density in the ring. Not unexpectedly both the chemical shifts of the methoxyl resonances of complexes **1–6** (τ 6.92–7.08 ppm) and the magnitude of the upfield shifts ($\Delta\delta$ 1.00–1.49 ppm)[4,5] are relatively insensitive to the position or nature of the aromatic substituents. However, the chemical shift of the H-3,5 resonances and the difference in the chemical shifts ($\Delta\delta$)[4,5] increase as a function of increasing substitution of cyano groups in the ring. HMO calculations have shown that the negative charge of Meisenheimer complexes is primarily delocalized over the nitro groups.[13] Since charge delocalization by cyano groups should be less than that by nitro groups, an increase in π-electron density, and hence in the upfield shifts, as a function of increasing cyano substitution is quite reasonable. Indeed, we have found a linear relationship between the H-3,5 chemical shifts of complexes **1–6** and the respective equilibrium constants for complex formation, *K* (Figure 3). No linear relationship exists, however, between the H-3,5 chemical shifts of the anisoles and *K* and thus the corresponding plot for $\Delta\delta$ and *K* exhibits a poor linear relationship. These results suggest that contributions other than electron density to the H-3,5 chemical shifts of complexes **1–6**, such as anisotropy, are either constant or relatively small and that approximate equilibrium constants for complexes containing other substituents at C-2, -4, and -6, *e.g.*, CF_3, could be predicted from the pmr spectra of the complex.

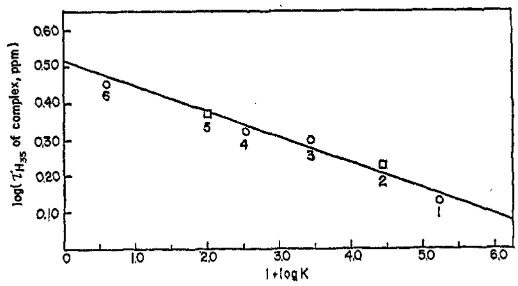

Figure 3.—Plot of log ($\tau_{H_{35}}$, ppm) for complexes **1–6** in DMSO-d_6 *vs.* log *K* for complex formation in methanol at 25.00°: ○, $\tau_{H_{35}}$; □, $(\tau_{H_3} + \tau_{H_5})/2$.

In the case of 2,4,6-trinitroanisole,[4,16] 2-cyano-4,6-dinitro- and 4-cyano-2,6-dinitroanisole,[4] and 2,4-dicyano-6-nitroanisole,[5] initial attack of methoxide ion was found to occur at C-3, an unsubstituted aromatic carbon atom para to a nitro group. In order to investigate this possibility and the existence of any other fairly stable transients involved in the interaction of methoxide ions with **7**, we examined the formation of **6** *in situ* in DMSO-d_6 using pmr spectroscopy. On the time scale necessitated by this technique,[4,5] no transients could be detected prior to or concurrent with the formation of **6**. On a much longer time scale (>24 hr at 42°), partial decomposition of **6** was found to occur.

Registry No.—**6**, 29826-25-3; **7**, 29897-71-0; **7** $O^{14}CH_3$, 29897-72-1; **8**, 13520-05-3.

Acknowledgment.—This study was supported, in part, by a grant from the U. S. Atomic Energy Commission, and a portion of the pmr studies were carried out with instrumentation provided by a grant (FR-00292) from the National Institutes of Health.

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[16] K. L. Servis, *J. Amer. Chem. Soc.*, **89**, 1508 (1967).

Kinetics and Mechanism of Methyl Transfer from Sulfonium Compounds to Various Nucleophiles

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A series of substituted phenyldimethylsulfonium perchlorates has been prepared and the reaction of these compounds with various nucleophiles has been investigated. With oxygen nucleophiles in water, elevated temperatures are required to effect methylation, whereas a slow reaction is observed with amines in water at 25°. A large solvent effect associated with these reactions permits the convenient study of the methylation of amine nucleophilies in acetonitrile at 25°. The values of ρ obtained from Hammett plots of the kinetic data are quite similar, using either hydroxide ion, pyrrolidine, or *n*-butylamine as the added nucleophile. Activation parameters and data derived from various linear free-energy relationships for the reaction of methylsulfonium compounds with nucleophiles are compared with data for the analogous reactions in which methyl iodide acts as the methylating agent. These data are discussed in relation to enzyme-catalyzed transmethylations which use the sulfonium compound *S*-adenosylmethionine as the methyl donor.

The process of transferring one-carbon moieties is ubiquitous in biological systems.[1] A considerable amount of information has been accumulated concerning the mechanism by which the folate enzymes activate formaldehyde and effect one-carbon transfer.[2] Equally important and even more widespread in their distribution in metabolic pathways are the reactions involving transfer of intact methyl or methylene groups.[3] Acceptors of these one-carbon moieties include such diverse molecules as catecholamines,[4] nucleic acids,[5] histones,[6] quinones and fatty acids,[7] to name but a few. The remarkable feature of biological transmethylations, involving such a wide variety of acceptor molecules, is that the donor of the "activated" methyl group is universally (−)-*S*-adenosyl-L-methionine[1] (**1**), hereafter referred to as SAM. The reaction of SAM with a nucleophilic acceptor results in the formation of *S*-adeno-

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[1] (a) S. H. Mudd and G. L. Cantoni in "Comprehensive Biochemistry," Vol. 15, M. Florkin and E. H. Stotz, Ed., Elsevier, New York, N. Y., 1964, p 1; (b) D. M. Greenberg, *Advan. Enzymol.*, **25**, 395 (1963).

[2] R. L. Blakley, "The Biochemistry of Folic Acid and Related Pteridines," Wiley-Interscience, New York, N. Y., 1969.

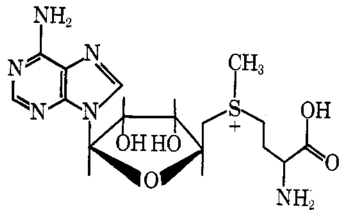
[3] S. K. Shapiro and F. Schlenk, Ed., "Transmethylation and Methionine Biosynthesis," University of Chicago Press, Chicago, Ill., 1965.

[4] J. Axelrod, *Recent Progr. Horm. Res.*, **21**, 597 (1965).

[5] E. Borek, *Annu. Rev. Biochem.*, **35**, 275 (1966).

[6] E. L. Gershey, G. W. Haslett, G. Vidali, and V. G. Allfrey, *J. Biol. Chem.*, **244**, 4871 (1969).

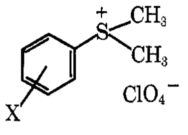
[7] E. Lederer, *Quart. Rev. Chem. Soc.*, **4**, 453 (1969).



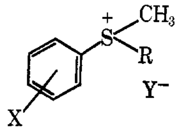
1

sylhomocysteine plus the methylated acceptor.[3] *A priori*, it would appear that this results from a simple nucleophilic attack on the methyl group in the same manner as nucleophilic attack occurs on the more common methylating agent, methyl iodide.[8] However, as discussed by Schlenk in a comprehensive review,[9] the chemistry of SAM and related sulfonium compounds is obviously more complex than methyl iodide.

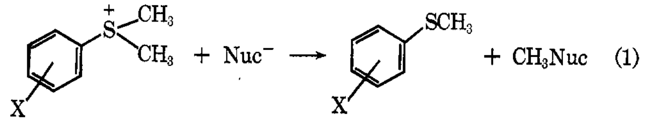
In order to have a chemical basis for understanding the specificity of enzyme-catalyzed transmethylation reaction between SAM and various acceptor molecules, a detailed mechanistic description of the nonenzymic process, similar to that which has been described for pyridoxal and related compounds,[10,11] is desirable. However, the chemical instability of SAM in aqueous media at pH > pK_a of the COOH group[12] renders this type of approach more difficult for SAM than for the less labile cofactors. The use of more stable sulfonium salts for kinetic studies of nonenzymic transmethylation can provide information about the chemistry of trivalent sulfur compounds, which is presently unavailable. A survey of the literature indicates that nucleophilic attack on sulfonium compounds takes place only under forcing conditions and that attack on the methyl group is rarely observed (see Discussion section). Furthermore, no detailed kinetic study of such a reaction has been undertaken. In order to study exclusive methyl transfer with a wide variety of nucleophiles, and to study substituent effects on the trivalent sulfur atom of the sulfonium compound, a series of 13 substituted phenyldimethylsulfonium compounds (2) were synthesized, and a kinetic investigation of the reaction of these compounds with oxygen and nitrogen nucleophiles according to eq 1 was carried out in water and acetonitrile.



2a, X = H
b, X = p-NO_2
c, X = p-Cl
d, X = p-COOH
e, X = p-OH
f, X = p-OCH_3
g, X = p-CH_3
h, X = p-CO_2CH_5
i, X = o-CH_3
j, X = o-CO_2H
k, X = o-$COCH_3$
l, X = o-$CH_2NH_2 \cdot HClO_4$



3a, X = H;
R = C_6H_5;
Y = ClO_4^-
b, X = H;
R = OCH_3;
Y = BF_4^-



2

Experimental Section

Materials.—The sulfonium salts used in this study together with their physical properties are listed in Table I. Except as noted below, all of these compounds were prepared by reacting the corresponding thioether with a slight excess of methyl iodide in the presence of anhydrous silver perchlorate, using ethylene chloride or acetonitrile as the solvent.[13] The precipitated silver iodide was removed from the reaction mixture by filtration. The filter cake was washed with solvent, and the combined filtrates were concentrated *in vacuo* to give the product either as a crystalline solid or as an oily residue, which readily crystallized from alcohol or alcohol–ether. The precursor thioethers were either commercially available or were prepared by literature methods. In the case of **21** (X = o-CH_2NH_2), methylation of the corresponding o-(aminomethyl)thioanisole would presumably result in a mixture of products due to competing N- and S-methylation; therefore, the amino group was blocked as the carbobenzyloxy derivative by treatment with carbobenzyloxy chloride in the usual manner.[14] The crude crystalline product, obtained on work-up of the reaction mixture (mp 56–59°), was suitable for use in further transformations. Methylation of this material with methyl iodide, as described above, gave an oily product which could not be crystallized. Cleavage of the carbobenzyloxy group with 70% perchloric acid gave the desired compound (**21**), as the bisperchlorate, mp 211–212.5° dec.

All attempts to prepare molecules of type **3**, in which the methyl group would be more susceptible to nucleophilic attack than in **3a** or **3b**, failed to give the desired materials. Thus, treatment of phenyl trifluoromethyl sulfide or bis(p-nitrophenyl) sulfide with either methyl iodide or dimethyl sulfate, under a variety of conditions, gave only unchanged thioethers on work-up of the reaction mixtures, and afforded none of the desired **3**, X = H and R = CF_3, or X = NO_2 and R = p-$O_2NC_6H_4$, respectively. Apparently the strong electron-withdrawing properties of the substituent group, which were expected to facilitate the transmethylation reaction by rendering the sulfur atom more electron poor, prevents the formation of the sulfonium compound *via* nucleophilic attack on the methylating agent by the sulfur atom.

Sodium hydroxide (Fisher) and all other inorganic salts were reagent grade and were used without further purification. All amines, except 1-phenylethanolamine (*vide supra*), were refluxed over calcium hydride or sodium and sodium hydroxide, and then distilled to give pure, anhydrous amines with boiling points and refractive indices in agreement with literature values. 1-Phenylethanolamine (Aldrich) could not be recrystallized or distilled without decomposition, and was used without further purification. It was shown to be a pure compound as judged by its chromatographic behavior, R_f 0.73 [2-propanol–acetic acid–H_2O (70:5:25)].[15] Acetonitrile (Fisher certified 99+%) was used without further purification, as it has been shown to be free of trace contaminants by polarography.[16]

Spectral Characteristics.—The infrared spectrum of all sulfonium compounds described in Table I showed a broad band centered at *ca.* 9 μ and extending from 8.5 to 10 μ. This enables one to readily distinguish the starting thioether from the desired sulfonium salt. Attempts to obtain meaningful nuclear magnetic resonance spectra (60 MHz) of these compounds were not successful in aqueous medium, since the maximum solubility of the compounds in water is only *ca.* 10^{-1} M. The ultraviolet spectra of the sulfonium compounds are quite different from the parent thioether as shown in Table II. In addition, the sulfonium com-

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[8] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, Chapter VII.

[9] F. Schenk, *Fortschr. Chem. Org. Naturst.*, **23**, 61 (1965).

[10] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, New York, N. Y., 1966, Chapter 8.

[11] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 133.

[12] (a) L. W. Parks and F. Schlenk, *J. Biol. Chem.*, **230**, 295 (1958); (b) J. Baddiley, W. Frank, N. A. Hughes, and J. Wieczorkowski, *J. Chem. Soc.*, 1999 (1962).

[13] T. Hashimoto, K. Ohkuho, H. Kitano, and K. Fukui, *Nippon Kagaku Zasshi*, **87**, 456 (1966); *Chem. Abstr.*, **65**, 15259*h* (1966).

[14] D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

[15] Lit. R_f 0.73: W. Drell, *J. Amer. Chem. Soc.*, **77**, 5429 (1955).

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TABLE I

PHYSICAL PROPERTIES AND ANALYSES OF SULFONIUM COMPOUNDS[a]

Sulfonium salt	X	Mp, °C	Lit mp, °C	Calcd, % C	Calcd, % H	Calcd, % Cl	Found, % C	Found, % H	Found, % Cl
2a	H	160–161.5	158–160[b]						
2b	p-NO_2	126–128		33.87	3.56	12.51	34.04	3.54	12.41
2c	p-Cl	153–155		35.19	3.70	25.96	35.40	3.90	25.81
2d	p-COOH	175–176		38.24	3.93	12.56	38.46	3.94	12.44
2e	p-OH	157–159	155–157[c]						
2f	p-OCH_3	84–86	84–86[c]						
2g	p-CH_3	123–124.5		42.78	5.18	14.05	42.88	5.38	14.29
2h	p-CO_2CH_3	131–134		40.48	4.42	11.96	40.63	4.30	11.92
2i	o-CH_3	101–103		42.78	5.18	14.05	42.89	5.19	14.27
2j	o-CO_2H	164–168		38.24	3.93	12.56	38.35	3.86	12.59
2k	o-$COCH_3$	179–181		42.79	4.67	12.65	43.01	4.75	12.59
2l	o-$CH_2NH_2 \cdot HClO_4$	211–212.5		29.37	4.10	19.26	29.37	3.90	19.15
3a	H (R = C_6H_5)	76–78.5	73–74[d]						
3b	H (R = OCH_3)	98–101	92–94[e]						

[a] Melting points are uncorrected. All analyses were performed by A. Bernhardt, 5251 Elbach über Engelskirchen, West Germany. [b] F. G. Bordwell and P. J. Boutan, *J. Amer. Chem. Soc.*, **78,** 87 (1956). [c] K. Hirose and S. Ukai, *Yakagaku Zasshi*, **86,** 187 (1966); *Chem. Abstr.*, **64,** 19466t (1966); compound prepared *via* different procedure. [d] See ref 13. [e] C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, **32,** 1926 (1967).

TABLE II

ABSORPTION MAXIMA OF SULFONIUM COMPOUNDS AND THE CORRESPONDING DEMETHYLATED THIOETHERS

Compd	λ^{S}_{max}, nm[a]	λ^{T}_{max}, nm[b]
2a	218	253
2b	248	342
2c	232	258
2d	230[c]	275
2e	242[d]	260
2f	243	253[e]
2g	227	255
2h	232	288
2i	222	247
2j	. . .[f]	255
2k	245	235
2l	222	250
3a	233	249

[a] Absorption maximum for sulfonium compound; c = *ca.* 10^{-4} M in water. [b] Absorption maximum for thioether product arising from demethylation of the numbered sulfonium compound; c = *ca.* 10^{-4} M in 1% acetonitrile:1 M NaOH (v:v). Nearly identical values of λ^{T}_{max} were obtained in 100% acetonitrile for compounds with no ionizable substituent. [c] In basic medium, no maximum with $\epsilon > 10^3$ was observed above the cutoff point of 230 nm. [d] In basic medium, λ_{max} 268 nm. [e] Reaction followed at 260 nm, the wavelength of maximum difference between the absorption spectra of **2f** and the product, p-methoxythioanisole. [f] In both neutral and basic media, no maximum of $\epsilon > 10^3$ was observed above the cutoff point of 230 nm.

pounds characteristically exhibit a weak doublet ($\epsilon < 10^3$) in the region *ca.* 50 nm above the λ_{max} (*i.e.*, generally *ca.* 265–275 nm).

Kinetics.—The kinetic measurements described herein were carried out in aqueous media and in pure acetonitrile solutions. The reactions in water were studied at 57.1 ± 0.3, 68.5 ± 0.3, and 78.8 ± 0.5°, and the temperature was maintained by allowing the reaction to proceed in sealed ampoules in a large round-bottom flask containing either acetone, n-hexane, or ethanol, respectively, at reflux. Because of the high temperatures involved, the strongly basic solutions attacked the glass of all sealed ampoules which were available commercially. Therefore, ampoules were made from Corning alkali-resistant tubing (no. 79900). These ampoules were not degraded by 1 M sodium hydroxide solution at 78° for a period of at least 1 week. The reactions in water were sufficiently slow so that the following experimental procedure was employed. A solution of sodium hydrxide of known normality was mixed with an aqueous solution (*ca.* 10^{-2} M) of the sulfonium salt, in a ratio which gave a final substrate concentration of *ca.* 10^{-4} M. Since the concentration of hydroxide was always at least 0.5 M, pseudo-first-order kinetics were obtained in all cases. The solution of substrate and hydroxide was then divided into 12–15 ampoules, which were sealed and placed in the refluxing solvent. Within 3–5 min, the bath temperature returned to the desired point (solvent reflux temperature), and the ampoules were allowed to equilibrate in the system for a total of 20 min. The first ampoule was then removed and opened, and the absorbance of the solution was recorded at 25.0 ± 0.1° as the initial data point. Additional samples were removed periodically and their absorbances recorded in a similar manner.

The measurements made in acetonitrile were carried out at 25.0 ± 0.1°. Since the reaction rates were considerably faster in this system than in the aqueous solutions described above, a slightly different procedure was employed to initiate the reactions and to monitor their progress. A solution (*ca.* 10^{-2} M) of the substrate in acetonitrile was added from a 20-μl pipet to a cuvette containing 3.0 ml of a solution of the amine nucleophile in acetonitrile, previously equilibrated at 25.0 ± 0.1°. The cuvette was inverted several times and immediately returned to the thermostated cell housing of the spectrophotometer for recording the change in absorbance. A similar procedure was employed to study the reaction of **2b** with inorganic anions in water except that the temperature of the cell housing was maintained at 78.5 ± 0.5°. The concentration of the sulfonium compound in the cuvette was *ca.* 6×10^{-5} M, and the concentration of added nucleophile was at least 0.01 M, so that pseudo-first-order kinetics were obtained in all cases.

The appearance of the thioether product was followed spectrophotometrically by recording the increase in optical density with time at the λ_{max} of the particular thioether (Table II). Repetitive scans of the ultraviolet and/or visible region of the spectrum showed clean isosbestic points, indicating no buildup of an intermediate which absorbed in the region scanned. The values of pseudo-first-order rate constants (k_{obsd}) were calculated from plots of log ($OD_\infty - OD_t$) *vs.* time.[17] First-order plots were linear for a minimum of two half-lives, and in most cases for more than three half-lives.

Apparatus.—Ultraviolet and visible spectra were measured on a Cary 15 recording spectrophotometer, which was used for all repetitive scans of the initial kinetic runs. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer. All kinetic measurements were carried out on a Gilford 2400 recording spectrophotometer (or a Beckman DU monochromator equipped with a Gilford automatic cuvette positioner and photometer). The temperature in the spectrophotometer cell compartments was maintained with water from a large thermostated circulating bath.

Results

The reaction of sulfonium compounds **2** with nucleophiles follows the rate law of eq A, which yields eq B

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[17] Reference 11, p 558.

$$dP/dt = v = k_2[\mathrm{S}][\mathrm{Nuc}] \qquad \text{(A)}$$

$$k_{\mathrm{obsd}} = k_{\mathrm{OH}}[\mathrm{OH}] \qquad \text{(B)}$$

when hydroxide is used as the nucleophile under the pseudo-first-order conditions employed. A plot of the data of Table III shows the dependence of k_{obsd} on hydroxide ion concentration for the decomposition of **2c**. The observed rate constants in 1 *M* hydroxide are given in Table IV. Unfortunately, the slow rates of reaction of these compounds with hydroxide ion precluded measurement of rates in solutions containing less than 1 *M* hydroxide for compounds other than **2c**. A Hammett plot[18] of the data for the para-substituted compounds in Table IV is shown in Figure 1. The value for ρ is 1.60; only the sulfonium compound containing the charged *p*-carboxylate substituent (**2d**) deviates from the line. Similarly, the effect of temperature on the rate of decomposition of **2c** by hydroxide ion is shown in Table V. An Arrhenius plot of these data (Figure 2) allows the calculation of E_a = 25.6 kcal/mol. From these data, the values of $\Delta F^{\ddagger}$ = 26.3 kcal/mol, $\Delta H^{\ddagger}$ = 24.8 kcal/mol, and $\Delta S^{\ddagger}$ = −5.0 eu can be obtained.

TABLE III

EFFECT OF HYDROXIDE ION CONCENTRATION ON THE RATE OF DECOMPOSITION OF **2c**[a]

[OH⁻], *M*	$k_{\mathrm{obsd}} \times 10^4$, sec⁻¹ [b]	$k_{\mathrm{OH}} \times 10^4$, *M*⁻¹ sec⁻¹
1.0	2.45 ± 0.10	2.45 ± 0.10
0.75	1.54 ± 0.06	2.05 ± 0.08
0.5	0.85 ± 0.07	1.70 ± 0.14

[a] Temperature 78.8 ± 0.5°; μ = 1.0 with $NaClO_4$. [b] Average of at least three determinations.

TABLE IV

OBSERVED RATE CONSTANTS FOR HYDROXIDE ION CATALYZED DECOMPOSITION OF **2**[a]

Compd	X	σ_{para}[b]	$k_{\mathrm{obsd}} \times 10^4$, sec⁻¹
2a	H	0	1.14 ± 0.10
2c	*p*-Cl	0.23	2.45 ± 0.10
2d	*p*-COO^-	0.13[c]	2.20 ± 0.14
2f	*p*-OCH_3	−0.27	0.39 ± 0.00
2g	*p*-CH_3	−0.17	0.58 ± 0.06
2i	*o*-CH_3		1.01 ± 0.08
2j	*o*-COO^-		0.72 ± 0.04
2l	*o*-CH_2NH_2		1.68 ± 0.09

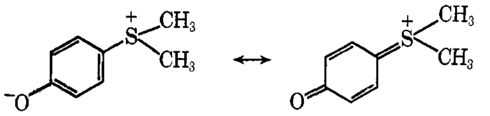
[a] Temperature 78.8°; μ = 1.0. [b] σ values from C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964) except for *p*-COO^-. [c] H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

TABLE V

EFFECT OF TEMPERATURE ON THE RATE OF DECOMPOSITION OF **2c** BY HYDROXIDE ION

Temp, °C	$k_{\mathrm{obsd}} \times 10^5$, sec⁻¹
57.1 ± 0.3	2.35 ± 0.16
68.5 ± 0.3	7.58 ± 0.25
78.8 ± 0.5	24.5 ± 1.0

The reaction of several sulfonium ions of type **2** failed to give the products expected from eq 1. For example, the *p*-hydroxy compound (**2e**) is almost totally unreactive under the conditions used in this study. The fact that the *p*-methoxy derivative (**2f**) reacts with hydroxide, as expected, to form the corresponding thioether and methanol indicates that the oxyanion of **2e** is particularly resistant to hydrolysis. This is presumably due to the large contribution of the inert quinoid form in the resonance hybrid shown below. This type of hybrid has been proposed previously[19] on the basis of pK_a and ultraviolet absorption spectral measurements. Similarly, the reaction of **2k** with hydroxide failed to give the corresponding thioether but, rather, led to a thianaphthene derivative. This reaction is not without precedent, having been observed previously for the corresponding *p*-methyl derivative.[20]



The reaction of the *p*-nitro compound (**2b**) with hydroxide ion leads to the formation of *p*-nitrophenolate ion and dimethyl sulfide, indicated by the development of an intensely yellow colored solution during reaction and an ultraviolet spectrum with $\lambda_{\max}$ 400 nm. No reaction of **2b** with other oxygen nucleophiles could be detected at 25° in aqueous media. However, at 78° a slow reaction was observed with carbonate ion according to eq 1 to give *p*-nitrothioanisole ($\lambda_{\max}$ 350 nm). Only when a nucleophile is employed which has an appreciable degree of polarizability (*i.e.*, a soft nucleophile[21]) does transmethylation occur as in eq 1. This type of reaction was originally observed with thiocyanate as the nucleophile[22] and was referred to as an "abnormal reaction," in that the nucleophile attacked the methyl group in a simple S_N2 reaction rather than the aromatic nucleus *via* an addition–elimination mechanism. It is well known[23] that nucleophiles such as iodide, thiocyanate, etc., attack a saturated sp^3 carbon in preference to an sp^2-hybridized carbon atom. For this reason, the reaction of **2b** with several inorganic nucleophiles was studied and the rate data are shown in Table VI. A plot of these data by the Swain–Scott procedure[24] is shown in Figure 3. The slope of the line of this plot is equal to 1.14.

TABLE VI

REACTION OF **2b** WITH VARIOUS INORGANIC NUCLEOPHILES IN WATER[a]

Nucleophile	n[b]	k_2, *M*⁻¹ sec⁻¹
SCN^-	4.77	1.35×10^{-3}
I^-	5.04	2.21×10^{-3}
$S_2O_3^{2-}$	6.36	8.58×10^{-2}

[a] Temperature 78.5 ± 0.5°; reaction run in 0.2 *M* HCO_3^-–CO_3^{2-} buffer (1:1), pH 9.66; μ = 1.0 with $NaClO_4$. Added nucleophile concentration = 3.3×10^{-2} to 6.0×10^{-1} *M*. [b] Nucleophilicity constant of Swain and Scott.[24]

The inability to observe facile transmethylations in aqueous media prompted investigation of the reactions of **3** containing strongly electron-withdrawing R groups. All attempts to isolate such compounds failed (see

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[18] L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, Chapter II.

[19] C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, p 152.

[20] (a) F. Krollpfeiffer, H. Hartmann, and F. Schmidt, *Justus Liebigs Ann. Chem.*, **563**, 15 (1949). (b) R. A. Guerra, *Acta Salmanticensia, Ser. Cienc.*, **6**, 7 (1963); *Chem. Abstr.*, **63**, 5581h (1965).

[21] R. G. Pearson, *Surv. Progr. Chem.*, **5**, 1 (1969).

[22] B. A. Bolto and J. Miller, *J. Org. Chem.*, **20**, 558 (1955).

[23] (a) Reference 10, Vol. I, p 42; (b) ref 11, p 85.

[24] C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 141 (1953).

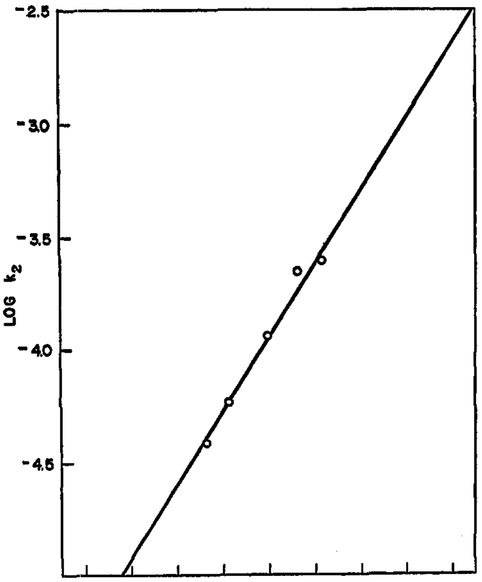
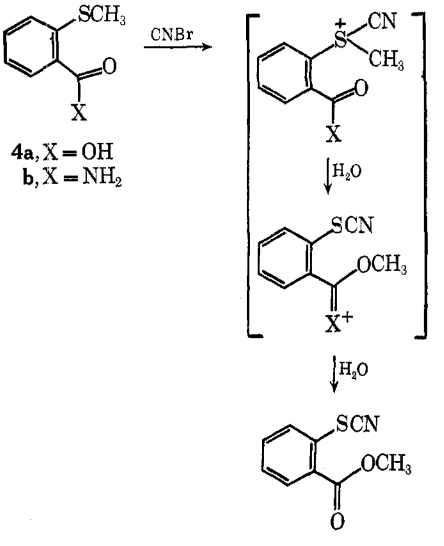


Figure 1.—Hammett plot for the hydroxide ion catalyzed hydrolysis of **2** in water at 78.5 ± 0.5°.

Experimental Section). We attempted to generate a more reactive sulfonium ion *in situ*, by reaction of a thioether with cyanogen bromide, a method which has been used extensively for selective cleavage of methionine-containing peptides.[25] The reaction anticipated in the current work is shown in eq 2.



4a, X = OH
b, X = NH$_2$

(2)

5

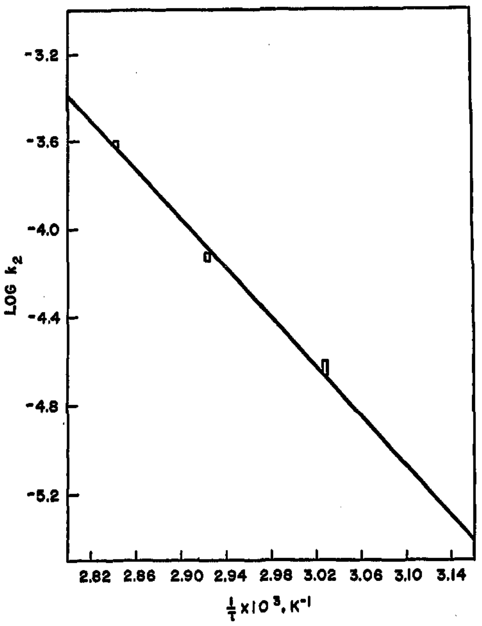


Figure 2.—Arrhenius plot for the hydroxide ion catalyzed hydrolysis of **2c** in water.

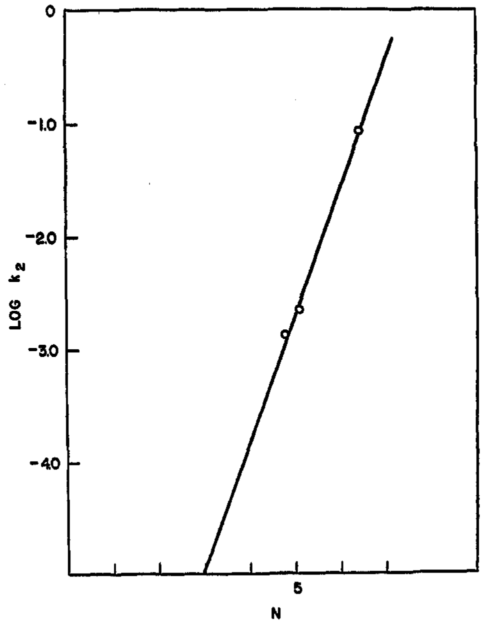


Figure 3.—Swain-Scott plot for the reaction of **2b** with nucleophiles in water at 78.5 ± 0.5°.

Repetitive scanning of the solution of **4** in 0.1 *M* CNBr and 0.1 *M* HCl[26] showed no change in the ultraviolet spectrum at ambient temperature over a period of up to 6 hr. The ultraviolet absorption spectrum of **4** had λ_{max} 257 nm, whereas the ultraviolet absorption spectrum of **5**, synthesized by an independent route,[27] had λ_{max} 245 and 222 nm. Thus, in contrast to the facile cleavage under these conditions of methionine-containing peptides, no analogous conversion of **4** to **5** was detectable. The reactions of **2j** and **2l** were also investigated in an attempt to effect transmethylation from a methylsulfonium compound to an adjacent carboxylate or amine nucleophile. No evidence for a facile intramolecular reaction could be obtained. Studies in this area are continuing and the results will be reported in a future paper.

Large solvent effects in reactions involving decomposition of formally charged molecules to neutral molecules have been noted for some time.[28] In order to investigate the reaction of sulfonium compounds with nucleophiles in a nonaqueous medium, it was decided to work with amine nucleophiles in acetonitrile. A major factor in this decision was the fact that the pK_a of many representative amines have been determined in aceto-

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[25] B. Witkop, *Advan. Protein Chem.*, **24**, 91 (1970), and references therein.

[26] E. Gross and B. Witkop, *J. Biol. Chem.*, **237**, 1856 (1962).

[27] R. K. Olsen and H. R. Snyder, *J. Org. Chem.*, **30**, 187 (1965).

[28] Reference 8, p 457.

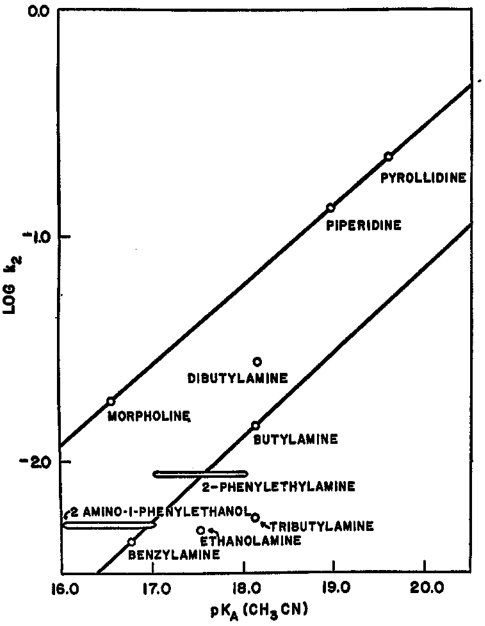


Figure 4.—Brønsted plot for the reaction of **2b** with various amine nucleophiles in acetonitrile at 25 ± 0.1°.

nitrile.[29] The second-order rate constants for reaction of the *p*-nitrophenyldimethylsulfonium compound, **2b**, with various amines are given in Table VII. A Brønsted plot[30] of these data is shown in Figure 4, and a value $\beta = 0.36$ is obtained from the slopes of the lines, primary and secondary amines being clearly separated. Two representative amines, namely, pyrrolidine and *n*-butylamine, were used as nucleophiles in order to study most of the sulfonium ions of types **2** and **3**. These data are presented in Table VIII and the Hammett plots[18] given in Figure 5. It can be seen that the slopes of the lines ($\rho = 1.74 \pm 0.05$) for both sets of data are quite similar and are in good agreement with the value obtained for the reaction of hydroxide ion with **2** in water (Figure 1).

TABLE VII

REACTION OF **2b** WITH AMINES IN ACETONITRILE[a]

Amine	$pK_a^{CH_3CN}$ [b]	k_2, M^{-1} sec^{-1}
n-Butylamine	18.26	1.43×10^{-2}
Di(*n*-butyl)amine	18.31	2.74×10^{-2}
Tri(*n*-butyl)amine	18.09	5.71×10^{-3}
Ethanolamine	17.53	4.88×10^{-3}
Benzylamine	16.76	4.36×10^{-3}
β-Phenylethylamine	17.5 ± 0.5[c]	8.65×10^{-3}
Phenylethanolamine	16.5 ± 0.5[c]	5.17×10^{-3}
Morpholine	16.61	1.85×10^{-2}
Piperidine	18.92	1.45×10^{-1}
Pyrrolidine	19.58	2.20×10^{-1}

[a] Temperature 25 ± 0.1°. [b] $pK_a^{CH_3CN}$ from ref 29, unless noted otherwise. [c] $pK_a^{CH_3CN}$ estimated from a plot of $pK_a^{H_2O}$ *vs.* $pK_a^{CH_3CN}$ for those amines whose pK_a's were known in both solvents. There is considerable uncertainty in these values.

TABLE VIII

EFFECT OF SUBSTITUENTS ON THE RATE OF REACTION OF SULFONIUM COMPOUNDS WITH *n*-BUTYLAMINE AND PYRROLIDINE IN ACETONITRILE[a]

Compd (X)	σ_{para}[b]	$k_{2p} \times 10^2$,[c] M^{-1} sec^{-1}	$k_{2b} \times 10^3$,[d] M^{-1} sec^{-1}
2a (H)	0	1.04	0.55
2b (NO_2)	0.78	22.0	14.3
2c (Cl)	0.23	2.46	1.61
2g (CH_3)	−0.17	0.54	
2h (CO_2CH_3)	0.45	5.68	3.38
2i (*o*-CH_3)		1.05	
3a		22.5	11.8

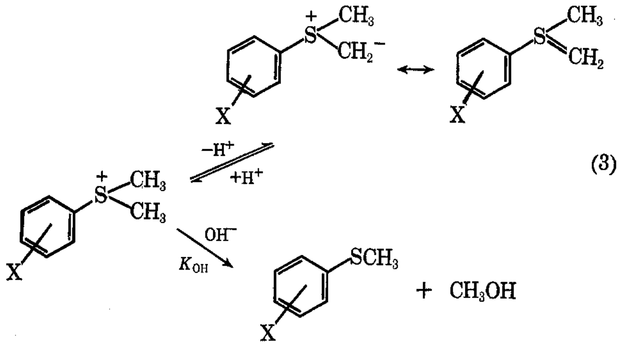
[a] Temperature 25 ± 0.1°. [b] See footnote *b*, Table IV. [c] Second-order rate constant using pyrrolidine as added nucleophile over the concentration range 10^{-2} to 10^{-1} *M*. [d] Second-order rate constant using *n*-butylamine as added nucleophile over the range 10^{-2} to 10^{-1} *M*.

Discussion

It has been known for some time that sulfonium compounds are extremely resistant to attack by oxygen nucleophiles.[31] The sulfonium compounds employed in the present study also require vigorous conditions to effect transmethylation with oxygen nucleophiles in water but, as will be discussed below, changes in solvent and/or nucleophile drastically alter the rate of nonenzymic transmethylation. The acidity of protons attached to the α carbon of sulfonium compounds permits the formation of sulfonium ylides.[32] In the present work this ylide would not be reactive and the reaction scheme of eq 3 would apply. This is a system of the general type shown below, *i.e.*, preequilibrium ionization

$$E^- \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} EH \xrightarrow{k_{rate}} \text{product}$$

of an acidic group to give an unreactive moiety at the expense of the reactive species. This type of kinetic scheme predicts that k_{obsd} will be insensitive to increasing concentrations of hydroxide ion at pH > pK_a of EH since the enhanced rate of reaction due to the increased concentration of OH^- will be equally offset by the decreased concentration of the reactive species, EH.[33] As can be seen by the data of Table III, the values of k_{obsd} are strongly dependent on the concentration of hydroxide ion, and there is no indication of a hydroxide-independent rate in the region studied. This indicates that the pK_a of compounds of type **2** is considerably higher than 14. Johnson[32] has estimated the pK_a of the methyl protons of **6** to be >17.3 based on the



(3)

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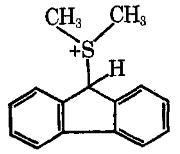
[29] J. F. Coetzee, *Progr. Phys. Org. Chem.*, **4**, 45 (1967).

[30] Reference 11, p 170.

[31] (a) J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 236 (1935); (b) F. Challenger, R. Bywood, P. Thomas, and B. J. Hayward, *Arch. Biochem. Biophys.*, **69**, 514 (1957).

[32] A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 9.

[33] Reference 10, Vol. I, Chapter 1.



6

assumption that the tertiary proton at the peri positive of 6 (measured pK_a in aqueous dioxane = 7.3[34]) is at least 10^{10} more acidic than the methyl protons.

Franzen and Driessen[35] have shown that the preparation of ylides from dimethylphenylsulfonium salts requires strong bases (*e.g.*, *tert*-butoxide) in rigorously anhydrous dimethyl sulfoxide. In the work reported herein, the presence of the relatively strong acid, water, would result in immediate protonation of any ylide formed. In deuterated water, this would result in exchange of the acidic protons. Attempts to measure this rate of exchange by nuclear magnetic resonance spectroscopy were unsuccessful owing to the low solubility of 2 in D_2O (see Experimental Section). Although there are several references in the literature to the facile exchange of α protons of sulfonium compounds in aqueous media,[36] the conclusion from the present work is that these exchange processes involve kinetically insignificant amounts of the ylide in a rapid equilibrium at pH 14. Thus, the data of Table IV is unencumbered by any preequilibria considerations, and the ρ value of 1.55 obtained from Figure 1 is a direct measure of the effect of the substituent group on the rate of hydrolysis.

The activation parameters derived from the data of Table V and Figure 2 afford insight into the reasons for resistance of 2 to hydrolytic decomposition. The thermodynamic parameters ΔG, ΔH, and ΔS for the process of transforming a sulfonium compound to a thioether have been known for some time.[37] Although the values have been revised on several occasions, the free energy of reaction is *ca.* -7 to -10 kcal/mol, which is of the same order as the so-called high-energy bond of ATP. However, it can be seen that, although the process of transforming a sulfonium compound to a thioether is thermodynamically favored, large activation parameters prevent the reaction from going to completion in water, except under forcing conditions.

The reaction of **2b** with several inorganic nucleophiles gives the kinetic data of Table VI, which is shown graphically in Figure 3. The linear free-energy relationship of Swain and Scott[24]

$$\log k_n = \log k_0 + sn$$

where n is the nucleophilicity constant for the particular nucleophile employed and s is the susceptibility of the substrate undergoing nucleophilic attack. The value of s obtained from Figure 3 (1.14 ± 0.06) is close to that arbitrarily assigned for the reaction of methyl bromide with various nucleophiles.[24] Since the reation of methyl bromide with added nucleophiles is known to be a simple S_N2 displacement reaction,[38] the similar magnitude of the s values (*ca.* 1.0) for both methyl bromide and **2b** would suggest that in both cases bond-breaking is not far advanced in the transition state; *i.e.*, little development of positive charge has occurred on the carbon undergoing attack. By contrast, recent studies on several types of methylsulfonium compounds provide information on the mechanism of transalkylation for alkyl groups capable of forming more stable incipient carbonium ions. The generalized structures studied are shown in 7–9, and the alkyl residue attacked

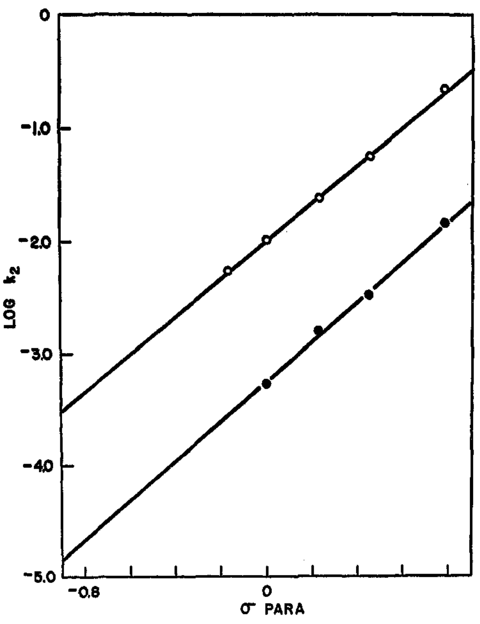
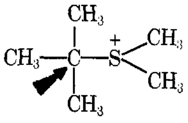


Figure 5.—Hammett plot for the reaction of 2 with pyrrolidine (O) and n-butylamine (●) in acetonitrile at 25°.



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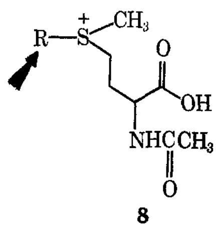

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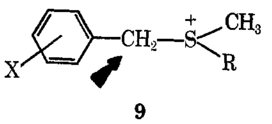

9

in each case is indicated by the arrow. In no case is the methyl group "transferred" to the attacking nucleophile at elevated temperatures (60–70°). The decomposition of 7 in aqueous ethanol or other mixed solvents was studied by Hyne and Jensen[39] and, in a related case, Jendrek[40] studied the decompositon of **8**, where R is allyl, cinnamyl, and substituted benzyl. These reactions obey the Swain–Scott relationship,[24] and, although neither group of workers discussed the significance of the s values derived from their data, both plots clearly

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[34] A. W. Johnson and R. B. LaCount, *Tetrahedron*, **9**, 130 (1960).

[35] V. Franzen and H. E. Driessen, *Chem. Ber.*, **96**, 1881 (1963).

[36] (a) W. von E. Doering and A. K. Hoggman, *J. Amer. Chem. Soc.*, **77**, 521 (1955); (b) ref 3, p 61; (c) ref 9, p 70.

[37] (a) S. H. Mudd, W. A. Klee, and P. D. Ross, *Biochemistry*, **5**, 1653 (1966); (b) J. Durell, M. Rawitscher, and J. M. Sturtevant, *Biochem. Biophys. Acta*, **56**, 552 (1962); (c) J. Durell and J. M. Sturtevant, *ibid.*, **26**, 282 (1957).

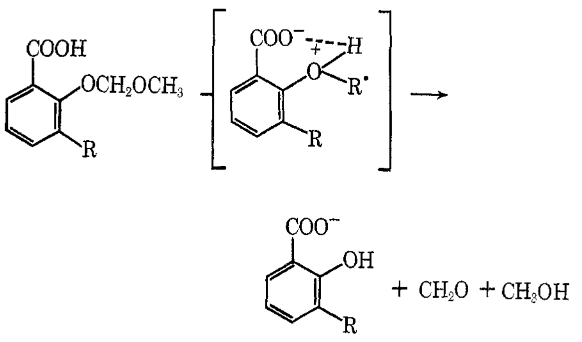
[38] C. A. Bunton, "Nucleophilic Substitution at Saturated Carbon," Elsevier, Amsterdam, 1963.

[39] (a) J. B. Hyne and J. H. Jensen, *Can. J. Chem.*, **43**, 57 (1965), and references therein; (b) J. H. Jensen, Ph.D. Thesis, University of Alberta, Calgary, Alberta, 1964.

[40] J. F. Jendrek, Ph.D. Thesis, Tulane University, New Orleans, La., 1967; *Diss. Abstr.*, *B*, **28**, 4031 (1968).

show a very low sensitivity of rate to the added nucleophilic species, and a value of $s = 0.16 \pm 0.02$ is obtained. It is apparent that in molecules such as **7** and **8**, which contain groups capable of forming stable carbonium ions, low s values are obtained, indicative of considerable development of carbonium ion character in the transition state; *i.e.*, bond-breaking of the C–S bond is far advanced in the transition state. Similarly, the decomposition of **9** studied by Schowen[41] proceeds with exclusive attack of OH^- on the benzylic carbon to the complete exclusion of the transmethylation reaction. This would suggest the development of considerable bond-breaking in the transition state, but a more rigorous proof is not immediately discernible from the available data.

In order to explain the observed rate-enhancing effect of the *o*-methyl substituent (**2i**, Table IV), steric factors must be considered. The fact that the ortho-substituted compound (**2i**) is hydrolyzed *ca.* twice as fast as the corresponding para isomer (**2g**) must be due to the steric bulk of the *o*-methyl group. This substituent presumably forces the dimethylsulfonio group out of the plane of the aromatic ring, thus decreasing orbital overlap and making delocalization of the positive charge less likely. Of interest in this regard are the recent data of Dunn and Bruice,[42] which demonstrate a similar rate enchancement by ortho substituents for the reaction shown in eq 4. The similarity between the oxonium ion transition state of eq 4 and the sulfonium ions of the present work is obvious, and it is not surprising that similar rate effects on hydrolytic reactions should be observed with bulky ortho substituents. In the course of investigating possible intramolecular transmethylation reactions, the reactions of **2j** (o-COO^-) and **2l** (o-CH_2NH_2) with hydroxide ion were studied. The data of Table IV show a 50% rate enhancement for the more bulky o-CH_2NH_2 substituent (**2l**) in comparison to the o-CH_3 group (**2i**). This is to be expected based on the steric considerations discussed above. However, the decreased rate of hydrolysis observed for **2j** (o-COO^-) *vs.* **2i** is not predicted on steric grounds.[42] The *o*-carboxylate anion seems to stabilize the sulfonium compound against hydrolytic decomposition, presumably by an electrostatic interaction between the adjacent formally charged groups. This type of interaction has been suggested by Casanova and coworkers[43] to explain the large decrease in pK_a for *o*-(dimethylsulfonio)phenylacetic acid in comparison with the para isomer. In contrast, the data of Dunn and Bruice for the reaction shown in eq 4 indicate a large rate enhancement when $R = COO^-$. The important difference between the two cases is that in eq 4 steric acceleration by the bulky *o*-carboxylate group results in a more facile reaction, while in the present work stabilization of the formally charged sulfonium ion by the *o*-carboxylate in the ground state results in an increase in the activation energy, and therefore a slower rate of reaction.



(4)

The reaction of sulfonium compounds with amines in acetonitrile was studied in the same way as described above for the hydroxide-catalyzed reactions in water, and the derived data are shown in Tables VII and VIII. The relative insensitivity of k_2 to changes in pK_a of the attacking nucleophile (Figure 4), as indicated by the low β value of 0.35, shows that the transfer of the electrophilic methyl group of **2b** is not far advanced in the transition state, in accord with the conclusion deduced from data obtained for hydroxide ion and compounds of type **2** in water. The fact that the data of Figure 4 clearly separates into two lines, one for primary amines and the other for secondary amines, is of interest since this type of behavior is generally attributed to solvation effects in aqueous media.[44] However, as has been pointed out by Gregory and Bruice,[44a] these examples involve substrates in which bond formation between nucleophile and the substrate is not very complete in the transition state. By contrast, a substrate in which bond formation is much more complete in the transition state (*e.g.*, phenyl acetate[45]) does not distinguish between primary and secondary amines. The fact that sulfonium ions such as **2** exhibit this type of discrimination is further evidence that bond-making between the nucleophile and sulfonium methyl group is not far advanced in the transition state. The deviation of di(*n*-butyl)amine from the line for secondary amines is presumably due to steric hindrance to nucleophilic attack by an acyclic secondary amine in comparison to a more facile attack by the exposed nitrogen lone pair of cyclic secondary amines. This type of steric inhibition to nucleophilic attack should be even more pronounced in the case of tri(*n*-butyl)amine, which is considerably slower than di(*n*-butyl)amine in this reaction. However, one of the products formed in the reaction of tri(*n*-butyl)amine with **2b** is tri(*n*-butyl)methylammonium perchlorate. The formation of this formally charged ammonium compound could be retarded in an aprotic solvent such as acetonitrile, thus leading to a depressed rate of reaction in comparison to other amines of similar pK_a. An explanation for the slight negative deviation of ethanolamine from the line for primary amines is not readily apparent at this time. Considering the uncertainties in the estimated pK_a values for β-phenylethylamine and β-phenylethanolamine, the rate data show that these amines react at a rate consistent with their base strength. Unfortunately, it was not possible

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(41) (a) C. G. Swain, W. D. Burrows, and B. J. Schowen, *J. Org. Chem.*, **33**, 2534 (1968). (b) B. J. Schowen, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1964; Abstracts of Theses, 1964–1965, MIT Press, Cambridge, Mass., 1969, p 240.

(42) B. M. Dunn and T. C. Bruice, *J. Amer. Chem. Soc.*, **92**, 2410, 6589 (1970).

(43) J. Casanova, Jr., N. D. Werner, and H. R. Kiefer, *ibid.*, **89**, 2411 (1967).

(44) (a) M. J. Gregory and T. C. Bruice, *ibid.*, **89**, 2327 (1967); (b) S. J. Benkovic and P. A. Benkovic, *ibid.*, **88**, 5504 (1966); (c) A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3209 (1965); (d) R. G. Pearson and F. V. Williams, *ibid.*, **76**, 258 (1954).

(45) T. C. Bruice, A. R. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).

TABLE IX

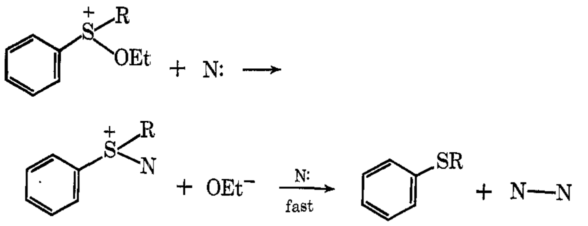
COMPARISON OF KINETIC DATA FOR 2 AND METHYL IODIDE[a]

Nucleophile	OH⁻				R₃N		Inorganic anions				
Substrate	k_{OH}^{298}	E_a	$\Delta F_{298}^{\ddagger}$	$\Delta S_{298}^{\ddagger}$	k_{R_3N}	β	s	k_{SCN}^{298}	E_a	$\Delta F_{298}^{\ddagger}$	$\Delta S_{298}^{\ddagger}$
$CH_3S^+{<}^{CH_3}_{C_6H_4R(p)}ClO_4^-$	3.05×10^{-7} [b]	25.6	26.3	−5.0	1.61×10^{-3} [c]	0.35	1.14	5.01×10^{-6} [d]	23.8	24.6	−4.7
CH_3I	6.52×10^{-5} [e]	22.2[e]	23.1	−5.0	3.1×10^{-3} [f]	0.22[f]	1.15[e]	4.68×10^{-4} [g]		21.9	

[a] Reactions carried out in water, except when noted otherwise. All rate data are in units of M^{-1} sec^{-1}; E_a and ΔF are in units of kcal/mol, and ΔS values are in entropy units (gibbs). [b] R = Cl; extrapolated from Figure 2. [c] R = Cl; data for *n*-butylamine from Table VIII; reaction carried out in 100% acetonitrile. [d] R = NO_2; extrapolated from data of ref 22 and this research. [e] Data from a compilation of earlier work cited in ref 49. [f] Derived from data of ref 48; k_{R_3N} is for methylamine at 30°. [g] Value obtained from data of footnote *e* for other inorganic nucleophiles and assuming that k_{SCN} lies on the Swain–Scott[24] line of slope, s = 1.15.

to study the reaction of norepinephrine in this system because of the low solubility of the amine in acetonitrile.

In Figure 5, the rate data of Table VIII for reaction of **2** with pyrrolidine and *n*-butylamine are plotted by the method of Hammett.[18] The similarity in the slopes of the lines obtained with two different amine nucleophiles, in addition to the similar slope using hydroxide ion as the nucleophile (Figure 1), serves to indicate that the substituent effect on the rate of attack at the methyl group of **2** are not sensitive to the nature of the attacking nucleophile. The effect of a change in substituent directly attached to the trivalent sulfur is shown by comparing the data in Table VIII for **2a** and **3a**. Using either pyrrolidine or *n*-butylamine as the added nucleophile, k_2 for **3a** is *ca.* 20 times that for **2a**, indicating the large rate-enhancing effect of placing a more electron-withdrawing group directly on the already electron-deficient sulfur atom. This substituent effect could not be investigated more completely because of the inability to synthesize **3** containing R groups more electron deficient than phenyl. No reaction could be detected between **3b** and *n*-butylamine in acetonitrile at ambient temperature by repetitive scanning in the ultraviolet and visible region of the spectrum. This is in contrast to the observation of a facile reaction between *p*-toluenethiolate anion and ethoxydiphenylsulfonium tetrafluoroborate in ethanol at −10 to −5°.[46] The mechanism proposed for this reaction involves the initial attack by thiolate anion on the trivalent sulfur atom, displacing ethoxide ion as shown in eq 5. The lack of



(5)

reactivity of **3b** toward an amine nucleophile presumably is due to the inability of the amine to displace ethoxide ion in acetonitrile.

Of primary interest in the present study is the delineation of the kinetic parameters for methylations involving methylsulfonium compounds *vis-à-vis* those reactions utilizing other methylating agents such as methyl iodide. A summary of some comparative data is given in Table IX. It can be seen that in all cases the reaction of a given nucleophile with methyl iodide is *ca.* 10 to 100 times faster than with **2**. In the case of the hydroxide-catalyzed hydrolyses, similar entropies of activation are calculated for the two reactions, and the rate differences therefore must arise from the more positive energy of activation for **2** *vs.* methyl iodide. These data provide additional evidence for the bimolecular nature of the reaction of **2** with nucleophiles, since negative entropies of activation of this magnitude are associated with many bimolecular processes.[47] The value of β for the reaction of amines with **2** is similar to that observed in the aminolysis of methyl iodide in water, where the low β value of 0.2 has been taken as evidence indicating little bond formation between amine and methyl iodide in the transition state.[48] The reaction of methyl iodide with mercaptoethylamine has been shown to occur very readily at 25° in aqueous media,[49] and recent observations in this laboratory have demonstrated a similar facile reaction between thiols and **2**.[50] These qualitative and quantitative similarities in the kinetic properties of **2** and methyl iodide indicate that the mechanism of transmethylation from simple sulfonium compounds to a variety of added nucleophiles is very similar to that involved in nucleophilic attack on methyl iodide, *i.e.*, a classic SN2 displacement mechanism. Of interest in terms of enzyme-catalyzed transmethylation is the relative reactivity of added nucleophiles (O < N < S) observed in the system described in eq 1. Schlenk and coworkers[51] have recently delineated the requirements for the sulfonium methyl donor in three enzyme-catalyzed reactions, involving methyl transfer to oxygen, nitrogen, and sulfur nucleophiles. The data for the enzymic processes clearly show a strict requirement for the usual methyl donor, SAM, in the *O*-methylase reaction (acetylserotonin methyltransferase), whereas the *N*-methylase (histamine *N*-methyltransferase) will carry out the reaction, albeit quite inefficiently, using the inosine analog of SAM as the methyl donor. These findings are in accord with the present work in that the more reactive amine nucleophile involved in an *N*-methylase can be expected to be less discriminating in its reactions than the much less reactive oxygen nucleophiles. Similarly the highly reactive thiol group should be even less discriminating toward methylsulfonium compounds, and the *S*-methylases use a number of derivatives of SAM *in vitro*.[51] *In vivo*, even simple thetins and *S*-methylmethionine are effective with the *S*-methylase.[9]

From the current work, it is concluded that the transition state for nucleophilic attack on **2** by a variety of nucleophiles is as shown in **10**. It seems reasonable to

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(46) S. Oae and Y. H. Khim, *Bull. Chem. Soc. Jap.*, **42**, 3528 (1969).

(47) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

(48) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967).

(49) R. E. Davis, S. P. Molnar, and R. Nehring, *ibid.*, **91**, 97 (1969).

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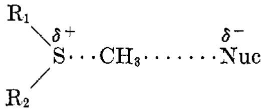

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assume that a similar transition state is involved in methyl transfer from any methylsulfonium compound. In order to test this hypothesis, we are continuing the study of nonenzymic transmethylation on molecules which are more closely related to SAM in structure, but which are not so readily decomposed in basic media.

Registry No.—**2a**, 29898-80-4; **2b**, 29843-53-6; **2c**, 29898-81-5; **2d**, 29898-82-6; **2e**, 5556-64-9; **2f**, 5556-65-0; **2g**, 29913-34-6; **2h**, 29913-35-7; **2i**, 29913-36-8; **2j**, 29913-37-9; **2k**, 29913-38-0; **2l**, 29890-17-3; **3a**, 10504-64-0; **3b**, 706-63-8.

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Catalysis of Nucleophilic Substitutions by Micelles of Dicationic Detergents[1]

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Dicationic detergents (I), $\mathrm{RN^+Me_2(CH_2)_nN^+Me_2R\ 2Br^-}$ (where R = cetyl and n = 4 and 6), readily micellize, and the micelles are effective catalysts of the reactions of hydroxide ions with chloro- and fluoro-2,4-dinitrobenzene and hydroxide and fluoride ions with *p*-nitrophenyl diphenyl phosphate. With n = 4 and 6, those detergents are two- to fivefold better catalysts than cetyltrimethylammonium bromide, CTABr. The dicationic detergent $\mathrm{RN^+Me_2CH_2C{\equiv}CCH_2N^+Me_2RBr_2^-}$ also micellizes, but it and I (n = 2) are not markedly better catalysts than CTABr.

Catalysis by ionic micelles and polyelectrolytes is well established and has been extensively reviewed.[3-6] The catalysis can be explained qualitatively in terms of the ionic and hydrophobic interactions of the reactants and transition state with the micelle, and, although strong binding is observed between substrate and many micelles,[7,8] micellar catalysis is generally relatively small *e.g.*, in the 10–100 range. Micellar catalysis can be increased by introducing the reagent into the micelle,[9] either by chemical binding or by comicellization,[10] and modification of the micellar structure is another approach.[8c] Polyelectrolyte catalysis is often much larger than micellar catalysis.[3] Micelles have very mobile structures,[11] whereas the charged groups in a polyelectrolyte are linked by alkyl or other chains, and we have therefore prepared a series of dicationic detergents (I and II), which combine some features of polyelectrolytes and detergents and compared their effectiveness as catalysts with that of cetyltrimethylammonium bromide (CTABr) for anionic nucleophilic attack upon uncharged substrates in the hope of increasing the effectiveness of micellar catalysis and the ease of micellization. The reactions used were those of hydroxide ion with chloro- and fluoro-2,4-dinitrobenzene (2,4-DNCB and DNFB),[8a,12] and hydroxide and fluoride ion with *p*-nitrophenyl diphenyl phosphate.[8b,c] There was also a possibility that some of these dicationic detergents might not form micelles because of constraints imposed by the bridging methylene chains, or the butyne group, and therefore the critical micelle concentrations (cmc) were also measured. We found that these dicationic detergents were sometimes catalytically active at very low concentrations and more effective than CTABr.

$$\underset{\mathrm{I}}{\mathrm{RMe_2\overset{+}{N}(CH_2)_n\overset{+}{N}Me_2R\ 2Br^-}} \qquad \underset{\mathrm{II}}{\mathrm{RMe_2\overset{+}{N}CH_2C{\equiv}CCH_2\overset{+}{N}Me_2R\ 2Br^-}}$$

R = cetyl; n = 2, 4, 6 for Ia, b, c, respectively

Experimental Section

Materials.—The *N,N'*-tetramethyldiamines were commercial products (Aldrich) and were redistilled before use. They were quaternized with a 10% excess of cetyl bromide in refluxing ethanol under nitrogen for 2–3 days (12 days for the ethane derivative, Ia). The detergents were precipitated with ether after evaporation of the bulk of ethanol, washed well with ether, and recrystallized from aqueous ethanol. The values of the cmc and the elemental analyses are given in Table I.

In order to make certain that both amino groups were quaternized, we showed spectrophotometrically that the reaction of hydroxide ion with the fluoro- or chloro-2,4-dinitrobenzene gave 2,4-dinitrophenol rather than the dinitroaniline which would have been formed had the solution contained free amine.

Kinetics.—The reactions were followed spectrophotometrically using a Gilford spectrophotometer with a water-jacketed cell compartment at 25.0° following methods already described.[8,12] *p*-Nitrophenyl diphenyl phosphate was added as a solution in purified dioxane, so that the final solution contained 0.5%

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