Molecular Modeling Calculations on the Acylation of β-Cyclodextrin by Ferrocenylacrylate Esters

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Abstract: Molecular modeling calculations have been performed on the complex of methyl ferrocenylacrylate with β-cyclodextrin, on the tetrahedral intermediates for acylation of the 2 or 3 hydroxyl groups of the cyclodextrin, and on the product 2 and 3 ferrocenylacrylate esters of β-cyclodextrin. The detailed results depend on the parameters chosen in the calculations; in all cases the product ester is twisted out of full conjugation, but with the most likely parameters this twisting is significantly centered at the ester group. These results are in general agreement with the conclusions of related calculations by Menger and Sherrod, although the initial assumptions and parameters were rather different. This agreement suggests that these calculations may validly reflect the physical reality, although they do not incorporate hydrophobic binding forces. The results suggest the reason that the very large rate accelerations in these acylations seen with good leaving groups such as *p*-nitrophenyl are greatly diminished with poorer leaving groups, when the transition state increasingly resembles the product ester.

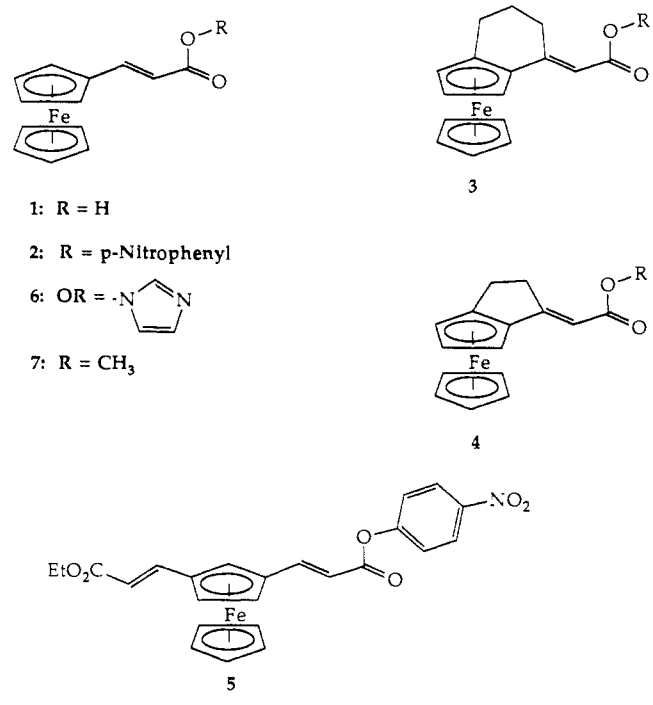
We have described a series of studies of the acylation of β-cyclodextrin by *p*-nitrophenyl esters.[1-5] In the pioneering work of Bender,[6] acylations of cyclodextrin by bound substrates were at most 200 times faster than was the hydrolysis of the same substrate in the absence of the cyclodextrin. Molecular models suggested that in his examples the substrate could bind into the cavity but the tetrahedral intermediate (a rough approximation of the transition state for acylation) was pulled largely out of the cavity. To solve this problem we prepared a series of *p*-nitrophenyl esters whose acyl groups could bind into the β-cyclodextrin cavity and stay more or less bound throughout the acylation reaction.[1-5] As hoped, some of these compounds showed much larger rates of acylation relative to the rate of hydrolysis under the same conditions (hydrolysis is of course not exactly analogous to acylation of a sugar hydroxyl group, but it corrects the acylation data for the intrinsic chemical reactivity of the substrate).

The most spectacular accelerations were seen with derivatives of ferrocenylacrylic acid (**1**). The *p*-nitrophenyl ester **2** had a $k_{acylation}/k_{hydrolysis}$ of 332000, while the related fused ring derivatives **3** and **4** had even larger rate ratios of 3 200 000 and 5 900 000, respectively.[3,5] We had added various projections to our other substrates to help define the geometries of their binding into the cyclodextrin cavity. We also added a projection onto the ferrocene ring, in compound **5**, and found that its $k_{acylation}/k_{hydrolysis}$ was 57000, only 6-fold less than that of **2**.[5] Thus the geometry involved in the reaction of **2** was not strongly blocked in **5**.

We hoped that the enormous accelerations seen with these active esters would also carry forward to less reactive compounds, such as amides. There is no real interest in producing catalysts for the hydrolysis of *p*-nitrophenyl esters; this is one reason that we did not worry about catalyzing a second step, in which the cyclodextrin ester is hydrolyzed back to cyclodextrin. If an amide of the ferrocene acids also showed a 10^5 or 10^6 acceleration in the acylation of β-cyclodextrin, then it would be worth hydrolyzing the product ester to achieve overall turnover catalysis of amide hydrolysis. However, we found that with poorer leaving groups, as in amides, the acceleration was greatly decreased.

We reported[1,5] that acylimidazole **6** derived from ferrocenylacrylate showed a $k_{acylation}/k_{hydrolysis}$ of only 1200 with β-cyclodextrin, much less than the 332000 with the *p*-nitrophenyl ester.

Chart I



We also found[7] that with anilides instead of esters there was no appreciable acylation of β-cyclodextrin under conditions that should have led to fast rates if they showed the 10^5-fold acceleration of the nitrophenyl esters. Thus it seemed clear that some geometric problem arises as the reaction goes from an early transition state, for highly reactive esters with good leaving groups, to a late transition state, with poorer leaving groups. In particular, it seemed likely that the transition state comes *before* the tetrahedral intermediate with a *p*-nitrophenyl ester, since that intermediate should mostly partition to product, but *after* the tetrahedral intermediate with poorer leaving groups. The huge rate accelerations with *p*-nitrophenyl esters occurred because the β-cyclodextrin complex was well bound and unstrained all the way from substrate to tetrahedral intermediate. A problem arising during the conversion of tetrahedral intermediate to product slowed the rates of those less reactive substrates whose transition states lie on that later part of the overall path.

The very fast acylation of β-cyclodextrin by substrates **2-4** reflects the rigid binding of substrate into the cyclodextrin cavity so that a cyclodextrin hydroxyl group is in the right position to attack the ester carbonyl. Furthermore, all the way to the resulting

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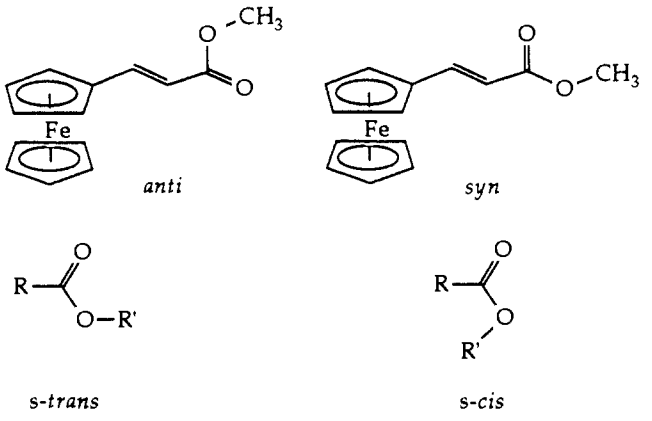

Figure 1. Conformations of ferrocenylacrylate esters.

tetrahedral intermediate this rigid geometry is essentially maintained. However, we realized[5] that there is a general problem in any acylation of an oxygen (or nitrogen) nucleophilic atom. The nucleophile must attack the carbonyl group along a p-orbital, perpendicular to the plane of the ester group, but in the product that nucleophile is now part of an ester group (or amide group) and should be in the carbonyl plane, not perpendicular to it. Thus the rigid geometry allowed in the path between substrate and tetrahedral intermediate cannot be maintained in the next part of the path. Some rotation or distortion is needed.

To illustrate this we assumed that the ferrocene nucleus adopts and maintains an orientation with its principal axis parallel to the cavity axis and that the product is an undistorted ester.[5] If so, the product ferrocenylacrylate ester of β-cyclodextrin would have to rotate either the carbonyl group or the entire acrylate chain by 90°. In either case this path would be destabilized because it breaks up the conjugated ferrocene:olefin:carbonyl system.

Recently Menger has reported the study of a series of esters of ferrocenylacrylic acid with β-cyclodextrin.[8] He found that the large acceleration seen with good leaving groups becomes considerably smaller with esters of less acidic alcohols than *p*-nitrophenol and suggested that there was a specific geometric problem with the product acylcyclodextrins, namely the formation of a planar s-cis ester (cf. Figure 1). The s-cis conformation is well-known to be less stable than the normal s-trans arrangement for esters.[9] Unfortunately, he did not mention the fact that we had already noted the diminished acceleration with poorer leaving groups,[1,5] albeit with a much less complete set of data than he supplied. He also did not refer to our prior different explanation[5] of this diminished acceleration.

Molecular models had guided our suggested explanation. They indicated that the products from acylation at the cyclodextrin C-2 hydroxyl were not conjugated and s-cis but were s-trans and twisted out of full conjugation. However, this seemed an interesting case for molecular modeling calculations. Thus we have applied the powerful MacroModel[10] program of Clark Still to this problem. While we have performed a number of such calculations, dealing with various stereochemical aspects of our experimental work, we will address here only the limited question of the reason that the ferrocenylacrylate ester of β-cyclodextrin is destabilized, a destabilization reflected in any late transition state that resembles this product. For computational simplicity we calculated reactions of the methyl ester **7** of ferrocenylacrylic acid, not the *p*-nitrophenyl ester **2** that was actually used in our experiments.

Menger has recently performed similar calculations,[11] since he also has an interest in clarifying the geometric factors involved in his experimental findings. Although we did not use the same set of parameters and assumptions, the results of his work and of our best calculations are in good qualitative agreement. Both conclude that the ferrocenylacrylate ester of β-cyclodextrin is destabilized principally by twisting, not by the formation of an untwisted s-cis ester. However, in contrast to our previous suggestion the twisting, by these calculations, is partly within the ester group itself.

Our calculations predict that in most cases examined the product has a rotated orientation in the cavity, so that the ferrocene axis is not parallel to the cavity axis. Since these calculations do not include the water medium and the principal binding force in the real physical system is hydrophobic, it is possible that the calculations overestimate the flexibility of orientation of the ferrocene unit of the substrate. If the hydrophobic packing forces held the ferrocene with its axis unrotated in the cyclodextrin cavity, even greater twisting of the acrylate chain would indeed be necessary.

Table I. Ferrocene Substructures Used (Written in MacroModel Atom Types)

Cyclopentadiene Rings[a]			
	Å	mdyn/Å	
C2*C2[b]	1.440	5.0	
C2–H1	1.104	4.6	
	deg	mdyn/rad²	
C2*C2*C2	108.0	0.42	
C2*C2–H1	126.0	0.36	
	V1 (kcal)	V2 (kcal)	V3 (kcal)
H1–C2*C2–H1	0.0	10.0	0.0
C2*C2*C2*C2	0.0	10.0	0.0
C2*C2*C2*H1	0.0	10.0	0.0+
charges: H, +0.19; C, −0.31			
Iron–Carbon Bond			
	Å	mdyn/Å	
C2–Fe	2.0643	4.0	
	deg	mdyn/rad²	
C2–Fe–C2	0.0	0.0[g]	
C2–Fe–C2	130.0	0.2[h]	
C2*C2–Fe	69.4	0.4	
H1–C2–Fe	126.9	0.0	
	V1 (kcal)	V2 (kcal)	V3 (kcal)
Fe–C2*C2*00	0.0	0.0	0.0
Out-of-Plane Bend			
	deg	mdyn/rad²	
C2*C2–Fe*00	0.0	0.0	
Fe: charge +1.23; van der Waals rad[c] 1.40 Å; ε[c] 0.63 kcal/mol			
Ferrocenylacrylate (Cyclopentadienyl Parameters as Above)			
	V1 (kcal)	V2 (kcal)	V3 (kcal)
8–7–6–5[d]	0.0	1.75	0.0
8–7–6–6′	0.0	1.75	0.0
Charges (atoms not mentioned as above or symmetry related):[e] **2**, −0.0662; **3**, +0.0979; **4**, −0.2506; **5**, +0.1014; **6**, +0.2784			
Tetrahedral Intermediates			
charges: **1a**, +0.036; **1′a**, +0.097; **1**, −0.036; **1′**, +0.097; **2**, 0.2720 **2a**, −0.2720; **3**, +0.359; **4**, −0.354; **4′**, 0.3060			

[a] For sources of data, see Methods section. [b] C2 is sp^2-hybridized carbon; H1 is hydrogen on an electroneutral atom; Fe is a wildcard atom, described in MM2 as Z0. [c] Taken from a Zn^{2+} parameter (W. C. Still, Columbia University); Fe^{2+} and Zn^{2+} have identical radii. [d] Numbered as in Figure 2. [e] From AM1 calculations on model compounds; see Methods for details. [f] From an AM1 calculation on 1,1-dimethoxy-1-hydroxyprop-2-ene. [g] Both C2 in the same ring. [h] C2 in different rings.

Methods

The calculations were performed with Clark Still's program[10] MacroModel V2.0 on a Microvax II and a Vax 11/780, with an Evans and Sutherland Model PS-390 graphics terminal. The MM2 force field was used, including Osawa's modifications,[12] Kroon-Batenburg lone pair

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Table II. Calculated Rotation Barriers and Energy Differences (in kcal/mol) for the Substrate Analogue, Methyl Ferrocenylacrylate[a]

	single-bond rotation barrier		
	7–6	5–3	3–2
initial parameters (V1.5, butadiene-like)	2.31	5.39	9.67 (anti) 8.57 (syn)
energy advantage, s-trans vs s-cis		1.86 (syn) 3.79 (anti)	
final parameters (V2.0, NMR derived)	7.06	7.42	8.36 (anti)
energy advantage, s-trans vs s-cis		3.68 (anti)	

[a] For the numbering scheme, see Figure 2.

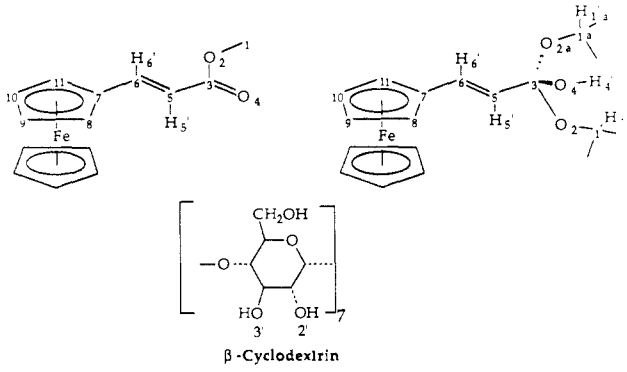

Figure 2. The numbering scheme for ferrocencylacrylate esters and derived tetrahedral intermediates and for β-cyclodextrin.

parameters,[13] and Still-Goldsmith carbonyl parameters.[14]

Ferrocene parameters were obtained from published crystal structure data and ab initio calculations[15] and are listed in Table I. Ferrocene itself cannot be simply modeled by the original MM2 force field. The structure was approximated by using three σ bonds from iron to each ring (atoms are allowed a maximum of six bonds in MacroModel).

Charges on the atoms of the α,β-unsaturated ester group were estimated from AMPAC calculations on model methyl 2- and 3-thienylacrylate esters and on the corresponding pyrrolylacrylic esters, with full geometry optimization. The charges selected were the average for these two thiophene and pyrrole systems, adjusted to retain overall neutrality. The torsional barriers resulting from these calculations were unrealistically low and were discarded. Thus the initial set of parameters used butadiene-like torsional parameters to describe the single bond torsion between cyclopentadienyl and the double bond of the acrylate moiety. The results of these initial calculations are listed in parentheses in Table III. The later calculations, whose results are listed without parentheses in Table III, used a torsional parameter for the 6–7 single bond estimated from an NMR coalescence study (vide infra).

The rotational barriers were checked by constraining the respective dihedral angles to different values with very high force constants (1000 kJ/rad^2) followed by minimization of the structure. After removal of the constraints, the energy of the molecules was computed and compared to the energy of the unstrained molecule. β-cyclodextrin was grown in the carbohydrate mode of MacroModel, with the standard parameters, and minimized to a gradient of 0.010 kJ/Å.

All complexes were created by rigid-body docking of a minimized ferrocenylacrylate to a minimized β-cyclodextrin. The resulting structures were then minimized to gradients of about 3 kJ/Å, checked by another cycle of docking, and finally minimized to gradients smaller than 0.02 kJ/Å (typically 0.01 kJ/Å) using predominantly the conjugate gradient routines provided by the program package.

The low-temperature NMR experiment was done on a Varian 400-MHz spectrometer. A solution of ethyl ferrocenylacrylate in 1/1 THF-d_8 and diethyl ether-d_{10} was examined for decoalescence of the NMR signals of H_8 and H_{11} at low temperature. The barrier height was estimated from the equation[16]

$$\Delta G(\text{activation}) = 19.23 T_c(9.87 + \log (T_c/\Delta\nu))\ \text{J/mol}$$

This low-temperature barrier was used for the second set of calculations, whose results are listed in Table III.

Results and Discussion

Prior to the investigation of guest–host complexes with β-cyclodextrin, the rotational barriers in methyl ferrocenylacrylate were calculated (Table II). We found all within the expected limits except the 6–7 torsional barrier, which seemed unnaturally low. A low-temperature proton NMR study was performed on ethyl ferrocenylacrylate. At −120 °C full separation of the peaks was achieved ($\Delta\nu$ = 136.6 Hz) and coalescence of the peaks corresponding to the 8 and 11 positions of cyclopentadienyl was reached at −112 °C. From these data, the rotational barrier for the 6–7 single bond was estimated to be 7.35 kcal/mol. No other peaks in the spectrum showed coalescence. As a result of the NMR study, the parameter describing the 6–7 single bond torsion was adjusted to the value in Table I to give results in good agreement with the NMR experiment (Table II).

Ferrocenylacrylate was docked to the secondary side of cyclodextrin and minimized according to the procedure outlined in the Methods section. After the first complex had been minimized, the structure was checked for singularity by performing random translations (0.05 to 0.15 Å) and rotations (20–180° along all coordinates) of the ferrocene derivative in the cavity followed by minimization. Rotations around the 3–5 and 6–7 single bonds were also specified between 30 and 180°. No minimum lower in energy than the two complexed starting syn and anti structures could be found. The next minima occur at 2.5, 3.3, and 20.9 kcal above the global minimum for the anti conformers and 2.7 kcal for the syn conformers, enough difference to assure reaction mainly from the global minima.

The minimum structures for the cyclodextrin complexes of both the syn and anti substrate conformers (Figure 3) show full penetration of the ferrocene unit into the cyclodextrin cavity and a slight rotation of the entire substrate around the acrylate sidearm long axis. Both conformers show only minor deviations from planarity in the acrylate sidearm (Table III). In both the syn and anti complexes a cyclodextrin 2′-hydroxyl is well positioned for attack on the carbonyl group.

The 2′-hydroxyls of cyclodextrin are known[17] to be more acidic than the 3′-hydroxyls, so 2′ is probably the reactive position under basic conditions (as it is in glucosides generally). Unfortunately, the product esters equilibrate between the 2′- and 3′-positions and make it difficult to establish clearly that the 2′-hydroxyl is indeed the first nucleophile. In the past we have seen a bound substrate donate a (non-equilibrating) tosyl group to the cyclodextrin C-2 hydroxyl,[18] but direct tosylation of a C-3 hydroxyl with a different substrate has also been reported.[19] For this reason we have calculated the geometries for both C-2 and C-3 acylation by our bound substrate ester. In the tetrahedral intermediates (Figure 2) the carbonyl-derived oxygen on the tetrahedral intermediate was modeled as protonated, since a negative charge in this position would certainly be solvated or hydrogen bonded in solution.

The results are rather similar with either set of starting parameters. In the complex of the substrate, in either its anti or syn form, the partial single bonds whose coplanarity is promoted by conjugation between the electron-donating ferrocene unit and the electron-accepting carbonyl group are twisted by at most 8.5°, and generally less. On conversion to the tetrahedral intermediate all the conformations are more free to rotate. The 3–5 bond twists as much as 57° while even the still weakly conjugated 6–7 bond twists by up to 34° with our initial parameters, 25° with the stiffer torsional constant for this bond (the stiffer constant, derived from NMR studies on an ester, should probably not be used for a tetrahedral intermediate).

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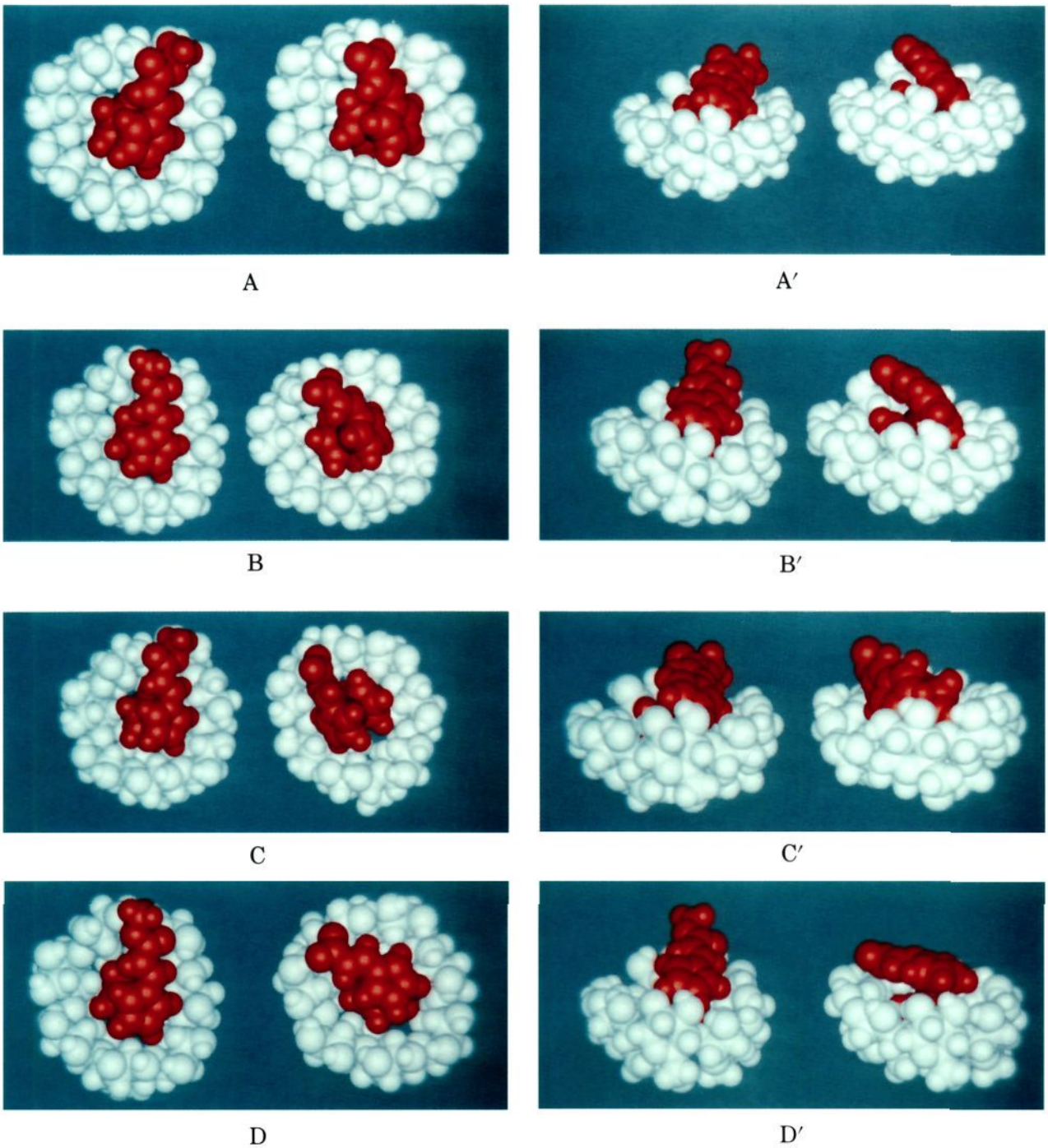

Figure 3. Computer-generated CPK models of the calculated minimum energy conformations for ferrocenylacrylate esters bound in a β-cyclodextrin cavity and for the derived acylcyclodextrin product, showing the conformational changes involved in the overall reaction. Each photograph shows the bound substrate (on the left) and the product (on the right) in top view (unprimed) and side view (primed). The sequence is as in Table III: A and A′, acylation at the 2′-hydroxyl by the anti ester; B and B′, acylation at the 2′-hydroxyl by the syn ester; C and C′, acylation at the 3′-hydroxyl by the anti ester; D and D′, acylation at the 3′-hydroxyl by the syn ester. Note the change from syn to anti during B and from anti to syn during C. There is a considerable tipping of the ferrocene ring during the reaction of cases B and C, but less during the reactions of cases A and D. Case C also has significant twisting in the acrylate chain of the product, as does D. The ferrocenylacrylate units are shown in red and the cyclodextrin in white.

Four product structures were considered: cyclodextrin esters derived from the syn or anti conformation of the substrate, and acylated on either the 2′- or 3′-hydroxyl of the cyclodextrin. For simplicity we did not also examine the mirror image substrate conformations, although the resulting complexes are diastereomeric. The choice of parameters made some difference.

Acylation at 2′ with either starting ester conformation led to a product that was essentially an s-trans ester, but with distortion. The products are both calculated to be anti, and with closely similar but not identical geometries (Figure 3 and Table III). As calculated, a significant barrier separates these similar conformations. With our original parameters the ester group itself was twisted around the 2–3 bond by 30 to 33°, so the carbonyl group was not fully stabilized by the alkoxy group. With the newer parameters the twist was even greater, by 46 to 49°. This twisting, which partially deconjugates the ester itself, is the main problem that destabilizes the product and diminishes the acceleration with poorer leaving groups. There is also some twisting within the

Table III. Calculated Relative Energies (in kcal/mol), Selected Dihedral Angles (in deg), and Twist Away from Full Conjugation (in deg) in the Cyclodextrin–Substrate Complexes, the Tetrahedral Intermediates, and the Acylated Cyclodextrin Products for Reaction of the Anti and the Syn Conformations of the Substrate with the 2′- or 3′-Hydroxyl Groups of β-Cyclodextrin

	E_{rel}	7–6	twist	5–3	twist	3–2	twist
complex (anti)[b]	0	175.7 (174.0)	4.3 (6.0)	−171.5 (−172)	8.5 (8.0)	−0.1	0.1
tet. int. (2) (anti)	11.9 (14.6)	172.2 (−156)	7.8 (24.0)	−174.7 (−172)	*a*	21.4	*a*
prod. (2) (anti)	13.3 (19.6)	176.4 (−170)	3.6 (10.0)	173.6 (177)	6.4 (3.0)	−49.0 (−30)[c]	49.0 (30)
complex (syn)	0.7 (1.4)	174.0 (−173)	6.0 (7.0)	5.6 (9.0)	5.6 (9.0)	−1.4	1.4
tet. int. (2) (syn)	10.6 (15.3)	156.8 (−172)	24.2 (8.0)	−47.3 (−45)	*a*	168.0	*a*
prod. (2) (syn)	10.7 (14.8)	165.4 (−175)	15.6 (5)	175.7 (177.0)[d]	4.3 (3.0)	−46.3 (−33)	46.3 (33.0)
tet. int. (3) (anti)	2.0 (5.4)	−168.6 (164.0)	11.4 (6.0)	−153.6 (−123)	*a*	−105.5	*a*
prod. (3) (anti)	9.3 (10.0)	151.3 (144.0)	28.7 (36.0)	−33.0 (−35.0)[e]	33.0 (35.0)	168.0 (172.0)[f]	12.0 (8.0)
tet. int. (3) (syn)	6.0 (4.2)	155.5 (161.0)	24.5 (29)	−30.3 (−27)	*a*	95.9	*a*
prod. (3) (syn)	22.9 (16.0)	169.3 (170.0)	10.7 (10.0)	−153.7 (−154.0)[d]	26.3 (26.0)	−133.1 (−130)	46.9 (50)

[a] Definition of a twist angle away from full conjugation is meaningless here. [b] Complex: ferrocenylacrylate with β-cyclodextrin; assignments of anti and syn are with respect to the conformation of the acrylate in the complex from which the structure is derived. Tet. Int.: tetrahedral intermediate resulting from attack of a secondary hydroxyl (2′ or 3′ is marked in parentheses) on the ester carbonyl. Prod.: the ferrocenylacrylate ester of β-cyclodextrin acylated at C-2 or C-3 with a ferrocenylacrylate ester substrate originally in the anti or syn conformation. Energies and angles in parentheses result from the initial set of parameters. [c] A distorted s-trans conformation (<90°). [d] The conformation has changed to anti (>90°). [e] The conformation has changed to syn (<90°). [f] A distorted s-cis conformation (>90%).

ferrocenylacrylate unit in all cases.

In the products derived from acylation at the 3′-hydroxyl group the situation is different. Now the esters are more or less s-cis, but twisted by up to 50° away from full conjugation (a 90° twist would make the ester halfway between s-cis and s-trans). In this case the product derived from either substrate conformer now has a reversed conformation (Figure 3 and Table III): syn and anti interconvert during the acylation reaction.

The geometric difference on acylation at 2′ vs 3′ is not surprising. The 2′-hydroxyls of cyclodextrin point into the cavity, so a (twisted) s-trans ester is easily formed; the 3′-hydroxyls point away from the cavity, so the product resembles s-cis.

The relative energies of these conformations are probably not a good guide to the path actually used. In the transition state for formation of a tetrahedral intermediate the attacking cyclodextrin oxygen carries appreciable negative charge, so the greater acidity of the 2′-OH group should favor acylation at C-2. However, in reactions with a poor leaving group, in which the transition state occurs after reversible formation of a tetrahedral intermediate, acylation could well occur at C-3 if it is favored for conformational reasons. Thus we cannot yet rule out a change in the *position* of acylation when the substrate is changed.

These calculations, and those of Menger,[11] show that the distortion in reactions with late transition states involves twisting within the ester group, not just twisting of the acrylate unit. Thus it was of interest to see how the system solved the problem we first posited: attack of the cyclodextrin hydroxyl *perpendicular* to the plane of the conjugated system, but a final product with the cyclodextrin oxygen *within* that plane. This is possible without twisting the acrylate unit because in three of the four cases the calculations predict a complex in which the product is *tipped* within the cavity (Figure 3) by rotation around the acrylate sidearm axis. In one case only (case D of Figure 3) can the system stay in more or less its original binding attitude by precessing.

With likely parameters, the calculated energy needed to twist the acrylate unit completely out of conjugation is even worse. However, as mentioned earlier this calculated tipping of the ferrocene unit in the cavity may reflect the fact that in the calculations only van der Waals and charge interactions are included as attractive forces between the substrate and the cyclodextrin. In the real system hydrophobic binding is the principal force producing a complex. It could well be that the tipping shown in Figure 3 would not be seen if hydrophobic binding were successfully modeled; in that case the acrylate conjugated system would have to twist even more in the product than the amounts (up to 35° at some bonds) calculated here.

Furthermore, even a late transition state will not be identical with the product ester but will occur on the way from intermediate to product. In a case like C of Figure 3, and in general when a syn substrate produces an anti product, or vice versa, a late transition state could have even more twist in the developing acrylate conjugated system than is seen in the final product.

Thus the geometric problem predicted earlier[5] for the product ester is certainly present. It is solved by some combination of twisting within the ester group, twisting of the acrylate conjugated system, and rotation of the entire ferrocenylacrylate unit within the cyclodextrin cavity.

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