Cyclodextrin Inclusion Complexes. MM2 Calculations Reproducing Bimodal Inclusions

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MM2 calculations correctly reproduce both the X-ray geometry of γ-cyclodextrin and its ability to distinguish between various alkyl substituents on a substrate, leading to different host–guest complexes. The theoretical results show a clear correlation with experiments. Solvent effects seem to be unimportant for the complexation preference within a series of compounds. The inclusion process is mainly, but not exclusively, controlled by van der Waals attractions.

Cyclodextrins (CD) are cyclic compounds composed of D-glucose residues linked by α(1,4) bonds. The manner in which the glucose polymer is ordered gives the CD a toroidal shape.[1-3] The inner cavity of a CD is known to be hydrophobic in character, allowing the formation of inclusion complexes with a wide variety of organic molecules. This feature has stimulated much interest in cyclodextrin in recent years, because of its implication in enzyme–substrate interactions[4] and molecular recognition,[5-7] and has contributed to the development of cyclodextrin chemistry as an important field of supramolecular chemistry.[8] Many articles dealing with the formation of inclusion complexes between CD and a substrate can be found in the literature. Nevertheless, the determination of the factors that control the process has yet to be done.

Many methods have been used to study cyclodextrins and their inclusion complexes, including X-ray crystallography,[9] NMR spectroscopy,[10] ESR spectroscopy,[11] and electrochemical methods.[12] Several tools have been used to analyze the geometries of CD complexes in solution, among them ^1H and ^{13}C chemical shifts[10,13] and kinetic and thermodynamic measurements.[14-18] CD complexes are usually studied by NMR spectroscopy, but the kinetics of complex formation introduces some difficulty in the extraction of conclusions from these experiments.[25] Theoretical methods offer another approach to determine these geometries, and recently CNDO[19,20] and molecular mechanics calculations have been published.[21-26,39] The combination of an experimental method with molecular mechanics calculations can be a useful means of learning the geometry of a host–guest complex. Agreement between the two lends better understanding of the evolution of CD inclusions complexes.

The ability of γ-cyclodextrin **1** to distinguish between various alkyl groups in a substrate like **2** and thus form different host–guest complexes was recently studied by fast electron spin resonance.[27] Two kinds of complexes were observed when a molecule like **2** was mixed with γ- or β-cyclodextrin.[28] The two complexes were assigned to the structures either with the *tert*-butyl (complex **A**) or the alkyl group (complex **B**) inside the cavity. A third possible mode of inclusion, in which the 2,4,6-trimethoxyphenyl group is inside the cavity, was excluded[27] due to the size of this group (about 8 Å while the γ-CD internal width is 6.5–7.5 Å). Experimentally, complex **A** is preferred for R = Me, Et, Pr, *i*-Pr, *n*-Bu, and *n*-pentyl, while complex **B** is the most stable for R = cyclohexyl, and no clear preference is observed for R = *n*-hexyl, cyclopentyl, and phenyl.

In this paper, we present a model of the complexation process between **1** and **2** as indicated in Figure 1. The process was studied by molecular mechanics calculations in order to continue exploring the behavior of Allinger's

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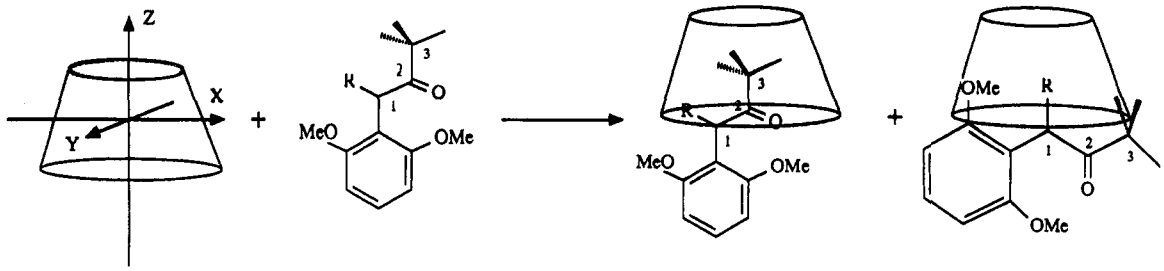
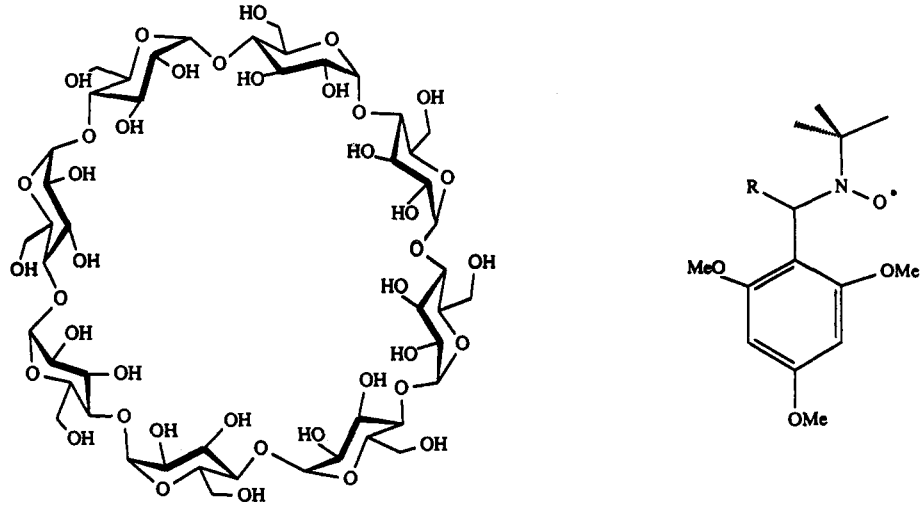


R	Me	Et	Pr	i-Pr	n-Bu	n-Pent	Cyc-5	n-Hex	Cyc-6	Ph	1-Ada
3	a	b	c	d	e	f	g	h	i	j	k

Figure 1. Computer model for the experimentally determined bimodal inclusion of γ-CD, 1, with nitroxides 2.[27]

Chart 1



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MM2(85) force field[29] and its applications to host–guest chemistry, as well as to obtain information on the complexation driving-force.

Computational Method

For the sake of generality, the standard Allinger program was used throughout.

Guest Geometry. The N–O bond was modeled by the C=O bond (i.e. 2 was modeled by 3) because of their similar geometries[30] and the lack of corresponding parameters in the MM2 force field. The phenyl *p*-methoxy substituent of 2 was also ignored since it is expected to have no influence on the complexation process. A full conformational study was undertaken on all the isolated guests, and the most stable conformation of each guest was used in two different orientations, as complexes **A** and **B**.

Orientations. The two orientations for each guest were considered in which two of its atoms were kept on the *Z* axis: (i) atoms C_2 and C_3 in the case of the orientation giving rise to complex **A**; (ii) atoms C_1 and the terminal carbon atom of the R group in the case of the orientation corresponding to complex **B**. The guest position throughout the study is referred to by the *Z* coordinate of its C_2 or C_1 atom for complexes **A** and **B**, respectively.

Host and Complexation Process. One MM2 fully optimized (in this work) geometry of γ-CD, 1, was used. The γ-CD molecule was oriented having all glycosidic oxygens nearly in the *XY* plane and the CH_2OH groups on the positive (upper) region of the *Z* axis, and the origin of coordinates was located at the center of the octagon formed by the eight glycosidic oxygens. The γ-CD was kept in this position, but geometry and energy were optimized, while the guest molecules approached from "infinity" (14.0 Å) and passed through the cavity along the *Z* axis (Figure 1). At the lowest point of energy, all of the fixed atoms of the guest were released and the complex geometry was fully optimized again.

Neglect of the Solvent. All the calculations were performed without consideration of solvent, although the limitations of such a simplification are acknowledged. First, the removal of highly ordered water molecules from the CD cavity is usually considered to be a main contribution to the driving force for complex formation. Second, once the complex is formed, the cavity of the γ-CD is wide enough to accommodate a number of water molecules and the γ-CD is known to form a number of ternary complexes. Nevertheless, our approach may be justified considering

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Table 1. Experimental (X-ray) and Calculated (MM2) Geometrical Data for γ-CD, 1 (distances are in angstroms and angles in degrees)

	avg distances[a]			avg angles[a]			dihedral angles	
	exptl	calcd		exptl	calcd	TAI[b]	exptl	calcd
C1–C2	1.53	1.525	C1–C2–C3	111	110.7	G1	99.8	99.6
C2–C3	1.53	1.527	C2–C3–C4	110	109.8	G2	107.0	107.2
C3–C4	1.52	1.518	C3–C4–C5	110	109.7	G3	113.1	113.1
C4–C5	1.53	1.528	C4–C5–C6	114	114.1	G4	119.9	120.1
C5–C6	1.51	1.512				G5	112.0	111.8
			C2–C1–O5	111	110.9	G6	97.0	96.4
C1–O4	1.42	1.421	C2–C1–O4	109	108.7	G7	120.4	120.9
C1–O5	1.41	1.406	C1–C2–O2	110	110.3	G8	116.5	116.9
C2–O2	1.42	1.423	C3–C2–O2	111	110.5			
C3–O3	1.44	1.435	C2–C3–O3	109	109.4			
C4–O4	1.44	1.439	C4–C3–O3	109	109.3			
C5–O5	1.46	1.457	C3–C4–O4	107	106.0			
C6–O6	1.42	1.430	C5–C4–O4	110	109.7			
			C4–C5–O5	108	107.6			
			C6–C5–O5	106	105.8			
O4–orig	5.88	5.80	O5–C1–O4′	111	110.9			
O4···O4′	4.50	4.46	C5–O5–C1	115	114.5			
O2···O3′	2.82	2.93	C1–O4′–C4	117	116.8			

[a] Average values considering the eight glucose units. [b] Torsion angle index (TAI) is defined as $\Phi = |O5–C1–C2–C3| + |C1–C2–C3–C4| + |C4–C5–O5–C1| + |C5–O5–C1–C2| - |C2–C3–C4–C5| - |C3–C4–C5–O5|$.

the following. Since the γ-CD cavity is wider than those of the α and β oligomers, the water molecules inside are expected to be less ordered and their displacement might result in a lesser energetic gain.[3] The considerable energy gap due to the fit between the guest and its host might therefore be a factor of primary importance in controlling the complexation process. On the other hand, the literature suggests that the ternary complexes formed with CD always involve small polar organic substrates, such as light alkanols.[31] However, in the case of nonprotic guests like 12-crown-4, the X-ray structures of inclusion compounds reveal that the water molecules are located outside the CD cavity, despite sufficient internal free volume to accommodate some solvent.[32] This suggests that upon complexation of rather hydrophobic guests, all the water molecules might be expelled from the internal cavity to the CD periphery. Similar behavior has been recently reported in the case of ternary complexes between β-CD, pyrene, and various alkohols.[33] In such systems, part of one pyrene molecule occupies a portion of the CD cavity and the hydrophobic alkyl group of the alcohol extends into the remaining volume. The polar hydroxyl group is positioned outside the cavity, wherein only hydrophobic interactions seem to occur. These results support the assumption that complexation of medium- to large-sized organic hydrophobic substrates might lead essentially to nonhydrated inclusion compounds. Nevertheless, there is little doubt that introduction of small guests into the wide γ-CD cavity should not displace all of the water. An assessment of the number of remaining water molecules in CD complexes via theoretical (MM) calculations could be problematic since there is no evidence to support that the unoccupied internal volume would be entirely filled with solvent (*vide supra*). Furthermore, recent neutron diffraction[34] and deuterium magnetic resonance[35] studies of CD-deuterated alcohol hydrate crystals have shown that the included molecules are dynamically disordered and have fast reorientational rates, the water molecules occupying several, alternative, discrete sites. It is clear that MM methods would be unable to consistently model such behavior. Considering the hydrophobic character of the guest molecules under investigation, we thus decided to ignore the water that is included in CD complexes, throughout this study.

Results and Discussion

Calculations of γ-CD. The published X-ray coordinates[36] for uncomplexed hydrated γ-CD, 1, were used as starting point after removal of the water molecule coordinates. The MM2(85) fully optimized γ-CD structure agrees remarkably well with that determined experimentally, as indicated in Table I. This indicates that realistic molecular geometries of hydrated CD compounds can be reproduced without taking account of included water molecules.

Conformational Study of the Guest Molecule. A compound like 2 presents at least six bonds (when R = H or Me) that can give rise to rotational isomers. This number of bonds provides a minimum of $3^6 = 729$ conformers.[37] Compound 2 was modeled by 3, and to reduce the number of rotamers, only the Ar–C_1, C_1–C_2, and C_1–R (for R other than methyl) bonds were considered to be rotatable. The number of conformers is thus reduced to 27. Complete explorations of the potential energy surfaces were preferred to multiple minimum search procedures implemented in various other molecular mechanics programs. One torsional energy surface was obtained for all of the studied guests, **3a–j**, by driving C_1–R and C_1–C_2 bonds with the standard two-bond drive technique. Driven bonds were changed from −180° to 180° in 10° steps. Figure 2b shows the energy surface obtained for **3b** (R = Et) (structure shown in Figure 2a) as an example. The 2,6-dimethoxyphenyl group was then

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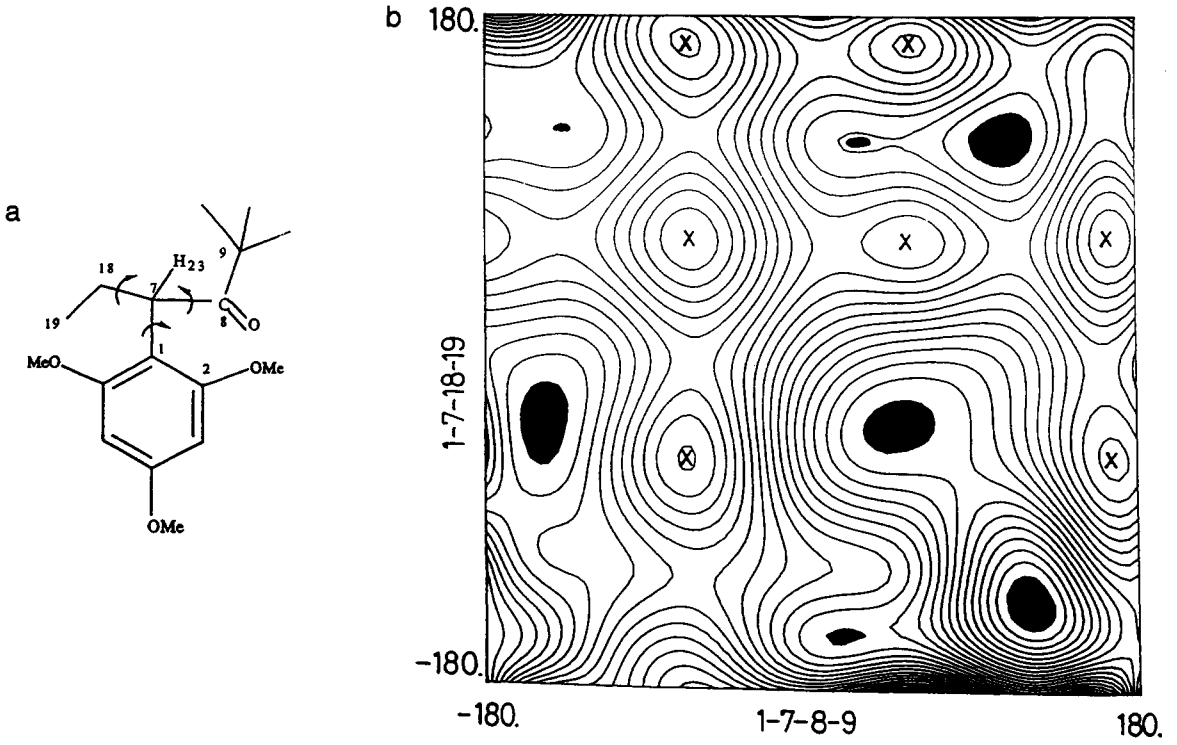


Figure 2. Schematic representation of the theoretical conformational analysis of **3b** by the MM2(85) force field. Variables are the two rotatable bonds indicated in Figure 2a. Black zones denote energy maxima regions, and *x* indicates energy minima.

Table 2. Relative Steric Energy (kcal/mol), Population (%), and Values for the Three Dihedral Angles Characterizing the Calculated Conformers for Compound 3b

conformer	dihedral angle (deg) 1-7-8-9	1-7-18-19	2-1-7-23	rel *E* (kcal/mol)	population (%)
1	-64.1	58.6	15.0	0.0	72.7
2	-67.5	164.6	15.0	0.7	22.3
3	-66.0	-59.5	15.1	1.8	3.5
4	-64.7	161.7	-179.9	2.3	1.5
5	169.6	50.1	0.0	4.5	0.0
6	54.9	165.8	135.0	5.8	0.0
7	-168.1	123.3	0.0	7.5	0.0
8	-129.5	-112.9	165.0	8.0	0.0
9	179.6	-66.1	15.0	8.1	0.0
10	173.1	133.5	14.9	8.7	0.0
11	-142.0	-82.9	120.0	9.3	0.0
12	34.0	-102.5	135.1	13.1	0.0

rotated around the C_1–Ar bond by the one-bond drive technique, in each of the obtained minima. All of the newly obtained energy minima was then fully optimized without restrictions. Table 2 contains the geometric and energetic data obtained for **3b**.

The results of these conformational analyses allowed us to take the most stable conformer for each guest, given the common skeleton. When the R group was an *n*-alkyl chain, only the all-*anti* conformation was considered; when R was cyclopentyl and cyclohexyl, the envelope and the chair conformations, respectively, were exclusively considered.

Calculations on the Inclusion Process. γ-Cyclodextrin has a toroidal shape with two differently sized entrances. The diameters of both entrances (about 6.5 and 7.5 Å between van der Waals radii of inner hydrogens) are large enough to accept the guest. The MM2(85) calculations for the process of inclusion of a guest into the CD cavity through both entrances have been carried out for only the simplest guest, **3a** (R = Me).

The energy variation of **3a** entering into **1** is shown in Figure 3. A total of four possible orientations were considered: the R and the *tert*-butyl group through the wider and the narrower entrances. It is worth noting that the curve corresponding to the inclusion of the guest by the *tert*-butyl group through the wider entrance gave the lowest energy value. Calculations suggest, then, that the complexation of **3a** takes place preferentially in the wider *tert*-butyl orientation, as illustrated by complex type **A** of Figure 3.

At least two minima, separated by energy barriers, were obtained for all compounds studied.[38] These barriers were produced by the strong nonbonding repulsive interactions between the guest and the host when the 2,6-dimethoxyphenyl group came in contact with **1**. The global energy minimum is at the −1 Å point for complex **A** and at the 0 Å point when complex **B** is formed. It is noteworthy that the most stable geometry for the complex, when the guest approaches the γ-CD with the narrower rim facing the methyl group, is nearly the same as the most stable orientation for the guest approaching with the wider rim facing the *tert*-butyl group.

For the rest of the compounds, only the approaches through the wider rim were considered. The same pattern is observed for almost all of the other R groups studied (see Table II), exceptions being when R is cyclopentyl and cyclohexyl. In these cases, a reversal in the relative energies of the minima is observed. Figure 4 shows the energy variation obtained for **3i** (R = cyclohexyl). The global energy minimum for the inclusion of the cyclohexyl group

(38) The shapes of the curves obtained are dependant on the computational method used. In fact, constraining two atoms of the guest to the *Z* axis during the inclusion process (see Computational Method—Orientations) results in high, unrealistic energy barriers. Release of the restriction on one of the two atoms allows the guest to pivot to avoid strong repulsive interactions of its substituents with the host. However, these barriers are always produced after the energy minima and have no influence on the energetics of the inclusion complexes.

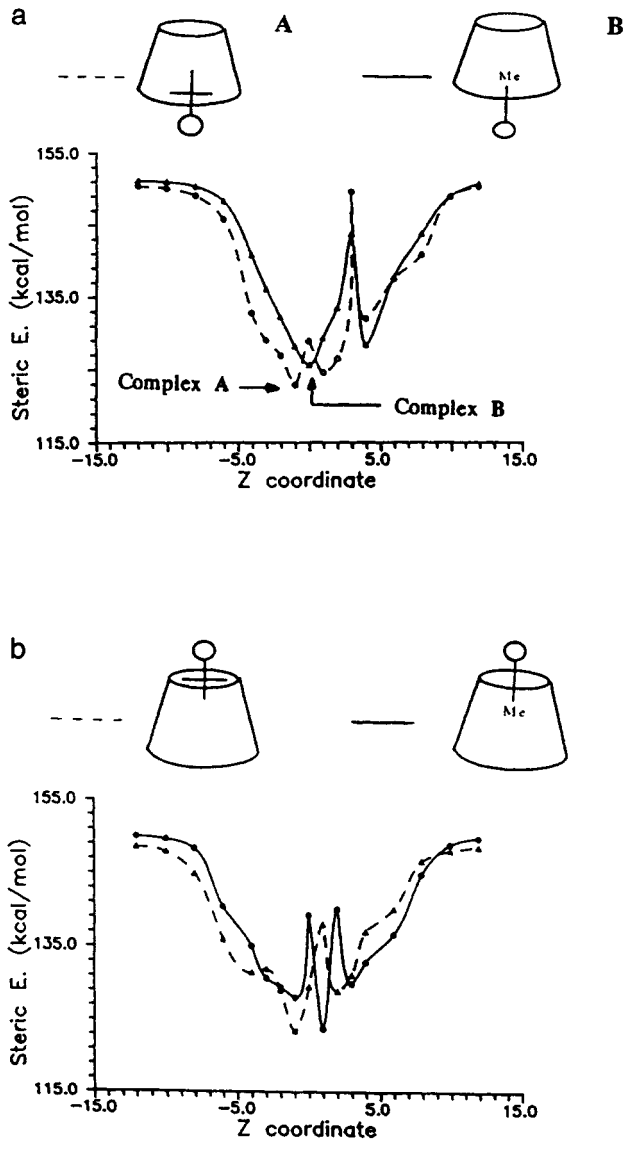


Figure 3. Plotting of calculated ΔE *versus* the Z coordinate of predetermined atoms (see text for explanation) for the modeling of complex formation between γ-CD, 1, and **3a**, through the wider (a) and the narrower (b) rims. In both figures, the solid and dashed lines are for the methyl and the *tert*-butyl inclusions, respectively.

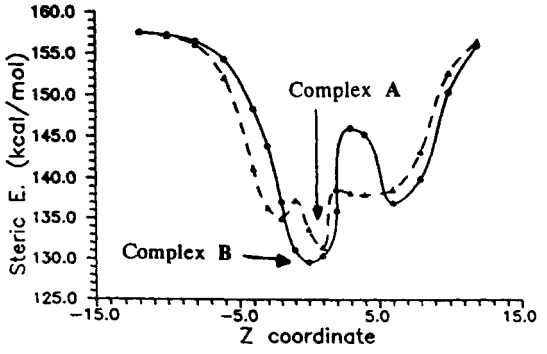


Figure 4. Plotting of calculated ΔE *versus* the Z coordinate of predetermined atoms (see text for explanation) for the modeling of complex formation between γ-CD, 1, and **3j**. The dashed line is for complex **A** and solid line is for complex **B**.

(complex **B**) is much lower than the minimum obtained for the inclusion of the *tert*-butyl group (complex **A**). The guest molecule is centered inside the cavity in the two minima (located at the 0 Å and +1 Å points, respectively). Drawings of the structures of these two complexes are shown in Figure 5.

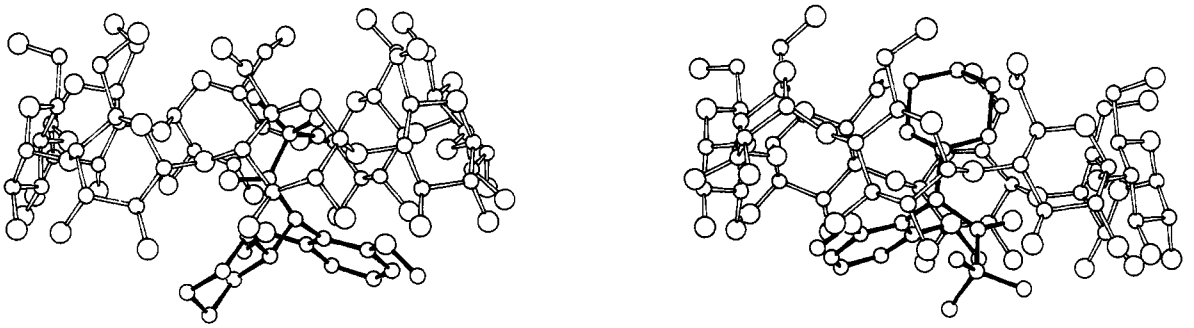
As deduced from Table 3, all of the results of molecular mechanics calculations are in qualitative harmony with the experimental association contant values. The question arises as to whether a quantitative relation exists.

Thermodynamics correlates the equilibrium constant with ΔG of a process by the expression $\Delta G = -RT \ln K$. Upon comparison of two different chemical equations, the following expression is derived: $\Delta G_2 - \Delta G_1 = -RT \ln(K_2/K_1)$. The MM2 calculations give the steric energy E (kcal/mol) of the complexes **A** and **B**, obtained for the two inclusion modes. Since the complexes derived from the same molecule are stereoisomers, the difference in steric energy ($\Delta E = E_B - E_A$) can be equated to the enthalpy difference ($\Delta\Delta H = \Delta H_B - \Delta H_A$). Besides, the main contribution to the entropic difference term ($\Delta\Delta S = \Delta S_B - \Delta S_A$) may be due to the difference in the number of water molecules expelled from the CD cavity upon complexation of **3** (*vide supra*). One might expect this number to vary to some extent from one isomer to another. However, this study ignores the solvent molecules involved in the inclusion process, so the differences in entropic effects for pairs of complexes were neglected and the $\Delta\Delta G$ approximated the ΔE. It is stressed that rigorous calculations of free enthalpies require computation of the frequencies associated with all the molecular vibration modes of the inclusion complexes. This cannot be achieved with the MM2 program since it does not perform frequency calculations. The ultimate MM3 program does, but could not be applied in this case, due to the size of the systems under investigation. Plotting the calculated energy difference between the two complexes of the same molecule ($\Delta E_B - \Delta E_A$) divided by RT *versus* the logarithm of the ratio of the experimental association constants (K_A/K_B), produced a good correlation ($r = 0.98$) (points for **3a** and **3b** were excluded because their $K_B = 0$), showing that ΔE increases when K_A/K_B increases.

Due to the nonpolar character of the guest functionalities that enter the γ-CD cavity, the importance of the attractive van der Waals interactions may be expected. However, analysis of MM2 energy results show no direct relation between the van der Waals term (E_{VDW}) and the stability of the complex. The attractive van der Waals host–guest interactions are the most important driving force for the inclusion process. Nevertheless, the final shape of the "reaction curve" is defined by several energetically less important factors (such as changes in torsional angles, bending angles, etc.).

As shown in Table 3, the experimental association constants for type **A** complexes do not vary much, but they vary considerably for type **B** complexes (from zero for methyl to 750 M^{-1} for cyclohexyl). The experimental inclusion tendency increases with the chain length when changing R, a fact properly reproduced by our calculations. The calculated preference for complex **A** varies from 2.82 to only 0.21 kcal/mol when R changes from *n*-butyl to *n*-hexyl. Moreover, the ratio K_A/K_B is nearly 2 for R = *n*-propyl, *n*-butyl, and *n*-pentyl, but is about 6 for R = isopropyl; the calculated energetic preference for complex **A** over complex **B** also denotes this difference (nearly 2.7 and 4.1 kcal/mol, respectively).

Whenever the experimental association constants are similar, the calculated preference is small (about 0.3 kcal/



A B

Figure 5. The structures of energy minima for the two inclusion modes of **3i** (R = cyclohexyl) in γ-cyclodextrin: complex **A** (inclusion of the *tert*-butyl group); complex **B** (inclusion of the cyclohexyl group). Guest molecules are shown with full bonds. Hydrogens atoms are not drawn for the sake of clarity.

Table 3. Calculated (MM2(85)) Relative Steric Energies (kcal/mol) and Experimental[26] Association Constants for Complex Types A and B of Molecules 3a–j, with γ-CD, 1

		rel *E* (kcal/mol)		association constant (M^{-1})	
molecule	R	complex A	complex B	complex A	complex B
3a	methyl	0.00	2.69	150	0
3b	ethyl	0.00	1.63	150	0
3c	propyl	0.00	2.70	130	50
3d	*i*-propyl	0.00	4.08	120	20
3e	*n*-butyl	0.00	2.82	120	60
3f	*n*-pentyl	0.00	2.79	140	70
3g	cyclopentyl	0.38	0.00	130	130
3h	*n*-hexyl	0.00	0.21	170	150
3i	cyclohexyl	1.38	0.00	130	750
3j	phenyl	0.00	0.89	160	130
3k	adamantyl	1.92	0.00	-	-

mol) with the exception of R = Ph, but this case perhaps deserves special treatment. The possibility of hydrogen bond formation between the phenyl group and either the primary hydroxyl groups or the solvent must be considered.

The effect of branching is clear; the inclusion of the branched substituents is always preferred over the inclusion of the *tert*-butyl group except in the **3d** case (R = isopropyl). The linear alkyl groups are, on average, centered inside the CD cavity, while branched groups position some methylene groups nearer to the CD internal walls, slightly increasing the attractive van der Waals contribution. On comparing **3c** (R = propyl) with **3d** (R = isopropyl), it seems that the isopropyl group is not large enough to overcome the preference for having a methyl group (the end of the propyl chain) in the narrower part of the toroidal cavity, with the subsequent increase in attractive interactions. The case of **3i** (R = cyclohexyl) shows the greatest complex **B** preference, with its large, branched substituent positioning methylenes in the narrower side of the cavity. We therefore performed calculations on the adamantyl-substituted guest **3k**, which has not been studied experimentally. As expected, the presence of the three adamantyl methylene groups inside the CD cavity induces an even higher energy difference, in favor of complex **B**. These trends confirm the importance of the van der Waals attractive interactions between lipophilic parts of the guest and the host cavity in controlling the inclusion process.

Conclusions

In spite of its lack of consideration of solvent effects in the host-guest complexation process, MM2(85) seems to correctly reproduce experimental data. This suggests that, although the solvent may be important in complex formation, the bimodal inclusion process of compound **2** is essentially governed by the energetics of the fit between the host and the guest. The good correlation obtained between the calculated energetic preference of the complexes and their experimental association constants allowed us to predict the association constant values for different R groups, considering only the results of molecular mechanics calculations. Moreover, the good correlation between theory and experiments (r = 0.98) suggests the absence of differential solvent effects in this series of molecules on preferred complexation. According to our calculations, it is clear that the direction of the inclusion should be through the wider rim of the CD molecule.

These results, together with others,[24,25,39] indicate that molecular mechanics (MM2) may be used in a predictive way in host–guest chemistry, although care must be taken in the molecules selected.

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