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ADDITIONAL FLEXIBILITY SOLVES THE LEAVING GROUP PROBLEM IN CYCLODEXTRIN ACYLATION

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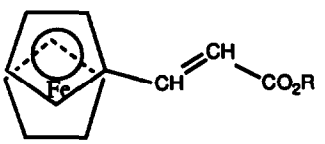
Summary: The rate of acylation of β-cyclodextrin by substituted phenyl esters of adamantanepropiolic acid shows a normal dependance on the basicity of the leaving group. This shows that the abnormal behavior in acylation by ferroceneacrylate esters can be solved with additional flexibility, which allows the geometry to change in response to the demands of the reaction path.

Cyclodextrins can be acylated by bound substrates. We have reported a series of substrates with very large values of $k_{acylation}/k_{hydrolysis}$.[1,2] The most striking values were obtained with some derivatives of ferroceneacrylic acid (1), whose p-nitrophenyl ester 2 showed a 360,000-fold acceleration with β-cyclodextrin (cycloheptaamylose).[1] Even larger values were observed with fused ring derivatives of 2.[2]



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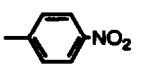
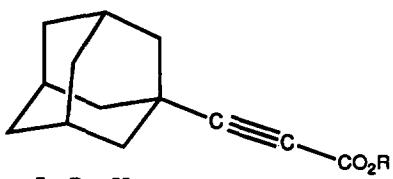
2 R = 



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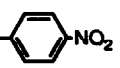
6 R = 

If in the complex (3) of 2 the ferrocene nucleus binds with its rotational axis parallel to the rotational axis of the cyclodextrin, conjugation holds the ester group so that a cyclodextrin oxyanion O^- can approach perpendicular to the ester plane, as it should to form the tetrahedral intermediate (Scheme 1). If formation of this intermediate is rate limiting (with rate constant k_1), the fast reaction is reasonable.

However, the tetrahedral intermediate must expel the leaving group (with rate constant k_2) to form the acylated cyclodextrin, and for this the geometry is no longer ideal. This geometric problem explains our finding,[2] and that of Menger,[3] that $k_{acylation}/k_{hydrolysis}$ decreases strongly as the leaving group is made more basic than p-nitrophenoxide ion. With poor leaving groups the decomposition of the tetrahedral intermediate can become rate limiting, and the geometric problem with this step will be expressed.

We suggested[2] that the geometric problem is twisting: the product acrylate cyclodextrin ester **4** now has the cyclodextrin oxygen in the plane of the ester, instead of perpendicular to it as in the first step. This will require twisting of or within the conjugated acrylate unit, or of the ferrocene ring. Menger[3] ascribed the problem to a syn conformation of the ester group in **4** rather than the preferred anti conformation.

Our Macromodel calculations[4] showed that indeed the conversion of **3** to **4** has a geometric problem, and that the problem was twisting within the conjugated acrylate ester unit, and twisting of the substrate within the cavity. Related calculations by Menger led to similar results.[5] Thus we decided to test the question with a substrate related to **2** in which the required twisting is not restricted by conjugation.

We had reported the acylation of β-cyclodextrin by the p-nitrophenyl ester (**6**) of adamantanepropiolic acid (**5**), and ascribed its $k_{acylation}/k_{hydrolysis}$ of only 2,000-fold to a greater geometric freedom in the complex relative to that of **2**.[1] When the adamantane nucleus binds to the cyclodextrin cavity the propiolic ester group is free to rotate, and the spherical adamantane unit itself can rotate freely into a variety of bound conformations. This freedom makes formation of the tetrahedral intermediate slower, but it should let the second step proceed with no special problem in the product ester **7**.

We have now prepared the esters listed in Table 1, and studied their acylation reactions with β-cyclodextrin. The esters were prepared as pure crystalline solids by dicylohexylcarbodiimide coupling of acid **5**[1] with the appropriate phenols, and characterized by HNMR. All kinetic studies were performed at 25.0 ± 0.1 °C in 40% H_2O/60% DMSO (v/v) with buffers calibrated with a glass electrode. We had found[1,2] that k_{CD} is not subject to buffer catalysis but that k_{un} is a function of buffer concentration. Thus k_{un} for each pH was determined at five different buffer concentrations and extrapolated to zero buffer. The pK_a's listed in Table 1 were determined in the same medium at 25.0 ± 0.1 °C by spectroscopic titration. In a preparative run ester **6** was allowed to react with β-cyclodextrin in buffered aqueous DMF, and the product ester **8** was isolated. It had the expected HNMR, and MS (FAB) of 1321 (m + 1).

The kinetic results are listed in Table 1, and plotted in Fig. 1A. With leaving groups of $pK_a < 11.7$ the first step is rate determining; k_1 decreases modestly for both the CD and the uncatalyzed reaction, with a Brønsted α of 0.24 reflecting the decreased

reactivity of carbonyls with better electron donor substituents. Above pK_a 11.7 both the CD and the uncatalyzed reaction rates decrease more strongly with poorer leaving groups, as the second step becomes rate determining. However, the ratio k_{CD}/k_{un} falls only modestly. By contrast, with the ferrocene system (Fig. 1B) the CD rate falls off sharply with increasing leaving group basicity through the entire range. The geometric problems developed in ester **4** make the second step rate determining even with good leaving groups. The k_{un} has no such problem, and shows a normal curve. As a result, with an unsubstituted phenoxide ester the k_{CD}/k_{un} for the adamantanepropiolate derivative is now 6 times larger than that for the ferrocene compound, while with the p-nitrophenyl esters it was 2000 times smaller.

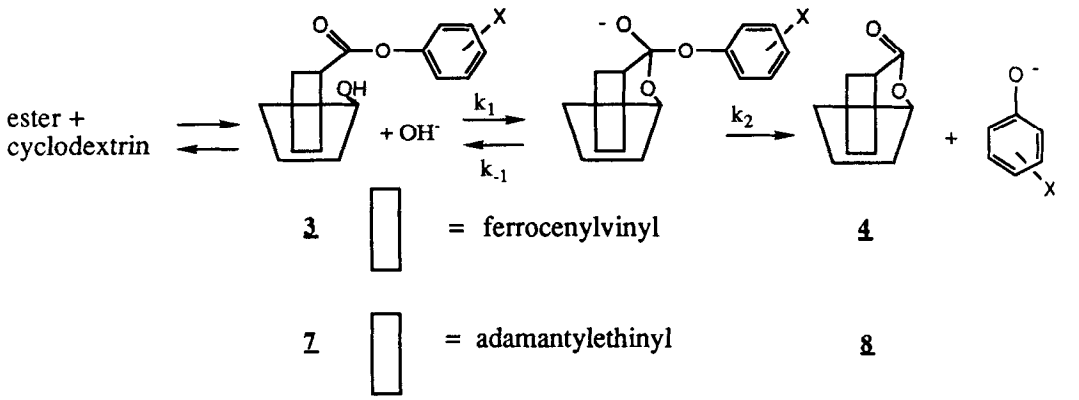


Table 1. Kinetic Data for Esters 7 (10^{-4} sec^{-1})

Substrate 7	pK_a of ArO^-	k_{un} (pH)	k_{CD} (pH)	k_{un} (pH 10)	k_{CD} (pH 10)	k_{CD}/k_{un}
2,5-dinitro	6.15	57(11.9)	96.3(8.77)	0.72	1645	2280
4-nitro	8.32		881(10.3)	0.21	442	2150
4-cyano	9.45	38(12.5)	414(10.24)	0.114	238	2090
3-nitro	10.0	39(12.45)	318(10.17)	0.138	215	1560
3-chloro	11.1	6.5(12.4)	65(10.13)	0.026	48.1	1857
4-chloro	11.6	7.1(12.4)	43.8(10.1)	0.0276	32.5	1178
H	12.55	2.1(12.58)	232(11.7)	0.0055	4.84	877
2,4-diMe	13.2	0.28(12.4)	58.5(11.9)	0.0012	0.64	547

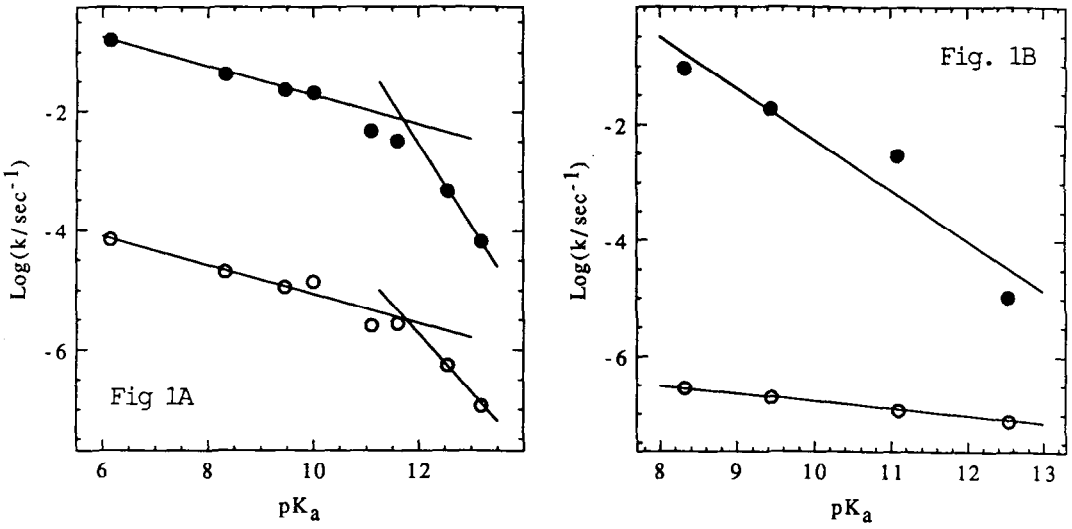


Figure 1. Pseudo-first-order rate constants for the reaction of substrates within the cyclodextrin complex (upper curves) and with OH^- alone (lower curves) *vs.* the pK_a's of the phenol derivatives. The data on the left refer to the adamantane series, and come from Table 1. The data on the right refer to the ferrocene series, and come from ref. 3.

These results point to the way to even better substrates. More generally, they illustrate the problem when a system has too much rigidity, as in 2. For fast reactions an enzyme, or an enzyme model, must have the freedom to adjust to the geometric demands that develop along the reaction pathway; all other irrelevant degrees of freedom are best frozen out. Thus it is not enough to "bind the transition state." Some residual freedom is needed so that the reaction does not simply create a new high energy point along the pathway, a new transition state.

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