The exact ratio of alcohols in the product could not be determined because considerable dehydration (to the diene, identified by IR and mass spectroscopy) accompanied gas chromatography. Both alcohols dehydrate, as shown by rechromatography of GLC-collected pure samples. (These alcohols are high enough in molecular weight to require high injector and column temperatures for gas chromatography.) While the experiments were not designed to measure the singlet O_2 trapping efficiency of the resin ester, a rough calculation suggests that, at a concentration of 0.057 mequiv of ester/20 mL, $\sim 4/1000$ of the $^1O_2$ formed was trapped. If the methyl ester had been dissolved at the same concentration, ~3% should have been trapped; thus the resin bound ester is (*very* roughly) $1/10$ as efficient as the methyl ester (β = 0.11 M) at trapping $^1O_2$ under these conditions.

(12) Gas-phase photolyses were run in 500-mL round-bottom flasks loaded with 100 mg of each polymer-bound species. The flask was evacuated to 10 μ and then refilled to the desired pressure using an oxygen-filled balloon. The flask was then irradiated with a 650-W Sylvania DWY tungsten–halogen lamp through a 2% sodium dichromate filter solution ~0.5 cm from the beads. The CCl_4-phase run was carried out using 200 and 50 mg of polymer-bound acceptor **1a** and sensitizer, respectively, in 20 mL of CCl_4 with the same lamp and filter setup. Products were analyzed as described in ref 11.

(13) P. B. Merkel and D. K. Kearns, *J. Am. Chem. Soc.*, **94**, 7244 (1972).

(14) T. Frankiewicz and R. S. Berry, *J. Chem. Phys.*, **58**, 1787 (1973). Quenching of $^1O_2$ by N_2 is negligible; the rate constant for quenching by O_2 is 2.2×10^{-18} cm^3/molecule s.

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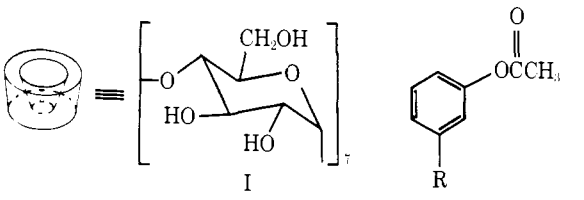
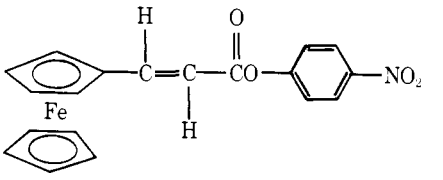
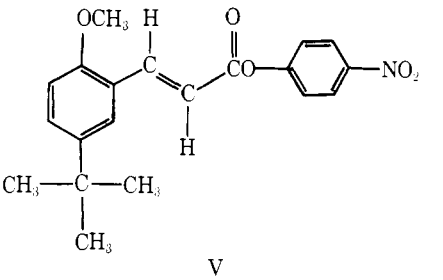


I

II, R = NO_2
III, R = $C(CH_3)_3$



IV



V

Very Fast Acylation of β-Cyclodextrin by Bound *p*-Nitrophenyl Ferrocinnamate

Sir:

In the study of the cyclodextrins as enzyme models, particular interest has surrounded reactions in which a substrate, bound into the cavity of the cyclodextrin, reacts with one of the hydroxyl groups on the rim of the molecule.[1] For example, Bender[2] has studied the acylation of β-cyclodextrin (I) by bound *m*-nitrophenyl acetate (II), *m-tert*-butylphenyl acetate (III), and related compounds. In water solution at pH 10.6, he reports that ester III acetylates a β-cyclodextrin hydroxyl group 250 times as rapidly as it acetylates water (hydrolyzes) in the absence of cyclodextrin at the same pH. We have reported[3] that such reactions are accelerated if the solvent is changed to 60% Me_2SO/H_2O, with the acylation of cyclodextrin by III being 500 times as fast as hydrolysis in this medium, and 13 000 times as fast in this medium as is hydrolysis with the same buffer in H_2O solvent.

On the basis of such data some pessimists have concluded that cyclodextrins can give selective reactions, but with only modest rate accelerations over the control. However, it seemed to us that the optimal[4] systems had not yet been examined. Entropy factors should be more favorable for acylation processes in which the acyl group, not the leaving group, is bound into the cyclodextrin cavity. Furthermore, molecular models suggest that certain derivatives of ferrocene should be particularly well held by binding to β-cyclodextrin. We have previously shown[3] that ferrocene itself is strongly bound. We now wish to report that the acylation of β-cyclodextrin by the *p*-nitrophenyl ester of ferrocinnamic acid[5] (IV) is accelerated by over 50 000-fold compared with hydrolysis by buffer alone. The actual rate achieved is comparable with that for acylation of the enzyme chymotrypsin by *p*-nitrophenyl acetate.

The substrate IV was prepared from ferrocinnamic acid[5] and *p*-nitrophenol with dicyclohexylcarbodiimide. Its hydrolysis in 60% of dimethyl sulfoxide/40% H_2O (v/v) at 30.0 °C with a 4 mM phosphate buffer was monitored at 410 nm (*p*-nitrophenoxide ion). With a buffer[6] which in H_2O has pH 6.8, the pseudo-first-order hydrolysis rate constant of IV was 3.5×10^{-6} s^{-1}, while *p*-nitrophenyl acetate under the same conditions has a rate constant of 74×10^{-6} s^{-1}, 21-fold faster. The reaction of cyclodextrin with IV (0.10 mM) in the same medium was monitored at 410 nm with β-cyclodextrin concentrations ranging from 0.20 mM to 20 mM. The data (20 points) fit an Eadie plot which demonstrates that 1:1 complex is being formed, and rigorously excludes other stoichiometries.[7] The K_d is 7 mM, while V_{max} is 0.18 s^{-1}. V_{max} is first order in hydroxide ion and unaffected by doubling the buffer concentration. Thus, the process being observed is the acylation of cyclodextrin *anion* by bound substrate IV, as had been shown[2,3] for substrates II and III at much higher pH's. As expected from this, the product isolated is a cyclodextrin ferrocinnamate ester (λ_{max} 474 nm) which is slowly hydrolyzed on treatment with aqueous sodium hydroxide to the salt of ferrocinnamic acid (λ_{max} 451 nm).

The acylation reaction is 51 000 times faster than hydrolysis of IV in our medium; this is two orders of magnitude larger than the best previous cyclodextrin acceleration. Furthermore, our V_{max} of 0.18 s^{-1} for IV with pH 6.8 buffer, and thus 1.8 s^{-1} at pH 7.8, should be compared with that of the acetylation of chymotrypsin with *p*-nitrophenyl acetate over this same pH range in water, in which V_{max} is essentially constant at 3.1 s^{-1}.[8] Our reaction is clearly comparable in rate, even though IV is 21-fold *less* reactive than is *p*-nitrophenyl acetate in a simple hydrolysis. This is more remarkable since β-cyclodextrin lacks the principal catalytic groups of the enzyme.

The comparison with the enzyme includes the effect of a solvent change meant to mimic the interior of the protein. In fact, taking our 26-fold acceleration[3] produced by this solvent in the simple hydrolysis of III and applying it here, one can argue that the full acceleration on going from an aqueous hydrolysis to a cyclodextrin acylation in 60% Me_2SO is more than 1.3 million. Regardless of the details of this comparison, it is apparent that our system shows an impressive acceleration.

Although several factors can be invoked to explain this improvement over other substrates, we believe that the geometry of IV is particularly important. Molecular models suggest that IV can go to the tetrahedral intermediate in ester exchange with full retention of the optimum binding geometry in the cyclodextrin cavity, while this is *not* the case for *m*-nitrophenyl

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acetate (II) or *m-tert*-butylphenyl acetate (III) reactions (the aromatic ring is pulled somewhat out of the cavity). In line with this, the ester V shows a K_d of 10 mM but V_{max} of only 4.1×10^{-3} s^{-1} in our Me_2SO buffer system. In this medium the pseudo-first-order rate constant for hydrolysis of V is 6.5×10^{-6} s^{-1}, so the acylation of β-cyclodextrin by V is only 630 times faster than hydrolysis. The *tert*-butylphenyl and ferrocene system have comparable binding constants, as we have seen previously[3] (while the binding constant of the *p*-nitrophenyl group shows that it would not be bound in this concentration range). V_{max} for V *should* be smaller than for IV, since models show that, with V, the conversion to a tetrahedral intermediate pulls the *tert*-butylphenyl group partly out of the cavity. Studies on other related substrates[9] will be needed to clarify all this, and even to show whether IV is yet the optimal substrate. However, it now seems clear that cyclodextrin-based catalysts have the potential to act as artificial enzymes with accelerations of enzymatic magnitudes.

Acknowledgment. This work was supported by the National Institute of Health.

References and Notes

(1) For a recent review, see M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry", Springer-Verlag, New York, 1977.
(2) R. L. Van Etten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *J. Am. Chem. Soc.*, **89**, 3242 (1967).
(3) B. Siegel and R. Breslow, *J. Am. Chem. Soc.*, **97**, 6869 (1975).
(4) At this stage of the development of artificial enzymes, it seems best to optimize the *substrate* for a given catalyst. In a later stage the catalyst would be modified to fit a substrate of particular interest.
(5) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 906 (1957); the authors do not name the compound. We propose that ferrocinnamic acid is appropriate. Our NMR studies establish that the double bond is trans.
(6) Prepared by titrating KH_2PO_4 with NaOH. The solvent change alters pH's and p*K*'s as part of the total solvent effect.
(7) This plot excludes in particular a 2:1 cyclodextrin–substrate transition state involving both aromatic groups even if one cyclodextrin were fully bound throughout our concentration range. Known binding constants[1,3] also exclude such possibilities.
(8) H. Gutfreund and J. M. Sturtevant, *Biochem. J.*, **63** 656 (1956).
(9) As one example, we have already looked at the *N*-acylimidazole of ferrocinnamic acid as a substrate for β-cyclodextrin. It shows an acceleration of only 1200-fold over hydrolysis in the same 60% Me_2SO medium.
(10) National Science Foundation Postdoctoral Fellow.

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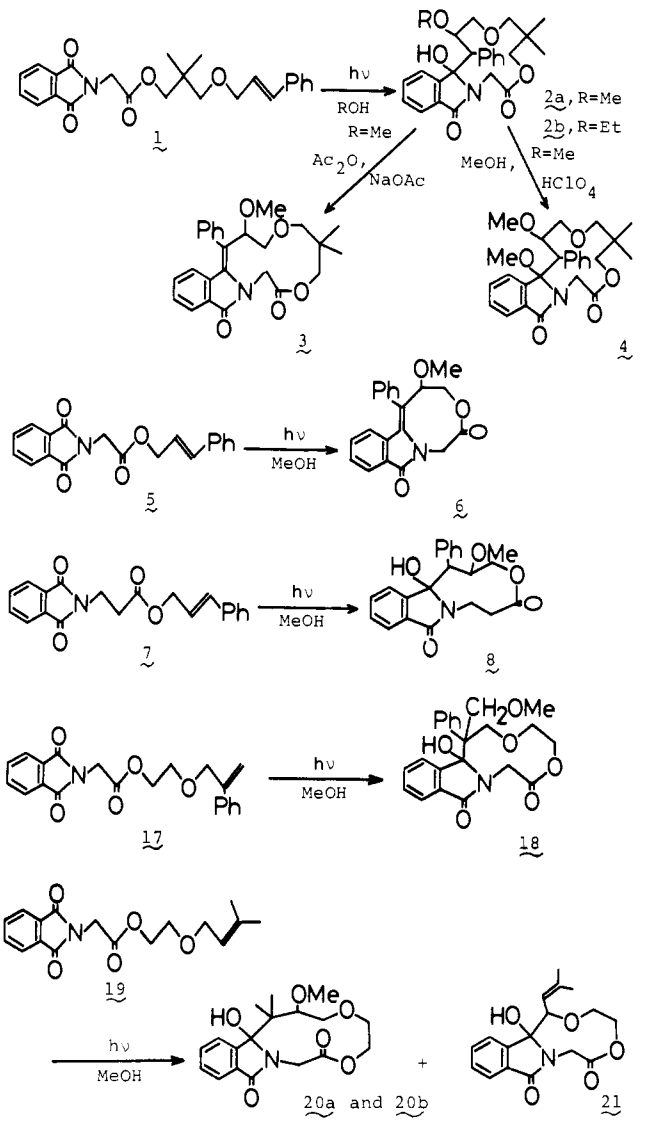
Solvent-Incorporated Medium to Macrocyclic Compounds by the Photochemical Cyclization of *N*-Alkenylphthalimides

Sir:

During recent years some examples of intramolecular photochemical cyclomerization between two chromophoric units bridged by more than four bonds have been reported by a few groups.[1] Compound formation between internal chromophores separated by 17–35 bonds has been successfully studied by Ors and Srinivasan in the cases of α,ω-dicinnamates.[1a,b] De Schryver and his co-workers were also successful in the cases of 7 7′-polymethylenedioxycoumarins with separation up to 14 bonds.[1c]

We report, for the first time, the photochemical solvent-incorporated medium to macro ring cyclomerizations between two chromophores separated by 6–13 bonds in the cases of *N*-alkenylphthalimides. A methanol solution of **1**[2,2] (2 mM) was irradiated for 3 h with a Eiko Sha PIH 300-W high-pressure Hg lamp through quartz. After evaporation of the solvent, a product (**2a**) crystallized (65%) (Scheme I). **2a:** mp 174–176 °C (from methanol); ^1H NMR ($CDCl_3$) δ 0.83 (s, 3 H), 1.05 (s, 3 H), 2.41 (s, 3 H, OMe), 2.8–3.1 (m, 3 H), 3.2–3.6 (m, 4 H), 3.78 and 4.30 (AB q, J = 12 Hz, 2 H), 3.98 and 4.26 (AB q, J = 16 Hz, 2 H), 7.2–7.8 (m, 9 H); IR (KBr) 3270 (OH), 1739 (ester), 1694 (amide) cm^{-1}; *m/e* (rel intensity) (20 eV) 439 (M^+, 6), 407 (M^+ − MeOH, 100), 273 (74); satisfactory elemental analysis for $C_{25}H_{29}NO_6$. Confirmatory evidence for the structure of **2a** was obtained by dehydration and methyl etherification as follows. The product **2a** was dehydrated by refluxing in acetic anhydride with a trace of sodium acetate to give **3** (30%). **3:** mp 157–159 °C; ^1H NMR ($CDCl_3$) δ 0.88 (s, 6 H), 3.1–3.5 (m, 4 H), 3.46 (s, 3 H, OMe), 3.80 and 4.49 (AB q, J = 12 Hz, 2 H), 4.41 and 5.78 (AB q, J = 18 Hz, 2 H), 5.00 (dd, J = 6, 8 Hz, 1 H), 5.68 (d, J = 8 Hz, 1 H), 6.9–7.9 (m, 8 H); IR (KBr) 1732 (ester), 1705 (amide) cm^{-1}; *m/e* (rel intensity) (20 eV) 421 (M^+, 59), 305 (94), 246 (100). On treatment with a trace amount of $HClO_4$ in methanol, **2a** was converted to its methyl ether **4. 4:** mp 175–176 °C; ^1H NMR ($CDCl_3$) δ 0.84 (s, 3 H), 1.11 (s, 3 H), 2.46 (s, 3 H, OMe), 2.60 (s, 3 H, OMe), 2.8–4.0 (m, 8 H), 4.54 (d, J = 12 Hz, 1 H), 4.61 (d, J = 17 Hz, 1 H), 7.2–8.1 (m, 9 H); IR (KBr) 1756 (ester), 1710 (amide) cm^{-1}; *m/e* (rel intensity) (20 eV) 453 (M^+, 3), 305 (100). Similar chemical manipulations were applied to the photoproducts of *N*-2-alkenylphthalimides.[4] Irradiation of **1** in ethanol gave the corresponding product **2b**, mp 200–203 °C (65%).

Scheme I



The photochemical solvent-incorporated cyclomerization was quite general in the cases of *N*-alkenylphthalimides with

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