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EXPLORATION OF CYCLOMALTO-OLIGOSACCHARIDE (CYCLODEXTRIN) CHEMISTRY WITH MOLECULAR MECHANICS: DOCKING CALCULATIONS ON THE COMPLEXATION OF FERROCENES WITH CYCLODEXTRINS

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ABSTRACT

The ability to design effective "enzyme mimics", such as those based on cyclodextrins (CDs), requires an understanding of the relationship between molecular structure and chemical reactivity. Wide variations in the rates of hydrolysis of ferrocenylacrylate esters, when complexed with cyclomaltoheptaose (βCD), raised questions about the geometry of the ester/CD complex and the acylated CD products. Sets of molecular mechanic parameters have been developed for use with MACROMODEL, which permit the computational modelling of ferrocene and ferrocenylacrylate esters. Calculated structures for the complexation of ferrocene with αCD, βCD, and γCD are consistent with experimental data. Extension of the methodology to the complexes of ferrocenylacrylate esters with βCD, as well as the resulting tetrahedral intermediates and acylated CDs, demonstrated that the 3×10^5-fold difference in the rates for the ethyl and *p*-nitrophenyl esters cannot be attributed to structural or steric differences. The results confirm that the formation of a highly strained acyl CD adversely affects the partitioning of the tetrahedral intermediate towards products unless the substrate has a particularly good leaving group.

INTRODUCTION

Cyclodextrins (cyclomalto-oligosaccharides, hereafter abbreviated as CDs) have served as mainstays in the field of enzyme mimetic chemistry since the pioneering work of Bender[1]. The ability of CDs to complex with organic molecules and accelerate the rates of a variety of reactions has been investigated by the research groups of Breslow[2], Tabushi[3a], and many others.

CDs provide models of the active sites of enzymes for a variety of reasons[1a]. The rigid, hydrophobic cavity attracts and binds many types of guest molecules. This alone often suffices to promote chemical reactivity, as in the case of CD-induced acceleration of Diels–Alder (**1**) cycloadditions in aqueous solution[4]. The

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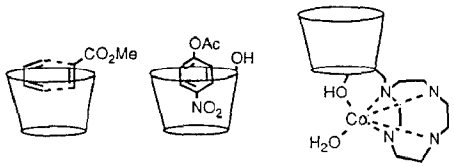
hydroxyl groups on either side of the CD cavity can also increase the reactivity of functional groups attached to included molecules. Aromatic esters, for example, are hydrolyzed rapidly when complexed (**2**) with αCD[1a,5]. In addition, CDs can be tailored for specific purposes, by functionalizing either the primary or secondary hydroxyls with a variety of substituents. Czarnik[6] has blended both host–guest chemistry and transition metal catalysis by attaching a cobalt–tetra-amine complex to the primary side of βCD (**3**) and observed the accelerated hydrolysis of phosphate esters.



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Obtaining an understanding of enzymic catalysis, through the study of enzyme models such as those based on CDs, is essentially a problem in determining the effects of host–guest geometry on chemical reactivity[7]. In particular, how does the relative orientation of the substrate and CD host affect the reactive functionalities? Answers to these questions will permit the design and construction of efficient and specific catalysts for many reactions[3b].

Reaching this goal requires an efficient and accurate methodology for determining and testing the geometries of host–guest complexes. X-Ray crystallography requires the synthesis and isolation of the host–guest complex. CPK models provide rapid assessment of the relative space-filling properies of guest and host, but cannot reflect interatomic forces. The application of computational methods to problems in molecular structure[8] seems to offer the best combination of speed and accuracy.

We present herein the observed rates of hydrolysis for a variety of ferrocenylacrylate esters when complexed with cyclomaltoheptaose (βCD)[9], and the utilization of molecular mechanics to examine the relationship between reactivity and the geometry of the host–guest complex[10].

*The "*p*-nitrophenyl ester effect".* — The *p*-nitrophenyl ester of 3-ferrocenylacrylic acid exhibits a remarkable 3.3×10^5-fold rate acceleration for hydrolysis when the ester is complexed with βCD[11]. Examination of space-filling models led Breslow *et al.*[11] to propose that the ferrocenylacrylate ester binds to βCD in an axial arrangement to form the tetrahedral intermediate, and then collapses to the "twisted" acyl CD, as shown in Fig. 1.

Menger and Ladika[9] studied ferrocenylacrylates in which the leaving group was varied from ethyl alcohol to *p*-nitrophenol (see Table I). The hydrolysis of the uncomplexed ethyl ester was found to be only 56 times slower than that of the *p*-nitrophenyl ester, yet the rate difference was $\sim 10^7$ in favor of the *p*-nitrophenyl

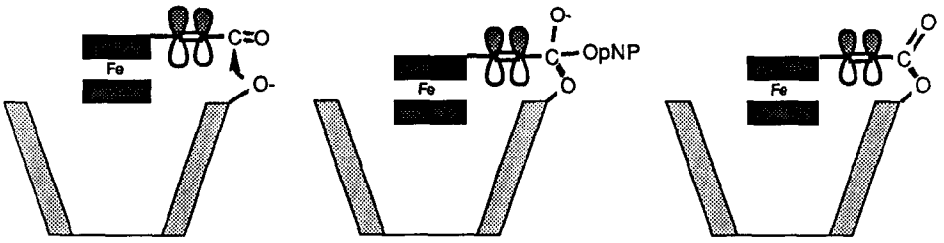

Fig. 1. Schematics for the axial binding and acylation of ferrocenylacrylate esters by βCD showing the "twisted" acylated product.

ester when complexed with βCD. Furthermore, the *p*-nitrobenzyl ester is stable for 10 days under reaction conditions which would hydrolyze the *p*-nitrophenyl ester completely in <1 min.

The marked difference in reactivity for the complexes was attributed to a partitioning effect. Only tetrahedral intermediates having leaving groups with a pK_a of <9 can collapse to the acylated CD, while others revert to the reactants. βCD therefore appears to be a much better leaving group than indicated by its pK_a. Menger and Ladika[9] proposed that the acylated βCD adopted a "high energy s-cis" conformation (**4**) which inhibited its formation[9].

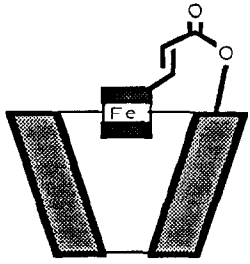

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TABLE I

RATE DATA FOR THE HYDROLYSIS OF FERROCENYLACRYLATE ESTERS (*F*CH=CHCOOR) AS COMPLEXES WITH βCD ($k_{complex}$) AND AS FREE SUBSTRATES (k_{un})[a,b]

R	pK_a *of ROH*	$k_{un} \times 10^8$ (s^{-1})	$t_{1/2complex}$	$k_{complex}/k_{un}$
Ethyl	15.9	0.5	>2 years	<2
Benzyl	15.2	0.7	>1 year	<2
p-Nitrobenzyl	14.6	0.9	>1 year	<2
Phenyl	9.9	7.9	18 h	140
m-Chlorophenyl	9.1	12	3.9 min	0.26×10^5
p-Cyanophenyl	8.0	20	37 s	0.95×10^5
p-Nitrophenyl	7.2	28	7.4 s	3.3×10^5[c]

[a]Ref. 9. [b]Reaction conditions: 3:2 Me_2SO and phosphate buffer (pH 10), [β-CD] 6.4×10^{-2} M. [c]Ref. 11.

Detailed information about the structure of the complexes between βCD and ferrocenylacrylates or of the acylated cyclodextrins is not currently available. If the geometries of the ethyl and *p*-nitrophenyl ferrocenylacrylate complexes were significantly different, then their reactivities would be expected to differ. A large difference in rate could also result from the ethyl tetrahedral intermediate being significantly more strained than the tetrahedral intermediate of the *p*-nitrophenyl ester. Finally, the structure of the acylated CD is not known, and the existence of an unstrained conformation for this molecule would demand another explanation for the observed partitioning behavior.

In order to resolve these uncertainties, sets of molecular mechanics parameters were developed for ferrocene and its acrylate ester derivatives, using MACROMODEL[12] to study the complexation between ferrocene and αCD, βCD, and γCD. These computer-generated structures were consistent with available experimental data, allowing the methodology to be extended to the interaction of ferrocenylacrylate esters with βCD.

EXPERIMENTAL

Computational methodology. — Calculations were performed with MACROMODEL[12], using a modified version of the MM2[8a] force field, and executed on either a VAX 11/785 or MicroVax II computer. An Evans and Sutherland PS390 graphics terminal was used to generate and view the structures. Computations utilized MACROMODEL default values for the dielectric constant and non-bonded cut-off distances*. All structures were optimized until the root mean square of the gradient vectors was <0.01 kcal/Å. ORTEP-style line drawings were prepared by CHEM3D (Cambridge Scientific Computing, Inc., Cambridge, MA, U.S.A.) after the structure data files had been converted into the appropriate format. In such illustrations, hydrogens attached to the carbons of the CDs have been omitted in order to improve the clarity of presentation.

The sets of parameters duplicate ferrocene and ferrocenylacrylate esters, utilizing only electrostatic and van der Waals (VDW) forces in order to retain the proper relative geometry between the iron atom and cyclopentadienyl anion rings. The "target geometry" for unsubstituted ferrocene was the X-ray crystal structure reported by Seiler and Dunitz[13], which gives C–C bond lengths of 1.431 Å, and C–Fe distances of 2.059 Å. Similarly, geometric parameters for the ferrocenylacrylate esters were based on an X-ray crystal structure of β,β-dicyano-α-methylvinylferrocene[14], which showed that electron-withdrawing groups on a vinyl-substituted ferrocene cause a slight shrinkage in the ferrocene C–C and C–Fe distances to 1.4164 and 2.046 Å, respectively.

MACROMODEL is not parameterized for cyclopentadienyl anion carbons

*VDW cut-off distance, 6.0 Å; electrostatic cut-off distance, 12 Å. Electrostatic interactions are treated as point charges ($q_i q_j / \varepsilon R_{ij}$) with distance-dependent dielectrics ($\varepsilon = R_{ij}$).

or for Fe^{2+}. This difficulty was skirted by deleting all parameters from the external constants file (MM2.FLD) for atom types Si (silicon) and Z0 (a "wild-card" metal), and entering the parameters shown in Tables A-I or A-II of the Appendix. These substitutions have the effect of redefining silicon atoms as the aromatic cyclopentadienyl anion carbons (with point charges of -0.2) and the wild-card metal atom as $Fe2^+$ (with a point charge of 2.0). The VDW parameters for $Fe2^+$ were selected to achieve the proper C–Fe distance as given in the crystal structures. The geometry and point charges for the nitro group of *p*-nitrophenyl were taken from an X-ray structure[15] and an AMPAC (AM1)[8c] calculation, respectively. All other force field parameters were taken from analogous parameters for sp^2 carbons already extant in MACROMODEL.

These complexes were too large to make a rigorous conformational search for the global minimum practical*. Therefore, the new parameter sets were used first to generate crude "energy *vs.* distance" curves for the insertion of ferrocene into the cavity of each CD. The relative position of ferrocene corresponding to the minimum energy along these curves provided reasonable starting geometries for further computation. At least three different initial geometries were considered for a given host–guest complex, each generated by a random rotation of the guest relative to the host. The resulting geometries and energies were often similar, and the geometry of lowest energy is reported in the discussion section and listed in the Appendix. Where some ambiguity existed in identifying the geometry of lowest steric energy, additional random starting conformations were generated and optimized. This procedure was repeated until the global minimum was located with confidence.

There are three limitations to the accuracy of the computations. First, the effects of solvent are neither explicitly nor implicitly accounted for, when in fact, the complexation phenomenon is driven by hydrophobic forces[16]. This omission of solvent, unfortunately, is a traditional limitation of computational chemistry. Second, the conformational complexity of the CD hosts leads to the possibility of millions of conformers. Fortunately, the differences in energy between rotamers are small, and the problem of "local minima" was avoided by consistently beginning each particular calculation with the same set of optimized CD geometries. Finally, MACROMODEL has no means of emulating π-bonding in the ferrocene moiety, and only electrostatic and VDW forces were used to hold the unit together. Consequently, the model detects essentially no energy difference between eclipsed and staggered ferrocene, when spectroscopic studies show the staggered conformation to be ~1 kcal/mol less stable[17]. Since binding energies for the complexes were calculated to be ~20 kcal/mol in the gas phase, the underestimation of the rigidity of ferrocene is not serious, and the space-filling properties of ferrocene are adequately represented.

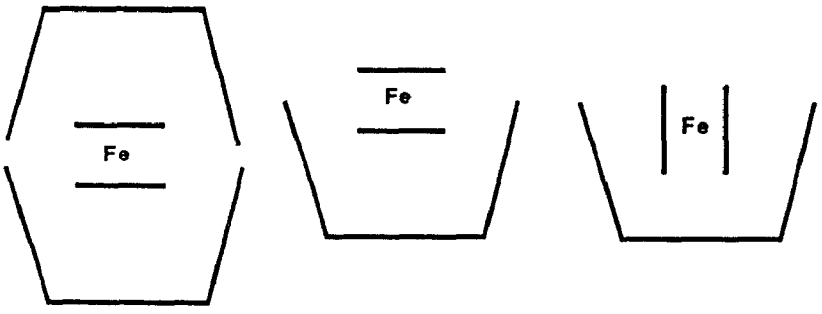
*Considering *only* skewed conformations for the hydroxyl hydrogens of βCD gives an upper limit of 1.05×10^{10} possible conformations.

Steric energies and gas-phase binding energies for all structures are provided in Table A-III of the Appendix.

RESULTS AND DISCUSSION

Complexes between ferrocene and CDs. — The structures of αCD, βCD, and γCD structures were generated using the "grow" feature of the "carbohydrate submode" of MACROMODEL. Particular care was taken during the early stages of optimization (steepest descents, no line search) in order to ensure that the molecules retained a high degree of radial symmetry. The resulting geometries, shown in Fig. 2, agree well with published crystal structures[15,18]. The calculated structures of ferrocene, ethyl ferrocenylacrylate, and *p*-nitrophenyl ferrocenylacrylate, as calculated by the new parameter sets, are shown in Fig. 3. The computer-generated structures for the esters show the cyclopentadienyl anion rings to be several degrees away from being perfectly parallel, a feature also present in the X-ray structure of the vinyl-substituted ferrocene[14].

Apparently, no X-ray structures for complexes between ferrocene and CDs have been reported. Harada and Takahashi[19a] used spectroscopic data and mechanical modelling to propose the structures **5–7**. Solid-state ^{2}H-n.m.r. studies by Clayden *et al.*[19b] provide supporting evidence for the proposed structures of **6** and **7**.



5 **6** **7**

Docking calculations proved ferrocene to be too large to fit entirely within the cavity of αCD, and to be positioned at an angle of ~45° at the top of the cavity. About half of the ferrocene molecule is exposed, thereby encouraging the association of another αCD molecule to form the much more stable 2:1 complex (Fig. 4). The calculated gas-phase binding energies (defined as $\Sigma E_{components} - E_{complex}$) increase from 20 kcal/mol to ~78 kcal/mol upon forming the 2:1 complex. Attractive VDW, electrostatic, and hydrogen-bonding interactions of the secondary hydroxyls of the CDs contribute to the enhanced stability of the 2:1 complex **5**.

Both axial and near-equatorial complexes were located for the complex

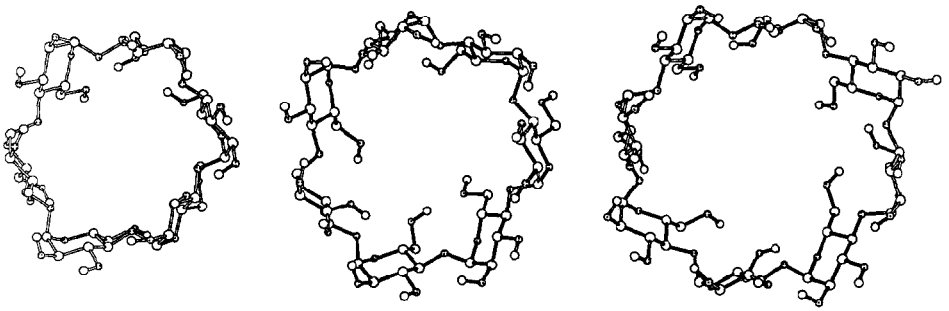


Fig. 2. Computer-generated CD structures.

between ferrocene and βCD (Fig. 5). The equatorial complex was calculated to be ~0.5 kcal/mol more stable, an energy difference too small to be significant. Therefore, solvation (or crystal packing forces) and molecular vibrations will determine the binding geometry. When the size of the ferrocene was reduced slightly (by using shorter bond lengths, *etc.*), the equatorial guest was favored by ~2 kcal/mol. Likewise, an *increase* in the size of the ferrocene led to the axial complex being more stable by ~2 kcal/mol. Thus, the relative size of the guest to the host cavity places the preferred orientation in a delicate balance. At ambient temperatures, the dynamic motion of the molecules will make the ferrocene effectively larger with regard to the βCD cavity, and the axial geometry should be the preferred binding mode.

Two stable complexes of similar energy were also located for the complex

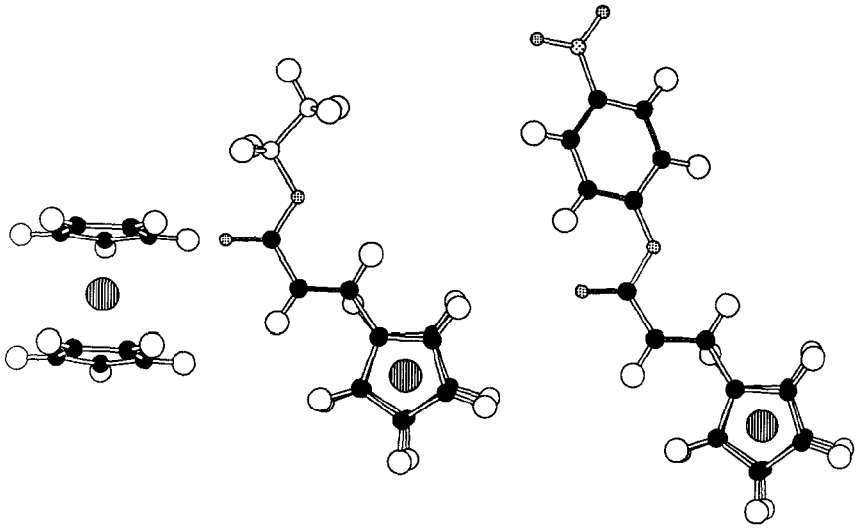


Fig. 3. Structures for ferrocene, ethyl ferrocenylacrylate, and *p*-nitrophenylacrylate as calculated by the modified MM2 force field.

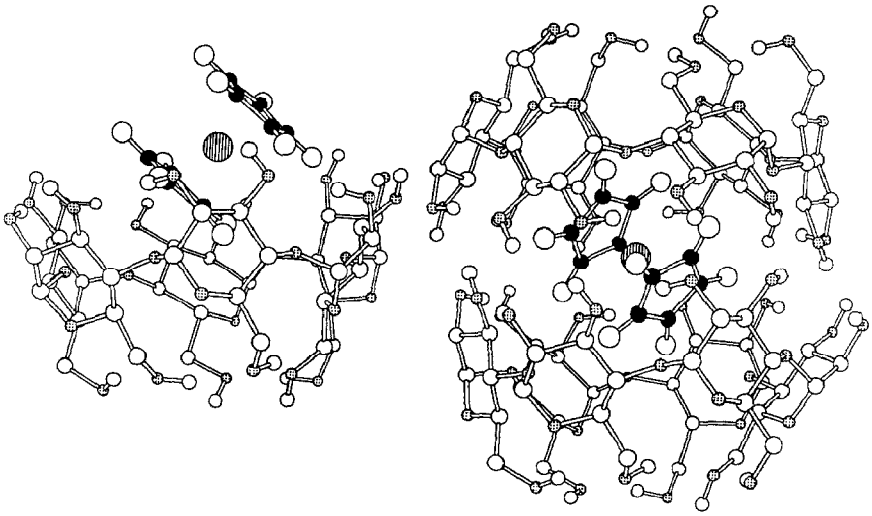


Fig. 4. Calculated structures for the 1:1 and 2:1 complexes between αCD and ferrocene.

between γCD and ferrocene. Each was essentially equatorial in binding geometry, and the interconversion of the two forms appears sterically unrestrained, as shown in Fig. 6.

Complexes between βCD and ferrocenylacrylate esters. — The complexes between βCD and ethyl or *p*-nitrophenyl ferrocenylacrylates had approximately the same geometry of binding and similar binding energies (Fig. 7). This strongly preferred binding mode has the ferrocene moiety bound equatorially within the cavity, and the acrylate linkage poised over the rim of the βCD (structures of axial starting geometry invariably collapsed to this equatorial arrangement). This structure is consistent with that proposed by Kobayashi and Osa[20] for the complexation of ferrocene carboxylic acid with βCD.

Table II shows the geometric relationship of the carbonyl carbon of both

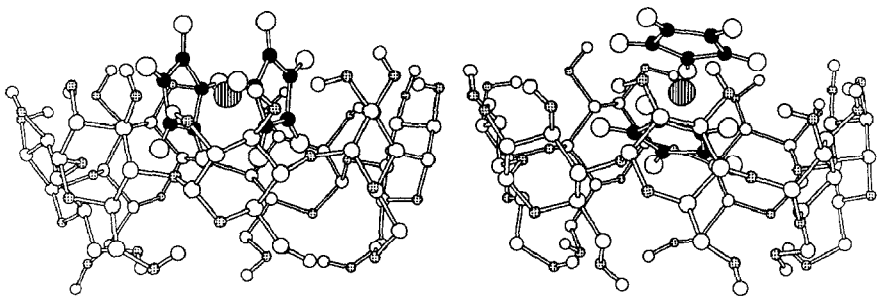


Fig. 5. Computer-generated structures for the equatorial (left) and axial (right) complexes between ferrocene and βCD.

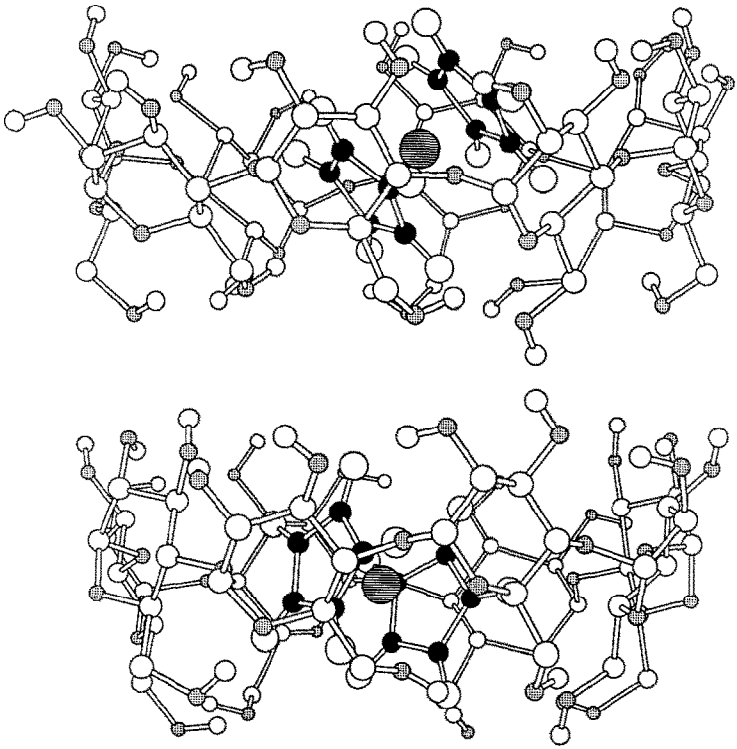


Fig. 6. Two equatorial conformations found for the complex between ferrocene and γCD. The lower structure is slightly more stable.

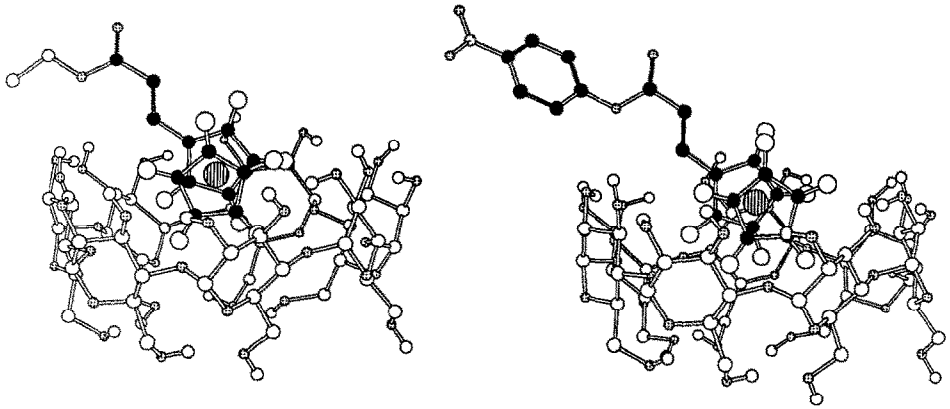


Fig. 7. Calculated geometries for the complexation of ethyl and *p*-nitrophenyl ferrocenylacrylates with βCD.

TABLE II

COMPARISON OF BINDING GEOMETRIES FOR ETHYL AND *p*-NITROPHENYL FERROCENYLACRYLATES WITH β-CD

	Ethyl	p-*Nitrophenyl*
Distance (Å)		
O-2···C(=O)	4.264	4.156
O-3···C(=O)	4.714	4.900
Angle (°)		
O-2···C=O	153.5	151.6
O-3···C=O	135.9	134.9

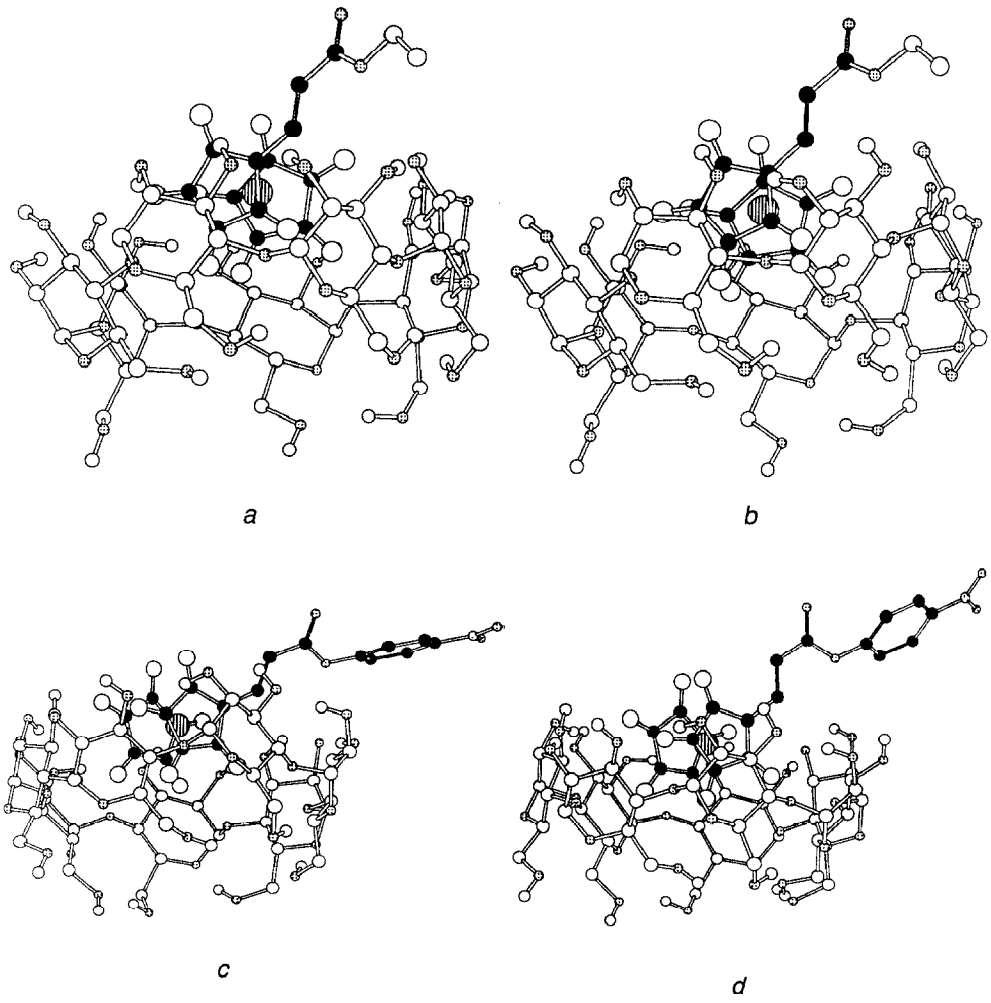


Fig. 8. Computer-generated structures for the O-2 and O-3 βCD anion complexes with ethyl ferrocenylacrylate (*a* and *b*, respectively), and the corresponding anionic complexes with *p*-nitrophenyl ferrocenylacrylate (*c* and *d*).

TABLE III

COMPARISON OF BINDING GEOMETRIES FOR ETHYL AND *p*-NITROPHENYL FERROCENYLACRYLATES WITH β-CD ANIONS

	Ethyl O-2/O-3 Anion	p-*Nitrophenyl O-2/O-3 Anion*
Distance (Å)		
O-2···C(=O)	3.824/3.384	4.343/4.067
O-3···C(=O)	5.039/4.955	5.900/5.066
Angel (°)		
O-2···C=O	133.5/127.8	151.4/152.2
O-3···C=O	115.4/113.0	155.5/145.4

esters with HO-2 and HO-3 on the nearest glucose residue. The relative binding geometries of the ethyl and *p*-nitrophenyl ferrocenylacrylates are similar in terms of (O=)C···O distances and approach angles, and the carbonyl carbon is closest to HO-2. This structural similarity provides strong evidence that the 3.3×10^5-fold acceleration for the *p*-nitrophenyl ester is *not* due to differences in binding orientation.

Complexes between anionic βCD and ferrocenylacrylate esters. — Under the reactions conditions, it is likely that anionic βCD serves as the nucleophile. MACROMODEL contains approximate parameters for alkoxides, which allowed the examination of the complexation between the ferrocenylacrylate esters and anionic βCD. Optimization of these structures (Fig. 8) showed that the geometries and binding energies change slightly from those of the neutral complexes. No counter-ion or related solvent shell was considered, thus the calculated "approach geometries" for the anionic complexes are simply listed in Table III. The pK_a of the HO-2 is lower than that of HO-3[21], and this factor, along with the geometric considerations above, should make HO-2 the preferred site of initial acylation.

"Tetrahedral Intermediates". — The approximate alkoxide parameters in MACROMODEL also allowed the structures of the tetrahedral intermediates for both the ethyl and *p*-nitrophenyl ferrocenylacrylates to be crudely modelled (Fig. 9). The ethyl intermediate was found to be ~3 kcal/mol higher in relative energy than the *p*-nitrophenyl intermediate. This energy difference, however, can only account for a small portion of the 10^7-fold difference in rate between the two esters observed by Menger and Ladika[9], assuming that this strain differential is maintained in the rate-determining transition structure.

Ferrocenylacrylate esters of βCD. — Three stable acylated CDs for which the ferrocene remained bound within the cavity of βCD were located (Fig. 10): one involved acylation at HO-2 (e_{rel} 0.0 kcal/mol), and two involved acylation of HO-3 (e_{rel} = −3.0 and −5.0 kcal/mol). The first two conformations show significant distortion about the O=C–O–C torsional angle (Table IV), and the geometries of all three esters closely resemble the proposed "s-*cis*" conformation proposed by Menger and Ladika[9]. However, the strong binding interaction of the ferrocene with

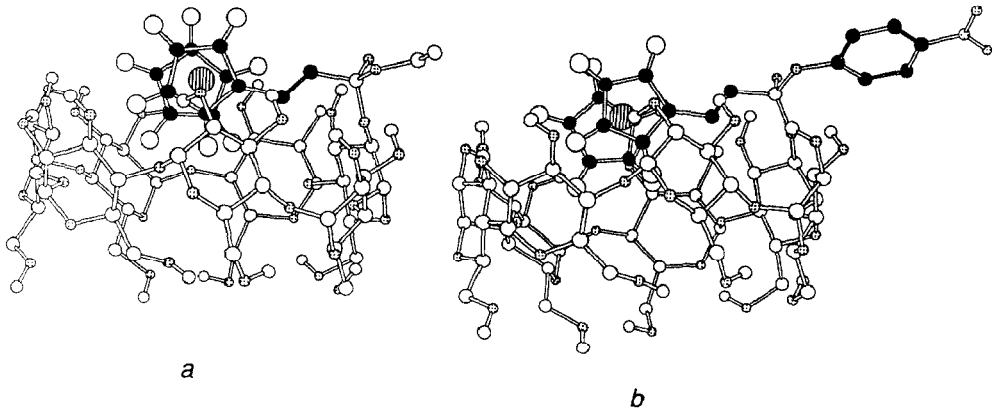


Fig. 9. Calculated structures for the βCD O-2 anion "tetrahedral intermediates" with ethyl (*a*) and *p*-nitrophenyl ferrocenylacrylate (*b*).

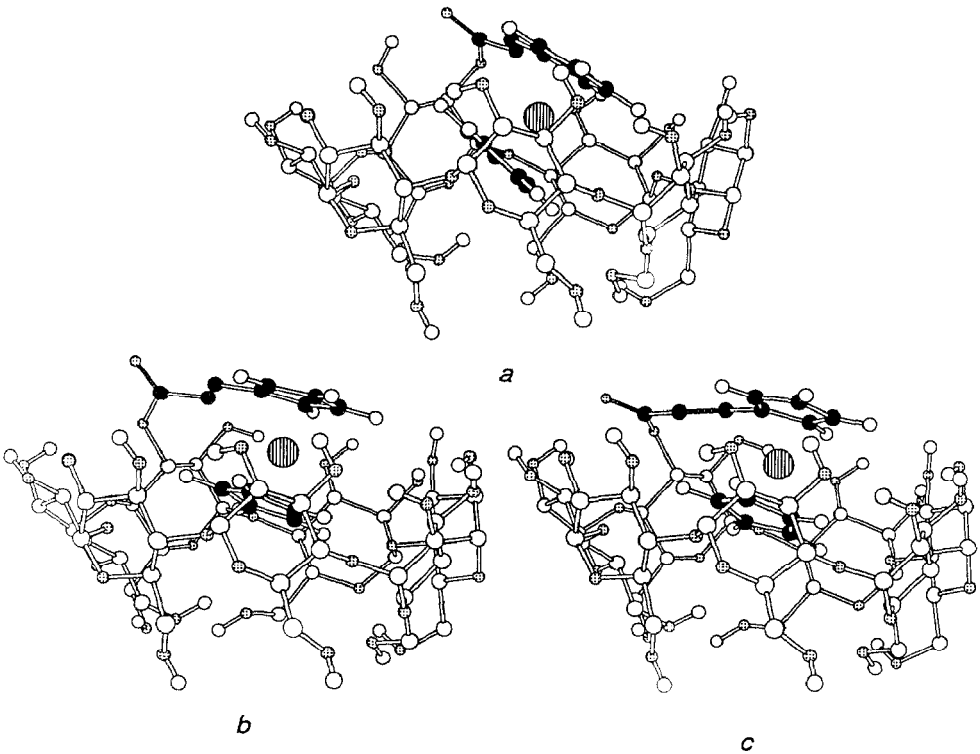


Fig. 10. Computer-generated structures for acylated βCD: *a* is the O-2 ester, and *b* and *c* are the O-3 esters; *c* is the most stable acylated βCD.

TABLE IV

COMPARISON OF TORSIONAL ANGLES (DEGREES) FOR ACYLATED β-CDs[a]

Torsional angle	*O-2 Ester*	*O-3 Ester-1*	*O-3 Ester-2*
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.

the CD distorts this ester linkage away from planarity, making the ester even less stable than that proposed[9].

Theim *et al.*[21] noted that acylated CDs seem to equilibrate rapidly among the secondary hydroxyl groups, and the current calculations provide both a geometric and thermodynamic rationale for this phenomenon. As mentioned above, distance and pK_a considerations favor attack by HO-2 on the carbonyl, but the resulting 2-ester was calculated to be the *least* stable configuration available to the acyl-CD. This strained linkage could be hydrolyzed readily under the basic reaction conditions to initiate the rapid equilibration.

Conclusions. — This computational study demonstrates the application of molecular mechanics to provide meaningful structural information on the host–guest interactions of CDs and ferrocenes. Calculated structures reveal no compelling steric or geometric source for the ~10^7-fold difference in rates of hydrolysis for the complexes of ethyl and *p*-nitrophenyl ferrocenylacrylates with βCD. The tetrahedral intermediate tends to revert back to reactants in order to avoid the severely distorted ester linkage in the acylated CD, and only if the leaving group has a pK_a <9 will partitioning favor the formation of the βCD–ferrocenylacrylate ester.

APPENDIX

TABLE A-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	Q_0	K_Q	
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*	*Epsilon*	*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]H1 is a "normal" hydrogen (*e.g.*, a C–H hydrogen). [c]Z0 is considered by MACROMODEL to be a "wild card" metal ion, in this case defined as Fe^{2+}.

TABLE A-II

FORCE FIELD FOR FERROCENYL ACRYLATE ESTERS

BONDS

Symbol	R_0	K_R	*Dipole moment*
C2–Si[a,b]	1.470	5.000	0.0
Si–Si	1.4164	9.600	0.0
H1–Si[c]	1.101	4.600	0.0
C-2–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–C-2–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*	*Epsilon*	*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 *sp2* hybridized carbons; C2 refers to carbons either in the acrylate linkage or in the *p*-nitrophenyl ring. [c]H1 is a "normal" hydrogen (*e.g.*, a C–H hydrogen). [d]Atom type N0 is a "generalized" nitrogen in MACROMODEL, specifically defined here as the nitrogen in the nitro substituent in the *p*-nitrophenyl group. [e]"Z0" is considered by MACROMODEL to be a "wild card" metal ion, in this case defined as Fe^{2+}.

TABLE A-III

STERIC AND BINDING ENERGIES OF STRUCTURES

Steric energy[a] *(kcal/mol)*	*Binding energy*[b] *(kcal/mol)*	*Descriptor*
−238.38		Eclipsed ferrocene
−238.42		Staggered ferrocene
−237.98		Ethyl ferrocenylacrylate
−232.02		*p*-Nitrophenyl ferrocenylacrylate
−134.08		αCD
−157.41		βCD
−186.39		γCD
−392.27	19.77	Ferrocene/αCD 1:1 complex
−584.61	78.03	Ferrocene/αCD 1:2 complex
−410.83	15.00	Ferrocene/βCD complex-axial binding
−411.30	15.47	Ferrocene/βCD complex-equatorial binding
−441.36	16.55	Ferrocene/γCD complex-axial binding
−441.02	16.21	Ferrocene/γCD complex-tilted binding
−413.97	18.58	Ethyl ferrocenylacrylate/βCD complex
−407.88	18.45	*p*-Nitrophenyl ferrocenylacrylate/βCD complex
−144.14		βCD"O2"anion
−148.35		βCD"O-3"anion
−402.32	20.20	Ethyl ferrocenylacrylate/βCD"O-2" anion complex
−408.19	21.86	Ethyl ferrocenylacrylate/βCD"O-3" anion complex
−396.35	20.19	*p*-Nitrophenyl ferrocenylacrylate/βCD"O-2" anion complex
−401.34	20.97	*p*-Nitrophenyl ferrocenylacrylate/βCD"O-3" anion complex
−398.80		βCD"O-2"ferrocenylacrylate
−401.78		βCD"O-3"ferrocenylacrylate, 1
−403.95		βCD"O-3"ferrocenylacrylate, 2
−208.47		Ethyl ferrocenylacrylate "tetrahedral intermediate"
−213.75		*p*-Nitrophenyl ferrocenylacrylate "tetrahedral intermediate"
−389.22		βCD/ethyl ferrocenylacrylate "tetrahedral intermediate" at O-2
−386.22		βCD/*p*-nitrophenyl ferrocenylacrylate "tetrahedral intermediate" at O-2
−382.64		βCD/ethyl ferrocenylacrylate "tetrahedral intermediate" at O-3
−378.81		βCD/*p*-nitrophenyl ferrocenylacrylate "tetrahedral intermediate" at O-3

[a]As calculated by the modified version of MACROMODEL. [b]Calculated as ($\Sigma Energy_{Components} - Energy_{Complex}$). Thus, the higher the number, the stronger the binding.

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