Nucleophilic Ion Pairs. I. Enhanced Esterolytic Reactivity of Hydrophobic Ion Pairs in Micellar Systems*

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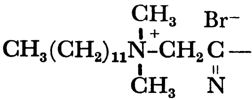
The reaction of the dodecyl(2-hydroxyimidophenethyl)dimethylammonium bromide(DHDB) and *N*-methylmyristohydroxamate (MMHA) anion with *p*-nitrophenyl acetate was studied mostly in the presence of aqueous nonionic micelles. Addition of a hydrophobic ammonium ion, TMAC, considerably enhanced the reactivity of MMHA but not that of DHDB (a zwitterion). The rate enhancement for MMHA-TMAC and DHDB in nonionic micelles were almost comparable to those in cationic(CTAB) micelles. It was proposed that the large enhancement observed for some anionic nucleophiles in cationic micelles is to a great extent caused by the formation of hydrophobic, desolvated ion pairs.

The importance of micellar catalyses which influence rates and equilibria of organic reactions and yield data pertinent to enzyme-catalyzed reactions has been reported.[1,2] Anionic nucleophiles such as alkoxide,[3,4] oximate,[5,6] hydroxamate,[7–10] thiolate[11,12] and imidazole anions[13,14] are considerably activated in the presence of cationic micelles and cationic polysoaps. The reactions studied involve nucleophilic attack toward phenyl esters,[1–8, 10, 11, 13, 14] nucleophilic substitution of 2,4-dinitrofluorobenzene[12] and hydrogen abstraction from carbon acids.[9] The nucleophilicity of some hydroxamate anions toward *p*-nitrophenyl acetate(PNPA) is enhanced by two or three orders of magnitude as compared with those predicted from the Brönsted relationship, the reaction rate exceeding even that of α-chymotrypsin and PNPA.[7,8] In contrast, the activation does not occur in anionic micelles,[15] and neutral nucleophiles such as amines and imidazoles are not subjected to activation by cationic micelles.[16]

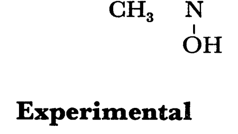
In an attempt to elucidate the mechanism of these micellar effects, we investigated the reaction of *N*-methylmyristohydroxamic acid(MMHA) and dodecyl-(2-hydroxyimidophenethyl)dimethylammonium bromide (DHDB) with PNPA in nonionic micelles. The latter nucleophile was specially designed to allow ready formation of the intramolecular ion pair between the oximate anion and the ammonium moiety on the basis of the CPK model building. The use of nonionic micelles as the reaction environment can avoid complicating influences of the high charge density at the surface of cationic micelles.

MMHA:



$$\mathrm{CH_3(CH_2)_{12}CO\underset{\displaystyle CH_3}{\underset{|}{N}}OH}$$

DHDB:



Experimental

Materials. Preparation of MMHA has been described.[8] *N*-Phenacyl-*N*,*N*-dimethyldodecylammonium bromide; *N*,*N*-dimethyldodecylamine(0.1 mol) and phenacyl bromide (0.1 mol) in 200 ml alcohol were allowed to react with stirring at room temperature for 4 days. The solvent was evaporated *in vacuo*, and the residual solid was recrystallized from ethyl acetate; mp 118—119 °C, yield 95%, IR (KBr); 1690 cm^{-1} (ketone).

Dodecyl (2 - hydroxyimidophenethyl) dimethylammonium bromide (DHDB); 4.1 g (10 mmol) of the ketone and 1.4 g (20 mmol) of hydroxylamine hydrochloride were dissolved in a mixture of 10 ml of pyridine and 10 ml of alcohol, and the solution was heated at 60 °C for 20 hr. The solvent was evaporated *in vacuo*, and the residual viscous oil was taken into 100 ml of acetonitrile. The insoluble crystals(pyridine hydrochloride) were filtered, and the solution was concentrated. The colorless liquid thus obtained was crystallized from ethyl acetate; mp 89—90 °C, IR (KBr): 1630 cm^{-1} (oxime), 3400 cm^{-1} (hydroxyl). Found: C, 61.68; H, 9.50; N, 6.35%. Calcd for $C_{22}H_{39}N_2OBr$: C, 61.75; H, 9.12; N, 6.55%.

p-Nitrophenyl acetate(PNPA) was prepared by acetylation of *p*-nitrophenol with acetic anhydride, and recrystallized from cyclohexane, mp 78 °C (lit,[17] 81—82 °C).

Nonionic surfactants, SDS and CTAB were obtained from Wako Pure Chem. Ind., and other reagents from Tokyo Kasei Ind. CTAB was recrystallized from ethanol before use, and the other surfants were used without further purification.

Kinetics. All the reactions were followed at 30± 0.1 °C with a Hitachi 124 spectrophotometer equipped with a thermostated cell-holder. The rate of nucleophilic reactions with PNPA was determined by following the increase in the absorption of the *p*-nitrophenolate anion (401 nm). All the kinetic experiments were performed at a calculated ionic strength of 0.01 (with KCl) unless otherwise stated. Buffers employed were Tris and phosphate. The pH of the medium (assumed to be equal to the value measured by a glass electrode) was confirmed not to vary before or after the reaction.

Results

The total phenol release followed the pseudo-first-order kinetics up to more than 90% reaction, if a large excess of a reactant was used over the other. The pseudo-first-order rate constant(k_{obsd}) for the reaction of MMHA and DHDB with PNPA were evaluated after correction for spontaneous hydrolysis (k_{sp}): $k_{obsd}=k_{total}-k_{sp}$. The rate of *p*-nitrophenol release was confirmed to be first-order with respect to nucleophile and substrate under the experimental conditions employed (Fig. 1); the apparent second-order rate constants($k_{a,\ obsd}$) were then evaluated, by dividing k_{obsd} by concentratuons of nucleophile or substrate.

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* Contribution No. 379 from this department.

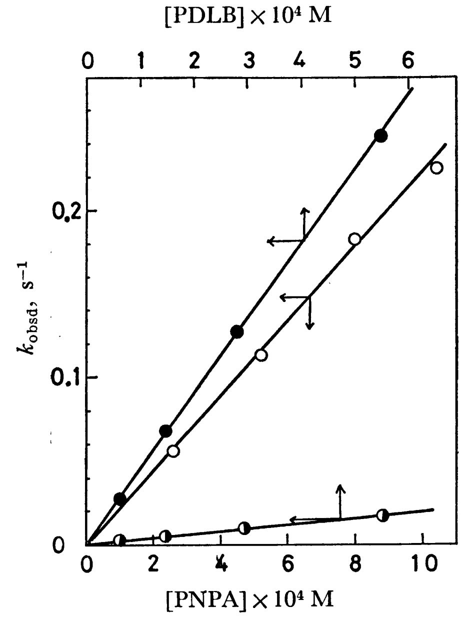
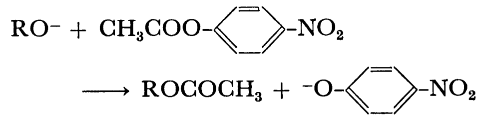


Fig. 1. Reaction of MMHA+TMAC and DHDB with PNPA in the presence of a nonionic micelle (POOA). 30 °C, $\mu=0.01$ with KCl, 3 v/v% ethanol, $[POOA]=1.0\times10^{-3}$ M.
○; $[MMHA]=1.0\times10^{-5}$ M, $[TMAC]=1.02\times10^{-4}$ M, pH=8.56±0.05 with 0.01 M borate. ●; $[PNPA]=2.13\times10^{-5}$ M, pH=9.10±0.04 with 0.01 M borate ◑; POOA was not added. $[PNPA]=2.13\times10^{-5}$ M, pH=9.10±0.04 with 0.01 M borate.



(1)

Reaction of MMHA with PNPA. The reaction of MMHA and PNPA was first carried out in the presence of nonionic micelles (Tween 80, Triton X-100, POOA**, Brij-35) above their cmc.[1] The influence of addition of quaternary ammnoium salts was also evaluated. If the $k_{a,obsd}$ value of MMHA in the absence of a nonionic micelle is approximated by that of aqueous *N*-methylisobutyrohydroxamic acid,[18] the presence of nonionic micelles results in a 2—9 time increase of $k_{a,obsd}$ (Table 1). The rate enhancement is much greater in cetyltrimethylammonium bromide(CTAB) micelle (more than 200 fold)[7]. In contrast, anionic sodium dodecyl sulfate-(SDS) suppressed the reactivity of MMHA. The reactivity of MMHA can be further enhanced in nonionic micelles by addition of trioctylmethylammonium chloride(TMAC) (Fig. 2). The reaction rates increased almost linearly with increasing TMAC and then gradually levelled off. Maximal augmentation of 18-fold was brought about by addition of TMAC. Addition of $Et_4N^+Br^-$ and $Bu_4N^+Br^-$ caused no effect. TMAC, typical phase transfer catalyst, is much more hydrophobic than the latter two, but cannot form a micelle by itself. In fact, it exists as an oily suspension in as aqueous medium without nonionic micelles. Thus, TMAC should be trapped in and/or on the nonionic micelles. The micelle consisting of a nonionic surfactant plus TMAC can be envisioned as an analogue of cationic micelles which possesses a much lower positive-charge density. On the contrary, addition of an inorganic salt inhibited the reaction (*vide post*). It is noteworthy that a minute amount of TMAC caused the rate enhancement of more than one-order of magnitude and that only the hydrophobic ammonium salt was effective.

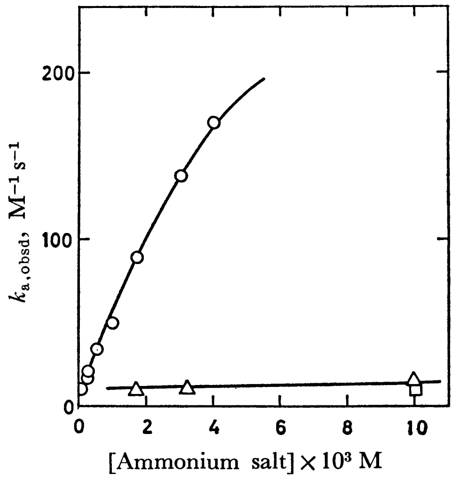


Fig. 2. Influence of quaternary ammonium salts on the reaction of MMHA and PNPA in the presence of a nonionic micelle (POOA).
30 °C, $\mu=0.01$ with KCl, 3 v/v% ethanol, pH=8.35 ±0.04 with 0.01 M borate, [POOA]=0.01 M, $[MMHA]=4.39\times10^{-5}$ M, $[PNPA]=1.17\times10^{-3}$ M. ○; TMAC, □; $Et_4N^+Br^-$, △; $Bu_4N^+Br^-$.

Table 1. APPARENT SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF MMHA AND DHDB WITH PNPA[a]

Additives	$k_{a,obsd}$ (M⁻¹ s⁻¹) MMHA	MMHA +TMAC	DHDB
None	*ca.* 4[b]		5.3
SDS	1.38		0.7
CTAB	821		1030
Tween 80	19.0	83.6	71.6
Triton X-100	34.2	280	55.6
POOA	36.8	210	306(311)[d]
POOA[c]	9.82		
Brij-35	19.1	117	92.3
Poly(*N*-vinylpyrrolidone)			6.39
β-cyclodextrin			2.63
Poly(ethyleneimine)			5.53

a) 30°C, $\mu=0.01$ with KCl, pH=8.5±0.1 for MMHA and 8.1±0.1 for DHDB with 0.01 M borate. $[MMHA]=1.0\times10^{-5}$ M, $[DHDB]=1.4\times10^{-4}$ M, $[TMAC]=1.0\times10^{-4}$ M, $[additives]=1.02\times10^{-3}$ M. b) Estimated with *N*-methylisobutyrohydroxamic acid.[18] c) [POOA] =0.01 M. d) DHDB+TMAC (1.0×10^{-4} M).

The $k_{a,obsd}$ values at a constant surfactant concentration are recorded for comparison in Table 1. The reactivity of MMHA in the presence of nonionic micelles which contain TMAC is enhanced up to

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** Polyoxyethylene(n=10) oleyl alcohol.

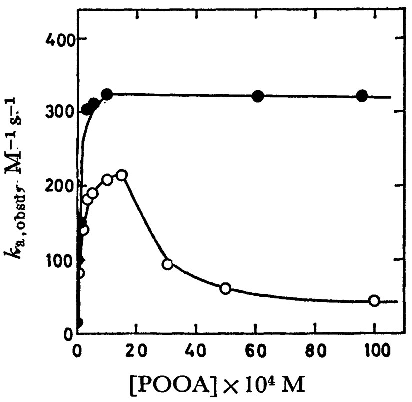

Fig. 3. Apparent second-order rate constants for the reactions of MMHA+TMAC and DHDB with PNPA as a function of the concentration of a nonionic surfactant (POOA).
30 °C, $\mu=0.01$ with KCl, 3 v/v% ethanol.
○; $[\text{MMHA}]=1.0\times10^{-5}$ M, $[\text{PNPA}]=2.62\times10^{-4}$ M, $[\text{TMAC}]=1.02\times10^{-4}$ M, pH=8.60±0.04 with 0.01 M borate. ●; $[\text{DHDB}]=1.40\times10^{-4}$ M, $[\text{PNPA}]=2.13\times10^{-5}$ M, pH=8.87±0.04 with 0.01 M borate.

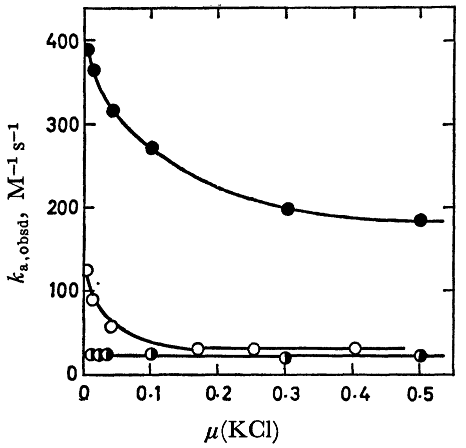

Fig. 4. Apparent second-order rate constants for the reactions of the MMHA+TMAC and DHDB with PNPA as a function of ionic strength.
30 °C, 3 v/v% ethanol.
○; $[\text{MMHA}]=4.39\times10^{-5}$ M, $[\text{PNPA}]=1.17\times10^{-3}$ M, $[\text{TMAC}]=1.67\times10^{-3}$ M, $[\text{POOA}]=0.01$ M, pH=8.35±0.04 with 0.01 M borate. ●; $[\text{DHDB}]=1.40\times10^{-4}$ M, $[\text{PNPA}]=2.19\times10^{-5}$ M, $[\text{POOA}]=1.0\times10^{-3}$ M, pH=8.90±0.02 with 0.02 with 0.01 M borate. ◑; $[\text{DHDB}]=1.40\times10^{-4}$ M, $[\text{PNPA}]=2.19\times10^{-5}$ M, pH=8.8±0.1 with 0.01 M borate. POOA was not added.

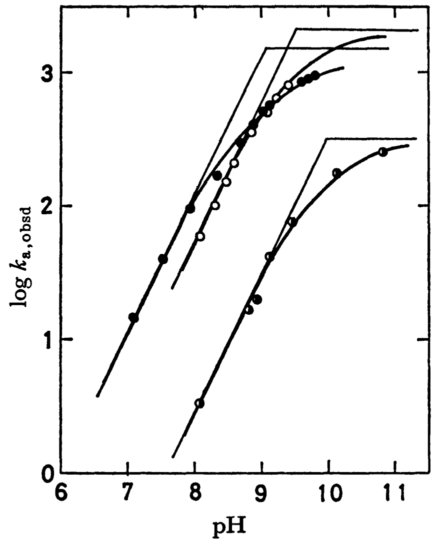

Fig. 5. pH Dependence.
30 °C, $\mu=0.01$ with KCl, 3 v/v% ethanol, $[\text{POOA}]=1.0\times10^{-3}$ M.
○; $[\text{MMHA}]=1.0\times10^{-5}$ M, $[\text{PNPA}]=2.62\times10^{-4}$ M, $[\text{TMAC}]=1.0\times10^{-4}$ M. ●; $[\text{DHDB}]=(0.8—5.6)\times10^{-4}$ M, $[\text{PNPA}]=(1.7—8.5)\times10^{-5}$ M. ◑; POOA was not added. $[\text{DHDB}]=(2.8—5.6)\times10^{-4}$ M, $[\text{PNPA}]=(4.3—8.5)\times10^{-5}$ M.

20—70 times as compared with that for the nonmicellar system, the maximum value (280 M^{-1} s^{-1} in Triton X-100) amounting to one-third of that in CTAB.

Reaction of DHDB with PNPA. Similar experiments were carried out for a zwitterionic nucleophile. The reaction was quenched by SDS micelle and enhanced in the presence of CTAB micelle(*ca.* 200 times), as is the case for the reaction of MMHA and PNPA. On the other hand, considerable rate enhancements (10—60 times) were readily achieved in the presence of nonionic micelles alone. Addition of TMAC caused no increase in the reaction rate. The maximum rate constant observed for DHDB (306 M^{-1} s^{-1} in POOA) is about one-third of the value in the CTAB micelle. Other additives such as poly(ethyleneimine), β-cyclodextrin and poly(*N*-vinylpyrrolidone) were found to be ineffective.

Influence of Surfactant Concentration and Ionic Strength. The dependence of the reactivities of MMHA-TMAC and DHDB on the concentration of POOA is given in Fig. 3. The cmc of POOA is estimated to be 10^{-6} M.[1] The $k_{a,obsd}$ value for the MMHA-TMAC system first increased and then decreased gradually with increasing POOA concentrations, the maximum $k_{a,obsd}$ value being observed at $[\text{POOA}]=1.5\times10^{-3}$ M. On the other hand, the reactivity of zwitterionic nucleophile rapidly increased and reached a constant value. The difference reflects the intermolecular *vs.* intramolecular nature of these ion pairs.

The reactivities of MMHA-TMAC and DHDB toward PNPA were also examined at different ionic strength (Fig. 4). The $k_{a,obsd}$ value for DHDB in the nonmicellar system was hardly affected by the salt(KCl) concentration. On the other hand, the enhanced reactivities of these catalytic systems attained in the presence of nonionic micelles were gradually lost with increasing salt concentrations. The largest rate decrease was about 4-fold. Similar results are frequently obtained in micellar catalysis.[1]

pH Dependence. The micellar reaction of MMHA-TMAC and DHDB with PNPA was carried out in the pH range 7—10. The log $k_{a,obsd}$ values are plotted against pH, which show linear increase with slope 1.0 followed by gradual saturation in the high pH region (Fig. 5). The reaction rates were found to be too great to be measured in the pH region higher than that in Fig. 5. The acid dissociation constants(K_a) and the true second-order rate constants(k_a) were determined by two methods: (a) fitting of the theoretical curves (Eq. (2)) to the experimental plots, and (b) finding pK_a values which give straight lines for α(degree of dissociation$=K_a/(K_a+a_H)$) *vs.* $k_{a,obsd}$ plots by trial-and-error computation. The values of K_a and k_a calculated by both methods were found to be agree within 5%.

$$k_{a,obsd} = k_a \frac{K_a}{K_a+a_H} \tag{2}$$

The results are given in Table 2, together with data we obtained recently.

Table 2. Second-order rate constants for the reactions of hydroxamates and oximates with PNPA at 30 °C

Catalyst		pK_a	k_a $M^{-1}s^{-1}$
1.	MMHA+POOA	9.5	2310
1.′	MMHA+POOA+TMAC	9.5	4900[a)]
2.	DHDB+POOA	9.1	1150
3.	MMHA+CTAB	*ca.* 10.3	26800
4.[b)]	DBHA+CTAB	9.72	6000
5.	DHDB	10.0	300
6.[c)]	*N*-methylisobutyrohydroxamic acid	9.05	32.6
7.[c)]	*N*-phenylisobutyrohydroxamic acid	8.81	25.1
8.[c)]	*N*-methylnaphthohydroxamic acid	8.23	10.5

a) k_a'' (the true second-order rate constant for MMHA paired with TMAC). b) DBHA (N-dodecylbenzohydroxamic acid)[10)]; 3 v/v% ethanol, $\mu=0.5$ (KCl). c) 1.4 v/v% CH_3CN, $\mu=0.1$ (KCl).[18)]

Discussion

Reactions performed in the presence of ionic micelles are influenced by various micellar effects.[1,2)] Straightforward kinetic analysis is often difficult because of complications characteristic of ionic micelles. One may simplify this situation by appropriate use of nonionic micelles, as independently shown by Brown *et al.* for a general-base catalyzed reaction toward phenyl phosphate.[19)] The nucleophilicity of some anions such as hydroxamates and oximates is highly enhanced in cationic micelles. We have attempted to elucidate the mechanism of these rate enhancement. We assumed that the rate enhancement of anionic nucleophiles in cationic micelles could be reduced to the problem of nucleophilic ion pairs. An anionic nucleophile forms an ion pair with a cationic surfactant molecule in a highly hydrophobic environment of micelles, the high charge density at the surface of cationic micelles playing only a secondary role. Nonionic micelles are convenient systems for testing the hypothesis, since nucleophilic ion pairs can be studied as species isolated from other charged species.

The nucleophilicity of MMHA anion as expressed by the $k_{a,obsd}$ value (Table 1) is enhanced in cationic and nonionic micelles relative to the nonmicellar system. Although the observed rate enhancement is much greater in the cationic(CTAB) micelle than in nonionic micelles, the difference can be made smaller by adding 1.0×10^{-4} M of TMAC, which is highly hydrophobic and not much soluble in water. Thus, the highly increased nucleophilicity of MMHA can be related to the formation of hydrophobic ion pairs solubilized in nonionic micelles. The absence of rate increase upon addition of less hydrophobic $Et_4N^+Br^-$ and $Bu_4N^+Br^-$ supports this view.

The apparent rate constant showed a maximum when the POOA concentration was varied. Supposedly, the hydrophobicity of POOA micelles increases with increasing POOA concentrations, and the formation of hydrophobic ion pairs becomes increasingly favorable. Further increase in the POOA concentration causes dissociation of MMHA-TMAC, resulting in rate decrease. This is consistent with the fact that no rate decrease was observed with increasing POOA concentrations in the case of intramolecular ion pair DHDB.

$k_{a,obsd}$ in the POOA micelle simply increased with increasing TMAC concentration (Fig. 2). This kinetic situation can be quantitatively treated by the following equation, provided that MMHA anion and TMAC cation form a 1 : 1 ion pair only, and that addition of TMAC does not change the micellar structure such as to affect the reaction rate.

$$\text{MMHA} + \text{TMAC} \overset{K}{\rightleftharpoons} \text{MMHA-TMAC} \tag{3}$$

$$\text{MMHA} \xrightarrow{k'_{a,obsd}\cdot[\text{PNPA}]} \text{products} \tag{4}$$

$$\text{MMHA-TMAC} \xrightarrow{k''_{a,obsd}\cdot[\text{PNPA}]} \text{products} \tag{5}$$

where K is the association constant for MMHA–TMAC, $k'_{a,obs}$ is the apparent second-order rate constant for MMHA which is not paired with TMAC and $k''_{a,obs}$ is that for MMHA paired with TMAC.

According to Mollica and Connors,[20)] the following equation is derived for [MMHA]$\ll$[TMAC].

$$\frac{k'_{a,obsd}}{k_{a,obsd}-k'_{a,obsd}} = \frac{1}{q\cdot K[\text{TMAC}]} + \frac{1}{q} \tag{6}$$

where $k_{a,obsd}$ is the rate constant obtained at a given TMAC concentration and $q=(k''_{a,obsd}/k_{a,obsd})-1$.

K and q were determined by plotting $k'_{a,obsd}/(k_{a,obsd}-k'_{a,obsd})$ against 1/[TMAC], which gives a straight line ($r=0.99$) for [TMAC]$>1.0\times10^{-3}$ M: $K=104\ M^{-1}$ and $q=0.0225$. The $k''_{a,obsd}$ value thus determined (447 $M^{-1}s^{-1}$) is more than 50% of the corresponding value in the CTAB micelle (821 $M^{-1}s^{-1}$, Table 1). The reactivity of MMHA increased from 36.8 to 447 $M^{-1}s^{-1}$ upon pairing with TMAC, if the other changes which may be caused by the addition of TMAC (*e.g.* micellar structure) are negligible.

The rate-enhancing effect of a countercation trapped in the hydrophobic environment is more clearly shown by using a zwitterionic nucleophile with a long alkyl group, DHDB. The $k_{a,obsd}$ value of DHDB in a nonmicellar system does not differ much from that expected from Brönsted relationship (see below), but it is enhanced in nonionic micelles (Table 1 and Fig. 3) more effectively than that of MMHA. This means that the presence of an intramolecular countercation

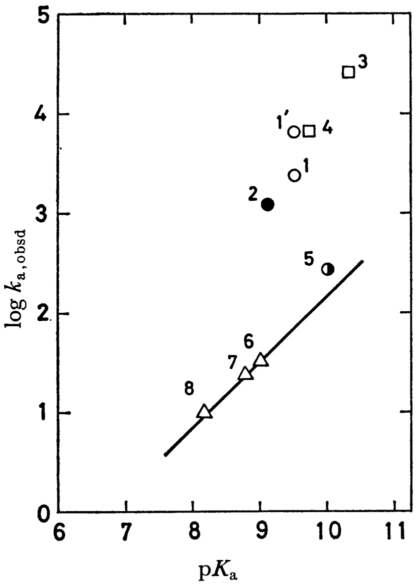

Fig. 6. Brönsted plots.
Numbers indicate those recorded in Table 2.

does not result in the increased reactivity of anionic nucleophiles unless they are placed in a hydrophobic environment. The addition of TMAC did not affect the reactivity of DHDB, reflecting the fact that DHDB forms a stable intramolecular ion pairs, as also inferred from the CPK model building.

It is thus concluded that the reactivity of an anionic nucleophile (hydroxamate and oximate) undergoes considerable augmentation in the presence of a hydrophobic countercation in a hydrophobic environment.

Figure 6 shows the Brönsted relationship for the data of Table 2. The plot for nonmicellar DHDB is located fairly close to the relationship obtained for simple hydroxamic acids. The data obtained in the CTAB micelle are placed above the Brönsted line by two orders of magnitude, though they are scattered due to varying reaction conditions. The polts for MMHA and DHDB in the nonionic micellar system are placed not far below those in the CTAB micelle.

The data (Tables 1 and 2) clearly indicate that the reactivity enhancement for intermolecular(MMHA–TMAC) and intramolecular(DHDB) ion pairs in nonionic micelles is almost comparable to those in cationic micelles. The remarkable rate enhancement in the cationic micelles has been attributed to concentration effect, proximity effect, peculiar environments of the micellar surface, desolvation of nucleophiles and to other factors, in the absence of definitive experimental evidence.

The entropic factors such as concentration effect and proximity effect cannot contribute to the large enhancement, since this has been observed not only in cationic micelles but also in anionic and conventional noninoic micelles. Characteristics peculiar to cationic micelles such as high charge density at the micellar surface do not appear to be a prerequisite for the rate enhancement, since the present investigation showed that the presence of a single countercation causes a sufficiently large enhancement. Thus, it is proposed that the rate acceleration observed for anionic nucleophiles in cationic micelles is largely derived from the formation of hydrophobic ion pairs between anionic nucleophile and cationic surfactant in a highly hydrophobic environment. The anion included in a hydrophobic ion pair will attain its high reactivity from desolvation, as already known for other nucleophilic reactions.[9,12)]

The importance of hydrophobic (dehydrated) ion pairs in the nucleophilic attack is also suggested by other data obtained recently. The reaction rate of the MMHA anion and PNPA in an aqueous system increased by 100-fold in the presence of partially benzylated poly(4-vinylpyridine).[21)] The polymer can provide a hydrophobic environment but cannot form a micellar structure. Kirsh *et al.*[22)] reported that the reactivity of the *N*-(2-hydroxyimidophenethyl)-pyridinium unit anchored to poly(4-vinylpyridine) is higher by a factor of 100 than for the monomeric analog. The micellar structure is not required for the activation of anionic nucleophiles in these cases.

We have found that tetraethylammonium *N*-methylmyristohydroxamate(MMHA–NEt_4) shows very large reactivities toward PNPA in dry, aprotic solvents, the reaction being efficiently suppressed (*ca.* 100 times rate decrease) by the addition of 10^{-3}—10^{-4} M of H_2O.[23)] The result shows the importance of the hydration term in considering the nucleophilic reactivity of some anions.

In conclusion, a remarkable rate enhancement of some anionic nucleophiles observed in cationic micelles arises from the formation of hydrophobic ion pairs (both intermolecular and intramolecular) in highly hydrophobic environments. The reactivity of these ion pairs is enhanced probably by desolvation of the anion. The micellar effect would constitute a part of a more general microenvironment effect, which is conceivably a major source of enzymatic efficiency.

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