(b) G. J. Lloyd, C.-M. Hsu, and B. S. Cooperman, *ibid.*, **93**, 4889 (1971); (c) C.-M. Hsu and B. S. Cooperman, *ibid.*, preceding paper in this issue; (d) J. M. Steffens, J. J. Siewers, and S. J. Benkovic, *Biochemistry*, **14**, 2431 (1975); (e) E. J. Sampson, J. Fedor, P. A. Benkovic, and S. J. Benkovic, *J. Org. Chem.*, **38**, 1301 (1973); (f) Y. Murakami and J. Sunamoto, *Bull. Chem. Soc. Jpn.*, **44**, 1827 (1971).
(3) (a) B. S. Cooperman in "Metal Ions in Biological Systems", Vol. V, H. Sigel, Ed., Marcel Dekker, New York, N.Y., (1976); (b) S. J. Benkovic in "Comprehensive Chemical Kinetics", C. H. Banford and. F. Tipper, Ed., Elsevier, New York, N.Y., 1972; (c) A. S. Mildvan, *Annu. Rev. Biochem.*, **43**, 357 (1974); (d) J. F. Morrison and E. Heyde, *ibid.*, **41**, 29 (1972); (e) T. G. Spiro, "Inorganic Biochemistry", G. L. Eichhorn, Ed., Elsevier, Amsterdam, 1973.
(4) R. Klement and K. H. Becht, *Z. Anorg. Chem.*, **254**, 217 (1947).
(5) R. W. Chambers and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 3751 (1958).
(6) (a) S. J. Benkovic and E. J. Sampson, *J. Am. Chem. Soc.*, **93**, 4009 (1971); (b) N. H. Stokes, *Am. Chem. J.*, **15**, 198 (1893).
(7) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).
(8) Instruction Manual for Radiometer pH meter PHM 26c, Section D.
(9) D. Chipman and R. Breslow, *J. Am. Chem. Soc.*, **87**, 4195 (1965).
(10) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **87**, 3199 (1965).
(11) J. E. Malmin, Ph. D. Thesis, Columbia University, 1969.
(12) G. W. Jameson and J. M. Lawlor, *J. Chem. Soc. B*, 53 (1970).
(13) A. J. Kirby and M. Younas, *J. Chem. Soc. B*, 1165 (1970).
(14) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. 1, W. A. Benjamin, New York, N.Y., 1966, pp. 119–201.
(15) A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc. B*, 135 (1968).
(16) A. Williams and K. T. Douglas, *J. Chem. Soc., Perkin Trans 2*, 1727 (1974).

Aromatic Nucleophilic Substitution in Nucleophilic Surfactants. Comparison with Alkoxide Reactions

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Abstract: The reactions of 2,4-dinitrochloro- and fluorobenzene (DNC and DNF) with the alkoxide ions of choline, propargyl alcohol, and 2,2,2-trifluoroethanol give ether intermediates which react readily with hydroxide ion. The nucleophilicities of the alkoxides toward DNC and DNF (in parentheses) are: $Me_3N^+CH_2CH_2O^-$ 19 (27), $HC{\equiv}CCH_2O^-$ 63 (132), $CF_3CH_2O^-$ 11 (10), relative to OH^- in water at 25.0 °C. The second-order rate constants (10^4k^{OH}, l. mol^{-1} s^{-1}) for reaction of DNF, DNC, or the ethers toward OH^- are: DNF, 1200; DNC, 1.42; $-OCH_2CF_3$, 9.1; $-OCH_2C{\equiv}CH$, 3.7; $-OCH_2CH_2N^+Me_3$, 9.1. Micelles of hexadecyl(2-hydroxyethyl)dimethylammonium bromide (n-$C_{16}H_{33}N^+Me_2CH_2CH_2OH$ Br^-, Ia) are effective reagents toward DNC and DNF at high pH and for ionization of the hydroxy group $pK_a \sim 12.3$, estimated kinetically for reactions of DNF and DNC in Ia and up to 0.15 M OH^-. In 0.01 M OH^- the reactivity of the 2,4-dinitrophenyl ether of Ia in micelles of Ia is 260 times that of the corresponding ether of choline in water, and the overall rates of nucleophilic attack on DNF and DNC in micelles of Ia are 6000 and 14 000, respectively, relative to reaction in water.

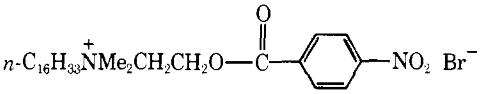
Cationic micelles of the hydroxyethyl surfactants (Ia, b) and related surfactants are effective reagents in reactions of phosphate[2] and carboxylate esters[3,4] and of alkyl halides[5] and carbocations.[6] It was suggested that the alkoxide moiety of the zwitterion (II) acted as a good nucleophile.[2,4,6]

$$R\overset{+}{N}Me_2CH_2CH_2OH \rightleftharpoons R\overset{+}{N}Me_2CH_2CH_2O^- + H^+$$

Ia, R = n-$C_{16}H_{33}$ II
b, R = n-$C_{12}H_{25}$
c, R = Me

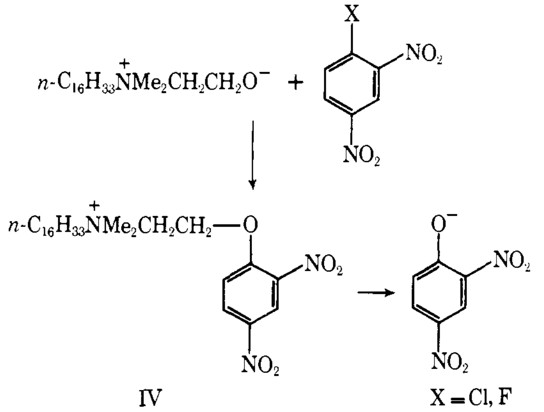
The pK_a of choline (Ic) is 13.9,[7] so that II should be generated at high pH, especially if R is sufficiently hydrophobic for micelles to form, because micellization should increase ionization of I. Micelles of Ia, b are crude models for a catalytically active serine residue in an enzyme.[8,9]

The catalytic effectiveness of micelles of Ia, b could be explained in terms other than nucleophilic attack. For example general acid or base catalysis could be important, and it has been suggested that hydroxide ions at the surface of micellized I could be especially reactive.[5] However the solvent deuterium isotope effects in phosphate ester hydrolyses are those expected for nucleophilic attack by the alkoxide moiety of II,[2c] and micellized Ia is no better a catalyst than the nonfunctional surfactant cetyltrimethylammonium bromide (CTABr) for reaction of hexadecyl(2-hydroxyethyl)dimethylammonium bromide p-nitrobenzoyl ester (III).[13]


III

Berezin and his co-workers have shown that p-nitrophenyl esters will acylate surfactants similar to I,[4] but their experiments were done using an excess of carboxylic ester over the functional surfactant, so that the substrate could markedly perturb the micellar structure.

Our aim was to demonstrate formation of an intermediate formed by nucleophilic attack by micellized II under conditions in which the substrate concentration is much lower than that of the surfactant. The micellar structure should then be little affected by the substrate, and direct comparison can be made with other reactions of micellized I or similar surfactants at high pH.[2-6] The most convenient substrates are 2,4-dinitrochloro- and fluorobenzene (DNC and DNF), because nucleophilic attack upon them should give the ether (IV) which could then be hydrolyzed to 2,4-dinitrophenoxide ion,[14] and perhaps be spectroscopically detectable.


IV X = Cl, F

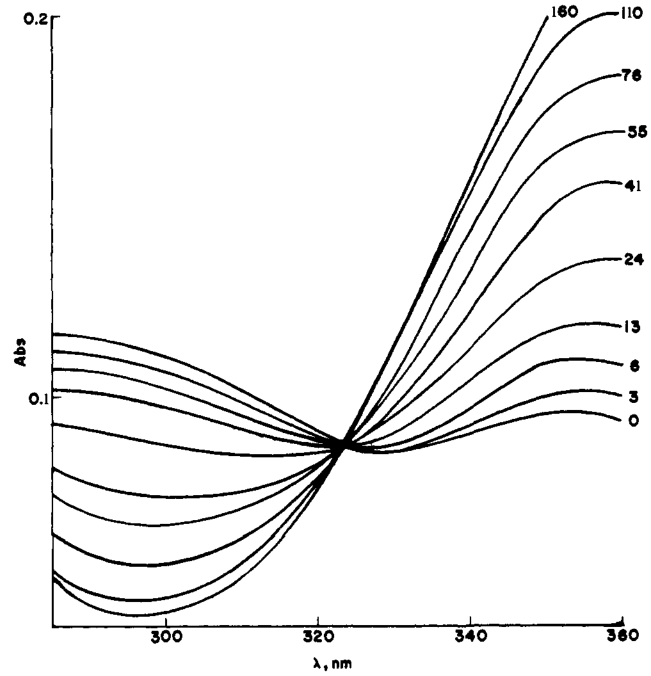


Figure 1. Repetitive scans for the reaction of DNF with 0.1 M choline chloride and 0.01 M OH$^-$ at 24.3 °C. The reaction times (min) are shown.

Detection would demonstrate nucleophilic participation by the hydroxyethyl head group of I, because other types of participation, e.g., general base catalysis, should give 2,4-dinitrophenoxide ion directly, and the relations between reaction rate and pH in micelles of Ia should be similar for aromatic nucleophilic substitution and for reactions of triaryl phosphates.[2b]

Alkoxide ions are often much better nucleophiles than lyate ions, in terms of their basicities, for nucleophilic attack on carboxylate[17] and phosphate esters[2] and carbocations,[6] so we also examined reactions of DNC and DNF with choline, propargyl alcohol, and 2,2,2-trifluoroethanol at high pH in the absence of micelles, because perhaps the high reactivities of micellized Ia, b are caused by the favorable environment provided by the micelle or by the inherently higher nucleophilicities of alkoxide over hydroxide ions (cf. ref 17).

Experimental Section

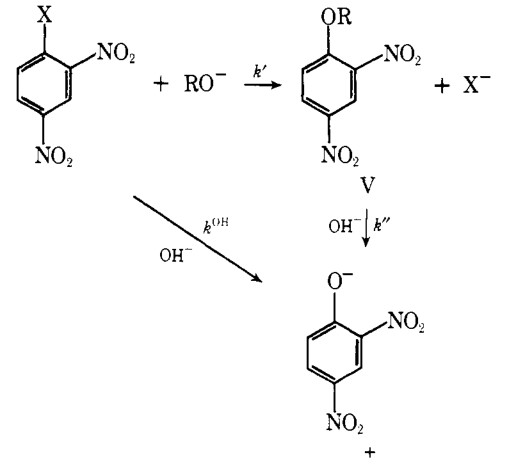
Materials. The preparation of hexadecyl(2-hydroxyethyl)dimethylammonium bromide (Ia) has been described.[2b] Choline chloride (Ic) (Eastman) was recrystallized and was dried in vacuo, and propargyl alcohol and 2,2,2-trifluoroethanol were redistilled before use.

Kinetics. The slower reactions were followed in a Gilford spectrophotometer with water-jacketed cells at 25.0 °C, and a Durrum stopped-flow spectrophotometer with a logarithmic amplifier and a Biomation 805 Waveform Data Acquisition unit was used for the faster runs. The first-order rate constants, k_ψ, are in s^{-1}, and concentrations of DNC and DNF were 5–8 × 10^{-6} M.

The reactions were followed at 358 nm, λ_{max} for 2,4-dinitrophenoxide ion, or at the isosbestic points between the intermediate ethers and 2,4-dinitrophenoxide ion. These isosbestic points are at 322.5, 322.5, 318.5, and 321.5 nm for the intermediates generated by the surfactant Ia, choline, trifluoroethanol, and propargyl alcohol, respectively.

When reactions were slow enough to be scanned repetitively (Cary 118), we observed isosbestic points between an intermediate and 2,4-dinitrophenoxide ion. An example is shown in Figure 1. The reactions followed at 358 nm which gave sigmoidal plots of absorbance against time due to build up of an intermediate were treated using an EAI TR-20 analog computer (Appendix). A minor problem with the runs in the stopped-flow spectrophotometer was that foaming of the surfactant caused irregular traces, but these irregularities were obvious. The problem was most serious with 4 × 10^{-3} M Ia.

Scheme I



(R = CF_3CH_2–, HC≡C–CH_2–, $Me_3\overset{+}{N}CH_2CH_2$–)

Products. Because aryl ethers of Ia, or other reaction intermediates, might decompose by an elimination reaction at high pH, we searched for n-hexadecyldimethylamine in the products. We used Si-gel plates (Eastman) and eluted the products of reactions of DNF and DNC in 0.15 M OH$^-$ and 4 × 10^{-3} M Ia using 20% MeOH–80% $CHCl_3$, and found a spot corresponding to 2,4-dinitrophenol (R_f 0.23), but no trace of the amine. Under these conditions n-$C_{16}H_{33}NMe_2$ has R_f 0.35.

Results

The reactions of the alkoxide or zwitterions in the absence of micelles and those of the functional micelles of Ia are considered separately, because the values of pK_a are known for the alcohols in water.

Nonmicellar Reactions. For reactions of DNF and DNC with, for example, choline in dilute hydroxide ion, spectra of the mixture can be scanned repetitively (Figure 1), and isosbestic points are observed (Experimental Section). When reactions of DNC are followed at 358 nm (λ_{max} for 2,4-dinitrophenoxide ion), there is an induction period, but the final parts of the reactions follow first-order kinetics, which are also observed if the reactions are followed at the isosbestic points. There are two routes for product formation: (i) direct reaction with hydroxide ion and (ii) formation and decomposition of the ether (V); Scheme I.

For reaction followed at the isosbestic point:

$$k_\psi = k^{OH}[OH^-] + k'[RO^-] \qquad (1)$$

where k_ψ is the observed first-order rate constant and the concentrations are actual, not stoichiometric.

The second-order rate constants, k^{OH}, in water are: 0.12 and 1.42 × 10^{-4} l. mol^{-1} s^{-1} at 25.0 °C for DNF and DNC, respectively,[18] and the concentrations of cholinate zwitterion and hydroxide or alkoxide ion can be calculated from the pK_a of the alcohols (Tables I and II). (The pK_a are: 2,2,2-trifluoroethanol, 12.37;[19] propargyl alcohol, 13.55;[19] choline, 13.9.[7]) There is a linear relation between cholinate zwitterion or alkoxide ion concentration and k_{corr}, the overall first-order rate constants corrected for reaction of OH$^-$ (cf. Tables I and II). In this treatment we ignore medium effects due to choline chloride or the alcohol, which should be small. For example, for reactions of hydroxide ion with DNF and DNC, 1 M Me_4NCl increases the rate by a factor of less than 50%.[18]

For reactions of DNF formation of the intermediate is much faster than the second decomposition step, so that the two reactions can be followed separately, and the net rate constants for the formation of the intermediate and direct formation of 2,4-dinitrophenoxide ion can be measured either at the isos-

Table I. Reactions of Alkoxides with DNC[a]

[Choline], M	$[HC{\equiv}CCH_2OH]$, M	$[CF_3CH_2OH]$, M	$10^2[RO^-]$, M	10^5k_ψ, s^{-1}	10^5k_{corr},[b] s^{-1}
0.1			1.02	3.83	2.55
0.2			1.86	5.97	4.81
0.3			2.57	8.25	7.19
	0.01		0.204	3.65	2.26
	0.02		0.442	5.19	3.83
	0.03		0.665	7.23	5.90
	0.1		1.87	16.3	15.1
	0.2		3.21	31.1	30.1
	0.3		4.21	40.1	39.3
		0.1	6.19	10.5	9.96
		0.2	8.33	12.0	11.8
		0.3	9.00	13.7	13.6

[a] At 25.0 °C with $[OH^-] + [OR^-] = 0.1$ M; for reaction with OH^-, $k^{OH} = 1.42 \times 10^{-4}$ l. mol^{-1} s^{-1}. The reactions were followed at: choline, 322.5 nm; propargyl alcohol, 321.5 nm; trifluoroethanol, 318.5 nm. [b] $k_{corr} = k_\psi - k^{OH}[OH^-]$.

Table II. Reactions of Alkoxides with DNF[a]

[Choline], M	$[HC{\equiv}C\text{-}CH_2OH]$, M	$[CF_3CH_2OH]$, M	$10^3[RO^-]$, M	10^3k_ψ, s^{-1}	10^3k_{corr},[b] s^{-1}
0.01			0.12	1.88	0.70
0.02			0.24	2.37	1.20
0.03			0.59	3.82	2.69
0.10			1.11	4.76	3.69
0.20			2.00	6.97	6.01
0.30			2.72	10.0	9.13
	0.10		2.16	9.00	8.06
	0.20		3.56	13.2	12.4
	0.30		4.60	19.1	18.5
	0.10[c]		18.7	92.1	82.3
	0.20[c]		32.1	142	134
	0.30[c]		42.1	191	184
		0.02	4.05	6.55	5.84
		0.03	5.15	7.02	6.44
		0.10	7.93	11.0	10.8
		0.20	8.91	10.9	10.8
		0.30	9.25	10.8	10.7

[a] At 25.0 °C with $[OH^-] + [OR^-] = 0.01$ M except where specified; for reaction with OH^-, $k^{OH} = 0.12$ l. mol^{-1} s^{-1}. The reactions were followed at: choline, 358 nm; propargyl alcohol, 321.5 nm; trifluoroethanol, 318.5 nm. [b] $k_{corr} = k_\psi - k^{OH}[OH^-]$. [c] $[OH^-] + [OR^-] = 0.1$ M.

Table III. Reactions of the Ether Intermediates with OH^- [a]

[Choline], M	$[HC{\equiv}CCH_2OH]$, M	$[CF_3CH_2OH]$, M	$10^2[OH^-]$, M[b]	10^5k_ψ, s^{-1}	$10^4k_\psi/[OH^-]$
0.09			9.08	9.42	10.4
0.18			8.30	7.38	8.9
0.27			7.63	6.17	8.1
	0.10		8.13	3.03	3.73
	0.20		6.79	2.51	3.70
	0.30		5.79	2.14	3.70
		0.10	3.81	3.69	9.69
		0.20	1.67	1.49	8.92
		0.30	1.00	0.87	8.70

[a] At 25.0 °C and followed at 358 nm after formation of ethers from DNF. The concentrations of the alcohols are stoichiometric. $[RO^-] + [OH^-] = 0.1$ M. [b] Calculated using stoichiometric $[OH^-]$ and pK_a of the alcohols.

bestic point or at λ_{max} for 2,4-dinitrophenoxide ion (358 nm).

The second-order rate constants for decomposition of the intermediate ethers (V), Scheme I, can be calculated by following formation of 2,4-dinitrophenoxide ion at 358 nm after allowing sufficient time for the substrate (DNF) to disappear. These second-order rate constants are given in Table III.

We also used a competition method to determine k' independently. The concentration of 2,4-dinitrophenoxide ion $[DNP^{10}]$ determined at 358 nm after 10 half-lives for the first step of the reaction of DNF (Scheme I) is a relative measure of the direct reaction with hydroxide (with second-order rate constant, k^{OH}) and can be compared with the concentration after complete reaction $[DNP^\infty]$ (obtained either by waiting or by increasing $[OH^-]$), so that k' and k^{OH} are given by eq 2 for reactions of DNF:

$$\frac{[DNP^{10}]}{([DNP^\infty] - [DNP^{10}])} = \frac{k^{OH}[OH^-]}{k'[RO^-]} \tag{2}$$

(The concentrations of hydroxide and cholinate ion are calculated from the stoichiometric concentrations and pK_a of choline, and [DNP] is proportional to the absorbances, A.) There is satisfactory agreement between these values (Table IV) and those determined directly.

When the total reaction of DNC is followed at 358 nm (λ_{max} for 2,4-dinitrophenoxide ion), we observe a sigmoidal curve

Table IV. Estimation of Rate Constants from Product Composition in Reaction of DNF with Choline Chloride[a]

[Choline], M	A^{10}	A^{∞}	$10^3k'[OR^-]$, s^{-1}
0.10	0.031	0.148	4.0 (3.69)
0.20	0.026	0.196	5.5 (6.01)
0.30	0.210	0.220	8.3 (9.13)

[a] At 25.0 °C with $[OH^-] + [OR^-] = 0.01$ M. A^{10} and A^{∞} are the absorbances at 358 nm after complete formation of the intermediate and complete reaction, respectively. The values in parentheses are determined directly (Table II).

Table V. Estimation of Fitted Second-Order Rate Constants for Overall Reaction of Cholinate Ion with DNC[a]

$[\text{Choline}]_{\text{HCl}}$, M	10^2· [Cholinate]	$10^3k'$, l. mol^{-1} s^{-1}	$10^3k''$, l. mol^{-1} s^{-1}	10^3k^{OH}, l. mol^{-1} s^{-1}
0.1	1.02	2.57 (2.50)	1.11 (1.04)	0.16 (0.14)
0.2	1.86	2.69 (2.59)	0.90 (0.89)	0.19 (0.14)
0.3	2.57	2.68 (2.80)	0.81 (0.81)	0.20 (0.14)

[a] At 25.0 °C with $[OH^-] + [OR^-] = 0.1$ M, calculated using the analog program given in the Appendix. The values in parentheses are from direct measurement under the reaction conditions (Table I and ref 18). The direct determination of k'' was made on intermediate generated from DNF under similar conditions (Table III).

which is typical of a reaction in which an intermediate builds up in concentration. The kinetics can be treated by fitting the data to Scheme I using an analog computer. (The program is given in the Appendix.) The estimated values of k', k'', and k^{OH} are given in Table V. In this table, we compare these fitted values with k', determined at the isosbestic point (Table I), or k'' for decomposition of the intermediate choline ether, determined from reaction with DNF (Table III) or k^{OH}. The agreement is reasonable although the estimated values of k^{OH} are larger than that measured directly, but part of the difference could be due to a positive salt effect of choline chloride. In addition, the computer fit of the rate plot is especially insensitive to small variations in k^{OH}. We could not use the analog computer to treat the kinetics of the reactions of DNF, because formation of the intermediate is considerably faster than its breakdown to products.

In treating these reactions we assume that the formation of the ethers (V), Scheme I, is irreversible because our estimated values of k'' are the same for both DNC and DNF. We exclude attack of chloride ion (from choline chloride) upon V in reactions of DNF because this would lead to formation of relatively unreactive DNC.

Micellar Reactions. Reactions with the hexadecyl surfactant (Ia) are complex because at low surfactant concentrations much of the surfactant can be as monomer, but the critical micelle concentration (cmc) of Ia decreases at high pH because of formation of its zwitterion,[20] so that the micellar structure is pH dependent, and the substrate, DNC, or DNF, will be distributed between the aqueous and micellar phases. Therefore we largely used relatively high surfactant concentrations ($>10^{-3}$ M), so that the bulk of the surfactant will be micellized at high pH with most of the substrate in the micelles.

Under these conditions the first step of reaction with DNF is fast and has to be followed on a stopped-flow spectrophotometer, but we observe an isosbestic point between an intermediate and 2,4-dinitrophenoxide ion at 322.5 nm for both DNC and DNF.

Methods similar to those used in the absence of surfactant were used to extract the rate constants for the various reactions.

When reaction of DNF was followed at 358 nm using a Gilford spectrophotometer we observed good first-order rate constants which were the same as those found for the later part of the reaction of DNC. (This is true only for relatively high surfactant concentrations, and reaction at low surfactant concentrations is considered later.) Therefore these rate constants (Figure 2) are for decomposition to products of an intermediate which we assume is the ether (IV). Neglecting reactions in the aqueous phase and with hydroxide ion in the micellar phase, the rate constants for the formation of Int_m from DNC in the micelles can be estimated for the reactions in Scheme II, using the following relations:

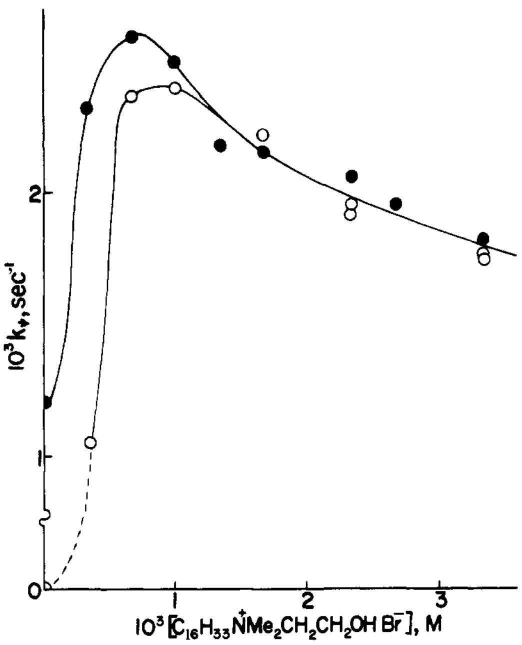
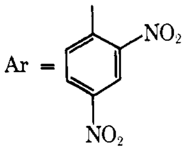


Figure 2. Formation of 2,4-dinitrophenoxide ion from micellized intermediate ether formed from DNC (○) and DNF (●) in 0.01 M at 25.0 °C.

Scheme II

$$(\text{Ia, II}) + \text{DNC}_m \xrightarrow{k_m'} \underset{\text{IV}}{\text{Int}_m} \xrightarrow{k_m''} \text{ArO}^- + (\text{Ia, II})$$



$$[\text{dArO}^-]/\,\text{d}t = k_m''[\text{Int}] \tag{3}$$

$$[\text{DNC}]_t = [\text{DNC}]_o - ([\text{ArO}^-]_t + [\text{Int}]) \tag{4}$$

(The subscript m denotes that reaction is occurring in the micelle, k_m' and k_m'' are first-order rate constants, and o and t are reaction times.)

The concentration of Int is calculated from the initial part of a plot of $[ArO^-]$ against time and the value of k_m'' determined either from the later part of the reaction or from reaction with DNF, and the value of k_m' is then calculated from a plot of ln [DNC] against time (Figure 3).

This approach requires the direct formation of 2,4-dinitrophenoxide ion in the aqueous phase to be much slower than the micellar reaction via the intermediate ether (IV), Scheme II, and in water at 25.0 °C the second-order rate constant $k^{OH} = 1.42 \times 10^{-4}$ l. mol^{-1} s^{-1} for reaction of DNC with hydroxide ion in the absence of surfactant.[18]

The situation is more complex with DNF where reaction in water is relatively rapid even in the absence of surfactant. (At 25.0 °C, $k^{OH} = 0.12$ l. mol^{-1} s^{-1} with hydroxide ion;[18] Scheme

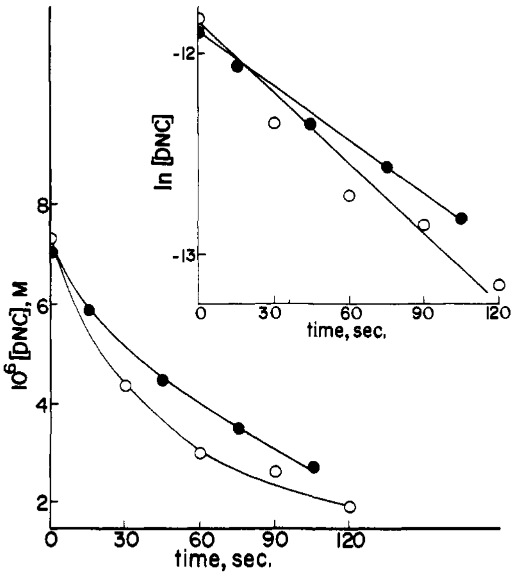


Figure 3. Estimation of rate constants k_m' for reactions of DNC with micellized Ic in 0.01 M OH^- using eq 3 and 4; (●) 1.33×10^{-3} M Ia; (○) 1.67×10^{-3} M Ia.

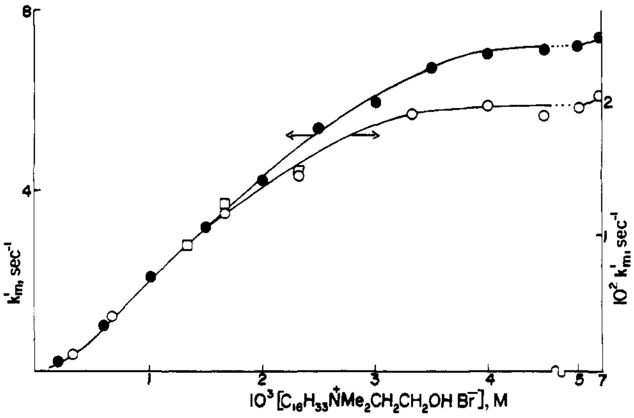
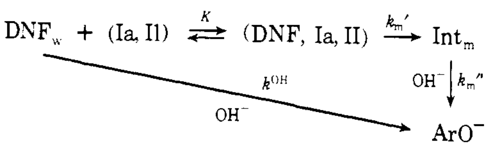


Figure 4. Variation of k_m' with concentration of Ia at 25.0 °C with 0.01 M OH^-; (●) DNF; (○, □) DNC; (●, ○) reactions followed at 322.5 nm, (□) reaction followed at 358 nm, and k_m' calculated using eq 3 and 4.

Scheme III



III.) In formulating Scheme III we assume that reaction via Int_m will be wholly in the micelles, because reaction of DNF with choline in dilute alkali is much slower than these micellar reactions. (The subscripts w and m denote reactions in water and the micelles, respectively.)

At low surfactant concentration there is sufficient DNF in the water for its direct reaction with hydroxide ion to contribute appreciably to the overall reaction. The formation of 2,4-dinitrophenoxide ion is then faster than its formation by decomposition of the intermediate (Int_m), and we cannot readily analyze the rate data.

If reaction is followed at 322.5 nm, the isosbestic point for intermediate and products, the rate constants, k_m', for formation of the intermediate are determined directly, and this procedure was followed for reaction of DNC using a Gilford spectrophotometer. The formation of Int from DNF and micellized II is very much faster than its decomposition to products, but it can be followed at the isosbestic point using a stopped-flow spectrophotometer.

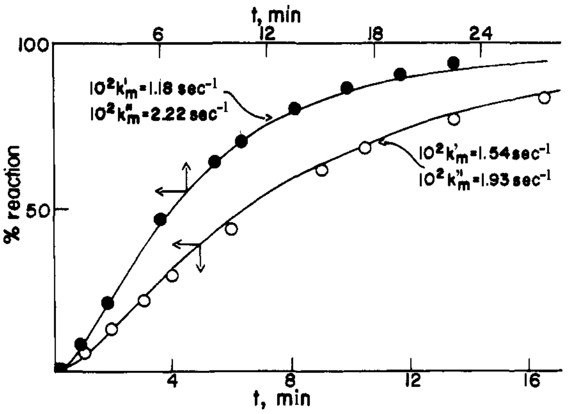


Figure 5. Fitting of formation of 2,4-dinitrophenoxide from DNC in micelles of Ia to values of k_m' and k_m'' in 0.01 M OH^- at 25.0 °C; (●) 1.67×10^{-3} M Ia; (○) 2.33×10^{-3} M Ia. The points are experimental.

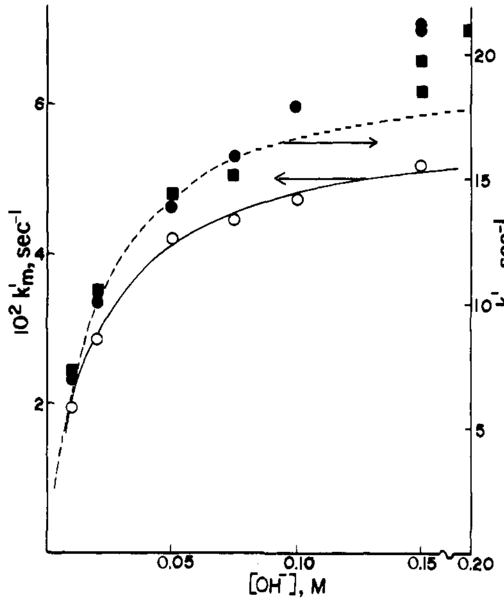


Figure 6. Variation of k_m' with micelles of Ia for reactions of DNF (●, ■, and broken line) and DNC (○ and solid line) with 4×10^{-3} M (● and ○) or 5×10^{-3} M (■) surfactant. The lines are calculated using eq 5 taking $k^- = 20\ s^{-1}$ and $5.8 \times 10^{-2}\ s^{-1}$ for reactions of DNF and DNC, respectively.

The various values of k' for the reactions of DNF and DNC are given in Figure 4.

We also used an analog computer (Appendix) to fit the experimental plots of absorbance at 358 nm against time using the directly determined values of k_m' and k_m''. This fitting was done only with DNC and under conditions such that it should be completely in the micelles. The agreement is shown in Figure 5.

Effect of Hydroxide Ion on the Micellar Reactions of DNF and DNC. Hydroxide ion speeds the formation of ether (IV) by reactions of DNF or DNC with micellized (Ia, II) (Figure 6). These experiments were done with relatively high concentrations of the surfactant so that the substrates are wholly in the micelles and reaction in the aqueous phase is unimportant.

As in other reactions in micelles of Ia, the rate constants tend to level off as the concentration of hydroxide ion increases and the cationic surfactant (Ia) is converted into its zwitterion (II)[2b,c,6]

$$\underset{\text{Ia}}{(n\text{-}C_{16}H_{33}N^+Me_2CH_2CH_2OH)_m} \rightleftarrows \underset{\text{II}}{(n\text{-}C_{16}H_{33}N^+Me_2CH_2CH_2O^-)_m} + H^+$$

If all the substrate is in the micelle, the variation of rate constant with hydroxide ion concentration can be treated using Scheme IV,[2a,b] where D = $C_{16}H_{33}N^+Me_2CH_2CH_2$- and S_m

Scheme IV

$$(DOH)_n + OH^- \overset{K'}{\rightleftarrows} (DOH)_{n-1}DO^-$$

$$(DOH)_{n-1}DO^- + S_m \xrightarrow{k^-} \text{products}$$

is micellized substrate and $K' = K_a/K_w$. The rate constant k^- refers to reaction with DO^- in the micelle. Scheme IV leads to the following equation:

$$k_m' = \frac{k^-[OH^-](K_a/K_w)}{1 + [OH^-](K_a/K_w)} \quad (5)$$

(k_m' is the observed first-order rate constant for formation of the intermediate ether measured at high surfactant concentration.) The assumptions made in this treatment have been discussed, and its application to reactions of phosphate esters gives pK_a = 12.4.[2b]

We estimated independent values of K_a using eq 6

$$\log k_m' = \log [OH^-] + \log k^- + \log \frac{K_a/K_w}{1 + [OH^-]K_a/K_w} \quad (6)$$

and plotting log k_m' against log [OH$^-$] for arbitrarily chosen values of K_a, and obtained linear plots with slopes close to unity for pK_a in the range 12.2-12.5. The best fits, up to 0.1 M hydroxide ion, were obtained with pK_a ~12.3, and the calculated lines (Figure 6) fit the experimental points using values of k^- = 20 and 5.8×10^{-2} s^{-1} for DNF and DNC, respectively, for [OH$^-$] < 0.1 M. The fit is insensitive to small variations in pK_a, but it agrees with the value obtained earlier for phosphate ester hydrolysis,[2b] and for reaction of *p*-nitrobenzoyl phosphate with micellized Ia.[22]

This treatment breaks down at relatively high concentrations of hydroxide ions for several reasons,[2] including: (i) electrolyte effects are neglected and (ii) the treatment ignores the changing micellar structure with conversion of the cationic surfactant into its zwitterion.[20] Our estimation of pK_a depends on the dubious assumption that K_w at the micellar surface is the same as in water, and it ignores the problem of the distribution of ionic reagents between micelle and bulk solvent,[23,24] so that K_a are apparent rather than true dissociation constants.

There is no evidence for additional reactions, e.g., elimination (Experimental Section) at high concentration of hydroxide ion,[25] and in 0.01-0.3 M OH$^-$ and 4×10^{-3} M Ia, DNF is converted wholly into an intermediate and then to 2,4-dinitrophenoxide ion.

The hydroxyethyl group in micellized Ia might give electrophilic assistance to the loss of fluoride ion from DNF, but the similarities in the catalysis of the reactions of DNF and DNC suggest that this assistance is unimportant.

Most of our experiments on the decomposition of the ether (IV) in micellized Ia were in dilute hydroxide ion. This reaction is mildly speeded by increasing the hydroxide ion concentration. In 0.12 M OH$^-$ with 4×10^{-3} M Ia, $10^3k_m''$ = 6.75 and 7.25 s^{-1} for decomposition of IV generated from DNF and DNC, respectively, whereas in 0.01 M OH$^-$ $10^3k_m''$ ~ 2 s^{-1} (Figure 2). Attack of external OH$^-$ upon the micellized intermediate ether (IV) will become more difficult as the cationic micelles of Ia are converted into zwitterionic micelles with increasing pH.

Table VI. Reactivities of Alkoxide toward DNC and DNF[a]

Nucleophile	pK_a[b]	DNC	DNF
OH^-		1.4×10^{-4} (1)[c]	0.12 (1)[c]
$Me_3N^+CH_2CH_2O^-$	13.9	2.7×10^{-3} (19)	3.2 (27)
$HC{\equiv}CCH_2O^-$	13.6	9×10^{-3} (63)	17.1 (132)
$CF_3CH_2O^-$	12.4	1.5×10^{-3} (11)	1.2 (10)

[a] Values of second-order rate constants at 25.0 °C; the values in parentheses are relative to hydroxide ion. [b] Of the alcohol. [c] Reference 18.

Discussion

Reactivities in the Nonmicellar Reactions. Cholinate zwitterion and the alkoxide ions of 2,2,2-trifluoroethanol and propargyl alcohol are considerably more nucleophilic toward DNC and DNF relative to OH$^-$ than would be expected in terms of their basicities (Tables I, II, and VI), as for nucleophilic addition to carbonyl carbon[17] and to triarylmethyl carbocations,[6] as well as for attack on a phosphoryl group.[2a]

This apparent low nucleophilicity of lyate ions could be ascribed to their strong solvation which should reduce nucleophilicity more than basicity[26] and bulky substituents could reduce hydration of the alkoxide moiety, but should also hinder attack on the substrate.

In problems of this type it is difficult to decide whether effects are related to changes in the initial or transition states, but for these aromatic substitutions we believe that transition state effects cannot be ignored because the 2,4-dinitrophenyl ethers are unexpectedly reactive toward hydroxide ion (Table III). They are less reactive than DNF, but more reactive than DNC (Table VII). The reactivities of various alkoxy and aryloxy ethers toward OH$^-$ or OMe$^-$ have been compared with those of the corresponding halides.[15,28] In aqueous dioxane the sequence of reactivities is F ≫ MeO > Cl > OEt ~ OPh, with small differences between the reactivities of the chloride and the ethers, and ethers are more reactive for reactions of 2,4,6-trinitro derivatives.[28] However, with methoxide ion in methanol the chlorides are considerably more reactive than the ethers so that these relative reactivities depend markedly upon the solvent and the nucleophile.[15,28] However, the reactivity differences between DNC and some of our ethers (Table VII) are larger than those observed earlier for dinitrophenyl methoxy and ethoxy ethers.[15,28] (Bunnett has pointed out that rates of aromatic nucleophilic substitution are relatively insensitive to the nature of the leaving group when addition is the rate-limiting step of reaction,[15] although leaving group effects are large for nucleophilic attack at acyl groups.)

There are similarities between the transition states for reactions of hydroxide ion with the ethers and alkoxide attack upon the halobenzenes, and in Scheme V we show the tetrahedral intermediates (VII and VIII) for these reactions. (The structures of the intermediates should be similar to those of the transition states for overall reaction.)

This comparison suggests that the intermediates for both these reactions (and their related transition states) are stabilized by similar interactions. For example, interactions involving the delocalized forming negative charge should stabilize the transition states for both reactions, by changing the angle strain at the carbon atom at the reaction center, or because of favorable ion-ion or ion-dipole interactions.[29] However, the substituent effects are larger for attack of the alkoxides upon DNC or DNF (Tables I, II, and VI) than for reaction of the 2,4-dinitrophenyl ethers with hydroxide ion (Tables III and VII), and solvation effects should be completely different for these reactions.

Table VII. Reactivities of 2,4-Dinitrophenyl Compounds toward Hydroxide Ion

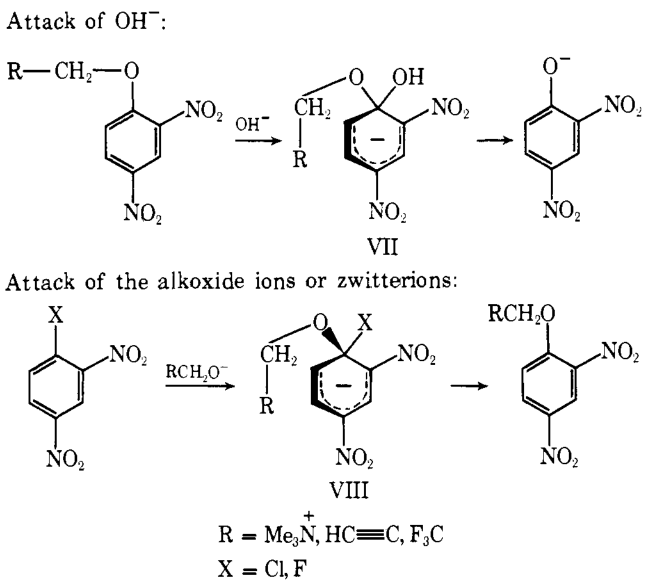
Leaving group	$-Cl$	$-F$	$-OCH_2CF_3$	$-OCH_2C{\equiv}CH$	$-OCH_2CH_2N^+Me$
10^4k^{OH}, l. mol^{-1} s^{-1}	1.42	1200	9.1	3.7	9.1
Rel rates	1	850	6.4	2.6	6.4

Table VIII. Reactivities of 2,4-Dinitrophenyl Compounds toward Hydroxide Ion in Micelles[a]

Leaving group	$-OCH_2CH_2N^+Me_3$	$-F$	$-Cl$	$-OCH_2CH_2N^+Me_2C_{16}H_{33}$
Medium	H_2O	H_2O-CTABr[c]	H_2O-CTABr[c]	H_2O-Ia[d]
10^3k_ψ[b]	0.0091	67	0.116	2.4[e]

[a] In 0.01 M OH^- unless specified. [b] Observed first-order rate constants, s^{-1}. [c] 0.02–0.03 M surfactant. [d] 10^{-3} M surfactant. [e] In 0.12 M OH^-, $k_\psi \sim 7 \times 10^{-3}$ s^{-1}.

Scheme V



All our experiments were in water whose structure should encourage the intermediates to take up the conformations shown in Scheme V, and there is extensive evidence for interactions between quaternary ammonium ions and aromatic groups.[31,32]

Coulombic interactions between hydroxide ion and the cationic choline ether (V, R = $Me_3N^+CH_2CH_2$–) might assist reaction, but there is evidence against this hypothesis based on reactions of carboxylic esters.[33]

The higher reactivities of fluoro- over chlorobenzenes are predicted from electronegativities,[15,16] but these and other results show that other effects are of great importance. For many carboxyl reactions the nucleophilicites of oxyanions are nicely correlated with basicity, except for small high charge density ions such as hydroxide or methoxide[17,34] (cf. ref 27), but this correlation fails for nucleophilic aromatic substitution, where the phenoxide ion is more reactive than hydroxide ion in aqueous solvents. For reaction with DNC in aqueous dioxane phenoxide is approximately tenfold more reactive than hydroxide ion,[35] and with DNF in water the factor is approximately five.[36] However, phenoxide is less reactive than methoxide ion for reaction with DNC in methanol,[28] probably because anionic solvation is important.[26] (In water phenoxide ions are very reactive toward carbocations.[37])

The sequences of nucleophilicities of the alkoxides and the reactivities of the corresponding ethers are different from that of the pK_a of the alcohols (Tables VI and VII). Some differences are to be expected because solvation of a nucleophilic anion should reduce nucleophilicity more than basicity, but should have no marked effect on formation of an addition complex in aromatic nucleophilic substitution at an ether. The alkoxide ion of propargyl alcohol is a much better nucleophile than expected in terms of basicity, perhaps because of the polarizability of the linear acetylenic moiety, and the higher reactivity of the choline ether (Table VII) could be ascribed to interactions between the aromatic residue and the quaternary ammonium ion.

These complexities suggest that no nucleophilicity scale based on a single factor such as pK_a, solvation, or Hardness and Softness will be completely valid (cf. ref 17, 27, 34, and 38).

Reactions with Functional Micelles of Ia. Interactions similar to those involving the trimethylammonium group of choline should also be important in reactions with micelles of the hexadecyl surfactant (Ia) because aromatic compounds interact strongly with cationic micelles.[32]

It is difficult to compare directly rates of reactions in the presence and absence of micelles because of the generally unknown distribution of a hydrophilic reagent, e.g., hydroxide ion, between water and the micelles,[23,24] and the problem is even more complex with functional micelles where the reagent group is chemically incorporated into the surfactant.

Decomposition of Micellized Ether (IV). The simplest reactivity comparisons are those for the reactions of hydroxide ion with the choline ether (V) in the absence of micelles and with IV in micelles of Ia and with DNF and DNC in the nonfunctional micelle, CTABr. (There is no net chemical change in a reaction of IV with the hydroxyethyl head group of Ia.) There is an element of arbitrariness in these comparisons, because of necessity we use different micelles, but we compare the maximum first-order rate constants in the presence of the surfactant using 0.01 M hydroxide ion (Table VIII), where most of the hydroxyethyl surfactant (Ia) will be present as cation rather than zwitterion.

The ether (IV) in micelles of Ia is less reactive than DNF in CTABr, but considerably more reactive than DNC in CTABr,[18,23] as for reaction of the choline ether in water (Tables VII and VIII), although the differences are greater for reactions in the micelle. The micellar catalysis of hydrolysis of the ether (IV), relative to hydrolysis of the choline ether (V) in water, is also large.

The reactivity differences between DNF, DNC, and the hexadecyl ether (IV) should not be related to the partitioning between the aqueous and micellar phases because at relatively high surfactant concentrations, the bulk of the substrate should be in the micelles, but the hydrophobic hexadecyl group of the ether (IV) should draw the reaction center more deeply into the micellar surface and thereby assist reaction (cf. ref 10–12, 39).

Reactivities in Micellar Reactions of DNF and DNC. It is difficult to compare the rates of nucleophilic attack upon DNF and DNC by hydroxide ion in the presence of CTABr and by the alkoxide moiety in the zwitterionic surfactant (II) because one reaction is second order and the other first, and there is an acid–base equilibrium between Ia and II.

Table IX. Micellar Rate Enhancements of Reactions of DNC and DNF[a]

Surfactant	DNC	DNF
n-$C_{16}H_{33}N^{+}Me_2CH_2$-$CH_2OH\ Br^{-}$	1.4×10^4 (0.005)	6×10^3 (0.005)
CTABr + OH^{-} [b]	82 (0.02)	56 (0.025)

[a] At 25.0 °C in 0.01 M, OH^- and at the optimum surfactant molarities (in parentheses), relative to the reactions in water. [b] Reference 17.

However, nucleophilic attack upon DNF or DNC by functional micelles of Ia is very much faster than that of hydroxide ion in the nonfunctional surfactant, CTABr, in 0.01 M OH^- (Table IX), and the differences would be even larger if we allowed for the incomplete ionization of Ia (in 0.01 M NaOH only ca. 30% of Ia is present as the reactive zwitterion). Another approach is to treat reactions in micelles of Ia as if they were intramolecular and to compare the second-order rate constants (i.e., the first-order rate constants in 1 M OH^-) with the first-order rate constants for reaction of DNF and DNC in the functional micelle (cf. ref 34 and 40).

The values of k^- for reactions with the zwitterion (II) in micelles of Ia (Scheme IV) are 5.8×10^{-2} s^{-1} for DNC and 20 s^{-1} for DNF (Figure 6), so that the magnitudes of these first-order rate constants are the same as those of the (hypothetical) first-order rates in 410 M OH^- for DNC and 170 M OH^- for DNF in water, thus the rate enhancements by functional micelles of Ia are similar to those often found in intramolecular reactions involving reactions at acyl groups.[34,40]

These rate enhancements are much larger than those for reactions of phosphate esters and carbocations,[2,6] and indeed for many reactions with functional micelles in water.[10-12] (Very large rate enhancements have been found with functional surfactants derived from hydroxamic acids.[41])

Several factors can be involved in catalysis by both nonfunctional and functional micelles of reactions of nucleophiles or bases.[10-12]

(i) A hydroxide or alkoxide ion should be less solvated at the micellar surface than in the more polar aqueous bulk solution (cf. ref 42).

(ii) The anionic transition state, with its delocalized charge should interact more favorably than the smaller nucleophilic anion with cationic head groups.

(iii) Incorporation of the reactants at the micellar surface will increase their concentrations over those in bulk solution and will decrease the entropy loss occasioned by bringing the reactants together. It may not be profitable to attempt to separate these two effects, but they should be more important with functional than nonfunctional micelles. For examples in intramolecular reactions, see ref 34, 40, and 43, and in an intermolecular micellar catalyzed reaction, see ref 44.

The importance of (ii), interaction of a transition state with cationic head groups,[10-12,32b] is important in these aromatic nucleophilic substitutions because the rate enhancements by both functional and nonfunctional micelles are much larger than those found in nucleophilic attack on phosphoryl groups,[2] where the negative charge is located on phosphoryl oxygen atoms. The maximum rate enhancements of the reaction of p-nitrophenyl diphenyl phosphate in sodium hydroxide are by factors of 11 and 300 in micellized CTABr and Ia, respectively,[2b] as compared with those of $6-14 \times 10^3$ (Table IX).

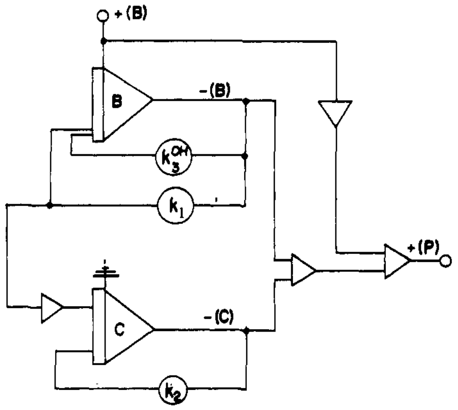
The micellar rate enhancements of these reactions of dinitrohalobenzenes are larger than those found for reactions of carboxylic esters with micelles of functional surfactants containing an ethanolamine head group,[3-5] although differences in the surfactants and reaction conditions complicate comparison.

Acknowledgments. Support of this work by the National Science Foundation and the Arthritis and Metabolic Diseases Institute of the U.S. Public Health Service is gratefully acknowledged.

Appendix

Computer program for fitting to Schemes I-III is given in Scheme VI.

Scheme VI



For reactions in the absence of micelles, the first-order rate constants are: $k_1 = k'[OR^-]$, $k_2 = k''[OH^-]$, $k_3^{OH} = k^{OH}[OH^-]$ (Scheme I). For reactions in the presence of micelles of Ic: $k_1 = k_m'$, $k_2 = k_m''$, $k_3^{OH} = 0$ (Schemes II and III), with B = substrate, C = intermediate ether, and P = 2,4-dinitrophenoxide ion.

References and Notes

(1) On leave from the Faculty of Physical and Mathematical Sciences, University of Chile, Santiago, Chile, under the University of Chile–University of California Cooperative Program supported by the Ford Foundation.

(2) (a) C. A Bunton, L. Robinson, and M. Stam, *J. Am. Chem. Soc.*, **92**, 7393 (1970); (b) C. A. Bunton and L. G. Ionescu, *ibid.*, **95**, 2912 (1973); (c) C. A. Bunton and S. Diaz, *J. Org. Chem.*, **41**, 33 (1976).

(3) M. Chevion, J. Katzhendler, and S. Sarel, *Isr. J. Chem.*, **10**, 975 (1972); G. Meyer, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, **276**, 1599 (1973).

(4) K. Martinek, A. V. Levashov, and I. V. Berezin, *Tetrahedron Lett.*, 1275 (1975).

(5) G. Meyer, *Tetrahedron Lett.*, 4581 (1972); V. Gani, C. Lapinte, and P. Viout, *ibid.*, 4435 (1973).

(6) C. A. Bunton and C. H. Paik, *J. Org. Chem.*, **41**, 40 (1976).

(7) R. M. C. Dawson, D. C. Elliott, and K. M. Jones, "Data for Biochemical Research", Clarendon Press, Oxford, 1959.

(8) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Chemistry", Benjamin, New York, N.Y., 1966, Chapter 2; (b) E. C. Webb and B. Zerner, *Biochemistry*, **8**, 2026 (1969).

(9) For discussions of micellar catalysis, see ref 10–12.

(10) E. H. Cordes and R. B. Dunlap, *Acc. Chem. Res.*, **2**, 329 (1969); E. H. Cordes and C. Gitler, *Prog. Bioorg. Chem.*, **2**, 1 (1973).

(11) E. J. Fendler and J. H. Fendler, *Adv. Phys. Org. Chem.*, **8**, 271 (1970).

(12) C. A. Bunton, *Prog. Solid State Chem.*, **8**, 239 (1973).

(13) C. A. Bunton and M. McAneny, *J. Org. Chem.*, 41, 36 (1976).

(14) For discussions of aromatic nucleophilic substitution, see ref 15 and 16.

(15) J. F. Bunnett, *Q. Rev., Chem. Soc.*, **12**, 1 (1958).

(16) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, New York, N.Y., 1968.

(17) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **84**, 2910 (1962); T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, **1**, 7 (1962).

(18) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **90**, 5965 (1968); *J. Org. Chem.*, **34**, 780 (1969).

(19) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **81**, 1050 (1959); **82**, 795 (1960).

(20) The cmc of Ic is 8×10^{-4} M in water and approximately 3.5×10^{-5} M in 0.1 M NaOH.[6] The cmc of the corresponding chloride is 1.2×10^{-3} M in water.[21]

(21) P. Mukerjee and K. J. Mysels, "Critical Micelle Concentrations of Aqueous Surfactant Systems", National Bureau of Standards, Washington, D.C., 1971.

(22) M. McAneny, unpublished results.

(23) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **90**, 5972 (1968).

(24) C. A. Bunton and B. Wolfe, *J. Am. Chem. Soc.*, **95**, 3742 (1973).

(25) The possibility of an elimination pathway was pointed out to us by Professor Liotta.

(26) Ritchie has suggested that variations of nucleophilicity as measured by the N^+ scale toward carbocations can be explained in terms of solvation of the nucleophile.[27]

(27) C. D. Ritchie, *Acc. Chem. Res.*, **5**, 348 (1972); *J. Am. Chem. Soc.*, **97**, 1170 (1975).

(28) Reference 16, Chapter 5.

(29) For an example of intermolecular interactions between aniline and DNC, see ref 30.

(30) S. D. Ross and I. Kuntz, *J. Am. Chem. Soc.*, **76**, 3000 (1954).

(31) E. M. Arnett, M. Ho, and L. L. Schaleger, *J. Am. Chem. Soc.*, **92**, 7039 (1970); S. J. Rehfeld, *ibid.*, **95**, 4489 (1973); J. W. Larsen and L. J. Magid, *ibid.*, **96**, 5774 (1974); E. F. J. Duynstee and E. Grunwald, *Tetrahedron*, **21**, 2401 (1965); J. Gordon and R. L. Thorne, *J. Phys. Chem.*, **73**, 3643, 3652 (1969); J. Gordon, J. C. Robertson, and R. L. Thorne, *ibid.*, **74**, 957 (1970).

(32) (a) J. G. Eriksson and G. Gillberg, *Acta Chem. Scand.*, **20**, 2019 (1966); (b) C. A. Bunton, M. J. Minch, J. Hidalgo, and L. Sepulveda, *J. Am. Chem. Soc.*, **95**, 3262 (1973); (c) J. W. Larsen and L. Magid, *J. Phys. Chem.*, **78**, 834 (1974); (d) C. A. Bunton and M. J. Minch, *ibid.*, **78**, 1490 (1974); (e) J. H. Fendler, E. J. Fendler, G. A. Infante, L. K. Patterson, and P.-S. Sheih, *J. Am. Chem. Soc.*, **97**, 89 (1975).

(33) B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.*, **91**, 2982 (1969).

(34) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms", Benjamin, New York, N.Y., 1966, Chapter 1.

(35) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **76**, 3011 (1954).

(36) H. Chaimovich, A. Blanco, L. Chayet, L. M. Costa, P. M. Monteiro, C. A. Bunton, and C. Paik, *Tetrahedron*, **31**, 1139 (1975).

(37) C. A. Bunton and S. K. Huang, *J. Am. Chem. Soc.*, **95**, 2701 (1973).

(38) R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967).

(39) J. Baumrucker, M. Calzadilla, M. Centeno, G. Lehrmann, M. Urdaneta, P. Lindquist, D. Dunham, M. Price, B. Sears, and E. H. Cordes, *J. Am. Chem. Soc.*, **94**, 8164 (1972).

(40) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, Chapter 1.

(41) I. Tabushi, Y. Kuroda, and S. Kita, *Tetrahedron Lett.*, 643 (1974).

(42) P. Mukerjee and A. Ray, *J. Phys. Chem.*, **70**, 2144 (1966); M. Grätzel and J. K. Thomas, *J. Am. Chem. Soc.*, **95**, 6885 (1973).

(43) T. C. Bruice and W. C. Bradbury, *J. Am. Chem. Soc.*, **87**, 4846 (1965); **90**, 3808 (1968); M. I. Page, *Chem. Soc. Rev.*, **2**, 295 (1973).

(44) C. A. Bunton and R. J. Rubin, *Tetrahedron Lett.*, 55 (1975); *J. Am. Chem. Soc.*, **98**, 4236 (1976).

Alkylation of Pyridine 1-Oxides and Related Compounds with Activated Acetylenes. A Novel Molecular Rearrangement of Heteroaromatic *N*-Oxides[1]

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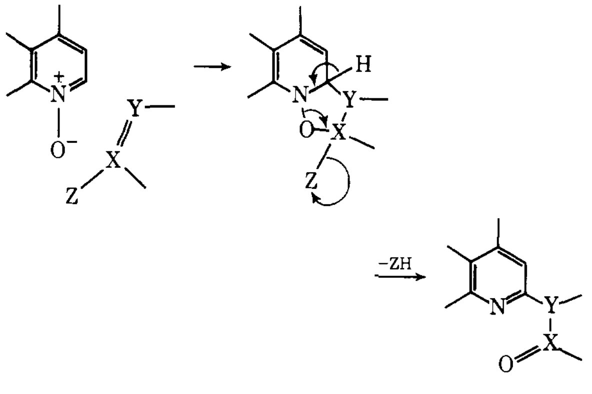
Abstract: The reaction of pyridine 1-oxide with phenylcyanoacetylene gives the 3-alkylated derivative **5** as the main product together with minor amounts of the 2-alkylated product **3**, the ylide **4**, and the divinyl ether **6**. With substituted pyridine 1-oxides and with quinoline 1-oxide the products of 3-alkylation are also formed unless the 3 and 5 positions are blocked. Isoquinoline 1-oxide gives only the corresponding ylide **18**. The structures of the products were confirmed by spectroscopic methods and by the synthesis of authentic samples. Reaction of α-cyanophenacylphenyliodonium ylide with pyridines, quinoline, and isoquinoline gives the *N*-ylides only, but decomposition of benzoylcyanodiazomethane in pyridine gives both the ylide **4** (main product) and **5** via benzoylcyanocarbene. The mechanism of formation of the products is discussed and it is felt that the 3-alkylated products arise from the initial 1,2-dihydro adduct **27** by a $[{}_\sigma2_s + {}_\pi2_a + {}_\pi4_s]$ rearrangement to **29**, followed by regiospecific cyclopropane ring opening to derivatives of **5**.

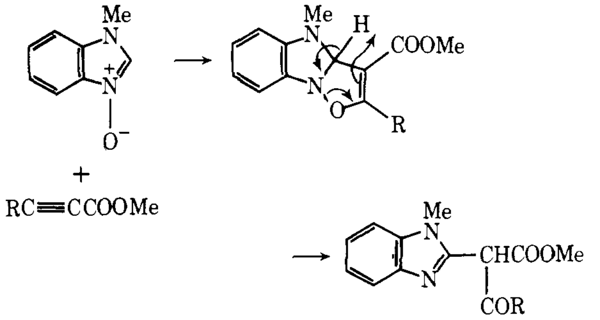
The direct α acylamination of heteroaromatic *N*-oxides using imidoyl chlorides or nitrilium salts[2] probably involves nucleophilic addition of the oxide group to the imidoyl carbon, followed by (or in the case of nitrilium salts perhaps concerted with) intramolecular nucleophilic attack of the nitrogen upon the α position of the pyridine ring, and then aromatization. A related reaction is that of *N*-oxides with isocyanates[3] and the reaction of pyridine 1-oxide with perfluoropropene to give 2-(1,2,2,2-tetrafluoroethyl)pyridine and carbonyl fluoride.[4]

This led us to consider the possibility of a general reaction, as shown in eq 1. In principle, Z could be either a good anionic leaving group or another π bond to Y. The present paper describes an example of the latter situation in which the reactions of some six-membered heteroaromatic *N*-oxides were treated with phenylcyanoacetylene (**1**).



(1)

Nitrones undergo 1,3-dipolar cycloaddition with suitable acetylenes[5] and this reaction has been applied successfully to imidazole 3-oxides (eq 2).[6]



(2)

Results

The reaction of pyridine 1-oxide (**2**) with **1** gave three 1:1 adducts and one 1:2 adduct (eq 3). One of the 1:1 adducts, α-cyanophenacylpyridinium ylide (**4**), was a very minor (0.4%) product at best. Its spectral properties were consistent with the

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