49(2), 59 (1940), or Z. P. Chirikova, L. A. Galama, Z. N. Komova, and L. C. Kofman, *Zh. Fiz. Khim.*, **40**, 918 (1966).
(27) There is some evidence which suggests the existence of an open-chain/cyclic dimer equilibrium: L. J. Bellamy, R. F. Lake, and R. J. Pace, *Spectrochim. Acta*, **19**, 443 (1963); M. A. Goldman and M. T. Emerson, *J. Phys. Chem.*, 77, 2295 (1973).
(28) J. C. Petersen, *J. Phys. Chem.*, **75**, 1129 (1971).
(29) For a review, see: (a) S. D. Christian, A. A. Taha, and B. W. Gast, *Q. Rev. Chem. Soc.*, **24**, 20 (1970); (b) M. Maclean Davis, *Natl. Bur. Stand. (U.S.) Monogr.*, **No. 105** (1968).
(30) (a) S. D. Christian, J. E. Affsprung, and S. A. Taylor, *J. Phys. Chem.*, **67**, 187 (1963); (b) L. Barcza, A. Buvari, and M. Vajda, *Z. Phys. Chem. (Frankfurt am Main)*, **102**, 35 (1976); (c) Y. Fujii and M. Tanaka, *J. Chem. Soc., Faraday Trans. 1*, **73**, 788 (1977); (d) Y. Fujii, K. Sobve, and M. Tanaka, *Ibid.*, 1467 (1978).
(31) O. Bensaude, M. Chevrier, and J. E. Dubois, *Tetrahedron Lett.*, 2221 (1978).
(32) For a review, see: (a) J. Elguero, C. Marzin, A. R. Katrizky, and P. Linda, *Adv. Heterocycl. Chem., Suppl. No. 1* (1976); (b) P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977).
(33) In model I, the "*a*" hydration constant is defined by the activity of water at which $K_{app} = 2K_T$. The activity coefficients of water in the acetonitrile/water system are found in: (a) V. de Landsberg, *Bull. Soc. Chim. Belg.*, **49**(2), 59 (1940); (b) Z. P. Chirikova, L. A. Galama, Z. N. Komova, and L. C. Kofman, *Zh. Fiz. Khim.*, **40**, 918 (1966). The "*b*" hydration constant used is obtained from the kinetic experiments in the propylene carbonate–water system, because the interesting point to establish is to account for experimental data rather than to get precise hydration constant values.
(34) R. M. Moravie, J. Corset, M. L. Josien, G. Nee, G. Lessy, and B. Tchoubar, *Tetrahedron*, **32**, 693 (1976).
(35) H. H. Limbach, *Ber. Bunsenges. Phys. Chem.*, **81**, 1112 (1977).
(36) For a review, see: (a) M. D. Joesten and L. J. Schaad, in "Hydrogen Bonding", Marcel Dekker, New York, 1974, pp 185–190; (b) P. Schuster, P. Wolschann, and K. Tortschanoff, in *Mol. Biol., Biochem. Biophys.*, **24**, 151–154 (1977).
(37) (a) G. G. Hammes and H. O. Spivey, *J. Am. Chem. Soc.*, **88**, 1621 (1966); (b) G. G. Hammes and A. C. Park, *Ibid.*, **91**, 956 (1969); (c) G. G. Hammes and P. J. Lillford, *J. Am. Chem. Soc.*, **92**, 7578 (1970).
(38) Infrared evidence of water/2-hydroxypyridine association can be detected; O. Bensaude, J. Guillerez, and M. Chevrier, manuscript in preparation.
(39) (a) T. Yasunaga, S. Nishikawa, and N. Tatsumoto, *Bull. Chem. Soc. Jpn.*, **44**, 2308 (1971); (b) P. Hemmes, K. Sherr, A. Jarmas, and E. U. Monse, *Adv. Mol. Relaxation Interact. Processes*, **12**, 333 (1978).
(40) In inert solvent, the base pairing is rate-encounter controlled. See: G. C. Hammes and A. C. Park, *J. Am. Chem. Soc.*, **90**, 4151 (1968), and R. Hopman, *Ber. Bunsenges. Phys. Chem.*, 77, 52 (1973). For a discussion on the base-pairing kinetics in aqueous solutions, see: M. Eigen, in *Naturwissenschaften*, **58**, 494–498 (1971); D. Craig, D. Crothers, and P. Doty, *J. Mol. Biol.*, **62**, 383 (1971); D. Pörschke and M. Eigen, *ibid.*, **62**, 361 (1971).
(41) For a review, see: R. P. Bell, in "The Proton in Chemistry", 2nd ed., Cornell University Press, Ithaca, N.Y., 1973, Chapter 8.
(42) (a) A. M. Kjaer, P. E. Sorensen, and J. Ulstrup, *J. Chem. Soc., Perkin Trans. 2*, 51 (1978); (b) C. S. Chin and H. H. Huang, *ibid.*, 474 (1978).
(43) T. M. Lowry, *J. Chem. Soc.*, 2554 (1927).
(44) J. Hine, *J. Am. Chem. Soc.*, **94**, 5766 (1972).

Micellar Catalysis and Reactant Incorporation in Dephosphorylation and Nucleophilic Substitution

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Abstract: The rate–surfactant profiles for the dephosphorylation of *p*-nitrophenyl diphenyl phosphate by phenoxide and *p*-cresyl oxide ions and the reaction of phenoxide ion with 2,4-dinitrofluorobenzene (DNF) in micelles of cetyltrimethylammonium bromide (CTABr) can be treated quantitatively in terms of the distribution of both reactants between the aqueous and micellar pseudophases. Distributions were measured directly under the reaction conditions. A similar treatment can be applied to the reaction of aniline with DNF catalyzed by micelles of CTABr or sodium lauryl sulfate (NaLS). For reactions of aryl oxide ions the rate enhancements of up to 4×10^3-fold can be explained almost completely in terms of increased reactant concentrations in the micellar pseudophase, but for the reaction of aniline this rate-enhancing effect is opposed by a negative "solvent" effect of the micelles stemming from the low polarity of their surface.

The extent of micellar catalysis of bimolecular reactions depends upon the incorporation of both reactants into the micelle and the rate constant in the micellar pseudophase.[4] The dependence of the overall rate constant upon surfactant concentration can, in principle, be treated quantitatively in terms of the distribution of the substrate between water and the micellar pseudophase for both spontaneous unimolecular reactions and for micellar-inhibited bimolecular reactions.[8,9] But for micellar-catalyzed bimolecular reactions observed rate constants generally go through maxima with increasing surfactant concentration and the observed second-order rate constants at or near the maxima are usually dependent on reactant concentration.[5-7]

These maxima arise because increasing surfactant concentrations increase the concentration of micelles and therefore the amounts of reactants in the micellar pseudophase. But increasing the concentration of micellized surfactant means that the reactants are distributed over a larger amount of micelles which leads to a "dilution" of reactants in the micellar pseudophase and a decrease in the observed rate constants. This explanation is consistent with the observation that added electrolytes typically reduce micellar catalysis of bimolecular reactions involving ion attack upon a substrate by competing with that ion for the micelle.[10]

These problems have been treated in several ways. Romsted has developed equations which relate the concentrations of both reagents in the micelle to those in water by treating micellar incorporation of hydrophilic ions in terms of a simple ion exchange process and his equations empirically fit the rate constant–surfactant profiles which are typical of bimolecular micellar-catalyzed reactions.[11]

Another approach, which has been applied to reactions involving hydrogen ions, is to use a specific ion electrode to estimate the amount of reactive ion in the water, and therefore by difference in the micelle, and to show that when the substrate is largely in the micelle the calculated second-order rate constants for reaction occurring in the micellar pseudophase are independent of surfactant or total hydrogen ion concentration.[12] A similar approach has been applied to reactions of carbocations with anionic nucleophiles, except that here the amount of micellar-bound anion was estimated indirectly.[13]

A number of workers have analyzed micellar catalysis of reactions of substrates with hydrophobic reagents by calculating, directly or indirectly, the amounts of each reactant in the micellar pseudophase, assuming that one reactant does not affect incorporation of the other.[11,13-19]

This method can be applied directly to reactions of nonionic nucleophiles,[13,15,18] and to deacylation by thiolate ions,[17] be-

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Table I. Reaction of *p*-Nitrophenyl Diphenyl Phosphate in the Presence of Thiophenoxide Ion[a]

10^3[CTABr], M	10^3[PhS⁻], M			
	0	0.6	1.5	3.0
	0.07		0.12[b]	
1.0	1.77	1.21		
2.0	1.70	1.01	0.95	1.07
2.5			1.09	1.01
3.0	1.39	0.87	0.83	1.01
3.5			0.97	1.11
4.0	1.19		0.90	1.05
5.0			0.84	1.03
6.0	1.01		0.87	0.97
8.0			0.79	0.83
10.0	0.70		0.76	0.72

[a] Values of $10^3 k_\Psi$, s^{-1}, at pH 9.5 in 0.05 M borate at 25.0 °C with 10^{-5} M substrate. [b] Obtained by extrapolation from reactions in dioxane–H_2O.

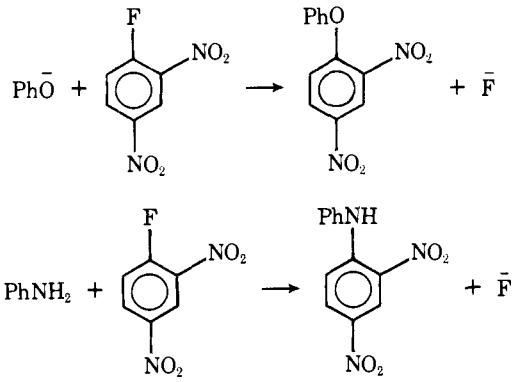
cause the thiol is fully ionized under the reaction conditions. But there is a problem with anionic nucleophiles which are generated by dissociation of weak acids, because the micelles almost certainly affect the acid dissociation, and it may be difficult to measure directly the extent of incorporation of the reactive anion in the micelle. For example, anions of imidazoles are excellent nucleophiles, but their incorporation into cationic micelles has not been measured directly.[14,19] Instead it has been estimated from the binding constant of the nonionic imidazole and the micellar effect upon the apparent pK_a of the imidazole and the pH of the solution. But this indirect method involves assumptions about the significance of "pH" at the micellar surface and is suspect because the measurements lead to the improbable conclusion that the extent of binding of, for example, the benzimidazole anion to a cationic micelle *decreases* at high surfactant concentration.[14,19,20]

One aim of our work was to measure the concentration of reactive anion directly under the reaction conditions. We used phenoxide ions as nucleophiles and were able to measure directly their binding to cationic micelles under conditions in which the phenol was only partially ionized. The rate and binding studies were made over a range of pH and nucleophile concentration, so that they provide a stringent test of the kinetic model. In most experiments to date only the surfactant concentration has been varied and the reactant concentrations and pH have been kept constant.

Most of the work was on dephosphorylation of *p*-nitrophenyl diphenyl phosphate (PNPDPP):

$$ArO^- + p\text{-}O_2NC_6H_4OPO(OPh)_2 \rightarrow ArOPO(OPh)_2 + p\text{-}O_2NC_6H_4O^-$$

but some experiments were done on nucleophilic aromatic substitution of 2,4-dinitrofluorobenzene (DNF) (cf. ref 15, 22, and 23).



Most models of micellar catalysis treat the micelle as a submicroscopic reaction medium, but a micelle is not homogeneous; for example, its interior is probably hydrocarbon-like, and its surface is hydrophilic, and for an ionic micelle is partially saturated by counterions.[24,25] However, micellar-bound polar solutes appear to residue largely in the Stern layer at the micellar surface, and reactions of polar solutes probably occur in this region.[5-7] In estimating reactant concentrations in the micellar pseudophase one has to make assumptions about the volume element for the reaction. We can, for example, assume that the reactants are localized within the Stern layer,[12,13] or estimate concentrations in terms of the total volume of the micelle.[14-17]

Most of our experiments were in solutions of cetyltrimethylammonium bromide (CTABr), but for the aniline reactions we also used sodium lauryl sulfate (NaLS). Recently Piskiewicz has suggested a different treatment of micellar catalysis based on the Hill equation which is used to treat enzymic catalysis.[26] This treatment leads to equations whose form is similar to that of the equations derived using the distribution model, but the parameters in the equations have different significance, and the treatment assumes cooperativity of substrate binding to the micelle whereas the models discussed in ref 12–19 do not make this assumption.

Experimental Section

Rate Measurements. Reactions were followed spectrophotometrically at 25.0 °C by methods already described.[22,23,27] The pH of the solutions was maintained using 0.01 M borate buffer and the pH of the reaction solutions was adjusted in the presence of surfactant. The first-order rate constants, k_Ψ, are in s^{-1}.

Effect of Thiophenoxide Ion on Reaction Rate. We had hoped to induce attack of thiophenoxide ion on PNPDPP in micelles of CTABr which are effective catalysts of the reaction of PhS^- with DNF.[23] However, attack of PhS^- is too slow to be observed in water or in the presence of CTABr (Table I). Apparently the reactions are simply those of hydroxide ion and water, and PhS^- is a slight inhibitor of these reactions. Because of the low solubility of thiophenol in water the rate constants in the absence of surfactant were determined by extrapolation of data obtained in the presence of 24–40% of dioxane.

Binding of Solutes to the Micelle. If the surfactant, (detergent), D, is in large excess over the solute, S, the binding constant, K_s, is given by[8]

$$K_s = [S_M]/[S_W]([D] - \text{cmc}) \quad (1)$$

where the subscripts denote solute in the micellar and aqueous pseudophases, and cmc is the critical micelle concentration, i.e., the concentration of monomeric surfactant. It is often convenient to define the fraction of bound solute, f, as

$$f = [S_M]/([S_M] + [S_W]) \quad (2)$$

In some cases the surfactant is not in large excess over S_M, and then we modify eq 1 as

$$K_s = [S_M]/[S_W]([D] - [S_M] - \text{cmc}) \quad (3)$$

to allow for the amount of surfactant attached to solute.

Solubility. Existing procedures were followed.[27-29] For a solute which could be hydrolyzed during the solubilization, e.g., DNF, we first measured the absorbance of hydrolysis product, i.e., 2,4-dinitrophenoxide ion, and then hydrolyzed the solute quantitatively and measured the absorbance. This method was used to determine the extent of binding of DNF and PNPDPP to CTABr. The solutions contained 10^{-3} M HBr to suppress reaction with OH^-. This low concentration of HBr should have little effect on the binding of nonionic solutes.

Ultrafiltration. The general method of Dougherty and Berg was followed using an Amicon 52 cell with a PM10 membrane.[15] The concentrations of solute in the filtrate and filtrand were determined spectrophotometrically, if necessary after quantitative hydrolysis, as described for the solubility method. This method was used with both aniline and DNF, but it failed with PNPDPP, which appeared to bind very strongly to the membrane. The experiments with DNF were made in 10^{-4} M HBr.

Table II. Reaction of Phenoxide Ions with *p*-Nitrophenyl Diphenyl Phosphate in Water[a]

reagent[b]	$10^4 k_\Psi$, s^{-1}	$10^2 k_W$, $M^{-1} s^{-1}$
	1.19	
0.0104 M PhOH	2.79	3.21
0.0103 M *p*-MeC_6H_4OH	2.56	3.44

[a] At 25.0 °C, pH 10, and 0.01 M borate buffer. [b] Stoichiometric concentrations.

Table III. Binding Constants[a]

solute	K, M^{-1}	solute	K, M^{-1}
$PhNH_2$	39[b]	DNF	54[d]
$PhNH_2$	36[c]	PNPDPP	16×10^3 [d]
$PhNH_2$	(14)[b]		

[a] In CTABr except for the values in parentheses, which are in NaLS. [b] By ultrafiltration. [c] By spectrophotometry. [d] By solubility.

A correction has to be applied for transport differences of water and the solutes through the membrane.[15] These factors follow: 0.02 M aniline, 1.01; 0.04 M aniline, 1.04; 6×10^{-5} M DNF, 1.19. The concentration of aniline was determined spectrophotometrically at 380 nm and of DNF at 358 nm after complete hydrolysis.

Spectrophotometry. The extent of micellar binding can readily be estimated from the spectral shifts provided that the spectra of the fully micellar incorporated solute can be measured.[30] Provided that Beers law is obeyed we obtain

$$f = (A - A_W)/(A_M - A_W) \quad (4)$$

where A is the observed absorbance and A_W and A_M are the absorbances in water and of the fully micellar-bound solute.

When this method was used to determine the incorporation of aniline into CTABr micelles we could not measure A_M directly, because of the relatively low binding of aniline to CTABr. Equations 2-4 can be rewritten to give

$$(A - A_W)/([D] - cmc) = K_s A_M - K_s A \quad (5)$$

provided that the concentration of bound aniline is small compared with [D]. This procedure allows estimation of K_s without the measurement of A_M.

Micellar Binding of Phenols and Their Anions under Kinetic Conditions. The rates were measured at pH 9-10, where both phenol and aryl oxide ion are present. There are spectral shifts when phenols and aryl oxide ions are bound to micelles of CTABr, but there is an apparent isosbestic point (ip) at which free and micellar-bound aryl oxide ions have the same extinction coefficients, and fortunately phenols do not absorb at this wavelength, so that the absorbance gives the total concentration of aryl oxide ion. The amounts of aryl oxide in the aqueous and micellar pseudophases can then be calculated from absorbances at a wavelength at which free and bound ions have different absorbances.

In practice we estimated the concentration of aryl oxide ion in two ways.

Method A. The binding constants of the aryl oxide ions to micellized CTABr were measured spectrophotometrically at pH 12, and then the total amount of aryl oxide ion was measured under the kinetic conditions (CTABr, pH 9-10) at the isosbestic point for free and bound aryl oxide ion. It was assumed that the binding of aryl oxide ion to micelles of CTABr (but not the total concentration of arlyl oxide ion) would be independent of pH.

The binding constant, K, is related to $[Ar\overline{O}_M]$ by

$$\frac{[Ar\overline{O}_M]}{[Ar\overline{O}_T]} = \frac{K([D] - cmc - [Ar\overline{O}_M])}{1 + K([D] - cmc - [Ar\overline{O}_M])} \quad (6)$$

where $[Ar\overline{O}_M]$ is the concentration of micellar-bound $Ar\overline{O}$ written in terms of the total volume of the solution, and $[Ar\overline{O}_T]$ is the total concentration of aryl oxide ion.

This quadratic equation can be solved for K. (When $[D] \gg [Ar\overline{O}_M]$ eq 6 takes a simpler form.)

This method is illustrated by the following data for 2×10^{-4} M total phenol at pH 9.2. The binding constant of phenoxide, K, is 1980 M^{-1}, measured at high pH, and $[Ar\overline{O}_T]$ at pH 9.2 was estimated from the absorbance at the apparent isosbestic point at 287.5 nm, where $\epsilon_{ip} = 2385$.

This method was used for the experiments at pH 9.2 and for the experiments at pH 10 and 2×10^{-4} M total phenol.

Method B. In this method all measurements are made under the kinetic conditions. The total concentration of aryl oxide ion is calculated from the absorbances at the apparent isosbestic point between free and micellar bound aryl oxide ion, and the fraction of micellar-bound aryl oxide ion is calculated from the absorbances at wavelengths at which the free and micellar-bound aryl oxide ions have different absorbances. The disadvantage of this method is that it relies upon small changes in absorbance.

This method was used only for the experiments at pH 10 with 6.67×10^{-4} M total phenol or *p*-cresol. The results of methods A and B agreed for the phenol solutions, although only the data from method B are used in the kinetic analysis.

The apparent isosbestic point between aryl oxide ion in water and in the micelles is at 287.5 nm for phenoxide ion (ϵ 2385) and at 297 nm for *p*-cresyl oxide ion (ϵ 2250), which allows estimation of the total amount of aryl oxide ion. The distribution of aryl oxide ion between the aqueous and micellar pseudophases is calculated from the absorbances at 300 nm for phenoxide ion, for which ϵ 2330 in CTABr micelles and ϵ 1000 in water, and at 312 nm for *p*-cresyl oxide ion, for which ϵ 1890 in CTABr micelles and ϵ 620 in water.

Table IV. Micellar Catalysis of Aryl Oxide Reactions[a]

reaction	k_W, $M^{-1} s^{-1}$ [b]	$10^2 k_\Psi$ max, s^{-1} [c]	k_{rel}
$Ph\overline{O}$ + DNF	0.68	16 (0.022)	750
$Ph\overline{O}$ + PNPDPP	0.032	2.9 (0.001)	~3000
p-$MeC_6H_4\overline{O}$ + PNPDPP	0.034	3.9 (0.001)	~4000

[a] At 25.0 °C in CTABr solutions, pH 10 and 6.67×10^{-4} M total phenol. [b] Reaction in absence of surfactant. [c] Maximum first-order rate constants; the values in parentheses are the estimated first-order rate constant for reactions of the phenols in water at pH 10.

Results

Nonmicellar Reaction of Aryl Oxide Ions with PNPDPP. The overall first-order rate constants, k_Ψ, and the second-order rate constants, k_W, for reaction in water, calculated in terms of the concentration of aryl oxide ion, are in Table II. The values of k_W take into account the contribution of the reactions with OH^- and H_2O and the incomplete ionization of the phenols.

Under these conditions these ions are poorer nucleophiles than hydroxide ion, as expected from the pK_a values; cf ref 31. For reaction of hydroxide ion the second-order rate constant is 0.33 $M^{-1} s^{-1}$.[32]

Binding Constants. The binding constants for the substrates and aniline are in Table III. Where comparisons can be made these values are in reasonable agreement with existing values. For example, our value for DNF in CTABr is similar to that of 2,4-dinitrochlorobenzene in CTABr,[28] and our value for aniline in NaLS is similar to that of Dougherty and Berg.[15] The value of K_s for PNPDPP is similar to those found earlier in NaLS and Igepal.[27]

The extents of binding of aryl oxide ions to CTABr are considered together with discussion of the rate measurements.

Overall Micellar Catalysis of Aryl Oxide Reactions. The maximum observed rate enhancements of the reactions with the aryl oxide ions at pH 10 and 6.67×10^{-4} M stoichiometric phenol are in Table IV, and the individual rate constants are in Figure 1 and Table V. The rate constants for reaction of phenoxide ion with DNF are larger than those reported earlier,[23] probably because in the present experiments we adjusted the pH for each surfactant concentration, whereas in the earlier experiments CTABr was added to borate buffer at pH 10. The overall rate enhancements given in Table IV are based on the observed first-order rate constants for reactions with the

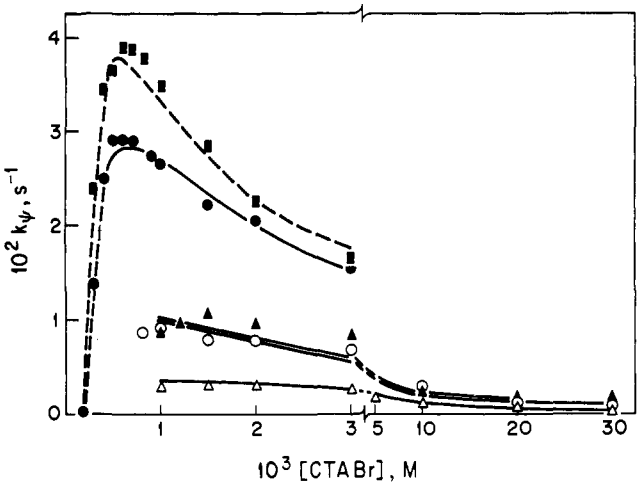


Figure 1. Micellar effects upon the first-order rate constants of dephosphorylation at 25.0 °C. The lines are calculated. Solid points, pH 10; open points, pH 9.2. Phenoxide ions, ▲△, 2×10^{-4} M; ●, 6.67×10^{-4} M. Cresylate ions, ■, 6.67×10^{-4} M.

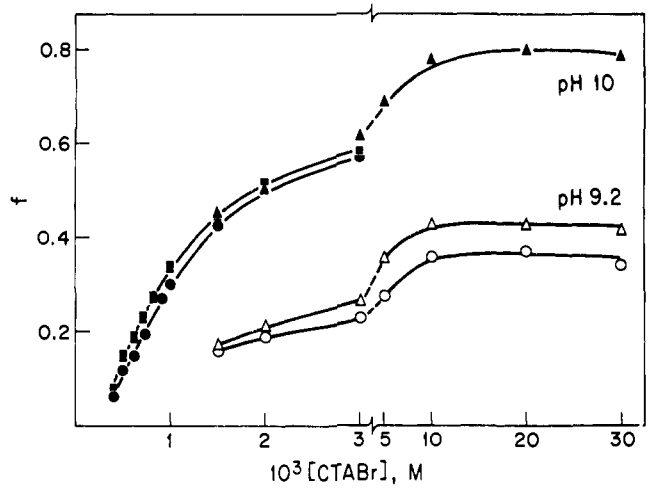


Figure 2. Fraction, f, of stoichiometric phenol bound as aryl oxide ion to CTABr micelles. Key as in Figure 1.

Table V. Values of Second-Order Rate Constants for Reaction of DNF with Phenoxide Ion[a]

10^3[CTABr], M	f	k_2, M^{-1} s^{-1} obsd	k_2, M^{-1} s^{-1} calcd
4	0.68	240	224
5	0.70	220	220
6	0.72	205	217
7	0.73	205	211
8	0.74	211	205
10	0.75	202	193
12	0.76	194	182
13	0.76	180	176
15	0.77	152	167
16	0.78	170	164
18	0.79	171	157
20	0.79	143	148

[a] At 25.0 °C, pH 10, and 6.67×10^{-4} M stoichiometric phenol.

phenols in water and aqueous CTABr at pH 10 and part of the rate enhancement is due to increased ionization of the phenol in the presence of CTABr. In estimating the rate enhancements for reactions of PNPDPP we correct for the contribution due to reaction with OH^-, which is significant in water but not in aqueous CTABr. This correction is very small for reactions with DNF.

Analysis of the Rate–Surfactant Profiles. Dephosphorylation. For reactions of either phenoxide or *p*-cresyl oxide in CTABr we neglect contributions of reactions with either water or hydroxide ion and reactions in water (Table II and ref 27). This approximation is least satisfactory at very low surfactant concentration where there is a certain amount of substrate in the water, and we do not attempt to analyze these data. In addition, there are problems when the surfactant concentration is close to the critical micelle concentration (cmc), because the reactants may interact with the surfactant to form submicellar aggregates or comicelles.[26,27,33]

The fractions, f, of total phenol which are bound to the micelle as aryl oxide ion are given in Figure 2 and Table V. It is important to note that the values of f do not go through maxima at high [CTABr], although the indirect method of calculating these values using the apparent dissociation constants (cf. ref 14 and 19) suggests that they should.

The observed first-order rate constant can be written as

$$k_\psi = k_M' K_s([D] - cmc)/(1 + K_s([D] - cmc)) \quad (7)$$

where K_s is the binding constant of the substrate, expressed in terms of concentration of micellized surfactant, and k_M' is the first-order rate constant in the micellar pseudophase, with respect to substrate,[8] and

$$k_M' = k_M m_N^s \quad (8)$$

where m_N^s is the concentration of micellar-bound nucleophile, N, relative to micellized surfactant:[12,13]

$$m_N^s = [Ar\bar{O}_M]/([D] - cmc) \quad (9)$$

so that

$$k_\psi = \frac{k_M K_s [Ar\bar{O}_M]}{1 + K_s([D] - cmc)} \quad (10)$$

$$[Ar\bar{O}_M]/k_\psi = 1/k_M K_s + ([D] - cmc)/k_M \quad (10a)$$

Assumptions are made in applying this treatment to the kinetics: (1) that each reactant does not affect the binding of the other, and (2) that the cmc under the experimental conditions gives the concentration of monomeric surfactant over all the experimental conditions, despite changes in relative concentrations of surfactant and added solute (cf. ref 13). The problem is greatest at low surfactant concentration, because of the form of the approximations, and here there could also be a cooperativity phenomenon, as discussed by Piskiewicz,[26] or possibly reaction in submicellar aggregates.[27,33] In addition, eq 7 applies only when there is a large excess of micellized surfactant over substrate, so that it fails at low surfactant concentration. For these reasons we could not apply the treatment to reactions in very dilute surfactant. (This problem has been discussed earlier.[13]) Also we did not attempt to study the rate–surfactant profile for reactions at pH 9.2 or with 2×10^{-4} M total phenol at low [CTABr] because under these conditions the spectral shifts are small and it is then difficult to estimate the concentration of bound pheonoxide ion. The form of eq 10a allows estimation of k_M from the slope of a plot of $[Ar\bar{O}_M]/k_\psi$ against [CTABr] without knowledge of the cmc, but the intercept is so small that we did not attempt to estimate K_s kinetically.

The estimated values of k_M are in Table VI. These rate constants and the independently measured values of $[Ar\bar{O}_M]$ (Figure 2) and K_s for PNPDPP in CTABr (Table III) can be used to predict values of k_ψ (Figure 1). In making the calculations we took the cmc of CTABr at pH 10 and 6.67×10^{-4} M total phenol to be 2.5×10^{-4} M, based on the spectral shift measurements (Experimental Section). The calculations are relatively insensitive to the value of the cmc except at the very low surfactant concentrations. The predicted and observed values of k_ψ agree reasonably well, except at low surfactant concentrations, because eq 10 is derived on the assumption that

Table VI. Values of Rate Constants for Dephosphorylation by Aryl Oxide Ions in CTABr

Ar	$10^4([ArO_T] + [ArOH_T])$, M	pH	k_M, s^{-1}
C_6H_5	6.67	10	0.11
p-MeC_6H_4	6.67	10	0.12
C_6H_5	6.67	9.2	0.11
C_6H_5	2.00	10	0.13
C_6H_5	2.00	9.2	0.14

the surfactant is in large excess over the reactants, but also because of perturbation of the micelles by the solutes which is most serious in dilute surfactant.

The values of k_M for phenoxide and p-cresyl oxide ion are very similar (Table VI), so that the greater micellar catalysis of the reaction of p-cresyl oxide ion (Table IV and Figure 1) is simply due to its more extensive incorporation in the micelle (cf. ref 11).

The values of k_M for phenoxide ion are only slightly affected by changes in pH or the phenoxide concentration (Table VI) even though these changes markedly affect the concentration of undissociated phenol. Therefore it seems that the presence of undissociated phenol has no major effect upon the micellar catalysis. A decrease in the stoichiometric concentration of phenol seems to increase k_M slightly (Table VI) but the differences are probably within the experimental error because estimation of the concentration of micellar-bound phenoxide ion depends on measurement of small spectral shifts.

Reaction of DNF with Phenoxide Ion. Phenoxide ion is so much a better nucleophile than hydroxide ion toward DNF that we neglect the contribution of the hydroxide ion reaction, but initially we include the contribution of reaction of phenoxide ion in water, so that the first-order rate constant for reaction in the presence of CTABr is given by[8]

$$k_\Psi = \{k_W' + k_M'K_s([D] - cmc)\}/\{1 + K_s([D] - cmc)\} \quad (11)$$

where $k_W' = [PhO_W]k_W$, $[PhO_W]$ is the molar concentration of phenoxide ion in water, and k_W is a second-order rate constant, M^{-1} s^{-1}. The other symbols have been defined. Rearrangement of these equations gives

$$k_2\{1 + K_s([D] - cmc)\} = k_W n + (k_M K_s - k_W)f \quad (12)$$

where

$$k_2 = k_\Psi/([ArOH_T] + [ArO_T]) \quad (13)$$

$$n = [ArO_T]/([ArOH_T] + [ArO_T]) \quad (14)$$

and

$$f = [ArO_M]/([ArOH_T] + [ArO_T]) \quad (15)$$

where the subscripts T and M denote total and micellar incorporated materials, respectively, the concentrations are in moles per liter of total solution, and values of f are in Figure 2 and Table V.

Our experiments were done at sufficiently high [CTABr] that $k_W n$ can be neglected, so that eq 11 gives

$$f/k_2 = 1/(k_M K_s - k_W) + ([D] - cmc)/k_M \quad (16)$$

A plot of f/k_2 against [CTABr] is linear and from the slope $k_M = 7$ s^{-1}. In order to estimate K_s kinetically we need the cmc under kinetic conditions and we used a value of 2.5×10^{-4} M, based on the original kinetic measurements,[23,34] and from the intercept we estimate $K_s = 57$ M^{-1}, which is in good agreement with that of 54 M^{-1} determined by solubility (Table III). The values of k_2 predicted by these parameters agree reasonably well with the observed values (Table V).

Table VII. Kinetic Analysis of the Reaction of Aniline with DNF in CTABr[a]

[CTABr], M	f	k_M, s^{-1}	k_2, M^{-1} s^{-1} calcd	k_2, M^{-1} s^{-1} obsd[b]
0.010	0.12	0.0334	0.173	0.164
0.025	0.30	0.0323	0.256	0.234
0.040	0.40	0.0364	0.255	0.262
0.040[c]	0.44	0.0378	0.277	0.295
0.050[d]	0.36	0.0354	0.229	0.228
0.050	0.47	0.0372	0.252	0.264

[a] At 25.0 °C with 0.05 M aniline unless specified. [b] Reference 22. [c] 0.025 M aniline. [d] 0.075 M aniline.

Table VIII. Kinetic Analysis of the Reaction of Aniline with DNF in NaLS[a]

[NaLS], M	f	k_M, s^{-1}	k_2, M^{-1} s^{-1} calcd	k_2, M^{-1} s^{-1} obsd[b]
0.010	0.07	0.020	0.058	0.050
0.025	0.17	0.0251	0.082	0.080
0.040	0.24	0.0254	0.089	0.088
0.040[c]	0.26	0.0254	0.094	0.093
0.040[d]	0.22	0.0250	0.082	0.080
0.050	0.29	0.0274	0.091	0.097

[a] At 25.0 °C with 0.05 M aniline unless specified. [b] Reference 22. [c] 0.025 M aniline. [d] 0.075 M aniline.

Reaction of Aniline with DNF. Most examples of micellar effects upon bimolecular reactions involve ionic reactants, so that micelles of opposite charge catalyze and of like charge inhibit reaction. In addition, if acid–base equilibria are involved they may be affected by the micelles. The reaction of aniline with DNF is very convenient in that it is catalyzed by both cationic and anionic micelles,[22] and is a convenient system for the application of equations analogous to eq 6–11.[15] Cationic micelles of CTABr are more effective catalysts than anionic micelles of NaLS, and reactant incorporation and reactivity in the micelle have to be considered. Extending eq 6, 7, and 11 to this reaction we obtain

$$(k_2\{1 + K_s([D] - cmc)\} - k_W)/f = k_M K_s - k_W \quad (17)$$

where k_2 is the overall second-order rate constant with respect to the total concentrations of the reactants, and $f = [PhNH_{2M}]/[PhNH_{2T}]$.

Equation 17 allows us to calculate k_M provided that K_s, k_W, f, and the cmc are known. The binding constants K_s of DNF to CTABr and NaLS are in Table III and $k_W = 0.03$ M^{-1} s^{-1}.[22] The values of f for aniline estimated from spectral or ultrafiltration measurements in Tables VII and VIII were measured directly under the reaction conditions. We used the cmc in water, simply because our surfactant concentrations are much larger than the cmc so that even if this value is too high no serious error will be introduced.

The treatment of the data is illustrated in Tables VII and VIII, and our values of k_M and the other parameters predict values of the second-order rate constants, k_2, which agree with experiment. The only data point which does not fit within experimental error is that at the lowest concentration of NaLS, where the treatment is least satisfactory.

The mean values of k_M are respectively in CTABr 0.035 s^{-1} and in NaLS 0.026 s^{-1} (omitting the first data point).

Discussion

Validity of the Model. The variation of observed rate constant with surfactant concentration can be fitted to a simple model of micellar catalysis which treats the micelle as if it were a separate phase and assumes that the reactants are distributed between it and water.[5-12]

Table IX. Comparison of Second-Order Rate Constants in Aqueous and Micellar Pseudophases

substrate	nucleophile	surfactant	k_W, M^{-1} s^{-1}	k_2^m, M^{-1} s^{-1}
PNPDPP	PhO^-	CTABr	0.032	0.017[a]
PNPDPP	p-$MeC_6H_4O^-$	CTABr	0.034	0.017
DNF	PhO^-	CTABr	0.68[b]	1.0
DNF	$PhNH_2$	CTABr	0.03[c]	0.0050
DNF	$PhNH_2$	NaLS	0.03[c]	0.0036

[a] Mean of data from experiments at pH 9.2 and 10 and 2 and 6.67 $\times 10^{-4}$ M total phenol. [b] Reference 23. [c] Reference 22.

The treatment is simplest for the reaction of aniline with DNF, because here the surfactant concentrations are well above the cmc, so that our conclusions are little affected by changes in the cmc, and thereby in the amount of micellized surfactant. Aniline is not strongly incorporated in the micelles so that we use relatively large amounts of surfactants.

The reactions of aryl oxides fit the model reasonably well over a range of pH and nucleophile concentration, except at low surfactant concentrations, where it is most likely to fail. In addition such relatively hydrophobic solutes as phenols and their anions and PNPDPP could alter micellar structure.

We feel that there may be a major problem in the estimation of the binding constants of hydrophobic anions from micellar effects upon the apparent pK_a and the binding constant of the nonionic conjugate acid. For example, this method, as applied to micellar binding of benzimidazole anions, predicts that the extents of incorporation *decrease* at high concentration of cationic surfactant.[14,19] This conclusion is probably an artifact stemming from the maxima which are often observed in plots of apparent K_a of weak acids against surfactant concentration. We find such maxima in plots of K_a against [CTABr] for phenols and oximes under conditions in which the measured pH is kept constant, but there are no maxima in the directly measured amounts of bound aryl oxide or oximate anion.[21] Almost certainly this behavior is caused by exclusion of hydrophilic ions, e.g., hydroxide or the buffer, from the micellar surface by the bromide ions which build up with increasing [CTABr], cf. ref 11, and does not indicate reduced incorporation of the hydrophobic nucleophilic anion (Figure 2).

Another problem in the rationalization of rate-surfactant profiles is that their form is approximately quadratic (cf. ref 11, 14, and 28), and they can often be fitted using a range of values of binding constants of the reactants, and it is therefore desirable, where possible, to estimate these binding constants independently of the kinetics. In addition, it is relatively easy to fit the rate-surfactant profiles to empirical equations using disposable parameters.[26,28]

Rate Constants of Reactions in the Micelle. Use of the pseudophase model in principle allows comparison of the rate constants in the micelles and in the aqueous solvent. For unimolecular reactions the rate constants are independent of concentration and the comparison can be made directly,[9] but for bimolecular reactions we must choose concentration units. The concentration of reactant in the micellar pseudophase can be calculated in terms of the total volume of the micelles[14-16] or of the Stern layer.[12,13] We use this second approach and on the assumption that the approximate volume of the Stern layer in 1 mol of micellized CTABr or NaLS is 0.14 L the second-order rate constant, k_2^m, M^{-1} s^{-1}, in the micelles is given by

$$k_2^m \approx 0.14 k_M \qquad (18)$$

The second-order rate constants k_2^m and k_W for reaction in the micellar and aqueous pseudophase are compared in Table IX. The calculation of k_2^m inevitably involves assumptions about the volume element of reaction, and it may not be reasonable to treat the Stern layer as if it were a homogeneous reaction medium, but the data in Table IX provide further evidence that concentration of reactants is a major source of micellar rate enhancements. The differences between k_W and k_2^m for reactions of aryl oxide ions are understandable in view of uncertainties in the units of concentration in the micellar pseudophase and the possibility that the reactants have different average locations in the micelle.

The values of k_2^m are less than k_W for the reaction of aniline with DNF, so that the micelle has a rate-inhibiting "solvent" effect. Such a submicroscopic "solvent" effect is understandable because the extensive incorporation of the reactants in the micelle implies a strong initial state stabilization which may well be more important than any stabilization of the transition state. In addition, reactions of amines with nonionic substrates are markedly slowed by nonpolar solvents,[35] and there is considerable evidence that the polarity of the Stern layer of an ionic micelle is less than that of water.[5,36] This submicroscopic solvent effect upon reactions between nonionic reagents seems to be general.[14,37]

Our second-order rate constants for reactions of aryl oxide ions in the micelle are very similar to those in water (Table IX). Berezin and his co-workers report rate constants for deacylations by the benzimidazole anion which are considerably larger in micelles of CTABr than in water.[14] It is possible that this apparent positive "solvent" effect of the micelle arises from the method of estimating the concentration of benzimidazole anion in the micelle from the values of the apparent K_a in the presence of cationic micelles and the extent of incorporation of the nonionic benzimidazole.

Our spectrophotometric method of estimating the extents of micellar incorporation of anions of weak acids is useful only when the reactants have chromophoric groups which undergo spectral shifts on micellar incorporation and we are examining the relation between micellar binding and the apparent K_a of phenols.

There is now considerable evidence that second-order rate constants in the micellar pseudophase are not especially larger than in water, and are indeed often smaller. For example, the rate constant of the reaction of thiophenoxide ion with p-nitrophenyl diphenyl phosphate is vanishingly small in water, and both reactants are taken up strongly by cationic micelles so that the rate constant must also be vanishingly small in the micellar pseudophase. Although micellar incorporation can sharply speed bimolecular reactions, it appears to speed existing reactions rather than introduce new reaction paths.

So far as we are aware the only failures in the pseudophase model of micellar catalysis occur with bimolecular reactions in which a negative nucleophilic anion, e.g., OH^- or F^-, is the only counterion to the micelle, and here the reaction rates do not correlate with the concentrations of substrate and nucleophile in the Stern layer.[38]

Acknowledgments. Support of this work by the National Science Foundation is gratefully acknowledged. The collaboration with Professor Luis Sepulveda[3] was developed with the support of the University of Chile-University of California Cooperative Program.

References and Notes

(1) On leave from the Institute of Organic Chemistry, University of Rome, with support of a NATO Fellowship.
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(3) On leave from the Faculty of Science, University of Chile, Santiago, Chile.
(4) For discussions of micellar catalysis see ref 5–7.
(5) E. H. Cordes and C. Gitler, *Prog. Bioorg. Chem.*, **2**, 1 (1973).
(6) J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, 1975.
(7) C. A. Bunton in "Application of Biomedical Systems in Chemistry", Part II, J. B. Jones, Ed., Wiley, New York, 1976, Chapter IV, p 731; *Pure Appl. Chem.*, **49**, 969 (1977).

(8) F. M. Menger and C. E. Portnoy, *J. Am. Chem. Soc.*, **89**, 4698 (1967).
(9) C. A. Bunton, E. J. Fendler, L. Sepulveda, and K-U. Yang, *J. Am. Chem. Soc.*, **90**, 5512 (1968).
(10) C. A. Bunton in "Reaction Kinetics in Micelles", E. H. Cordes, Ed., Plenum Press, New York, 1973, p 73.
(11) L. S. Romsted in "Micellization, Solubilization and Microemulsions", Vol. 2, K. L. Mittal, Ed., Plenum Press, New York, 1977, p 509.
(12) C. A. Bunton and B. Wolfe, *J. Am. Chem. Soc.*, **95**, 3742 (1973); C. A. Bunton, F. Ramirez, and L. Sepulveda, *J. Org. Chem.*, **43**, 1166 (1978); C. A. Bunton, L. S. Romsted, and H. J. Smith, *Ibid.*, **43**, 4299 (1978).
(13) C. A. Bunton, N. Carrasco, S. K. Huang, C. H. Paik, and L. S. Romsted, *J. Am. Chem. Soc.*, **100**, 5420 (1978).
(14) K. Martinek, A. K. Yatsimirski, A. V. Levashov, and I. V. Berezin, ref 11, p 489.
(15) S. J. Dougherty and J. C. Berg, *J. Colloid Interface Sci.*, **48**, 110 (1974); **49**, 135 (1975).
(16) J. Epstein, J. J. Kaminski, N. Bodor, R. Enever, J. Sowa, and T. Higuchi, *J. Org. Chem.*, **43**, 2816 (1978).
(17) I. M. Cuccoria, E. M. Schroter, P. M. Monteiro, and H. Chaimovich, *J. Org. Chem.*, **43**, 2248 (1978).
(18) K. Martinek, A. Osipov, A. K. Yatsimirski, and I. V. Berezin, *Tetrahedron*, **31**, 709 (1975).
(19) K. Martinek, A. P. Osipov, A. K. Yatsimirski, and I. V. Berezin, *Tetrahedron Lett.*, 1729 (1975).
(20) The values of the apparent K_a for a number of weak acids, including Imidazoles[14,19] and phenols,[21] go through maxima as the concentration of cationic surfactant is increased, but these results are probably caused by changes in the extent of incorporation of hydroxide or buffer anions in the micellar pseudophase, cf, ref 11, because the *directly measured* extents of micellar incorporation of aryl oxide ions do not decrease at high surfactant concentration.
(21) L. Sepulveda, unpublished results.
(22) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **92**, 356 (1970).
(23) H. Chaimovich, A. Blanco, L. Chayet, L. M. Costa, P. M. Monteiro, C. A. Bunton, and C. Paik, *Tetrahedron*, **31**, 1139 (1975).
(24) D. Stigter, *J. Phys. Chem.*, **68**, 3603 (1964); C. Tanford, *Science*, **200**, 1012 (1978).
(25) Reference 6, Chapter 3; R. Mukerjee, J. R. Cardinal, and N. Desai in ref 11, Vol. 1, p 241.
(26) D. Piskiewicz, *J. Am. Chem. Soc.*, **99**, 7695 (1977).
(27) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773, 780 (1969).
(28) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **90**, 5972 (1968).
(29) L. Sepulveda and R. Soto, *Makromol. Chem.*, **179**, 765 (1978).
(30) L. Sepulveda, *J. Colloid Interface Sci.*, **46**, 372 (1974).
(31) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 343 (1964); T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", W. A. Benjamin, New York, 1966, Chapters 1 and 5.
(32) C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).
(33) P. Shiffman, C. Rav-Acha, M. Chevion, J. Katzhendler, and S. Sarel, *J. Org. Chem.*, **42**, 3279 (1977); Y. Okahata, R. Ando, and T. Kunitake, *J. Am. Chem. Soc.*, **99**, 3067 (1977).
(34) The cited value of the cmc is consistent with those estimated from the spectral shifts of phenoxide under the kinetic conditions.
(35) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1969, Chapter 7.
(36) P. Mukerjee and A. Ray, *J. Phys. Chem.*, **70**, 2144 (1966).
(37) Although comparison of second-order rate constants in water and in the micellar pseudophase depends on an arbitrary measure of concentration, there is no such problem when the relative rates of reactions of different charge types in the two media are compared, provided that we assume that the site of reaction in the micelle does not change.
(38) C. A. Bunton, L. S. Romsted, and G. Savelli, *J. Am. Chem. Soc.*, in press.

Synthesis in the Tropane Class of Alkaloids. Pseudotropine and *dl*-Cocaine

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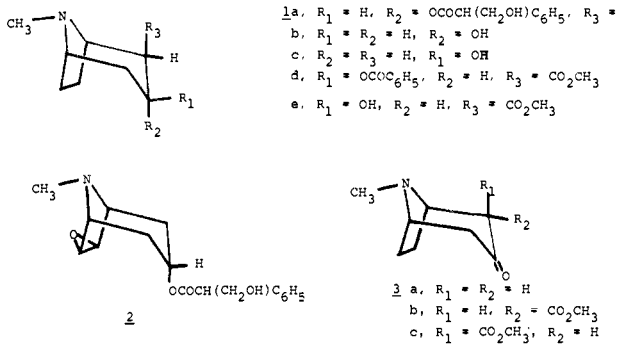
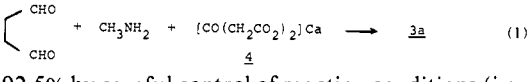
Abstract: A nitrone-based entry into the tropane class of alkaloids is described. Syntheses of pseudotropine and *dl*-cocaine are discussed. The synthetic utility and the high degree of regiochemical and stereochemical control inherent in the nitrone cycloadditions are stressed.

Introduction

The tropane alkaloids (e.g., atropine (**1a**), scopolamine (**2**), pseudotropine (**1c**), cocaine (**1d**)) incorporate an 8-azabicyclo[3.2.1]octane moiety, usually esterified at the 3 position in combination with a tropic acid.[1,2] These alkaloids, isolated from a variety of plant sources (e.g., *Hyoscyamus niger*, *Atropa belladonna*), have a long and important history in medicine. *Hyoscyamus* was mentioned in the Ebers papyrus (ca. 1550 B.C.) as a treatment for abdominal distress and to expel "magic of the belly".[3] Belladonna extract is still widely used for its antispasmodic, antisecretory, and sedative action in the symptomatic treatment of functional gastrointestinal disorders.[4] Cocaine, a notorious member of this alkaloidal family, is found in *Erythroxylon coca*, indigenous to the higher elevations of Peru. The natives of this region, descendants of the Incas, still chew the coca leaf for its stimulatory properties. The drug has significant historical importance in the pioneering development of local anesthesia; however, owing to its unpredictability, toxicity, and addictive nature, its medicinal use has been limited to topical application, primarily in ophthalmology.[3]



Synthesis in the tropane family was initiated by Willstatter's preparation of tropinone (**3a**) in an extended series of transformations starting from cycloheptanone.[1a,5] Soon thereafter, Robinson devised an efficient, superbly elegant approach involving the condensation of succindialdehyde, methylamine, and the calcium salt of 1,3-acetonedicarboxylic acid (**4**) to afford (eq 1) tropinone (**3a**) in 42% yield.[6] This yield was increased to 92.5% by careful control of reaction conditions (i.e., pH, temperature, etc.).[7] Efforts to extend the Robinson synthesis to cocaine encountered stereochemical complication. Thus, condensation of the monomethyl ester of acetonedicarboxylic acid, methylamine, and succindialdehyde led to a



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