

Influence of the Water Molecule on Cation– π Interaction: Ab Initio Second Order Møller–Plesset Perturbation Theory (MP2) Calculations

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The influence of introducing water molecules into a cation– π complex on the interaction between the cation and the π system was investigated using the MP2/6-311++G** method to explore how a cation– π complex changes in terms of both its geometry and its binding strength during the hydration. The calculation on the methylammonium–benzene complex showed that the cation– π interaction is weakened by introducing H₂O molecules into the system. For example, the optimized interaction distance between the cation and the benzene becomes longer and longer, the transferred charge between them becomes less and less, and the cation– π binding strength becomes weaker and weaker as the water molecule is introduced one by one. Furthermore, the introduction of the third water molecule leads to a dramatic change in both the complex geometry and the binding energy, resulting in the destruction of the cation– π interaction. The decomposition on the binding energy shows that the influence is mostly brought out through the electrostatic and induction interactions. This study also demonstrated that the basis set superposition error, thermal energy, and zero-point vibrational energy are significant and needed to be corrected for accurately predicting the binding strength in a hydrated cation– π complex at the MP2/6-311++G** level. Therefore, the results are helpful to better understand the role of water molecules in some biological processes involving cation– π interactions.

Introduction

Cation– π interaction between cations and aromatics was found to be common in biomolecular systems such as proteins and receptor–ligand complexes.^{1–9} Extensive experimental and theoretical investigations revealed its important role in biological processes such as molecular recognition, drug action, and protein folding.^{1,10–19} For example, the investigation on the X-ray structures of *Torpedo californica* acetylcholinesterase (AChE) complexes with inhibitors showed that 14 conserved aromatic residues, along the narrow active-site gorge, facilitate transfer of cationic substrates into the active site.^{5,6} In addition, the interaction is responsible for the selectivity sequence of the monovalent cations of lithium, sodium, potassium, and rubidium to potassium channels.¹¹ It is also the reason tetraethylammonium ion and other quaternary ammonium ions can block potassium channels.²⁰

In the previous theoretical investigations of cation– π interactions,^{1,7,12,20–29} many efforts had been devoted to its characters in the gas phase, while less attention has been paid to such interactions in aqueous environment. Recent studies, however, have showed that cation– π interactions are also found on the protein surface and exposed to aqueous solution.^{2,30} In all the crystal structures of the AChE–huperzine A (HupA),³¹ AChE–tacrine,⁶ and AChE–huprine X³² complexes, two or three water molecules are found within 3.5 Å of the ammonium group of the inhibitors and are in favor of forming hydrogen bonds with the ammonium group of the inhibitors. Furthermore, our previous steered molecular dynamics simulations revealed that there are always two or three water molecules surrounding the

ammonium group of HupA and moving along with HupA during the processes of binding and unbinding of this natural AChE inhibitor to the deep active-site gorge of AChE lined by aromatic residues.³³ The case is similar in other cation channel proteins where water molecules definitely play their roles when cations go through the protein channels into or out of cells. Most recently, Kohtani et al. found that water adsorption to the protonated dipeptide, Gly-Trp+H⁺, results in weakening of cation– π interactions.³⁴ In addition, several studies observed that the cation– π interactions between divalent metal ions and π systems are affected by the metal hydration extent.^{35,36} Therefore, the investigation on a cation– π complex with water molecule at atomic and electronic levels will help us to better understand the role of the water molecule and its influence on cation– π interaction. Although there are some investigations on cation– π complexes in aqueous media,^{2,30,37–42} for example, Gallivan and Dougherty predicted a cation– π interaction of –5.5 kcal/mol for the methylammonium–benzene complex in aqueous solution using the SM5.42R/HF solvation model,³⁰ they focused only on the whole effect of water solution as a medium on the cation– π interactions. Hence, it is of importance to study the influence of individual water molecules on cation– π interaction during the continuous hydration of a cation– π complex by using the quantum chemistry method.

In this paper, the methylammonium–benzene cation– π complex was selected as a model system to explore how the water molecule affects cation– π interaction. Obviously, methylammonium (A, hereafter) is a better model cation than ammonium. The water molecules were introduced into the A–benzene complex (A–B complex, hereafter) one by one to mimic the dynamic process of water molecules binding to a cation– π complex. The purposes of this study are (1) to study

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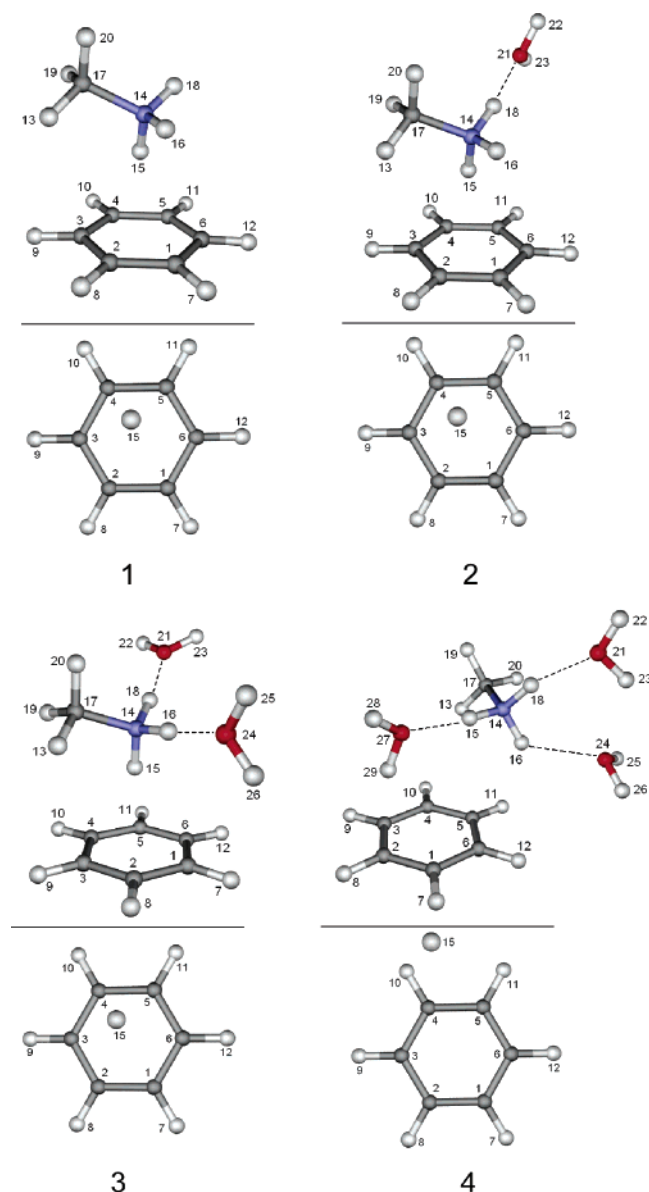


Figure 1. Structures of the complexes formed by methylammonium, benzene, and water molecules and the projection of hydrogen 15 on the benzene ring.

the geometrical characteristic of a cation- π complex with different numbers of water molecules and (2) to investigate how the binding of a water molecule to an existing cation- π complex affects the cation- π interaction.

Molecular Models and Computational Methods

According to our previous calculation results^{21,22,27} that two hydrogen atoms of a NH_4^+ point toward the benzene with identical distances in a $\text{NH}_4^+-\text{C}_6\text{H}_6$ complex, the initial structure of the A-B complex was designed with two hydrogen atoms pointing toward the benzene (structure 1, Figure 1). The geometry optimization for the initial structure was carried out at the MP2/6-31G** level. Then, one, two, and three water molecules were separately introduced into the optimized structures, followed by another cycle of geometry optimization at the same level for finding the stable structures of the hydrated A-B complexes with different numbers of water molecules. Frequency calculations were carried out using the same method, to verify the stability of the optimized structures and to estimate zero-point vibrational energy (ZPVE) and thermal energy.

Finally, the MP2/6-311++G** method was adopted to optimize all the structures obtained at the MP2/6-31G** level to calculate the geometric parameters and the interaction energies. Meanwhile, the basis set superposition error (BSSE) correction was also estimated at the MP2/6-311++G** level for obtaining accurate binding strength using the counterpoise method of Boys and Bernardi⁴³ through the following equation:

$$\text{BSSE} = [E_a - E_{a(b)}] + [E_b - E_{b(a)}] \quad (1)$$

where $E_{a(b)}$ (or $E_{b(a)}$) is the energy of fragment a (or b), based on the geometry extracted from the optimized structure, with its own basis set augmented by the basis set of b (or a). E_a or E_b is the energy of the isolated fragment a (or b), with just its own basis set.

All calculations were carried out on a Power Challenger R-10000 supercomputer and a 128-CPU Silicon Graphics (Mountainview, CA) Origin3800 server with the program Gaussian 98.⁴⁴

Results and Discussion

Optimized Structures. Figure 1 depicted the four optimized structures at the MP2/6-311++G** level, which are the A-B complex (structure 1, Figure 1); A-B-W complex (2, Figure 1) formed by introducing one water molecule into the A-B complex; A-B-2W (3, Figure 1) obtained by A-B-W with another water molecule; and A-B-3W (4, Figure 1) formed by inserting one more water molecule into A-B-2W. Some important structural parameters of the optimized structures 1-4 are summarized in Table 1. No significant changes were found in the C-C and C-H bond lengths, but the interaction distance between N14 and the centroid of the benzene (R14-centroid) increases from 2.964 Å in structure 1 to 3.900 Å in 4 (Table 1), suggesting that the cation- π binding between A and B is weakened as water is introduced into the complex. The distances between the centroid of the benzene and the projection of N14 onto the benzene plane (R) are 0.081, 0.055, 0.078, and 2.103 Å for structures 1-4, respectively, indicating that the projection of N14 in structure 4 is outside of the benzene ring. The significant lengthening of the R14-centroid and the increasing of the R value suggest that the cation- π interaction between A and B in structure 4 is almost eliminated. This conclusion is supported by the calculated binding strengths (see discussion below).

Although the two methylammonium hydrogen atoms (H15 and H16) still point toward the benzene in the optimized structure 1, the perpendicular distances of H15 and H16 to the benzene (R15-benzene and R16-benzene) are not identical any more, which are different from the result of the $\text{NH}_4^+-\text{C}_6\text{H}_6$ complex.^{22,27} The shorter R15-benzene (1.993 Å) than R16-benzene (2.903 Å) in complex 1 indicates that H15 contributes much more to the cation- π interaction between A and B than H16. A similar trend was found in complexes 2-4. Additionally, the projections of H15 onto the benzene plane in complexes 1-3 are within the benzene ring except in complex 4 (Figure 1), indicating again that the cation- π interactions between A and B in structure 4 are almost destroyed.

On the other hand, the cation- π interaction also affects the hydrogen bonding between the water molecule and methylammonium. The hydrogen bond length between H18 and O21 is 1.704 Å in the $\text{H}_2\text{O}-\text{CH}_3\text{NH}_3^+$ complex. However, the length in all the hydrated A-B complexes ranges from 1.754 to 1.803 Å, demonstrating that the cation- π interaction between A and

TABLE 1: Some Structural Parameters at the MP2/6-311++G Level^a**

atom	1 (A-B)	2 (A-B-W)	3 (A-B-2W)	4 (A-B-3W)	A-W	A
R14-centroid ^b (Å)	2.964	3.015	3.073	3.900		
R ^c (Å)	0.081	0.055	0.078	2.103		
R15-benzene ^d (Å)	1.993	2.039	2.070	2.417		
R16-benzene ^d (Å)	2.903	2.992	3.213	3.305		
R14-15 (Å)	1.031	1.030	1.026	1.021	1.024	1.019
R14-16 (Å)	1.020	1.023	1.035	1.033	1.019	1.021
R14-18 (Å)	1.021	1.038	1.031	1.030	1.040	1.023
R14-17 (Å)	1.496	1.492	1.487	1.487	1.495	1.504
R18-21 (Å)		1.754	1.803	1.777	1.704	
R16-24 (Å)			1.794	1.737		
R15-27 (Å)				2.247		
A14-18-21 (deg)		172.9	173.9	158.4	175.3	
A14-16-24 (deg)			172.6	166.7		
A14-15-27 (deg)				130.9		

^a Refer to Figure 1 for atomic numbering. ^b The distance from the nitrogen atom 14 of methylammonium to the centroid of benzene. ^c The distance between the centroid of benzene ring and the projection of nitrogen atom 14 of methylammonium onto the benzene plane. ^d The perpendicular distances of atoms 15 and 16 to the benzene plane, respectively.

TABLE 2: Energetic Parameters of Methylammonium-Benzene Complexes with Water Molecules at the MP2/6-311++G Level (kcal/mol)**

	1 (A-B)	2 (A-B-W)	3 (A-B-2W)	4 (A-B-3W)	A-W
$\Delta E_{\text{inter}}^a$	-19.03	-17.33	-17.14	-7.96	-19.66
BSSE	3.25	3.59	4.04	3.60	1.98
$\Delta E_{\text{thermal}}^b$	1.77	1.34	1.95	1.98	1.94
ZPVE ^b	0.77	0.74	0.69	1.66	1.68
ΔE_{corr}^c	-13.25	-11.66	-10.46	-0.73	-14.06
ΔH^d	-13.84	-12.26	-11.05	-1.32	-14.65
$\Delta E_{\text{A-W}}^e$		-19.52	-36.57	-49.63	-19.66
$\Delta E_{\text{B-W}}^e$		0.53	1.25	-3.43	

^a The interaction energies between methylammonium and benzene in complexes **1-4** and between methylammonium and water for the methylammonium-water dimer. ^b Calculated at the MP2/6-31G** level based on the structure optimized at the same level. ^c $\Delta E_{\text{corr}} = \Delta E_{\text{inter}} + \Delta E_{\text{thermal}} + \text{BSSE} + \text{ZPVE}$. ^d $\Delta H = \Delta E_{\text{corr}} + \Delta(PV)$. ^e The energy was obtained by calculating the energy of the methylammonium-water or benzene-water complex that is extracted from the optimized structure for calculating ΔE_{inter} .

B weakens the H bond of the water molecule with the methylammonium.

Energetic Properties. Table 2 presents the calculated thermochemical parameters of the A-B and the hydrated A-B complexes at the MP2/6-311++G** level. Although the water molecules interact with A through hydrogen bonding, they also interact with the benzene, especially in structure **4**. The calculated binding energy between the water molecules and the benzene in structure **4**, $\Delta E_{\text{B-W}}$, is -3.43 kcal/mol, while those in structures **2** and **3** are 0.53 and 1.25 kcal/mol, respectively, demonstrating that the interaction between water and benzene is attractive in structure **4** but repulsive in structures **1** and **2**. This repulsion could be one of the reasons why introducing water molecule(s) into cation- π systems leads to weakening of the cation- π binding between A and B. Anyway, the $\Delta E_{\text{B-W}}$ and ΔE_{corr} values demonstrate that the main interaction in structure **4** is the usual hydrogen bond between water molecules and B.

The ΔE_{corr} values in Table 2, which are corrected by thermal energy, ZPVE, and BSSE, are -13.25, -11.66, -10.46, and -0.73 kcal/mol for structures **1-4**, respectively, demonstrating that as the water molecule is introduced into the A-B complex one by one, the binding strength between A and B becomes weaker and weaker. The addition of the first water molecule to A-B will reduce the cation- π binding strength by ~ 1.6 kcal/mol, which is very close the result of the B3LYP method by

Kohtani et al.³⁴ The addition of the second water molecule leads to a reduction of ~ 1.2 kcal/mol in the cation- π interaction. In other words, introduction of the water molecule into a cation- π complex etches the cation- π binding. On the other hand, the interaction between methylammonium and water molecule(s) gets strengthened from -19.52 and -36.57 to -49.63 kcal/mol, while the binding strength between benzene and water molecule(s) fluctuates from 0.53 and 1.25 to -3.43 kcal/mol for structures **2-4**, respectively. Thus, as indicated in other studies,³³⁻³⁶ it should be the water screening effect that weakens the cation- π interaction. The influence of introducing the third water molecule is so intense that the cation- π interaction fades out its role as a main binding component. Taking into account its optimized geometry, structure **4** should not be considered as a typical cation- π complex any more. Meanwhile, we would like to point out that as the real biological system is much more complex than our model, the relative positions of cation/cationic groups, aromatic systems, and water molecules in biological systems might be significantly different from our model due to, for instance, geometrical constrain. Thus, a cation- π interaction could be either in the binding cavity or on the protein surface in a biological system even for a hydrated cation or cationic group with three water molecules as long as a suitable geometry for cation- π interaction is kept. On the other hand, the cation- π binding strength of the methylammonium-benzene complex in aqueous solution was estimated as -5.5 kcal/mol by Gallivan and Dougherty, significantly lower than our value for complex **4** (-0.73 kcal/mol).³⁰ To further study the stability of the cation- π complex in aqueous solution, a Carr-Parrinello molecular dynamics simulation on ammonium-benzene and other systems in aqueous solution has been performed that seems support these findings (to be published).

As seen from Table 2, the estimated BSSE, ranging from 3.25 to 4.04 kcal/mol, is rather large relative to the binding energy, and it is as much as 45% of the raw binding energy in structure **4**. The estimated $\Delta E_{\text{thermal}}$ and ZPVE also apparently affect the calculated binding strength. Therefore, the BSSE correction, $\Delta E_{\text{thermal}}$, and ZPVE estimations are necessary steps for accurately predicting binding strength for the hydrated cation- π system if the MP2/6-311++G** method is employed.

Charge Population Analysis. ChelpG,⁴⁵ Mulliken,⁴⁶ and Natural Population Analysis⁴⁷ atomic charges were calculated at the MP2/6-311++G** level on all optimized structures to investigate the possible charge transfer during the complexation and hydration reactions. Each complex was divided into three parts: methylammonium (A), benzene (B), and water (W). The

TABLE 3: Atomic Charges (Q/e) at the MP2/6-311++G Level**

charges	molecule	1 (A-B)	2 (A-B-W)	3 (A-B-2W)	4 (A-B-3W)	A-W
Mulliken	A	0.9124	0.9263	0.9225	0.9543	0.9743
	B	0.0876	0.0495	0.0222	-0.0465	
	W		0.0242	0.0553	0.0922	0.0257
NBA	A	0.9649	0.9349	0.9149	0.9133	0.9528
	B	0.0351	0.0265	0.0205	0.0106	
	W		0.0385	0.0643	0.0758	0.0469
ChelpG	A	0.7040	0.7525	0.7829	0.7887	0.9976
	B	0.2960	0.2611	0.2378	0.1620	
	W		-0.0136	-0.0207	0.0493	0.0024

TABLE 4: Electrostatic, Induction, and Dispersion Energies in kcal/mol Calculated by Orient 3.2

energy	1 (A-B)	2 (A-B-W)	3 (A-B-2W)	4 (A-B-3W)	A-W
E_{ele}	-9.71	-7.50	-5.00	-3.53	-10.12
E_{rep}	2.43	2.03	1.90	1.43	4.34
E_{ind}	-4.16	-3.26	-2.22	-1.14	-1.22
E_{dis}	-1.83	-1.71	-1.82	-1.77	-1.37
E_{total}	-13.27	-10.43	-7.14	-5.01	-8.37

sums of total atomic charges on the three parts are listed in Table 3. Apparently, these three different kinds of atomic charges suggest that one unit of the positive charge is delocalized onto two parts or three parts. However, the transferred positive charge to benzene decreases on moving from structure **1** to structure **4**, indicating that the cation- π interaction becomes weaker and weaker from structure **1** to structure **4**. This is consistent with the changes of the interaction distances and the cation- π binding energies (Tables 1 and 2). Therefore, the transferred charge could be an indicator of how strong a cation- π binding is, which was also observed in our previous studies on other cation- π systems.^{22,48} In structure **4**, the positive charge on water molecules is significantly greater than that in the structures **2** and **3**, suggesting that hydrogen bonding plays a more and more important role in the structures from **2** to **4**.

Electrostatic, Induction, and Dispersion Energy. As discussed above, the binding energies between A and B decreased from structure **1** to structure **4**, suggesting a weakening of the cation- π interaction during its hydration. To further clarify the exact cause of the influence of introducing a water molecule into the complex A-B on the binding between A and B, a decomposition of the binding energy was performed using the program ORIENT 3.2 developed by Stone et al.,⁴⁹ in which a precise distributed multipoles model is obtained from the MP2/6-31G** wave functions using CADPAC, version 6.⁵⁰ The program employs site-site potential to calculate various interactions for an assembly of interacting molecules, such as electrostatic energy, induction energy, repulsion energy, dispersion energy, and so on. The distributed multipoles are used for the calculation of electrostatic energy, and the distributed polarizabilities are used for the calculation of other interacting energies. In all these calculations, we defined benzene as fragment 1 and all the others, including the cation and water, as fragment 2. The data are shown in Table 4. The total interaction energies between the two fragments (E_{total}) are -13.27, -10.43, -7.14, and -5.01 kcal/mol for structures **1-4**, respectively, which is remarkably in agreement with the sum of ΔE_{inter} and $\Delta E_{\text{B-W}}$ in Table 2, namely, -13.25, -11.13, -9.21, and -4.16 kcal/mol. In addition, the E_{dis} is almost a constant, suggesting that the hydration of the cation- π complex does not affect the dispersion energy. However, the electrostatic energy (E_{ele}) and induction energy (E_{ind}) decrease sharply as the water molecule is introduced into A-B. They might result from the lengthening of the interaction distance through

structures **1-4**. Therefore, the effect of the hydration on cation- π interaction is brought about through the electrostatic and induction interactions.

Conclusions

The MP2/6-311++G** calculations on the complexes composed of methylammonium, benzene, and water molecules showed that the cation- π interaction between methylammonium and benzene is etched by the introduction of water molecule into the cation- π system. As the water molecule is introduced into the cation- π complex, the hydrogen bonding between the methylammonium and water leads to the lengthening of the interaction distances between the cation and benzene. The longer interaction distance causes less transferred charge from the cation to the benzene. Meanwhile, the longer interaction distance also results in weaker electrostatic and induction interactions and, therefore, weaker overall cation- π binding strength between the methylammonium and the benzene. The introduction of the third water molecule leads to a dramatic change in both the complex structure and total binding energy, resulting in a significant destruction of the cation- π interaction. Therefore, the study would be helpful to better understand the great role of water molecules in some biological processes involving cation- π interactions.

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