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CATALYSIS OF THE DEACYLATION OF p-NITROPHENYL HEXADECANOATE BY 11-AMINO[20]PARACYCLOPHAN-10-OL IN NEUTRAL AND ALKALINE MEDIA

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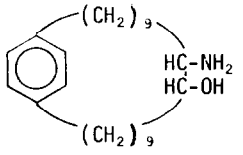
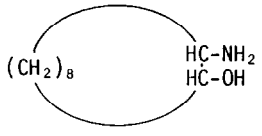
Simulation of the polyfunctional features of various enzymes by synthetic model compounds is quite interesting from bioorganic viewpoint. Mechanistic investigations on various reactions as catalyzed by such enzyme model systems will make plausible approaches to the elucidation of enzymatic catalysis. Nevertheless, synthetic macrocycles of polyfunctional nature have not so far been successfully prepared. We have recently prepared various [20]paracyclophanes which are furnished with one or two suitable catalytic groups.[1~3] Those macrocycles were effective for the deacylation of *p*-nitrophenyl carboxylates bearing a long alkyl chain.[2] (10-Hydroxyimino[20]paracyclophan-22-(23)-yl-methyl)trimethylammonium chloride enhanced much significantly the deacylation of hydrophobic esters by concurrent nucleophilic-electrostatic bifunctional catalysis.[1] In the present work, 11-amino[20]paracyclophan-10-ol (*1*)[3] has been examined kinetically to characterize it as another bifunctional catalyst in the deacylation of *p*-nitrophenyl hexadecanoate (PNPP) in a neutral to alkaline region.



(*1*)



(*2*)

The decomposition rate of PNPP, as determined spectrophotometrically at 400 nm, was markedly accelerated in a whole pH range investigated (6 through 12) by an equimolar or a less amount of paracyclophane *1* (Fig. 1). The catalytic efficiency was compared with that of 2-aminocyclodecanol (*2*) (Table 1). Thus, cyclodecanol *2* has no ability to incorporate PNPP into its cavity. A great effectiveness of *1* as compared with *2* clearly suggests that the following factors are important for the development of catalytic effect, (i) sufficient hydrophobicity must be provided by a macrocycle, (ii) a functional group or groups of a macrocycle must be oriented geometrically in favor of the pseudo-intramolecular reaction between the functional group or groups and the ester bond of the bound substrate. The hydrophobic incorporation of a substrate into the paracyclophane cavity prior to rate-determining acyl transfer process has been rationalized by observation of the saturation kinetics in the present reaction as well as in the previous ones.[1~3]

The pH-rate profile for the deacylation of PNPP as effected by *1* demonstrates a double sigmoid shape (Fig. 1). In reference to the chemical structure of paracyclophane *1*, the first

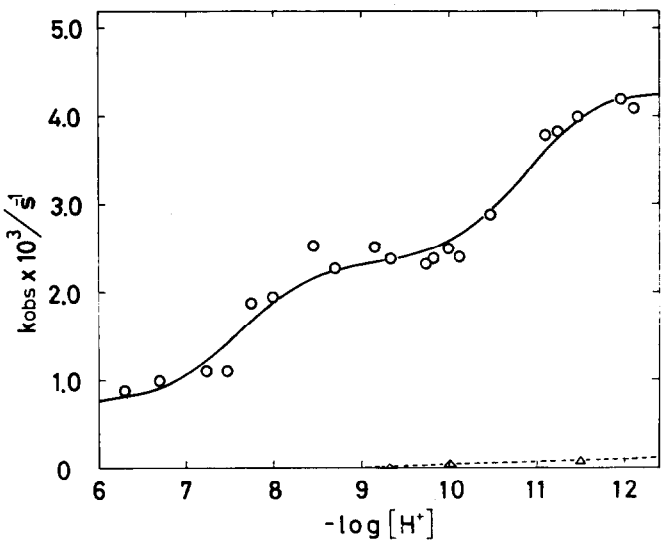


Fig. 1. pH-rate profile for the deacylation of PNPP (1.00×10^{-5} M) in 10.9%(v/v) aqueous ethanol at 40.0±0.1° and μ=0.10 (KCl) in the absence (Δ) and presence of *1* (o, 1.03×10^{-5} M). Solid line is a theoretical curve calculated using the equations: $k_{calc}=k_1X_1 + k_2X_2 + k_3X_3$, $X_1=[H^+]^2/(K_1K_2 + K_1[H^+] + [H^+]^2)$, $X_2=X_1K_1/[H^+]$, $X_3=X_1K_1K_2/[H^+]^2$, and $X_1 + X_2 + X_3 = 1.0$, where Xs, Ks, and ks stand for the mole fractions, acid dissociation constants, and first-order rate constants of ionic species suffixed to them; 1, 2, and 3 refer to cationic, neutral, and anionic species, respectively. Parameters used to calculate the theoretical curve are as follows: $k_1=7.40\times10^{-4}$ s^{-1}, $k_2=23.6\times10^{-4}$ s^{-1}, $k_3=43.7\times10^{-4}$ s^{-1}, $K_1=2.46\times10^{-8}$ M^{-1}, and $K_2=1.29\times10^{-11}$ M^{-1}.

Table 1. Catalytic efficiency of *1* and *2* in the deacylation of PNPP at 40.0±0.1°, μ=0.10 (KCl), and -log[H^+]=9.18 in 10.9%(v/v) aqueous ethanol[a)]

[Catalyst]×10⁵/M	$k_{obs}\times10^4/s^{-1}$	k_c[b)]$/s^{-1}M^{-1}$	Rate ratio[c)]
None	0.22±0.04	0.50±0.09	
1 : 0.931	26.4 ±0.5	282 ±5	~10³
2 : 1.06	0.25±0.06	0.28±0.3	

a) Each first-order rate constant is an average of triplicated runs and the estimated uncertainty is not greater than ±6%. Initial substrate concentration, 1.00×10^{-5} M. b) $k_c=(k_{obs} - k_{hyd})/[1$ or $2]$; $k_c=k_{hyd}/[OH^-]$ for simple alkaline hydrolysis. c) $k_{c(1)}/k_{c(2)}$.

process is caused by the protonated amino-group and the second one by the hydroxy-group. The pK_a values evaluated computationally from the pH-rate profile were 7.6 and 10.9 for the amino- and hydroxy-groups, respectively. They seem too low for pK_a values of functional groups under consideration unless some effect comes into play. The primary factor which facilitates the dissociation of these protons is most likely the hydrophobic field effect provided by the inclusion complex. On the basis of the concept of hydrophobic interaction, water molecules surrounding an apolar species would be highly structured (iceberg formation), resulting in the enhancement of the basicity of water molecules.[4~6] The unusual nucleophilic reactivity exerted by the unionized hydroxyimino group of 10-hydroxyimino[20]paracyclophane toward PNPP was also attributed to the increased basicity of highly structured water molecules surrounding the inclusion complex.[7] The increased basicity was found to facilitate the dissociation of the hydroxy-imino-proton. In addition to the hydrophobic field effect, an intramolecular hydrogen bonding between the ammonium- and hydroxy-groups tends to retard the acid dissociation of the ammonium group; pK_a 7.1 for 10-amino[20]paracyclophane[8] and 7.6 for the present paracyclophane in a manner as observed for the combination of *threo*-2-aminocyclopentanol (pK_a 8.85) and its *erythro*-isomer (pK_a 9.1).[9] On the other hand, the hydrogen bonding between the free amino- and secondary hydroxy-groups should facilitate the acid dissociation of the hydroxyl group to stabilize the producing alkoxide group.[10]

It must be pointed out here that the hydrolysis of PNPP, neither the aminolysis nor the other acyl transfer reactions, was markedly accelerated in a neutral pH region (6-7). In the absence of *1*, the hydrolysis did not proceed to any detectable extent under the same reaction conditions. The profound rate enhancement must be attributed either to an electrostatic catalysis which results in the stabilization of the anionic tetrahedral intermediate,[1] or to a pseudo-intramolecular general acid catalysis by the ammonium group of protonated species 1_a. In a pH range above 9, the acyl transfer was found to take place between *1* and PNPP. The acyl group is transferred to the amino-group of neutral paracyclophane (1_b) to afford the *N*-acylated paracyclophane (aminolysis) in a manner as observed previously for 10-amino[20]paracyclophane.[8] As pH goes up to a region of 11-12 where the anionic paracyclophane (1_c) is present as the predominant species, the alkoxide group becomes the principal nucleophile and the transesterification occurs from PNPP to 1_c.[11]

In order to clarify the catalytic roles of both functional groups, the amino- and hydroxy-groups were independently modified with 2,4-dinitrofluorobenzene (DNFB) and diisopropylphosphorofluoride (DFP), respectively.[12] Catalytic effects of the modified paracyclophane are listed in Table 2. Upon phosphorylation of the hydroxy-group of *1*, the catalytic efficiency decreases to about one third of that shown by the un-modified catalyst. This result indicates that the amino-group acts as an effective nucleophile in place of the deactivated hydroxy-group in such a high pH range. The paracyclophane dinitrophenylated at the amino-group, on the other hand, does not show any catalytic efficiency and the decomposition rate of PNPP decreases nearly to the catalyst-absence level. Substitution with the bulky 2,4-dinitrophenyl group at the amino nitrogen seems to interfere effectively with the approach of PNPP to the nucleophilic secondary hydroxy-group.

Table 2. Catalytic effects of the chemically modified 11-amino[20]paracyclophan-10-ol on the deacylation of PNPP at 40.0±0.1° and μ=0.10 (KCl) in 10.9%(v/v) aqueous ethanol[a)]

$[1]\times10^5$/M	[Modification reagent]$\times10^5$/M	$-\log[H^+]$	$k_{obs}\times10^4/s^{-1}$
None	None	11.50	0.72±0.04
0.995	None	11.22	39.3 ±0.4
0.995	DFP : 5.09[b)]	11.22	17.8 ±0.8
0.995	DNFB : 5.68[b)]	11.30	1.39±0.21

a) Initial concentration of substrate, 1.00×10^{-5} M. b) The chemical modification of *1* with DFP or DNFB was carried out as follows: an aqueous solution containing appropriate amounts of *1*, DNFB (or DFP), ethanol, and potassium chloride was allowed to stand at room temperature for 24 hr, pH being maintained at 10.4 with borate-carbonate buffer.

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11) When the reaction was carried out at pH 11.6 where 1_c is predominant, a new absorption band appeared at 231.4 nm during the course of reaction. On the other hand, an absorption band at 227.0 nm increased as the reaction proceeded in the presence of 1_b. We regard this slight difference in absorption maximum was caused by the alteration of the attacking nucleophile from the amino- to the alkoxide-group. In the case of cycloamylose-catalyzed hydrolysis, the acyl group was transferred to a secondary hydroxy-group of cycloamylose (R. L. VanEtten, G. A. Clowes, J. F. Sebastian, and M. L. Bender, *J. Amer. Chem. Soc.*, 89, 3252 (1967)).

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