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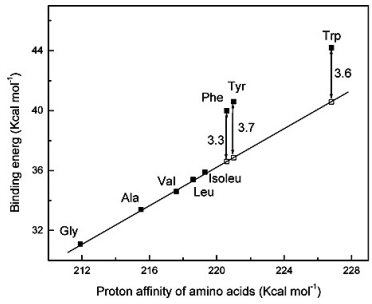
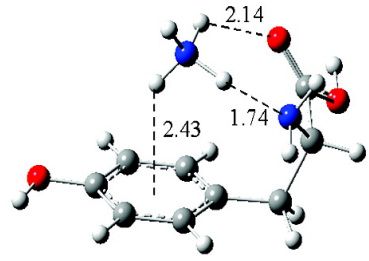
Ronghu Wu, and Terry B. McMahon

J. Am. Chem. Soc., **2008**, 130 (38), 12554-12555 • DOI: 10.1021/ja802117s • Publication Date (Web): 29 August 2008





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Published on Web 08/29/2008

Investigation of Cation-π Interactions in Biological Systems

Ronghu Wu and Terry B. McMahon*

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

Received March 21, 2008; E-mail: mcmahon@uwaterloo.ca

Aromatic residues in biological systems can play a significant energetic and structural role. Approximately 20 years ago Burley et al.[1a] and Singh et al.[1b] surveyed a number of X-ray structures to demonstrate a marked tendency for positively charged amino groups to preferentially localize near the π-electron cloud of the aromatic rings in the three aromatic amino acids, Phe, Tyr, and Trp. The interactions between charged groups, such as organic ions or metal ions, and aromatic residues have been denoted as cation$-\pi$ interactions.[2] The cation$-\pi$ interaction has come to be recognized as an important noncovalent binding force in biological systems.[3,4] The distance between atoms in such species may be determined relatively accurately by X-ray diffraction;[5] however the experimental energetics of these cation$-\pi$ interactions between aromatic amino acids and cations in the isolated state have remained elusive. Although the experimental cation$-\pi$ interaction strengths of $\sim$20 kcal mol^{-1} between benzene and either the ammonium ion or Na^+ have been reported many years ago,[6] these are markedly different from those in the biological systems, because the cation interacts with several groups simultaneously in the latter. The investigation of these interactions thus has the potential to provide further insight into the structures and functions of biological molecules.

High Pressure Mass Spectrometry (HPMS) is a very powerful tool for the investigation of ion$-$molecule interactions.[7] It permits the direct determination of the accurate interaction strength between ions and molecules. The binding energetics of a number of protonated aliphatic and aromatic amino acids with ammonia have been determined by HPMS. Using the proton affinity (PA) differences between the amino acids and ammonia (204 kcal mol^{-1}),[8] the binding energies between the neutral amino acids and ammonium ion can be obtained, and these are summarized in Table S1, together with the calculated binding energies.

Quantum chemical calculations[9] have revealed a number of different stable isomers of protonated aromatic amino acids and ammonia. Conformations for $TyrNH_4^+$ and $TrpNH_4^+$ are very similar to those of $PheNH_4^+$. Therefore only different isomers of $PheNH_4^+$ are shown in Figure S1, with the calculated enthalpy and entropy changes corresponding to formation of different isomers summarized in Table S2. The most stable isomers of protonated Tyr with ammonia or methylamine are given in Figure 1. It is evident that a proton transfer from the protonated amino acid to ammonia or methylamine occurs, despite the fact that the proton affinity of the amino acid is higher than that of either ammonia or methylamine. This endothermic proton transfer is driven, at least in part, by cation$-\pi$ interaction between the neutral Tyr and ammonium ion. The most stable isomers of the clusters of Phe and Trp have the same type of structures as those of Tyr.

In hydrogen bonded dimers of the form $BH^+ \cdot A$, the binding energy decreases as the PA difference increases, which may be understood as the result of partial proton transfer from BH^+ to A within the cluster.[10] Partial proton transfer will be facilitated either as BH^+ becomes a more efficient proton donor or as A becomes a more efficient proton acceptor. The binding energies between protonated

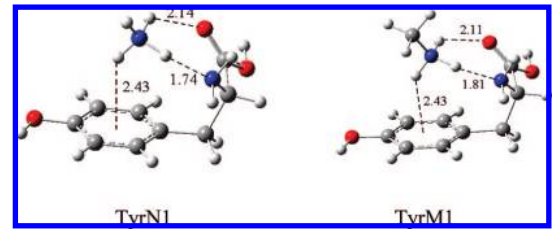

Figure 1. Structures of the most stable isomers of protonated Tyr and ammonia or methylamine obtained by B3LYP/6-31+G(d). The hydrogen bonds are expressed as dotted lines and the units of bond lengths are Å.

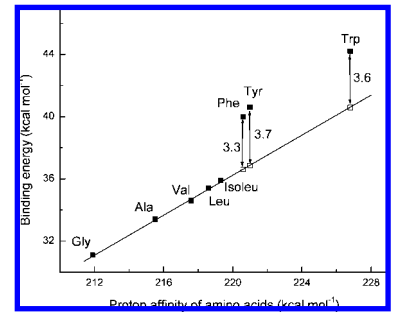

Figure 2. Binding energies with NH_4^+ vs PAs of amino acids. Intercept(y) $= -104.846 \pm 3.31$, slope $= 0.6415 \pm 0.0153$, and $R^2 = 0.9983$.

Gly, Ala, Val, Leu, Ile, Phe, Tyr, and Trp and ammonia are plotted as a function of PAs of amino acids in Figure S2. The plot for the neutral amino acids and NH_4^+ is given in Figure 2. For the series of aliphatic amino acids, Gly, Ala, Val, Leu, and Ile, a very good linear relationship exists between the binding energies and their PAs, where the only interactions between the cation and amino acid backbones are likely to be present, consistent with the trend discussed above. However, the three aromatic amino acids represent an exception to this trend. This can be attributed to the presence of the additional H-bond interaction between one of the ammonium ion hydrogens and the ring of the aromatic amino acids. This is shown clearly in Figure 1 for the adducts of Tyr in which a hydrogen of either of the ammonium ions is positioned nearly vertically with respect to the center of the ring. The deviation from the linear trend in Figure 2 permits a deduction of the enhancements arising from this cation$-\pi$ hydrogen bond interaction as 3.3, 3.7, or 3.6 kcal mol^{-1} for the NH_4^+ clusters of Phe, Tyr, or Trp, respectively. It is important to note that the actual magnitude of the cation$-\pi$ hydrogen bond interaction will be greater than this value since, to achieve the geometry benefiting from this interaction, an inherently less favorable conventional hydrogen bonded structure must be adopted.

The cation$-\pi$ hydrogen bond interaction strengths have not been obtained for $CH_3NH_3^+$ clusters of all amino acids. However, they can be inferred from an analysis of the structural differences computed between NH_4^+ and $CH_3NH_3^+$ clusters (see Table S3). For the $CH_3NH_3^+$ clusters, the π hydrogen bond lengths ($R_{H\cdots Bc}$),

10.1021/ja802117s CCC: $40.75

Table 1. Binding Energies and Cation-π Interaction Strengths (kcal mol^{-1}) between Phenylalanine, Tyrosine, and Tryptophane and NH_4^+ or Na^+

	NH_4^+			Na^+				
				expt				
	expt[a]	calcd[b]	cation−π	kinetic method	TCID[12f]	FTICR	calcd	cation−π
Phe	40.0 (0.5)[a]	41.6	3.3	41.5 (5),[12a] 47.3 (2)[12b]	49.8 (1.6)	44.8 (2),[12c] 47.3 (3)[12e]	44.9,[12e] 48.0,[12d] 48.1[12g]	7.0
Tyr	40.6 (0.5)	41.4	3.7	41.8 (5),[12a] 48.0 (2)[12b]	50.8 (2.3)		48.3[12d]	7.8
Trp	44.2 (0.5)	43.6	3.6	43.0 (5),[12a] 50.2 (2)[12b]	52.6 (1.8)	49.0 (3)[12e]	51.9,[12e] 52.0[12d]	6.8

[a] Uncertainties are in parentheses. [b] MP2/6-31+G(d, p)//B3LYP/6-31+G(d) including the ZPEs and thermal energy corrections at 298 K.

which are defined as the distances between hydrogen and the center of the benzene ring, are 2.41, 2.43, and 2.61 Å, respectively, for the three aromatic amino acids, which are very nearly the same as those for the corresponding NH_4^+ clusters of 2.45, 2.43, and 2.60 Å. This demonstrates that the cation−π interaction strengths in the $CH_3NH_3^+$ clusters should be very similar to those of the corresponding NH_4^+ clusters. $CH_3NH_3^+$ serves as an excellent model for protonated amine functions in biomolecular species such as amino acids, peptides, and proteins. Thus, these data for the cation−π interaction should provide meaningful insight into the importance of this phenomenon in biomolecules. They are close to recently calculated energies for this type of interaction in proteins and protein−ligand complexes.[11]

The interactions between aromatic amino acids and sodium ion have also been extensively investigated by both theoretical and experimental methods.[12] Some experimental and calculated data are summarized in Table 1, together with the values for NH_4^+. A recent study using threshold collision induced dissociation (TCID) techniques has given sodium cation binding energies of 49.8, 50.8, and 52.6 kcal mol^{-1}, respectively, for Phe, Tyr, and Trp.[12f] These interaction energies are ~9 kcal mol^{-1} greater than the corresponding values for NH_4^+. Several computational and experimental methods have been used to attempt to determine the strengths of the cation−π interactions between Na^+ and the aromatic amino acids.[12a,c,d] Using computational data, the most stable isomers of the Na^+ cluster with the aromatic amino acids, including the cation−π interaction, have been compared with the corresponding isomers in which the side chain is rotated out of chelation. The cation−π interaction has also been estimated to be 5−8 kcal mol^{-1} in the Na^+/Phe complex from a comparison of the difference in gas phase Na^+ binding energies between Ala and Phe obtained from FTICR equilibrium measurements.[12c] It had been presumed that the difference in these two Na^+ binding energies would be mainly due to the cation−π interaction, with small additional contributions from differential polarization interactions and internal chelation in neutral Phe. In addition, to obtain the cation−π interaction energy, it had been necessary to make assumptions considering entropic differences involved in addition of Na^+ to Ala and Phe.

Given the evident advantage demonstrated above for the cation−π interaction enhancement obtained from a correlation of NH_4^+ binding energies with PAs, it is of considerable interest to use the same protocol to obtain enhancements due to Na^+−π interactions. The most extensive set of sodium cation binding energies to amino acids is that of Kish et al.[12b] obtained by the kinetic method. A plot of these Na^+ binding energies as a function of PA is shown in Figure S3. The cation−π interaction enhancements can be obtained as 4.5, 5.1, and 4.4 kcal mol^{-1} for Phe, Tyr, and Trp, respectively. However, these kinetic method data did not account for any entropic differences associated with addition of Na^+ to aliphatic or aromatic amino acids. According to our HPMS experimental results, addition of NH_4^+ to Phe is 7 cal mol^{-1} K^{-1} less favorable entropically than to Ala. If instead, the TCID data of Ruan and Rodgers[12f] for Phe, Tyr, and Trp are used, cation−π interaction enhancements of 7.0, 7.8, and 6.8 kcal mol^{-1}, respectively, are obtained. The uncertainty of the cation−π strengths obtained here is very dependent on the accuracy of the experimental data adopted. Thus even though Na^+ binding energies to the aromatic amino acids are roughly 9 kcal mol^{-1} greater than those for NH_4^+, the cation−π interaction enhancements differ by only ~3 kcal mol^{-1}.

In conclusion, a new protocol has been developed to measure the enhancements in binding energies due to cation−π interactions between the aromatic residues of amino acids and organic or metal ions. Investigation of cation−π interactions also aids in a further understanding of why nature selects aromatic amino acids as fundamental building blocks of life.

Acknowledgment. The generous financial support by the Natural Sciences and Engineering Research Council of Canada (NSERC) is gratefully acknowledged.

Supporting Information Available: Tables S1−S3, Figures S1−S3, and the complete refs 5 and 9. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA802117S