Docking Calculations on Ferrocene Complexation with Cyclodextrins

F. M. Menger* and M. J. Sherrod

Contribution from the Department of Chemistry, Emory University, Atlanta, Georgia 30322.
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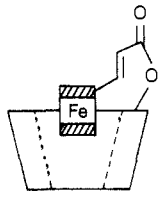
Abstract: A molecular mechanics force field was developed that provided calculated geometries for complexes between ferrocene and α-, β-, and γ-cyclodextrin. Docking calculations on the association of 3-ferrocenylacrylate esters with β-cyclodextrin, and the acylcyclodextrin derived therefrom, were also preformed. They showed that the (3×10^5)-fold difference in acceleration between the *p*-nitrophenyl and ethyl ester, occurring when the esters enter the cyclodextrin cavity, is not related to a C=C/C=O perpendicular "twist". Nor is the difference due to "attack" angles and distances that are almost identical for the two esters. Instead, the results affirm our previous contention that formation of a distorted ester in the acylcyclodextrin adversely affects partitioning of a tetrahedral intermediate unless the substrate is endowed with a particularly good leaving group. An enzyme-catalyzed ester or amide cleavage need not suffer this limitation.

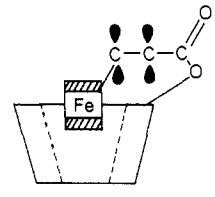
The *p*-nitrophenyl ester of 3-ferrocenylacrylic acid experiences a 3.3×10^5 acceleration in reactivity when it binds to β-cyclodextrin.[1] On the other hand, no acceleration can be observed with the complex between the corresponding ethyl ester and β-cyclodextrin. We recently attributed the difference among bound esters to partitioning of the tetrahedral intermediate which is controlled, in part, by formation of a lactone-like s-cis acylcyclodextrin (drawn below).[2] Only if the ester leaving group has a pK_a less than 9 does the tetrahedral intermediate partition favorably toward the acylcyclodextrin.[2]



An enzyme-catalyzed ester cleavage need not, of course, suffer this limitation.

The above rationale[2] assumes that host–guest complexes of all the ester substrates we investigated have the same basic structure. Thus, the argument would collapse if, for example, the carbonyl of the *p*-nitrophenyl ester within the complex were held 3 Å away from the nearest cyclodextrin hydroxyl, whereas the ethyl were 5 Å away. We felt, intuitively, that such a possibility was unlikely because the ferrocene moiety adsorbs tightly to the cyclodextrin cavity and, therefore, a remote substitutent should not grossly distort the complex. Nonetheless, the assumption of a constant geometry among our complexes warrented examination in a rigorous fashion, a fact that motivated the docking calculations described herein. We hoped, additionally, that the calculations would provide information on host–guest association not previously available.

Yet another factor was important in motivating our calculations. Previous to our own cyclodextrin studies, Breslow et al.[1] had suggested that acceleration and leaving-group were related. No specific experimental data were provided except for a footnote citing a 1200-fold increase in hydrolysis rate when 3-ferrocenylacryloylimidazole binds to β-cyclodextrin[3] (compared to $>10^5$ for the *p*-nitrophenyl ester complex). Owing to the uncertainties in comparing an acylimidazole with a *p*-nitrophenyl ester (espiecially since the former is subject to nucleophilic catalysis while the latter often responds to a general base mechanism),[4] it was felt that a more extensive study was necessary.[2] Moreover, Breslow et al., in explaining the relationship between acceleration and leaving-group ability, invoked a "twisted" intermediate where the π-orbitals of the double bond and the carbonyl are perpendicular and totally out of conjugation (drawn below). This structure appeared to us far less likely a rationale for the observations than a s-cis ester upon which we focused our previous analysis.[2] In any event, a more quantitative assessement of the situation seemed desirable, and we therefore undertook the calculations reported below. As will be shown, they provide no evidence for the proposed "twisted" acylcyclodextrin.



We report here the construction of an MM2 force field for use with MACROMODEL,[5] which allowed computations on ferrocene and ferrocene derivatives. This force field was applied to complexes between ferrocene and α-, β-, and γ-cyclodextrin (with six, seven, and eight glucose units, respectively). Complexes of ethyl and *p*-nitrophenyl 3-ferrocenylacrylate with β-cyclodextrin, and the acylcyclodextrin derived therefrom, were also examined.

Computer Methodology

Calculations were performed wtih MACROMODEL[5] executed on a VAX 11/785 or MicroVax II computer. An Evans and Sutherland PS390 graphics terminal was used to generate and view the structures. Unless mentioned to the contrary, energy minimizations were carried out with MACROMODEL's default values for the dielectric constant and nonbonded cutoff distances.[6] All structures were minimized until the root mean square of the gradient vectors was less than 0.01 kcal/Å.

Our first objective was to duplicate the ferrocene structure with a molecular mechanics force field using electrostatic and van der Waals interactions to retain the rings in the proper geometry. We chose the X-ray structure of Seiler and Dunitz,[7] with C–C distances of 1.431 Å and C–Fe distances of 2.059 Å, to serve as our "target geometry" for modelling purposes.

MACROMODEL is not parameterized for cyclopentadienyl anion carbons and iron atoms. We skirted this difficulty by deleting all parameters from the external data file for Si (silicon) and ZO (a "wildcard" metal) and, in their place, entering the parameters given in Table I. The substitutions had the effect of redefining silicon atoms as the ring carbons, with

(1) Breslow, R.; Trainor, G.; Ueno, A. *J. am. Chem. Soc.* **1983**, *105*, 2739.
(2) Menger, F. M.; Ladika, M. *j. Am. Chem. Soc.* **1987**, *109*, 3145.
(3) Czarniecki, M. F.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 7771. See footnote 9 (and footnote 14 in ref 1 where anilides, also very different esters, are mentioned without specifics).
(4) Fife, T. H. *J. am. Chem. Soc.* **1965**, *87*, 4597.
(5) W. Clark Still, Columbia University.
(6) Dielectric contant = 1.0 (distance dependent). VDW cutoff distance = 6.00 Å. Electrostatic cutoff distance = 12.00 Å.
(7) Seiler, P.; Dunitz, J. D. *Acta Crystallogr.* **1982**, *B38*, 1741.

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Table I. Force Field for Unsubstituted Ferrocene

Bonds

symbol	R_0	K_R	dipole moment
Si-Si[a]	1.431	9.600	0.0
H1-Si[b]	1.101	4.600	0.0

Bond Angles

symbol	Θ_0	K_Θ
H1-Si-Si	126.0	0.40
Si-Si-Si	108.0	0.60

Torsional Angles

symbol	V1	V2	V3
H1-Si-Si-H1	0.0	15.0	0.0
H1-Si-Si-Si	0.0	15.0	0.0
Si-Si-Si-Si	0.0	15.0	0.0

VDW Parameters

symbol	radius	ϵ	charge
Si	1.94	0.044	−0.20
Z0[c]	1.10	0.500	+2.00

[a] The parameters for atom type Si (silicon) were changed in order to redefine this atom type as the aromatic cyclopentadienyl anion carbons. [b] Atom type H1 is a "normal" hydrogen (e.g., a C–H hydrogen). [c] Atom type Z0 is considered by MACROMODEL to be a "wildcard" metal ion, in this case defined as Fe^{2+}.

point charges of −0.2, and of designating the "wildcard" metal atom as Fe^{2+}. The VDW values or Fe^{2+} in Table I were selected to establish the correct C–Fe distance of 2.059 Å, the remainder of the parameters (taken from analogous sp^2 carbon interactions aleady in the force field) being necessary to secure the proper geometry for the cyclopentadienyl anion rings.

Esters of 3-ferrocenylacrylic acid were modelled in a similar fashion with the parameter set in Table II. A crystal structure of β,β-dicyano-α-methylvinylferrocene[8] showed that electron-withdrawing groups on a vinyl substituent cause a slight contraction in the C–C bonds of the rings. We therefore fixed the C–C bond lengths in the ferrocene ring at 1.4164 Å and adjusted the VDW radius of iron to obtain a C–Fe distance of 2.046 Å (as in the X-ray structure). The geometry and bond moments of the nitro group were taken from an X-ray[9] and an AMPAC calculation, respectively. Other required parameters had already been entered into the "MM2.FLD" file of MACROMODEL.

Three limitations to the accuracy of our computational results must be mentioned. (a) Calculations were performed for systems in the gas phase; solvation effects were neither explicity nor implicity considered. In this regard, of course, we are in the company of most theoreticians. Ignoring the solvent could, among other consequences, cause the complexes to appear more flexible than they are in reality. This is because complexation is driven by hydrophobic forces that are not incorporated in our calculations. In defense of the computations, however, it should be stated that we are treating large rate variations (>10^5-fold) that exist between the ethyl and *p*-nitrophenyl esters. Relevant geometries (e.g., those of the s-cis and s-trans configurations) differ by several kcal/mol. In contrast, currently fashionable gas-phase "calculations" of product ratios in solution involve energy differences of less than 1 kcal/mol. The reader, however, should not find comfort in this comparison but, as with all such computations, maintain a wholesome sense of doubt. (b) Another difficulty derives from the rotational freedom of a multitude of hydroxyls (21 for β-cyclodextrin). Fortunately, energy differences among the rotamers are small and, in any case, we mitigated the problem by consistently initiating our calculations with the identical set of "minimized" cyclodextrin geometries. (c) Finally, owing to the absence of π-bonding in the MM2-based model, we held the ferrocene structures together solely by electrostatic and VDW forces. Consequently, our simulation detects virtually no energy difference between eclipsed and staggered rings when in fact the former is favored by 1 kcal/mol.[10] Since, however, the binding energies for ferrocene–cyclodextrin complexation far exceed 1 kcal/mol, a small underestimation of rigidity is not serious, and the space-filling properties of ferrocene are thus adequately represented.

Table II. Force Field for Ferrocenylacrylate Esters

Bonds

symbol	R_0	K_R	dipole moment
C2—Si[a,b]	1.470	5.00	0.0
Si—Si	1.4164	9.600	0.0
H1—Si[c]	1.101	4.600	0.0
C2—N0[d]	1.469	6.400	0.0
O2=N0	1.237	8.000	−1.7

Bond Angles

symbol	Θ_0	K_Θ
C2=C2—Si	120.0	0.43
Si—C2—H1	120.0	0.36
C2—Si—Si	126.0	0.55
H1—Si—Si	126.0	0.40
Si—Si—Si	108.0	0.60
C2=C2—N0	120.0	0.43
C2—C2—N0	120.0	0.43
C2—N0=O2	118.0	0.55
O2=N0=O2	124.0	0.55

Torsional Angles

symbol	V1	V2	V3
C2—C2=C2—Si	−0.93	15.0	0.0
H1—C2=C2—Si	0.0	15.0	0.0
H1—C2—Si—Si	0.0	1.1	0.0
C2=C2—Si—Si	1.0	1.25	0.0
H1—Si—Si—C2	0.0	15.0	0.0
C2—Si—Si—Si	0.0	15.0	0.0
H1—Si—Si—H1	0.0	15.0	0.0
H1—Si—Si—Si	0.0	15.0	0.0
Si—Si—Si—Si	0.0	15.0	0.0
C2*C2—N0=O2	0.0	5.0	0.0

VDW Parameters

symbol	radius	ϵ	charge
N0	1.82	0.055	0.0
Si	1.94	0.044	−0.20
Z0[e]	1.085	0.500	+2.00

[a] The parameters for atom type Si (silicon) are changed in order to redefine this atom type as the aromatic cyclopentadienyl anion carbons. [b] "C2" is the symbol given by MACROMODEL to represent sp^2 hybridized carbons. In this table C2 refers to carbons either in the acrylate linkage or in the *p*-nitrophenyl ring. [c] Atom type H1 is a "normal" hydrogen (e.g., a C–H hydrogen). [d] Atom type N0 is a "generalized" nitrogen in MACROMODEL. Here it is specifically defined as the nitrogen in the nitro substituent in the *p*-nitrophenyl group. [e] "Z0" is considered by MACROMODEL to be a "wildcard" metal ion, in this case defined as Fe^{2+}.

Results and Discussion

Complexes of Ferrocene. α-, β-, and γ-Cyclodextrin structures were generated with use of the "Grow" feature of the "Carbonhydrate submode" of MACROMODEL.[5] Particular care was taken during the early stages of minimization (steepest descents, no line search) to ensure that the molecule retained a high degree of radial symmetry for the sugar units as a whole and for the hydroxyls on either side of the "doughnut". About five CPU days on the Microvax II were required to achieve a minimized structure for the γ-compound. The resulting geometries, shown in Figure 1, agree well with published X-ray pictures.[9,11] Structures in Figure 1 served as starting conformations for all subsequent docking calculations.

To our knowledge, complexes between ferrocene and the cyclodextrins have not been investigated by X-ray analysis. In 1984 Harada and Takahashi,[12] using spectroscopic data and mechanical modelling, suggested the structures shown below. It was pointed out that since ferrocene is too large to be totally incorporated within the α-cyclodextrin cavity, two α-cyclodextrins are needed

(8) Rybakov, V. B.; Aslanov, L. A.; Eremin, S. A. *J Struct. Chem.* **1983**, *24*, 495.
(9) Harata, K. *Bull. Chem. Soc., Jpn.* **1977**, *50*, 1416.
(10) Carter, S.; Murrell, J. N. *J. Organomet. Chem.* **1980**, *192*, 399.
(11) Hybl, A.; Rundle, R. E.; Williams, D. E. *J. Am. Chem. Soc.* **1965**, *87*, 2779. Fugita, K.; Matsunaga, A.; Imoto, T.; Hirotsu, K.; Kanitori, S.; Higuchi, T. *J. Am. Chem. Soc.* **1985**, *107*, 1970.
(12) Harada, A.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 645.

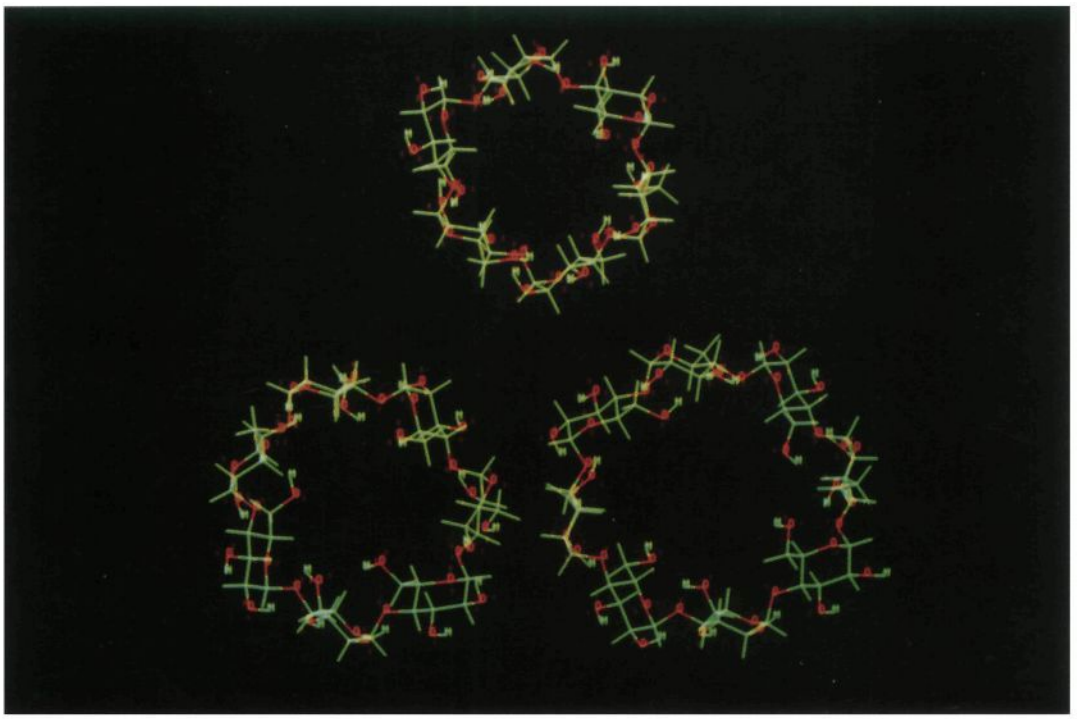


Figure 1. Computer-generated structures of α-cyclodextrin (top), β-cyclodextrin (bottom left), and γ-cyclodextrin (bottom right).

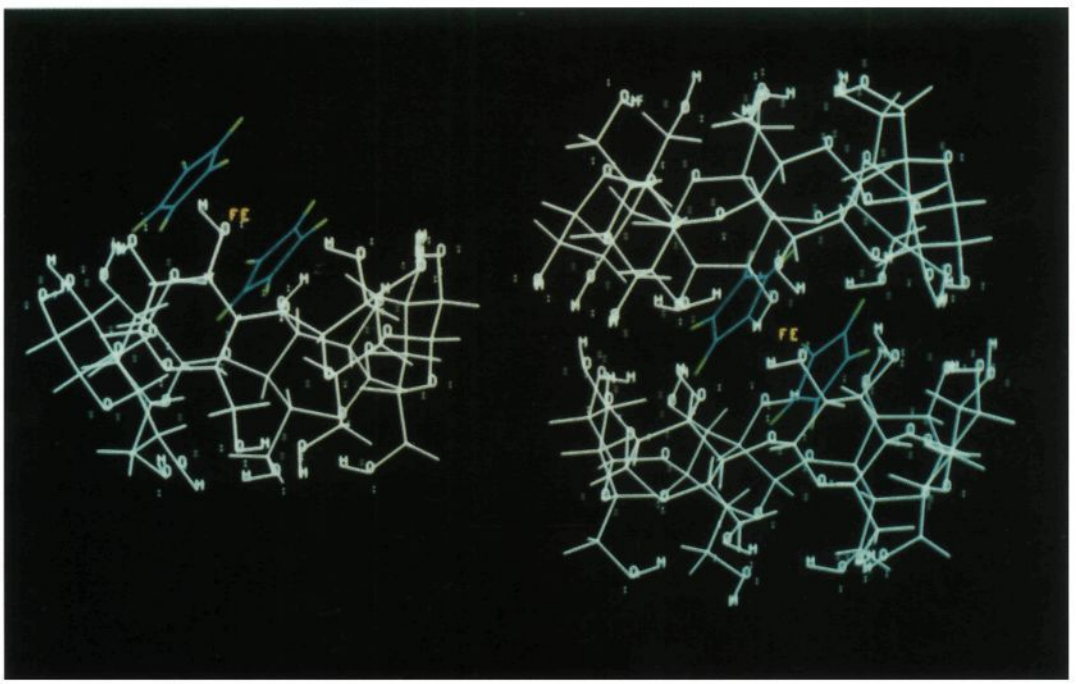
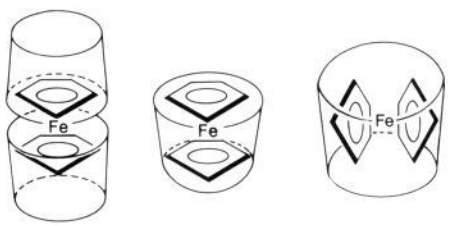


Figure 2. Computer-generated structures of the 1:1 complex (left), and 2:1 complex (right) between α-cyclodextrin and ferrocene.



to envelop the guest. A 2:1 host–guest complex was actualy isolated. In contrast, β-cyclodextrin forms a tight 1:1 complex having a proposed "axial" geometry. γ-Cyclodextrin has a sufficiently large cavity to accommodate an "equatorial" orientation of ferrocene, a binding mode that received indirect support from ORD spectra.[12]

Initially, our new force field was used to obtain rough "distance vs energy" curves for the docking of ferrocene into the cyclodextrins. Thus, the energy decreases as the ferrocene enters the cavities until one "pushes too far" and the energy shoots up dramatically. Initial distances in our calculations approximated the minimum-energy distances revealed from the plots. Calculations were then run repeatedly while varying both axial and equatorial geometries and while randomly rotating the guest relative to the host. Ultimately, at the cost of considerable computer time, we located the lowest energy complexes.

Minimization of 1:1 and 2:1 complexes between ferrocene and

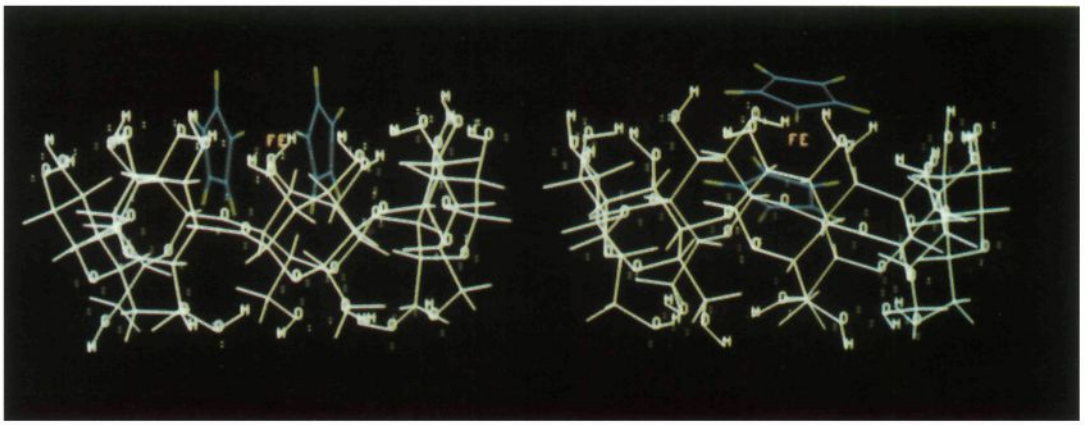


Figure 3. Computer-generated structures of an equatorial (left) and axial (right) complex between β-cyclodextrin and ferrocene.

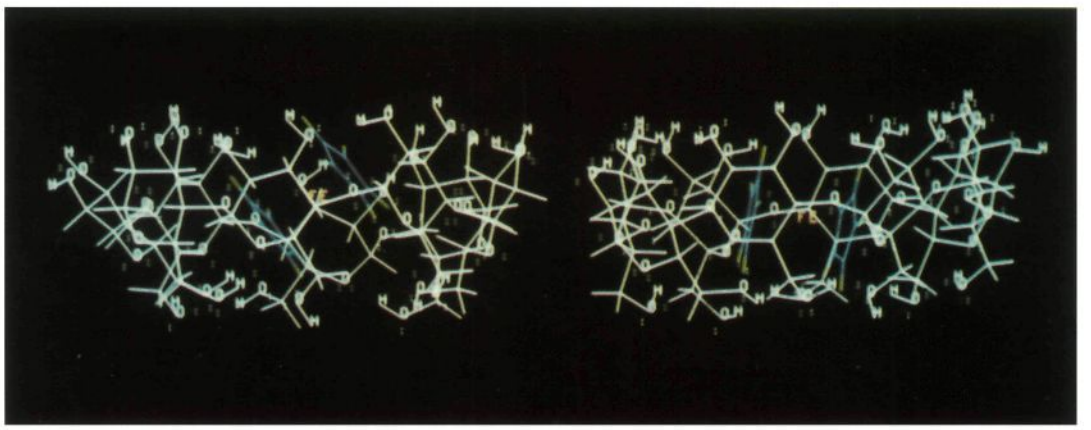


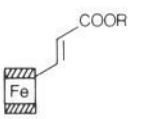
Figure 4. Computer-generated structures of two complexes detected for γ-cyclodextrin and ferrocene.

α-cyclodextrin gave the structures shown in Figure 2 regardless of whether the input geometry was axial or equatorial. The ferrocene guest within the 1:1 complex, finding too little space to penetrate deeply, tilts 40–45° at the upper rim of the α-cyclodextrin cup. This exposes a large section of ferrocene to the outside, thereby permitting (as Harad and Takahashi[12] demonstrated experimentally) coordination to a second host molecule. The tilt is maintained in the 2:1 complex. Gas-phase binding energies (defined here as $E_{components} - E_{complex}$) increase from 20 to 78 kcal/mol upon addition of a second α-cyclodextrin, the enhanced stability arising from favorable intermolecular interactions among the hydroxyls and from electrostatic and VDW terms generated by completely surrounding the guest. It may be added parenthetically that minimization of the 2:1 complex was so demanding of computer memory that the electrostatic cutoff had to be reset from 12 to 8 Å in order to avoid overloading the interaction array; the above energies, however, were calculated with standard default values.

Ferrocene binds to β-cyclodextrin in *both* an axial and equatorial orientation (Figure 3). Equatorial complex is favored by 0.5 kcal/mol, an energy difference too small to be significant. Packing forces in a crystal, or solvation effects in solution, could well determine the preferred binding mode with real systems. In this connection, we deliberately imposed slight modifications upon the ferrocene structure in order to determine their effect on guest orientation. When the ferrocene was slightly contracted (i.e., C–C bonds and C–Fe distances reduced by 0.015 Å as occurs with ferrocenes having electron-withdrawing substituents),[8] the equatorial guest was favored by 2 kcal/mol. Lengthening the bonds by the same amount led to a 2 kcal/mol more stable axial complex. Size and orientation here are in a delicate balance.

Two geometries of virtually identical energies were also found for ferrocene plus γ-cyclodextrin (Figure 4): an equatorial form and a second one tilted about 40° from horizontal. "Wobbling" back and forth between conformations appears sterically unrestrained. The equatorial complexes of β- and γ-cyclodextrin differ in binding energy by less than 1 kcal/mol.

Complexes of Ethyl and *p*-Nitrophenyl 3-Ferrocenylacrylate with β-Cyclodextrin. Both the ethyl and *p*-nitrophenyl esters showed a strong preference for binding to β-cyclodextrin in an equatorial



R = Et, *p*-NO_2Ph

orientation (Figure 5). When the computer was purposely given an axial input geometry, the guest spontaneously reoriented itself to produce the geometries shown in the photograph. Neither the schematics of Breslow[1] nor those of Menger[2] adequately portray the true host–guest relationships deduced by our calculations.

The carbonyls of the ester appendages are seen to position themselves above the edge of the cyclodextrin cup. Table III lists the distances separating the carbonyl carbons from the nearest cyclodextrin hydroxyls that, we presume, ultimately attack the esters. Two points are relevant to reactivity vs structure: (a) If distance determines the reactivity site, then one would predict that the C_2–OH, rather than the C_3–OH, should become acylated by the guest (the distances being 4.2–4.3 and 4.7–4.9 Å, respectively). The acylation site has yet to be elucidated experimentally. (b) The ethyl and *p*-nitrophenyl ester complexes differ only slightly in their geometric properties. Thus, both have planar –CH=CHCOO– moieties. Moreover, both have similar distances separating the C=O carbon from the C_2–OH (i.e., 4.26 and 4.16 Å, respectively). Finally, the "attack angle" (defined here as C_2–*O*H/*C*=O/C=*O* in accordance with previous work[13]) is 154°

(13) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128.

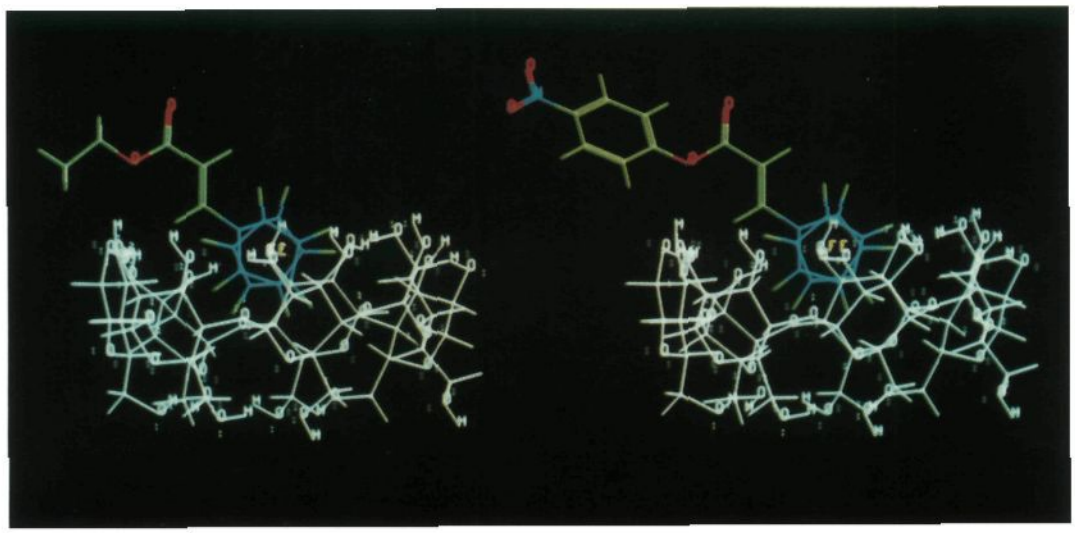


Figure 5. Computer-generated complexes between the ethyl ester (left) and *p*-nitrophenyl eater (right) of 3-ferrocenylacrylic acid and β-cyclodextrin.

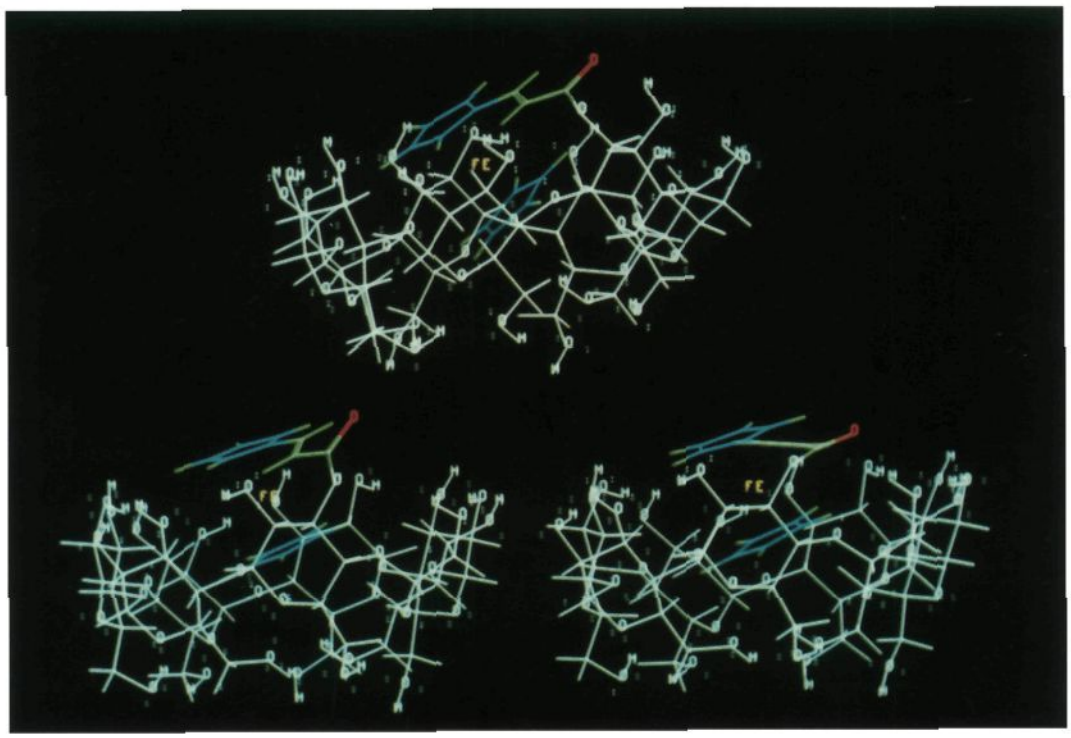


Figure 6. Computer-generated acyl-β-cyclodextrins with the acyl group on a 2-hydroxyl (top) and a 3-hydroxyl (bottom).

Table III. Comparison of Binding Geometries for Ethyl- and *p*-Nitrophenyl Ferrocenylacrylates with β-Cyclodextrin

	ethyl	*p*-nitrophenyl
distance (Å)		
O_2···C(=O)	4.264	4.156
O_3···C(=O)	4.714	4.900
angle (deg)		
O_2···C=O	153.5	151.6
O_3···C=O	135.9	134.9

and 152° for the ethyl and *p*-nitrophenyl esters, respectively. These data are important because they constitute proof that the 3.3×10^5 differential in acceleration between *p*-nitrophenyl and ethyl esters, occurring when the esters bind to β-cyclodextrin and subsequently cleave, is unrelated to structural variations in the initial complexes. This leads support, by a process of elimination, to our alternate rationale:[2] Favorable partitioning of a tetrahedral intermediate to an energetic, nontransoid ester linkage, within the acyl-cyclodextrin, requires a leaving group of pK_a less than 9.

Kinetic studies on ester–cyclodextrin complexes by Breslow et al.[1] and by ourselves were carried out under basic conditions where, no doubt, an alkoxide anion rather than a hydroxyl serves as the nucleophilic entity. Hence, calculations were performed on anionic β-cyclodextrin (i.e., the cyclodextrin bearing a single C_2–OH in the anionic form). Since, however, MACROMODEL parameterization of alkoxides is almost certainly approximate, we report here only a few general observations. Upon removing a proton from the C_2–OH of an empty β-cyclodextrin, the glucose residue with the C_2–O^- tilts 5–10° inwardly relative to its original position. When the C_2–OH closest to the carbonyl of an ester–cyclcodextrin complex was exchanged for a C_2–O^-, the hydroxyl–carbonyl distance increased slighly for the *p*-nitrophenyl ester to 4.3 Å, whereas the distance decreased for the ethyl ester to 3.8 Å. The

Table IV. Comparison of Torsional Angles for Acyl-β-cyclodextrins[a]

torsional angle (deg)	O_2 ester	O_3 ester	O_3 ester
$C_F—C_F—C=C$	3.1	−21.0	12.2
$C=C—C=O$	12.0	−152.3	33.8
$O=C—O—C_C$	−71.0	−134.8	−170.8
$C_{(=O)}—O—C_C—C_C$	4.5	−150.2	−103.4

[a] C_F refers to ferrocene carbons and C_C to carbons on the upper rim of the cyclodextrin.

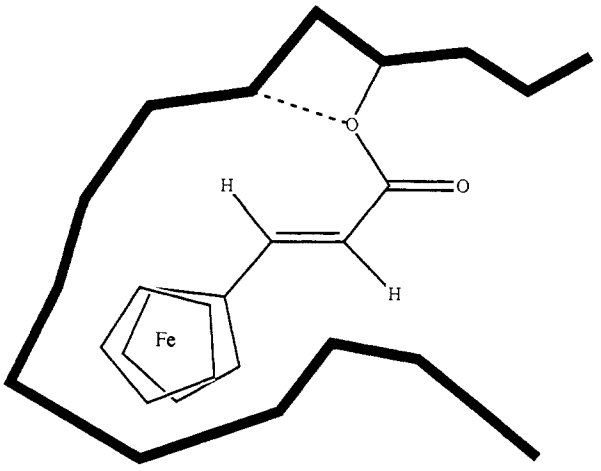
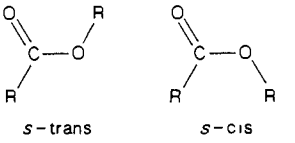


Figure 7. An acylenzyme having a planar s-trans ester configuration. The dotted line indicates the distorted ester geometry observed with acylcyclodextrins, which accounts in part for the unfavorable partitioning of tetrahedral intermediates in model systems unless a very good leaving group (e.g., *p*-nitrophenol) is present.

data indicate, once again, that distance effects are *not* the source of the high *p*-nitrophenyl reactivity; if anything, distance favors the ethyl ester within an anionic host.

Reaction of 3-ferrocenylacrylate esters with β-cyclodextrin generates acylcyclodextrin as the primary product.[1,2] Three low-energy acylcyclodextrins were located (Figure 6): a single C_2–OAc conformation (E_{rel} = 0.0 kcal/mol) and two C_3–OAc conformations (E_{rel} = −3.0 and −5.0 kcal/mol). Table IV lists relevant torsional angles for the three cyclodextrin derivatives. The most likely acylcyclodextrin, C_2–OAc, has the following properties: (a) The C=C of the ferrocenyl sidechain is within 3° of being coplanar with the five-membered ring to which it is attached. (b) The C=C and C=O are within 12° of being coplanar, thus casting serious doubt on Breslow's "twist" proposal[1] in which perpendicular C=C and C=O groups are invoked to rationalize acylation kinetics among the host–guest complexes. (c) By far the greatest distortion from normal occurs, as we previously suggested,[2] at the ester site. The O=C—O—C torsional angle was found to equal 71° compared to 0° for s-trans and 180° for s-cis as defined below. It is clear, at at least for the



C_2–OAc species, that the product is less stable (by ca. 2–3 kcal/mol) than the s-cis ester we had postulated earlier[2] to explain why *p*-nitrophenyl esters cleave so rapidly within the cyclodextrin cavity. Thus, the tetrahedral intermediate tends (even more than we initially surmised) to revert back to reactants in order to avoid the distorted ester linkage. Only if the leaving group is *p*-nitrophenyl (or one with a $pK_a < 9$) will partitioning favor the formation of acylcyclodextrin.[2] This, rather than geometric factors or a perpendicular C=C/C=O "twist",[1] accounts in large measure for the accleration observed with the *p*-nitrophenyl ester but not with the ethyl ester.

Acylation at the C_3–OH site creates two acylcyclodextrins which manifest torsional displacements from normal at all single bonds of the ferrocene side chain. The C=C linkage is out-of-plane with both the five-membered ring and the carbonyl (although nowhere near perpendicular to the latter). The ester site is closer to an s-cis than in the C_2–OAc compound. It is difficult to judge from the data at hand the importance of the C_3–OAc products, relative to C_2–OAc, because no attempt was made to simulate transition structures. But, as already mentioned, geometric factors favor C_2–OAc formation.

Acylenzymes, formed by serine proteases, can achieve s-trans configurations and thus *not* be destabilized by contortions at the ester site (Figure 7). Chemists desiring to emulate enzymatic rates must ultimately design more sophisticated "models" that are capable of encircling the substrate sufficiently to generate to low-energy s-trans ester intermediate.[14]

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(14) **Note Added in Proof**: We call attention to the calculations of Breslow et al., described in an article following this one, that confirms our main conclusions.