Theoretical binding affinities and spectroscopy of complexes formed by cyclobis(paraquat-p-anthracene) with amino acids

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The theoretical binding affinities and spectroscopy of complexes formed by cyclobis(paraquat-p-anthracene) with amino acids have been studied using the semi-empirical AM1 method and density function theory. Based on the B3LYP/3-21G optimized geometries, the energies of the complexes have been calculated at B3LYP/6-31G(d) level. The binding energies of the complexes have been obtained after the correction of basis set superposition error. The energy gaps of the complexes are decreased due to the formation of hydrogen bonds. The stretching vibration frequencies of the C-H bonds in the IR spectra of the complexes calculated with AM1 method are red shifted as compared with those of the host. The chemical shifts of the carbon atoms adjacent to the hydrogen bonds, calculated at B3LYP/3-21G level, generally move downfield, whereas those of the carbon atoms next to the nitrogen atoms move upfield. Most of the complexes are less aromatic than the host, based on the nuclear independent chemical shifts calculated at B3LYP/3-21G level.

Keywords: Theoretical chemistry, Spectroscopy, Binding affinities, Density function theory, Aromaticity, Cyclobis(paraquat-p-anthracene), Amino acids

Cyclobis(paraquat-p-phenylene) (CBPQT⁴⁺) is a tetracationic cyclophane and one of the most important building blocks, which can furnish the functional system in supramolecular chemistry. CBPQT⁴⁺ can be synthesized from 1,4-phenylene-bridged bis(4,4′-bipyridinium) salt and 1,4-dibromomethylbenzene. CBPQT⁴⁺ can bind many kinds of guest molecules such as rotaxane and catenane via CH-π, CH-O, and π-π stacking interactions. The complexes formed by CBPQT⁴⁺ with the guest molecules can be used as molecular switches. CBPQT⁴⁺ also exhibits an excellent binding affinity to amino acids, which can be used to detect and quantify the amino acids dissolved in water. Furthermore, CBPQT⁴⁺ can bind 1,4-dialkoxypyrenyl and 1,5-dialkoxynaphthalene derivatives as well as neurotransmitters (dopamine, epinephrine, norepinephrine, and serotonin) and some aromatic compounds like indole and catechol. The binding process of CBPQT⁴⁺ to benzidine and 4,4′-biphenol indicates that the host can act as a redox-switchable donor station in controllable molecular shuttle structures. CBPQT⁴⁺ also binds triethylene glycol substituted by monopyrrolotetrafulvalene and tetrafulvalene derivatives, which can improve the stabilities of the molecular switches. CBPQT⁴⁺ can form complexes with tetrafulvalene and symmetric aromatic compounds. Moreover, the complexes are also formed between CBPQT⁴⁺ and phenyl glycopyranoside, which is related to the aqueous binding diastereoselectivity.

Another important host similar to CBPQT⁴⁺ is cyclobis(paraquat-p-anthracene). Neelakandan et al. have investigated the interactions between the host and guest molecules such as phosphate, adenosine, AMP, ADP and ATP. They have found that the host can selectively bind ATP from other nucleosides, nucleotides, and phosphate anion under physiological pH conditions. However, the interactions between the host and amino acids have not been studied yet. Based on this study of Neelakandan et al., herein the binding energies of the complexes formed by cyclobis(paraquat-p-anthracene) with the amino acids are investigated theoretically. The regularities of the spectroscopic properties and aromaticities for the complexes are explored.

Theoretical

The electrons in a supramolecular complex are generally considered to be moving in the orbitals of the whole system, and the minimum total energy of the complex on the potential curve can be found. The binding energies of the complexes are defined as the
difference of the energies between the complexes and the two separated monomers. Cyclobis(paraquat-p-antithracene) was used as a host. Sixteen amino acids, viz., D-cysteine, D-alanine, D-proline, D-glutamine, D-arginine, D-tyrosine, D-threonine, D-valine, L-cysteine, L-alanine, L-proline, L-glutamine, L-arginine, L-tyrosine, L-threonine, L-valine were the guest molecules (Fig. 1). Complexes 1-16 were formed by the host with the above sixteen guest molecules in 1:1 proportion. In the initial inputs for complexes 1-16, the guest molecules were inserted into the cavity of the host with separation of at least 0.20 nm.

Full geometry optimization for the host and guests as well as complexes 1-16 without any symmetric restriction was performed using semiempirical AM1 method. Further optimization of these complexes was carried out with Becke three parameters and Lee, Yang and Parr’s (B3LYP) method with STO-3G and 3-21G basis sets in density function theory. Then the energies of the complexes was calculated at B3LYP/6-31G(d) level. The binding energies of the complexes were obtained after basis set superposition error (BSSE). These methods in GAUSSIAN 03 have been successfully used to elucidate the electronic structures of the supramolecular complexes, hydrogen-bonding systems, fluorescent materials, fullerene derivatives and other organic or inorganic compounds.

On the basis of the B3LYP/3-21G optimized geometries, the IR spectra of the complexes have been computed using AM1 method. The 13C and 3He NMR spectra have been calculated using the geometry-independent atomic orbitals (GIAO) at B3LYP/3-21G level. The implementation of the GIAO method has been described by Wolinski et al. The NICS value of a complex was computed using 3He as a mass center of the geometry. Then the aromaticity of the complex was measured as proposed by Schleyer et al.

According to Koopmans’ theory, vertical ionization potential (IP) is approximately defined as the negative value of the energy for the highest occupied molecular orbital (HOMO). Similarly, vertical electron affinity (EA) is considered as the negative value of the energy for the lowest unoccupied molecular orbital (LUMO). Absolute hardness (η) is equal to the half of the difference between IP and EA. Absolute electron negativity (χ) equals half of the sum for IP and EA. These chemical indexes have been calculated at B3LYP/6-31G(d) level.

**Results and Discussion**

**The binding energies of the complexes**

To examine the reliability of the method, we have compared the calculated results with those reported in the literature. The calculated length and width of the host (I) are 1.042 and 0.734 nm respectively, which are in agreement with the experimental values of 1.04 nm and 0.71 nm (ref. 12), respectively. The structures of B3LYP/3-21G optimized geometries of complexes 1-16 are shown in Fig. 1. The stabilities of the complexes depend on the absolute values of the binding energies. The binding energies ΔE of complexes 1-16 (Table 1) are negative, indicating that the complexes can be formed thermodynamically. According to the optimized geometries of the complexes, there are three types of binding situations between the host and guest molecules (Fig. 1). In the first type, the complexes are formed by the host with the guest molecules centrally located in the cavity of the host e.g., complexes 5, 6 and 13. The binding energy of complex 5 is -0.672 eV, which is close to the experimental value of -0.243 eV of the complex formed by CBPQT4+ with D-glucuronide. In the second type, the complexes such as 3, 4, 7, 10 and 16, are generated by the hydrogen bonds between the N or O atom in the guest molecules and the two or three hydrogen atoms at the corner of the geometry for the host. The binding energy of complex 10 is -1.194 eV, which is consistent with the experimental value of -1.238 eV of the complex formed by CBPQT4+ with β-glucoside. In the third type, e.g., complexes 1, 2, 8, 9, 11, 12, 14 and 15, the complexes are produced by the hydrogen bonds between the N or O atom in the guest molecules and the hydrogen atoms on the pyridine rings in the host.

Generally, the binding energies of the complexes increase with the increase in the number of the hydrogen bonds formed. In the second type, four hydrogen bonds are found in complex 16, whereas...
Fig. 1 — The optimized geometries of complexes 1-16 at B3LYP/3-21G level.
those in complex 3 are seven. Thus more hydrogen bonds lead to the higher binding energy of complex 3 and than that of complex 16. Complex 7 has six effective hydrogen bonds, more than complex 10, thus it is more stable. The number of hydrogen bonds in complex 4 reaches as many as eight, including the five O–H bonds with the lengths of 0.222, 0.224, 0.237, 0.265 and 0.294 nm as well as the three N–H bonds with the lengths of 0.247, 0.284 and 0.288 nm. Thus, complex 4 is highly stable.

The effectiveness of the hydrogen bonds also plays an important role in the binding process of the complexes. In the first type, complex 5 has six hydrogen bonds, four of which are the N–H bonds. These N–H bonds are not as strong as the O–H bonds with the length 0.204 nm in complex 6. Thus, complex 6 is more stable than complex 5. Complex 13 has hydrogen bonds with the lengths of 0.202, 0.201 and 0.248 nm, which are more powerful than those in the other complexes of this type. Therefore, complex 13 has a higher binding energy than complex 6 although the number of the hydrogen bonds in complex 13 is less. In the third type, the hydrogen bonds with the lengths in the range 0.191-0.289 nm in the complexes are more efficient than those in the other two types. The pyridine rings in the host of this type are almost planar, which is favorable to forming the hydrogen bonds. Thereby, the complexes in the third type basically display the high stabilities.

Besides, the host basically shows better binding affinities to L-amino acids than to D-amino acids (Fig. 2). Among eight pairs of the amino acids, complexes 10-14 with the L-amino acids are more stable than complexes 2-6 with the corresponding D-amino acids. Since these five amino acids (alanine, proline, glutamine, arginine and tyrosine) are relatively bulky, the steric effect can be reduced in L-amino acids. The small steric effect is beneficial to the formation of the hydrogen bonds.

### Some chemical indexes

The stabilities and reactivities of complexes are affected by the LUMO-HUMO energy gaps. The energy gaps of the complexes are basically narrower than that of the host except those of complexes 6 and 13. The interaction between the host and guest molecules leads to the extension of the conjugation system and decrease in the energy gaps. Complexes 6 and 13 have six and three hydrogen bonds respectively. They have at least one hydrogen bond which is short (length 0.210 nm). These efficient hydrogen bonds cause the flow of electrons from the guest to the host, which intensifies the electron flow.

#### Table 1—Chemical indexes of the host and complexes (1-16) calculated at B3LYP/6-31G(d) level

<table>
<thead>
<tr>
<th></th>
<th>∆E (eV)</th>
<th>Energy gap a (eV)</th>
<th>IP (eV)</th>
<th>EA (eV)</th>
<th>η (eV)</th>
<th>χ (eV)</th>
<th>NICS b</th>
</tr>
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<tbody>
<tr>
<td>Host</td>
<td>1.641</td>
<td>14.550</td>
<td>12.909</td>
<td>0.821</td>
<td>13.730</td>
<td>-3.668</td>
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<td>2</td>
<td>-0.688</td>
<td>0.457</td>
<td>14.275</td>
<td>13.818</td>
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<td>14.047</td>
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<td>3</td>
<td>-0.973</td>
<td>0.395</td>
<td>14.006</td>
<td>13.611</td>
<td>0.197</td>
<td>13.809</td>
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<tr>
<td>4</td>
<td>-1.670</td>
<td>0.659</td>
<td>14.240</td>
<td>13.581</td>
<td>0.329</td>
<td>13.911</td>
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<tr>
<td>5</td>
<td>-0.672</td>
<td>0.732</td>
<td>14.419</td>
<td>13.687</td>
<td>0.366</td>
<td>14.053</td>
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<tr>
<td>6</td>
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<td>0.774</td>
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<td>14.164</td>
<td>12.735</td>
<td>0.714</td>
<td>13.449</td>
<td>-3.582</td>
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a ∆E is binding energy. The energy gap is the difference between $E_{\text{LUMO}}$ and $E_{\text{HOMO}}$. IP, EA, η and χ are vertical ionization potential, vertical electron affinity, absolute hardness and absolute electronegativity, respectively. IP = $-E_{\text{HOMO}}$, EA = $-E_{\text{LUMO}}$, η = (IP-EA)/2, and χ = (IP+E)A)/2.

b The NICS values are calculated at B3LYP/3-21G level.

Fig. 2 — Comparison 1, 2 the binding energies between D- and L-amino acids.
density on the host and widens the energy gaps of complexes 6 and 13.

Complexes 1-16 possess lower IP data than that of the host, and thus they are ready to lose the electrons. The electron density on the host in complex 10 is greatly increased owing to the three effective hydrogen bonds with the lengths 0.191, 0.211, and 0.223 nm. Therefore, the low IP and $\chi$ values of complex 10 result in the sensitive oxidation. The large IP data of complexes 5 and 8 lead to high stabilities.

The interactions caused by the hydrogen bonds in complexes 5 and 8 are relatively weak, and thus the HOMO energies are little affected. Complexes 2, 3, 4, 5 and 8 with higher EA data than that of the host are more likely to be reduced, whereas the other complexes with the lower EA values are not. The conjugation systems in the guest molecules of complexes 2, 3, 4, 5 and 8 lead to the powerful electron transfer from the guests to the host through the ligation bonds, which forms the partial positive ions on the end of the guest molecules. The thermal stabilities of complexes 6 and 13 with the larger $\eta$ values than that of the host are high since several hydrogen bonds exist in the two complexes. The other complexes with the low $\eta$ values are less stable than the host. Complex 10 is the least stable one of the ten complexes, which is related to its narrow energy gap.

**IR spectra**

The stabilities of complexes are related to density of electrons and strength of bonds in the complexes, which can be reflected in IR spectra. The main absorptions of the host (Fig. 3a) are located at 3309, 1791, and 1547 cm$^{-1}$, which are ascribed to the stretching vibrations of the C-H, C=N, and C=C bonds. The bending vibrations of the C-H and N-H bonds are situated at 866 cm$^{-1}$. The C-H stretching vibrations in complex 1 (Fig. 3b) compared with those of the host are weakened to 3307 and 3085 cm$^{-1}$. This is due the overlapping of the electron cloud between the host and guest as well as the enlargement of the conjugation system upon the formation of the hydrogen bonds. The decrease in the symmetry of the complex leads to the splitting of the absorptions. The absorptions at 1794 and 2056 cm$^{-1}$ of complex 1 in contrast to those of the host are blue-shifted because

![IR spectra](image_url)
the oxygen atom in the furan ring enlarges the electron density on the guest molecule.

The first IR absorptions at 3311, 3312, 3313, and 3310 cm\(^{-1}\) of complexes 2 (Fig. 3c), 7, 15 (Fig. 3d), and 16 in comparison with that of the host are blue-shifted. Some of the C-H bonds except those neighboring the hydrogen bonds in the host are intensified owing to the growing electron density. The absorptions near 2000 cm\(^{-1}\) of complexes 2-16 are caused by the stretching vibrations of the C=O bonds on the delocalized carboxyl groups in the amino acids. The similar absorptions of the C=O bonds and red-shifted C-H bond in complexes 2-16 as compared with those in complex 1 are produced within 1926-2106 cm\(^{-1}\) and 3055-3183 cm\(^{-1}\).

**NMR spectra**

The electron density on the carbon atoms is changed because of the formation of the complex, which can be displayed in the NMR spectrum. The calculated chemical shift of the \(sp^3\)-C atom appears at 71.5 ppm (Fig. 4a), which is close to the experimental value\(^{12}\) 72.9 ppm. The chemical shifts of the \(sp^2\)-C atoms on the pyridine rings are located at 130.1-175.0 ppm, basically consistent with the experimental values\(^6\) at 128.3-154.0 ppm. The absorptions in the NMR spectra of complexes 1-16 are split compared with those of the host, and more absorption peaks within the ranges 5-45, 55-75 and 120-180 ppm are generated. This is because of the presence of the \(sp^3\)-C and \(sp^2\)-C atoms on the guest molecules as well as the decrease in the molecular symmetries of the complexes. In complex 2, the absorptions of \(sp^3\)-C are split to 52.5, 56.1, 57.0, and 58.2 ppm, which move upfield as compared with 71.5 ppm of the host. Additionally, the absorptions of \(sp^2\)-C in complex 2 are widened to 121.3-183.8 ppm due to the decrease in the molecular symmetry. The peak at 80.1 ppm of complex 3 arises from \(sp^2\)-C on the carboxyl group in the guest. The absorption at 119.2 ppm of complex 6 is generated from \(sp^2\)-C on the benzene rings in the guest. Moreover, the peaks at 101.1 and 100.6 ppm in complexes 5 and 13 are caused by \(sp^2\)-C connected with the three nitrogen atoms in the guest molecules.

The chemical shifts of the carbon atoms adjacent to the hydrogen bonds generally moved downfield, whereas those of the carbon atoms next to the nitrogen atoms move upfield. In complex 1 (Fig. 4b), the absorptions of C(16), C(17), and C(33) move downfield to 152.8, 160.8, and 153.0 ppm, relative to the original values of 146.7, 148.1, and 148.1 ppm. These three carbon atoms are adjacent to the three

![Fig. 4](image-url) — The \(^{13}\)C NMR spectra of some complexes at B3LYP/3-21G level. [(a) host; (b) complex 1; (c) complex 2; (d) complex 10].
hydrogen bonds between the host and guest in complex 1. Also, the oxygen atom in the guest molecule decreases the electron density on C(16), C(17) and C(33). In complex 2 (Fig. 4c), the absorptions of C(17) and C(33) also move downfield to 151.7 and 167.2 ppm as compared with 148.1 and 146.7 ppm, whereas the chemical shift of C(34) moves upfield from 148.1 ppm to 140.6 ppm because N(32) with the strong electron attracting effect increases the electron density on C(34). Besides, the chemical shift of C(29) in complex 2 appears at 183.8 ppm since C(29) is used to form the C=C bond and the electron cloud is decreased in the presence of the adjacent hydrogen bond. Similarly, the absorptions of C(31) and C(55) in complex 10 (Fig. 4d) move downfield to 156.2 and 144.8 ppm, relative to the original values 138.6 and 138.9 ppm, whereas the chemical shift of C(35) moves upfield from 71.5 ppm to 66.4 ppm.

Conclusions
The host cyclobis(paraquat-p-anthracene) binds amino acids via hydrogen bonds between the atom N or O in the guest molecules and the atom H in the host. The binding energies of the complexes are mainly affected by the number and effectiveness of the hydrogen bonds. The IR stretching vibrations of the C-H bonds adjacent to the hydrogen bonds are weakened. The chemical shifts of the carbon atoms next to the hydrogen bonds generally move downfield, whereas those of the carbon atoms adjacent to the nitrogen atoms move upfield. Some of the complexes are less aromatic. Thus, how to improve the aromaticities and stabilities of the complexes is still a problem. As an electron-deficient macromolecule, cyclobis(paraquat-p-anthracene) is predicted to show binding affinities to other electron efficient guest molecules such as pharmaceutical molecules.

References
14. (a) Gaussian 03, Rev B 01, (Gaussian Inc, Pittsburgh, PA) 2003; (b) See Gaussian website: http://www.gaussian.com/g_whitepaper/nmrcmp.htm.


