THEORETICAL AM1 STUDIES OF INCLUSION COMPLEXES OF α- AND β-CYCLODEXTRINS WITH METHYLATED BENZOIC ACIDS AND PHENOL, AND γ-CYCLODEXTRIN WITH BUCKMINSTERFULLERENE

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ABSTRACT

Semiempirical AM1 calculations have been performed on the inclusion complexes of α- and β-cyclodextrin with benzoic acid and phenol and β-cyclodextrin with methylated benzoic acids in the "head first" and "tail first" positions. The results show that α-cyclodextrin complexes with phenol and benzoic acid guests in the "head first" position are more stable than in the "tail first" position, while β-cyclodextrin complexes with the same guests prefer the "tail first" position. The preferred orientation for β-cyclodextrin with methylated benzoic acids is determined by the position of the methyl substituent(s). In general, para-methyl benzoic acid derivatives prefer the "tail first" position. γ-cyclodextrin forms a slightly unstable 1:1 complex with C_{60} (3.4 kcal/mol), but two γ-cyclodextrins provide enough stabilization by about 10 kcal/mol to "cage-in" the C_{60}.

1. INTRODUCTION

The hydrophobic character of the central cavity of cyclodextrins (CDs) enables them to form inclusion complexes with many different molecules. As a result, many poorly water soluble drugs can be administered in solution in the complex form by taking advantage of the well-established low toxicity of most CDs. Therefore, investigations of the driving forces of complexation and the structures of inclusion complexes are very important. Modern computers with graphical capabilities are valuable tools for studying the structures of inclusion complexes.

Various investigators have applied theoretical methods such as molecular mechanics, molecular dynamics, and CNDO with fixed-geometry to CD inclusion complexes. There are very few quantum mechanical calculations on CDs using the most advanced semi-empirical method, AM1 [1] with fully unrestricted geometry optimization [2].

2. MATERIALS AND METHODS

Phenol, benzoic acid, and methylated benzoic acids were studied using the MOPAC programs on a Tektronix CAChe workstation. The AM1 fully optimized geometries

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with no symmetry constraints for α-CD and β-CD were taken from our previous calculations [2]. AM1 calculations on all the inclusion complexes of α- and β-CD with phenol and benzoic acid, β-CD with methylated benzoic acids, γ-CD, buckminsterfullerene, γ-CD dimer, and γ-CD with buckminsterfullerene were performed using a modified version of the AMPAC program from QCPE [1]. In all cases, considerable computer power is required in order to obtain reliable fully optimized structures.

3. RESULTS AND DISCUSSION

AM1 calculations for the inclusion complexes of α- and β-CD with phenol and benzoic acid and β-CD with methylated benzoic acid have been performed for the "head first" and "tail first" orientations (Fig. 1).

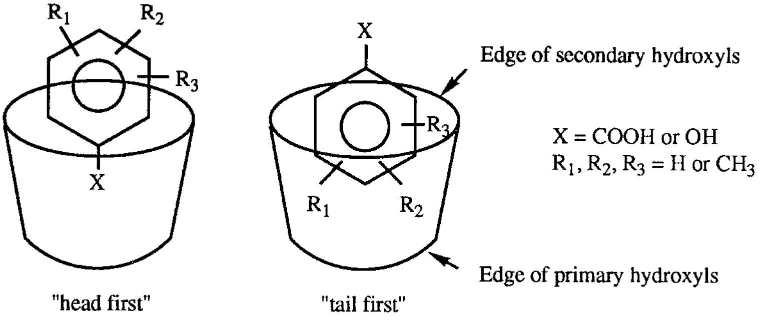

Figure 1. The two possible penetration pathways for benzoic acid, phenol and methylated benzoic acids.

The calculated partition coefficients, volume, surface area, and ovality are based on our previously developed BLOGP program [3]. These properties, the heats of formation, dipole moment, HOMO energy, and the lengths of the guest molecules are listed in Table 1. As expected, increased molecular complexity introduced by homologue extension increases the lipophilicity of the benzoic acid and decreases the water solubility. From our previous studies [2], α-CD and β-CD have calculated heights of 6.2-6.5 Å, heats of formation -1414.0 and -1647.5 kcal/mol, dipole moment 10.4 and 7.5 Debye, and HOMO energies of -10.21 and -10.35 eV respectively.

The AM1 heats of formation, dipole moment, HOMO energy, and stabilization energy for different inclusion complexes in the "tail first" and "head first" positions are shown in Table 2. From Table 2, we can draw a few conclusions: (1) phenol and benzoic acid form more stable complexes with α-CD in the "head first" position and form more stable complexes with β-CD in the "tail first" position; (2) among o-, m-, and p-methyl benzoic acid, o- and m-methyl benzoic acid form more stable complexes with β-CD in the "head first" position and p-methyl benzoic acid forms a more stable complex with β-CD in the "tail first" position; (3) among all the dimethyl benzoic acids, 2,3-dimethyl, 2,5-dimethyl, 2,6-dimethyl, and 3,4-dimethyl benzoic acid form more stable complexes with β-CD in the "head first" position, and 2,4-dimethyl and 3,5-dimethyl benzoic acid form more stable complexes with β-CD in the "tail first" position; (4) of the trimethyl benzoic acids, only 2,3,5-trimethyl, 2,4,5-trimethyl and 3,4,5-trimethyl benzoic acids form stable complexes with β-CD. The first one prefers the "head first" position and the others prefer the "tail first" position.

TABLE 1. Heats of formation (ΔH_f, kcal/mol), dipole moment (D, Debye), HOMO energy (eV), the calculated partition coefficients, volume (V, Å^3), surface area (S, Å^2), ovality (O), and length (Å) of phenol, benzoic acid, all the possible one, two, and three methylated benzoic acids (BA).

Compound	ΔH_f	D	HOMO	LogP	V	S	O	Length
phenol	-22.2[a]	1.2	-9.11	1.30[b]	91.84	120.50	1.22	5.662
benzoic acid (BA)	-68.0[a]	2.4	-10.08	1.61[b]	110.74	143.02	1.28	7.012
2-methyl BA	-73.6	2.4	-9.73	2.04	126.83	160.07	1.31	7.077
3-methyl BA	-75.6	2.7	-9.75	2.02[b]	127.39	164.42	1.34	7.011
4-methyl BA	-75.8	2.8	-9.82	2.02[b]	127.49	164.57	1.34	7.922
2,3-dimethyl BA	-79.5	2.6	-9.55	2.39	143.45	180.84	1.36	7.039
2,4-dimethyl BA	-81.5	2.7	-9.63	2.43	143.57	181.82	1.37	7.981
2,5-dimethyl BA	-81.3	2.4	-9.45	2.45	143.60	181.77	1.37	7.075
2,6-dimethyl BA	-79.3	2.0	-9.53	2.42	143.42	179.57	1.36	7.024
3,4-dimethyl BA	-81.0	3.0	-9.61	2.41	143.62	182.78	1.38	7.910
3,5-dimethyl BA	-83.1	2.7	-9.58	2.47	144.18	185.98	1.40	7.009
2,3,4-trimethyl BA	-86.0	2.9	-9.50	2.74	159.76	199.18	1.40	7.989
2,3,5-trimethyl BA	-87.2	2.6	-9.33	2.81	160.01	201.57	1.41	7.052
2,3,6-trimethyl BA	-85.8	2.1	-9.32	2.78	160.15	201.16	1.41	7.013
2,4,5-trimethyl BA	-88.5	2.7	-9.37	2.82	160.14	201.63	1.41	7.987
2,4,6-trimethyl BA	-87.1	2.3	-9.49	2.81	160.03	200.50	1.41	7.994
3,4,5-trimethyl BA	-89.1	3.1	-9.56	2.81	160.35	202.98	1.42	7.954

[a] Experimental ΔH_f for phenol and benzoic acid are -23.0 kcal/mol and -70.3 kcal/mol (Pedley, J. B.; Rylance, G. "Sussex-N.P.L. Computer Analysed Thermochemical Data: Organic and Organometallic Compounds", Sussex University, 1977). [b] Experimental LogP values for phenol, benzoic acid, 3-methyl BA, and 4-methyl BA are 1.49, 1.95, 2.37, and 2.27 respectively (Hansch, C. and Leo, A. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley: New York, 1979).

The hydroxyl groups of phenol and carboxylate group of benzoic acid in the "head first" position in α-CD inclusion complexes could possibly form hydrogen-bond with the primary OH-s. Using cut-off criteria from Steiner and Saenger [4-7], namely a hydrogen bond is an O-H...O interaction in which the H...O distance is less than or equal to 3.00 Å and the angle at H is larger tha 90°, we found that there are two possibilities for hydrogen bonds between α-CD and phenol in "head first" position and no hydrogen bond with phenol in "tail first" position. There are three possible positions for hydrogen bonds between β-CD and phenol in the "tail first" position, and no hydrogen bonds with phenol in the "head first" position. There is one possible hydrogen bond between β-CD and benzoic acid in the "tail first" position and no hydrogen bond with benzoic acid in the "head first" position. For the inclusion complex of α-CD with benzoic acid, we found there is one hydrogen bond in both "head first" and "tail first". Beyond the hydrogen bond factor, there is a strong dipole-dipole interaction between the host and guest in the "head first" orientation of the α-CD (10.4 Debye) with benzoic acid (2.4 Debye), which is in agreement with the previous CNDO studies [8-11] which indicated that dipole moments of guest molecules are antiparallel to the dipole moment of host α-CD in the crystalline state.

TABLE 2. Heats of formation (ΔH_f, kcal/mol), dipole moment (D, in Debye), HOMO energy (eV) for AM1 optimized geometries of which are complexes of α- and β-CD with phenol and benzoic acid (BA), and β-CD with methylated benzoic acids in "tail first" and "head first" positions. The stabilization energies ($\Delta\Delta H_f$) are in kcal/mol.

Compound	$\Delta H_f^t(\Delta\Delta H_f)$	D^t	$HOMO^t$	$\Delta H_f^h(\Delta\Delta H_f)$	D^h	$HOMO^h$
α-CD + phenol	-1434.2(2.0)	8.9	-9.32	-1439.4(-3.2)	6.6	-9.28
β-CD + phenol	-1673.2(-3.5)	8.6	-9.46	-1672.6(-2.9)	8.1	-9.42
α-CD + BA	-1482.0(0.0)	5.1	-10.26	-1489.1(-7.1)	11.4	-10.08
β-CD + BA	-1716.9(-1.4)	8.3	-10.30	-1716.1(-0.6)	6.8	-10.34
β-CD + 2-Me BA	-1721.8(-0.7)	6.6	-10.03	-1728.1(-7.0)	7.2	-10.00
β-CD + 3-Me BA	-1723.4(-0.3)	8.6	-10.15	-1729.8(-6.7)	8.2	-9.99
β-CD + 4-Me BA	-1725.2(-1.9)	8.3	-10.21	-1723.5(-0.2)	8.2	-10.12
β-CD + 2,3-diMe BA	-1726.2(0.8)	6.1	-9.78	-1729.6(-2.6)	6.5	-9.74
β-CD + 2,4-diMe BA	-1735.9(-6.9)	6.8	-9.97	-1729.6(-0.6)	8.1	-9.95
β-CD + 2,5-diMe BA	-1726.8(2.0)	5.9	-9.76	-1734.0(-5.2)	6.2	-9.66
β-CD + 2,6-diMe BA	-1728.5(-1.7)	6.5	-9.85	-1730.2(-3.4)	6.4	-9.82
β-CD + 3,4-diMe BA	-1735.1(-6.6)	5.1	-9.94	-1735.9(-7.4)	7.0	-9.89
β-CD + 3,5-diMe BA	-1740.4(-9.8)	5.9	-9.98	-1738.4(-7.8)	8.1	-9.80
β-CD + 2,3,4-triMe BA	-1731.7(1.8)	7.3	-9.76	-1731.4(2.1)	5.5	-9.68
β-CD + 2,3,5-triMe BA	-1731.6(3.1)	6.5	-9.62	-1737.3(-2.6)	5.8	-9.50
β-CD + 2,3,6-triMe BA	-1729.4(3.9)	7.8	-9.62	-1727.8(5.5)	5.6	-9.35
β-CD + 2,4,5-triMe BA	-1743.9(-7.9)	3.8	-9.72	-1734.3(1.7)	6.9	-9.57
β-CD + 2,4,6-triMe BA	-1733.0(1.6)	6.8	-9.79	-1726.3(8.3)	6.5	-9.68
β-CD + 3,4,5-triMe BA	-1740.0(-3.4)	5.6	-9.87	-1737.7(-1.1)	7.8	-9.59

The guest HOMO energies are somewhat affected by complexation. For example isolated 3,4,5-trimethyl benzoic acid has a HOMO energy of -9.56 eV, while in "tail first" and "head first" complexes with β-CD the HOMO energies are -9.87 and -9.59 eV, respectively.

The reasons for the orientational preferences of the methylated guests are a combination of hydrogen bonding, steric hindrance, van der Waals interactions, and hydrophobic interactions. All the mono-, di-, and trimethyl benzoic acids can form weak hydrogen bonds between the carboxylate group and the primary or secondary hydroxylic rim of the β-CD. The H-bonding affects the relative positions. Methyl substituent in the ortho and meta position cause more steric hindrance than in the para position. Since the energy of interaction between the guest and host is a van der Waals-London dispersion forces interaction, maximization of contact within the attraction distance between the benzoic acid derivatives and the β-CD cavity will enhance complexation. For increased van der Waals interaction, the 2- and 3-methyl benzoic acids would prefer the "head first" position, since when the methyl group of the guest molecule is near the primary hydroxylic rim, the distance between the cavity wall and the substrate is smaller than when it is near the secondary hydroxylic rim and consequently there is a larger van der Waals interaction. In the case of the di- and trimethyl substituted benzoic acids, a balance between the various forces will determine the optimum position.

Since the first report [12] on a water soluble γ-CD and C_{60} fullerene complex, we were intrigued by the potential structure of it. The complex was reportedly prepared by boiling aqueous C_{60} with with a 0.08 mol dm^{-3} aqueous solution of γ-CD for at least 48 h. The X-ray structure of the complex is not available. Indirect evidence for complexation is from UV-VIS and NMR spectroscopy [12-13] and photophysical [14-15] studies. The most likely complex is suggested to be a 2 : 1 adduct of γ-CD and C_{60}, in which both γ-CD's interact with C_{60} at their secondary hydroxyl sides [16-18].

The heats of formation from AM1 fully unrestricted geometry optimization for γ-CD, C_{60}, and their 1 : 1 complex are -1890.4, 973.4, and -913.6 kcal/mol respectively, which shows that the 1 : 1 complex, although a minimum on the potential surface, is slightly unstable by 3.4 kcal/mol. Our previous studies [2] suggested that intermolecular interactions between β-cyclodextrin molecules are at an about 34 kcal/mol level, explaining the stability of the crystals. Relatively strong interactions between CD molecules could also exist in solution, leading to some special spacial arrangements around the water insoluable C_{60}. Two γ-CD-s could surround C_{60} and interact with each other to form a stable 2 : 1 complex. In order to support this concept, we have calculated the stabilization energy between two γ-CD-s arranged with their secondary OH-s facing each other. The dimer is by 13.8 kcal/mol (γ-CD dimer ΔH_f = -3668.0 kcal/mol and monomer ΔH_f = -1827.1 kcal/mol) more stable than two γ-CD-s and would allow to accomodate a C_{60} molecule "cage-in" between them.

4. CONCLUSION

In conclusion, we have studied the inclusion complexes of α-CD and β-CD with benzoic acid and phenol, and β-CD with methylated benzoic acids in the "head first" and "tail first" positions. The preferred position for the guest compound inside the cavity depends on a combination of steric, hydrogen bonding, van der Waals, and hydrophobic effects. The stabilization energy from the dimerization of γ-CD through the secondary hydroxylic rims may render the 2 : 1 adduct of γ-CD and C_{60} more stable than the 1 :1 adduct or isolated molecules.

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