Substrate Specificity in Ester Hydrolysis by a New Water-Soluble Heterocyclophane

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Abstract: A new water-soluble heterocyclophane, *N,N,N′,N′,N″,N″,N‴,N‴*-octamethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophanetetraammonium tetrafluoroborate (**1**), was found to catalyze the hydrolysis reaction of three aromatic chloroacetates, $ClCH_2CO_2R$ [R = *p*-nitrophenyl (**7a**), α-naphthyl (**7b**), or β-naphthyl (7c)], very effectively and specifically. The rate accelerations judged from the rate constant ratio of k_2/k_0 were 25 ± 3 (**7c**), 6 ± 0.5 (**7b**), or 2.6 (**7a**) at pH 8.10 in phosphate buffer and 18 ± 2 (**7c**), 11 ± 1 (**7b**), or 2.4 (**7a**) at pH 6.96 in phosphate buffer, strongly indicating that the "inclusion-electrostatic" catalyst **1** is more effective and discriminating than any of CTAB micelle, simple cyclodextrin inclusion, or an open-chain analogue (**9**). Very interestingly, however, a unique inhibition by **1** was found with a substrate of the α-chloro-β-naphthyl type (**14**), showing a rate constant ratio of $k_{inh}/k_0 = 0.084 \pm 0.023$ ($^1/_{12}$ deceleration). In order to elucidate the basis of this interesting discriminative catalysis or inhibition by **1**, mechanistic studies were carried out. Temperature-jump experiments by the use of a model compound for substrate, sodium hydroxynaphthalenecarboxylate (**11**, **12**), had shown that the present host-guest inclusions are satisfactorily fast ($k_A = 1.8 \times 10^7$ to $4.4 \times 10^7\ s^{-1}\ M^{-1}$; $k_D = 1.6 \times 10^4$ to $3.8 \times 10^4\ s^{-1}$), allowing the host and guest to search for the most appropriate arrangement for the slow subsequent hydrolysis. The absence of any systematic correlation between log (k_2/k_0) vs. pK_a of the leaving phenol or naphthol or a small basicity dependence of the N^+–aryloxyl interaction leads to the conclusion that the very discriminative catalysis by **1** was developed mostly from specific substrate binding, in a sense that the N^+–oxyanion interaction, at the transition state for the tetrahedral intermediate formation, remarkably depends on the substrate structure. The one-twelfth deceleration observed for **14** was, therefore, attributed to the inhibition of this N^+–oxyanion interaction due to either the mechanism of "reverse binding" of the substrate or the "induced disfit".

Basic characteristics of enzymes, such as saturation kinetics or large catalytic constants, have been successfully modeled by the use of naturally occurring compounds[1] or synthetic molecules[2] during the past decade. Substrate specificity, on the other hand, is one of much more complicated features of enzymes than these kinetic resemblances in a sense that specificity is generated by enzymes in regard to the reaction pathway,[3a] the geometry of the substrate,[3b] the shape and size of the substrate, and/or the optical discrimination,[3c] for this reason, greater sophistication is necessary in enzyme models for advanced understanding of enzymatic mechanisms involving how specificities are controlled or reconciled to one another. Discriminative binding of substrate[1,2] or proximity effect[3d] had been well documented in previous studies as the origin of substrate specificity manifested by most of previous enzyme models.

Substrate specificity is understood to indicate that a specific substrate has a "best fit" to a unique array of binding-site residues[4] and that the spatial arrangement of atoms relevant to the catalysis is particularly favorable for the stabilization of the transition state.[3] Among the variety of ways in which such stabilization can arise, electrostatic stabilization is very important, especially in a very hydrophobic environment,[5] as seen in most enzymatic reactions involving various charged transition states. In an active site, cationic residues of protonated basic amino acids, such as $LysH^+$ or $ArgH^+$, can stabilize an anion developing in the transition state of an enzyme-catalyzed reaction.[6] For example, in ribonuclease catalysis, stabilization of a dianionic pentacoordinate intermediate is assumed to be provided by a cationic residue in close proximity (probably protonated Lys).

In previous communications,[7a–d] we reported that water-soluble heterocyclophanes **1** and **2** are excellent inclusion hosts toward certain organic substrates, and a unique substrate specificity was observed in ester hydrolysis catalyzed by **1**, among α-naphthyl, β-naphthyl, and *p*-nitrophenyl chloroacetates,[7d] in a marked contrast to much smaller specificity of other catalysts such as CTAB micelles[7d,8] or cyclodextrins.[8] In this article is presented

(1) (a) F. Cramer and W. Kampe, *J. Am. Chem. Soc.*, **87**, 1115 (1965); (b) R. L. van Etten, J. F. Sebastian, G. A. Groves, and M. L. Bender, *ibid.*, **89**, 3242 (1967); (c) D. L. Vander Jagt, F. L. Killian, and M. L. Bender, *ibid.*, **92**, 1016 (1970); (d) T. S. Straub and M. L. Bender, *ibid.*, **94**, 8875 8881 (1972); (e) R. Breslow and P. Cambell, *Bioorg. Chem.*, **1**, 140 (1971); (f) I. Tabushi, K. Fujita, and H, Kawakubo, *J. Am. Chem. Soc.*, **99**, 6456 (1977).

(2) (a) F. Cramer and G. Mackenson, *Angew. Chem.*, **78**, 641 (1966); (b) F. Cramer and G. Mackenson, *Chem. Ber.*, **103**, 2138 (1970); (c) R. Breslow and L. W. Overman, *J. Am. Chem. Soc.*, **92**, 1075 (1970); (d) W. B. Gruhn and M. L. Bender, *Bioorg. Chem.*, **4**, 219, 237 (1975); (e) R. Breslow, J. B. Doherty, G. Guillot, and C. Lipsey, *J. Am. Chem. Soc.*, **100**, 3277 (1978).

(3) (a) A pyridoxal phosphate dependent enzyme catalyzes a certain pathway among racemization, transamination, decarboxylation, α,β-elimination, and synthesis of amino acids: see, for example, E. Zeffren and P. L. Hall, "The Study of Enzyme Mechanism", Wiley-Interscience, New York, 1973, pp 156–162. (b) Fumarate hydratase shows a specificity toward fumarate among geometrical isomerism of cis or trans. Another example of geometrical discrimination is seen for glycerol kinase, which phosphorylates assymetrically a symmetric substrate, glycerol: M, Dixon et al., "Enzymes", Longman, London, 1979, pp 238–240. (c) M. L. Bender, "Mechanism of Homogeneous Catalysis from Protons to Proteins", Wiley-Interscience, New York, 1971, pp 484–485. (d) T. C. Bruice, *Enzymes, 3rd Ed.*, **2**, 217–279 (1970).

(4) In our recent theoretical study on chemical model of biological molecular recognition, the observed free-energy change for inclusion complexing of a hydrophobic molecule by α-cyclodextrin in water was successfully reproduced. In this theoretical work, we had clarified that the free-energy change for the "best fit" of a substrate to the cyclodextrin's cavity involves very complicated terms as follows: (1) van der Waals interaction between the guest and α-cyclodextrin; (2) extrusion of bound (structured) water molecules of α-cyclodextrin into the bulk water; (3) the collapse of the water structure which originally developed around the hydrophobic guest; (4) a very large entropy decrease due to the loss of motional freedoms, together with several other terms. See I. Tabushi, Y. Kiyosuke, T. Sugimoto, and K. Yamamura, *J. Am. Chem. Soc.*, **100**, 916 (1978).

(5) (a) I. Tabushi, J. Imuta, N. Seko, and Y, Kobuke, *J. Am. Chem. Soc.*, **100**, 6287 (1978); (b) I. Tabushi, Y. Kobuke, and J. Imuta, *Nucleic Acid Res., Symp. Ser.*, **6**, s 175 (1979); (c) Arg-145 of carboxypeptidase is known to strongly interact, through electrostatic interaction, with the terminal carboxylate group of the substrate in the hydrophobic active site: J. A. Hartsuch and W. N. Lipscomb, *Enzymes, 3rd Ed.*, **3**, 1, (1971), references cited therein; (d) see also ref 6.

(6) D. Robertus, *Biochemistry*, **11**, 4293 (1972).

(7) (a) I. Tabushi, H. Sasaki, and Y. Kuroda, *J. Am. Chem. Soc.*, **98**, 5727 1976); (b) I. Tabushi, Y. Kimura, and Y. Kuroda, *Tetrahedron Lett.*, 3327 (1976); (c) I. Tabushi and Y. Kuroda, *Shokubai*, **16**, 78 (1974); (d) I. Tabushi, Y., Kimura, and K. Yamamura, *J. Am. Chem. Soc.*, **100**, 1304 (1978).

(8) Present study. α-Cyclodextrin catalysis: **7b**, $k_{cat} = (k_{obsd} - k_0)/[\text{catalyst}] = 2.0\ s^{-1}\ M^{-1}$; **7c**, $k_{cat} = 1.45\ s^{-1}\ M^{-1}$. β-Cyclodextrin catalysis: **7b**, $k_{cat} = 1.05\ s^{-1}\ M^{-1}$; **7c**, $k_{cat} = 1.15\ s^{-1}\ M^{-1}$. See Table I and text for CTAB catalysis.

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the complete account of "inclusion-electrostatic" catalysis manifested by a new water-soluble heterocyclophane, **1**, in which four quaternary ammonium residues (catalytic site) are fixed at the definite position of the macrocycle (binding site), thus constituting a unique active site. Based on the results of the present mechanistic studies, we have succeeded in demonstrating the following functions of heterocyclophane **1**: (1) the very strong inclusion binding of ester substrates (**7a–c**) by **1**; (2) the rate-determining step is the attack of nucleophile to the carbonyl group to form a tetrahedral intermediate in the inclusion complex; and (3) the quaternary ammonium residue of **1** manifested its catalytic action by stabilizing the negatively charged transition-state complex, and the relative ease of such stabilization was of primary importance to the substrate specificity disclosed herein. Furthermore, an interesting inhibition mechanism was found with substrate(s) of the α-chloro-β-naphthyl type (**14**), in which "reverse binding" of the substrate or the "induced disfit" uniquely interrupted the "electrostatic-inclusion" stabilization very effectively, providing a 300-fold difference in reactivity between β-naphthyl chloroacetate, a specific substrate (25-fold acceleration), and α-chloro-β-naphthyl chloroacetate, an inhibitor ($^1/_{12}$-fold deceleration).

Results and Discussion

A cyclic tetraamine, **6**, was prepared[7] by condensation of terephthaloyl chloride (**3**) and N,N'-dimethyl-p-xylylenediamine (**4**) using the high-dilution technique, followed by $LiAlH_4$ reduction, with slight modification of a reported procedure[9] (Scheme I). Permethylation of **6** with Me_3OBF_4[8] in CH_2Cl_2 was complete within 1 h at room temperature, affording white precipitates of tetraammonium heterocyclophane **1** (Scheme I), which was further purified by successive recrystallization from CH_3CN-H_2O. Spectroscopic characteristics (NMR, IR) and elemental analyses of **1** were satisfactory, strongly supporting the unique structure, cyclic tetraammonium, of heterocyclophane **1**.

1 was very soluble in water, and solid **1** was hygroscopic, forming $\mathbf{1}\cdot 2H_2O$ (elemental analysis). The electronic absorption spectrum of the aqueous solution of **1**, 262 nm (ϵ 2620), 268 (3070), 274 (2490), was practically unchanged over a pH range of 4 to 13, strongly indicating that **1** is very stable in an aqueous medium of such a wide pH region, while sulfonium heterocyclophane **2** was unstable in aqueous solution above pH 9 where a remarkable change of the electronic spectrum was observed, together with precipitation of a degraded product.

Hydrolysis was conducted for three aromatic chloroacetates [**7**: R = p-nitrophenyl (**7a**, p-NpClA), α-naphthyl (**7b**, α-NpClA), or β-naphthyl (**7c**, β-NpClA)] in the presence or absence of heterocyclophane **1** at pH 8.10 and 6.96, 20 °C. Spectroscopic determination of p-nitrophenol (**8a**), α-naphthol (**8b**), or β-naphthol (**8c**) was carried out at 400, 321, or 328 nm, respectively. In the presence of a 1.49×10^{-5} to 5.93×10^{-5} M concentration of **1**, the hydrolysis rates of **7** were much faster than those of the corresponding uncatalyzed (spontaneous) hydrolyses. The increase of the catalyst (**1**) concentration from 1.49×10^{-5} to 5.93×10^{-5} M exhibited a saturation of the pseudo-first-order rate constant k_{obsd}, strongly indicating an aspect of enzyme-like catalysis as depicted in eq 1, where the pathway k_0 refers to the uncatalyzed (spontaneous) hydrolysis. The observed rate constant k_{obsd} was, therefore, analyzed by use of the Lineweaver–Burk type equation[11] (eq 2), where K_m is the Michaelis constant defined as $K_m = (k_{-1} + k_2)/k_1$. The satisfactory Lineweaver–Burk type plot, $1/(k_{obsd} - k_0)$ vs. $1/[C]$, observed over a reasonable range of heterocyclophane concentrations (Figure 1a) strongly supported the above mechanism. The kinetic parameters determined are given in Table I.

$$\mathrm{S} + \mathrm{C} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{CS} \xrightarrow{k_2} \mathrm{C} + \mathrm{P}; \quad \mathrm{S} \xrightarrow{k_0} \mathrm{P} \tag{1}$$

$$\frac{1}{k_{obsd} - k_0} = \frac{K_m}{(k_2 - k_0)[\mathrm{C}]} + \frac{1}{k_2 - k_0} \tag{2}$$

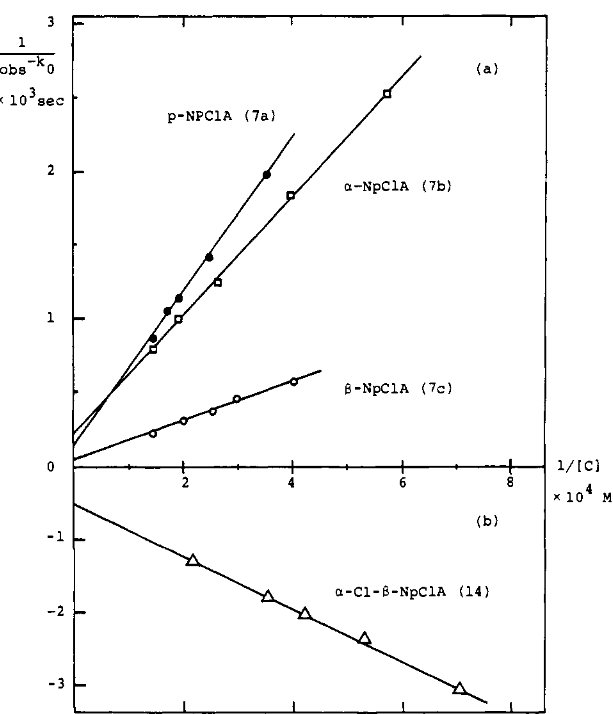


Figure 1. The Lineweaver–Burk type plot. (a) p-NPClA (**7a**), α-NpClA (**7b**), and β-NpClA (**7c**): 4.9×10^{-6} M, pH 8.10, $^1/_{15}$ M phosphate buffer, 20.2 °C. (b) α-Cl-β-NpClA (**14**): 4.76×10^{-6} M, pH 8.10, $^1/_{15}$ M phosphate buffer, 20.2 °C.

Scheme I[a]

ClOC–C₆H₄–COCl (3) + CH₃NH–CH₂C₆H₄CH₂–NHCH₃ (4) —a→ 5 —b→ 6 —c→ 1

[a] a = Et_3N/benzene; b = $LiAlH_4$/dioxane; c = Me_3OBF_4/CH_2Cl_2.

(9) The first preparation of **6** was reported in Y. Urushigawa, T. Inazu, and T. Yoshino, *Bull. Chem. Soc. Jpn.*, **44**, 2546 (1971).

(10) H. Meerwein, *Org. Synth.*, **46**, 120 (1966).

(11) R. L. VanEtten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *J. Am. Chem. Soc.*, **89**, 3242 (1967).

Table I. Catalytic Hydrolysis of Aromatic Esters (7a-c and 14) by Water-Soluble Heterocyclophane (1)[a]

catalyst	substrate	pH	buffer[b]	k_0, ×10^{-3} s^{-1} [c]	k_2, ×10^{-3} s^{-1}	K_m, mM	k_2/k_0
1	β-NpClA (7c)	8.10	p	0.77 ± 0.01	19.2 ± 2.4	0.54 ± 0.05	25 ± 3
			b	0.51 ± 0.05	9.7 ± 0.8	0.90 ± 0.04	19 ± 4
		6.96	p	0.10 ± 0.01	1.85 ± 0.08	2.23 ± 0.22	18 ± 2
			b	0.12	2.12	1.89	17
	p-NPClA (7a)	8.10	p	5.54	14.6	0.51	2.6
			b	6.01	10.5	0.91	1.7
		6.96	p	2.55 ± 0.06	6.0	0.90	2.4
			b	0.89	1.6	2.4	1.8
	α-NpClA (7b)	8.10	p	0.82 ± 0.01	4.9 ± 0.3[d]	0.18 ± 0.02[d]	6.0 ± 0.5
		6.96	p	0.16 ± 0.01	1.7 ± 0.1	0.60 ± 0.02	10.6 ± 1.4
	α-Cl-β-NpClA (14)	8.10	p	2.60 ± 0.13	0.22 ± 0.05	0.20 ± 0.02	0.085 ± 0.024
9	7c	8.10	p	0.82 ± 0.01	1.32	2.62	1.6
CTAB	7c	8.25	p	0.87 ± 0.01	5.9	0.03	6.8
	7b	8.25	p	0.81 ± 0.01	4.5	0.024	5.6

[a] Average of at least three independent kinetic runs, 20.2 ±0.2 °C. [b] Abbreviations p and b refer to phosphate ($^1/_{15}$ M) and borate ($^1/_{15}$ M) buffers, respectively. [c] Uncatalyzed hydrolysis rate constant. [d] For α-naphthyl substrate (7b) at pH 8.10, a seriously deviated point of rate was found at the lowest concentration of catalyst which should accompany a large experimental error. Thus, reanalysis by excluding these data and by addition of several new measurements gave the present rate data (4.9 ± 0.3) × 10^{-3} s^{-1}, instead of those reported in ref 7d, (3.53 ± 0.26) × 10^{-3} s^{-1}.

Chart I[a]

k_2/k_0 (pH 8.10)	25 ± 3	6 ± 0.5	2.6
(pH 6.96)	18 ± 2	10.6 ± 1.4	2.4

[a] R = CH_2Cl.

It is evident from Table I that heterocyclophane catalyst **1** accelerated the hydrolysis rate of each substrate, the rate constant ratio, k_2/k_0, being 25 ± 3 for **7c**, 6.0 ± 0.5 for **7b**, and 2.6 for **7a** at pH 8.10 in phosphate buffer and 18 ± 2 for **7c**, 10.6 ± 1.4 for **7b**, and 2.4 for **7a** at pH 6.96 in phosphate buffer (Table I), revealing an interesting substrate specificity in the rate acceleration of the order depicted in Chart I.

Much smaller catalytic effects were observed for **9**, an open-

$(CH_3)_3N^+$ ... $^+N(CH_3)_3$ $2BF_4^-$

9

chain analogue, where the k_2/K_m value for **7c** was 0.5 s^{-1} M^{-1} (Table I), an ca. $^1/_{70}$ times smaller value than k_2/K_m = 35.5 s^{-1} M^{-1} (**7c**) for **1**. Simple inclusion catalysis alone, such as α-or β-cyclodextrin,[8] again shows a much smaller catalytic effect judging from the k_2/K_m values ranging from 1.0 to 2.0 s^{-1} M^{-1} for **7b** and **7c**. Therefore, it is concluded that the rate accelerations seen with **1**, together with the catalytic specificity disclosed above (Chart I), are due not just to simple electrostatic catalysis but also to inclusion-electrostatic catalysis.

Mechanistic Study on Substrate Binding and Inclusion-Electrostatic Catalysis. Since the CTAB micelle is known to catalyze ester hydrolysis reactions,[12] its catalytic action on hydrolyses of **7a–c** was investigated. Assuming that one micelle particle is the catalytic unit,[13] rate data were analyzed also by using eq 2, and k_2 values of 5.9 × 10^{-3} and 4.5 × 10^{-3} s^{-1} were obtained for **7c** and **7b**, respectively, at pH 8.25 (Table I). It is apparent that the CTAB micelle is 0.3 times less effective than the heterocyclophane catalyst (**1**) and exhibits practically no substrate specificity, the rate ratio of k_2/k_0 being 5.6 and 6.8 for α-naphthyl (**7b**) and β-naphthyl substrates (**7c**), respectively.

The Michaelis constant (K_m) obtained for **7a** and **7c** were 0.51 and 0.54 mM, respectively (Table I), indicating that the binding of p-nitrophenyl (**7a**) and β-naphthyl substrates (**7c**) by **1** was almost equally effective. In the subsequent hydrolysis, however, a marked specificity was seen as described in Chart I, strongly indicating that the spatial arrangement of the quaternary ammonium residue of the macrocycle (**1**) should be directly responsible for the large and discriminating accelerations seen with **7a–c**. The K_m values for the α-naphthyl substrate (**7b**), 0.18 and 0.60 mM at pH 8.10 and 6.96, respectively, were found to be smaller than the K_m values found for the β-naphthyl substrate (**7c**) under the corresponding conditions (K_m for **7c**, 0.54 mM at pH 8.10; 2.23 mM at pH 6.96). Despite the better binding of the α-naphthyl substrate (**7b**) than the β-naphthyl substrate (**7c**) by **1**, the latter was subsequently hydrolyzed 5.4 times faster than **7b**. Therefore, the heterocyclophane catalyst (**1**) manifested kinetic specificity. This observation is in good accord with an idea that the correct fit for reactivity is not a prerequisite for binding.[3] It is strongly suggested, therefore, that the quaternary ammonium residue of the host (**1**) in the inclusion complex markedly favors the stabilization of the negatively charged quasi-tetrahedral transition state for the best substrate, as shown in eq 3.

$$E{-}N^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{-}N^+ \; O{=}C(CH_2Cl)(OR) \; X^- \xrightarrow{k_2} E{-}N^+ \; {}^-O{-}C(CH_2Cl)(X){-}O{-}R \quad (3)$$

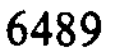
$E{-}N^+ \; {}^{\delta-}O{\cdots}C(CH_2Cl)(OR){\cdots}OH^{\delta-}$ quasi-tetrahedral transition state

Very Rapid Preequilibrium Host–Guest Inclusion. The strong interaction between the host (**1**) and a hydrophobic guest in aqueous medium is suggested by several observations. Judging from the space-filling molecular model (CPK), a benzene ring fits the cavity of **1** nicely. A naphthalene ring, which is ~8.6 Å in width, is somewhat too big to be inserted "sideways" into the cavity (5.5–7 Å) of **1**. However, a naphthalene ring can be included nicely by heterocyclophane **1**, if the insertion is in a "perpendicular" manner (**10**).

The rate of the inclusion equilibrium between the host, **1**, and hydrophobic guest, 2-hydroxy-3-naphthalenecarboxylate (**11**) or

(12) (a) A. Ochoa-Solano, G. Romero, and C. Gitler, *Science*, **156**, 1243 (1967). (b) J. H. Fendler and E. J. Fendler, "Catalysis in Micelar and Macromolecular Systems", Academic Press, New York, 1975, Chapter 5.

(13) (a) Aggregation number of 61 was used for a CTAB micellar particle: see ref 12b. (b) Since four ammonium residues constitute single catalytic and binding site, one CTAB micellar particle is assumed to have at least 61/4 = 15 catalytic units on the same standard.



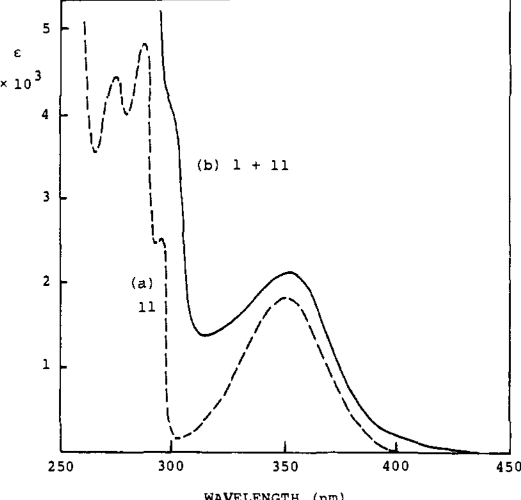


Figure 2. The electronic absorption spectrum of (a) 2-hydroxy-3-naphthalenecarboxylate (**11**), 0.75 × 10^{-4} M, and (b) 2-hydroxy-3-naphthalenecarboxylate (**11**), 0.75 × 10^{-4} M plus heterocyclophane (**1**), 1.0 × 10^{-3} M. Phosphate buffer ($^1/_{15}$ M), pH 7.0.

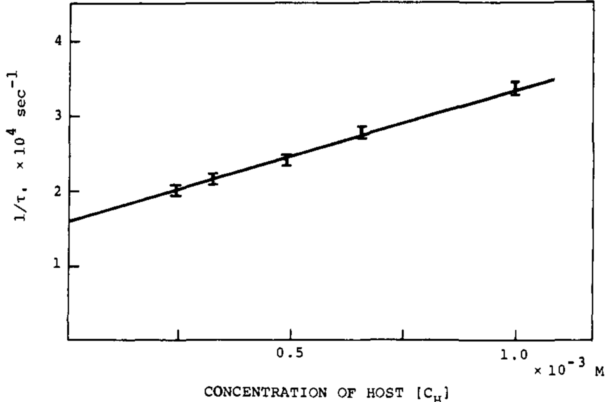
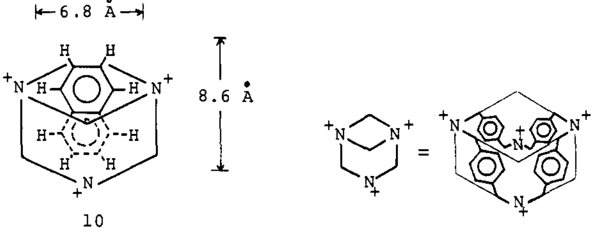


Figure 3. The temperature-jump experiment. The plots of eq 5 for the inclusion of **11** by **1**: **11**, 0.75 × 10^{-4} M; **1**, 0.25 × 10^{-3} to 1.0 × 10^{-3} M in $^1/_{15}$ M phosphate, 0.1 M KCl buffer at pH 7.0, 27 °C.



1-hydroxy-2-naphthalenecarboxylate (**12**), was investigated by the temperature-jump technique.[14] A hyperchromic shift in the electronic absorption band of **11** (Figure 2) was observed when 1 × 10^{-3} M host **1** was added into the solution of **11** in borate buffer, showing that **11** is strongly bound by **1** in aqueous solution.[15] For a 1:1 complexation reaction, the relaxation time τ is given by eq 4, where k_A and k_D are the association and dissociation rate constant, respectively, C_H is the host concentration, and C_G is the guest concentration. When $C_H >> C_G$, eq 4 reduces

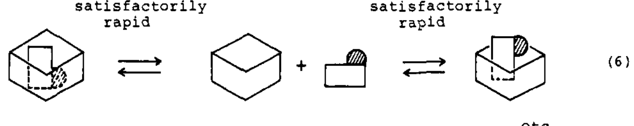
$$1/\tau = k_A(C_H + C_G) + k_D \quad (4)$$

$$1/\tau = k_A C_H + k_D \quad (5)$$

to eq 5, and by plotting $1/\tau$ against C_H (Figure 3), the rate constants k_A and k_D were determined from the slope and the intercept of the straight line, respectively.[16] Thus, k_A values of 1.8 × 10^7 and 4.4 × 10^7 s^{-1} M^{-1} were obtained for **11** and **12**, respectively (Table II), revealing a reasonably fast association of host **1** and hydrophobic guest molecules.[17] When compared with α-cyclodextrin whose k_A for the binding of **12** was 0.40 × 10^7 s^{-1} M^{-1} (Table II), the k_a value of **1** (4.4 × 10^7 s^{-1} M^{-1}) was 11 times larger than the former, despite the similarity between the hole size of **1** (5.5–7 Å) and α-cyclodextrin (6 Å).[16] The k_A for **1** was even larger than the k_A for β-cyclodextrin [**12**: k_A = 1.21 × 10^7 s^{-1} M^{-1} (Table II)], whose hole size is 7.5 Å;[16] therefore, these results are reasonably interpreted as a result that (a) it is easier for the heterocyclophane (**1**) than the cyclodextrins to take an appropriate conformation very favorable for the inclusion binding because of the somewhat more flexible nature of the macrocycle (**1**) and/or that (b) the positive charges of **1** accelerate the association with the guest molecules.

The change of the geometrical position of the hydroxyl group from the α (**12**) to the β position (**11**) resulted in a small decrease of k_D from 3.8 × 10^4 (**12**) to 1.6 × 10^4 s^{-1} (**11**) (Table II). These k_D values are 10^6 to 10^7 times larger than the k_2 values in the subsequent catalysis, and k_A values are even larger.

Thus, the Boltzmann distribution should be attained for the present host–guest inclusions (eq 6) before catalysis takes place,



allowing the host and the guest to search for the most appropriate spatial arrangement for the stabilization of the transition state.

Moreover, the almost equally "effective" binding of two isomeric hydroxynaphthalenecarboxylates, **11** and **12**, by **1** was clarified, where the binding constants for **11** (K_{assoc} = 1130 M^{-1}) and for **12** (K_{assoc} = 1150 M^{-1}) were obtained by using the following equation: $K_{assoc} = k_A/K_D$ (Table II). Therefore, these results of

Table II. Association Rate Constant (k_A) and Dissociation Rate Constant (k_D) of Inclusion Binding of **11** and **12** by the Heterocyclophane **1** and Cyclodextrins[a,b]

host	guest	k_A, 10^7 s^{-1} M^{-1}	k_D, 10^4 s^{-1}	K_{assoc},[c] M^{-1}
1	(**11**)	1.77 ± 0.13	1.56 ± 0.09	1130 ± 140
	(**12**)	4.40 ± 0.12	3.83 ± 0.02	1150 ± 240
α-CD[d]	**12**	0.40 ± 0.01	5.9 ± 0.1	69 ± 4
β-CD[d]	**12**	1.21 ± 0.03	1.10 ± 0.13	1130 ± 170

[a] In $^1/_{15}$ M phosphate buffer, 0.1 M KCl, pH 7.0, 27 °C. Monitor wavelength: **11**, 347 nm; **12**, 342 nm. [b] Average of at least seven independent temperature-jump experiments. [c] The association constant, K_{assoc}, was calculated by using the equation $K_{assoc} = k_A/k_D$. [d] Inclusion binding of **11** by cyclodextrins gave a much smaller hyperchromic shift in the spectrum of **11**, resulting in great difficulty in the determination of k_A and k_D by the temperature-jump technique.

(14) (a) M. Eigen and L. de Maeyer, "Investigation of Rates and Mechanisms of Reactions", G. G. Hammes, Ed., Wiley-Interscience, New York, 1974, Chapter 3; (b) G. G. Hammes, *ibid.*, chapter 4.

(15) A hyperchromic shift of the electronic absorption spectrum of **11** was also observed in a 25% aqueous dioxane solution of **11**.

(16) F. Cramer and H.-Ch. Spatz, *J. Am. Chem. Soc.*, **89**, 14 (1967).

(17) The determination of k_A and k_D values for bindings of **11** and **12** by the CTAB micelle were unsuccessful by using the temperature-jump technique, because of very small absorbance changes at the low CTAB concentrations which are most appropriate to detect the most rapid relaxation (10 μs) accessible by our temperature-jump apparatus.

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Table III

pK_a of leaving phenol or naphthol	7.15	8.14	9.34	9.56
[CTAB] 2.9×10^{-3} M	6.75	7.55		9.34
5.9×10^{-3} M	6.69	7.51		9.23
k_0, 10^{-3} s^{-1}	5.54	2.60 ± 0.13	0.82 ± 0.01	0.77 ± 0.01
k_2/k_0	2.6	0.085 ± 0.024	6.0 ± 0.5	25 ± 3
$1/K_m$, M^{-1}	1960	5000 ± 560	5460 ± 790	1850 ± 190

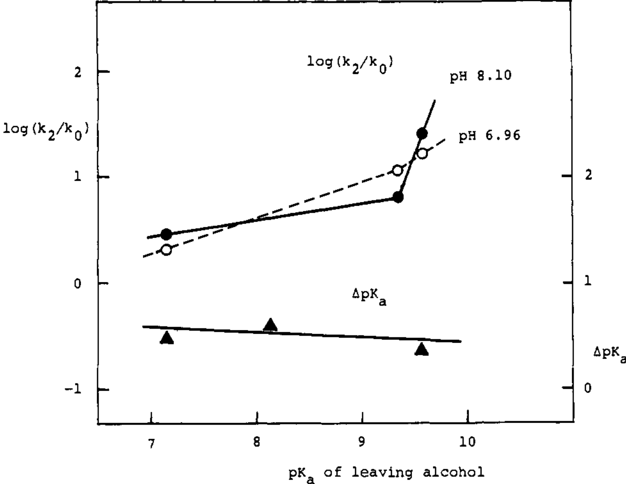

Figure 4. The plots of log (k_2/k_0) and ΔpK_a against the pK_a value of the leaving phenol (**8a–c** and **13**).

the temperature–jump experiment gave a satisfactorily detailed feature of very fast preequilibrium of inclusion binding of **7a–c** (or **11** and **12**) by **1**. The effective and discriminating acceleration of subsequent catalysis by the N^+ residue should have been accomplished in either of the following two ways: (1) N^+ stabilizes the oxyanion generating at the carbonyl oxygen to lead to the accelerated formation of a tetrahedral intermediate and/or (2) N^+ strongly interacts with the oxyanion of the leaving aryloxy l to lead to the facilitated cleavage of phenolate or naphtholate from the tetrahedral intermediate.

Very Specific Rate Acceleration in the Inclusion Complex by 1 and a Unique Inhibition Mechanism. We have discussed hitherto about a great possibility that the effective and discriminating catalysis manifested by **1** was developed from the very strong interaction between the quaternary N^+ of **1** and the oxyanion at the transition state. In order to correlate these catalytic effects with appropriate equilibrium data for similar N^+–oxyanion interactions, we have investigated the effect of CTAB on the pK_a values of *p*-nitrophenol (**8a**), α-chloro-β-naphthol (**13**), and β-naphthol (**8c**). Thus, the proton dissociation equilibrium of three phenols (**8a**, **13**, and **8c**) in the presence of a 5.85×10^{-4} M concentration of CTAB was investigated by electronic absorption spectroscopy, and apparent pK_a values of 6.69, 7.51, and 9.23 were obtained for **8a**, **13**, and **8c**, respectively (Table III). Therefore, the apparent pK_a decreases from the original pK_a [**8a**, 7.15; **13**, 8.14; **8c**, 9.56 (Table III)] to $\Delta pK_a = 0.46$ (**8a**), 0.63 (**13**), and 0.33 (**8c**), respectively. Evidently, from the absence of any systematic correlation between ΔpK_a vs. pK_a (Figure 4), the N^+–oxyanion interaction on the CTAB micellar surface is almost independent of the sort on phenolate or naphtholate. Therefore, the highly discriminating catalysis by **1** [see plots of log (k_2/k_0) vs. pK_a (Figure 4)] is not due to the basicity difference of aryloxyls interacting with N^+, strongly eliminating the possibility of case 2 (loc. cit.) where the breakdown of the tetrahedral intermediate is rate determining. Judging from the minor importance of the N^+-aryloxyl interaction seen in the CTAB micelle, it is reasonable that hydrolytic catalysis by the CTAB micelle is mostly due to the enhanced reactivity of the naked anion (OH^-). Such a naked anion (OH^-) may be likewise supplied by heterocyclophane **1** by desolvating the anion (OH^-) in its hydrophobic cavity.

The fluorescence intensity and λ_{max} of sodium 1-anilino-8-naphthalenesulfonate (1,8-ANS) is very sensitive to the hydrophobicity of medium. The fluorescence λ_{max} of uncomplexed 1,8-ANS in water (pH 7.0) shifted from 526 nm to 510 nm with an increased intensity when complexed by **1** (1×10^{-3} M), providing a blue shift of fluorescence λ_{max} by 16 nm. However, in the presence of CTAB (1×10^{-3} M), the fluorescence λ_{max} appeared at 483 nm with a greater intensity than the former; thus, the blue shift was 43 nm, i.e., the CTAB micelle is much more hydrophobic than **1**, strongly indicating that CTAB should be more effective in desolvating (activating) the anion for catalysis than **1**. Nevertheless, the catalytic ability of heterocyclophane **1** was ca. 3.6 times greater than the CTAB micelle as seen for the substrate **7c** (Table I); i.e., the desolvation is not a sole mechanism of the cyclophane catalysis. Therefore, it is concluded that the effective and discriminating catalysis by **1** (Figure 4) was developed mostly from substrate specificity in the binding; i.e., the N^+–oxyanion interaction remarkably depends on the substrate structure (shape and size) and the difference of which stabilization had reflected on the discriminating catalytic effect (Figure 4).

α-Chloro-β-naphthyl chloroacetate (**14**) hydrolyzes spontaneously with $k_0 = (2.60 \pm 0.13) \times 10^{-3}$ s^{-1} at pH 8.10 in phosphate buffer, showing a 3.4 times greater reactivity than β-naphthyl chloroacetate (**7c**) (Table I). However, when the hydrolysis of **14** was conducted in the presence of heterocyclophane **1**, a considerable retardation of the hydrolysis rate was observed. The Lineweaver–Burk type treatment (Figure 1b) gave $k_2 = 0.22 \pm 0.05 \times 10^{-3}$ s^{-1} and $K_m = 0.20 \pm 0.02$ mM for **14**, revealing the reduced rate ratio $k_2/k_0 = {}^1/_{12}$ (Tables I and III).

There is no anomaly in the k_0 values of the four substrates (**7a–c** and **14**) used, since the larger spontaneous (uncatalyzed) hydrolysis rate constant (k_0) was seen for the better leaving ability of the phenol group (see k_0 in Table III). Therefore, the considerable retardation (${}^1/_{12}$-fold) seen for **14**, despite its moderately fast spontaneous hydrolysis, is attributable to the prohibition of oxyanion–N^+ interaction by inclusion binding. This is most easily understood by "reverse binding" (or "nonproductive binding") of a substrate (Scheme IIa) in which the ester moiety is incorporated into the binding site of **1**, leading to inhibition of the N^+–aryloxyl interaction. An alternative explanation may be possible by an induced-disfit mechanism, which implies that the binding of **14** induced a conformational change in **1** as well as in **14**, leading to an inappropriate fit for catalysis. This conformational change is correlated with a somewhat flexible nature of the conformation of free cyclophane observed by tempera-

Scheme II

(a) reverse binding

K_b ; v_c ; 15 nonproductive binding ; product ; catalysis 16 productive binding

$v = K_b \cdot v_c$

if $K_b \ll 1$ $v \to 0$

$K_b \gg 1$ $v \to v_c$

(b) induced disfit

1 ; 17 ; poor catalysis

ture-dependent ^{1}H NMR experiments.[20] A much stronger binding of the α-chloro-β-naphthyl type inhibitor ($1/K_m = 5000 \pm 560$ M^{-1}) compared with the bindings of substrates **7a–c** (Table III) suggests that the reverse binding mechanism is more important, although it is possible that the induced-disfit mechanism can additionally operate in the productive binding mode:

$$k_{cat}/K_m = \left(\frac{1}{K_{m,app}}\right) f^{npb} k^{npb} + \left(\frac{1}{K_{m,app}}\right) f^{pb} k_{cat}^{pb}$$

where f^{npb} and f^{pb} denote the fraction of the nonproductive binding and that of the productive binding, respectively, and k^{npb} and k_{cat}^{pb} are the corresponding rate constants, being $k^{npb} \ll k_{cat}^{pb}$. Since we do not have any direct measurement for the productive and nonproductive binding in this stage, we can not differentiate between these two terms. We might say that at one extreme, $f^{pb} \ll f^{npb}$ with moderate k_{cat}^{pb} (nonproductive binding mechanism), and that at the other extreme, $f^{pb} > f^{npb}$, but k_{cat}^{pb} (disfit) $< k_{cat}$ (expected) (induced-difit mechanism). The true picture may exist between the two extremes. In any occasion, it seems to be reasonable to conclude that the difference between a 25-fold acceleration for the β-naphthyl substrate (**7c**) and a $^1/_{12}$-fold deceleration for the α-chloro-β-naphthyl inhibitor (**14**) is due to the difference in the stabilization of the quasi-tetrahedral transition state (eq 3).

Experimental Section

General. Proton nuclear magnetic resonance spectra were obtained with a Varian HA-100D or EM-360 spectrometer using tetramethysilane as an internal standard, and the chemical shifts are given in δ values. Infrared spectra were recorded on a Hitachi Model 215 spectrometer. Measurements of mass spectra were carried out at the Analytical Laboratory of Kyushu University or at the Institute of Chemical Research of Kyoto University. pH measurements were carried out with a Hitachi Horiba F-7SS pH meter. Fluorescence spectra were recorded on a Union FS-301 high-sensitivity fluorescence spectrophotometer. Temperature-jump experiments were carried out with a Union Giken rapid-reaction analyzer RS-1200. Electronic absorption spectra were measured with a Hitachi 340 spectrophotometer or with a Union high-sensitivity spectrophotometer SM-401. Analytical thin-layer chromatography was performed using Merck silica gel GF-254, and preparative column chromatography was performed using Merck silica gel 60. Microanalyses were performed by the Microanalytical Laboratory of Kyoto University or by the Analytical Laboratory of Kyushu University.

Materials. *p*-Nitrophenyl chloroacetate (**7a**), α-naphthyl chloroacetate (**7b**), and β-naphthyl chloroacetate (**7c**) were prepared by treatment of the corresponding alcohol with chloroacetyl chloride for 12 h at 5–10 °C in pyridine according to the reported procedures.[18a–c] α-Chloro-β-naphthyl chloroacetate (**14**) was prepared from α-chloro-β-naphthol[19] and chloroacetyl chloride according to the procedure reported for the preparation of α-chloro-β-naphthyl acetate.[18d] Purification of these esters were carried out by recrystallizations from *n*-hexane (**7b**, **7c**, and **14**) or benzene (**7a**): mp, **7a**, 94–95 °C (lit.[18a] 94 °C); **7b**, 46.5–47.5 °C (lit.[18b] 50 °C); **7c**, 94–96 °C (lit.[18c] 95–96 °C). Trimethyloxonium fluoroborate was prepared according to the reported procedure.[10] Buffer solutions were made from distilled, deionized water and Na_2HPO_4–NAH_2PO_4 or H_3BO_3–NaOH (analytical grade).

***N,N'*-Dimethyl-*p*-xylylenediamine (4).** Gaseous methylamine generated from aqueous methylamine solution (40%) and solid KOH was passed through a drying tube (KOH) and introduced into a 2-L three-neck flask cooled at ca. −40 to −50 °C. To 150 g (5.17 mol) of liquid methylamine thus trapped in the flask was slowly added a solution of 66 g (0.25 mol) of *p*-xylylene bromide in 600 mL of THF in 10 h under stirring at ca. −20 to −15 °C. THF and the excess amount of methylamine were evaporated, and the residue was made strongly alkaline with 30% aqueous NaOH solution, which was followed by extraction with 3 × 200 mL of ether. Dry HCl gas was introduced into the combined ethereal solution to obtain precipitates of the 2HCl salt of **4**, which, after filtration, was further purified by recrystallization from 3:1 (v/v) ethanol–water. Yield of **4**·2HCl was 48.4 g (81.7%). **4**: IR (KBr) 2925, 2780, 1565, 1460, 1410 cm^{-1}; NMR (D_2O) δ 7.50 (4 H, singlet, aromatic), 4.75 (4 H, singlet, CH_2), 2.83 (6 H, singlet, CH_3).

***N,N',N'',N'''*-Tetramethyl-1,12,19,30-tetraoxo-2,11,20,29-tetraaza-[3.3.3.3]paracyclophane (5).** This cyclic tetraamide was prepared by using the following high-dilution technique. Dry benzene (1.25 L) and dry triethylamine (1.25 L) were placed in a 5-L four-neck flask equipped with a mechanical stirrer, two dropping funnels, and a drying tube (P_2O_5). Reactant solutions [(A) 12.2 g (0.06 mol) of terephthaloyl chloride (**3**) in 200 mL of dry benzene and (B) 9.8 g (0.06 mol) of *N,N'*-dimethyl-*p*-xylylenediamine (**4**) in 200 mL of dry triethylamine] were placed in each dropping funnel, and these two solutions were added dropwise over 8 h, whose dropping rates were maintained as equal as possible, at room temperature under gentle mechanical stirring. After the addition was complete, the mixture was stirred for an additional 10 h, and the solvents were evaporated to dryness. Chloroform (500 mL) was added to dissolve the residual solid, and this chloroform solution was washed with 3 × 300 mL of water to remove the triethylamine hydrochloride produced. The chloroform layer was concentrated again to complete dryness, and the residual mixture was separated by column chromatography on silica gel using chloroform as the eluent. Recrystallization from 20:1 (v/v) chloroform–methanol gave colorless crystals of **5**: yield 1.85 g (10.5%); mp > 280 °C; ν_{max} 2930, 2860, 1630, 1507, 1415, 1395, 1360, 1260 cm^{-1}; MS, *m/e* (relative intensity) 588 (*p*, 4), 589 (P + 1), 590 (P + 2), 560 (4), 456 (20), 323 (43), 133 (100).

***N,N'N'',N'''*-Tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (6).** A mixture of 0.24 g (6 mmol) of lithium aluminum hydride and 50 mL of dry dioxane was refluxed in a 200-mL flask equipped with a P_2O_5 drying tube. To this mixture was added 1.5 g (2.6 mmol) of the cyclic tetraamide (**5**) in small portions for ca. 30 min, and the refluxing was continued for an additional 12 h. Into the reaction mixture cooled with ice was added 60 mL of ethyl acetate and 5 mL of 15% NaOH aqueous solution. After the mixture boiled for 0.5 h, insoluble materials which remained were filtered off, and the filtrate was concentrated in vacuo to one-fifth by volume, made alkaline by adding a 5-mL aqueous solution of 15% NaOH, and extracted with 5 × 20 mL of methylene chloride. The methylene chloride solutions were combined, dried on anhydrous Na_2SO_4, and concentrated to dryness. Recrystallization from chloroform gave colorless crystals of **6**: yield 0.235 g (17%); mp 199–201 °C; IR (KBr) ν_{max} 1515 (ring), 1445, 1360 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 16 H, arom), 3.33 (s, 16 H, CH_2), 2.33 (s, 12 H, CH_3); MS, *m/e* (relative intensity) 632 (P, 28), 533 (P + 1), 534 (P + 2), 400 (P − C_9H_9N, 9.7), 397 (11.5), 296 (17), 294 (18.6), 266 (39), 265 (33), 237 (53), 133 (100).

***N,N,N',N',N'',N'',N''',N'''*-Octamethyl-2,11,20,29-tetraaza[3.3.3.3]-paracyclophanetetrammonium Tetrafluoroborate (1).** The cyclic tetraamine **6** (0.15 g, 0.28 mmol) and dry methylene chloride (100 mL) were placed in a 200-mL round-bottom flask equipped with a drying tube (P_2O_5), and 0.20 g (1.35 mmol) of trimethyloxonium tetrafluoroborate was added in several portions under stirring with a magnetic bar. After 2 h at room temperture, the product precipitated from the solution as a white powder. The precipitates were filtered and combined with additional crop, which was obtained by concentration of the filtrate solution in vacuo to approximately one-fifth by volume. Recrystallization from

(20) (a) I. Tabushi, H. Yamada, Z. Yoshida, R. Oda, *Tetrahedron*, **27**, 4875 (1971); (b) I. Tabushi, H. Yamada, K. Matsushita, Z. Yoshida, Y Kuroda, and R. Oda, *ibid.*, **28**, 3381 (1972); (c) I. Tabushi, H. Yamada, and Y. Kuroda, *J. Org. Chem.*, **40**, 1946 (1976); (d) I. Tabushi and H. Yamada, *Tetrahedron*, **33**, 1101 (1977).

1:1 (v/v) acetonitrile–water gave colorless crystals of **1**: yield 0.11 g (40%); mp 273–277 °C dec; IR (KBr) ν_{max} 3020, 2960, 1480, 1300, 1130, 1040 cm^{-1}; NMR (Me_2SO-d_6) δ 7.30 (s, 16 H, arom), 3.96 (s, 16 H, CH_2), 3.18 (s, 24 H, CH_3). Anal. Calcd for $C_{40}H_{56}N_4B_4F_{16}\cdot 2H_2O$: C, 49.08; H, 6.15. Found: C, 49.22; H, 5.78.

***N,N,N',N',N'',N''*-Hexamethyl-*p*-xylylenediammonium tetrafluoroborate (9)** was prepared from 1.54 g (8 mmol) of *N,N,N',N'*-tetramethyl-*p*-xylylenediamine and 2.5 g (17 mmol) of trimethyloxonium tetrafluoroborate in dry methylene chloride in a similar manner as described for **1**. Recrystallization from 1:1 (v/v) acetonitrile–water gave colorless needles of **9**: yield 2.53 g (80%); mp >280 °C dec.

Kinetic Measurements. A 2.0-mL solution of 9.9×10^{-6} M *p*-nitrophenyl chloroacetate (**7a**), α-naphthyl chloroacetate (**7b**), β-naphthyl chloroacetate (**7c**), or α-chloro-β-naphthyl chloroacetate (**14**) in a phosphate ($^1/_{15}$ or $^1/_{60}$ M) (pH 6.96 or 8.10) or in a borate ($^1/_{15}$ or $^1/_{60}$ M) buffer solution (pH 6.96 or 8.10) was put into a quartz cuvet. The cuvet was placed in a cell holder of a Union high-speed UV spectromonitor Model SM-303, a cell chamber of which was thermostated at 20.2 ± 0.1 °C by circulating thermostated water. Heterocyclophane (7.4×10^{-5} to 3.0×10^{-5} M) was added to the above solution of the ester substrate to start the hydrolysis. The reaction was followed by monitoring the increase in the absorbance of phenol (*p*-nitrophenol, α-naphthol, β-naphthol, and α-chloro-β-naphthol) at 400, 321, 328, and 331 nm, respectively. Each kinetic run followed pseudo-first-order kinetics up to the second half-life: correlation coefficients of the lines obtained were 0.9999–0.9770 (8 points). The dependence of pseudo-first-order rate constants on the heterocyclophane concentration was analyzed by the use of eq 2.

Kinetic measurements for CTAB-catalyzed hydrolyses of ester substrates (**7b–c**) were similarly carried out as described above under the following conditions of concentrations: ester substrate, 9.9×10^{-6} M; CTAB, 9.5×10^{-3} to 3.7×10^{-3} M. The effective concentration of micellar particles was calculated by the following equation

$$[\text{micellar particles}] = \frac{[\text{CTAB}] - [\text{cmc}]}{\text{aggregation no.}}$$

where a reported value of 5×10^{-5} M was used as the critical micellar concentration, [cmc], and a reported number, 61, was employed for the aggregation number. Treatment of kinetic data was the same as described above for the heterocyclophane-catalyzed hydrolysis reactions.

Temperature–Jump Experiments. Temperature–jump experiments were carried out with a Union rapid-reaction analyzer RA-1200. A solution of 0.5×10^{-4} M sodium hydroxynaphthalenecarboxylate (**11** or **12**) and the water-soluble heterocyclophane (1.0×10^{-3} to 0.167×10^{-3} M) in 0.067 M borate + 0.1 M KCl buffer solution at pH 7.0 was put into the temperature–jump cell, and the cell compartment was thermostated at 27 °C by circulating thermostated water. Under a standard experimental condition, a 27-kV voltage was applied to raise the temperature of the solution by ca. 2 °C in a few microseconds. The signal output from the photomultiplier was recorded with a Hitachi memoriscope V-038.

Communications to the Editor

[2,3]-Wittig Rearrangement of Unsymmetrical Bis-Allylic Ethers. A Facile Method for Regio- and Stereoselective Synthesis of 1,5-Dien-3-ols

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Conceptually, the [2,3]-Witting rearrangement[1] of bis-allylic ethers is a convenient, general vehicle to 1,5-dien-3-ols which are valuable as substrates for the oxy-Cope rearrangement.[2] In order to establish the feasibility of such an approach within *unsymmetrical* frameworks, however, many questions must be elucidated which remain largely unexplored.[3,4] There are positional ambiguities at both the migrating termini in terms of the possibilities for [2,3] vs. [1,2] shift[5] and for α vs. α' lithiation, providing at least four reaction pathways (Scheme I). Furthermore, stereochemical problems also arise when the migrating allylic moiety has substituents at the α and/or γ position; the [2,3]-process might produce geometric and/or diastereomeric isomers.

Scheme I

As part of our general interest in the synthetic potential of [2,3]-sigmatropic rearrangements,[6] we have now systematically studied carbanion rearrangements of unsymmetrical bis-allylic ethers having different substitution patterns. Herein we wish to report that these rearrangements proceed exclusively in a [2,3]-sigmatropic fashion with remarkably higher levels of regio- and stereoselectivity than previously anticipated. The genuine [2,3]-Wittig process provides an exceedingly facile procedure for regio- and stereocontrolled synthesis of a broad variety of 1,5-dien-3-ols from nonidentical allylic alcohols which in many instances will be superior to current procedures.[7]

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