A Theoretical Study on the Inclusion Complexation of Cyclodextrins with Inorganic Cations and Anions

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Abstract

PM3 and B3LYP/3-21+g(d) calculations were performed on the inclusion complexation of α- and β-cyclodextrin with inorganic cations and anions including Li^+, Na^+, F^-, and Cl^-. Both the gas-phase interaction and solvent effect were taken into consideration. The CD complex with an anion was more stable than that with a cation, which was in agreement with the experimental findings. It was proposed that hydrogen bonding between the anion and the cyclodextrin cavity was the physical origin of such behavior.

Introduction

Cyclodextrins (CDs), cyclic oligomers of α-D-glucose units connected through glycosidic α-1,4 bonds, can form inclusion complexes with a variety of organic compounds [1]. CD chemistry has attracted much attention, not only due to its applications to pharmaceutical science and separation technology, but also because inclusion represents an ideal model mimicking enzyme-substrate interactions [2]. CD inclusion complexes are also valuable models for understanding non-covalent intermolecular interactions because of their relatively simple and rigid structures [3]. The major driving forces leading to complexation have been proposed to include electrostatic interaction, van der Waals interaction, hydrophobic interaction, and hydrogen bonding [4, 5].

The electrostatic interaction energy is the energy of interaction between the undistorted charge distributions of the two molecules interacting with each other. It includes all electrostatic forces between permanent charges, dipoles and higher multipoles present in the system. Normally, three types of electrostatic interactions are the most important, i.e., ion-ion interaction, ion–dipole interaction, and dipole–dipole interaction. As CDs are neutral molecules, the ion-ion interaction does not occur in CD complexation, unless the CD is appropriately modified with charged groups [6]. On the other hand, the ion-dipole interaction is expected to take place in CD complexation apparently because CDs are polar molecules. However, the occurrence of this interaction is difficult to show.

Nevertheless, CD complexes with inorganic ions should be a good system where the ion–dipole interaction is expected to be important. Fortunately, the CD-ion binding constants have also been known to be measurable in water

with various methods such as conductometry, potentiometry, spectrophotometry, and polarography [7]. In particular, the binding of CDs with anions (e.g., F^- and Cl^-) were found to be much stronger than the binding of CDs with cations (e.g., Li^+ and Na^+) [8]. This is a very interesting yet unaddressed phenomenon especially when one notices that Na^+ and F^- are isoelectronic. Therefore, it prompted us to carry out a theoretical study on the inclusion complexation of CDs with inorganic ions in order to understand the underlying interactions.

Clearly, our theoretical study on CD complexation would rely much on the gas phase interactions. The solvation effect could be included using various continuum solvation models, but whether these models could give reasonable results remains to see. Nevertheless, it should be mentioned that the CD inclusion complexes have been successfully detected in the gas phase recently using various techniques including electrospray ionization, matrix assisted laser desorption ionization, and fast atom bombardment mass spectroscopy [9]. Considering the importance of simple cations and anions in modern mass spectroscopy techniques, it would also be valuable to study the gas phase CD-ions interactions.

In fact, as early as 1994, Lebrilla *et al.*, studied the CD complexes with cations including Li^+, Na^+, K^+, and Cs^+ in the gas phase using liquid secondary ion mass spectrometry [10]. They found that decay rates of the CD complexes decrease as the size of cations increase. In 1997, Bowers *et al.* studied gas phase structrues of sodiated α-cyclodextrin in the gas phase using both experimental and theoretical methods [11]. Their results suggested that the CD-Na^+ complex should be an inclusion one because Na^+ is located in the CD cavity. However, it was proposed that in the complex CD was highly distorted and Na^+ could interact with four sugar units. Moreover, in 1999 Kojima *et al.* studied the CD complexes with triply charged metal ions such as Sc^{3+} and

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Y^{3+} [12]. All these studies indicate that besides the hydrophobic effect, which cannot take place in the gas phase, other interactions should also be important for CD complexation.

Methods

All the calculations were done with GAUSSIAN 98 [13]. α- and β-CD were built and optimized with PM3 from the crystal structure [14]. The glycosidic oxygens were placed onto the XY plane and their center was defined as the center of the coordination system. The primary OH groups were placed pointing toward the positive Z-axis. The inclusion complex was constructed from the PM3-optimized CD and the inorganic substrate. The position of the substrate was defined by its Z coordinate. The inclusion complexation was emulated by entering the substrate from one end of the CD and then letting it pass through the CD by steps. At each step, the geometry of the complex was completely optimized with PM3 without any restriction. DFT single-point calculation at the level of B3LYP/3-21+g* was then performed on all the PM3-optimized species to obtain more accurate total energies, both *in vacuo* and in water solution by using the Onsager continuum solvation model based on the self-consistent reaction field (SCRF) method [15]. It should be mentioned that this continuum solvation model only considers the solvent as a continuous dielectric with a cavity accurately modeled for the solute. In the model, the solvent reacts against the solute charge distribution, generating a reaction field, and the electrostatic interaction between the solute and the solvent is introduced as a perturbation operator in the solute hamiltonian.

Results and discussion

The graphic presentation of the energy changes produces roughly V-shape curves for the inclusion complexation of ions into CDs, typically as shown in Figure 1. From these curves, it is clear that computation on CD complexation is a multiple-minimum problem, because every spot on the curve is a real minimum on the potential surface. Therefore, a thorough examination of the potential surface is necessary using the systematic multi-step technique as mentioned above. The resulting energy curves show that the complex is the most stable when the substrate approaches to the center of the host cavity.

Nevertheless, we are more interested in the global minimum spot on the potential surface, whose position can be easily found according to Figure 1. Using this method, we obtained the optimal structures of the CD-ion complexes as shown in Figure 2. The energetic aspects of all the complexes are summarized in Table 1. From Figure 2, it can be seen that CDs indeed are able to form inclusion complexes with inorganic ions. The negative binding energies as shown in Table 1 clearly demonstrate that these inclusion complexes are also stable, at least in the gas phase. Notably, the stabilization energies upon complexation calculated with PM3 are qualitatively close to those with B3LYP/3-21+g*.
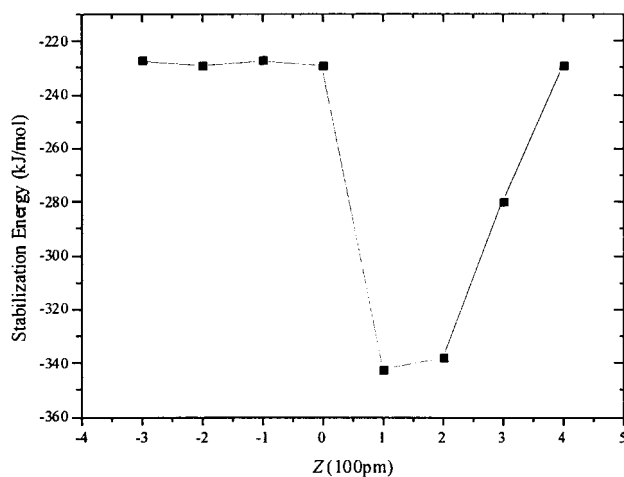
(a)
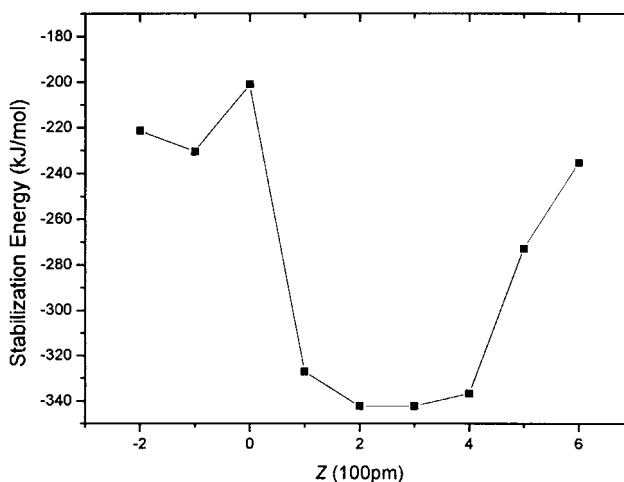
(b)

Figure 1. Graphic presentations for the inclusion complexation of fluoride anion into (a) α-CD and (b) β-CD cavities.

Thus, optimization with PM3 on CDs is not only feasible but also qualitatively reliable.

However, when continuum solvation effects are taken into consideration by SCRF calculations, the binding energies become a little larger. The magnitudes of the binding energies in water, 40-350 kJ/mol, clearly would predict much larger binding constants than those ever measured for the ions (<100 L/mol). Therefore, the continuum solvation model completely fails for the CD-ion complexes. It is conceivable that the ions should be complexed to water molecules before they bind to CDs. Breaking these water-ion complexes would need considerable free energy, which is not taken into consideration by the continuum solvation model [16].

Nevertheless, a binding energy of 40–350 kJ/mol is reasonable for a gas phase molecule-ion complex. Therefore, we expect that our calculations of the CD-ion complexes
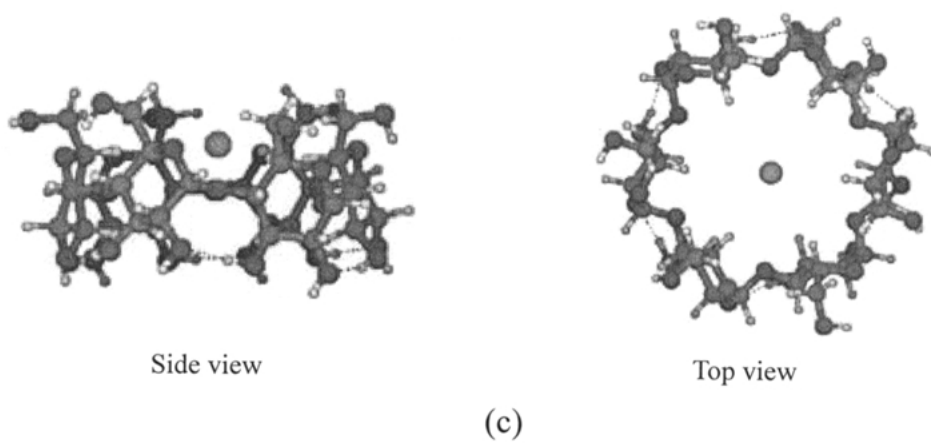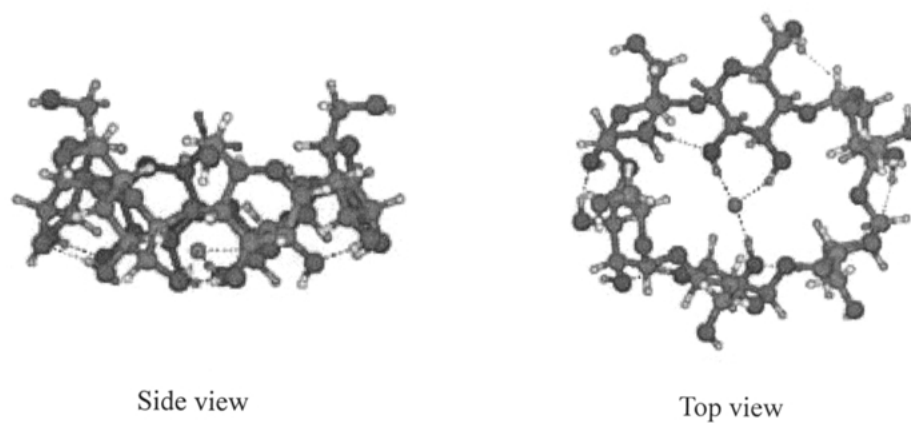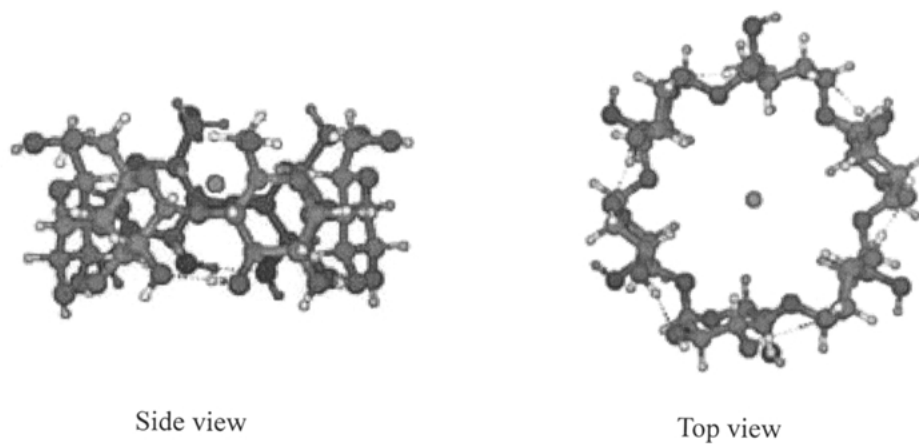
Side view   Top view

(a)

Side view   Top view

(b)

Side view   Top view

(c)

Figure 2. PM3 optimized structures of the complexes of α-CD with (a) lithium cation (b) fluoride anion. (c) sodium cation (d) chloride anion, and β-CD with (e) lithium cation (f) fluoride anion. (g) sodium cation and (h) chloride anion.
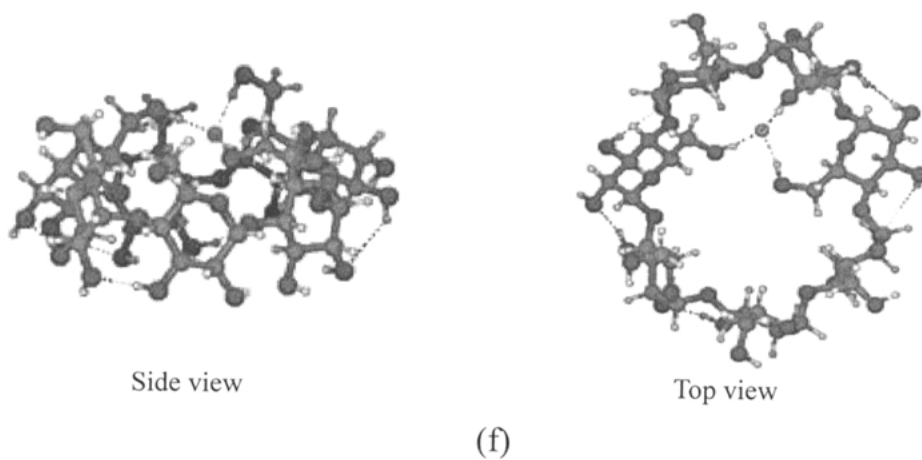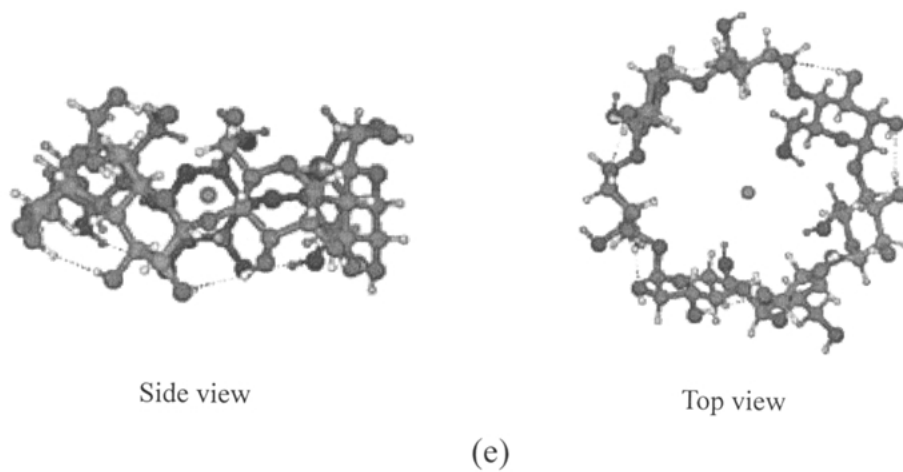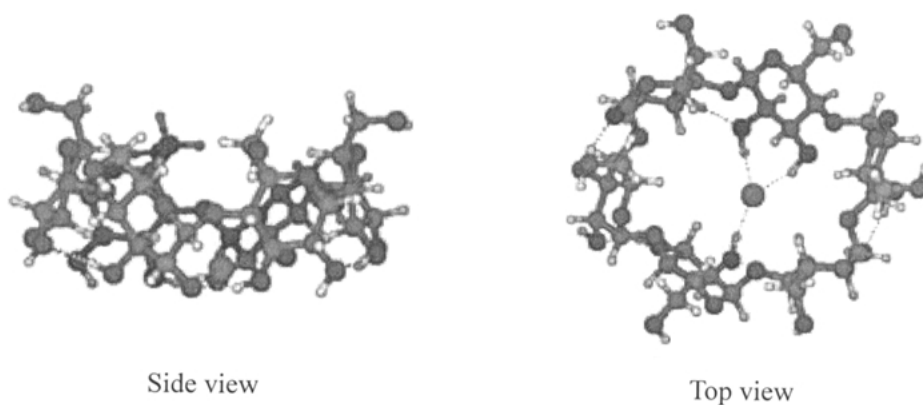
Side view

Top view

(d)

Side view

Top view

(e)

Side view

Top view

(f)

Figure 2. Continued.

Side view   Top view
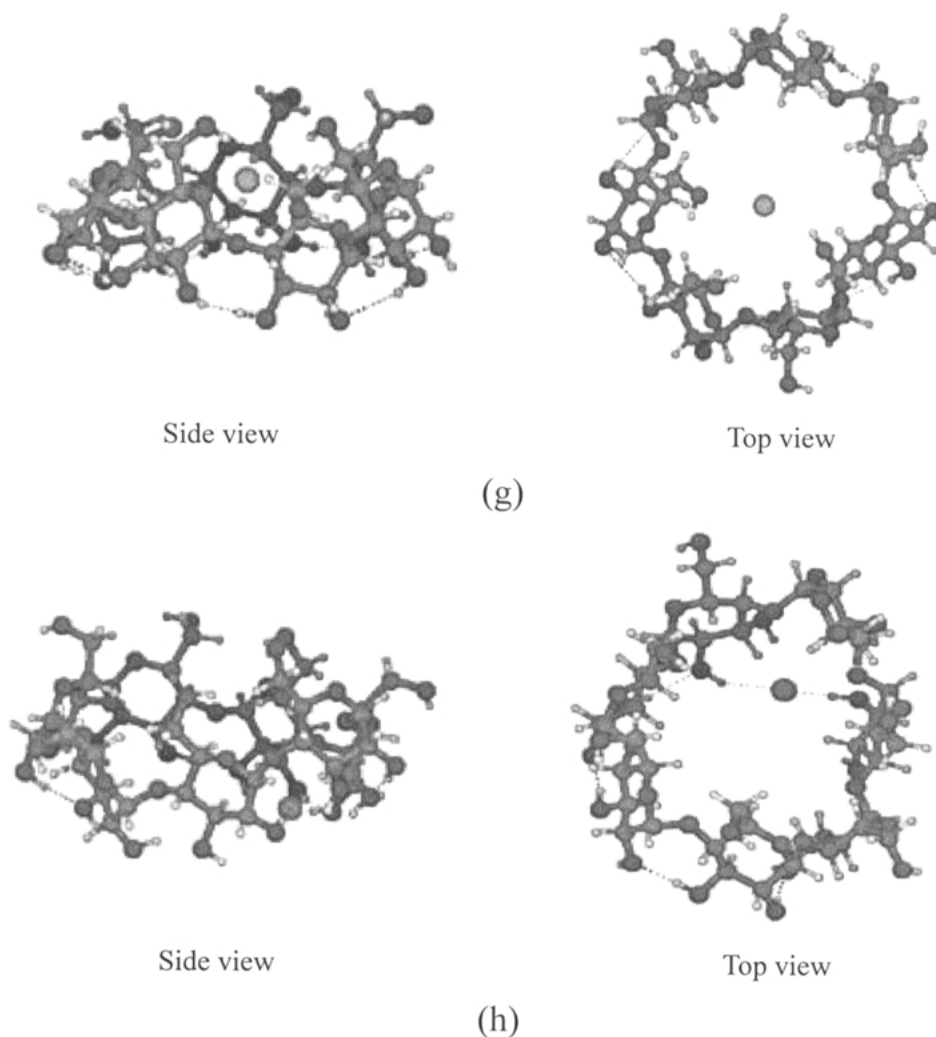
(g)

Side view   Top view

(h)

Figure 2. Continued.

in vacuum should provide valuable insights into the real interactions whose many aspects are hard to reveal experimentally. For example, from calculations it is clear that in both the α- and β-CD complexes, F^- always has a larger binding energy than Cl^-. This observation is interesting, because according to the experimental measurements (in water, however) the binding constants of CDs with halide anions should decrease in the order $I^- > Br^- > F^- > Cl^-$.

Obviously, the reason that iodide binds more strongly than other halide anions lies in the larger size of iodide which enhances the van der Waals interaction between the substrate and CD [5]. The same mechanism can also be used to explain the stronger binding of bromide anion than fluoride and chloride anions. However, the situation changes when we compare the fluoride and chloride anions. The only possible reason for this behavior should be the hydrogen bond.

According to Figure 2, fluoride and chloride anions are located in the cavity of α-CD near its secondary rim. Three hydrogen bonds are identified between the anion and the secondary hydroxyl groups of α-CD. On the other hand, in the β-CD complexes, fluoride is hydrogen bonded to three hydroxyl groups of the primary rim, whereas chloride is hydrogen bonded to two hydroxyl groups of the secondary rim. The fact that β-CD is more flexible than α-CD clearly is the reason for the more complicated modes of binding seen with the β-CD. Nevertheless, because the $F^- \ldots$ H–O hydrogen bonding (101.7 kJ/mol for $F^- \ldots$ H–O–CH$_3$ by PM3) is much stronger than the $Cl^- \ldots$ H–O one (e.g., 73.2 kJ/mol for $Cl^- \ldots$ H–O by PM3), it is understandable than the fluoride-CD complex should be more stable than the chloride one although the latter enjoyed a larger van der Waals force.

In contrast to CD binding with anions, CDs bind much more weakly with cations. The same trend is also observed experimentally, although the medium is water. Obviously, the reason for the weaker binding is the lack of any hydrogen bond. In fact, in all the cation-CD complexes, the cation is located right at the center of the CD cavity surrounded by six or seven glycosidic oxygens. The conformation of the CD cavity is not significantly distorted by the binding, either. Also interestingly, according to Table 1 the CD–Na$^+$ complexes are more stable than the CD–Li$^+$ complexes. Presumably, the larger size of Na$^+$ causes larger van der Waals interaction in the sodium complex than the lithium one.

Table 1. Energies of the complexes of CDs with inorganic ions (kJ/mol)

Complex	Method	Total energy of ion	Total energy of CD	Total energy of complex	Binding energy
α-CD-Li$^+$	PM3	–	−5212.44	−5056.02	–
	B3LYP/3-21+g* (in vacuo)	−18974.53	−9560937.40	−9579970.45	−58.5
	B3LYP/3-21+g* (in water)	−18974.53	−9560938.89	−9579970.70	−57.3
α-CD-Na$^+$	PM3	–	−5212.44	−5217.37	–
	B3LYP/3-21+g* (in vacuo)	−422498.51	−9560937.40	−9983534.72	−98.8
	B3LYP/3-21+g* (in water)	−422498.51	−9560938.89	−9983534.96	−97.6
α-CD-F$^-$	PM3	−130.55	−5212.44	−5685.33	−342.3
	B3LYP/3-21+g* (in vacuo)	−260638.47	−9560937.40	−9821832.57	−256.8
	B3LYP/3-21+g* (in water)	−260638.47	−9560938.89	−9821839.07	−261.7
α-CD-Cl$^-$	PM3	−214.14	−5212.44	−5655.29	−228.7
	B3LYP/3-21+g* (in vacuo)	−1201841.9	−9560937.40	−10762905.11	−125.8
	B3LYP/3-21+g* (in water)	−1201841.9	−9560938.89	−10762914.66	−133.9
β-CD-Li$^+$	PM3	–	−6082.82	−5921.47	–
	B3LYP/3-21+g* (in vacuo)	−18974.53	−11154227.99	−11173154.52	−45.8
	B3LYP/3-21+g* (in water)	−18974.53	−11154228.73	−11173410.25	−48.2
β-CD-Na$^+$	PM3	–	−6082.82	−6082.82	–
	B3LYP/3-21+g* (in vacuo)	−422498.51	−11154227.99	−11576795.37	−68.9
	B3LYP/3-21+g* (in water)	−422498.51	−11154228.73	−11576798.66	−71.4
β-CD-F$^-$	PM3	−130.55	−6082.82	−6554.96	−341.6
	B3LYP/3-21+g* (in vacuo)	−260638.47	−11154227.99	−11415250.19	−383.7
	B3LYP/3-21+g* (in water)	−260638.47	−11154228.73	−11415253.08	−385.9
β-CD-Cl$^-$	PM3	−214.14	−6082.82	−6529.79	−232.8
	B3LYP/3-21+g* (in vacuo)	−1201841.9	−11154227.99	−12356347.05	−277.2
	B3LYP/3-21+g* (in water)	−1201841.9	−11154228.73	−12356350.04	−279.4

Conclusions

PM3 and B3LYP/3-21+g* calculations in vacuum and in water were performed on the complexation of CDs with inorganic cations and anions. The results suggested that the complexation of CDs with the anions was more favorable than that with cations. Hydrogen bonding between the anion and CD cavity was proposed as the physical origin of such a behavior.

Acknowledgement

References

1. (a) P.A. Kollman: *Acc. Chem. Res.* **10**, 365 (1977). (b) H.-J.Schneider: *Angew. Chem. Int. Ed. Engl.* **30**, 1417 (1991). (c) K. A. Connors: *Chem. Rev.* **97**, 1325 (1997). (d) K.Muller-Dethlefs and P. Hobza: *Chem. Rev.* **100**, 143 (2000).
2. (a) R. Breslow: *Science* **218**, 532 (1982). (b) I. Tabushi: *Acc. Chem. Res.* **15**, 66 (1982). (c) R. Breslow: *Supramol. Chem.* **1**,111 (1993). (d) K. Takahashi: *Chem. Rev.* **98**, 2013 (1998). (e) A.R. Hedges: *Chem. Rev.* **98**, 2035 (1998). (f) K. Uekama, F. Hirayama, and T. Irie: *Chem. Rev.* **98**, 2045 (1998).
3. (a) R. Breslow: *Pure Appl. Chem.* **66**, 1573 (1994). (b) R. Breslow: *Acc. Chem. Res.* **28**, 146 (1995). (c) R. Breslow and S.D. Dong: *Chem. Rev.* **98**, 1997 (1998).
4. (a) Á. Buvári, L, Barcza: *J. Incl. Phenom.* **7**, 379 (1989). (b) H.-J. Schneider: *Angew. Chem. Int. Ed. Engl.* **30**, 1417 (1991). (c) M.V. Rekharsky and Y. Inoue: *Chem. Rev.* **98**, 1875 (1998). (d) L. Liu, K.-S. Song, X.-S. Li, Q.-X. Guo: *J. Incl. Phenom.* **40**, 35 (2001).
5. (a) D.W. Griffiths and M.L. Bender: *Adv. Catal.* **23**, 209 (1973). (b) I. Tabushi, Y. Kuroda and T. Mizutano: *Tetrahedron* **40**, 545 (1984). (c) Y. Inoue: *Ann. Rep. NMR Spectrosc.* **27**, 59 (1993). (d) L. Liu, W.-G. Li , Q.-X. Guo, Y.-C. Liu: *J. Incl. Phenom.***34**, 291 (1999). (e) L. Liu, Q.-X. Guo: *J. Phys. Chem. B.* **103**, 3461 (1999). (f) L. Liu, Q.-X. Guo: *J. Incl. Phenom.* **42**, 1 (2002).
6. (a) Y. Matsui and A. Okimoto: *Bull. Chem. Soc. Jpn.* **51**, 3030 (1978). (b) A. K. Yatsimirskii and A. V. Eliseev: *J. Chem. Soc. Perkin Trans. 2* 1769 (1991). (c) Y. Liu and C.C. You: *Chin. J. Chem.* **19**, 533 (2001).
7. (a) H. Schlenk and D. M. Sand: *J. Am. Chem. Soc.* **89**, 14 (1967). (b) J. F. Wojcik and R. P. Rohrbach: *J. Phys. Chem.* **79**, 2251 (1975). (c) R. I. Gelb, L. M. Schwartz, M. Radeos, and D. A. Laufer: *J. Phys. Chem.* **97**, 3349 (1983). (d) A. Hersey, and B. H . Robinson: *J. Chem. Soc. Faraday Trans. 1*. **82**, 1271 (1986). (e) Y. Yamashoji, M. Fujiwara, T. Matsushita, and M. Tanaka: *Chem. Lett.* 1029 (1993). (f) Y. Matsui, M. Ono, and S. Tokunaga: *Bull. Chem. Soc. Jpn.* **70**, 535 (1997).
8. I. Sanemasa, M. Fujiki, T. Deguchi: *Bull. Chem. Soc. Jpn.* **61**, 2663 (1998).
9. C. B. Lebrilla: *Acc. Chem. Res.* **34**, 653 (2001).
10. L. C. Ngoka, J. F. Gal, and C. B. Lebrilla: *Anal. Chem.* **66**, 692 (1994).
11. S. Lee, T. Wyttenbach, and M. T. Bowers: *Int. J. Mass Spectrom. Ion Proc.* **167/168**, 605 (1997).
12. T. Kojima, I. Kudaka, T. Sato, T. Asakawa, R. Akiyama, Y. Kawashima, K. Hiraoka. *Rapid Commun. Mass Spectrom.* **13**, 2090 (1999).
13. Gaussian 98, Revision A.7, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara,

C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, B. W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, C. E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.

14. (a) X.-S. Li, L. Liu, Q.-X. Guo, S.-D. Chu, and Y.-C. Liu: *Chem. Phys. Lett.* **307**, 117 (1999). (b) L. Liu, X.-S. Li, Q.-X. Guo, and Y.-C. Liu: *Chin. Chem. Lett.* **10**, 1053 (1999). (c) K.-S. Song, L. Liu, X.-S. Li, and Q.-X. Guo: *Res. Chem. Intermed.* **26**, 319 (2000). (d) L. Liu, X.-S. Li, and Q.-X. Guo: *J. Mol. Struct. (THEOCHEM)* **31**, 530 (2000).

(e) X.-S. Li, L. Liu, T.-W. Mu, and Q.-X. Guo: *Monatsh. Chem.* **131**, 849 (2000). (f) K.-S. Song, C.-R. Hou , L. Liu, X.-S. Li, and Q.-X. Guo: *J. Photochem. Photobiol. A.* **139**, 105 (2001).

15. (a) L. Onsager: *J. Am. Chem. Soc.* **58**, 1486 (1936). (b) M. W. Wong, M. J. Frisch and K. B. Wiberg: *J. Am. Chem. Soc.* **113**, 4776 (1991). (c) M. W. Wong, K. B. Wiberg and M. J. Frisch: *J. Chem. Phys.* **95**, 8991 (1991).

16. T.-W. Mu, L. Liu, X.-S. Li, Q.-X. Guo: *J. Phys. Org. Chem.* **14**, 559 (2001).