Competition between π and Non-π Cation-Binding Sites in Aromatic Amino Acids: A Theoretical Study of Alkali Metal Cation (Li^+, Na^+, K^+)–Phenylalanine Complexes

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Abstract: To understand the cation–π interaction in aromatic amino acids and peptides, the binding of M^+ (where $M^+ = Li^+$, Na^+, and K^+) to phenylalanine (Phe) is studied at the best level of density functional theory reported so far. The different modes of M^+ binding show the same order of binding affinity ($Li^+ > Na^+ > K^+$), in the approximate ratio of 2.2:1.5:1.0. The most stable binding mode is one in which the M^+ is stabilized by a tridentate interaction between the cation and the carbonyl oxygen (O=C), amino nitrogen ($-NH_2$), and aromatic π ring; the absolute Li^+, Na^+, and K^+ affinities are estimated theoretically to be 275, 201, and 141 kJ mol^{-1}, respectively. Factors affecting the relative stabilities of various M^+–Phe binding modes and conformers have been identified, with ion–dipole interaction playing an important role. We found that the trend of π and non-π cation bonding distances (Na^+–π > Na^+–N > Na^+–O and K^+ –π > K^+–N > K^+–O) in our theoretical Na^+/K^+–Phe structures are in agreement with the reported X-ray crystal structures of model synthetic receptors (sodium and potassium bound lariat ether complexes), even though the average alkali metal cation–π distance found in the crystal structures is longer. This difference between the solid and the gas-phase structures can be reconciled by taking the higher coordination number of the cations in the lariat ether complexes into account.

Keywords: alkali metals · binding affinities · cation–pi interactions · molecular modeling · phenylalanine

Introduction

Noncovalent cation–π interactions, which involve binding of a cation to the π-face of the aromatic amino acids phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trp), have recently attracted much attention as a new type of binding force important in molecular recognition.[1,2] Such interactions have been implicated in the biological functions of the nicotinic acetylcholine receptor,[3] trimethylamine dehydrogenase,[4] human butyrylcholinesterase,[5] voltage-gated Na^+ channels,[6] and the stabilization of cell membrane proteins.[7] In addition, recent studies have suggested that the interactions between aromatic amino acids and various cationic centers are common motifs in protein structures.[8,9]

Sodium and potassium cations are amongst the most abundant metal cations found in biological systems.[10] Potassium cation–π interaction has been suggested to play an important role in the selective transport of K^+ across cell membranes.[11,12] A Na^+–tryptophan binding site in the crystal structure of lysozyme has been reported recently.[13] A putative Na^+/K^+ cation–π (tryptophan) binding site in the enzyme tryptophanase has also been suggested by Gokel and co-workers.[14] Despite this newfound importance, reports on alkali metal cation–π interactions in peptides/proteins have been sparse. Direct observation of cation–π interactions in vivo is experimentally difficult, and the situation could be complicated by competitive binding of the alkali metal cations to the many non-π, O/N heteroatom binding sites of peptides/proteins at the same time. In X-ray crystallographic studies, these cations have been described as the "lost cations",[15] since their scattering powers, most notably that of Na^+, are similar to that of water.[16] Hence, with the exception of lysozyme and tryptophanase, as cited

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above,[13,14] very few alkali metal cation–π binding sites have been definitively identified in peptide/protein crystal structures. Up to now, the interactions between alkali metal cations and aromatic amino acids have mostly been demonstrated on synthetic host–guest receptors, from which experimental data could be more easily gathered in both the solid and the solution states.[1,2,14,17,18] In particular, experimental evidence in support of Na^+/K^+ binding to phenylalanine, tyrosine, and tryptophan for a series of diaza-18-crown-6 lariat ethers has recently been reported.[19]

To gain a better understanding of the biological role of cation–π interactions, the local interactions between alkali metal cations and aromatic amino acids first have to be established. While there are some theoretical[20–25] and experimental[21,22,26–29] studies on alkali metal cation–π interactions,[20–29] these studies are focused on the interactions between the cations and small model molecules such as substituted benzenes, aromatics, and nitrogen heterocycles. As these ligands have only one or two potential sites of binding, it has been found—with the exception of pyridine (and its methyl and other related derivatives)—that the alkali metal cations often binds to the π ring. Experimental methods for measurement of M^+ free energies/enthalpies (affinities) of binding (where $M^+ = Li^+$, Na^+, and K^+) values by different mass spectrometric techniques have also been reported.[26–29] The theoretical study demonstrated that cation–π binding is indeed involved in the most stable forms of these cationized aromatic amino acid complexes, even though the factors affecting the competition between the π and non-π binding modes have not been explored in detail.

Our current study intends to fill this gap in the literature. Here, we report a detailed theoretical study on M^+–Phe (where $M^+ = Li^+$, Na^+, and K^+) complexes at the best level of theory so far reported for these systems. Using the M^+–Phe system, we aim to identify the physicochemical and structural factors that determine the relative stabilities of various π and non-π binding modes in alkali metal cationized aromatic amino acids. The ion selectivity (that is, the effect of ionic size on the relative stabilities of different binding modes) is discussed.

Computational Methods

Standard ab initio molecular orbital calculations were carried out with the aid of the GAUSSIAN 98[30] package of programs on SGI Indigo 2/Octane workstations and Origin 2000/Compaq GS320 high-performance computers.

Unless otherwise noted, all structures reported here were fully optimized geometries at the B3-LYP/6–31G(d) level. For all atoms except potassium, the standard 6–31G(d) basis sets in GAUSSIAN 98 were used. For potassium, the 6–31G(d) basis sets developed by Blaudeau et al. were utilized.[31] The optimized structures are numbered according to their order of appearance in the text. For phenylalanine in the free ligand form, the different conformers are prefixed by "Phe". For the cationized phenylalanine complexes (M^+–Phe, $M^+ = Li^+$, Na^+, or K^+), they may be in the "charge-solvation" (where the amino acid is a free acid) or the "zwitterionic" (where the amino acid is dipolar) forms. In this paper, these two types of complexes are differentiated by the abbreviations "CS" and "ZW" for the charge-solvation and zwitterion form, respectively. Furthermore, in order to distinguish between the same binding mode with different cations (Li^+, Na^+, or K^+), the form label is prefixed by the atomic symbol of the cation. For example, while "CS1" is used as a collective description for the three cations complexes with the same charge-solvation binding mode, "K^+-CS1" refers exclusively to the potassium cation complex in the CS1 binding mode. The Cartesian coordinates of all cationized phenylalanine complexes (M^+–Phe, $M^+ = Li^+$, Na^+, or K^+) reported in this paper can be found in the Supporting Information, Table 1S).

The alkali metal cation (M^+) binding affinity of a ligand (L) is defined as the enthalpy change of Equation (1), ΔH, and is calculated by Equation (2):

$$M^+L \rightarrow M^+ + L \quad (1)$$

$$\Delta H = E(M^+) + E(L) - E(M^+L) + ZPE(L) - ZPE(M^+L) \quad (2)$$

The electronic energies $E(M^+)$, $E(L)$, and $E(M^+L)$ in Equation (2) were calculated at the B3-LYP/6-311+G(3df,2p) level of theory based on fully optimized B3-LYP/6-31G(d) geometries. The effect of zero point energy (ZPE) was corrected by using the HF/6-31G(d) frequencies, scaled by 0.8929. The theoretical values at 0 K (ΔH_0) were converted into affinities at 298 K (ΔH_{298}) by standard statistical thermodynamics relationships[32] calculated from the scaled HF/6-31G(d) vibrational frequencies.

We recently utilized the above protocol to obtain the K^+ binding affinities of 136 ligands, for which 70 experimentally ascertained values are available for comparison.[33] We found that the theoretical estimates and the experimental affinities are in good general agreement (mean-absolute-deviation (MAD) of 4.5 kJ mol^{-1} for 65 model ligands).[33] In that work,[33] the effects of ZPE (HF versus B3-LYP, with the 6-31G(d) basis), basis set superposition error (BSSE), and the use of different theoretical models for single-point calculations (B3-P86 versus B3-LYP, with the 6-311+G(3df,2p) basis) were also studied. We found that these refinements/corrections are small, and may not lead to better agreement with experimentally obtained data, even though B3-P86 affinities have a tendency to be slightly lower than the B3-LYP values. Here we have carried out further analysis for 40 M^+–Phe (where $M^+ = Li^+$, Na^+, and K^+) complexes. The conclusion was similar to what we had found previously in reference [33]: BSSE is on average 3 kJ mol^{-1}, and B3-P86 affinities are on average about 5 kJ mol^{-1} lower. In terms of *relative* affinities, however, B3-P86 and B3-LYP are almost identical (with a MAD of 0.4 kJ mol^{-1}). In addition, we had previously found that, for Na^+–Phe complexes, relative B3-LYP affinities were in good agreement (within 3 kJ mol^{-1}) with values obtained by the computationally more expensive MP2 calculations.[34] From all the above considerations, we concluded that, as different theoretical models yield the same trend in terms of relative stability, the reported *relative* affinities are unlikely to carry an error bar exceeding 2–3 kJ mol^{-1}. In terms of *absolute* Li^+, Na^+, and K^+ affinities, we propose assigned error bars of ±20, ±16, and ±6 kJ mol^{-1}, respectively, for our reported B3-LYP affinities (see the section on Absolute Affinities of M^+–Phe Complexes for details).

Results and Discussion

Phenylalanine (Phe) conformers: By using the protocol outlined in the Supporting Information, and on the basis of previously reported structures for alanine,[35] we located six stable phenylalanine conformers at the B3-LYP/6-31G(d) level of theory, the relative stabilities of which were determined at the B3-LYP/6-311+G(3df,2p) level. The stabilities of these conformers are very close, spanning a narrow range of only 12 kJ mol^{-1}. The two most stable conformers (Figure 1) are more stable than that obtained by Dunbar (structure Phe(a) in ref. [25]) by at least 5 kJ mol^{-1}. The most stable conformer we obtained, Phe1, has an intramolecular hydrogen bond between the hydroxyl hydrogen and the amino nitrogen. On the other hand, there are two sets of stabilizing intramolecular interactions in Phe2. It appears

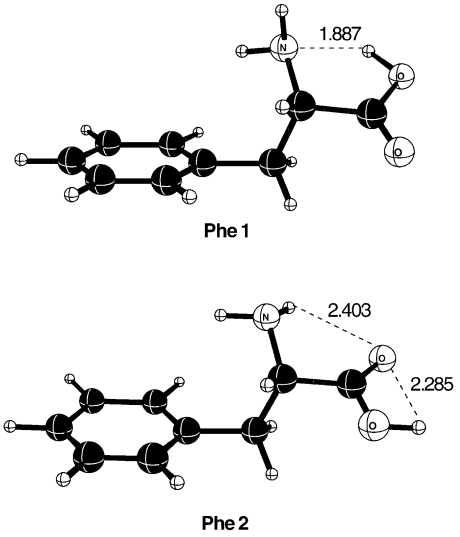


Figure 1. The optimized geometries of the two most stable conformers of phenylalanine (Phe) obtained at the B3-LYP/6-31G(d) level of theory. The hydrogen bonds/intramolecular interactions are indicated by dotted lines, with distances given in Å.

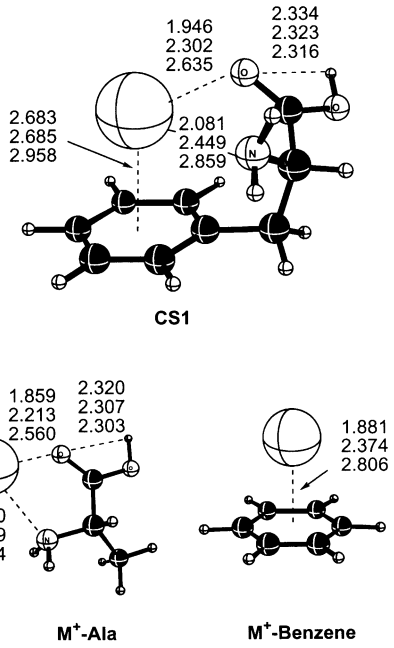


Figure 2. The optimized geometries of CS1 (the most stable M^+–phenylalanine (Phe) isomer), M^+–alanine (Ala), and M^+–benzene at the B3-LYP/6-31G(d) level of theory. All the bond lengths [Å] and angles [°] are given in the order (from top to bottom) $M^+ = Li^+$, Na^+, K^+. In CS1, the cation–π bonding distances are calculated on the basis of the separation between the M^+ and the centroid of the phenyl π ring. The angles between M^+, ring centroid, and the base normal are 21.1°, 11.3°, and 5.4° for Li^+, Na^+, and K^+–Phe complexes, respectively. For comparison, the corresponding angles in the M^+–benzene complexes are 0°.

that the stability of Phe1 over Phe2 (by 4 kJ mol^{-1}) arises from the presence of one shorter (stronger) intramolecular interaction rather than two longer (weaker) sets of interaction in Phe2 (Figure 1).

We note with interest that the preferred hydrogen-bonding patterns of alanine (Ala)[35] and of phenylalanine are different. In the case of alanine, the nitrogen lone pair is pointing away from the carbonyl oxygens so that both amino hydrogens ($-NH_2$) are accessible to the carbonyl oxygen (O=C). Such a conformation would be destabilizing in the case of phenylalanine as the nitrogen lone pair may interact unfavorably with the electron-rich phenyl π ring.

The most stable M^+–Phe conformers: By using the method outlined in the Supporting Information, the candidate M^+–Phe structures were selected on the basis of previous literature K^+–glycine structures.[36,37] All three alkali metal cations prefer to bind to phenylalanine (in the charge-solvation (CS) form) through a tridentate binding mode: carbonyl oxygen (O=C) and amino nitrogen ($-NH_2$) with additional stabilization from the cation–π interaction (Figure 2). This binding mode was also identified as the most stable in Dunbar's study of the Na^+/K^+–Phe systems.[25] However, our work has demonstrated that this preference is also extendable to the smallest alkali metal cation, Li^+.

Phenylalanine may be viewed as a substituted alanine in which one of the C_β hydrogens of alanine is replaced by a phenyl group (see Scheme 1 in the Supporting Information). If we compare M^+–Phe with M^+–Ala and M^+–benzene, we find that the bonding distances between M^+ and O=C, $-NH_2$, and the phenyl π ring (measured from the center of the phenyl π ring) have all increased (Figure 2). This suggests that the interactions between M^+ and the individual binding sites (functional groups) are weaker in Phe than in the cases of alanine and benzene. However, this weakening of binding strength at individual coordination sites is compensated by the increased coordination number of the cation, with three phenylalanine binding sites in the CS1 conformation. This relation between bond length/bond strength and number of coordination sites is further discussed in a later section, in which our theoretical structures are compared with the crystal structures of model synthetic receptors.

Other less stable charge-solvation (CS) M^+–Phe conformers: In addition to K^+-CS1, we have also located ten multidentate isomers with binding affinities smaller than that of K^+-CS1 within a range of 59 kJ mol^{-1}. If isomers arising from minor conformational differences (with the same binding sites) are ignored, there are seven more CS isomers (K^+-CS2 to K^+-CS8, Figure 3). Two zwitterionic (ZW) isomers (K^+-ZW3 and K^+-ZW5) were also found, but discussion of these complexes is postponed until the next section. The binding sites and the relative affinities (with reference to CS1) of the various isomers are summarized in Table 1.

In theory, the four electron-rich sites in phenylalanine could generate one tetradentate, four tridentate, six bidentate, and four monodentate modes. Our calculations suggest that the tetradentate mode (in which M^+ binds simultaneously to O=C, $-OH$, $-NH_2$, and the phenyl π ring), and the two tridentate modes (in which the M^+ interacts with O=C, $-OH$, and $-NH_2$ and with $-OH$, $-NH_2$, and the phenyl π ring) are not stable. Theoretical studies on K^+–Gly[36,37] have already suggested that K^+ may not bind simultaneous-

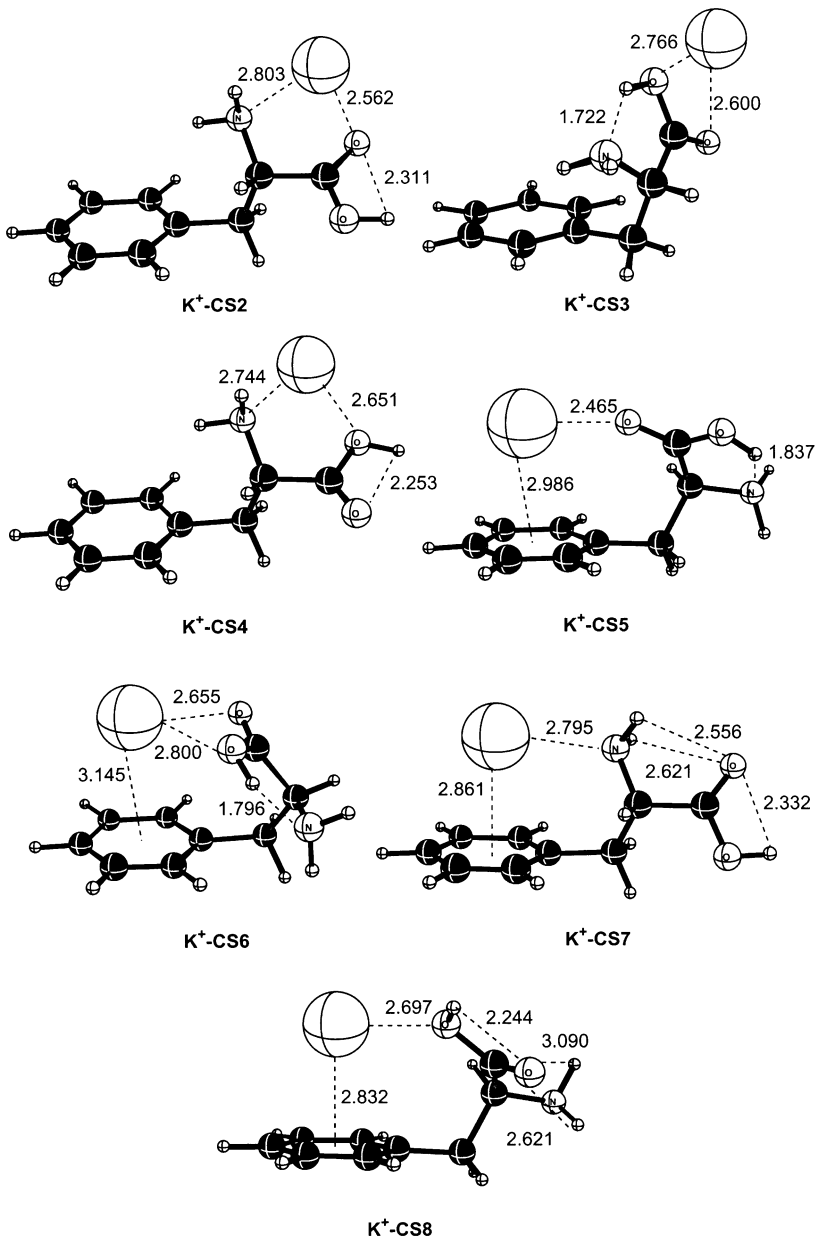


Figure 3. The optimized geometries for isomers K^+-CS2 to K^+-CS8 at the B3-LYP/6-31G(d) level of theory. The interaction between K^+, N/O/π binding sites and hydrogen bonds/intramolecular interactions are indicated by dotted lines, with distances given in Å. For the cation–π binding site, the distances between K^+ and the centroid of the π ring are indicated. The angles between K^+, ring centroid, and the base normal are 5.3°, 3.7°, 3.8°, and 1.1° for CS5, CS6, CS7, and CS8, respectively.

ly to O=C, −OH, and $-NH_2$, as such a binding mode would induce too much structural strain on the glycine. If this is the case, then, the tetradentate binding mode, in which the M^+ binds to O=C, −OH, $-NH_2$, and the phenyl π ring, would be even less stable. Moreover, we have failed to locate a Li^+-CS6 complex (in which Li^+ binds tridentately to π, O=C, and −OH), as this species collapses to Li^+-CS5 (in which Li^+ binds only bidentately to π and O=C). We note that the binding of Li^+ to both O=C and −OH appears to be quite unfavorable, as no such complex was found either in the Li^+–Gly system in a previous study.[38]

In the following discussion, the factors affecting the relative stability of π versus non-π modes of binding in alkali metal cationized phenylalanine complexes are analyzed in detail. The observed binding affinities of M^+–ligand complexes can be regarded as a balance of stabilizing and destabilizing interactions. In these M^+–Phe conformers, the key stabilization force is the electrostatic attraction between the positively charged metal cation and the electron-rich binding site in phenylalanine. The strength of this stabilization force is dependent on many factors, such as the coordination number of the cation, the intrinsic binding strength at each binding site, and the distances between the cation and the binding sites. In previous theoretical studies on cation–π interactions, the major focus has been on the ion–quadrupole interaction between the cation and the aromatic-π binding site.[1] This is understandable, as the dipole moment tends to be small, if not zero, in the model aromatic molecules studied, and the first non-vanishing and significant permanent molecular multipole in these small ligands is the quadrupole moment. However, as shown in the following discussion, ion–dipole interaction appears to play a significant role in determining the stability of various π and non-π modes of binding for a multi-functional ligand such as phenylalanine.

In this work, we have applied classical electrostatic theory to model the strength of the ion–dipole interaction.[39] On the basis of classical electrostatics, we define the *dipole interaction parameter* (DIP) for the ion–dipole interaction in a M^+–Phe conformer as in Equation (3),

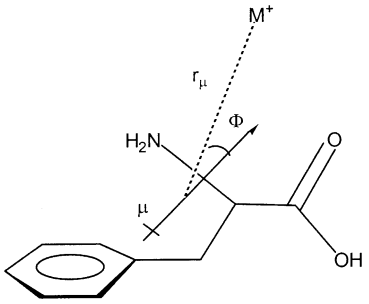
$$\mathrm{DIP} = \mu\cos(\Phi)/r_\mu^2 \qquad (3)$$

where μ is the permanent molecular dipole moment of the deformed ligand (i.e., Phe with the geometry in the various M^+–Phe complexed states, in Debye), Φ is the angle of deviation between the metal cation and the molecular dipole vector (in °), and r_μ is the distance between M^+ and the center of the dipole moment vector (in Å) (Scheme 1). As DIP has the effects of binding geometries incorporated

Table 1. Relative binding energies [kJ mol^{-1}] and properties of various charge-solvation (CS) and zwitterionic (ZW) M^+–Phe (M^+ = Li^+, Na^+, and K^+) complexes

Species	Binding sites	Hydrogen bond/ intramolecular interactions	Li^+			Na^+			K^+		
			$\Delta(\Delta H_0)$[a]	DIP[b]	E_{def}[c]	$\Delta(\Delta H_0)$[a]	DIP[b]	E_{def}[c]	$\Delta(\Delta H_0)$[a]	DIP[b]	E_{def}[c]
CS1	O=C, π, NH_2	OH···O=C	0.0	0.47	47.5	0.0	0.42	39.7	0.0	0.28	35.2
CS2	O=C, NH_2	OH···O=C	11.5	0.20	36.9	16.9	0.17	29.2	15.0	0.14	25.5
CS3	O=C, OH	OH···NH_2	55.0	0.27	19.9	32.5	0.23	9.3	16.0	0.19	4.5
CS4	NH_2, OH	OH···O=C	53.2	0.11	34.2	55.9	0.08	27.0	51.5	0.05	24.0
CS5	O=C, π	OH···NH_2	4.7	0.89	30.5	7.9	0.57	23.6	3.1	0.40	21.1
CS6	O=C, π, OH	OH···NH_2	–[d]	N/A	N/A	36.2	0.55	31.6	21.5	0.46	29.5
CS7	π, NH_2	OH···O=C; NH_2···O=C	34.5	0.36	27.5	33.5	0.23	18.1	29.2	0.16	15.2
CS8	π, OH	OH···O=C; NH_2···O=C	67.0	−0.23	25.6	67.1	−0.16	18.3	58.6	−0.12	14.7
ZW3	COO^-[e]	NH_3^+···$^-$O–C	24.0	0.37	88.2	20.2	0.32	77.2	16.1	0.27	71.2
ZW5	CO^-[f], π	NH_3^+···$^-$O–C	11.7	2.19	127.6	43.3	0.72	95.7	40.8	0.53	90.2

[a] Relative binding affinities at 0 K with reference to CS1. The binding affinities of Li^+-, Na^+-, and K^+-CS1 are 275, 201, and 141 kJ mol^{-1}, respectively. [b] Dipole interaction parameter (defined by Equation (3)]) of phenylalanine, in units of Debye Å^{-2}, with its geometry in the complexed form, calculated at the B3-LYP/6-31G(d) level of theory. [c] Deformation energies of phenylalanine (in kJ mol^{-1}), calculated at B3-LYP/6-31G(d) level of theory. [d] No minimum could be found for this conformer. [e] M^+ binds to *both* carboxylate oxygens. [f] M^+ binds to *one* of the carboxylate oxygens only.



Scheme 1. The definition of *dipole interaction parameter* (DIP), for the ion–dipole interaction in a M^+–Phe conformer, where μ is the permanent molecular dipole moment (in Debye) of the deformed ligand (i.e., Phe with the geometry in the various M^+–Phe complexed states), Φ is the angle of deviation between the metal cation and the molecular dipole vector (in °), and r_μ is the distance between M^+ and the center of the dipole moment vector (in Å).

(through Φ and r_μ), it would be expected to provide a more accurate representation of the ion–dipole interaction (in terms of classical electrostatics) than the crude molecular dipole moment (μ) itself.

To accommodate the metal cation, the ligand needs to deform itself upon complexation and hence is destabilized. The destabilization is due to factors such as structural distortion (introduction of strain in the phenylalanine ligand upon complexation), disruption of intramolecular hydrogen bonding, and electrostatic repulsion arising from various electron-rich cation binding sites in the ligand. To gain an insight into the overall effect of these destabilizing factors, we define the deformation energy of the M^+–Phe complex, E_{def}, as in Equation (4),

$$E_{def} = E(\text{Phe in the complexed form}) - E(\text{Phe in the most stable uncomplexed form}) \quad (4)$$

where E is the energy of the species calculated at the B3-LYP/6-31G(d) level. We found the E_{def} values determined at the B3-LYP/6-31G(d) and B3-LYP/6-311+G(3df,2p) levels differed by less than 1 kJ mol^{-1} in a few test cases. Hence, given the savings in computational time, we estimated the destabilization effect at the B3-LYP/6-31G(d) level.[36] As the ligand has to adopt a less favorable (stable) conformation in order to complex with the cation, E_{def} is always a positive quantity.

Our aim is to investigate how ion–dipole interaction (in terms of DIP) and ligand deformation (in terms of E_{def}) would affect the preference for various π and non-π cation binding sites. These two parameters for various CS and ZW species are summarized in Table 1. The variations in DIP [Eq. (3)], E_{def} [Eq. (4)], and ΔH [Eq. (2)] in various modes of binding are plotted in Figure 4a, Figure 4b, and Figure 4c, respectively. As Li^+-CS6 could not be located, we have omitted this species in the discussion below.

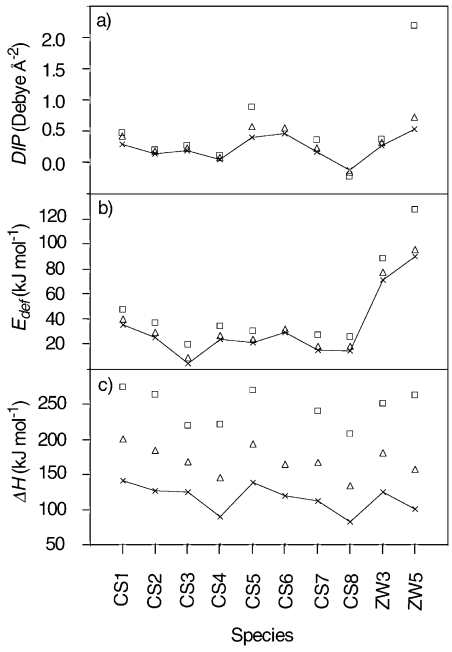


Figure 4. Variations in: a) dipole interaction parameter [Debye Å^{-2}], b) deformation energy [kJ mol^{-1}], and c) binding affinity [kJ mol^{-1}] for different M^+–Phe conformers. The Li^+-, Na^+-, and K^+-bound complexes are denoted by squares (□) , triangles (△), and crosses (×), respectively. Data points associated with K^+ complexes are connected to aid visualization of trends.

In general, as can be seen in Figure 4a, the magnitude of the dipole interaction parameter for a given binding mode is quite independent of the size of M^+, except for CS5 and ZW5. The molecular dipole moment of the deformed ligand (μ) is quite large in CS5 (≈6 Debye). Converting CS5 into its corresponding zwitterionic ZW5 mode induces even greater charge separation, and thus further increases the molecular dipole moment to over 9 Debye. The larger molecular dipole moment in turn amplifies the cationic size effect, which leads to the largest range of DIP observed in the ZW5 mode. Regardless of the absolute magnitude for the dipole interaction parameter, DIP is of the general order $Li^+ > Na^+ > K^+$, reflecting the $1/r_\mu^2$ dependence of the parameter [Eq. (3)]. The only exception is found in the case of CS8, in which the order is reversed, as discussed below.

The deformation energy, E_{def}, is relatively small for CS complexes, but large for the ZW species (Figure 4b). This reflects the intrinsic instability of phenylalanine in the zwitterionic form in the gas phase. As in the case of DIP, for a given binding mode, E_{def} also follows the order $Li^+ > Na^+ > K^+$. This general decreasing trend of DIP and E_{def} with increasing cationic radius is consistent with the qualitative picture that, whereas a smaller cation interacts more favorably with Phe, it also, at the same time, induces a larger deformation in the ligand. Given these two opposing but comparable effects, the relative affinity for a given binding mode or conformation shows little metal cation (M^+) dependence. The ratio of average $Li^+/Na^+/K^+$ binding affinity for the nine binding modes is 2.2:1.5:1.0, which is quite typical for electrostatically bound complexes of alkali metal cations,[34,40–42] except that the Li^+/K^+ affinity ratio is particularly small for CS3 (1.8:1.0), and exceptionally large for ZW5 (2.6:1.0). Given these observations, we focus our discussion on how structural and electronic factors affect the relative stability of various binding modes of K^+ complexes. The effect of cationic size is discussed for the CS3 and ZW5 modes of binding only.

The CS2 binding mode: Structurally, the major difference between the bidentate CS2 and the most stable tridentate CS1 is that the phenyl π ring does not interact with the metal cation in the CS2 complex (Figure 2 and Figure 3). In the absence of cation–π interaction, the CS2 complex is less strained, as reflected in the smaller E_{def} (Table 1). Despite this, the CS2 mode is still less stable than CS1 by 12 to 17 kJ mol^{-1}, depending on the nature of M^+. Thus, in terms of stabilization energy, the reduction in E_{def} cannot compensate for the loss of the cation–π binding site in CS2. Another important factor is the dipole interaction parameter. As the Phe ligand is adopting a more "open" conformation in CS2, the distance r_μ (the distance between the center of the dipole moment vector and the M^+) is found to be much larger, indicating a weaker ion–dipole interaction in this complex.

The CS3 binding mode: Non-π bidentate binding between M^+ and Phe is involved in both the CS2 and CS3 conformers (Figure 3). While M^+ in CS2 binds to O=C and $-NH_2$ to form a five-membered ring moiety, in CS3 it binds to O=C and −OH to form a four-membered ring moiety. Despite a smaller deformation energy and a stronger ion–dipole interaction (larger DIP), the CS2 conformer tends to be more stable than CS3. However, the relative stabilities of CS2 and CS3 exhibit a strong dependence on cation size.

This preference for the five-membered ring moiety in CS2 over the four-membered ring motif in CS3 has also been discussed by Hoyau and Ohanessian[37] in the case of M^+–Gly (structures 1 versus 3 in ref. [37]). As the preference was found to decrease with increasing cationic size from Li^+ to Cs^+, it was suggested that the increase in cation binding distances led to the destabilization of the five-membered ring moiety (CS2) relative to other modes of binding. Our calculations provide further insight into the origin of this destabilization. We note that the difference in E_{def} between CS2 and CS3 is virtually independent of cationic size, suggesting that the relative destabilization of the CS2 mode is *not* caused by strains derived from binding to larger cations. One of the major differences between CS2 and CS3 is that $M^+\cdots NH_2$ binding is involved in CS2, while $M^+\cdots OH$ binding is involved in CS3. Comparing ammonia with water, alkali metal cation affinities for NH_3 are always larger than for H_2O, but the difference decreases with increasing cationic radius.[41] We believe that the same factor is at work here. For the M^+–Phe complexes, as the size of the cation is increased, the preference for $-NH_2$ over −OH binding becomes smaller. This preference is counterbalanced by the difference in E_{def} between CS3 and CS2 in the case of K^+, and K^+-CS3 becomes marginally less stable than K^+-CS2.

The CS4 binding mode: Comparison of the two non-π binding modes of CS4 and CS2 is particularly revealing. These two modes of binding have almost identical E_{def} values (Table 1). In fact, CS4 is related to CS2 through a simple rotation around the C–C bond so that M^+ is bound to $-NH_2$ and O=C in CS2 but to $-NH_2$ and −OH in CS4. However, CS4 is less stable than CS2 by ≈40 kJ mol^{-1}. We attribute this difference in relative stability to the particularly small dipole interaction parameter of Phe in the CS4 conformation, leading to a much smaller cation–dipole interaction than in CS2. This also suggests that the conformation of the carboxylic acid functional group has a significant effect on the molecular dipole moment (in terms of both magnitude and direction) of Phe.

The CS5 binding mode: In complexes CS5 to CS8, the phenyl–π ring is involved in M^+ coordination (Figure 3). Species CS5 is very stable and it is in fact the second most stable M^+–Phe complex found. This is quite surprising, given that CS1 is stabilized by tridentate binding between M^+ and phenylalanine (O=C, π, and $-NH_2$), but only bidentately (O=C and π) in CS5. Our model suggests that the relatively high stability of CS5, in relation to CS1, is the result of a combination of three factors: a much larger dipole interaction parameter (Figure 4a), a smaller E_{def} (Figure 4b), and stronger intramolecular hydrogen bonding (Figure 3).

The CS6 binding mode: The CS6 conformer is, like CS1, a tridentate complex involving a cation–π binding site. De-

spite a smaller E_{def} and a larger DIP, CS6 is much less stable than CS1. Apart from the intrinsically weaker M^+ affinity for $-OH$ binding than for $-NH_2$ binding, it seems that the cation–π interaction in CS6 is also weaker; we found evidence in, for example, the K^+–phenyl π distance, which is approximately 0.2 Å longer in K^+-CS6 than in K^+-CS1 (Figure 3).

The CS7/CS8 binding modes: The CS7 and CS8 conformers have M^+ bound to the phenyl-π face, but differ in that M^+ is bound to the $-NH_2$ group in CS7, and to the carboxylic $-OH$ group in CS8 (Figure 3). The CS7 isomer is found to be more stable than CS8 for all M^+. Because CS7 and CS8 have similar deformation energies (Table 1), the relative stability of CS7 over CS8 must be governed by some favorable interactions. We suggest that the stability of CS7 is partly due to the greater intrinsic binding strength of $M^+\cdots NH_2$, in relation to the $M^+\cdots OH$ interaction. However, the difference in binding affinity for CS7/CS8, unlike the CS2/CS3 and CS1/CS6 pairs, shows very little cation dependence. This suggests that other factors are at work here. We note that the alignment angle of the dipole moment vector (Φ in Scheme 1) increases from 149° for Li^+ to 173° for K^+ for the CS8 binding mode. In other words, the positive end of the molecular dipole moment is in fact pointing towards the cation. This is electrostatically unfavorable, in particular for the larger potassium cation. Hence, it appears that in CS8, to bind both the phenyl π ring and to the $-OH$ site, the M^+ is interacting repulsively with the molecular dipole moment, resulting in a relatively unstable binding mode.

Stability of zwitterionic (ZW) M^+–Phe complexes: With the relative stability of various charge-solvation (CS) modes established in the previous section, we now turn our attention to the zwitterionic (ZW) modes of binding. Only two zwitterionic M^+–Phe conformers (ZW3 and ZW5) were found, with non-π binding sites involved in ZW3, and cation–π binding involved in ZW5 (Figure 5). Because of the separation of positive and negative charges in their structures, these two zwitterionic binding modes are associated with much larger deformation energies (71 and 90 kJ mol^{-1} for K^+-ZW3 and K^+-ZW5, respectively, Table 1) than the CS binding modes, with deformation energies in the range from 4 to 35 kJ mol^{-1}.

We have discussed the role of the phenyl ring in the stability of cation–π (CS5/ZW5) and non cation–π modes (CS3/ZW3) of binding in Na^+–Phe system previously.[34] In this report we focus on the effect of cationic size on the stability of these modes.

The ZW3 binding mode: Both CS3 (O=C, $-OH$) and ZW3 (COO^-) are non-π binding modes. In order to elucidate the role of the phenyl-π side chain in governing the relative stabilities of CS3/ZW3 complexes, we carried out methyl stabilization analysis[43] for the CS3/ZW3 complexes for the Li^+ and K^+ reactions ([Eq. (5) and Eq. (6)]):

$$\mathrm{Ala(CS3)} + \mathrm{CH_3C_6H_5} \rightarrow \mathrm{CS3} + \mathrm{CH_4} \quad (5)$$

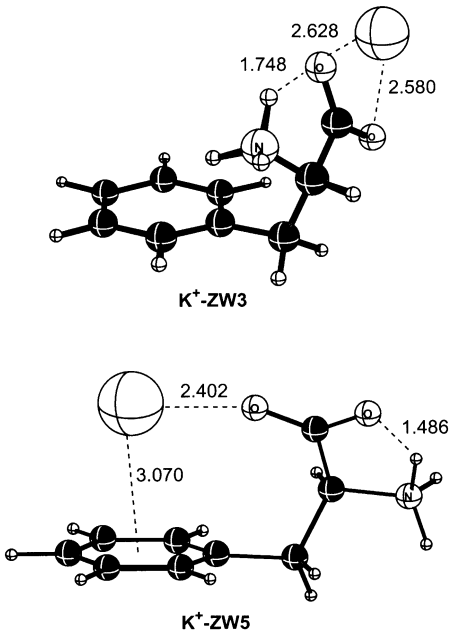


Figure 5. The optimized geometries of K^+-ZW3 and K^+-ZW5 conformers at the B3-LYP/6-31G(d) level of theory. For the cation–π binding site in the K^+-ZW5 complex, the distance between K^+ and the centroid of the π ring is indicated, and the angle between K^+, ring centroid, and the base normal in this species is 5.3°.

$$\mathrm{Ala(ZW3)} + \mathrm{CH_3C_6H_5} \rightarrow \mathrm{ZW3} + \mathrm{CH_4} \quad (6)$$

In the case of K^+, similar to what was found for Na^+,[34] the reactions depicted in Equation (5) and Equation (6) are exothermic. This suggests that the phenyl group in phenylalanine stabilizes both the CS3 and ZW3 forms relative to toluene (methylbenzene). As the phenyl group is not interacting with the alkali cation in the CS3 and ZW3 modes (Figure 5), one would expect that this stabilization should be quite independent of the cationic size. This is indeed what we observed here, as the *difference* in exothermicity between the reaction shown in Equation (5) and that in Equation (6) is the same for the Na^+ and K^+ complexes, at 8 kJ mol^{-1} (Figure 6).

For Li^+, we were unable to find a stable Li^+–Ala(CS3) complex. The small radius of Li^+ results in a bidentate binding mode to the two carboxylic oxygens that is not stable. Similar results for Li^+–Gly complexes have been reported by Jensen.[38] Hence, the energetics of the reaction shown in Equation (5) cannot be determined for Li^+. For that shown in Equation (6), the exothermicity is found to decrease slightly with increasing cationic radius, with the stabilization energy being in the order of Li^+ (22 kJ mol^{-1}) > Na^+ (19 kJ mol^{-1}) > K^+ (17 kJ mol^{-1}). In other words, there is a slight preference for the smaller cation to bind in the ZW3 mode, due to the phenyl–π stabilization effect. On the other hand, we found that the energy difference between CS3 and CS1 (Table 1) decreases rapidly with increasing ionic size: Li^+ (56 kJ mol^{-1}) ≫ Na^+ (33 kJ mol^{-1}) ≫ K^+ (16 kJ mol^{-1}), indicating that the larger cation has a strong preference for the CS3 mode. Because of these two opposing trends, ZW3 is more stable than CS3 by 32 and 12 kJ mol^{-1} for Li^+ and

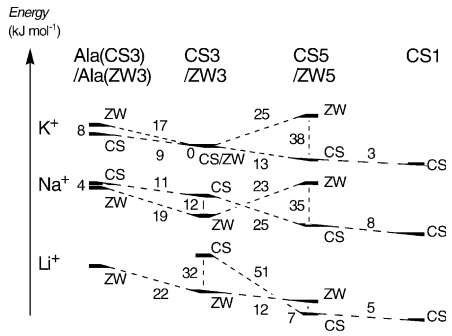


Figure 6. Energy level diagram for M^+–alanine (Ala) and M^+–phenylalanine (Phe) complexes with reference to the most stable conformer CS1. In order to conserve the type and number of atoms so that different systems can be compared on the same potential surface, the following species are added: $CH_3C_6H_5$ for Ala(CS3)/Ala(ZW3) and CH_4 for the remaining systems, together with the alkali metal cations, where Ala(CS3) and Ala(ZW3) are the charge-solvation and zwitterionic forms of Li^+-/K^+–alanine complexes in the same binding mode as CS3 (O=C and −OH) and ZW3 (COO^-), respectively.

Na^+, respectively, but becomes comparable for K^+ (Figure 6).

The ZW5 binding mode: Cation–π binding is involved in both CS5 and ZW5 modes of binding. For all three alkali metal cations, CS5 is more stable than the non cation–π CS3 mode. We found that the preference for CS5 over CS3 decreases from Li^+ (51 kJ mol^{-1}) to Na^+ (25 kJ mol^{-1}), and to K^+ (13 kJ mol^{-1}). This can be attributed to the conspicuous decrease in deformation energies with increasing cationic radius in the CS3 complexes, which is not so obvious in the CS5 complexes (Figure 4b).

If the components of the ZW3/ZW5 pair (Figure 6) are compared, the presence of strong cation–π binding leads to an overall stabilizing effect in the case of Li^+-ZW5 (by 12 kJ mol^{-1}). Contrarily, we found that it is destabilizing for Na^+ (−23 kJ mol^{-1}) and K^+ (−25 kJ mol^{-1}). When phenylalanine binds to the larger cations in the ZW5 mode, the distance between the negatively charged carboxylate COO^- site and the phenyl π ring increases. Hence, we would expect the repulsion between these binding sites to decrease, and this is indeed reflected in the decrease of E_{def} from 128 to 90 kJ mol^{-1} for Li^+-ZW5 and K^+-ZW5 (Figure 4b), respectively. This change is particularly significant in view of the very similar E_{def} values for the CS5 complexes (21 to 30 kJ mol^{-1}) for different cations (Figure 4b). On the basis of this factor alone, one would predict K^+-ZW5 to be quite stable, as this species has a lower E_{def} than Li^+-ZW5. However, this is found not to be the case, hence suggesting that other factors are at work here. We would like to offer the following rationale: as charge density decreases with increasing cation size, the attractive and repulsive interactions between metal cations and the various binding sites are also weakened at the same time. For K^+, it appears that the decrease in stabilizing interactions (in terms of crude binding affinity, and including the cation–π interaction) far exceeds the decrease in destabilizing interactions (in terms of repulsion between charged binding sites, and deformation energies) in ZW5, so that the zwitterionic complex becomes much less stable (by 38 kJ mol^{-1}) relative to CS5.

In summary, for the ZW3 non-π binding mode, despite the stabilization effect of the phenyl π ring, the relatively large deformation energy is the predominant factor affecting the stability of this binding mode. For the ZW5 cation–π binding mode, electrostatic repulsion between negatively charged sites strongly destabilizes this binding mode. Hence, we found both ZW3 and ZW5 modes are less stable than CS1 for all alkali cations studied here.

General conclusions on the stabilities of M^+–Phe complexes: From the above analysis, it is evident that the observed strengths of various π and non-π binding modes are determined by a delicate balance of various interaction factors. Nevertheless, the following general conclusions can be drawn:

1) The energetically preferred binding site in phenylalanine appears to be the carbonyl oxygen (O=C), as such a binding motif can be found in five of the most stable M^+–Phe complexes (CS1, CS2, CS3, CS5, and CS6). These conformations tend to have large dipole interaction parameters, suggesting that the alignment of the molecular dipole moment to the binding of alkali metal cation, and hence the ion–dipole interaction, is an important factor contributing to the stabilities of these complexes.
2) Binding to the carbonyl oxygen (O=C) and the phenyl π ring appears to be the most favorable bidentate site, as such a motif is found in the two most stable complexes (CS1 and CS5). As these two modes allow M^+ to interact with the O=C as well as the quadrupole moment of the phenyl π ring, these binding sites are particularly stabilizing.
3) Cation binding to $-NH_2$ versus the phenyl π ring in phenylalanine is comparable in strength, as indicated by the relatively small difference (< 14 kJ mol^{-1}) in stability of the CS4/CS8 and CS2/CS5 pairs. This is in line with the similar intrinsic M^+ affinities found for ammonia and benzene.[41] For the CS4/CS8 pair, M^+ binding to $-NH_2$ (in CS4) is slightly more stable than binding to phenyl-π (in CS8), with the two modes sharing a common −OH binding motif. On the other hand, the order of relative binding affinity is reversed in favor of phenyl-π binding in CS5 for the CS2/CS5 pair (with common O=C group binding). We attribute this reversal in the order of binding affinity to the geometrical effects of different binding modes. While M^+ can position itself freely to maximize its alignment with the nitrogen lone pair in NH_3, such optimal binding to an amine nitrogen ($-NH_2$) may not always be possible in the multidentate binding modes of the M^+–Phe complex.
4) If $-NH_2$ and −OH are compared, M^+ binding to −OH is less favorable than binding to $-NH_2$, as is demonstrated by the relative stabilities of the CS1 > CS6, CS2 > CS3, and CS7 > CS8 isomer pairs.
5) The zwitterionic complexes (ZW3 and ZW5) are energetically not competitive with the most stable charge-solvated CS1 species. The ZW5 binding mode is particular-

ly unstable, presumably due to greater electrostatic repulsion between the negatively charged carboxylate oxygens and the electron-rich phenyl π ring in the ZW5 conformation.

6) It seems that the different modes of binding in phenylalanine show little ion selectivity for the three alkali metal cations. The only exception is found for Li^+, as this cation appears to have a smaller tendency to bind simultaneously to O=C and −OH. We find evidence in CS3 (O=C and −OH) as the Li^+/K^+ affinity ratio (1.8:1.0) is particularly small in relation to other modes of binding, and the fact that species Li^+-CS6 (in which the Li^+, if found, would interact with π, O=C, −OH) could not be located at all.

Comparison with model synthetic receptor systems: In a previous study, diaza[18]crown-6 lariat ethers with two flexible side arms (two-carbon spacers) were used as model receptors for Na^+/K^+ cation–π binding. It was found that complexation with Na^+/K^+ led to a dramatic change in the conformation at the side arms of these ligands. The geometry of K^+-bound **10**·KI and **11**·KI complexes, the side arms of which contain a phenyl and a phenol π group, respectively,[19] are particularly relevant to our current study. The crystal structures revealed that the potassium cation binds simultaneously to the nitrogens and oxygens of the crown ether, while attaining further stabilization through two sets of cation–π interactions between the K^+ and the phenyl or phenol π groups in the side arms. The observed trend of bonding distances in these crystal structures (K^+–π > K^+–N > K^+–O) is in agreement with the most stable K^+-CS1 ground state structure we obtained theoretically.

A point of interest arises on *quantitative* comparison. The distances between K^+ and all binding sites (–π, –N, and –O) are longer in the crystal structure of K^+–lariat ether complexes[19] than in the isolated, theoretical structures of the various K^+–Phe complexes. Notably, the K^+–aromatic π distances in the crystal structures of the **10**·KI and **11**·KI complexes (≈3.4 Å, ref. [19]) are longer than the theoretical K^+–aromatic π bonding distance of 2.96 Å in K^+-CS1 (Figure 2). This discrepancy could be attributable to deficiencies in our theoretical model in describing the geometry of noncovalent interaction, and to the presence of packing forces in the crystal structure. However, we believe that a plausible reason is that as the K^+ tries to attain optimal coordination in the lariat ether complex, the individual binding sites of the ligands are all weakened, leading to longer interaction distances.

If K^+–benzene (Figure 2) is compared with various π-bonded K^+–Phe structures (CS1, CS5, CS6, CS7, and CS8), we find that the K^+–aromatic π distances have increased from benzene to phenylalanine. On average, on the basis of the differences of bonding distances in these species, we estimated that each additional binding to an O/N heteroatom site increases the K^+–aromatic π distances by 4%. In the lariat ether complex, K^+ binds to four oxygen and two nitrogen atoms, so we might expect that the K^+–aromatic π distances would increase by 24%. On this basis, the estimated K^+–π distance would be about 3.4 Å, in excellent agreement with the experimentally observed binding distances in the synthetic receptor complexes.[19]

Similar analysis for the Na^+–Phe complexes suggests that each additional binding to an O/N heteroatom site would increase the Na^+-aromatic π distances by 6%. In the very recently reported sodium lariat ether complex (**1**·Na),[44] the cation binds to four oxygens and one nitrogen. With the optimal Na^+–benzene of 2.374 Å as the reference, binding to five N/O heteroatoms may result in a lengthening of the Na^+–π distance by 30%, thus yielding a predicted Na^+–π bonding distance of ≈3.1 Å in **1**·Na. This estimate is significantly greater than the reported distance of 2.8 Å. Given the crudeness of our simple model, the disagreement may not be surprising. However, the agreement between our rough estimate and the experimentally measured cation–π interaction distance is clearly less satisfactory in the case of Na^+–π[44] than for the K^+–π distance[19] discussed above. This could be due to the variation in the nature of ligand, thus leading to differing extents of how crystal packing forces affect the experimental cation–π distances, and/or the weaker scattering power of Na^+, leading to larger uncertainty in resolution of the position of the cation. Another possibility is that the agreement is related to the binding strength between the cations and binding sites. In the case of K^+, we found that the binding distance between the cation and the phenyl π ring of Phe in CS1 is fairly similar to that in K^+–benzene (differs by 0.15 Å). However, the differences in binding distances are increased to 0.31 and 0.80 Å for Na^+–Phe/benzene and Li^+–Phe/benzene, respectively. Thus, the binding of K^+ to a multidentate ligand (e.g., K^+ binding to Phe in the CS1 mode) would be not much different from K^+ binding to a cluster of ligands with the same coordination number and basic sites (e.g., K^+ binding simultaneously to a benzene and an alanine). In other words, given the weaker interaction between K^+ and ligands in general, one may expect less variation in the cation–π distance for K^+ with different ligands than in the case of Na^+ and Li^+. Regardless of the plausible reasons, the simple analysis here supports the claim that cation–π interaction is strong enough that it can be observed even when the binding geometry is not optimal.[19]

Absolute affinities of M^+–Phe complexes: The absolute Li^+, Na^+, and K^+ affinities are estimated to be 275, 201, and 141 kJ mol^{-1}, respectively (Table 2). In order to estimate error bars of the absolute affinities we had determined for M^+–Phe, we applied the same DFT protocol to the M^+–benzene (M^+–Bz) and M^+–alanine (M^+–Ala) systems. The theoretical affinities of these species are compared against existing experimentally measured values and summarized in Table 2.

In the case of benzene, the agreement between theory and experiment is good; the deviations are within ± 7 kJ mol^{-1}. For Phe, Ryzhov et al.[26] first reported the Na^+ and K^+ affinities (298 K) obtained by kinetic method measurements at 174 and 104 kJ mol^{-1}, respectively. However, questions have been raised with regard to the reliability of the reference values used,[45] and these reported values have been put in doubt by subsequent studies.[27,28] The Na^+–Phe

Table 2. Experimental and calculated M^+ (M^+ = Li^+, Na^+, and K^+) binding affinities [kJ mol^{-1}] of phenylalanine (Phe), benzene (Bz), and alanine (Ala).

M^+	Phe		Bz		Ala	
	Calcd[a]	Exptl	Calcd[a]	Exptl	Calcd[a]	Exptl
Li^+	275	246[b]	156	161[g]	253	219[b]
	[279]		[159]		[257]	[220][i]
Na^+	201	[174][c]	100	93[g]	175	159[d]
	[203]	188[d]	[101]		[177]	[167][e]
		[198][e]			[167][h]	[165][i]
K^+	141	104[c]	67	73[g]	123	123[j]
	[143]	139[f]	[68]		[124]	
					[126][h]	

[a] This work, ΔH_0 (affinity at 0 K) estimated at the B3-LYP/6-311+G(3df,2p)//B3-LYP/6-31G(d) level, by Equation (2). The affinities at 298 K (ΔH_{298}) are shown in square brackets. [b] Ref. [29], corrected from ΔG_{373} to ΔH_0 in this work. [c] Ref. [26], kinetic method ΔH_{298} values. [d] Ref. [27], ligand exchange equilibrium/FT-ICR ΔH_0 values: [e] Ref. [28], kinetic method ΔH_{298} values. [f] Ref. [50], kinetic method values, assumed to be $\approx \Delta H_0$. [g] Ref. [51], threshold-CID ΔH_0 values. [h] Ref. [53], ΔH_{298} values. [i] Ref. [47], kinetic method ΔH_{298} values. [j] Ref. [52], kinetic method values, assumed to be $\approx \Delta H_0$.

affinity was later revised upwards to 188 and 198 kJ mol^{-1} in separate redeterminations in the laboratories of Dunbar[27] and of Wesdemiotis,[28] respectively. Omitting the first reported experimentally ascertained Na^+–Phe affinity (174 kJ mol^{-1}), we found our theoretical Na^+ affinities tend to be higher than the experimentally determined values for Ala and Phe, up to a maximum deviation of 16 kJ mol^{-1} in the case of Na^+–Ala (Table 2).

Recently, we also noted that the first reported K^+–Phe affinity at 104 kJ mol^{-1} is unreasonably low, because it is even less than the threshold-CID value of K^+–glycine (126 kJ mol^{-1} at 298 K) reported by Kebarle and co-workers.[46] If this K^+–Phe affinity is omitted, then our theoretical K^+ affinities for Ala and Phe are in excellent agreement (within ±2 kJ mol^{-1}) with the experimental (kinetic methods) values obtained in our laboratory (Table 2).

For Li^+, however, our calculated Ala and Phe affinities are 29–37 kJ mol^{-1} too high in relation to the experimentally determined values of Bojesen et al.[47] and Feng et al.,[29] who reported very similar Li^+–Ala values (Table 2). We note that the experimentally measured Li^+–Ala/Phe ΔG_{373} value of Feng et al. was anchored to an "average ΔG_{373}" value of Li^+–glycine, which was in turn obtained (among other measurements) with reference to a ΔG_{373} value of *N*,*N*-dimethylacetamide at 179 kJ mol^{-1},[48] a value ≈ 17 kJ mol^{-1} *lower* than a ΔG_{373} value of 196 kJ mol^{-1} validated experimentally in a recent study by our group.[49] Hence, the reported experimentally ascertained Li^+–Ala/Phe affinity values could be too low by about 17 kJ mol^{-1} because of the chosen anchoring ΔG_{373} value of *N*,*N*-dimethylacetamide. At the same time, the protocol we used could be overestimating the Li^+–Ala/Phe affinity, as is found for Na^+–Ala/Phe (≈16 kJ mol^{-1}). Thus, the relatively large discrepancies (≈37 kJ mol^{-1}) are likely to arise from a combination of errors in the experimental measurements and in the theoretical estimation.

Overall, our estimated M^+–Phe affinity is likely to be on the high side in relation to reported experimentally determined values. This may be due to BSSE and other differences (correlation method and basis sets) employed in the theoretical model. From the maximum deviations found in a comparative study on M^+–Bz/Ala/Phe affinities as shown in Table 2, the theoretical absolute Li^+, Na^+, and K^+ affinities of Phe reported in this study are assigned error bars of ± 20, ±16, and ±6 kJ mol^{-1}, respectively. The performance of the protocol appears to be dependent on the nature of the alkali metal cation. It is more satisfactory for K^+ affinity determination: the maximum error for K^+–Bz/Ala/Phe (± 6 kJ mol^{-1}) is comparable to the mean-absolute-deviation of 4.5 kJ mol^{-1} we reported for 65 model ligands in reference [33].

Conclusion

We have carried out detailed theoretical studies on M^+–Phe (where M^+ = Li^+, Na^+, and K^+) complexes at the best level of theory reported thus far. Our study has confirmed that, for these alkali metal cations, cation–π binding modes are competitive with non-π binding modes in phenylalanine in the gas phase. The various stabilizing and destabilizing factors in different modes of binding have been discussed in detail. The absolute theoretical affinities are in reasonable agreement with available experimentally determined values, hence providing support for the reliability of the model presented here.

In view of the widespread presence and biological functions of alkali metal cations in living systems, it has been postulated that more Na^+/K^+ cation–π binding sites of functional importance will be found in proteins as the resolution and data screening techniques for X-ray structures improve in the future.[14,16] Hence, our reported geometries and bonding distances for the M^+–Phe complexes may serve as structural references for optimal interaction between alkali metal cations and the various π and non-π binding sites around aromatic amino acid residues in peptides/proteins.

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