Metal Ligand Aromatic Cation−π Interactions

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Cation–π interactions are important noncovalent bonding forces. This review covers a special type of cation–π interactions, the metal ligand aromatic cation–π (MLACπ) interaction, where ligands that are coordinated to a metal ion interact with aromatic groups. These interactions have been observed in metalloproteins, metal complexes, biomimetic metal complexes, and when DNA and RNA interact with metal cations. The energy of MLACπ interactions in different systems has been calculated by quantum chemical methods and was found to vary from 1 to 30 kcal/mol.

1. Introduction

Noncovalent interactions are very important for molecular systems ranging from molecular biology to material science.[1] Cation−π interactions are now recognized as important noncovalent binding forces.[2] In their review, Ma and Dougherty provided an overview of cation−π interactions that covered the nature of the interactions, and described cation−π interactions in artificial receptors and in biological structures.[2]

Since that review was published, a large number of papers have appeared that deal with cation−π interactions, especially in biological systems. Investigations on cation−π interactions in proteins and polypeptides have shown that cation−π interaction pairs contribute at least as much to protein stability and the structural motifs of a native protein as do more conventional noncovalent interactions.[3] In a few recent review articles, some theoretical and experimental aspects of cation−π interactions have been considered.[4]

In this review, a special type of cation−π interaction is considered, namely that in which the cation is part of a metal complex (Figure 1). In this type of cation−π interaction, the ligands that are coordinated to a metal ion interact with π systems. In the case of an aromatic π system, we called this interaction a metal ligand aromatic cation−π (MLACπ) interaction. Figure 1 depicts the NH_3 ligands of the $[Co(NH_3)_6]^{3+}$ cation interacting with benzene. Please note that we do not consider direct interactions of a π system with a transition metal atom, as exist in ferrocene and other sandwich compounds, where the π system interacts with the metal's d orbitals. A number of papers that deal with MLACπ interactions have appeared in the last few years.

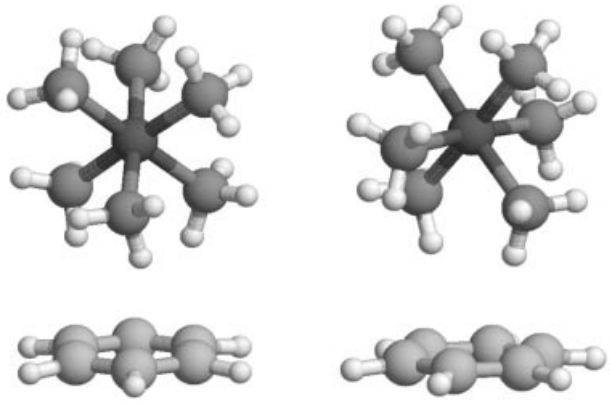

Figure 1. The η_3 and η_2 structures of $[Co(NH_3)_6]^{3+}-C_6H_6$ complexes

In all cases of MLACπ interactions that we report in this article, the ligand participating in the interaction possesses a hydrogen atom pointing towards the π system. By coordinating to a metal cation, ligands acquire partial positive charge that is located mainly on the hydrogen atoms of the ligand that interact with the π system.

Because hydrogen atoms of ligands are interacting with π systems (Figure 1), this interaction may be considered to be an X−H···π bond.[5,11] Because of the positive charge on

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the ligands in these MLACπ interactions, the X−H···π bonds are charge-assisted, which increases the strength of the X−H···π bonds and makes these bonds among the strongest of known X−H···π bonds.

Interactions of transition metal complexes with π systems have been predicted by quantum chemical calculations. It was anticipated that predicting the strengths of these interactions would be possible because theoretically calculated bonding energies for cation−π systems are in agreement with experimental data.[6] By using DFT (Density Functional Theory) calculations it has been shown that a cationic metal complex interacts strongly with the π system of benzene.[7] Based on these calculations, we proposed[7] that the cation−π interaction may exist when ligands coordinated to a metal ion can get in close contact with a π system. MLACπ interactions can occur in metalloproteins, metal complexes, supramolecular structures, and when DNA and RNA interact with metal cations.

These theoretical predictions have been supported by experimental evidence. Experimental findings of the interactions between nucleobases of DNA and RNA and cationic metal complexes[8] were published virtually simultaneously with the theoretical results.[7] MLACπ interactions in metalloproteins,[9] metal complexes,[10,11] and biomimetic metal complexes[5a] have been found also in crystal structures. MLACπ interactions in the gas phase[12] and in solution[11] have been investigated by spectroscopic methods in a few examples of metal complexes.

2. Calculations of MLACπ Interactions with Benzene

Calculations that predict a strong interaction of transition metal complexes with π systems have been performed for the interactions of the $[Co(NH_3)_6]^{3+}$ cation with benzene.[7,14] The DFT method was used for these calculations, as the most convenient form of quantum chemical methods, because it is suitable for transition metal complexes. In particular, DFT methods have given good results for all transition metal complexes, including transition metal complexes of the first row.[15] It has also been shown that the DFT method is suitable for studying cation−π interactions. Using the B3LYP method, calculations on the bonding energy of the $NH_4^+-C_6H_6$ complex were in agreement with experimental data.[7] In other calculations, reliable results with the DFT method were obtained also for cation−π systems.[16] Geometries were optimized with a the LANL2DZ basis set, while energies were calculated in a larger basis set (6-31G** basis set for all atoms, except for cobalt where LANL2DZ was used).[14]

The $[Co(NH_3)_6]^{3+}-C_6H_6$ cation−π complex has many possible conformers. Three conformers may exist by considering the number of NH_3 groups of the $[Co(NH_3)_6]^{3+}$ cation interacting with the benzene molecule, namely where the number of NH_3 groups involved in bonding is one (η_1), two (η_2) or three (η_3). The total number of possible conformers is larger, however, because for each of these structures, η_1, η_2 and η_3, the benzene molecule may adopt different orientations.

An η_1 conformer was not obtained as a stable structure in the calculations. Starting with this structure, geometry optimization terminated with a conformer of type η_3. The calculations showed that stationary points were obtained for several η_2 and η_3 structures. In all calculated η_2 and η_3 structures, only one hydrogen atom from each of the participating NH_3 groups interacts with the benzene unit. The geometries and energies of two η_2 structures are very similar; the only difference is in the orientation of the benzene ring. The four optimized η_3 structures are also similar to each other. The difference in energy between the η_3 and η_2 structures is approximately 2 kcal/mol. The most stable η_3 structure has a bonding energy of 32.18 kcal/mol, after basis-set-superposition error (BSSE) correction. Frequency calculations on all the optimized geometries showed that only this structure is an energy minimum. The most stable η_2 and η_3 structures are shown in Figure 1, and their bonding energies and geometric data are shown in Table 1.

Table 1. The bond lengths (in the case of the η_3 structures, the data are average bond lengths, except for H···centroid of the benzene ring) and bonding energies of η_2 and η_3 structures (the most stable conformers for η_2 and η_3 structures, shown in Figure 1) of $[Co(NH_3)_6]^{3+}-C_6H_6$ complex

	η_2 structure	η_3 structure
$N-H_{int}$ [Å]	1.040	1.037
$Co-N_{int}$ [Å]	2.023	2.015
$Co-N_{(cis)nonint}$ [Å]	2.025	
$Co-N_{(trans)nonint}$ [Å]	2.052	2.043
$C_{(benzene)}\cdots H_{int}$ [Å]	2.224	2.299
$H_{(1)int}$···centroid of benzene ring [Å]	2.513	2.676
$H_{(2)int}$···centroid of benzene ring [Å]	2.513	2.680
$H_{(3)int}$···centroid of benzene ring [Å]		2.727
ΔE_2 [a] [kcal/mol]	−31.37	−34.16
ΔE_{2B} [b] [kcal/mol]		−32.18

[a] Bonding energies without BSSE correction. [b] Bonding energies with BSSE correction.

In the calculated cation−π complexes there are changes caused by the cation−π interaction in the calculated geometries of the $[Co(NH_3)_6]^{3+}$ cation and of the benzene ring. The bond lengths change in the $[Co(NH_3)_6]^{3+}$ cation. Changes are largest for the Co−N bonds directed at the benzene ring (shortened by more than 0.01 Å) and the N−H bonds of hydrogen atoms that are directly involved in the interactions (lengthened by more than 0.01 Å). The hydrogen atoms in the benzene molecule are bent away from the cation. The cation−π interaction also causes some C−C bonds of the benzene ring to lengthen up to 0.008 Å.

Comparing the charges of a separate $[Co(NH_3)_6]^{3+}$ cation and a benzene molecule with the charges of the cation−π complex shows that there is an electron transfer from the π system to the cation. The average charge on the benzene unit in the η_2 structures of the $[Co(NH_3)_6]^{3+}-C_6H_6$ complex is +0.3077, and in the η_3 structures it is +0.3316.[14] The increase in charge transfer

corresponds to an increase in the strength of the interaction.

The calculated strong interactions existing between the transition metal complex and the aromatic molecule indicate that these interactions can exist in all cases where ligands coordinated to a metal center can get in close contact with aromatic groups. The small difference in energy among different conformers indicates the large number of mutual orientations that can be adopted by the interacting ligands and benzene, and the large degree of variability in conformations that are possible in MLACπ interactions.

Interactions of the $[Co(NH_3)_6]^{3+}$ cation with ethylene and acetylene were also calculated and the bonding energies obtained were 17.02 and 18.30 kcal/mol, respectively.[17]

Calculations on the interactions of $[Mg(H_2O)_6]^{2+}$ with benzene were done using the Hartree−Fock (HF) method and 6-31G* basis set for geometry optimization.[18] Single-point energies at the optimized geometries were calculated by the MP2 method. The calculated bonding energies were corrected for BSSE. In the optimized geometry, three coordinated water molecules are oriented towards the benzene molecule. The hydrogen atoms of the water molecules point towards the C−C bonds of the benzene unit, with the H···C distance to the two closest carbon atoms being 2.56 and 2.79 Å. The elongation of the O−H bonds involved in the O−H···π contact is ca. 0.004 Å. The calculated bonding energy is 21.5 kcal/mol. Similar calculations with $[Zn(H_2O)_6]^{2+}$ gave almost the same geometry and bonding energy (21.3 kcal/mol). For the benzene−sodium hexahydrate complex, the bonding energy was reduced to 9.1 kcal/mol.[18]

It is interesting to compare calculations of the interactions of metal complexes with benzene with those of non-metal cations [$(CH_3)_4N^+$ and NH_4^+] with benzene. In calculated structures where metal complexes or $(CH_3)_4N^+$ interact with benzene, there are three NH_3 ligands or three CH_3 groups oriented towards benzene, while in the NH_4^+−benzene complex there are two hydrogen atoms that interact with benzene.[6h] The calculated bonding energy of benzene−sodium hexahydrate complex (9.1 kcal/mol) is similar to that of the $(CH_3)_4N^+$−benzene complex (ca. 10 kcal/mol),[6h] while the energy of interaction of the NH_4^+−benzene complex is large (ca. 18 kcal/mol).[6h,19a] The energy of interaction of the NH_4^+−benzene complex is relatively close to the bonding energy of metal complexes having a charge of +2, which shows that the positive charge is less dispersed in the NH_4^+ cation than it is in the metal complex cations and $(CH_3)_4N^+$.

In the NH_4^+−benzene complex the closest distance between an H atom (from the cation) and a C atom (from benzene) is 2.436 Å,[19b] and in the $[Co(NH_3)_6]^{3+}$−benzene complex that distance is 2.299 Å.[14] In both of these systems there is electron transfer; in the former, the charge of the benzene unit is 0.265,[19b] and in the latter, as was mentioned previously, it is 0.331.[14] Both features — the interacting distances and charges — are in agreement with the belief that the stronger interactions occur in the $[Co(NH_3)_6]^{3+}$−benzene system than in the NH_4^+−benzene complex.

3. MLACπ Interactions in Metal Complexes

Geometries in Crystal Structures

Intramolecular

Crystal structures of metal complexes containing a phenyl ring and coordinated nitrogen or oxygen atoms, obtained from the Cambridge Structural Database (CSD), were screened for intramolecular cation−π interactions between ligands coordinated to the metal center and the aromatic groups (MLACπ).[10] Geometric criteria were used for screening such that structures were chosen in which the distance between the metal ion and the centroid of the aromatic ring is less than d_0 = 5.5 Å (Figure 2). No restrictive criteria were used for the angle of the normal of the aromatic ring plane with the distance vector between the centroid of the aromatic ring and the metal ion, since intramolecular interactions were being investigated. It was found that the interaction is stronger if the hydrogen atom that interacts with the aromatic group is closer to the metal center,[9] and hence, structures were considered only in which there are two bonds between the hydrogen atom and the metal ion.

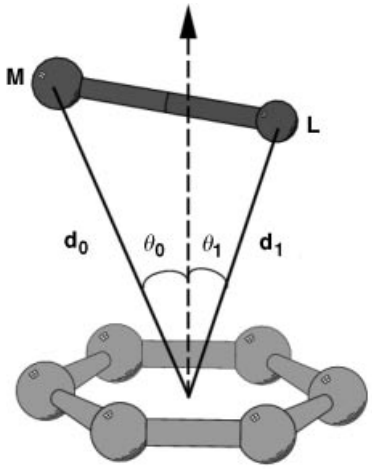

Figure 2. Distances (d_0, d_1), and angles (θ_0, θ_1) used to search for and characterize MLACπ interactions; M is a metal cation, L is a non-hydrogen atom ligand (L) closest to the ring centroid; the dashed line is the normal of the aromatic ring plane

It was found that intramolecular MLACπ interactions, between a coordinated ligand and the aromatic ring in the same complex, were observed in a number of crystal structures of transition metal complexes. Data concerning the MLACπ interactions in different crystal structures are compiled in Tables 2 and 3. The data show that there are numerous metal complexes in which there is close contact between an aromatic ring and a ligand and that different metal ions and ligands can be involved.

Table 2. Intramolecular metal ligand aromatic cation−π (MLACπ) interactions in complexes with two bonds between the aromatic ring and the metal ion

RFCODE	Metal ion	X[a]	X···centroid of ring[b] [Å]	H···centroid of ring[c] [Å]	X···C[d] [Å]	H···C[e] [Å]	Y[f]	Ref.
BZSACS	Co^{3+}	N	3.98	3.82	3.27	3.16	S	[20]
				3.35		2.83		
CUBXAY	Co^{3+}	N	3.39	3.54	3.22	3.00	P	[21]
				3.64		2.94		
		N	4.11	3.49	3.37	3.44	P	
				4.17		2.89		
JORJAB	Co^{2+}	N	3.35	3.17	3.02	2.72	N	[22]
JUJPEJ	Cu^{2+}	N	3.92	3.22	3.36	2.82	N	[23]
TSACOP	Co^{3+}	N	3.79	3.45	3.12	2.96	S	[24]
				3.39		2.80		
TULBEH	Mn^{1+}	N	3.77	2.95	3.19	2.51	P	[25]
GAFKED10	Cd^{2+}	N	3.65	2.81	3.33	2.52	N	[26]
HELYUS	Ru^{2+}	N	3.83	3.06	3.18	2.61	S	[27]
PAXCAS	Mo^{4+}	N	3.89	3.13	3.07	2.43	S	[28]
PIRKAC	Ru^{1+}	N	3.55	3.39	3.14	2.92	P	[29]
				3.29		3.02		
TOJCIE	$Ru^{1/5+}$	O	3.94	3.00	3.27	2.37	P	[30]
VERGEE	Tc^{5+}	N	3.73	2.80	3.08	2.30	S	[31]
		N	3.72	2.80	3.04	2.25	S	
WEFLOI	Ru^{2+}	N	4.02	3.36	3.28	2.71	Si	[32]
AQTORU	Ru^{2+}	O	3.58		3.03		P	[33]
		O	2.74		3.09		P	
KAJROC	Rh^{2+}	N	4.48	3.59	3.46	2.67	Sb	[34]
		N	4.15	3.26	3.36	2.63	Sb	
BAXJOZ	Re^{4+}	O	3.98		3.34		P	[35]
CIRNUM	$Os^{2/3+}$	O	3.73		3.23		P	[36]
DIKMUF	Os^{2+}	O	3.64		3.14		P	[37]
		O	3.64		3.14		P	
PEDXAX	Ir^{3+}	N	3.63	2.76	3.01	2.25	P	[38]
		N	3.71	3.05	3.09	2.64	P	
				3.64		2.82		
PEWRUE	Re^{5+}	N	3.75		3.17		P	[39]
WAXGIL	Re^{3+}	N	3.53	2.69	3.14	2.48	P	[40]

[a] Heavy atom to which the interacting hydrogen atom is bound. [b] The distance between the heavy atom and the centroid of the aromatic ring. [c] The distance between the interacting hydrogen atom and the centroid of the aromatic ring. [d] The distance between the heavy atom and the closest carbon atom of the aromatic ring. [e] The distance between the interacting hydrogen atom and the closest carbon atom of the aromatic ring. [f] The atom between the metal ion and the aromatic ring.

In most of the complexes there are two or four bonds between the metal ion and the aromatic ring. The aromatic ring of an organic ligand can interact with a hydrogen atom of the other ligand, or with a hydrogen atom of the same ligand.

In complexes where there are only two bonds between the aromatic ring and the metal ion (Table 2) there is the possibility for the MLACπ interaction only with the ligand coordinated in the *cis* position and there is no possibility for an MLACπ interaction within the same ligand. In this group of complexes there is little freedom for the ligands to adjust their mutual orientations.

In structures with more than two bonds between the metal ion and the aromatic ring (Table 3) there is the possibility for MLACπ interactions with the hydrogen atom of the other ligand, but also with the hydrogen atom of the same ligand. There are fewer steric constraints in cases where there are interactions with hydrogen atoms of another ligand, and in these cases the distances of the interaction to the center of the ring are shorter.

These results show that steric constraints in the intramolecular MLACπ interactions in the complexes have an important influence on their geometry and, probably, the strength of these interactions.

Kumita et al. studied intramolecular interactions between a ligand and an aromatic ring using different experimental methods.[11] They observed these interactions in the crystal structures of K[Co(L)(aa)] [L = *N*,*N*-bis(methoxycarbonyl)-(*S*)-phenylalanine; aa = (*S*)-Phe, (*R*)-Phe, (*S*)-Trp] complexes. In these structures there are intraligand interactions with the distances between amino hydrogen atoms and the plane of the phenyl ring in the range 2.61−2.82 Å. Similar interactions were observed in the complex K[Co{*N*,*N*-bis(methoxycarbonyl)-(*S*)-leucine}-(*S*)-Phe].[61] Although there is the possibility, however, for intraligand interactions in complexes with aromatic amino acids as ligands, they do not always occur[62] since they depend very much on the interplay with other ligands in the complex; this feature shows that these interactions are in balance with other noncovalent interactions.

Table 3. Intramolecular metal ligand aromatic cation−π (MLACπ) interactions in complexes with several bonds between the aromatic ring and the metal ion

RFCODE	Metal ion	X[a]	X···centroid of ring[b] [Å]	H···centroid of ring[c] [Å]	X···C[d] [Å]	H···C[e] [Å]	Ref.
CEBREG	Cu^{2+}	N	4.00	3.42	3.06	2.66	[41]
FUCSIF	Cu^{2+}	N	3.90	3.29	2.96	2.58	[42]
NEFRAR	Co^{3+}	N	3.90	3.22	2.99	2.54	[43]
POKAD02	Co^{3+}	N	3.75	3.08	2.90	2.56	[44]
		N	3.75	3.08	2.90	2.56	
TONPUH	Cu^{2+}	N	3.88	2.99	2.99	2.23	[45]
VAFSIE	Co^{3+}	N	3.85	3.03	2.92	2.33	[46]
RUFKUY	Rh^{3+}	N			2.93	2.46	[47]
NEGREW	Re^{1+}	N	3.81	3.16	2.82	2.38	[48]
			3.55	2.87	3.29	2.51	
DUSJIK	Ni^{3+}	N	3.27	2.21	3.46	2.54	[49]
DEMHAE	Ni^{2+}	N	3.55	2.87	3.29	2.62	[50]
			3.55	2.87	3.29	2.51	
DIXHAT	Cu^{2+}	N	4.48	3.79	3.84	3.18	[51]
		N	4.53	3.84	3.84	3.18	
GLTRCU01	Cu^{2+}	O	3.25	2.31	3.37	2.52	[52]
LETYCU10	Cu^{2+}	O	3.32	2.58	3.39	2.66	[53]
NALPIZ	Fe^{2+}	N	3.63	2.63	3.16	2.72	[54]
		N	3.63	2.63	3.16	2.29	
NOVBAB	Ni^{2+}	O	4.06	3.28	3.53	2.76	[55]
		O	3.93	3.23	3.27	2.49	
NUTKES	Mn^{2+}	O	3.24	2.36	3.32	2.74	[56]
		O	4.13	3.22	3.52	2.65	
TONPOB	Cu^{2+}	O	3.17		3.31		[45]
FOBTAR	Mo^{4+}	N	3.42	2.84	3.26	2.53	[57]
SIRCOL	Mo^{4+}	N	3.91	2.97	3.50	2.67	[58]
		N	3.91	2.97	3.50	2.67	
ZURREJ	Cd^{2+} Ni^{2+}	N	3.77	2.91	3.55	2.68	[59]
NOLQIO	Mo^{6+}	N	3.47	2.94	3.33	2.85	[60]

[a] Heavy atom to which the interacting hydrogen atom is bound. [b] The distance between the heavy atom and the centroid of the aromatic ring. [c] The distance between the interacting hydrogen atom and the centroid of the aromatic ring. [d] The distance between the heavy atom and the closest carbon atom of the aromatic ring. [e] The distance between the interacting hydrogen atom and the closest carbon atom of the aromatic ring.

Some C−H···π interactions, where the C−H unit is part of the ligand, have also been observed in metal complexes.[63] If the C−H groups are not very close to the metal ion there is no difference between these C−H···π interactions and those in organic molecules.[63a,64]

Intermolecular

Intermolecular interactions between hydrogen atoms and π systems have been observed in organometallic crystals.[5a] Investigation of these interactions show that they are common and appear to be typical hydrogen bonds. Many of these organometallic structures are ionic compounds. In most cases it has been shown that charge-assisted ($X-H^{\delta+}\cdots\pi^{\delta-}$) interactions possess shorter distances than neutral X−H···π bonds. It should be noted that in this study an X−H group was not always part of a ligand coordinated to a metal ion, but instead was part of any other molecule in the crystal structure.[5a]

Calculated Intramolecular MLACπ Interactions

DFT calculations were done on model systems with relatively small ligands to evaluate the energy of intramolecular MLACπ interactions.[10] The geometries and energies were calculated for structures with various conformations of the aromatic ring in the model systems. Based on the difference in energy for conformers with and without MLACπ interactions, the energy of the interactions was evaluated for model systems of cationic complexes of Co^{III} having a total charge of +1.

The calculations on complexes with two bonds between the aromatic ring and the metal ion were done on the model system $[CoCl_2(NH_3)_3(C_6H_5NH_2)]^+$. The coordinated aniline unit is in the *cis* position relative to the two NH_3 and two Cl^- ligands. The energy was calculated for the structure where the aromatic ring is positioned above either an NH_3 or Cl ligand. Based on the difference in energy between these two conformers, the energy of the MLACπ interaction was evaluated to be ca. 4 kcal/mol for this model system.

The $[CoCl(NH_3)_3Phe]^+$ complex was used as a model system to study the interactions in complexes having several bonds between the aromatic ring and the metal ion (Figure 3). There are three possible conformations of the phenyl ring in the coordinated phenylalaninato ligand. In one conformer there are no MLACπ interactions, in the second there is only an intraligand interaction, and in the third

there are intraligand and interligand interactions. Based on the differences in the energy of these conformers, the energies of intraligand and interligand interactions were evaluated to be ca. 3.5 and 4 kcal/mol, respectively.[10]

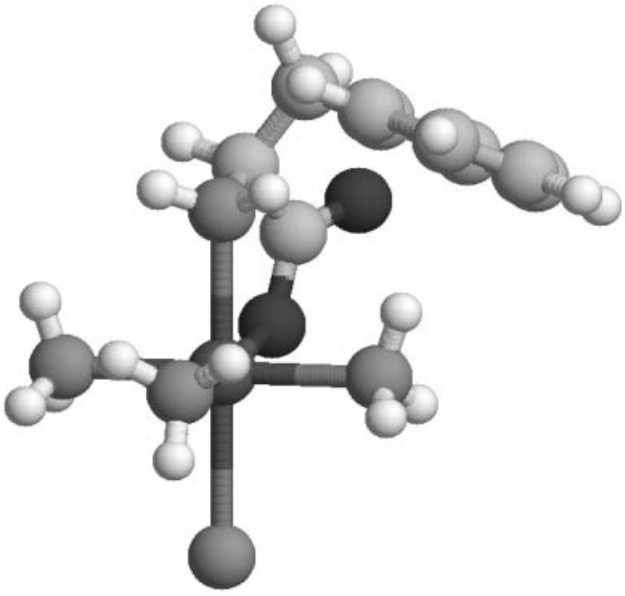

Figure 3. Model systems $[CoCl(NH_3)_3Phe]^+$ used for calculations of intramolecular metal ligand aromatic cation−π (MLACπ) interactions in metal complexes

Spectroscopic Evidence

IR Spectra

Interactions of a benzene unit with water molecules coordinated to K and Na ions were observed using infrared spectroscopy in gas-phase cluster ions of the form $M^+(C_6H_6)_n(H_2O)_m$, with M = Na or K.[12,13] Vibrational-predissociation spectroscopy indicates details of the structure because the OH stretching frequency of water is extremely sensitive to changes in its bonding environment. In the $K^+(C_6H_6)_3(H_2O)_1$ complex the stretching modes of water are very similar to that of free water. The introduction of a fourth benzene molecule significantly affects the OH spectrum, which is indicative of hydrogen bond formation.[12]

The O−H···π hydrogen bond was observed also in $K^+(C_6H_6)_5(H_2O)$, where a water molecule and three benzene molecules are bonded directly to the K^+ ion, and the fourth and fifth benzene molecules are bound to the coordinated water molecule. The interaction of the benzene molecules with the coordinated water molecule is observed by a shift in vibrational frequencies of the O−H stretching mode towards smaller wavenumbers by ca. 70 cm^{-1}. Vibrational spectra can also indicate differences in the strengths of hydrogen bonds in cases when there is a neutral benzene−water complex, and when water is bonded to a K^+ ion. The bonding of a water molecule to the ion enhances the π−hydrogen bond between the water and benzene molecules, leading to an additional shift in the OH stretching frequency.[12]

In the case of Na^+ ions, the most interesting complex is the self-assembled cluster ion, $Na^+(C_6H_6)_8(H_2O)_4$, which has a single structure of an inner shell of four water molecules and an outer layer of eight benzene molecules, each of the latter being fixed by a π−hydrogen atom bond to one of the eight interior O−H groups. The intense narrow bands observed in the vibrational spectra of $Na^+(C_6H_6)_8(H_2O)_4$ indicate a stable cluster ion configuration with eight H−π bonds.[13]

CD Spectra

The CD spectra of *trans*-(N)−K[Co(bcmpa)(aa)] (aa = amino acid) complexes were measured in a study of N−H···π interactions in Co^{III} complexes with amino acids.[11] The CD spectra of these complexes have four components in the d−d region. For one of these bands, there are indications that its origin can be attributed to a chiral amino acid, and the same band exhibited a solvent effect that is related to the vicinal effect of chiral amino acids. For complexes with aromatic amino acids [(*S*)-Trp, (*S*)-Phe, (*S*)-Tyr], there is a significant difference in the intensity of the band in aqueous and ethanol solutions, while the complexes with aliphatic amino acids [(*S*)-Ala, (*S*)−Leu, (*S*)-Pro] did not exhibit this solvent effect. The solvent effect in complexes with aromatic amino acids is a consequence of the N−H···π bond in solution, since the strength of the N−H···π bond varies in different solvents.[11]

^{1}H NMR Spectra

NMR spectroscopy is a powerful method for studying weak interactions in solution. ^{1}H NMR spectra of *trans*-(N)−K[Co(bcmpa)(aa)] (aa = amino acid) complexes were measured to obtain detailed structural information of the N−H···π interaction in solution.[11] If the N−H protons approach an aromatic system closely, they are expected to shift to higher field as a result of the ring-current effect. Indeed, in NMR spectra of metal complexes with aromatic amino acids, the peaks of NH protons at a higher field exhibited significant upfield shifts. Namely, for the Co^{III} complexes with aromatic amino acids, the two peaks of the amino protons at the higher and lower fields were observed in the ranges δ = 5.34−5.81 and 7.02−7.26 ppm, respectively, while those for the complexes with aliphatic amino acids were detected in the ranges δ = 6.01−6.29 and 7.22−7.40 ppm, respectively. In the crystal structure, one of the two coordinated amino protons is located exactly in the position expected for it to be affected by the shielding effect of an aromatic ring, but another one is slightly deviated from such a position. Since the geometry in solution is probably very similar to that observed in the crystal, the signals for these two protons are shifted differently because of their different shielding. Moreover, the values of chemical shift of the peaks at higher field for the Co^{III} complexes with *p*-X-substituted phenylalanines (X = OH, CH_3, H, Cl) demonstrate a significant substituent effect, which indicates that greater electron density on the aromatic ring results in a larger shielding effect. This observation suggests that the

Table 4. Interactions of C−H groups of ligands with the π system of a chelate ring (data for normalized positions of the H atom)

CSD refcode	H···centroid of ring [Å]	C···centroid of ring [Å]	Chelate ring	Ref.
ACIPTI	2.43	3.51	TiOCCCO	[67]
BEPZOL	2.48	3.56	CuNCNCN	[68]
COTQAD	2.38	3.39	ZrNCCCN	[69]
COTQEH	2.36	3.38	HfNCCCN	[69]
FEBTAH	2.39	3.45	NiNCCCN	[70]
GORYER	2.46	3.54	MnOCCCN	[71]
GOXDAY	2.48	3.46	FeNCCCN	[72]
HALWAS	2.40	3.36	ZnNCCCN	[73]
HAMDAA	2.40	3.38	ZnNCCCN	[73]
HAMGUX	2.46	3.43	ZnNCCCN	[73]
JOXGIM	2.59	3.68	CuOCCCN	[74]
LICSEV	2.31	3.32	CuNCCCN	[75]
LOFZOV	2.36	3.35	NiOCCCN	[76]
MAMTOJ	2.46	3.52	CoOCCCN	[77]
MAMTUP	2.32	3.38	CuOCCCN	[77]
PIQZUK	2.45	3.53	ReOCCCN	[78]
SUMXIH	2.50	3.45	FeNCCCN	[79]
VAFQIC	2.30	3.38	ZnNCCCN	[80]
YINLUC	2.54	3.60	NiOCCCO	[81]
ZAXDOR	2.30	3.31	ZnOCCCN	[82]
ZONQOI	2.34	3.32	CoNCCCN	[83]
ZOPYUY	2.34	3.37	CuOCCCN	[84]

attractive interaction is maintained even in polar solvents such as DMSO.[11]

4. Interaction with a Chelate Ring

Geometries in the Crystal Structures

There is a special type of X−H···π interaction in which a hydrogen atom from a ligand coordinated to a metal ion interacts with a chelate ring that has delocalized π bonds.[65] It is considered that the metal atom is involved in π delocalization and that these rings can have aromatic character.[66] A search for crystal structures of transition metal complexes from the CSD showed that interactions between C−H groups and the π system of chelate rings are observed in many crystal structures. Geometrical parameters for some examples are shown in Table 4. All of these examples have a very short distance between the interacting hydrogen atom and the centroid of the chelate ring (< 2.6 Å), and the hydrogen atom is located in a position almost centered over the chelate ring's centroid. From a geometrical point of view, interactions in these structures are similar to strong C−H···π interactions in organic molecules.[63a,64]

These interactions occur in metal complexes of different metals and various chelate rings. In Table 4 most of these interactions listed are intermolecular ones, with only the compound ACIPTI presenting an intramolecular interaction.

It is very interesting to notice that in all cases shown in Table 4 the complexes are neutral and both the chelate ring and the C−H group belong to the same molecule. In cases of intermolecular interactions, the interaction occurs between two identical molecules: the C−H group of one molecule interacts with the chelate ring of the second molecule. It is assumed that the neutrality of the complexes is important for these types of interactions because it enables a chelate ring not to have a partial positive charge, which would be the case if the complex was positively charged. On the other hand, the π system of the chelate ring would not interact with a negatively charged complex. In the case of a neutral complex, the interacting H atom has a partial positive charge, which is enough charge for a weak C−H···π interaction to occur.

Calculation of the Energy of Interaction

DFT calculations were performed on model systems from crystal structures to evaluate the energy of these types of interactions. The calculated energies of these interactions are approximately 1 kcal/mol.[65] The calculated values for interacting energies are similar to the values calculated for C−H···π interactions in organic molecules.[63a,64] One of the model systems based on the crystal structure YINLUC in shown in Figure 4.

5. MLACπ Interactions in Biomimetic Metal Complexes

Interactions of the MLACπ type were found in the crystal structure of biomimetic zinc complexes that are related to the enzyme/substrate complexes in biological systems with mononuclear zinc species.[5b] In the structures of $[Zn(X_6Me_3ImMe_3)L]^{2+}$ (L = EtOH, NH_2CHO) the neutral ligand $X_6Me_3ImMe_3$ forms a cavity that mimics the enzyme pocket and stabilizes four coordinated zinc species N_3ZnL^{2+}. These complexes were the first obtained of four-coordinated zinc dicationic complexes involving either a terminal aliphatic alcohol or an amide ligand. In the X-ray

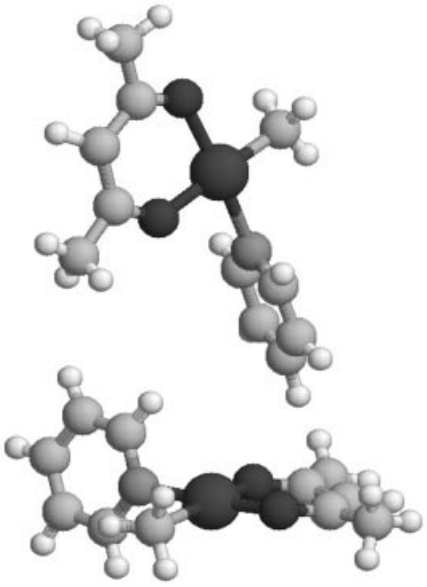

Figure 4. A model system, based on the crystal structure of YINLUC, used for calculations of the energy of C−H···π interactions with a chelate ring

structures of these complexes there are hydrogen bonds and CH···π interactions between the calix[6]arene hosts and the guests L. The CH groups that are directly connected to the oxygen atom have increased partial-positive charge because they are coordinated to an oxygen atom bonded to the metal ion. These CH groups interact with the aromatic group in the calixarene structure. The distance of the hydrogen atom closest to the centroid of the aromatic ring is 2.92 Å for $-CH_2OH$ (L = EtOH) and 2.70 Å for $-CH{=}O$ (L = NH_2CHO). These interactions, together with hydrogen bonds, play an important role in stabilizing the complex between the calix[6]arene host and the guest molecules L.[5b]

6. MLACπ Interactions in DNA and RNA Structures

Geometries in Crystal Structures

Cations play a very important role in the structure, stability, and reactivity of nucleic acids.[85] Among other noncovalent interactions, cation−π interactions between cations and nucleic acid bases have been observed in crystal structures of DNA and RNA.[8] Cation−π interactions with cationic metal complexes have been found by searching crystal structures of DNA and RNA using geometrical criteria.[8] These criteria was based on the geometries of a number of cation−π pairs in the human growth hormone/receptor complex (PDB entry 3HHR). These criteria requested that the distance between the metal ion and the centroid of the aromatic ring be smaller than 5.2 Å, and that the angle between the normal to the centroid and the centroid−metal ion bond be less than 52° (Figure 2).

It was assumed that cations interact favorably with π systems of nucleic acid bases, since cation−π interactions were detected in crystal structures of DNA and RNA. In the DNA structures of NDB entries BDL084[86] and BDJ025[87] a hydrated magnesium ion is located in the major grove and interacts with the π system of a cytosine unit (Figure 5). It was suggested that partial unstacking observed in the crystal structure was caused by cation−π interactions. The anticodon arm of yeast tRNA (NDB entry TRNA10[88]) contains one hydrated magnesium ion that is involved in MLACπ interactions. The water molecules coordinated to the magnesium ion form seven cation−π interactions, involving four tRNA bases. In the crystal structure of the tetrahymena group I intron P4−P6 domain (NDB entry URX053[89]), several magnesium ions are involved in cation−π interactions. In the same crystal structure it was also observed that the ligands of $[Co(NH_3)_6]^{3+}$ engage in MLACπ interactions with the RNA bases.

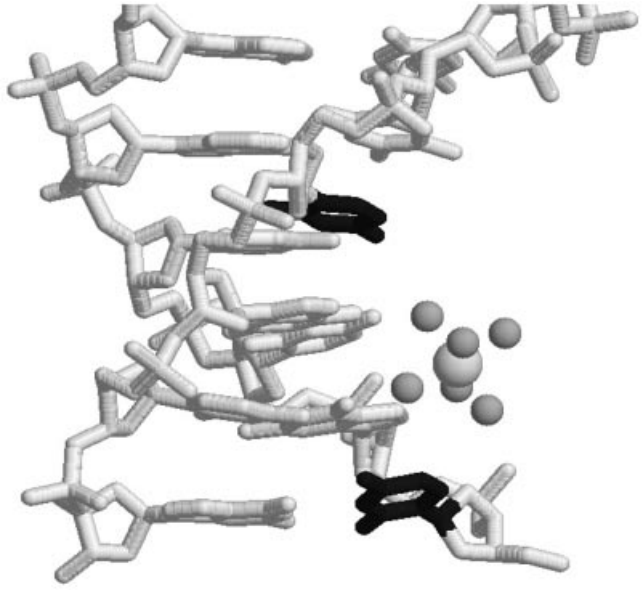

Figure 5. Part of the DNA crystal structure of BDL084[20] (NDB entries) showing the interaction of $[Mg(H_2O)_6]^{2+}$ with two cytosine units

The observation of cation−π interactions suggest a number of new mechanistic roles for cations in DNA bending, DNA−protein recognition, base flipping, RNA folding, and catalysis.[8]

Calculations

Ab initio (MP2) calculations were used to study local interactions between $[Mg(H_2O)_6]^{2+}$ and DNA bases observed in crystal structures.[18,90,91] The possibility of cation−π interactions was analyzed by assuming idealized[18] and crystal-structure geometries[18,90] of the interacting species.

The calculations on idealized geometries showed that hydrated metal cations can interact strongly with nucleobases in a cation−π manner.[18] Calculations on $[Mg(H_2O)_6]^{2+}$ with the cytosine π system were done with constraints that forced the magnesium hexahydrate unit to interact with the cytosine aromatic system and, at the same time, kept all of the cytosine atoms coplanar. The calculated interaction

energy was 20.2 kcal/mol. This value is very close to the calculated interaction energy with a benzene molecule (see Section 2).[18] In the optimizations without any constrains, however, the complex undergoes a quick rearrangement to the conventional through-water, in-plane bonding pattern of magnesium ions, with strong hydrogen bonds to the N and O atoms of the cytosine unit. The interacting energy for this structure is much larger (68.2 kcal/mol) than that of the one above. Hence, in spite of relatively strong cation−π interaction between $[Mg(H_2O)_6]^{2+}$ and the cytosine π system, this configuration is very unstable because there is a much more stable alternative configuration in which the hydrated metal cation is in the plane of the nucelobases and forming conventional hydrogen bonds. To make cation−π interactions with nucleobases, the cation must be kept above the plane of the nucleobase by another strong interaction, which can be the case in certain biopolymers.

Calculations on the crystal-structure geometry were performed for the dodecamer BDL084[86] (NDB entry) to evaluate interacting energies in the crystal. Contacts of the magnesium hexahydrate unit with two cytosine molecules were observed in this structure, and it was suggested that both contacts can be considered as cation−π interactions.

Calculations were performed by two groups in two different ways. In the calculations of Šponer et al., the position of the Mg^{2+} ion was kept fixed with respect to the cytosine ring according to the geometry found in the crystal, while the cytosine ring and the positions of all six water molecules were fully relaxed.[18] In the optimized geometries for both contacts, the cytosine rings are substantially deformed with pyramidal amino groups. There is one water molecule interacting with the cytosine amino group, which can be considered to be an amino−acceptor interaction. The interaction energies are 13.5 and 8.1 kcal/mol. Crystal geometries were also optimized while the cytosine unit was kept planar. This constraint abolished the amino−acceptor interaction and the water molecules reoriented. The calculated interaction energies were very small (2.5 and 0.3 kcal/mol).[18]

In the second calculation, all atoms were kept at the same position as in the crystal structure and only the positions of the added hydrogen atoms were optimized.[90] The calculated bonding energies range from 1 to 3 kcal/mol. To see the effect of the magnesium ion on these interactions, the interacting energies between cytosine and loose water molecules were calculated in the presence and absence of the otherwise pentahydrated magnesium ion. The presence of the magnesium ion increased the interacting energy by ca. 1 kcal/mol.

The calculations on the interactions of $[Mg(H_2O)^6]^{2+}$ with DNA showed that the interaction energies in the crystal structures are very small. This energy is not sufficient to compensate for the decrease in energy resulting from the lack of alternative hydrogen bonding and the bending of the bond angle related to unstacking of the bases and, hence, this interaction cannot cause the bases to unstack. Further investigations[91] have shown that there are strong hydrogen bonding interactions between these cations and another base, and that these interactions are keeping the cation in its position, above the aromatic plane, observed in the crystal structure. This localization could have resulted in a favorable cation−π interaction.

7. MLACπ Interactions in Metalloproteins

Geometries in Crystal Structures

Using geometric criteria, crystal structures of metalloproteins from the PDB were screened for cation−π interactions between ligands coordinated to the metal ion and aromatic residues.[9] The criteria used were the same as those proposed by McFail-Isom et al.[8] for screening crystal structures of DNA and RNA for possible cation−π interactions, as was mentioned above. The screening was performed for the aromatic groups of phenylalanine, tyrosine, and tryptophan, but not for histidine. Histidine is very often directly coordinated to a metal ion and, therefore, a large number of structures would be obtained that do not contain the interactions of interest.

The MLACπ interactions with the aromatic rings of phenylalanine, tyrosine and tryptophan can be observed in a number of crystal structures of metalloproteins. Data concerning the interactions in different crystal structures are compiled in Table 5, which shows that this type of interaction exists in numerous metalloproteins. Practically all metals commonly occurring in enzymes can participate in such interactions. The ligands involved in the MLACπ interactions can be amino acids, water, substrates and inhibitors.

The positions of the hydrogen atoms are not available in the crystal structures of the protein structures listed in Table 5 and, hence, the geometry of the MLACπ interaction is characterized by the distance d_1 between the center of the aromatic ring and the non-hydrogen atom ligand closest to the ring centroid (Figure 2). In Table 5, the value of d_1 varies between 3.09 and 4.41 Å. The angle θ_1 is often smaller than 30°, but can be as large as 45°.

For the same protein, the data in Table 5 show that all crystal structures exhibit the same pattern of MLACπ interactions, although the redox state and coordination number may vary. In some metalloproteins, there are different ligands in different crystal structures, but they interact with the same aromatic group, as in the case of alcohol dehydrogenase (ADH). In other proteins there is more than one MLACπ interaction at one metal center. In some cases two ligands interact with the same aromatic group, while in other cases two ligands interact with two aromatic residues of amino acids. It was concluded from the atomic distances that, among the aromatic amino acids, it is tryptophan that forms the strongest MLACπ interaction, and that, among the ligands, water molecules form the strongest interactions.

This conclusion is in agreement with previous results that indicate that tryptophan is able to make relatively strong interactions.[2,3b,6c,6d] It demonstrates that the nature of the MLACπ interaction, of the ligands coordinated to a metal ion interacting with aromatic molecules, is related to other

Table 5. Metalloproteins with metal ligand aromatic cation−π (MLACπ) interactions

Name/PDB code	Metal	Ligands/bond number	Aromatic residues	Distance d_1[a] [Å]	Angle θ_1 [a] [°]	Ref.
ADH/1adc	Zn^{2+}	Ethanol/2	Phe93	4.21	35.8	[92]
ADH/1ldy	Zn^{2+}	His67/2	Phe93	4.28	35.2	[93]
		CXF378/3		3.46	19.6	
ADH/1axe	Zn^{2+}	His67/2	Trp93	3.77	21.5	[94]
		ETF404/2	Trp93	3.65	40.9	
ADH/1axg	Zn^{2+}	His67/2	Phe93	3.94	16.6	[94]
		ETF404/2		3.94	44.6	
ADH/2ohx	Zn^{2+}	His67/2	Phe93	4.41	33.6	[95]
AO/1asp	Cu^{2+}	His62/3	Phe102	4.11	42.9	[96]
CBP/2cbp	Cu^{2+}	His39/2	Phe13	4.12	33.5	[97]
CheY/1chn	Mg^{2+}	H_2O300/1	Phe14	4.12	27.7	[98]
		H_2O301/1		3.50	24.9	
D9D/1afr	Fe^{2+}	Glu143/3	Trp139	3.93	26.0	[99]
EndN/1ak0	Zn^{2+}	His15/2	Tyr16	3.69	14.1	[100]
FBC/1hfc	Zn^{2+}	His168/2	Phe174	4.00	38.0	[101]
GLI1/2gli	Co^{2+}	His129/2	Trp108	3.09	17.9	[102]
HeC/1lla	Cu^{+}	His364/2	Phe360	3.50	16.9	[103]
MMP-8/1mmb	Zn^{2+}	His147/2	Phe153	3.82	34.9	[104]
NPR/1npc	Ca^{2+}	Thr195/3	Tyr194	3.58	16.0	[105]
SBA/1sbd	Ca^{2+}	Asn130/3	Trp132	3.37	27.7	[106]
SOD/1avm	Fe^{3+}	H_2O1/1	Trp163	3.35	16.3	[107]
		Asp161/3	Trp126	3.75	21.5	
SOD/1mmm	Fe^{2+}	H_2O207/1	Trp169	3.12	14.4	[108]
		Asp167/3	Trp128	3.53	16.0	
SOD/1ap5	$Mn^{2+(3+)}$	H_2O200/1	Trp161	3.52	25.4	[109]
		Asp159/3	Trp123	3.66	15.0	
SOD/1ar4	$Mn^{2+(3+)}$	H_2O1/1	Trp163	3.29	19.7	[110]
		Asp161/3	Trp126	3.75	21.7	
SOD/1mng(L)	Mn^{3+}	H_2O205/1	Trp168	3.57	19.7	[111]
		Asp166/3	Trp132	3.59	14.7	
SOD/1mng(U)	Mn^{3+}	H_2O205/1	Trp168	3.52	26.9	[111]
		Asp166/3	Trp132	3.54	15.4	
TNC/1tn4	Ca^{2+}	H_2O5/1	Tyr109	4.03	42.6	[112]

[a] Definitions of geometric parameters are given in Figure 2.

cation−π interactions that have already been observed and investigated.

The MLACπ interaction generally will be stronger when there are fewer bonds between the atom of the ligand coordinated to the metal ion and the interacting hydrogen atom. The water molecule, when acting as a ligand, has just a single bond between the H atom and the O atom attached to the metal ion and, thus, it is not surprising that the MLACπ interactions are the strongest when a water molecule is a ligand.

In the cases of SOD and AHD enzymes, there are indications that MLACπ interactions might be relevant for enzyme function.[9] The MLACπ interaction in the case of alcohol dehydrogenase is very interesting. In the crystal structure of the AHD−alcohol complex (PDB code 1adc/B),[92] the zinc(II) ion is tetracoordinated. Three of the ligands are amino acids, two cysteine units (Cys46 and Cys174) and one histidine unit (His67). The fourth ligand is the bound ethanol (Figure 6). Close to the metal ion is the aromatic ring of Phe93 that is in contact with the coordinated ethanol. The hydrogen atoms were modeled into this structure. For the CH_2 group of the ethanol unit, the shortest distance between a hydrogen atom and the centroid

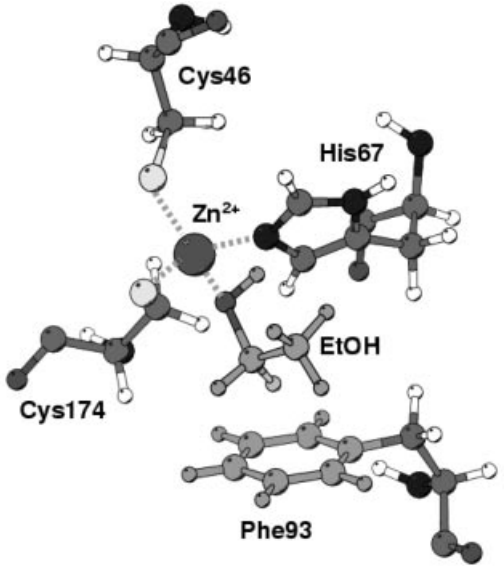

Figure 6. Part of the crystal structure of alcohol dehydrogenase (PDB code 1adc/B); all ligands are displayed that are coordinated to the metal ion and the aromatic residue (Phe93) displaying MLACπ interactions

of the phenyl ring is 3.19 Å, and its distance to the closest carbon atom of the phenyl ring is 2.64 Å.

In other structures of alcohol dehydrogenases, which we have found by searching for MLACπ interaction, there are interactions of different ligands coordinated to the zinc atom that interacts with Phe93 (Table 5). These ligands are His, trifluoroethanol (ETF), and cyclohexylformamide (CXF), respectively. In the ADH structure 1axe/B,[94] there is a Phe93Trp mutation. Trp93 is involved in cation−π interactions with the coordinated ligands, His67 and ETF. The distance of the cation−π interactions with Trp93 are shorter, and probably are stronger than the interactions with Phe93. It was found experimentally that the mutation from Phe93 to Trp93 increases the tunneling of a hydrogen atom in the hydride transfer reaction from alcohol to NAD.[94] It could be that there is a connection between a stronger cation−π interaction and an increase of hydrogen atom tunneling. We assume that the cation−π interaction of the alcohol with Phe93 may play a role in the reaction mechanism of the enzyme ADH.

Calculations

The energy of the MLACπ interactions in metalloproteins was evaluated by DFT calculations on model systems built from the crystal structure of SOD. The calculated interacting energy of the metal ion complex (an iron ion with its coordinated ligands) with he indole ring of Trp163 was 10.09 kcal/mol.[9]

8. Concluding Remarks

This article has given an overview of MLACπ interactions that have been observed in different molecular systems, mainly in crystal structures, but also in solution and in the gas phase. The overview also includes calculations of MLACπ interactions that are primarily important for estimating interaction energies. MLACπ interactions play a role in the stability of metalloproteins, metal ion complexes, and biomimetic metal ion complexes. For some metalloenzymes these interactions are probably important for the mechanisms of enzymatic reactions.

MLACπ interactions are weaker than interactions of simple metal cations with the same charge, because the transition metal complexes are relatively large, and the charge is more dispersed. The calculated energies of MLACπ interactions vary from 1 to 30 kcal/mol. This range shows that, in some cases, these interactions are among the strongest noncovalent interactions, and can play an important stabilizing role.

The largest calculated energies were for the interactions in the optimized geometries of the $[Co(NH_3)_6]^{3+}$, $[Mg(H_2O)_6]^{2+}$, and $[Zn(H_2O)_6]^{2+}$ cations with benzene (32.2, 21.5, and 21.3 kcal/mol, respectively). A comparison of these three numbers indicates that the charge of the complex is a very important factor. Calculated energies of interactions in crystal structures are smaller, ranging from 1 to 10 kcal/mol. The main reason why these energies are smaller is that the geometries in the crystal structures do not optimize the MLACπ interactions because of constraints caused by other interactions. Also, most of the calculations were performed for metal complexes with a small charge. The weakest interactions, of ca. 1 kcal/mol, are calculated when a C−H group of the ligand interacts with a chelate ring. In these cases the charge of complexes is zero, and that is the reason why the calculated energy of the interaction are very small.

The range of energies of MLACπ interactions is similar to the range of energies of hydrogen bonds, and strong MLACπ interactions are among the strongest X−H···π bonds.

From the studies that are reviewed in this paper, the nature of MLACπ interactions is related to the other cation−π interactions, as is indicated by calculated values of charge transfer. Among the aromatic amino acids, tryptophan forms the strongest MLACπ interactions. To clarify these findings, more studies regarding the nature of MLACπ interactions are needed.

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