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Molecular modeling methodology of β-cyclodextrin inclusion complexes

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Abstract

A docking approach for molecular mechanics optimization of β-cyclodextrin complexes is described. Because of the specific geometry of the cyclodextrins and the class of guests (relatives of *tert*-butyl benzene), the guest molecule is moved along a vector going through the middle of the cavity. This vector is perpendicular to the mean plane of the acetal oxygen atoms that link the glucose units. At each step along this vector, the geometry of the bimolecular assembly was optimized to give a minimum in the molecular mechanics steric energy. As expected, the energy decreases as the guest molecule enters the cyclodextrin cavity, and again increases as the guest exits from the other side of the cavity. Rotation of the guest within the cavity prior to energy minimization did not result in lower energies; the minimization process found the best rotational orientation of the guest. On the other hand, it was necessary to drive the guest along the vector; the energy minimization process did not pull the guest into an optimal depth of penetration into the cavity. The binding energies calculated at two different dielectric constants were almost identical, indicating that the complex formation is stabilized by dispersive or Van der Waals forces and not electrostatic (dipole–dipole or hydrogen bonding) forces.

Keywords: Guest–host interaction; Inclusion complex; MM3; Molecular mechanics calculation

1. Introduction

Cyclodextrins, especially cycloamyloses, are receiving increased attention for their ability to form inclusion complexes. Their unique bell-shaped structures with hydrophilic groups on the exterior and a hydrophobic cavity renders them very useful in many areas of chemistry, biochemistry and pharmacology [1]. They also serve as very relevant models for complexes of polymeric amylose. Cyclodextrins are relatively easy to crystallize, compared to other oligosaccharides of comparable size, and much useful information has been obtained from such studies. Still, computer modeling studies of cyclodextrin complexes are an important avenue to the understanding of the mechanism of complex formation, for interpretation of the more limited data from experiments in solution, and for extrapolation to amylose which has, to date, yielded far fewer of its structural secrets to experiment.

Of the available computational approaches, ab initio methods, especially with suitably high levels of theory and large basis sets, are limited to molecules no bigger than monosaccharides with state-of-the-art

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supercomputers [1]. Semiempirical quantum mechanical methods can accommodate cyclodextrin complexes when sufficient computational resources are available. However, they have not proven adequate to reproduce various aspects of carbohydrate structures and energies within the relatively small ranges required for making selections among various conformers, and apparently should be avoided for such calculations [1,2]. Molecular mechanics, on the other hand, can easily handle structures as large as cyclodextrin complexes, even on personal computers. Related to this problem, there are many computational studies of modeling crown ether complexation [2]. This method has been able to reproduce a large number of carbohydrate structures and has been applied to cyclodextrin complexes previously by other workers [3]. The present study is unique, as far as we know, in that the complexes were fully energy minimized at each stage of the study with MM3. Crystalline cyclodextrin complexes often have substantial differences in their molecular conformation, when complexed, that depend on the exact guest. To us, that indicates a requirement for relaxation of the cyclodextrin molecule during modeling studies, even though that is computationally more expensive.

As part of a wider project on nonbonding interactions and enantiomeric recognition, we were confronted with the problem of finding the energy minima on the potential energy surface of enantiomeric guests in cyclodextrin hosts. The compounds of interest in our studies have a hydrophobic phenyl moiety and a bulky group containing a hydrophilic peptide linkage. Because of the large number of degrees of freedom, numerous local minima are possible in the modeling of such complexes. In the present work, the degrees of freedom are reduced somewhat by our choice of *tert*-butyl benzene as a guest. It has several characteristics in common with the molecules of more specific interest, but has no important internal degrees of freedom. Still, the energy differences of binding different enantiomers inside the cyclodextrin cavity are very small (usually below 1 kcal mol^{-1}) so a systematic approach is necessary to get as close as possible to the global minimum.

2. Methods

In our approach, there are three main variables that define the relationship of the guest to the cyclodextrin. The first is the orientation of guest, namely whether the guest entered the larger side of the cavity (the side with the O2 and O3 hydroxyl groups) with the *tert*-butyl group first, or the benzene ring was first. Secondly, the depth of penetration must be varied. The rotational orientation of the plane of the guest's benzene ring with respect to the host's glucose residues is an obvious concern, as is the angle of the plane of the benzene ring to the mean plane of the linkage oxygen atoms of the cyclodextrin.

In the present work, the rather planar shape of the guest and the somewhat cylindrical shape of the host conspire to hold the guest nearly perpendicular to the plane of the cyclodextrin linkage oxygens. Therefore, only the depth of penetration and rotational orientation of the guest are important variables. For the first variable, the guest was initially placed at a distance of 20 Å from the mean plane of the linkage oxygen atoms. It was centered on a vector perpendicular to that mean plane, and was moved in decreasing increments, phenyl group first, toward the center of the cavity. At each step the entire structure was optimized without any restriction or constraint. Once the guest began to penetrate the host, the increments were reduced to 0.5 Å, threading it more slowly through the cavity of the host. Then, the increments were increased and the guest moved away from the host. When the guest had been translated to 20 Å beyond the plane of the linkage oxygens, the procedure was terminated. It was then repeated with the benzene group first.

Models of all compounds were created and visualized with CHEM-X [4] running on a 486/66 IBM PC compatible computer. All energies and computed geometries were obtained with MM3(92) [5] running on a VAX station 4000/90 or a VAX 7620, using the default energy-based termination criterion (0.00008n kcal mol^{-1}, where n is the number of atoms). All calculations were performed at dielectric constants of both 3.0 and 80.0.

The limitations of accuracy for our models must be acknowledged. The calculations were for molecules in the gas phase, neglecting the fact that complex formation results from differences in solvation energies of the host and the guest, compared with the solvation energies of the host–guest complex. There are convincing evidences for reorganization caused by

guest hydrogen bonding to the solvent molecules [6]. Furthermore, the energy differences between the initial (or final) widely separated species and the optimized complex are likely to be exaggerated compared to the experimental free energies of complex formation in solution. Also, the energies of carbohydrate models depend to a certain degree on the orientations of the hydroxymethyl and hydroxyl groups. A total of 328 combinations of 3-fold staggered orientations is possible, a number beyond any hope of explicit consideration. In the present work, only a single combination of the group orientations was considered. The same initial conformation of the cyclodextrin was used for each minimization. This provided a consistent indicator but strongly reduces the chance of hydrogen bond formation between the host and the guest. Fortunately, the evidence from crystallography suggests that hydrogen bond formation to larger guests is fairly rare, so this should be a good approximation.

3. Results and discussion

The results are presented in Fig. 1 and Fig. 2 where the calculated energy is plotted as a function of the distance between host and guest molecules. As the guest molecule approaches the cyclodextrin the energy of the system begins to decrease. Once inside the cavity there is a range of positions that it can assume with rather close energy values, indicating

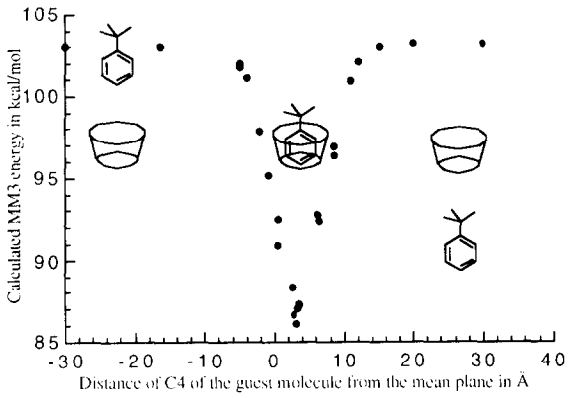

Fig. 1. Final steric energy of the complexes, as a function of the distance of the C4 of the guest molecule to the mean plane of the oxygen atoms, linking the glucose units with phenyl ring down.

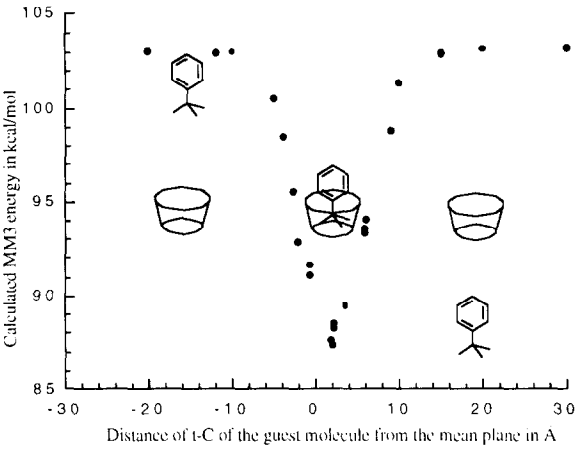

Fig. 2. Final steric energy of the complexes, as a function of the distance of the guest molecules to the mean plane of the oxygen atoms, linking the glucose units with *tert*-butyl group down.

that it has some freedom of movement within certain limits [7,8]. Moving it deeper inside and away from the cavity, the energy again increases reaching an initial value.

The binding energies obtained from the difference of the structure with lowest steric energy (when the guest molecule is in the cyclodextrin cavity) and when the two are separated are 17.1, 19.3, 15.8 and 15.5 kcal mol^{-1}, respectively. The value of the binding energy obtained both at dielectric constant of 3 and 78 is about the same, indicating that only non-hydrogen bonding interactions are involved. The model compound does not have any groups that could get involved in hydrogen bonding interactions, so this result is not surprising. Also, the binding energies confirm the fact that the guest molecule preferentially (by about 2 kcal mol^{-1}) enters with the phenyl group first in the larger opening of the cavity.

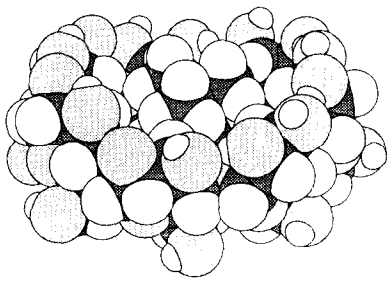

Fig. 3. Structure of the MM3 optimized β-cyclodextrin inclusion complex with *tert*-butylbenzene.

Table 1
Some structural characteristics of the MM3 optimized complexes.

		Ref.[8]	D030	b-CD	D035
			e = 3	e = 3	e = 78
Primary OH	< 0	-64.09			
torsion angle	> 0	64.33	65.19	65.56	67.53
Chair conformation	C1	36.28	50.21	50.03	50.30
(flap angle)	C4	37.78	50.79	50.07	51.50
Out-of-plane deviation of	< 0	-0.05	-0.22	-0.03	-0.17
linkage oxygens	> 0	0.05	0.29	0.04	0.13
Acetal oxygen	< 0	-3.11	-9.55	-1.80	-6.68
torsion angles	> 0	2.66	12.13	1.20	8.43
Orthogonality of glucose	< 0	-7.34	-9.78	-11.35	-20.52
plane from mean plane	> 0	5.56	20.30	14.40	1.10
Angle of deformation	< 0	-2.44	-4.30		-7.20
from C7 symmetry	> 0	2.14	4.60	0.57	4.93
Distance from macrocycle centroid to glucose centroid		5.69	5.63	5.72	5.64

The guest in the structure with minimal energy was rotated inside the cavity in order to find an even more stable structure of the complex. All obtained energies were within a very limited range indicating that MM3 forces the guest molecule at a angle with minimal steric energy, no matter what the initial position was.

The structure with minimal energy is presented in Fig. 3, showing that the phenyl group is well into the cavity of β-cyclodextrin. Some other characteristics of the obtained structures and the mean values for solid-state β-cyclodextrin complexes are presented in Table 1.

It has been established that symmetry breaking lowers the energy of these molecules and that the highly symmetric cyclodextrin structures, portrayed in the literature, are to be regarded as time-averaged structures only [9]. Our optimized structures clearly support this assertion. The optimized cyclodextrin without a guest inside is much more symmetrical than the ones with the guest inside. The values of some of the parameters for our optimized complexes are different than the average values, but they are not outside the range of recorded data.

It has been suggested that in guest–host complexes, the size of the best guest is about 20% smaller than the CPK models [10]. More recent results show the cavity should be somewhat larger i.e. the attraction between two neutral atoms is maximum at a separation 1.24 times larger than the sum of their Van der Waals radii [11]. Thus, the attraction between two hydrogen atoms is maximal at a distance of 2.815 Å, and between an oxygen and a hydrogen atom at a distance of 3.047 Å. Table 2 lists the distances between the guest hydrogen atoms to the closest host hydrogen and oxygen atoms in the minimized complex. Only one distance in each series is significantly below the optimum value, and a number of them are very close to this ideal distance contributing to the stabilization energy of the whole complex.

4. Conclusion

The study of cyclodextrin inclusion adducts indicates that the initial position of the guest molecule is critical in the molecular modeling of such complexes. The calculations clearly indicate that MM3 can find a local minimum for a great number of positions of the

Table 2

H···HH	2.174	2.263	2.386	2.451	2.471	2.654	2.691	2.792	2.873	2.888	2.895	2.927	2.937	3.003	3.082 3.202
H···O	2.832	3.003	3.063	3.245	3.350	3.365	3.503								

guest into the host molecule, and just inserting the guest inside the cavity in the hope that the program will place it properly i.e. find the global minimum is erroneous. The distance of the guest molecule from the mean plane, formed by the linker oxygen atoms in cyclodextrin, is critical in the search of the global minimum. For this reason, it is important to optimize the whole complex as the guest molecule is inserted deeper and deeper into the cyclodextrin cavity. On the other hand, the rotation of the guest inside the cavity can be accomplished by MM3 and for symmetrical, monosubstituted benzenes doesn't seem to justify a systematic rotational search.

References

[1] (a) S.E. Barrows, F.J. Dulles, C.J. Cramer, A.D. French and D.G. Truhlar, Carbohydr. Res., 188 (1995) in press; (b) See for example, M.L. Bender and M. Komiyama, Cyclodextrin Chemistry, Springer-Verlag, New York, 1978, p. 205; R.J. Clarke, J.H. Coates and S.F. Lincoln, Inclusion complexes of the cyclomalto–oligosaccharides (cyclodextrins), in R.S. Tipson and D. Horton (Eds.), Advances in Carbohydrate Chemistry and Biochemistry, Academic Press, New York, 1988; J.F. Stoddart, Angew. Chem. Int. Ed. Engl., 31 (1992) 846.

[2] (a) K. Guntertofte, J. Palm, I. Patterson and A. Stamvik, J. Comput. Chem., 12 (1991) 200; (b) Y.J. Zheng, S.J. Le Grand and K.M. Merz Jr., J. Comput. Chem., 13 (1992) 772; (c) R.B. Schirts and L.D. Stolworthy, J. Incl. Phenom. Mol. Rec. Chem., 20 (1995) 297.

[3] (a) K.B. Lipkowitz, J. Org. Chem., 56 (1991) 6357; (b) A.D. French and M.K. Dowd, J. Mol. Struct. (Theochem), 286 (1993) 186.

[4] Chem-X is available from Chemical Design Inc., 200 Route 17 South, Suite 120, Mahwah, NJ 07430.

[5] N.L. Allinger, Y.H. Yuh, and J.H. Lii, J. Am. Chem. Soc., 111 (1989) 8551. The MM3 program is available for academic users from QCPE.

[6] Y. Inoue, T. Hakushi, Y. Liu, L.-T. Tong, B.-J. Shen and D.-S. Jin, J. Am. Chem. Soc., 115 (1993) 475.

[7] V. Tran, M.M. Delage and A. Buléon, J. Incl. Phenom. Mol. Rec. Chem., 14 (1992) 271.

[8] M.C. Godet, V. Tran, M.M. Delage and A. Buléon, Int. J. Biol. Macromol., 15 (1993) 11.

[9] K.B. Lipkowitz, K. Green and J. Yang, Chirality, 4 (1992) 205.

[10] F. Diederich, F. Angew. Chem. Int. Ed. Engl., 100 (1988) 362.

[11] J. Israelachvili, Intermolecular and Surface Forces, 2nd edn., Academic Press, London, 1992.