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Catalytic Efficiency of [20]Paracyclophane Oxime and Cycloheptaamylose in the Decomposition of Carboxylate and Carbonate Esters

by

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The hydrolytic decomposition of dodecyl *p*-nitrophenyl carbonate (LPNC) and *p*-nitrophenyl dodecanoate (PNPL) as mediated by 10-hydroxy-11-hydroxyimino[20]-paracyclophane (Oxime-I) and cycloheptaamylose (*β*-CD) has been investigated in aqueous media containing 9.9% (v/v) ethanol and 1.0% (v/v) acetonitrile to gain an insight into the reaction and/or substrate specificity. Both LPNC and PNPL were decomposed effectively by an equimolar amount of Oxime-I. It turned out from the analysis of kinetic data that the binding of LPNC to Oxime-I is 2.5 times tighter than that of PNPL, but the subsequent catalysis is 3.3 times more favorable for PNPL than for LPNC. Hence, the overall efficiency of Oxime-I is 1.3 times greater for PNPL, as changed from a 13-fold difference between both substrates in the simple alkaline hydrolysis. *β*-CD was found to be effective also in the decomposition of LPNC when added in large excess over substrate. Comparison of kinetic parameters between the two systems, Oxime-I and *β*-CD, indicated that the former is better in both binding and catalytic effects toward the extremely hydrophobic substrates.

Among the various enzyme models so far developed, macrocyclic compounds are especially interesting and important from mechanistic viewpoints, since they bear a stable reaction site which is hardly affected by medium, temperature, and so forth. Cycloamyloses are the most thoroughly investigated macrocycles and they showed enzyme-like behaviors in many organic reactions.[1,2] Despite the great efforts to improve catalytic activity by introducing suitable catalytic groups to the amylose skeleton, [3-7] or capping,[8,9] the modified amyloses are not still satisfactory. Murakami and coworkers developed totally synthetic macrocycles bearing an effective nucleophile such as hydroxyimino or amino moiety and being furnished with a cavity of sizable diameter into which substrate can be incorporated through hydrophobic interactions.[10] These macrocyclic catalysts also showed enzyme-like properties in the decomposition of carboxylate and sulfate esters.[11-16]

In the present paper, the decomposition of alkyl *p*-nitrophenyl carbonate catalyzed by 10-hydroxy-11-hydroxyimino[20] paracyclophane (Oxime-I) has been investigated kinetically to

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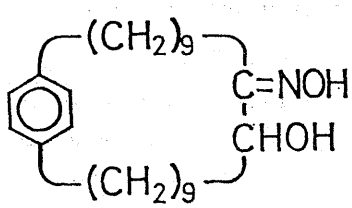
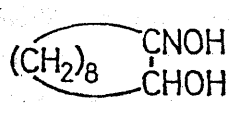
gain an insight into the reaction and/or substrate specificity which can be performed by [20]paracyclophanes. To our knowledge the reaction of a highly nucleophilic oximate group with carbonate esters has never been examined. Another aim of the present work is to compare the catalytic activity of our macrocycles with that of cycloamyloses. These studies will serve to elaborate more sophisticated enzyme models in the future.

Experimental

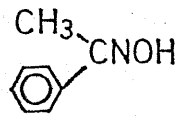
The synthesis of dodecyl- (LPNC) and methyl *p*-nitrophenyl carbonate (MPNC) has been described.[17] *p*-Nitrophenyl dodecanoate (PNPL), 10-hydroxy-11-hydroxyimino[20]paracyclophane (Oxime-I), sebacoin oxime (Oxime-II), and acetophenone oxime (Oxime-III) were the same as those used in the previous studies.[11-16] Cycloheptaamylose was a generous gift from Teijin Co. Ltd. and it was purified by repeated recrystallizations from water as described.[1] The method and apparatus adopted for kinetic measurements were the same as before.[16]



Oxime-I

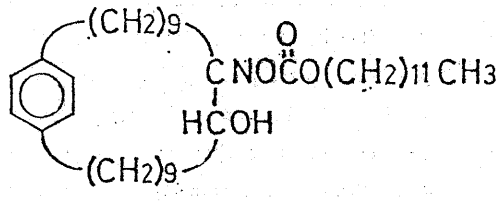


Oxime-II



Oxime-III

Product Analysis. LPNC (15.8 mg) was reacted with Oxime-I (10.5 mg) for 48 h under the conditions identical to those for kinetic experiments. The reaction solution was extracted with 300 ml of chloroform. After washing with water, the extract was dried over sodium sulfate. Removal of the solvent afforded an oily material, which was analyzed by means of TLC and HPLC (Toyo Soda HLC-802) The sample gave four spots on TLC (silica gel) with benzene when detected by chromic acid. Three of them were easily identified by comparison with authentic samples as LPNC, Oxime-I, and dodecanol. High performance liquid chromatography on TSK gel LS-310 (4×600 mm) with hexane-ethanol (98:2 by volume) as an eluant revealed four peaks, three of which were identified again as LPNC, Oxime-I, and dodecanol. The fourth peak came off last under these conditions. In summary, an unidentified material was obtained on both TLC with $R_f = 0.50$ and HPLC. Although we failed to purify or characterize this material rigorously, we tentatively regarded it to be dodecyloxycarbonylated Oxime-I (Oxime-Ia).



Oxime-Ia

Results

Alkaline Hydrolysis of LPNC and PNPL. Alkaline hydrolyses of LPNC and PNPL were investigated at 25.0 °C in 9.9% (v/v) ethanol-1.0% (v/v) acetonitrile aqueous solution over a range of pH 10-12. Pseudo-first-order rate constants for both substrates showed first-order dependence on hydroxide ion concentration and the second-order rate constants, k_{OH}, were obtained by simply dividing the observed first-order rate constants by the stoichiometric hydroxide ion concentration. They are listed in Table 2.

Reaction of Carbonates with Oximes. Cata-

Table 1 Effects of oximes on the decomposition of carbonate esters at 25.0 °C and μ=0.10 (KCl) in 9.9% (v/v) ethanol-1.0% (v/v) acetonitrile

Substrate	[Catalyst]×10^5, M	pH	k_{obs}×10^4, s^{-1}	k_c[c] M^{-1} s^{-1}	k_c/k_{OH}
LPNC[a]	Oxime-I: 0.991	12.11	24.3	246	22000
LPNC[a]	Oxime-II: 1.00	12.13	2.17	8.2	770
LPNC[a]	Oxime-III: 1.02	12.14	2.08	7.2	760
MPNC[b]	None	10.71	52.4		
MPNC[b]	Oxime-I: 0.991	10.74	59.5		
MPNC[b]	None	11.17	149		
MPNC[b]	Oxime-I: 0.991	11.11	150		

a) [LPNC]=0.991×10^{-5} M
b) [MPNC]=0.994×10^{-5} M
c) $k_c = (k_{obs}-k_{hyd})/[\text{Catalyst}]$

lysis of the degradation of carbonate esters, MPNC and LPNC, by three oximes has been studied under the same reaction conditions as those adopted for the alkaline hydrolyses of substrates. Oxime-I enhanced the decomposition rate of LPNC to a considerable extent, while the effect of Oxime-II and Oxime-III was much smaller (Table 1). The pH-rate profile for the catalytic decomposition of LPNC by an equimolar amount of Oxime-I clearly indicates the existence of an acid-dissociable group, *i.e.*, the hydroxyimino moiety of Oxime-I (Fig. 1). It is also evident that the oximate ion is catalytically active, while the contribution of free oxime moiety is negligible in the catalysis. Analysis of the pH-rate profile along this line allowed to calculate the dynamic acid dissociation constant for this group to be 12.4. Based on this pK_a-value a theoretical curve is drawn to fit the data best as shown in Fig. 1. For the decomposition of MPNC even Oxime-I could not enhance the rate to a meaningful extent (Table 1). It is obvious from these results that both substrate and catalyst must have sufficient hydrophobicity for the catalysis to take place. Similar phenomena have already been noticed by Murakami *et al.*[12,13,16] and by others[18,19] for several reactions.

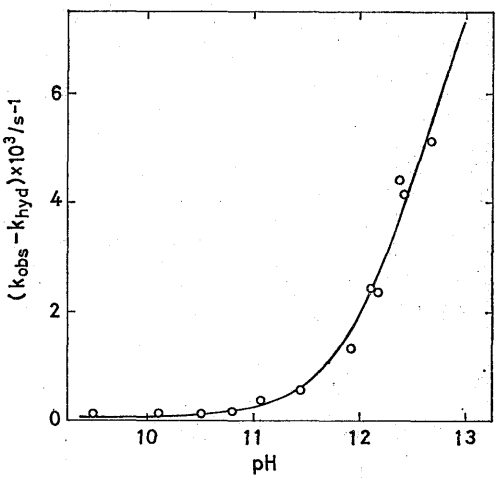


Fig. 1. pH-Rate profile for the catalytic decomposition of LPNC (9.91×10^{-6} M) by an equimolar amount of Oxime-I in aqueous media containing 9.9% (v/v) ethanol-1.0% (v/v) acetonitrile at 25.0 °C. The solid line is the calculated one based on pK_a=12.4.

The catalytic rates of LPNC decomposition leveled off over the slightly excess molar ratio of Oxime-I to substrate as shown in Fig. 2. The similar saturation kinetics have been observed in the reaction of [20]paracyclophane oxime and *p*-nitrophenyl carboxylates bearing a long alkyl chain.[11-13] This is good evidence to

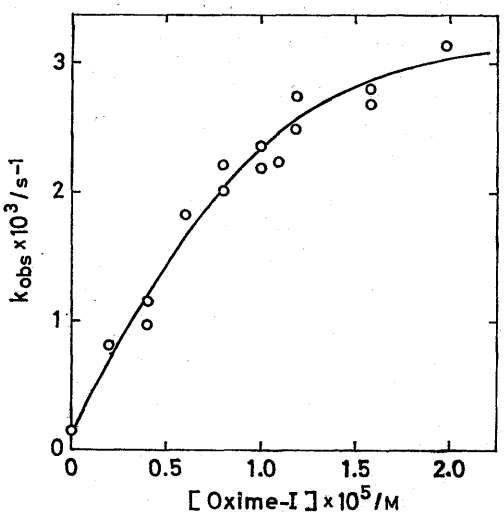
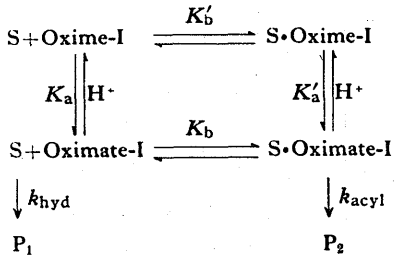


Fig. 2. Saturation kinetics for the catalytic decomposition of LPNC (9.91×10^{-6} M) by Oxime-I in aqueous media containing 9.9% (v/v) ethanol-1.0% (v/v) acetonitrile at 25.0 °C. The calculated line is drawn on the basis of the kinetic parameters listed in Table 2.

suggest that the Oxime-I-catalyzed decomposition of LPNC occurs via a substrate-catalyst complex formed at the pre-equilibrium stage. Thus, the whole reaction scheme may be depicted as follows:[12]



P_1: *p*-nitrophenolate ion, dodecanol, and carbon dioxide

P_2: *p*-nitrophenolate ion and dodecyloxycarbonylated Oxime-I

Since it was shown that the substrate binding is independent of the protonation state of Oxime-I,[20] K_b' was taken to be equal to K_b in the further treatment. Based on the above scheme the kinetic data were analyzed according to the method developed previously for the analysis of reaction system of 10-amino[20]-paracyclophane and carboxylate esters.[16] The method, which is applied under the specific conditions of comparable molar ratio of catalyst to substrate, includes an iterative calculation of non-linear least squares by the aid of an electronic computer. The obtained kinetic parameters (K_b and k_{acyl}) enabled to construct a theoretical line to fit the experimental points fairly well as illustrated in Fig. 2.

Reaction of Carboxylate Esters with Oximes. In order to compare critically the reactivity of Oxime-I to the present substrate with that to PNPL, the reaction of PNPL with Oxime-I was reinvestigated at the same solvent composition and temperature as those used for LPNC. The pH-rate profile for the reaction of PNPL with an equimolar amount of Oxime-I was essentially the same as that for the reaction of LPNC with Oxime-I. The pK_a of 12.4 obtained dynamically for the oxime group is identical to that obtained in the reaction of LPNC with Oxime-I. This result indicates that the acid dissociation of the oxime group of Oxime-I is unaffected by the structure of the incorporated substrates. This is provided by the similar hydrophobicity and bulkiness of both substrates. However, the pK_a-value of Oxime-I obtained in this work shifted by nearly one pH unit from those obtained for PNPL in the previous work.[12] This can be ascribed to the difference in the reaction temperature and solvents between the two systems.

The rate dependence on the catalyst concentration was essentially the same in shape as that seen in the previous study (see Fig. 2 of Ref. 12). It seems, therefore, that the change in the solvent system from 10.9% (v/v) acetone to 9.9% (v/v) ethanol-1.0% (v/v) acetonitrile did not bring about a serious difference in binding properties of Oxime-I. This, in fact, was confirmed quantitatively by

the analysis of kinetic data. The binding constant of 1.8×10^5 M^{-1} for the previous system is in good agreement with the present value of 2.2×10^5 M^{-1}, if the difference in temperature at which kinetic measurements were made is taken into account.

Catalysis by β-CD. The reaction of LPNC and PNPL with cycloheptaamylose (β-CD) was examined under the same reaction conditions as those described above. For both substrates, a large excess of β-CD over substrates was necessary for the decomposition. In the reaction of LPNC and β-CD the plot of the logarithmic rate constants *vs.* pH revealed a linear dependency on the hydrogen ion concentration below pH 10.6 and then negatively deviated at higher pH, as already observed by Bender and his coworkers for the reaction of β-CD with *m*-tolyl acetate and its related substrates.[2] This behavior of β-CD has been interpreted in terms of the decrease in the number of secondary hydroxy groups left to ionize at higher pH, just as done by Bender *et al.* for their system.[2] The slope at the linear part (1.04) was basically the same as that for the alkaline hydrolysis of the substrate (1.06). Using a 100-fold excess of β-CD, the rate acceleration amounted to 140-fold in this linear region. The pK_a (11.5) dynamically obtained from analysis of the pH-rate profile is fairly close to the value (12.1) for the system of β-CD and *m*-tolyl acetate in 1% (v/v) aqueous acetonitrile.[2]

The decomposition rate of LPNC in 9.9% (v/v) ethanol-1.0% (v/v) acetonitrile leveled off with respect to the concentration of β-CD only when the catalyst was used in large excess over the substrate. This means that the binding ability of β-CD toward the present substrate is relatively poor compared with Oxime-I. In the system of β-CD and LPNC the binding constant obtained from the saturation kinetics was as 1.2×10^2 M^{-1} (Table 2). By reference to the stoichiometry obtained for the binding of palmitoyl-CoA to β-CD,[21] more than two β-CD molecules (possibly three) might be involved in the inclusion of LPNC. If this is the case, the binding constant should be tripled as 3.6×10^2 M^{-1}.

Discussion

All the kinetic parameters obtained in the present investigation are compiled on Table 2 along with the previous data for the reaction

Table 2 Kinetic parameters for the reaction of LPNC and PNPL with macrocycles at 25.0 °C and μ=0.10 (KCl) in 9.9% (v/v) ethanol-1.0% (v/v) acetonitrile (unless otherwise stated)

Substrate	Catalyst	pK_a	K_b, M^{-1}	k_{acy}, s^{-1}	$K_b \cdot k_{acyl}$ $M^{-1}\ s^{-1}$	k_{OH}, $M^{-1}\ s^{-1}$
LPNC	Oxime-I	12.4	5.4×10^5	1.7×10^{-2}	9.2×10^3	1.07×10^{-2}
LPNC	β-CD	11.5	1.2×10^2	8.3×10^{-3}	1.0	1.07×10^{-2}
LPNC[a]	β-CD	11.0	5.7×10^2	6.7×10^{-3}	3.8	6.22×10^{-2}
PNPL	Oxime-I	12.4	2.2×10^5	5.6×10^{-2}	12.3×10^3	14.2×10^{-2}
PNPL[b]	Oxime-I	11.4	1.8×10^5	7.8×10^{-3}	1.40×10^3	
PNPL[c]	Oxime-IV	11.36	~5.2×10^3	2.1×10^{-1}	~1.4×10^3	4.3×10^{-2}

a) Medium, 3.0% (v/v) ethanol-1.0% (v/v) acetonitrile.
b) Medium, 10.9% (v/v) aqueous acetone at 34.0 °C. Ref. 12.
c) Medium, 1.0% (v/v) methanol-1.0% (v/v) acetone aqueous solution at 30.0 °C. Ref. 13.

of PNPL and {10(11)-hydroxyimino[20]-paracyclophan-22-yl-methyl}trimethylammonium chloride (Oxime-IV) studied by Murakami and coworkers.[14] Two points have been made clear. First, Oxime-I specifically catalyzes the decomposition of LPNC and PNPL, but it shows no catalytic effect on the decomposition of anilides such as *N*-methyl-*N*-dodecanoyl-*p*-nitroanilide (data not shown). Secondly, under the present reaction conditions Oxime-I is more effective toward the hydrophobic substrates than β-CD.

In Table 2, a more critical comparison among the specific substrates for Oxime-I reveals that LPNC is more effectively decomposed by Oxime-I than PNPL. The rate of alkaline hydrolysis of PNPL is faster by a factor of 13 than that of LPNC. Nevertheless, this difference is diminished to 1.3-fold in the Oxime-I-catalyzed reactions in terms of $K_b \cdot k_{acyl}$. The binding process (K_b) is favorable for LPNC, while the subsequent group transfer step is more favorable for PNPL. It is interesting to note that the ratio of k_{acyl}-value of LPNC to that of PNPL (3.3) is fairly close to the intrinsic reactivity ratio of *p*-nitrophenyl acetate and MPNC against nitrogen or oxygen nucleophiles (1.3-2.4).[22]

Let us now compare the catalytic activity of Oxime-I to that of β-CD. Whereas cycloamyloses have been reported to include a variety of organic compounds with a modest binding constant (10^2–10^3 M^{-1}),[1,2,23] the binding of the extremely hydrophobic substrates such as LPNC and PNPL to β-CD was found not to be very strong. This appears rather unusual at first sight, because Bergeron *et al.* observed a tight binding of palmitoyl-CoA to β-CD in a 1:3 stoichiometry.[21] The 10.9% contamination by organic solvents may be responsible in part for this unexpected result.[2] The increase in the binding ability of β-CD toward the present substrates was, in fact, attained by decreasing the apolar component from 10.9% aq. ethanol to 1.0% (v/v) ethanol-1.0% (v/v) acetonitrile aq. solution (Table 2). Another reason would be the less hydrophobic nature of the cavity of β-CD. Although the cavity of cycloamyloses is relatively hydrophobic as long as water molecules are excluded, it is also expected to be somewhat polar owing to the presence of hydroxy groups in the periphery of the cavity.[24] On the other hand, the cavity of [20]paracyclophanes is regarded to be completely hydrophobic because it is composed entirely of hydrocarbon groups such as benzene ring and polymethylene chains. It may be, thus, concluded that the intrinsic hydrophobicity of the cavity of paracyclophanes is superior to that of cycloamyloses. In order for a substrate bearing a long alkyl chain to be incorporated into a cavity, the alkyl chain in the aqueous media must be fully extended in the first place. In the case of cyclophanes, energetic loss in this process must be readily overcome by the gain in the subsequent inclusion of elongated chain into the cavity. However this is not the case for amyloses. This difference would be the principal reason for the difference in binding properties of both macrocycles. In addition to the binding ability, the catalysis of the decomposition of bound LPNC is accomplished more efficiently by Oxime-I than by β-CD. Thus, the oximate ion of Oxime-I is twice as reactive as the alkoxide ion of β-CD. If one takes into account that β-CD has seven equivalent hydroxy groups, this difference may be magnified to 14-fold. It is obvious that the higher basicity of the hydroxyimino moiety of Oxime-I is responsible for it. In addition, the α-effect must be working in the oximate group to increase nucleophilicity of the oxygen atom.[25]

In summary, Oxime-I showed a marked specificity for the highly hydrophobic substrates in their binding. The subsequent catalysis was

also specific for those substrates that have a good leaving group. Stereospecificity is an important aspect of enzymic catalysis and it has already been reported that β-CD also shows some stereospecificity.[26] Thus, an approach to this goal should be an interesting next target in the [20]paracyclophane systems as well.

Acknowledgment

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