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Interactions of Some Organic Compounds with α-, β- and γ-Cyclodextrins: A Molecular Mechanics Study

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In the present work, molecular mechanics calculations using amber force field were conducted to study the complexation of some organic compounds varied in structure and functional groups with α-, β- and γ-cyclodextrins to evaluate host-guest binding energies. Results indicate that guest-host interactions have a significant role as a driving force in complex formation but not the dominant one. Also mode of solute interaction with cyclodextrin in the optimal complex geometry are not the same for different types of cyclodextrins. Results also indicate that relaxation of the macrocycle structure of the host is important as a driving force for complexation with α- and β-cyclodextrins, where for γ-cyclodextrin, this factor is low.

Key Words: Molecular mechanics, Amber force field, Cyclodextrins, Inclusion complexes.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligomers of α-(1-4)-linked D-glucose units linked in a macrocyclic ring. They are tours shaped molecules with hydrophobic cavities and hydrophilic exterior edges[1, 2]. CDs can form inclusion complexes with neutral organic molecules of different size and functionality[2]. As a consequence of inclusion process, there are extensive applications of CDs in various fields[3]. The most important contribution to the complexation thermodynamics of cyclodextrins are believed to originate from hydrophobic interactions, van der Waals interactions and hydrogen bonding between host and guest[4, 5].

Molecular mechanics is an empirical method for predicting the geometry of molecular systems. It is a useful tool for understanding the guest-host complexation phenomena, as well as prediction of the optimal geometry of the complexes[6–10]. Many attempts to apply molecular mechanics calculations were made to investigate the molecular interactions in inclusion complexes of cyclodextrins.

In this work molecular mechanical modeling of the complexes of anthracene (AN), 4-nitrophenol (NP), flurbiprofen (FP) and bromodiphenhyramine (BH) (**Scheme-1**) with α-, β-, γ-cyclodextrins will be examined using amber force fields[11]. These computational results predict the optimal structure and geometry of the complexes and estimate the binding energy between guest and host. The results obtained were compared with literature values of the formation constants of these complexes.

Theoretical Methods

The calculations were performed with Hyperchem® (release 6, Hyperchem Inc., Waterloo, Canada). Amber force field was used in these calculations. Partial atomic charges needed for molecular mechanics calculations were obtained by performing AM1 semi-empirical calculations[12]. Energy minimization was performed using the conjugate gradient algorithm (0.01 kcal/mol Å gradient). Different starting conformations, intended to minimize into 1 : 1 inclusion complexes, were built by systematically applying different relative orientations between guest and α-, β-, γ-CD. All starting conformations were minimized in two steps. First all atoms of CD were fixed in their positions and the guest molecule was energy minimized. Then the whole inclusion complex was minimized (CD was allowed to relax). All minimizations were done by applying a dielectric constant of 78 (water environment).

The nonbonded interaction between the guest and cyclodextrin, or binding energy, $E_{binding}$, was obtained as[8-10]:

$$E_{binding} = E_{guest:CD} - (E_{isolated\ guest} + E_{isolated\ CD}) \quad \ldots (1)$$

The terms on the right hand side represent the potential energy of the guest : CD system, in addition to the sum of potential energies of isolated guest and cyclodextrin in the same conformations (terms in brackets).

Contribution of the relaxation of CD macrocycle to the binding energy was calculated as follows:

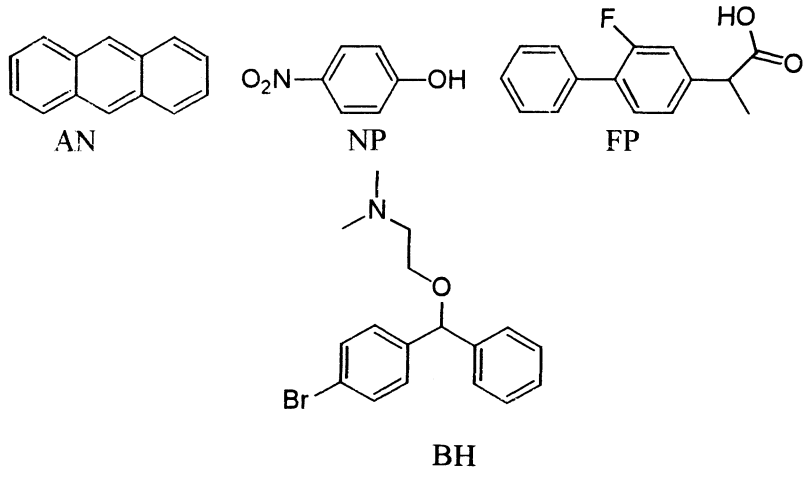
$$\%\ \text{relaxation} = (E_{free\ CD} - E_{restrained\ CD})/E_{free\ CD} \cdot 100\% \quad \ldots (2)$$

where $E_{free\ CD}$ is the binding energy obtained from calculation of the complex when the CD is totally free during minimization, and $E_{restrained\ CD}$ is obtained when CD is totally restricted.

RESULTS AND DISCUSSION

The binding energy of the most probable complex geometry for each solute obtained through molecular mechanical modeling (Amber force field) is presented in Table-1. For each solute two values of binding energy are given; one corresponds to rigid CD structure maintained through minimization process and the other for free CD.

The most probable structures of NP with α-, β-and γ-CD complexes are presented in Fig. 1. It appears that the geometry of NP : α-CD complex involves partial inclusion of NP into the cavity where the nitro group remains outside. However, there is complete inclusion of the guest in the case of β- and γ-CD, where the nitro group probably interacts with the primary hydroxyl groups suited at the narrow rim. This is apparently due to small cavity of α-CD compared to β- and γ-CD. Although the mode of inclusion is similar in β- and γ-CD, the obtained value of binding energy is higher for β-CD (≈ 5.0 kcal/mol), and this is attributed to larger size of the cavity in γ-CD, since nonbonded interactions are strongly depend on distance. There is quite similarity in binding energy trend (β-complex > α-complex > γ-complex) and the correspondence complex formation constant[5], which suggest the significance of the nonbonded interaction between the guest and the host in these type of complexes.



Scheme 1. Structures of guest molecules

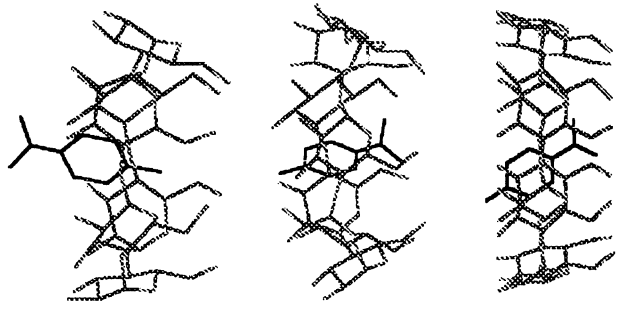


Fig. 1. Side views of optimal configurations of NP : α-CD complex (a), NP : β-CD complex (b) and NP : γ-CD complex (c).

AN is partially included in α-CD cavity, where a higher degree of penetration occurrs in β- and γ-CD (Fig. 2). AN is almost perpendicular to the cavity axis in β-CD and with a slope in γ-CD. As in NP, the increase in binding energy of AN with the examined CDs correlates well with the experimental values of formation constant (Table-1).

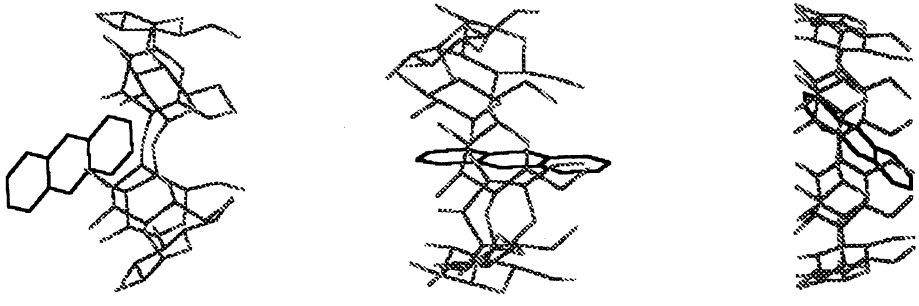


Fig. 2. Side views of optimal configuration of AN : α-CD complex (a), AN : β-CD complex (b) and AN : γ-CD complex (c).

TABLE-1
BINDING ENERGIES (kcal/mol) OF THE MOST PROBABLE STRUCTURES OF GUEST : CD COMPLEXES

Compound	Binding energy (kcal/mol)[a]			Binding energy (kcal/mol)[b]			log K[c]		
	α-CD	β-CD	γ-CD	α-CD	β-CD	γ-CD	α-CD	β-CD	γ-CD
NP	-15.64	-17.48	-15.81	-19.76	-21.44	-16.28	2.25	2.48	1.79
AN	-17.46	-21.42	-20.77	-19.79	-28.27	-20.84	1.87	3.31	2.78
FP	-15.63	-26.09	-25.56	-24.82	-30.77	-26.78	1.84	3.29	3.48
BH	-20.07	-30.44	-28.88	-30.34	-37.28	-29.45	3.13	3.33	3.39

[a]Geometry of CD is totally restricted during calculation [b]Geometry of CD is free [c]Ref 5.

Results indicate that binding energy of FP with β-CD > γ-CD > α-CD where the order of complex formation constant is γ-CD > β-CD > α-CD. Fig. 3 depicts side view of the optimal configurations of FP : CD complexes. It seems that FP behaves in different manner in interaction with different cyclodextrins. In α-CD, the carboxyl group of FP interacts with hydroxyl groups in the wide rim, where the biphenyl is located outside the cavity. In Both β- and γ-CDs, it appears that the carboxyl group interacts with the hydroxyl groups in the narrow rim, probably by hydrogen bonding forces, where the fluoro interacts with the secondary hydroxyl groups in the wide rim. This proves the significance of dipolar interactions to complex stability.

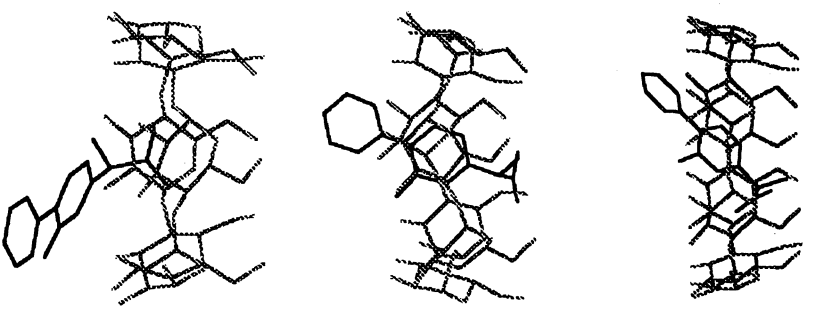


Fig. 3. Side views of optimal configurations of FP : α-CD complex (a), FP : β-CD complex (b) and FP : γ-CD complex (c).

The results of geometry optimization through molecular mechanical modeling of BH complex indicate (Fig. 4) that optimal interaction involves bromophenyl included in α-CD cavity letting the amine chain and phenyl outside the cavity. For β-CD, the bromophenyl is also included, but there was room for partial inclusion of the other phenyl group. For γ-CD, the amine and phenyl were included in the cavity, letting the bromophenyl near the wide rim. It can be concluded that in spite of the similarity of α, β- and γ-CD structures, the size of the cavity is essential in deciding the most probable complex structure.

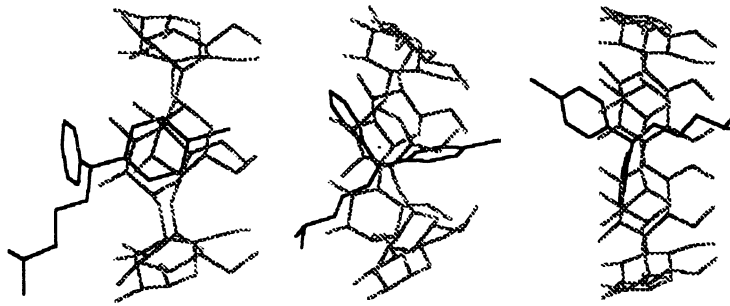


Fig. 4. Side views of optimal configurations of BH : α-CD complex (a), BH : β-CD complex (b) and BH : γ-CD complex (c).

As in FP the binding energies of BH with CDs do not correlate well with the complex formation constants, this is, may be due to presence of different polar functional groups that stabilize complex not just for intermolecular interactions with CD but with water. In this theoretical work the non-specific interactions between guest or host with water molecules were included in calculation, while the specific interactions were not included. Also FP and BH bear a flexible structure, that the entropic effects must be considered in complex stability.

The contribution of relaxation of the CD macrocycle to binding energy is reproduced in Fig. 5. It is observed that the relaxation of the α, β- and γ-CD macrocycles contribute roughly about 25, 20 and 2% respectively, to the overall binding energy between the examined solutes and CDs. this is quite significant in stabilizing α- and β-CD complexes, but insignificant in γ-CD complex stability.

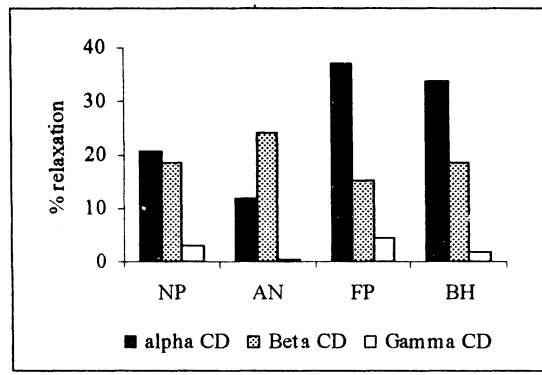


Fig. 5. % Contribution of the relaxation of CD macrocycle to the binding energy.

To ascertain whether the guest-host interaction is the major driving force for solute: β-CD complexation in aqueous solution, a plot of log K against binding energy is depicted in Fig. 6 for all solutes examined in this work it appears no one-to-one correspondence between log K and binding energy. This suggests that through there is a general increase in complex stability with increase of binding

energy, hence, the guest-host interaction does have a role to play, it is by no means the sole driving force for complexation, while hydrophobic, desolvation, entropic factors and geometric fit are also important.

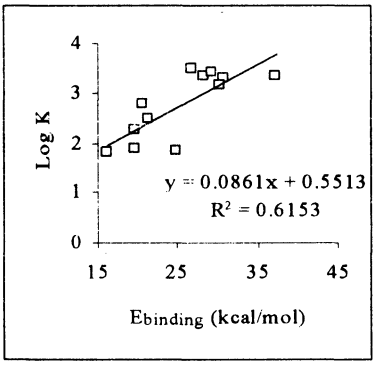


Fig. 6. Plot of log K *vs.* binding energy.

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