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MICELLAR ALKYLATION: A METHYLATING SURFACTANT

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Summary. Micellar $\underline{n}$-$C_{16}H_{33}\overset{+}{N}(CH_3)_2CH_2CH_2\overset{+}{S}(CH_3)_2$, $2CF_3SO_3^-$ rapidly methylates bound thiophenoxide ions.

Biological methylation generally involves S_N2 reactions between nucleophilic sites and the sulfonium reagent S-adenosyl-L-methionine.[1] Our interest in micellar alkylation reactions[2] stimulated development of a simple model for such processes. Accordingly, we now describe initial studies of a highly reactive, methylating sulfonium surfactant.[3]

Thioacetate surfactant, I,[2] was deprotected with 1 equiv of NaH in CH_3OH, and the resulting thiolate surfactant was methylated *in situ* (60 min, 25°) with excess CH_3I. Removal of volatiles, followed by 3 recrystallizations from 2:1 CH_2Cl_2/ether, gave 94% of sulfide surfactant II.[4,5] Treatment of II with 3-fold excess methyl triflate in CH_2Cl_2 (60 min, 25°) gave, after

$$\underset{\text{I}}{\overset{+}{R}N(CH_3)_2CH_2CH_2SCOCH_3,\ CF_3SO_3^-} \xrightarrow[(2)\ CH_3I]{(1)\ NaH/CH_3OH} \underset{\text{II}}{\overset{+}{R}N(CH_3)_2CH_2CH_2SCH_3,\ CF_3SO_3^-}$$

$$\xrightarrow[CH_2Cl_2]{CH_3OSO_2CF_3} \underset{\text{III}}{\overset{+}{R}N(CH_3)_2CH_2CH_2\overset{+}{S}(CH_3)_2,\ 2CF_3SO_3^-} \quad (\underline{\text{Note}}: R=\underline{n}\text{-}C_{16}H_{33}) \qquad (1)$$

repetition of the previous work-up, 88% of sulfonium/ammonium surfactant III;[4,6] *cf.*, eq. (1). In a similar manner, commercial S-acetylthiocholine bromide was converted (89%) to nonsurfactant analog IV.[4,7]

$$\underset{\text{IV}}{(CH_3)_3\overset{+}{N}CH_2CH_2\overset{+}{S}(CH_3)_2,\ 2CF_3SO_3^-} \qquad \underset{\text{V}}{\underline{n}\text{-}C_{16}H_{33}\overset{+}{N}(CH_3)_2CH_2CH_2OSO_2CH_3,\ Cl^-}$$

Reactivities of III and IV were determined in S_N2 displacements with thiophenol (pH 8.0,[8] 25°), following the disappearance of thiophenoxide absorption at 273 nm (micellar reactions) or 263 nm (nonmicellar reactions). Good psuedo-first-order behavior was observed ($\underline{r}$ >0.999); kinetic data are tabulated in Table I, along with comparable data for surfactant V.[2] Preparative scale reactions between III and thiophenoxide, monitored by nmr, demonstrated the formation of thioanisole and II as the only products, indicating methyl transfer as the central chemical process.

Both III and IV are reactive methylating reagents under mild conditions. Thiophenoxide ions are strongly bound by cationic comicellar CTACl and III.[10] Note that a 3-fold increase in [III] does not enhance k_ψ (*i.e.*, $C_6H_5S^-$ reacts only in CTACl/III comicelles), whereas a similar increase in [IV], which cannot bind thiophenoxide, elicits a corresponding increase in k_ψ.

Table I. Reactions of Alkylating Agents with Thiophenoxide Ion.[a]

Reagent	Concn, M	Additive (concn, M)	k_ψ, sec^{-1}	av. devn.
III	0.0033	CTACl[b] (0.010)	0.167	0.002
III	0.010	CTACl (0.010)	0.157	0.005
III	0.010	None	0.120	c
IV	0.0033	NaCl (0.010)	0.0126	0.0001
IV	0.010	NaCl (0.010)	0.0416	0.0007
V[d]	0.010	None	0.00162	

[a]Reactions of III and IV were done in 0.01M pH 8.0 phosphate buffer; V was studied in 0.01M pH 9 borate buffer. All reactions were done at 25°, with 5×10^{-5}M thiophenol. [b]CTACl = cetyltrimethylammonium chloride. [c]Average deviations refer to duplicate runs. [c]Single run. [d]See ref. 2.

Micellar III methylates bound thiophenoxide ~100 times more rapidly than micellar V alkylates this nucleophile,[2] and is at least 13 times more reactive in methyl transfer (0.167/0.0126) than its non-micellar analog, IV. This reflects the advantage of binding thiophenoxide ions to the cationic micelles, resulting in the conversion of a bimolecular reaction (IV + $C_6H_5S^-$) to a quasiunimolecular one.[11]

In preliminary studies, surfactant III appears to react readily with the much weaker[12] nucleophile, p-nitrophenoxide and also with guanylic acid. We are continuing our studies of these novel micellar methylation reactions.

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3. Lauryldimethylsulfonium halide yields oxiranes by "CH_2" transfer upon reaction with carbonyl substrates in C_6H_6/15 N NaOH. Prior formation of a sulfonium ylide is involved. Cf., Y. Yano, T. Okonogi, M. Sunaga, and W. Tagaki, Chem. Commun., 527 (1973).
4. A satisfactory elemental analysis was obtained.
5. Mp, 175° (liquid crystal, ~60°). Nmr $\delta^{TMS}_{CDCl_3}$: 0.88 ("t", 3H, cetyl CH_3), 1.28 (s, 28H, $(CH_2)_{14}$), 2.25 (s, 3H, SCH_3), 3.06-2.70 (m, 2H, CH_2S), 3.27 (s, 6H, $\overset{+}{N}(CH_3)_2$), 3.83-3.27 (m, 4H, $\underline{CH_2}\overset{+}{N}(CH_3)_2\underline{CH_2}$).
6. Mp, 150° (liquid crystal, 115°). Nmr $\delta^{TMS}_{(CD_3)_2CO}$: 0.87 ("t", 3H, cetyl CH_3), 1.28 (s, 28H, $(CH_2)_{14}$), 3.32 (s, 6H, $\overset{+}{S}(CH_3)_2$), 3.45 (s, 6H, $\overset{+}{N}(CH_3)_2$), 3.90-3.45 (m, 2H, $C_{14}\underline{CH_2}\overset{+}{N}$), 4.27 (s, 4H, $\overset{+}{N}\underline{CH_2}\underline{CH_2}\overset{+}{S}$).
7. Mp, 195-197°. Nmr $\delta^{TMS}_{(CD_3)_2CO}$: 3.33 (s, 6H, $\overset{+}{S}(CH_3)_2$), 3.53 (s, 9H, $\overset{+}{N}(CH_3)_3$), 4.30 (s, 4H, $N\underline{CH_2}\underline{CH_2}\overset{+}{S}$).
8. Thiophenol (pK_a = 6.43, 25°, μ=1.0)[9] is largely ionized at pH 8.
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