104-110 °C (0.02 mm); NMR (CCl_4) δ 1.79 (m, 2 H), 1.85 (s, 3 H), 2.50 (m, 2 H), 2.76 (d of d, 2 H), 5.01 (m, 1 H), 7.05 (s, 5 H), 7.10 (s, 5 H).

1,4-Bis(4-nitrophenyl)-2-butanol. 1,4-Diphenyl-2-butyl acetate (15.39 g, 0.057 mmol) was treated with a nitrating mixture of 17.5 mL of fuming HNO_3 and 56.5 mL of Ac_2O.[10] After 4 h at −45 °C, the mixture was poured into H_2O and the organics were extracted into ether. The organic phase was neutralized with Na_2CO_3 and dried over $MgSO_4$. Removal of the solvent left about 15 mL of yellow oil, which was dissolved in the minimum amount of hot CH_3OH and treated with 15% NaOH solution. After acidification with concentrated HCl and concentration of the solution, crystals of the desired alcohol were obtained. Recrystallization from CH_2Cl_2 gave 0.90 g (6.5%) of the desired alcohol: mp 151-154 °C; NMR ($CDCl_3$) δ 1.80 (m, 3 H), 2.86 (m, 4 H), 3.80 (m, 1 H), 7.75 (AB q, 8 H). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.60; H, 4.97; N, 8.79.

1,4-Bis(4-nitrophenyl)-2-butyl Tosylate (4f). A solution of 0.8975 g (2.84 mmol) of 1,4-bis(4-nitrophenyl)-2-butanol was treated with 0.78 g (4.1 mmol) of tosyl chloride in the manner described above. Recrystallization of the resulting crude tosylate gave 0.913 g (68%) of pure tosylate: mp 149-152 °C; NMR ($CDCl_3$) δ 2.05 (m, 2 H), 2.42 (s, 3 H), 2.80 (m, 2 H), 3.06 (d, 2 H), 4.82 (t, 1 H), 7.62 (m, 12 H). Anal. Calcd for $C_{23}H_{22}N_2O_7S$: C, 58.71; H, 4.71; N, 5.96. Found: C, 58.81; H, 4.69; N, 5.96.

***erythro*-1,4-Diphenyl-3-acetoxy-2-butyl Tosylate.** A solution of 0.75 g (3.1 mmol) of *meso*-1,4-diphenyl-2,3-butanediol in pyridine was treated with 0.65 g (3.4 mmol) of tosyl chloride according to the usual procedure. After workup the residue was treated with an excess of Ac_2O, to which 1 drop of concentrated H_2SO_4 had been added.[14] This solution was stirred overnight, and the excess anhydride was hydrolyzed with water. The organics were extracted into ether, washed with saturated $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent left a viscous oil, which crystallized upon cooling. Three recrystallizations from ether/hexane gave 0.646 g (46%) of the desired erythro acetoxy tosylate: mp 86.5-88 °C; NMR ($CDCl_3$) δ 1.86 (s, 3 H), 2.36 (s, 3 H), 2.90 (m, 4 H), 5.00 (m, 2 H), 7.12 (m, 14 H). Anal. Calcd for $C_{26}H_{26}O_5S$: C, 68.46; H, 5.98. Found: C, 68.84; H, 6.07.

References and Notes

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Remarkable Activation of Anionic Nucleophiles toward *p*-Nitrophenyl Acetate by Aqueous Trioctylmethylammonium Chloride: A New Class of the Hydrophobic Aggregate[1]

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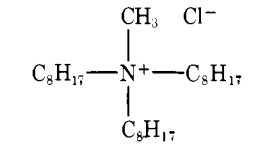
Abstract: Trioctylmethylammonium chloride (TMAC), a typical phase transfer catalyst, forms aggregates in aqueous solutions at very low concentrations (10^{-4}-10^{-5} M). The aggregate was inferred to be much smaller than the conventional globular micelles from the data of surface tension and specific conductance. The dissociation of 2,6-dichlorophenolindophenol, which is commonly used for detection of the critical micelle concentration of the cationic micelle, was enhanced in proportion to the TMAC concentration at 10^{-4}-10^{-5} M. This lack of the critical phenomenon suggests the progressive formation of the tight ion pair between the phenolate anion and the cationic TMAC aggregate. The reactivity of lauryl-substituted hydroxamate and imidazole nucleophiles toward *p*-nitrophenyl acetate was remarkably enhanced in the presence of 7×10^{-5} M TMAC in water at 30 °C, pH 9. The rate enhancements amounted to 500 to 10^4 times, and were much larger than those produced by the conventional hexadecyltrimethylammonium bromide (CTAB) micelle. Less hydrophobic hydroxamate and imidazole nucleophiles were not activated by addition of TMAC. The dissociation of the hydrophobic nucleophiles was promoted in the presence of the TMAC aggregate and, for example, $pK_{a,2}$ of the lauryl-substituted imidazole was lowered by 2.5 pK units relative to that of the hydrophilic counterpart. Therefore, the large rate enhancement observed is produced by adsorption of hydrophobic nucleophile onto TMAC aggregates by which highly nucleophilic ion pairs are formed. Finally, the acetylimidazole intermediate is hydrolyzed very rapidly, and the imadazole-TMAC system is an extremely efficient catalyst for the hydrolysis of phenyl esters.

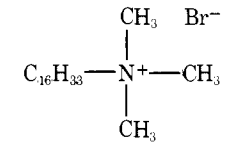
In recent years, a wide variety of reactions have been studied in aqueous micellar systems, in connection with the enzyme reaction mechanism.[2] Particularly interesting is the large rate enhancement observed for the reaction of anionic nucleophiles with phenyl esters in the presence of cationic micelles. These nucleophiles include hydroxamate,[3,4] oximate,[5] thiolate,[6] and

imidazole anions.[7-10] We have studied some of these reactions in aqueous nonionic micelles[11] and in organic media,[12] and concluded that the activation of nucleophiles in cationic micellar systems can be attributed to the formation of the hydrophobic ion pair.[13] The peculiar nature of the cationic micelle such as the high charge density of the micellar surface is apparently not required for the rate enhancement. Thus it is expected that any aqueous system which can produce hydrophobic ion pairs from anionic nucleophiles would give rise to rate enhancements.

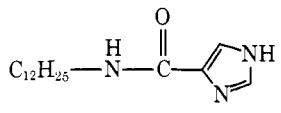
We found that aqueous trioctylmethylammonium chloride (TMAC, **1**) forms aggregates which are in many respects different from the conventional globular micelle. This aggregate accelerates the reaction of hydrophobic imidazole and hydroxamate nucleophiles with *p*-nitrophenyl acetate. However, the reaction was not appreciably accelerated with less hydrophobic nucleophiles. We will discuss in this paper the nature of the TMAC aggregate and the mechanism of its catalysis in some nucleophilic acyl transfer reactions. In the following are shown the structures of the surfactants and nucleophiles employed.



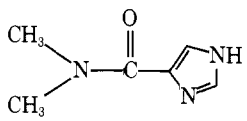
TMAC (**1**)



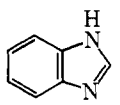
CTAB (**2**)



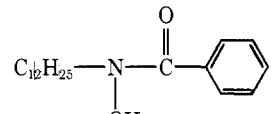
LImAm (**3**)



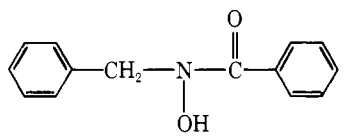
DMImAm (**4**)



BzIm (**5**)



LBHA (**6**)



BBHA (**7**)

Experimental Section

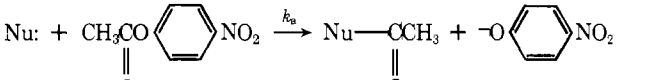
***N*-Laurylimidazole-4-carboxamide) (LImAm, 3).** Imidazole-4-carbonyl chloride (2 g, 0.014 mol)[14] and 1.3 g (0.007 mol) of laurylamine were refluxed in chloroform solvent for 6 h in the presence of 4 g (0.04 mol) of triethylamine. The solvent was removed, and the oily residue was extracted by hot acetonitrile and recrystallized from acetonitrile, mp 128-130 °C, pale yellow powders. Anal. ($C_{16}H_{30}N_3OCl$), C, H, N.

Other Materials. *p*-Nitrophenyl acetate (PNPA) was prepared from *p*-nitrophenol and acetic anhydride, mp 78 °C. Commercial CTAB (**2**) was twice recrystallized from water, and TMAC (**1**) (Dojin Chemicals, Japan) and tetrabutylammonium bromide were used without further purification. Benzimidazole (BzIm, **5**) was recrystallized from alcohol, mp 170 °C. The following compounds were prepared as described before: *N*,*N*-dimethyl(imidazole-4-carboxamide) (DMImAm, **4**),[15] mp 196-198 °C; *N*-laurylbenzohydroxamic acid (LBHA, **6**),[4] mp 75-76 °C; *N*-benzylbenzohydroxamic acid (BBHA, **7**),[16] mp 108-109 °C.

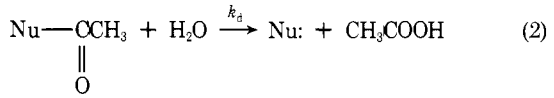
Rate Measurement. The reaction of PNPA with nucleophiles was performed in 3 v/v % EtOH-H_2O, μ = 0.01 (KCl), 0.01 M borate buffer (pH 7-11) at 30 ± 0.1 °C, and followed by using the absorption of the *p*-nitrophenolate anion at 401 nm with a Hitachi 200 UV-visible spectrophotometer. The pH of the medium was constant within ±0.05 before and after the reaction (Toa Electronics, HM10B digital pH meter).

Results

Kinetics. The reaction of PNPA with nucleophiles (Nu:) such as imidazole and hydroxamate proceeds according to eq 1 and 2.



(1)



(2)

The reaction was always carried out with excess substrate ([PNPA] = (1.02-2.04) × 10^{-5} M; [nucleophile] = (1.64-9.86) × 10^{-6} M). The total rate constant k_{total} was corrected for the spontaneous hydrolysis as follows.

$$k_{obsd} = k_{total} - k_{spont} \quad (3)$$

In the case of the hydroxamate reaction, the k_{obsd} value was obtained from the initial rate of reaction (conversion <10%) and divided by the total hydroxamic acid concentration to give the apparent second-order rate constant of the acyl transfer, $k_{a,obsd}$.

The reaction with the imidazole nucleophiles proceeded according to the pseudo-first-order kinetics up to more than 90% conversion of the substrate. This indicates that the acylimidazole intermediate is not detectably accumulated, and the rate constant of acylation becomes equal to that of turnover. The apparent rate constant, $k_{Im,obsd}$, was obtained by dividing k_{obsd} by the imidazole concentration.

Hydrolysis of PNPA. The hydrolysis of PNPA by hydroxamate and imidazole nucleophiles was performed in the presence of (2.07-20.3) × 10^{-5} M of aqueous TMAC (**1**). The apparent second-order rate constants $k_{a,obsd}$ and $k_{Im,obsd}$ thus obtained were plotted against the TMAC concentration in Figure 1. The rate constants for hydrophobic LImAm (**3**) and LBHA (**6**) increased in proportion to the TMAC concentration.

Rate increases were considerable; for instance, $k_{Im,obsd}$ = 1900 M^{-1} s^{-1} for LImAm (**3**) and $k_{a,obsd}$ = 9200 M^{-1} s^{-1} for LBHA (**6**) at [TMAC] = 1.04 × 10^{-4} M. On the other hand, there were no rate accelerations when less hydrophobic nucleophiles (DMImAm (**4**), BzIm (**5**), and BBHA (**7**)) were employed.

The maximal solubility of TMAC in water at 30 °C was in the range of 10^{-2}-10^{-3} M and the solution became turbid at higher TMAC concentrations. Therefore, the reaction was carried out at [TMAC] <5 × 10^{-4} M.

The reaction rate was dependent on the relative concentration of nucleophiles and TMAC. When, for instance, the concentration of LImAm (**3**) was increased from 1.64 × 10^{-6} M to 2.30 × 10^{-5} M at a fixed TMAC concentration of 1.03 × 10^{-4} M, the reactivity of LImAm (**3**) decreased to ca. 50% of the initial value (see Figure 1). That is, the maximum reactivity of LImAm (**3**) was obtained when its concentration was 10% or lower than that of TMAC. The subsequent experiments were therefore carried out at [LImAm (**3**)] = (1.64-6.57) × 10^{-6} M and [TMAC] = 7.27 × 10^{-5} M.

The spontaneous hydrolysis of PNPA was affected very little by the addition of TMAC.

The reactivity of LBHA (**6**) and LImAm (**3**) was not appreciably enhanced when CTAB (**2**) and tetrabutylammonium bromide were used instead of TMAC in the same concentration range (2 × 10^{-4} to 2 × 10^{-5} M). However, the micellar CTAB (1.02 × 10^{-3} M) increased the rate constants for

Table I. Reaction of Hydroxamate and Imidazole Nucleophiles with PNPA in the Presence of Ammonium Salts[a]

Nucleophile	× 10^6 M	$k_{a,obsd}$ or $k_{Im,obsd}$,[b] M^{-1} s^{-1}				
		None	TMAC (1)	$Bu_4N^+Br^-$	CTAB (2)	Micellar CTAB (2)[c]
LImAm (3)	1.64	0.09	1200	0.10	3.2	105
DMImAm (4)	9.52	0.07	0.08	0.06	0.05	0.09
Benzimidazole (5)	5.36	0.09	0.08	0.08	0.08	5.8
LBHA (6)	4.82	15	6700	18	35	1900
BBHA (7)	9.52	14	18	15	18	870

[a] Conditions: 30 °C, pH 9.0 ± 0.1, 3 v/v % EtOH-H_2O, μ = 0.01 (KCl), 0.01 M borate buffer, 7.27 × 10^{-5} M ammonium salts. [b] $k_{a,obsd}$ for hydroxamates and $k_{Im,obsd}$ for imidazoles. [c] 1.02 × 10^{-3} M CTAB.

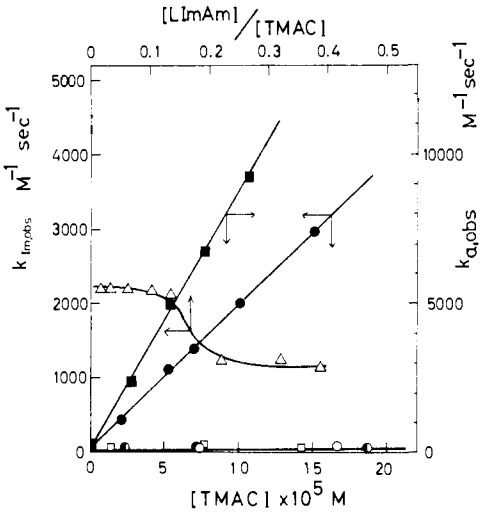


Figure 1. Dependence of the apparent rate constant ($k_{a,obsd}$ and $k_{Im,obsd}$) on the TMAC concentration. Conditions: 30 °C, pH 9.0 ± 0.1, 3 v/v % EtOH-H_2O, μ = 0.01 (KCl), 0.01 M borate buffer; substrate, 1.02 × 10^{-5} M PNPA. Nucleophiles: ■, 4.82 × 10^{-6} M LBHA (**6**); □, 9.52 × 10^{-6} M BBHA (**7**); ●, 1.64 × 10^{-6} M LImAm (**3**); ◐, 9.52 × 10^{-6} M DMImAm (**4**); ○, 5.36 × 10^{-6} M BzIm (**5**); △, (1.64-23.0) × 10^{-6} M LImAm (**3**) and 1.03 × 10^{-4} M TMAC.

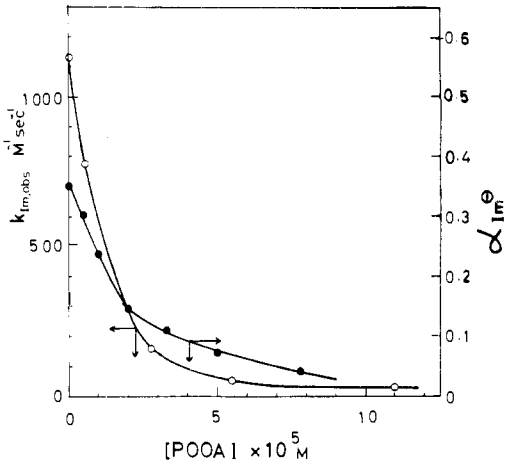


Figure 2. Influence of a nonionic surfactant (POOA) on the reaction rate and the dissociation of the imidazole group. Conditions: 30 °C; pH 9.0; 3 v/v % EtOH-H_2O; μ = 0.01 (KCl); 0.01 M borate buffer. ○: 1.64 × 10^{-6} M LImAm (**3**); 7.27 × 10^{-5} M TMAC; 1.02 × 10^{-5} M PNPA. ●: 3.28 × 10^{-6} M LImAm (**3**); 7.27 × 10^{-5} M TMAC. α_{Im^-} is the mole fraction of the anionic species of LImAm (**3**); see eq 4.

LBHA (**6**) and LImAm (**3**) by factors of 10^2 and 10^3, respectively. It was also effective for less hydrophobic BBHA (**7**) and BzIm (**5**), but not for DMImAm (**4**). These results are summarized in Table I.

Influence of Ionic Strength. The reactivity of anionic nucleophiles in cationic micelles decreases with increasing ionic strength.[4,9] Similar results were obtained in the TMAC system. The $k_{Im,obsd}$ value for LImAm (**3**) (1.64 × 10^{-6} M) in the presence of 7.27 × 10^{-5} M TMAC at pH 9.0 was 1200 M^{-1} s^{-1} at μ = 0.01 and 70 M^{-1} s^{-1} at μ = 0.5.

Influence of Nonionic Micelle. The influence of the hydrophobic microenvironment produced by the nonionic micelle of polyoxyethylene (n = 10) oleyl alcohol (POOA) was investigated in the LImAm (**3**)-TMAC system. The results are shown in Figure 2. The critical micelle concentration of POOA was estimated to be 10^{-6} M.[17] $k_{Im,obsd}$ decreased appreciably by addition of a minute amount of POOA and the rate constant in the presence of 1.09 × 10^{-4} M POOA was only 1/38 of that in the absence of POOA.

In order to find out the cause of this rate decrease, the dissociation behavior of LImAm (**3**) was investigated in the presence of TMAC and POOA. The electronic spectrum of LImAm (**3**) in the presence of TMAC (7.02 × 10^{-5} M) gives λ_{max} at 258 nm due to the imidazole anion in 1 N aqueous NaOH and at 233 nm due to the neutral imidazole species at pH 6.7. Thus, the extinction coefficient at 270 nm was employed for determining the mole fraction of the anionic species, α_{Im^-}

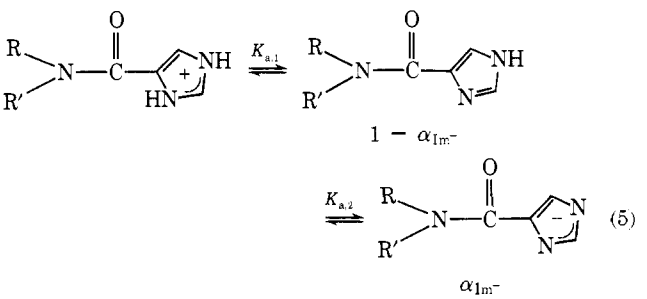
$$\alpha_{Im^-} = \frac{\epsilon_I - \epsilon}{\epsilon_I - \epsilon_M} \quad (4)$$

where ϵ_I and ϵ_M are extinction coefficients at 270 nm of the imidazole anion (obtained in 1 N aqueous NaOH) and the neutral species (obtained at pH 6.7, phosphate buffer).

At pH 9.0, the fraction of the anionic species is 0.35 in the absence of POOA, but it decreased remarkably with increasing POOA concentrations (Figure 2). A parallel trend is clearly noticed between the variations of $k_{Im,obsd}$ and α_{Im^-}.

pH-Rate Profile. The pH dependence of $k_{Im,obsd}$ in the LImAm (**3**)-TMAC system was compared with those in the LImAm (**3**)-CTAB (micellar) system and in the DMImAm (**4**) (without hydrophobic aggregates) system.

The dissociation behavior of imidazolecarboxamides is given by eq 5.



(5)

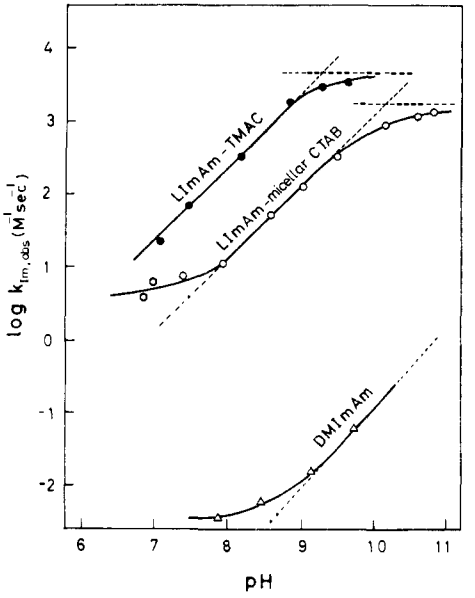


Figure 3. pH-rate profile of the reaction of imidazole nucleophiles with PNPA. Conditions: 30 °C; 3 v/v % EtOH-H_2O; μ = 0.01 (KCl); 0.01 M borate buffer. ●: (1.64-4.93) × 10^{-6} M LImAm (**3**); 7.27 × 10^{-5} M TMAC; 1.02 × 10^{-5} M PNPA. ○: 4.41 × 10^{-5} M LImAm (**3**); 1.03 × 10^{-3} M CTAB; 8.83 × 10^{-5} M PNPA. The data for DMImAm (**4**) are taken from ref 15; 30 °C; 28.9 vol/vol % EtOH-H_2O; μ = 0.1 (KCl).

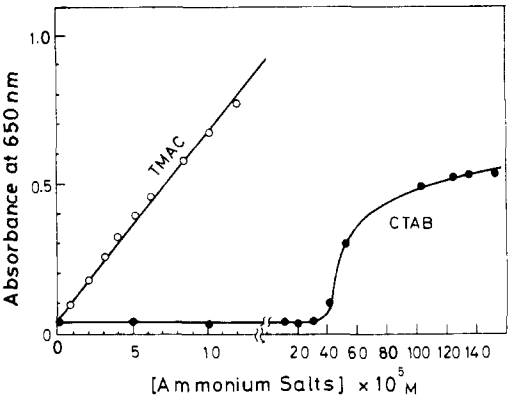


Figure 4. Influence of hydrophobic ammonium salts on the dissociation of 2,6-dichlorophenolindophenol. Conditions: 30 °C, 3 vol/vol % EtOH-H_2O; μ = 0.01 (KCl); 1.00 × 10^{-4} M 2,6-dichlorophenolindophenol (as sodium salt); 3.00 × 10^{-4} M hydrochloric acid.

The cationic species must be virtually absent under the hydrolysis conditions, since $pK_{a,1}$ of DMImAm (**4**) (R = R′ = CH_3) is 4.30 in 28.9 v/v % EtOH, 30 °C, μ = 0.1 (KCl).[15] Then, the apparent rate constant is given by

$$k_{Im,obsd} = (k_{anion} - k_{neutral})\alpha_{Im^-} + k_{neutral} \qquad (6)$$

where k_{anion} and $k_{neutral}$ are the true second-order rate constants of catalysis by anionic and neutral species, respectively. The solid lines in Figure 3 were obtained by assuming appropriate $pK_{a,2}$ values and rate constants which would give best fits with experiments. They are summarized in Table II.

The $pK_{a,2}$ value for the LImAm (**3**)-CTAB system determined from kinetics as mentioned above agrees with that determined by the photometric titration at 270 nm. It is to be noted that the $pK_{a,2}$ value was lowered in the order DMImAm (**4**) > LImAm (**3**)-CTAB > LImAm (**3**)-TMAC. On the other hand, the k_{anion} value increased in the order DMAmIm (**4**) ≪ LImAm (**3**)-CTAB < LImAm (**3**)-TMAC. These results are contrary to that expected from the Brönsted relation.

Dye Absorption by Hydrophobic Aggregates. The spectral changes of methyl orange and 2,6-dichlorophenolindophenol were studied in the presence of hydrophobic ammonium salts under conditions similar to those of the hydrolysis.

The absorption maximum of methyl orange shifts to shorter wavelengths with decreasing polarity of the medium (464 nm in H_2O and 420-430 nm in organic solvents). Therefore, the λ_{max} value is sometimes used as an index of the hydrophobicity of the microenvironment surrounding the dye molecule. For instance, the absorption maximum is observed at 420-430 nm when methyl orange is absorbed to aqueous bovine serum albumin and lauroylpolyethylenimine.[18]

The λ_{max} value (methyl orange, 5.34 × 10^{-6} M, 30 °C, 3 v/v % EtOH-H_2O, μ = 0.01 (KCl)) shifted abruptly from 466 to 430 nm when the TMAC concentration was made larger than 2 × 10^{-5} M. Thus, TMAC can provide hydrophobic microenvironments at the concentration employed in the hydrolysis: [TMAC] = (2-16) × 10^{-5} M.

2,6-Dichlorophenolindophenol is often used for the measurement of the cmc of cationic micelles.[19] This compound is red (neutral species, λ_{max} 500-520 nm) in dilute hydrochloric acid, but turns blue (anionic species, λ_{max} 600-650 nm) by addition of cationic micelles.

Table II. Acidity and Rate Constants for Imidazole Nucleophiles[a]

Catalytic system	$pK_{a,2}$[b]	k_{anion},[c] $M^{-1}s^{-1}$	$k_{neutral}$,[c] $M^{-1}s^{-1}$
LImAm (**3**)-TMAC[d]	9.30	5200	
LImAm (**3**)-micellar CTAB[e]	10.25 (10.25)	1620	2-3
DMImAm (**4**)[f]	ca. 12	13	10^{-2}

[a] Conditions: 30 °C, 3 v/v % EtOH-H_2O, μ = 0.01 (KCl). [b] For the second dissociation of the imidazole group. See eq 5. Determined from pH-rate profiles. The data in parentheses were obtained by the phototitration of the imidazole anion at 270 nm. [c] See eq 6. [d] 7.27 × 10^{-5} M TMAC. [e] 1.03 × 10^{-3} M CTAB. [f] Conditions: 30 °C, 28.9 v/v % EtOH-H_2O, μ = 0.1 (KCl). See ref 15.

Figure 4 shows the absorbance change of the indophenol at 650 nm in the presence of hydrophobic ammonium salts. As expected, the absorbance increased abruptly at ca. 5 × 10^{-4} M CTAB. Therefore, this must be the cmc for CTAB in the medium employed: 30 °C, 3 v/v % EtOH-H_2O, μ = 0.01 (KCl). The cmc determined by a similar method at 30 °C in pure water was 8 × 10^{-4} M. The presence of ethanol and KCl seems to have lowered the cmc.[20]

On the other hand, the absorbance at 650 nm increased linearly with the TMAC concentration. CTAB did not produce an absorbance increase at the same concentration range. Thus, aqueous TMAC apparently provides hydrophobic microenvironments which strongly bind the anionic indophenol.

Surface Tension. The surface tension of aqueous ammonium salts was measured in 0.5 v/v % EtOH-H_2O at 18 °C by the Wilhelmy method (Kyowa Kagaku Co., Digi-O-Matic ESB-IV). The surface tension without ammonium salts was 71.0 ± 0.5 dyn/cm, which is in agreement with that of pure water. The dependence of surface tension on the concentration of ammonium salts is summarized in Figure 5. The surface tension of 0.5 v/v % EtOH-H_2O was affected very little by the addition of tetrabutylammonium bromide, which indicates the lack of the surface-activating capacity for this less hydrophobic salt. The cmc of aqueous CTAB was determined from Figure 5 to be 8 × 10^{-4} M, in agreement with the published data. In the case of TMAC, the general trend is similar to that of aqueous CTAB; however, the critical concentration is less clear and much lower than that of CTAB.

Specific Conductance. The specific conductance of aqueous ammonium salts was measured in 0.5 v/v % EtOH-H_2O at 18

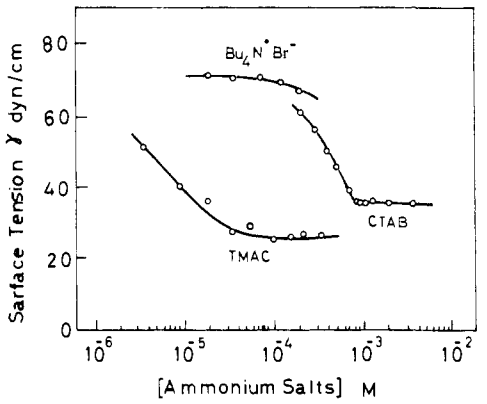


Figure 5. Surface tension of aqueous ammonium salts. Conditions: 18 °C; 0.5 vol/vol % EtOH-H_2O.

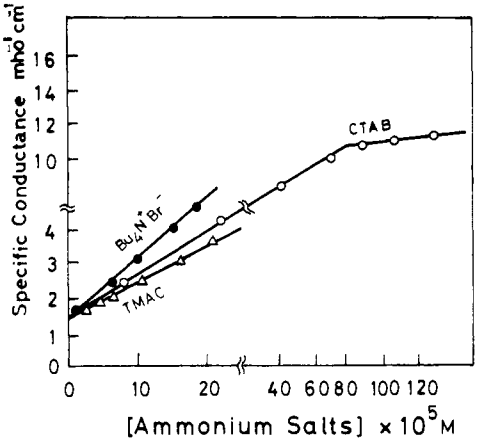


Figure 6. Specific conductance of aqueous ammonium salts. Conditions: 30 °C; 0.5 vol/vol % EtOH-H_2O.

°C. The results are given in Figure 6. There is a break point for the CTAB curve at 8×10^{-4} M, whereas the specific conductance for $Bu_4N^+Br^-$ and TMAC increased in proportion to their concentrations up to 2×10^{-4} M.

Discussion

Nature of TMAC Aggregates. The solubility of trioctylmethylammonium chloride in water is 10^{-2}–10^{-3} M. Organic droplets separate at larger concentrations. Clear solutions are obtained at TMAC concentrations of less than 10^{-3} M; however, the TMAC molecule is apparently not molecularly dispersed. The physicochemical measurements carried out in this study indicate the formation of aggregated TMAC molecules. The surface tension data show that TMAC forms some kind of aggregates at concentrations much lower than the cmc of CTAB. The decreased increment in the specific conductance is observed for conventional micelles at cmc and is attributed to the formation of multicharged micelles (macroions) which suppress the ion mobility. However, the specific conductance of the TMAC solution increased linearly in the same concentration range, thus excluding the critical formation of macroions. Based on these two kinds of physicochemical data, TMAC is presumed to form fairly small aggregates at very low concentrations (0–20×10^{-5} M). The ion mobility may not be suppressed when the aggregation number is small.

The formation of TMAC aggregates is consistent with the data of Figure 4. The dissociation of 2,6-dichlorophenolindophenol is promoted by its adsorption to positively charged micelles, as shown by the CTAB curve. Since the absorbance increases linearly, there appears to be no critical concentration for the aggregation. Seemingly, the number and/or size of aggregates increase gradually with the increase in the TMAC concentration without a critical change. It is worthy to emphasize that TMAC are much more efficient than CTAB for adsorption of this dye, and this fact is related to the enormous rate enhancement for anionic nucleophiles observed in the TMAC system.

Activation of Anionic Nucleophiles. As mentioned in the introduction, various anionic nucleophiles are remarkably activated in the presence of cationic micelles. The data summarized in Table I indicate that TMAC activates hydrophobic nucleophiles (LBHA (**6**) and LImHA (**3**)) much better than the CTAB micelle. The rate difference becomes even greater if the effect of the hydrophobic ammonium salts (TMAC and CTAB) is compared at the same concentration (7.27×10^{-5} M). These kinetic results are in accord with the physicochemical data obtained for aqueous TMAC, in that TMAC forms aggregates (hydrophobic microenvironments) at concentrations much lower than the cmc of the CTAB micelle.

However, the activation by the TMAC aggregate seems possible only for very hydrophobic nucleophiles such as LImAm (**3**) and LBHA (**6**). Moderately hydrophobic BzIm (**5**) and BBHA (**7**) were not at all activated. Interestingly, the CTAB micelle produced considerable rate enhancements for these nucleophiles, although nonmicellar CTAB was not effective. It appears that moderately hydrophobic nucleophiles bind with micellar CTAB better than with TMAC aggregates.

The nature of the TMAC aggregate can also be inferred from the detailed kinetic study of the LImAm (**3**)-TMAC system. The rate constant for the nucleophilic reaction was proportional to the TMAC concentration (Figure 1). This indicates that the nucleophiles are activated increasingly as the number and/or size of the TMAC aggregate increase. The reactivity of a given LImAm (**3**) molecule appears to be fairly constant, once it is adsorbed onto the TMAC aggregate, since the anionic species of LImAm (**3**) increased linearly with the increase in the TMAC concentration. The latter trend is similar to the dissociation behavior of 2,6-dichlorophenolindophenol, shown in Figure 4.

The maximum activation was attained at small molar ratios of the nucleophile and TMAC. When more than 10 mol % of LImAm (**3**) is present relative to TMAC, its reactivity decreases to almost one-half (Figure 1). Addition of POOA (nonionic surfactant) in a similar concentration ratio caused an analogous decrease in the rate constant (Figure 2). Again, the rate suppression due to added POOA was accompanied by the decrease in the dissociated fraction of LImAm (**3**). The dissociation of the nucleophile must be promoted most efficiently in the presence of tight TMAC aggregates. Addition of POOA appears to dilute the aggregate and lower the reactivity of bound nucleophiles.

Concluding Remark. The remarkable activation of hydrophobic, anionic nucleophiles described in this study is attributed to the adsorption of these nucleophiles onto TMAC aggregates. Two major factors which contribute to the rate enhancement are the increase in the anionic species of the nucleophile and the enhanced reactivity of a given anionic nucleophile (see Table II). These are made possible by formation of the tight ion pair in the hydrophobic microenvironment. The tight ion pair is formed by the cooperative action of hydrophobic and coulombic forces. Therefore, the use of the reaction condition which weakens the tightness such as addition of nonionic surfactants and the increase in the ionic strength will supress the reactivity. It is important that the rate enhancement was attained in the presence of hydrophobic aggregates other than the conventional globular micelle. As we disscussed previously,[4,11] the enhanced reactivity of anionic nucleophiles in the presence of cationic micelles is explained by the formation of hydrophobic ion pairs, and the peculiar structural characteristics of globular micelles are not required. This

proposition was amply supported by the present study. TMAC forms aggregates in aqueous systems with characteristics much different from those of the conventional cationic micelle. And yet TMAC aggregates are much more efficient than the latter.

All the imidazole compounds act as true catalysts for the hydrolysis of PNPA in the present system. Therefore, both of the acylation and deacylation processes are accelerated by the TMAC aggregate. The turnover rate of the LImAm (**3**)-TMAC system is thus much larger than that of α-chymotrypsin under comparable conditions. We will be able to develop many other catalytic systems by combinations of anionic nucleophiles with appropriate hydrophobic aggregates.

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A Stereochemical Investigation of the Formation and Cyclization of Allenic Phosphonic Acids. Preparation of 4-Substituted 1,2-Oxaphosphol-3-enes[1]

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Abstract: Allenic phosphonic acid **4a**, previously found to be inert toward proton-catalyzed cyclization, reacted with bromine (chloroform) and mercuric acetate (acetic acid, chloride ion) to form the 4-bromo (**7a**-Br) and 4-chloromercuri (**7a**-HgCl) derivatives of 2-hydroxy-3,5-di-*tert*-butyl-1,2-oxaphosphol-3-ene 2-oxide in good yield. The reaction of optically pure (*R*)-(+)-2,2,6,6-tetramethyl-4-heptyn-3-ol (**1a**) with phosphorus trichloride gave, after hydrolysis, 102 ± 2% optically pure *R*-(−)-**4a**, indicating that the propargyl phosphite → allenic phosphonate rearrangement occurs via a concerted [3,2] sigmatropic shift with complete stereospecificity. Reaction of optically pure *R*-(−)-**4a** with mercuric acetate-chloride ion led to *R*-(+)-**7a**-HgCl of 86 ± 2% optical purity, while reaction with bromine gave *R*-(+)-**7a**-Br of >41 ± 2% optical purity. Thus, electrophile-promoted cyclizations proceed by moderately to highly stereospecific trans addition. The ^{1}H NMR spectrum of **7a**-HgCl exhibits five-bond Hg-H coupling and apparent restricted rotation of the upfield *tert*-butyl group.

For several years we have been investigating those factors which control the formation of phosphorus-containing products in the reaction of propargyl alcohols with phosphorus trihalides.[2-5] Most recently[5] we described how a series of propargyl alcohols could be made to undergo the transformations shown below.

The formation of dichlorophosphite (**2**) was found to be immediate at room temperature in all cases studied. The success of the rearrangement leading to **3** was critically dependent on efficient removal (*not* neutralization) of the HCl liberated in the first step. The half-life of this rearrangement ranged from ca. 20 min (24 °C) when R_1 = H and $R_2 + R_3 = (CH_2)_4$ to ca. 3 h (60 °C) when $R_1 = R_2 = R_3$ = H. The facility of the acid-catalyzed cyclization was highly dependent on R_2 and R_3 (and to a lesser extent on R_1). When R_2 and R_3 were both alkyl, cyclization proceeded readily at 60 °C in 2 M acid. However, if either R_2 or R_3 were H, the cyclization was completely suppressed, even at >90 °C in 35% perchloric acid. This