A Theoretical Study on the Stereoisomerism in the Complex of Cucurbit[8]uril with 2, 6-Bis(4, 5-dihydro-1H-imidazol-2-yl)naphthalene

Ting Wei MU, Lei LIU, Ke Chun ZHANG, Qing Xiang GUO*

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

Abstract: Semiempirical PM3 and density function theory B3LYP/3-21g* calculations in vacuum and in water indicated that the "*syn*" orientation was preferred in the 1:2 complex of cucurbit[8]uril with protonated 2, 6-bis(4, 5-dihydro-1H-imidazol-2-yl)naphthalene. The π-π stacking interaction between the two substrate molecules was proposed as the physical origin of such a behavior.

Keywords: Cucurbiturils, inclusion complexation, PM3, B3LYP, π-π stacking.

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]. 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-dipole interactions.
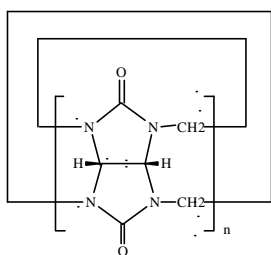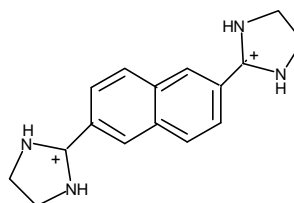
CB[n]   **1**

Very recently, Kim *et al* reported the synthesis of CB [5], CB [7], and CB [8][3]. They found that CB [8] can form 1:2 complex with protonated 2, 6-bis (4, 5-dihydro-1H-imidazol-2-yl) naphthalene **1**, which interestingly has a new type of stereoisomerism. In the complex, the two naphthalene rings are either in "*syn*" orientation with full overlap or "*anti*" orientation with partial overlap. Though the NMR study indicated that the complex stays in only one orientation in water, it remains unknown which one of the above two orientations is preferred.

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* E-mail: qxguo@ustc.edu.cn

Theoretical studies might help in illustrating which orientation is favored in energy. However, as it was mentioned that a π-π stacking interaction is involved in the system, the molecular mechanics methods might have difficulty in modeling the complex. Thus, we herein performed a quantum chemistry study on the above problem.

Methods

All the calculations were done with GAUSSIAN 98. CB [8] was optimized with PM3 from the crystalline structure. The inclusion complex was constructed from the PM3-optimized CB [8] and **1**. Both the 1:1 and 1:2 complexes were constructed, and for the 1:2 complex both the "*syn*" and "*anti*" orientations were considered. Interestingly, when different starting geometries were used, the optimized structures were always the same for every complex. Presumably, the high symmetry of the cavity and the strong interaction between the carbonyl groups of the host and the protonated imidazoles of the guest cause such a behavior.

Results and Discussion

In **Table 1** are listed the calculated energies upon complexation by PM3. The corresponding optimized structures are shown in **Figure 1**. As all the stabilization energies are negative, it can be concluded that CB [8] can form stable inclusion complex with **1**. Interestingly, though in the 1:2 complex each substrate molecule cannot stay in the most favorable place as that in the 1:1 complex because of their repulsion to each other, the stabilization energy of the 1:2 complex is roughly twice of that of the 1:1 one. This means that a strong π-π stacking interaction takes place between the two guest molecules in the 1:2 complex, as suggested by Kim *et al*[3]. It also indicates that the 1:2 complex is much easier to form than the 1:1 one, in accordance with the experimental observation.

Table 1 Stabilization energy upon complexation of the complexes (kJ/mol)

| Complex	PM3	B3LYP/3-21g* (in vacuum)	B3LYP/3-21g* (in water)
1:1	-388.7	-512.9	-513.2
1:2 "*syn*"	-748.7	-1209.8	-1211.4
1:2 "*anti*"	-712.3	-1127.2	-1131.1

From **Table 1**, the stabilization energy of the "*syn*" 1:2 complex is somewhat more negative than that of the "*anti*" one. Therefore, it seems that the "*syn*" orientation should be more favored than the "*anti*" one, which answers the question raised by Kim *et al*[3]. The result is reasonable, because it is obvious that in the "*syn*" complex the overlap between the aromatic rings is better and hence the π-π stacking interaction is stronger.

To confirm the above results, we performed density function theory B3LYP/3-21g* calculations on the PM3-optimized species, whose results are also summarized in **Table 1**. As seen, though there is some difference between the PM3 and B3LYP/3-21g* results, all the conclusions from the PM3 calculation remain correct at least qualitatively. Thus,

it seems that PM3 is a qualitatively reliable method to be used in the study of cucurbituril chemistry.

Undeniably, it is always interesting to see if the solvation has any effect on the energetics of the complexation. Thus, we calculated the stabilization energies upon complexation in water using the Onsager continuum solvation model based on the self-consistent reaction field (SCRF) method. As seen from **Table 1**, the results are very close to those calculated in vacuum. It indicates that either the solvation does not have much influence on the inclusion complexation of CB [8] with **1**, or the continuum theory of solvation cannot fully describe the solvation effect in present system[5].

Figure 1 Optimized "*syn*" (a) and "*anti*" (b) complexes of CB [8] with **1**.
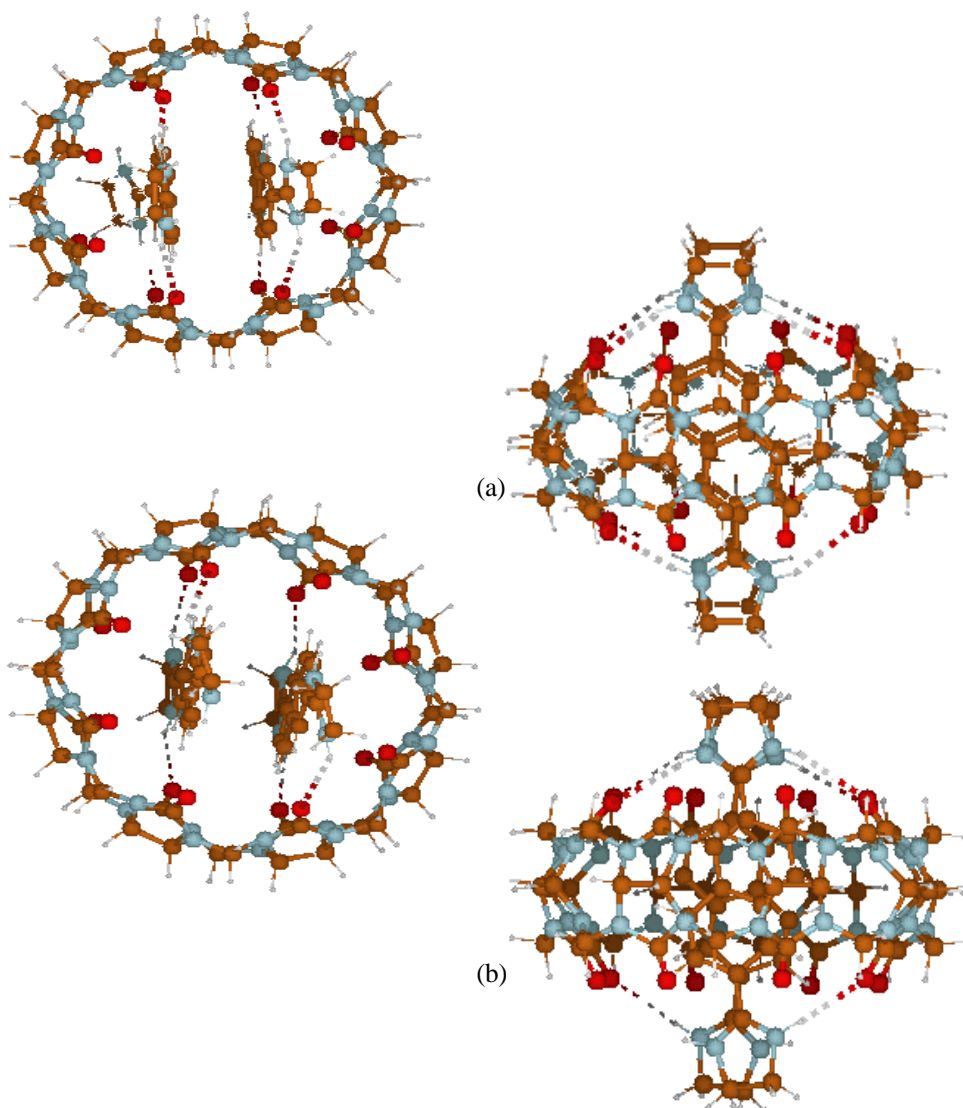
Conclusion

PM3 and B3LYP/3-21g* calculations confirm that CB [8] can form stable inclusion complexes with protonated 2, 6-bis(4, 5-dihydro-1*H*-imidazol-2-yl)naphthalene. Due to the strong π-π stacking interaction, the 1:2 complex is more favored in energy than the 1:1 one. Furthermore, the calculation indicates that the "*syn*" orientation is probably more stable than the "*anti*" one in the 1:2 complex.

Acknowledgment

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