Secondary Valence Force Catalysis. XII. Enhanced Reactivity and Affinity of Cyanide Ion toward N-Substituted 3-Carbamoylpyridinium Ions Elicited by Ionic Surfactants and Biological Lipids[1]

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Abstract: Rate and equilibrium constants for the addition of cyanide ion to a series of *N*-alkyl-3-carbamoylpyridinium ions are markedly increased by dilute solutions of *n*-alkyltrimethylammonium bromides. For example, 0.02 *M* hexadecyl surfactant increases the rate constant for addition of cyanide to the *N*-hexadecyl substrate 950-fold and increases the corresponding association constant about 25,000-fold. More concentrated solutions of these surfactants also elicit marked increases in rate and equilibrium constants for the same reactions although the increases are not quite so pronounced as with more dilute solutions. This may, in part, reflect inhibition by the surfactant counterion since it has been established that the surfactant-dependent reactions are sensitive to inhibition by anions. The effectiveness of anions as inhibitors increases in the order $F^- < NO_3^- < Cl^- < Br^-$. The extent of surfactant facilitation of the addition of cyanide ion to the pyridinium ions increases with increasing hydrophobicity in both surfactant and substrate, suggesting that hydrophobic interactions may contribute to the activation energies. The zwitterionic surfactant dodecyldimethylammoniopropane sulfonate increases the rate and equilibrium constants for addition of cyanide ion to *N*-dodecyl-3-carbamoylpyridinium bromide by 40- and 5000-fold, respectively. Finally, this same reaction is subject to promotion by sonicated aqueous dispersions of lecithin, lysolecithin, and sphingomyelin.

A series of studies in the past several years has established that rate and equilibrium constants for a number of organic reactions are sensitive functions of the concentration of ionic surfactants.[3] In most such cases the observed effects are the consequence of adsorption of one or more of the reacting species onto or into micelles formed from the surfactants. Electrostatic and hydrophobic interactions between the substrates and the components of the micelle dominate both the adsorption process itself and the rate and extent of bond-changing reactions which follow.

Since those factors which influence rates and equilibria of organic reactions may not only provide additional insight into the reaction mechanisms concerned but also yield data pertinent to enzyme-catalyzed reactions, it appears profitable to pursue the study of organic reactions in the presence of surfactants more fully. Moreover, recent results suggest that the presence of ionic micelles may be important in determining the *course* of organic reactions, as well as their rate and extent.[4] In this study, the rate and equilibrium constants for the addition of cyanide ion to a series of N-substituted 3-carbamoylpyridinium ions have been determined in the presence of a series of *n*-alkyltrimethylammonium ions, one zwitterionic surfactant, and several biological lipids. The effects of surfactant concentration, substrate structure, and concentration of added salts have been investigated. The reactions studied prove to be among the most sensitive known to promotion by ionic surfactants. A preliminary account of this work has been published.[5]

Experimental Section

Materials. A series of *n*-alkyltrimethylammonium bromides was prepared from commercially obtained *n*-alkyl bromides, redistilled before use, and trimethylamine according to the method of Scott and Tartar.[6] The salts were recrystallized from anhydrous ethanol–ether mixtures a minimum of two times prior to use in kinetic studies. Dodecyldimethylammoniopropane sulfonate was a generous gift from Procter and Gamble, Inc.

N-Alkyl-3-carbamoylpyridinium bromides were prepared from the appropriate *n*-alkyl bromides and commercially obtained nicotinamide.[7] A 1:2 molar ratio of the *n*-alkyl bromide and nicotinamide was refluxed in a minimum volume of tetrahydrofuran at 66° for 24 hr. The shiny white precipitate was filtered from the hot solution and extracted with hot acetone. The acetone-insoluble portion dried on standing to form a white crystalline powder melting within 0.5° between 223 and 224° for each product in the series.

Egg lecithin was prepared and purified by the method of Singleton, *et al.*, from egg yolk, recrystallized twice from acetone–hexane, and stored in a dark container at −20°.[8] The white powder gave a single spot when subjected to thin layer chromatography (tlc) in 90% methanol–10% chloroform. Synthetic L-α-lecithin (β,γ-dipalmitoyl), A grade, was obtained from Calbiochem. Chromatographically pure bovine brain sphingomyelin was obtained from the Pierce Chemical Co. Lysolecithin, prepared from purified egg lecithin by treatment with phospholipase A, and pur-

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(3) For a comprehensive review, see: E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970). A brief review of this field is also available: E. H. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, 2, 329 (1969).

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(6) A. B. Scott and H. V. Tartar, *J. Amer. Chem. Soc.*, 65, 692 (1943).

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ified so as to yield a single spot on tlc, was also obtained from the Pierce Chemical Co.

The water employed throughout was distilled through a Corning all-glass distillation apparatus, Model AG-1a. The inorganic salts used were of commercial reagent grade. Spectra of the substrates and products were recorded on a Cary 14 recording spectrophotometer and Perkin-Elmer 137 infrared spectrophotometer. Melting points were taken on a Thomas-Hoover Uni-melt.

Preparation of Lipid Suspensions. Preparation of the stock suspension of sonicated lipids began the day previous to the sonication by suspending sufficient lecithin in 1.00 *M* sodium chloride solution so that the final lecithin concentration would be roughly 0.001 *M*. An average molecular weight of 768 was calculated from the fatty acid composition given in ref 8. Just before sonication, the suspension was made basic by adding an equal volume of 0.02 *M* triethylamine buffer, pH 10.0. This procedure minimizes the possibility of base-catalyzed hydrolysis of suspended lipid. Following the swelling process, the suspensions were sonicated four–six times for 45-sec periods. Sonications were performed in the cold room and the dispersions were cooled between each period of sonication, either in an ice bath or by standing a few minutes at the ambient temperature. A maximum temperature of about 35° was reached during sonication. Sonication was performed at maximum intensity and a frequency of 20 kHz on a Biosonik ultrasonic system, Model BP-II or BP-III, manufactured by Bronwell Scientific. Neither sphingomyelin nor the synthetic lecithin swelled in the salt solution to the same extent as the ovolecithin, necessitating relatively more sonication to obtain stable suspensions with sufficiently low values of optical density. An upper limit to the concentrations of phospholipid that could be employed was imposed by the light scattering at 340 nm after sonication (except for the optically clear lysolecithin micelles).

Kinetic measurements were carried out spectrophotometrically with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell holder through which was circulated water from a thermostated bath maintained at 25 or 30°. The cyanide addition reaction was followed by observing the appearance of the 1,4-adduct absorption maximum near 340 nm.[9] The reaction solution initially contained *ca.* 1×10^{-4} *M* pyridinium ion substrate, and the reaction was initiated by the addition of 0.1 ml of cyanide or substrate solution to 2.9 ml of reaction solution. First-order rate constants were obtained from plots of log ($OD_\infty - OD_t$) against time in the usual fashion. In a few cases, a secondary reaction, probably reflecting formation of the 2 or 6 adducts,[9] made determination of the infinite time optical density values difficult. In these cases, the infinite time value was estimated from the extinction coefficient of the adducts, available from reactions in which complications did not occur, and initial substrate concentration. Several infinite time optical density values near this estimate were employed to calculate the rate constant and that value which minimized deviations from first-order kinetic behavior was chosen. Such rate constants are considered accurate to ±15%.

Second-order rate constants were calculated from first-order rate constants, the cyanide concentration, and the dissociation constant for the overall reaction, K_{diss}, according to the following equation

$$k_2 = k_{obsd}/([CN^-] + K_{diss})$$

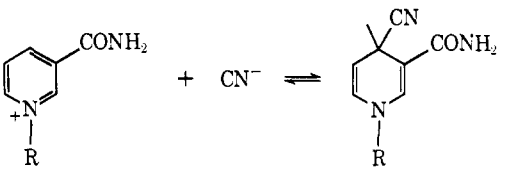
Equilibrium constants were evaluated from the equation

$$K_{eq} = \frac{[\text{adduct}]}{[\text{substrate}][CN^-]}$$

in which the [substrate]/[adduct] ratio is determined directly from the infinite time optical density values for reactions which go to completion at high cyanide concentrations, and from corresponding values obtained for these reactions at lower cyanide concentrations. In the case of addition of cyanide to *N*-benzyl-3-carbamoylpyridinium bromide in the absence of surfactants, it is experimentally impossible to employ concentrations of cyanide sufficiently high to force the reaction to completion. In these cases, equilibrium constants for adduct formation were obtained graphically as previously described.[9]

Results

A. Studies in Dilute Solutions of Cationic Surfactants. Addition of cyanide ion to N-substituted pyridinium ions in purely aqueous solution, yields, as the initial products, the adducts at the 4 position.[9]



(1)

These products may be isolated and characterized and have absorption maxima in the 330–340-nm range. The initial adducts undergo a slow rearrangement to spectrophotometrically distinct products, probably the adducts at the 2 and/or 6 positions.[9] In the presence of surfactants, the course of addition of cyanide to pyridinium ions is not substantially altered. The 4 adducts are again the first products and, on standing, the reaction solutions exhibit changes in their absorption spectra similar to those observed for the same reactions in the absence of surfactants. The relative rate of formation of the initial products and their rearrangement is increased in the presence of cationic surfactants, especially when present in high concentrations. Hence, the secondary reactions cause fewer problems for assessment of rate and equilibrium constants for the formation of the 4 adducts in the presence of cationic surfactants than in their absence.

In Table I, second-order rate constants for the addition of cyanide to certain N-substituted 3-carbamoylpyridinium ions measured at 25° and pH 11 are collected as a function of the concentration of dodecyltrimethylammonium bromide. Although these rate constants are much larger than those in the absence of surfactant, note that they have reached maximal values at a concentration of 0.01 *M* surfactant or less. Above this concentration, the rate constants actually decrease slightly with increasing surfactant concentration. In view of these results, a surfactant concentration of 0.02 *M* was chosen for detailed study of the influence of substrate and surfactant structure on the rate and equilibrium constants for these reactions. This concentration is sufficiently high to ensure, at least for those substrates and surfactants possessing C_{12} or longer chains, that substantially all of the substrate is incorporated

Table I. Second-Order Rate Constants for Addition of Cyanide to N-Substituted 3-Carbamoylpyridinium Bromides at 25° as a Function of the Concentration of Dodecyltrimethylammonium Bromide[a]

Substrate	Surfactant concn, *M*	k_2, M^{-1} sec^{-1}
Dodecyl	0.005	4.6
	0.010	5.9
	0.020	5.9
	0.030	5.6
Tetradecyl	0.005	14.1
	0.010	13.2
	0.020	8.6
	0.030	6.3
Hexadecyl	0.005	18.7
	0.010	15.1
	0.020	14.1
	0.030	8.2

[a] pH maintained near 11 through the addition of dilute solutions of sodium hydroxide.

(9) R. N. Lindquist and E. H. Cordes, *J. Amer. Chem. Soc.*, 90, 1269 (1968).

into the micellar phase. Thus, rate and equilibrium constants measured at this surfactant concentration will be those characteristic of the reactions in the micellar phase and will not noticeably depend on the equilibrium constants for incorporation of the substrates into the micelles.

In Table II, rate and equilibrium constants for the addition of cyanide to a series of N-substituted 3-carbamoylpyridinium ions in the presence of 0.02 M solutions of a series of n-alkyltrimethylammonium bromides at 25° are collected. In all cases, the pH was maintained near 11 through addition of dilute sodium hydroxide. This concentration is greater than the critical micelle concentration for all of the surfactants employed. Each rate and equilibrium constant was measured at at least five cyanide concentrations; the indicated values are averages of the five determinations. For the most part, these systems are well behaved although the association constants do tend to increase slightly with increasing cyanide concentration. A representative set of data is provided in Table III.

Table II. Rate and Association Constants for the Addition of Cyanide to a Series of N-Substituted 3-Carbamoylpyridinium Ions in the Presence of a Series of n-Alkyltrimethylammonium Bromides in Aqueous Solution at 25° [a]

Substrate	Surfactant: Decyl	Dodecyl	Tetradecyl	Hexadecyl
Octyl				0.21; 135
Decyl			1.10; 530	1.35; 710
Dodecyl		2.5; 1100		5.8; 4000
Tetradecyl	0.28; 330		6.6; 3600	10.4; 4500
Hexadecyl		6.4; 4500		13.3; 4800

[a] Surfactant concentration is 0.02 M throughout. In each case, the entries in the table are second-order rate constants in units of M^{-1} sec^{-1} followed by association constants in units of M^{-1}.

Clearly, both the affinity and reactivity of cyanide toward the pyridinium ions increase with increasing hydrophobicity of both surfactant and substrate. For example, employing a constant concentration of the hexadecyl surfactant, rate constants for cyanide addition increase by almost two orders of magnitude as the substrate hydrophobicity is varied from octyl to hexadecyl. As noted above, much of the change (and perhaps all of it) reflects differences in substrate reactivity following incorporation onto the micelle, not differences in equilibrium constants for this incorporation. Note also that the concentration of surfactant is about 200 times greater than that of substrate. Consequently, it is likely that the substrates themselves do not alter the micelle structures significantly; most micelles will have only one substrate molecule associated with them.

The insolubility of the cyanide adducts of the substrates employed in this study in the absence of surfactants makes determination of the rate and equilibrium constants for the cyanide-addition reaction in surfactant-free solutions experimentally difficult. However, suitable control values are available from previous studies employing closely related substrates.[9] For example, these constants for addition of cyanide to N-propyl-3-carbamoylpyridinium bromide in aqueous solution at 25°, ionic strength 0.5, are known: k_2 = 0.014 M^{-1} sec^{-1} and K_{eq} = 0.185. Thus, the largest association constant found, 4800 M^{-1}, for the reaction of the N-hexadecyl substrate in the presence of the n-hexadecyl surfactant, is more than 25,000 times larger than that for the model reaction. The largest second-order rate constant observed, 13.3 M^{-1} sec^{-1}, for the same reaction is 950 times greater than that for the same model reaction.

In an effort to detect possible changes in the localization of the reactive pyridinium functionality within the micelle as a function of the length of the N substituent, the absorption maxima of the corresponding bromides (9.9×10^{-5} M) in the presence of 0.02 M hexadecyltrimethylammonium bromide were measured employing a scanning spectrophotometer. The following maxima were obtained: decyl, 271.3 nm; dodecyl, 271.6 nm; tetradecyl, 271.8 nm; and hexadecyl, 272.3 nm. Although the changes in wavelength of maximum absorption are small, there is a regular increase toward a higher wavelength with increasing substrate hydrophobicity suggesting that the effective local environment of the chromophore becomes increasingly polar.[10]

Effects of the concentration of four anions on the first-order rate constants and equilibrium constants for addition of cyanide to N-dodecyl-3-carbamoylpyridinium bromide in the presence of 0.02 M tetradecyltrimethylammonium bromide were studied in the presence of 0.001 M total cyanide, pH 10.4, at 30°. The results are collected in Table IV. Bromide, chloride, nitrate, and fluoride all appear to decrease both the rate and extent of the surfactant-dependent reaction although the effect of fluoride is barely detectable. Bromide is the most effective inhibitor. The extent of these decreases is more marked at the higher salt concentrations although the effects do not become particularly large up to concentrations of 0.5 M. The largest rate decrease observed is about threefold and the largest extent decrease is about sixfold.

Table III. Rate and Equilibrium Constant Data for Addition of Cyanide to N-Decyl-3-carbamoylpyridinium Bromide in the Presence of 0.02 M Hexadecyltrimethylammonium Bromide at 25°

Cyanide concn, M	Infinite time optical density	K_{diss}, M	k_{obsd}, sec^{-1}	k_2, M^{-1} sec^{-1}
1.0×10^{-1}	0.739			
1.0×10^{-2}	0.690		1.75×10^{-2}	1.54
5.0×10^{-3}	0.615	0.93×10^{-3}	8.05×10^{-3}	1.26
4.0×10^{-3}	0.550	1.37×10^{-3}	5.86×10^{-3}	1.08
3.0×10^{-3}	0.502	1.42×10^{-3}	5.01×10^{-3}	1.13
2.0×10^{-3}	0.423	1.47×10^{-3}	4.20×10^{-3}	1.23

(10) P. Mukerjee and A. Ray, *J. Phys. Chem.*, 70, 2144 (1966).

Table IV. The Influence of Salts on Rate and Equilibrium Constants for Addition of Cyanide to *N*-Dodecyl-3-carbamoylpyridinium Bromide in the Presence of 0.02 *M* Tetradecyltrimethylammonium Bromide at 30° [a]

Salt	Concn, *M*	$k_{obsd} \times 10^2$, sec^{-1}	K_{eq}, M^{-1}
NaBr	0.01	0.84	1290
	0.03	0.76	925
	0.05	0.68	910
	0.07	0.56	645
	0.10	0.46	650
	0.20	0.42	445
	0.50	0.32	220
NaCl	0.01	0.91	1260
	0.03	0.81	990
	0.05	0.83	
	0.07	0.64	670
	0.10	0.67	
	0.20	0.52	500
	0.50	0.38	295
$NaNO_3$	0.01	0.92	1220
	0.03	0.77	1150
	0.05	0.90	1400
	0.07	0.62	830
	0.20	0.48	590
	0.50	0.43	590
NaF	0.01	0.94	1090
	0.03	1.01	1330
	0.05	0.90	1190
	0.07	0.85	800
	0.10	1.01	1220
	0.20	0.84	900
	0.50	0.76	730

[a] Cyanide concentration is 0.001 *M* throughout; pH 10.4 maintained with 0.01 *M* triethylamine–ammonium buffer.

B. Studies in Concentrated Solutions of Cationic Surfactants. As the concentration of the cationic surfactants employed in this work is increased, the aggregation number of the individual micelles increases; that is, the micelles increase in size.[11] Moreover, for hexadecyltrimethylammonium bromide at least, and perhaps the tetradecyl compound as well, the micelle structure changes from spherical to rod-shaped and, at sufficiently high concentrations, a liquid crystalline phase is formed (consisting of infinitely long cylinders organized at the apices of a hexagonal lattice).[12,13] In an effort to establish the effect of micelle size and shape on the kinetics of surfactant-dependent reactions, a study of the rate and extent of addition of cyanide ion to pyridinium ions at high surfactant concentrations was undertaken.

In Table V, rate and equilibrium constants for addition of cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide are collected as a function of the concentration of tetradecyltrimethylammonium bromide at 25°. Note that both rate and equilibrium constants increase with increasing surfactant concentration up to about 0.02 *M* (see also Table I) but decrease thereafter; the data for first-order rate constants are shown graphically in Figure 1.

A more detailed study of these reactions was carried out at 30° employing the whole series of substrates with the whole series of surfactants, at fixed, high surfactant concentrations. Both rate and equilibrium constant data are summarized in Table VI. Note that the results are qualitatively similar to those obtained employing more dilute surfactant solutions. Increasing hydrophobicity in both substrate and surfactant increases the rate and equilibrium constants. But quantitatively the dependence of these constants on substrate and surfactant structure is less marked than at the lower concentration. The absolute values of both sets of constants are lower at 0.19 *M* surfactant than at 0.02 *M*, and are lower at 0.27 *M* surfactant than at 0.19 *M*, in agreement with expectations based on the data of Table V and Figure 1.

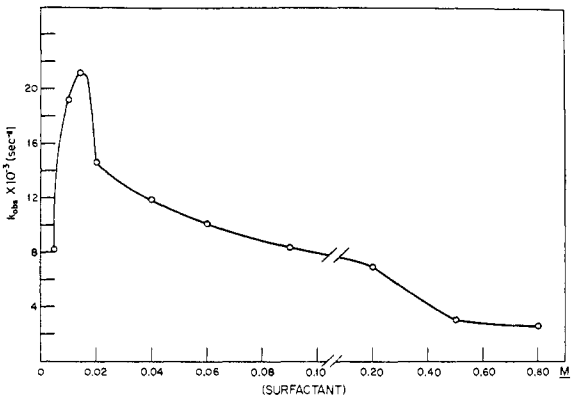


Figure 1. First-order rate constants for the addition of 0.004 *M* cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide at 25° as a function of the concentration of *n*-tetradecyltrimethylammonium bromide.

Table V. Rate and Equilibrium Constants for Addition of Cyanide Ion to *N*-Dodecyl-3-carbamoylpyridinium Ion as a Function of the Concentration of Tetradecyltrimethylammonium Bromide at 25° [a]

Surfactant concn, *M*	$(OD)_\infty$	K_{eq},[b] M^{-1}	k_{obsd}, sec^{-1}	k_2, M^{-1} sec^{-1}
0.0050	0.569	990	8.25×10^{-3}	1.47
0.0075	0.611		1.22×10^{-2}	
0.010	0.621		1.92×10^{-2}	
0.015	0.614		2.17×10^{-2}	
0.020	0.576	1060	1.47×10^{-2}	2.58
0.040	0.569	990	1.19×10^{-2}	2.13
0.060	0.549	840	1.01×10^{-2}	1.89
0.090	0.525	700	8.35×10^{-3}	1.63
0.20	0.460	455	6.85×10^{-3}	1.40
0.50	0.413	345	3.01×10^{-3}	0.66
0.80	0.424	370	2.57×10^{-3}	0.57

[a] [Cyanide ion] = 0.004 *M* throughout. [b] Calculated from OD_∞ = 0.712 when reaction goes to completion.

C. Studies in the Presence of Zwitterions. In Table VII, rate and equilibrium constants for addition of cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide in water at 25° in the presence of 0.02 *M* dodecyldimethylammoniopropane sulfonate (a zwitterionic surfactant) are collected as a function of cyanide concentration. Note that the calculated second-order rate constants diminish as the cyanide concentration increases indicating that the system is kinetically more complex than in the case of related systems employing cationic surfactants. Nevertheless, it is quite clear that this zwitterionic surfactant strongly promotes the reaction. Comparison of these constants with those for the

(11) F. Reiss-Husson and V. Luzzati, *J. Colloid Interface Sci.*, **21**, 534 (1966).
(12) F. Reiss-Husson and V. Luzzati, *J. Phys. Chem.*, **68**, 3504 (1964).
(13) P. Debye and E. W. Anacker, *J. Phys. Colloid Chem.*, **55**, 644 (1951).

Table VI. Rate and Association Constants for the Addition of Cyanide to a Series of N-Substituted 3-Carbamoylpyridinium Ions in the Presence of High Concentrations of a Series of *n*-Alkyltrimethylammonium Bromides at 30° [a]

Substrate	Surfactant					
	Decyl (0.193)	Dodecyl (0.193)	Dodecyl (0.270)	Tetradecyl (0.193)	Tetradecyl (0.270)	Hexadecyl (0.174)
Octyl		0.47, 108	0.46, 103	0.58, 178	0.56, 192	0.57, 244
Decyl	0.61, 145	0.82, 200	0.74, 180	1.44, 476	1.07, 370	1.57, 602
Dodecyl	0.92, 200	1.00, 196	0.77, 213	1.86, 610	1.26, 500	2.05, 960
Tetradecyl		1.22, 286		2.28, 900	1.72, 830	2.14, 1070
Hexadecyl		1.39, 345	1.23, 244	2.57, 1160		2.79, 1490
Octadecyl		1.37, 384	0.93, 288	2.76, 1060	1.72, 770	3.19, 2000

[a] The surfactant concentration (M) is given in parentheses following the surfactant name. The entries in the table are second-order rate constants in units of M^{-1} sec^{-1} followed by association constants in units of M^{-1}.

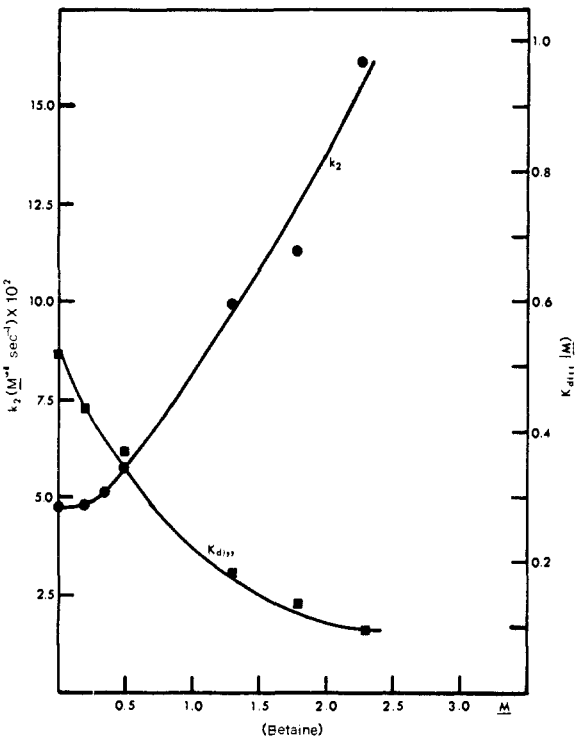


Figure 2. Second-order rate constants (●) and dissociation constants (■) for addition of 0.033 M cyanide to *N*-benzyl-3-carbamoylpyridinium bromide plotted as a function of betaine concentration at 25°, pH 10.1. Ionic strength was maintained at 2.3 through addition of sodium chloride.

Table VII. Rate and Equilibrium Constants for the Addition of Cyanide to *N*-Dodecyl-3-carbamoylpyridinium Bromide in the Presence of 0.02 M Dodecyldimethylammoniopropane Sulfonate at 25° and pH 10

$[CN^-]$, M	k_{obsd}, sec^{-1}	K_{eq}, M^{-1}	k_2, M^{-1} sec^{-1}
0.0035	0.0069	1000	1.54
0.010	0.0160	950	1.45
0.017	0.0245		1.36
0.035	0.038		1.05
0.069	0.058		0.83
0.103	0.079		0.76
0.138	0.095		0.69
0.172	0.096		0.56
0.206	0.107		0.52
0.241	0.124		0.52
0.276	0.128		0.47
0.310	0.163		0.52

model reaction (*vide infra*) indicates that 0.02 M surfactant increases the equilibrium constant some 5000-fold and the second-order rate constant about 40-fold. This surfactant is, in fact, nearly as good a promoter for the addition of cyanide to the dodecyl substrate as is *n*-dodecyltrimethylammonium bromide (Table II).

In an effort to understand the basis for the increased affinity and reactivity of cyanide toward pyridinium ions elicited by the zwitterionic surfactant, the effect of a simple zwitterionic substance, betaine, on this type of reaction was probed. *N*-Benzyl-3-cyanopyridinium bromide was chosen as substrate for these studies because of its increased reactivity toward cyanide compared to *N*-alkyl derivatives[9] and because of the solubility of its cyanide adduct in water. The betaine was obtained in the form of its hydrochloride and was neutralized with sodium hydroxide prior to use. This procedure results in the formation of stoichiometric quantities of sodium chloride; in order to avoid variation of ionic strength as a function of betaine concentration, total ionic strength was maintained at 2.3 throughout by addition of sodium chloride. In Figure 2, dissociation and second-order rate constants for addition of cyanide ion to *N*-benzyl-3-carbamoylpyridinium bromide are shown as a function of betaine concentration in 0.033 M triethylamine–ammonium buffer, pH 10.1, at 0.033 M cyanide. Increasing concentrations of betaine increase both the affinity and reactivity of cyanide toward the pyridinium ion substrate, although the effects observed are clearly smaller than those elicited by the zwitterionic surfactant.

D. Studies in the Presence of Biological Surfactants. The observation of promotion of cyanide addition to pyridinium ions due to the presence of zwitterionic species suggested that biological surfactants of zwitterionic nature might promote these reactions as well. Lecithin, lysolecithin, and sphingomyelin, which form distinct types of structures in aqueous systems. were chosen to test this suggestion.

Values for first-order rate constants and total optical density change at 340 nm for the addition of cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide in aqueous solution at 25° employing 0.093 M triethylamine–ammonium buffer and in the presence of 1.0×10^{-4} M sonicated lecithin are plotted as a function of cyanide concentration in Figure 3. The pH was maintained at 10 or above throughout and the reaction mixtures contained 0.47 M sodium chloride. Two observations indicate that the reaction kinetics in this system are complex. First, as may be directly appreciated from Figure 3, the first-order rate constants do not vary in a linear manner with cyanide concentration. Second, calculation of the equilibrium constant for the reaction from the optical density values of Figure 3 does not

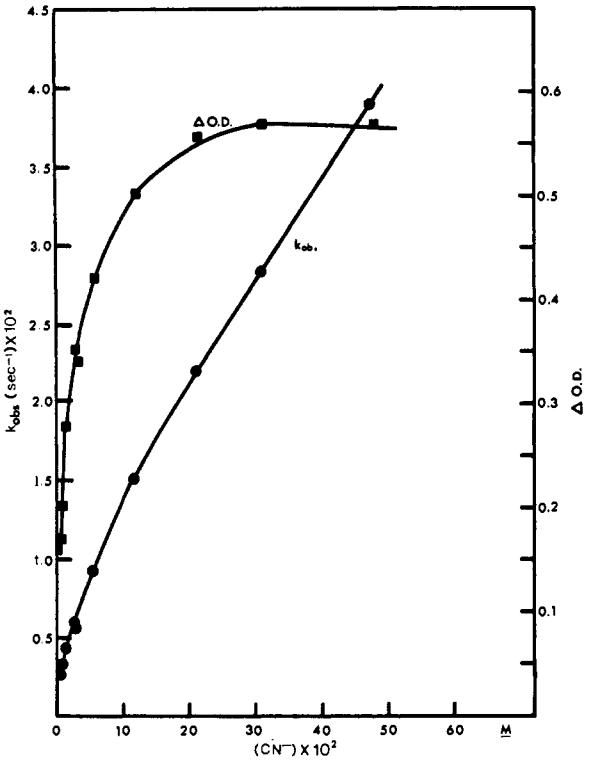


Figure 3. First-order rate constants (●) and total change in optical density at 340 nm (■) for addition of cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide as a function of the concentration of cyanide at 25°. The reaction mixtures contained 1.0×10^{-4} *M* ovolecithin present as a sonicated dispersion; pH was maintained above 10 through use of a 0.093 *M* triethylamine buffer. Total sodium chloride concentration was 0.47 *M*.

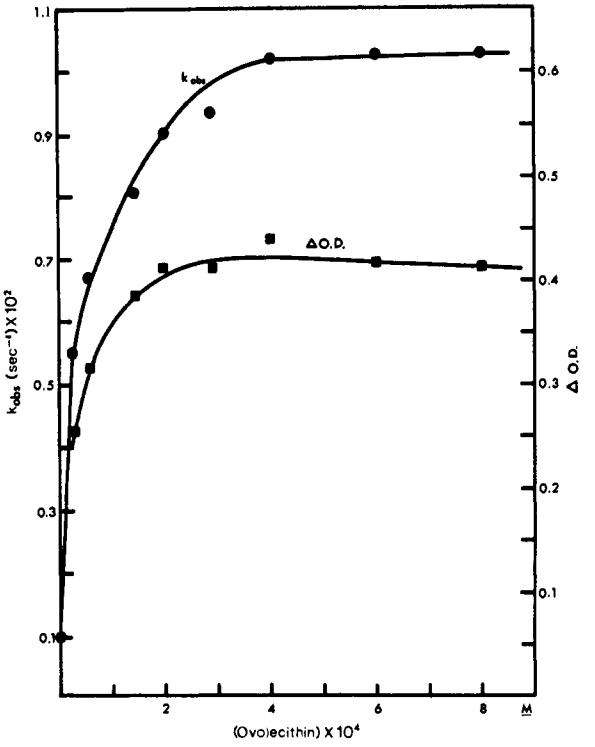


Figure 4. First-order rate constants (●) and total change in optical density at 340 nm (■) for addition of 0.033 *M* cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide as a function of the concentration of ovolecithin, present in the form of a sonicated dispersion at 25° and pH 10.04. Total sodium chloride concentration was 0.47 *M*.

lead to consistent values. Consequently, calculation of meaningful equilibrium constants and second-order rate constants for the reaction under these conditions is impossible. For further study, a cyanide concentration of 0.033 *M* was chosen and qualitative effects on the rate and extent of the reaction are based on first-order rate constants and total changes in optical density at 340 nm.

In Figure 4, these parameters are plotted against the concentration of sonicated lecithin concentration for the addition of 0.033 *M* cyanide to the *N*-dodecyl substrate at 25° and pH 10.04, in the presence of 0.47 *M* sodium chloride. Both the rate and extent of the reaction increase with increasing lecithin concentration up to a concentration near 3×10^{-4} *M*, above which no further changes are observed. The overall change in rate constant is near tenfold, as judged from the previously measured constant for the *N*-propyl substrate under similar conditions but in the absence of lecithin.[9] Note that about 80% of the total rate change observed is realized at a 1:1 mole ratio of lecithin to substrate and the maximal rate change is achieved at a 4:1 mole ratio. Under a similar set of experimental conditions, including lecithin up to a concentration of 25×10^{-4} *M*, no reaction is observed when the *N*-dodecyl-3-carbamoylpyridinium bromide is replaced by the corresponding *N*-methyl compound, emphasizing the importance of hydrophobic interactions between the substrate and lecithin. When ovolecithin was replaced by a synthetic lecithin containing exclusively palmitoyl fatty acyl residues, the kinetic behavior for these reactions became quite complicated so that even reliable first-order rate constants were difficult to obtain. Further studies employing this surfactant were not carried out.

Addition of cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide in the presence of sonicated ovolecithin dispersions is rather insensitive to both the nature and concentration of added anions and cations. The pertinent data are collected in Tables VIII and IX. High concentrations of anions do lessen the reactivity and affinity of cyanide toward the pyridinium ions although the effect is less marked than that in the presence of cationic surfactants (compare the data in Table VIII

Table VIII. Effect of Anions on First-Order Rate Constants and Total Change in Optical Density for Addition of Cyanide to *N*-Dodecyl-3-carbamoylpyridinium Bromide in a Sonicated Dispersion of 1.05×10^{-4} *M* Ovolecithin at 25°, pH 10.09 ± 0.08[a]

Added salt,[b] 0.434 *M*	k_{obsd}, sec^{-1}	ΔOD_{340}
Na_2SO_4	0.0080	0.392
NaF	0.0072	0.350
NaCl	0.0060	0.297
NaBr	0.0051	0.275
NaBr[c]	0.0053	0.249
NaI[d]	0.0041	0.200

[a] All reactions were carried out in the presence of 0.093 *M* triethyl amine–ammonium chloride buffer. Initial concentrations of substrate and NaCN were 1.0×10^{-4} and 0.033 *M*, respectively. [b] Additional 0.033 *M* NaCl is present in each case from the original liposome dispersion. Systems were incubated with the added salt for 20 min before initiation of the reaction, except when noted otherwise. [c] Incubated less than 0.5 min. [d] Incubated 30 min.

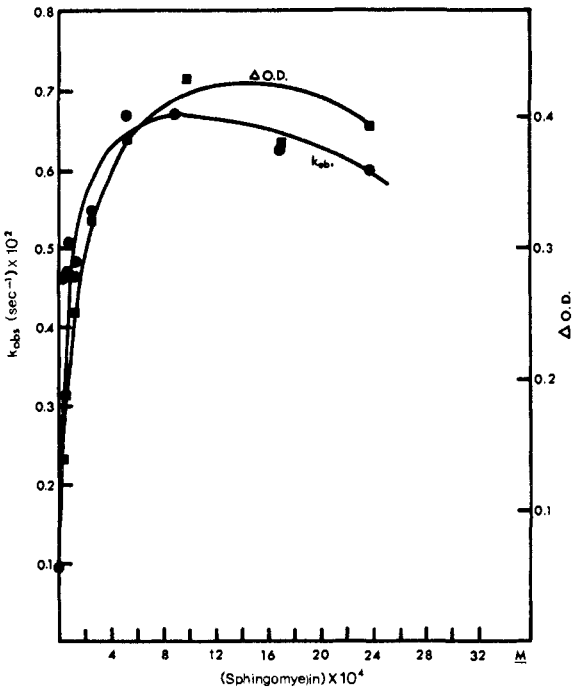


Figure 5. First-order rate constants (●) and total change in optical density at 340 nm (■) for addition of 0.033 *M* cyanide to *N*-dodecyl-3-carbamoylpyridinum bromide at 25° plotted as a function of the concentration of a sonicated dispersion of bovine brain sphingomyelin in 0.47 *M* sodium chloride, pH 10.03.

Table IX. Effect of Cations on First-Order Rate Constants and Total Change in Optical Density for Addition of Cyanide to *N*-Dodecyl-3-carbamoylpyridinium Bromide in a Sonicated Dispersion of 1.05 × 10^{-4} *M* Ovolecithin at 25°, pH 10.03 ± 0.03[a]

Added salt,[b] 0.434 *M*	k_{obsd}, sec^{-1}	ΔOD_{340}
LiCl	0.0059	0.289
NaCl	0.0057	0.293
KCl	0.0058	0.297
CsCl	0.0054	0.288
CaCl	0.0054	0.285

[a] All reactions were carried out in the presence of 0.093 *M* triethylamine–ammonum chloride buffer. Initial concentrations of substrate and NaCN were 1.0 × 10^{-4} and 0.033 *M* respectively. [b] Additional 0.033 *M* NaCl is present in each case from the original liposome dispersion. Systems were incubated with the added salt for 20 min before initiation of the reaction.

with that in Table IV). Cations appear to be without detectable effect.

Finally, a series of experiments very similar in design to those involving lecithin was performed employing sphingomyelin and lysolecithin as biological surfactants. The first-order rate constants and total optical density changes at 340 nm for addition of 0.033 *M* cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide as a function of the concentration of these species are provided in Figures 5 and 6. Note that both surfactants promote the reaction and do so to about equal extents. The reaction in the presence of lysolecithin is inhibited to a minor degree in the presence of high concentrations of sodium chloride (Figure 6).

Discussion

The optical density changes following the addition of mildly alkaline solutions of cyanide to *N*-alkyl-3-carbamoylpyridinium ions in the presence of micelle-forming surfactants are similar to those observed for the same reactions in the absence of surfactants.[9] Thus, the surfactants markedly affect the extent and rate of the addition reaction but not its course (eq 1).

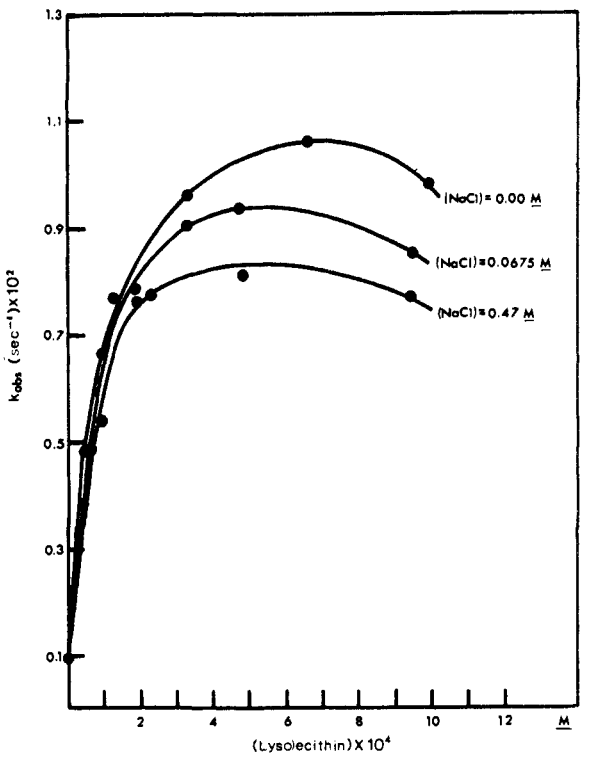


Figure 6. First-order rate constants for addition of 0.033 *M* cyanide to *N*-dodecyl-3-carbamoylpyridinium bromide plotted as a function of lysolecithin concentration at 25° and pH 10.01 at three concentrations of sodium chloride.

The data in Tables I and II establish that dilute solutions of simple cationic surfactants strikingly promote the addition of cyanide to pyridinium ions. In fact, this reaction is one of the most sensitive, if not the most sensitive, reactions known to promotion by micelles. There appear to be at least three sources which contribute to the increases in reactivity and affinity observed. First, the positively charged micellar surface should electrostatically destabilize the positively charged substrate with respect to the zwitterionic transition state and uncharged products. The *N*-alkylpyridinium ions almost certainly associate with the micelles with the hydrophobic chains in the micellar interior and the head group at or near the micellar surface. In fact, the pyridinium ions employed in this study themselves form micelles, although the critical micelle concentrations are higher than the concentrations used in these studies.[14]

Second, the negatively charged cyanide ion may be electrostatically stabilized by the surface of the cationic micelle. That such effects are important is testified to by the related studies from the laboratory of Bunton. Specifically it has been established that reaction between hydroxide ion and 2,4-dinitrochlorobenzene and 2,4-dinitrofluorobenzene as well as those involving glycinate and glycylglycinate and the latter substrates are subject to catalysis by cationic surfactants and to in-

(14) B. M. Anderson and C. D. Anderson, *Biochim. Biophys. Acta*, 205, 161 (1970).

hibition by anionic ones.[15-17] Since these substrates lack a positive charge, electrostatic destabilization of the substrate cannot be an important factor. But electrostatic effects on the nucleophiles do accord with the experimental observations.

Third, hydrophobic interactions between micelle and substrate clearly contribute to the overall changes in rate and equilibrium constants. With a given substrate, increasing hydrophobicity of the surfactant increases both the rate and extent of the addition reaction (Tables II and VI). Similar observations have been made for a number of systems in earlier studies.[18-20] This result may reflect the increasing importance of electrostatic effects resulting from the formation of better organized micellar surfaces with increasing alkyl chain length or may reflect direct contribution of hydrophobic forces to the activation energy and overall free-energy change.[19] Some insight into these matters may be gained from the observation that, with a given surfactant, increasing substrate hydrophobicity also results in accentuation of the effects on rate and equilibrium constant (Tables II and VI). A related observation has been made by Gitler and Ochoa-Solano.[19] Since the molar ratio of surfactant to substrate is at least 200, not more than one substrate molecule will be incorporated into each micelle. Thus, it seems unlikely that the large effects observed result from changes in micelle properties with changes in the nature of the substrate. It seems likely, therefore, that the hydrophobic interactions themselves contribute to overcoming the energy barrier to reaction.[19] One way in which the binding interactions between substrate and micelle could contribute to activation energy is through changing the location of the reactive head group with respect to the micellar surface. Thus, the increasing importance of hydrophobic interactions between micelle and substrate may have the effect of bringing the pyridinium group increasingly close to the micellar surface, thus increasing the electrostatic destabilization of this group. The changes in spectra observed in the presence of bromide ion are consistent with and provide mild support for this point of view.

Two observations suggest that yet additional factors also influence the rate and equilibrium constants for cyanide addition to pyridinium ions in the presence of cationic surfactants. First, the observation that zwitterionic species also increase the rate and equilibrium constants for these reactions is not readily explained in terms of the factors discussed thus far. Second, Bunton and Robinson have established that addition of aniline to 2,4-dinitrofluorobenzene is catalyzed by cationic, nonionic, and (slightly) anionic surfactants.[16] Again, arguments based on electrostatic interactions do not account for this finding.

Anions inhibit the cationic micelle promoted addition of cyanide to pyridinium ions (Table IV). Both the fact of inhibition and the order of effectiveness of the anions accord with previous investigations of related systems.[15,21-25] Quantitatively, the salt effects are not as large as those observed in some previous cases.

High concentrations of cationic surfactants are less effective than lower ones in promoting addition of cyanide to pyridinium ions (Figure 1 and Table VI). In part, this may reflect the higher concentration of bromide ion in the system, a necessary consequence of adding the surfactants as the bromide salt. It is also possible that changes in micellar structure from spherical to rod shaped with increasing concentration may influence the rate and equilibrium constants. However, this effect cannot be very important since the consequences of higher surfactant concentration employing long-chain surfactants, which undergo this structure change, are similar to those for shorter chain ones, which probably do not.[12,13] It would appear that small spherical micelles and large rod shaped ones are roughly equally effective in promoting addition of cyanide ion to pyridinium ions.

The observation of strong promotion of cyanide addition to pyridinium ions elicited by a zwitterionic surfactant is surprising. Generally, surfactants bearing no net charge have little effect on reaction rates and equilibria. In some cases, modest catalytic effects are observed in the presence of nonionic surfactants.[16,26] It is possible that, because of the positioning of the substrate with respect to the micellar surface, the zwitterionic micelle may have some net electrostatic effect on the reaction but it seems unlikely that this effect could explain the degree of catalysis observed. It is also possible, perhaps likely, that hydrophobic interactions account for a part of the observed effects. But it seems most reasonable to conclude that medium effects at the micellar surface are responsible for the greater part of the promotion. This explanation is supported by the observation that the simple molecule betaine, in high concentrations (Figure 2), is also a promoter for the reaction. Solutions of betaine in water have very high dielectric constants;[27] unfortunately the polarity of the surface of micelles formed from zwitterionic surfactants is not known. While this factor itself may be important, it is not clear why an increasing dielectric constant should increase the reactivity and affinity of cyanide for pyridinium ions.

The observation that aqueous suspensions of biological lipids promote addition of cyanide to pyridinium ions (Figures 4–6) is the first case in which these complex surfactants have been observed to function in this manner. That they might be effective for this reaction was suggested by the observation that the simple zwitterionic surfactant was an effective promoter. Of the three biological surfactants studied, only lysolecithin forms micelles in the usual sense; lecithin and sphingomyelin, when sonicated in aqueous media, form more complicated structures, frequently referred

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(23) C. A. Bunton, L. Robinson, and L. Sepulveda, *J. Org. Chem.*, **35**, 108 (1970).
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(27) J. T. Edsall and J. Wyman, Jr., *J. Amer. Chem. Soc.*, **57**, 1964 (1935).

to as liposomes or Bangosomes.[28] These spherical bilayer structures have many of the properties of biological membranes. Due to the complexity of the structures present in these systems, it is not surprising that kinetic anomalies were observed. The source of the effects on the rate and extent of addition of cyanide to pyridinium ions elicited by these surfactants is unclear though those factors which are important in the case of the simple zwitterionic surfactant may be important here as well.

Finally, we may note that in a basic way the reactions studied in this investigation mimic enzymatic reactions involving the nicotinamide nucleotide coenzymes. The importance of electrostatic factors in promoting the simple organic reactions suggests that such factors may be important for the enzymatic ones as well.

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Group VI–Halogen Adducts. Trisubstituted *vs.* Tetrasubstituted Structures in Solution[1a]

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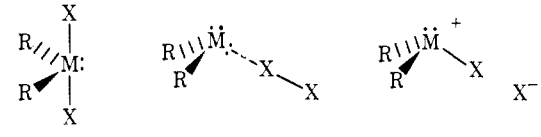
Abstract: The structures of the complexes between group VI heterocycles (thiane or selenane) and halogens (bromine or iodine) have been determined in solution. Analysis of coupling-constant ratios for both the 2,3 and 3,4 segments of the ring characterize the selenane–bromine complex as a trigonal bipyramid (tetrasubstituted) and the selenane–iodine and both thiane complexes as simple charge-transfer molecular adducts (trisubstituted). The ionic character of the complexes was assessed by conductance measurements. The thiane–bromine complex is highly ionic, the selenane–bromine complex exhibits a very low conductance, and the iodine complexes are intermediate in behavior. Ionic character was placed on a relative scale by comparison with the halosulfonium and haloselenonium tetrafluoroborates, which are entirely ionic.

Dialkyl sulfides, selenides, and tellurides react instantaneously with molecular halogens to form Lewis acid–base complexes of the σ–σ type (eq 1). The

$$R_2\ddot{M}: + X_2 \longrightarrow R_2\dot{M}X_2 \qquad (1)$$

ease of formation and isolation, the brilliant colors of some of the adducts, and their structural complexity have made these compounds a constant object of study for over a century. Husemann reported and characterized possibly the first such adduct (iodine and 1,4-dithiane) in 1863.[2] The major thrust of the structural work to date has consisted of X-ray crystallographic determinations,[3] particularly by the groups of Hassel and McCullough. Some attention has been devoted recently to the measurement of equilibrium constants for complex formation in solution.[4] We report herein the first quantitative efforts to define the structures of these adducts in solution.

From the mass of structural data reported on these group VI–group VII complexes, two general classes of bonding situations have emerged: those (**1**) in which the group-VI atom (M) lies between the two halogen atoms (X—M—X), and those (**2**) in which M



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is at the terminus (M···X—X). In the former class ("tetrasubstituted"), the atom M forms the center of a trigonal bipyramid with covalent bonds to both halogen atoms. In the latter class of simple charge-transfer molecular complexes ("trisubstituted"), the bonding between M and the halogen molecule has been likened to that in the hydrogen bond.[3] The M···X—X angle is very close to 180°, and the strength of the complex may be related to the deviations of the X—X bond from its natural length. These two classes grade naturally into each other.[3,5]

In addition to classification as either molecular complexes (MC) or trigonal bipyramids (TB), these molecules may be characterized according to the ionic or covalent nature of the bonds. Organic chemists, in fact, have favored depicting many of these molecules as halosulfonium or haloselenonium halides (**3**).[6] The

(1) (a) This work was supported by the National Science Foundation (Grant No. GP-22942), the Advanced Research Projects Agency of the Department of Defense through the Northwestern University Materials Research Center, and the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4,5); (b) National Institutes of Health Fellow, 1967–1971; (c) National Science Foundation Trainee, 1968–1969.

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(6) For example, see D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969).