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Selective Esterolysis of Nitrophenyl Acetates in Crystalline α-Cyclodextrin Complexes

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Abstract. The esterolysis of *m*-nitrophenyl acetate (*m*NPA) and *p*-nitrophenyl acetate (*p*NPA), complexed with α-cyclodextrin, was investigated in the solid state. At 117 and 140°C, the initial half-times of *m*NPA esterolysis were 30 and 24 h, respectively, whereas *p*NPA esterolysis was undetectably slow. At 117°C, the *m*NPA reaction proceeded to completion, and cyclodextrin acetate and *m*-nitrophenol products were identified. At 140°C, the initial rate was followed by a slow phase with a half-time of 130 h, evidently due to a structural change in the complex. The *meta*/*para* selectivity of the solid-state reaction is considerably enhanced over the selectivity reported in aqueous solution.

Key words. Solid-state esterolysis, α-cyclodextrin, nitrophenyl acetates.

1. Introduction

The reactivity of cyclodextrin (CD) complexes has been widely investigated in the liquid phase, i.e., in aqueous and organic solutions [1, 2]. In the solid phase, guests in CD complexes are subjected to additional interactions, not present in liquids, tending to orient them relative to the host lattice. Therefore, it seems likely that reactions in solid CD complexes would display enhanced selectivity relative to the liquid-phase CD systems. A few recent reports of solid-state CD reactivity [3–9] support this hypothesis, for example in halogenation of complexed alkenes [3–5] and in photolysis of dibenzyl ketones [6].

One of the classic examples of liquid-phase CD–guest reactivity is the selective esterolysis of *meta*- and *para*-substituted phenyl acetates. Thus, VanEtten *et al.* [10] showed that α-cyclodextrin (α-CD) catalyzes the esterolysis of *m*-nitrophenyl acetate (*m*NPA), with a rate ratio of 27 : 1 relative to *p*-nitrophenyl acetate (*p*NPA) in alkaline aqueous solution (pH 10.6, 25°C). This selectivity was attributed to the directing effect of the *meta* nitro group on complexation geometry, bringing the carbonyl of *m*NPA into close proximity with a nucleophilic α-CD secondary hydroxyl group [11].

We have now examined the solid-phase counterpart of this reaction. Selective reactivity of solid α-CD·*m*NPA and α-CD·*p*NPA complexes is reported here. To our knowledge, this is the first report of an esterolysis reaction in a solid CD complex.

2. Experimental

α-Cyclodextrin hydrate (α-CD·6 H_2O) was a product of Amerchol Corporation and was recrystallized from water before use. Infrared spectra were obtained on a Nicolet 5DX

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Fourier transform spectrometer. Generally, 100 scans were accumulated on a sample containing 1–2 mg of α-CD complex in a 200 mg KBr pellet. Under these conditions, absolute absorbances were reproducible to ±10% and relative absorbances of peaks within a spectrum to within ±2%. ^{1}H-NMR spectra were obtained at 360 MHz in DMSO-d_6 solvent (recovered CD samples) or in $CDCl_3$ (recovered nitrophenol product). Ultraviolet spectra were obtained in 0.015 M pH 4.42 HOAc/NaOAc buffer at 1.0×10^{-4} M α-CD concentration, or in $CHCl_3$ for recovered nitrophenyl acetates or nitrophenols. X-ray powder diffraction patterns were determined with Co$K\alpha_1$ radiation at room temperature.

2.1. PREPARATION OF COMPLEXES

Solid α-CD·*m*NPA was typically prepared by stirring a solution of 5.00 g of α-CD·6 H_2O in 10 mL of water with 0.838 g of *m*NPA [12] and 0.1 mL of chloroform at 50°C for 48 h. The mixture was cooled and filtered, and the precipitate was washed alternately with several aliquots of cold water and ethanol, followed by chloroform, and was dried *in vacuo*.

Solid α-CD·*p*NPA was typically prepared by allowing a solution of 1.00 g of α-CD·6 H_2O in 4 mL of water to stand in contact with a solution of 1.00 g of *p*NPA in 2.00 mL of chloroform at 58°C for 24 h. The resulting precipitate was filtered, washed, and dried as above.

2.2. SOLID-STATE REACTIONS

Reactions were monitored by heating 10–100 mg samples of the powdered CD complexes in an open system under an inert atmosphere. In order to ensure conditions of good heat and mass transfer, the samples were contained in thin layers (~ 1 mm) in open glass dishes on an aluminum plate, which was inserted into a glass tube through which a slow stream of nitrogen was passed. The glass tube was heated from the exterior by vapors of refluxing butanol (117°C) or *o*-xylene (140°C). The temperature inside the tube was uniform within ±0.1°C. Samples were withdrawn periodically and were analyzed by IR and UV spectroscopy.

Control experiments established that reaction rates and selectivities were qualitatively similar when the samples were heated in air or in vacuum, in an ordinary oven (90–140°C), or in the form of preformed KBr pellets rather than powders. Rates were more reproducible in the dry powder system under a nitrogen atmosphere, however.

In additional control experiments, reactions were examined at 117°C in a nitrogen stream moistened with 8700 Pa partial pressure of water vapor by passage through a thermostatted saturator.

CDs and guests were recovered from solid samples by dissolving 63 mg of each sample in 5 mL of water and extracting with three 3 mL portions of chloroform. The aqueous and chloroform phases were evaporated, and the residues were redissolved and examined by UV and ^{1}H-NMR spectroscopy.

3. Results and Discussion

3.1. PREPARATION AND CHARACTERIZATION OF COMPLEXES

Crystalline α-CD·*m*NPA and α-CD·*p*NPA were prepared by cocrystallization of α-CD and the respective nitrophenyl acetates from aqueous solution. The formation of inclusion

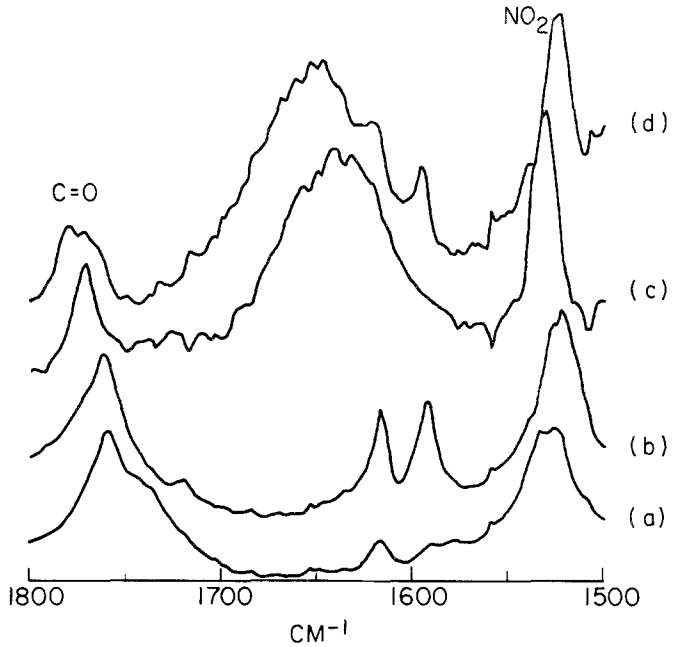

Fig. 1. Infrared absorption spectra (KBr pellets) of (a) *m*NPA, (b) *p*NPA, (c) α-CD·*m*NPA, and (d) α-CD·*p*NPA. Note shifts of carbonyl band indicating complexation.

complexes was confirmed by IR spectroscopy (Figure 1) and by X-ray powder diffraction (Figure 2). Thus, the IR spectrum of solid α-CD·*m*NPA exhibited carbonyl absorption at 1773 cm^{-1} as opposed to 1759 cm^{-1} in uncomplexed *m*NPA. (In one preparation, a second phase of α-CD·*m*NPA absorbing at 1781 cm^{-1} was obtained. This phase appeared to be less reactive in the solid-phase esterolysis and was not further investigated.)

The IR spectrum of α-CD·*p*NPA exhibited two carbonyl absorptions at 1781 and 1773 cm^{-1}, in comparison to 1761 cm^{-1} for uncomplexed *p*NPA (Figure 1). It is not clear whether this material was a single phase with two different *p*NPA environments or a heterogeneous mixture of two α-CD·*p*NPA phases.

In both the *m*NPA and *p*NPA complexes, small shifts of the α-CD IR absorptions relative to α-CD·6 H_2O were observed. Of particular note is the weak absorption of α-CD·6 H_2O at 711 cm^{-1}, which has been assigned to a CD ring vibrational mode [13]. This absorption is shifted to 704 cm^{-1} in both α-CD·*m*NPA and α-CD·*p*NPA. In other work, we have observed that this absorption is sensitive to complexation of a variety of guests in α-, β-, and γ-CD systems [14].

The stoichiometry of the complexes was established by UV analysis. Both *m*NPA and *p*NPA gave complexes containing ~0.2 molecules of guest per α-CD, despite numerous attempts to increase guest concentrations by variation of crystallization conditions. The X-ray powder diffraction patterns established that the low guest/host ratios were not caused by dilution of the samples with α-CD·6 H_2O (Figure 2). Guest/host ratios of this magnitude have been observed in a number of CD systems, particularly with guests that are too large to fit entirely into the CD cavity [8, 15].

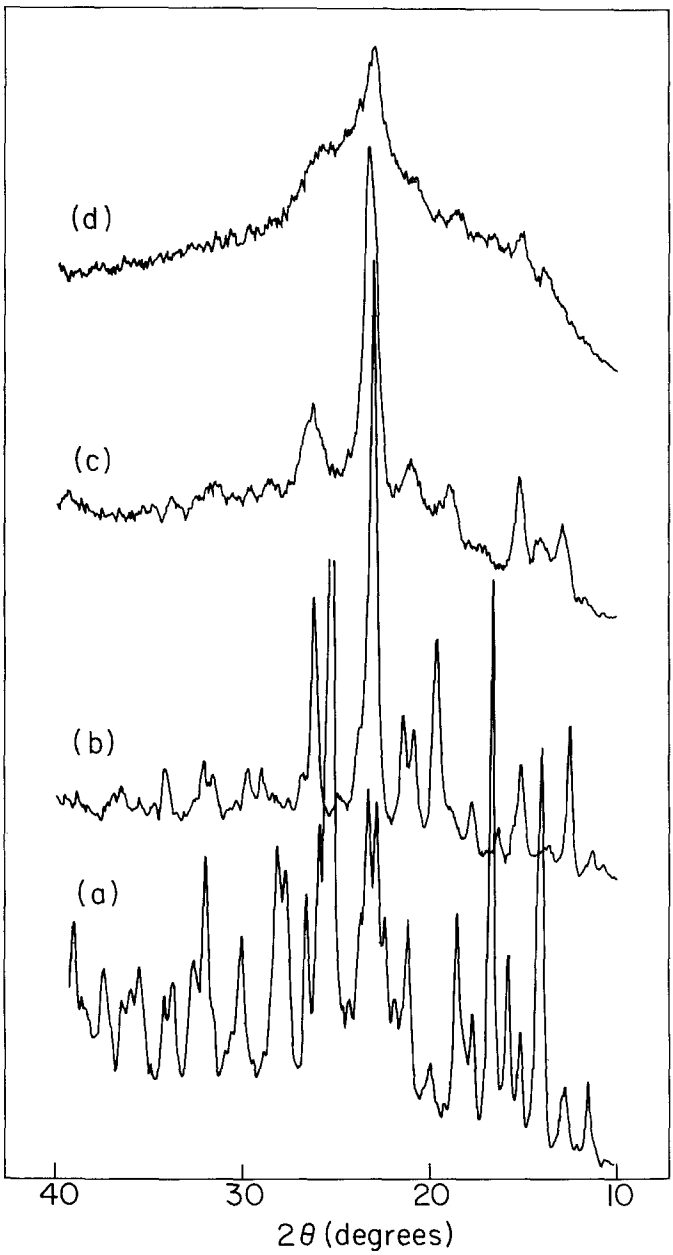

Fig. 2. X-ray powder diffraction patterns at room temperature of (a) α-CD·6 H_2O, (b) α-CD·*m*NPA, (c) α-CD·*m*NPA after heating at 117°C (53% conversion) and (d) α-CD·*m*NPA after heating at 140°C (55% conversion).

3.2. ESTEROLYSES

In contrast to the alkaline conditions of the aqueous CD esterolyses [10], the solid complexes did not contain a basic catalyst. The solid reactions were therefore expected to be slow, and were investigated at elevated temperatures.

Solid α-CD·*m*NPA was heated at 117–140°C under a dry nitrogen atmosphere. Under these conditions, the 1773 cm^{-1} carbonyl absorption of the phenyl ester disappeared, and was replaced with a broad absorption at 1730 cm^{-1}, consistent with formation of α-cyclodextrin monoacetate (Figure 3). After the reaction, the solid product was dissolved, and UV spectroscopy confirmed the formation of *m*-nitrophenol (λ_{max} 273 and 330 nm as opposed to 263 nm for *m*NPA). The host and guest constituents of the product were separated by extraction. ^{1}H-NMR and UV spectroscopy of the recovered guest confirmed formation of *m*-nitrophenol.

The ^{1}H-NMR spectrum of α-CD, recovered after reaction, displayed two new resonances of comparable intensities at δ 2.02 and 2.03 ppm. Esterolysis reactions catalyzed by α-CD in aqueous solution are known to occur by acyl transfer to the α-CD secondary hydroxyls [1, 11, 16]. Breslow and coworkers [16] have reported NMR evidence that the same ester substrate can acylate both the 2-hydroxyl and the 3-hydroxyl of β-CD. By analogy, we suggest that the resonances of the solid state reaction product at 2.02 and 2.03 ppm are due to the methyl hydrogens of α-CD 2- and 3-acetates. The intensities of these resonances were consistent with this assignment, with the stoichiometry and degree of conversion of the starting complex taken into account. Thus, it is likely that the course of the solid-state esterolysis is similar to that in aqueous solution, involving acyl transfer from *m*-nitrophenol to the α-CD hydroxyls.

Reaction rates were estimated from the ratio of the 1773 cm^{-1} phenolic ester carbonyl absorbance to the 1532 cm^{-1} nitro absorbance in the solid state IR spectrum. The latter absorbance remained essentially unchanged throughout the reaction, and thus provided an internal calibration standard. The validity of this method was confirmed by UV and ^{1}H-NMR analysis of selected samples. At 117°C, the initial reaction half-time was approximately 30 h, and the reaction appeared complete at 137 h. At 140°C, the reaction kinetics were biphasic (Figure 4), with an initial rate corresponding to a half-time of 24 h, followed

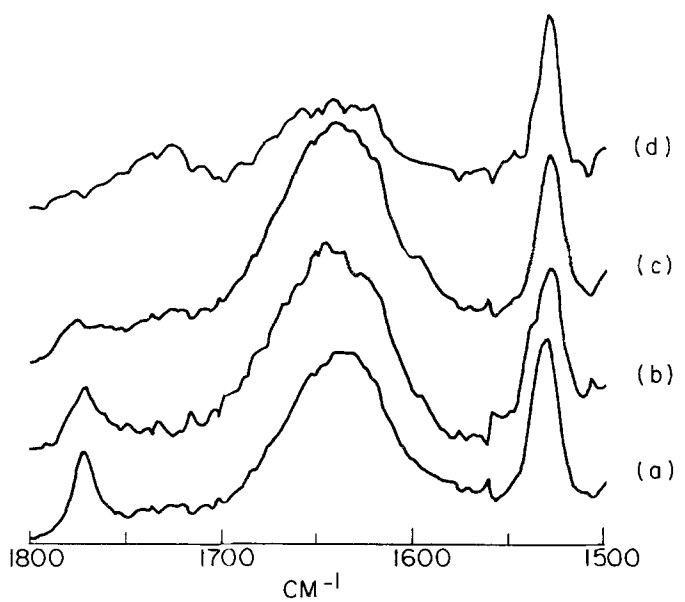

Fig. 3. Infrared absorption spectra of (a) fresh α-CD·*m*NPA, and after heating at (b) 140°C for 23 h (23% conversion), (c) 140°C for 216 h (72% conversion), and (d) 117°C for 137 h (100% conversion).

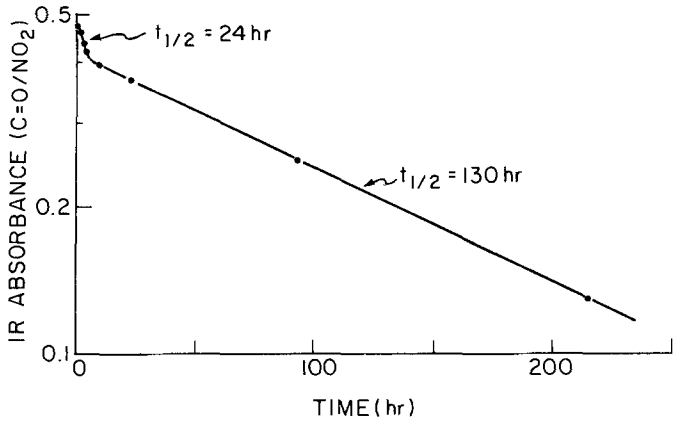

Fig. 4. First-order kinetic plot of α-CD·*m*NPA esterolysis at 140°C. *m*NPA conversion estimated from the ratio of phenolic ester to nitro IR absorbance. Extrapolated reaction half-times in each straight line region are indicated.

by a change at ~16% conversion to a much lower rate (half-time 130 h). At 140°C, the reaction reached only 72% conversion even after a 216 h reaction period (Figure 3).

A further difference in behavior at 117°C and 140°C was observed in the X-ray powder diffraction patterns (Figure 2). At 53% conversion, a sample heated at 117°C exhibited a powder pattern similar to that of the starting α-CD·*m*NPA; band broadening indicated a slight loss of crystallinity. At the same conversion, a sample heated at 140°C was largely amorphous.

Evidently, the thermal reaction of α-CD·*m*NPA is accompanied by a structural transformation to an amorphous complex, at a temperature dependent rate. Loss of crystallinity was also observed in the solid-state bromination of α-CD·cinnamic acid and α-CD·ethyl cinnamate complexes [3, 4]. Possibly, these structural transformations are induced by incompatibility of the reaction product with the starting crystal lattice. Crystal structure transformations during the course of organic solid-state photoreactions have often been attributed to this cause [17].

The observed structural transformation can explain the biphasic kinetics at 140°C, if it is assumed that the amorphous complex is less reactive than the starting crystalline form. At 117°C, the rate of transformation to the amorphous complex is reduced relative to the esterolysis reaction, and the reaction is not substantially retarded.

In contrast to α-CD·*m*NPA, the solid α-CD·*p*NPA complex gave no detectable esterolytic reaction. The infrared spectrum of α-CD·*p*NPA retained phenolic ester IR absorption and provided no evidence for cyclodextrin acetate formation during a 137 h period at 117°C or during a 171 h period at 140°C (Figure 5). It was noted, however, that the ratio of the 1781 to 1773 cm^{-1} carbonyl absorbance increased significantly during the heating period, possibly due to a change of conformation or orientation of *p*NPA within the complex. Minor changes in the X-ray powder diffraction pattern also suggested a slight structural change during heating. UV analysis of the complex after heating provided no evidence for *p*-nitrophenol formation; from the sensitivity of the UV analysis, it was inferred that the half-time for *p*-nitrophenol production was >3000 h.

Previous work had established that cyclodextrin crystals at these temperatures in a dry atmosphere lose most of their water of crystallizaion [18]. In order to determine the effect of hydration, reactions were carried out in a nitrogen atmosphere moistened with water

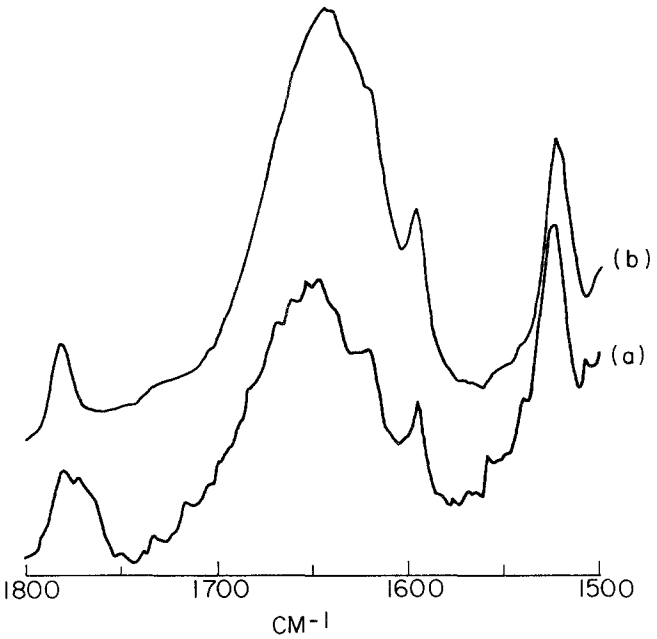

Fig. 5. Infrared absorption spectra of (a) fresh α-CD·*p*NPA and (b) after heating at 140°C for 171 h.

vapor (8700 Pa partial pressure). As in the dry system, no detectable α-CD·*p*NPA reaction was observed. The rate of α-CD·*m*NPA reaction was slightly decreased relative to the dry system. These observations are consistent with the NMR evidence that the reaction involves acyl transfer to the α-CD hydroxyls, rather than attack on the ester by water.

In control experiments, it was confirmed that neither *m*NPA nor *p*NPA reacted at 117°C in the absence of α-CD. The uncomplexed esters are liquids at this temperature, and both were recovered unchanged.

It is concluded that α-CD catalyzes the esterolysis of *m*NPA in the solid state, whereas *p*NPA esterolysis is undetectably slow under the same conditions. The solid-state *m*NPA/*p*NPA rate ratio was >100, in contrast to the ratio of 27 observed under alkaline conditions in aqueous solution [10]. The results demonstrate the potential of solid-state CDs for enhanced esterolytic selectivity.

Acknowledgements

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