Ph. D. Thesis

THEORETICAL AND EXPERIMENTAL STUDY OF COOPERATIVITY EFFECTS IN NONCOVALENT INTERACTIONS

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Theoretical and Experimental Study of Cooperativity Effects in Noncovalent Interactions

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CERTIFICAN:

Que la Memoria que lleva por título *Theoretical and Experimental Study of Cooperativity Effects in Noncovalent Interactions* presentada por Carolina Estarellas Martín para obtener el grado de Doctor en Ciencia y Tecnología Química, ha sido realizado bajo nuestra dirección conjunta en el Departamento de Química (Área de Química Orgánica) de la Universitat de les Illes Balears durante los años 2008-2012, y cumple los requisitos para optar a Mención Europea.

Palma de Mallorca, 07 de Junio de 2012.

Dr. Pere M. Deyà Serra

Dr. Antonio Frontera Beccaría

A mis padres y
mis abuelos,

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(T.S. Elliot)

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PROLOGUE

The present thesis is organized as a compendium of articles derived from the investigation carried out during the last four years. The objective of this prologue is to clarify the outline of this thesis.

Chapter 1 collects a detailed introduction to focalize the main subject of this research, ranging from the wide field of Supramolecular Chemistry to the particular analysis of the anion–π interaction, which is the protagonist of this investigation. Additionally, an extensive description of different noncovalent interactions and physical forces that govern them can be found.

In *Chapter 2* the general objectives and motivation of this research are summarized.

The thesis is organized around three main objectives that I desired to achieve in this research. Every objective occupies a chapter and it is treated in detail. For this reason, in Chapters 3, 4 and 5 the reader will find the same distribution for his/her comfort. It starts with a background about the main issue summarizing the motivation and previous results about the topic. The second part gathers the results and discussion section where I have tried to recapitulate the most important facts of the research during my training. In the same section the published articles with all the information about the investigation are included. Each chapter finalizes with the main conclusions.

Chapter 3 is divided into two parts. Firstly, the theoretical part implies the design and the study of the most convenient moiety to establish π interactions and its possible competition with σ interactions. Secondly, the transfer of theoretical knowledge previously obtained into the experimental field has been carried out. Four papers have been published from this research.

In *Chapter 4* all studies devoted to analyse different combinations of noncovalent forces are presented, where one of the most important parts imply the formula, concepts and parameters used for the assessment of the cooperativity effects. Due to the quantity of information included in this chapter the most important features have been highlighted to facilitate the reading. It is the chapter which we have studied more in-depth, clearly reflected by the publication of eight papers.

Chapter 5 represents the culmination of this work, with the theoretical study of anion–π interactions in biological systems. This chapter is divided into two more differentiated sections. On the one hand, the examples of biological systems that present anion–π interaction, and on the other hand, one more extended concept of the anion–π, i.e., the radical anion–π interactions and the influence of transition-metal ions on anion–π interactions. From this stage, we have published four papers, two related to biological systems and two related to extended varieties of anion–π interaction.

Finally, *Chapter 6* assembles all main conclusions derived from this thesis.

At the end, all bibliographic sources in reference to the subject are also included. Besides, a set of annexes that contain information about the computational methods and experimental section, as well as published works derived from this research or from the collaboration with different research groups carried out during this period, can be found.

TABLE OF CONTENTS

ABBREVIATIONS

Aπ	Anion–π Interaction
AIM	Atoms in Molecules
ASE	Aromatic Stabilization Energy
a. u.	Atomic Units
AU	Absorbance Units
B3LYP	Becke, three parameter, Lee-Yang-Parr
BCP	Bond Critical Point
BF_4^-	Tetrafluoroborate anion
BLYP	Becke-Lee-Yang-Parr
BNZ	Benzene
BP86	Becke-Perdew
Bptz	3,6–bis(2–pyridyl)–1,2,4,5–tetrazine
BQ	Benzoquinone
Br^-	Bromide anion
BSSE	Basis Set Superposition Error
Cπ	Cation–π Interaction
CBS	Complete Basis Set
CC	Coupled Cluster
CCP	Cage Critical Point
CD	Circular Dichroism
$CDCl_3$	Chloroform
CHπ	C–H··· π Interaction
CHelp	Charges from Electrostatic Potential
CI	Configuration Interaction
Cl^-	Chloride anion
COSMO	Conductor-Like Screening Model
CP	*Counterpoise* Technique
CSD	Cambridge Structural Database
DAB	1,4-diaminobenzene
DCM	Dichloromethane

DFT	Density Functional Theory
DMSO	Dimethylsulfoxide
EDA	Electron Donor-Acceptor Complex
EF	Edge-to-Face
ESI–FTICR–MS–MS	Electrospray Ionization Fourier–Transform Ion Cyclotron Resonance Mass Spectrometry
ESI–MS	Electrospray Ionization Mass Spectrometry
ESP	Electrostatic Surface Potential
EtOAc	Ethyl Acetate
F^-	Fluoride anion
fc	Frozen core
FF	Face to Face
fu	Full core
GGA	Generalized Gradients Approximations
GIAO	Gauge Invariant Atomic Orbitals
GTO	Gaussian Type Orbitals
$HAT(CN)_6$	1,4,5,8,9,12-Hexaazatriphenylenehexacarbonitrile
HB	Hydrogen Bond
HF	Hartree-Fock
HFB	Hexafluorobenzene
HOMA	Harmonic Oscillator Model of Aromaticity
HOMO	High Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
I^-	Iodide anion
ITC	Isothermal Titration Calorimetry
K_a	Association Constant
kcal mol^{-1}	Kilocalorie per mole
LDA	Local Density Approximations
l.p.–π	Lone pair–π Interaction
LUMO	Low Unoccupied Molecular Orbital
MEP	Molecular Electrostatic Potential
MIP	Molecular Interaction Potential
MIPp	Molecular Interaction Potential with polarization
MK	Merz-Kollman
MP2	Møller-Plesset 2

Mull	Mulliken
NDIs	Naphthalenediimides
NICS	Nucleus-Independent Chemical Shift
NO_3^-	Nitrate anion
NPA	Natural Population Analysis
OFF	Offset Face-to-Face
O–NDIs	Oligonaphthalenediimides
ππ	π–π Stacking Interaction
PBE	Perdew-Burke-Ernzerhof
PDB	Protein Data Bank
PDPNL	3,3'-(1,4-phenylene)dipropiolonitrile
PF_6^-	Hexafluorophosphate anion
Pol	Polarization
PYR	Pyrazine
Q_{zz}	Quadrupole moment
q	Point Charge
QM	Quantum Mechanics
RCP	Ring Critical Point
RI	Resolution of the Identity
SAPT	Symmetry-Adapted Perturbation Theory
SCF	Self-Consistent Field
sIND	4,7-dihydro-1H-dipyrrolo[2,3-2:2',3'-g]indole
SOMO	Single Occuppied Molecular Orbital
TBA	*n*–tetrabutylammonium salts
TFB	1,3,5-Trifluorobenzene
TMS	Tetramethylsilane
TPAL	Terephthaldehyde
TPNL	Terephthalonitrile
μ_z	Dipole Moment
vdW	van der Waals
XB	Halogen Bond

ABSTRACT

Ten years ago, the interaction between anions and hexafluorobenzene, where the anion is positioned over the ring along to the C_6 axis, was named "Anion–π Interaction" by our research group. At the same time, two other research groups demonstrated, theoretically, that the interaction of anions with electron-deficient aromatic rings is favourable. Since then, many efforts have been made to study its physical nature until its actual understanding.

In the last years, it has begun the evaluation of, on the one hand, the force of this interaction in combination with other noncovalent interactions and, on the other hand, the existence of this interaction experimentally. This thesis is based on these key topics, which are summarized as follows.

In the early stages of this thesis the theoretical design of building blocks to obtain the more favourable anion–π interaction by means of computational calculations was developed. After that, this knowledge was transferred into the experimental field to, subsequently; assess the force of the interaction in solution by experimental techniques.

Later, the research was mainly centred in the evaluation of the interplay between many combinations of noncovalent interactions and in the study of the existence of cooperativity effects. Herein, the definition of formulas to calculate the synergetic effects between the forces and new concepts as synergetic stability is described. This field is crucial for Supramolecular Chemistry and Molecular Recognition since it involves the intelligent utilization of noncovalent interactions between the molecules assembled. Additionally, the cooperativity effects have a key role in biological systems and crystal engineering. In the former area the importance is because these systems are based on impressively efficient and intricate combinations of noncovalent interactions. In the latter field, the crystal structure prediction needs a precise understanding and a complete control over the interplay of weak interactions responsible for crystal packing, since they are operating simultaneously.

Finally, we have focused our attention in the impact of the anion–π interaction in biological systems, showing the first theoretical example where the presence of this interaction between an inhibitor and an enzymatic substrate is proposed to be crucial in the inhibition of an enzyme. In the last stage of this research, we have extended the study of the anion–π interaction to innovative and different versions of this force from a theoretical point of view, focusing mainly on the influence that new modifications cause in the physical nature of the

interaction. The results derived from this investigation are related to the radical anion–π and the study of this interaction when a transition-metal ion belongs to the anion.

RESUMEN

Diez años atrás, nuestro grupo de investigación definió la interacción entre aniones y la molécula de hexafluorobenzeno como "Interacción Anión–π", cuando el anión se localizaba sobre el eje de simetría C_6 de la molécula. Al mismo tiempo, otros dos grupos de investigación se sumaron a la investigación de esta nueva interacción, demostrando teóricamente que la interacción entre aniones y anillos aromáticos electrodeficientes era favorable. Desde entonces se han realizado grandes esfuerzos para estudiar su naturaleza física hasta su actual comprensión.

En los últimos años se ha empezado a evaluar; por un lado, la fuerza de esta interacción en combinación con otras interacciones no covalentes; y por otro lado, la existencia de la interacción experimentalmente. Esta tesis se basa en estos puntos clave, resumidos a continuación.

En un principio, la investigación se dirigió hacia el diseño teórico de motivos estructurales para dar lugar a la interacción anión–π más favorable. Este proceso se llevó a cabo mediante herramientas computacionales. A continuación, se transfirieron los conocimientos adquiridos mediante los cálculos a un laboratorio experimental, donde se cuantificó la interacción anión–π en disolución mediante espectroscopia de resonancia magnética nuclear de protón.

Posteriormente, la investigación se centró principalmente en la evaluación de las interrelaciones entre un gran número de combinaciones de interacciones no covalentes y, en el estudio de la existencia de efectos cooperativos entre ellas. Aquí se definen nuevos conceptos como el de estabilidad sinérgica y se proponen diferentes fórmulas para calcular los efectos de cooperatividad, que son muy importantes en Química Supramolecular y Reconocimiento Molecular. Además, los efectos de cooperatividad tienen un impacto importante en sistemas biológicos o en ingeniería de cristales. En el primero, la importancia se debe a que estos sistemas están basados en una combinación muy complicada de interacciones no covalentes, que funcionan de manera altamente eficiente. En el caso de la ingeniería de cristales, la predicción de estructuras cristalinas necesita una comprensión precisa y un control completo sobre las relaciones de las interacciones débiles, responsables del empaquetamiento cristalino, que operan simultáneamente.

Finalmente, en el último estadio de esta investigación, nos hemos centrado en el impacto de la interacción anión–π en sistemas biológicos, presentando el primer ejemplo teórico donde

la presencia de una interacción de esta naturaleza entre el inhibidor y el sustrato enzimático se propone como un paso vital en la inhibición del enzima. En esta última etapa, también se ha extendido el estudio de la interacción anión–π a diferentes e innovadoras versiones de esta fuerza. Se ha llevado a cabo un estudio teórico centrándonos principalmente en la influencia de las nuevas modificaciones sobre la naturaleza física de la interacción. Los trabajos derivados de esta investigación están relacionados por un lado, con la interacción anión–π radical, y por otro lado, con el estudio de la interacción anión–π cuando en el anión está presente un metal de transición.

Chapter 1. Introduction

CHAPTER 1. INTRODUCTION

Chemistry is a multidisciplinary field that lets us generate new molecules and new materials with a multitude of applications in several fields.

1.1. SUPRAMOLECULAR CHEMISTRY

Molecular Chemistry studies molecules based on covalent bonding without considering the interactions that can be established between different molecules, as shown in Figure 1.1.

Synthetic chemistry only based on covalent bonding cannot generate big complex structured molecules with capacity to respond to physics and/or chemical stimuli. Until recent years, this kind of chemistry centres its attention in the study of the covalent interactions with the idea to obtain new molecules. The capacity of biomolecules, as proteins or nucleic acids, to selectively recognize and link to other species forming larger complexes is a key element in Chemistry. Therefore a bigger interest arose in mimic processes involving the mutual recognition of two molecules by means of the formation of noncovalent unions between them. With the objective of carrying out the new purposes, a new discipline emerged: the Supramolecular Chemistry[1,2] (*supra*, in Latin means *above*), dedicated to the study, design and synthesis of molecular structures linked between them by means of noncovalent interactions. This subject was initiated from the pioneer works of Jean-Marie Lehn in 1969 about the idea of molecular recognition and led him to obtain the Nobel Prize in 1987 together with Donald J. Cram and Charles J. Pedersen.

J.-M. Lehn defined the Supramolecular Chemistry as "Chemistry of the union between molecules through the intermolecular bonds",[2] "Chemistry beyond the molecules" or "Chemistry of noncovalent bonding". More recently, Lehn has added a more functional definition which includes previous definitions: "Supramolecular Chemistry directs to the development of big complexed chemical systems, from the components that interact between them by means of intermolecular noncovalent forces"[3] and has opened a new field where the interests of various disciplines of Chemistry converge, including Biorganic and Bioinorganic Chemistry, Biochemistry, Materials Science and Nanotechnology.

[1] J. M. Lehn, *Supramolecular Chemistry. Concepts and Perspectives*, VCH: Weinheim ed., Germany, **1995**.
[2] J. W. Steed; J. L. Atwood, *Supramolecular Chemistry*, John Wiley & Sons: West Sussex ed., UK, **2000**.
[3] J. M. Lehn, *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 4763-4768.

Figure 1.1. Molecular and Supramolecular Chemistry.

Therefore, the Supramolecular term introduced by J.M. Lehn[4] in the year 1978 refers to the ordered sets of molecules that maintain linked by a variety of interactions of noncovalent nature.

One supramolecule is obtained from the formation process of one molecule that acts as receptor (*host*) and another that acts as substrate or *guest*, binding to the first one to obtain a receptor-substrate complex.[5,6] Normally, the receptor is a big molecule or aggregate, as an enzyme or macrocycle, with an adequate cavity. The substrate can be an inorganic single ion or a more complex molecule, as for example a hormone or neurotransmitter. The associations between the receptor and substrate molecules are based on intermolecular interactions that are, in general, weaker than covalent bonds. For this reason, several simultaneous interactions are established between the complexation sites of both molecules which are the normal procedure in biological systems, ensuring the efficiency of the replication process, the enzyme-substrate interactions or antigen-antibody, as in other important biological functions. In summary, the receptor would be the molecule formed by covalent bonds able to complex the substrate through intermolecular noncovalent interactions allowing the formation of a supramolecule.

An important requirement for the multiarea combination is the complementarity between the complex places of the receptor and substrate molecules, the better they fit together the more efficient the complexation will be. This is the general concept of the key-lock proposed by E. Fisher,[7] who explains the notable specificity of the enzyme catalysis one century ago, establishing the basis that today are known as Molecular Recognition.

The first studies in the Supramolecular Chemistry field are centred in the selective gathering of alkaline cations by macrocyclic ligands and natural or synthetic macropolycyclics,[8,9,10,11] as crown ethers[12,13,14] and kriptands.[15] This new research field

[4] J. M. Lehn, *Angew. Chem., Int. Ed. Engl.* ***1988****, 27, 89-112.*
[5] D. J. Cram, *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009-1020.
[6] D. J. Cram, J. M. Cram, *Science* **1974**, *183*, 803-809.
[7] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2985-2993.
[8] Y. A. Ovchinnikov; V. T. Ivanov; A. M. Scrob, *Membrane Active Complexones*, Elsevier ed., New York, USA, **1974**.

experienced fast growth in the development of new synthetic receptor molecules. The new receptors are prepared to selectively capture cationic, anionic or neutrals substrates and can be of organic, inorganic and biological nature through electrostatic, van der Waals, metal coordination and/or hydrogen bonding intermolecular interactions.

While the complexation of cations has been object of studies since one century ago, the anion complexation in Supramolecular Chemistry[16,17,18] has received very little attention until recently. The appearance of synthetic molecules capable of complexing cations or anions was almost simultaneous. In 1967 C. J. Pedersen prepared the first organic synthetic ligand capable of complexing cations.[13] One year after C. H. Park and H. E. Simmons synthesized the first one able to complex anions denominated katapinate (*katapnosos*, in Greek means *swallow*).[19] Both receptors present in Figure 1.2.

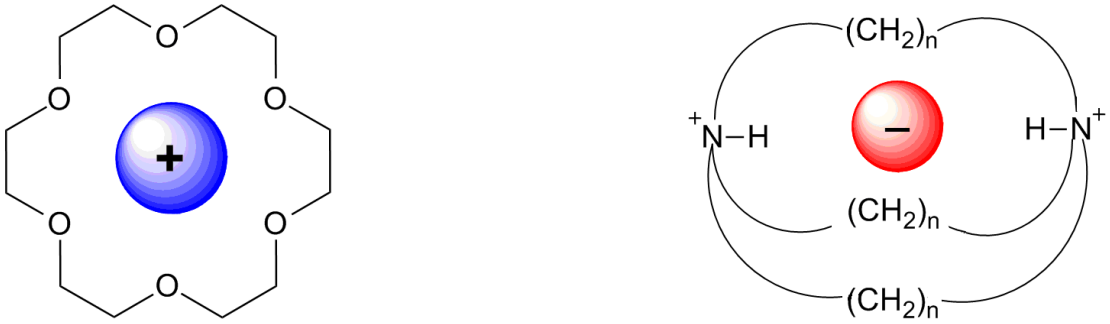

Figure 1.2. The 18-crown-6 ether compound, synthesized by Pedersen, is able to complex alkaline cations. The katapinate synthesized by Park and Simmons is able to complex halide anions.

Despite this almost simultaneous discovery, the field of anions complexation remained relatively unexplored in contrast with the cations, maybe due to the intrinsic peculiarities associated with the anions (solubility, hydration energy, size and the big variety of geometrical forms).

[9] B. C. Pressman, *Annu. Rev. Biochem.* **1976**, *45*, 501-530.
[10] M. M. Shemyakin, N. A. Aldanova, E. I. Vinogradova, M. Y. Feigina, *Tetrahedron Lett.* **1963**, 1921-1925.
[11] B. C. Pressman, *Proc. Natl. Acad. Sci. U. S. A.* **1965**, *53*, 1076-1083.
[12] C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 2495-2496.
[13] C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 7017-7036.
[14] C. J. Pedersen, *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021-1027.
[15] J. M. Lehn, *Science* **1985**, *227*, 849-856.
[16] A. Bianchi; K. Bowman-James; E. García-España, *Supramolecular Chemistry of Anions*, Wiley-VCH ed., New York, USA, **1997**.
[17] P. D. Beer, P. A. Gale, *Angew. Chem., Int. Ed.* **2001**, *40*, 486-516.
[18] F. P. Schmidtchen, *Anion Sensing* **2005**, *255*, 1-29.
[19] C. H. Park, H. E. Simmons, *J. Am. Chem. Soc.* **1968**, *90*, 2431-2432.

In the last years, the investigation of anions in Coordination Chemistry field has experienced a great growth,[20] as a result of the importance of anions in the biological world as, for example:

- The transport of genetic information through the DNA, which is a polianion,
- The biocatalyzed processes through anionic cofactors and substrates.

Moreover, the anions are the leads in environmental subjects as:

- Phosphate anions in case of the eutrophication of rivers,[21]
- Nitrate anions, whose carcinogenic metabolites[22] can be present in waters as consequence of a high use of fertilizers,
- Pertecnate radioactive anion ($^{99}TcO_4^-$), subproduct of nuclear process, dumping at sea.[23]

Other key concept in Supramolecular Chemistry is the self-assembly that can be defined as the process through the supramolecular species are spontaneously formed from their components. It is necessary to highlight, that this process is not only reserved for Supramolecular Chemistry, but is present in nature: the DNA structure, the formation of lipid bilayers, the secondary, tertiary and quaternary conformations of proteins, among other examples. The common factor to all these self-assembly processes is the requirement of chemical and structural complementarity of different components through the numerous noncovalent interactions, as mentioned above, the multiarea combination.

Before completing this section, the difference between the supramolecule and supermolecule terms should be clarified. The supramolecular word is a term of ample meaning, concerning all the fields of Chemistry that presents more or less organized polimolecular associations. On the other hand, in Theoretical Chemistry, the computational procedure that treats the molecular associations just as if they were a unique entity described by a unique wave function is denominated supermolecular approach.[24]

Therefore, the key and repetitive feature in all supramolecular compounds is the fact that the union between the various components is done through noncovalent interactions.

[20] F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609-1646.
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1.2. NONCOVALENT INTERACTIONS

Noncovalent interactions have a constitutive role in the science of intermolecular relationships. Chemical and biological assembly processes orchestrated by noncovalent bonding are directed by elegant expressions of collective behaviour on the molecular scale.[25] In nature, these interactions are the foundation of the life process itself, the ultimate function articulation, both mechanical and cognitive. In synthetic chemistry, interactions between rationally designed molecular subunits drive the assembly of nanoscopic aggregates with targeted functions. Research in this area is inspired by everything from the basic mechanisms of function to structural feature of biological systems. [2,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41] A clear understanding and accurate description of the full compass of interactions between molecules is essential for the development of Supramolecular Chemistry, particularly the elucidation of the mechanisms of biological functions and the development of new synthetic applications in Catalysis, Materials Science and Medicine.

Noncovalent interactions involving aromatic rings play an essential role in chemistry and biology.[33] This role becomes prominent in drug receptor interactions, crystal engineering and protein folding.[42] It has been estimated that around 60% of aromatic amino acid side chains (histidine, phenylalanine, tyrosine, and tryptophan) participate in π–π stacking interactions in proteins.[43] The role of stacking interactions in DNA and RNA is also of undisputed importance, wherein nucleobase intra- and interstrand stacking help to stabilize the structure of DNA duplexes.[43,44] Moreover, biological processes involved in the control and regulation of gene expression are dependent on protein–DNA aromatic interactions, as the action of intercalating

[25] H. J. Schneider, *Angew. Chem., Int. Ed.* **2009**, *48*, 3924-3977.
[26] F. Vögtle, *Supramolecular Chemistry: An Introduction*, Wiley ed., New York, **1993**.
[27] G. V. Oshovsky, D. N. Reinhoudt, W. Verboom, *Angew. Chem., Int. Ed.* **2007**, *46*, 2366-2393.
[28] P. D. Beer; P. A. Gale; D. K. Smith, *Supramolecular Chemistry*, Oxford University Press ed., Oxford, **1999**.
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[30] *Y. Inoue; G. Gokel; M. Dekker, Cation Binding by Macrocycles New York, **1990**.*
[31] M. Kruppa, B. Konig, *Chem. Rev.* **2006**, *106*, 3520-3560.
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[33] E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem., Int. Ed.* **2003**, *42*, 1210-1250.
[34] R. W. Saalfrank, H. Maid, A. Scheurer, *Angew. Chem., Int. Ed.* **2008**, *47*, 8794-8824.
[35] L. R. Nassimbeni, *Acc. Chem. Res.* **2003**, *36*, 631-637.
[36] C. A. Hunter, *Angew. Chem., Int. Ed.* **2004**, *43*, 5310-5324.
[37] H. J. Schneider, *Chem. Soc. Rev.* **1994**, *23*, 227-234.
[38] H. J. Schneider, A. K. Yatsimirsky, *Chem. Soc. Rev.* **2008**, *37*, 263-277.
[39] H. Gohlke, G. Klebe, *Angew. Chem., Int. Ed.* **2002**, *41*, 2645-2676.
[40] R. R. Arvizo, A. Verma, V. M. Rotello, *Supramol. Chem.* **2005**, *17*, 155-161.
[41] D. H. Williams, E. Stephens, D. P. O'Brien, M. Zhou, *Angew. Chem., Int. Ed.* **2004**, *43*, 6596-6616.
[42] K. Muller-Dethlefs, P. Hobza, *Chem. Rev.* **2000**, *100*, 143-167.
[43] S. K. Burley, G. A. Petsko, *Science* **1985**, *229*, 23-28.
[44] S. Li, V. R. Cooper, T. Thonhauser, B. I. Lundqvist, D. C. Langreth, *J. Phys. Chem. B* **2009**, *113*, 11166-11172.

drugs.[45] Another related function occurs within the active sites of various DNA repair enzymes that excise alkylated purines via a recognition mechanism based on π–π interactions with aromatic amino acid residues.[46] These interactions also play a key role in the repair process where aromatic amino acids are inserted into the DNA strand to maintain the stability when the damaged base is flipped out of the duplex and into the active site of the repair enzyme.[46]

Noncovalent interactions include a wide range of attractive and repulsive forces of different nature, force and directionality.

In this case, it is convenient first to describe the different features of the interactions, including their classification and focusing to the ones studied in this thesis.

Covalent bonds determine the disposition of atoms inside the molecule, but the bonds responsible for the conformation of the molecules or the molecular aggregations are the molecular interactions.

Intra- and intermolecular interactions play an important role in chemical reactions and Molecular Recognition, then the specificity and the efficiency of these chemical processes are obtained by means of combinations of weak molecular interactions. An interaction covers all the effects that can occur between two bodies, including the forces between them. Although not having the same meaning, the terms of interaction and force are usually used undistinguishably. Only, from the elucidation of the electronic structure of atoms and molecules and the development of the quantum theory in 1920, it was possible to start understanding the origin of intermolecular forces. Early, it was established that the origin of all molecular forces was essentially electromagnetic. This affirmation is implicit in the Hellman-Feynman theorem,[47] which postulates that the intermolecular forces can be calculated based on classic electrostatics, once the electronic distribution is known from the Schrödinger equation resolution. Although other magnetic or gravitational forces exist, not originally electrostatic, their magnitudes are negligible compared to electrostatic forces (even when the cooperativity nature of ferromagnetism plays a role, magnetic forces are weaker).

[45] D. Y. Kim, N. J. Singh, J. W. Lee, K. S. Kim, *J. Chem. Theory Comput.* **2008**, *4*, 1162-1169.
[46] J. T. Stivers, Y. L. Jiang, *Chem. Rev.* **2003**, *103*, 2729-2759.
[47] R. P. Feynman, *Phys. Rev.* **1939**, *56*, 340-343.

One of the first classifications of the components of the interaction energy was carried out by C. A. Coulson.[48] In this, the electrostatic contribution, the delocalization and the repulsion are distinguished. Later, a fourth contribution was added due to the dispersion.

Another very popular classification[49,50,51] refers to two great groups of forces: "long range" and "short range". The interaction energy of long range forces is a function of r^{-n}, while short range forces depend on $e^{-\alpha r}$, consequently this division has a theoretical fundament.

1.2.1. LONG RANGE FORCES

The energy associated to these forces is a function of the inverse power of the distance between interacting molecules. The attractive component of the long range forces is significant when the electronic cloud superposition is small.

There are five contributions to the long range interaction energy, whose degree of participation depends on the nature of the molecules:

- Electrostatic,
- Induction,
- Dispersion,
- Resonance,
- Magnetic.

The last two effects occur when one of the molecules is in a degenerate state (usually an excited state) or when both molecules have unpaired spins, respectively, but it will not be explained because is not the case of this study.

1.2.1.1. Electrostatic Forces

The electrostatic effects emerge from the classic interaction between specific charges (monopoles) or from the distribution of static charges of two molecules (multipoles), not from charge distributions modified by interactions. For this reason the total charge distribution must be determined from the charge distribution of free molecules. In Figure 1.3 different charge distributions are shown as a result of a series of electric moments.

[48] C. A. Coulson, *Research* **1957**, *10*, 149.
[49] A. D. Buckingham; P. Claverie; R. Rein; P. Schuster; B. Pullman, *Intermolecular Interactions: From Diatomics to Biopolymers. Chapter 1 Basic Theory of Intermolecular Forces: Applications to Small Molecules.*, John Wiley & Sons: ed., Chichester, UK, **1978**.
[50] G. C. Maitland; M. Rigby; E. B. Smith; W. A. Wakeham, *Intermolecular Forces: Their Origin and Determination*, Clarendon Press ed., Oxford, UK, **1987**.
[51] A. J. Stone, *The Theory of Intermolecular Forces*, Clarendon Press ed., Oxford, UK, **2000**.

POINT CHARGE (q): As a result of the situation of a molecule having a different number of protons and electrons, resulting in a net charge supported by the molecule. The units are: *e* (ua) or Coulomb (SI); 1 $e = 1.602 \cdot 10^{-19}$ C.

DIPOLE MOMENT (μ_z): The interaction between two charges of equal magnitude but of opposite sign generates a dipole. The direction of the dipole is from the negative to positive charge centres. The permanent dipole moments result from the different electronegativities of the atoms in a molecule necessarily asymmetric. In general, to describe a molecule as being polar it is equivalent to say that it possesses a permanent dipole moment. The units are: ea_0 (ua), Cm (SI) or Debye; $1ea_0 = 2.5418$ D $= 8.478 \cdot 10^{-30}$ Cm.

QUADRUPOLE MOMENT (Q_{zz}): A molecule possesses a non-zero electric quadrupole moment when it presents symmetric non-spherical charge distribution. This can be achieved from four charges arranged in a two-dimensional space that sum zero without generating a net dipole. The units are: ea_0^2 (ua), Cm^2 (SI) or Buckingham; 1 $ea_0^2 = 1.3450$ B $= 4.4865 \cdot 10^{-40}$ Cm^2.

The following higher order multipole moments are the octupole and hexadecapole, that can be expressed as eight and sixteen charges arranged in the space, although the series continues indefinitely.

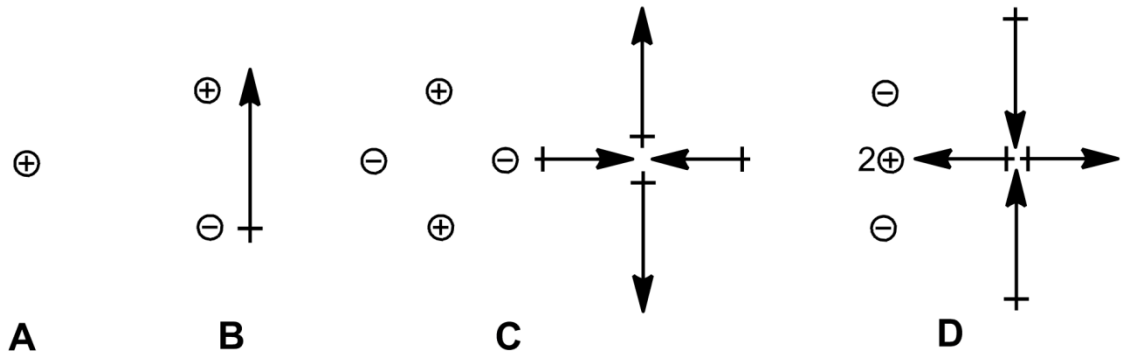


Figure 1.3. A) Point charge. B) Dipole moment. C) and D) Quadrupole moments generated by the disposition of point charges in the space.

One electrostatic interaction can take place between two charges, between one charge and one multipolar moment, or between two multipole permanent moments. The forces that derive from purely electrostatic interactions are strictly additive and can be of attractive or repulsive character.

When two molecules that possess net charge interact, the main force involved is derived from the interaction between both charges, although other interactions can also participate (i.e. between multipole moments), they will be weaker and for this reason, often neglected.

The central multipole expansion[52] (Equation 1.1) shows the electrostatic potential at point P by means of the sum of a finite series of charge-charge, charge-dipole, dipole-dipole, charge-quadrupole, dipole-quadrupole, quadrupole-quadrupole interactions. The electrostatic potential (V(r)) calculated a distance **r** from the centre of mass is represented in Figure 1.4

$$V(r) = \frac{1}{4 \cdot \pi \cdot \varepsilon_0}\left(\frac{q}{r} + \frac{\mu_z \cdot cos\,\theta}{r^2} + \frac{Q_{zz}(3\,cos^2\,\theta - 1)}{2r^3} + \cdots\right)$$

Equation 1.1

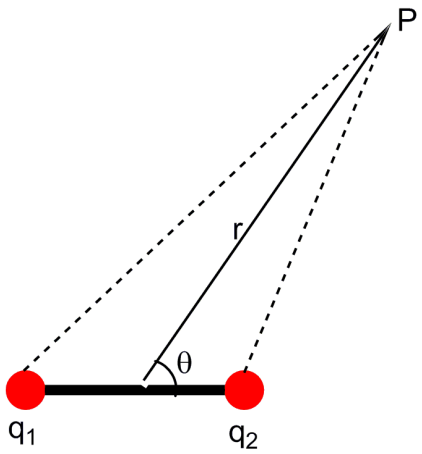


Figure 1.4. Electrostatic potential due to two point charges.

Depending on the interacting systems, more terms of multipole expansion can be added as needed to properly define the interaction. For example, in ionic solids, the term charge-charge is the dominant (r^{-1}); in polar fluids a sufficient approximation is to use the dipole-dipole energy (r^{-3}) and in centre-symmetric molecules (as H_2 or N_2, in any state of the matter), the quadrupole-quadrupole interaction (r^{-5}) is a good representation of the electrostatic energy.

Through the central multipole expansion, it is possible to predict the more favourable orientations when a series of multipoles are facing as shown in Figure 1.5.[53]

[52] J. O. Hirschfelder; C. F. Curtiss; R. B. Bird, *Molecular Theory of Gases and Liquids*, Wiley ed., New York, USA, **1964**.
[53] A. D. Buckingham, *Quarterly Reviews* **1959**, *13*, 183-214.

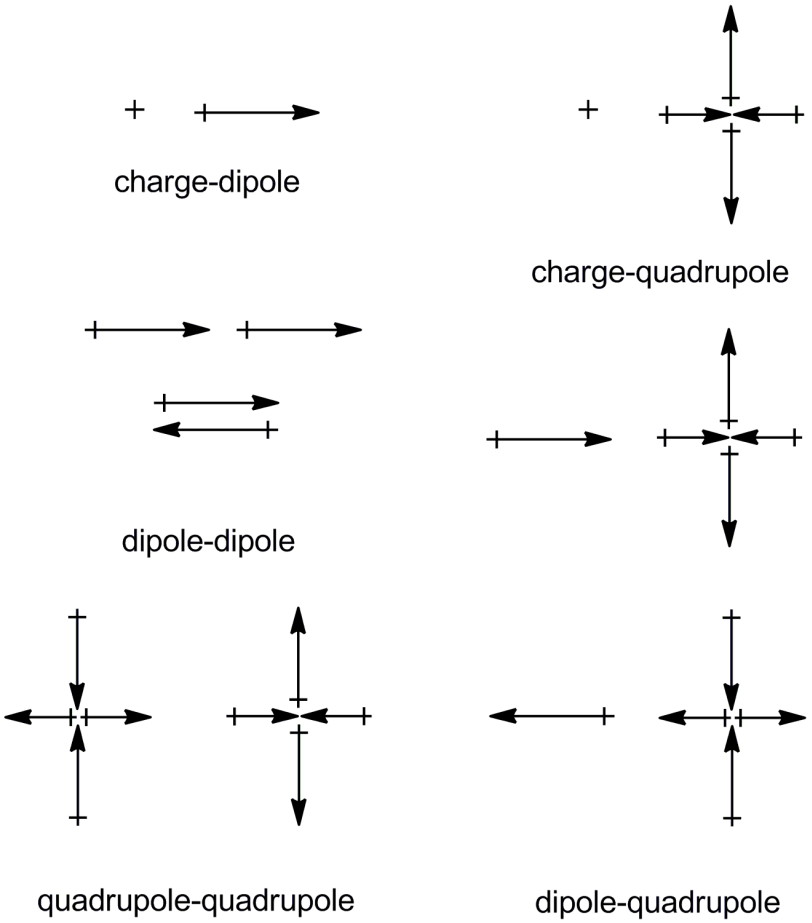


Figure 1.5. More favoured orientations for interactions between several electric moments.

1.2.1.2. Inductive Forces

Inductive effects arise from the deformation of the charge distribution of a molecule caused by an external electric field generated by neighbouring molecules. In the interaction between a dipolar and an apolar molecule, the electric field of the former molecule distorts the electronic charge distribution of the latter molecule generating an induced dipolar moment. Then, this induced dipole moment interacts with the permanent dipole resulting in an attractive force. This concrete case is named interaction of Debye since it was described by him.[54]

When some of the interacting molecules have permanent electric moment, induction interactions are present, although become less relevant if the electrostatic contribution is large. Since induction energy is the result of the deformation of the charge distribution in response to an external field, it is always negative for molecules in their fundamental electronic states.

[54] P. Debye, *Polar Molecules, Chemical Catalog Company*, New York, USA, **1929**.

The molecular polarizability (α in Equation 1.2) is the trend of a molecule to be polarized, i.e., the facility of creating a dipole induced moment ($\mu_{induced}$) because of electric external fields produced by neighbouring molecules. The polarizability in the atoms and molecules is defined in agreement with the force that acquires the dipole induced moment in the electric field, being the constant of proportionality between the external field and the induced moment in the non-polar molecule.

$$\mu_{induced} = \alpha \cdot E$$

Equation 1.2

The polarizabilities of all molecules, apart from those of spherical symmetry, are anisotropic and have different values in the different directions. In linear molecules, there are only two independent components of the polarizability. The dipole moment of a molecule varies according to the expression in Equation 1.3:

$$\mu_{effective} = \mu + {}^{1}/_{2}\,\alpha E + {}^{1}/_{6}\,E\beta E + \cdots$$

Equation 1.3

Where;

- μ is the permanent dipole moment,
- α is the molecular polarizability,
- β is the molecular hiperpolarizability (non-linear polarizability).

In fact all the electric moments are altered by the presence of external electric field; however, tending to focus the attention in the dipolar polarizability, as well as in permanent electric moments, an induced dipole has a bigger influence in the interaction energy than an induced quadrupole.

1.2.1.3. Dispersive Forces

The origin of attractive forces between non-polar molecules was a serious problem at the beginning of twentieth century, until 1930, when F. London[55,56] described them using a second order perturbational theory, pointing to a relationship between these forces and the optic dispersion in gases, namely dispersion forces. Also they are named London forces and are the only long range forces present in all molecular interactions; in fact they are the only long range

[55] F. London, *Z. Phys. Chem.* **1930**, *63*, 245-279.
[56] F. London, *Z. Phys. Chem.* **1930**, *11*, 222-251.

forces present in the case of interaction between neutral apolar molecules, representing the most important contribution to van der Waals forces, except in small polar molecules.

The dispersion energy cannot be analysed in classic terms due to having its origin in quantum mechanics, and comes from the continuous fluctuation of charge distribution of molecules due to electron movement. These movements are correlated and the resultant effect is a diminution in the energy, consequently the dispersive forces are always attractive and practically additive.

Due to electronic density of molecules varying continuously in time and space, generated instantaneous electric moments can induce an electric moment in a second molecule. Between the induced multipole of the second molecule and the inductor of the first one an attractive force emerges instantaneously named dispersion force.

In general mode, the dispersion energy is attributed to the interaction of different instantaneous multipoles of the molecules, as described in the Drude model[57] expanded in series (Equation 1.4).

$$E = \frac{C_6}{r^6} + \frac{C_8}{r^8} + \frac{C_{10}}{r^{10}} + \cdots$$

Equation 1.4

The coefficients C_n are negative and correspond to the attractive interaction placed between the series of instantaneous multipoles: dipole-dipole (C_6), dipole-quadrupole (C_8), quadrupole-quadrupole (C_{10}), etc.

Since polarizability is a measure of the charge fluctuation in a molecule, the instantaneous and induced multipoles can be related with their polarizabilities, so that the higher the polarizabilities of molecules, the stronger the dispersion interactions.

1.2.2. SHORT RANGE FORCES

The forces that participate in the interaction energy as a consequence of orbitalic overlap constitute the group of short range forces, they are only important at short distances.

The most important contribution to the energy of short range normally is described as exchange-repulsion. This is a double effect combination. The interchange energy is a consequence of the Pauli principle that, due to the prohibition of putting two electrons in a system with the same set of quantum numbers, reduces the electrostatic repulsion between

[57] P. K. L. Drude, *The Theory of Optics* Longman ed., London, UK, **1933**.

electron pairs resulting in attractive term. The repulsion energy between two molecules comes from, on the one hand, the electrostatic repulsion of electrons of the molecules and, on the other hand, from the nuclei that are not totally protected. When the electronic clouds of two molecules are close enough to overlap, Pauli's principle of exclusion prohibits some electrons to occupy the same region of space, reducing the electronic density in this region; for this reason, the atomic nuclei are partially unprotected one from the other, generating repulsion between them.

Moreover we can find two important effects in the short range forces: charge transfer and charge penetration.

The **charge transfer** is an effect that considers part of the induction forces that act at short-range. The charge transfer model was introduced by Mulliken[58,59,60] in complexes that have an electron-rich (donor, D) and an electron-poor (acceptor, A) component. The acceptor component strongly attracts electrons and therefore these complexes are also known as electron donor-acceptor complexes (EDA).[61,62] In terms of resonance, the EDA complexes are represented as a hybrid of two structures as shown in Figure 1.6.

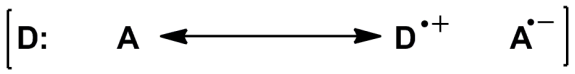


Figure 1.6. Representation of EDA complexes.

The structure on the left presents both components in a neutral state, while the one on the right, known as charge transfer structure, has had a total transfer of one electron. The last one contributes slightly to the total electronic structure. As the quantity of charge transfer in a complex from one component to the other is not an observable quantity, the obtained values will depend on the applied models. It has been demonstrated[63] that the charge transfer component in the interaction energy is generally small in comparison with other contributions, according to the experimental results.[64]

The **charge penetration** is an attractive effect of purely electrostatic origin that takes place at electronic distances where the interacting molecules overlap. Conceptually, it can be understood as the attraction that experiments the atomic nuclei partially unprotected of one

[58] R. S. Mulliken, *J. Am. Chem. Soc.* **1950**, *72*, 600-608.
[59] R. S. Mulliken, *J. Am. Chem. Soc.* **1952**, *74*, 811-824.
[60] R. S. Mulliken, *J. Phys. Chem.* **1952**, *56*, 801-822.
[61] H. A. Bent, *Chem. Rev.* **1968**, *68*, 587-648.
[62] Banthorp.Dv, *Chem. Rev.* **1970**, *70*, 295-322.
[63] A. J. Stone, *Chem. Phys. Lett.* **1993**, *211*, 101-109.
[64] F. Cozzi, M. Cinquini, R. Annuziata, J. S. Siegel, *J. Am. Chem. Soc.* **1993**, *115*, 5330-5331.

molecule to the electronic cloud associated to another molecule. As a consequence of this interaction, the multipolar expansion ceases to be valid at short distances.

Below a brief description of some important noncovalent interactions is included, where the forces explained above have a significant contribution. Some of the interactions explained here, have been studied and analysed in this thesis.

1.2.2.1. Ion-Ion Interaction

They are attractive interactions of electrostatic nature that occur between ions of different charge sign. The strength of these interactions are comparable to covalent bond. (Bonding energy = 25-85 kcal·mol^{-1}).

An example of a supramolecular system characterized by this interaction is observed in Figure 1.7. The interaction between the ligand tris(diazabicycleoctane)$^{3+}$ and the anion $[Fe(CN)_6]^{3-}$ is only observed in the solid state, since in solution solvation effects dominate and the complex is not formed.[65]

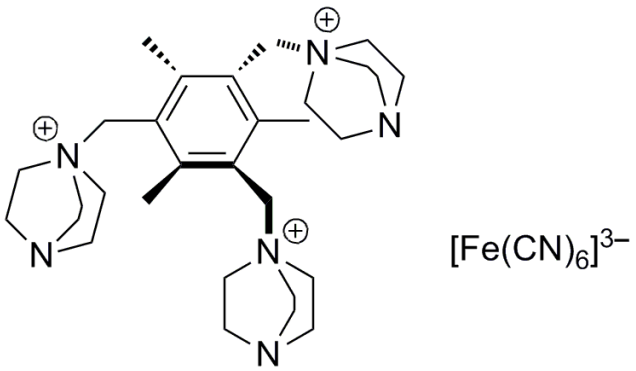


Figure 1.7. Ion-ion interaction between tris(diazabicycleoctane)$^{2+}$ and $[Fe(CN)_6]^{2+}$.

1.2.2.2. Ion-Dipole Interaction

This interaction takes place between an ion and a polar molecule. It exists in solid state and in solution and is weaker than the ion-ion interaction (bonding energy = 10-50 kcal·mol^{-1}). A classic model is the solvation process of an ion, as for example, Na^+ cation in water. The complexes formed by crown ethers and alkaline ions are other examples of ion-dipole interactions (see Figure 1.8). This complex has a marked ionic character due to the interaction between a small polarising cation and the lone pairs of the oxygen atoms.

[65] P. J. Garratt, A. J. Ibbett, J. E. Ladbury, R. O'Brien, M. B. Hursthouse, K. M. A. Malik, *Tetrahedron* **1998**, *54*, 949-968.

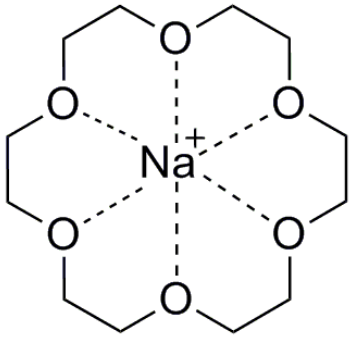


Figure 1.8. Crown ether within Na^+ cation in its interior.

1.2.2.3. Dipole-Dipole Interaction

They are attractive interactions of electrostatic nature between dipoles, due to the alignment of the opposite poles of both. They are weak interactions (Bonding energy = 1-10 kcal·mol^{-1}), especially in solution (see Figure 1.9).

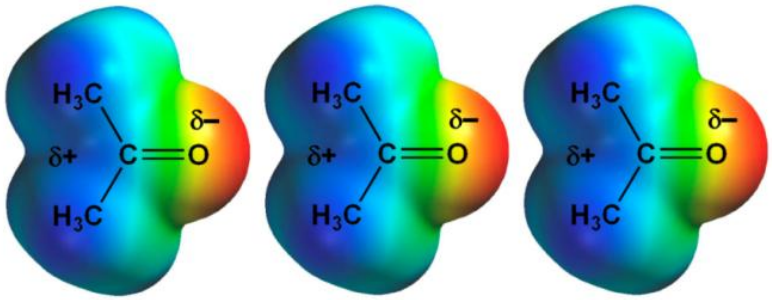


Figure 1.9. Dipole-dipole interactions in carbonylic compounds.

1.2.2.4. Hydrogen Bond, HB

It is a particular dipole-dipole interaction that takes place between an electronegative atom and a hydrogen atom linked to other electronegative atom or charge acceptor group. Usually, the HB is explained in function of the electron-donor or proton acceptor capability of involved groups. Based on this, it can be said that the hydrogen bond consists of a kind of dipole-dipole interaction between a functional group A (hydrogen acceptor) and an atom or atom groups D-H (hydrogen donor), so that both A and D must have certain electronegative character.

HB are directional and reversible interactions, whose force is variable (Bonding energy = 1-30 kcal·mol^{-1}) and very dependent of the electronegative character of the involved atoms and their environment (bond distances and angles with the hydrogen atom).[66,67,68,69,70,71]

[66] G. R. Desiraju, *Acc. Chem. Res.* **1991**, *24*, 290-296.
[67] S. Subramanian, M. J. Zaworotko, *Coord. Chem. Rev.* **1994**, *137*, 357-401.
[68] C. A. Hunter, *Chem. Soc. Rev.* **1994**, *23*, 101-109.

The hydrogen bonding can be appearing in different conformations that can influence their strength. The most common can be observed in the Figure 1.10 and would be:

- Simple,
- Bifurcated,
- Trifurcated,
- Bridge Cyclic,
- Cyclic dimer.

The hydrogen bond has a very important electrostatic component, but there are numerous cases where the hydrogen bonding has a very significant covalent nature.[72] Very strong interactions take place when the donor and acceptor groups are highly electronegative and both have the same electronegativity; therefore the hydrogen atom is practically located halfway. Strong hydrogen bonds character is mainly electrostatic in nature and occurs when both the donor and acceptor systems are hard bases of very electronegative character (N, O, F). The weak hydrogen bond takes place when the donor and acceptor groups are not so strong bases and have a marked van der Waals character, although the electrostatic component that follows is predominant. Two examples of weak hydrogen bond interactions with marked van der Waals character are the C-H···X and X-H···π contacts.[73,74,75,76]

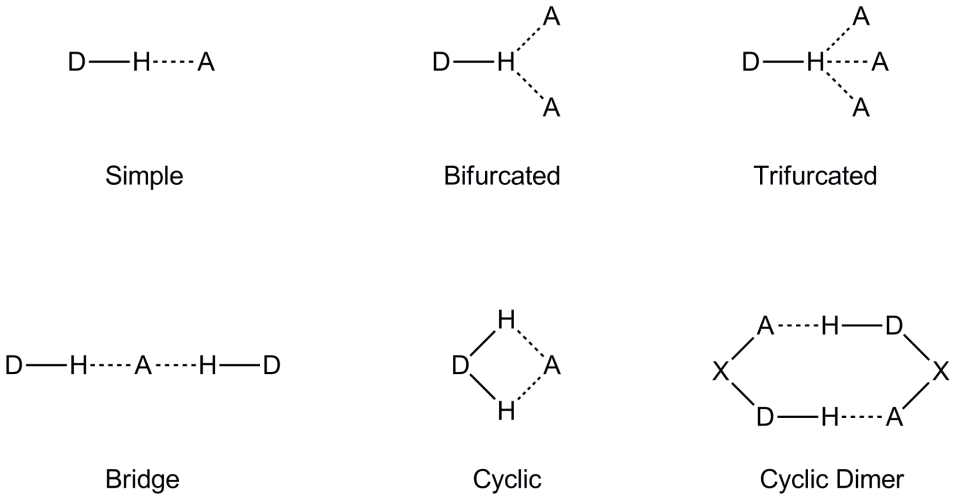


Figure 1.10. Most common conformations for Hydrogen-Bonding.

[69] H. Adams, F. J. Carver, C. A. Hunter, N. J. Osborne, *Chem. Commun.* **1996**, 2529-2530.
[70] G. R. Desiraju; T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Oxford University Press ed., Oxford, **1999**.
[71] V. R. Vangala, A. Nangia, V. M. Lynch, *Chem. Commun.* **2002**, 1304-1305.
[72] S. J. Grabowski, *Chem. Rev.* **2011**, *111*, 2597-2625.
[73] S. Tsuzuki, K. Honda, T. Uchimaru, M. Mikami, K. Tanabe, *J. Am. Chem. Soc.* **2000**, *122*, 11450-11458.
[74] T. Steiner, G. Koellner, *J. Mol. Biol.* **2001**, *305*, 535-557.
[75] H. Maeda, Y. Kusunose, *Chem.--Eur. J.* **2005**, *11*, 5661-5666.
[76] R. B. Bedford, M. Betham, C. P. Butts, S. J. Coles, M. B. Hursthouse, P. N. Scully, J. H. R. Tucker, J. Wilkie, Y. Willener, *Chem. Commun.* **2008**, 2429-2431.

A classification of hydrogen bond in function of their strength in strong, moderate and weak can be done using as a reference the values of bond distances and bond angles that involve the three atoms D-H···A.[77,78] Below, a classification table of hydrogen bond as a function of different parameters is shown.

As can be observed in Table 1.1, the hydrogen bond can be relatively strong and shows a marked directionality. This type of interactions becomes a key part in Supramolecular Chemistry. Also the weak hydrogen bond is important, being a crucial part in the stabilization of structures when a large number of them participate.[79]

Table 1.1. Classification of Hydrogen Bonds according to their strength and geometric parameters.

	Strong	**Moderate**	**Weak**
D-H···A Interaction	Important Covalent component	Electrostatic mainly	van der Waals
Bond length	D-H ≈ H···A	D-H < H···A	D-H << H···A
H···A (Å)	~ 1.2 – 1.5	~ 1.5 – 2.0	2.0 – 3.0
D···A (Å)	2.2 – 2.5	2.5 – 3.2	3.0 – 4.0
Bond angles (°)	175 – 180	130 – 180	90 – 150
Bond energy (kcal·mol^{-1})[a]	14 – 40	4 – 15	<4
^{1}H NMR Chemical shift (ppm)	14 – 22	< 14	---

[a] Proposed by Emsley (1980).

A more detailed analysis and classification of different hydrogen bond interactions point out that there are three different kinds of HBs: typical hydrogen bonds, designated as D–H···A, with the positive charge of H-atom; inverse (or hydride) bonds where a negatively charged hydrogen atom is situated between electropositive atoms; and dihydrogen bonds (DHBs) D–H···H–A containing both protic and hydric H-atoms.[80] Generally, it seems that the properties of DHBs do not differ much from typical H-bonds and its formation usually causes changes similar to those of conventional hydrogen bonds. The meaning and understanding of H···H contacts was changed and verified in the 1990s when this new type of interaction (DHB)[81] was

[77] G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press ed., Oxford, **1997**.
[78] G. R. Desiraju, *Hydrogen Bonding, in Encyclopedia of Supramolecular Chemistry, Vol. 1*, J. L. Atwood; J. W. Steed ed., **2004**.
[79] L. F. Scatena, M. G. Brown, G. L. Richmond, *Science* **2001**, *292*, 908-912.
[80] I. Alkorta, J. Elguero, S. J. Grabowski, *J. Phys. Chem. A* **2008**, *112*, 2721-2727.
[81] T. B. Richardson, S. deGala, R. H. Crabtree, P. E. M. Siegbahn, *J. Am. Chem. Soc.* **1995**, *117*, 12875-12876.

detected in different organometallic crystal structures.[82] This interaction was designated as D−H···H−A, where D−H denotes a typical proton donating bond such as O−H or N−H with the excess of positive charge on hydrogen atom. The second hydrogen atom possesses a negative charge and is connected with the acceptor center A (A could be a transition metal or a boron atom). Other systems were also analyzed and classified as DHBs, even some C−H···H−C interactions were described as possessing the characteristics of dihydrogen bonds. Numerous calculations on dihydrogen bonded systems were performed finding that their binding energies in some cases exceed 10 kcal/mol.[83]

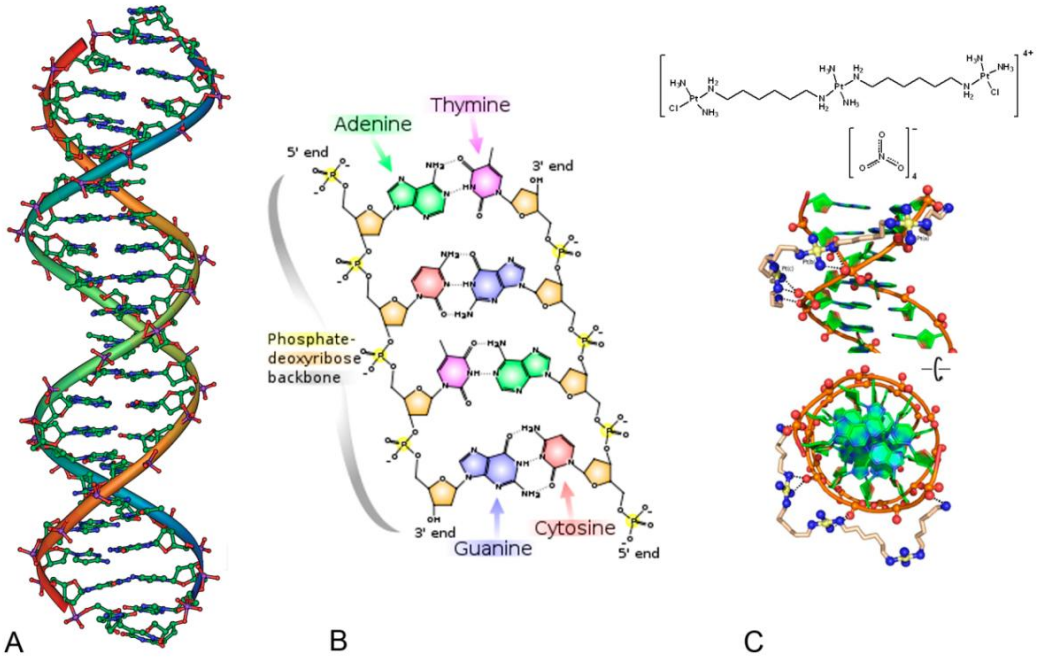


Figure 1.11. A) Double-helix of DNA structure. B) Chemical structure of DNA and hydrogen bonds between base pairs. C) The TriplatinNC coupling of DNA by means of hydrogen bond generates structural changes in double-helix.[85,86]

The hydrogen bond has a great importance in biological systems. For example, it plays a fundamental role in the stabilization and formation of tridimensional structures of proteins and nucleic acids.[84] In these biological macromolecules, the coupling between different parts of the same macromolecule origins a specific structure that determines the biological and physiological role. A characteristic example and of great importance is the structure of double helix of DNA that is mainly due to the formation of complementary hydrogen bonds between nucleotide base-pairs and π–π stacking interactions between them. Some anticancer drugs that are currently used are based on their intercalation in the DNA through hydrogen bond

[82] C. J. Cramer, W. L. Gladfelter, *Inorg. Chem.* **1997**, *36*, 5358-5362.
[83] M. J. Calhorda, P. E. M. Lopes, *J. Organomet. Chem.* **2000**, *609*, 53-59.
[84] Y. Mandelgutfreund, O. Schueler, H. Margalit, *J. Mol. Biol.* **1995**, *253*, 370-382.

generating structural changes resulting in an inhibition or slowdown of the transcription and replication processes in the DNA of cancer cells,[85,86] *i.e.*, are used as drugs acting as selective mutagens based on hydrogen bond (See Figure 1.11).

Neurodegenerative diseases such as Alzheimer are due to, among others, errors in the complementarity of hydrogen bond involved in protein folding therefore preventing them to carry out their function.

The importance of this interaction goes further. The formation of complementary hydrogen bonding has also found application in diverse fields, highly topical and with wide applications in the fields of catalysis, molecular machines, supramolecular systems, among others. Chan and collaborators[87] have carried out theoretical calculations that corroborate the *orto*-F···H(β) contacts ligand-polymer proposed by Fujita.[88] In the last years, molecular machines have been designed and synthesized (see Figure 1.12) based on the controlled formation/destruction of hydrogen bonds mediated by different extern stimuli such as changes in the potential or pH, light, presence of other reagents, etc.[89,90,91]

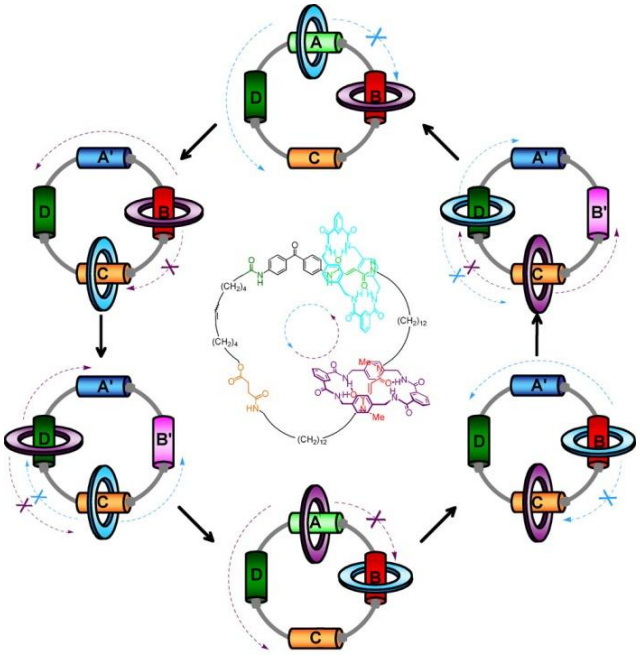


Figure 1.12. Operating scheme of molecular motor based on hydrogen bond.[90]

[85] S. Komeda, T. Moulaei, K. K. Woods, M. Chikuma, N. P. Farrell, L. D. Williams, *J. Am. Chem. Soc.* **2006**, *128*, 16092-16103.
[86] P. C. A. Bruijnincx, P. J. Sadler, *Curr. Opin. Chem. Biol.* **2008**, *12*, 197-206.
[87] M. C. W. Chan, *Macromol. Chem. Phys.* **2007**, *208*, 1845-1852.
[88] M. Mitani, R. Furuyama, J. Mohri, J. Saito, S. Ishii, H. Terao, T. Nakano, H. Tanaka, T. Fujita, *J. Am. Chem. Soc.* **2003**, *125*, 4293-4305.
[89] F. G. Gatti, D. A. Leigh, S. A. Nepogodiev, A. M. Z. Slawin, S. J. Teat, J. K. Y. Wong, *J. Am. Chem. Soc.* **2001**, *123*, 5983-5989.
[90] D. A. Leigh, J. K. Y. Wong, F. Dehez, F. Zerbetto, *Nature* **2003**, *424*, 174-179.
[91] J. V. Hernandez, E. R. Kay, D. A. Leigh, *Science* **2004**, *306*, 1532-1537.

1.2.2.5. C–H···π Interaction, C–H···π

This interaction consists of the attraction between C–H group and the π electronic density of an aromatic ring. Normally the range of distance between the hydrogen atom and the centroid of the ring is 2.4–3.2 Å.

Often, it has been considered a kind of weak hydrogen bond, due to the structural similitude between both kinds of interactions.[92,93,94,95] Recently, theoretical studies and experimental results in gas phase[96,97] propose that the nature of C-H···π interaction is totally different to the conventional hydrogen bonds. While the hydrogen bonds are due to electrostatic attractions, the electrostatic component in the C–H···π interactions is minimum, being the van der Waals interactions the main cause of formation. Only, in case of some activated C–H···π interactions with very acidic C–H bonds (acetylene, chloroform,…) the electrostatic interaction is the most important contribution.

Other fundamental difference is the directionality that both interactions exhibit. While the fundamental hydrogen bond feature is its high directionality due to the electrostatic contribution, the C–H···π presents very small electrostatic contribution. This fact confirms the different nature of both interactions.

1.2.2.6. Cation–π Interaction, Cπ

This kind of interaction takes place between a cation and one of the faces of an electron-rich aromatic system, as could be benzene and its derivatives or π systems as ethylene (see Figure 1.13). This interaction has basically an electrostatic origin, which implies the attraction of a cation to the electron density associated to a π system.

[92] H. Suezawa, S. Ishihara, O. Takahashi, K. Saito, Y. Kohno, M. Nishio, *New J. Chem.* **2003**, *27*, 1609-1613.
[93] Y. Umezawa, M. Nishio, *Biopolymers* **2005**, *79*, 248-258.
[94] M. Harigai, M. Kataoka, Y. Imamoto, *J. Am. Chem. Soc.* **2006**, *128*, 10646-10647.
[95] A. Gil, V. Branchadell, J. Bertran, A. Oliva, *J. Phys. Chem. B* **2007**, *111*, 9372-9379.
[96] A. Fujii, K. Shibasaki, T. Kazama, R. Itaya, N. Mikami, S. Tsuzuki, *Phys. Chem. Chem. Phys.* **2008**, *10*, 2836-2843.
[97] S. Tsuzuki, A. Fujii, *Phys. Chem. Chem. Phys.* **2008**, *10*, 2584-2594.

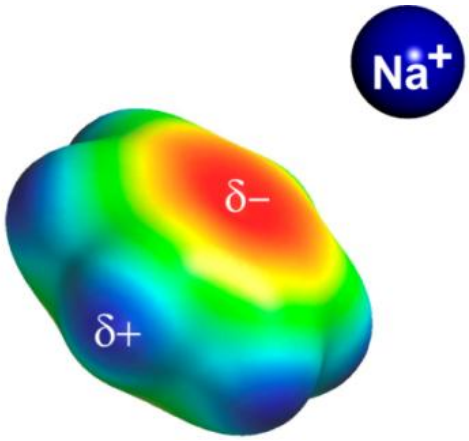


Figure 1.13. Cation–π interaction for benzene aromatic ring. The colour code for potential surfaces is ranging from –5 (red colour, rich places in electronic density) to +5 (blue, electron-deficient regions) in kcal·mol^{-1} for benzene.

This interaction is of great interest in biological systems[98] (Bond energy = 1-20 kcal·mol^{-1}). Most of neurotransmitters have a cationic group that permits them a selective anchorage to their receptors by cation–π interaction. In fact, cation–π bonding is an important and widely recognized noncovalent interaction that involves aromatic rings.[99] The cation–π interaction has important applications in the field of Supramolecular Chemistry. Supramolecular aggregates like dendrimers,[100] molecular tweezers, rotaxanes,[89] catenanes,[101] and foldamers,[102] have been associated by cation–π interactions.[103,104] Numerous studies have reported the occurrence of cation–π interactions in protein structures[98, 105] and in protein–ligand[33, 106] and protein–DNA[107,108] complexes. These analyses have revealed the preferential localization of amino groups in the area of aromatic rings.[105,109] This interaction is calculated to be even more stabilizing than an analogous salt bridge, and it is not so strongly attenuated in water.[110] The side–chains of the aromatic amino acid residues, Phe, Tyr, and Trp, provide a surface of negative electrostatic potential than can bind to a wide range of cations through a predominantly electrostatic interaction.[111, 112] A remarkable case is the acetylcholine

[98] J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, *97*, 1303-1324.
[99] P. B. Crowley, A. Golovin, *Proteins: Struct., Funct., Bioinf.* **2005**, *59*, 231-239.
[100] A. J. Lovinger, C. Nuckolls, T. J. Katz, *J. Am. Chem. Soc.* **1998**, *120*, 264-268.
[101] P. L. Anelli, P. R. Ashton, N. Spencer, A. M. Z. Slawin, J. F. Stoddart, D. J. Williams, *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1036-1039.
[102] F. M. Raymo, K. N. Houk, J. F. Stoddart, *J. Org. Chem.* **1998**, *63*, 6523-6528.
[103] X. F. Bao, I. Isaacsohn, A. F. Drew, D. B. Smithrud, *J. Org. Chem.* **2007**, *72*, 3988-4000.
[104] J. M. Heemstra, J. S. Moore, *Chem. Commun.* **2004**, 1480-1481.
[105] J. P. Gallivan, D. A. Dougherty, *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 9459-9464.
[106] C. Biot, E. Buisine, M. Rooman, *J. Am. Chem. Soc.* **2003**, *125*, 13988-13994.
[107] R. Wintjens, J. Lievin, M. Rooman, E. Buisine, *J. Mol. Biol.* **2000**, *302*, 395-410.
[108] J. S. Lamoureux, J. T. Maynes, J. N. M. Glover, *J. Mol. Biol.* **2004**, *335*, 399-408.
[109] S. K. Burley, G. A. Petsko, *FEBS Lett.* **1986**, *203*, 139-143.
[110] J. P. Gallivan, D. A. Dougherty, *J. Am. Chem. Soc.* **2000**, *122*, 870-874.
[111] N. S. Scrutton, A. R. C. Raine, *Biochem. J.* **1996**, *319*, 1-8.
[112] N. Zacharias, D. A. Dougherty, *Trends Pharmacol. Sci.* **2002**, *23*, 281-287.

nicotinamide receptor whose mechanism of molecular recognition to their substrate (acetylcholine, positively charged molecule) is based on only cation–π interactions, as can be observed in Figure 1.14.[113]

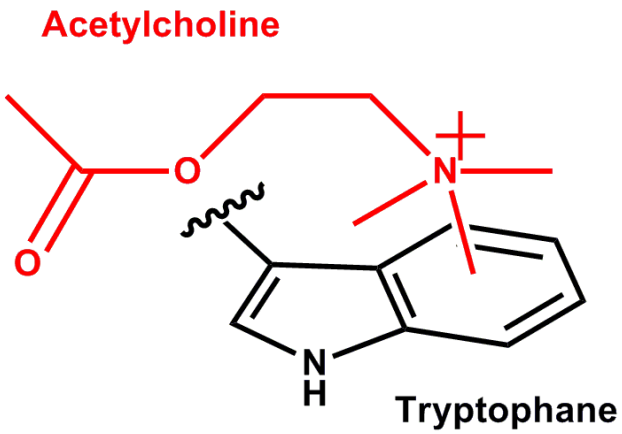


Figure 1.14. Cationic acetylcholine bonded to a tryptophan fragment of acetylcholine nicotinamide receptor by cation–π interaction.

Furthermore, systems with molecular structure as crown ether with π systems strategically located have shown to be very effective binding places for alkaline cations.[114]

Additionally, cation–π interactions have also been used to increase the π–face selectivity in catalysts in asymmetric catalysis.[115]

1.2.2.7. π–π Stacking Interactions, π–π

This type of interaction takes place between the π electron densities of stacked aromatic systems. Normally, one of the rings is electron-rich, while the other is electron-poor, although cases have been described where both rings have the same electron wealth, this would be weak interactions (Bonding energy = 0-10 kcal·mol^{-1}) of great importance from a biological and supramolecular points of view.

This kind of interaction plays an important role in the stabilization of DNA, together with hydrogen bond, resulting in pair-bases stacking and generating its characteristic helicoidal structure. Based on this, a number of intercalating drugs have been designed. On the other hand, π–π stacking interactions have a lot of applications in Supramolecular Chemistry, especially for host-guest systems. A remarkable case is the one described by Sygula and

[113] D. L. Beene, G. S. Brandt, W. G. Zhong, N. M. Zacharias, H. A. Lester, D. A. Dougherty, *Biochemistry* **2002**, *41*, 10262-10269.
[114] G. W. Gokel, L. J. Barbour, R. Ferdani, J. X. Hu, *Acc. Chem. Res.* **2002**, *35*, 878-886.
[115] S. Yamada, C. Morita, *J. Am. Chem. Soc.* **2002**, *124*, 8184-8185.

collaborators[116] who have synthesized a buckycatcher based on a multitude of conjugated aromatic rings that adopt a concave conformation matching perfectly with a fullerene C_{60} molecule (see Figure 1.15), acting as receptor of this molecule through π–π stacking interactions.

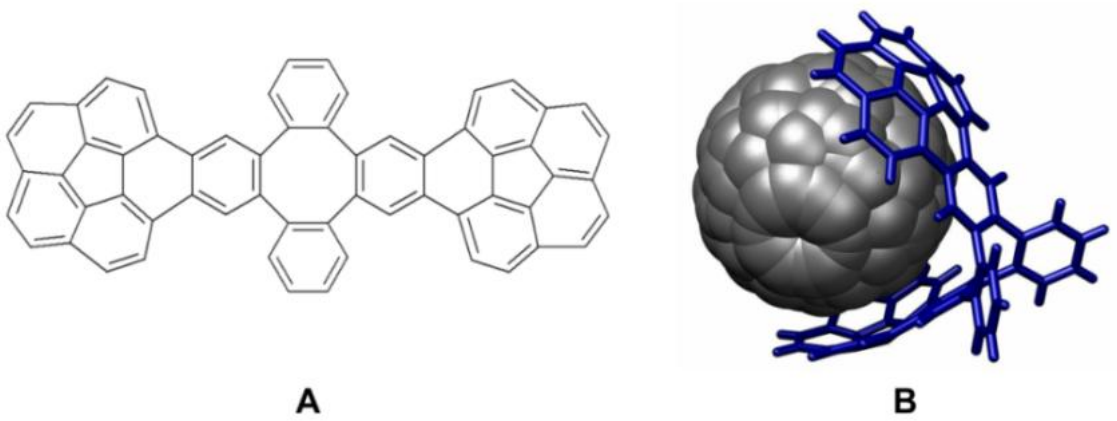


Figure 1.15. A) Buckycatcher structure. B) Crystalline structure of fullerene linked to buckycatcher by π–π stacking interaction.[116]

This kind of interaction is also of great utility in liquid crystals for the formation of columnar structures supported by the stacking of aromatic rings (see Figure 1.16).[117]

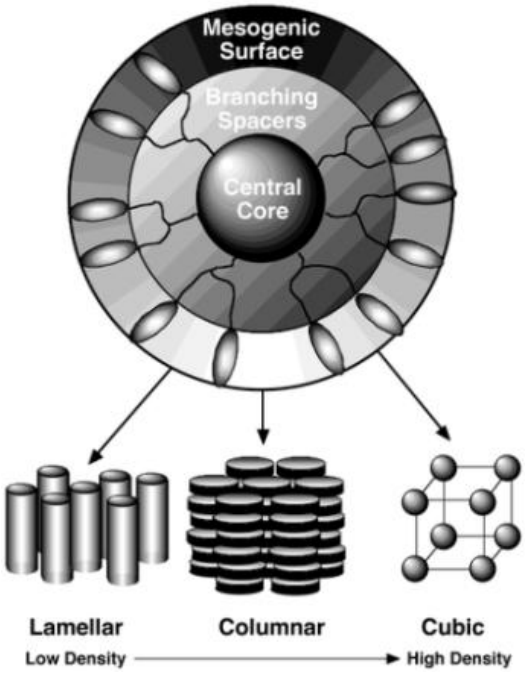


Figure 1.16. Disk detail in liquid crystal mesogen and various types of arrangement of liquid crystal mesogenic disks.[117]

[116] A. Sygula, F. R. Fronczek, R. Sygula, P. W. Rabideau, M. M. Olmstead, *J. Am. Chem. Soc.* **2007**, *129*, 3842-3843.
[117] J. W. Goodby, D. W. Bruce, M. Hird, C. Imrie, M. Neal, *J. Mater. Chem.* **2001**, *11*, 2631-2636.

Three general kinds of π–π stacking interaction can be distinguished, as shown in Figure 1.17:

- Face to face (FF),
- Offset face-to-face or parallel-displaced (OFF),
- Edge-to-face or T-shaped (EF).

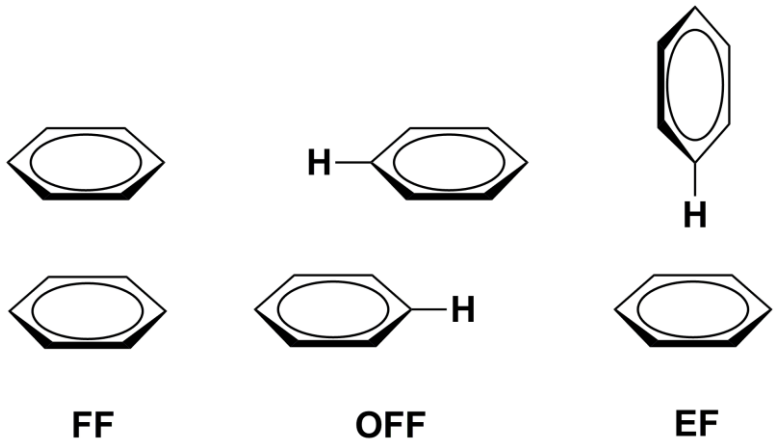


Figure 1.17. Types of π–π stacking interactions between aromatic rings.

The edge-to-face stacking is a particular case of C–H···π interaction, since it has the same nature and similar strength and takes place when the distance that separates the hydrogen atom and the ring centroid is 2.4–3.2 Å (C–π distance = 3.2–3.7 Å).

There has been some controversy concerning the physical nature of this kind of interaction. In 1990, Hunter and Sanders proposed a simple model based on the competition between the electrostatic and the van der Waals forces to explain the variety of geometries observed for these interactions and to quantitatively predict their interaction energies.[118] These authors postulate the existence of an attractive overlap by van der Waals interactions, which are proportional to the surface contact area between both π systems. This overlap is due to an attraction between the π electronic cloud negatively charged of one of the rings and the σ electronic cloud positively charged from the other. The relative orientation of both rings is determined by electronic repulsions between both π systems negatively charged.

For this reason, when an aromatic system is stacked in a parallel way, it is normally observed that the rings are not totally aligned, with one slightly displaced with respect to the other, minimizing the π–π repulsion and maximizing the σ–π attraction. In fact, few examples exist where the aromatic rings are arranged totally overlapping.[119,120] The most common

[118] C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525-5534.
[119] M. D. Blanchard, R. P. Hughes, T. E. Concolino, A. L. Rheingold, *Chem. Mater.* **2000**, *12*, 1604-1610.
[120] A. N. Sokolov, T. Friscic, L. R. MacGillivray, *J. Am. Chem. Soc.* **2006**, *128*, 2806-2807.

arrangements are the offset and T-shaped disposition, because σ–π attractions predominate in both (see Figure 1.18).

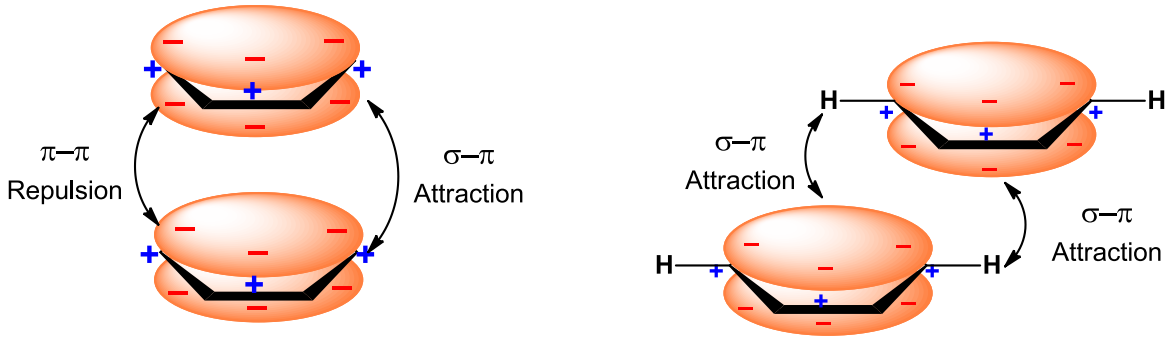


Figure 1.18. Scheme of existing forces between aromatic rings.

In cases of stacking in offset disposition, a range of guide values for distances and angles can be established between layers of both rings within the existence of π–π stacking interactions are considered demonstrated.[121,122] Fundamentally, the parameters to take into account are:

- Centroid-centroid distance (3.3–4.1 Å),
- Centroid-plane distance (3.3–4.1 Å),
- Dihedral angle that forms both planes of both rings (α=0–19°).

To measure the displacement of one ring over the other, γ and β angles are used, being the angles formed between the centroid-centroid vectors and centroid-layer for both rings. Normally, these angles have values between 16 and 40°. Above 40° the rings are considered to be too laterally displaced with respect of one to the other for the π–π stacking interaction being effective. When the rings are totally parallel (α = 0°), β and γ are equal. These features can be better observed in the Figure 1.19.

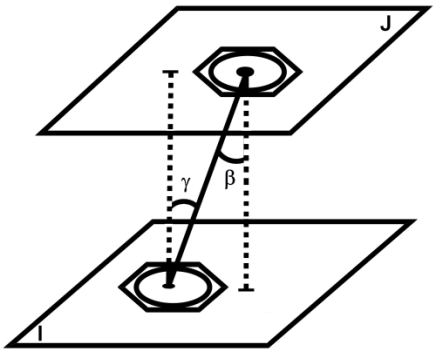


Figure 1.19. Main parameters for π–π stacking interaction.

[121] C. Janiak, *Dalton Trans.* **2000**, 3885-3896.
[122] U. Mukhopadhyay, D. Choquesillo-Lazarte, J. Niclos-Gutierrez, I. Bernal, *CrystEngComm* **2004**, *6*, 627-632.

It is worth mentioning that the strength of these interactions is highly affected by different factors, such as the presence of electron-donor or electron-acceptor substituents in the rings, the existence of heteroatoms forming part of the ring and, even, the condensation grade of the involved rings in the stacking. Thereby, the higher the number of condensed rings, the more favourable the stacking.[123] Regarding the substitution effect, it has been demonstrated that the presence of electron-attractor substituents in the ring increases the strength of this kind of interactions since the electronic density of π cloud of the ring decreases, minimizing the π–π repulsions between the rings.[64,124]

When the stacking is produced between aromatic heterocycles the strength of these interactions increases, since the substitution of a carbon atom of the ring by a nitrogen atom in six-mebered ring like in pyridine for example, causes a decrease of the electronic π density in the carbon atoms of the ring, which leads to a stabilization of the system and decreases the π–π repulsion forces as mentioned above.[125] It is observed that a cooperativity effects exist between π–π stacking interactions and anion–π or cation–π interactions.[126]

Regarding this, a stability order to the stacking of π systems can be established: π-deficient··· π-deficient system > π-deficient··· π-excess > π-excess··· π-excess.[64,118]

1.2.2.8. Anion–π Interactions, Aπ

The anion–π interactions are attractive noncovalent interactions between electron-poor aromatic rings and an anion, although there is evidence that, even non-deficient aromatic rings can present these interactions, especially if these rings are involved in cation–π interactions on the other side.[127] These interactions are more intense when the aromatic ring is more electron-deficient. Therefore, the presence of electron-withdrawing substituents (halogen, nitro or cyano groups) in the ring favours the formation of anion–π complexes, as well as the existence of nitrogen atoms in the ring (pyridine, triazine, tetrazine, among others). Theoretical studies have revealed that this kind of interaction is dominated by electrostatic forces, although the contribution of induced polarization by the anion[128,129,130] is also important

[123] R. Goddard, M. W. Haenel, W. C. Herndon, C. Kruger, M. Zander, *J. Am. Chem. Soc.* **1995**, *117*, 30-41.
[124] C. A. Hunter, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584-1586.
[125] K. Kano, H. Minamizono, T. Kitae, S. Negi, *J. Phys. Chem. A* **1997**, *101*, 6118-6124.
[126] A. Frontera, D. Quiñonero, A. Costa, P. Ballester, P. M. Deyà, *New J. Chem.* **2007**, *31*, 556-560.
[127] C. Garau, D. Quiñonero, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *New J. Chem.* **2003**, *27*, 211-214.
[128] D. Quiñonero, C. Garau, C. Rotger, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *Angew. Chem., Int. Ed.* **2002**, *41*, 3389-3392.
[129] C. Garau, A. Frontera, D. Quiñonero, P. Ballester, A. Costa, P. M. Deyà, *ChemPhysChem* **2003**, *4*, 1344-1348.
[130] D. Quiñonero, A. Frontera, C. Garau, P. Ballester, A. Costa, P. M. Deyà, *ChemPhysChem* **2006**, *7*, 2487-2491.

and crucial in cases where the electrostatic is small or null.[131] The molecular polarizability of the aromatic ring is one of the factors that affect the magnitude of the induced polarization.The bond energy is around 5-10 kcal·mol^{-1}.

To consider that the interaction exists, the distance between the anion and an atom of the aromatic ring must be inferior to the sum of van der Waals radii. However, Gámez and collaborators have carried out an analysis of structures retrieved from Cambridge Structural Database (CSD) presenting anion–π interactions. They have established parameters that allow determining the existence and strength of the anion–π interaction for six-membered rings.[132] They propose:

- The distance between a given atom of the anion, in case of this being polyatomic, and any atom of the aromatic ring must be equal or less than 4 Å. This distance is named ***d***.
- The distance between one of the atoms of the anion (in case of polyatomic anion we must get the same referenced atom) and centroid of the ring must be equal or less to 4 Å. This distance is represented as ***D***.

From these criteria, the conclusion that they reach from their search is that the number of anion–π interactions are bigger when the distance ***d*** is 3.82 Å.

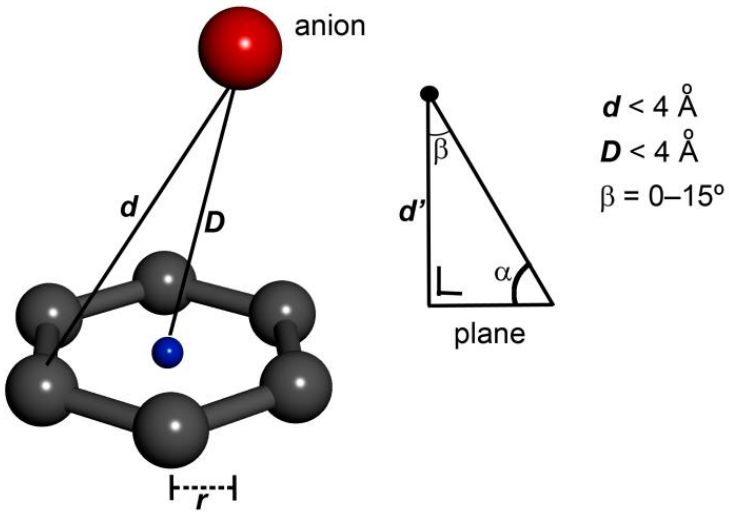


Figure 1.20. Representation of used parameters to define the anion–π contacts and average values for every one of them.

Furthermore, the lateral displacement of the anion with respect to the ring is quantified with the following parameters (see Figure 1.20):

[131] A. Clements, M. Lewis, *J. Phys. Chem. A* **2006**, *110*, 12705-12710.
[132] T. J. Mooibroek, C. A. Black, P. Gamez, J. Reedijk, *Cryst. Growth Des.* **2008**, *8*, 1082-1093.

- ***r*** defined as the parallel displacement between the vectors anion-centroid, ***D***.
- ***β*** is defined as the angle between the vectors anion-ring layer, ***d'***. It has been observed that the strong anion–π interactions present angles β = 0–15°. Interactions with lower angles represent a significant lateral displacement which leads to a decrease in the strength of them.

The anion–π interaction can be established between an aromatic system and an anion either mono- or polyatomic. In the latter case, there can be more than one interaction between different atoms of the anion and the aromatic ring. Some examples are found with the following anions: ClO_4^-, BF_4^-, PF_6^- or NO_3^-. However, not only the possibility of multiple interactions with the same rings exists, but also occurs between the same anion and different aromatic rings.

In the last years there has been a growing interest in this kind of interactions due to the great range of possible implications, as later shown. They are present in:

- Process of environmental importance to the elimination of nitrate or phosphate ion of fresh water,[133,134,135]
- Biological systems (ionic synthetic channels or membranes)[64] and catalysts systems.

This interaction is the main force for which this thesis is based on. Section 1.3 of Chapter 1 explains in detail the great progress and impact of the anion–π interaction in recent years.

1.2.2.9. Lone pair–π Interactions, l.p.–π

It is the interaction between lone pair electrons of an atom belonging to a neutral electron-rich molecule (H_2O, R_2CO, R_2O, RCN, etc.) and an electron-poor aromatic ring. There are a lot of similitudes between this one and the anion–π interaction, explained above. In fact the parameters used to determine its existence and their strength are the same and have very similar values.[136,137,138,139]

[133] C. Garau, A. Frontera, P. Ballester, D. Quiñonero, A. Costa, P. M. Deyà, *Eur. J. Org. Chem.* **2005**, 179-183.
[134] A. P. Davis, D. N. Sheppard, B. D. Smith, *Chem. Soc. Rev.* **2007**, *36*, 348-357.
[135] V. Gorteau, G. Bollot, J. Mareda, A. Perez-Velasco, S. Matile, *J. Am. Chem. Soc.* **2006**, *128*, 14788-14789.
[136] M. Egli, S. Sarkhel, *Acc. Chem. Res.* **2007**, *40*, 197-205.
[137] C. Q. Wan, X. D. Chen, T. C. W. Mak, *CrystEngComm* **2008**, *10*, 475-478.
[138] P. J. Kitson, Y. F. Song, P. Gamez, P. de Hoog, D. L. Long, A. D. C. Parenty, J. Reedijk, L. Cronin, *Inorg. Chem.* **2008**, *47*, 1883-1885.
[139] T. J. Mooibroek, P. Gamez, J. Reedijk, *CrystEngComm* **2008**, *10*, 1501-1515.

In both cases this interaction is mainly electrostatic in nature. However, the electron-rich atom induces polarization in the ring, which can be important. In the following Figure 1.21 the characteristic parameters of these interactions are schematized.

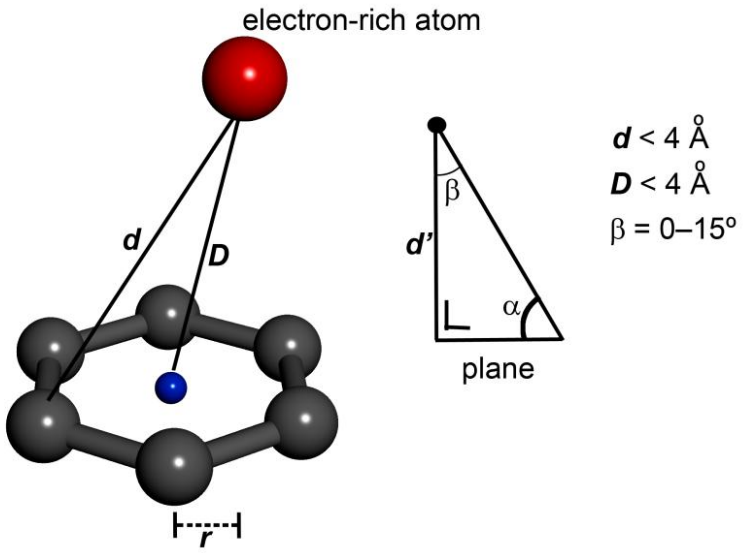


Figure 1.21. Representation of used parameters to define the l.p.–π interactions and average values of every one of them.

It has been observed that the lone pair–π interactions are of great importance in the stabilization of biological macromolecules and for the anchorage of the biochemical inhibitor receptors.[140,141,142] Sankararamakrishnan and collaborators have carried out an investigation using the crystallographic database CSD for protein searching the l.p.–π interactions of carbonyl group and have found more than 250 proteins where this kind of interaction is present[143] showing the biological importance of these interactions. Recently, their presence in small "host-guest"molecular systems have been confirmed,[137,144] and have even demonstrated their contribution in electron transfer together with proton transfer.[145]

1.2.2.10. Halogen Bond, XB

Halogen bond is a noncovalent interaction where a halogen atom is involved acting as electron-acceptor. The interaction can be schematized as:

D···X-Y

[140] S. Sarkhel, A. Rich, E. Martin, *J. Am. Chem. Soc.* **2003**, *125*, 8998-8999.
[141] J. C. Calabrese, D. B. Jordan, A. Boodhoo, S. Sariaslani, T. Vannelli, *Biochemistry* **2004**, *43*, 11403-11416.
[142] J. Li, J. Zhang, J. Chen, X. M. Luo, W. L. Zhu, J. H. Shen, H. Liu, X. Shen, H. L. Jiang, *J. Comb. Chem.* **2006**, *8*, 326-337.
[143] A. Jain, C. S. Purohit, S. Verma, R. Sankararamakrishnan, *J. Phys. Chem. B* **2007**, *111*, 8680-8683.
[144] Z. L. Lu, P. Gamez, I. Mutikainen, U. Turpeinen, J. Reedijk, *Cryst. Growth Des.* **2007**, *7*, 1669-1671.
[145] G. A. DiLabio, E. R. Johnson, *J. Am. Chem. Soc.* **2007**, *129*, 6199-6203.

X is a halogen with electronic deficiency and acts as a Lewis acid,

D is any electron donor, and acts as a Lewis base,

Y can be a carbon, nitrogen or halogen atom.[146,147,148,149]

This interaction presents a lot of similarities with the hydrogen bond,[150] both geometrically and in the arrangement of atoms involved energetically, although it is more affected by the steric constraints due to the bigger size of halogens regarding the hydrogen atom. Moreover halogen bond exhibits a wide range of energies similar to those of hydrogen bonding (Bond energy = 1–45 kcal·mol^{-1}). The nature of this interaction is a sum of different attractive forces: charge transfer, electrostatic effects, polarizability, and London dispersion. For this reason, the nature of involved atoms determines the relevance of each contribution.

The strength of the D···X interaction increases when the electron density in D is large and is small around X. For this reason, when electron-donor groups are bound to the halogen (X) and electron-acceptor groups are bound to D, the interaction is stronger. Analyses of structural data have concluded that the angle formed between the covalent bonding and noncovalent bonding around the halogen in D···X-Y is approximately 180°. This is consistent with the theoretical calculations that postulate that the electron density is distributed anisotropically around the halogen nuclei and the atomic radius along the X-Y bond being smaller than in the orthogonal direction of this axis.

This interaction presents a huge potential because it can create supramolecular architectures with application in different fields such as liquid crystals or organic semiconductors,[151,152,153,154] without forgetting the application in biological systems as their use to optimize the ligand anchorage to a specific receptor, molecular packing and drug design.[155,156,157]

[146] A. C. Legon, *Chem.--Eur. J.* **1998**, *4*, 1890-1897.
[147] P. Metrangolo, H. Neukirch, T. Pilati, G. Resnati, *Acc. Chem. Res.* **2005**, *38*, 386-395.
[148] P. Politzer, P. Lane, M. C. Concha, Y. G. Ma, J. S. Murray, *J. Mol. Model.* **2007**, *13*, 305-311.
[149] P. Metrangolo, F. Meyer, T. Pilati, G. Resnati, G. Terraneo, *Angew. Chem., Int. Ed.* **2008**, *47*, 6114-6127.
[150] P. Metrangolo, G. Resnati, *Science* **2008**, *321*, 918-919.
[151] H. L. Nguyen, P. N. Horton, M. B. Hursthouse, A. C. Legon, D. W. Bruce, *J. Am. Chem. Soc.* **2004**, *126*, 16-17.
[152] M. Fourmigue, P. Batail, *Chem. Rev.* **2004**, *104*, 5379-5418.
[153] A. W. Sun, J. W. Lauher, N. S. Goroff, *Science* **2006**, *312*, 1030-1034.
[154] E. Cariati, A. Forni, S. Biella, P. Metrangolo, F. Meyer, G. Resnati, S. Righetto, E. Tordin, R. Ugo, *Chem. Commun.* **2007**, 2590-2592.
[155] M. Adler, M. J. Kochanny, B. Ye, G. Rumennik, D. R. Light, S. Biancalana, M. Whitlow, *Biochemistry* **2002**, *41*, 15514-15523.
[156] P. Auffinger, F. A. Hays, E. Westhof, P. S. Ho, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 16789-16794.
[157] Y. Jiang, A. A. Alcaraz, J. M. Chen, H. Kobayashi, Y. J. Lu, J. P. Snyder, *J. Med. Chem.* **2006**, *49*, 1891-1899.

1.2.2.11. Hydrophobic Effect

The hydrophobic effect is a property that presents molecules or non-polar molecular fragments that have a tendency to form intermolecular aggregates when is found in a polar media, generally aqueous, hence the name. The hydrophobic effects can produce effects resembling attraction between one organic molecule and another, although there are in addition van der Waals and π–π stacking attractions between the organic molecules themselves. The hydrophobic effect is very important in biological systems in the creation and maintenance of protein and polynucleotide structure, among other functions. They are of crucial importance in the binding of organic guests by cyclodextrins and cyclophane hosts in water and may be divided into two energetic components: enthalpic and entropic.

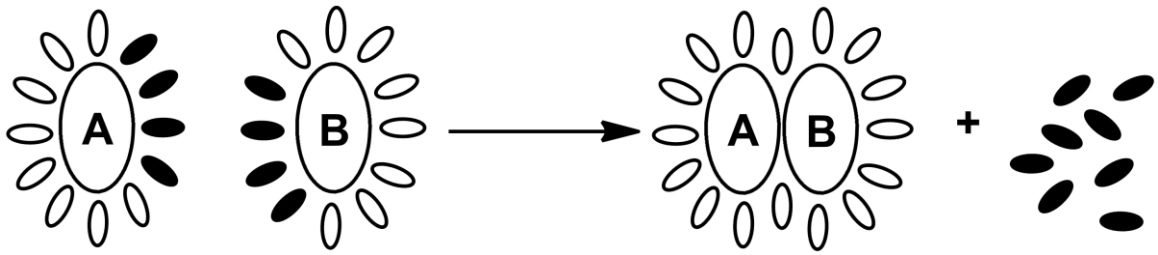


Figure 1.22. Release of solvent molecules by association of two molecules of solute A and B.

The enthalpic hydrophobic effect involves the stabilization of water molecules that are driven from a host cavity upon guest binding. Because host cavities are often hydrophobic, intracavity water does not interact strongly with the host walls and is therefore of high energy. Upon release into the bulk solvent, it is stabilized by interactions with other water molecules. The entropic hydrophobic effect arises from the fact that the presence of two (often organic) molecules in solution (host and guest) creates "two holes" in the structure of bulk water. Combining host and guest to form a complex results in less disruption to the solvent structure and hence an entropic gain (resulting in a lowering of overall free energy).[2] The process is represented schematically in Figure 1.22, where the formation of these apolar aggregates results favorably from a thermodynamic point of view.[158]

1.2.3. VAN DER WAALS FORCES

The electrostatic and inductive forces are of great importance when some of the molecules possess a dipolar permanent moment. However, other forces act between the molecules of the system. The combination of other forces, known as van der Waals forces, is responsible for the deviation of the behaviour of gases regarding an ideal system.

[158] D. Chandler, *Nature* **2005**, *437*, 640-647.

In contrast to gravitational or coulombic forces, the van der Waals forces are generally not additive. Therefore, the force between two molecules is affected by the presence of other nearest molecules, and it is not possible to add all the potential pairs of one molecule to obtain its net interaction energy with other molecules. This absence of additivity is due to the field that emerges from any molecule, that reaches a second molecule in a direct and also indirect way, i.e., by reflection from other molecules that also are polarized by the field of the first one.[159]

The van der Waals forces can be repulsive or attractive, and the empiric expression most used is the Lennard-Jones potential present in Equation 1.5.[160]

$$V(r) = 4\varepsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$$

Equation 1.5

The parameter $\boldsymbol{\sigma}$ is the collision diameter, which is the distance where the energy is zero and is equal to $2^{-1/6}\mathbf{r_m}$ ($\mathbf{r_m}$ is the distance where the potential is minimum). The $\boldsymbol{\varepsilon}$ parameter is the depth of the potential well.

As we can see in the Lennard-Jones equation (Equation 1.5 and Figure 1.23), the van der Waals forces are divided into two contributions. The attractive component comes from the dispersive effects and has the basis in the dominant term of Drude (r^{-6}). However, the repulsive component emerges from the compliance of the exclusion principle of Pauli when the electronic clouds of two atoms interpenetrate, although theoretical arguments do not exist for r^{-12} term, since the quantum mechanics suggest an exponential law.

Due to the previous discussion, it can be concluded that the van der Waals interactions are weak (bond energy < 1 kcal·mol^{-1}) and not directional. These forces have been observed in supramolecular systems, especially in inclusion processes, where generally organic molecules (as solvents), are occluded in the crystalline packing or in the cavities of macrocycles.

[159] J. N. Israelachvili, *Intermolecular and Surface Forces*, Academic Press ed., San Diego (California), USA, **2000**.
[160] J. E. Lennard-Jones, *Proc. R. Soc. London, A* **1924**, *106*, 463-477.

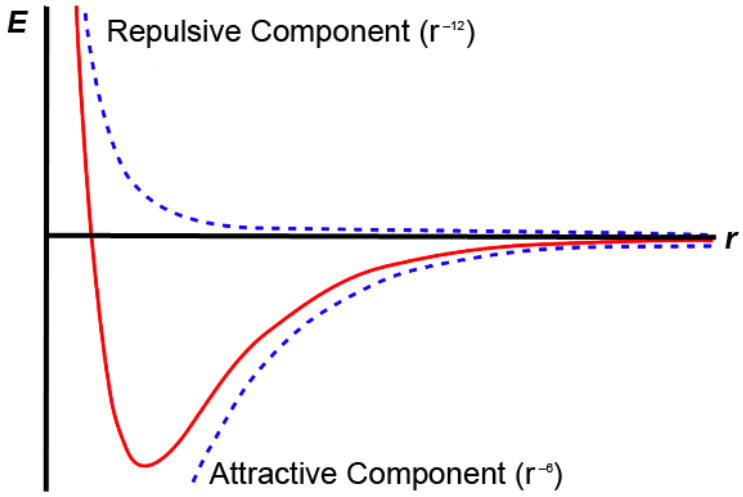


Figure 1.23. Lennard-Jones Potential Energy.

The noncovalent interactions above mentioned are summarized in Table 1.2, where bond energy and nature of all of them are collected.

Table 1.2. Scheme-table of binding energies and nature of noncovalent interactions.

Interactions	Bonding Energy (kcal·mol^{-1})	Nature of the Interaction
Ion–Ion	25 – 85	Electrostatic
Ion–Dipole	10 – 50	Electrostatic and Induction
Dipole–Dipole	1 – 10	Electrostatic and Induction
Hydrogen Bond	1 – 30	Electrostatic (dipole-dipole)
C–H···π	1	Weak Hydrogen Bond
Cation–π	1 – 20	Electrostatic and Induction
π–π Stacking	1 – 10	Weak Electrostatic and Dispersion
Anion–π	5 – 10	Electrostatic and Induction
Lone pair–π	1 – 5	Electrostatic
Halogen Bond	1 – 45	Weak Electrostatic
Hydrophobic Effect	< 1	Thermodynamic
van der Waals Forces	< 1	Dispersion

1.3. TUNING THE ANION–π INTERACTIONS

Supramolecular Chemistry is a field of scientific exploration that probes into the relationship between molecular structure and function. It is the chemistry of the noncovalent bond, which forms the basis of highly specific recognition, transport, and regulation events that actuate biological processes as mentioned previously. The classic design principles of Supramolecular Chemistry include strong, directional interactions like hydrogen bonding, halogen bonding, and cation–π complexation, as well as less directional forces like ion pairing, π–π, solvophobic, and van der Waals potentials. In recent years, the anion–π interaction (an attractive force between an electron-deficient aromatic π system and an anion) has been recognized as a *hitherto* unexplored noncovalent bond, the nature of which has been interpreted through both experimental and theoretical investigations. The design of selective anion receptors and channels based on this interaction represent important advances in the field of Supramolecular Chemistry.

Noncovalent interactions involving aromatic rings in particular play an essential role in chemistry and biology.[33] This role becomes prominent in drug receptor interactions, crystal engineering and protein folding.[42] Cation–π bonding is an important and widely recognized noncovalent interaction that involves aromatic rings as mentioned previously. In recent years, the inverse of the cation–π bonding, *i.e.* close contact between an anion and the region above the plane of an electron-poor aromatic ring, has been recognized as a noncovalent bonding interaction. The nature of this interaction, called an "anion–π bond,"[128] has been described by numerous theoretical studies, which demonstrate that it is energetically favourable,[45,128,161,162] in addition to several experimental investigations.[163,164,165,166,167] Anion–π interactions continue to gain attention as their role in chemical and biological processes is being increasingly recognized.[168,169] Moreover, their application to the design of highly selective anion receptors and channels[135,170,171,172] is establishing their importance in the field of Supramolecular

[161] M. Mascal, A. Armstrong, M. D. Bartberger, *J. Am. Chem. Soc.* **2002**, *124*, 6274-6276.
[162] I. Alkorta, I. Rozas, J. Elguero, *J. Am. Chem. Soc.* **2002**, *124*, 8593-8598.
[163] S. Demeshko, S. Dechert, F. Meyer, *J. Am. Chem. Soc.* **2004**, *126*, 4508-4509.
[164] B. L. Schottel, J. Bacsa, K. R. Dunbar, *Chem. Commun.* **2005**, 46-47.
[165] P. de Hoog, P. Gamez, H. Mutikainen, U. Turpeinen, J. Reedijk, *Angew. Chem., Int. Ed.* **2004**, *43*, 5815-5817.
[166] C. Estarellas, M. C. Rotger, M. Capo, D. Quiñonero, A. Frontera, A. Costa, P. M. Deyà, *Org. Lett.* **2009**, *11*, 1987-1990.
[167] M. Mascal, I. Yakovlev, E. B. Nikitin, J. C. Fettinger, *Angew. Chem., Int. Ed.* **2007**, *46*, 8782-8784.
[168] C. Caltagirone, P. A. Gale, *Chem. Soc. Rev.* **2009**, *38*, 520-563.
[169] C. Estarellas, A. Frontera, D. Quiñonero, P. M. Deyà, *Angew. Chem., Int. Ed.* **2011**, *50*, 415-418.
[170] J. Mareda, S. Matile, *Chem-Eur J* **2009**, *15*, 28-37.
[171] A. Perez-Velasco, V. Gorteau, S. Matile, *Angew. Chem., Int. Ed.* **2008**, *47*, 921-923.
[172] R. E. Dawson, A. Hennig, D. P. Weimann, D. Emery, V. Ravikumar, J. Montenegro, T. Takeuchi, S. Gabutti, M. Mayor, J. Mareda, C. A. Schalley, S. Matile, *Nature Chem.* **2010**, *2*, 533-538.

Chemistry. The closely related lone pair–π interaction has been observed in biological systems. For instance, Egli *et. al.* have reported an interesting case of O–π interactions involving an RNA pseudoknot.[136]

In this section more detailed forefront advances in the anion–π interaction will be described.[173] This interaction has increased its popularity in the last years as demonstrated by the increase of published papers both experimental and theoretical. This section will be divided into three parts. Firstly, to discuss current thinking on the nature of this interaction, secondly, to survey key experimental work in which anion–π bonding is demonstrated. This part is subdivided into three sections, *i.e.* complexes in solution, the solid state, and the gas phase. Thirdly, to provide insights into the directional nature of anion–π contact in X-ray crystal structures.[174]

1.3.1. PHYSICAL NATURE OF THE ANION–π INTERACTION

The general concept of anion–aromatic bonding is depicted graphically in Figure 1.24. Thus, while cation–π complexes are described by a single type of minimum energy structure, interactions between anions and aromatic rings can be manifested in any one of three modes of contact. First, when hydrogen atoms are present on the ring, hydrogen bonding can occur. Alternatively, a lone pair of the anion may interact with a π* orbital in such a way as to give a nascent Meisenheimer–type complex, often called a σ complex. Finally, the anion may position itself at or near the ring centroid to describe a structure analogous to the cation–π complex.

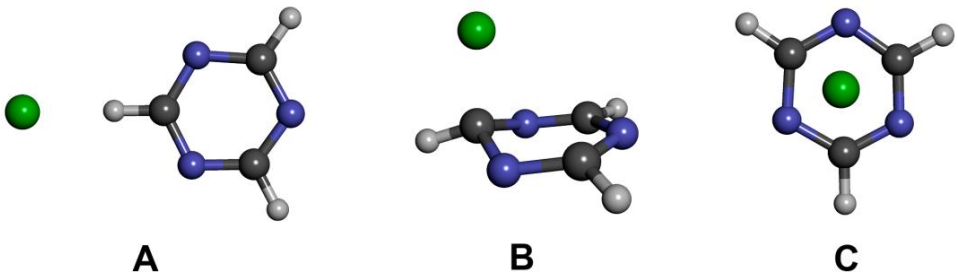


Figure 1.24. Depiction of three modes of contact between an electron poor aromatic ring and an anion (1,3,5-triazine and F^- in this case). A) H-bonding. B) σ-type interaction. C) anion–π bonding.

The physical nature of the anion–π interaction has been extensively analyzed.[45,128,161,162] From these studies, it has been concluded that electrostatic forces and ion–induced polarization are the main energetic contributors to the anion–π complex.[129, 175] The electrostatic term is explained by means of the permanent quadrupole moment of the arene,

[173] A. Frontera, P. Gamez, M. Mascal, T. J. Mooibroek, J. Reedijk, *Angew. Chem., Int. Ed.* **2011**, *50*, 9564-9583.
[174] F. H. Allen, *Acta Crystallogr., Sect. B: Struct. Sci.* **2002**, *58*, 380-388.
[175] D. Quiñonero, C. Garau, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *Chem. Phys. Lett.* **2002**, *359*, 486-492.

which is the first non-zero multipole moment in symmetric arenes. The negative quadrupole moment of benzene can be turned positive by attaching electron-withdrawing substituents to the ring (Figure 1.25). Consequently, the *a priori* electrostatically repulsive interaction between an anion and an aromatic ring can become attractive. The polarization of the π–electron system by the anion is significant, whereas the reverse effect (distortion of the electronic distribution of the anion) is generally negligible. Therefore, a polarization contribution to the total interaction energy is derived from the interaction of the anion with the induced dipole in the π–system. On the other hand, dispersion interactions, which are generally important in weak interactions involving aromatic rings, play only a modest role in anion–π bonding.[45,176]

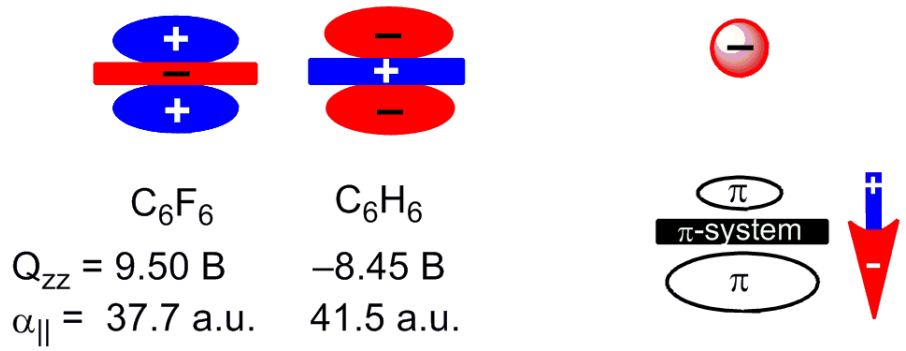


Figure 1.25. Schematic representation of the quadrupole moments of hexafluorobenzene and benzene (left) and the anion-induced dipole (right). The values of the quadrupole moments (Q_{zz}) in Buckingham (B) and molecular polarizabilities parallel to the main symmetry axis ($\alpha_{||}$) in atomics units (a.u.) are given.

This understanding of the physical nature of the interaction has been used in a predictive way. For example, a dual bonding mode exhibited by aromatic rings with negligible quadrupole moments has been identified.[177,178] Since both anion–π and cation–π interactions are dominated by electrostatic and polarization effects, molecules such as 1,3,5–trifluorobenzene (Q_{zz}= 0.57 B) and *s*–triazine (Q_{zz}= 0.90 B) must be able to interact with both anions and cations since the polarization term is always favourable. This is because the sign of the induced dipole is always opposite the sign of the ion. Thus, the modelled, gas-phase interaction energies for complexes of *s*–triazine with the chloride anion and lithium cation are –5.2 and –6.2 kcal·mol^{-1}, respectively.[177] Another example involves the interaction of anions with electron–rich aromatic rings such as benzene, which is expected to be strongly repulsive. However, this supposition turned out to be false due to the opposing effects of electrostatic (unfavourable) and ion–induced polarization (favourable) forces, which largely cancel each other out. Thus, the interaction energies of both benzene with chloride or hexafluorobenzene with sodium are

[176] D. Y. Kim, N. J. Singh, K. S. Kim, *J. Chem. Theory Comput.* **2008**, *4*, 1401-1407.
[177] C. Garau, D. Quiñonero, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *Org. Lett.* **2003**, *5*, 2227-2229.
[178] C. Garau, A. Frontera, D. Quiñonero, P. Ballester, A. Costa, P. M. Deyà, *J. Phys. Chem. A* **2004**, *108*, 9423-9427.

negligible.[127] An interesting example of this compensating effect is observed in complexes of anions with isocyanuric acid when the oxygen atoms are replaced by sulfur to give thiocyanuric acids (Figure 1.26).[179] The binding energy of the complexes of chloride with the four possible (thio)cyanuric acids is essentially constant (~15 kcal·mol^{-1}). This can be explained by the fact that while the quadrupole moment progressively decreases on going from isocyanuric acid to trithiocyanuric acid, the molecular polarizability increases.

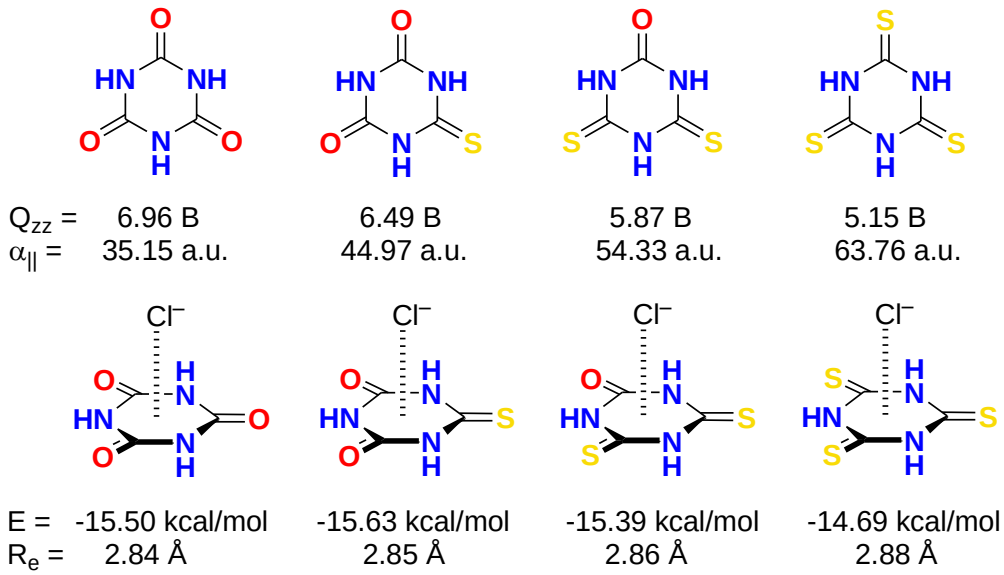


Figure 1.26. Top: Variation of the quadrupole moment (Q_{zz}) and molecular polarizability ($\alpha_{||}$) in cyanuric acid derivatives with increasing substitution of sulfur for oxygen. Bottom: Interaction energies (E) and equilibrium distances (R_e) of the chloride–(thio)cyanuric acid anion–π complexes.[179]

From the considerations described above, it is apparent that to engineer a strong anion–π interaction, the aromatic ring should have a large and positive quadrupole moment as well as a large molecular polarizability. Secondly, depending on the magnitudes of these two physical properties, the interaction can be dominated by either electrostatic or polarization forces. In some cases, induction effects can dominate the interaction. For example, the molecular polarizability of 1,4,5,8,9,12–hexaazatriphenylene is almost three times the value of benzene, while the quadrupole moment is about the same as that of benzene. As a result, its interaction energy with bromide is -5.2 kcal·mol^{-1}, while that of bromide with benzene is +1.9 kcal·mol^{-1}.[133]

The properties of the anion are also an important consideration for applications of anion–π bonding in Supramolecular Chemistry. Both the electrostatic and polarization contributions to the total interaction energy depend strongly upon the ion–arene distance. Small anions are more polarizing and present short equilibrium distances and, consequently, giving rise to more

[179] A. Frontera, F. Saczewski, M. Gdaniec, E. Dziemidowicz-Borys, A. Kurland, P. M. Deya, D. Quiñonero, C. Garau, *Chem.--Eur. J.* **2005**, *11*, 6560-6567.

negative interaction energies (Table 1.3). In addition, planar and linear anions such as NO_3^- or N_3^- can interact with the aromatic ring via π–π stacking. This theoretically predicted binding mode has been confirmed experimentally between nitrate ion and pyrimidinium rings.[180]

Side-by-side comparison of analogous cation–π and anion–π complexes generally show the anion–π distance to be longer and the interaction to be energetically weaker.[133] However, a different picture emerges when charged aromatic rings participate in anion–π complexes. Positive charges are easy to introduce onto azine rings by simply adjusting the pH of the medium, and this can be used to increment the anion binding ability of the ring (denoted as anion–π^+ interaction). There is no simple analogue of this effect in cation–π bonding. The geometric and energetic features of anion–π^+ complexes between several aromatic cations (tropylium, quinolizinylium, protonated 2–aminopyrimidine, protonated adenine) and various anions have been reported along with crystallographic structures that support the theoretical findings (Figure 1.27).[180,181,182] As expected, in these complexes the binding energies are large (> 80 kcal·mol^{-1}) and electrostatic effects dominate the anion–π^+ interaction.

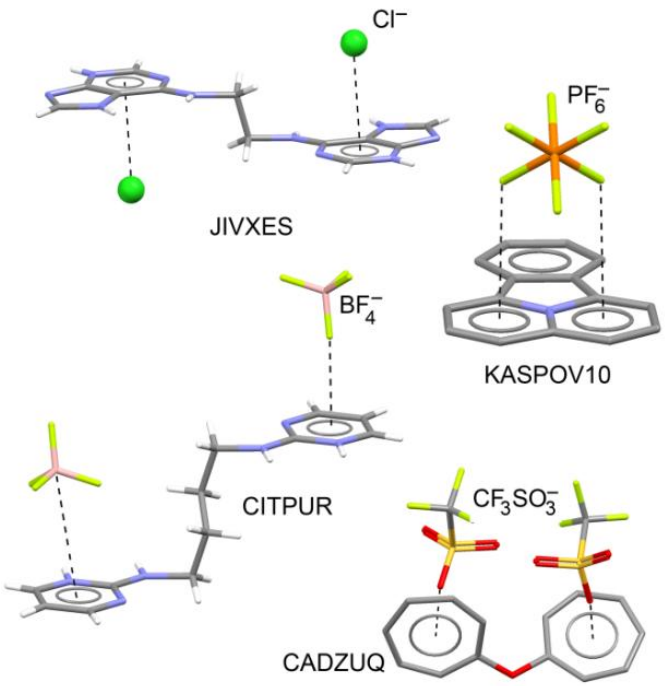


Figure 1.27. X-ray structures retrieved from the CSD in which anion–π^+ interactions are exhibited, with distances in Å.[180,181,182] The CSD reference codes are indicated.

[180] A. Garcia-Raso, F. M. Alberti, J. J. Fiol, A. Tasada, M. Barcelo-Oliver, E. Molins, C. Estarellas, A. Frontera, D. Quiñonero, P. M. Deyà, *Cryst. Growth Des.* **2009**, *9*, 2363-2376.
[181] A. Garcia-Raso, F. M. Alberti, J. J. Fiol, A. Tasada, M. Barcelo-Oliver, E. Molins, D. Escudero, A. Frontera, D. Quiñonero, P. M. Deyà, *Inorg. Chem.* **2007**, *46*, 10724-10735.
[182] C. Estarellas, A. Frontera, D. Quiñonero, P. M. Deyà, *J. Chem. Theory Comput.* **2008**, *4*, 1981-1989.

Another key aspect of the use of electron deficient rings as design principles in the construction anion receptors is the additivity of the anion–π interaction. Using *s*–triazine and trifluoro–*s*–triazine as examples, the additivity of the bonding interaction with halides has been studied[183] showing that the interaction energies of the ternary complexes (X^-–π_2) are essentially twice the interaction energies of the corresponding binary complexes (X^-–π). For the quaternary complexes (X^-–π_3), secondary interactions enter the picture.

The influence of ion–arene contact on the aromaticity of benzene rings has also been studied. It has been reported that when the ring participates in anion–π interactions, its aromaticity increases.[178,184] Interestingly, the behaviour in cation–π complexes is the opposite. This effect is the result of a modulation of the C–C bond energy of the aromatic ring. Regarding charge transfer effects on anion–π interactions, the theoretically predicted values strongly depend on the method used to derive the atomic charges. In general, NPA and AIM charges predict negligible charge transfer effects, and Merz–Kollman and CHelpG charges predict values ranging from 0.1–0.25 e. A molecular orbital description of the anion–π interaction has also been developed[178,185] and compared with the cation–π interaction, and again a totally different picture emerges, in that the atomic orbitals of the cation do not participate in the molecular orbitals of the cation–π complex, whereas the atomic orbitals of the anion have an active participation in the molecular orbitals of the anion–π complex.

An alternative description of the nature of anion–π interactions involving benzene rings was recently offered by Wheeler and Houk,[186] who examined substituent effects in $Cl^-\cdots C_6H_{6-n}X_n$ complexes using density functional theory (DFT) and robust *ab initio* methods paired with large basis sets. The predicted interaction energies for a large number of model $Cl^-\cdots C_6H_{6-n}X_n$ complexes span a *ca.* 40 kcal·mol^{-1} range and show an excellent correlation (r = 0.99) with computed electrostatic potentials. They proposed that substituent effects in these systems can be attributed mainly to direct interactions between the anion and local C–X dipoles. Specifically, interaction energies for $Cl^-\cdots C_6H_{6-n}X_n$ complexes could be matched using a model system in which the substituents are isolated from the aromatic ring and π–resonance effects are impossible. Additionally, they demonstrated that the interaction energy for $Cl^-\cdots C_6H_{6-n}X_n$ complexes follows a linear relationship with the electrostatic potential evaluated at the position of Cl^-. The resulting equation has a scaling factor between the interaction energy and electrostatic energy close to 1 ($E = 0.98E_{ele} - 7.27$). Therefore, the differences in the interaction

[183] C. Garau, D. Quiñonero, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *J. Phys. Chem. A* **2005**, *109*, 9341-9345.
[184] C. Garau, A. Frontera, D. Quiñonero, P. Ballester, A. Costa, P. M. Deyà, *Chem. Phys. Lett.* **2004**, *392*, 85-89.
[185] C. Garau, A. Frontera, D. Quiñonero, P. Ballester, A. Costa, P. M. Deyà, *Chem. Phys. Lett.* **2004**, *399*, 220-225.
[186] S. E. Wheeler, K. N. Houk, *J. Phys. Chem. A* **2010**, *114*, 8658-8664.

energies of the complexes reflect the differences in the electrostatic contributions to the total interaction energy. It is also worth noting that the *y* intercept of the equation reported by Wheeler and Houk is –7.3 kcal/mol. This value corresponds to the sum of all other energy components apart from the electrostatic term.

Table 1.3. Interaction energies (E, kcal·mol^{-1}) with basis set superposition error correction and zero-point corrections and equilibrium distances (R_e) measured from the anion to the centre of the ring at the MP2/6-31+ +G** level of theory for several anion–π complexes.[127,128,177,177]

Anion	E	R_e
Hexafluorobenzene		
H^-	–12.1	2.693
F^-	–18.2	2.570
Cl^-	–12.6	3.148
Br^-	–11.6	3.201
NO_3^-	–12.2	2.917
CO_3^{2-}	–34.7	2.720
Trifluorobenzene		
H^-	–4.4	3.021
F^-	–7.8	2.748
Cl^-	–4.8	3.323
Br^-	–4.5	3.359
NO_3^-	–5.6	3.471
CO_3^{2-}	–17.3	2.814
***s*–Triazine**		
H^-	–4.8	2.982
F^-	–9.7	2.592
Cl^-	–5.2	3.223
Br^-	–5.0	3.339
NO_3^-	–5.3	3.003
CO_3^{2-}	–16.9	2.751
Trifluoro–*s*–triazine		
H^-	–16.9	2.504
F^-	–24.2	2.390
Cl^-	–15.0	3.009
Br^-	–14.0	3.137
***s*–tetrazine**		
H^-	–60.9	1.520
F^-	–19.3	2.243
Cl^-	–10.9	2.858
Br^-	–7.8	3.239
isocyanuric acid		
H^-	–18.5	2.345
F^-	–28.1	2.191
Cl^-	–16.8	2.799
Br^-	–15.5	3.001

1.3.2. INTERPLAY BETWEEN THE ANION–π INTERACTION AND OTHER WEAK INTERACTIONS

Manifestations of weak noncovalent interactions turn up in all areas of chemistry.[1,33,36,39] They determine material properties, orchestrate chemical reactions, drive molecular recognition, and are active in the regulation of biochemical processes.[27,34] In these nanoscopic events, success relies on specificity and efficiency, which is accomplished by balancing intricate combinations of intermolecular attractive and repulsive forces. The organization of multicomponent supramolecular assemblies is often governed by multiple noncovalent interactions. In biological systems and particularly in the solid state, a lot of interactions may operate simultaneously giving rise to cooperativity effects. A recent review examined pairwise combinations of several weak interactions, including anion–π bonding, and described the synergy that operates between them.[187,188]

1.3.2.1. Interplay between Anion–π and Cation–π Interactions

A large and positive quadrupole moment guarantees that an aromatic ring can participate in strong anion–π bonding. The presence of charge on the aromatic ring (anion–π^+) can further increase the strength of the interaction. Conversely, it is also possible to establish a strong anion–π interaction between anions and arenes bearing no polarizing substituents. This can be achieved in the situation where the aromatic ring simultaneously interacts with both a cation and an anion on opposite sides of the ring.[127,189,190,191] The aromatic system mediates the transfer of information between the charged systems. For these ternary complexes the interaction energies are large and negative (Table 1.4), and the equilibrium distances are shorter than the corresponding distances of either binary ion–π complex, indicating a reinforcement of both interactions. In addition, this behaviour does not depend upon the nature of the arene, since a negative interaction energy (*E*) and short equilibrium distances (R_e) values were obtained for three aromatic rings spanning the range of quadrupole moments (C_6H_6, Q_{zz}= –8.45 B; $C_6F_3H_3$, Q_{zz} = 0.19 B; C_6F_6, Q_{zz} = 9.50 B).

Experimental work that supports the above theoretical findings has been published by Atwood and co-workers.[192,193] Using X–ray crystallography and ^{1}H–NMR titration experiments,

[187] I. Alkorta, F. Blanco, P. M. Deyà, J. Elguero, C. Estarellas, A. Frontera, D. Quiñonero, *Theor. Chem. Acc.* **2010**, *126*, 1-14.
[188] A. Frontera, D. Quiñonero, P. M. Deyà, *WIREs Comput. Mol.Sci.* **2011**, *1*, 440-459.
[189] I. Alkorta, F. Blanco, J. Elguero, C. Estarellas, A. Frontera, D. Quiñonero, P. M. Deyà, *J. Chem. Theory Comput.* **2009**, *5*, 1186-1194.
[190] I. Alkorta, J. Elguero, *J. Phys. Chem. A* **2003**, *107*, 9428-9433.
[191] D. Quiñonero, A. Frontera, P. M. Deyà, I. Alkorta, J. Elguero, *Chem. Phys. Lett.* **2008**, *460*, 406-410.
[192] J. W. Steed, R. K. Juneja, J. L. Atwood, *Angew. Chem., Int. Ed. Engl.* **1995**, *33*, 2456-2457.

they have shown that the host–guest behaviour of calixarenes and cyclotriveratrylenes can be inverted by complexation of the arene rings with transition metals (Ru, Ir, Rh), allowing anionic guest species (instead of cationic) to be included within the molecular cavity. One such example is shown in Figure 1.28 (left). Likewise, Fairchild and Holman[194,195] have reported that the metalation of the exterior arene faces of the molecular capsule cryptophane–E with $[Cp^*Ru]^+$ moieties (Figure 1.28, right) results in a π–acidic cavity capable of encapsulating anions. The anion complexes have been crystallographically characterized and the encapsulation of anions by the metalated cryptophane has been established by ^1H and ^{19}F NMR spectroscopy.

Table 1.4. Interaction energies of binary and ternary complexes (E, kcal·mol^{-1}), and the total interaction energy minus the isolated $Na^+\cdots X^-$ electrostatic bonding term with basis set superposition error correction (E_{int}, kcal·mol^{-1}) and equilibrium distances (R_e, Å) for several cation–π–anion complexes at the MP2/6-31+ +G** level of theory.[127]

Anion–π–Cation	E	E_{int}	R_e (cation–π)	R_e (anion–π)
$Na^+\cdots C_6H_6$	-21.0	-	2.429	-
$Na^+\cdots C_6F_3H_3$	-8.21	-	2.552	-
$Na^+\cdots C_6F_6$	+3.5	-	2.652	-
$C_6H_6\cdots F^-$	+2.8	-	-	3.162
$C_6H_6\cdots Cl^-$	+2.4	-	-	3.731
$C_6H_6\cdots Br^-$	+1.9	-	-	3.840
$Na^+\cdots C_6H_6\cdots F^-$	-93.10	-22.39	2.280	2.482
$Na^+\cdots C_6H_6\cdots Cl^-$	-85.11	-21.93	2.304	3.049
$Na^+\cdots C_6H_6\cdots Br^-$	-84.26	-22.12	2.313	3.157
$Na^+\cdots C_6F_3H_3\cdots F^-$	-90.94	-19.48	2.353	2.368
$Na^+\cdots C_6F_3H_3\cdots Cl^-$	-80.35	-17.14	2.389	2.925
$Na^+\cdots C_6F_3H_3\cdots Br^-$	-78.89	-16.00	2.399	3.006
$Na^+\cdots C_6F_6\cdots F^-$	-88.42	-17.09	2.437	2.286
$Na^+\cdots C_6F_6\cdots Cl^-$	-75.63	-12.05	2.488	2.835
$Na^+\cdots C_6F_6\cdots Br^-$	-74.04	-11.23	2.495	2.913

Further experimental evidence of the interplay between anion–π and cation–π interactions in solution has published by Dougherty and co-workers.[196] Using ^1H–NMR spectroscopy, they have demonstrated that cyclophane receptors that present carboxylate groups in the annular periphery have higher cation binding affinities than those without the anionic groups. This effect was attributed to the induced dipole generated in the aromatic ring by the presence of the carboxylate anion.

[193] M. Staffilani, K. S. B. Hancock, J. W. Steed, K. T. Holman, J. L. Atwood, R. K. Juneja, R. S. Burkhalter, *J. Am. Chem. Soc.* **1997**, *119*, 6324-6335.
[194] K. T. Holman, M. M. Halihan, S. S. Jurisson, J. L. Atwood, R. S. Burkhalter, A. R. Mitchell, J. W. Steed, *J. Am. Chem. Soc.* **1996**, *118*, 9567-9576.
[195] R. M. Fairchild, K. T. Holman, *J. Am. Chem. Soc.* **2005**, *127*, 16364-16365.
[196] S. M. Ngola, P. C. Kearney, S. Mecozzi, K. Russell, D. A. Dougherty, *J. Am. Chem. Soc.* **1999**, *121*, 1192-1201.

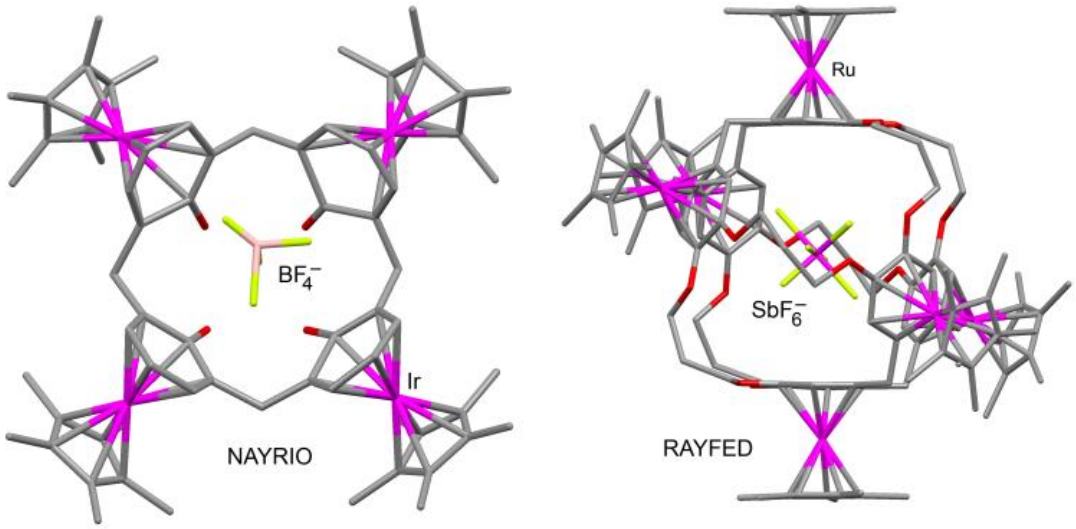


Figure 1.28. X-ray crystal structures of transition-metal complexed macrocycles NAYRIO[193] and RAYFED[194] exhibiting anion–π–cation bonding.

1.3.2.2. Interplay between Anion–π and Hydrogen Bonding Interactions

The interplay between the anion–π and H–bonding interaction has been also studied theoretically.[197,198,199] It has been demonstrated that a reinforcement of both interactions is observed when the aromatic ring is also engaged as a hydrogen bond acceptor, for example in pyrazine or pyridazino[4,5-*d*]pyridazine. In contrast, a weakening of both interactions is observed in complexes where the aromatic ring is a hydrogen bond donor, for instance pyromellitic diimide. From the partitioning of the interaction energy, it has been shown that this synergy is basically due to electrostatic effects.[197] These reciprocal effects were first reported for relatively small aromatic systems, where water molecules were used to generate the hydrogen bonding interactions with the arene at the normal H-boding distances. In a second report, the aromatic systems studied were larger and the distance from the anion to the water molecules was as long as 11 Å.[199] Even in these cases, a remarkable interplay between both interactions was observed.

[197] D. Escudero, A. Frontera, D. Quiñonero, P. M. Deyà, *J. Comput. Chem.* **2009**, *30*, 75-82.
[198] D. Quiñonero D. Escudero; X. Lucas; C. Estarellas; A. Frontera, P. M. Deyà, *Trends Phys. Chem.* **2008**, *13*, 31.
[199] X. Lucas, C. Estarellas, D. Escudero, A. Frontera, D. Quiñonero, P. M. Deyà, *ChemPhysChem* **2009**, *10*, 2256-2264.

1.3.2.3. Interplay between Ion–π and π–π Interactions

Since ion–π and π–π interactions are very important and omnipresent in a great variety of biological systems, the study of the mutual influence of both interactions is crucial. It has been recently demonstrated the interplay between ion–π and π–π interactions, which can lead to strong cooperativity effects.[126,130,200] The aromatic systems studied and some complexes are shown in Figure 1.29. The cooperativity effects can be favourable or unfavourable depending on the nature of the aromatic ring and the sign of the ion (see Table 1.5).

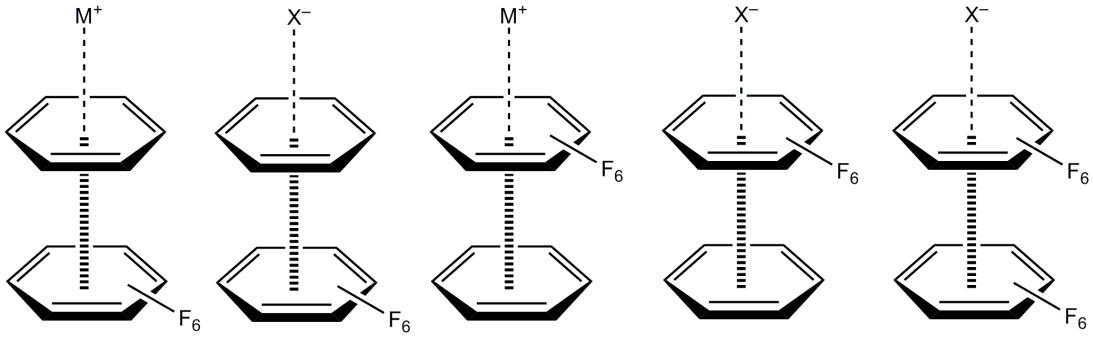


Figure 1.29. Ion–π–π complexes studied theoretically.

Table 1.5. Interaction (BSSE corrected) and cooperativity energies (E and E_{coop}, respectively in kcal/mol) and equilibrium distances (R_e, Å) of ion–π–π complexes at the MP2/6-31++G** .

Complex	E	E_{coop}	R_e (ion–π)	R_e (π–π)
$Li^+\cdots C_6H_6\cdots C_6F_6$	–35.5	0.3	3.37	1.90
$Na^+\cdots C_6H_6\cdots C_6F_6$	–23.0	0.0	3.39	2.39
$K^+\cdots C_6H_6\cdots C_6F_6$	–17.6	–0.3	3.38	2.91
$F^-\cdots C_6H_6\cdots C_6F_6$	–6.5	–2.6	3.35	3.00
$Cl^-\cdots C_6H_6\cdots C_6F_6$	–6.0	–2.6	3.36	3.59
$Br^-\cdots C_6H_6\cdots C_6F_6$	–6.2	–2.5	3.36	3.59
$Li^+\cdots C_6F_6\cdots C_6H_6$	–12.2	–4.5	3.25	2.10
$Na^+\cdots C_6F_6\cdots C_6H_6$	–6.1	–3.9	3.27	2.57
$K^+\cdots C_6F_6\cdots C_6H_6$	–4.9	–2.9	3.31	3.16
$F^-\cdots C_6F_6\cdots C_6H_6$	–21.8	0.5	3.48	2.59
$Cl^-\cdots C_6F_6\cdots C_6H_6$	–16.3	0.2	3.46	3.16
$Br^-\cdots C_6F_6\cdots C_6H_6$	–16.1	0.4	3.44	3.31
$F^-\cdots C_6F_6\cdots C_6F_6$	–24.4	–0.8	3.40	2.53
$Cl^-\cdots C_6F_6\cdots C_6F_6$	–17.4	–1.5	3.38	3.08
$Br^-\cdots C_6F_6\cdots C_6F_6$	–17.1	–1.0	3.39	3.24

[200] A. Frontera, D. Quiñonero, C. Garau, A. Costa, P. Ballester, P. M. Deyà, *J. Phys. Chem. A* **2006**, *110*, 9307-9309.

The theoretical results on ion–π–π complexes have been used to explain an unexpected experimental finding regarding the face-to-face stacking of pentafluorophenyl groups in substituted ferrocenes. In Figure 1.30 we show the three ferrocene derivatives studied by Blanchard et al.[119] in the conformation observed in their crystal structures. The conformation adopted in the crystal of the substituted ferrocenes **A** and **B** can be explained intuitively, while the conformation of **C** is in principle counterintuitive, as stated by the authors, showing face-to-face π–stacking of two pentafluorophenyl groups. This unexpected face-to-face stacking of the pentafluorophenyl groups can be explained considering the cooperativity energies of the anion–π–π complexes where both π–systems are hexafluorobenzene rings (see Table 1.5). They are negative and the equilibrium distances are shorter than in the related 1:1 complexes indicating that cooperativity effects are also found between anion–π and π–π interactions when both π–systems are HFB. These results are useful to explain the behaviour of structure **C** of Figure 1.30. The presence of the cyclopentadienyl anion interacting with a pentafluorophenyl group induces the face-to-face stacking interaction with the other pentafluorophenyl unit. Lastly, several recently reported works[201,202] have given experimental evidence of the interplay between anion–π and π–π interactions in π–acidic rings, in particular between two *s*-tetrazine rings and anions. This interplay may influence self-assembly reactions.

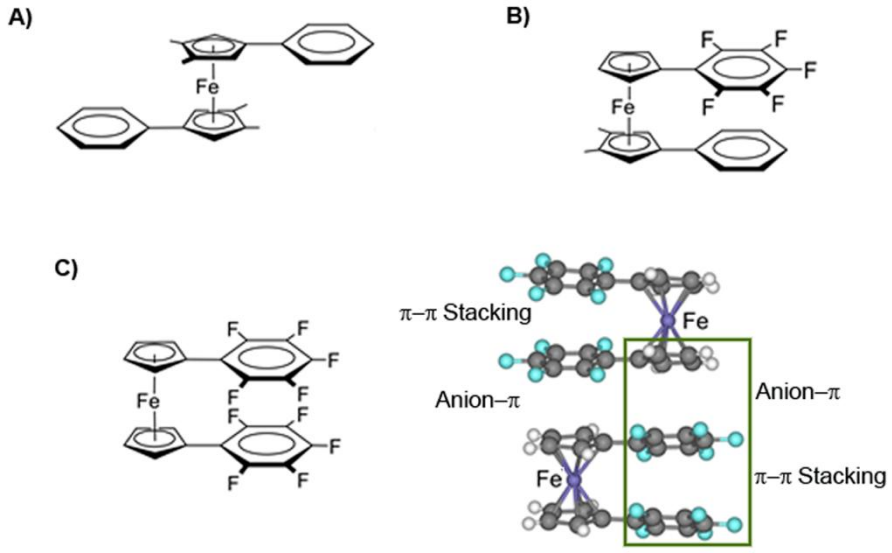


Figure 1.30. Ferrocene derivatives synthesized by Blanchard et al.[119] and a fragment of the X-ray structure of C are shown.

[201] B. L. Schottel, H. T. Chifotides, M. Shatruk, A. Chouai, L. M. Perez, J. Bacsa, K. R. Dunbar, *J. Am. Chem. Soc.* **2006**, *128*, 5895-5912.
[202] L. A. Barrios, G. Aromi, A. Frontera, D. Quiñonero, P. M. Deya, P. Gamez, O. Roubeau, E. J. Shotton, S. J. Teat, *Inorg. Chem.* **2008**, *47*, 5873-5881.

1.3.2.4. Influence of Metal Coordination on the Anion–π Interaction

The influence of metal coordination to heteroaromatic rings on the energetics of anion–π interactions has been analysed in two recent papers.[203,204] One of them[204] combines theory and experiment to demonstrate that *s*–tetrazine is a powerful anion–π acceptor when it is coordinated to four Ag^{I} atoms. The calculated interaction energy of *s*–tetrazine with nitrate ion is –9.6 kcal·mol^{-1}, and when tetracoordinated to Ag^{I} the interaction energy becomes –62.4 kcal·mol^{-1}. A significant shortening of the equilibrium distance is also predicted. Experimentally, very close contact is observed between the anion and the *s*–tetrazine ring in the X–ray structures (Figure 1.31) indicating strong anion–π interactions, in agreement with the theoretical predictions.

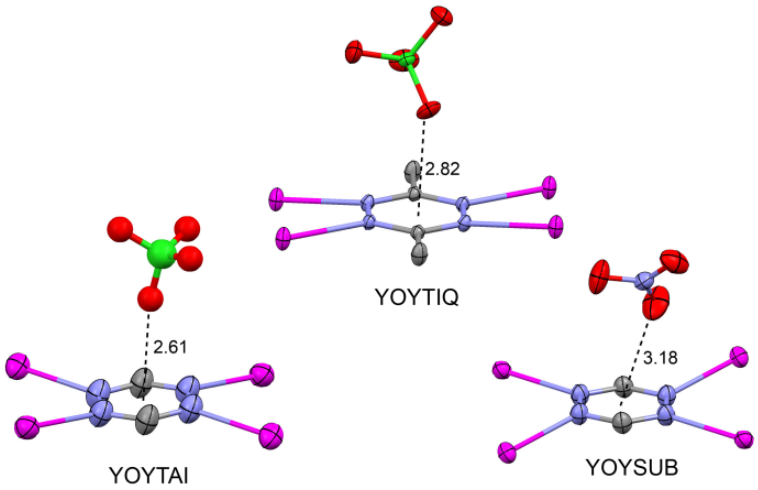


Figure 1.31. Fragments of the X-ray crystal structures containing μ_4-coordination of 1,2,4,5-tetrazine and the relevant anion–π interactions, with distances in Å.[204] The CSD reference codes are indicated.

1.3.3. DIRECTIONALITY OF THE ANION–π INTERACTION

It is important to define rational criteria which can be used to classify a given anion–aromatic contact as an anion–π interaction. In the same sense that the hydrogen bond should not be restricted to linear X-H···Y contacts at X–Y distances greater than the sum of the van der Waals radii (<ΣvdW), it is clearly incorrect to limit the anion–π interaction to situations where the anion is exactly over the centre of the ring at anion-centroid distances <ΣvdW radii. In fact, since aromatic rings are often electronically asymmetric, the most favourable location is generally not directly above the centre of the ring. Furthermore, anion–π complexes are generally observed in the solid state, and isotropy is almost never experienced in the local

[203] D. Quiñonero, A. Frontera, P. M. Deyà, *ChemPhysChem* **2008**, *9*, 397-399.
[204] I. A. Gural'skiy, D. Escudero, A. Frontera, P. V. Solntsev, E. B. Rusanov, A. N. Chernega, H. Krautscheid, K. V. Domasevitch, *Dalton Trans.* **2009**, 2856-2864.

environment of a crystal, where counterions, possibly solvent molecules and, of course, other rings are packed into a lattice. Thus, the equilibrium position of the anion with respect to the aromatic ring will vary with the particular circumstances. Since the π–system encompasses the entire ring, the broadest, but arguably most appropriate, criterion would be to invoke anion–π bonding when the anion is located anywhere within the ring boundary at distances ≤ ΣvdW radii + d, where "d" is an increment distance that has to be defined. In a high-level study of the energetics of anion–π bonding, our group recommended a value of 0.8 Å for *d*.[205] In time, other values may be put forward. Looking again to the hydrogen bond as an example, it is described by a wide range of interaction distances and angles, and for this reason is classified as strong, moderate and weak. However, neither the name, nor the nature of the interaction changes. The occurrence of the hydrogen bonding is generally rationalized using the concept of lone pairs of electrons as the acceptor, and thus hydrogen bonds involving carbonyl groups commonly have C=O···H angles near 120°. However, this is not a strict condition, and a wide scatter found in C=O···H angle histograms in different hydrogen bonded systems.[206]

The directionality of the anion–π interaction has been recently investigated and compared with that of the cation–π interaction. In previous report,[207] the authors stated that "anion–π interactions involving close interactions of anions with the centre of neutral aryl ring are uncommon in the CSD". Given the restrictive geometric search criteria used in that work, and the fact that the majority of X-ray crystal structures in which anions and aromatic rings appear together involve charged aromatics (usually N-heterocycles), this was an inevitable conclusion. However, as noted above, the equilibrium position of an anion is often displaced away from center of the ring. Conversely, in cation–π interactions, cations show a stronger preference for the centre of the ring. This behaviour can be explained by analysing how the interaction energy is affected by incrementally moving an anion from the centre to the periphery of the ring in an anion–π complex and comparing it to the same movement in a cation–π complex. The directionality observed for the chloride–hexafluorobenzene complex has been compared to that of the sodium–benzene complex. The results reported in the study[205] are useful to explain the experimental (crystallographic) differences between these ion–π interactions. The analysis shows that the interaction energy of anion–π complexes shows only a very modest changes (less than 1 kcal·mol^{-1}) when the anion moves along the *x* and *y* axes. The analogous results obtained for the cation–π complex show that the energy loss is substantially greater than that obtained for the anion–π interaction. This result offers an explanation for the

[205] C. Estarellas, A. Bauza, A. Frontera, D. Quiñonero, P. M. Deyà, *Phys. Chem. Chem. Phys.* **2011**, *13*, 5696-5702.
[206] P. A. Kollman, *J. Am. Chem. Soc.* **1972**, *94*, 1837-1842.
[207] B. P. Hay, R. Custelcean, *Cryst. Growth Des.* **2009**, *9*, 2539-2545.

experimental findings[207] that show more scatter in the location of the ion in anion–π *versus* cation–π complexes when analysing the crystal structures in the Cambridge Structural Database (CSD).

1.3.4. SELECTED EXPERIMENTAL EXAMPLES OF THE ANION–π INTERACTION

While molecular modelling can provide valuable insights into the nature and energetics of previously unrecognized modes of bonding, the model remains a purely theoretical one in the absence of experimental validation and predictive ability. Crystal structures are the traditional proving ground for structural evidence of unconventional bonding relationships, and often reveal features that had not been noticed by the authors who published the data. Since the earliest papers which described the anion–π interaction,[128,161,162] the Cambridge Structural Database (CSD)[174] has been used to provide experimental evidence of its occurrence in the solid state. To date, a great deal of experimental work has provided strong evidence of this emerging noncovalent interaction. In the following sections, we describe some selected experimental examples where anion–π interactions are strongly evident. These examples are organized with respect to the experimental medium (solution, solid state, and gas phase) in which they occur.

1.3.4.1. Evidence of Anion–π Interactions in Solution

In the last years the numbers of papers that experimentally demonstrate the anion–π in solution have increased. However one of the pioneering works was reported by Berryman and co-workers, which prepared a receptor incorporating two-point recognition motif involving a hydrogen bond donor and a perfluorophenyl ring (Figure 1.32).[208] As a control, an analogue lacking the fluoro substituents was also studied. Any enhanced affinity for anions that the former receptor exhibits over the latter should be the result of a favourable anion–π interaction. This was the first neutral receptor molecule designed to make use of the anion–π interaction to bind anions in solution. ^{1}H NMR spectroscopic titration experiments were performed for both receptors with *n*–tetrabutylammonium chloride, bromide and iodide salts in $CDCl_3$. The reported K_a values are included in Figure 1.32, and show a significant difference between the association constants of the receptors with a given halide. The receptor incorporating the electron–deficient ring binds all the halides with a measurable, albeit modest association constant. However, in the case of the receptor where no electron–deficient ring is present, there is no measurable association with any of the halides. These data provide good

[208] O. B. Berryman, F. Hof, M. J. Hynes, D. W. Johnson, *Chem. Commun.* **2006**, 506-508.

support for anion–π bonding in solution, highlighting the possibility of utilizing the interaction in receptor design.

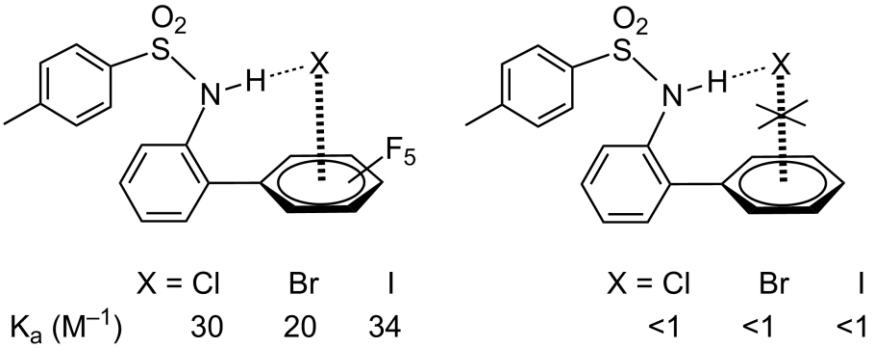


Figure 1.32. Anion receptors synthesized by Berryman et. al.[208] and their association constants (K_a) with halides in $CDCl_3$.

Berryman and co-workers have also published an experimental and theoretical study on a series of neutral tripodal hosts that solely employ electron–deficient arenes to bind halides in solution (Figure 1.33).[209] The authors prepared 2,4,6–trisubstituted 1,3,5–triethylbenzene derivatives differing only in the position of their nitro substituents, which provided access for anions to interact with the electron–deficient cavities either by the π–system or by C–H···X^- hydrogen bonding (Figure 1.33, left and middle receptors). The structures incorporate "steric gearing" to preorganize the electron–deficient cavity, and represent the first receptors designed to quantitatively measure weak bonding interactions between anions and arenes. ^{1}H–NMR spectroscopy was used to measure the anion binding constants (K_a) and to determine the nature of the interaction. The key feature in the design strategy is that the middle receptor of Figure 1.33 cannot form hydrogen bonds to anions due to the bulky nitro groups being positioned *ortho* to the aryl hydrogens, thereby allowing the study of the interaction between the anion and the π–system. The receptor on the right was used as a control. The association constants determined for the hosts based on electron–deficient arenes was 11–53 M^{-1}, while the control molecule exhibited no measurable binding. These results support the hypothesis that electron–deficient aromatic rings are required to bind anions in this neutral system. Significantly larger ^{1}H chemical shift changes were observed for the left receptor over those of the middle receptor, consistent with the fact that the former can participate in aryl C–H···X^- H–bonds while the latter cannot. The highly electron-deficient middle receptor was determined to adopt a binding motif involving weak σ-type anion–π contact. The receptors exhibited the strongest interactions with Cl^- followed by Br^- and I^-, and the largest association constants

[209] O. B. Berryman, A. C. Sather, B. P. Hay, J. S. Meisner, D. W. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 10895-10897.

were observed when the halide was forced to interact solely through contacts to the π–system (Figure 1.33, middle receptor).

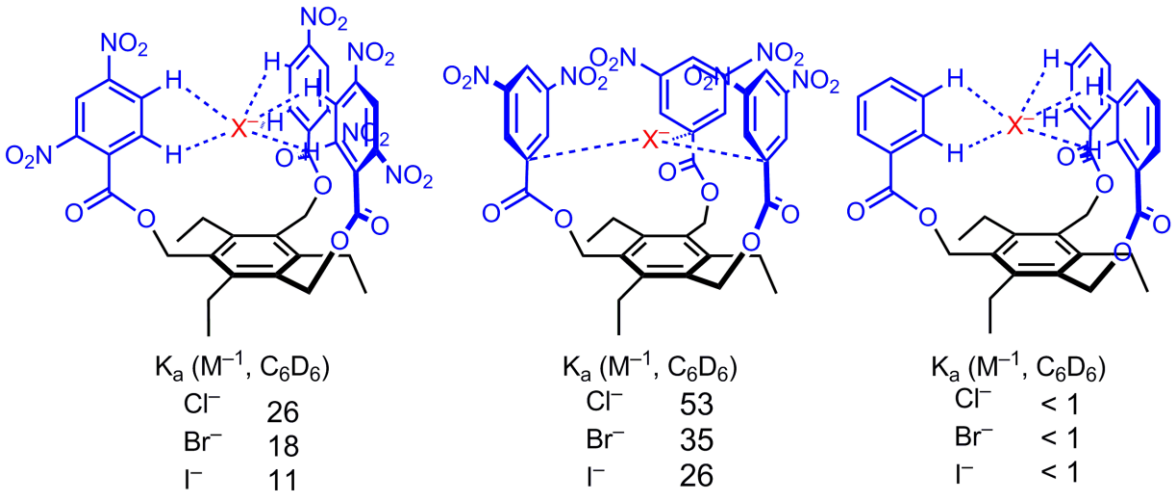
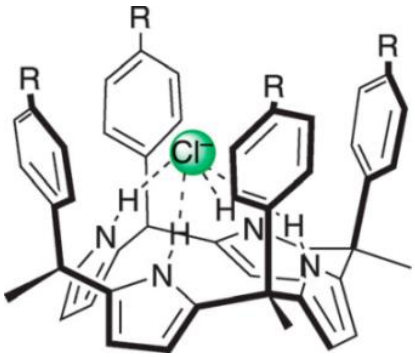


Figure 1.33. Anion-receptor synthesized by Berryman et. al.[209] and their association constants (K_a) with halides in C_6D_6.

Yet another study devoted to measuring the binding energy of anion–π interactions within neutral receptors has been published by Ballester and collaborators (see Figure 1.34).[210] In this work, a series of mesotetraaryl calix[4]pyrrole receptors were used as model systems to quantify chloride–π interactions in solution. By means of ^{1}H–NMR spectroscopy and X–ray crystallography it was demonstrated that chloride–arene interactions observed in these complexes are established exclusively with the aromatic π system. The derived quantitative Hammett free–energy relationship was used to show that the observed chloride–π interactions were dominated by electrostatic effects.

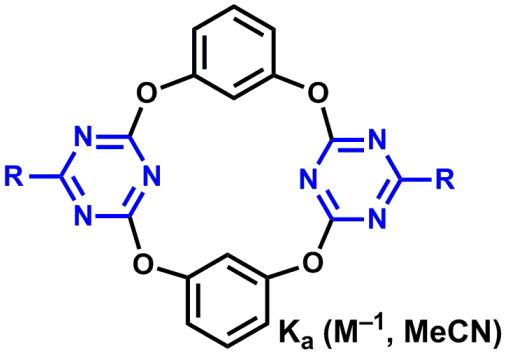


R	K_a (M^{-1}, CD_3CN)
OMe	1.3×10^2
H	2.5×10^2
Br	3.8×10^3
CN	3.3×10^4
NO_2	1.8×10^5

Figure 1.34. Meso-tetraaryl calix[4]pyrrole receptors synthesized by Ballester *et. al.*[210] and their association constants (K_a) with chloride in CD_3CN.

[210] G. Gil-Ramirez, E. C. Escudero-Adan, J. Benet-Buchholz, P. Ballester, *Angew. Chem., Int. Ed.* **2008**, *47*, 4114-4118.

Heteroatom–bridged heteroaromatic calixarenes are an emerging class of macrocycles that have been utilized recently as versatile host molecules in Supramolecular Chemistry.[211,212] A representative example is tetraoxacalix[2]arene[2]triazine (Figure 1.35), which preferentially adopts a 1,3–alternate conformation, forming a cleft between the two π–electron deficient triazine rings. Recently, Wang *et. al.*[213] reported halide recognition by tetraoxacalix[2]arene [2]triazines, in which significant substituent effects were observed. Thus, macrocycles with N,N–dimethylamino substituents showed no change in either the absorption or emission spectrum when titrated with fluoride, chloride, or bromide. The unsubstituted calixarene interacted weakly with fluoride but not with chloride or bromide. However, the chlorine–substituted host formed 1:1 complexes with both fluoride and chloride, with binding constants of 4036 ± 36 M^{-1} and 4246 ± 83 M^{-1}, respectively. This effect was attributed by the authors to the electron–withdrawing nature of the chloro substituent.



R	F^-	Cl^-	Br^-
Cl	4036	4246	–
H	68	–	–
NMe_2	–	–	–

Figure 1.35. Macrocyclic anion receptors synthesized by Wang *et. al.* and their association constants (K_a) with Bu_4N^+ halides in MeCN.[213]

The work of Matile's group on the application of anion–π interactions to selective anion transport across lipid bilayer membranes merits special mention here.[135,170,171,172] In biology, the selectivity of ion transport is of vital importance, and in the case of cations is generally achieved by ion coordination to preorganized arrays of oxygen lone pairs, with cation–π interactions also playing a potential role.[214,215] In biological anion channels, hydrogen bonding, ion pairing, and anion–dipole interactions contribute to selectivity. Up to now, no anion–π

[211] M. X. Wang, X. H. Zhang, Q. Y. Zheng, *Angew. Chem., Int. Ed.* **2004**, *43*, 838-842.
[212] H. Y. Gong, Q. Y. Zheng, X. H. Zhang, D. X. Wang, M. X. Wang, *Org. Lett.* **2006**, *8*, 4895-4898.
[213] D. X. Wang, Q. Y. Zheng, Q. Q. Wang, M. X. Wang, *Angew. Chem., Int. Ed.* **2008**, *47*, 7485-7488.
[214] R. A. Kumpf, D. A. Dougherty, *Science* **1993**, *261*, 1708-1710.
[215] D. A. Dougherty, *Science* **1996**, *271*, 163-168.

bonding has been observed in natural anion channels. However, the challenge of bringing anion–π interactions to bear on transmembrane anion transport has been taken on by Matile group. To achieve this, anion recognition must be combined with anion translocation. The combination involves a delicate balance of effects, because tight binding tends to hinder ion movement. In biological ion channels, the placement of multiple binding sites in series combines selectivity with favourable kinetics.[216,217] The cooperative transport of ions by this means is referred to as multi–ion hopping.[170,171] To achieve significant transmembrane transport using anion–π interactions, it is therefore necessary to present multiple π–acidic aromatic binding sites along the channel. Anions could then be transported quickly and selectively along these anion–π "slides". Inspired by an earlier, closely related approach to transmembrane potassium ion transport via cation–π interactions,[218] Matile and co-workers prepared π–acidic, shape-persistent, rigid–rod oligonaphthalenediimides (O–NDIs) for chloride–selective multi–ion hopping across lipid bilayers (see Figure 1.36). Results from end–group engineering and covalent capture as O–NDI hairpins have suggested that self–organization into transmembrane O–NDI bundles is essential for activity. The reported halide topology implies strong anion binding along the anion–π slides with weaker contributions from size exclusion. Anomalous mole fraction effects supported the occurrence of multi–ion hopping along the O–NDI rods.

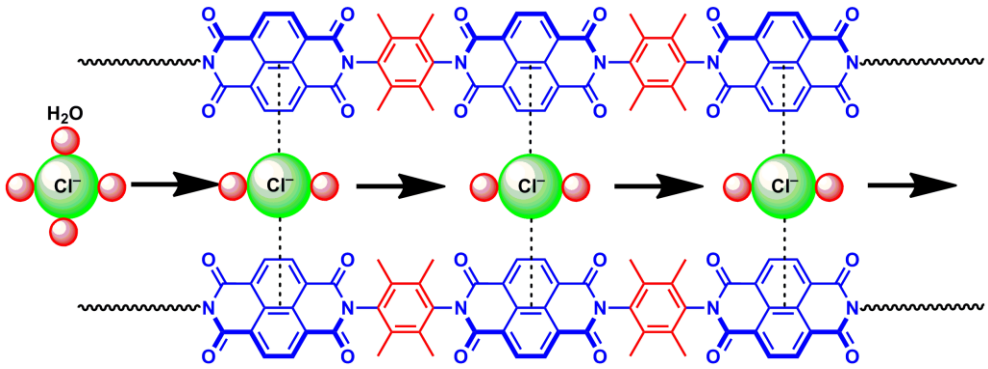


Figure 1.36. Schematic representation of the anion–π "slide" based on O-NDIs used by Matile and co-workers.[219]

Matile *et. al.* [220] have also introduced simple sulfur redox chemistry into the naphthalenediimide framework[221,222,223,224,225] in order to 1) generate enhanced π acidity, 2)

[216] D. A. Doyle, J. M. Cabral, R. A. Pfuetzner, A. L. Kuo, J. M. Gulbis, S. L. Cohen, B. T. Chait, R. MacKinnon, *Science* **1998**, *280*, 69-77.
[217] R. Dutzler, E. B. Campbell, R. MacKinnon, *Science* **2003**, *300*, 108-112.
[218] M. M. Tedesco, B. Ghebremariam, N. Sakai, S. Matile, *Angew. Chem., Int. Ed.* **1999**, *38*, 540-543.
[219] V. Gorteau, G. Bollot, J. Mareda, S. Matile, *Org. Biomol. Chem.* **2007**, *5*, 3000-3012.
[220] J. Misek, A. V. Jentzsch, S. I. Sakurai, D. Emery, J. Mareda, S. Matile, *Angew. Chem., Int. Ed.* **2010**, *49*, 7680-7683.
[221] E. L. Dane, S. B. King, T. M. Swager, *J. Am. Chem. Soc.* **2010**, *132*, 7758-7768.

demonstrate the functional relevance of the system by anion transport experiments,[135,170,171,172,225] and 3) to create switchable, chiral π–acidic surfaces that may be used for applications in asymmetric anion–π actuated catalysis. Thioether core–substituted naphtalenediimides (cNDIs)[226,227] were oxidized to give chiral sulfoxide and then further to sulfone derivatives (Figure 1.37). Optoelectronic properties, anion transport activity and computational studies reveal that the tetrasulfone is the most π–acidic cNDI known, with a LUMO energy level 0.43 eV below that of NDI itself.

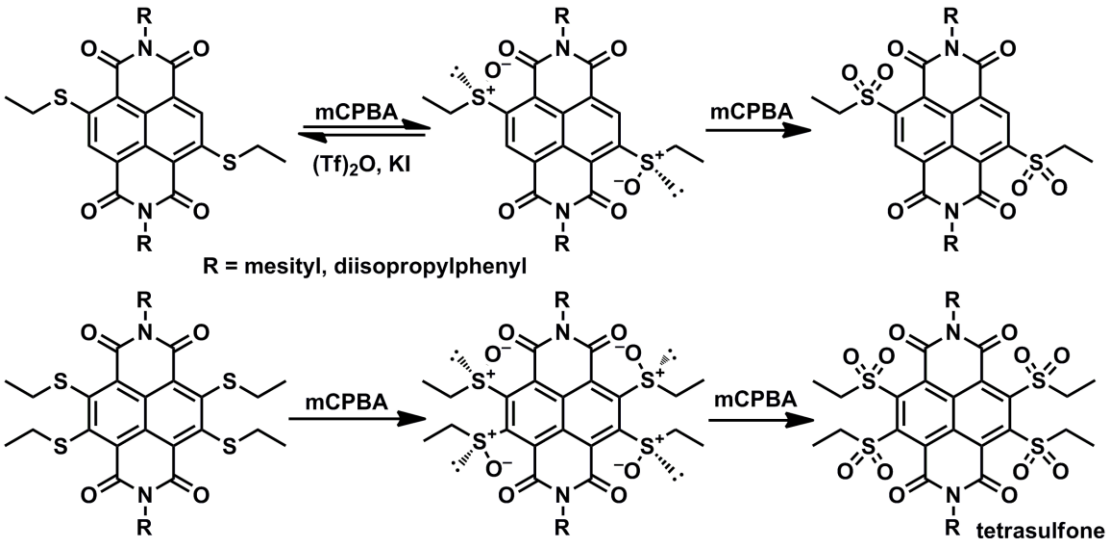


Figure 1.37. Structures of thioether, sulfoxide, and sulfone core-substituted naphthalenediimides, the anion affinity of which is dependent on the oxidation state of sulfur.[220] (mCPBA=meta-chloroperbenzoic acid).

Chifotides and co-workers[228] have carried out an insightful study of an extended π electron deficient molecule with multiple sites available for interactions with anions, namely $HAT(CN)_6$ (HAT = 1,4,5,8,9,12-hexaazatriphenylenehexacarbonitrile). The high π–acidity, high molecular polarizability, and positive quadrupole moment of $HAT(CN)_6$ render it an attractive, neutral heterocyclic system for exploring anion–π and lone pair–π bonding. Interactions between $HAT(CN)_6$ and the halide salts $[nBu_4N][X]$ ($X = Cl^-, Br^-, I^-$) were unequivocally confirmed in solution by UV/Vis, ^{13}C–, and halogen NMR spectroscopy. Experimentally, by means of Job plots, the authors found evidence of a 2:3 stoichiometric ratio of $[HAT(CN)_6]:[X^-]$ suggesting

[222] M. M. Oliva, J. Casado, J. T. L. Navarrete, S. Patchkovskii, T. Goodson, M. R. Harpham, J. S. S. de Melo, E. Amir, S. Rozen, *J. Am. Chem. Soc.* **2010**, *132*, 6231-6242.
[223] C. Wolschner, A. Giese, H. A. Kretzschmar, R. Huber, L. Moroder, N. Budisa, *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 7756-7761.
[224] N. Sakai, S. Matile, *J. Am. Chem. Soc.* **2002**, *124*, 1184-1185.
[225] N. Sakai, D. Gerard, S. Matile, *J. Am. Chem. Soc.* **2001**, *123*, 2517-2524.
[226] A. Blaszczyk, M. Fischer, C. von Hanisch, M. Mayor, *Helv. Chim. Acta* **2006**, *89*, 1986-2005.
[227] C. Roger, F. Wurthner, *J. Org. Chem.* **2007**, *72*, 8070-8075.
[228] H. T. Chifotides, B. L. Schottel, K. R. Dunbar, *Angew. Chem., Int. Ed.* **2010**, *49*, 7202-7207.

multicentre binding in an unprecedented η^2,η^2–fashion (Figure 1.38). The measured association constants in THF at 25 °C are 3780, 2200 and 940 M^{-1} for Cl^-, Br^-, and I^- respectively. These large K_a values are attributed to the high stability of the charge transfer (CT) complexes of $HAT(CN)_6$ and its exceptional acceptor strength, which render it a sensitive, selective molecular scaffold for the effective recognition of anions and a promising colorimetric anion sensor.

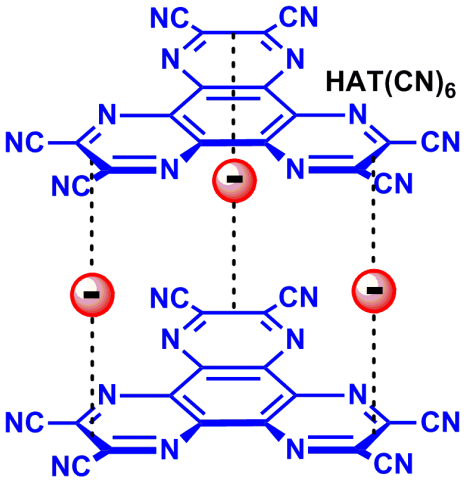


Figure 1.38. Schematic representation of multisite anion contacts observed in $[HAT(CN)_6]_2[X^-]_3$ complexes reported by Chifotides, *et. al.*[228]

1.3.4.2. Evidence of Anion–π Interactions in the Solid State

The first experimental work devoted to the study of anion–π interactions to appear after the publication of the original theoretical manuscripts was reported by Demeshko *et. al.*[163] The synthesis and X–ray characterization of a host molecule based on the electron–deficient *s*–triazine ring was reported, where two triazine rings are arranged in an almost perfect face–to–face arrangement (Figure 1.39). The most interesting feature of the crystal structure are the positions of the charge–compensating chloride and $[CuCl_4]^{2-}$ ions. The chloride anion resides above one of the triazine rings, where the distance between the ring centroid and the Cl^- is 3.17 Å. The angle of the $Cl^-\cdots$centroid axis to the plane of the ring (87°) shows that the chlorine is almost ideally located on the C_3–axis above the ring. Both values are in agreement with those obtained from *ab initio* molecular orbital calculations for the parent 1,3,5–triazine–chloride complex.[161] In a likewise manner, the opposite triazine face of the host is capped by the $[CuCl_4]^{2-}$ ion at a distance of 3.11 Å between one chlorine of the complex ion and the ring centroid. Another interesting work was published by de Hoog *et. al.*,[165] who described the synthesis and X–ray characterization of a tetranuclear copper complex of a single dendritic

ligand, where four *s*–triazinyl groups stack two by two in a parallel fashion and the copper ions are coordinated by two dipyridylamino substituents of the stacked *s*–triazine rings.

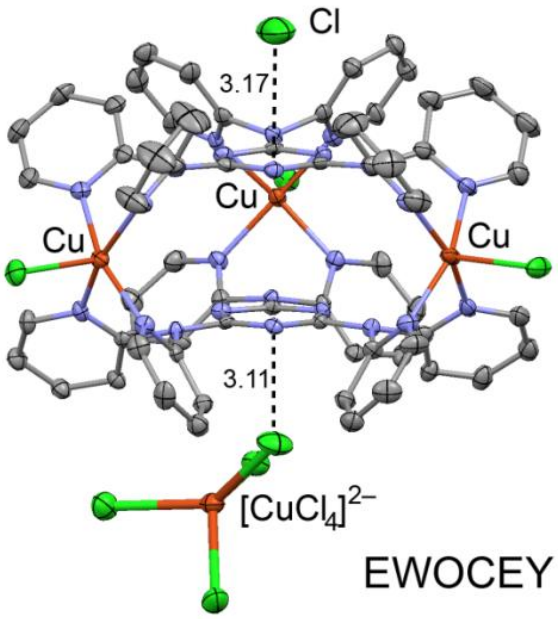


Figure 1.39. Fragment of the X-ray structure EWOCEY showing the *s*–triazine-based host interacting with Cl^- and $CuCl_4^{2-}$ ions through anion–π interactions.[163]

An elegant piece of work by Dunbar and collaborators[229] describes the comprehensive investigation of an anion–templated self–assembly reaction between first row transition metal ions M(II) (M = Ni, Zn, Mn, Fe, Cu) and the bis–bipyridine ligand 3,6–bis(2–pyridyl)–1,2,4,5–tetrazine (bptz; Figure 1.40). The formation of polygonal complexes was observed in the presence of certain anions (BF_4^-, ClO_4^-, SbF_6^-), which were found to selectively determine the aggregation state both in the solid and solution. The formation of molecular squares is dominant in the presence of the BF_4^- and ClO_4^- ions, while the SbF_6^- ion templates a pentagonal oligomer (Figure 1.40). The competing influence of the anions in stabilizing the different cyclic entities was also studied by mass spectrometry and X–ray crystallography. For example, the $[Ni_5]^{10+}$ pentagon was found to be less thermodynamically stable than $[Ni_4]^{8+}$. Ion signals corresponding to the molecular square begin to appear in the ESI–MS spectrum after addition of n–Bu_4N^+ BF_4^- or n–Bu_4N^+ ClO_4^- to a solution of $[(Ni_5(bptz)_5(CH_3CN)_{10})\subset SbF_6]^{9+}$, and complete conversion of the Ni(II) pentagon to the square is accomplished by adding an excess of either tetrahedral anion (Figure 1.40). It was concluded from this study that the nuclearity of the cyclic products is dictated by the identity of the anion present in solution during the self–assembly process. This can be attributed to a template effect that stabilizes one particular

[229] C. S. Campos-Fernandez, B. L. Schottel, H. T. Chifotides, J. K. Bera, J. Bacsa, J. M. Koomen, D. H. Russell, K. R. Dunbar, *J. Am. Chem. Soc.* **2005**, *127*, 12909-12923.

cyclic structure over another due to favourable anion–π interactions between the anion inside the cavity and the bptz ligands.

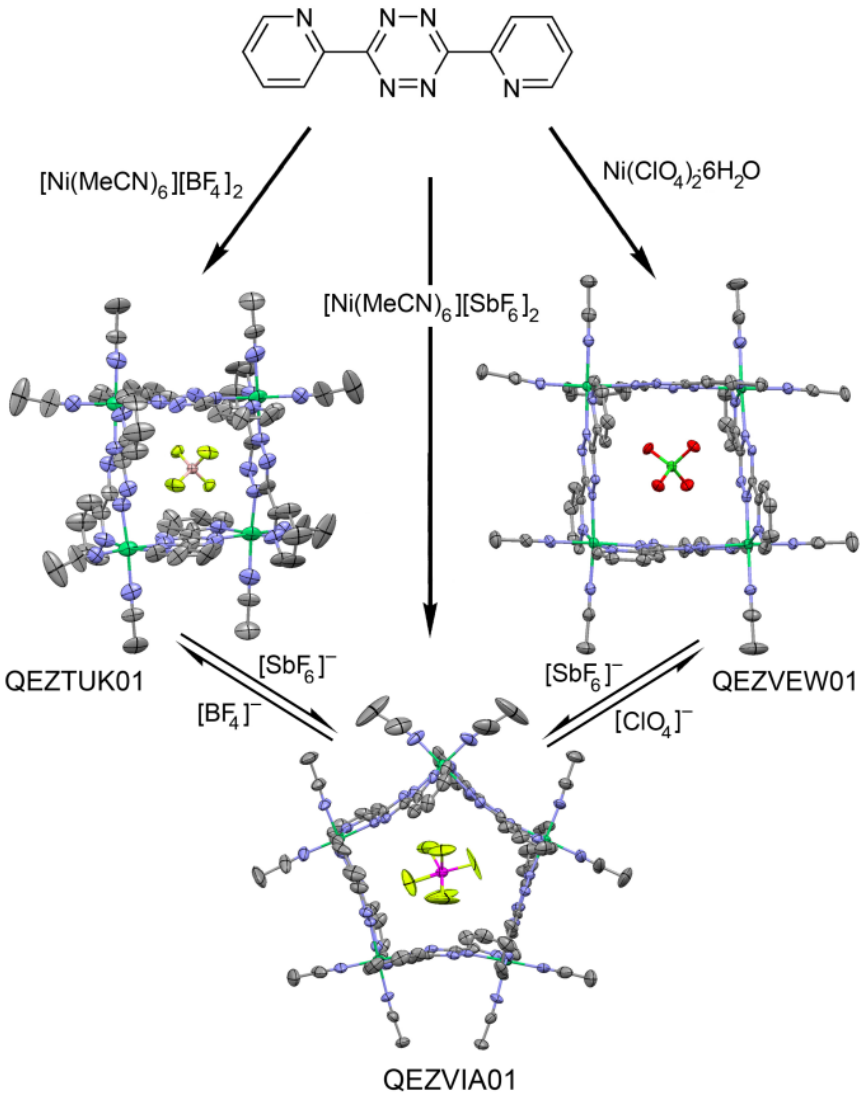


Figure 1.40. Representation of the cationic units $[(Ni_5(bptz)_5\text{-}(CH_3CN)_{10})\subset SbF_6]^{9+}$ (QEZVIA01), $[(Ni_4(bptz)_4(CH_3CN)_8)\subset ClO_4]^{7+}$ (QEZVEW01), and $[(Ni_4(bptz)_4(CH_3CN)_8)\subset BF_4]^{7+}$ (QEZTUK01) and their scheme of interconversion.[229]

An additional example of the self–assembly of Ag(I) coordination networks directed by anion–π interactions has been published by Zhou *et. al.*[230] In their study Ag(I) complexes with 2,4,6–tri(2–pyridyl)–1,3,5–trazine (tpt). They found that polyatomic anions (ClO_4^-, BF_4^-, and PF_6^-) direct the self–assembly of Ag–tpt coordination polymers through anion–π interactions. It has been proved that factors such as reaction temperature, ratio of reactants, counterions, and solvents influence the self-assembly of resulting supramolecular compounds.

[230] X. P. Zhou, X. J. Zhang, S. H. Lin, D. Li, *Cryst. Growth Des.* **2007**, *7*, 485-487.

Mascal and co-workers recently described an application of π–anion–π sandwich bonding in the design[231] and synthesis[161] of a selective fluoride host. A theoretical treatment of the receptor (Figure 1.41), described two key design principles that work together to establish selectivity. On the one hand, it is known that fluoride ion benefits from both π–X–π and $^{+}NH\cdots X^{-}$ hydrogen bonding interactions making them stronger than the next closest ion in size (chloride). Next, the tight steric fit of fluoride in the cavity suggested that the complexation of any other anion was simply not feasible. The molecular framework on which the receptor is based is the cylindrophane macrobicycle, in which two planar, six-membered rings are bridged in a three-fold symmetric manner by linking chains. In this case, the rings are π–acidic triazinetriones, and the linkers are trialkylamines. Protonation of the amine groups "arms" the receptor for inclusion via a combination of anion–π interactions and ion–pair–reinforced hydrogen bonding. Complexation studies were carried out by electrospray mass spectrometry, in which 1:1 binding of the receptor with fluoride was established, while no affinity for chloride was observed. An X–ray crystal structure of the complex shows fluoride occupying the centre of the cavity, in very close agreement with the theory. Although a number of halide complexing agents have been described,[232] this receptor introduces a new genre of anion binding, wherein anion–π interactions operate alongside conventional ion pairing, hydrogen bonding, and the classic "preorganization" effect.

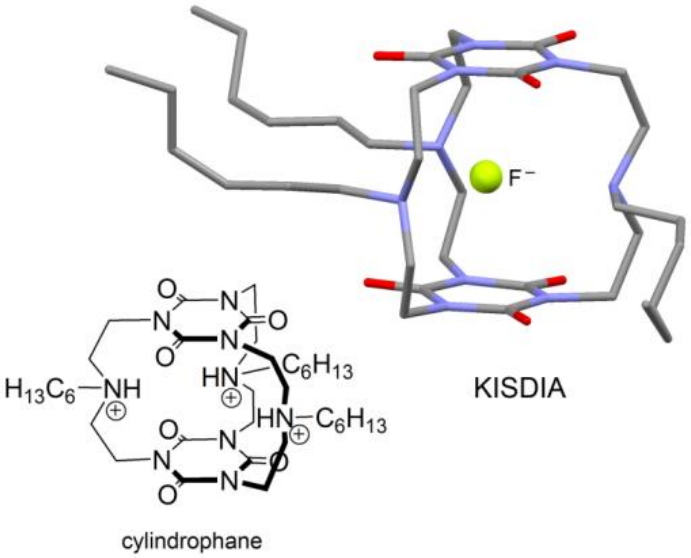


Figure 1.41. Structure of the fluoride-binding cylindrophane macrocycle and the experimental X-ray structure of the F^{-} complex (KISDIA).[161,231]

As described in the previous section, Wang and coworkers[213] reported halide recognition by tetraoxacalix[2]arene[2]triazine host molecules in solution based on anion–π interactions. X–

[231] M. Mascal, *Angew. Chem., Int. Ed.* **2006**, *45*, 2890-2893.
[232] K. Bowman-James, *Acc. Chem. Res.* **2005**, *38*, 671-678.

ray crystallography revealed the concurrent formation of noncovalent halide–π and lone pair–π electron interactions between water, halide ion, and the dichlorosubstituted host (Figure 1.42). Some interesting structural features are that in both complexes, the calixarene moiety adopts a 1,3–alternate conformation with the two benzene rings being nearly face–to–face while the two π–deficient triazine rings form a V–shaped cleft. Both chloride and bromide anions form classic anion–π interactions with the triazine rings. Furthermore, both host–halide complexes co–crystallize with water molecules, one of which forms a ternary complex between the halide and host (Figure 1.42). Finally, the hydrogen–bonded water molecule in both cases forms a lone pair–π interaction between the oxygen atom and the triazine ring, as evidenced by the location of the water molecule directly above the triazine centroid at a very short distance of 2.83–2.85 Å. Such a close contact excludes the possibility of an O–H···π interaction.

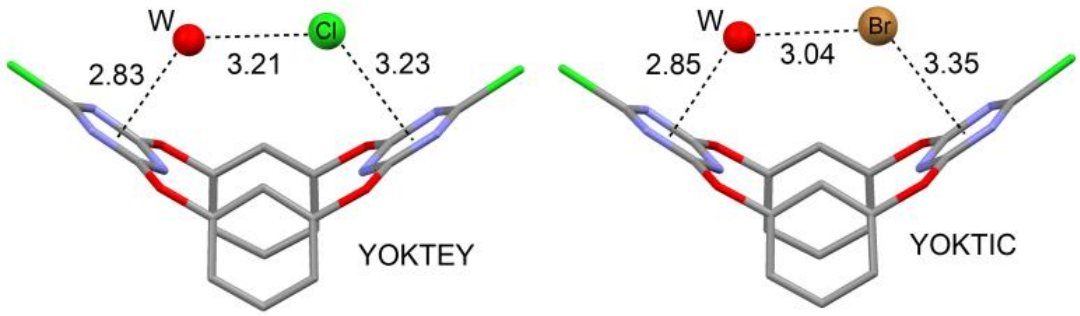


Figure 1.42. X-ray crystal structures of the complexes between tetraoxacalix[2]arene[2]triazine hosts and chloride (left) and bromide (right), with distances in Å.[213] The CSD reference codes are indicated.

1.3.4.3. Evidence of Anion–π Interactions in the Gas Phase

Anion–π complexation in the gas phase has been investigated principally by electrospray ionization mass spectrometry (ESI–MS) experiments. Mass spectrometry offers the advantage that non–solvated complexes are observed, which can be more easily compared to quantum chemical calculations than the corresponding complexes in solution. Two important works that characterize anion–π complexes by this technique are described here. The first involves $[HAT(CN)_6]:[X^-]$ complexes, which also combines evidence for anion–π bonding from the solution and the solid state.[228] Results obtained from the ESI–MS measurements provided additional strong evidence that anion–π interactions between halides and $HAT(CN)_6$ persist in the gas phase by observation of $([HAT(CN)_6]:[X])^-$ complex ions for X = Cl, Br, and I. A second work employs electrospray ionization Fourier–transform ion cyclotron resonance tandem mass

spectrometry (ESI–FTICR–MS–MS),[233] which can be used to determine anion affinity sequences quantitatively. Equimolar solutions of naphthalenediimides (NDIs) **A**–**E** (Figure 1.43) and salts of different anions were electrosprayed from acetonitrile under mild ionization conditions. NDI–anion complexes of **A**–**D** were confirmed for Cl^-, Br^- and NO_3^-. For macrocycle **E**, the binding of an additional series of anions was reported. A preference for chloride among halides and nitrate among oxyanions was obtained from competition experiments, which also revealed a selectivity sequence for chloride of **D** > **C** > **B** > **A**, demonstrating an increasing anion affinity with increasing π–acidity and decrowding of the anion–π binding site.

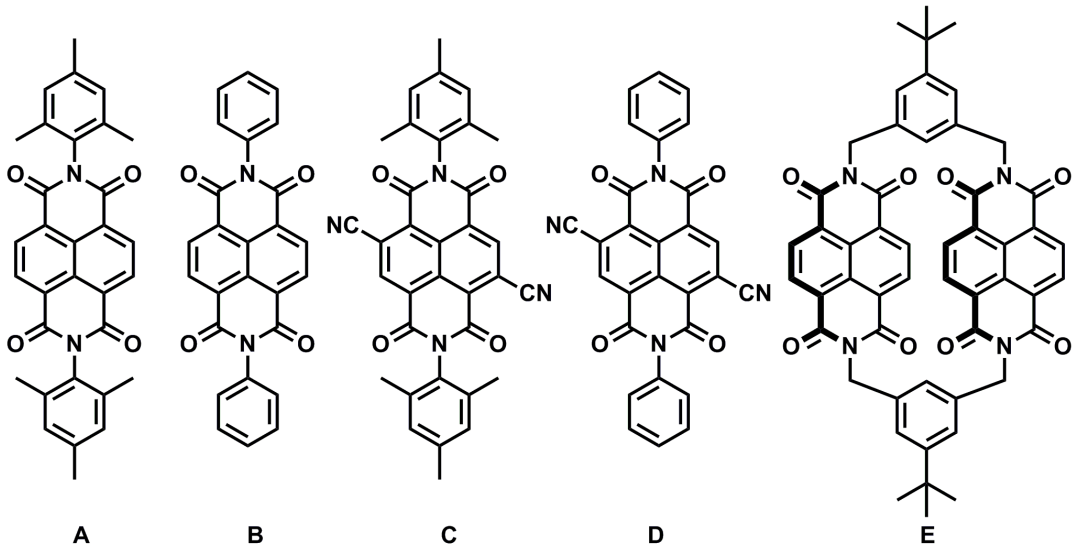


Figure 1.43. Representation of the structures of NDIs **A**–**E** used by Matile and coworkers[172] to probe gas-phase anion affinity.

1.3.5. RECENT ADVANCES IN THE INVESTIGATION OF ANION–π INTERACTION

Over the past ten years, the anion–π interaction has been recognized as an important weak force that occur between anionic systems and electron-deficient aromatics. Lately, this supramolecular contact has experienced a rapidly growing interest, as reflected by numerous recent literature reports. The progress achieved in the field is examined in this section by emphasizing a few important studies involving anion–π interactions published in 2011 and early 2012.

Ion transport systems that operate in lipid bilayer membranes[172,220,234,235] are emerging as attractive tools to probe the functional relevance of weak interactions that are otherwise difficult to observe. This approach builds on the notion that transport and catalysis operate

[233] M. Kogej; C. A. Schalley, *Analytical Methods in Supramolecular Chemistry*, Wiley-VCH ed., C. A. Schalley, Weinheim, **2007**.
[234] Y. Tanaka, Y. Kobuke, M. Sokabe, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 693-694.
[235] S. Matile, A. V. Jentzsch, J. Montenegro, A. Fin, *Chem. Soc. Rev.* **2011**, *40*, 2453-2474.

best with weaker interactions than the ones that are required for detection in binding studies. Earlier important work has confirmed that transport efficiency is not proportional with the stronger binders.[236] Based on this idea, very recently Matile and co-workers[237] have studied a series of calix[4]arenes derivatives (**I**-**VI**) to dissect the individual contributions of halogen bonds, hydrogen bonds and anion–π interactions to anion transport (see Figure 1.44). They used these receptors as new ditopic ion transport systems to demonstrate the general functional relevance of anion–π interactions and to achieve, for the first time, anion transport based on halogen bonds. Calix[4]arenes cones receptors were selected because they offer a series of advantageous properties suitable for the construction of ditopic transporters. The modular anion-binding site can vary in nature and number of possible anion–π (**I**), halogen bond (**II**, **IV**, **V**) or hydrogen bonding (**III**, **VI**) interactions with anions systematically and without global structural changes. After the evaluation of their activity as membrane transporters by means of ^{19}F NMR and Hill analysis, the activity for the best anion transporter (receptor **I**, $K_{a,exp}$ = 55 M^{-1} for complex Cl^-@**I**) was about as modest as expected from literature.[234,235] This work represents a nice example of the functional relevance of anion–π interactions, independent of the motif in which they are involved and the thermodynamically weak complexes that they produce.

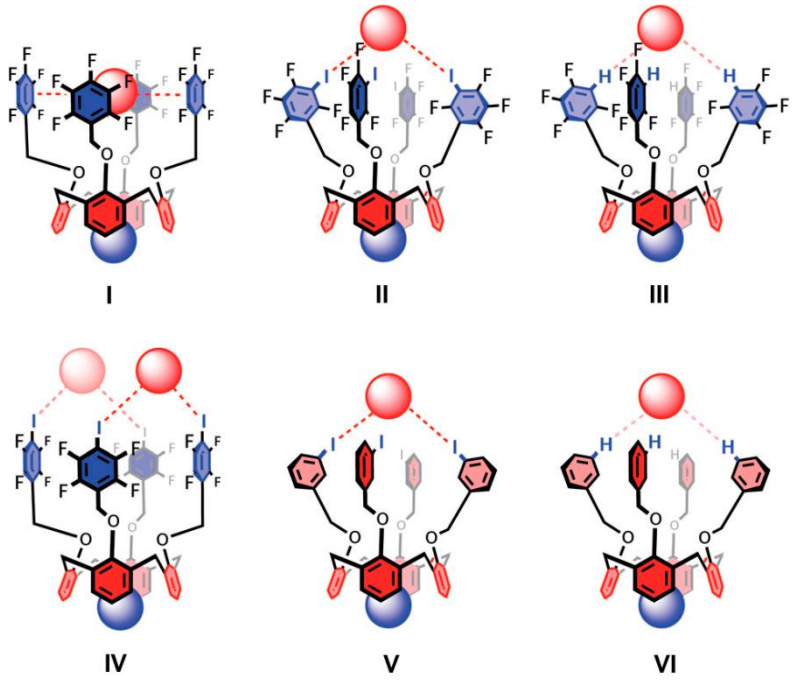


Figure 1.44. Ditopic ion transport systems made to study anion–π interactions and halogen bonds. Red colours indicate electron-rich, blue color electron-poor regions. Red balls indicate anions, blue balls TMA cations and dotted red lines possible anion–π (**I**), halogen bonds (**II**, **IV**, **V**) or hydrogen-bonding (**III**, **VI**) interactions between anions and transporters.[237]

[236] J. P. Behr, M. Kirch, J. M. Lehn, *J. Am. Chem. Soc.* **1985**, *107*, 241-246.
[237] A. V. Jentzsch, D. Emery, J. Mareda, P. Metrangolo, G. Resnati, S. Matile, *Angew. Chem., Int. Ed.* **2011**, *50*, 11675-11678.

Chen and co-workers[238] have reported the stable 1:2 host-guest complex in both solution and solid sate. The complex is performed between a triptycene-derived macrotricyclic host containing two dibenzo-[30]-crown-10 moieties and the guest, which includes paraquat derivatives and hexafluorophosphate anion (PF_6^-). The anion–π interactions between the anion and the bipyridinium rings of paraquat play an important role. Stable ternary host-guest complexes in which a host includes two different guest organic molecules are usually formed by the effective charge transfer, electrostatic or hydrogen bonding interactions between the two guests. However the inclusion of two identical organic guests in the cavity of a host is relatively difficult due to the lack of effective interaction between the guests. In this work the authors describe the possibility of including two identical guests into the host thanks to the anion–π interaction between the bipyridinium rings of the π-electron deficient systems (guest) and hexafluorophosfate anions (see Figure 1.45). This is an important example of experimental anion–π interactions based on charged electron deficient aromatic rings and polyatomic anion different to the experimented halide anions. They demonstrated the formation of 1:2 complexes in solution by ^{1}H NMR, in gas phase by ESI-MS and in solid state by means of X-Ray structure determination, where the anion–π interactions between PF_6^- and the bipyridinium rings played an important role in the formation of the stable complexes, among other noncovalent interactions.

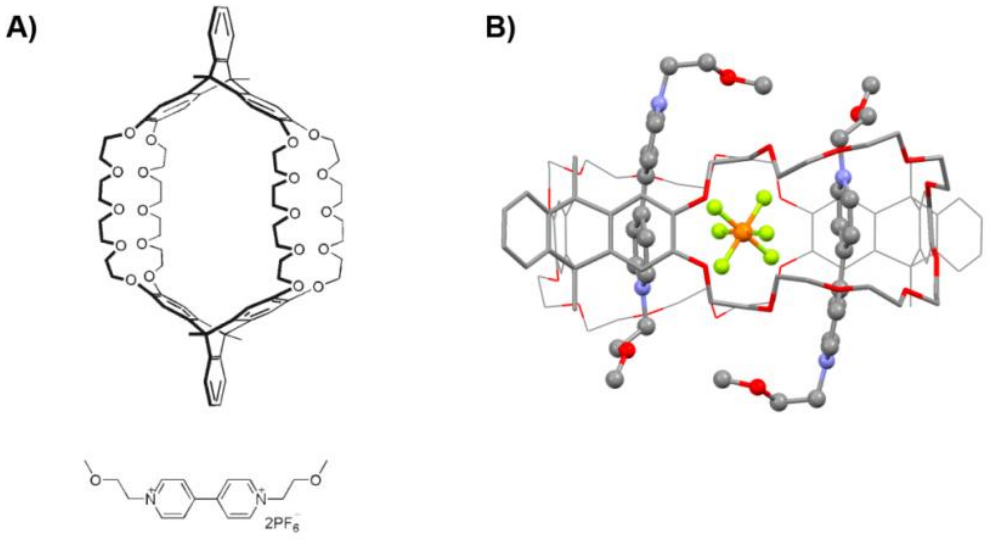


Figure 1.45. A) Structure of triptycene-derived macrotricyclic host and one of the paraquat derivatives guests. B) View of the crystal structure of host-guest complex of molecules represented in A. Solvent molecules, PF_6^- ions, and hydrogen atoms not involved in the noncovalent interactions are omitted for clarity.[238]

[238] J. B. Guo, Y. Han, J. Cao, C. F. Chen, *Org. Lett.* **2011**, *13*, 5688-5691.

Other interesting work was described by Albrecht and co-workers[239] where they report an analysis of anion–π interaction in solid state as a consequence of the last controversial discussions about this interaction. The early reports suggest that anion–π interactions are commonplace in the crystal but were overlooked for long time. However, structure based data mining with more restricted parameters indicate that η^6-type interactions with anions, specifically with halides and neutral aromatics are extremely rare. The authors have carried out a computational and experimental study where they analyse the position of the halide in C_6F_5 moieties in order to investigate if η^6-type anion–π interactions are based on attractive anion–π interactions or if it is only due to crystal packing. After the analysis in a several ammonium salts they conclude that the anion–π interaction exists in the crystal and is strongly dependent on the electron density at the aromatic moiety. This result is independently observed both by computational methods and detailed solid state structural studies.

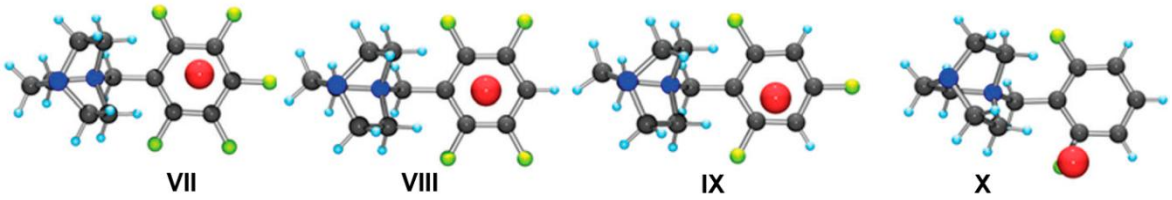


Figure 1.46. Top view of part of the crystal structures of ammonium bromides **VII**-**X** showing the ion pair with the bromide located above the plane of the π system.(C: black, H: light blue, N: blue, F:yellow).[239]

Wang and collaborators[240] have reported novel macrocyclic anion receptors based on the principle of anion–π interactions. The functionalized oxocalix[2]arene[2]triazines bearing two other electron-deficient heteroaromatic rings on the lower rim were efficiently synthesized (see Figure 1.47). The resulting macrocycle receptors adopt 1,3-alternate conformation, yielding an expanded electron-deficient cavity on the lower rim position of benzene rings consisting in two triazine and two appending aromatic rings. UV-Vis Spectroscopic titration study showed the selective interaction of the pentafluorophenyl-substituted oxocalix with azide and fluoride anions in solution with binding constants ranging from 1 to $3.5x10^3$ M^{-1}. In this way, they conclude that the perfluorophenyl-appending to oxacalix[2]arene[2]triazine host molecules formed 1:1 noncovalent anion–π complexes with azide and fluoride anions in diluted acetonitrile solution giving high association constants.

[239] M. Giese, M. Albrecht, C. Bannwarth, G. Raabe, A. Valkonen, K. Rissanen, *Chem. Commun.* **2011**, *47*, 8542-8544.
[240] S. Li, S. X. Fa, Q. Q. Wang, D. X. Wang, M. X. Wang, *J. Org. Chem.* **2012**, *77*, 1860-1867.

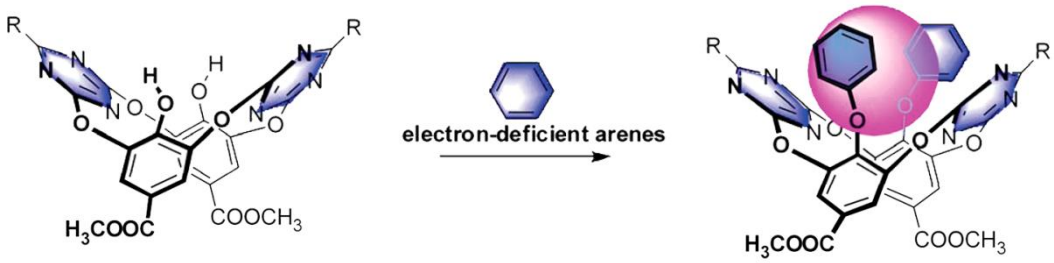


Figure 1.47. Construction of macrocycle hosts of an expanded π-electron deficient cavity.[240]

Yong and co-workers[241] report a new electron-deficient π system, namely carboxycarbonyl substituted imidazo[1,2-*a*]pyridinium which exhibits various noncovalent interactions with chloride and perchlorate anions. Crystallographic results demonstrate that the interaction types of chloride anion and π receptors systems can be tuned from anion–π interaction to η^1-type anion–π interactions. The new receptors exhibit different phosphorescent colors in the solid state influenced by anion–π interactions, which is still very unusual, and may be due to charge transfer to electron-deficient pyridinium. These new properties, where the solid phosphorescent color changes, are induced by relevant anion–π interactions.

The work of Dutasta and Martinez[242] reports the synthesis of hemicryptophane (host) and its binding properties toward selected zwitterionic neurotransmitters in a competitive aqueous medium. Biologically relevant zwitterions like GABA or taurine play an important role in the transfer of neuronal information, which is the subject of numerous studies involving chemical, biochemical and clinical approaches. These guests are strongly solvated species in aqueous media. Their biomimetic encapsulation through endohedral weak interactions in a hydrophobic neutral molecular pocket is still a challenge. The authors claim that they obtained a cavity able to bind the positive and negative charge of these zwitterionic neurotransmitters combining cation–π and anion–π interactions. ^{1}H NMR experiments and quantum calculations are presented to emphasize the competing cation–π and anion–π interactions involved simultaneously in the recognition process. They demonstrated that hemocryptophane was able to encapsulate biologically relevant zwitterionic guests as taurine in a competitive aqueous medium only through endohedral weak interactions. High affinities have been obtained and ^{1}H NMR experiments and DFT calculations emphasize the different interactions involved in these recognition processes. The combination of experimental and theoretical methods emphasizes the fact that cation–π and anion–π interactions can be associated to concomitantly stabilize a host-guest complex.

[241] G.-Y. Yong Y.-M. Zhang, W.-L. She, *CrystEngComm* **2012**, *14*, 3923-3929.
[242] O. Perraud, V. Robert, H. Gornitzka, A. Martinez, J. P. Dutasta, *Angew. Chem., Int. Ed.* **2012**, *51*, 504-508.

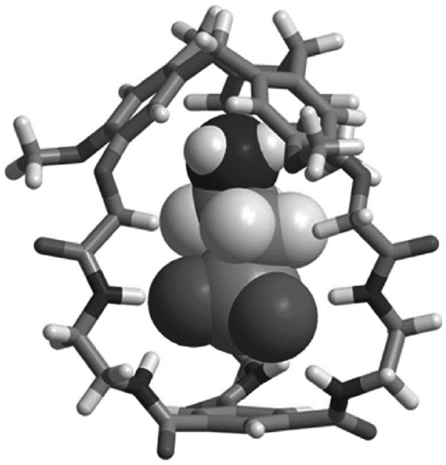


Figure 1.48. DFT optimized structure of taurine@hemicryptophane.[242]

Matile and co-workers[243] have also described the design, synthesis and the study of planar naphthalendiimides (NDIs) with one shielded and one free chiral π-surface to direct self-assembly into dimers. The objective is the achievement of self-sorting into π-stacks or bundles in solution. The self-sorting at interfaces is one of the big challenges to prepare functional organic materials of the future. The stereoisomers are isolated by chiral, preparative HPLC and characterized by X-Ray crystallography. The NMR studies show that racemates with almost planar, nearly identical π-surfaces prefer uniform self-sorting into homodimers at large differences in π-acidity, and alternate self-sorting into heterodimers at small differences in π-acidity. In contrast, enantiomers self-sort into heterodimers and diastereomers show moderate preference for homodimers. Whereas the lessons learned from dimerization are directly applicable to self-sorting of π-stacks on surfaces, anion transport in lipid bilayers is shown to require a more subtle, somewhat inverse interpretation, with diastereomeric transporters differing dramatically in activity but the least visible supramolecule being confirmed as the best performer.

[243] N. T. Lin, A. V. Jentzsch, L. Guenee, J. M. Neudorfl, S. Aziz, A. Berkessel, E. Orentas, N. Sakai, S. Matile, *Chem. Sci.* **2012**, *3*, 1121-1127.

Finally, I would like to emphasize that the purpose of this section entitled "Tuning the anion–π interaction" was to showcase the bonding relationship between anions and π systems by describing work at the experimental and theoretical forefront of this interaction and demonstrating its potential to impact the field of Supramolecular Chemistry. In this section we have given some overview of the importance and functional relevance of this interaction, which otherwise and despite the excellent results is difficult to detect. Then, with this background, in this thesis we would like to contribute in several aspects of this fascinating field.

Chapter 2. Motivation and Objectives

CHAPTER 2. MOTIVATION AND OBJECTIVES

The motivation of this thesis has evolved during these four years due to the progression of the research and the high activity within the Supramolecular Chemistry field.

This project is based on the study of the anion–π interaction and the interplay between noncovalent interactions. After the discovery of the anion–π interaction, a thorough examination of the physical nature of the interaction was performed. Thereafter, the scientific community echoed about the newer noncovalent interaction, appearing first evidences of the interaction in solution and solid state. Until now, experimental examples in solution where a receptor is able to interact with an anion only by means of single or multiple anion–π interactions are scarce in the literature and therefore, it is a challenge.

Supramolecular Chemistry is based on the interplay between noncovalent interactions, i.e., the systems are not really isolated, but the molecules form part of a network with other interactions. Therefore, taking into account these statements and due to the growth of anion–π interaction, the next step in the evolution of this interaction and one of our motivations was carried out; i.e., studying the weak interactions and the interplay between them. Understanding these interactions and their interrelation is of crucial importance in the development of Chemistry, Biology, Biochemistry or Engineering Sciences. The questions that we ask during this stage were:

- Which is the reason that such complex systems work so efficiently?
- Is it possible that a complex system can be held solely by noncovalent interactions?
- Which is the contribution of the interactions involved?
- Are they equal when isolated or interacting with other systems? Are their properties modified?

Once understood what happens when more than one interaction is involved and if cooperativity effects exist between them, we could advance and answer more complicated issues. The examples of utmost and puzzling supramolecular systems are the enzymes. Herein the questions are endless, but some of them raised in this thesis are:

- When an enzyme does its function, are there changes in noncovalent interactions of the active centre enabling or inhibiting the action of the system?
- Are these changes due to cooperative effects between different noncovalent interactions that come into play?

- What forces are involved? Is there a predominant interaction?
- If we substitute one molecule for another changing the interactions, will the reaction continue to proceed?
- And otherwise, is the anion–π present in biological systems? Is the anion–π interaction involved in the function of the enzyme?

Finally, it is not possible to finish this thesis without thinking in the following stage, which is related to future directions of the anion–π interactions research.

All these questions have motivated us to develop this thesis and are orchestrated under three main objectives as consequence of our main motivations. All of them conducted under the same baton of the computational chemistry.

The first objective is to study theoretically competitive interactions in order to design the most convenient building block to particularly favour the anion–π interaction, and ultimately, transfer our knowledge into the experimental field trying to quantify the anion–π interaction.

The second objective is the theoretical study of different noncovalent interactions and the interplay between them to analyse:

- Cooperativity effects emerged from different combinations,
- What interactions are reinforced or weakened.

The third objective is to extent the concept of anion–π interaction to new fields:

- The searching of anion–π interactions in biological systems, analysing cooperativity effects with other noncovalent interactions in order to demonstrate the most likely function of this interaction in the enzyme.
- The study of alternative anion–π interactions. Specifically, the influence of open-shell systems and transition-metal ions in the strengthening of the interaction.

To achieve these three objectives, it is necessary to address the following issues:

1.- Analysis of Molecular Interaction Potential (MIP) of molecules candidates to form the different noncovalent interactions, ion–π and σ bonds.

2.- Optimization and characterization of complexes between the ions and aromatic systems with different substituents at different levels of theory.

3.- Analysis of electron density from the optimized geometry of complexes and assessment of the interactions between different components.

4.- Examination of different contributions to the interaction energy (electrostatic, induction, dispersion, charge transfer) by means of different methods.

5.- Analysis of the aromaticity and its variation depending on the molecules and the network of interactions studied.

6.- Analysis of orbitalic and spin densities to examine open-shell complexes and systems containing heavy metals.

7.- Exploration of more favourable energetic and geometric ternary, quaternary,… complexes combining different noncovalent interactions.

8.- Study of synergy of complexes important in chemical and biological systems and the search of experimental evidences in biological (Protein Data Bank, PDB) and crystallographical (Cambridge Structure Database, CSD) databases.

9.- Investigation, obtaining and studying new energetic terms (cooperativity, synergetic and non-additivity energies) that are useful to analyse cooperativity effects.

10.- Synthesis and characterization of a potential receptor to assess the anion–π interaction in solution.

Chapter 3. Anion–π Interaction: From the Theoretical Design to the Experimental Assessment

CHAPTER 3. ANION–π INTERACTION: FROM THE THEORETICAL DESIGN TO THE EXPERIMENTAL ASSESSMENT

Chapter 3 is an example of multidisciplinary research because it involves two areas of chemistry: computational and experimental. The aim of this work consists of the selection, by means of computational chemistry, of molecular building blocks capable of establishing favourable anion–π interaction, followed by the experimental assessment of its anion-binding properties in solution using tetraalkylammonium halides as anion precursors. The synthesis of macrocyclic receptors based on the selected binding units was also undertaken. The binding properties of the prepared receptors with several halides are described.

3.1. BACKGROUND

After the initial documentation of the existence of attractive anion–π interactions, a thorough analysis of the physical nature of this interaction was performed using computational methods for structure determination. The results obtained in these theoretical studies provoked interest in experimental research groups and induced them to design and synthesize several receptors (charged and uncharged systems) capable of interacting with anions by means of anion–π interactions. From the first experimental report quantifying an attractive anion–π interaction in 2004[244,245] to the data available from the more recent studies, it can be concluded that the energy gain that can be associated with anion–π interactions in solution is relatively small compared to the computational estimates. For this reason, the search of new building blocks that can offer stronger anion–π interactions and that can be easily incorporated in the design of neutral receptors for anion binding is a daunting task.

Several steps are required in the design of more effective anion binding receptors based on anion–π interactions. First, one needs to computationally explore a set of molecules satisfying the requirements of establishing strong anion–π interaction, as well as design synthetic methods to easily implement them in the synthesis of the receptors.

Based on previous knowledge, appropriate candidates for aromatic binding sites for anions should exhibit the following properties:

[244] H. Maeda, H. Furuta, *J. Porphyrins Phthalocyanines* **2004**, *8*, 67-75.
[245] H. Maeda, A. Osuka, H. Furuta, *J. Inclusion Phenom. Macrocyclic Chem.* **2004**, *49*, 33-36.

- Electron-deficient π systems,
- Aromatic rings with strong electrostatic ($Q_{zz}>0$) and high polarizability ($\alpha_{||}$) components.

Once several aromatic units are selected based on the principles discussed above, a detailed computational study needs to be performed. At this stage, the selected aromatic binding blocks are interrogated, using computational methods, for the strength of their interactions with anions. Designed receptors derived from the more promising aromatic blocks are also investigated. After an in depth analysis of the energetic and geometrical properties obtained in the theoretical evaluations of the anion–π interactions discussed above, a decision must be taken with respect to the systems that are going to be investigated experimentally in solution. This decision ususally implies the consideration not only of effective anion–π interactions but also the existence of a reasonable synthetic route to access the desired molecular receptor.

Second, the development of the experimental part of the study involves the following steps:

- Synthesis, purification and characterization of the designed receptor.
- Experimental assessment of the value of the interaction.

The selection of appropriate experiments and spectroscopic techniques to perform this latter task will highly dependent on the chemical properties of the system under study (strength of the interaction, solubility properties in different polar and non polar solvents, etc).

The strategy mentioned above is applied in the results presented in this Chapter and outcomes, in a multidisciplinary investigation of the anion–π interaction. In short, the main objective of the work undertaken in this chapter is the discovery of building blocks from which effective receptor for anions can be easily prepared. In our aim for the ideal anion–π experimental receptor we considered that only anion–π interactions must be involved in the complexation of the anion. Therefore, other electrostatic forces like hydrogen bonding or charge-charge interactions are premeditatedly not considered in our experimental assessment.

3.2. RESULTS AND DISCUSSION

This section is divided in three parts. The first one is based on the theoretical study to evaluate several potential building blocks suitable to be incorporated in the design of anion receptors. The second part includes the theoretical assessment of anion–π interactions using the designed receptors. The aromatic units that are studied can also be easily installed in the scaffold of a molecular receptor using simple synthetic protocols. Moreover, this section describes the experimental attempts performed to evidence anion–π interaction in solution using the designed and synthesized receptors. The last part refers to experimental evidences of anion–π interaction in solution and solid state.

3.2.1. ANION–π INTERACTION: DUAL σ/π ANION BINDING AFFINITY

The relevance of the interactions involving aromatic rings as important binding forces, both in chemical and biological systems, has been emphasized throughout this thesis. The anion–π interaction is one of the forces implying aromatic rings. The fact that anion–π interactions are observed experimentally gives strong support to the effectiveness of theoretical predictions. In the same vein, it also provides a promising potential for the development of anion receptors based exclusively on this type of interaction. To achieve this goal, it is first necessary to study different kinds of aromatic rings capable of being involved in strong anion–π interactions.

Until 2008 the number of studies involving aromatic rings, substituted with carboxyl electron-withdrawing groups (EWG), which are capable of establishing anion–π interactions was scarce. These substituted π systems were thought as possible building blocks for the design and synthesis of receptors for anions. One of the reasons for the selection of these aromatics units refers to the structural criteria based on electron-deficient arenes. The presence of electron-withdrawing groups increases the acidity of the arene allowing the interaction with the anion. Other possible aromatic systems suitable to form favourable anion–π interactions include positively charged-rings. In fact, cationic aromatic rings can be considered as one extreme in the scale of increasing acidity of the arenes. Despite we have theoretically studied direct charge-charge interactions involving the complexation of anions with aromatic rings they were not considered in the experimental evaluation, as above mentioned.

However, previous to the analysis of the ability of these molecules to act as binding sites for anions and building blocks of the corresponding receptors, another complementary theoretical study is needed: the evaluation of their dual σ/π–anion binding properties. This study was

performed because electron-withdrawing groups (EWG) have a double effect in arene C–H donors. On the one hand, the decoration of an aromatic system with EWG favours the establishment of anion–π interaction. On the other hand, however, the presence of EWG increases the strength of hydrogen bonding interaction between the anion and the arene C-Hs. For this reason, it is important to study if these types of aromatic systems are suitable for the formation of strong anion–π interaction. The presence of hydrogen atoms in the aromatic ring could induce the formation of alternative hydrogen bonding interactions with the anion.

As a consequence of this study two papers were published.

3.2.1.1. C. Estarellas, D. Quiñonero, A. Frontera, P. Ballester, J. Morey, A. Costa, P.M. Deyà. MP2 Study of the Dual σ/π Anion-Binding Affinity of Fluorinated Phthallic Acid Anhydrides. *J. Phys. Chem. A*, **2008**, *112*, 1622–1626.

3.2.1.2. C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Theoretical and Crystallographic Study of the Dual σ/π Anion Binding Affinity of Quinolizinylium Cation. *J. Chem. Theory Comput.*, **2008**, *4*, 1981–1989.

The first report (article 3.2.1.1) is based on uncharged phthallic anhydride and several fluorinated derivatives. In this study it is observed that as the number of fluorine atoms increases in the aromatic ring both anion–π and hydrogen bonding interactions increase their strength. From the results obtained we concluded that the most substituted derivative is the most favourable building block for anion–π interaction because in the partially substituted ring the σ interaction, CH-anion hydrogen bond, is stronger.

The second article (3.2.1.2) describes the theoretical analysis of quinolizinylium cation, a positively charged aromatic ring. In this case the study includes the assessment of different monoatomic and polyatomic anions, as well as the evaluation of the strength between σ and π interactions. The outcomes show that polyatomic anions establish preferably π interactions while monoatomic anions arrange more favourable interactions with the system by means of hydrogen bonds. Moreover, the ability of quinolizinylium cation to establish anion–π interactions is corroborated from crystal structures found in Cambridge Structural Database (CSD).

3.2.2. ANION–π INTERACTION: FROM THE THEORETICAL SELECTION OF BUILDING BLOCKS TO THE EXPERIMENTAL ASSESSMENT OF BINDING AFFINITIES

In this section, I explain the complete procedure followed to reach the goals of the chapter. During the theoretical evaluation of aromatic building blocks (Section 3.2.1), we learnt their dual σ/π ability. We selected the building blocks represented in Figure 3.1 to be included in the theoretical study and the subsequent experimental quantification of anion–π interaction. These building blocks comply with the requirements of being electron-deficient arenes with high quadrupole moments and molecular polarizabilities.

3.2.2.1. Design of the Receptor

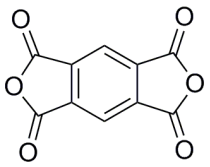
The challenge in the design of a receptor for anions based exclusively on anion–π interactions relied on finding a building block that can establish these types of interactions in a very effective manner. Therefore, the binding units and the receptor itself have to be "neutral" systems, for instance:

- Molecules containing uncharged aromatic rings,
- Molecules lacking of transition metal centres or other additional binding sites for the anions that could act as handles for an "enforced proximity" strategy for anion binding.

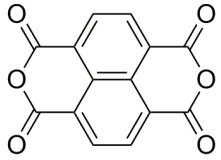
Generally, the "enforced proximity" methodology is used to force the anion–π interaction due to the presence of additional forces.[246] However, our basic idea is trying to obtain a building block able to establish effective anion–π interactions without the help of additional reversible interactions.

Furthermore and based on the considerations mentioned above, it is important to take into account that selected binding units will be used in the synthesis of a molecular receptor capable of establish multiple anion–π interactions in the host-guest complex. Considering these features, the design of receptors is based on pyromellitic (PMDA) and 1,4,5,8-naphthalenetetracarboxylic (NTCDA) dianhydride building blocks (see Figure 3.1).

[246] J. Rebek, B. Askew, P. Ballester, C. Buhr, S. Jones, D. Nemeth, K. Williams, *J. Am. Chem. Soc.* **1987**, *109*, 5033-5035.



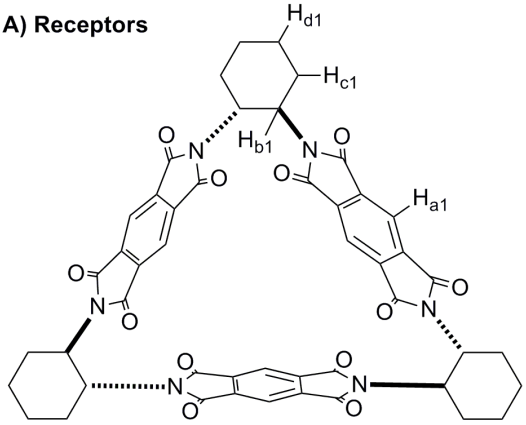
Pyromellitic dianhydride
Benzene-1,2,4,5-tetracarboxylic dianhydride
(PMDA)

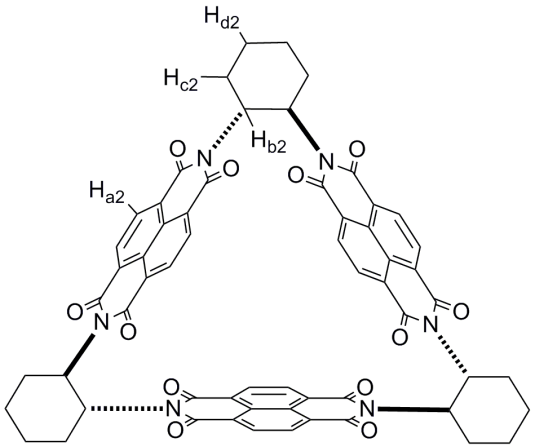


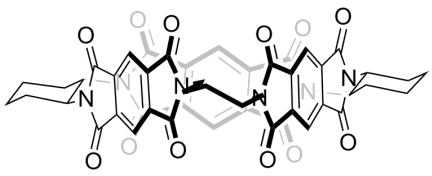
1,4,5,8-Naphthalenetetracarboxylic dianhydride
(NTCDA)

Figure 3.1. Representation of neutral building blocks to be used in the synthesis of new anion–π receptor. Left: Pyromellitic dyanhidride. Right: 1,4,5,8-naphthalenetetracarboxylic dianhydride.

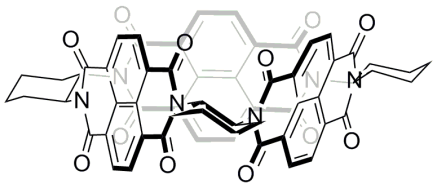
A) Receptors





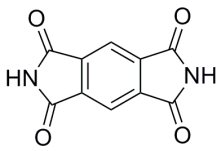


Cyclic trimeric pyromellitic diimide, **1**

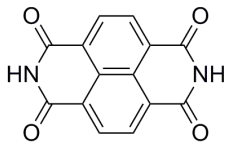


Cyclic trimeric naphthalene diimide, **2**

B) Building blocks motifs



Benzene-1,2,4,5-tetracarboxylic diimide
Pyromellitic diimide



1,4,5,8-Naphthalenetetracarboxylic diimide

Figure 3.2. A) Structures of the receptors studied in this work, cyclic trimeric pyromellitic diimide (**1**) and cyclic trimeric naphthalene diimide (**2**). B) Building blocks motifs present in the receptors.

Inspired by previous work of Gawronski and co-workers,[247] which describes the reaction of PMDA with diamines to yield a triimide macrocycle represented in Figure 3.2.A left (receptor **1**), we designed the synthesis of the analogous macrocycle 3.2.A right using NTCDA instead (receptor **2**). Both macrocyclic trimers are neutral and can be considered as potential receptors for establishing effective anion–π interactions. The reduced conformational flexibility of both receptors produces an intrinsic aromatic cavity in their structures (see Figure 3.2). The walls of this cavity are formed by three aromatic-rigid bis-imides covalently connected by diaminocyclohexane spacer molecules. The aromatic walls are oriented in such a way that the electron density of their π cloud is pointing both outwardly and inwardly to the cavity. However, the macrocyclic structure of the trimeric receptors provides a convergent disposion of the electron densities directed towards the interior of the cavity.

In principle, the molecular scaffolds of both receptors fulfil the requirements mentioned above for an anion receptor based exclusively on anion–π interactions:

- They provide a confined space within the macrocycle's interior to include the anion, in which the three π clouds of the aromatic binding units converge.
- The three binding units feature the characteristics required for aromatic rings capable of establishing strong anion–π interaction.

Consequently, the structures of the cyclic trimers **1** and **2**, which are depicted in Figure 3.2, were selected as synthetic targets. These compounds are appealing potential anion receptors suitable for the experimental assessment of anion–π interactions in solution. The binding of the anions by these receptors must take place exclusively through anion–π interactions and does not involve the intermediacy of other additional intermolecular forces.

3.2.2.2. Theoretical Binding Studies

A theoretical study was performed to analyze the anion binding affinities. This study can be divided in two parts:

- The examination of binding affinities of pyromellitic and naphthalene tetracarboxylic diimides towards anions.
- The geometrical and energetic features exhibited by the complexes of the macrocyclic receptors with monoatomic and polyatomic anions.

[247] J. Gawronski, M. Brzostowska, K. Gawronska, J. Koput, U. Rychlewska, P. Skowronek, B. Norden, *Chem.--Eur. J.* **2002**, *8*, 2484-2494.

The analysis performed for the simple monomeric diimides (binding units) implies the evaluation of their anion-binding affinity properties. It is known that the anion–π interaction is dominated by electrostatics and anion-induced polarization terms.[128,162] The strength of the electrostatic term depends on the value of the quadrupole moment (Q_{zz}) and the polarization component correlates well with the molecular polarizability values of the aromatic units ($\alpha_{||}$). We carried out this study by computing two-dimensional MIPp (Molecular Interaction Potential with polarization) maps, as well as the values of the quadrupole moment and molecular polarizability of the two aromatic units (see Figure 3.3). In these aromatic units the value of the quadrupole moment is high; which is a clear indication that they are good candidates to establish favourable anion–π interaction.

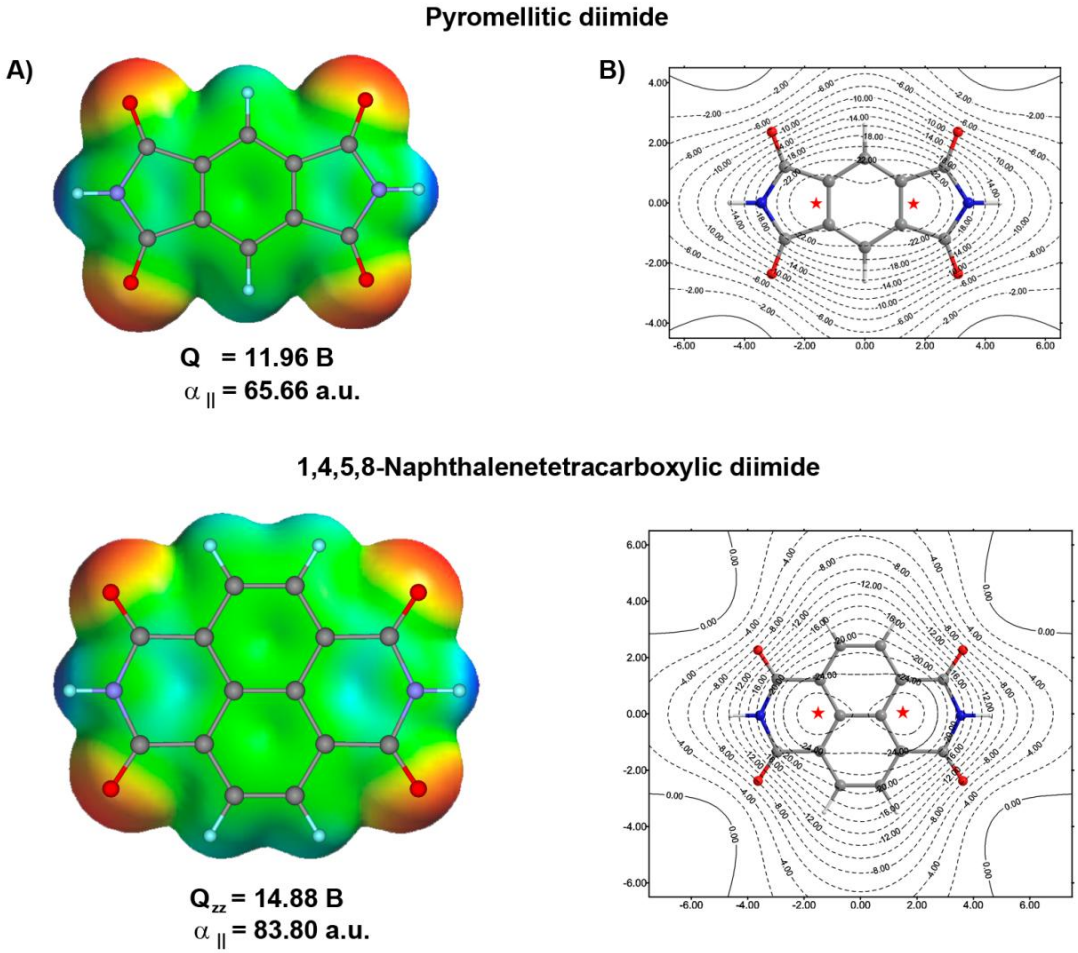


Figure 3.3. A) Up: MEP of the optimized geometry of pyromellitic diimide. Bottom: MEP of the optimized geometry of 1,4,5,8-naphthalenetetracarboxylic diimide. The colour code for potential surfaces of building blocks is ranging from –42 (red colour, rich places in electronic density) to +42 (blue, electron-deficient regions) kcal·mol^{-1}. Quadupole moments (Q_{zz}, B) are calculated at RI-BP86/6-31++G** level of theory. Molecular polarizabilities ($\alpha_{||}$, a.u.) are calculated at MP2/6-31++G** level of theory. B) 2D-MIPp(Cl^-) energy maps computed for pyromellitic diimide (top) and naphthalenetetracarboxylic dimide (bottom) at 3 Å above the molecular plane. Isocontour lines are plotted every 2 kcal mol^{-1}. Dashed lines correspond to negative values and solid lines to positive values of the potential energy. The minimum is represented by a red star. Axes units are Å and energies in kcal mol^{-1}.

Moreover, Figure 3.3 depicts the two-dimensional MIPp (2D-MIPp) maps obtained for pyromellitic and naphthalenetetracarboxilic diimide. In order to study the anion-binding ability of these aromatic units via anion–π interactions, we computed the MIPp at 3.0 Å over the molecular plane and parallel to it. In both cases, the maps presented two minima (indicated by a red star) located approximately over the centre of C–C common bonds in the pyromellitic derivative (~ –24 kcal mol^{-1}) and over the C atom shared by three rings in the naphthalene diimide derivative (~ –26 kcal mol^{-1}).

After having obtained positive results for favourable anion–π interaction between the binding units and anions, the following step consisted in the quantitative evaluation of the binding affinities of the receptors towards anions. Table 3.1 reports the interaction energies at RI-BP86/TZVP level of theory corresponding to the interaction for the optimized structures of the complexes between the receptor **1** and monoatomic (Cl^-, Br^-, I^-) or polyatomic (BF_4^-, PF_6^-, NO_3^-) anions (see Figure 3.4). For all complexes, the interaction energies are large and negative, indicating that the interaction between anions and the receptor **1** is favourable. From the inspection of the energetic results, we conclude that the most favourable interaction takes place with chloride as monoatomic anion, while nitrate is the best polyatomic anion in establishing attractive interactions.

The results obtained for receptor **2** are very similar to those obtained for receptor **1** (see Table 3.1). Interestingly, the computed binding energy values are lower for receptor **2** than for receptor **1**, even though the naphthalene diimide unit showed an improved potential for anion binding (MIPp, quadrupole and polarizability values) compared to the pyromellitic diimide counter part. A likely explanation has to do with the fact that receptor **2** presents a bigger cavity than receptor **1**. Therefore the anion can interact more favorably with the three aromatic walls in receptor **1** than in receptor **2** (see Figure 3.5).

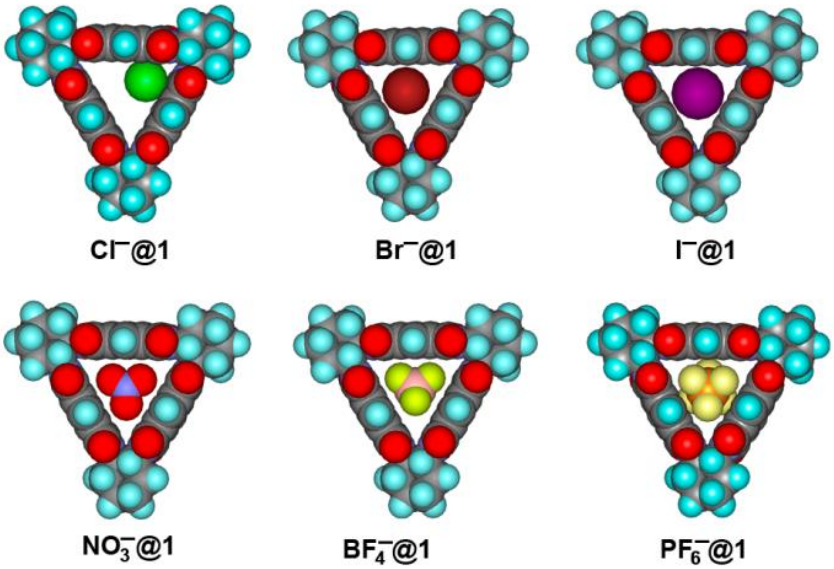


Figure 3.4. Optimized geometry of complexes between several anions and receptor **1** (cyclic trimer derived from pyromellitic diimide) represented in CPK.

From the obtained theoretical results we concluded that these macrocycles constitute potential receptors for the study of anion–π interactions using host-guest chemistry. It is worth noting that based on previous experimental results of anion–π binding in solution we should expect to experimentally measure association binding constant values lower than the ones that can be directly derived from the computed binding energies.

Table 3.1. Interaction energies at the RI-BP86/TZVP level of theory with basis set superposition error BSSE corrections (ΔE, kcal mol^{-1}) for the anion–π complexes between receptor **1** and **2**, respectively, and a series of monoatomic and polyatomic anions.

Complex	ΔE	Complex	ΔE
1 + Cl^-	–33.68	**2** + Cl^-	–31.10
1 + Br^-	–26.15	**2** + Br^-	–26.39
1 + I^-	–21.39	**2** + I^-	–21.84
1 + NO_3^-	–28.48	**2** + NO_3^-	–26.83
1 + BF_4^-	–21.99	**2** + BF_4^-	–21.62
1 + PF_6^-	–14.06	**2** + PF_6^-	–14.76

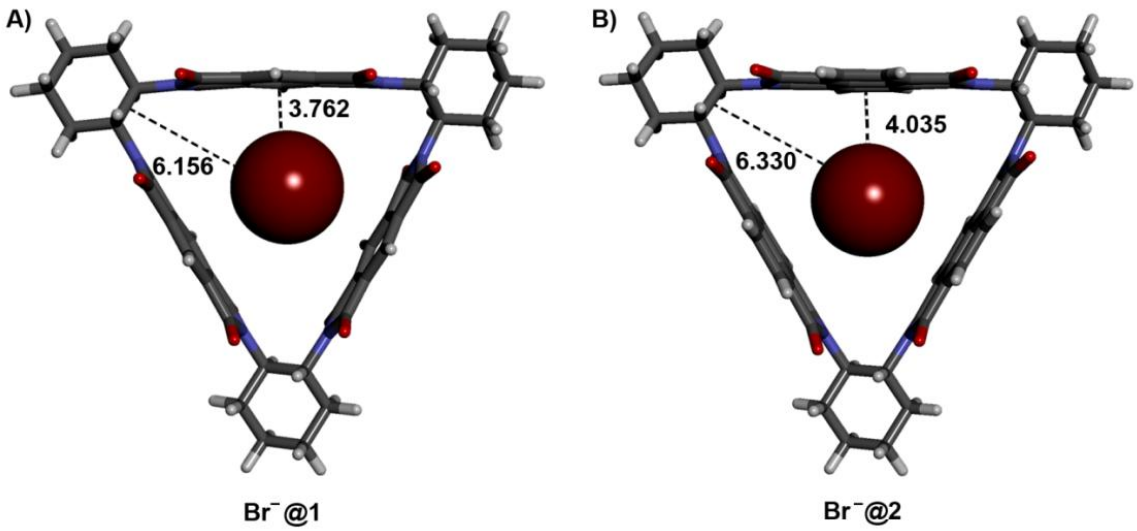


Figure 3.5. Comparison between host-guest complex for A) receptor **1** and B) receptor **2** with bromide anion. The receptors are represented in stick and the bromide anion is represented in CPK.

3.2.2.3. Synthesis of the Receptors

The results described in sections 3.2.2.3 and 3.2.2.4 were obtained in the Institute of Chemical Research of Catalonia (ICIQ) under the supervision of Prof. Pau Ballester.

The receptors **1** and **2** used in the binding studies were obtained using slightly modified reaction conditions to the ones reported for the preparation of **1**.[247] Receptor **2** was synthesized for the first time by us and was completely characterized using high resolution spectroscopic techniques and X-ray diffraction analysis. The general synthesis consists of the reaction of equimolar quantities of (1*R*,2*R*)-1,2-diaminocyclohexane and the corresponding dyanhidride for 4 hours at DMF reflux. After purification using column chromatography the overall yield of both receptors was close to 10%.

The ^{1}H-NMR spectra of receptors **1** and **2** at 400 MHz displayed a single signal for the aromatic protons (H_a). Three different signals (b, c and d) can be observed for the protons of the diaminocyclohexane spacer. The signal for proton H_b is diagnostic for both receptors (see Figure 3.6).

For receptor **2**, the detailed synthetic procedures together with the characterization data of the product such as ^{1}H NMR, ^{13}C NMR spectra, as well as X-Ray crystal structure can be found in Annex II.

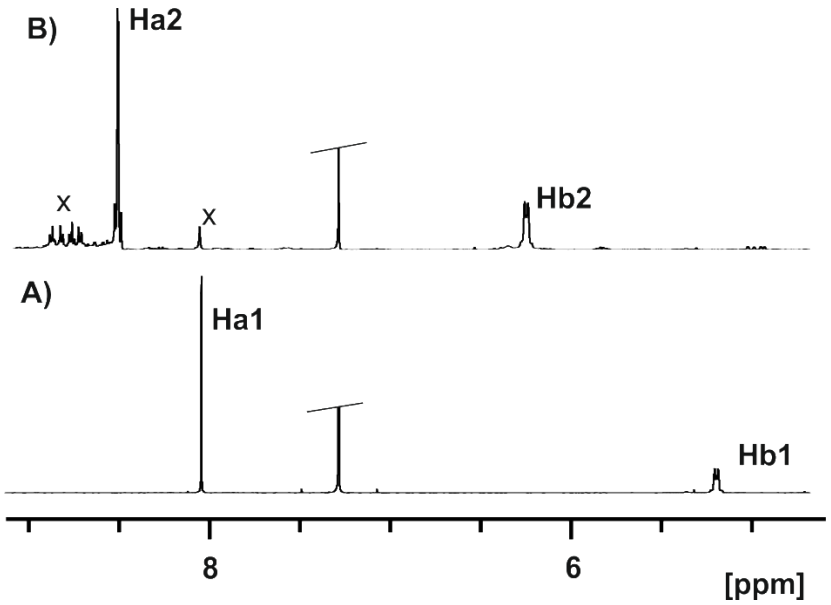


Figure 3.6. Selected regions of the ^{1}H-NMR spectra in $CDCl_3$ at 298 K of: A) receptor **1**; B) receptor **2**. See Figure 3.2 for proton assignment. Impurities marked with x.

3.2.2.4. Anion Binding Studies in Solution

In this section we describe the results obtained in the binding studies performed with receptors **1** and **2** and several halides. Initially, the complexation was probed using proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). Before starting the complexation study we performed a solubility study. We wanted a solvent able to solubilize our receptor at concentrations high enough to be easily detected using ^{1}H NMR spectroscopy (~ 1x 10^{3} M). Our first option was to use acetonitrile. Acetonitrile is a polar solvent and induces ion-pair dissociation. However it does not solvate any of the ions (cation and anion) very well. Unfortunately, our receptor was not soluble in this solvent. It is known that large aromatic systems are difficult to solubilise in acetonitrile due to their tendency to stack forming aggregates and decreasing their solubility.[248] Finally, chloroform was selected as the solvent to carry out the binding studies because it could dissolve our receptors. Chloroform is a polar non-protic solvent, and as such it does not promote a significant dissociation of ionic-pairs. All experiments were carried out using receptor concentration in the range of 0.5 to 1.0 mM. We decided to use the tetrabutylammonium salts of the anions as their precursors for the following reasons:

- These salts are widely used in anion-binding studies,
- They have an acceptable solubility in organic solvents allowing the use of ^{1}H-NMR spectroscopy to study the binding process.

[248] P. Mukerjee, J. R. Cardinal, *J. Pharm. Sci.* **1976**, *65*, 882-886.

The complexation behaviour of receptors towards chloride and fluoride anions was studied by adding incremental amounts of a chloroform-*d* stock solution of its tetrabutylammonium salts (10 mM) to a NMR tube containing the receptor also dissolved in chloroform-*d* (0.6–1 mM). After each addition of the anion salt the NMR spectrum of the mixture was recorded. In order to keep constant the concentration of the receptor all along the titration, the anion salt was dissolved using a chloroform-*d* solution containing the receptor in the same concentration than the NMR tube.

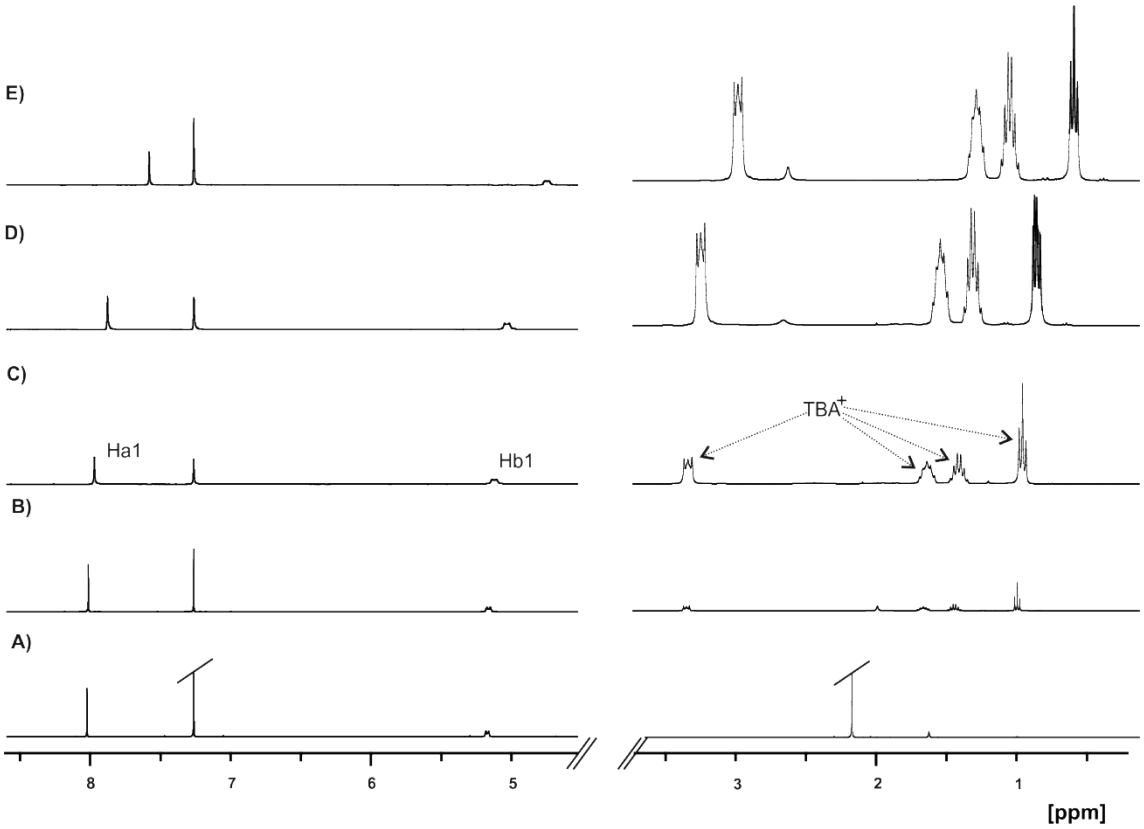


Figure 3.7. Selected expansion of ^{1}H-NMR spectra obtained during the titration of receptor **1** in $CDCl_3$ with TBACl at 298 K. A) **1**. B) **1** + 3 eq. of TBACl. C) **1** + 50 eq. of TBACl. D) **1** + 160 eq. of TBACl. E) **1** + 300 eq. of TBACl. See Figure 3.2 for proton assignment. [**1**] = 0.63 mM.

During the titration experiment of receptor **1** we did not observe any change in the chemicals shifts of its proton signals (see Figure 3.7). Only after the addition of extremely high quantities of guest (100-300 equivalents) the proton signal H_a moved slightly upfield. We observed chemical shift changes in all signals of the protons of the receptors and also in the tetrabutylammonium salt signals when the solution contained high concentration of the salt (see Figure 3.7). A likely explanation is that the observed chemical shift changes are caused by the modification of dielectric constant of the solution due to the increase of the salt concentration. We concluded that the binding affinities of receptor **1** for chloride anion are too low to be measured under these conditions. The use of high concentrations of the salt induced

secondary effects on the chemical shift changes of the signals of the protons of the receptors that probably are not related with anion binding.

Based on recent results described by Saha and co-workers,[249] suggesting the existence of an electron-transfer process induced by the anion–π interaction of naphthalene diimide receptors with tetrabutylammonium fluoride salt (TBAF·3H_2O), and our negative results in detecting anion–π interactions between receptor **1** and TBACl salt, we decided to perform a titration of receptor **2** with TBAF·3H_2O salt.

During the NMR titration experiment of receptor **2** with fluoride anion in chloroform-*d*, we did not observe chemical shift changes of the signals for the protons H_{a2} and H_{b2} (see Figure 3.8). However, if one considers the signals of the ^{13}C spinomers of the non-deuterated residual chloroform proton as a reference, it must be concluded that the signals of the protons of the receptors decreased in intensity during the incremental addition of the fluoride anion. That is, in order to plot the H_{a2} signal of receptors with the same relative intensity in the sequential additions, the signals of the ^{13}C spinomers of chloroform proton becomes significantly increased.

Due to working with the fluoride anion we could, additionally, follow the titration by ^{19}F-NMR spectroscopy. This is shown in Figure 3.9. The A spectrum corresponds to the ^{19}F NMR of a mixture containing the receptor and 1 equiv of tetrabutylammonium fluoride. Surprisingly, after the addition of 1 equivalent of fluoride anion in the host solution, we could no detect a signal for the fluoride anion. In fact, we needed to add up to 3 equivalents of tetrabutylammonium fluoride (Spectrum C, Figure 3.9) to observe a signal corresponding to the fluoride anion of tetrabutylammonium salts in chloroform solution. The addition of more than 3 equivalents of fluoride anion does not produce significant changes on the ^{19}F NMR spectra. Therefore, the expected concentration of the fluoride anion in the solution does not correspond to our observations. The results obtained in ^{19}F NMR and in ^{1}H NMR titrations (shown in Figure 3.8) suggested that a chemical reaction is taking place between the fluoride and the receptor and both species are detected in solution at lower concentration than expected.

[249] S. Guha, S. Saha, *J. Am. Chem. Soc.* **2010**, *132*, 17674-17677.

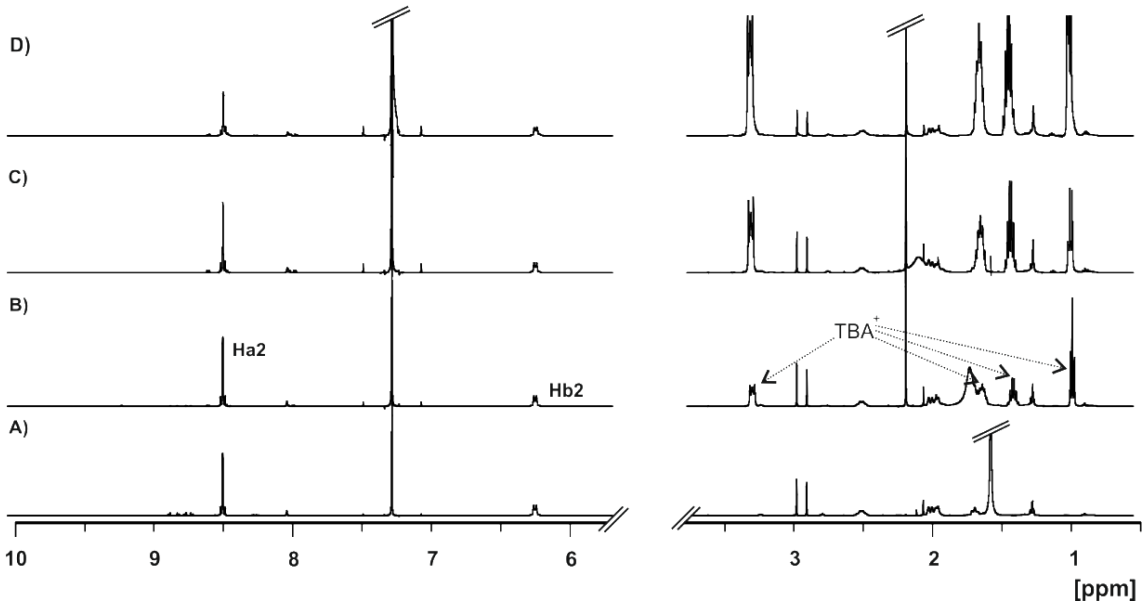


Figure 3.8. Selected expansion of ^{1}H-NMR spectra obtained during the titration of receptor 2 in $CDCl_3$ with TBAF·3H_2O at 298 K. A) **2**. B) **2** + 0.9 eq. of TBAF·3H_2O. C) **2** + 2.9 eq. of TBAF·3H_2O. D) **2** + 5.8 eq. of TBAF·3H_2O. See Figure 3.2 for proton assignment. [**2**] = 1 mM.

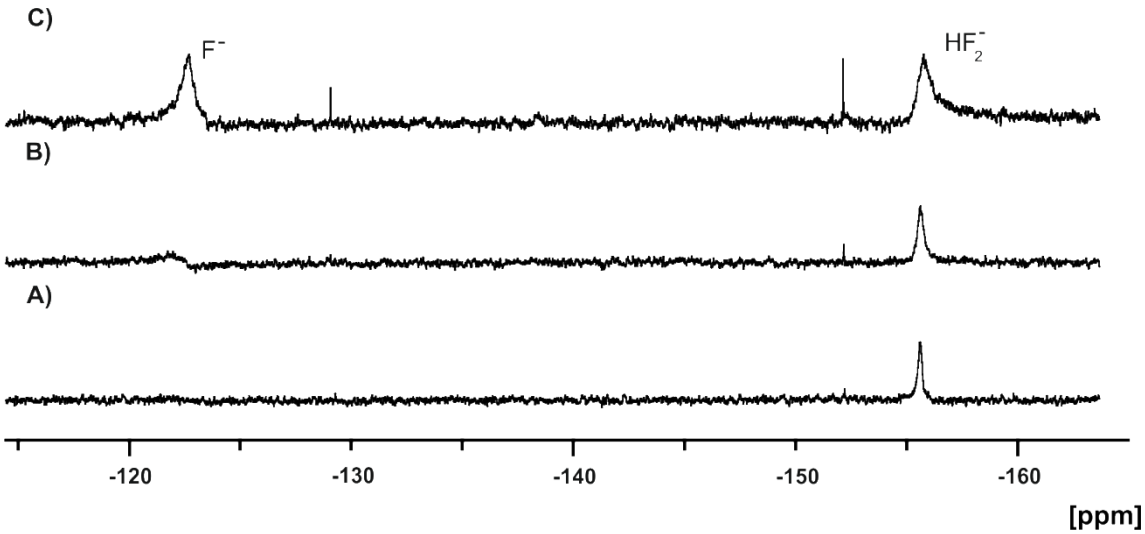


Figure 3.9. Selected expansion of ^{19}F-NMR spectra obtained during the titration of receptor **2** in $CDCl_3$ with TBAF·3H_2O at 298 K. A) **2** + 0.9 eq. of TBAF·3H_2O. B) **2** + 1.7 eq. of TBAF·3H_2O. C) **2** + 2.9 eq. of TBAF·3H_2O. [**2**] = 1 mM.

As a consequence of this result, which we cannot explain and based on the report of Saha *et. al.*[249] we decided to repeat the titration using the same conditions, but changing the solvent from chloroform ($CDCl_3$-*d*) to dimethylsulfoxide (DMSO-d_6).

When using DMSO-d_6 as solvent, the ^{1}H-NMR spectrum of the mixture after the addition of 1.8 equiv of tetrabutylammonium fluoride showed the dissapearence of the signal for the proton H_{a2} in the free receptor resonating at δ = 8.4 ppm, and a significative broadening for the signal at δ = 6 ppm (H_{b2}). In addition, a change of colour in the solution of the mixture is also observed. This change in colour was already observed for the preparation of the stock solution

of the fluoride. As mentioned above, in order to keep constant the concentration of the receptor along the titration, the anion salt was dissolved using a solution containing the receptor at the same concentration that the NMR tube solution. When the TBA salt of fluoride was dissolved in a DMSO solution containing the receptor **2** the solution changed dramatically from colorless to blue. This colour was maintained during few minutes and then the solution turns yellowish. After the first addition of 1 equivalent of fluoride, the solution in the NMR tube acquires an orange colour. At the end of the titration, the solution had a dark green colour. Taking into account these observations and the results described by Saha and co-workers,[250] we speculate that the addition of the fluoride also promotes the formation of radical-anion or diradical dianion species of receptor **2**. These molecular species are paramagnetic providing very fast relaxation times to their nuclear proton spins and avoiding their observation by ^{1}H NMR spectroscopy. Probably, this is the reason why the aromatic protons of receptor **2** are not observed in the ^{1}H NMR spectrum B. The incremental addition of the fluoride salt induces the appearance of new sets of signals that we were not able to assign. It is worth mentioning here that the ^{1}H NMR spectra after 3 equivalents (spectrum C, Figure 3.10) and after 8 equivalents (spectrum D, Figure 3.10) of fluoride salt were added showed practically the same signals but with different relative intensities.

Figure 3.11 shows the ^{19}F NMR spectra acquired during the titration of receptor **2** with tetrabutylammonium fluoride in DMSO. These spectra are very similar to the ones registered in the same titration using chloroform as solvent (see Figure 3.9 for comparison purposes). In this case at hand, the signal of the fluoride anion did not appear until 5 equivalents of the salt were added. Therefore, we surmise that a similar process is occurring in both solvents, chloroform and DMSO. In chloroform, the intensity of the unknown process is in some way reduced.

[250] S. Guha, F. S. Goodson, S. Roy, L. J. Corson, C. A. Gravenmier, S. Saha, *J. Am. Chem. Soc.* **2011**, *133*, 15256-15259.

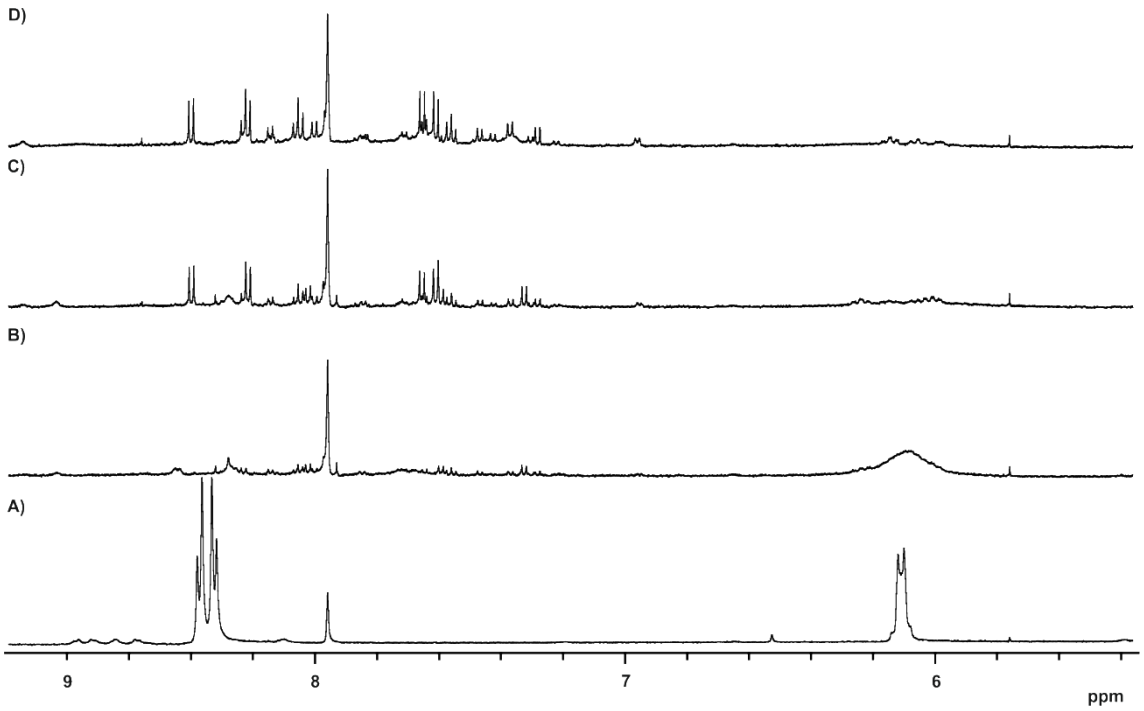


Figure 3.10. Selected expansion of ^{1}H-NMR spectra obtained during the titration of receptor **2** in DMSO with TBAF·3H_2O at 298 K. A) **2**. B) **2** + 1.8 eq. of TBAF·3H_2O. C) **2** + 3.1 eq. of TBAF·3H_2O. D) **2** + 8.2 eq. of TBAF·3H_2O. See Figure 3.2 for proton assignment. [**2**] = 1 mM.

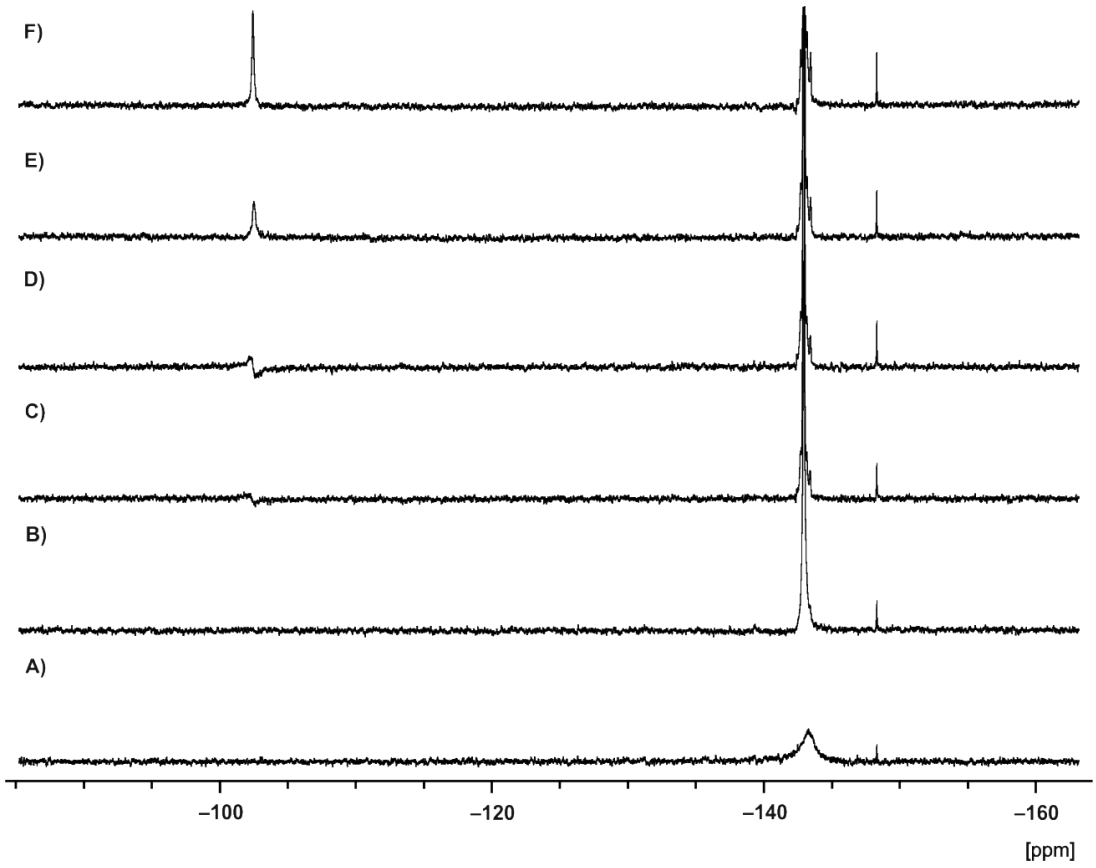


Figure 3.11. Selected expansion of ^{19}F-NMR spectra obtained during the titration of receptor **2** in DMSO with TBAF·3H_2O at 298 K. A) **2** + 1.8 eq. of TBAF·3H_2O. B) **2** + 3.1 eq. of TBAF·3H_2O. C) **2** + 4.03 eq. of TBAF·3H_2O. D) **2** + 4.7 eq. of TBAF·3H_2O. E) **2** + 5.3 eq. of TBAF·3H_2O. F) **2** + 6.3 eq. of TBAF·3H_2O. [**2**] = 1 mM.

The results obtained in this study are not entirely surprising because the generation of experimental data in solution phase for the quantification of noncovalent interactions between anions and charge-neutral arenes is difficult. In addition, fluoride usually behaves quite differently from the other halides when interacting with aromatic systems. Computational and experimental studies support this statement. Most of the experimental studies dealing with anion–π interactions in solution are based on receptors that combine other noncovalent interaction with single or multiple anion–π interactions. In these cases, the strength of the anion–π interaction is detected indirectly as a modulation of the secondary interaction, known as "enforced proximity" approach. But this modulation not always reveals an attractive anion–π interaction and therefore great care must be taken selecting the appropriate model.

The design and synthesis of receptors capable of binding anions efficiently in solution only with multiple anion–π interactions are challenging tasks. In fact, this work was undertaken to substantiate in solution our theoretical results obtained with receptors **1** and **2**. Unfortunately, it has not been possible to detect the interaction between anions and these receptors in solution. Among the many factors that can contaminate and difficult the observation of anion–π interactions in solution we want to highlight:

- Solvation effects,
- The use of salts (ion-pairs) as precursors of anion for the recognition, which complicates the analysis of the titration data and the assignment of the complex.

Therefore, the solvent and the counter-ion must be considered as important variables impacting on the estimation of energy values of anion–π interactions in solution.[251] Finally, despite that anion–π interactions have been widely demonstrated theoretically, the challenge to do so experimentally with systems that can only bound anions by means of single or multiple anion–π interactions is still in force.

3.2.3. EXPERIMENTAL EVIDENCES OF ANION–π INTERACTION

In this section we describe the positive results obtained in two additional experimental investigations of anion–π interactions.

The first example is related to the evaluation of anion–π interaction in solid state. In this case the experimental work was performed by the components of the experimental part of our Supramolecular Chemistry research group. The molecules we worked with are squaramide

[251] P. Ballester, *Acc. Chem. Res.* **2012**. DOI: 10.1021/ar300080f

molecules and derivatives. In this case, I have only carried out the computational study. As a consequence of this work we published an Organic Letters paper (3.2.3.1).

The examples that state the importance of anion–π interaction in the solid state have increased during last years. Generally, many of these examples involve electron-deficient six- and five-membered aromatic rings. In this article we reported the first description of anion–π interaction in four-membered aromatic rings. The simplest four-membered ring, cyclobutadiene (see Figure 3.12, up), is not a good candidate to participate in the anion–π interaction since it is antiaromatic and is not electron-deficient. However, this interaction can be achieved taking advantadge of the aromatization of cyclobutadiene when it is η^4-coordinated to a transition metal (Figure 3.12.A) or the substitution of cyclobutadiene in cyclobutene-1,2-diones due to partial contribution of a resonance structure (Figure 3.12.B). The manuscript is divided into three parts to illustrate the importance of anion–π interaction in four-membered rings. In first instance, the interaction is evidenced by the synthesis and X-Ray characterization of two new squaramide salts that exhibit anion–π interaction in solid state. Additionally, the search of additional examples in the CSD database and the theoretical study supports the experimental observations. It is worth mentioning that theoretical results have it greatest experimental accomplice in solid state, since the environment in two cases is more similar.

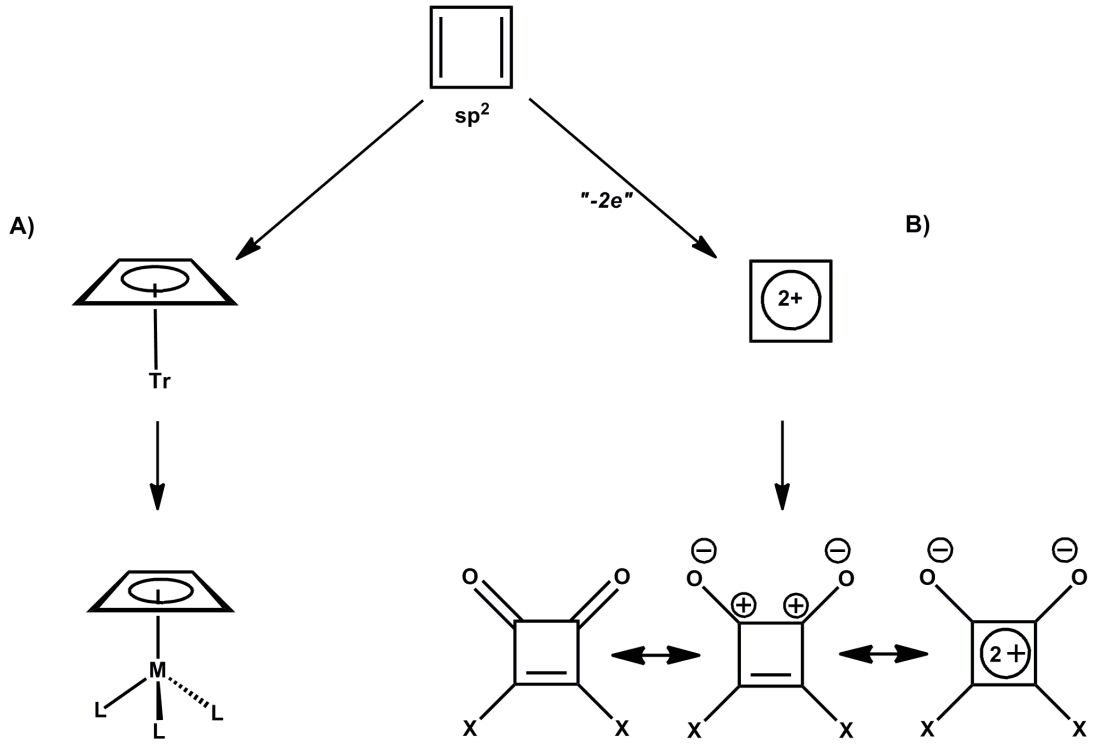


Figure 3.12. A) η^4 Coordination of Cyclobutadiene with a transition metal. B) Resonance forms of cyclobutene-1,2-dione derivatives.

The second example implies the evaluation of anion–π interaction in solution. In this case the experimental and theoretical work was performed by myself. The experimental issues were carried out at ICIQ under the supervision of Prof. Pau Ballester. After the previous experience acquired and briefly described in section 3.2.2 of this chapter, we continue with the determination to quantify the binding association constant between anion and receptors taking into account the previous learning. As mentioned above we were unable to quantify anion–π interactions in pure neutral receptors that only establish this interaction. For this reason, we have used the tuneable calix[4]pyrrole scaffold to quantify anion-binding affinity with an oxoanion. These receptors have been widely studied by Ballester's research group, and have been used to the experimental measure of anion–π interaction between chloride anion and a series of *meso*-tetraaryl calix[4]pyrrole receptors.[210] The conelike conformation of the receptor contains a deep aromatic cavity capable of including anions. The formation of four hydrogen bonds between a halide ion and the NH groups of the scaffold constitutes a reliable interaction which positions the anion above the planes of the π system (enforced proximity) shown in Figure 3.13.[246]

In our case, we have studied experimentally the anion-binding affinity between nitrate anion and mixed series of *meso*-tetra and diaryl-extended calix[4]pyrrole receptors by means of ^{1}H-NMR titrations. These receptors can achieve the electronic modification of the aromatic cavity by placing different substituents on the *meso*- phenyl rings of the calix[4]pyrrole skeleton. We have performed the study with electron-withdrawing substituents in the phenyl ring, however some electron-rich substituents have been taken into account for comparison purposes. For the sake of comparison, it is important to maintain the rest of the variables as similar as possible. We assume that the substitution at the phenyl rings (upper rim) has a negligible effect on the macrocyclic pyrrole unit (lower rim) of the receptor (see Figure 3.13). Consequently, the hydrogen bond binding properties of the receptor for the anion are assumed to be kept constant in the series.

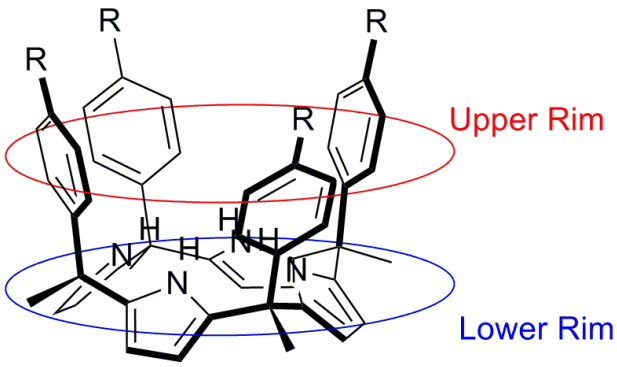


Figure 3.13. Schematic representation of the upper and lower rims of an aryl extended calix[4]pyrrole.

The theoretical study is related to the analysis of binding energy between the nitrate anion and calixpyrroles experimentally studied, taking into account solvation effects. Additionally, a comprehensive examination of possible binding modes of the nitrate anion has been performed with the aim to know the best orientation of the anion to establish the anion–π interaction. The results of this investigation are collected on a "*submitted paper*" (3.2.3.2).

3.2.3.1.- C. Estarellas, M.C. Rotger, M. Capó, D. Quiñonero, A. Frontera, A. Costa, P. M. Deyà. Anion–π Interactions in Four-Membered Rings. *Org. Lett.*, **2009**, *11*, 1987–1990.

3.2.3.2.- C. Estarellas, D. Quiñonero, A. Frontera, P.M. Deyà, P. Ballester. Assessment of Anion–π Interactions between aryl-extended calix[4]pyrrole and oxoanions. *In preparation*.

3.3. CONCLUSIONS

In this chapter the main objective was to theoretically design and experimentally assess the capacity of a receptor to establish interactions with anions only by single or multiple anion–π interactions. Keeping in mind this idea, two more goals are underlined. Firstly, to perform a theoretical design of a receptor that gathers a series of requirements necessary to perform an attractive anion–π interaction, based on electron-deficient arenes with high quadrupole moment and molecular polarizability. Secondly, the experimental assessment by means of NMR spectroscopy of anion–π interaction is established using the synthesized receptor previously designed. The receptor can only establish interactions with the anion through the anion–π interaction.

Regarding the experimental assessment of anion–π interaction shown in this chapter several points arise. Firstly, we have synthesized and characterized a new macrocycle receptor that can only interact with anions by means of multiple anion–π interactions. Regretably, with this receptor we could not experimentally assess the interaction in solution. However, we have quantified the anion–π interaction in solution using receptors that combine several noncovalent interaction (i.e. anion–π plus hydrogen bond), although the binding energies obtained are small. The detection is difficult because solvation effects can contaminate the measure, as well as the formation of ion-pairs difficults the analysis of titration data.

Regarding the theoretical study, this chapter has shown the practical importance of electrostatic and polarization components, which have been taken into account to design the receptor. Additionally, we have performed a σ/π binding ability analysis of the arenes to help us to decide the stability of the potential building block.

Chapter 4. Interplay between Noncovalent Interactions

CHAPTER 4. INTERPLAY BETWEEN NONCOVALENT INTERACTIONS

In Chapter 4 the research dedicated mainly to the study of the interplay between noncovalent interactions such as cation–π, hydrogen-bond, halogen bond, π–π stacking, lone-pair–π and anion–π interactions is collected. This chapter is organized in three parts. Firstly, a brief background presenting the motivation and reasons of this research is exposed. Secondly, the list of published articles obtained is presented. To facilitate the reading and understanding of this part, the reader can find a summary of the most important items to consider. Finally, the conclusions of this chapter are presented.

4.1. BACKGROUND

The understanding of noncovalent interactions and the interplay among them are of pivotal importance to the development of fields such as Supramolecular Chemistry and Molecular Recognition. The interaction involving aromatic rings are crucial binding forces in both chemical and biological systems. They are important in deciding the conformation of many molecules. They are also relevant in chemical reactions and regulation of biochemical processes. These chemical processes are accomplished with specificity and efficiency by means of intricate combinations of weak intermolecular interactions of various sorts. Noncovalent interactions such as hydrogen bond, cation–π, anion–π, and other weak forces govern the organization of multicomponent supramolecular assemblies. It is for this reason that a deep understanding of these interactions is of outstanding importance in the rationalization of effects observed in several fields, such as biochemistry or material science. A quantitative description of these interactions can be performed by taking advantage of quantum chemical calculations on small model systems. In complex biological systems and in the solid state a multitude of these noncovalent interactions may operate simultaneously, giving rise to interesting cooperativity effects. For instance, it is well-known that the hydrogen-bonding shows highly cooperative behaviour. The cumulative strength of networks of hydrogen bonds is larger than the sum of the individual bond strengths when they work simultaneously.[252] Our group has recently reported experimental[181,202] and theoretical[126,130] evidence of interesting synergetic effects between ion–π and π–π interactions, demonstrating that there is a remarkable interplay between these noncovalent interactions in complexes where both

[252] R. Ludwig, *Angew. Chem., Int. Ed.* **2001**, *40*, 1808-1827.

coexist. We have also demonstrated interesting synergetic effects between ion–π and hydrogen-bonding interactions leading to strong cooperativity effects.

For this reason, one of our main objectives was to carry out a complete study of cooperativity effects between different combinations of noncovalent interactions. In this manner, a useful set of computational tools for the evaluation of synergetic effects are proposed and a set of suggestions are established to predict the better combination of weak interactions to generate the strongest supramolecular complex.

4.2. RESULTS AND DISCUSSION

In this section I would like to emphasize the most important issues about this research and some concepts that we have learnt through several investigations.

4.2.1. BEFORE STARTING THE STUDY…

In this research we wanted to perform the most comprehensive analysis about the interplay of the noncovalent interactions. The forces studied throughout this work are: cation–π (Cπ), anion–π (Aπ), lone-pair–π (lp–π), π–π stacking (π–π), hydrogen bond (HB), dihydrogen bond (dHB) and halogen bond (XB) interactions. We have used several combinations of these forces, some of them shown in Figure 4.1.

The systems studied involve a wide range of electron-deficient and electron-rich aromatic rings (see Figure 4.2.A), used in order to evaluate different interactions and to investigate if the interaction depends on the nature of the aromatic ring. Some of the systems used are benzene; 1,3,5-trifluorobenzene; hexafluorobenzene; 1,4-diaminobenzene; 1,4-dicyanobenzene; pyrazine; terephthaldehide, among others. The aromatic rings are chosen based on their electrostatic and polarizability features defined by a quadrupole moment and molecular polarizability, respectively. The extension of π system and the aromaticity characteristics are also crucial. Normally the molecules used for the study, both aromatic and ionic or neutral interacting particles (ions or neutral molecules, see Figure 4.2.B), are chosen with the aim to study different features that can modulate the strength of the interaction. For instance, we normally use a set of anions such as Cl^-, Br^- or I^-, to study the size or polarization effects of the anions. In some studies, the strength of interaction between monotatomic or polyatomic anions is also compared. In other reports, cations with different charge such as Na^+ and Mg^{2+} have been used to test the influence of the charge. To establish lone pair interactions

H_2O and NH_3 molecules are suitable to assess the directionality of the interaction. However, in halogen bonding interactions the molecules used are ClF and BrF.

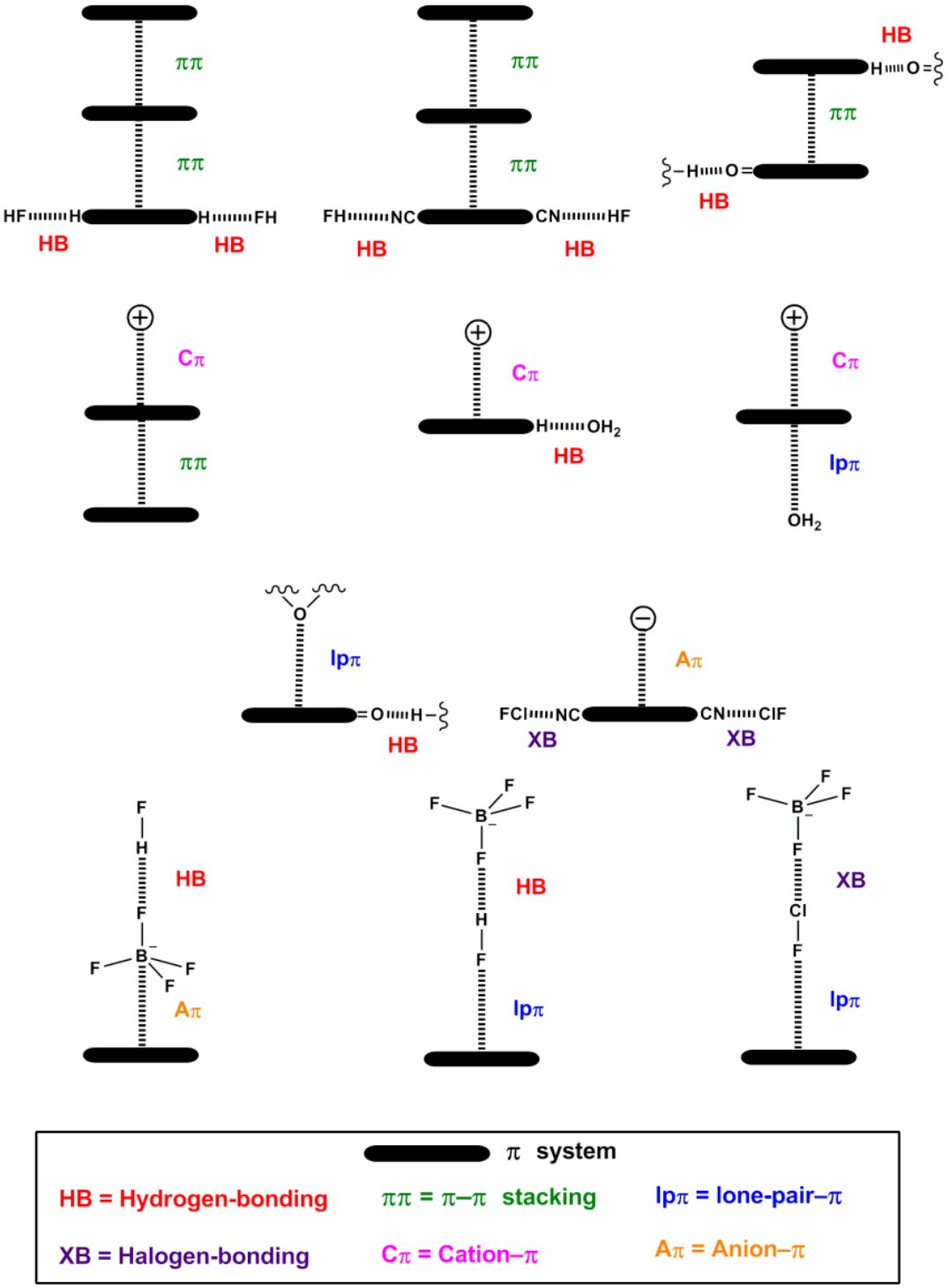


Figure 4.1. Representation of noncovalent interactions and combinations of them studied in this chapter.

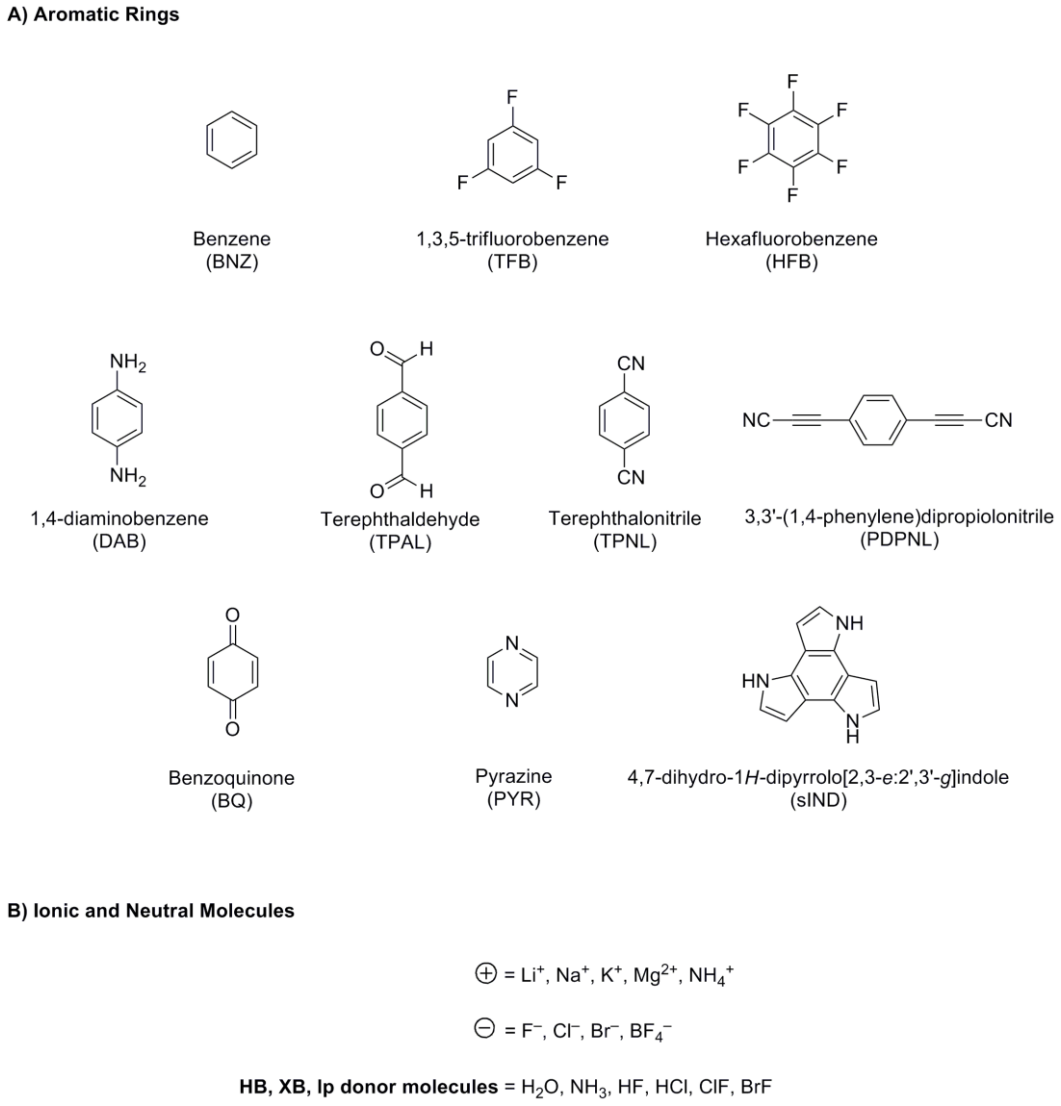


Figure 4.2. Compounds used to generate the combination of complexes studied in this chapter.

One of the most important interests of a theoretical researcher is that its investigation can be corroborated experimentally and that the results presented are realistic and relevant. With these purposes in most of our research we appeal to the experimental crystallography structures from Cambridge Structural Database (CSD), giving sense to the models of systems studied to analyse the interplay of noncovalent interaction. Other important parameter is the solvation effect that offers more realistic values of binding energies in comparison to the results obtained in the gas phase. For this reason, it is interesting to consider a solvation continuum model like, for instance, the Conductor-Like Screening Model (COSMO), which decreases interaction energies and are closer to the experimental association constants values. Moreover, the assessment of interplay between noncovalent interactions can give the confirmation of the existence of synergetic effects even in the presence of a solvent.

4.2.2. COOPERATIVITY STUDY I: FUNDAMENTAL CONCEPTS

In this chapter the papers related to cooperativity are collected. All of them are based on the same idea, i.e., to study different combinations of noncovalent interaction and evaluate the existence of synergetic or cooperativity effects in those systems. From these studies, we have extracted a set of tools, formulas and concepts, which are summarized below. They are useful for analysing cooperativity effects when different weak forces are combined.

4.2.2.1. How to calculate Cooperativity Effects?

In general, to calculate the cooperativity and synergetic effects we have used the formulas explained below. In some articles, we have defined other complementary systems to calculate synergetic effects enabling us to learn what interaction is more reinforced additionally to know if exists cooperativity effects through equations. The use of these complementary systems depends on:

- The combination of interactions studied,
- The objectives of the study, and
- The previous results obtained,

For a comprehensive explanation of these systems two examples present in the articles of this chapter have been used. Throughout this research we have used three methods to calculate the cooperativity effects. For a better understanding, the situations studied are schematized in Figure 4.3. Let us consider a ternary complex formed by three components A, B and C that are establishing two noncovalent interactions.

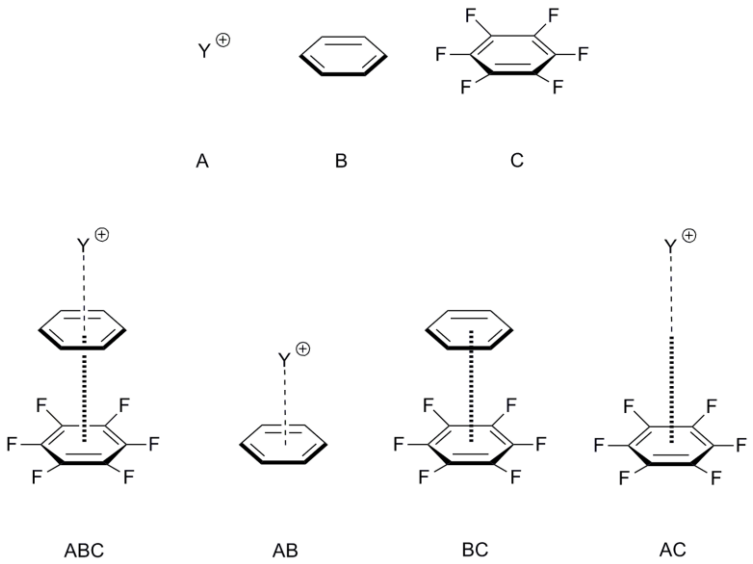


Figure 4.3. Schematic representation of ternary and binary complexes used to calculate cooperativity effects.

The first method is named synergetic energy, and is calculated as the total energy of the optimized system, i.e., the energy of the ternary complex ($E_{BSSE}(ABC)$) minus the energy of each optimized binary complex derived from the ternary complex ($E_{BSSE}(AB)$ and $E_{BSSE}(BC)$).

Synergetic Energy

$$E_{syn} = E_{BSSE}(ABC) – E_{BSSE}(AB) – E_{BSSE}(BC)$$

Equation 4.1

Another method based on synergetic energy is the cooperativity energy, calculated by adding one term to the synergetic energy, which takes into account the interaction energy between the components A and C ($E_{BSSE}(AC)$) from the geometry of the ternary complex.

Cooperativity Energy

$$E_{coop} = E_{BSSE}(ABC) – E_{BSSE}(AB) – E_{BSSE}(BC) – E_{BSSE}(AC)$$

Equation 4.2

In addition to cooperativity energy, we have used a third method, the non-additivity energy. The terms of its equation are very similar to those found in the cooperativity energy. The difference is that, in cooperativity energy, the binary complexes have been previously optimized. However, in non-additivity formula, the energy of all binary combinations is obtained from single point calculations of the optimized ternary complex.

Non-additivity energy

$$E\text{-}E_A = E_{BSSE}(ABC) – E_{BSSE}(AB) – E_{BSSE}(BC) – E_{BSSE}(AC)$$

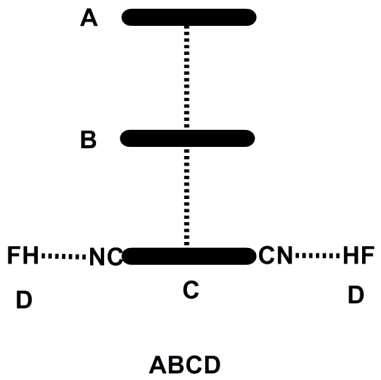
Equation 4.3

The equation of non-additivity energy is also useful for systems with a lot of components because we take into account the complete system and the energy of all possible pairs.

However, depending on the studied systems (quaternary or quinnary complexes) these equations can suffer modifications, as in *Comput. Theor. Chem., **2011**, 975, 106* article present in this chapter, where we have calculated E_{syn}' for quinnary complexes with more than one aromatic ring. The synergetic energy can be calculated as shown in Figure 4.4. The E_{syn}' provides us the effect of the substitution in the aromatic ring **C** through the space over the first π system **A** (see Figure 4.4).

Below two different schemes to study cooperativity effects and which interaction is more reinforced are described. From the above mentioned equations, we can know what

combination of noncovalent interactions would be more favourable; but in this way we do not know which noncovalent interactions would be more reinforced.

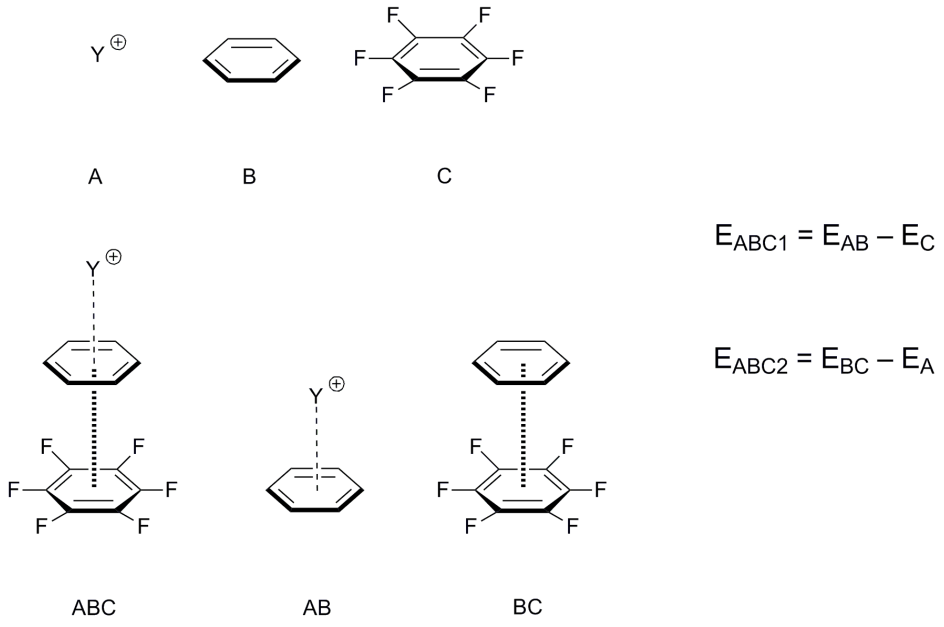


$$E_{syn} = E_{ABC2D} - E_{AB} - E_{BC} - E_{C2D}$$

$$E_{syn}' = E_{ABCD} - E_{ABC} - E_{C2D}$$

Figure 4.4. Scheme of different ways to calculate synergetic energy for quinnary complex.

One alternative way to do this is calculating the binding energy of ternary complexes from binary complexes as shown in Figure 4.5. In case of E_{ABC1} we consider that the cation–π interaction (complex AB) is previously formed. Here, we are evaluating the effect to create a π–π stacking interaction, which is formed by the addition of molecule C. However, the equation E_{ABC2} is the contrary. Firstly the π–π stacking interaction (complex BC) is formed and then, we added the cation. Therefore, we are evaluating the effect generated from forming a cation–π over the π–π stacking.



$$E_{ABC1} = E_{AB} - E_{C}$$

$$E_{ABC2} = E_{BC} - E_{A}$$

Figure 4.5. Schematic representation of ternary and binary complexes used to calculate which noncovalent interaction is more reinforced in the ternary complex.

An additional way to evaluate the mutual influence of noncovalent interactions in the same system (see Figure 4.6) is explained in the *ChemPhysChem, **2011**, 12, 2742* article present in this chapter, where anion–π and halogen bond interactions coexist in the same system:

- ΔE_{XB2} reflects the binding energy of the halogen bond when the anion–π interaction is previously formed, and therefore we are evaluating the halogen bond interaction in the ternary complex.
- $\Delta E_{A\pi 2}$ reflects the binding energy of the anion–π interaction when the halogen bond interaction is previously formed, and therefore we are evaluating the anion–π interaction in the ternary complex.
- In all cases we are using the binding energies with the BSSE correction from the binary complexes.

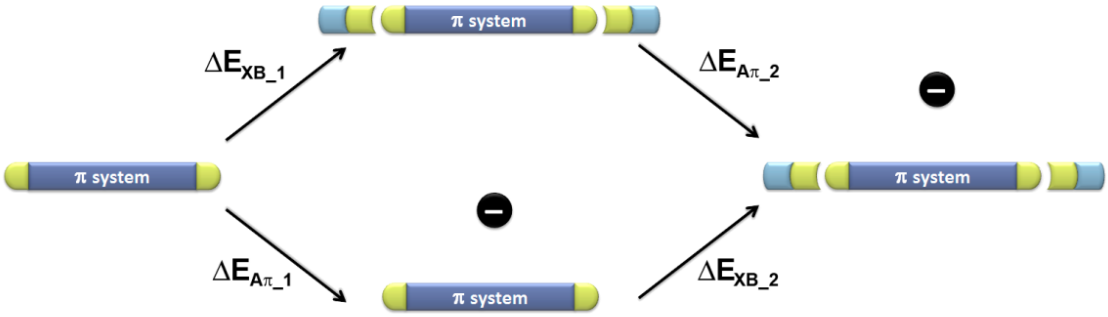


Figure 4.6. Schematic representation of the two routes to form the anion–π–XB complex that allows computation of the $\Delta E_{XB2}/\Delta E_{XB1}$ and $\Delta E_{A\pi 2}/\Delta E_{A\pi 1}$ ratios.

From the comparison of the values of ΔE_{XB2} with ΔE_{XB1} using the relation $\Delta E_{XB2}/\Delta E_{XB1}$ to know what interaction is reinforced, we obtain that:

- If $\Delta E_{XB2}/\Delta E_{XB1} > 1$, the XB is strengthened by the anion–π interaction previously formed in binary complex.
- If $\Delta E_{A\pi 2}/\Delta E_{A\pi 1} > 1$, the Aπ is strengthened by the halogen bond interaction previously formed in binary complex.
- If both relations are greater than one (>1), means that both interactions present synergy between them. If the value of the relations is the same, the interactions are unaltered.
- If one ratio is greater than one (>1) and the second ratio is less than one (<1), one interaction is reinforced at the expense of the other, i.e., if $\Delta E_{A\pi 2}/\Delta E_{A\pi 1} > \Delta E_{XB2}/\Delta E_{XB1}$, that means that anion–π is more reinforced than XB and *vice versa*.

Therefore, following this scheme we can analyse whether there are cooperativity effects or not and what interaction is more reinforced.

4.2.2.2. Useful Parameters to confirm Cooperativity Effects

In addition to energetics, there are other parameters that are very useful in the determination of cooperativity effects.

One of these parameters is geometry related. For example, if the equilibrium distances of ternary complex are shorter than the distances in the binary complexes, it means that both interactions are reinforced in the ternary complex. However, if there is one distance that is shorter and the other is longer in ternary complex than in binary complexes, this fact means that the first interaction is reinforced at the expense of the second interaction. In this case the existence of cooperativity effects depends on the strength of the reinforced interaction. Finally, the lengthening of both distances in the ternary complex with respect to the two binary complexes implies a weakening of both interactions and no existence of cooperativity effects.

The analysis of Bader's theory of "Atoms-in-molecules" (AIM) is also a useful tool to determine the existence of cooperativity effects. In this case we discuss about critical points of AIM instead of equilibrium distances, but the idea is very similar. Normally, the noncovalent interactions studied can be classified into two groups. The first one is related to the interactions in σ orientation such as HB, dHB or XB, mainly defined by a Bond Critical Point (BCP). The second group implies interactions with aromatic rings such as anion–π, cation–π or π–π stacking, defined by a Cage Critical Point (CCP). The value of the electron density at BCP and CCP is determined by rho (ρ). Therefore, the higher the electron density value (ρ), the stronger the noncovalent interaction. The additivity of interactions forming the ternary complexes is confirmed by the difference of electron density values between the noncovalent interactions in binary complex with respect to the same noncovalent interaction present in ternary complex ($\Delta\rho$). The same reasoning can be applied for charge transfer properties.

Finally, in most of the studies carried out in this chapter we have used the Molecular Interaction Potential with polarization tool (MIPp). It is very useful for us because it allows the separation of the total interaction energy into different contributions such as electrostatic, polarization and van der Waals allowing us to study the origin of cooperativity effects in terms of these contributions.

4.2.2.3. Synergetic Stability Concept

We have also defined the concept of Synergetic Stability. *A priori* the stability of one complex is proportional to the complexation energy, which at the same time is proportional to the strength of noncovalent interactions.

In cooperativity studies, normally we combine two noncovalent interactions and we expect that some of the following situations could occur:

- Strengthening of both,
- Weakening of both,
- Strengthening of first one and weakening of the second interaction.

The definition of synergetic stability has a special interest. Initially, the complex with both strongest interactions should be the most energetically favourable and the most stable synergetically. However, in our study reflected in *J. Phys. Chem. A, **2009**, 113, 3266*, the most stable complex energetically implies a weakening of the two studied interactions. This fact led us to define the new concept of synergetic stability, where the strengthening of both interactions does not imply the combination of energetically more stable complex.

4.2.3. COOPERATIVITY STUDY II: RESULTS OBTAINED

Under these lines, the publications in Scientific Journals derived from this research are listed, in addition to a brief summary of the subject of matter.

4.2.3.1.- C. Estarellas, A. Frontera, D. Quiñonero, I. Alkorta, P.M. Deyà, J. Elguero. Energetic vs. Synergetic Stability: A Theoretical Study. *J. Phys. Chem. A*, **2009**, *113*, 3266–3273.

4.2.3.2.- C. Estarellas, D. Escudero, A. Frontera, D. Quiñonero, P.M. Deyà. Theoretical ab initio study of the interplay between hydrogen bonding, cation–π and π–π interactions. *Theor. Chem. Acc.*, **2009**, *122*, 325–332.

4.2.3.3.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Interplay between cation–π and hydrogen bonding interactions: Are non-additivity effects additive? *Chem. Phys. Lett.*, **2009**, *479*, 316–320.

4.2.3.4.- D. Escudero, C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Cooperativity effects between non-covalent interactions: are they important for Z-DNA stability? *Chem. Phys. Lett.*, **2009**, *485*, 221–225.

4.2.3.5.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Can lone pair–π and cation–π interactions coexist? A theoretical study. *Cent. Eur. J. Chem.*, **2011**, *9*, 25–34.

4.2.3.6.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Unexpected Nonadditivity Effects in Anion–π Complexes. *J. Phys. Chem. A*, **2011**, *115*, 7849–7857.

4.2.3.7.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Theoretical ab initio study of substituted benzene trimer: Interplay between hydrogen bonding and π–π interactions. *Comput. Theor. Chem.*, **2011**, *975*, 106–110.

4.2.3.8.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Theoretical Study on Cooperativity Effects between Anion–π and Halogen-Bonding Interactions. *ChemPhysChem*, **2011**, *12*, 2742–2750.

The article numbered as 4.2.3.1 implies the definition of the new synergetic stability concept, which has been used in some of the subsequent articles.

The articles 4.2.3.2, 4.2.3.5, 4.2.3.7 and 4.2.3.8 are referred to the study of cooperativity effects between different noncovalent interactions. In all of them, we have studied all the physical effects that can modify the interplay between the forces. For example in the article 4.2.3.8., where we study the halogen bond and its influence on the anion–π interaction, we have taken into account the interaction with nitrogen and oxygen atoms, as well as the force of the interaction when the atom is in the ring (pyrazine) or outside the ring (terepthalonitrile, see Figure 4.2).

The article 4.2.3.3 is a singular report, where the additivity between the cation–π and hydrogen-bonding is studied. It can be observed by means of non-additivity effects that, as the number of HB increases, the cation–π interaction is reinforced.

The article 4.2.3.4 shows a clear example of the importance of cooperativity effects in a biological system as Z-DNA, where this interplay contributes to their stability.

Finally, the article 4.2.3.6 is an unusual paper in this chapter, but at the same time very relevant. On the one hand, we have only analysed the anion–π interaction. But on the other hand, we have studied several important subjects. The additivity effects are studied varying the number of double bonds and the number of fluorine atoms substituted in the molecules examined, without varying the stoichiometry.

In this way, we can study the first issue: the aromaticity and conjugation of π system. The second issue is to learn the behaviour of additivity effects in aromatic and in non-aromatic

systems. Finally, the analysis of the anion–π interactions in these complexes leads to a scheme of partition energy into different contributions. From this point, we observe that our study provides very similar results that the theory proposed by Houk and co-wokers.[186] However going a step further, we conclude that additionally to the substituent effect and electrostatic contribution, it is important to take the polarization term into account.

4.3. CONCLUSIONS

The results reported stress the importance of interplay between noncovalent interactions.

From a general point of view, we have defined three different formulas to study the cooperativity effects and the new concept that is the synergetic stability. Apart from the equations described there are two more methodologies to know not only if there are cooperativity effects, but also what interaction is reinforced. In addition, there are geometric and electrostatic information that confirm the results obtained through the equations and MIPp tool.

Moreover, from all the studies where the partition scheme for the interaction energy is analysed, we can conclude in general terms that electrostatic and polarization terms are crucial for the favourable interaction energy. The polarization term acquires more importance in systems where the electrostatics is small, invariant or when the aromatic system is highly extended and it is more polarizable. However in systems where the electrostatics is important (i.e., from quadrupole moment values of 9B), this is the most relevant contribution.

If now, we focus on each of the articles discussed the conclusions are the following.

Paper 4.2.3.1 shows how the most stable complex is at the same time the least synergetically favourable complex, leading to the concept of Synergetic Stability, *ergo* the least stable complex in terms of interactions involved becomes the most favourable in terms of cooperativity effects. The same study, performed with COSMO approximation, shows how some synergetic stable complexes are also the most energetically favourable. This is a key article because synergetic stability can be understood as the balance between cooperativity and anti-cooperativity effects.

The set of articles (4.2.3.2-4.2.3.5 and 4.2.3.7-4.2.3.8) that treat physical aspects between the systems that form noncovalent interaction, are responsible for us being able to establish useful tools, parameters and formulas to evaluate the synergetic effects. Moreover, they provide important effects such as:

- The additivity of non-additivity effects in article 4.2.3.3,
- The corroboration of these effects are important in biological systems shown in paper 4.2.3.4,

- The knowledge of that the synergy is transmitted through the extended π system even when two noncovalent interactions present in the system are at long distances (article 4.2.3.8).

The article 4.2.3.6 shows the importance of the aromaticity in the π interactions, and it is another example of the importance of the polarization term in the π interactions. Our main conclusion in this study is to reflect our accordance with the model proposed by Houk and co-workers[186] but it is important to emphasize that the electrostatic model is not sufficient to provide an accurate description of anion–π interaction. Additional effects like aromaticity and polarizability effects are required for a good and total description of the interaction.

Chapter 5. Anion–π Interactions: One Step Further

CHAPTER 5. ANION–π INTERACTIONS: ONE STEP FURTHER

Chapter 5 can be divided basically into two ideas. On the one hand, we emphasize the presence of anion–π interaction in biological systems and its possible function into sophisticated molecules as proteins or enzymes. On the other hand, we explain new concepts as radical anion–π interaction and its detection in a biological system or the study of the interaction when a transition-metal ion belongs to the anion.

5.1. BACKGROUND

Ten years after the publication of the first article devoted to the anion–π interaction, the study of this interaction has now taken a new direction. In the last years, the scientific community has dedicated his efforts to:

- The study of its physical nature,
- The interplay with other noncovalent interactions in complex systems, and
- The demonstration of its vital importance in experimental field.

However, now we need to go one step further. One way to achieve this objective is studying the interaction in biological systems. Another way is translating the concept of anion–π interaction into different questions, as for example in the field of open-shell systems and transition-metal ions.

The interest of the presence of anion–π interaction in biological systems was born because these systems are based on efficient connections between noncovalent interactions, leading complex functions in highly organized molecular systems. Anion–π interaction might be one of these interactions. Moreover, in last years the importance of anion–π interaction has been demonstrated by a great deal of theoretical and experimental investigations, gaining significant recognition and interest. However, a clear evidence of anion–π interaction that likely plays a key role in enzymes is lacking in the literature. For this reason, we have carried out a search with the objective to find this interaction in a biological system. The critical step to evidence the importance of this interaction is to demonstrate its relevant function in these scenarios.

Regarding an alternative way of anion–π interaction, here we have firstly considered open-shell systems. We present the first study of radical anion–π interaction. This study emerges as a result of recent experimental works where several authors demonstrate the importance of anion–π interaction in reactions involving aromatic rings. For this reason, we wanted to study the chemical sense, the importance and the possible repercussion of the open-shell version of the anion–π, as well as, the cation–π interaction. During the last years the influence of transition-metal ion on the anion–π interaction when it is coordinated to the aromatic ring has been studied showing a strengthening of the binding.[203,204] However, in this study we want to analyse the influence of transition-metal ion on the interaction when it belongs to the anion.

5.2. RESULTS AND DISCUSSION

In the last stage of the research that has been developed during this thesis, we realized that the anion–π interaction needs to expand its frontiers and needs to diversify. Based on this impression, the works commented below try to study the anion–π interaction from other perspectives.

In this chapter the main objective is to demonstrate an original idea that has the anion–π interaction as a protagonist. The tools used to get this aim are the usual in computational chemistry that the reader can find fully described in the Annex I of the present thesis. For this reason, below, there is the list of the studied subjects carried out together with a brief summary of the most important facts of each published article.

5.2.1. ANION–π INTERACTION IN BIOLOGICAL SYSTEMS

One of the ideas that we have pursued in the investigation was based on the question of whether anion–π interaction is present in biological systems and carries out important functions. With this objective, we started the search for anion–π interaction in biological systems through the Protein Data Bank (PDB) database.

As a result of this research, we have found a fascinating example, where the anion is in the active centre of the Urate Oxidase enzyme (UOX) interacting with the aromatic substrate (uric acid) by means of an anion–π interaction. X-Ray analysis of several UOX complexed structures reveals the existence of anion–π interactions between both uric acid and 8-azaxantine with cyanide and chloride anions (PDB codes 3BJP and 3CKU, respectively).

The urate oxidase is a homotetrameric cofactorless enzyme, which in the presence of molecular oxygen catalyses the hydroxylation of uric acid to *s*-allantoin through 5-hydroxyisourate intermediate. In the X-Ray structure (PDB code 3BJP) the cyanide anion (inhibitor) is establishing an anion–π interaction with the substrate (uric acid). The anion probably replaces the molecular oxygen involved in the reaction mechanism, and therefore, hinders any access to the peroxo site in the course of the reaction, inhibiting the enzyme. High level *ab initio* study on the anion–π complex shows negative interaction energy indicating that the binding of cyanide anion with the uric acid is favourable. The additional inhibitor complex (PDB ID: 3CKU) between chloride anion and 8-azaxantine inhibitor has been also calculated for comparison purposes. The theoretical study has been extended to the analysis of the anion-binding ability of uric acid in its anionic form (observed in the active centre, see Figure 5.1.A) interacting with models of the amino acids of the enzyme active centre in order to know if the anion–π interaction is also favourable. The binding energy is smaller for this model than the one corresponding to the non-anionic form of uric acid; however it is still favourable, indicating that the anion–π interaction is stabilizing even in the anionic form. The theoretical study finalizes with the study of the anionic model interacting at the same time with the cyanide anion and with a phenylalanine (Phe159) at the opposite side of the anion (see Figure 5.1.B). The Phe159 establishes a π–π stacking interaction with the substrate. The interaction energy of this ternary complex is slightly more negative than the interaction without phenylalanine, indicating that the presence of Phe159 enhances the interaction energy of the anion with the urate π-system.

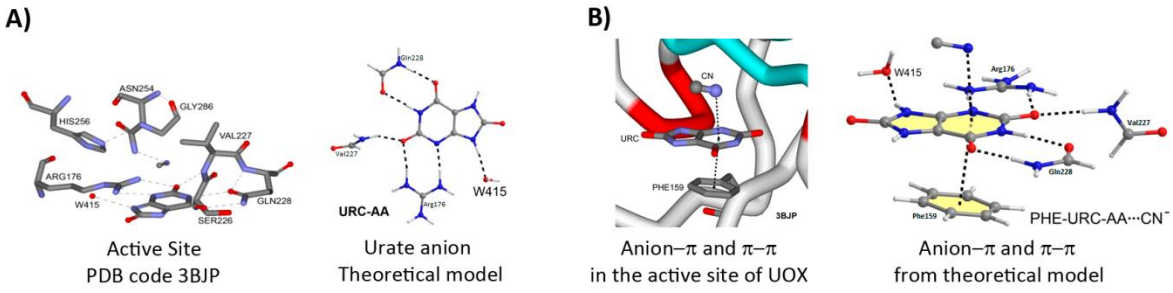


Figure 5.1. A) Active site with indication of amino acids of one subunit of UOX (PDB code 3BJP) together with the URC-AA theoretical model used to evaluate the anion–π interaction with urate anion. B) Representation of the anion–π and π–π interactions observed in the active site of UOX (B, left) and in the theoretical model (B, right).

In summary, we concluded that the cyanide anion could act as the inhibitor of the protein function, which is indeed the most relevant fact. This becomes the first reported example where the existence of the anion–π interaction in a biological system is demonstrated and

moreover where this interaction is probably the responsible of the inhibition of the enzyme. As a result of this research we published one article (5.2.1.1).

During the search of the existence of anion–π in biological systems, we have discovered a repeated pattern that involves the presence of cofactors as Flavin Adenine Dinucleotide (FAD) or Flavin Mononucleotide (FMN). Therefore, from this finding we performed an exhaustive study of the presence of anion–π interactions in flavoproteins. In this case, it is extremely important to distinguish between the results:

- Where the anion is involved in an anion–π interaction, but the presence of the anion is only due to biological or crystallographical conditions to obtain the structure of the protein or,
- Where the anion is located over the isoalloxidine aromatic ring of the cofactor because in this position it is making an important function.

Taking into account these facts, we wanted to emphasize an interesting example where the anion–π interaction participates in the enzymatic process of the tryptophan-7-halogenase (PrnA) enzyme (PDB ID 2AR8, see Figure 5.2.A). The PrnA is a flavin-dependent halogenase that catalyzes the regioselective chlorination of tryptophan at seventh position (C7). The chloride anion is bound on one face of the isoalloxidine ring and is positioned to make a nucleophilic attack on the flavin peroxide resulting in the formation of hydroxilated FAD and hypochlorous acid (HClO) as shown in Figure 5.2.B. The HClO travels through a tunnel of 10Å that connects the FAD and tryptophan binding sites. In solution tryptophan is not chlorinated by hypochlorous acid because is less reactive than other aromatic rings. However, in the tryptophan binding site a lysine (Lys79) establishes a hydrogen bond with HClO activating the chlorine atom by increasing its electrophilicity and allowing to chlorinate tryptophan (Figure 5.2.C).

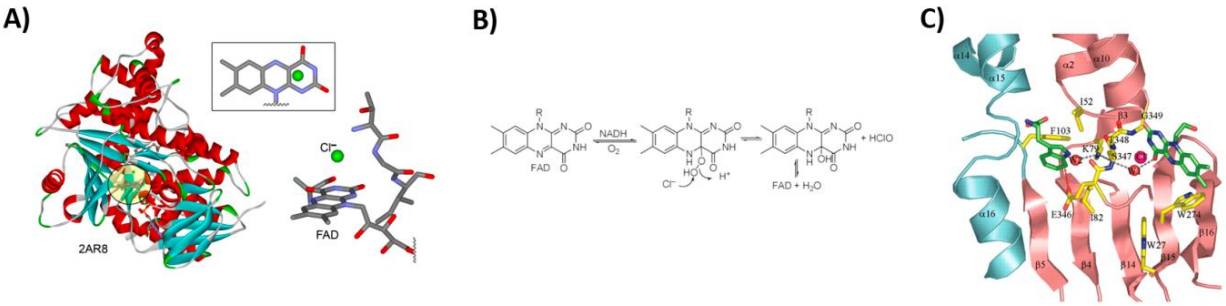


Figure 5.2. A) 3D X-Ray structure of PrnA (PDB code 2AR8) and the position of the FAD-Cl– complex. B) Mechanism of formation of HClO. C) Scheme of the enzymatic mechanism of formation of 7-chlorotryptophane.

From this research we have published one article that collects several examples of anion–π interactions in flavoproteins and the PrnA is the outstanding example (5.2.1.2).

5.2.1.1.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Relevant anion–π interactions in biological systems: the case of urate oxidase. *Angew. Chem. Int. Ed.*, **2011**, *50*, 415–418.

5.2.1.2.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Anion–π Interactions in Flavoproteins. *Chem.- Asian J.*, **2011**, *6*, 2316–2318.

5.2.2. ALTERNATIVE ANION–π INTERACTION

The alternative anion–π interaction refers to the analysis of this interaction and how it is affected when the anion is modified; in one case because the anion is an open-shell system (radical anion) and, in other case due to the introduction of a transition-metal ion in its structure.

The first study implied open-shell systems. It is interesting to note that, this research was born from the knowledge that they have been experimentally observed in reaction pathways where radical ion and aromatic systems are involved. Is a radical anion–π interaction possible? What are the implications of this new concept of anion–π interaction? These are some of questions that we try to answer in this study by means of physical nature analysis. With this aim, and additionally to the geometric and energetic study, we have performed an orbital, spin density and AIM analysis. This investigation has been extended to the cation–π interaction, for comparison purposes. Moreover, the work published ends with the description of the presence of radical cation–π interaction in an enzyme, providing great significance to this study (5.2.2.1).

The last report considered has implied the influence of transition-metal ion in the anion–π interaction. The origin of this investigation comes from the examples found in the literature, both experimental and theoretical, where transition-metal ions are present in systems experiencing anion–π interaction. Generally, in these studies the metal is coordinated to π systems producing stronger anion–π interactions. However, in this research we have studied the effect of transition metal ion when it belongs to the anion. To evaluate the effect we have performed a systematic study, where we have taken into account different metals with different coordination indices, and therefore different geometries. This point gives us the opportunity of studying anion–π for different orientations. An additional point is to consider electron-acceptor and electron-donor aromatic rings to study if the presence of transition-metal ion can strengthen the less favoured anion–π interactions.

5.2.2.1.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. Radical cation ($C^{\cdot+}$–π) and radical anion ($A^{\cdot-}$–π) interactions with aromatic rings: energetic, orbitalic and spin density considerations. *Phys. Chem. Chem. Phys.*, **2011**, *13*, 16698–16705.

5.2.2.2.- C. Estarellas, A. Frontera, D. Quiñonero, P.M. Deyà. The key role of Transition-Metal Ions in Anion–π Interactions: Theoretical Study. *Submitted*.

5.3. CONCLUSIONS

The investigation presented here emphasizes the new horizon of the anion–π interaction.

We can divide the new way into two, one related to the study on biological systems, and the other in relation with a new perspective in its physical nature.

Regarding the existence of anion–π interaction in biological systems (articles 5.2.1.1 and 5.2.1.2), in this chapter we have exposed the first studies when the interaction is present in the active site of enzymes playing a relevant action in their function.

Regarding article 5.2.1.1, two important statements can be found. On the one hand, we have proved that the anion–π interaction is present in the active site of the UOX enzyme and is energetically favourable. On the other hand, this is the first example where the presence of an anion–π interaction between an inhibitor and an enzymatic substrate is proposed to be crucial in the inhibition of an enzyme.

The paper 5.2.1.2 shows a systematic search of anion–π interactions in flavin-dependent enzymes. As a consequence of this search a significant number of strutures exhibit this interaction between FAD or FMN and a series of monoatomic and polyatomic anions. However, the search goes one step further finding an enzyme where the anion binds the cofactor at the enzymatic centre by means of an anion–π interactions and it participates in the enzymatic process instead of inhibiting it.

Concerning the new perspective of anion–π interaction (papers 5.2.2.1 and 5.2.2.2), this chapter shows two studies that involve the evaluation of the interaction when the anion is modified, firstly turning it into an open-shell system as radical anion and, secondly, adding into its structure the presence of a transition-metal cation. In both reports, the final aim is to assess the influence of different factors on the binding ability of the anion–π interaction.

In paper 5.2.2.1 the radical anion–π interaction is less favourable than the anion–π interaction, while the contrary is observed for radical cation–π interaction that is more favoured than cation–π interaction. These energetic features are confirmed by both orbital and spin density analyses. Moreover, the significance of radical cation–π interaction can be corroborated by its presence and function of the tetrahydrobiopterin biological system.

The article 5.2.2.2 shows that the anion–π interaction is more favoured thanks to the presence of transition-metal ions, independently of the type and coordination index of the metal or different orientations adopted.

Chapter 6. Conclusions

CHAPTER 6. CONCLUSIONS

This chapter gathers main conclusions and learning of this thesis grouped by main objectives raised.

The first objective was to find a convenient binding site to be used for constructing a receptor that establishes single or multiple anion–π interactions without other noncovalent interactions.

This objective was born as a result of first experimental evidences, where in general, the binding association constants were small and difficult to measure. Therefore, the following step would be to find a good candidate to build a receptor able to establish strong anion–π interactions mainly in solution, which is the limiting step.

Bearing in mind this objective, it was necessary to carry out a complete work in both theoretical and experimental fields.

Computationally the main work is the design of the building block; study its properties and finally assess the binding energy between several anions and the receptor. A building block has to gather several requirements to perform strong and favourable anion–π interactions. Firstly, we need an electron-deficient aromatic ring. We can get this kind of π systems with heteroaromatic rings or increasing the number of electron-withdrawing substituents. In this manner the π acidity of aromatic ring increases. Moreover, we know from previous theoretical studies that the anion–π interaction is regulated by electrostatic and anion-induced polarization terms,[128,129,130] which at the same time are governed by quadrupole moment (Q_{zz}) and molecular polarizability ($\alpha_{||}$), respectively. The larger Q_{zz} and $\alpha_{||}$ values, the better the anion–π interaction in this moiety.

In addition, the study of dual σ/π ability of building blocks for the selection of the best moiety has also been important. From computational studies we conclude:

- The increasing of electron-withdrawing groups (EWG) in aromatic rings that have –CH groups provides two effects. On the one hand, it favours hydrogen bond (σ interactions) interaction between the aromatic ring and the anion. On the other hand, the π acidity of aromatic ring increases, favouring the anion–π interaction. The best building block would be the aromatic ring that has more EWG enabling the

anion–π interaction and minimizing the possibility to perform other competitive interactions.

- It is important to consider both mono- and polyatomic anions to perform anion–π interactions. Depending on the model system, the anion–π interaction can be favoured by monoatomic anion instead of polyatomic anion and *vice versa*.

Once all candidates have been analysed computationally, the best candidate to obtain a receptor suitable for interacting with anions by means of anion–π interaction is decided. The experimental work starts with the synthesis and characterization of the receptors. The following step is the measurement of anion binding constant in solution. Unfortunately, with the designed receptors we were not able to detect the interaction by means of NMR spectroscopy. The measurement is difficult due to the solvent, the model system and the ion-pairs present in the solution.

For these reasons, the most appropriate way to measure anion–π interaction in solution is still depending on the presence of "enforced proximity". Consequently, using a receptor that provides an additional help, as calix[4]pyrrole we were able to measure anion–π interactions in solution between tuneable four and two-wall calix[4]pyrrole receptors and nitrate anion. Favourable anion–π interactions can be observed in aryl-extended calix[4]pyrrole systems substituted with more electron-withdrawing groups.

Additionally, an example of anion–π interaction in solid state is shown. Curiously, it is the first example of an anion–π interaction between an anion and a four-membered ring, concretely with squaramide and its derivative systems.

Finally, regarding the first objective the general conclusions that we obtain are the following. Experimentally the detection of anion–π interaction in solution by means of a receptor able to do solely single or multiple anion–π interactions continues being a challenge. On the other hand, computational chemistry is a useful tool. However, hard working is still required to provide accurate results comparable to the experimental findings. It is necessary to join forces to perform multidisciplinary studies.

The second objective of this thesis was to evaluate the interplay between noncovalent interactions.

This objective was born due to the importance of noncovalent interactions in Supramolecular Chemistry and Molecular Recognition. In fact, complex biological systems are also based on intricate combinations of several noncovalent interactions, which act very efficiently. Specifically, the interactions involving aromatic rings are crucial binding forces in both chemical and biological systems. For this reason, it is an exciting research trying to understand and control the interplay of weak interactions responsible of complicated functions in Nature.

Taking into account this statement, to achieve this goal we have performed an extended theoretical study where we have combined several noncovalent forces resulting in ternary, quaternary and quinnary complexes.

The study has two goals:

- The evaluation of the existence of cooperativity effects in different combination of interactions.
- And then, once demonstrated cooperativity effects, analyse if one interaction is more reinforced than the other.

To perform this study we have used a series of equations and schemes that let us shed light to this topic understanding why this effect is produced, i.e., the physical nature. Regarding this subject, we can confirm that:

- Synergy, Cooperativity and Non-Additivity Energy equations are useful to identify if a complex where two or more noncovalent interactions are present have cooperativity effects. Also, these formulas are also effective to know what are the best combinations of noncovalent interactions in case that more than one organisation could exist.
- However, to identify if one interaction is more reinforced than others present in the complex, these formulas are not sufficient. For this, we have appealed to another startegy. It is based on the evaluation of the energetic cost of formation of the second interaction when the first interaction is previously formed, in case of complex being formed by two interactions. To complete the study it is necessary to invert the order.

- Finally, to complete the study it is important to know the physical nature of interactions that allows the existence of cooperativity effects. After several studies we conclude that obviously, the electrostatic term is essential for strong noncovalent interactions, mainly in those where one component is charged such as anion–π or cation–π interaction. In the same way, in cases where electrostatic is not crucial, there are two more factors to take into account: the polarizability term and the aromaticity. In some models studied in this thesis the extended π system is a beneficial to strengthen π interactions.

Finally, the general conclusion of the second objective is that we have demonstrated the importance of studying the different combination of noncovalent interactions, the general trends are:

- The strongest interaction present in a given complex usually dominates the interaction; however it is less reinforced by the presence of a weaker interaction.
- Cooperativity effects can be explained using the electrostatic term, although depending on systems and interactions, this trend can change.

Therefore, the equations and tools described in Chapter 4 are really valuable to know the best combination of forces.

The third objective was the evaluation of the influence of anion–π interactions in other Chemistry fields.

This objective was born because of the need to evolve in the research of anion–π interaction. We need to go one step further. It was necessary to investigate if anion–π interaction is relevant in different fields of chemistry such as Biological Chemistry or Chemistry of Excited States.

With these questions in mind, we performed two different studies to achieve our third objective.

One of these studies was the search of anion–π interaction in a biological system where it has a relevant function, for instance in the inhibition or activation of the enzyme. This objective was achieved with the finding of anion–π interactions in the urate oxidase enzyme and in flavoproteins. Specifically, in the urate oxidase the anion participates in the inhibition of the enzyme, which is located at the active centre of the protein by means of anion–π interaction. This example is an illustration of the significance that anion–π could have in Enzymatic Chemistry, which is a basically unexplored field.

The second study is related to the analysis of alternative modes of anion–π interactions that can be useful to definitely expand the anion–π interaction to other fields. Above all, in this case we have modified the nature of the anion. In one case the anion is an open-shell system instead of a habitual close-shell, and in the other case a transition-metal ion is incorporated to the anion. The results obtained show that the anion–π interactions are less favourable when the anion is an open-shell system. However, the interaction is stronger in anionic transition metal complexes than in standard anion–π interactions. This opens the possibility to introduce anion–π interactions in Catalysis.

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Annexes

ANNEX I. COMPUTATIONAL METHODS

Computational chemistry has become a very important tool in modern chemistry to understand the structure, properties and reactivity of chemicals. Below is a brief description of computational methods used during the development of this thesis. For more extensive treatment general literature is available.[i.1,i.2,i.3]

I.I. LEVELS OF THEORY

I.I.1. QUANTUM MECHANICS

Quantum mechanics (QM) is the correct mathematical description of the nuclei and electrons behaviour at an atomic level. QM was born at the beginning of the 20th century[i.4] and as the application of new quantum concepts to study atomic and molecular systems has a fast and wide acceptance. In its early stages, some semi-empirical approximations were developed as Hückel[i.5,i.6,i.7] and extended-Hückel methods.[i.8]

The microscopic systems, which present corpuscular and wave behaviour, obey the quantum mechanics laws. These were discovered by Heisenberg, Born and Jordan in 1925 and by Schrödinger in 1926. Using the quantum mechanics the interpretation and prediction of the molecular structure and properties as well as chemical reactivity is possible.

The molecular systems are defined by a wave function, which Schrödinger equation accomplishes:

$$H\Psi = -\left(h/_i\right)\left(\partial\Psi/_{\partial t}\right)$$

Equation I.1

When the solution to this equation is found without using any empiric data, the methods used are named *ab initio* (from Latin, *at the beginning*). Equation I.1 can only solve one-electron systems in their exact form, however, for multiple electron systems it is always necessary to make approximations to simplify the calculations, which lead to different theoretical methods useful in treating molecular systems, so solving the Schrödinger equation in its time-independent form,[i.9] becomes a milestone equation, under the Born-Oppenheimer approximation. The wave function (Ψ) is related with ρ by definition. The electron density is defined as a multiple integral over the spin coordinates of all electrons and moreover one of the spatial variables (Equation I.2).

$$\rho(\vec{r}) = N \int \dots \int |\Psi(\overrightarrow{x_1}, \overrightarrow{x_2}, \dots, \overrightarrow{x_N})|^2 \, ds_1 d\vec{x}_2 \dots d\vec{x}_N$$

Equation I.2

The electron density ρ determines the probability of finding one of the *N* electrons within an infinitesimal element of space with arbitrary spin while the other electrons have arbitrary positions and spin in the state represented by the wave function Ψ.

I.I.1.1. Ab Initio Calculations

As mentioned above, for many-body problems there is not a "correct" solution; we therefore require some means to decide whether one proposed wave function is "better" than another. The *variation theorem* provides us with a mechanism for answering this question. The theorem states that the energy calculated from an approximation to the true wave function will always be greater than the true energy. Consequently, the better the wave function, the lower the energy. The "best" wave function is obtained when the energy is a minimum. At the minimum, the first derivative of the energy, δE, will be zero. The Hartree-Fock (HF) equations (Equation I.4) are obtained by imposing this condition on the expression for the energy, subject to the constraint that the molecular orbitals remain orthonormal. The orthonormality condition is written in terms of the overlap integral, S_{ij}, between two orbitals *i* and *j* (see Equation I.3).

$$S_{ij} = \int x_i x_j \, d_\tau = \delta_{ij}$$

Equation I.3

$$\delta E - 2\delta \sum_i \sum_j \varepsilon_{ij} S_{ij} = 0$$

Equation I.4

The solution of this equation is rather complicated. However, a qualitative picture is possible. The major difference between polyelectronic systems and systems with single electrons is the presence of interactions between the electrons, which are expressed as Coulumb and exchange integrals. Suppose we are given the task of finding the "best" (i. e. lowest energy) wave function for a polyelectronic system. We wish to retain the orbital picture of the system. The problem is to find a solution which simultaneously enables all the electronic motions to be taken into account. After the mathematical treatment, we arrive to an equation where each electron has been assumed to move in a "fixed" field comprising the nuclei and

the other electrons. This has important implications for the way in which we attempt to find a solution, for any solution that we might find by solving the equation for one electron will naturally affect the solutions for the other electrons in the system. The general strategy is called a *self-consistent field* (SCF) approach. The SCF method gradually refines the individual electronic solutions that correspond to lower and lower total energies until the point is reached at which the results for all the electrons are unchanged, when they are said to be *self-consistent.*

The most significant drawback of Hartree-Fock theory is that it fails to adequately represent electron correlation. In the self-consistent field method the electrons are assumed to be moving in an average potential of the other electrons, and so the instantaneous position of an electron is not influenced by the presence of a neighboring electron. In fact, the motions of electrons are correlated and they tend to "avoid" each other more than Hartree-Fock theory would suggest, giving rise to a lower energy. The correlation energy is defined as the difference between the Hartree-Fock energy and the exact energy. Neglecting electron correlation can lead to some clearly anomalous results, especially as the dissociation limit is approaching. The electron correlation is crucial in the study of dispersive effects, which play a major role in intermolecular interactions.

Møller and Plesset proposed an alternative way to tackle the problem of electron correlation. Their method is based upon Rayleigh-Schrödinger perturbation theory, in which the "true" Hamiltonian operator (*H*) is expressed as the sum of "zeroth-order" Hamiltonian (H^0) and a perturbation (*H'*). The parameter λ further indicates the smallness of the perturbation (see Equation I.5). In order to calculate higher-order wave functions we need to establish the form of the perturbation. This is the difference between the "real" Hamiltonian and the zeroth-order Hamiltonian.

$$H = H^0 + \lambda H'$$

Equation I.5

On the other hand, the sum of the zeroth-order and first-order energies thus corresponds to the Hartree-Fock energy. To obtain an improvement on the Hartree-Fock energy it is therefore necessary to use Møller-Plesset perturbation theory to at least second order. This level of theory is referred to as MP2. Third- and fourth-order Møller-Plesset calculations (MP3 and MP4) are also available as standard options in many *ab initio* packages. The advantage of many-body perturbation theory is that it is size-independent. However, Møller-Plesset

perturbation theory is not variational and can sometimes give energies that are lower than the "true" energy. These calculations are computationally intensive; however, they are the most popular way to incorporate electron correlation into molecular quantum mechanical calculations.

To carry out the geometry optimizations of the studied compounds in this thesis, as well as the single point calculations done, different levels of theory have been used. Initially, most of the molecular species have been optimized using the Hartree-Fock methodology (HF). The geometries obtained with this method are used as the initial point in high-level optimizations, e.g., electron correlation methods.

As commented above, the MP2 method[i.10] is the most popular and simple method that includes electron correlation, by means of the perturbation theory application (in this case, of second order) to the HF determinant. In spite of the high computational cost of the Møller-Plesset (MP2) methodology in comparison with HF theory, other post-HF methods such as Configuration Interactions (CI) or Coupled Cluster (CC) require more computational resources, intractable in medium-large system sizes. The RI-MP2 method (*Resolution of the Identity* MP2)[i.11,i.12] also treats the electron correlation and, thanks to the use of auxiliary basis set to avoid dealing a complete set of two-electron repulsion integrals, is a calculistic methodology that consumes less time and resources than MP2.

It is very normal to use the *frozen core* (FC) approximation that only estimates the electron correlation energy associated to the valence electrons, since the important chemical changes take place in the valence orbitals while the intern orbitals are practically constant. In general, the calculations performed in this thesis are done using the *frozen core* approximation. However, in the concrete cases where we have included all electrons of the system in the calculation of electron correlation energy, this is explicitly indicated as *full electron* (full).

I.I.1.2. Density Functional Theory

Density Functional Theory (DFT) represents an alternative methodology for evaluating the energy and other properties of a polyelectronic system.[i.13] Rather than having to work with a complex and non-observable Ψ, DFT uses functional of the electron density (ρ), which is directly related with Ψ, physically observable and easy to handle, presenting the basis for DFT. This methodology introduces the electron correlation effects in the Schrödinger equation resolution by means of approximate alternative methods.

The two major theoretical pillars of the DFT were established by Hohenberg and Kohn theorem postulated in 1964.[i.14] The first Hohenberg-Kohn theorem states that the external potential (e. g. due to the nuclei) is a unique function of the ground state electron density; since, in turn an external potential fixes the Hamiltonian and determines the energy of the system and all other ground state electronic properties. The second theorem states that in any system the ground state functional for energy delivers the lowest energy if and only if the input density is the true ground state density. This theorem is only the extension of variational principles to the density functional theory. In 1965 Prof. Kohn and Prof. Sham suggested an avenue for how the unknown universal functional in DFT can be approached.[i.15] Their approach consists of reducing the intractable many-body problem of interacting electrons in a static external potential to a tractable problem of non-interacting electrons moving under an effective potential. The typical representation of Kohn-Sham equations is presented in Equation I.6.

$$F[\rho(\vec{r})]\varphi_i(\vec{r}) = \varepsilon_i\varphi_i(\vec{r})$$

Equation I.6

$F[\rho(\vec{r})]$ is the Kohn-Sham functional and ε_i is the orbital energy of the corresponding Khon-Sham orbital φ_i. The Kohn-Sham functional can be divided in different parts as presented in the following Equation I.7,

$$F[\rho(\vec{r})] = T_s[\rho(\vec{r})] + J[\rho(\vec{r})] + E_{xc}[\rho(\vec{r})] = T_s[\rho(\vec{r})] + J[\rho(\vec{r})] + (T_c[\rho(\vec{r})] + E_{ncl}[\rho(\vec{r})])$$

Equation I.7

$T_s[\rho(\vec{r})]$ is the kinetic energy in a non-interacting system, $J[\rho(\vec{r})]$ is the classical coulomb interaction and $E_{xc}[\rho(\vec{r})]$ is the exchange-correlation energy. This term is defined as the sum of two terms: the residual part of the true kinetic energy, $T_c[\rho(\vec{r})]$ and the non-classical electrostatic contributions $E_{ncl}[\rho(\vec{r})]$. In other words, the exchange-correlation energy $E_{xc}[\rho(\vec{r})]$ is the functional which contains everything that is unknown or we do not know exactly how to handle. The Kohn-Sham approach moves the search of an unknown universal functional to a search of an unknown universal exchange-correlation functional.

The Kohn-Sham approach establishes the guidelines for the construction of the universal functional however the unknown exchange-correlation energy has to be approximated. The most relevant approximations are LDA, GGA, meta-GGA and hyper-GGA. These approximations are the first steps on the Jacob's ladder of exchange-correlation functional. This is an imaginary ladder drawn by Perdew[i.16] that connects the "Hartree world" where there is no exchange or

correlation energy with the "Heaven of Chemical Accuracy" where the error in bonding energies is less than one kcal·mol^{-1}.

The central idea of **Local Density Approximation** (LDA) is a hypothetical uniformed electron gas. In this system the electrons move around a distribution of positive background charges that make the system electrically neutral. The number of electrons *N* and the volume of the gas *V* are considered to approach infinity and the electron density attains a constant value anywhere in *V*. The LDA functional considered exchange-correlation has a local effect and only depends on the electron density value in each point in the space. The LDA exchange part is represented by the known exchange energy of one electron in a uniform electron gas at one particular density. There is no analytical expression for the correlation part; moreover there are very accurate Monte-Carlo simulations for a homogeneous electron gas.[i.17] Even the relative simplicity of LDA functional, acceptable results are achieved, but their moderate accuracy is certainly insufficient for most chemical applications.

In the 80's, the **Generalized Gradients Approximations** (GGA) methods were developed. They introduced the density gradient ($\nabla\rho$) as well as the electron density (ρ) at each point in space. The corrections from the gradient are added to the local definition of exchange-correlation redefining $E_{xc}[\rho(\vec{r})]$ functional. Nowadays, there are many GGA functionals based on different formulations of the exchange and correlation parts as Becke-Perdew (BP86),[i.18] Perdew-Burke-Ernzerhof (PBE),[i.19] Becke-Lee-Yang-Parr (BLYP),[i.20] etc.

The corrections introduced by GGA highly improved the results with respect to LDA, achieving an acceptable accuracy. The deviations on bond energies are partially corrected and accordingly the total and bonding energies too. This derives in molecular geometries that are in better agreement with the experimental ones. Although the GGA functionals have problems in the description of "weak" interactions as dispersion,[i. 21] π–stacking,[i. 22] etc., that are completely neglected in their formulation, these functionals are widely used in computational chemistry for systems without relevant "weak" interactions, e.g., many organometallic complexes.

The main errors of the previous functionals are found in the exchange part description because it is usually known that the exchange contributions are significantly larger in absolute numbers than the corresponding correlation effects. The **hybrids functionals are** an approach to minimize this problem with a partial incorporation of the Hartree-Fock exact exchange-energy in the previous functional. There are many hybrids functionals with different percentage of exact exchange (ee). Today, one of the most used hybrid functionals is the

B3LYP (20% of ee).[i.23] It has become a reference in computational chemistry showing remarkable results in a wide variety of properties and reactions. Its exchange part is made up of 80% of Becke, 3-parameters exchange functional and 20% Hartree-Fock exact exchange.[i.24] The Becke's functional[i.20,i.25,i.26] includes three semi-empirical parameters adjusted in order to minimize the atomization and ionization energies error as well as the proton affinities in the G2 set of molecules. The correlation part is constructed by Lee-Yang-Parr (LYP) correlation functional.[i.27]

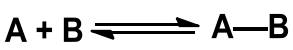
I.I.2. BASIS SET FUNCTION

One of the inherent approximations for all *ab initio* methods is the introduction of a finite set of function basis. An exact representation of a molecular orbital can only be achieved using a complete basis set, i.e., infinite, which is practically impossible. Obviously, the bigger the basis set, the better the representation, but the computational cost is larger; therefore, the idea is to use the smallest basis set possible without compromising the efficiency of the calculation.[i.28]

Due to computational efficiency, the Gaussian type orbitals or GTO are the most used basis set in electronic structure calculations. Moreover, it has previously been shown that cation–π and anion–π interactions can be correctly studied by means of this kind of function. For this reason, the 6-31++G** basis set of Pople has been widely used throughout this thesis, which includes polarization and diffuse functions for all atoms. The former functions are necessary to take into account the polarization component, which plays a transcendent role in the interactions studied. The latter functions are added to correctly represent the greater electron density in further areas of the atomic nuclei. These functions are necessary when the complexes studies present ionic species. However, to perform RI-MP2 calculations with TURBOMOLE[i.29] programme, the auxiliary basis set 6-31++G** necessary to perform the calculation is not included, and therefore the VDZ auxiliary set of Alrichs[i.30] is used instead. In addition to basis set of Pople, in some studies the double and triple-zeta basis sets of Dunning (aug-cc-pVXZ, X = D, T) has been used.

I.I.3. BASIS SET SUPERPOSITION ERROR (BSSE)

Suppose we wish to calculate the energy of formation of a bimolecular complex, such as the specific supramolecular system (AB) obtained from the following reaction between A and B:



One might expect that this energy value could be obtained by first calculating the energy of a single A and B molecules, then calculating the energy of the dimer (AB), and finally subtracting the energy of the two isolated molecules (the 'reactants') from that of the dimer (the 'products').

Its interaction energy can be obtained according to the approximation (Equation I.8):

$$\Delta E_{interac.} = E(AB)^{*}_{ab} - E(A)_{a} - E(B)_{b}$$

Equation I.8

Where:

- * indicates that the optimized geometry complex is used,
- *a*, *b* and *ab* subscripts mean that the energy calculation have been done using the basis set of *A*, *B* and *AB*, respectively.

The favourable complexation processes present negative energies, so the more negative the energies, the more favourable the formation of complex. It is worth mentioning that during the thesis, the terms “greater” and “smaller” have been used in their absolute value. Therefore, if we compare the favourable formation of two complexes and one possesses greater interaction energy then it is more favourable.

However, the energy difference obtained by such an approach will invariably be an overestimate of the true value. Ideally, the best solution would be to use a *complete basis set* (CBS) to avoid this overestimation. Since this solution is not possible, the first condition is to use the same basis set to perform all the calculations and compare interaction energies. The discrepancy arises from a phenomenon known as *basis set superposition error* (BSSE). As the two A and B molecules approach each other, the energy of the system falls not only because of the favourable intermolecular interactions but also because the basis functions on each molecule provide a better description of the electronic structure around the other molecule. Hence, in a complex, the basis set of one molecule can help to compensate the incomplete basis set of another molecule and *vice versa*. In this way the energy is artificially greater (more negative) and the interaction energy is overestimated.

It is clear that the BSSE would be expected to be particularly significant when small, inadequate basis sets are used (e.g. the minimal basis STO-nG basis sets) which do not provide for an adequate representation of the electron distribution far from the nuclei, particularly in the region where noncovalent interactions are strongest.

The most used method to correct this error is the *Counterpoise* technique (CP).[i.31] By this method, the BSSE is estimated as the difference between the energies of the monomers with the regular basis set and the energies calculated with the complete basis set for the entire complex (Equation I.8).

To estimate how much of this energy of complexation is due to the BSSE, it takes four additional energy calculations. Using the basis set *a* for A, and basis set *b* for B, are calculated each of the two fragments in the geometry of the complex with the complete basis set *ab*. For example, the energy of A is calculated in the presence of normal basis set functions *a* and with the basis set functions *b* of fragment B located in the corresponding nuclear positions, but without B nuclei present. These basis set functions located at fixed points of the space is often referred to as ghost orbitals. The energy of fragment A will be lowered due to ghost functions, since the basis set becomes more complete. The correction of *Counterpoise* (CP) is defined as shown the Equation I.9.

$$\Delta E_{CP} = E(A)^*_{ab} + E(B)^*_{ab} - E(A)^*_a - E(B)^*_b$$

Equation I.9

The interaction energy corrected by means of *Counterpoise* technique is expressed as follows in Equation I.10. With the notation used before, the interaction energy can also be written as shown in Equation I.11.

$$\Delta E^{BSSE}_{interac.} = \Delta E_{interac.} - \Delta E_{CP}$$

Equation I.10

$$\Delta E^{BSSE}_{interac.} = E(AB)^*_{ab} - [E(A)^*_{ab} + E(A)_a - E(A)^*_a] - [E(B)^*_{ab} + E(B)_b - E(B)^*_b]$$

Equation I.11

When the complex is formed from three components, the interaction energy is calculated as:

$$\Delta E_{interac.} = E(ABC)^*_{abc} - E(A)^*_a - E(B)^*_b - E(C)^*_c$$

Equation I.12

In these cases, the BSSE estimation is much more complicated to calculate,[i.32] although some approximations[i.33] were proposed that result in a simple calculation without the introduction of big errors, as expressed in Equation I.13.

$$\Delta E_{CP} = E(A)^*_{abc} + E(B)^*_{abc} + E(C)^*_{abc} - E(A)^*_a - E(B)^*_b - E(C)^*_c$$

Equation I.13

Therefore, the corrected interaction energy is (Equation I.14):

$$\Delta E_{interac.}^{BSSE} = E(ABC)_{abc}^{*} - E(A)_{a} - E(A)_{abc}^{*} + E(A)_{a}^{*} - E(B)_{b} - E(B)_{abc}^{*} + E(B)_{b}^{*} - \\ -E(C)_{c} - E(C)_{abc}^{*} + E(C)_{c}^{*}$$

Equation I.14

Fortunately, the complexes that present monatomic ions, it holds that $(N)_{n}^{*} = E(N)_{n}$ and the corrected energy calculation is less arduous.

I.I.4. MOLECULAR INTERACTION POTENTIAL

The molecular electrostatic potential (MEP)[i. 34] can be defined as the electrostatic component of the interaction energy between the charge distribution of one molecule and a positive point charge (and therefore Q_B = +1), and can be calculated from Equation I.15:

$$V_{MEP} = \sum_{A}\sum_{B}\frac{Q_B Z_A}{|R_B - R_A|} - \sum_{B} Q_B \sum_{i}^{occupied}\sum_{\mu}\sum_{\vartheta} c_{\mu i} c_{\vartheta i} \left\langle \varphi_{\mu} \middle| \frac{1}{R_B - r} \middle| \varphi_{\vartheta} \right\rangle$$

Equation I.15

Where:

- Z_A is the atomic number of atom A,
- Q_B is the classical point charge,
- r indicates the electron position,
- R_A indicates the nuclei location of atom A,
- R_B indicate the position of classical atom B,
- φ is the basis set used for molecule A,
- $c_{\mu i}$ is the orbital atomic coefficient μ in the molecular orbital i.

The first term represents the nuclear electrostatic repulsion between the nuclei A and a classical particle; while the second corresponds to the electrostatic attraction originated between the electrons of A and the classical particle B.

The MEP formalism enables the rigorous calculation of electrostatics interactions between any classical charge and a perturbed molecule, without considering the induction, dispersion or repulsion effects. This defect can be solved by means of the addition of the classic term of Lennard-Jones,[i.35] which is mathematically simple but promotes a good description of van der

Waals forces. The addition of this term to the MEP expression defines what is called **Molecular Interaction Potential** known as MIP.[i.36]

$$V_{MIP} = V_{MEP} + \sum_{A} \left(\frac{\varepsilon_{AB}}{\gamma_{AB}^{12}} - \frac{2\varepsilon_{AB}}{\gamma_{AB}^{6}} \right)$$

Equation I.16

The Lenard-Jones potential term is shown in Equation I.16, where ε_{AB} and γ_{AB} are calculated as the following classical formulas (see Equation I.17Equation I.18):

$$\varepsilon_{AB} = \sqrt{\varepsilon_A \varepsilon_B}$$

Equation I.17

$$\gamma_{AB} = \frac{R_{vw}^{A} + R_{vw}^{B}}{R_{AB}}$$

Equation I.18

- ε_A and R_{vw}^{A} are the hardness and the van der Waals radius of atom A, respectively.
- ε_B and R_{vw}^{B} are the hardness and the van der Waals radius of atom B, respectively.

In the programme used to do this calculations (MOPETE),[i.37] these parameters have been taken from TRIPOS/5 force field.[i.38] However, to do the present studies, some modifications over the classical atoms have been included with the aim to treat correctly anionic atoms. Thus, *in house* parameterization of fluoride anion has been done, assigning the values: R_{vw} = 2.170 Å and ε_B = 0.061 kcal·mol^{-1}. The van der Waals radii of the anions chloride and bromide (2.470 and 2.575 Å, respectively) was estimated following the methodology developed by G. Ujaque and collaborators,[i.39] while their hardness were taken from the TRIPOS/5 force field[i.38] (0.314 and 0.287 kcal·mol^{-1}, respectively). Finally, for the cations the van der Waals radii and hardness parameters values were taken from OPLS[i. 40] and CHARMM27[i. 41] force fields, respectively, being R_{vw} = 1.869 Å and ε_B = 0.048 kcal·mol^{-1} for Na^+ and R_{vw}=2.467 Å and ε_B=0.087 kcal·mol^{-1} for K^+ cation.

Additionally, if we include polarization effects calculated by means of second-order perturbation treatment[i.42] we obtain the **Molecular Interaction Potential with polarization** or MIPp definition (Equation I.19):[i.43]

$$V_{MIPp} = V_{MIP} + \sum_{j}^{virtual} \sum_{i}^{occupied} \frac{1}{\varepsilon_i - \varepsilon_j} \left\{ \sum_{\mu} \sum_{\vartheta} c_{\mu i} c_{\vartheta j} \left\langle \varphi_\mu \left| \sum_{B} \frac{Q_B}{|R_B - r|} \right| \varphi_\vartheta \right\rangle \right\}^2$$

Equation I.19

Where ε is the energy of virtual (j) and occupied (i) molecular orbitals.

Along these lines, the total interaction energy calculated with the MIPp is the sum of the three mentioned contributions: electrostatic, van der Waals and polarization, as shown in Equation I.20.

$$E_t^{MIPp} = E_e + E_{vw} + E_{pol}$$

Equation I.20

I.I.5. AROMATICITY: NUCLEUS-INDEPENDENT CHEMICAL SHIFT

The aromaticity plays an important role in Chemistry. In fact, the stability of some molecular structures, as well as the success or failure of some chemical reactions is due to the gain or loss of aromaticity. Despite the lack of clear and unambiguous definition of aromaticity, this chemical concept is deep-seated in the chemical community.[i.44] The aromaticity is not an observable parameter, and cannot measure directly. For this reason there are several definitions of aromaticity based on structural (*Harmonic Oscillator Model of Aromaticity*), magnetic (*Nucleus-Independent Chemical Shift*) and/or energetic criteria (*Aromatic Stabilization Energies, ASE*). Below, the magnetic criterion is described in more detail because it is used in this thesis.

I.I.5.1. Nucleus-Independent Chemical Shift (NICS)

Most of the organic molecules do not possess permanent magnetic moments and, consequently, are weakly diamagnetic. In this case, in a magnetic field small magnetic fields are generated opposite to the first. Marked diamagnetic anisotropy is presented by aromatic molecules, which is known as diamagnetic ring flow. The ring flow induced by external magnetic fields is much bigger than small flows associated to σ electrons. For this reason, the magnetic indexes of aromaticity are based on this ring flow due to the π electrons.[i.45] The atypical chemical shift in Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H-NMR) of aromatic molecules has been used as indicators of the ring flow effects.[i.46]

If a magnetic flow goes through the aromatic ring, a secondary and opposite magnetic field is induced inside and intensified outside of the ring. As can be observed in Figure I.1, in regions above, below and in the ring, the apparent field is weakened, increasing the shield, whereas the opposite occurs in the outer regions of the ring.

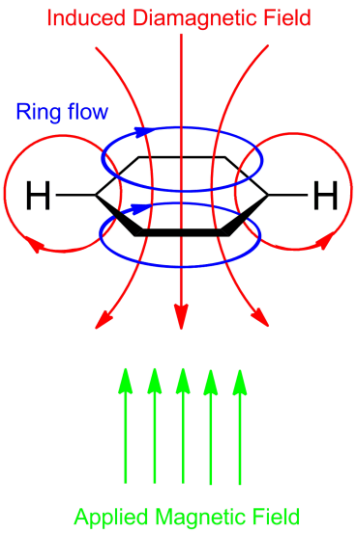


Figure I.1. Model of ring flow in aromatic systems.

Probably, the most widely used index based on magnetic criteria is the Nucleus-Independent Chemical Shift (NICS) proposed by P. v. R. Schleyer *et. al*.[i.47] The NICS criterion is the negative value of absolute magnetic shielding, which originally was evaluated in the ring centre. Negative values involve strong shielding produced by diatropic ring flow and are associated to aromaticity. However, positive values correspond to anti-aromaticity (paratropic ring flow). The values of NICS in the geometric centre of the ring are highly influenced by local paratropic effects that mainly emerge from σ bonds, especially in small rings. For this reason, NICS values in this thesis have been estimated at 0.6 and 1 Å above the geometric centre with the aim to reflect essentially the π effects derived from ring flow.[i.48,i.49] NICS index was calculated using the GIAO methodology (*Gauge Invariant Atomic Orbitals*)[i.50] at the HF/6-31++G** level of theory.

I.I.6. ATOMS IN MOLECULES THEORY (AIM)

The R.F.W. Bader's theory of **Atoms in Molecules** (AIM)[i.51,i.52] is an intent to rigorously define the atom and chemical bond from the polielectronic wave function. Principally being based on Hellman-Feynman theorem,[i.53] it shows that all properties of one molecule are determined by the electron density distribution (ρ). Hence, the AIM theory is a formalism that permits defining the atom concepts in molecule, chemical bond, molecular structure and

stability, structural change and, moreover, give descriptions of different kinds of bonding and atomic interactions according to the ideas of descriptive chemistry.

An important part of the AIM theory is the topological analysis of ρ, which can give a good description, depending on its gradient vector and stationary points. The ρ gradient ($\nabla\rho$) or trajectory is a vector that is directed in the direction of the greater slope towards the maximum. In a molecule, all the trajectories start at the infinity and finish at a nuclei, without crossing each other. In this way every nucleus acts as an attractor of different trajectories, which is named attractive basin. It has been demonstrated[i.54] that it can divide a system in regions or quantic subsystems in which all the total system magnitudes are well-defined through zero flux surfaces of $\nabla\rho$. In general, each and every one of the delimited volumes of these surfaces have single atomic nucleus, so are named atomic basin.

The stationary points of the electron density function ($\nabla\rho = 0$) are called critical points (CP). Their nature is determined by means of the hessian matrix of ρ, whose eigenvalues are named curvatures and their signs determine the kind of CP. A negative curvature indicates that ρ is a maximum in the direction of the associated eigenvector, while being a minimum when it is positive. The rank of a CP, described as ω, is the number of curvatures different from zero. Their classification designed as σ, is the sum of all their algebraic signs. CPs are labelled giving the pair value (ω, σ). The CPs of ω=3 correspond to ρ distributions in molecules with stable nuclear configurations and are the interest of this study. There are four possible types of CP of ω=3.

- (3,–3) is a local maximum of the electronic density and corresponds to nuclei.
- (3,–1) is an inflexion point and it is located between both bonded nuclei (BCP).
- (3,+1) is also an inflexion point and occurs as consequence of particular geometric distributions of bonds defining elements in molecular structure. When bonds are disposed in such a way that bonded atoms ring form, a ring CP (RCP) in its interior is generated.
- (3,+3) is a local minimum that is associated to the structural element generated when several rings form a cage and is therefore named cage CP (CCP).

Due to ρ(r) being a continuous function, the total number of CPs present in the system should satisfy the Poincaré-Hopf relation (Equation I.21):[i.55]

$$n - b + r - c = 1$$

Equation I.21

Where *n*, *b*, *r*, and *c* are the total number of nuclei, bond, ring and cage CPs, respectively.

I.I.7. ATOMIC CHARGES

The charge assigned over the atoms has been a valuable tool for chemists, despite the idea that the atomic charge in a molecule is not really an observable chemical quantity. The atomic charges have been a key concept in the understanding of many types of chemical reactions, and are of great importance in the interpretation of numerous phenomena such as the dipolar moment or chemical shift in NMR; moreover they are important parameters in structure-property and structure-activity relations. A lot of schemes have been proposed, both quantum-chemical and empirical, either to assign the electron density distribution between the atoms of a molecule or charges of these atoms. Traditionally, the Mulliken method[i.56,i.57] and electrostatic potential have been the most useful in defining atomic charges.

The methods based on the population analysis distribute the electronic density between nuclei, so that every atom has a specific number of electrons (not necessarily integer) associated to it. This partition provides a way to calculate the atomic charge over every nucleus. Nevertheless, no quantum-mechanics operator exists for the atomic charge and the partition scheme is arbitrary.

The Mulliken's population analysis[i.56,i.57] is a trivial calculation once it has reached the consistency in the Self Consistent Field (SCF) that the electronic population needs in every orbital ($P_{\mu\mu}$) and in the overlapping area ($S_{\mu\nu}$), as shown in Equation I.22 for the atomic charge over atom A:

$$q_A = Z_A - \sum_{\mu=1}^{K} P_{\mu\mu} - \sum_{\omega=1}^{K} \sum_{\vartheta=1,\vartheta\neq\mu}^{K} P_{\mu\vartheta} S_{\mu\vartheta}$$

Equation I.22

Thus, the atomic charge is estimated subtracting the electronic population in each of the orbitals of the atom from the nuclear charge and the overlapping population is divided equally between the two atoms, regardless differences in the type of atom (coefficient, electronegativity, etc). The Mulliken's population analysis is widely used due to its simplicity; however it presents a great dependency upon the basis set used.[i.58,i.59]

The electrostatic potential methods determine atomic charges fitting the electrostatic potential to a series of points surrounding the molecule. These points can be chosen in multiple ways, but they should be in a region where it is more important to define the molecular interactions correctly, that is to say over the van der Waals radii of the atoms. Once the electrostatic potential has been calculated (Equation I.15) at these points, by means of mathematical adjustment, the partial atomic charges that best reproduced the potential are derived. This procedure is done through the least-squares fit, that is normally combined with Lagrange multiplier as described in the literature.[i.60]

The CHelp (*CHarges from Electrostatic Potential*)[i.60] method uses spherical layers, 1 Å apart, centred in every atom with points symmetrically distributed on its surface. The points lie outside of the van der Waals surface and up to 3 Å from it. On the other hand, in the CHelpG method,[i.61] the points are regularly distributed in a cubic grid with a big density (are spaced 0.3-0.8 Å) and located from the van the Waals surface up to 2.8 Å distance from it.

The Merz-Kollman scheme[i.62] uses the Connolly algorithm[i.63] to generate five spherical surfaces of points around every atom. These surfaces are found at distances of 1.4, 1.6, 1.8 and 2.0 times the van der Waals atomic radius, all with a density of 1 point/Å^2. The molecular surface is built taking into account the union of all these surfaces for every atom and eliminating the points that are within of multipole of van de Waals radius of any atom. Both CHelp and Merz-Kollman methods are derived from electrostatic potential.

The AIM theory[i.51,i.52] gives an alternative way to assign electrons between the atoms of one molecule, based on the flux surfaces that determine the atomic basin. The assigned population of every atom is calculated by means of the numeric integration of ρ in its atomic basin. This approximation is very attractive, as it eliminates the arbitrary of atom division in the molecule. However, the procedure is computationally very complicated, and the resulting atomic charges do not reproduce well the electrostatic potential when they are used in a monopole approximation (as happens in a great number of simulation packages).[i.64]

I.I.8. CRYSTALLOGRAPHIC DATABASE

The Cambridge Structural Database or CSD[i.65,i.66,i.67,i.68] is an adequate tool to carry out searches of crystallographic structures.[i.69,i.70]

Throughout this thesis, the CSD tool has been used mainly to find molecular interactions between π systems and different electronegative, neutral or negatively charged atoms with the aim to complement the theoretical study.

These interactions must correspond to noncovalent bonds between the electronegative atoms and all the atoms that form the aromatic system to ensure a correct interaction. Therefore imposing the condition of contact between the interacting atom and all atoms of the π system, using the definition that includes the CSD in their leading searchers questv5, [i.71] it is detailed that the distance must be equal or less to the sum of van der Waals radii in contact, plus 1 Å. For a recent discussion on this topic see references i.72 and i.73.

I.I.9. COMPUTATION PROGRAMMES

In this section a brief description is found regarding levels of theory and programmes used along this thesis to calculate the complexes and their properties.

All the complexes studied are fully optimized. Most of the optimizations have been done with TUBOMOLE programme (versions 5.7 and 6.0)[i.29] at the RI-MP2 level, except in two cases properly indicated where the optimizations have been performed with Gaussian 03[i.74] and 09[i.75] at the MP2 level. The interaction energy with and without the *Basis Set Superposition Error* (BSSE) correction was calculated in all cases at the same level of theory than the geometric optimizations. In some specific cases, the interaction energy together with BSSE were calculated at a higher level of theory, explicitly indicated as for example RI-MP/aug-cc-pVTZ//RI-MP2/aug-cc-pVDZ. This notation means that the system has been optimized at the RI-MP2/aug-cc-pVDZ level and the single point calculation at the RI-MP/aug-cc-pVTZ level. Most of jobs carried out in this thesis have been performed with the *frozen core* approximation and therefore, in these cases it is not specified along the text. Conversely, when the calculations were performed with *full core* approximation, it is specified in the text. All the optimizations were performed at C_1 point group of symmetry, except in specific cases where other possible conformations of complexes have not been considered because the ultimate aim of that study is to verify the influence of several noncovalent interactions shown in the article. In these cases the highest possible abelian point group of symmetry is applied.

Calculations in the presence of solvent have been carried out using the Conductor-Like Screening Model (COSMO)[i.76] as implemented in TURBOMOLE programme.[i.29] In some studies, we have also extrapolated the complete basis set (CBS) limit using two points method of Helgaker and co-workers.[i.77]

The calculations of molecular interaction potential are done using the MOPETE programme,[i.37] at HF/6-31++G** level of theory. In some studies the triple-zeta basis set of Pople (6-311++G**) has been used.

The AIM analysis is carried out using the AIMPAC[i.78] or AIM2000 programmes[i.79] generally from wave function at same level of theory that the optimized structures obtained with Gaussian 03[i.74] or 09[i.75] programme. In all articles the level of theory used to calculate the wave function is indicated.

The quadrupole moments were estimated with the CADPAC[i. 80] and MOLPRO[i. 81] programmes. The charge transfer in complexes was evaluated by using the Merz-Kollman (Q_{MK}) scheme for deriving atomic charges at the same level of theory that optimized structures obtained with Gaussian 03[i.74] or 09[i.75] programmes. In most of the articles published Mulliken charges (Q_{Mull}) are also included for comparison purposes. The molecular polarizabilities were computed using Gaussian 09[i.75] programme at the MP2/6-31++G** level of theory. NICS values were computed at the GIAO-HF/6-31++G** level of theory,[i.50] because previous studies have demonstrated that reliable results are obtained at this level of theory.[i.49] The Molecular Electrostatic Potential Surfaces (MEP) calculated were performed with Spartan programme.[i.82]

Other interesting theoretical studies were related to the molecular natural orbitals and spin density calculations computed at the RI-MP2/aug-cc-pVDZ level of theory with TURBOMOLE programme.[i.29] To represent the molecular orbitals we have used the MOLDEN programme.[i.83]

The crystallographic search has been done using the Cambridge Structural Database[i.65] and with the leading searcher questv5[i.71] using the latest update available to extract the geometries: 5.29 version (February 2008) or 5.30 version (February 2009). The Mercury and Vista programmes[i.84,i.85, i.71] have also been used to visualize the geometries and to analyse the geometric parameters, respectively. The search of biological molecules has been done in the Protein Data Bank (PDB).[i.86]

All calculations have been carried out in our own workstation and the Centre de Tecnologies de la Informació of UIB. Some calculations have been also carried out at the Centre de Computació de Catalunya (CESCA).

I.II. NOTES AND REFERENCES

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ANNEX II. EXPERIMENTAL SECTION

II.I. GENERAL INFORMATION AND INSTRUMENTATION

Unless stated otherwise, all preparations were carried out under Argon inert atmosphere and using standard techniques. All reagents were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from a solvent purification system SPS-400-6 from Innovative Technologies, Inc.

All solvents were of HPLC grade quality, obtained commercially and used without further purification.

Routine ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 (300.1 MHz for ^{1}H-NMR) and Bruker Avance 500 (500.1 MHz for ^{1}H-NMR and 125.6 MHz for ^{13}C) ultrashield spectrometer. The deuterated solvents (Aldrich) used are indicated in the experimental part; chemical shifts, δ, are given in ppm, relative to TMS (^{1}H, ^{13}C). Coupling constants, *J*, are given in Hz.

Mass spectra were recorded on a Waters LCT Premier ESI-TOF spectrometer.

Isothermal titration calorimetry experiments (ITC) were performed using a MicroCal VP-ITC Microcalorimeter.

Crystal structure determination was carried out using a Bruker-Nonius diffractometer equipped with a APPEX 2 4K CCD are detector, a FR591 rotating anode with MoKα radiation, Montel mirrors as a monochromators and a Kryoflex low temperature device (T = 100K). Full sphere data collection omega and phi scans. Programs used: Data collection Apex2 V. 1.0-22 (Bruker-Nonius 2004), data reduction Saint + Version 6.22 (Bruker-Nonius 2001) and absorption correction SADABS V. 2.10 (2003). Crystal structure solution was achieved using direct methods as implemented in SHELXTL Version 6.10 (Sheldrick, Universität Göttingen (Germany), 2000) and visualized using XP program. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL Version 6.10 (Sheldrick, Universität Göttingen (Germany), 2000).

II.II. EXPERIMENTAL DETAILS OF SYNTHESIS AND CHARACTERIZATION OF MACROCYCLIC REPECEPTORS 1 AND 2

The experimental details presented here are related to section 3.2.2 of Chapter 3 of this thesis.

The cyclic trimeric pyromellitic diimide (receptor **1**) was synthesized following the procedure described in the report of Gawronski and coworkers[ii.1] with a yield of 11 % and with the same physical characteristics obtained previously by them.

Below the synthesis and characterization of cyclic trimeric 1,4,5,8-naphthalene tetracarboxylic diimide (receptor **2**) is described as well as their X-Ray structure determination.

II.II.1. SYNTHESIS AND CHARACTERIZATION OF THE CYCLIC TRIMERIC 1,4,5,8-NAPHTHALENE TETRACARBOXYLIC DIIMIDE, 2.

114 mg (1 mmol) of (*1R*,*2R*)-trans-diaminocyclohexane and 268 mg (1 mmol) of 1,4,5,8-naphthalenetetracaboxilic anhydride were refluxed in 10 mL of dimethylformamide anhydrous (DMF) for 4 hours. After the reaction the solvent was removed in vacuo. The residue was suspended in a dichloromethane (DCM) solution, and over this suspension, a column chromatography of the residue on silica gel eluting with CH_2Cl_2:3% AcOEt was done, afforded cyclic trimeric 1,4,5,8-naphthalenetetracarboxylic diimide **2** as a brownish solid; yield 10%. Additional attempts of the synthesis of the receptor **2** were not successful in good yields, probably because of impurity of the reagent (1,4,5,8-naphthalenetetracarboxylic dianhydride). m.p. >360°C; IR (KBr): $\tilde{\upsilon}$ = 2935.2, 2760.8 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 500.1 MHz δ = 1.70 (m, 12H, H-4', H-5'), 1.95 – 2.03 (m, 12H, H-3', H-6'), 6.24 (m, 6H, H-1', H-2'), 8.49 (s, 12H, H4, H5, H9, H10); ^{13}C NMR ($CDCl_3$, 125.6 MHz): δ = 25.7 (CH_2, C-4', C-5'(x3)); 29,9 and 29,7 (CH_2, C-3', C-6'(x3)); 53,9 (CH, C-1', C-2'(x3)); 125,8 and 126,1 (C, C-10b, C-10c(x3)); 126,5 (CH, C-4, C-5, C-9, C-10(x3)); 130,7 and 131,3 (C, C-3a, C-5a, C-8a, C-10a(x3)); 162,4 and 162,7 (C, CO (x12)).. ESI-TOF negative mode detection, m/z: 1038.3 $[M–H]^-$.

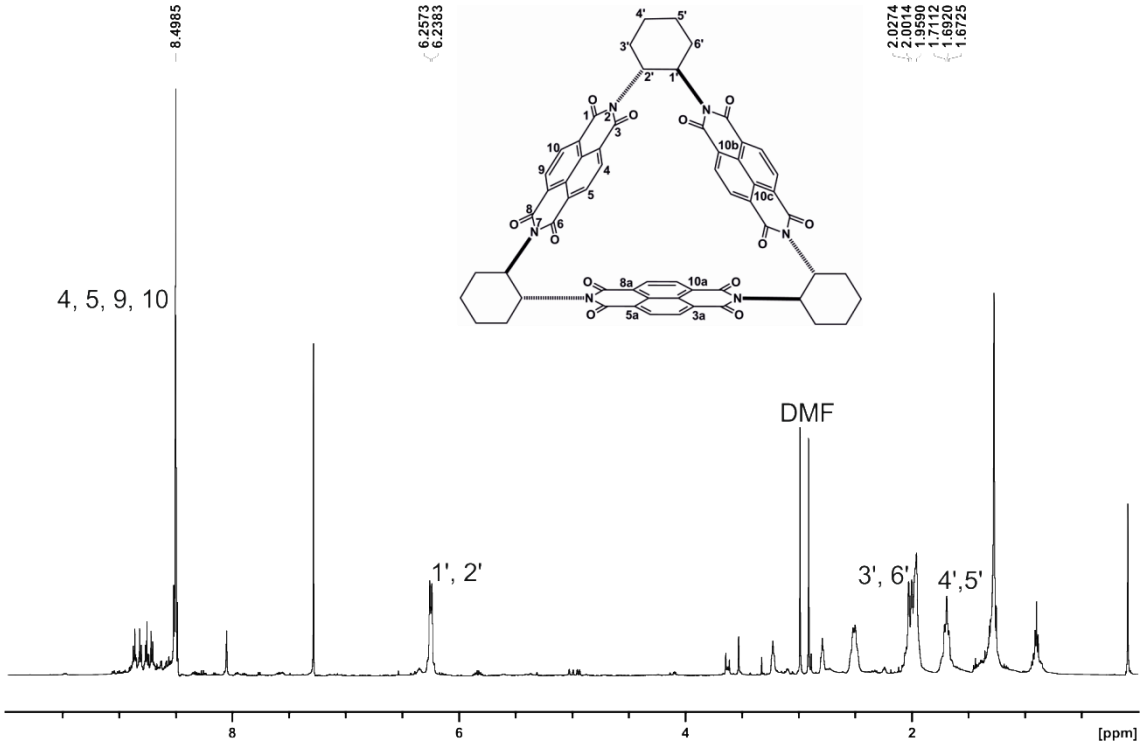

Figure II.1. ^{1}H NMR spectra for receptor **2** in $CDCl_3$.

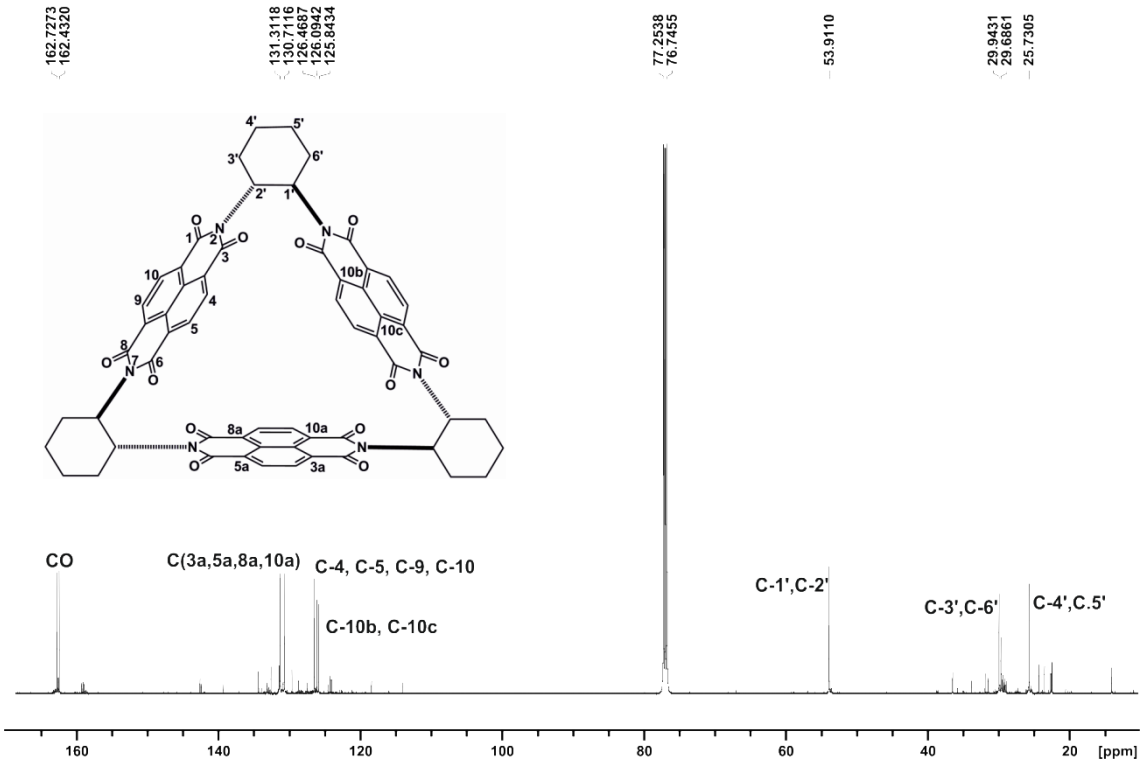

Figure II.2. ^{13}C NMR spectra for receptor **2** in $CDCl_3$.

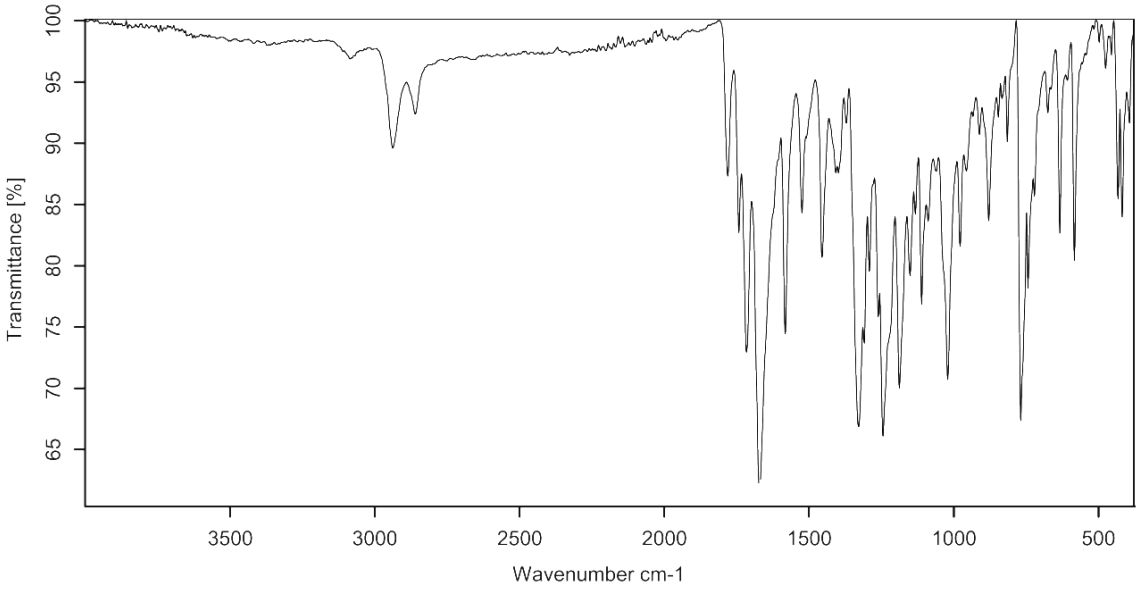

Figure II.3. Room Temperature IR-spectra of receptor **2**.

II.II.1.1.Crystal data for Receptor 2

Compound **2** crystallize in the triclinic cystal system. The ORTEP diagram of the compound is shown in Figure II.4. Crystallographic data collection and refinement parameters are listed in Table II.1.

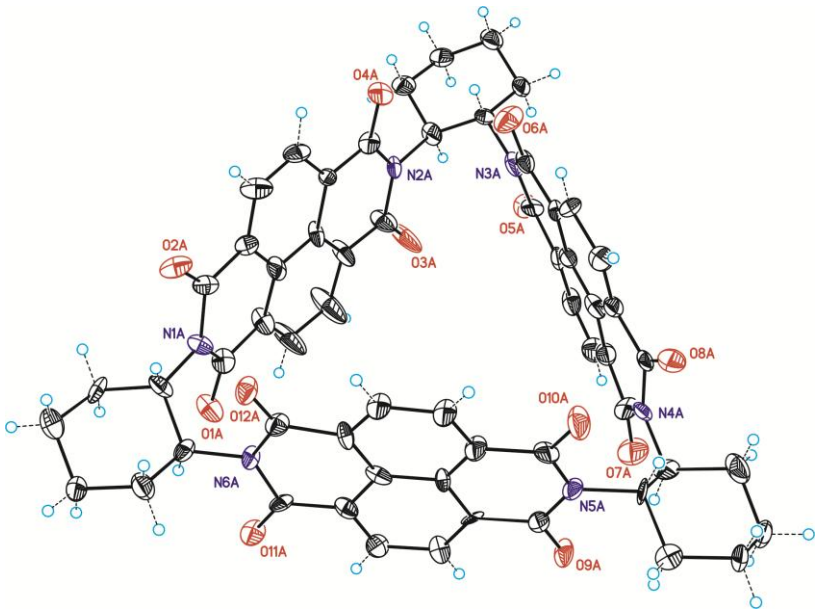

Figure II.4. ORTEP diagram of compound **2**. Thermal ellipsoids are drawn at the 50% probability level.

Table II.1. Crystallographic data and structure refinement for compound **2**.

Compound	**2**	
Empirical formula	$C_{43}H_{36.75}N_3O_6$	
Formula weight	691.50	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 14.761(2) Å	a= 77.857(7)°
	b = 15.706(2) Å	b = 88.863(7)°
	c = 15.867(2) Å	g = 76.803(7)°
Volume	3499.7(9) $Å^3$	
Z	4	
Density (calculated)	1.312 Mg/m^3	
Absorption coefficient μ	0.088 mm^{-1}	
F(000)	1455	
Crystal size	0.08 x 0.05 x 0.03 mm^3	
θ range for data collection	1.31 to 25.61°	
Index ranges	-17 <=h<=17	
	-18 <=k<=18	
	-19 <=l<=19	
Reflections collected	31348	
Independent reflections	22763 [R(int) = 0.0798]	
Completeness to ϑ =25.61°	0.974 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9974 and 0.9930	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	22763/556/2054	
Goodness-of-fit on F^2	0.960	
Final *R* indices [I>2σ(I)]	R_1 = 0.0899, wR_2 = 0.1794	
R indices (all data)	R_1 = 0.2408, wR_2 = 0.2666	
Flack parameter	x = -2.1(19)	
Largest diff. peak and hole	0.441 and -0.401 e $Å^{-3}$	

II.III. EXPERIMENTAL DETAILS OF QUANTIFICATION OF ANION–π INTERACTION BETWEEN CALIX[4]PYRROLE DERIVATIVES AND OXOXANIONS

The experimental details presented here correspond to section 3.2.3 of Chapter 3. Specifically, the data is the supporting information of the article *Assessment of Anion–π Interactions between aryl-extended calix[4]pyrrole and oxoanions* shown there.

II.III.1.1. Isothermal Titration Calorimetry Experiments

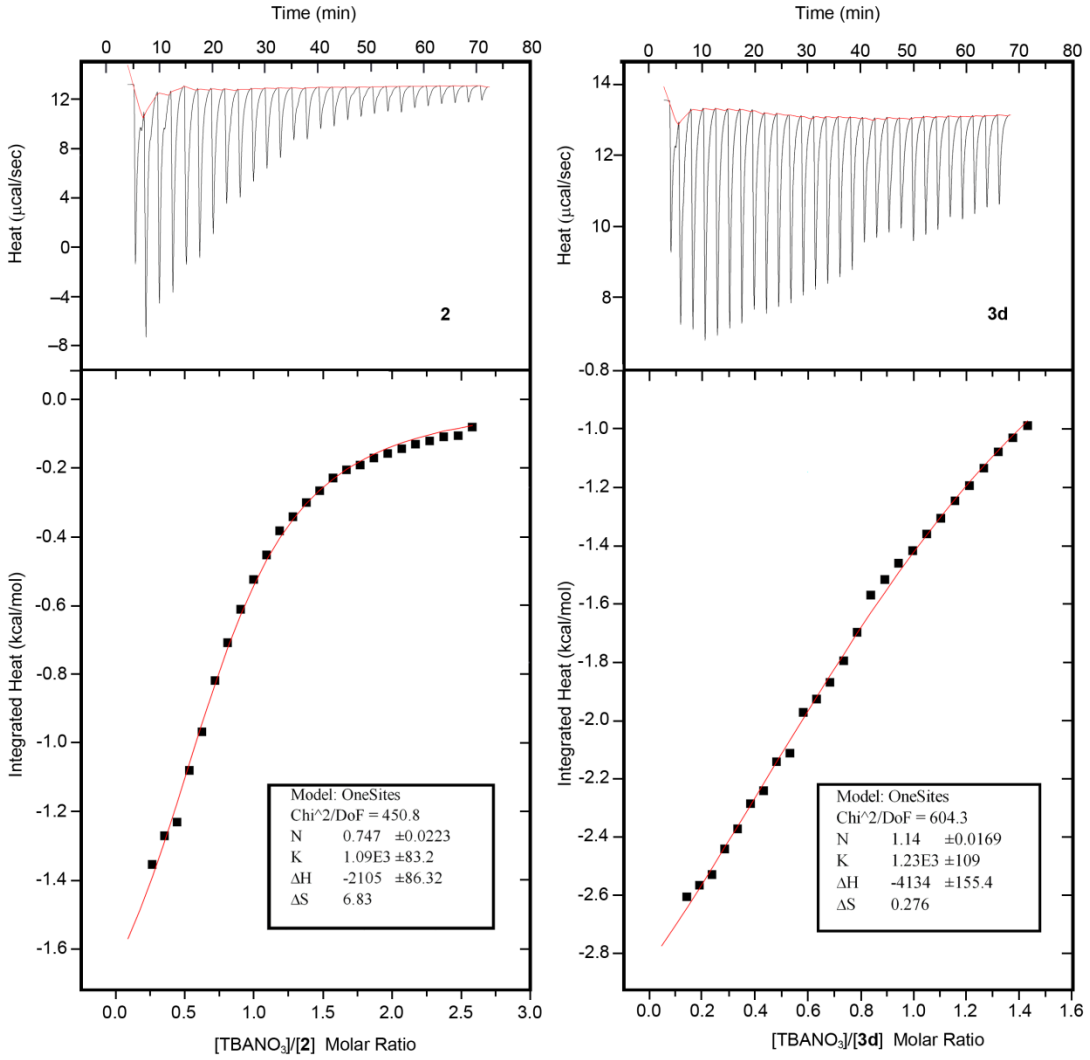

Figure II. 5. Representative ITC profile for tetra-*p*-nitrophenyl calix[4]pyrrole, receptor **2** (left) and di-*m*-dinitrophenyl calix[4]pyrrole, receptor **3d** (right). Top: The figure shows the Heat (µcal/sec) vs. Time (min) graphic for the titration of $TBANO_3$ in to each host, respectively, at 25°C. Bottom: Integrated Heat (kcal/mol) vs. Molar Ratio graphics are represented. The continuous line represents the least-square fit of the data to a single-site binding mode. The binding constant (K), number of binding site (N), enthalpy (ΔH) and entropy (ΔS) are provide in the box.

Titrations between tetrabutylammonium nitrate $TBANO_3$ (guest) and the hosts *meso*-tetra-*p*-nitrophenylcalix[4]pyrrole (**2**) and *meso*-di-*m*-dinitrophenylcalix[4]pyrrole (**3d**) were carried

out by adding small aliquots (5 μL) of an acetonitrile solution of the guest into a solution of the host in the same solvent. The solution of the guest was approximately ten times more concentrated than that of the host ([**2**]= 5.5mM, [**3d**]= 0.99mM). The association constants and the thermodynamic parameters were obtained from the fit of the titration data to a simple 1:1 binding mode using the Microcal ITC Data Analysis module.

II.III.1.2.^{1}H NMR Titrations

All titration were carried out on a Bruker 500 MHz spectrometer, at 298 K, in acetonitrile-d_3 (CD_3CN). The association constants were determined using 1-1.5 mM solutions of **2** and **3a-d** in CD_3CN at 298 K, and adding aliquots of a solution of the corresponding salt, approximately 20 or 30 times more concentrated, in the same solvent. The concentration of the receptor was maintained constant throughout the titration. The association constants between the receptor **1, 2** and **3a-d** and the nitrate anion were determined fitting ^{1}H NMR titration data using HypNMR software to a simple 1:1 binding model. For each titration, different protons were followed and fitted. Figure II.6 shows the adjustment of the experimental chemical shift fitted with respect to the calculated chemical shift for two different protons for receptor **2** and **3b**. The chemical shift followed during the experimental titration for H_c fitted completely with the fitting of chemical shift calculated by HypNMR software. The behavior of proton H_c (from group –NH of the pyrrol) is repeated for all receptors. In addition, the chemical shift for proton H_d has been also represented. This proton is one of the β-pyrrolic protons. The fitting of this proton with respect the theoretical chemical shift calculated by the software is good although not as accurate as for H_c proton. These representations indicate us that the values of association constant (K_a) from HypNMR software are very reliable. It is worth to mention that the value of K_a is obtained from the average of all chemical shifts of all protons that we followed during the titration, and taking into account the good fitting observed between the experimental and calculated data (σ values present in Figure caption of each receptor), we conclude that the values of association constants obtained in this way are really consistent.

It is also interesting the data obtained from speciation which informe us about the changes of the different initial species with respect to the concentration of the new specie formed. In Figure II.7 shows the speciation for each receptor. The green line indicates the change in the concentration of receptor free as the concentration of the complex increases (blue line). In Figure II.7 can be observed the total % of complex experimentally formed after the titration for each receptor. For receptor **1** and **3b**, at the end of the titration we got ~ 70% of the complex NO_3^-@**1** and NO_3^-@**3b**. For receptors 2, 3c and 3d receptors at the end of the titration we

reached ~ 90% of complexes NO_3^-@**2**, NO_3^-@**3c** and NO_3^-@**3d**, respectively. Only for receptor 3a after the titration, only we reached the 30% of complex NO_3^-@**3a**. This fact can be explained because the receptor **3a** is the less appropriate to establish strong anion–π interactions.

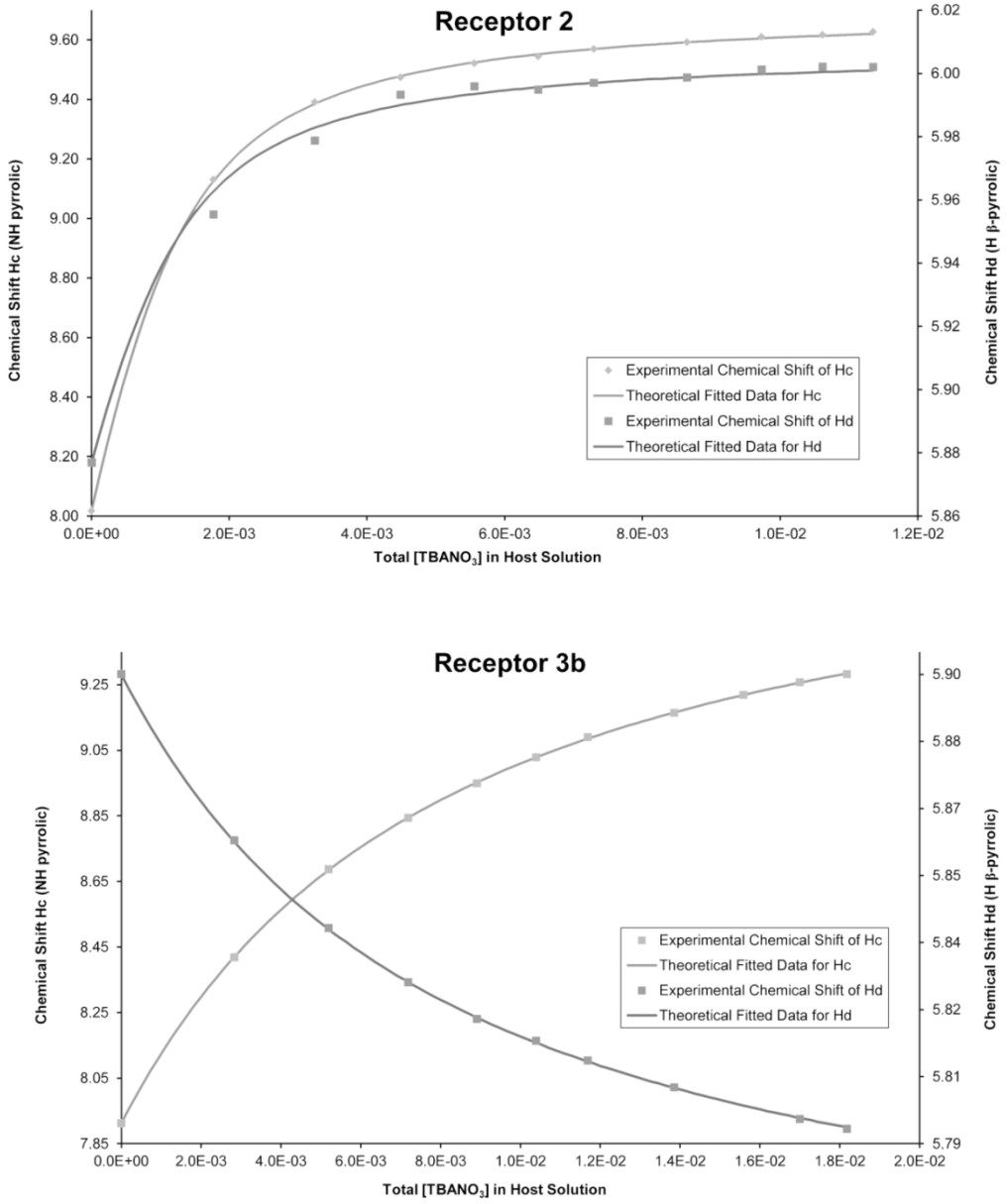

Figure II.6. The graphic shows the experimental chemical shift of proton signals H_c (proton of pyrrolic –NH) and H_d (proton β-pyrrolic) vs. the concentration of $TBANO_3$ salt, for A) receptor **2** and B) receptor **3b**.

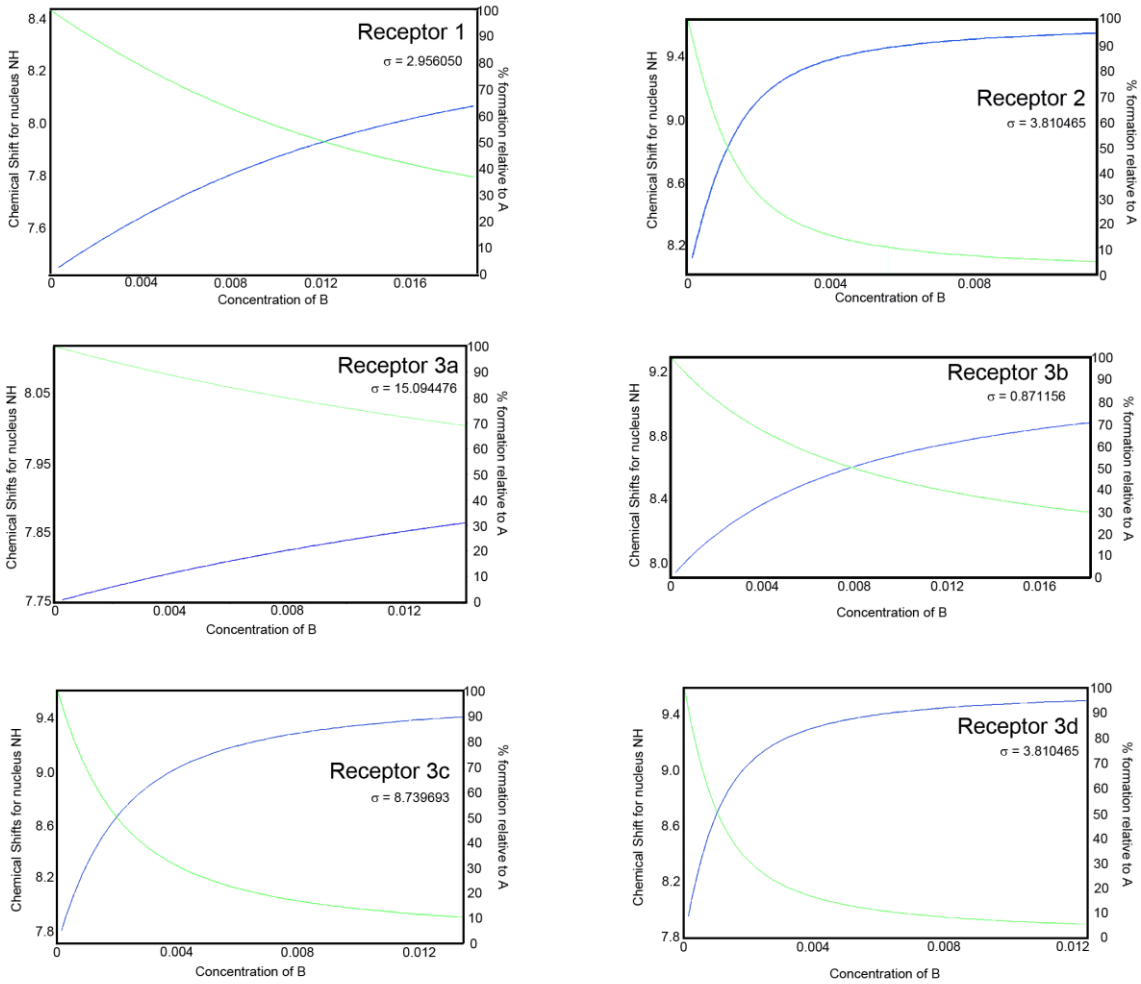

Figure II.7. Graphics of speciation that show the evolution of the titration. The graphics indicate at the end of the titration the percentage of receptor free (green line) and complex formed (blue line) for each receptor **1**, **2** and **3a**-**d**.

The calix[4]pyrrole receptors are really versatile systems. In the study performed and presented in the article 3.2.3.2 (*Assessment of Anion–π Interactions between aryl-extended calix[4]pyrrole and oxoanions*) we have analysed the behaviour of two kinds of calix[4]pyrroles; the *meso*-tetraarylextended calix[4]pyrrole, from now four walls calix[4]pyrrole, and the *meso*-diarylextended calix[4]pyrrole, from now two walls calix[4]pyrroles. The interaction between both kinds of calixpyrroles and halides (Cl^-) has been previously studied by Ballester's research group.[ii.2] In these previous studies have been analysed:

- The conformational changes of the receptor,
- The behaviour in solution,
- The aryl groups that more favourably interact with anions, and
- The quantification of anion–π interaction.

The calix[4]pyrroles can present three conformations: 1,2-alternate; 1,3-alternate and cone conformation. The most favourable conformations are the conelike and 1,3-alternate. From X-Ray structure determination[ii.2] we know that the complex between the anion and the receptor is produced when the calix[4]pyrrole is in cone conformation. In solution, it is necessary the equilibrium between the cone and 1,3-alternate conformation to exchange the solvent molecule that occupies the cavity for the anion present in the solution after its first addition. This conformational exchange is necessary to maintain the system thermodynamically stable during the output of the solvent and the entry of the anion. Depending on the energetic cost of the conformational equilibrium between cone and 1,3-alternate conformations, experimentally we can observe slow or fast equilibrium exchange. Therefore:

- More difficult change between cone and 1,3-alternate conformations, slower equilibrium exchange rate observed in NMR timescale. If this happens, the proton signals that characterized our receptor are splitted after the first addition of the guest, i.e, we can observe the proton signals for free receptor (before the complexation with the anion) and the same proton signals shifted for complexed receptor. As the titration progresses the intensity of signals splitted changes.
- Conversely, smaller energetic barrier for the conformational equilibrium and therefore, lower energetically transition state, greater equilibrium exchange rate. In NMR timescale the shifted of proton signals that characterized our receptor, but without splitted, is observed.

In the present study, we have chosen the arylextended calix[4]pyrroles that more favourably interact with halides, and we have quantified the anion–π interaction between these calix[4]pyrroles and nitrate anion. For comparison purposes we have worked with several receptors as octamethylcalix[4]pyrrole (receptor **1**) used as model reference, tetra-*p*-nitrophenyl calix[4]pyrrole (receptor **2**), the only four wall receptor chosen and a series of diarylextended calix[4]pyrrole, i.e., phenyl- (receptor **3a**), *p*-nitrophenyl- (receptor **3b**), pentafluorophenyl- (receptor **3c**) and *m*-dinitrophenyl- (receptor **3d**) calix[4]pyrrole.

Regarding four walls calix[4]pyrrole, from the titration data results between receptor **2** and nitrate anion, we can deduce that we worked with fast equilibrium exchange rate (see Figure II.10), i.e., for each typical proton only one signal is observed, and this signal is shifted during the titration. However, in previous study of Ballester and co-workers[ii.2] the titration between receptor **2** and chloride anion was characterized by slow equilibrium exchange rate in NMR timescale, and after the first addition of guest the proton signals of the receptor are splitted.

The difference observed for the same receptor under the same conditions, produced only by the change of chloride anion by nitrate anion is related to the geometry of cone conformation. As can be appreciated in Figure II.8, when the receptor **2** interacts with chloride anion, the calix[4]pyrrole adopts a more closed cone conformation (A). However, when the receptor **2** interacts with nitrate anion, the host adopts a more opened cone conformation (see B in Figure II.8). Therefore, in the latter case the cone conformation is more prepared to easily change at 1,3-alternate conformation, being the transition state in this case energetically lower than for chloride anion. For this reason, in the titration between receptor **2** and nitrate anion no splitted signals are observed (Figure II.10).

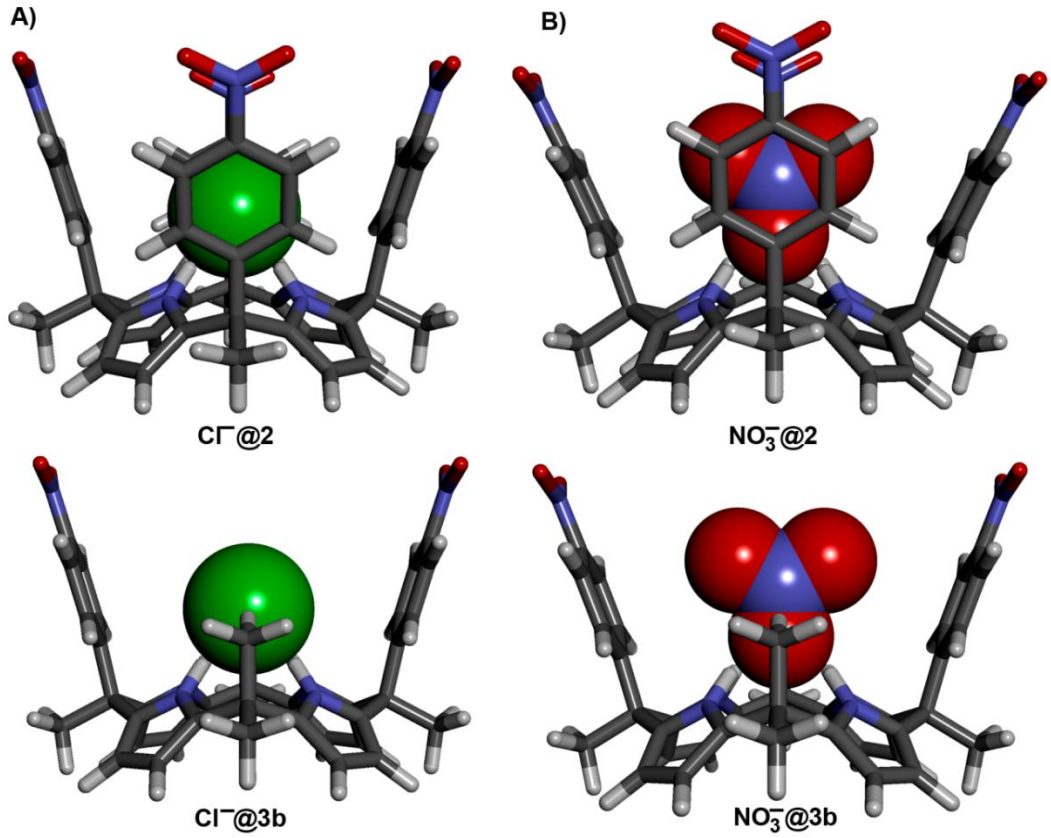

Figure II.8. Schematic representation of tetrarylextended calix[4]pyrrole (top) and diarylextended calix[4]pyrrole (bottom). A) Cone conformation of complexes Cl^-@**2** and Cl^-@**3b**. B) Cone conformation of complexes NO_3^-@**2** and NO_3^-@**3b**.

Regarding two walls calix[4]pyrrole systems, all of them present a fast exchange equilibrium rate during the titration with nitrate, showing the shifted of proton signals and without splitted (Figure II.11 –Figure II.14). This fact is easily explained because cone conformation for two walls receptors generates like a tunnel that facilitates the change between the solvent and the anion (see Figure II.8).

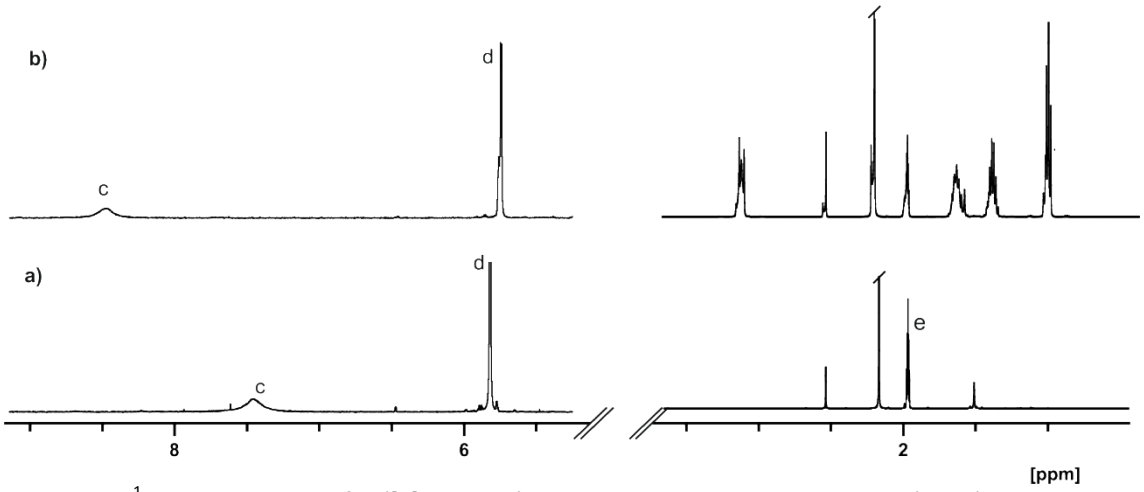

Figure II.9. ^{1}H NMR titration of **1** ([**1**] = 1 mM) with $TBANO_3$ in CD_3CN at 298 K. a) **1**. b) **1** + 15.73 eq. $TBANO_3$.

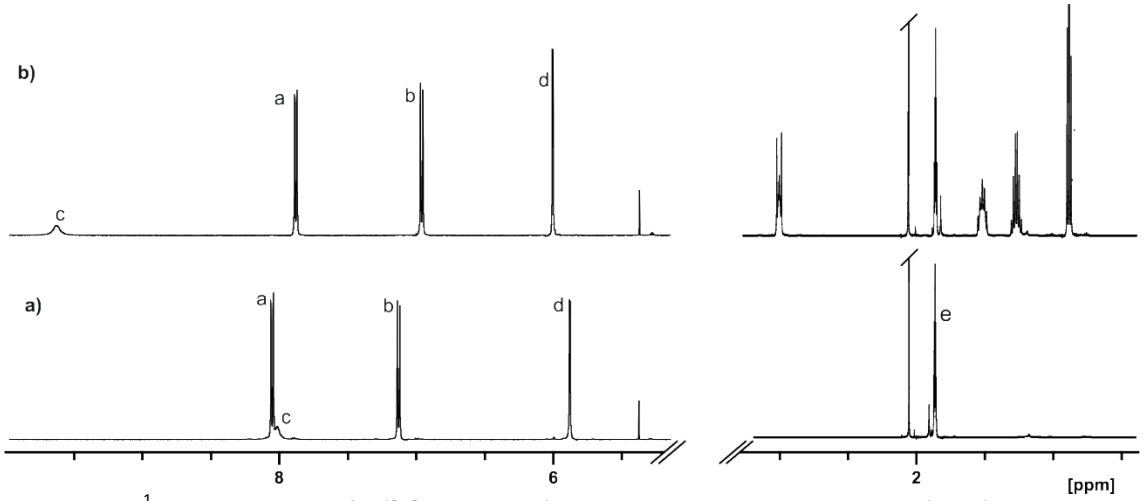

Figure II.10. ^{1}H NMR titration of **2** ([**2**] = 1.09 mM) with $TBANO_3$ in CD_3CN at 298 K. a) **2**. b) **2** + 43.13 eq. $TBANO_3$.

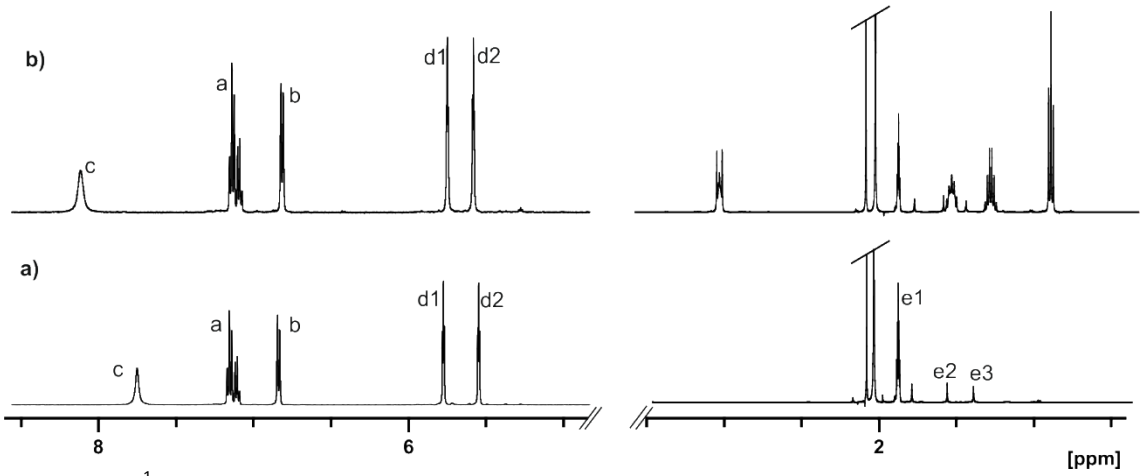

Figure II.11. ^{1}H NMR titration of **3a** ([**3a**] = 1.21 mM) with $TBANO_3$ in CD_3CN at 298 K. a) **3a**. b) **3a** + 7.47 eq. $TBANO_3$.

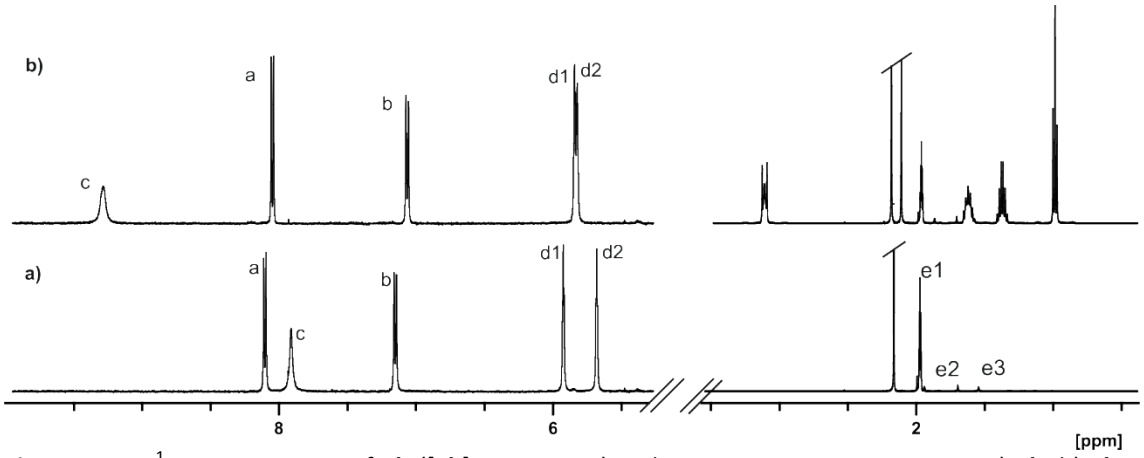

Figure II. 12. ^{1}H NMR titration of **3b** ([**3b**] = 0.95 mM) with $TBANO_3$ in CD_3CN at 298 K. a) **3b**. b) **3b** + 17.75 eq. $TBANO_3$.

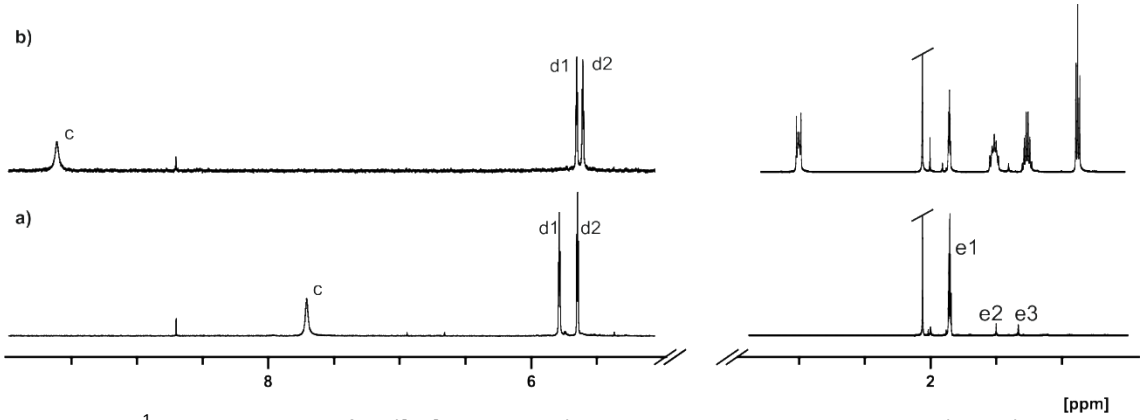

Figure II.13. ^{1}H NMR titration of **3c** ([**3c**] = 1.06 mM) with $TBANO_3$ in CD_3CN at 298 K. a) **3c**. b) **3c** + 11.82 eq. $TBANO_3$.

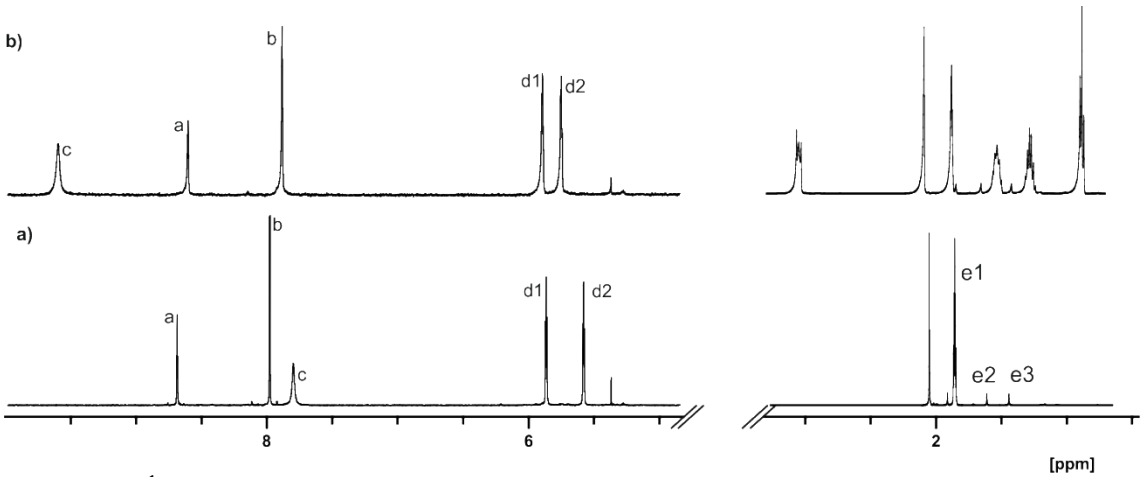

Figure II.14. ^{1}H NMR titration of **3d** ([**3d**] = 0.74 mM) with $TBANO_3$ in CD_3CN at 298 K. a) **3d**. b) **3d** + 15.46 eq. $TBANO_3$.

Table II.2. ^{1}H NMR chemical shifts $\Delta\delta$ (ppm, $\delta_{complex}$-δ_{host}) of calixpyrrole hosts **1**, **2** and **3a-d**; chemical shifts for the complex were obtained from the addition of an excess of $TBANO_3$ to a host solution in CD_3CN at 298 K.

	2	**3a**	**3b**	**3c**	**3d**	**1**
R	NO_2	H	NO_2	F_5	$(NO_2)_2$	-
$\Delta\delta_{NH}$	1.69	1.18	1.95	2.11	1.73	1.53
$\Delta\delta_{Ha}$	-0.18	-0.05	-0.08	--	0.59	--
$\Delta\delta_{Hb}$	-0.18	-0.08	-0.12	--	0.86	--
$\Delta\delta_{Hd1}$	0.13	-0.09	-0.14	-0.16	-0.15	-0.12
$\Delta\delta_{Hd2}$	--	0.11	0.23	-0.03	0.24	--

(ii.1) J. Gawronski, M. Brzostowska, K. Gawronska, J. Koput, U. Rychlewska, P. Skowronek, B. Norden, *Chem.--Eur. J.* **2002**, *8*, 2484-2494.
(ii.2) G. Gil-Ramirez, E. C. Escudero-Adan, J. Benet-Buchholz, P. Ballester, *Angew. Chem., Int. Ed.* **2008**, *47*, 4114-4118.

ANNEX III. OTHER PUBLICATIONS DERIVED FROM THIS THESIS

A.III.1.- Escudero, D.; Estarellas, C.; Frontera, A.; Quiñonero, D.; Deyà, P.M. Theoretical and Crystallographic Study of edge-to-face aromatic interactions between pyridine moieties and benzene. *Chem. Phys. Lett.*, **2009**, *468*, 280–285.

A.III.2.- Escudero, D.; Lucas, X.; Estarellas, C.; Frontera, A.; Quiñonero, D.; Deyà, P.M. Interplay between Ion–π and Hydrogen Bonding Interactions. *Trends in Phys. Chem.*, **2009**, *13*, 31–53.

A.III.3.- Alkorta, I.; Blanco, F.; Elguero, J.; Estarellas, C.; Frontera, A.; Quiñonero, D.; Deyà, P.M. Simultaneous Interaction of Tetrafluoroethene with Anions and Hydrogen-Bond Donors: A Cooperativity Study. *J. Chem. Theory Comput.*, **2009**, *5*, 1186–1194.

A.III.4.- Lucas, X.; Estarellas, C.; Escudero, D.; Frontera, A.; Quiñonero, D.; Deyà, P.M. Very long range effects: cooperativity between anion–π and hydrogen bonding interactions. *ChemPhysChem*, **2009**, *10*, 2256–2264.

A.III.5.- Alkorta, I.; Blanco, F.; Deyà, P.M.; Elguero, J.; Estarellas, C.; Frontera, A.; Quiñonero, D. Cooperativity in multiple unusual weak bonds. *Theor. Chem. Acc.*, **2010**, *126*, 1–14.

A.III.6.- Estarellas, C.; Lucas, X.; Frontera, A.; Quiñonero, D.; Deyà, P.M. Erroneous behaviour of the widely used MP2(full)/aug-cc-pVXZ (X = D, T) level of theory for evaluating the BSSE in ion-pi complexes. *Chem. Phys. Lett.*, **2010**, *489*, 254–258.

A.III.7.- Quiñonero, D.; Estarellas, C.; Frontera, A.; Deyà, P.M. A methodological analysis for the assessment of noncovalent π interactions. *Chem. Phys. Lett.*, **2011**, *508*, 144–148.

A.III.8.- Estarellas, C.; Bauzá, A.; Frontera, A.; Quiñonero, D.; Deyà, P.M. On the directionality of anion–π interactions. *Phys. Chem. Chem. Phys.*, **2011**, *13*, 5696–5702.

ANNEX IV. OTHER PUBLICATIONS DERIVED FROM COLLABORATION WITH NATIONAL RESEARCH GROUPS

A.IV.1.- García-Raso, A.; Albertí, F.M.; Fiol, J.J.; Tasada, A.; Barceló-Oliver, M.; Molins, E.; Estarellas, C.; Frontera, A.; Quiñonero, D.; Deyà, P.M. 2-Aminopyrimidine Derivatives Exhibiting Anion–π Interactions: A Combined Crystallographic and Theoretical Study. *Cryst. Growth Des.,* **2009,** *9*, 2363–2376.

A.IV.2.- Barceló-Oliver, M.; Estarellas, C.; García-Raso, A.; Terrón, A.; Frontera, A.; Quiñonero, D.; Molins, E.; Deyà, P.M. Lone pair–π vs π–π interactions in 5-fluoro-1-hexyluracil and 1-hexyluracil: a combined crystallographic and computational study. *CrystEngComm*, **2010**, *12*, 362–365.

A.IV.3.- Barceló-Oliver, M.; Estarellas, C.; García-Raso, A.; Terrón, A.; Frontera, A.; Quiñonero, D.; Mata, I.; Molins, E.; Deyà, P.M. Experimental and theoretical study of uracil derivatives: the crucial role of weak fluorine-fluorine noncovalent interactions. *CrystEngComm*, **2010**, *12*, 3758–3767.

A.IV.4.- Garcia-Raso, A.; Albertí, F.M.; Fiol, J.J.; Lagos, Y.; Torres, M.; Molins, E.; Mata, I.; Estarellas, C.; Frontera, A.; Quiñonero, D.; Deyà P.M. A Combined Experimental and Theoretical Study of Anion–π Interactions in N6- and N9-Decyladenine Salts. *Eur. J. Org. Chem.*, **2010**, 5171–5180.

A.IV.5.- García-Raso, A.; Fiol, J. J.; Albertí, F.M.; Lagos, Y.; Torres, M.; Barceló-Oliver, M.; Prieto, M. J.; Moreno, V.; Mata, I.; Molins, E.; Estarellas, C.; Frontera, A.; Quiñonero, D.; Deyà, P.M. New chlorido(dimethyl sulfoxide)iridium (III) complexes with N(6)-adenine substituted adenines-kinetic N(7) versus thermodynamic N(9) coordinated adenine isomers. *Eur. J. Inorg. Chem.*, **2010**, 5617–5628.

A.IV.6.- Barceló-Oliver, M.; Estarellas, C.; Terrón, A.; García-Raso, A.; Frontera, A. RNA's uracil quartet model with a non-essential metal ion. *Chem. Commun.*, **2011**, *47*, 4646–4648.

ANNEX V. OTHER PUBLICATIONS DERIVED FROM COLLABORATION WITH INTERNATIONAL RESEARCH GROUPS

A.V.1.- Das, A.; Choudhury, Somnath R.; Dey, B.; Yalamanchili, S. K.; Helliwell, M.; Gamez, P.; Mukhopadhyay, S.; Estarellas, C.; Frontera, A. Supramolecular Assembly of Mg(II) Complexes Directed by Associative Lone Pair–π/π–π/π–Anion–π/π–Lone Pair Interactions. *J. Phys. Chem. B*, **2010**, *114*, 4998–5009.

A.V.2.- Naiya, S.; Drew, M.G.B.; Estarellas, C.; Frontera, A.; Ghosh, A. Hydrogen-bond assisted stabilization of the less favored conformation of a tridentate Schiff base ligand in dinuclear nickel(II) complex: An experimental and theoretical study. *Inorg. Chim. Acta*, **2010**, *363*, 3904–3913.

A.V.3.- Biswas, S.; Naiya, S.; Drew, M.G.B.; Estarellas, C.; Frontera, A.; Ghosh, A. Trinuclear and Tetranuclear Adduct Formation Between Sodium Perchlorate and Copper(II) Complexes of Salicylaldimine Type Ligands: Structural Characterization and Theoretical Investigation. *Inorg. Chim. Acta*, **2010**, *366*, 219–226.

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A.V.6.- Biswas, R.; Drew, M. G. B.; Estarellas, C.; Frontera, A.; Ghosh, A. Synthesis and Crystal Structures of ¼-Oxido- and ¼-Hydroxido-Bridged Dinuclear Iron(III) Complexes with an N_2O Donor Ligand - A Theoretical Study on the Influence of Weak Forces on the Fe-O-Fe Bridging Angle. *Eur. J. Inorg. Chem.*, **2011**, 2558–2566.

A.V.7.- Seth, S. K.; Saha, I.; Estarellas, C.; Frontera, A.; Kar, T.; Mukhopadhyay, S. Supramolecular self-assembly of M-IDA complexes involving lone pair···π interactions: crystal structures, Hirshfield surface analysis, and DFT calculations [H_2IDA =iminodiacetic acid, M = Cu(II), Ni(II)]. *Cryst. Growth Des.*, **2011**, *11*, 3250–3265.

A.V.8.- Mandal, P.C.; Chakraborty, M.; Das, S.; Estarellas, C.; Quiñonero, D.; Frontera, A.; Mukhopadhyay, S. Kinetics and mechanism of the oxidation of hydroxylamine by a $[Mn_3O_4]^{4+}$ core in aqueous acidic media. *Dalton Trans.*, **2011**, *40*, 9571–9579.

A.V.9.- Mashraqui, S.H.; Chandiramani, M.A.; Ghorpade, S.S.; Estarellas, C.; Frontera, A. A Highly Selective Fluorescence Turn-on Probe for $Zn^{(2+)}$ Based on New Diaryloxadiazole Chelate. *Chem. Lett.*, **2011**, *40*, 1163–1164.

ANNEX VI. ARTICLES FEATURED ON THE COVER AND BACK COVER OF THE JOURNALS

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