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Experimental and theoretical study on the supramolecular complexes of 15-crown-5 with adrenaline

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ABSTRACT

The electron transfer properties of supramolecular complexes of 15-crown-5 (15C5) with protonated adrenaline (PAd^+) at different electrodes using cyclic voltammetry (CV) have been investigated in the article. The experimental results show that 15C5 will affect the electron transfer properties of adrenaline. The formed supramolecular complexes by ion-dipole and hydrogen bond interaction between PAd^+ and 15C5 will slow down the diffusion ability of adrenaline and make it hard to donate electron and be oxidized.

The interaction energies and NPA calculations for the supramolecular complexes of 15C5 with PAd^+ at B3LYP/6-31+G(d) level have been performed. The calculational results confirm the experimental fact that 15C5 can form stable supramolecular complexes with PAd^+.

Adrenaline (Ad), an important hormone secreted by the medulla of the adrenal glands, serves as a chemical mediator for conveying nerve pulses to efferent organs,[1,2] and is often used as one of the hormone drugs. It belongs to a group of compounds known as catecholamines, which play a particularly important role in the regulation of physiological processes in living systems. Adrenaline is not dissolved in water and organic solvents, but will be dissolved in the solvent that can donor proton and form protonated adrenaline (PAd^+). Adrenaline can be studied directly by electrochemical methods because of its structural similarity to *o*-dihydroxybenzene, and the –CH(OH)– group at the α carbon facilitates the easy donation of an electron. After Hawley's first study on the electrochemical reaction of adrenaline at a carbon paste electrode,[1] the nature of the electron transfer of adrenaline has been extensively studied.[2–7]

Crown ethers are the model compounds of biomolecule, and have the remarkable properties of recognizing and binding specific ions with a high degree of specificity in three-dimensional cavities. Therefore, since their discovery,[8] they have been found numerous applications in science and industry and stimulated the field of supramolecular chemistry (host–guest chemistry). Noncovalent interaction plays a key role in many areas of modern chemistry, especially in the field of supramolecular chemistry.[9] Crown ethers can form complex with organic ammonium (such as adrenaline) upon formation of hydrogen bonds,[10,11] so crown ethers can be used as hosts to form complexes with adrenaline and other organic ammoniums. Although a lot of experimental and theoretical studies have been reported in this field,[10–18] studies on the electron transfer properties and geometries of supramolecular complexes of adrenaline with crown ethers are still scant.

In the present article, we selected 15-crown-5 (15C5) as a model molecule of crown ethers to investigate the electron transfer properties and geometries of supramolecular complexes of 15C5 with protonated adrenaline by using cyclic voltammetry (CV) and by performing B3LYP calculations with a polarized basis set. We characterized the supramolecular complexes of 15C5 with adrenaline, and obtain the geometries and structure parameters of the supramolecular complexes. Our new findings will be useful to explore the synthesis of new adrenaline receptor[19–22] and the mechanism of electron transfer of adrenaline.

The glassy carbon electrode, polished using 6# grade Al_2O_3 polishing paper, ultrasonically washed with double distilled water for 10 min, and dried by highly pure nitrogen gas, was called a fresh non-treated electrode, denoted as bare GCE (BGCE). A modified glass carbon electrode, denoted as Al_2O_3/GCE or SiC/GCE, was obtained after BGCE had been modified with Al_2O_3 or SiC particles by polishing with Al_2O_3 or SiC emery paper, respectively. After the BGCE had been anodic (+1.75 V) polarized for 5 min and cathodic (−1.0 V) polarized for 1 min in a solution containing 0.05 mol/L

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KH_2PO_4 and 0.1 mol/L $NaClO_4$ solution,[23] the electrochemical pretreated glassy carbon electrode (EGCE) was obtained.

The supramolecular complexes of PAd^+ with 15C5 were obtained by geometry optimization calculations at the staring geometries of the complexes, which were tried from 15C5 part approaching to the phenolic hydroxyl, alcoholic hydroxyl and imine group of PAd^+ part, respectively. The interaction energy for the 2:1, 1:1, and 1:2 supramolecular complex of protonated adrenaline with 15-crown-5 (PAd^+–15C5) was assumed to be equal to the difference between the complex and the sum of the energies for the free PAd^+ and 15C5.

The NPA (Natural Population Analysis)[24–26] performed at B3LYP/6-31+G(d) level was used to characterize the electronic structures of the monomers and the supramolecular complexes. All calculations were carried out using GAUSSIAN 03 program,[27] and the NPA was performed with the NBO code[28] included in GAUSSIAN 03.

For evaluating interaction energies for the complexes in aqueous solution, we performed B3LYP/6-31+G(d) energy calculations for the complexes, PAd^+ and 15C5 in aqueous solution at their gas phase B3LYP/6-31+G(d) optimized geometries, and we used the PCM model (polarizable continuum model)[29–32] of the self-consistent reaction field theory to simulate solution effects.

15C5 can be dissolved in aqueous solution with ethanol volume fraction of 50%. BGCE, Al_2O_3/GCE, SiC/GCE, and EGCE are used as the working electrode, respectively. The CV curves of adrenaline at SiC/GCE in the solution with different concentration of 15C5 are presented in Figure 1. Peak 1 of curve a corresponds to the oxidation of adrenaline into adrenalinequinone (anodic peak), and peak 2 of curve a corresponds to the reduction of adrenalinequinone into adrenaline (canodic peak). It can be seen that with the addition of 15C5, the electron transfer ability of adrenaline decreases as follows: the anodic peak potential shifts positively, the canodic peak potential shifts negatively, the peak-to-peak potential separation between anodic and canodic peak potential increases, and the anodic and canodic peak current decreases significantly. The results demonstrate the inhibition effect of 15C5 on the electron transfer reaction of adrenaline. The supramolecular complexes of PAd^+–15C5 formed by ion-dipole and hydrogen bond interaction between PAd^+ and 15C5 will slow down the diffusion ability of adrenaline, protect the phenolic hydroxyl groups of adrenaline and make it hard to donate electron and be oxidized. The voltammetry responses of adrenaline at the other three glassy carbon electrodes are almost consistent with that at SiC/GCE, so we do not list them here.

CV experiment is also performed in the free adrenaline solution and the mixed solution of adrenaline and 15C5 with molar ratio of 2:1, 1:1, and 1:2, respectively, at the scan rate of range of 10–100 mV/s. Figure 2 displays the relationship between the oxidation peak current (i_{pa}) and the scan rate (v) of 1:1 PAd^+–15C5 complex in aqueous solution with ethanol volume fraction of 50%. The results show good linear relationship between i_{pa} and $v^{1/2}$, which indicates that the electron transfer process of PAd^+–15C5 supramolecular complexes is controlled by the diffusion in this system.

The diffusion coefficient of adrenaline is obtained by the peak currents of CV curves at different scan rates. As shown in Figure 1, the peak-to-peak potential separation of adrenaline at the glassy carbon electrode in ethanol aqueous solution is large and will become larger with the proportion of 15C5 increasing. According to the theory of irreversible electron transfer process,[33] the diffusion coefficient (D_R) of adrenaline can be calculated by Eqs. (1) and (2).

$$i_{pa} = 2.99 \times 10^5 (\beta n)^{1/2} n A D_R^{1/2} C^0 v^{1/2} \quad (1)$$

$$\Delta E_p = 0.048/\beta n \quad (2)$$

where i_{pa} (A) is oxidation peak current, A (cm^2) is the area of electrode, D_R (cm^2/s) is diffusion coefficient, β is electro-transfer coefficient, n is electro-transfer amount, C^0 (mol/L) is the concentration of bulk solution, v (V/s) is scan rate, and ΔE_p (V) is the difference between peak potential (E_{pa}) and half-peak potential ($E_{pa/2}$).

The average values of diffusion coefficient for adrenaline obtained by Eqs. (1) and (2) with different scan rates in the mixed solution are listed in Table 1. D_R of adrenaline is reduced with increasing concentration of 15C5, indicating further that PAd^+ can form supramolecular complexes with 15C5. The large size of PAd^+–15C5 complexes slow down the diffusion rate and make the complexes more stable. The slightly difference of diffusion coefficient at different electrode can attribute to the microenvironmental of electrode surface. The quinonyl group, phenolic group, and carboxyl group on the EGCE surface can play an enrichment role through absorbing adrenaline in solution, which is equivalent to increase the concentration of adrenaline and lead to the larger diffusion coefficient value. However, when the concentration of 15C5 is two times of that of PAd^+, 15C5 can protect the phenolic hydroxyl, alcoholic hydroxyl, and imine group of adrenaline effectively, and make them hard to interact with the groups on the electrode surface, so diffusion coefficient decreases greatly. Microporous catalysis effect at SiC/GCE causes the larger value of diffusion coefficient and the effect becomes weaker

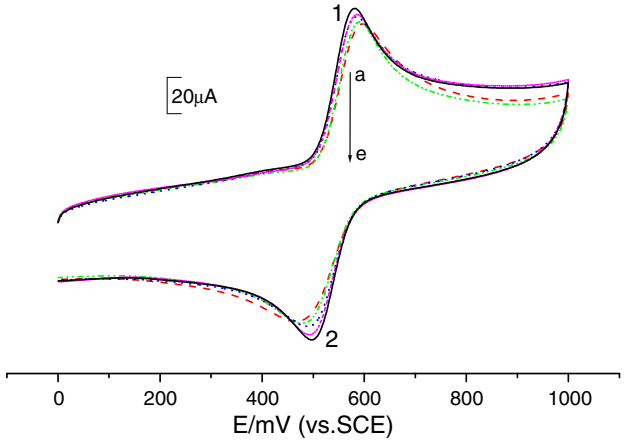

Figure 1. Cyclic voltammograms of 5.0 mmol/L adrenaline in aqueous solution with SiC/GCE as a working electrode. The voltammograms are obtained in the solution with different concentration of 15C5 and using a scan rate of 50 mV/s. The lines of a, b, c, d, and e denote the 15C5 concentration of 0, 2.5×10^{-3}, 5×10^{-3}, 7.5×10^{-3}, and 1×10^{-2} mol/L, respectively. The peak 1 denotes the anodic peak, and peak 2 denotes the canodic peak.

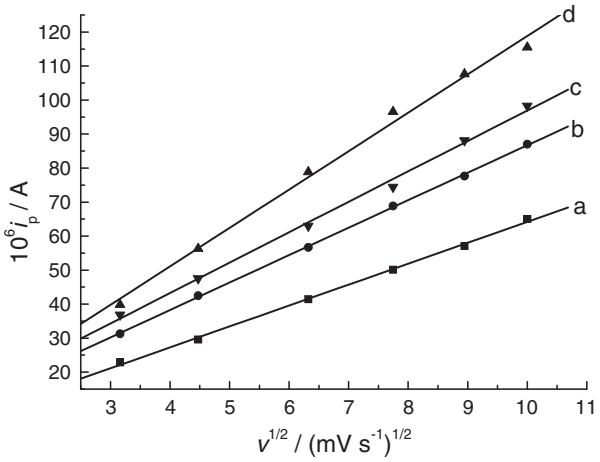

Figure 2. Relationship between oxidation peak current and scan rate of 1:1 complex of PAd^+ with 15C5 in aqueous solution with ethanol volume fraction of 50%.

with the size of supramolecular complexes increasing. There also exist microenvironmental effect at Al_2O_3/GCE, but the catalysis is not as strong as that at SiC/GCE. Accordingly, the values of diffusion coefficient at Al_2O_3/GCE are smaller. Surface action of BGCE is weak and the measured change values of diffusion coefficient are stable, which may basically reflect diffusion nature of adrenaline and its supramolecular complexes.

PAd^+ can form supramolecular complex with 15C5 at different ratio, while in this section, we will only discuss the most stable conformation of 2:1, 1:1, and 1:2 supramolecular complex of PAd^+ with 15C5, respectively (according to the ratio in the CV experiment stated above), and compare the calculational results with the experimental phenomena.

The most stable conformation of PAd^+–15C5 complex between two protonated adrenaline molecule and one 15C5 molecule is shown in Figure 3. The hydrogen bonds in the complex are formed between the oxygen atoms in 15C5 (O_C) and the hydrogen atoms at the oxygen atoms of phenolic hydroxyl in protonated adrenaline (the H_1 and H_2 atoms at the O_1 and O_2 centers in one protonated adrenaline molecule, and the H'_1 and H'_2 atoms at the O'_1 and O'_2 centers in another protonated adrenaline molecule, respectively). The hydrogen bond parts of the complex are described by the [O_1–$H_1\cdots O_C$], [O_2–$H_2\cdots O_C$], [O'_1—$H'_1\cdots O_C$], and [O'_2—$H'_2\cdots O_C$] formula, respectively, and the complex is denoted as AdC21 complex. Another 2:1 conformation of PAd^+–15C5 supramolecular complex (AdC21-2) is put in the Supplementary data (SI1). It will be expected that the hydrogen bonds established with a charged group as in AdC21-2 will be more stable, but the interaction energy for it is 2.01 kcal/mol (in the gas phase) higher than that for AdC21 complex shown in Figure 3. The phenomenon can be interpreted by the competition between ion-dipole interaction and hydrogen bond interaction. There might be other geometries for each of the two complexes, depending on how the 15C5 part 'approaches' to the PAd^+ part in the staring geometries of the complexes used in the geometry optimization calculations. Other geometries (if exist) might lead to different interaction energies from the geometry reported in the present Letter, but the differences are expected to be small.[34]

Table 2 displays the geometric parameters of the hydrogen bond parts in the B3LYP/6-31+G(d) fully optimized geometries of AdC21 complex, and the B3LYP/6-31+G(d) hydrogen bond interaction energies for the complex. In Table 2 we also give the hydrogen bond interaction energies for the complex in aqueous solution based on the PCM-B3LYP/6-31+G(d) energy calculations at the gas phase B3LYP/6-31+G(d) optimized geometries.

As shown in Table 2, the O–H bond lengths in the hydrogen bond parts of AdC21 complex are only slightly (0.012–0.017 Å) longer than the respective bond lengths in free PAd^+. The $H\cdots O_C$ distance values are within a range between 1.784 Å and 1.977 Å and the $OH\cdots O_C$ angles are larger than 148.0°.

As shown in Table 2, the interaction energy for AdC21 complex is significantly larger in the gas phase than in solution, and the interaction energy is predicted to be −4.27 kcal/mol in the gas phase (by the B3LYP/6-31+G(d) calculations) and to be −1.37 kcal/mol in aqueous solution (by the PCM-B3LYP/6-31+G(d)//B3LYP/6-31+G(d) calculations).

Table 1
The diffusion coefficients of PAd^+–15C5 complexes in aqueous solution with ethanol volume fraction of 50%

15C5:Ad	$10^6 D_R$ (cm^2/s)			
	BGCE	Al_2O_3/GCE	SiC/GCE	EGCE
0:1	3.20	3.19	3.26	3.24
1:2	3.10	3.12	3.22	3.17
1:1	2.86	2.84	2.76	3.13
2:1	2.79	2.50	2.54	2.68

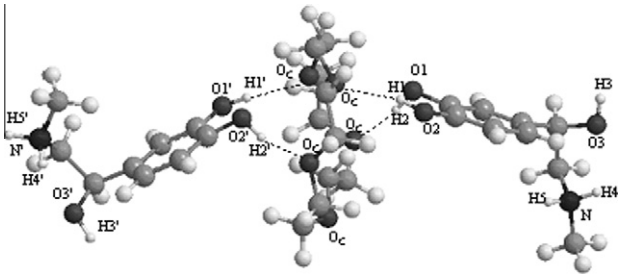

Figure 3. The B3LYP/6-31+G(d) optimized geometry of the AdC21 complex (the most stable 2:1 supramolecular complex of PAd^+ with 15C5).

The charges of the $O_1(O'_1)$, $O_2(O'_2)$, and N atoms in free PAd^+ and AdC21 complex, given by NPA analyses, are collected in Table 3. Because PAd^+ is hydrogen bond donors, there are negative charge transfers from 15C5 to PAd^+ through the phenolic hydroxyl groups. The charge accumulation on the phenolic hydroxyl groups pushes more negative charge away from the group. As shown in Table 3, one can notice that the charges on $O_1(O'_1)$ and $O_2(O'_2)$ are larger than those in the free PAd^+. The O–H bond lengthening in the complexes can be interpreted by the electrostatic interaction model,[35–37] according to which, the O_C of 15C5 pulls the hydrogen bond proton away from the phenolic hydroxyl oxygen in PAd^+, or the hyperconjugation model[38] which attributes the lengthening to the donation of O_C lone pair to the O–H anti-bonding orbital. With respect to the free PAd^+, the charges of N only change marginally. The charges of O_C atoms in PAd^+ and AdC21 complex are also shown in Table 3. One can notice that the negative charge (−0.6312 *e*) on O_C in AdC21 complex is larger than that (−0.6030 *e*) in the free 15C5, which is disagreement with the fact that 15C5 is the hydrogen bond acceptors.

The disagreements can be conciliated by considering the total charge on 15C5. Because, as the hydrogen bond formed, the whole electrons are reorganized to adapt the new chemical environment, all the atoms in 15C5 therefore also play roles and the charge of all the atoms on 15C5 are more informative. As shown in Table 3, the sum of charge of 15C5 part in AdC21 complex is positive (0.1264 *e*), which is larger than that (0 *e*) of free 15C5.

The most stable conformation of PAd^+–15C5 complex between one protonated adrenaline molecule and one 15C5 molecule in the gas phase and aqueous solution phase is given in Figure 4. The hydrogen bond in the complex is formed between the oxygen atoms in 15C5 (O_C) and the hydrogen atoms at the nitrogen atoms in protonated adrenaline (the H_5 atom at the N centers). The hydrogen bond of the complex is described by the [N–$H_5\cdots O_C$] formula, and the complex is denoted as AdC11 complex. Other three 1:1 conformations of PAd^+–15C5 supramolecular complex (AdC11-2–AdC11-3) are put in the Supplementary data (SI2). The interaction energies for the three structures in the gas phase are −11.08, −10.67, and −9.98 kcal/mol. Apparently, there is a competition between ion-dipole interaction and hydrogen bond interaction. As a consequence, the AdC11 complex is the most stable one in spite of only one hydrogen bond in it. In AdC11 complex, though the supramolecular complex will not protect the phenolic hydroxyl groups, the interaction energy for AdC11-2 (the hydrogen bonds are formed between the oxygen atoms in 15C5 and the hydrogen atoms at the oxygen atoms of phenolic hydroxyl in PAd^+) is only 0.11 kcal/mol higher than that for the most stable AdC11 complex, and AdC11-2 can also exist stable. On the other hand, the formed AdC11 complex makes the molecule size become larger, therefore, the diffusion ability of the complex decreases, and adrenaline becomes more stable and hard to be oxidized. The geometric parameters of the hydrogen bond part in the B3LYP/6-31+G(d) fully optimized geometries of AdC11 complex and the

Table 2
Geometric parameters[a,b] of the O(N)–H···O_C (or O′–H′···O_C) parts in the B3LYP/6-31+G(d) fully optimized geometries of the 2:1, 1:1, 1:2 complexes of PAd^+ with 15C5 (AdC21, AdC11, and AdC12) and the B3LYP/6-31+G(d) hydrogen bond interaction energies (in kcal/mol) for the complexes in the gas phase (ΔE_g) and in aqueous solution (ΔE_s)[c]

	R(O–H)/R(N–H)	R(O′–H′)	R(H···O_C)/R(H′···O_C)	∠OH···O_C/∠NH···O_C	∠O′H′···O_C	ΔE_g	ΔE_s
AdC21	0.983 (0.970)[d]	0.987 (0.970)	1.977/1.807	149.0	160.3	−4.27	−1.37
	0.991 (0.974)	0.986 (0.974)	1.784/1.961	161.8	148.2		
AdC11	1.056 (1.030)		1.739	172.7		−11.59	−3.01
AdC12	0.989 (0.970)		1.759	168.6		−32.18	−5.26
	0.986 (0.974)		2.014	149.5			
	1.037 (1.030)		2.194	141.2			

[a] For labelings, see Figures 3–5.
[b] Bond lengths are given in Å, and angles in degrees.
[c] Based on the PCM-B3LYP/6-31+G(d) energy calculations in aqueous solution at the gas phase B3LYP/6-31+G(d) optimized geometries.
[d] Values in parentheses are the bond lengths in the B3LYP/6-31+G(d) geometries of the free PAd^+.

Table 3
The natural bonding orbital (NBO) charges of the O_1, O_2, N, and O_C atoms calculated at B3LYP/6-31+G(d) level

	O_1/O_1'	O_2/O_2'	N	O_C	15C5
AdC21	−0.7368 (−0.7127)[a]	−0.7522 (−0.6800)	−0.6437 (−0.6443)	−0.6312 (−0.6030)	0.1264 (0)
	−0.7495 (−0.7127)	−0.7125 (−0.6800)	−0.6440 (−0.6443)		
AdC11	−0.7147 (−0.7127)	−0.6828 (−0.6800)	−0.6669 (−0.6443)	−0.6091 (−0.6030)	0.0742 (0)
AdC12	−0.7509 (−0.7127)	−0.7089 (−0.6800)	−0.6519 (−0.6443)	−0.6105 (−0.6030)	0.1104 (0)

[a] Values in parentheses are the NBO charges in the B3LYP/6-31+G(d) geometries of the free PAd^+.

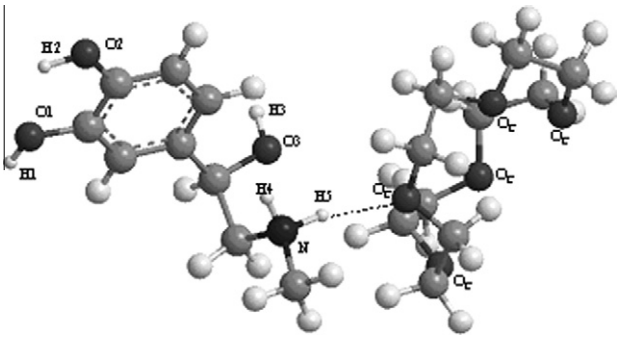

Figure 4. The B3LYP/6-31+G(d) optimized geometry of the AdC11 complex (the most stable 1:1 supramolecular complex of PAd^+ with 15C5).

B3LYP/6-31+G(d) hydrogen bond interaction energies for the complex in the two phases are given in Table 2.

As shown in Table 2, the N–H bond lengths in the hydrogen bond part of AdC11 complex are 0.026 Å longer than the respective bond length in free PAd^+. The H···O_C distance value is 1.739 Å and the NH···O_C angle is 172.7°.

As shown in Table 2, the interaction energy for the AdC11 complex is significantly larger in the gas phase (−11.59 kcal/mol) than in solution (−3.01 kcal/mol). Either in the gas phase or in aqueous solution, AdC11 complex is more stable than AdC21 complex.

Table 3 list the charges of the O_1, O_2, and N atoms in PAd^+ and AdC11 complex. With respect to the free PAd^+, the charges of O_1 and O_2 only change marginally. The charge on N atom in AdC11 complex (−0.6440 *e*) is larger than that in the free PAd^+ (−0.6443 *e*). The sum of the charges of 15C5 part in AdC11 complex is 0.0742 *e*, as shown in Table 3.

The most stable conformations of PAd^+–15C5 complex between one protonated adrenaline molecule and two 15C5 molecule in the gas phase and aqueous solution phase are given in Figure 5. The hydrogen bonds in the complex are formed between the oxygen atoms in 15C5 (O_C) and the hydrogen atoms at the oxygen and nitrogen atoms in protonated adrenaline (the H_1, H_2, and H_5 atoms at the O_1, O_2, and N centers, respectively). The hydrogen bond parts of the complex are described by the [O_1–H_1···O_C], [O_2–H_2···O_C], and [N–H_5···O_C] formula, respectively, and the complex is denoted as AdC12 complex. In Table 2 given are the geometric parameters of the hydrogen bond parts in the B3LYP/6-31+G(d) fully optimized geometries of AdC12 complex in the gas phase and aqueous solution phase, and the B3LYP/6-31+G(d) hydrogen bond interaction energies for the complex in the two phases.

As shown in Table 2, the O–H and N–H bond lengths in the hydrogen bond parts of AdC12 complex are 0.007–0.019 Å longer than the respective bond lengths in free PAd^+. The H(N)···O_C distance values are 1.759, 2.014, and 2.194 Å, respectively, and the O(N)H···O_C angles are larger than 141.0°.

As shown in Table 2, the interaction energy for the AdC12 complex is significantly larger in the gas phase (−32.18 kcal/mol) than in solution (−5.26 kcal/mol). Either in the gas phase or in aqueous solution, the 'clip' supramolecular complex with the proportion of adrenaline and 15C5 molecule of 1:2 is most stable, in which imine group of PAd^+ can react with 15C5 by ion-dipole effect. The computed order of stability of three supramolecular complexes (see Table 2) agrees with the order of the diffusion coefficients displayed in Table 1. The size of the supramolecular complex is larger, the value of diffusion coefficient is smaller, and the complex is more stable. For the 2:1 supramolecular complex, though the size is large, 15C5 cannot protect the active groups of adrenaline effectively, and the electron can transfer easily at the electrode surface, there-

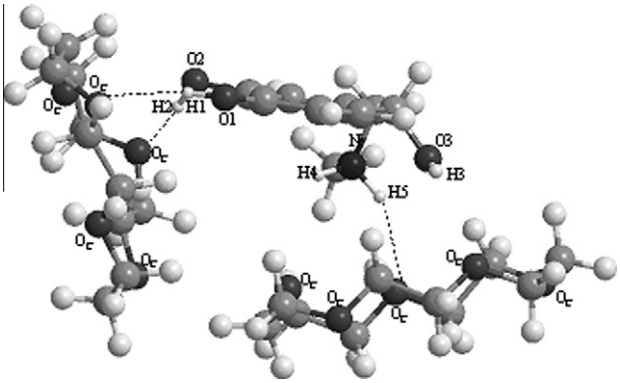

Figure 5. The B3LYP/6-31+G(d) optimized geometry of the AdC12 complex (the most stable 1:2 supramolecular complex of PAd^+ with 15C5).

fore, the value diffusion coefficient of 2:1 supramolecular complex is large.

Table 3 display the charges of the O_1, O_2, and N atoms in PAd^+ and AdC12 complex. With respect to the free PAd^+, the charge on O_1 and O_2 in AdC12 complex are larger than those in the free PAd^+, and the charges of N atoms only change marginally. The sum of the charges of 15C5 part in AdC12 complex is 0.1104 *e*, as shown in Table 3.

The calculational results are consistent with the experimental results that 15C5 can form stable supramolecular complexes with PAd^+. The supramolecular complexes will protect the phenolic hydroxyl groups of adrenaline, influence the electron transfer properties of adrenaline, and make them hard to donate electron and be oxidized. According to the classical drug design paradigm,[39,40] the effect of a drug in human body is a consequence of the molecular recognition between the drug and the biological target. The pharmacological activity of a drug is ultimately determined by the interactions between the drug and its target. Hydrogen bond is one of the major forces for the interactions. The formation of stable PAd^+–15C5 supramolecular complex by hydrogen bond interaction may be utilized in the drug design or the synthesis of new adrenaline receptor, which is, in part, the motivation of the present study.

Using cyclic voltammetry, we have investigated the electron transfer properties of supramolecular complexes of 15C5 with PAd^+ at BGCE, Al_2O_3/GCE, SiC/GCE, and EGCE, respectively. Our experimental data show that 15C5 affects the electron transfer properties of adrenaline. The supramolecular complexes of PAd^+–15C5 formed by ion-dipole and hydrogen bond interaction between PAd^+ and 15C5 will protect the phenolic hydroxyl groups of adrenaline and make them hard to donate electron and be oxidized.

Our interaction energies and NPA calculations for the supramolecular complexes of PAd^+–15C5 at B3LYP/6-31+G(d) level confirm the experimental results that 15C5 can form stable supramolecular complexes with PAd^+.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.098.

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