Chapter 16
Anion-π Interactions in Supramolecular Chemistry and Catalysis

Antonio Bauzá, Pere M. Deyà and Antonio Frontera

Abstract Non-covalent interactions play a major role in supramolecular chemistry and biochemistry by dominating the central parts of living systems since they dictate the functionality of many biological and host-guest systems. A good comprehension of the different non-covalent forces is necessary for the rational design of new drugs and developing improved synthetic receptors capable to function in competitive media. Interactions involving aromatic rings (or π-systems in general) are very relevant in supramolecular chemistry, exemplified by the cation–π interaction and its importance in protein structure and enzyme catalysis. From a traditional point of view, the π-system is usually considered as electron rich (π-basic). The naissance of the counterintuitive anion–π interaction –the attractive interaction between an anion and an electron poor π-system (π-acid)– was somewhat controversially discussed by the scientific community. However, in the last decade a great deal of theoretical and experimental investigations has time-honored the anion–π interaction as an important supramolecular bond. Herein we describe the physical nature of this noncovalent interaction and the different strategies that can be used to modulate its strength. Finally, selected state-of-the-art reports illustrating the rational utilization of the anion–π interaction in supramolecular chemistry (anion receptors), biological applications and catalysis are described in this chapter.

16.1 Introduction

Nowadays supramolecular chemistry is probably the most multidisciplinary field of research. It is exponentially growing as indicated by the large number of articles, reviews, and books published since the beginning of this millennium. The rapid development of supramolecular chemistry has a profound effect on the increasing efficiency for preparation of structures of different sizes, shapes and functionalities. Supramolecular chemists rely on the comprehension of the non-covalent forces, which form the basis of highly specific recognition, transport, and regulation

A. Frontera (✉) · A. Bauzá · P. M. Deyà
Departament de Química, Universitat de les Illes Balears, 07122 Palma de Mallorca, Baleares, Spain
e-mail: toni.frontera@uib.es

S. Scheiner (ed.), *Noncovalent Forces,* Challenges and Advances in Computational Chemistry and Physics 19, DOI 10.1007/978-3-319-14163-3_16

mechanisms. The orchestration of many chemical and biological processes is often dominated by an intricate combination of non-covalent interactions [1, 2], which are the foundation of the life process itself, the ultimate expression of function. In general host-guest chemistry, interactions between targeted guests and rationally designed receptors drive the formation of assemblies of different sizes, shapes and affinities [3–6]. The correct description of interactions between molecules is needed for the understanding and progress of the supramolecular chemistry that usually relies on strong, directional interactions such as hydrogen bonding and halogen bonding, and less directional forces like ion pairing. More recently, general σ-hole interactions are also considered as an important addition to the family of well-established directional non-covalent interactions [7–9]. In addition, non-covalent interactions involving aromatic rings are enormously significant in this field [10, 11]. They play a crucial role in chemistry and biology [12], in particular drug–receptor interactions, crystal engineering, enzyme inhibition and protein folding [12]. A clear example is the role of π–stacking interactions in DNA, RNA [14, 15] and protein-DNA aromatic interactions [16]. An important and widely recognized non-covalent attractive force that involves aromatic rings is the cation–π interaction [17, 18], of great significance in biology [19–21] and supramolecular chemistry [22–25]. Other weak interactions involving π-systems are also at the forefront of interdisciplinary research. For example, CH–π [26, 27], lone pair–π [28, 29] and salt-bridge–π [30] interactions have been recently used in several supramolecular chemistry fields, especially in crystal engineering and protein-ligand interactions.

In the last decade, the anion–π interaction [31–33], i.e. the attractive noncovalent force between an electron-deficient π–system and an anionic moiety [34, 35], has also been recognized as a non-covalent bonding interaction. Its nature has been described by a plethora of theoretical studies [36–39] in addition to an increasing amount of experimental investigations [40–44]. Anion–π interactions are expected to become noticeable players in fields as diverse as medicine, environmental chemistry and biochemical processes [31, 45–47]. Moreover, their application to the design of highly selective anion receptors and transport channels definitively confirms their significance in the field of supramolecular chemistry [48, 49].

As a matter of fact, the design and synthesis of selective receptors designed to bind anions is a topic of continuous interest [50–55]. The main reason is related to the vital function played by anions, which are ubiquitous throughout biological systems [56, 57]. In addition, some anions are increasingly recognized as problematic environmental contaminants. For example, the overuse of anionic pollutants (phosphate and nitrate) as fertilizers causes the disruption of aquatic ecosystems. The eutrophication caused by the fertilizing properties of these oxy-anions limits the populations of algae and phytoplankton in rivers and lakes [58]. Other anions, such as pertechnetate are generated from the re-processing of nuclear fuel [59] and their release to the sea is strictly controlled or prohibited. Another harmful anion is arsenate that caused the largest mass poisoning in human history (200 million) due to the dissolution in the groundwater of the Bengal basin [60]. Interestingly, a new class of anion receptors based on the anion–π interaction is emerging in the literature [31, 61]. For instance, an interesting receptor, that combines hydrogen bonding and anion–π interaction

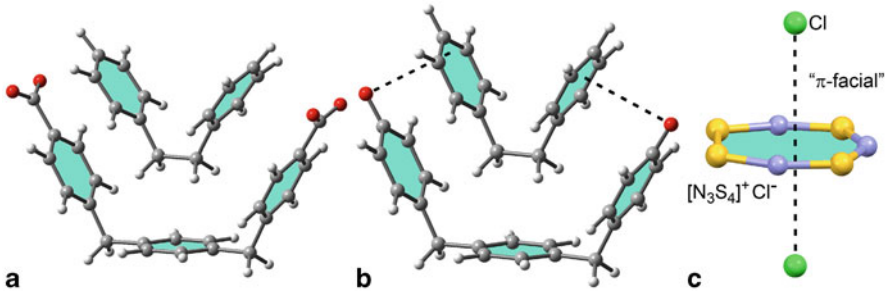

Fig. 16.1 **a** and **b** Host–Guest complexes reported by Schneider and coworkers. **c** Partial view of the X-ray structure of thiotrithiazylium chloride

for the binding of anions with neutral π-acceptors, has been recently published by Albrecht and collaborators [62] and its ability to trap anions both in solution and in the solid state. Similarly, Johnson and collaborators have developed receptors for selective nitrate binding in competitive hydrogen bonding solvents where anion–π interactions facilitate the selectivity [63].

This chapter is not intended to be a bibliographic survey of the literature related to anion–π interactions since several excellent reviews have been written for that purpose [31, 35, 64–66]. Instead, we intend to emphasize the bonding relationship between anions and π systems, at the experimental and theoretical forefront of this noncovalent interaction. The chapter is developed under five headings. First, we describe early publications on this topic, which have not been properly cited and adequately placed into perspective. Second, the physical nature of the interaction is explained for assimilation by a wide readership. Third, we highlight selected examples from the literature where molecular recognition driven by anion–π bonding is very relevant. Next, attractive applications and wonderful examples of anion–π bonding to catalysis are described. Finally, clear evidence that illustrates the increasing interest on the study of anion–π interactions in biological systems is provided.

16.2 Early Publications

Early reports on weak attractive interactions involving negatively charged residues and polarizable aryl groups in host–guest systems [67–69] were reported before the publication of a series of computational studies in 2002 [36–38] supporting the existence of attractive forces between anions and the positive electrostatic potential on the ring edge of electron-deficient aromatic groups.

In 1993 Schneider and coworkers demonstrated attractive interactions between simple organic host and guest molecules by means of NMR measurements [67]. Since their experiments were carried out in a highly competitive media (water) and the aryl groups that participate in the anion–π interaction were not electron deficient (see Fig. 16.1a and 16.1b), the calculated interactions energies were very modest,

reaching approximately 2 kJ/mol. A similar value was also obtained for the complex between a calixarene with 4-sulfonato groups and toluene, which is not an electron poor moiety. Thus, the attraction is only dominated by polarization effects (*vide infra*). Earlier to this work, Hiraoka et al. [70] demonstrated the formation of highly symmetric $X^- \cdots C_6F_6$ anion–π complexes in the gas-phase (X = CI, Br, and I). In addition, gas-phase clustering reactions $X^-@(C_6F_6)_{n-1} + C_6F_6 = X^-@(C_6F_6)_n$ for X = F, C1, Br, and I were studied by means of pulsed electron-beam high-pressure mass spectrometry. For fluoride a nucleophilic attack and covalent bond formation was observed and, conversely, noncovalent $X^- \cdots C_6F_6$ complexes were detected for X = CI, Br, and I where the anion was located along the C_6 main symmetry axis of C_6F_6.

Another early progress in this direction [71] was reported in 1996 by Woollins and collaborators. They named the anion–π interaction as "π-facial" [72] in their description of the close contact between chloride and the seven-membered aromatic $[S_4N_3]^+$ ring that they observe in the X-ray structure of thiotrithiazylium chloride (see Fig. 16.1c).

16.3 Physical Nature

The physical nature of the anion–π interaction has been widely studied using high level *ab initio* and Density Functional Theory (DFT) calculations. Moreover, several partition energy schemes have been used in order to decompose the total interaction energy into individual components [73, 74]. The general conclusion is that electrostatic forces and ion-induced polarization are the main forces that contribute to the anion–π interaction [75–77]. The electrostatic term is explained by means of the permanent quadrupole moment (Q) of the arene, which is the first non-zero multipole moment in symmetric arenes. Moreover, in most asymmetric arenes, where the dipole moment (μ) is non-zero, the μ_z component is approximately zero and, likewise symmetric arenes, the electrostatic attraction is basically due to the existence of the adequate component (perpendicular to the ring plane) of the quadrupole moment (Q_{zz}), which describes the charge distribution on both sides of the aromatic plane. The Q_{zz} of benzene is negative, but can be turned into positive by attaching electron withdrawing substituents to the ring (see Fig. 16.2a). Similarly, the Q_{zz} of pyridine is negative but can be turned into a positive value by attaching a coordination metal to the nitrogen atom [66]. Therefore, the electrostatic charge-quadrupole interaction between an anion and an aromatic ring can become attractive either attaching electron-withdrawing substituents or coordinating metal ions in case of heteroaromatic rings. The ion-induced polarization of the π-electron system by the anion is significant, inducing a dipole (see Fig. 16.2b). Therefore, a polarization contribution to the total interaction energy is derived from the interaction of the anion with the induced dipole [73–76]. An alternative explanation on the nature of anion–π interactions involving benzene rings has been proposed by Wheeler and Houk [78], who examined substituent effects in $Cl^- \cdots C_6H_{6-n}X_n$ complexes. In contrast

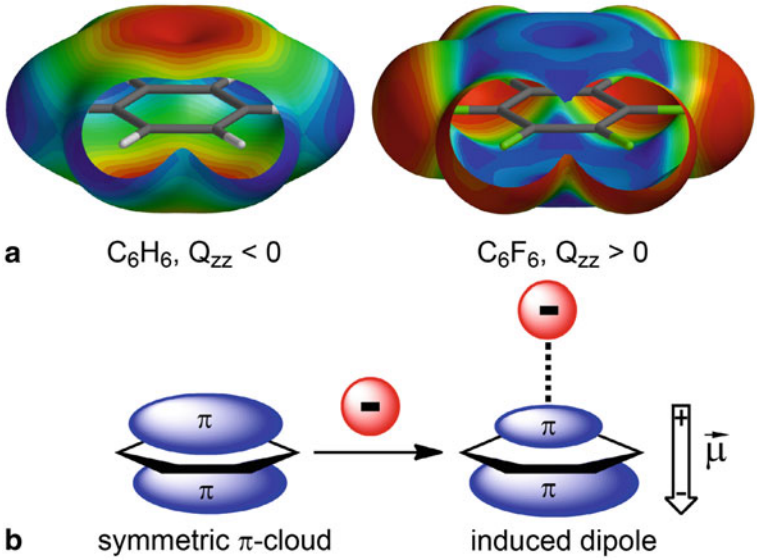

Fig. 16.2 **a** Molecular electrostatic potential of benzene and hexafluorobenzene. **b** Schematic representation of the ion-induced dipole

to the intuitive view where the substituent induces changes in the aryl π system, Wheeler and Houk propose a model where substituent effects in these systems can be attributed mainly to direct interactions between the anion and local C–X dipoles.

A proper understanding of the physical nature (*vide supra*) is necessary to explain, on one hand, the dual binding mode exhibited by arenes with negligible quadrupole moments [79, 80]. That is, since electrostatic and polarization terms are the main contributions to both anion–π and cation–π interactions, molecules with very small Q_{zz} values such as 1,3,5-trifluorobenzene ($Q_{zz} = 0.57$ B) and *s*-triazine ($Q_{zz} = 0.90$ B) are able to interact with both anions and cations because the electrostatic term is negligible and the interaction is dominated by the polarization term, which is always attractive. On the other hand, it is useful to rationalize the interaction of anions with electron-rich aromatic rings, such as benzene, which are not strongly repulsive. This is due to a compensating effect between the electrostatic (unfavorable) and ion-induced polarization (favorable) forces that roughly cancel each other out. For this reason, the anion–π interaction energy of benzene with chloride is very small, but favorable [81, 82].

The electrostatic term depends on the magnitude of the Q_{zz} and the polarization term on the magnitude of the molecular polarizability parallel to the main symmetry axis (denoted as $\alpha_{||}$) in symmetric arenes (or perpendicular to the ring plane in asymmetric arenes, denoted as α_{zz}), which are intrinsic properties of the π-system. Therefore, it is clear that in order to design an efficient anion receptor based on the anion–π interaction, the π–binding units should have a large and positive quadrupole moment and a large molecular polarizability. However, there is a limitation for the

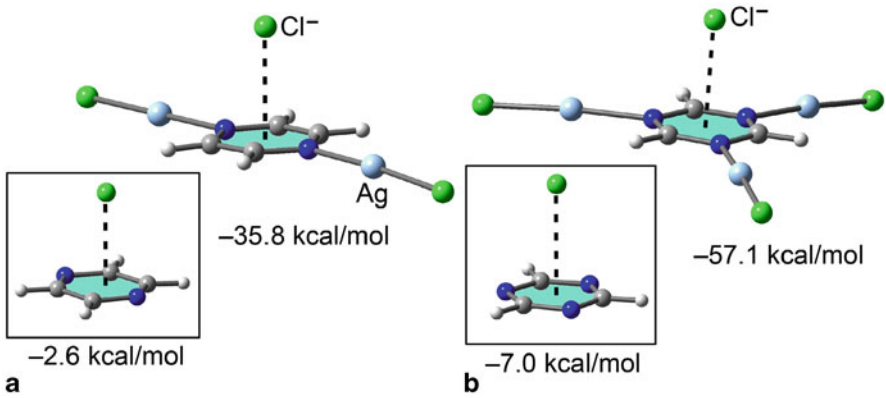

Fig. 16.3 Interaction energies of pyrazine **a** and triazine **b** anion–π complexes from references [84, 85]

first condition due to the reduced number of strong electron withdrawing groups available for constructing the binding blocks. To have a large value of Q_{zz}, the use of -NO_2 and -CN groups is required. However, it is synthetically complicated to attach more than three strong electron withdrawing groups and the spacer to the aromatic ring to build the receptor. An intelligent solution to this limitation is the utilization of heteroaromatic rings, especially di-, tri- and tetrazines. The metal coordination to heteroaromatic rings strongly increases the π-acidity of the ring, thus favoring the anion–π interactions [83, 84]. It has been demonstrated that the coordination of both pyrazine (Fig. 16.3a) and *s*-triazine (Fig. 16.3b) to Ag^I dramatically enhances their ability to establish anion–π binding [83, 85].

The same behavior has been demonstrated [84] for *s*-tetrazine using both theory and experiment. As a matter of fact, *s*-tetrazine coordinated to four Ag^I atoms is the most powerful anion–π acceptor binding block reported to date. Theoretically, the interaction energy of *s*-tetrazine with nitrate ion strengthens from − 9.6 kcal/mol to − 62.4 kcal/mol when the arene is tetracoordinated to Ag^I. Experimentally, several X-ray crystal structures of *s*-tetrazine μ_4–coordinated to Ag^I have been reported, exhibiting very close contacts between the anion and the *s*-tetrazine ring (see Fig. 16.4) indicating strong anion–π interactions, in agreement with theoretical predictions. Interestingly the anion–π distance for the perchlorate anion in the X-ray structure shown in Fig. 16.3a (2.61 Å) is the shortest reported to date.

The anion–π interaction has been also observed in the solid state of novel hybrid inorganic–organic assemblies generated from $H_4SiW_{12}O_{40}$ as Keggin-type polyoxometalates (POM) and several trinuclear lanthanide clusters of type $\{Na(H_2O)_3[Ln(HCAM)(H_2O)_3]_3\}^{4+}$ (Ln = La, Ce, Eu and H_3CAM = chelidamic acid or 2,6-dicarboxy-4-hydroxypyridine) [86]. These unprecedented anion–π interactions between the POM (a tetra-anion) and the coordinated aromatic ligand rings play a crucial role in the crystal packing formation (see Fig. 16.5). This investigation of the interaction in Keggin-type POM–based inorganic–organic frameworks also

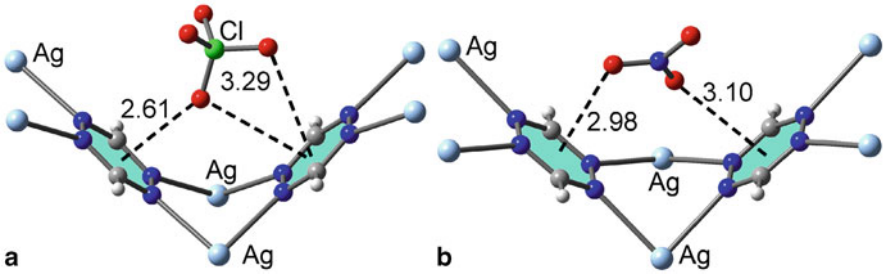

Fig. 16.4 Fragments of the X-ray crystal structures containing μ_4-coordination of 1,2,4,5-tetrazine from ref [84]. The relevant anion–π interactions are indicated by dashed lines (distances in Å)

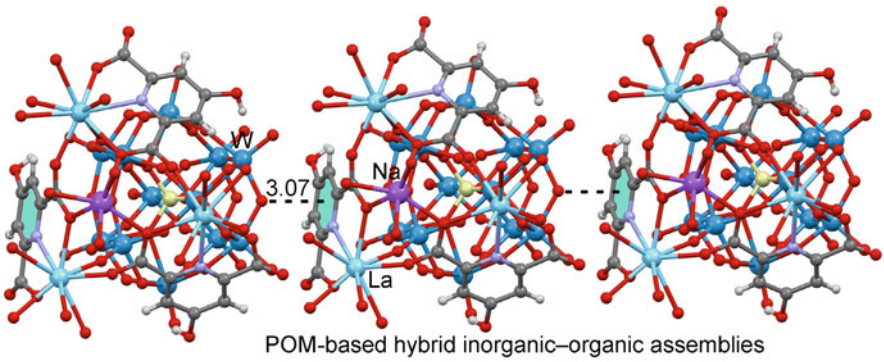

Fig. 16.5 Partial view of the crystal packing of compound $\{Na(H_2O)_3[La(C_7H_3NO_5)(H2O)_3]_3\}[SiW_{12}O_{40}]$ published by Mirzaei et al. [86] with indication of the intermolecular anion–π interaction established between the organic ligand and the POM (distance in Å)

includes a theoretical study devoted to analyze the effect of the ligand coordination to the metal center that increases the π-acidity of the aromatic ring, and consequently enhances its ability to establish anion–π interactions.

The coordination of the heteroaromatic ring to a transition metal is similar to the effect of protonation. For instance, pyridine, diazines, etc. can be easily protonated by simply adjusting the pH of the medium increasing the anion binding ability of the ring (anion–π^+ interactions). The geometric and energetic features of anion–π^+ complexes of several aromatic cations (tropylium, quinolizinylium) and various anions have been reported along with crystallographic structures [87, 88]. This field of research has recently attracted attention and several works have appeared in the literature [89, 91]. For instance, the anion–π^+ interaction participates in the formation of a robust recognition motif in the transition metal malonate complexes using protonated 2-amino-4-picoline and 2-aminopyridine as the auxiliary ligands [89, 90]. As expected, these complexes exhibit very large (>80 kcal/mol) interaction energies

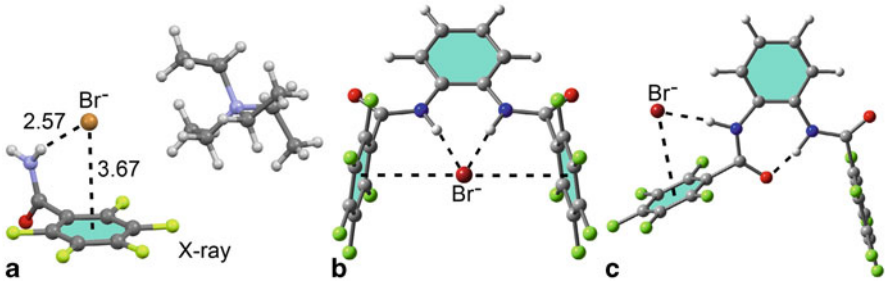

Fig. 16.6 **a** Partial view of the X-ray crystal structure reported by Giese et al. [62] showing the pentafluorobenzamide, the bromide and the tetraethylammonium cation. **b** and **c** Modeled binding motifs for the interaction of bromide with a receptor containing two pentafluorobenzamide moieties. Distances in Å

due to strong electrostatic effects that dominate the interaction. The anion–π^+ interaction in protonated purine and pyrimidine bases has been recently reviewed [91] demonstrating the importance of this interaction in biologically relevant compounds.

16.4 Anion-π Interactions in Supramolecular Chemistry

In this section of the chapter we describe very recent and especially relevant advances in this field. The quality of the works demonstrates that there is a continuous and increasing interest for investigating and developing novel anion-binding hosts and transporters based on electron deficient aromatic rings.

Giese et al. [62] have studied the binding of a series of anions with neutral π-acceptors by means of concurrent hydrogen bonding and anion-π interaction. Interestingly, latter interaction is demonstrated both in the solid state and in solution, and further evidenced by a computational study. The receptors are based on pentafluorobenzamides (see Fig. 16.6), which were found appropriate systems for studying anion-π interactions. In case of bromide, the anion–π complex was characterized by X-ray spectroscopy and it is the first solid state structure where anion-π interactions between an uncharged pentafluorophenyl derivative and an anion are observed. Moreover, the investigation in solution showed differences between electron rich and poor systems, which are explained by a cooperative effect of N–H · · · anion and anion–π interactions and the enhanced acidity of the amide proton by the electron-withdrawing C_6F_5-unit.

Remarkably, Watt et al. [63] have demonstrated that the selective nitrate binding in competitive media by a tripodal urea receptor (see Fig. 16.7) is facilitated by anion–π interactions. Using ^{1}H–NMR titrations they show that the higher affinity observed for nitrate over the halides for the fluorinated receptor is lost when the fluorine atoms are absent. An anion–π interaction between the nitrate and the π-system of the ethynyl-substituted arene is proposed as the source of this selectivity.

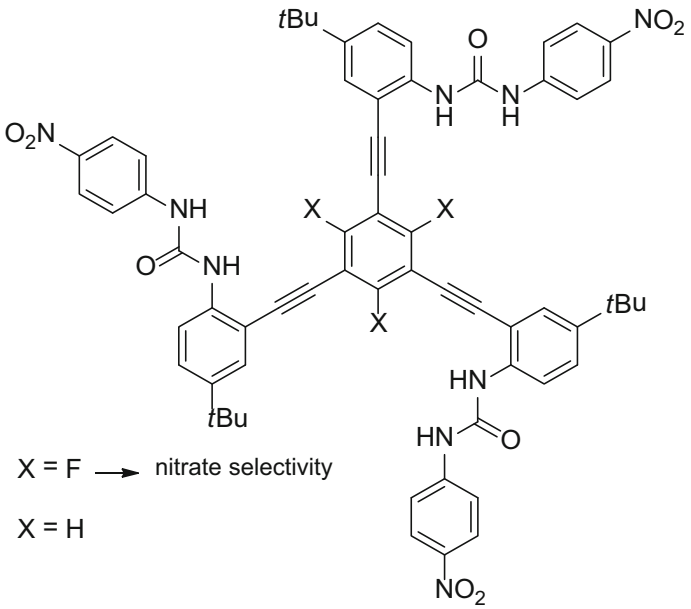

Fig. 16.7 Tripodal urea receptors synthesized by Watt et al. [63]

The fluorinated receptor trends: $NO_3^- > Cl^- > Br^- > I^-$, with a moderate selectivity for nitrate. The existence of the anion–π interaction is demonstrated using an indirect prove. That is, binding studies of the non-fluorinated receptor showed three important issues: first, the nitrate selectivity is lost; second, the association constant of nitrate is diminished compared to the fluorinated receptor; and, third, the binding mode of nitrate is different than that for halides. These data support a model in which nitrate binds to the receptors through a combination of hydrogen bonds with the urea moieties and an anion–π-type interaction regardless of the electronic nature of the central core, thus raising the association constant and selectivity for nitrate in the fluorinated receptor and the opposite in the non-fluorinated. Latter receptor is more selective for chloride since it binds the receptors via hydrogen bonding interactions, exclusively.

Anion–π interactions have been systematically studied by Wang and Wang [92] using tetraoxacalix[2]arene[2]triazine (see Fig. 16.8), an electron-deficient and neutral macrocyclic host. Using electrospray ionization mass spectrometry (ESI-MS), fluorescence titration and X-ray crystallography, the authors demonstrate the formation of 1:1 host-guest complexes with four typical polyatomic anions of different geometries and shapes in the gaseous phase, in solution, and in the solid state. The association constants for the formation of anion–π complexes in acetonitrile are impressive in some cases, ranging from 239 to 16950 M^{-1}, ($NO_3^- > BF_4^- > PF_6^- > SCN^-$). The X-ray molecular structures of the complexes show that two opposed triazine rings of the host interact with the anionic guests through cooperative anion–π and lp–π

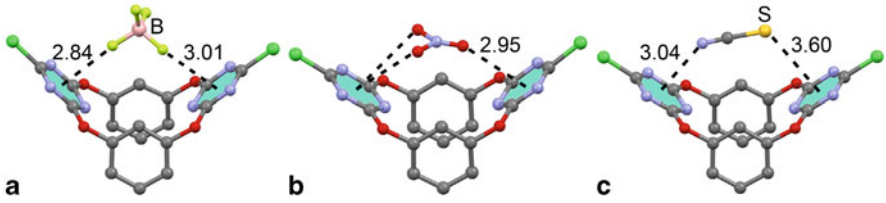

Fig. 16.8 Crystal structures of the 1:1 host-guest complexes reported by Wang and Wang [92] Distances in Å

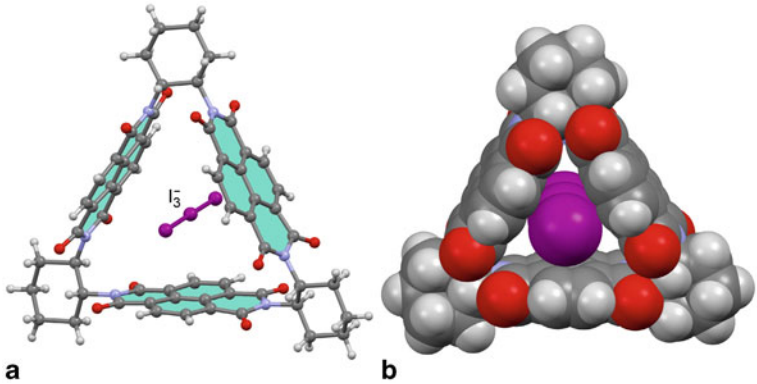

Fig. 16.9 Two views in ball and stick **a** and space filling **b** of the crystal structure of the triangular prism complexed to I_3^- reported by Stoddart and coworkers [93]

interactions. In this comprehensive study, the generality and diversity of anion–π interaction motifs certainly provide a new dimension to molecular recognition of anions and anion-governed self-assembly processes.

Stoddart et al. [93] have reported an interesting anion–π recognition study in molecular triangular prisms formed by naphthalenediimide redox centers. They have demonstrated, both experimentally and by the application of theory, through-space orbital interactions and electron sharing phenomena in their synthesized triangular, redox-active naphthalenediimide prisms (see Fig. 16.9). The resulting electronic communication among the naphthalenediimide units leads to an unusually large number of individually accessible redox states in the triangular prisms, opening the door to potential applications in the field of molecular electronics. The electron deficient cavities of the molecular prisms are ideal for studying anion–π interactions. This ability is demonstrated by the encapsulation of linear I_3^- anions inside the prismatic cavities, causing a profound change in the packing of the prisms in the extended solid-state architecture. The inclusion of I_3^- anions induces π–π stacking of the chiral prisms into supramolecular helices, providing a unique example of anion-induced self-assembly with potential applications as ion-channels. In addition, the chirality endowed by the six stereogenic centers in the occupied prisms dictates the either right- or left-handed associated with their packing in the solid state.

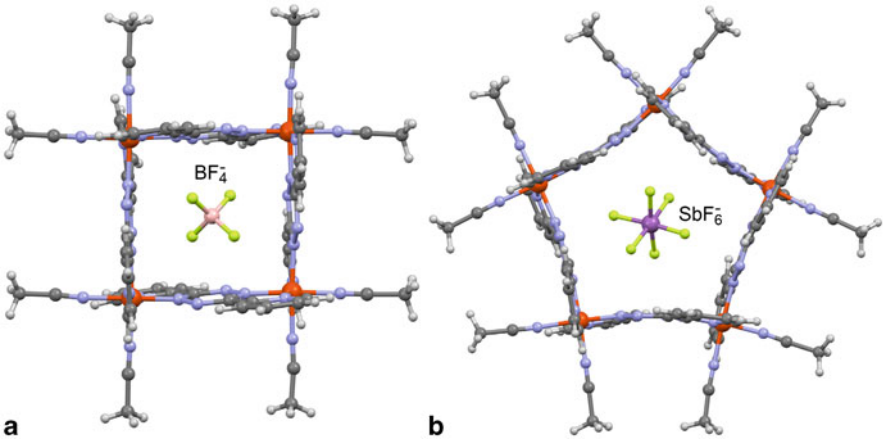

Fig. 16.10 Anion-templated X-ray structures of a molecular square **a** and a molecular pentagon **b** reported by Chifotides et al. [94]

Taking advantage of the enhanced π-acidity of organic ligands upon coordination to transition metals, Chifotides et al. [94] have reported supramolecular architectures with 3,6-bis(2-pyridyl)-*s*-tetrazine cavities where anion–π interactions participate in the remarkable stability of Fe(II) metallacycles in solution. This comprehensive investigation provides convincing evidence that anion–π interactions are the main driving force in the formation (in high yields) of self-assembled Fe(II)-templated metallacycles. Combining several technics, like X-ray crystallography, ^{1}H NMR, solution and solid-state ^{19}F NMR spectroscopies, cyclic voltammetry and mass spectroscopy, they demonstrated that the anion acts as a template occupying the π–acidic cavities and controlling the nuclearity of the cages. That is, $[BF_4]^-$ and $[ClO_4]^-$ anions template molecular squares (see Fig. 16.10a) and $[SbF_6]^-$, $[AsF_6]^-$ and $[PF_6]^-$anions template molecular pentagons (see Fig. 16.10b) establishing close directional F· · ·C *s*-tetrazine contacts with the *s*-tetrazine rings that are up to 0.4 Å shorter than the sum of the F· · ·C van der Waals radii (3.17 Å). The number and strength of F· · ·C tetrazine contacts are maximized. They have also performed unprecedented solid-state ^{19}F MAS NMR studies, where the templating anions showed downfield chemical shifts $\Delta\delta(^{19}F)$ ranging 3.5–4.0 ppm (compared to peripheral anions) due to their participation in anion–π interactions. NMR, cyclic voltammetry and mass spectroscopy studies also establish that the molecular squares and pentagons remain intact in solution. This study provides unambiguous evidence that anion–π interactions are the main driving force in the templation process leading to the formation of Fe(II) metallacycles with π-acidic cavities. The F atoms of the encapsulated anions are directly located over the more π-acidic *s*-tetrazine C atoms, establishing six simultaneous anion–π contacts with the metallacycle edges. More importantly, they evidenced the instrumental role of the templating anions in solution, thus favoring and stabilizing the Fe(II) metallacycles of specific nuclearities.

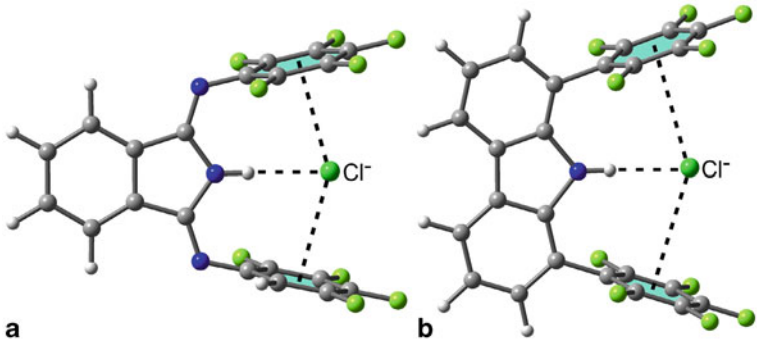

Fig. 16.11 Representation of the neutral hosts designed and synthesized by Meyer's group [95]

Meyer's group [95] has designed and synthesized pre-organized anion traps (Cl^- and Br^-) for exploiting anion–π interactions based on 1,3-bis(pentafluorophenyl–imino) isoindoline (Fig. 16.11a) and 3,6-di-*t*-butyl-1,8-bis(pentafluorophenyl)-9H–carbazole (Fig. 16.11b) in various solvents. Both neutral receptors provide a central N–H$\cdots$X$^-$ hydrogen bond that directs the halide anion into a pre-organized clamp formed by the two electron deficient arenes. Crystal structures of host–guest complexes reveal that in all cases the guest is located in the cleft between the perfluorinated flaps. In solution, association constants up to 960 M^{-1} have been determined depending on the solvent by NMR spectroscopy. Their study also includes a detailed computational analysis of the host–guest complexes and an energetic decomposition of the ring–anion interactions that confirm the contribution of the anion–π interactions to the stabilization of these complexes (∼50 % of the total energy). These receptors contribute to increasing the relative low number of examples of neutral receptors that are well pre-organized for exploiting anion–π interactions.

Ballester and his group have dedicated much effort to the experimental quantification of anion–π interactions in solution using neutral host–guest model systems [96]. The quantification of anion–π interactions is commonly provided by computational studies of simple models that are useful to estimate the binding energy. The scientific community has no doubt about the existence of attractive anion-π interactions in the gas phase and in the solid state. However, there are still few examples of attractive anion-π interactions in solution. Ballester's group has reported several examples of neutral molecular receptors that bind anions in solution as a combination of anion–π interactions and hydrogen bonding [97, 98]. The strength of the anion–π interaction is indirectly detected as a modulation of the stronger hydrogen bonding interaction. The dissection of the energy contribution of the anion–π interaction to the overall binding is complex and requires the use of appropriate reference systems. Ballester and coworkers have designed a model system based on a series of "four wall" aryl-extended calix[4]pyrrole receptors. They contain deep aromatic cavities with fixed walls (see Fig. 16.12a, for the nitro-derivative as example). The formation of four concurrent H-bonds between the anion and the NH groups of the calix[4]pyrrole

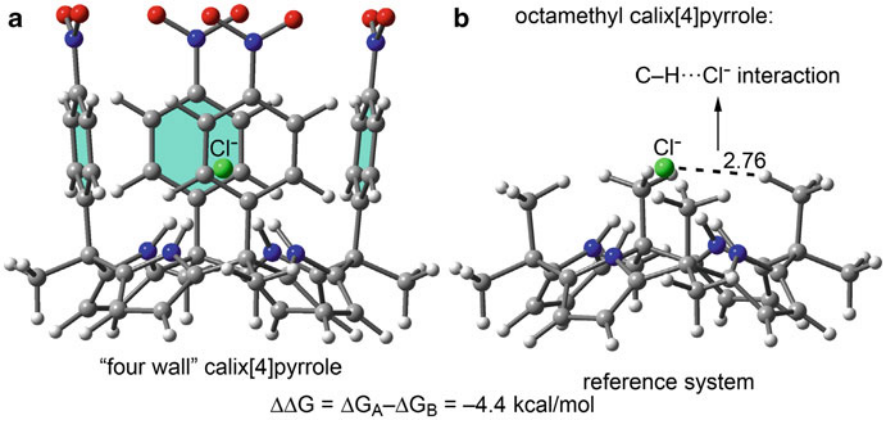

Fig. 16.12 Structures of a four wall calix[4]pyrrole **a** and the receptor used by Ballester's group [97] as reference **b** for the estimation of chloride–π interactions. Distance in Å

scaffold fixes the halide in the aromatic cavity, above the planes of the π-systems of the four meso-aryl substituents, as probed using ^{1}H NMR spectroscopy. Different *para* substituents in the aromatic walls were used to tune the electronic density of the aromatic rings and Cl^- as the interacting anion. Interestingly, the magnitude of the association constant was increased with the electron-withdrawing character of the *para*-substituent in the meso-aryl groups. The difference in free energy ($\Delta\Delta$G, see Fig. 16.12) of binding between different complexes provides a direct measurement of the relative interaction energy of the halide with the different aromatic systems. Using this approach, they determined a maximum contribution of −4.4 kcal/mol for the four chloride–π interactions to the overall binding free energy in the *para*-nitroaryl substituted receptor. This is likely an underestimation of the anion–π interaction energy because the reference system used by Ballester's group was octamethylcalix[4]pyrrole, which provides four C–H · · · Cl interactions (see Fig. 16.12b). Therefore, the estimated contribution of –4.4 kcal/mol likely means that each anion–π interaction is 1.1 kcal/mol more favorable than each C–H · · · Cl^- interaction that is established in the reference complex and, consequently, it cannot be used as an absolute estimate of the anion–π interaction in solution.

Calix[4]pyrrole based receptors featuring two additional pyrrole side arms have been also used by Chang et al. [99] for the molecular recognition of anions. This hexapyrroliccalix[4]pyrrole (see Fig. 16.13) has two additional pyrrole suspended above or below the calix[4]pyrrole core and presents *cis*/*trans* isomerism. Anion binding experiments revealed interesting differences in the binding mode depending on the isomer. That is, whilst the *trans* isomer displays only hydrogen bonding interactions, the *cis* isomer displays a mixed binding mode featuring a combination of hydrogen bonding and anion–π interactions resulting in an unexpected strong binding (see Fig. 16.13c). In fact, UV spectrophotometry and NMR titrations reveal

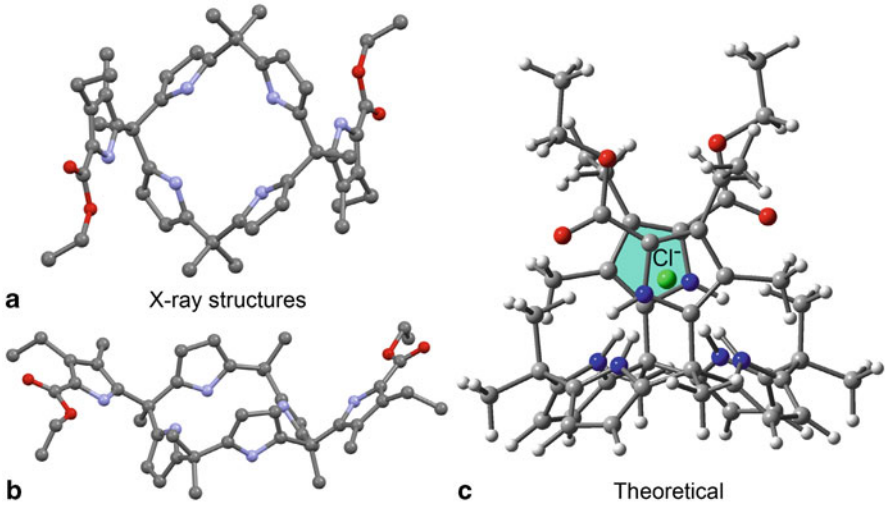

Fig. 16.13 X-ray structures of the trans **a** and cis **b** isomers of *meso*-substituted hexapyrrolic-calix[4]pyrrolereceptors reported by Chang et al. [99] and the modeled complex **c** between chloride and the *cis* isomer

that *cis* isomer displays higher affinity (105–106 M^{-1}) for anions while the *trans* isomer is more selective.

An interesting research has been recently published by He et al. [100] devoted to the study of the stability of size-regulable vesicles based on anion–π interactions Taking tetraoxacalix[2]arene[2]triazine as a functionalization platform (see Fig. 16.14), He et al. synthesized a series of new amphiphilic anion receptors that self-assemble into stable vesicles in a mixture of THF and water, with the surface of the vesicles engineered by electron-deficient cavities. Strikingly, several anions are able to influence the size of self-assembled vesicles selectively, following the order of $F^{\mu} < ClO_4^{\mu} < SCN^{\mu} < BF_4^{\mu} < Br^{\mu} < Cl^{\mu} < NO_3^{\mu}$, as revealed by dynamic light scattering (DLS) experiments and independently with the hydration cost. This order of selectivity agrees with the binding strength of anions with tetraoxacalix[2]arene[2]triazine receptor, demonstrating that the anion–π interaction most probably competed over other possible weak interactions and is responsible for this interesting selectivity. Furthermore, the chloride permeation process across the membrane of the vesicles was also studied by He et al. using fluorescent experiments. This investigation shows the potentiality of heteracalix aromatics as new models to construct functional vesicles and gives a new dimensionality to the anion–π interaction in aqueous medium and, potentially, in living systems.

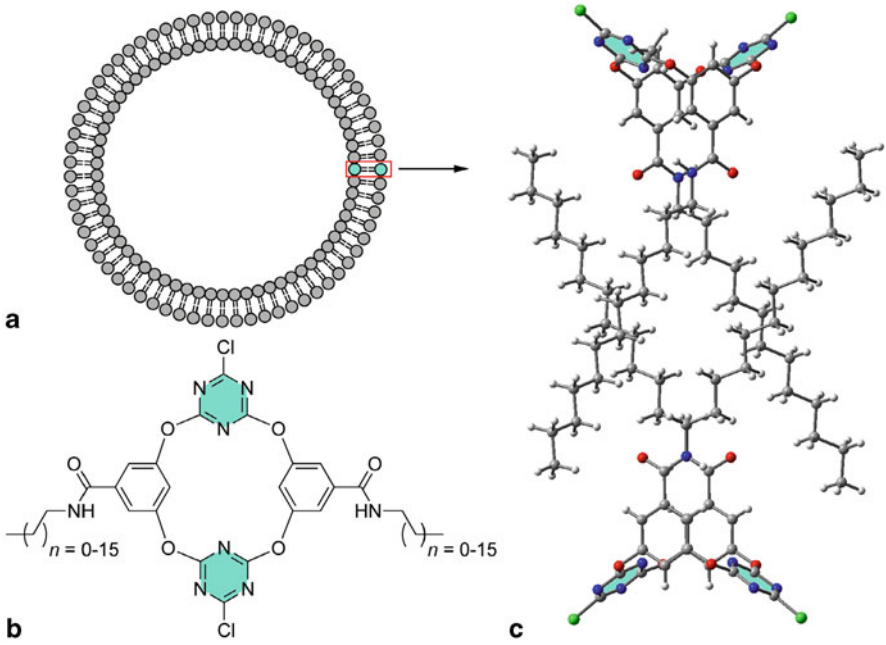

Fig. 16.14 Schematic illustration of the vesicle (**a** and **b**) and long alkyl chain derivatives of tetraoxacalix[2]arene[2]triazine compounds (**c**) reported by He et al. [100]

16.5 Catalysis

Zhao et al. reported in 2013 for the first time experimental evidence suggesting that anion–π interactions contribute to the catalysis of the Kemp elimination reaction (see Fig. 16.15) by π-acidic naphthalene diimides (NDI) leading to conceptually innovative design strategies to stabilize anionic transition states [101]. Subsequent studies [102] with modified sulfur-containing NDI catalysts confirmed the general validity of increasing transition-state stabilization while increasing π-acidity with regard to the Kemp elimination. Moreover, computational simulations are in excellent agreement with experimental results, confirming that the stabilization of the anionic transition states (but not the neutral ground states) increases with the π-acidity of the catalysts, i.e., the existence of anion–π catalysis. The proposed catalytic cycle is shown in Fig. 16.15 and the key point is the location of the carboxylate base on the π-acidic surface of catalyst NDI. The initial substrate-NDI complex (NDI + S) is likely stabilized by a combination of π–π and hydrogen bonding interactions. In the transition state (TS), the negative charge flows over the π-acidic surface from the carboxylate base over the carbanion of the conjugate base to the phenolate oxygen. The TS is stabilized by the π-acidic surface of the NDI. The proton transfer from the carboxylic acid to the phenolate in the intermediate (I) prevents product inhibition and regenerates the catalyst NDI. Therefore, in this catalytic cycle, the NDI stabilizes the

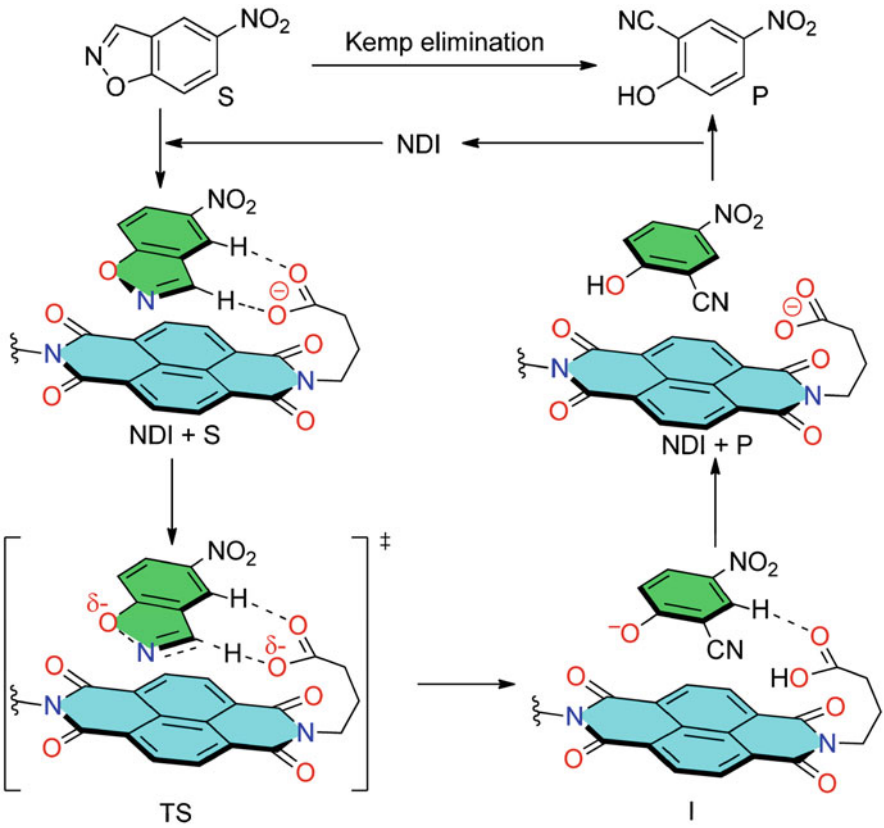

Fig. 16.15 Catalytic cycle proposed by Zhao et al. [101] (NDI + S = catalyst–substrate complex, I = reactive intermediate, NDI + P = catalyst–product complex)

anionic TS by means of anion–π interactions, which are proved by the acceleration of the Kemp elimination observed experimentally. Both pioneering works [101, 102] on catalysis with anion–π interactions are extremely important since clearly open a new avenue and move beyond the grand principles operating in nature.

The catalytic cycle shown in Fig. 16.15 has been analyzed theoretically to examine the most important aspects of the anion–π catalyzed Kemp elimination considering solvent effects in the calculations [102]. Already in the early stage of the reaction (NDI + S), the carboxylate anion is positioned so that an efficient intramolecular anion–π interaction with the most π-acidic part of the NDI surface takes place. The carboxylate group also anchors the benzisoxazole substrate above the NDI surface via two C–H · · · O interactions (see Fig. 16.15), therefore favoring the π–π interaction between the two parallel disposed aromatic systems. This facilitates the proton transfer between the catalyst and the substrate, leading to the transition state TS with the activation barrier of 15.05 kcal/mol (Fig. 16.16a). At this stage the electron

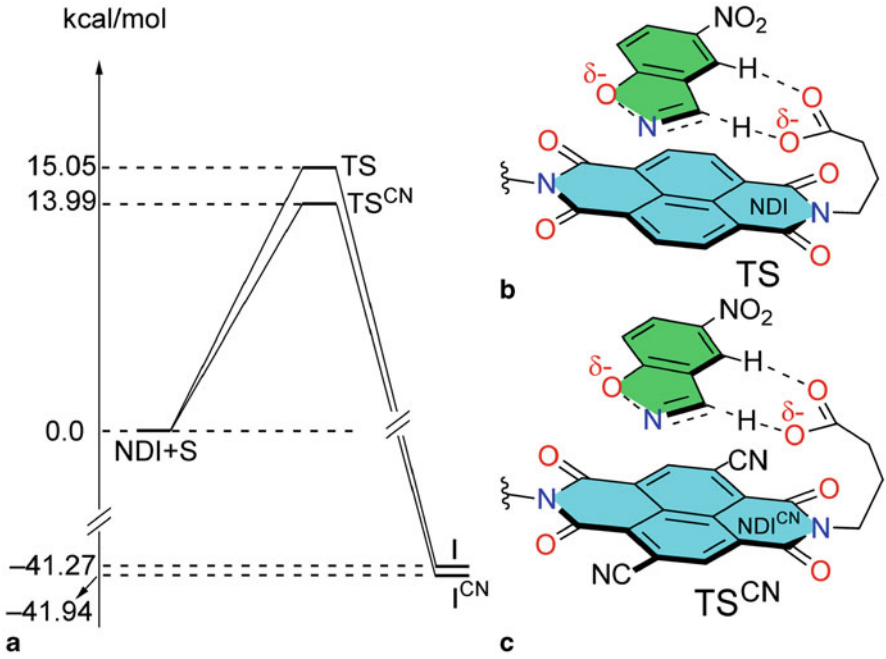

Fig. 16.16 **a** Free energy diagram (IEFPCM/M06-2X/def2-TZVP//B97-D/6-311G**) for the Kemp elimination with anion–π catalyst NDI and NDI^{CN}. **b** Transition state (TS) for the reaction catalyzed by catalyst NDI, negative charge transfer is highlighted in red. **c** Transition state (TS^{CN}) for the reaction catalyzed by catalyst NDI^{CN} [101]

transfer, which occurs over several atoms from carboxylate anion to phenolate oxygen, is efficiently stabilized by the π-acidic surface of NDI. The reaction progresses toward the anionic intermediate I, while the negative charge is fully transferred to the benzisoxazole substrate. The benzisoxazole oxygen accumulates most of the charge and its distance from the NDI surface decreases to 2.995 Å. The conformation of this complex once again favors anion–π interactions by placing the anionic oxygen right above the preferential binding site of NDI. Interestingly, the Kemp elimination in the presence of the 3,7-dicyano-substituted catalyst (NDI^{CN}, see Fig. 16.16c) follows a similar pathway. However, the increased π-acidity enhances the TS^{CN} transition-state stabilization by 1.06 kcal/mol when compared to TS (Fig. 16.16a). This stabilization enhancement of TS^{CN} by the more π-acidic NDI surface of NDI^{CN} confirms that anion–π interactions contribute significantly to this reaction. The comparison of certain geometric parameters during the reaction mechanism involving catalysts NDI and NDI^{CN} also reflects enhanced anion–π implication. For instance the more pronounced decrease of the distance between benzisoxazole oxygen and catalyst plane on going from the initial complex to the TS is correlated with the higher strength of the anion–π interaction in the NDI^{CN}.

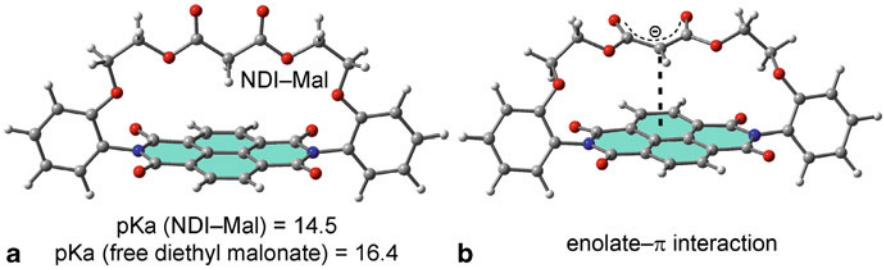

Fig. 16.17 **a** Malonate covalently bonded to NDI reported by Matile's group [103]. **b** DFT-optimized geometry obtained for the enolate–π interaction

Matile's group has taken one step further the research on anion–π catalysis [103] by extending it to enolate chemistry. They have covalently attached a malonate moiety to an NDI (see Fig. 16.17) and by means of ^{1}H NMR spectroscopy they have compared the chemical shift of the acidic hydrogen atoms of free diethyl malonate with the corresponding ones upon its attachment to the naphthalene diimide (denoted as NDI–Mal, see Fig. 16.17a). As a result, the chemical shift of 3.38 ppm for the acidic hydrogen atoms in free diethylmalonate changes to 1.78 ppm due to their exposure to the naphthalene ring current in NDI–Mal that causes the upfield shift (see Fig. 16.17a). This direct experimental evidence for the fixed covalent positioning of the malonate above the π–acidic surface is very important because it assures that any changes in acidity can be unambiguously attributed to the stabilization of the enolate by anion–π interactions (see Fig. 16.17b). In fact, they have demonstrated using ^{1}H NMR titrations that anion–π interactions stabilize the enolate by almost two pK_a units. Remarkably, the addition of these anion–π-stabilized reactive enolate intermediates to enones and nitroolefins occurs with significant transition-state stabilizations (up to 11 kJ/mol) [103]. Moreover, anionic cascade reactions that cover aldol condensation, elimination and transesterification also accelerate on π-acidic surfaces. These findings are very significant because enolate chemistry is fundamental in chemistry and biology. This research is expected to stimulate the use of anion–π interactions in catalysis in the broadest sense.

16.6 Biologically Relevant Anion–π Interactions

Clear evidence that illustrates the growing interest in the study anion–π interactions in biological systems is the development of software capable to search anion–π contacts in the PDB and related biological databases. To this respect, the STAAR (statistical analysis of aromatic rings) program [47] can identify anion–π interactions in a large structural database of biomolecules. The program is freely available for download through the web (http://staar.bio.utk.edu) and has been tested in a recent version of the PDB demonstrating the high prevalence and relatively strong anion–π

energies involving side-chain/side-chain interactions in biomolecules. The program is currently limited to phenylalanine residues and is expected to include tryptophan and tyrosine residues in the new version. The program also provides pairwise interaction energies with Asp and Glu as anions. Other future project for improving the program includes the possibility to investigate anion–π interaction in protein/ligand complexes.

A pioneering work on the study of anion-π interaction in biomolecular recognition was published in 2012 by Chakravarty et al. [46]. Combining theoretical and convincing experimental evidences they demonstrated that the interaction between an anion and an aromatic π system plays an important role in the formation and recognition of biomolecular structures. Though less frequent than its counterpart cation–π interactions, the examination of high-resolution structures of proteins and nucleic acids indicated the presence anion–π interactions. Interestingly, they have been observed unambiguously, occurring in protein/nucleic acid loops and often involving conserved/coevolving sites in proteins. These findings suggest that this interaction plays an important role in macromolecular folding and function. Two examples are highlighted in Fig. 16.18. In the first one, the anion–π interaction is observed in the nucleic acid backbone (tetraloop hairpin, 1m5o structure), where the guanine-nucleotide (G75) establishes a clear anion–π interaction with the oxygen atom of the phosphate anion. Apart from this interacting phosphate, the rest of the phosphate anionic oxygen atoms in the nucleic acid backbone face outward. Remarkably, the phosphate anion that faces inward is poorly solvated, facilitating the anion–π interaction (Fig. 16.18a, top). The nucleic acid base likely compensates for the energetic cost of the desolvation of the anion. In many RNA hairpins, even in structures with low resolutions the same interacting pattern is observed [46] suggesting that anion–π interactions may be a regular feature of nucleic acid loops. The second example involves an RNA-protein interaction that corresponds to a crucial biological process. It is well-known [104] that the RRM (RNA recognition motif) of the U1A protein binds to U1 snRNA hairpin II. The structure of the complex reveals that RRM Asp92 stacks in parallel to the Cytosine-12 residue of the hairpin loop, establishing an anion–π interaction. Amazingly, the same feature is observed in the structure of the RRM of U2B" bound to hairpin IV of U2 snRNP (Fig. 16.18b). U2B" Asp92 stacks on Guanine-12 of the hairpin loop of U2 and this arrangement is a conserved feature of spliceosomal RNA hairpins involving a C/G12 and Asp92-carboxylates.

Frontera and coworkers [45] have studied the important role of anion–π interactions in the active site of the urate oxidase enzyme (see Fig. 16.19). The inhibition of this enzyme by cyanide ions is caused by the existence of an anion–π interaction between the anionic inhibitor and the π-electron deficient enzymatic substrate (uric acid). They demonstrated using high level *ab initio* calculations that the anion–π interaction between the inhibitor and the substrate in a model of the active site is energetically favorable. In addition, a favorable cooperativity effect between a π–π stacking interaction involving the substrate and a phenylalanine residue (PHE159, see Fig. 16.19) and the anion–π interaction also contributes to the binding energy. This was the first example where the presence of an anion–π interaction between an inhibitor and an enzymatic substrate was proposed to be crucial in the inhibition of

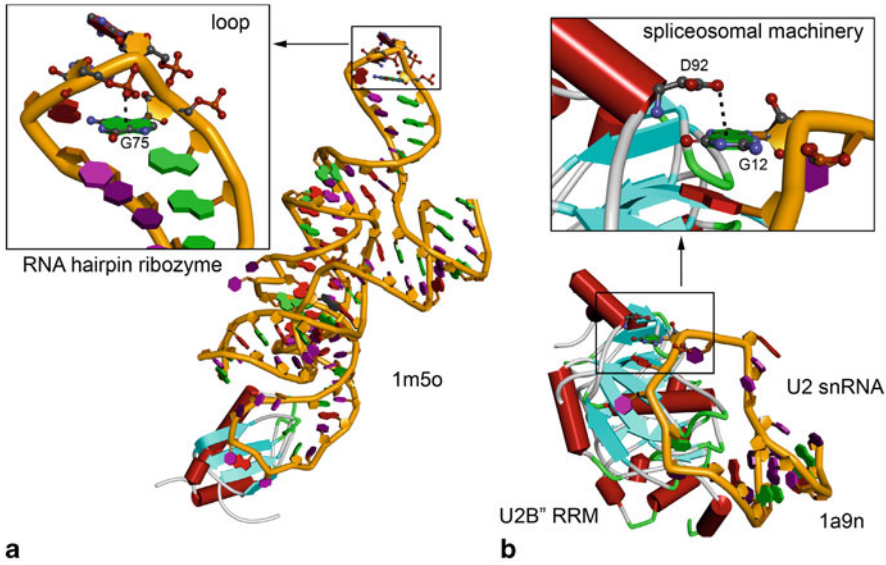

Fig. 16.18 **a** Anion–π interaction in nucleic acids between the base of the i^{th} nucleotide with the oxygen atoms of an $(i+2)^{th}$ phosphate of a tetraloop hairpin. **b** Anion–π in RRM (split-pea *green*, 1a9n) of U2B″ (spliceosomalmachinary) in complex with U2 snRNA

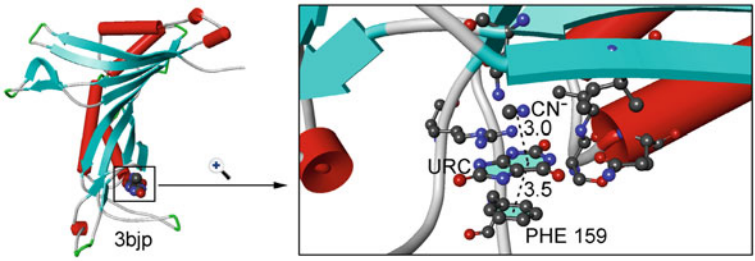

Fig. 16.19 The anion–π interaction between the CN^- inhibitor and the uric acid substrate (URC) found in the X-ray structure 3bjp studied theoretically by Frontera's group [45] is shown. Distances in Å

an enzyme. This investigation extended the relevance of anion–π interactions to an important field such as enzyme chemistry.

The relevance of anion–π interactions in flavoproteins has been analyzed by Estarellas et al. [105]. An initial search in the PDB provided evidence of anion–π interactions in a large number of proteins. Many of them are reductases that have affinity for small negatively charged ions such as acetate, chloride and thiocyanate, which are competitive inhibitors. Two interesting examples were described in their investigation. In the first one (2ar8, tryptophan 7-halogenase), the anion binds the FAD at the enzymatic center by means of an anion–π interaction and participates

in the enzymatic process [106]. This enzyme catalyzes the regioselective chlorination at the 7 position of tryptophan. The Cl^- is bound near to the entrance of the tunnel leading to the tryptophan and positioned to make a nucleophilic attack on the flavin peroxide resulting in the formation of hydroxylated FAD and HClO that is the real chlorination agent [106]. A close examination of the active site reveals that the anion is located above the most electron deficient ring of the FAD establishing an anion–π interaction. In the ternary complex (see Fig. 16.19a), the distance between the Cl^- anion and the ring centroid of the pyrimidinic ring of FAD is 3.3 Å in 2ar8. The second example is a FMN-dependent nitroreductase (1ylU) [107] that plays a prominent role in the reduction of the antibiotics nitrofuranone and nitrofurantoin to the hydroxylamine derivatives, which are the active antibacterial agents. Inhibition studies of nitroreductase (NTR) have demonstrated that acetate displayed competitive inhibition with respect to both the substrate and NADH [107]. More interestingly, it has been demonstrated that acetate binds only to the oxidized form of the enzyme. The crystal form of the enzyme complexed to the acetate and the FMN coenzyme shows one acetate molecule in each active site (see Fig. 16.20b). The acetate anion is bonded to the active site by means of a bifurcated hydrogen bond, a $-CH_3 \cdot \cdot \cdot \pi$ interaction and an anion–π interaction with the pyrimidinic ring of FMN. The distance between the acetate anion and the ring centroid is short (3.0 Å) indicating a strong interaction. This investigation further confirms the relevance of anion–π interactions in the scientific field of enzyme chemistry.

Bauzá et al. [108] have studied the importance of anion-π interactions in the mechanism of sulfide:quinone oxidoreductase. It is a flavin-dependent enzyme that plays a physiological role in two important processes. First, it is responsible for sulfide detoxification by oxidizing sulfide ions to elementary sulfur and the electrons are first transferred to flavin adenine dinucleotide (FAD), which in turn passes them to the quinone pool in the membrane [109]. Second, this enzyme plays a key role in the sulfide-dependent respiration and anaerobic photosynthesis, deriving energy for their growth from reduced sulfur in sulfidotrophic bacteria [110]. Two mechanisms of action for this enzyme have been proposed [108] that involve a common anionic intermediate that it is stabilized by a relevant anion–π interaction (INT–FAD, see Fig. 16.21). The formation of the intermediate is facilitated by reducing the transition state barrier, owing to an anion–π interaction that involves the π system of FAD. By analyzing the X-ray structures of SQRs available in the Protein Data Bank (PDB) and using DFT calculations, they have demonstrated the relevance of the anion–π interaction in the enzymatic mechanism.

In particular, Bauzá et al. [108], have demonstrated theoretically using DFT calculations (B3LYP/6-311++G**) that the energy barrier is reduced when the reaction occurs in the present of FAD, using cyclo-L-cysteine (see Figure 16.21b) as model of disulfide bond. In Fig. 16.22a the reaction coordinate diagram is represented where the relative energies of the different species involved in the mechanism are also indicated. It can be observed that the presence of FAD (in red) stabilizes all species. However, the most important result is that the stabilization of the transition state is higher than the stabilization of the intermediates, thus supporting the crucial role of FAD not only as an electron sink in subsequent enzymatic steps of

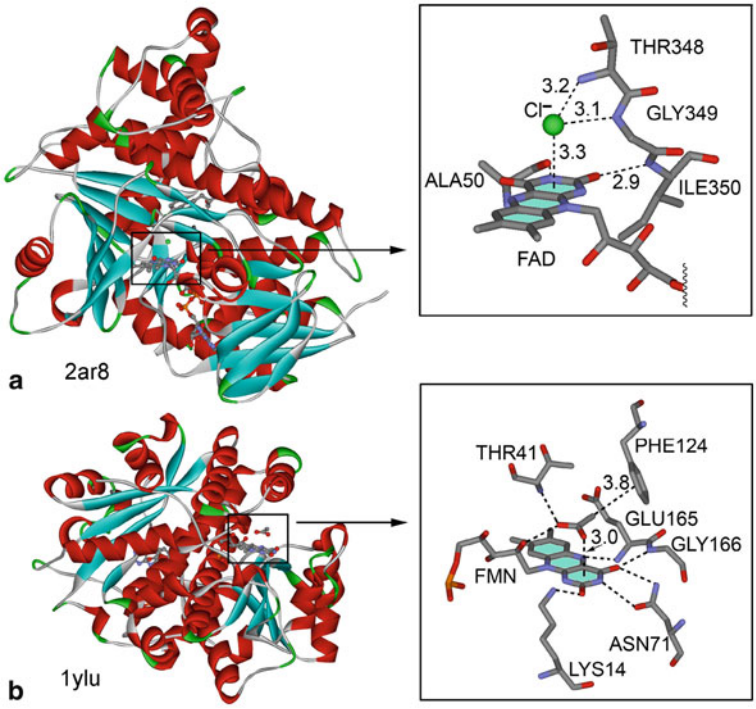

Fig. 16.20 3D X-ray structures of 2ar8 (**a**) and 1ylu (**b**) are shown and the anion–π interactions observed in the FAD-Cl^- (**a**) and FMN-acetate (**b**) complexes are highlighted. Distances in Å

the mechanism but also facilitating the initial addition-elimination reaction to take place. Moreover, the presence of FAD stabilizes the reaction product placing it in an ideal position either to attack or transfer an electron to the isoalloxazine ring. The theoretical study also includes the computation of the NCI (Non Covalent Interaction) plot to study the anion–π interactions observed in the structures retrieved from the PDB. This visualization index based on the electron density and its derivatives enables the identification and visualization of non-covalent interactions efficiently [111]. The isosurfaces correspond to both favorable and unfavorable interactions, as differentiated by the sign of the second density Hessian eigenvalue and defined by the isosurface color. In Fig. 16.22b the representation of the NCI plot computed around the FAD (within 4.0 Å) cofactor in 3SX6 protein is shown. Obviously, several non-covalent regions clearly appear between the FAD and the aminoacids. For instance, several green isosurfaces are found around the methyl groups of FAD, which are characteristic of hydrophobic interactions. Interestingly the trisulfide group (represented in ball and stick) originates an extended isosurface that covers two rings of FAD and confirms the importance of the anion–π interaction.

Finally, Bauzá et al. [112] have also studied long-range effects in anion–π interactions and their crucial role in the inhibition mechanism of mycobacterium

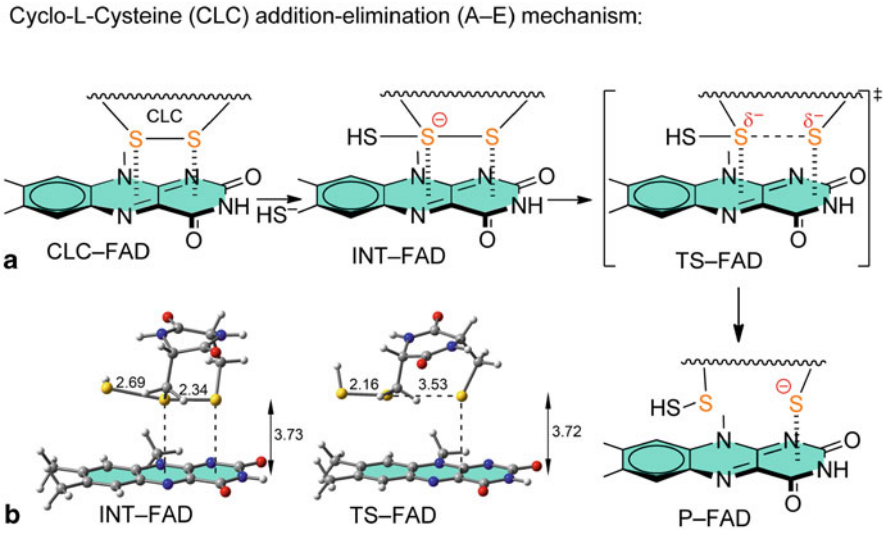

Fig. 16.21 **a** Addition-elimination mechanism in the presence of FAD. **b** B3LYP/6-311 + G* optimized complexes of INT-FAD and TS-FAD. Distances in Å

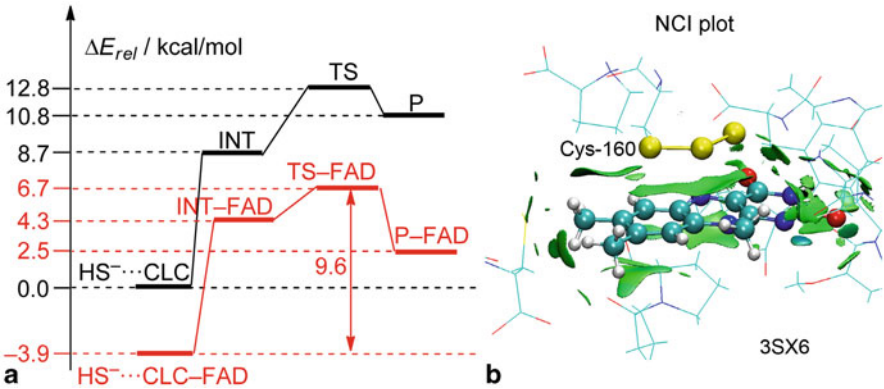

Fig. 16.22 **a** Addition-elimination mechanism in the presence of FAD. **b** B3LYP/6-311+G* optimized complexes of INT-FAD and TS-FAD. Distances in Å

tuberculosis malate synthase. This enzyme together with isocitrate lyase forms the glyoxylate shunt that is an anaplerotic bypass of the traditional Krebs cycle. It plays a prominent role in Mycobacterium tuberculosis virulence, so it can be exploited for the development of antitubercular therapeutics [113]. The shunt bypasses two steps of the tricarboxylic acid cycle, allowing the incorporation of carbon, and thus, refilling oxaloacetate under carbon-limiting conditions. A catalytic Mg^{2+} unit is located at the bottom of the cavity, and plays a very important role. Recently, the development of effective antituberculosis drugs based on phenyldiketo acids (PDKAs) has been

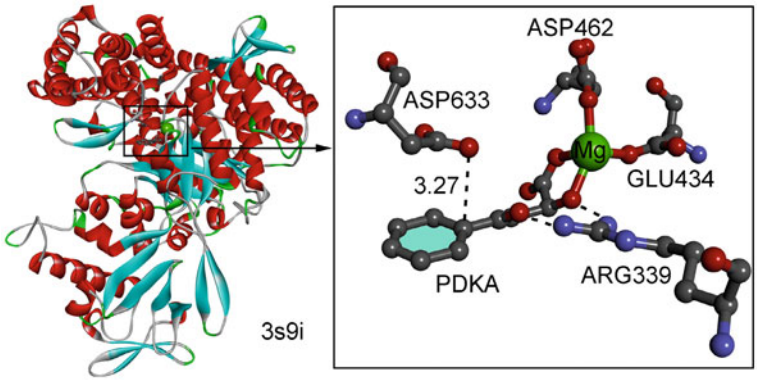

Fig. 16.23 3D X-ray structure of 3s9i is shown and the anion–π interaction observed in the active site between aspartate-633 and the PDKA inhibitor is highlighted. Distance in Å

reported [114]. Interestingly, all the crystal structures of malate synthase–inhibitor complexes exhibit close contact between the carboxylate of Asp633 and the face of the aromatic ring of the inhibitor (see Fig. 16.23). Remarkably, the replacement of the phenyl ring in PDKA by aliphatic moieties yields inactive inhibitors, suggesting that the aromatic moiety is crucial for inhibition. However, the aromatic ring of PDKA is not electron-deficient, and consequently, the anion–π interaction is expected to be very weak (dominated only by polarization effects). Combining an analysis of the recent X-ray structures of GlcB–PDKA complexes retrieved from the protein data bank (PDB) and computational *ab initio* studies (RI-MP2/def2-TZVP level of theory), Bauzá et al. [112] demonstrate the prominent role of the Mg^{2+} ion in the active site, which promotes long-range enhancement of the anion–π interaction.

Specifically, in the computational analysis of the long range effects, they have computed several theoretical models of the inhibitor and their complexes with formate (as model of aspartate) to demonstrate the long range effect and to estimate it energetically. Two possible enol forms (highlighted in green in Fig. 16.24) of the diketo acid denoted as PDKA-taut1 and PDKA-taut2 were considered in the energetic analysis, since it has been demonstrated experimentally that the PDKA chemical structure is in its enol tautomer by solution-phase ^{1}H– and 13C–NMR data [114]. In addition, a theoretical model of the inhibitor coordinated to the Mg^{2+} ion was also considered, denoted as PDKA-Mg. In this model (see Fig. 16.23c), a formate ligand was added in order to keep the model neutral and to exemplify the active site where the Mg^{2+} is coordinated to ASP462 (see Fig. 16.23). Interestingly, the interaction energy of the anion–π complex of formate with PDKA-taut1 is -4.5 kcal/mol and with PDKA-taut2 is almost negligible (-0.2 kcal/mol) indicating that the intramolecular hydrogen bonding is very important since it increases the electron withdrawing ability of the carbonyl group attached to the ring. Interestingly, in the PDKA-Mg complex, the interaction energy is large and negative (-10.6 kcal/mol), indicating a strong binding. Therefore, the theoretical study clearly demonstrates

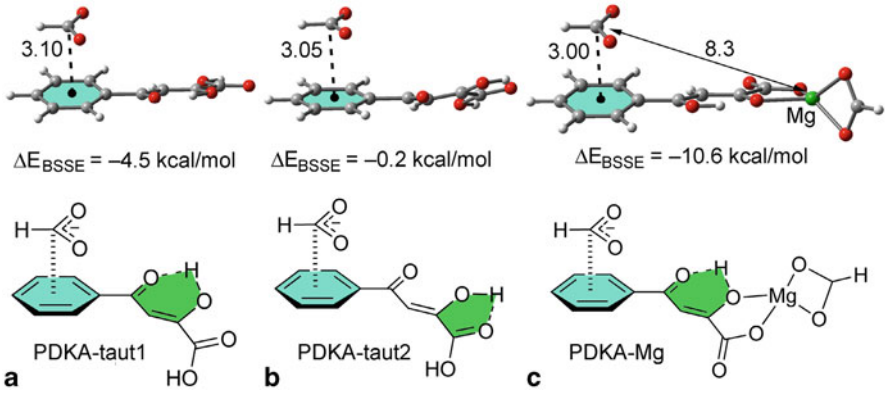

Fig. 16.24 Optimized formate complexes with the PDKA considering both tautomers (**a** and **b**) and with the PDKA coordinated to Mg^{2+} from reference [112]. The interaction energies (ΔE_{BSSE}) are indicated. Distances in Å

that the presence of the Mg ion coordinated to the inhibitor enhances the anion–π interaction. This long-range effect should be emphasized since the distance from the Mg ion to the interacting anion is 8.3 Å (see Fig. 16.24c).

16.7 Conclusions

The purpose of this chapter has been to expose the bonding relationship between anions and π systems by describing high quality work and demonstrating the extraordinary potential of this relatively new interaction to impact the field of supramolecular science, including catalysis and enzyme chemistry. It is now evident for the scientific community that anion–π interactions are prominent in a wide range of systems and should be considered as an important and general noncovalent binding force. The potential of the anion–π interaction is not limited to the design of novel hosts and sensors. Its important role in RNA recognition motifs, enzymatic chemistry, catalysts, and crystal engineering has provided a new dimension to this interaction. The effect of anion–π interactions should not be overlooked in chemical and biological systems that involve anion and electron-deficient aromatic species.

Acknowledgment We are grateful to Carol Garau, Xavier Lucas, Daniel Escudero and David Quiñonero with whom we have had the good fortune to work and their names are contained within the pertinent references. We thank CONSOLIDER-Ingenio 2010 (project CSD2010-0065) and the MICINN of Spain (project CTQ2011-27512 FEDER funds) for financial support. We thank the Direcció General de Recerca, Desenvolupament Tecnològic i Innovació del Govern Balear (project 23/2011, FEDER funds) for financial support.

References

1. Schneider HJ (2009) Binding mechanisms in supramolecular complexes. Angew Chem Int Ed 48:3924–3977
2. Schneider HJ, Yatsimirski A (2000) Principles and methods in supramolecular chemistry. Wiley, Chichester
3. Lehn JM (1995) Supramolecular chemistry concepts and perspectives. Wiley-VCH, Weinheim
4. Vögtle F (1993) Supramolecular chemistry: an introduction. Wiley, New York
5. Beer PD, Gale PA, Smith DK (1999) Supramolecular chemistry. Oxford University Press, Oxford
6. Steed JW, Atwood JL (2000) Supramolecular chemistry. Wiley, Chichester
7. Politzer P, Murray JS, Clark T (2010) Halogen bonding: an electrostatically driven highly direccional noncovalent interaction. Phys Chem Chem Phys 12:7748–7757.
8. Bundhun A, Ramasami P, Murray JS, Politzer P (2013) Trends in σ-hole strenghts and interactions of F_3MX molecules (M = C, Si, Ge and X = F, Cl, Br, I). J Mol Model 19:2739–2746
9. Bauzá A, Mooibroek TJ, Frontera A (2013) Tetrel–bonding: rediscovered supramolecular force? Angew Chem Int Ed 52:12317–12321
10. Meyer EA, Castellano RK, Diederich F (2003) Interactions with aromatic rings in chemical and biological recognition. Angew Chem Int Ed 42:1210–1250
11. Schneider HJ, Yatsimirsky A (2008) Selectivity in supramolecular host-guest complexes. Chem Soc Rev 37:263–277
12. Salonen LM, Ellermann M, Diederich F (2011) Aromatic rings in chemical and biological recognition: energetics and structures. Angew Chem Int Ed 50:4808–4842
13. Müller-Dethlefs K, Hobza P (2000) Noncovalent interactions: a challenge for experiment and theory. Chem Rev 100:143–167
14. Burley SK, Petsko GA (1985) Aromatic-aromatic interaction: a mechanism of protein structure stabilization. Science 229:23–28
15. Li S, Cooper VR, Thonhauser T, Lundqvist BI, Langreth DC (2009) Stacking interactions and DNA intercalation. J Phys Chem B 113:11166–11172
16. Rutledge LR, Campbell-Verduyn LS, Wetmore SD (2007) Characterization of the stacking interactions between DNA or RNA nucleobases and the aromatic amino acids. Chem Phys Lett 444:67–175
17. Tsuzuki S, Yoshida M, Uchimaru T, Mikami M (2001) The origin of the cation/π interaction: the significant importance of the induction in Li^+ and Na^+ complexes. J Phys Chem A 105:769–773
18. Ma JC, Dougherty DA (1997) The cation-π interaction. Chem Rev 97:1303–1324
19. Crowley PB, Golovin A (2005) Cation-π interactions in protein-protein interfaces. Proteins Struct Funct Genet 59:231–239
20. Gallivan JP, Dougherty DA (2000) A computational study of cation-π interactions vs salt bridges in aqueous media: implications for protein engineering. J Am Chem Soc 122:870–874
21. Lamoureux JS, Maynes JT, Glover JMN (2004) Recognition of 5′-YpG-3′ sequences by coupled stacking/hydrogen bonding interactions with amino acid residues. J Mol Biol 335:399–408
22. Frey J, Kraus T, Heitz V, Sauvage JP (2005) A catenane consisting of a large ring threaded through both cyclic units of a handcuff-like compound. Chem Commun 49:5310–5312
23. Masu H, Sakai M, Kishikawa K, Yamamoto M, Yamaguchi K, Kohmoto S (2005) Aromatic foldamers with iminodicarbonyl linkers: their structures and optical properties. J Org Chem 70 1423–1431
24. Bao X, Isaacsohn I, Drew AF, Smithrud DB (2007) Determining the binding and intracellular transporting abilities of a host-[3]rotaxane. J Org Chem 72:3988–4000
25. Heemstra JM, Moore JS (2004) Helix stabilization through pyridinium-π interactions. Chem Commun 40:1480–1481

26. Nishio M, Hirota M, Umezawa Y (1998) In the C–H/π interaction: evidence, nature, consequences. Wiley-VCH, New York
27. Nishio M (2004) CH/π hydrogen bonds in organic and organometallic chemistry. Cryst Eng Comm 6:130–156
28. Egli M, Sarkhel S (2007) Lone pair-aromatic interactions: to stabilize or not to stabilize. Acc Chem Res 40:197–205
29. Mooibroek TJ Gamez P Reedijk J (2008) Lone pair–π interactions: a new supramolecular bond? CrystEngComm 10:1501–1515
30. Mitra M, Manna P, Seth SK, Das A, Meredith J, Helliwell M, Bauzá A, Choudhury SR, Frontera A, Mukhopadhyay S (2013) Salt-bridge-π (sb-π) interactions at work: associative interactions of sb-π, π-π and anion-π in Cu(II)-malonate-2-aminopyridine-hexafluoridophosphate ternary system. CrystEngComm 15:686–696
31. Frontera A, Gamez P, Mascal M, Mooibroek TJ, Reedijk J (2011) Putting anion-π interactions into perspective. Angew Chem Int Ed 50:9564–9583
32. Schottel BL, Chifotides HT, Dunbar KR (2008) Anion-π interactions. Chem Soc Rev 37:68–83
33. Caltagirone C, Gale PA (2009) Anion receptor chemistry: highlights from 2007. Chem Soc Rev 38:520–563
34. Gamez P, Mooibroek TJ, Teat SJ, Reedijk J (2007) Anion binding involving π-acidic heteroaromatic rings. Acc Chem Res 40 435–444
35. Hay BP, Bryantsev VS (2008) Anion-arene adducts: C–H hydrogen bonding, anion-π interaction, and carbon bonding motifs. Chem Commun 44:2417–2428
36. Quiñonero D, Garau C, Rotger C, Frontera A, Ballester P, Costa A, Deyà PM (2002) Anion-π interactions: do they exist? Angew Chem Int Ed 41:3389–3392
37. Mascal M, Armstrong A, Bartberger MD (2002) Anion-aromatic bonding: a case for anion recognition by π-acidic rings. J Am Chem Soc 124:6274–6276
38. Alkorta I, Rozas I, Elguero J (2002) Interaction of anions with perfluoro aromatic compounds. J Am Chem Soc 124:8593–8598
39. Kim DY, Singh NJ, Kim KS (2008) Cyameluric acid as anion-π type receptor for ClO_4^- and NO_3^-: π-Stacked and edge-to-face structures. J Chem Theory Comput 4:1401–1407
40. Schottel BL, Bacsa J, Dunbar KR (2005) Anion dependence of Ag(I) reactions with 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (bptz): isolation of the molecular propeller compound $[Ag_2(bptz)_3][AsF_6]_2$. Chem Commun 41:46–47
41. Han B, Lu JJ, Kochi JK (2008) Anion recognitions via cocrystallizations with organic π-acids in the efficient self-assembly of nanoscopic one-dimensional molecular chains. Cryst Growth Des 8:1327–1334
42. Mascal M, Yakovlev I, Nikitin EB, Fettinger JC (2007) Fluoride-selective host based on anion-π interactions, ion pairing, and hydrogen bonding: synthesis and fluoride-ion sandwich complex. Angew Chem Int Ed 46:8782–8784
43. Götz RJ, Robertazzi A, Mutikainen I, Turpeinen U, Gamez P, Reedijk J (2008) Concurrent anion-π interactions between a perchlorate ion and two π-acidic aromatic rings, namely pentafluorophenol and 1,3,5-triazine. Chem Commun 44:3384–3386
44. Albrecht M, Müller M, Mergel O, Rissanen K, Valkonen A (2010) CH-directed anion-π interactions in the crystals of pentafluorobenzyl-substituted ammonium and pyridinium salts. Chem Eur J 16:5062–5069
45. Estarellas C, Frontera A, Quiñonero D, Deyà PM (2011) Relevant anion-π interactions in biological systems: the case of urate oxidase. Angew Chem Int Ed 50:415–418
46. Chakravarty S, Sheng ZZ, Iverson B, Moore B (2012) "η6"-Type anion-π in biomolecular recognition. FEBS Lett 586:4180–4185
47. Jenkins DD, Harris JB, Howell EF, Hinde RJ, Baudry J (2013) STAAR: Statistical Analysis of Aromatic Rings. J Comput Chem 34:518–522
48. Dawson RE, Hennig A, Weimann DP, Emery D, Ravikumar V, Montenegro J, Takeuchi T, Gabutti S, Mayor M, Mareda J, Schalley CA, Matile S (2010) Experimental evidence for the functional relevance of anion-π interactions. Nat Chem 2:533–538

49. Sakai N, Mareda J, Vauthey E, Matile S (2010) Core-substituted naphthalenediimides. Chem Commun 46:4225–4237
50. Gale PA, Caltagirone C (2014) Anion sensing by small molecules and molecular ensembles. Chem Soc Rev. doi:10.1039/c4cs00179f
51. Caballero A, Zapata F, Beer PD (2013) Interlocked host molecules for anion recognition and sensing. Coord Chem Rev 257:2434–2455
52. Gale PA (2011) Anion receptor chemistry. Chem Commun 47:82–86
53. Wenzel M, Hiscock JR, Gale PA (2012) Anion receptor chemistry: highlights from 2010. Chem Soc Rev 41:480–520
54. Gale PA, Quesada R (2006) Anion coordination and anion-templated assembly: highlights from 2002 to 2004. Coord Chem Rev 250:3219–3244
55. Bowman-James K, Bianchi A, García-Espaa E (2011) Anion coordination chemistry. Wiley-VCH, Weinheim
56. Berg JM (1995) Zinc finger domains: from predictions to design Acc Chem Res 28:14–19
57. Ashcroft FM (2000) Ion channels and disease. Academic, San Diego
58. Moss B (1996) A land awash with nutrients-the problem of eutrophication. Chem Ind 11:407–411
59. Asakura T, Kim SY, Morita Y, Ozawa M (2005) Reduction of pertechnetate in nitric extraction of rare metals for future reprocessing. J Nucl Radiochem Sci 6:267–269
60. Benner S (2010) Hydrology: anthropogenic arsenic. Nat Geosci 3:5–6
61. Frontera A, Quiñonero D, Deyà PM (2011) Cation-π and anion-π interactions. WIREs Comput Mol Sci 1:440–459
62. Giese M, Albrecht M, Krappitz T, Peters M, Gossen V, Raabe G, Valkonen A, Rissanen K (2012) Cooperativity of H-bonding and anion-π interaction in the binding of anions with neutral π-acceptors. Chem Commun 48:9983–9985
63. Watt MM, Zakharov LN, Haley MM, Johnson DW (2013) Selective nitrate binding in competitive hydrogen bonding solvents: do anion-π interactions facilitate nitrate selectivity? Angew Chem Int Ed 52:10275–10280
64. Gamez P, Mooibroek TJ, Teat SJ, Reedijk J (2007) Anion-π interactions involving π-acidic rings. Acc Chem Res 40:435–444
65. Ballester P (2008) Recognition of anions. Springer Berlin
66. Frontera A (2013) Encapsulation of anions: macrocyclic receptors based on metal coordination and anion-π interactions. Coord Chem Rev 257:1716–1727
67. Schneider HJ, Werner F, Blatter T (1993) Attractive interactions between negative charges and polarizable aryl parts of host-guest systems. J Phys Org Chem 6:590–594
68. Schneider HJ (1991) Mechanisms of molecular recognition—investigations of organic host guest complexes. Angew Chem Int Ed Engl 30:1417–1436
69. Hiraoka K, Mizuse S, Yamabe S (1987) High-symmetric structure of the gas-phase cluster ions $X^- \cdot \cdot \cdot C_6F_6$ (X = Cl, Br and I). J Phys Chem 91:5294–5297
70. Hiraoka K, Mizuse S, Yamabe S (1987) A determination of the stabilities and structures of F-(C_6H_6) and F-(C_6F_6) clusters. J Chem Phys 86:4102–4105
71. Bauzá A, Quiñonero D, Deyà PM, Frontera A (2013) Anion-π interactions in $[S_4N_3]^+$ rings. New J Chem 37:2636–2641
72. Galán-Mascarós JR, Slawin AMZ, Woollins JD, Williams DJ (1996) π-Facial interactions between Cl^- and $[S_4N_3]^+$. Polyhedron 15:4603–4605
73. Kim D, Tarakeshwar P, Kim KS (2004) Theoretical investigations of anion-π interactions: the role of anions and the nature of π systems. J Phys Chem A 108:1250–1258
74. Kim DY, Singh NJ, Lee JW, Kim KS (2008) Cyameluric acid as anion-π type receptor for ClO_4^- and NO_3^-: π-Stacked and edge-to-face structures. J Chem Theory Comput 4:1162–1169
75. Garau C, Frontera A, Quiñonero D, Ballester P, Costa A, Deyà PM (2003) A topological analysis of the electron density in anion-π interactions. Chem Phys Chem 4:1344–1348
76. Quiñonero D, Garau C, Frontera A, Ballester P, Costa A, Deyà PM (2002) Counterintuitive interaction of anions with benzene derivatives. Chem Phys Lett 359:486–492

77. Bauzá A, Deyà PM, Frontera A, Quiñonero D (2014) Substituent effects in cation-π interactions revisited: a general approach based on intrinsic properties of the arenes. Phys Chem Chem Phys 16:1322–1326
78. Wheeler SE, Houk KN (2010) Are anion/π interactions actually a case of simple charge−dipole interactions? J Phys Chem A 114:8658–8664
79. Garau C, Quiñonero D, Frontera A, Ballester P, Costa A, Deyà PM (2003) Dual binding mode of s-triazine to anions and cations. Org Lett 5:2227–2229
80. Garau C, Frontera A, Quiñonero D, Ballester P, Costa A, Deyà PM (2004) Cation-π versus anion-π interactions: energetic, charge transfer, and aromatic aspects. J Phys Chem A 108:9423–9427
81. Garau C, Quiñonero D, Frontera A, Ballester P, Costa A, Deyà PM (2003) Anion-π interactions: must the aromatic ring be electron deficient? New J Chem 27:211–214
82. Quiñonero D, Frontera A, Garau C, Ballester P, Costa A, Deyà PM (2006) Interplay between cation-π, anion-π and π-π interactions. Chem Phys Chem 7:2487–2491
83. Quiñonero D, Frontera A, Deyà PM (2008) High-level ab initio study of anion-π interactions in pyridine and pyrazine rings coordinated to Ag(I). Chem Phys Chem 9:397–399
84. Gural'skiy IA, Escudero D, Frontera A, Solntsev PV, Rusanov EB, Chernega AN, Krautscheid H, Domasevitch KV (2009) 1,2,4,5-Tetrazine: an unprecedented μ_4-coordination that enhances ability for anion-π interactions. Dalton Trans 38:2856–2864
85. Bauzá A, Quiñonero D, Deyà PM, Frontera A (2012) Tuning of the anion-π interaction. Theor Chem Acc 131:1219–1230
86. Mirzaei M, Eshtiagh-Hosseini H, Lotfian N, Salimi A, Bauzá A, Van Deun R, Decadt R, Barceló-Oliver M., Frontera A (2014) Syntheses, structures, properties and DFT study of hybrid inorganic-organic architectures constructed from trinuclear lanthanide frameworks and Keggin-type polyoxometalates. Dalton Trans 43:1906–1916
87. Estarellas C, Frontera A, Quiñonero D, Deyà PM (2008) Theoretical and crystallographic study of the dual σ/π binding affinity of quinolizilynium cation. J Chem Theory Comput 4:1981–1989
88. Quiñonero D, Frontera A, Escudero D, Ballester P, Costa A, Deyà PM (2007) Theoretical study of anion-π interactions in seven membered rings. Chem Phys Chem 8:1182–1187
89. Das A, Choudhury SR, Dey B, Yalamanchili SK, Helliwell M, Gamez P, Mukhopadhyay S, Estarellas C, Frontera A (2010) Supramolecular assembly of Mg(II) complexes directed by asociative lone pair-π/ π-π/ π-anion-π/ π-lone pair interactions. J Phys Chem B 114:4998–5009
90. Das A, Choudhury SR, Estarellas C, Dey B, Frontera A, Hemming J, Helliwell M, Gamez P, Mukhopadhyay S (2011) Supramolecular assemblies involving anion-π and lone pair-π interactions: experimental observation and theoretical analysis. Cryst Eng Comm 13:4519–4527
91. Fiol JJ, Barceló-Oliver M, Tasada A, Frontera A, Terrón A, García-Raso A (2013) Structural characterization, recognition patterns and theoretical calculations of longchain Nalkyl substituted purine and pyrimidine bases as ligands: on the importance of anion-π interactions. Coord Chem Rev 257:2705–2715
92. Wang DX, Wang MX (2013) Anion–π interactions: generality, binding strength, and structure. J Am Chem Soc 135:892–897
93. Schneebeli ST, Frasconi M, Liu Z, Wu Y, Gardner DM, Strutt NL, Cheng C, Carmieli R, Wasielewski MR, Stoddart JR (2013) Electron sharing and anion-π recognition in molecular triangular prisms. Angew Chem Int Ed 52:13100–13104
94. Chifotides HT, Giles ID, Dunbar KR (2013) Supramolecular architectures with π-acidic 3,6-bis(2-pyridyl)-1,2,4,5- tetrazine cavities: role of anion–π interactions in the remarkable stability of Fe(II) metallacycles in solution. J Am Chem Soc 135:3039–3055.
95. Bretschneider A, Andrada DM, Dechert S, Meyer S, Mata RA, Meyer F (2013) Preorganized anion traps for exploiting anion-π interactions: an experimental and computational study. Chem Eur J 19:16988–17000

96. Ballester P (2013) Experimental quantification of anion-π interactions in solution using neutral host-guest model systems. Acc Chem Res 46:874–884
97. Gil-Ramírez G, Escudero-Adán EC, Benet-Buchholz J, Ballester P (2008) Quantitative evaluation of anion-π interactions in solution. Angew Chem Int Ed 47:4114–4118
98. Adriaenssens L, Gil-Ramírez G, Frontera A, Quiñonero D, Escudero-Adán EC, Ballester P (2014) Thermodynamic characterization of halide-π interactions in solution using "two wall" aryl extended calix[4] pyrroles as model system. J Am Chem Soc 136:3208–3218
99. Chang KC, Minami T, Koutník P, Savechenkov PY, Liu Y, Anzenbacher P (2014) Anion binding modes in meso-substituted hexapyrrolic calix[4]pyrrole isomers. J Am Chem Soc 136:1520–1525
100. He Q, Han Y, Wang Y, Huang ZT, Wang DX (2014) Size-regulable vesicles based on anion-π interactions. Chem Eur J 20:7486–7491
101. Zhao Y, Domoto Y, Orentas E, Beuchat C, Emery D, Mareda J, Sakai N, Matile S (2013) Catalysis with anion-π interactions. Angew Chem Int Ed 52:9940–9943
102. Zhao Y, Beuchat C, Domoto Y, Gajewy J, Wilson A, Mareda J, Sakai N, Matile S (2014) Anion-π catalysis. J Am Chem Soc 136:2101–2111
103. Zhao Y, Sakai N, Matile S (2014) Enolate chemistry with anion-π interactions. Nature Comm 5:3911
104. Oubridge C, Ito N, Evans PR, Teo CH, Nagai K (1994) Crystal-structure at 1.92 Angstrom resolution of the RNA-binding domain of the U1a spliceosomal protein complexed with an RNA hairpin. Nature 372:432–438
105. Estarellas C, Frontera A, Quiñonero D, Deyà PM (2011) Anion-π interactions in Flavoproteins. Chem Asian J 6:2316–2318
106. Dong C, Flecks S, Unversucht S, Haupt C, van Pee KH, Naismith JH (2005) The structure of tryptophan 7-halogenase (PrnA) suggests a mechanism for regioselective chlorination. Science 309:2216–2219
107. Race PR, Lovering AL, Green RM, Ossor A, White SA, Searle PF, Wrighton CJ, Hyde EI (2005) Structural and mechanistic studies of *Escherichia Coli* nitroreductase with the antibiotic nitrofurazone. Reserved binding orientations in different redox states of the enzyme J Biol Chem 280:13256–13264
108. Bauzá A, Quiñonero D, Deyà PM, Frontera A (2013) On the importance of anion-π interactions in the mechanism of sulfide: quinone oxidoreductase. Chem Asian J 8:2708–2713
109. Cherney M, Zhang Y, Solomonson M, Weiner JH, James MNG (2010) Crystal structure of sulfide:quinone oxidoreductase from *Acidithiobacillus Ferrooxidans*: insights into sulfidotrophic respiration and detoxification. J Mol Biol 398:292–305
110. Pham VH, Yong JJ, Park SJ, Yoon DN, Chung WH, Rhee SK (2008) Molecular analysis of the diversity of the sulfide: quinone reductase (sqr) gene in sediment environments. Microbiol 154:3112–3121
111. Johnson E, Keinan S, Mori-Sánchez P, Contreras-García J, Cohen A, Yang W (2010) Revealing non-covalent interactions. J Am Chem Soc 132:6498–6506
112. Bauzá A, Quiñonero D, Deyà PM, Frontera A (2014) Long-range effects in anion-π interactions: their crucial role in the inhibition mechanism of *Mycobacterium Tuberculosis* malate synthase. Chem Eur J 20:6985–6990
113. McKinney JD, Höner zu Bentrup K, Muoz-Elías EJ, Miczak A, Chen B, Chan WT, Swenson D, Sacchettini JC, Jacobs WR Jr, Russell DG (2000) Persistence of *Mycobacterium Tuberculosis* in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase. Nature 406:735–738
114. Krieger IV, Freundlich JS, Gawandi VB, Roberts JP, Gawandi VB, Sun Q, Owen JL, Fraile MT, Huss SI, Lavandera JL, Ioerger TR, Sacchettini JC (2012) Structure-guided discovery of phenyl-diketo acids as potent inhibitors of *M. Tuberculosis* malate synthase. Chem Biol 19:1556–1567