Cyclodextrin Inclusion Complexes. Molecular Mechanics Calculations on the Modification of π-Face Selectivity†

Antonio Entrena‡ and Carlos Jaime*,§

Departament de Química, Facultat de Ciències, Universitat Autònoma de Barcelona, 08193 Bellaterra (Barcelona), Spain, and Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Granada, 18071 Granada, Spain

Received July 29, 1996⊗

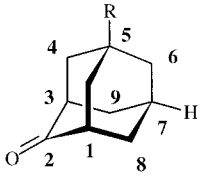
A theoretical model (considering bimodal inclusions) for the complexation of β-cyclodextrin and several 5-substituted 2-adamantanones is discussed. The change in the π-facial selectivity observed in their photochemical reactions with fumaronitrile was properly reproduced by either the original or the MacroModel version of MM3 force field.

Introduction

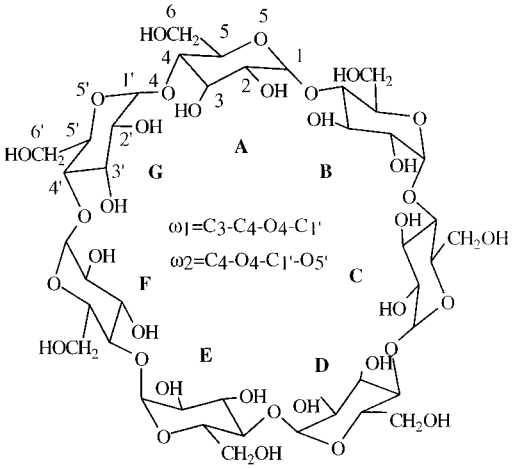
Cyclodextrins (CDs) are cyclic oligosaccharides formed by α(1→4) linked D-glucose units.[1,2] They are named α-, β-, and γ-CD depending on the number of glucose units in the macrocycle (six, seven, or eight, respectively). CDs are one of the most widely used systems in supramolecular chemistry,[3] since they include a large variety of organic compounds inside their hydrophobic, torus-shaped cavity.

The structural study of CDs and of their complexes has been carried out by different techniques such as X-ray analysis,[4] NMR spectroscopy,[5] EPR,[6] and electrochemical methods.[7] Chemical shifts[5−7] and kinetic and thermodynamic studies,[8] as well as computational methods (CNDO,[9,10] MD,[11,12] and MM[13−18]), have been used to study the complexation process.

CDs can be considered as models for enzyme−substrate interactions[19] or as standards for molecular recognition.[20]



1a: R= F **1d**: R= Ph
1b: R= Cl **1e**: R= *t*-Bu
1c: R= Br **1f**: R= OH



β-CD

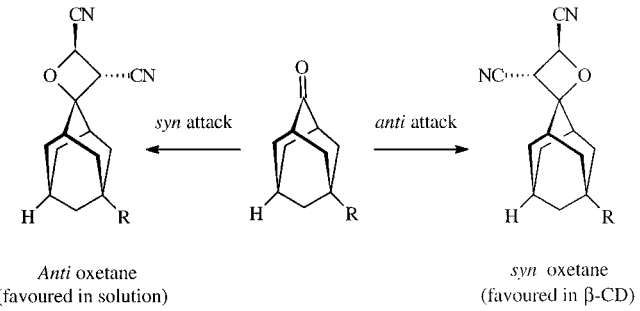
CDs have also been widely used as chiral stationary phases in chromatography,[21−23] and they are especially important as unique environments for certain chemical reactions. Their presence can change the reactivity or the stereochemical course of a determinate reaction. Photochemical reactions are probably the most widely studied. CDs prevent the movement of reactive intermediates,[24,25] increase Diels−Alder reaction rates,[26−28] and increase the *endo*/*exo* ratio.[26,27] A recent example shows the modification of the π-face selectivity in 7-norbornene reductions.[29]

† In remembrance of 'Pablito' Entrena.
‡ Universidad de Granada.
§ Universitat Autònoma de Barcelona.
⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(1) Bender, N. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: New York, 1978.
(2) Szejtli, J. *Cyclodextrin Technology*; Kluwer Academic Publishers: Dordrecht, 1988.
(3) Lehn, J. M. (Nobel Lecture) *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 88.
(4) Hamilton, J. A.; Steinrauf, L. K.; Van Etten, R. L. *Acta Crystallogr. Sect. B* **1968**, *B24*, 1560.
(5) Wood, D.; Hruska, F. E.; Saenger, W. *J. Am. Chem. Soc.* **1977**, *99*, 1735.
(6) Flohr, K.; Patton, R. M.; Kaiser, E. T. *J. Am. Chem. Soc.* **1975**, *97*, 1209.
(7) (a) Dong, S.; Zhang, D. *Acta Chim. Sinica* **1988**, *46*, 335. (b) Ismin, R.; Slam, C.; Kaifer, A. E. *J. Org. Chem.* **1991**, *56*, 35.
(8) Eftink, M. R.; Andy, M.; Byström, K.; Perlmutter, H. D.; Kristol, D. *J. Am. Chem. Soc.* **1989**, *111*, 6765.
(9) Kitagawa. M.; Hoshi, H.; Sakurai, M.; Ionue, Y.; Chûjô, R. *Chem. Lett.* **1988**, 895.
(10) Kitagawa, M.; Hoshi, H.; Sakurai, M.; Ionue, Y.; Chûjô, R. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2065.
(11) Koehler, J. E. H.; Saenger, W.; van Gunsteren, W. F. *J. Biomol. Struct. Dyn.* **1988**, *6*, 181.
(12) Ivanov, P. M.; Jaime, C. *An. Quím. Int. Ed.* **1996**, *92*, 13.
(13) Venanzi, C. S.; Canzius, P. M.; Zhang, Z.; Bunce, J. D. *J. Comput. Chem.* **1989**, *10*, 1038.
(14) Ohashi, M.; Kasatani, K.; Shinohara, H.; Sato, H. *J. Am. Chem. Soc.* **1990**, *112*, 5824.
(15) Lipkowitz, K. B. *J. Org. Chem.* **1991**, *56*, 6357.
(16) Jaime, C.; Redondo, J.; Sánchez-Ferrando, F.; Virgili, A. *J. Org. Chem.* **1990**, *55*, 4772.
(17) Jaime, C.; Redondo, J.; Sánchez-Ferrando, F.; Virgili, A. *J. Mol. Struct.* **1991**, *248*, 317.
(18) Fathallah, M.; Fotiadu, F.; Jaime, C. *J. Org. Chem.* **1994**, *59*, 1288.
(19) Tabushi, I. *J. Am. Chem. Soc.* **1977**, *99*, 7100.
(20) Atwood, J., Ed. *Inclusion Phenomena and Molecular Recognition*; Plenum Press: New York, 1990.
(21) Lough, W. J., Ed. *Chiral Liquid Chromatography*; Blackie and Son: London, 1989.
(22) Fischer, P.; Aicholz, R.; Bolz, U.; Juza, M.; Krimmer, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 427.
(23) Armstrong, D. W.; Li, W.; Chang, C. D.; Pitha, J. *Anal. Chem.* **1990**, *62*, 914.
(24) Ramamurthy, V.; Eaton, D. F. *Acc. Chem. Ress.* **1988**, *21*, 300.
(25) Syamala, M. S.; Rao, B. N. Ramamurthy, V. *Tetrahedron* **1988**, *62*, 914.
(26) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613.

S0022-3263(96)01439-9 CCC: $14.00

Scheme 1



Anti oxetane (favoured in solution) — *syn* oxetane (favoured in β-CD)

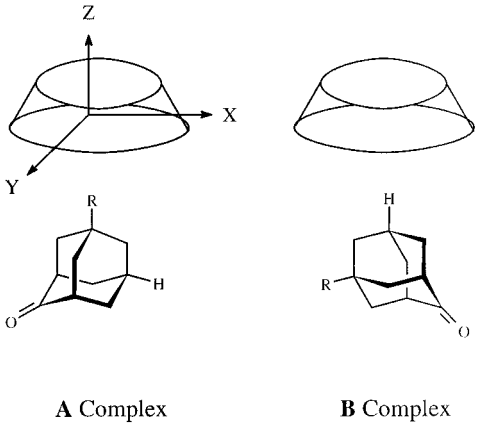
The purpose of this paper is to explain the change observed in the π-face selectivity when several 5-substituted 2-adamantanones and fumaronitrile undergo a photochemical cycloaddition.[30] Experimental results are summarized in Scheme 1: *syn* attack is favored in aqueous solution, and *anti*-oxetane is the major product, while *syn*-oxetane (formed by an *anti* attack) is formed in presence of β-CD. It has been assumed, but not proved, that the change in selectivity is produced by the difference in stability of two main inclusion complexes (bimodal complexes).

Results

Computational Methodology. Allinger's MM3 force field[31] was used for the inclusion process emulation and for the optimization of the complex structures. The MM3(92) program[32] was slightly modified to be able to use the full-matrix Newton−Raphson minimizer with molecules containing up to 210 atoms.

Previously published neutron diffraction coordinates of β-CD[33] have been used as starting coordinates for the host. The macrocycle was oriented so as to keep the glycosidic oxygens in the *XY* plane with the hydroxymethyl groups in the upper (positive) region of the *Z* axis.[16] The origin for the coordinate axis of reference was thus located at the center of the heptagon formed by the seven glycosidic oxygens. The host was kept at this position by restraining the movement of two neighboring glycosidic oxygens and the one opposite.[16−18]

Guest geometries were generated independently and optimized. Two orientations were considered (Figure 1) to produce inclusion complexes with the carbonyl group outside the cavity able to suffer the photochemical reaction. To emulate the formation of complex **A**, the guest was oriented with the C5−R bond over the *Z* axis pointing toward the positive end. For complex **B**, the C7−H bond was placed on the *Z* axis. Initially, guests were considered to be far from the host. The reference atom (C5 or C7 for **A** and **B** complexes, respectively) was located at the *Z* coordinate −15 (i.e., a distance of 15 Å separates the β-CD equatorial plane and the guest reference atom),[34] and its movement was



A Complex **B** Complex

Figure 1. Schematic representation for the two inclusion complexes (**A** and **B**) between β-CD and the 5-substituted 2-adamantanones **1a**−**f** considered in this study.

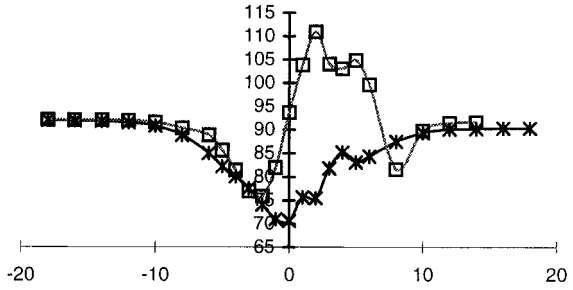


Figure 2. Graph of the variation of the total steric energy with the distance between the reference atom of the guest and the *XY* plane (equatorial plane of the β-CD). Energies (obtained with MM3 force field) involved in the formation of complexes **A** and **B** of **1d** are represented by * and □, respectively.

totally restricted. The inclusion was then achieved by increasing the *Z* coordinate of guest atoms by 1 Å increments until reference atoms reached the *Z* coordinate of +15.

The graph of the total steric energy against the C5 or C7 *Z* coordinate offered an overview of the guest inclusion. Figure 2 depicts that for compound **1d** as an example. The global energy minima in each of the curves obtained were reoptimized either with the block-diagonal method or with the tandem block-diagonal/full-matrix method[35] after eliminating the guest restraints.

Solvent (water) influence was simulated using two methods: (a) different dielectric constant values (1.5, 7.5, and 20) in the computation of the final energy minimum with the MM3 program[36] and (b) the GB/SA solvation model[37] together with the MM3* force field implemented in MacroModel package.[38] Under MacroModel, structures were optimized using a conjugate gradient or full-matrix optimizers.

Computational Results. Table 1 shows the energy of complex **B** relative to that of **A**, as well as their

(27) Schneider, H. J.; Sangwan, N. K. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 896.
(28) Komimaya, M.; Hirai, H. *J. Am. Chem. Soc.* **1988**, *45*, 17.
(29) Mehta, G.; Khan, F. A.; Lakshmi, A. *Tetrahedron Lett.* **1992**, 7977.
(30) Chung, W. S.; Turro, N. J.; Silver, J.; le Noble, W. J. *J. Am. Chem. Soc.* **1990**, *112*, 1202.
(31) Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551, 8566, and 8576.
(32) MM3(92) program is available from Technical Utilization Corp. Inc., 235 Glen Village Court, Powell, OH 43065.
(33) Betzel, C.; Saenger, W.; Hingerty, B. E.; Brown, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7545.
(34) Except for the type **A** complex of **1d** and **1e** in which the reference atom (C5) is initially located at 18 Å from the *XY* plane placing the closest guest atom as far from the host as to consider no interaction between both molecules.
(35) No restraints are considered whith the full matrix minimizer. See MM3 manual.
(36) Unfortunately, MM3(92) does not allow any other way to consider the solvent effect.
(37) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127.
(38) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Table 1. Relative Energies (kcal/mol)[a] and Population (%, in Parentheses)[b] for the Complex B between β-CD and 1a−f As Obtained with Different Force Fields and Methods

	MM3(92)					MacroModel	
compd	$\epsilon = 1.5$[c]	$\epsilon = 7.5$[c]	$\epsilon = 20$[c]	$\epsilon = 1.5$[d]	$\epsilon = 7.5$[d]	GB/SA[e]	GB/SA[d]
1a (R = F)	0.98 (16.1)	1.32 (9.7)	0.86 (8.9)	0.86 (8.9)	2.17 (2.5)	0.78 (21.1)	0.27 (38.8)
1b (R = Cl)	1.22 (11.3)	1.47 (7.7)	1.15 (12.5)	1.37 (9.0)	2.65 (1.1)	1.40 (8.6)	1.40 (8.6)
1c (R = Br)	1.37 (9.0)	0.93 (17.2)	0.69 (23.7)	1.81 (4.5)	0.80 (20.6)	1.86 (4.1)	1.97 (3.5)
1d (R = Ph)	3.75 (0.2)	4.21 (0.1)	3.64 (0.2)	5.29 (0.1)	4.20 (0.1)	6.42 (0.1)	5.36 (0.1)
1e (R = Bu^t)	3.54 (0.2)	0.70 (23.4)	0.21 (41.2)	3.67 (0.2)	0.16 (43.3)	5.42 (0.1)	5.53 (0.1)
1f (R = OH)	-0.74 (77.7)	0.16 (43.3)	0.07 (52.9)	0.18 (42.5)	1.77 (4.8)	1.19 (11.8)	1.18 (12.0)

[a] Relative energy is defined as the steric energy of complex **B** minus that for complex **A**. [b] The population was obtained using the Boltzmann's equation on the computed energy values at 298 K and without considering entropy contributions. [c] Block-diagonal minimizer. [d] Newton−Raphson minimizer. [e] Conjugate gradient minimizer.

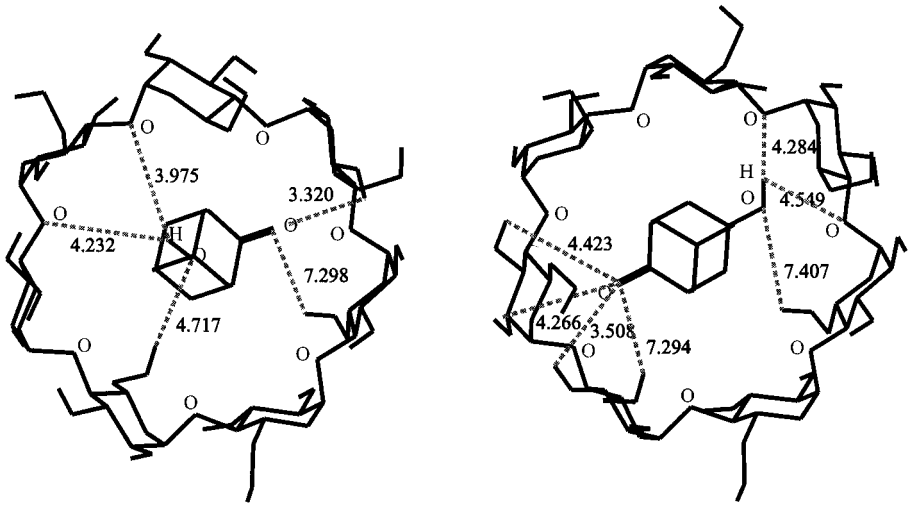


Figure 3. Computer drawings of the computed energy minimum for complexes **A** and **B** of **1f** showing selected intermolecular distances.

populations computed using Boltzmann's equation without considering entropy contributions. Differences are observed depending on the program used. Results from computations predict complex **A** to be always more stable than **B**. This complex was computed to be more stable than **A** only in one case (**1f**, X = OH, $\epsilon = 1.5$). The greater stability of complex **B** for **1f** could be a consequence of existence of hydrogen bonds between the secondary OH groups and that of **1f**, while complex **A** may present hydrogen bonds with the primary OH groups. The final optimized structure for both complexes as computed by MM3* in MacroModel is presented in Figure 3. As shown, any distance between host and guest is short enough as to produce hydrogen bonds between both molecules.

The relative energy for complex **B** increased with the substituent volume, especially when it was a halogen (Table 1). This tendency is due to smaller stabilizing host/guest interactions produced by this larger substituent size because when ϵ increases (7.5 or 20 D) the tendency decreased, achieving smaller values for **1c** than for **1a** (0.69 and 0.86 kcal/mol, respectively, $\epsilon = 20$). Under the MM3 scheme, large ϵ values produce reductions in the dipole−dipole and hydrogen bond interactions almost exclusively. These interactions are more important for the conformational integrity of the host than for the host−guest interactions. Since studied guests are relatively low polar, host−guest interactions are mainly governed by van der Waals forces.

Table 2. Experimental[30] Binding Constants (L/mol) and Initial and Calculated Concentrations (mM) for the β-CD/1a−d Complexes

entry	compd	K	$[\mathbf{1x}]_i$	$[\beta\text{-CD}]_i$	$[\mathbf{1x}]_{eq}$	$[\beta\text{-CD}/\mathbf{1x}]_{eq}$
1	**1a** (R = F)	8.7×10^2	5.0	5.0	1.89	3.11
2			1.5	7.5	0.24	1.26
3	**1b** (R = Cl)	8.7×10^2	5.0	5.0	1.89	3.11
4			1.5	7.5	0.23	1.27
5	**1c** (R = Br)	8.2×10^2	5.0	5.0	1.92	3.08
6			1.5	7.5	0.24	1.26
7	**1d** (R = Ph)	1.33×10^3	5.0	5.0	1.60	3.40
8			1.5	7.5	0.16	1.34

The substituent interacts with the CD wall during the formation of complex **B** (see Figure 2). These strong repulsive interactions are responsible for the higher energy of this complex. They also modify the cone-truncated shape of β-CD. When a large ϵ is used, the hydrogen bonds are weakened and the host modification is even larger.

Torsional angles centered on the glycosidic oxygens (ω_1 and ω_2) for the isolated β-CD present values around 120°, the largest deformations being 4.8° and 8.8° (for $\epsilon = 7.5$ and 20, respectively) (see the Supporting Information). The substituent points toward the interior of the cavity in complex **A**; values for ω_1 and ω_2 (and deformations) are thus similar to those found for the isolated host. The deformation of the macrocyclic structure is much larger in complex **B** (deviations of 13.6° and 15.6° are obtained for **1c**) than in complex **A**. Moreover, repulsive interactions between the substituent and the macrocycle wall

Table 3. Calculated (This Work) and Experimental[30] *Syn/Anti* Ratio for the Cycloaddition between Fumaronitrile and Several of the 2-Adamantanone Derivatives (1a−d) in the Presence of *β*-CD

		MM3(92)					MacroModel		
entry	compound	$\epsilon = 1.5$[a]	$\epsilon = 7.5$[a]	$\epsilon = 20$[a]	$\epsilon = 1.5$[b]	$\epsilon = 7.5$[b]	GB/SA[c]	GB/SA[b]	exp
1	**1a** (R = F)[d]	1.67	1.90	1.58	1.58	2.22	1.51	1.08	1.08
2	**1a** (R = F)[e]	2.64	3.46	2.38	3.47	4.97	2.19	1.23	1.23
3	**1b** (R = Cl)[d]	1.56	1.69	1.53	1.64	1.95	1.65	1.65	1.70
4	**1b** (R = Cl)[e]	2.74	3.23	2.60	3.04	4.59	3.09	3.09	2.85
5	**1c** (R = Br)[d]	1.69	1.43	1.26	1.85	1.34	1.87	1.89	2.03
6	**1c** (R = Br)[e]	3.77	2.20	1.75	3.82	1.95	3.90	4.03	4.00
7	**1d** (R = Ph)[d]	1.90	1.90	1.90	1.91	1.91	1.91	1.91	1.63
8	**1d** (R = Ph)[e]	5.64	5.74	5.74	5.74	5.74	5.74	5.74	3.35
9	σ_{ms}[f]	0.99	1.37	1.27	1.18	1.70	0.93	0.85	
10	σ_{ms}[g]	0.65	1.25	1.02	0.94	1.94	0.44	0.11	

[a] Block-diagonal minimizer. [b] Newton−Raphson minimizer. [c] conjugate gradient minimizer. [d] $[\beta\text{-CD}]_i$ and $[\mathbf{1d}]_i$ were equal to 5 mM. [e] $[\beta\text{-CD}]_i = 1.5$ mM and $[\mathbf{1d}]_i = 7.5$ mM. [f] Computed using all eight values. [g] Computed discarding values for compound **1d**.

tilt one of the glucose rings in complex **B** when high ϵ values are used.

Experimental results[30] indicate a *syn*/*anti* ratio that is always greater than one. This should correlate with a larger stability of complex **A** over **B**. Although a reasonable agreement was obtained when the MM3 force field was used, results were more coincident when the MM3* force field and the GB/SA solvation model were used. Small divergences were obtained depending on the optimization routine employed.

Discussion

Compounds **1a**−**f** can be considered as ideal structures to study the facial selectivity in carbonyl group addition reactions.[39] The rigidity of the adamantyl skeleton eliminates any conformational consideration, and both diastereotopic carbonyl faces are virtually identical from steric considerations. In such systems, reagents attack the carbonyl face that is antiperiplanar to the electronically richest neighboring bonds.[40−42] Cieplak's transition state hyperconjugation[43] has been invoked to explain the facial selectivity observed (*syn* attack) in the photocycloaddition of **1a**−**f** with fumaronitrile.[41,42] Cyclodextrins invert this facial preference by hindering one of the carbonyl faces.

The reaction should take place partly over the free guest (the *syn*/*anti* ratio increases with the *β*-CD/**1** molar ratio) and partly over the complex (binding constants for these complexes are small[30]). The *syn*/*anti* ratio obtained when the reaction is carried out in the presence of the *β*-CD, thus depends on three factors:

(a) The difference in the carbonyl face reactivity, which determines the *syn*/*anti* ratio obtained from the free guest; it should be similar to that observed in the absence of *β*-CD.

(b) The binding constant of the complexes, which determine the amount of free and complexed guest depending on the initial concentrations of guest and host.

(c) The stability difference of complexes **A** and **B**, which controls the *syn*/*anti* ratio obtained from the complexed guest.

We may, thus, write

$$[syn]_{total} = [syn]_{free} + [syn]_{complex} \qquad (1)$$

Considering a kinetic control of the reaction, the previous equation can be rewritten as

$$[syn]_{total} = K_{syn}[\mathbf{1}]_{free} + K_{syn}[\text{complex } \mathbf{A}] \qquad (2)$$

This equation considers that K_{syn} (kinetic constant for the *syn*-oxetane formation) is the same for the free and for the complexed guest. This assumption is valid because the change in the reactivity when *β*-CD is present is exclusively due to a selective hindrance over one carbonyl face and should not affect the carbonyl group intrinsic reactivity. The [complex **A**] can be estimated as the product of the concentration of the complexed guest, [*β*-CD/**1**], and its population, A_{pop}, obtained from the computed relative stability (Table 1); the same applies to [complex **B**]. The total *syn*/*anti* ratio can, thus, be obtained as follows:

$$\frac{[syn]_{total}}{[anti]_{total}} = \frac{K_{syn}}{K_{anti}} \frac{[\mathbf{1}]_{free} + [\beta - \text{CD}/\mathbf{1}]A_{pop}}{[\mathbf{1}]_{free} + [\beta - \text{CD}/\mathbf{1}]B_{pop}} = \frac{[syn]_{water}}{[anti]_{water}} \frac{[\mathbf{1}]_{free} + [\beta-\text{CD}/\mathbf{1}]A_{pop}}{[\mathbf{1}]_{free} + [\beta-\text{CD}/\mathbf{1}]B_{pop}} \qquad (3)$$

Finally, the K_{syn}/K_{anti} ratio is equal to the *syn*/*anti* ratio obtained in those reactions carried out in water and in the absence of *β*-CD, assuming a kinetic control.

Table 2 lists the concentrations for the free and complexed guests obtained from the experimental binding constants[30] and from the initial concentrations of host and guest. Only complexes with compounds **1a**−**d** are considered because binding constants for **1e,f** could not be determined experimentally.[30] Each compound presents two entries due to the consideration of two sets of initial concentrations for each compound.

Table 3 shows the experimentally determined *syn*/*anti* ratios,[30] those computed using eq 3 together with the values in Tables 1 and 2, and two root-mean-square (rms) values, one for all the four compounds (entry 9) and the other for only the three halogenated compounds (entry 10). A generally good agreement was obtained and that for MacroModel using the Newton−Raphson minimizer (rms = 0.85 and 0.11) was remarkably good. MM3 results always present poorer agreement with experiments. The best rms for MM3 calculations was obtained when a low ϵ value (1.5) was used. The good results obtained with MM3* and the GB/SA solvation model indicate the adequacy of the tandem for this case.

The calculated *syn*/*anti* ratio for compound **1d** is markedly higher than that determined experimentally (5.74 and 3.35, respectively). Two factors can produce this discrepancy: (a) an overestimation of the experimental binding constant and (b) an overestimation of the

(39) Song, I. H.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 58.
(40) Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001.
(41) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690.
(42) Mehta, G.; Khan, F. A. *Tetrahedron Lett.* **1992**, *33*, 3065.
(43) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

energy difference between the **A** and **B** complexes. We do not have enough data to determine which factor is the most important, but the extremely good agreement between the computed and experimental *syn*/*anti* ratios for compounds **1a**−**c** suggests the energy difference is properly computed for all the compounds.

The combination of eq 3 with the computed preference of complex **A** allows the prediction of those not determined binding constants for **1e,f**. Calculated values for compound **1f** (R = OH) are always in the range 101.5−452.5 M^{-1} (depending on the initial host and guest concentrations and on the force field used). These values are in the range of the experimentally observed binding constants for the other studied compounds. The calculated binding constant for **1e** (R = *t*-Bu) was only obtained in one case, being the value equal to 2900 M^{-1}. This is the largest constant for the whole series, and it qualitatively agrees with other experimentally determined binding preferences of cyclodextrins for molecules containing *tert*-butyl groups.[44]

Conclusions

Molecular mechanics calculations (MM3 or MacroModel programs) quantitatively explain the experimentally obtained *syn*/*anti* ratio for the photochemical cycloaddition of fumaronitrile with several 5-substituted 2-adamantanones in the presence of β-CD. Computations predict complex **A** to be always more stable than **B**. This assumption agrees well with experimental results. The preference of R = Ph and *t*-Bu for being included into the β-CD cavity is remarkable. The observed change in facial selectivity is thus produced by bimodal inclusion of guests inside the host, and computations can be used to predict or explain experimental results within this series of products with a large degree of confidence.

Acknowledgment. Financial support was obtained from DGICYT (Ministerio de Educación y Ciencia, Spain) through Grant PB92-0611.

Supporting Information Available: One table containing the glycosidic dihedral angles between different glucose units for isolated β-CD and for complexes **A** and **B** of **1c** (as an example) computed at different ϵ values with the MM3 force field (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9614396

(44) Kotake, Y.; Janzen, E. G. *J. Am. Chem. Soc.* **1989**, *111*, 5138.