Articles

A Theoretical Study on Cucurbit[7]uril and Its Inclusion Complexation

ZHANG, Ke-Chun(张科春)   MU, Ting-Wei(穆廷巍)   LIU, Lei(刘磊)   GUO, Qing-Xiang*(郭庆祥)

Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

PM3 and B3LYP/3-21g* calculations were performed on cucurbit[7]uril and its complex with protonated 2,6-bis(4,5-dihydro-1H-imidazol-2-yl)naphthalene. The results agreed well with the experimental observations. It indicated that in addition to van der Waals interaction and hydrophobic effect, hydrogen bonding is also an important driving force for the molecular recognition of cucurbiturils.

Introduction

Cucurbit[n]urils (**CB[n]**), macropolycyclic compounds self-assembled from an acid-catalyzed condensation of glycoluril and formaldehyde,[1] can form inclusion complexes with a number of organic substrates in water.[2] As novel cage compounds, their rigid structures and appropriate cavities make them useful molecular receptors with great potential applications in separation techniques, catalysis, molecular sensors, and drug delivery. Usually, **CB[6]** is used in the studies because of its easy synthesis, and the driving forces for its binding are considered to be the hydrophobic effect and dipole interactions.

Very recently, Kim *et al.* reported the synthesis of **CB[5]**, **CB[7]**, and **CB[8]**.[3] These molecules, whose cavities are of different sizes, are expected to have different binding properties and therefore many potential applications. For example, though it has been shown that the cavity of **CB[6]** is too small for a modestly large substrate such as protonated 2,6-bis(4,5-dihydro-1H-imidazol-2-yl)naphthalene (**1**), it turns out that **1** can form a very stable 1:1 complex with **CB[7]**.

Scheme 1
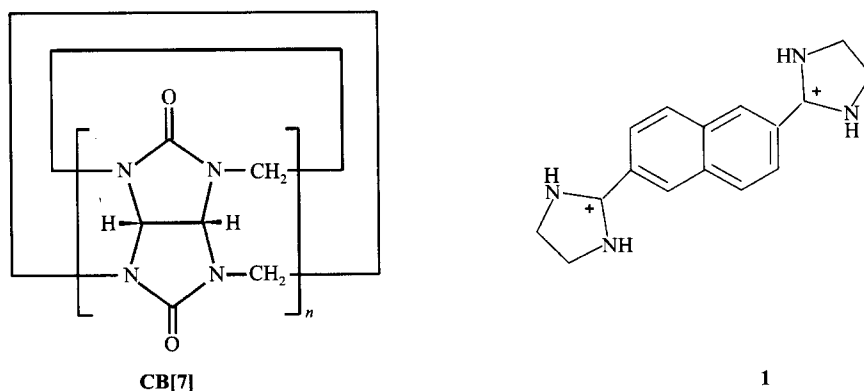
CB[7]   1

Herein, as a part of our continuing efforts in developing the theoretical host-guest chemistry,[4] we performed a quantum chemistry study on newly synthesized CB[7] and its inclusion complexation with 1. It is interesting to see that the quantum mechanic method can reproduce the experimental observations of such a large system.

Methods

All the calculations were done with GAUSSIAN 98.[5] The initial geometry of 1 was constructed with the help of MOLDEN. CB[7] was optimized by PM3 from the crystalline structure. The inclusion complex was constructed from the PM3-optimized CB[7] and 1, and several starting points were considered for the complex in which 1 was located at different places inside the cavity of CB[7]. The stationary point with the lowest energy was found. Finally, density functional theory method B3LYP/3-21g* was used to give a better estimation of the energies of the PM3-optimized species.

Results and discussion

Structure of CB[7]

The structure parameters of the PM3-optimized and crystalline CB[7] are listed in Table 1. Since both the structures are not symmetrical, only the average bond lengths, bond angles, and dihedral angles are listed, for which the denotations of elements are illustrated in Fig. 1. As seen from Table 1, the overall optimized geometry agrees well with the crystalline structure, which indicates that PM3 is applicable to such a large system.
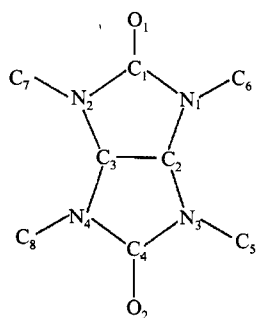

Fig. 1   Denotations of the elements of the CB[7] molecules.

Table 1   Bond lengths, bond angles and dihedral angles of the crystalline and PM3-optimized CB[7]

	Crystalline	PM3-optimized
Bond length (nm)		
C(1)—N(1)	0.1364	0.1450
N(1)—C(2)	0.1450	0.1497
C(2)—C(3)	0.1547	0.1562
C(3)—N(2)	0.1445	0.1491
C(3)—N(4)	0.1453	0.1498
N(4)—C(4)	0.1369	0.1452
C(4)—N(3)	0.1367	0.1444
C(6)—N(1)	0.1446	0.1479
C(5)—N(3)	0.1446	0.1474
C(7)—N(2)	0.1450	0.1475
C(8)—N(4)	0.1451	0.1479
O(1)—C(1)	0.1232	0.1212
O(2)—C(4)	0.1231	0.1212
Bond angel (deg)		
C(1)-N(1)-C(2)	112.1	109.2
C(3)-C(2)-N(1)	103.3	104.8
N(2)-C(3)-C(2)	103.3	104.2
N(4)-C(3)-C(2)	103.4	104.6
C(4)-N(4)-C(3)	112.1	109.5
N(3)-C(4)-N(4)	108.4	108.4
C(5)-N(3)-C(4)	122.5	122.2
C(6)-N(1)-C(1)	122.5	119.8
C(7)-N(2)-C(1)	123.0	121.9
C(8)-N(4)-C(4)	122.5	119.7
O(1)-C(1)-N(1)	125.6	125.6
O(2)-C(4)-N(3)	125.9	125.6
Dihedral angel (deg)		
C(3)-C(2)-N(1)-C(1)	3.6	13.3
N(2)-C(3)-C(2)-N(1)	4.2	15.6
N(4)-C(3)-C(2)-N(1)	118.4	110.3
C(4)-N(4)-C(3)-C(2)	3.8	14.2
N(3)-C(4)-N(4)-C(3)	4.2	8.2
C(5)-N(3)-C(4)-N(4)	170.3	162.2
C(6)-N(1)-C(1)-N(2)	166.9	147.7
C(7)-N(2)-C(1)-N(1)	170.4	161.0
C(8)-N(4)-C(4)-N(3)	167.5	152.1
O(1)-C(1)-N(1)-C(2)	175.7	171.6
O(2)-C(4)-N(3)-C(2)	175.8	173.9

Interestingly, although the PM3-optimized CB[7] is not fully circular, it is much more symmetric than that of the crystalline structure. The behavior might be caused by the lattice packing and hydration waters in the crystal environment, which can significantly distort the macrocyclic molecules from their most stable conformations in gas phase. Apparently, the free cucurbituril molecules in gas phase are expected to be less twisted

than their crystalline structures and consequently be more symmetric and circular. The symmetric and circular shape is also expected to be dominant for cucurbiturils in solution because unlike crystal, the solution provides a homogenous environment to the molecules in it. Thus, the PM3-optimized structure might better reflect the structure of **CB[7]** in the gas phase or in solution.

Inclusion complex

The PM3-optimized geometry of the complex of **CB[7]** with **1** is shown in Fig. 2, and the key features of the complex are summarized in Table 2.
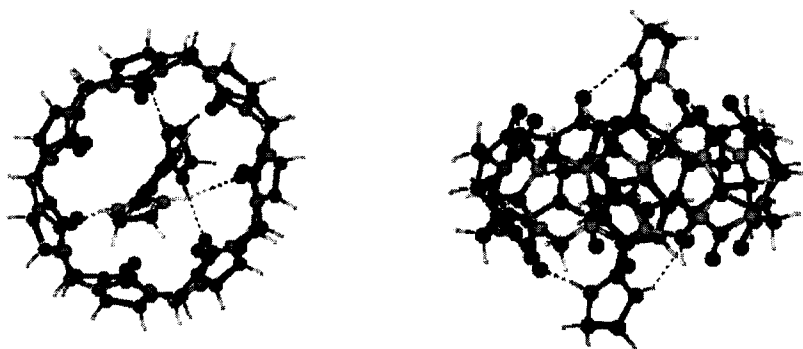

Fig. 2 PM3-optimized structure of the complex of **CB[7]** with **1**.

Table 2 PM3 calculation results for the host and guest molecules

Species	Heat of formation (hartrees)	HOMO (eV)	LUMO (eV)	Stabilization energy upon complexation (kJ/mol)
1	0.64700	− 0.55733	− 0.28512	—
CB[7]	− 0.57237	− 0.35203	0.01719	—
Complex	− 0.06882	− 0.46929	− 0.18566	− 376.29

From Fig. 2, it can be seen that the calculated structure is in good agreement with the prediction from the properties of the host and guest molecules. As known, the center of the cucurbiturils constitutes a lipophilic region, while the two portals laced with carbonyl groups are lipophobic. Therefore, it is expected that the naphthalene portion of **1**, which is highly hydrophobic, should be located inside the cavity. On the other hand, the protonated dihydroimidazole rings, which are very hydrophilic, should obviously reside outside the portal of the host molecule. Both the expectations are confirmed by the calculation. Interestingly, according to the calculated results, four hydrogen bonds are formed between **1** and the receptor, as is denoted by the distances between the hydrogens of N—H groups and the oxygens of the receptor: 0.1801 nm, 0.1818 nm, 0.2696 nm and 0.3103 nm. Thus, in addition to van der Waals interaction and hydrophobic effect,[1] it is clear that hydrogen bonding can also be an important driving force for the inclusion complexation of cucurbiturils.

Density functional theory calculation

In Table 3 the calculation results is listed with the density functional theory B3LYP/3-21g* method. Comparing Table 3 with Table 2, we can see that though there is some difference between the calculation results by PM3 method and B3LYP/3-21g* method, their results are qualitatively the same. Thus, it is expected that PM3 is at least qualitatively reliable in the study of the inclusion complexation of cucurbiturils. This information is important, because (1) the size of the cucurbituril complexes is too large for DFT methods at the present stage, and (2) as the substrates of cucurbiturils are usually organic cations,[2] the molecular mechanic methods might have difficulty in modeling the system. Thus, PM3 represents a feasible and reliable method to be used in the theoretical study of cucurbiturils at a level of quantum mechanics.

Table 3   B3LYP/3-21g* results based on PM3 optimized structure

Species	Heat of formation (hartrees)	HOMO (eV)	LUMO (eV)	Stabilization energy upon complexation (kJ/mol)
1	− 834.45984	− 0.46812	− 0.32407	−
CB[7]	− 4188.90617	− 0.22535	0.03850	−
Complex	− 5023.58663	− 0.35625	− 0.20097	− 578.68

Conclusion

PM3 is a feasible and reliable method to be used for the study of cucurbiturils. Modeling with PM3 on cucurbit[7]uril can well reproduce the X-ray structure. In the system of the complex of cucurbit [7] uril with 2,6-bis(4,5-dihydro-1H-imidazol-2-yl)naphthalene, the calculation indicates that in addition to van der Waals interaction and hydrophobic effect, hydrogen bonding is also an important driving force for the inclusion complexation.

Acknowledgement

References

1   (a) Freeman, W. A.; Mock, W. L.; Shih, N. Y. J. Am. Chem. Soc. **1981**, 103, 7367.
    (b) Cintas, P. J. Inclusion Phenom. **1994**, 17, 205.
2   (a) Mock, W. L.; Shih, N. Y. J. Org. Chem. **1983**, 48, 3618.
    (b) Mock, W. L.; Shih, N. Y. J. Am. Chem. Soc. **1988**, 110, 4706.
    (c) Mock, W. L.; Shih, N. Y. J. Am. Chem. Soc. **1989**, 111, 2697.
    (d) Buschmann, H.-J.; Schollmeyer, E. J. Inclution Phenom. **1997**, 29, 167.
    (e) Neugebauer, R.; Knoche, W. J. Chem. Soc., Perkin Trans. 2 **1998**, 529.
    (f) Buschmann, H.-J.; Jansen, K.; Schollmeyer, E. J. Inclution Phenom. **2000**, 37, 231.
3   Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. J. Am. Chem. Soc. **2000**, 122, 540.
4   (a) Liu, L.; Guo, Q.-X. J. Phys. Chem. B. **1999**, 103, 3461.
    (b) Li, X.-S.; Liu, L.; Guo, Q.-X., Chu, S.-D.; Liu, Y.-C. Chem. Phys. Lett. **1999**, 307, 117.
    (c) Song, K.-S.; Liu, L.; Li, X.-S.; Guo, Q.-X. Res. Chem. Intermed. **2000**, 26, 319.
    (d) Liu, L.; Li, X.-S.; Guo, Q.-X. J. Mol. Struct. (THEOCHEM) **2000**, 530, 31.
    (e) Li, X.-S.; Liu, L.; Mu, T.-W.; Guo, Q.-X. Monatsh. Chem. **2000**, 131, 849.
5   GAUSSIAN 98, Revision A.7, Frisch, M.J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, A.; Cheeseman, J. R.; Zakrzewski, V.G.; Montgomery, J. A. Jr., Stratmann, R. E.; Burant, J.C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, **1998**.