Micellar Methylating Agents: (Long-chain-alkyl)dimethylsulphonium Iodides

Kiyoshi Yamauchi,* Yorisato Hisanaga, and Masayoshi Kinoshita
Department of Applied Chemistry, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

Dodecyl-, hexadecyl-, and octadecyl-dimethylsulphonium iodide were found to methylate efficiently various nucleosides, hydroxy aromatic compounds, and thiols at pH 8—11 and 50—70 °C. The optimum conditions and the mechanism of the reaction are discussed briefly in relation to the micellar reaction characteristics.

Trimethylsulphonium iodide, $(CH_3)_3S^+ I^-$, has been shown previously to methylate various nucleosides in aprotic solvents.[1] However, the reagent was inactive in water. We therefore attempted to replace one of three methyl groups with a long-chain alkyl group in order to generate a functional micellar methylating agent, n-$C_mH_{2m+1}S^+(CH_3)_2 I^-$ (abbreviated to C_m-reagent, where m = 12, 16, and 18). Although n-$C_{16}H_{33}N^+(CH_3)_2CH_2CH_2S^+(CH_3)_2 \cdot 2CF_3CO_2^-$ has been used recently in a kinetic study of the micellar methylation of thiophenol,[2] our simple long-chain-alkyldimethylsulphonium iodides were prepared easily and were capable of methylating efficiently both water-soluble and -insoluble compounds.

Results and Discussion

The methylating activity of various alkyldimethylsulphonium iodides towards thymidine in water is shown in Table 1. Trimethyl- and n-butyldimethyl-sulphonium iodide did not methylate the nucleoside (runs 1 and 2). By contrast, the micelle-forming C_m-reagents (m = 12, 16, and 18) smoothly transformed thymidine into the 3-methyl derivative when the reagent concentration was higher than the critical micellar concentration (c.m.c.) (runs 5—9). The optimum pH value of the micellar solution was found to be *ca.* 10. At pH < *ca.* 8 the substrate was not methylated. It would appear most likely that the anions of thymidine (pK_a 8.9 at 70 °C) were concentrated on the surface of the cationic micelles, and reacted with the dimethylsulphonium ions in the Stern layer.

The appropriate values of the detergent concentration (C_d) and those of the substrate concentration (C_s) were 10—20-times the c.m.c. and one-third to one-fourth of the C_d value, respectively. Higher C_d values made the micellar solution viscous, and increasing C_s relative to the C_d did not enhance the yield of the product appreciably. Although the C_{16}- and C_{18}-reagent were active in concentrations below the c.m.c. of the C_{12}-reagent (runs 3, 7, and 8), the C_{12}-reagent was more useful than the C_{16}- and C_{18}-reagent from a synthetic point of view since it allowed reactions at higher concentrations of the substrate.

Micellar methylations of other compounds by the C_{12}-reagent are listed in Table 2. Aromatic amide, imide, and hydroxy groups as well as aliphatic and aromatic thiol groups were methylated easily to furnish the corresponding products. When the products are soluble in water, micellar methylation may be considered convenient with regard to product isolation, *i.e.* the C_m-reagents were stable in water, but decomposed rapidly in organic solvents such as chloroform and tetrahydrofuran (THF) at > *ca.* 50 °C, giving methyl iodide and the corresponding alkyl methyl sulphide. Hence, during work-up procedures, the excess of reagent in the micellar reaction mixture was converted into these compounds which were easily removed by extraction with chloroform. By contrast, many classical methylating agents such as dimethyl sulphate and methyl iodide generate water-soluble by-products (CH_3OSO_3H, HI, or their Na and K salts, *etc.*) which often cause a water-soluble product to be isolated in low yield. The kinetics of the micellar reactions will be reported elsewhere.

Experimental

^1H N.m.r. spectra were recorded on a JEOL-JNM-PS-100 spectrometer using dilute solutions in $CDCl_3$ with tetramethylsilane as internal standard. H.p.l.c. (high-performance liquid chromatography) was run on a Toyo-Soda 803 liquid chromatograph with a 254-nm u.v. flow-cell detector. For chromatographic conditions see refs. 1 and 3.

Preparation of the C_m-Reagents.—A mixture of an n-alkyl methyl sulphide and methyl iodide (1.2 equiv.) in THF

Table 1. Conversion of thymidine into 3-methylthymidine by alkyldimethylsulphonium iodides [a]

Run	Alkyl group in the reagent	10^3[Reagent] (M) [b]	10^3[Thymidine] (M)	pH	Reaction time (h)	Yield (%) [c]
1	CH_3	100	1.0	11	15	trace
2	n-C_4H_9	100	1.0	11	15	2
3	n-$C_{12}H_{25}$	5 (0.8)	0.5	11	10	0
4		69 (10)	6.9	7	10	0
5		69 (10)	6.9	11	6	90 (82 [d])
6		138 (20)	13.8	11	6	87
7	n-$C_{16}H_{33}$	5 (10)	0.5	11	6	95
8	n-$C_{18}H_{37}$	1 (10)	0.5	11	3	13
9		15 (150)	0.5	11	1.5	86

[a] Reaction temperature 70 °C. [b] C_d/c.m.c. Value given in parentheses. [c] Yields determined by means of u.v.–t.l.c. or h.p.l.c. [d] Yield of product isolated, m.p. 136.5—137 °C (from water) (H. T. Miles, *J. Am. Chem. Soc.*, 1957, **79**, 2565 reports m.p. 132—134 °C).

Table 2. Micellar methylation of various substrates by n-$C_{12}H_{25}S^+(CH_3)_2I^-$ [a]

Substrates	pH	Temperature (°C)	Time (h)	Product	Yield (%) [b]
Uridine (U)	10.5	70	15	3-Methyl-U	73 (65) [c]
Cytidine (C)	12	65	12	2′(3′)-*O*-Methyl-C	trace
Guanosine (G)	10.5	65	12	1-Methyl-G	34 (21) [d]
Inosine (I)	10.5	70	10	1-Methyl-I	84 (74) [e]
Adenosine (A)	10.5	70	10	No reaction	—
Phenol	9	70	5	Anisole	95
L-Cystein	8	70	2	*S*-Methyl-L-cysteine	(87) [f]
Aniline	10.5	70	11	No reaction	—

[a] [C_{12}-Reagent] 6.9×10^{-2}M; [substrate] 2.3×10^{-2}M. Amount of compound used 0.1—0.5 g. [b] Values in parentheses are the yields of isolated products. [c] M.p. 121.5—122.5 °C (from ethyl acetate) (H. T. Miles, *Biochim. Biophys. Acta*, 1956, **22**, 247 reports m.p. 119—120 °C). [d] M.p. 225—227 °C (from methanol) (A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, 1964, **3**, 494 report m.p. 225—227 °C). [e] M.p. 205—208 °C (from ethanol) (J. Zemlicka, *Collect. Czech. Chem. Commun.*, 1970, **35**, 3572 reports m.p. 209—210 °C). [f] M.p. 220—221 °C (from 95% aqueous ethanol) [J. F. Thompson, *Nature (London)*, 1956, **178**, 593 reports m.p. 220 °C].

(*ca.* 1 ml THF mmol^{-1} of the sulphide) was kept at *ca.* 10 °C for 5 d. The crystalline sulphonium iodide was filtered off with suction and recrystallized from acetone containing a small amount of water. The c.m.c. values were determined at 70 °C by means of the eosin dye method.[4]

C_{12}-Reagent: yield 71%, m.p. 85.5—86 °C (lit.,[5] 87 °C); c.m.c. 6.9×10^{-3}M; δ 0.88 (3 H, t, *J* 6.0 Hz, $CH_3[CH_2]_n$), 1.26 (18 H, s, $[CH_2]_9CH_3$), 1.81 (2 H, br m, SCH_2CH_2), 3.40 [6 H, s, $S(CH_3)_2$], and 3.85 (2 H, *J* 7.5 Hz, SCH_2).

C_{16}-Reagent: yield 37%, m.p. 88 °C; c.m.c. 6.1×10^{-4}M; the ^{1}H n.m.r. spectrum was essentially the same as that of the C_{12}-reagent except for the signal due to the polymethylene residue: δ 1.26 (26 H, s, $[CH_2]_{13}CH_3$) (Found: C, 52.5; H, 9.75. $C_{18}H_{39}IS$ requires C, 52.15; H, 9.48%).

C_{18}-Reagent: yield 38%, m.p. 82—103 °C (gel ⟶ liquid); c.m.c. 0.98×10^{-4}M; the ^{1}H-n.m.r. spectrum was almost identical with that of the C_{12}-reagent except for the signal due to the polymethylene residue: δ 1.26 (30 H, s, $[CH_2]_{15}$-CH_3) (Found: C, 54.5; H, 10.0. $C_{20}H_{43}IS$ requires C, 54.28; H, 9.79%).

General Methylation Procedure.—The substrate and the C_m-reagent were dissolved in water, and the pH was adjusted to an appropriate value with 2M potassium hydroxide. The solution was then warmed and shaken occasionally in a thermostatted water-bath (see Tables for more conditions). The progress of the methylation reaction was monitored by means of silica gel t.l.c. or ODS-silica gel h.p.l.c. The solution was then made neutral with 1M hydrochloric acid, mixed with ethanol, and concentrated at *ca.* 50 °C (rotatory evaporator). (The ethanol effectively suppressed foam formation during the concentration procedure.) The residue was then washed with chloroform. *S*-Methyl-L-cysteine was obtained as crystals by addition of ethanol to the residue, while methylated nucleosides were isolated by chromatography of the residue on a silica-gel column with gradient elution with chloroform–methanol (10 : 1 to 25 : 1 v/v). All products were identified by comparison of their m.p.s, and i.r., and n.m.r. spectra with those in the literature, or of authentic samples.

References

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