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Charge-transfer Interaction: A Driving Force for Cyclodextrin Inclusion Complexation

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Abstract

PM3 calculations were performed on the complexation of α-cyclodextrin (α-CD) with nitrobenzene, benzoic acid, benzoate anion, 4-nitrophenol, and 4-nitrophenolate anion. The results, in agreement with the experimental observations, indicated that the complex α-CD-benzoic acid was more stable than α-CD-nitrobenzene, and α-CD-4-nitrophenolate was more stable than α-CD-4-nitrophenol. Frontier orbital analysis suggested that charge-transfer interaction led to such behaviors, and hence constituted a nontrivial driving force in the molecular recognition of α-CD.

Introduction

Cyclodextrins (CDs) can form inclusion complexes with many compounds [1]. CD chemistry has caused much interest, not only due to its applications to pharmaceutical science and separation technology [2], but also because the inclusion represents an ideal model mimicking enzyme-substrate interactions [3]. CD inclusion complexes are also valuable models for understanding non-covalent intermolecular interactions [4].

The driving forces leading to the complexation are important in CD chemistry [5], which have been studied theoretically with quantum mechanical (QM) or molecular mechanical (MM) calculation [6–8], linear regression [9–11], and artificial neural networks [12]. The driving forces have been attributed to factors including van der Waals force [13], hydrophobic effect [14], and dipole-dipole interactions [15]. Quantitative models based on this theory [9–11] could well account for the observed trends in binding energy in general.

However, there are some intriguing behaviors hard to understand according to the above driving forces. One example is the complexation of α-CD with benzoic acid and with nitrobenzene. The two guest molecules are isoelectronic. They have similar volume and polarizability, reflected by the similar substituent molar refraction R_m constants (12.29 for NO_2, and 13.07 for COOH) [16]. They also have the same hydrophobic π constants (-0.28) [16]. Thus, if van der Waals forces and the hydrophobic effect dominate CD molecular recognition, the stability of the two complexes should not be significantly different. Besides, the dipole moment of nitrobenzene is larger than that of benzoic acid as reflected by their Hammett σ constants (0.78 for NO_2 and 0.41 for COOH) [16]. Thus, α-CD-nitrobenzene should be more stable than α-CD-benzoic acid, if dipole–dipole interaction affects CD complexation. However, experimentally the complexation of α-CD with benzoic acid was more favorable than that with nitrobenzene (see Table 1).

Another interesting example is the complexation of α-CD with 4-nitrophenol and with 4-nitrophenolate anion. Though 4-nitrophenolate is obviously much more hydrophilic than 4-nitrophenol, the complex α-CD-4-nitrophenolate is more stable than α-CD-4-nitrophenol (see Table 1). Some authors considered this as a result of stronger dipole-induced dipole interaction for the charged guest molecule [19]. It was also suggested to be due to the increased electron density and polarizability in the binding site of 4-nitrophenolate [20]. However, firm conclusions have not been reached.

Herein, the above problems were studied with quantum chemistry calculations [21], which have been shown to be reliable in the modeling of CD complexation [22]. Due to difficulties in modeling the solvation effect, only the gas-phase interaction between the host and guest was evaluated. However, the results of the gas-phase calculation are still valuable because of the following reasons. (1) As the solvation effect disfavors the complexation of CD with benzoic acid and 4-nitrophenolate more than that with nitrobenzene and 4-nitrophenol, it is expected that in the gas phase the complexation with the former two guest molecules should be more favorable than with the latter two. (2) As the dipole-dipole interaction does not favor the complexation with the former two guest molecules, it is interesting to see if calculation can indeed give a larger complexation energy for the first two guest compounds and what factor leads to such a result.

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Table 1. The experimental association constants for the complexation of α-CD with the guest molecules in aqueous solution at 298 K[17]

Guest molecule	Experimental association constant (K_a) (M^{-1})	K_a in average (M^{-1})	ΔG (298 K) (kJ/mol)
Nitrobenzene	48.6, 187, 89*	108	11.6
Benzoic acid	1400, 722, 810, 588, 783, 812, 800, 1000, 338, 1047, 751, 683*	811	16.6
Benzoate	38, 11.2, 12.8, 11, 10.5, 9.8, 12.3, 10.5, 11.4*	14	6.5
4-Nitrophenol	200, 245, 249, 249, 341, 210, 250, 200, 160, 189, 769, 126, 240, 204, 177, 158	248	13.7
4-Nitrophenolate	2200, 2408, 1887, 2000, 2270, 2290, 1800, 2500, 1587, 2704, 5000, 4167, 2500, 1770, 3550, 1545, 2440	2507	19.4

*Taken from Ref. 18.

Methods

All calculations were performed with GAUSSIAN 98 [23]. The initial geometry of nitrobenzene, benzoic acid, benzoate anion, 4-nitrophenol, and 4-nitrophenolate anion were constructed with MOLDEN and then optimized by PM3. Single point calculation with B3LYP/6-31g* method was performed on the guest compounds to obtain their dipole moments.

The structure of α-CD was built from the crystal structure [24]. It was fully optimized by PM3 without any symmetry constraint. The glycosidic oxygen atoms of CD were placed onto the *XY* plane and their center was defined as the center of the coordination system. The primary hydroxyl groups were placed pointing toward the positive *Z* axis. The inclusion complexes were constructed from the PM3-optimized α-CD and guest molecules. The NO_2 and COOH groups were always located pointing to the primary hydroxyls of α-CD according to the experimental observation [25]. The longer dimension of the guest molecule was initially placed onto the *Z* axis. The position of the guest was determined by the *Z* coordinate of one selected atom of the guest. The inclusion process was simulated by putting the guest in one end of CD and then letting it pass through the CD cavity by steps. In every step, the geometry of the host-guest complex was completely optimized by PM3 without any restriction. Frequency calculations using PM3 were also performed, and no negative eigenvalue was found for the final structures.

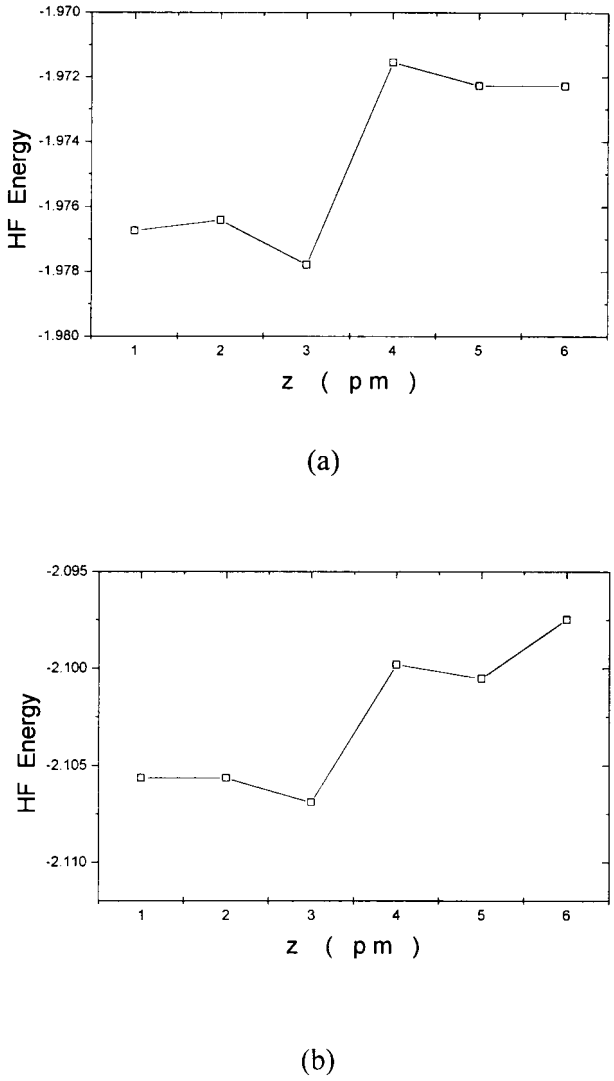

Figure 1. Graphic diagrams for the simulation of the inclusion complexation of the guest molecules into α-CD. The position of the guest was determined by the *Z* coordinate of one of the atoms in the guest molecule from the center of the glycosidic oxygens. (a) nitrobenzene, (b) benzoic acid.

Result and discussion

The optimizations

The details of the optimization can also be found in former reports [22, 26]. Herein, as examples, the results of α-CD-nitrobenzene and α-CD-benzoic acid are briefly discussed.

Graphic representation of the energy changes involved in the inclusion process produces two curves for nitrobenzene and benzoic acid, respectively (Figure 1). The PM3-optimized host–guest molecular structures of the two complexes at each energy minimum are shown in Figure 2.

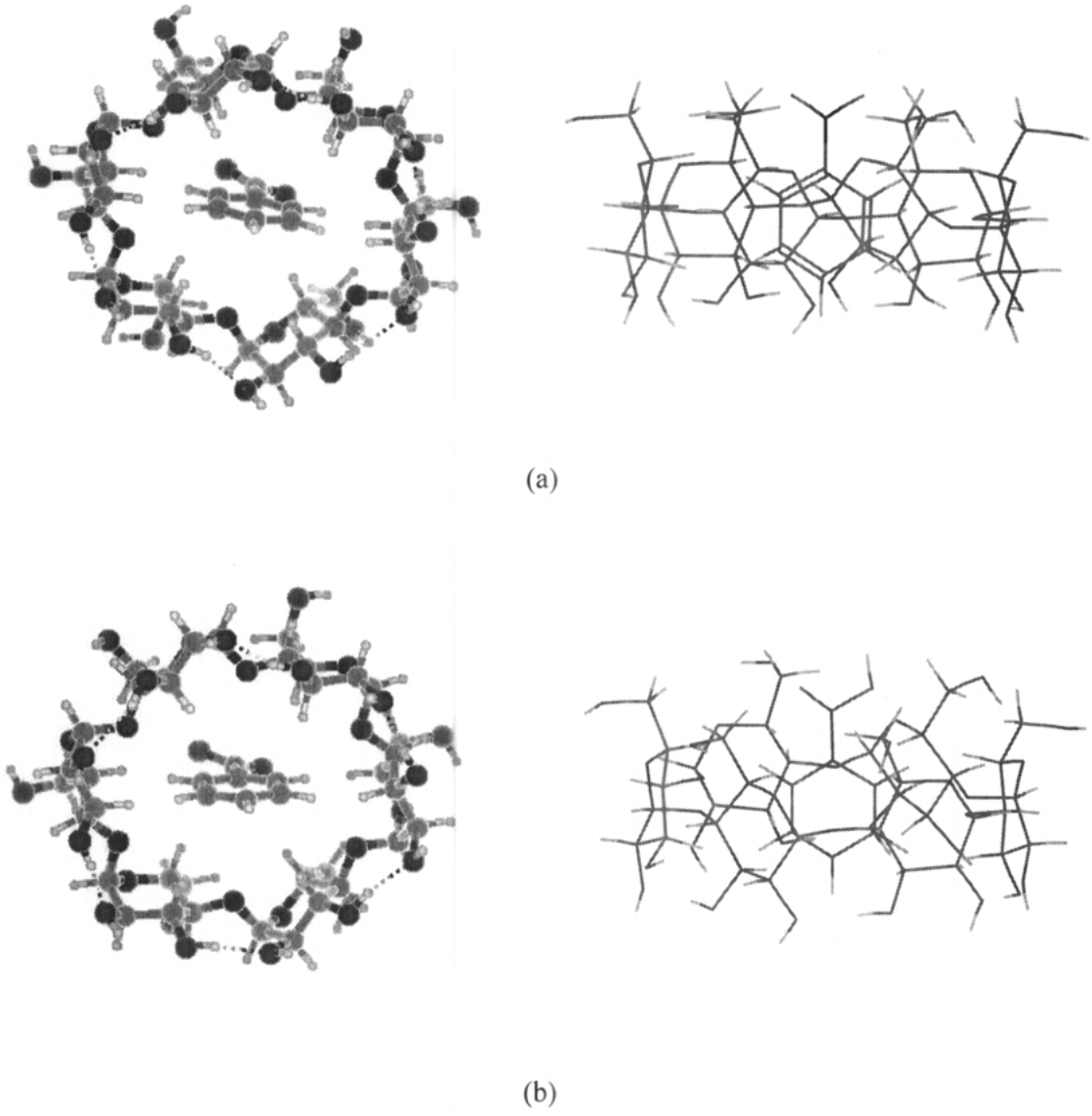

Figure 2. PM3-optimized structures of the α-CD complexes. (a) nitrobenzene, (b) benzoic acid.

From Figures 1 and 2, it can be seen that the guest molecules indeed form stable inclusion complexes with α-CD. Interesting, it can also be seen that the structures of α-CD-nitrobenzene and of α-CD-benzoic acid are very similar to each other. Presumably, the fact that the two guest molecules are isoelectronic causes the above behavior. Therefore, the structural difference is not likely a factor that makes the complexation energies of α-CD with the two guest molecules different.

Likewise, the structure of α-CD-4-nitrophenolate is similar to that of α-CD-4-nitrophenol.

The properties of the guest, host, and their complexes

In Table 2 are summarized the energy, HOMO, and LUMO of the guest compounds. The dipole moments from B3LYP/6-31G* calculation are also listed.

From Table 2, the dipole moment of nitrobenzene is significantly larger than that of benzoic acid. The dipole moment of 4-nitrophenol is also significantly larger than that of 4-nitrophenolate. These results are readily understandable. However, it is not straightforward why the complexations of α-CD with nitrobenzene and with 4-nitrophenol are less favorable than with benzoic acid and 4-nitrophenolate if the dipole-dipole interaction and hydrophobic interaction are the only driving forces in CD complexation.

In Table 3 are summarized the stabilization energies upon complexation, HOMO, and LUMO of the CD complexes. From Table 3, it can be seen that the complexation of α-CD with benzoic acid is indeed significantly more favorable than that with nitrobenzene. The complexation of α-CD with 4-nitrophenolate is also much stronger than that with 4-nitrophenol. Obviously, these results agree with the experimental observations.

The charge-transfer interaction in CD complexation

Though the results are not readily understandable according to the driving forces listed in the introduction, the Morokuma theory of energy decomposition analysis [27] can offer

Table 2. PM3 calculation results for the host and guest molecules

Compound	PM3 energy (kJ/mol)	HOMO (eV)	LUMO (eV)	LUMO-HOMO MO (eV)	Dipole moment (Debye)*
α-CD	−5212.4	−10.82	1.41	12.23	–
Nitrobenzene	60.2	−10.60	−1.13	9.47	4.58
Benzoic acid	−277.1	−10.13	−0.53	9.60	1.92
Benzoate	−375.3	−4.45	3.89	8.34	8.27
4-Nitrophenol	−133.1	−10.16	−1.08	9.08	5.34
4-Nitrophenolate	−341.5	−4.24	3.82	8.06	0.89

By B3LYP/6-31g method.

Table 3. PM3 calculation results for the α-CD complexes of the guest molecules

Guest molecule	Heat of formation (kJ/mol)	Stabilization energy upon complexation (kJ/mol)	HOMO (eV)	LUMO (eV)	LUMO-HOMO (eV)	Mulliken charge of α-CD in complex
Nitrobenzene	−5170.5	−18.3	−10.64	−1.27	9.37	−0.0044
Benzoic acid	−5521.0	−31.5	−10.21	−0.68	9.53	−0.0059
Benzoate	−5685.5	−97.8	−5.74	2.93	8.67	−0.0684
4-Nitrophenol	−5363.2	−17.7	−10.28	−1.23	9.05	−0.0042
4-Nitrophenolate	−5610.0	−56.1	−5.12	2.92	8.04	−0.0163

a reasonable explanation. According to the theory, when a supermolecule is formed electrons will lose their identity as belonging to one or other component molecule. Four types of interactions should be considered in the formation of a supermolecule: (a) electrostatic interaction, which is favored by large permanent charges and dipoles; (b) polarization interaction, which is favored by large volume and polarizability of the molecules; (c) exchange energy, or Pauli repulsion; and (d) charge-transfer interaction, which is contributed from the mixing of the filled orbitals of one component molecule with the vacant orbitals of the other. Evidently, charge-transfer interaction is always attractive, and the most important terms in this interaction are contributed from the charge-transfer between the HOMO of one component and the LUMO of the other.

These first three interactions constitute the canonical driving forces in CD chemistry, i.e. dipole–dipole interaction, dipole-induced dipole interaction, and steric effect. However, they cannot explain the unexpected experimental observations. Herein, QM studies indicate the importance of charge-transfer interaction as a non-trivial driving force in CD complexation.

Mulliken charge distribution analysis reveals that in the complexes, α-CD as a whole always obtains a nontrivial negative charge. Thus, charge-transfer takes place in CD complexation. In the present systems, α-CD is a Lewis acid accepting electrons, while the guest compounds act as Lewis bases donating electrons. Thus, the most important term in the charge-transfer energy comes from the interaction of the HOMO of the guest compounds and the LUMO of α-CD. The higher the HOMO of the guest molecule, the stronger is the charge-transfer interaction in the complexation.

As the HOMO of benzoic acid lies significantly higher than that of nitrobenzene (see Table 2), stronger charge-transfer interaction will take place in α-CD-benzoic acid than in α-CD-nitrobenzene. As a result, though benzoic acid and nitrobenzene, two isoelectronic molecules, have similar volumes, polarizability, and hydrophobicity, α-CD complexation with the former is stronger than that with the latter. Admittedly, the hydrogen bonding between benzoic acid and α-CD may also be able to cause the behavior. However, the present calculation shows that charge-transfer interaction can be an additional reason for the difference. Moreover, hydrogen bonding cannot bring about the difference between the binding energies of α-CD complexation with 4-nitrophenol and with 4-nitrophenolate.

Similarly, as the HOMO of 4-nitrophenolate lies significantly higher than that of 4-nitrophenol (See Table 2), a stronger charge-transfer interaction will take place in α-CD-4-nitrophenolate than in α-CD-4-nitrophenol. As a result, though 4-nitrophenolate is more hydrophilic and has a smaller dipole moment than 4-nitrophenol, α-CD complexation with the former can be more favorable than that with the latter.

It should be mentioned that the above comparison of the strength of charge transfer interaction is only useful when the guest molecules are isoelectronic. Otherwise, factors such as dipole moments and steric effect can greatly affect the stability of the complexes, which makes the comparison of charge transfer interaction less meaningful. Apparently, though charge transfer interaction is shown to be a driving force in CD complexation and can determine the strength of complexation for isoelectronic guest molecules, it is not expected to be a major driving force in CD complexation

as shown by the small Mulliken charge transferred from the guest to the host.

Interestingly, though the complexation of α-CD with 4-nitrophenolate is stronger than that with 4-nitrophenol, α-CD-benzoate is much less stable than α-CD-benzoic acid (see Table 1). Phenomenologically, this behavior is explained as a result of the different inclusion modes in the complexes [19]. In α-CD-benzoate, COO^- is located completely inside the CD cavity and does not interact with bulk water. On the other hand, in α-CD-4-nitrophenolate, O^- is located outside the CD cavity and still interacts with bulk water.

Herein, the complexation of α-CD with benzoate anion was also studied with PM3 (see Table 2 and 3). From the results, α-CD-benzoate is much more stable than α-CD-benzoic acid in the gas phase. This is again due to the high-lying HOMO of benzoate, which leads to the occurrence of a stronger charge-transfer interaction. Thus, the interaction between an anionic guest and CD is actually strong. Presumably, it is the hydrophilic effect that makes the α-CD-benzoate complex unstable.

Conclusion

The present study suggested that charge-transfer interaction was a nontrivial driving force in CD molecular recognition. This interaction could explain why the complexation of α-CD with benzoic acid was more favorable than that with nitrobenzene. It could also explain why α-CD-4-nitrophenolate was more stable than α-CD-4-nitrophenol.

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