Base-Catalyzed Hydrogen–Deuterium Exchange Reactions of Long-Chain Alkyldimethylsulfonium Halides

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Received July 25, 1972

Base-catalyzed H–D exchange reaction of sulfonium halides, $n\text{-}C_nH_{2n+1}S(CH_3)_2{}^+X^-$ (n = 1–12), has been studied by nmr technique. The rates of exchange of longer alkyl chain compounds (n = 10, 12) were found to be much larger than those of shorter chain compounds (n = 1–8). Under micellar conditions, the rates for lauryldimethylsulfonium salts (n = 12, X = Cl, Br, I) followed Michaelis–Menten type saturation kinetics with respect to hydroxide ion concentration, and they increase in the order of X = I < Br < Cl.

An enhanced reactivity of a nucleophile on a cationic micellar surface has been well documented for a number of micellar reactions[1] including our previous observations.[2] In most of these cases, except for a few functional micelles,[1a,2b,3,4] a detergent to form micelle is not directly involved in reaction but appears to affect the reactivity of a nucleophile through field effects such as electrostatic and microenvironmental solvent effects.

Direct reaction of micellar component is known in the hydrolysis of primary straight-chain alkyl sulfate in acidic, neutral, and basic aqueous solution.[5] Although this reaction exhibits a typical micellar effect, the detergent decomposes during the reaction. In this report, we describe the H–D exchange reaction of long-chain alkylsulfonium halides catalyzed by sodium deuterioxide in deuterium oxide solution. Such a direct reaction of micellar component with hydroxide ion, without changing the micellar properties during the reaction, may give more insight into the reactivity of a nucleophile on a cationic micelle.

Results and Discussion

The rate of H–D exchange reaction was followed by determining the relative intensities of the *S*-methyl protons of sulfonium salts and the methyl protons of 2-picoline used as an internal standard in a nmr tube according to our previous method.[6] The methyl protons of 2-picoline do not undergo any detectable exchange under the present reaction conditions. The exchange of the other protons of sulfonium salts are extremely slow and they can also be used as the internal standard. In all the experiments, the rates followed pseudo-first-order kinetics up to more than 90% completion of reaction. The results are shown in Table I and Figure 1.

Table I indicates that the rates for iodides increase slightly by increasing alkyl chain length from C_1 to C_8, then sharply for C_{10} and C_{12} compounds. It is well known that the *S*-methyl hydrogen of sulfonium salt undergoes ready base-catalyzed H–D exchange reaction[7,8] and the effect of structure of other alkyl portions on the rates is generally small.[8,9] Such a rate change associated with the change of alkyl chain length appears to be explained in terms of micellar effect, since both C_{10} and C_{12} compounds form micelles well below the substrate concentration of kinetics (0.1 M) while the micelle formation was not detected for the other shorter alkyl chain compounds. Micellar explanation also appears to be consistent with the effects of a base concentration and counteranion on the rates as described below.

Figure 1 indicates that the rates of C_1 and C_4 compounds increase in a first-order manner by increasing deuterioxide ion concentration. In addition, these rates are virtually unchanged with the change of counteranions (X = Cl, Br, I), and the slope of the line gives $k_2 = 6.76 \times 10^{-2}\ M^{-1}\ \text{min}^{-1}$. On the other hand, in the case of C_{12} compounds, such a linear plot of k_{obsd} *vs.* [OD$^-$] was not observed. Rather, the plots gave a saturation curve for each counteranion like in Michaelis–Menten type kinetics. Furthermore, there is an increase of reactivity in the order of X = I < Br < Cl.

For a non-micelle-forming salt, the ion pair can be considered to be fully dissociated in an aqueous media, and abstraction of hydrogen from the cation by deuterioxide ion proceeds through an ordinary bimolecular mechanism without undergoing appreciable interference with the counteranion. Whereas on a cationic micellar surface, the counteranions are thought to be bound to the surface relatively tightly.[1] Effects of ion pairing or micelle formation may be reflected in the chemical shift of *S*-methyl protons (δ_{CH_3}). As indicated in Table I, the δ_{CH_3} values are substantially larger and constant in $CDCl_3$ than in D_2O. The constancy of δ_{CH_3} in $CDCl_3$ may be reasonable since the ion pairing in less polar $CDCl_3$ should be more complete than in polar D_2O, and hence the δ_{CH_3} may be expected to be insensitive to the change of alkyl chain or the counteranion. The δ_{CH_3} values of C_{12} compounds in D_2O are intermediate between those in $CDCl_3$ and of C_4 compounds in D_2O. This suggests in accordance with the accepted view[1,10] that the polarity of the micellar surface of C_{12} compounds is considerably reduced and the ion pairing is more sensitive to the nature of counterion than in the case of a non-micelle-forming salt. Thus, for micelle-

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[2] (a) W. Tagaki, M. Chigira, T. Amada, and Y. Yano, *J. Chem. Soc., Chem. Commun.*, 219 (1972); (b) W. Tagaki, T. Amada, Y. Yamashita, and Y. Yano, *ibid.*, 1131 (1972).

[3] T. C. Bruice, J. Katzhendler, and L. R. Fedor, *J. Amer. Chem. Soc.*, **90**, 1333 (1968).

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TABLE I

EFFECTS OF BASE CONCENTRATION AND COUNTERANION ON THE H–D EXCHANGE RATES OF $n\text{-}C_nH_{2n+1}S(CH_3)_2{}^+X^-$ [a]

			Nmr, δ_{CH_3}, ppm[b]			
n	X	Registry no.	D_2O	$CDCl_3$	$[OD^-] \times 10^2$, M	k_{obsd}[c] $\times 10^2$, min^{-1}
1	Cl	3086-29-1	2.92	d	6.27	0.440
	Br	3084-53-5	2.92	d	6.27	0.424
	I	2181-42-2	2.92	d	3.78	0.253
					6.27	0.460
4	Cl	41580-82-9	2.83	3.38	17.9	1.20
	Br	41580-83-0	2.85	3.42	17.9	1.25
	I	37127-44-9	2.86	3.42	1.31	0.118
					3.78	0.295
					4.95	0.347
					7.15	0.493
					17.9	1.24
6	I	41580-85-2	2.90	3.42	3.78	0.312
8	I	41580-86-3	3.02	3.42	3.78	0.333
10[e]	I	41619-34-5	3.08	3.42	3.78	4.35
12	Cl	41580-87-4	2.90	3.39	1.35	5.81
					2.65	9.66
					3.91	15.5
					5.11	19.5
					6.27	21.1
					7.39	22.0
					9.38	29.5
					11.2	32.5
					14.6	35.3
					17.9	41.2
12	Br	41580-88-5	2.97	3.42	1.35	4.04
					2.65	6.86
					3.91	10.3
					5.11	11.9
					6.27	13.6
					7.39	16.4
					11.2	25.0
					14.6	26.9
					17.9	30.7
12	I	18412-81-2	3.10	3.42	0.792	1.95
					1.56	3.65
					2.57	5.72
					3.78	7.66
					4.95	8.46
					5.74	9.50
					7.15	11.7
					11.2	16.8
					14.6	17.9
					17.9	21.0

[a] Sulfonium salt = 0.1 M, 42 ± 0.5°. [b] From the peak of tetramethylsilane. [c] Mean deviations are less than 6%. [d] Hardly soluble in $CDCl_3$. [e] cmc = 1.72×10^{-2} M (in water). For C_{12} salts, see Figure 2.

forming salts, it can be assumed that deuterioxide ion abstracts hydrogen after a fast preequilibrium association with the micellar sulfonium cation, and a halide counteranion acts as an inhibitor in such a way as to occupy the active site for abstraction of hydrogen, competitively or noncompetitively. If the inhibition is competitive, the reaction can be described by eq 1–3,

$$S^+H + OD^- \xrightarrow{k_2} S^+D + OH^- \qquad (1)$$

$$S^+H_m + OD^- \underset{}{\overset{K}{\rightleftarrows}} S^+H_m\cdot OD^- \overset{k_m}{\rightleftarrows} S^+D_m\cdot OH^- \rightleftarrows S^+D_m + OH^- \qquad (2)$$

$$S^+H_m + X^- \overset{K_I}{\rightleftarrows} S^+H_m\cdot X^- \qquad (3)$$

where S^+H_m and S^+H are the micellar and nonmicellar components of sulfonium salt, respectively, K and K_I are the association constants, and k_m and k_2 are the rate constants for the hydrogen abstraction from the micellar and nonmicellar salt, respectively. The overall rate is then given by eq 4, where C_D is the initial stoichiometric concentration of substrate. Equation 4 can be transformed to eq 5 based on the assumptions

$$\text{rate} = k_{obsd}C_D = k_2[S^+H][OD^-] + k_m[S^+H_m\cdot OD^-] \qquad (4)$$

$$k_{obsd}C_D = k_2\text{cmc}[OD^-] + \left[\frac{(C_D - \text{cmc})}{N}\right]\cdot \left[\frac{k_mK[OD^-]}{(1 + K_I[X^-] + K[OD^-])}\right] \qquad (5)$$

and formulations reported by Bunton,[1b,11] where $[S^+H]$ = cmc, $[S^+H_m]_T = (C_D - \text{cmc})/N$ is the total concentration of micelle, and N is the aggregation num-

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[11] C. A. Bunton and L. Robinson, J. Amer. Chem. Soc., 90, 5512 (1968). They assume that a micelle and the substrate (here OD^-) forms a 1:1 complex and incorporation of substrate in the micelle prevents incorporation of inhibitor competitively. These assumptions are obviously oversimplified for the present case since a micelle should incorporate more than one counteranion.

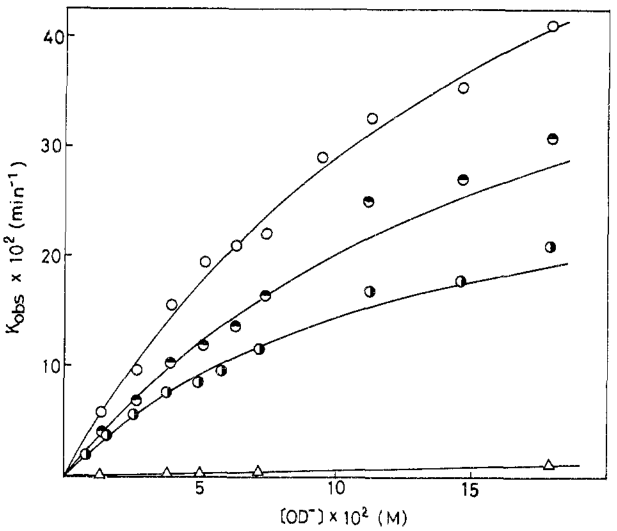

Figure 1.—Plots of k_{obsd} *vs.* base concentration: ○ (X = Cl), ◓ (Br), and ◑ (I) for n-$C_{12}H_{25}S(CH_3)_2{}^+X^-$; △, for n-$C_4H_9S(CH_3)_2{}^+I^-$. The solid lines are calculated from eq 7 using the intercepts and slopes in Figure 3.

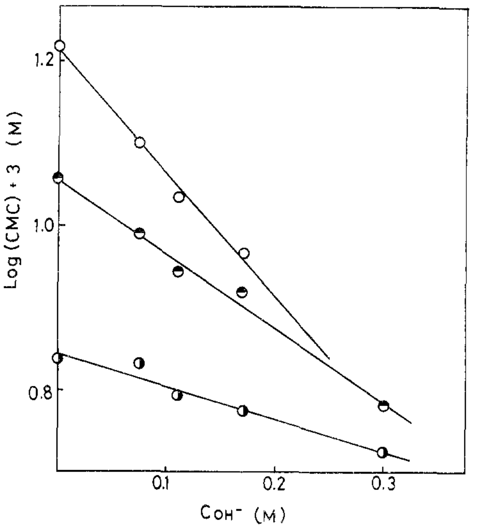

Figure 2.—Plots of log (cmc) *vs.* hydroxide ion concentration for n-$C_{12}G_{25}S(CH_3)_2{}^+X^-$: ○ (X = Cl), ◓ (Br), and ◑ (I). The cmc's in water are 1.65×10^{-2} M (X = Cl), 1.14×10^{-2} M (Br), and 0.689×10^{-2} M (I).

ber of micelle. In eq 5, it is difficult to determine the first nonmicellar term because of limitation of the present nmr method to carry out the kinetics with the salt concentration as low as the cmc. Another difficulty was the change of cmc with the change of base concentration. However, as shown in Figure 2, it was found that there is a linear relationship between log (cmc) and the base concentration, C_{OH^-} (eq 6),[12]

$$\log(\text{cmc}) = \log(\text{cmc})_0 - k_s C_{OH^-} \qquad (6)$$

which allows the contribution of cmc to the rates to be calculated. Furthermore, if the nonmicellar rate (k_2) is assumed to be the same as those of C_1 and C_4 compounds, the data in Table I and Figure 2 allow the contribution of the first term in eq 5 to be estimated to be negligible (less than 1% of the overall rate).

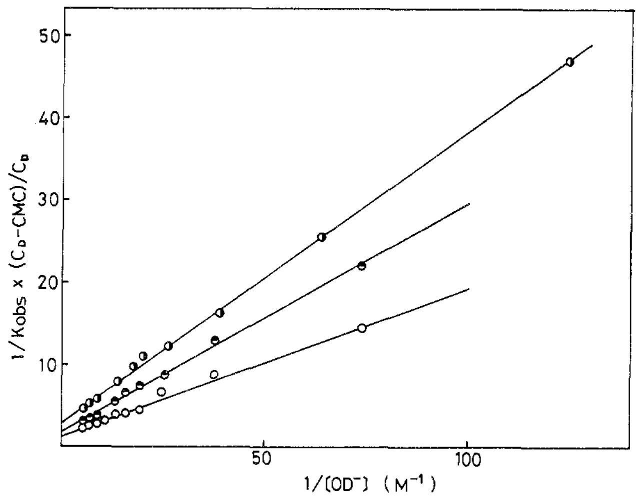

Figure 3.—Plots of data for n-$C_{12}H_{25}S(CH_3)_2{}^+X^-$ based on eq 7: ○ (X = Cl), ◓ (Br), and ◑ (I).

Thus, neglect of the first term and rearrangement of eq 5 leads to eq 7. The linearity of the plots based on

$$\left(\frac{1}{k_{obsd}}\right)\cdot\left(\frac{C_D - \text{cmc}}{C_D}\right) = \frac{N}{k_m} + \frac{N}{k_m K}(1 + K_I[X^-])(1/[OD^-]) \qquad (7)$$

eq 7 was confirmed as shown in Figure 3. Figure 3 indicates that the intercepts (N/k_m) are almost identical for the three counteranions within experimental error, and the identity may justify the assumption of competitive inhibition, although a small difference can also be argued to indicate other mechanism such as a noncompetitive inhibition. One may suspect that the change of cmc (Figure 2) is the corollary of the change of the size and the aggregation number (N) of micelle. The linearity in Figure 3 might indicate that either the change in N is small or k_m, K, and K_I also change in such a direction to cancel out the change of N. The reciprocal values of the slopes $\{k_m K/N(1 + K_I[X^-])\}$ in Figure 3 are 5.47 (X = Cl), 3.57 (Br), and 2.82 M^{-1} min^{-1} (I), and they should be comparable to the k_2 values of C_1 and C_4 compounds ($k_2 = 6.76 \times 10^{-2}$ M^{-1} min^{-1}) to give the ratios 81 (X = Cl), 53 (Br), and 42 (I), respectively. These ratios would be raised more if uninhibited rates of micellar reactions ($k_m K/N$) could be compared.[13] Furthermore, the reactivity of deuterioxide ion per one micelle ($k_m K$) should be even more pronounced since the aggregation number N may be expected to be larger than 10 for most C_{12} cationic detergents.[1]

The above results and discussion indicate that the reactivity of deuterioxide ion is enhanced more than 100-fold when bound on a cationic micellar surface of C_{12} sulfonium salt. An increase of local concentration of base near the reaction site may account for a part of rate enhancement. However, a more important factor may be an enhanced basicity of deuterioxide ion bound to a relatively nonpolar cationic micellar sulface.

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[12] See also P. Mukerjee, *J. Phys. Chem.*, **69**, 4038 (1965); A. Ray and G. Nemethy, *J. Amer. Chem. Soc.*, **93**, 6787 (1971); A. Hamabata, S. Chang, and P. H. von Hippel, *Biochemistry*, **12**, 1278 (1973).

[13] For such a comparison, one must measure the rates of exchange of the substrate of $X^- = OH^-$, or alternatively the K_I values must be known. However, we have encountered some difficulties in obtaining a pure sample of lauryldimethylsulfonium hydroxide. Furthermore, it may be difficult to obtain a reliable value of $K/(1 + K_I[X^-])$ since it is a ratio of the intercept and slope in Figure 3 which already involves a relatively large error due to the error (~6%) in the rate measurement by the present nmr method.

TABLE II

MELTING POINTS AND ELEMENTAL ANALYSES OF SULFONIUM HALIDES [n-$C_nH_{2n+1}S(CH_3)_2{}^+X^-$]

				Analyses, found (calcd), %		
n	X	S[a]	Mp,[b] °C (lit.)	C	H	S
1	Cl	M	176 (170–173)[d]			
	Br	M	196 (198)[e]	22.49 (22.94)	5.97 (5.78)	20.55 (20.41)
	I	M	205 (203–207)[f]	17.98 (17.66)	4.45 (4.44)	15.83 (15.71)
4	Cl[c]	AE	120			
	Br	MC	95–98	36.12 (36.19)	7.76 (7.59)	16.45 (16.09)
	I	A	80 (82)[g]	29.49 (29.28)	6.75 (6.14)	12.92 (13.03)
6	I	A	66–67 (68)[h]	35.20 (35.04)	7.51 (6.98)	11.74 (11.69)
8	I		*i*	39.55 (39.74)	7.98 (7.66)	11.10 (10.61)
10	I		*i*	43.41 (43.64)	8.72 (8.23)	10.03 (9.70)
12	Cl	A	64–66	62.80 (62.99)	11.78 (11.71)	12.03 (12.01)
	Br	A	68–70	53.67 (54.00)	10.16 (10.04)	10.05 (10.29)
	I	A	87	47.31 (46.93)	8.63 (8.71)	8.96 (8.95)

[a] Solvent for recrystallization: M, methanol; AE, acetone–ethanol; MC, methylene dichloride; A, acetone. [b] Uncorrected. [c] Microanalyses have not been done because these salts are very hygroscopic and difficult to weigh. However, chloride titration by silver nitrate and the nmr analyses suppported their purity and structure. [d] Y. Funazukuri, *Japan,* **2,** 173 (1961); *Chem. Abstr.*, **56,** 8566 (1962). [e] R. T. Major and H. J. Hess, *J. Org. Chem.*, **23,** 1563 (1959). [f] S. Miller, *Chem. Ber.*, **56,** 1923 (1923). [g] C. K. Ingold, J. A. Jessop, K. I. Kuriyan, and A. M. M. Mandour, *J. Chem. Soc.*, 533 (1933). [h] J. V. Braun, W. Teuffert, and K. Weissbach, *Justus Liebigs Ann. Chem.*, **472,** 121 (1929). [i] Wax form, no definite melting point.

Experimental Section

Materials.—Deuterium oxide (99.8%) was purchased from Showa Denkko Co. The sodium deuterioxide stock solution in deuterium oxide (0.5 *M*) was prepared by dissolving fresh sodium metal. 2-Picoline was distilled over potassium hydroxide pellets. It boiled at 128° and showed no impurities on vapor phase chromatography.

Sulfonium iodides were prepared by treating sulfides with methyl iodide, and sulfonium bromides were prepared from dimethyl sulfide and alkyl bromide, according to a literature method.[14] Sulfonium chlorides were prepared by the following two methods. (1) A sulfide was treated in a sealed tube with methanol (a large excess) saturated with hydrogen chloride for 15–24 hr at 60°. In the case of lauryl methyl sulfide, the reaction mixture was heterogeneous at the beginning, then became homogeneous at the end of reaction. After removal of excess methanol, the residue was washed with ether, dried, and recrystallized. (2) A sulfonium perchlorate (obtained from the corresponding iodide) was dissolved in methanol containing excess potassium chloride under stirring at room temperature. Potassium perchlorate that formed was removed by filtration, the filtrate was concentrated, and the residue was recrystallized. The solvents for recrystallization, the melting points, and the elemental analyses of these sulfonium halides are listed in Table II. The nmr δ_{CH_3} values of the salts are also given in Table I.

Critical micelle concentrations (cmc) of C_{10} and C_{12} salts were determined by titration of salt solutions with eosine solution, according to a literature method.[15] The dependency of cmc on base concentration is shown in Figure 2.

Exchange Kinetics.—The isotopic composition of solutions of sulfonium salts was determined by nmr spectroscopy with a Varian A-60 spectrometer according to our previous method.[6] 2-Picoline was used as an internal standard which showed the signal from the methyl group at δ 2.54 in D_2O. The control experiments showed no H–D exchange of methyl protons of 2-picoline under the present experimental conditions.

The reaction mixtures for the kinetics were prepared by weighing the sulfonium salt in nmr tubes and by adding 0.5 ml of D_2O containing 2-picoline. After equilibration at the reaction temperature, a calculated volume of the sodium deuterioxide stock solution was added into the tube quickly by a microsyringe and the stoppered tube was shaken by turning upside down. The control experiments using a larger volume of the reaction mixture indicated that the calculated base concentration was the same as that determined by titration and remained constant during the reaction. As the reaction proceeded initial singlet peak for the *S*-methyl proton changed to a small multiplet peak, and the peak area diminished, relative to that for the methyl protons of 2-picoline. The exchange of the other protons was extremely slow and not detected. The rate constants shown in Table I were calculated based on the following equation: $k_{obsd} = (2.303/t \log (r_0 - r_\infty)/(r_t - r_\infty)$, where r = (peak area for *S*-methyl)/(peak area for 2-picoline methyl). As expected, the accuracy of the present method is not high. Kinetic runs which showed more than 6% of mean deviation in k_{obsd} were discarded.

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[14] R. Kuhn and O. Dann, *Chem. Ber.*, **73,** 1092 (1940).

[15] M. L. Corrins and W. D. Harking, *J. Amer. Chem. Soc.*, **69,** 679 (1947).