Theoretical Studies on the Conformation of *mono*-**6-***O*-*p*-**nitrobenzoyl-**β-**cyclodextrin in Aqueous Solution**

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Abstract: The conformation of *mono*-6-*O*-*p*-nitrobenzoyl-β-cyclodextrin was studied with B3LYP/6-311g**//PM3 calculations in vacuum and in water solution. It was concluded that the *p*-nitrobenzoyl group of the molecule should be located above the primary hydroxyls of the cyclodextrin instead of being completely enclosed by the cavity. It was proposed that the behavior might be caused by the requirement of a *cis* ester bond in the self-included conformation of the molecule.

Keywords: cyclodextrin, self-inclusion, conformation, driving force, DFT.

It is well known that a substituted cyclodextrin (CD) can often form a self-included complex, in which the substituent group is incarcerated into the CD cavity[1]. The phenomenon is interesting, as the self-inclusion is a nice model of protein folding[2] and it has also been successfully used in the construction of various molecular devices[3]. Studies have showed that van der Waals force, hydrophobic effect, and electrostatic interaction are the major driving forces leading to the self-inclusion[4].

Recently, we studied the photoinduced electron transfer in supramolecular assemblies, in which *mono*-6-*O*-*p*-nitrobenzoyl-β-cyclodextrin (NBCD) was found a good electron donor[5]. Interestingly, the conformation of NBCD in aqueous solution is not as usually expected, because no self-inclusion of the *p*-nitrobenzoyl group can be detected from the 2D ^{1}H-^{1}H NOESY spectrum[5]. This behavior promoted us to perform a theoretical study on the conformation of NBCD. In fact, although many theoretical studies have been performed on CDs[6], little has been done on the structure of a substituted CD to date. In addition, the paper should also represent the first quantum chemistry study on the substituted CDs.

Experimental

All the calculations were performed with GAUSSIAN 98[7]. NBCD was optimized with PM3[8] and the energies of the optimized structures were evaluated at B3LYP/6-311g** level. The solvation effect was taken into account by using a continuum solvation model based on the

self-consistent reaction field (SCRF) method.   Three conformations of NBCD were considered. (**Figure 1**) In one conformation, the *p*-nitrobenzoyl group was far away from the cavity of NBCD so that the conformation was called an out-stretched one.   The second conformation was called a rim-covering one because in the conformation the *p*-nitrobenzoyl group was located covering the primary hydroxyls of NBCD. The third conformation was a self-included one as usually defined.

Results and discussion

In **Table 1** are listed the B3LYP/6-311g**//PM3 energies of the three conformations of NBCD, and the corresponding optimized structures are shown in **Figure 1**.   According to **Table 1**, it is obvious that the rim-covering conformation is the most stable.   Thus, self-inclusion does not occur in NBCD, which is in agreement with the experimental observations. The same results are obtained when the solvation effect is taken into consideration.

Table 1 The calculated energies of the three conformations of NBCD. (kJ/mol)

Conformation	Out-stretched	Rim-covering	Self-included
In vacuum	-12656907.4	-12656943.8	-12656831.1
In water	-12656913.2	-12656950.4	-12656835.0

Figure 1 The three optimized conformations of NBCD

(a)   (c)

(b)
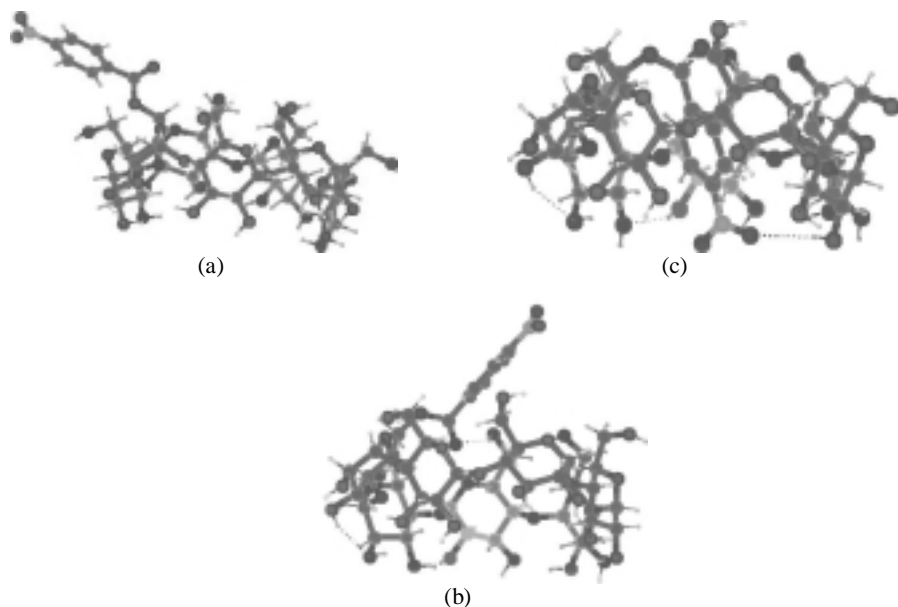
(a) Out-stretched. (b) Rim-covering. (c) Self-included.

The reason for the above behavior might be the preference of a *trans* conformation in an ester bond[9]. Herein, we calculated the energies of methyl *p*-nitrobenzoate and *tert*-butyl *p*-nitrobenzoate in their *trans* and *cis* conformations with B3LYP/6-311g** method, respectively. As seen from Table 2, the *trans* conformation is always much more stable than the *cis* one with a significant energy difference of 68.5 and 92.8 kJ/mol. These energy differences are apparently much larger than the usual binding energies of β-CD with 1,4-disubstituted benzenes[10]. Thus, NBCD cannot adopt the self-included conformation, because if it did so, it would unavoidably adopt a *cis* conformation at the *p*-nitrobenzoate ester bond, (Figure 2) and the energy contributed from the inclusion of the *p*-nitrobenzoyl group cannot compensate the loss of energy at the *cis* ester bond.

Table 2 The energies of *trans* and *cis* *p*-nitrobenzoate esters.

Energy (kJ/mol)	*Trans*	*Cis*
methyl *p*-nitrobenzoate	-1743775.6	-1743707.1
tert-butyl *p*-nitrobenzoate	-2053242.6	-2053149.8

Figure 2 The conformation of the ester bond in (a) self-included, and (b) rim-covering NBCD

(a)   (b)
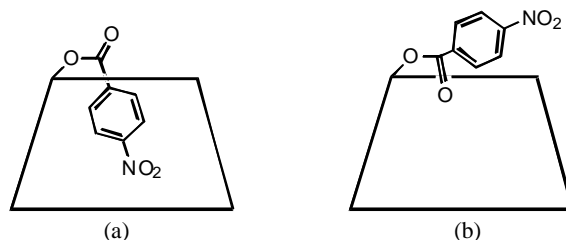
On the other hand, the adoption of the out-stretched or rim-covering conformation by NBCD simply requires a *cis* conformation at the *p*-nitrobenzoate ester bond. As the aggregation of the hydrophobic moieties is a usual behavior of organic compounds in aqueous solution, it is understandable that instead of being completely far away from the NBCD cavity, the *p*-nitrobenzoyl group is anticipated to be located closely above the β-CD moiety. Indeed, the out-stretched NBCD is calculated to be less stable than the rim-covering NBCD. This phenomenon, to some extent, mimics the folding behavior of peptides and proteins.

Conclusion

Theoretical calculations with high-level methods indicated that no self-inclusion occurs in NBCD in aqueous solution. It was concluded that the energy difference between the *trans* and *cis* ester bonds constitutes the reason why the *p*-nitrobenzoyl group only covers the primary hydroxyls of NBCD instead of being completely enclosed by the cavity.

Acknowledgment

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