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Dipolar Micelles. 5. Micellar Effects on the Hydrolysis of Neutral and Charged Esters

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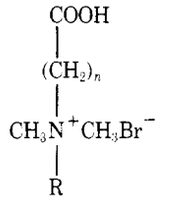
The specific base catalyzed hydrolyses of positively charged and neutral esters in three betainelike micelles of structures I–III, and five dipolar micelles IV–VIII, have been studied. These comprised nine different esters: $C_{10}H_{21}N^+(CH_3)_2ZBr^-$, Z = 2-(*p*-nitrobenzoyloxy)ethyl (CPNBA), Z = 3-(*p*-nitrobenzoyloxy)propyl (HCPNBA), Z = 3-(2,4-dinitrophenyloxycarbonyl)propyl (DNPDE$^+$); *p*-nitrophenyl acetate (PNPA); *p*-nitrophenyl hexanoate (PNPH); *p*-nitrophenyl decanoate (PNPD); 2,4-dinitrophenyl acetate (DNPA); 2,4-dinitrophenyl decanoate (DNPD); and decyl *p*-nitrobenzoate (DPNBA). Study has shown that the second-order rate coefficients of PNPA, PNPH, and PNPD enhance with increasing concentration of premicelle aggregates (subunits) and decrease in the presence of micelles. The betainelike micelles exhibit inhibitory effect on rates of hydrolyses of most substrates included in this study. The inhibitory efficiency was found to depend on the positions of both the reaction site and the carboxylate anion of the zwitterionic micelle. It is suggested that proximity of microenvironmental factors affects primarily the course of hydrolyses on the micellar surface.

In parts 3 and 4[1,2] we have shown that proximity and microenvironmental factors are important in determining the catalytic efficiency of micelle-forming cationic surfactants containing hydroxy head groups at various positions around the cationic surface. It is well known that reactions which occur at the micellar surface are highly affected by the hy-

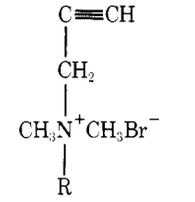
drophilic–lyophilic mode of the system. Therefore, the substrate–micelle intracomplexes may serve as attractive models[3-7] for a systematic study of reaction courses at the interfaces of biological systems.

Present study concerns the kinetic effects of dipolar micelles I–VIII on the hydrolyses of various esters A–E. The models included here were designed to furnish deeper insight on effects of conformation and electrostatic interactions on the catalytic reactivity of micelles. In view of the differences in the mechanistic routes between the micelles of the type discussed earlier in part 4[2] and those of I–VIII presented here, more information on reaction sites and structural effects is expected.

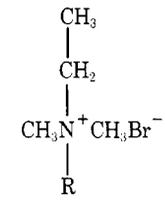
Surface Active Compounds



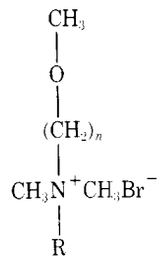
I, R = $C_{10}H_{21}$; n = 1
Ia, R = CH_3; n = 1
II, R = $C_{10}H_{21}$; n = 2
III, R = $C_{10}H_{21}$; n = 3



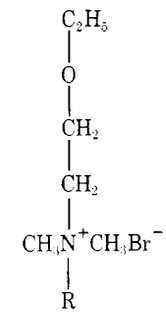
IV, R = $C_{10}H_{21}$
IVa, R = CH_3



V, R = $C_{10}H_{21}$

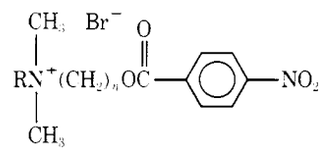


VI, R = $C_{10}H_{21}$, n = 1
VII, R = $C_{10}H_{21}$, n = 2

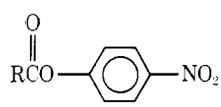


VIII, R = $C_{10}H_{21}$

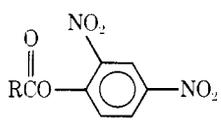
Esters



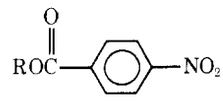
A: CPNBA, n = 2; R = $C_{10}H_{21}$
HCPNBA, n = 3; R = $C_{10}H_{21}$



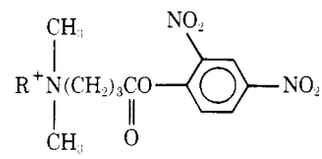
B: PNPA, R = CH_3
PNPH, R = C_5H_{11}
PNPD, R = C_9H_{19}



C: DNPA, R = CH_3
DNPD, R = C_9H_{19}



D: DPNBA, R = $C_{10}H_{21}$



E: DNPDE$^+$, R = $C_{10}H_{21}$

Experimental Section

Micelle Forming Agents. Compounds I–VIII were prepared according to procedures i or ii described in part 3[1] as outlined below:

(i) $CH_3(CH_2)_n(CH_3)_2N + Br(CH_2)_mX \rightarrow CH_3(CH_2)_n(CH_3)_2N^+(CH_2)_mX\ Br^-$

(ii) $CH_3(CH_2)_nBr + N(CH_3)_2(CH_2)_mX \rightarrow CH_3(CH_2)_nN^+(CH_3)_2(CH_2)_mX\ Br^-$

The preparation of *N,N*-dimethyldecylamine used in method i is according to Clarke et al.[8] Compounds I and III were prepared from the appropriate bromoesters (method i) and the esters formed were hydrolyzed either during the quaternization step (compound I) or in the final step with aqueous hydrobromic acid. The synthesis of II (method ii) is accompanied by a large amount of elimination product and the yield of the compound is only 10%.

***N,N*-Dimethyl-*N*-decyl-*N*-2-carboxyethylammonium Bromide (II).** Decyl bromide (48 g) was added to ethyl 3-dimethylaminopropionate (21.5 g). The solution was allowed to stand at room temperature for 2 days only, and the precipitate removed by filtration, followed by washing with ether (mp 55–70 °C).

After several recrystallizations from methanol–ether the quaternary ethyl ester of II melted at 65 °C. The ester hydrolyzed in aqueous HBr solution pH 1 at 50 °C over a period of 1 week followed by lyophilization. The residue was recrystallized from acetone and dried. For analytical properties see Table I.

Esters. All the esters were prepared as described[1,2] and purified prior to their use.

Kinetic Measurements. The hydrolyses of *p*-nitrobenzoate esters were followed by monitoring the release of *p*-nitrobenzoate anion at 250–260 nm as previously described.[2] A Unicam SP800 recording spectrophotometer with scale expansion was used. The temperature of 30 °C in the cell was maintained by circulation of water from an external thermostated bath. All the reactions were performed in a 0.05 M carbonate buffer at a pH range of 9.5–10.5, and in an ionic strength of 0.8 M (KBr). The concentration of esters in the equilibrated cell was 5×10^{-5} M. The second-order rate constants are assembled in Tables II and III. The plots of second-order rate coefficients of the short-chain esters against concentration of micelle-forming surfactants are presented in Figures 1–3.

Results and Discussion

From Figures 1–3 it can be seen that the rate constants of short-chain phenyl esters tend to increase first, and then decrease gradually as the detergent concentrations increase.[9a] The kinetic cmc values at the reaction maxima were found to be higher than those determined by the surface tension method. The corresponding cmc values of micelles I, IV, and V at 0.8 M (KCl) are 4–6 $\times 10^{-3}$, 9 $\times 10^{-3}$, and 5 $\times 10^{-3}$ M.

Scheme I describes in outline the intermediary species involved in the hydrolytic processes. In this scheme M and $(m)_x$ are the average concentrations of micelle units and subunits, respectively, and K_1 and K_2 are the corresponding association constants of the substrate.

At low concentrations of detergent and below the cmc the rate of hydrolysis depends on $(m)_x$ concentration (eq 1), while

Scheme I

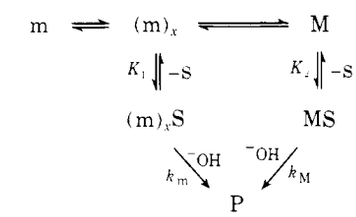


Table I. Analysis and Physical Constants of Compounds II, III, IV, IVa, VI, and VIII

Compd	Registry no.	Mp, °C	Method	Formula	Analysis C Calcd	C Found	H Calcd	H Found	N Calcd	N Found	Br Calcd	Br Found
II[b]	26543-24-8	138–140	ii	$C_{15}H_{32}NO_2Br$	53.25	53.11	9.46	9.44	4.19	4.09	23.67	23.82
III[c]	62851-20-1	92–93	ii	$C_{16}H_{34}NO_2Br$	54.54	54.58	9.65	9.47	3.97	4.14	22.72	22.81
IV[d]	62851-21-2	76	i	$C_{15}H_{30}NBr$	59.21	59.42	9.87	9.81	4.61	4.61	26.32	26.42
IVa[e,b]	7505-53-5	182	i	$C_6H_{12}NBr$	40.45	40.14	6.74	6.67	7.68	7.83	44.94	44.90
VI[a]	62851-22-3	99	ii	$C_{14}H_{32}NOBr$	54.19	53.71	10.32	10.16				
VIII[b]	62851-23-4	124	ii	$C_{16}H_{36}NOBr$	56.80	56.51	10.65	10.51	4.14	4.40	23.67	23.40

Recrystallized from: [a] methanol–ether; [b] acetone; [c] acetone–ether; [d] acetone–ethyl acetate; [e] methanol.

Table II. Rate Constants k_m, k_M (s^{-1} M^{-1}) and Association Constants of Substrates (PNPA, PNPH, DNPA) with Micelles III, IV, and V[a]

Micelles		Esters PNPA	PNPH	DNPA
	k_{OH}	12.1	7.9	64.9
III	Kinetic cmc	0.01	0.01	0.01
	k_{cmc}	24	13.8	12.0
	k_e	19	8.3	12.8
	k_m	62	60.4	390
	K_S		162	
	K_M		2.0	
IV	Kinetic cmc	0.02	0.02	0.03
	k_{cmc}	35	25.9	138
	k_e	90	79	15
	k_m	38	14.7	296
	K_S	74	178	43.8
	K_M	7.5	2.1	71
V[b]	Kinetic cmc	0.008	0.01	0.01
	k_{cmc}	24.8	10.5	130
	k_e	145		60
	k_m	41		301
	K_S	37	272	
	K_M	6.7	1.9	

[a] At 30 °C, μ = 0.8 M (KBr). [b] Registry no.: V, 39995-56-7.

at concentrations above the cmc the quantity of $(m)_x$ remains constant and the reaction rate varies with the micellar concentration (M) only (eq 2).

$$k_{obsd} = (k_{OH} + k_m Kem)^{-}OH/(1 + Kem) \ldots \quad (1)$$

$$Kem = K_1(m)_x = K_1(m/n)$$

where m is the detergent concentration based on monomers, and n is the average aggregation number of the subunits in the solution. k_{OH} denotes the second-order rate constant in the bulk solution, and k_m denotes the rate constant in the subunits.

$$k_{obsd} = [k_{cmc} + k_M K_S(m - cmc)]^{-}OH/[1 + K_S(m - cmc)] \ldots \quad (2)$$

$$K_S(m - cmc) = K_2M = K_2(m - cmc)/n'$$

where k_{cmc} is the second-order rate constant of the ester hydrolysis at the cmc, and k_M is the second-order rate constant of the substrate–micelle complex.

The parameters in eq 1 and 2 were derived by fitting the experimental plots to the theoretical ones, using a nonlinear least-squares program.

From Table II it can be noted that the ratio of the apparent association constants (K_e, K_s) varied in the range of 0.05–3.9. A ratio >1 does not indicate a better binding of the substrate to the subunit than to the micelle, since the two systems differ in their aggregation numbers. On the assumption that $n' > n$ in the three micelles III, IV, and V, it follows that the

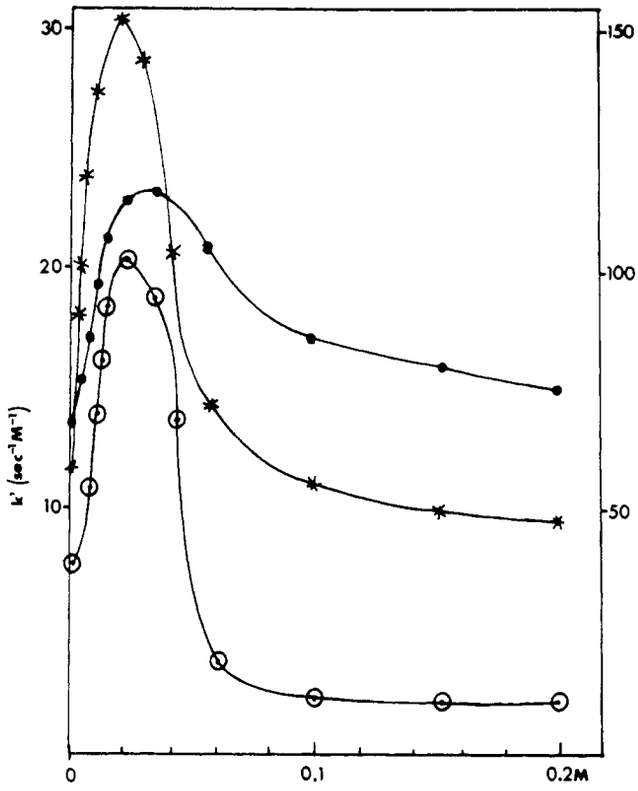


Figure 1. Second-order rate dependence of PNPH (⊙–⊙) and PNPA (★–★) (left-hand ordinate) and DNPA (●–●) (right-hand ordinate) on the concentration of micelle-forming agent (IV): T = 30 °C, μ = 0.8 M (KBr).

binding capacity of micelle's unit is greater than that of the premicelle aggregates. As anticipated, the binding of PNPH to the micellar phase compared with PNPA and DNPA is most efficient due to the greater extent of hydrophobic interactions. The data also indicate that micellar effects of III, IV, and V cannot be accommodated with those produced by other types of cationic micelles recorded in the literature.[10,11]

From Figures 1, 2, and 3 it is apparent that the effect of micelle III, IV, and V on the reaction rates above the cmc is that of an inhibition. Moreover, the better the penetration of the esters into the hydrophobic region of the micelle the greater the inhibitory effects. This is inferred from the decreasing ordering in the relative rates (k_{OH}/k_M) of PNPH, PNPA, and DNPA.

The above mentioned phenomenon is in contrast with the well-known behavior of cationic micelles, which accelerate the reaction rates of anionic nucleophiles due to the electrostatic stabilization of the transition state. Therefore, it can be assumed that in the case of the latter micelles, steric perturbations of the micellar head groups should be attributed to the

Table III. Second-Order Rate Constants k_M (s^{-1} M^{-1}) of Long-Chain Esters with Micelles I–VIII

Micelles	Esters					
	DPNBA	CPNBA	HCPNBA	DNPD	DNPDE+	PNPD
H_2O		13.0	1.7		1688	
I[b]	0.023	9.13	1.08	4.0	910	0.56
II		6.6	1.1	20	1950	2.05
III	0.020	9.3	1.4	20	2100	1.78
IV	0.022	19.5	1.91	19	2100	1.62
V	0.025	11.9	1.8	11.7	2200	1.43
VI	0.021	12.5	2.0	20.5	1533	2.88
VII[c]	0.025	13.9	1.55			1.43
VIII	0.023	14.4	2.0	11.1	1280	1.40

[a] At 30 °C, μ = 0.8 M (KBr). [b] Registry no.: I, 39995-54-5. [c] Registry no.: VII, 61063-28-3.

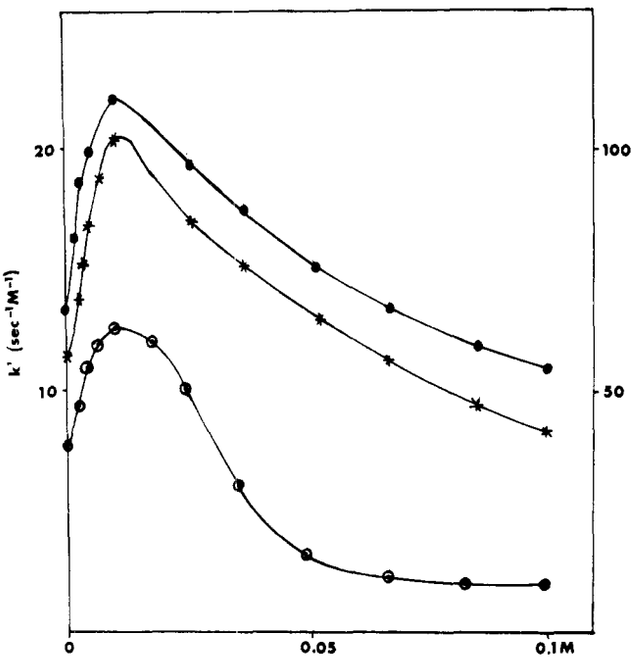


Figure 2. Second-order rate dependence of PNPH (⊙–⊙) and PNPA (★–★) (left-hand ordinate) and OPDNPA (●–●) (right-hand ordinate) on the concentration of micelle-forming agent (III): T = 30 °C, μ = 0.8 M (KBr).

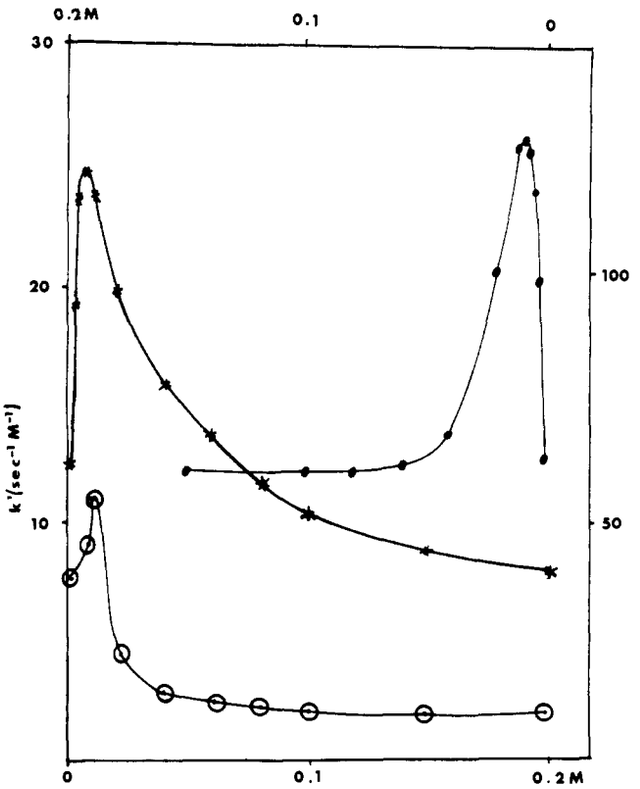


Figure 3. Second-order rate dependence of PNPH (⊙–⊙) and PNPA (★–★) (left-hand ordinate and lower abscissa) and DNPA (●–●) (left-hand ordinate, upper abscissa) in the presence of micelle-forming agent (V): T = 30 °C, μ = 0.8 M (KBr).

decrease in reaction rates. This factor must dominate the electrostatic effects of the positively charged surface.

In addition, the data recorded in Table III indicate that both polar and negatively charged head groups also exert an influence on the reaction rates. Accordingly, at various regions on the surface, the shielding and electrostatic effects contribute unequally to the microenvironment at the reaction site of the substrate. Hence, it seems that the reactivity of esters at the micellar surface depends mainly on the locality of the reaction site and on steric factors. Corroboration of this view is shown, thus: (a) It is most likely that hydrophobic interactions orient the reaction centers of both PNPD and PNPH to reside near the positively charged onium groups of micelles III, IV, and V. On the other hand, the electrostatic interactions of the functional head groups of the latter micelles with the surface seems to be negligible. This is adduced from the relative rate of PNPD in the betaine-like micelles I, II, and III (Table III). Consequently, the similarity in the rate coefficients between PNPD and PNPH in the presence of micelles III, IV, and V (see Tables II and III) can be related to the closeness of the microenvironment effect on the reaction sites of the two esters. (b) Although the rate constants (k_M) of DNPA and PNPA decrease as the micelle concentration increases above the cmc, the rate of PNPA only is suppressed below its value in water. This is reflected also in their K_s values (see micelle IV) and the origin of this behavior could stem from the difference in the position of the two esters on the surface. The molecules of DNPA are assumed to cluster around the water-rich region of the micelle and should conceivably be less affected than those of PNPA, which tend to penetrate into the interior region of the micelle.

The observed premicelle-induced augmentation in reaction rates could be interpreted in similar terms. In fact the subunits of III, IV, and V display kinetic characteristics which are peculiar to cationic micelles and the relative k_m/k_{OH} values lie in the range of 1.8–7.5 (Table II). This clearly indicates that the aliphatic head groups exert greater influence on the closed surface of the micelle rather than on the subunits. The differences between the systems could spring from differences in (a) shielding capacities, (b) surface shapes, (c) modes of binding, and (d) the effective charges. These reflect virtually all microenvironmental differences at the reaction sites.

The kinetic effects as displayed by the subunits of III, IV, and V (Table II) also indicate that substrate reactivity does not depend on the binding constants K_s. This again suggests

that orientation of the reaction site in a subunit system is a more important factor than the extent of the substrate interaction.

The increase in reaction rate of PNPA in the presence of IVa by a factor of 2.3 ($k = 28\ s^{-1}\ M^{-1}$) is worthy of note. The measurements were taken in the range 0.05–0.2 M, showing no dependence on concentration. The reaction rate of PNPA under similar conditions with Ia was unaffected. This emphasizes the contribution of electrostatic effect of both negative and positive ions on the specific base hydrolysis of esters.

The rate enhancement of anionic nucleophiles in cationic micelles was recently proposed to be due to hydrophobic desolvation of ion pairs.[9b] Our data presented above could not be accommodated with that proposal, since the low hydrophobic environment of the subunit actually increases substrate reactivity, whereas the high hydrophobic environment of the micelle decreases the reactivity.

Effect of Zwitterionic Micelles. An inspection of Table III reveals inconsistency in the kinetic effects of carboxylate anions (I, II, III) on the hydrolysis of the different esters. Substrates bearing good leaving groups, such as in DNPD, $DNPDE^+$, and PNPD, are inhibited by micelles of the type I, whereas the ester CPNBA is inhibited mainly by micelle I. Substrate of the kind of DPNBA is quite unaffected by zwitterionic micelles. The carboxylate-induced rate retardation in alkaline hydrolysis can be explained in terms of electrostatic interactions similar to that described for other micellar and bimolecular systems.[12-15]

The remarkable increase in reactivity of the nucleophilic reactions in cationic surfactant could be attributed to: (a) the effect of binding of the reactants to the micellar surface, which increases the effective concentration of the reacting species and as a consequence its proximity effects;[16,17] (b) electrostatic interactions between the negatively charged transition state and the micelle surface, which enhanced its stabilization relative to that of the ground state.[18,19] Following these considerations anionic micelles are to be expected to exert the opposite effect on reaction rates. However, the charge characteristic in zwitterionic micelles is not clear. There are three possibilities which must be reckoned. First, that zwitterionic micelles could affect the reaction rate like neutral micelles to retard the reaction rate. This could be envisioned either on the basis of the ground state (a decrease in binding of reactants) or on the basis of the transition state (a decrease in electrostatic stabilization) as compared to the situation in cationic micelles. Second, zwitterionic micelles could behave like cationic micelles in accelerating the reaction rates. This was actually the case when cyanide ion was added to pyridinium ion in the presence of dodecyldimethylammoniopropanesulfonate.[18a] Third, zwitterionic micelles may behave like anionic detergents which inhibit the reaction rate in alkaline hydrolysis, since 70–80% of the positive charge on the cationic group should be neutralized by the counterions[20] at high ionic strength (0.8 M).

The data presented here point out that additional factors are also responsible for the varied reactivity of zwitterionic micelles. The basic hydrolyses of DNPD and PNPD in the three zwitterionic micelles I, II, and III reveal the importance of the location of the reaction site relative to the positively and negatively charged groups on the micellar surface. The case of the latter esters in the presence of micelle I is that the site of reaction and of carboxylate anion are very close and therefore electrostatic interactions should destabilize the emerging negatively charged transition state of the ester, and dominate the stabilization effects induced by the cationic group. In the presence of zwitterionic micelles II and III the carboxylate anion is located more in the region of the bulk solution and thus the electrostatic stabilization of the transition state due to the positively charged surface is more pronounced, as compared to micelle I.

The proximity of the carboxylate group in the betaine series[21] to that of the ammonium head group is inferred from physical measurements. This is borne out also from the kinetic data. However, it might be quite different for the zwitterionic micelles II and III.

The significance of the location of the reaction site in the zwitterionic micelles is also noted in other types of esters. The anticipated inhibitory effect of micelle III on the hydrolysis of $DNPDE^+$ was not experimentally observed. In fact (see Table III), the relative rates of $DNPDE^+$ in the zwitterionic micelles I, II, and III resemble those of PNPD and DNPD, suggesting analogy between the latter and the former. Thus, it can be concluded that the reaction site in $DNPDE^+$ is most probably on or near the surface rather than in the bulk. Moreover, the tendency of aromatic compounds to solubilize on the surface of cationic micelles is well documented.[22-25] It is permissible, therefore, to conclude that $DNPDE^+$ exists in a folded conformation and that the phenyl moiety occupies a position between the positively charged groups.

On the basis of kinetic salt effects we have inferred earlier that this sort of conformation actually exists in the case of CPNBA, HCPNBA, and $DNPDE^+$. Accordingly, the abovementioned effects of the zwitterionic micelles on HCPNBA and CPNBA appear plausible. However, some differences could be observed upon comparing the latter with $DNPDE^+$: (a) All three zwitterionic detergents, I, II, and III, exert diminishing effects on rates of reaction of HCPNBA and CPNBA (compared to micelle V), but this is not the case with $DNPDE^+$. (b) The rate constant of HCPNBA is affected in the presence of micelles I and II, but in the case of $DNPDE^+$ only micelle I exhibited an inhibitory effect. (c) In the hydrolysis of CPNBA only micelle II was the most effective one. These kinetic differences could be attributed to small conformation variation in the folded forms of the esters, pointing the closeness of the reaction site to the carboxylate anion. The micellar effects of I, II, and III are rather modest and could also originate either from microscopic changes in the dielectric constant of the medium or from changes in solvation of the transition state. It could also be due to changes in the steric interactions within the micelles, but they all must be small.

On comparison between the rate constants of compounds V, VI, and VII, only little sensitivity to the polar groups along the surfactant chain was observed.

The absence of an inhibitory effect in the case of DPNBA in the presence of micelle I appeared rather unexpected at first glance, since it was thought to be similar to that of PNPD and DNPD. However, the electrostatic interactions of the charged groups in the zwitterionic micelle with the attacking nucleophile and the leaving group in the transition state of DPNBA relative to PNPD may account for the dissimilar effects in the esters.

More work on the transition state level is warranted toward this end.

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Registry No.—PNPA, 830-03-5; PNPH, 956-75-2; DNPA, 4232-27-3; DPNBA, 6500-30-7; CPNBA, 62851-24-5; HCPNBA, 62851-25-6; DNPD, 61063-34-1; $DNPDE^+$, 62905-89-9; PNPD, 1956-09-8.

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A New Synthesis of Benzo[*a*]pyrene. 7,10-Dimethylbenzo[*a*]pyrene[1]

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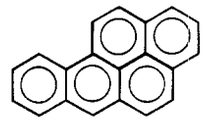
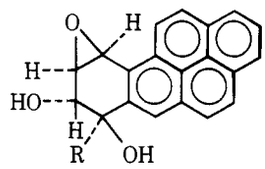
1-Acetylpyrene was reacted with the lithium enolate of ethyl acetate to yield the hydroxy ester which was dehydrated to 3-(1-pyrenyl)-2-butenoic acid. Reduction produced 3-(1-pyrenyl)butanoic acid which was reduced by $LiAlH_4$ to 3-(1-pyrenyl)butanol. Mesylation, cyanation, and hydrolysis afforded 4-(1-pyrenyl)pentanoic acid. This acid was produced in 15% yield but in one step by alkylation of pyrene with γ-valerolactone. Cyclization with HF produced 7-keto-10-methyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene from which 10-methylbenzo[*a*]pyrene was produced by reduction and dehydrogenation and 9,10-dimethylbenzo[*a*]pyrene by reaction with methyllithium followed by dehydration and dehydrogenation. Alternately 7,10-dimethylbenzo[*a*]pyrene was synthesized by reaction of 1-bromopyrene with 2,5-dimethylfuran (via 1-pyryne) to yield 7,10-dihydro-7,10-dimethyl-7,10-epoxybenzo[*a*]-pyrene which on reduction and acid-catalyzed dehydration yielded 7,10-dimethylbenzo[*a*]pyrene. The fact that 10-methylbenzo[*a*]pyrene is inactive as a carcinogen is discussed in terms of the effect of the 10-methyl group on the metabolism involved.

The metabolism of benzo[*a*]pyrene, **1**, in relation to carcinogenicity and mutagenicity has long interested scientists. Recently, the hypothesis has been advanced that one (or more) of the isomeric 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenes, **2**, is the ultimate carcinogen, and/or mutagen.[3] Presumably, epoxidation[4] of **1** to yield the 7,8-



1



2, R = H
4, R = CH_3

epoxide occurs first, followed by hydration to trans-7,8-diol which is then epoxized to **2**. Thus three enzyme-catalyzed processes occur consecutively to yield (presumably) the ultimate carcinogenic species.

In studies in the benz[*a*]anthracene series, we have hypothesized that the carcinogenic activity of many substituted benz[*a*]anthracenes can be rationalized if it is assumed that: (a) detoxification occurs by metabolic attack at position 7; and (b) carcinogenic activity arises by metabolism which is initiated by attack at position 5.[5,6] Each of these metabolic pathways can be blocked (or altered) by substitution of a methyl or fluoro group at the position involved. For example, 7,12-dimethylbenz[*a*]anthracene is a potent carcinogen but 5,7,12-trimethylbenz[*a*]anthracene[7] and 7,12-dimethyl-5-fluorobenz[*a*]anthracene[7,8] are inactive, probably because in each the 5 position is blocked.

Because of the results in the benz[*a*]anthracene series we became interested to find out if the current hypothesis concerning the ultimate carcinogen in the benzo[*a*]pyrene series could be tested by determining the carcinogenic activity of benzo[*a*]pyrenes having methyl groups in the benz ring.

For example, if a methyl group were substituted at the 7 position of benzo[*a*]pyrene would this block the epoxidation at the 7,8 position and render the compound inactive? Since 7-methylbenzo[*a*]pyrene, **3**, has been reported to be carcinogenic,[9] evidently the epoxidation at the 7–8 bond can occur as well as the hydration of the 7,8-oxide to the 7-methyl-7,8-*trans*-diol. The latter could then be epoxidized at the 9–10 bond to yield a 7,8-dihydroxy-9,10-epoxy-7-methyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene, **4**, which would be a corcinogenic substance analogous to the product, **2**, formed from **1**. The above reasoning assumes that the carcinogenic activity of **3** is due to the same type of metabolic processes responsible for the activation of **1**.

Accordingly, we wished to know if 10-methylbenzo[*a*]pyrene, **5**, and 7,10-dimethylbenzo[*a*]pyrene, **6**, would be carcinogenic. We have been informed that after 16 months, **5** has produced no tumors and hence must be considered inactive as a carcinogen.[7] One can assume that **5** is capable of being epoxidized and the epoxide hydrated to *trans*-7,8-dihydro-7,8-dihydroxy-10-methylbenzo[*a*]pyrene, **7**, but epoxidation at the 9,10 position is either blocked or the epoxide, if formed, does not interact with DNA as does **2**. Further experiments