Cleavage of Phosphate Esters by Hydroxyl-Functionalized Micellar and Vesicular Reagents

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In order to compare the kinetic efficiencies of hydroxyl-functionalized surfactant vesicles with those of comparably functionalized micellar reagents, we studied the cleavages of *p*-nitrophenyl diphenyl phosphate (**2**) at pH 9.0 and lithium 2,4-dinitrophenyl ethyl phosphate (**6**) in 0.1 M aqueous NaOH. The cleavage reagents included vesicular *N,N*-di-*n*-hexadecyl-*N*-methyl-*N*-(β-hydroxyethyl)ammonium bromide (**3**), *N*-*n*-hexadecyl-*N,N*-dimethyl-*N*-(β-hydroxyethyl)ammonium bromide (**4**), and *N*-*n*-hexadecyl-*N,N*-dimethyl-*N*-(*p*-hydroxybenzyl)ammonium bromide (**5**). The latter was used either as a covesicle with *N,N*-di-*n*-hexadecyl-*N,N*-dimethylammonium bromide or as a comicelle with cetyltrimethylammonium bromide. Rate constants were determined as a function of [surfactants], and the resulting k_ψ vs. [surfactant] profiles were analyzed to provide values of micellar or vesicular rate constants. Reagents **4** and **5** were moderately effective for the cleavage of neutral phosphate esters in either micellar or vesicular phases. There was, however, no intrinsic superiority of the vesicular systems (e.g., **3**) toward the neutral substrate, although the vesicular systems were more effective in cleaving anionic phosphate **6**.

Structure **1** is a general representation of a toxic orga-

1

nophosphorous compound, in which Z = O or S, R_1 and R_2 are groups which are not easily displaced from P (e.g., RO, R_2N, or R), and X can function as a leaving group (e.g., F or *p*-nitrophenoxyl).[2] The ability of these compounds to inhibit such enzymes as acetylcholinesterase, and thus to disrupt neurological function, forms the basis of their activity as pesticides and chemical warfare agents. These normally function by esterifying the active site serine hydroxyl of acetylcholinesterase, so that it is not surprising that attempts to develop useful decontaminants have concentrated on hydrolytic reagents for phosphates and phosphonates.

The triester *p*-nitrophenyl diphenyl phosphate (PNPDPP, **2**) is a useful model substrate which has been

$(C_6H_5O)_2P(O)OC_6H_4$-*p*-NO_2

2 (PNPDPP)

extensively studied to gauge the efficiency of phosphate cleavage reagents. In view of the well-known ability of cationic surfactant micelles to accelerate the cleavage of carboxylic esters, there have naturally been parallel studies of the micelle-catalyzed P–O scission of **2**,[3] and, recently, attention has centered on the use of functional micellar reagents.[4]

Thus, the fluoride counterion of micellar cetyltrimethylammonium (CTA) fluoride is an effective agent for the cleavage of **2**.[5] Hydroxyl-functionalized cationic surfactants[6] and aryloxide ions,[7] solubilized in CTABr micelles, also serve as nucleophilic reagents for the cleavage of **2** and related substrates. In its conjugate base (anionic) form, the =NOH moiety is perhaps the most effective agent yet introduced for the nucleophilic cleavage of phosphates; hydrophobic hydroxamic acids, oximes, and amidoximes, solubilized in micellar CTABr, all serve in this manner.[8] Specific application to the cleavage of the insecticide Paraoxon (**1**; Z = O, $R_1 = R_2$ = OEt, X = *p*-nitrophenoxyl) has appeared.[8a] Finally, the imidazole moiety, either included in functionalized surfactants or supplied as (e.g.) benzimidazole solubilized in CTABr, strongly catalyzes the hydrolysis of **2**.[9] The imidazole can function catalytically either as a general base to activate water or directly as a nucleophile. The mode of action depends on the structure of the catalyst.[9]

Most recently, chemical applications of surfactant vesicles have commanded wide attention.[10] These systems are more highly ordered than micelles and may offer unique properties as catalysts or reaction microenvironments. For example, we have observed distinct interior (endovesicular) and exterior (exovesicular) cleavages of activated esters by thiol-functionalized surfactant vesicles[11] and of phosphate ester **2** in either hydroxyl-functionalized or unfunctionalized surfactant vesicles.[12] The hydroxamate-catalyzed cleavage of alkyl bis(*p*-nitrophenyl) phosphates in dialkyldimethylammonium ion vesicles has also been reported.[13]

This topical interest in reagents for the cleavage of phosphates, coupled with our own interest in functional micelles and vesicles, led us to undertake a study of the

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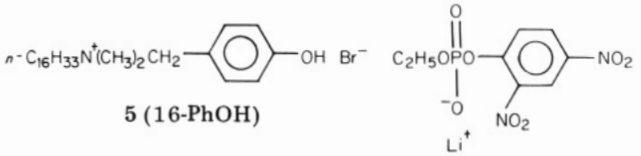
comparative cleavage efficiencies of the hydroxyl-functionalized vesicles derived from **3** (16_2OH) and the anal-

$(n\text{-}C_{16}H_{33})_2N^+(CH_3)CH_2CH_2OH\ Br^-$
3 (16_2OH)
$n\text{-}C_{16}H_{33}N^+(CH_3)_2CH_2CH_2OH\ Br^-$
4 (16-OH)

ogous micelles derived from **4** (16-OH). Additionally, we examined the related reactions of phenolic surfactant **5** (16-PhOH) and of substrate **6**, the 2,4-dinitrophenyl ethyl phosphate anion.



5 (16-PhOH) **6**

Results

Materials. PNPDPP (**2**) was prepared from *p*-nitrophenol and diphenyl chlorophosphate.[14] Substrate **6** required prior reaction of 2,4-dinitrophenol with diethyl chlorophosphate to give diethyl 2,4-dinitrophenyl phosphate, which was then cleaved to **6** with LiBr/acetone.[14,15] CTABr was a purified commercial sample, and dihexadecyldimethylammonium bromide (16_2) was a gift from Professor T. Kunitake. Surfactants **3**[11] and **4**[6b] were synthesized by appropriate cetylations of (methylamino)-ethanol and (dimethylamino)ethanol, respectively. Finally, phenolic surfactant **5** was prepared by quaternizing *N,N*-dimethyl-*n*-hexadecylamine with *p*-acetoxybenzyl bromide, followed by deacetylation with methanolic HBr.[16]

Kinetic Studies. Cleavage reactions of **2** or **6** were followed spectrophotometrically by monitoring the release of nitrophenolate ions at 400 nm. For the construction of k_ψ vs. [surfactant] profiles, we generally determined only single values of k_ψ at each surfactant concentration. However, spot duplications indicated reproducibilities of ±5% in k_ψ.

Standard reaction conditions were pH 9.0, 0.02 M Tris buffer (μ = 0.01, KCl), and 25 °C. Under these conditions, k_0 for the buffer cleavage of PNPDPP was $2.91 \pm 0.10_3 \times 10^{-5}$ s^{-1}. The substrate concentration was normally 1×10^{-5} M, and its introduction required the presence of 0.2% of CH_3CN. Vesicular solutions were prepared either by injection[11] of ethanolic surfactant solutions into aqueous buffer or by sonication[10] of the surfactants in the buffer; final ethanol concentrations were 4% by volume in each case. Vesicle formation from 16_2OH has been demonstrated by electron microscopy.[12] Reactions were initiated by the addition of substrate.

Table I (see supplementary material) collects pseudo-first-order rate constants for the cleavage of PNPDPP by micellar 16-OH and by vesicular 16_2OH as functions of [surfactant]. Figure 1 presents this data graphically. It is clear that micellar 16-OH is the more reactive system ($k_\psi^{max} = 2.0 \times 10^{-3}$ s^{-1} vs. $k_\psi^{max} = 0.93 \times 10^{-3}$ s^{-1} for vesicular 16_2OH) but that maximum cleavage rates are obtained at a lower concentration of vesicular 16_2OH.

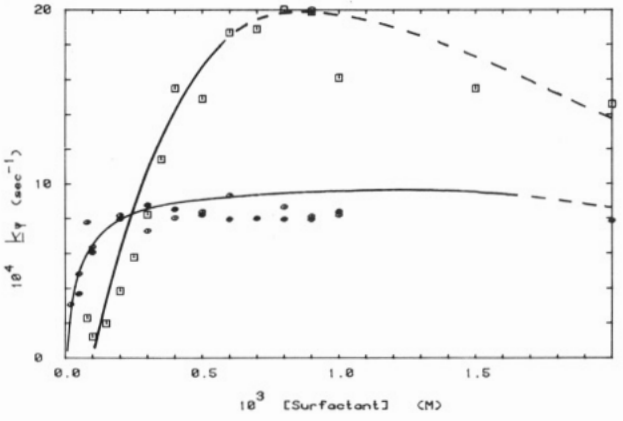


Figure 1. Pseudo-first-order rate constants (k_ψ, s^{-1}) for the cleavage of PNPDPP as a function of [surfactant] at pH 9.0 under standard conditions (see text): □, micellar 16-OH; ○, vesicular 16_2OH prepared by injection; ●, vesicular 16_2OH prepared by sonication. The solid lines were generated by using the Lineweaver–Burk parameters of Table V (see text and Table I).

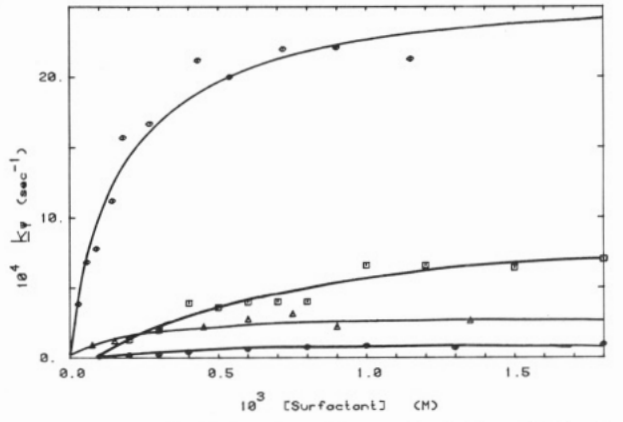


Figure 2. Pseudo-first-order rate constants (k_ψ, s^{-1}) for the cleavage of lithium 2,4-dinitrophenyl ethyl phosphate (**6**) as a function of [surfactant] in 0.10 M NaOH at 25 °C with [**6**] = 1.5×10^{-5} M: ○, vesicular 16_2OH (sonicated); □, micellar 16-OH; △, vesicular 16_2 (sonicated); ●, micellar CTABr. The solid lines were generated by using the Lineweaver–Burk parameters of Table V (see text and Table II).

An opposite picture is presented by the data of Table II (see supplementary material) for the strongly basic (0.1 M NaOH) cleavage of the anionic phosphate substrate **6**. Here, vesicular 16_2OH is a more efficient reagent than micellar 16-OH, eliciting a higher value of k_ψ^{max} ($\sim 2.2 \times 10^{-3}$ vs. 0.7×10^{-3} s^{-1}) at a lower concentration ($\sim 0.7 \times 10^{-3}$ vs. 1.8×10^{-3} M). The results are shown graphically in Figure 2, which also includes data obtained with nonfunctional micellar CTABr and vesicular 16_2. The latter are seen to be less reactive than either functional surfactant, although vesicular 16_2 is a better catalyst than micellar CTABr. k_0 for the cleavage of **6** in 0.1 M NaOH was $1.32 \pm 0.06_3 \times 10^{-5}$ s^{-1}.

We examined whether the method of assembling the 16_2OH vesicles had any effect on their reaction with anion **6**. With [16_2OH] = 9.0×10^{-4} M and [**6**] = 1.5×10^{-5} M, in 0.1 M, NaOH, there was no significant difference in k_ψ for the cleavage reactions whether the vesicles were constructed by injection or sonication or, in either method, whether the substrate was added before or after the vesicles had been formed. There was also no evidence for a second kinetic phase[11,12] in any of these reactions, but in some instances eventual precipitation of surfactant prevented the kinetics from being carried beyond 70–80% of

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Table V. Micellar and Vesicular Cleavages of Phosphates[a]

case	surfactant	substrate	$10^3 k_\psi^{max}$,[b] s^{-1}	$10^3 k_m$,[c] s^{-1}	K/N,[d] M^{-1}	k_ψ^{max}/k_0
1	16-PhOH/CTABr	PNPDPP	24.0 (4.0)[e]	29.8	716	825
2	16-PhOH/16_2	PNPDPP	2.08 (0.06)[f]	2.56	5900	71
3	16-OH	PNPDPP	2.00 (0.80)[g]	3.78	2000	69
4	16_2OH	PNPDPP	0.93 (0.60)[g]	0.94	22000	32
5	16_2OH	6	2.21 (0.90)[g]	2.66	5600	167
6	16-OH	6	0.70 (1.8)[g]	1.02	1300	53
7	16_2	6	0.26 (1.4)[g]	0.33	4300	20

[a] Kinetic data were taken from Tables I–IV (see supplementary material). Conditions are standard (see text): pH 9.0, Tris buffer for PNPDPP cleavages, and 0.10 M aqueous NaOH solution for 6. [b] k_ψ^{max} values are from Tables I–IV; values in parentheses are concentrations $\times 10^3$ (M) of *functional* surfactant at which k_ψ^{max} is observed. [c] Micellar (k_ψ = vesicular) rate constants derived from Lineweaver-Burk analysis of Tables I–IV (see text). *Total* surfactant concentrations were used in cases 1 and 2. [d] Ratio of binding constant to aggregation number derived from Lineweaver-Burk analysis. [e] 1:1 16-PhOH/CTABr; total [surfactant] = 8.0×10^{-3} M. [f] 1:10 16-PhOH/16_2; total [surfactant] = 6.6×10^{-4} M. [g] No additional surfactant was present.

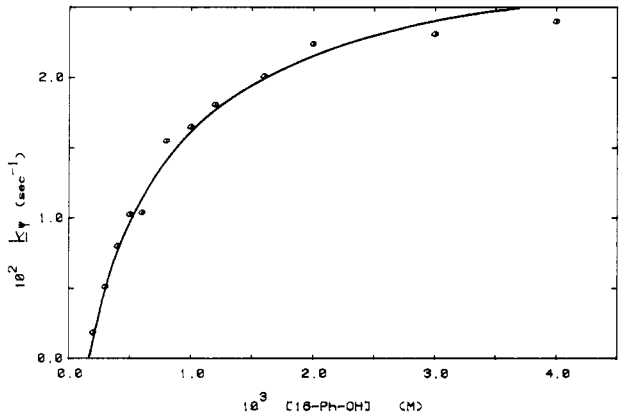

Figure 3. Pseudo-first-order rate constants (k_ψ, s^{-1}) for the cleavage of PNPDPP by comicellar 1:1 16-PhOH/CTABr as a function of [16-PhOH] at pH 9.0 under standard conditions (see text). The solid line was generated by using the Lineweaver–Burk parameters of Table V (see text and Table III).

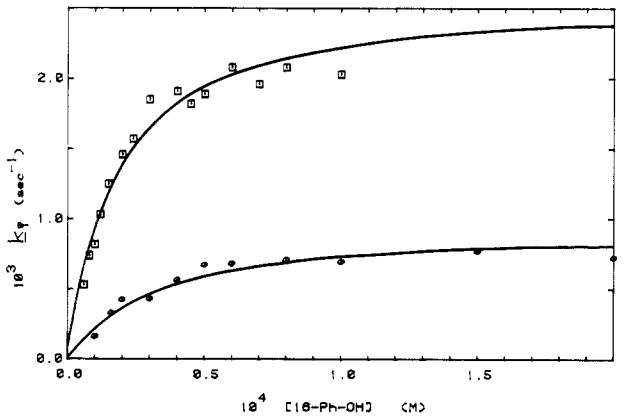

Figure 4. Pseudo-first-order rate constants (k_ψ, s^{-1}) for the cleavage of PNPDPP by 1:10 covesicular 16-PhOH/16_2 (sonication) and 1:10 comicellar 16-PhOH/CTABr as functions of [16-PhOH] at pH 9 under standard conditions (see text): □, 16-PhOH/16_2; ○, 16-PhOH/CTABr. The solid lines were generated by using the Lineweaver–Burk parameters of Table V (see text and Table IV).

reaction. Since slow "second phase" vesicular reactions often account for the last 10–20% of the overall reaction,[11,12] they would not have been observed under these circumstances.

The known efficiency of aryloxide ion micellar systems in the cleavage of phosphate substrates[7] led to a brief study of functional phenolic surfactant **5** (16-PhOH). Due to its limited solubility, these reactions were carried out in comicellar or covesicular solutions. In Table III (see supplementary material) we collect data for rate constant/[surfactant] profiles involving PNPDPP cleavage by 1:1 16-PhOH (or 16-OH)/CTABr comicelles. The 16-PhOH profile appears graphically in Figure 3. The 16-PhOH/CTABr system is about 80 times kinetically superior to the 16-OH/CTABr reagent.

Finally, covesicular 16-PhOH/16_2 was compared to comicellar 16-PhOH/CTABr in the cleavage of PNPDPP. These reactions employed 1:10 blends of functional and nonfunctional surfactants. The data are collected in Table IV (see supplementary material) and illustrated in Figure 4. The vesicular reagent appears to be ~3 times more reactive than its micellar analogue and reaches its maximum efficiency at about half the concentration of 16-PhOH (i.e., 0.60×10^{-4} M 16-PhOH in 16_2 vs. 1.5×10^{-4} M 16-PhOH in CTABr).

Discussion

A major aim of this study was to determine the comparative kinetic efficiencies of simple functional micelles and vesicles in the nucleophilic[6] cleavage of the representative phosphate substrates, **2** and **6**. Appropriate kinetic data have been presented in Tables I–IV and Figures 1–4. Maximum pseudo-first-order cleavage rate constants (and the concentrations of surfactant necessary to produce them) together with relative kinetic enhancements, k_ψ^{max}/k_0, are collected in Table V.

From Table V it is apparent that 1:1 comicellar 16-PhOH/CTABr is the most reactive system for the cleavage of the neutral phosphate substrate PNPDPP at pH 9, providing an 825-fold rate constant enhancement over buffer alone. The 1:10 vesicular 16-PhOH/16_2 (case 2) is not directly comparable because of its lower functionalization. (Higher ratios of 16-PhOH to 16_2 could not be used for fear of destroying the vesicles.) It provides only a 71-fold cleavage rate enhancement but reaches maximum efficiency at 0.66×10^{-3} M total surfactant concentration vs. 8.0×10^{-3} M for 1:1 16-PhOH/CTABr. The concentration "advantage" of the vesicular system is due to its greater K/N. Assuming $N \approx 14\,000$[19] for 16_2 and ~100 for 16-PhOH/CTABr,[3] we estimate K to be $\sim 10^3$ greater for the vesicular system. Figure 4 shows that 1:10 vesicular 16-PhOH/16_2 is kinetically superior to 1:10 micellar 16-PhOH/CTABr at comparable concentrations.

Micellar 16-OH and 1:10 vesicular 16-PhOH/16_2 appear from Table V to be kinetically comparable as PNPDPP cleavage reagents (cases 2 and 3). In the direct micelle vs. vesicle comparison, 16-OH is modestly superior to 16_2OH (factor of ~2 in k_ψ^{max}, cases 3 vs. 4). From Table V this advantage can be seen to consist of a 4-fold higher k_m,

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partially offset by more effective substrate binding by the vesicular system. Clearly, for efficient cleavage of the neutral PNPDPP substrate, there is no advantage in using vesicular 16_2OH over micellar 16-OH. These results should be compared with those for the cleavage of ethyl bis(*p*-nitrophenyl) phosphate by (e.g.) 5×10^{-5} M *N*-methyloctadecanehydroxamic acid in either 10^{-3} M CTABr micelles or 10^{-3} M $R_2NMe_2^+$ vesicles (pH 8.8, 30° C).[13] Here k_ψ is slightly greater for the vesicular system when R = n-$C_{12}H_{25}$ but slightly lower when R = n-$C_{16}H_{33}$. Again, there is no pronounced kinetic advantage to the use of the vesicular system.

The apparent kinetic advantage of micellar 16-PhOH/CTABr over 16-OH is most reasonably attributed to the greater acidity of the former, resulting in a greater proportion of the reactive, nucleophilic, phenoxide form present in pH 9 micellar solution, compared to the alkoxide form of 16-OH. The pK_a of 1:1 micellar 16-PhOH/CTABr is 8.04;[16] that of 16-OH was reported to be ~12.4 in the kinetic system here under study.[6b] However, in a recent kinetic study of the micellar cleavage of isobutyl *p*-nitrophenyl methylphosphonate, the pK_a of 16-OH was determined to be 9.5 from the dependence of k_{obsd} on pH.[6c] Additionally, $pK_a \approx 10.5$ was reported for the homologous *n*-octadecyl micellar reagent in a kinetic study of the esterolysis of *p*-nitrophenyl heptanoate.[20] Despite the manifest uncertainty in the pK_a of micellar 16-OH, it must clearly be higher than that of micellar 16-PhOH.

For cleavage of the *anionic* 2,4-dinitrophenyl ethyl phosphate (**6**), vesicular 16_2OH is the reagent of choice (cf. Table V and Figure 2). In 0.1 M aqueous NaOH solution, the functional vesicles generate a 167-fold rate enhancement, relative to bulk aqueous solution; the functional micellar analogue, 16-OH, is about one-third as reactive at twice the concentration (Table V, case 5 vs. 6). The vesicular system's advantage involves both more favorable k_m and K/N values. The reversal of kinetic advantages between micellar 16-OH and vesicular 16_2OH toward neutral PNPDPP (16-OH superior) and anionic **6** (16_2OH superior) has practical interest, but the kinetic differences are not very large, and the mechanistic reasons are still obscure.

It is of some interest to briefly compare the phosphate cleavage systems described here with literature examples. The most reactive of the present systems, 1:1 micellar 16-PhOH/CTABr, is comparable to phenoxide ions solubilized in CTABr.[7] Thus, 6.7×10^{-4} M phenoxide/phenol in ~10^{-3} M CTABr cleaves PNPDPP at pH 10 with k_ψ = 0.029 s^{-1}, whereas 8.0×10^{-3} M (total [surfactant]) of 1:1 16-PhOH/CTABr exhibits k_ψ = 0.024 s^{-1} toward the same substrate at pH 9. These reagents are also kinetically comparable to 10^{-4} M benzimidazole solubilized in ~10^{-3} M CTABr, which cleaves PNPDPP with $k_\psi \approx 0.02$ s^{-1} at pH 10.7,[9b] and to 10^{-3} M micellar imidazole-functionalized surfactant, n-$C_{16}H_{33}N^+Me_2CH_2Im,Cl^-$, where k_ψ = 0.045 s^{-1} for cleavage of PNPDPP at pH 9.[9a]

Oximate catalysts, however, are more reactive than the foregoing reagents. Thus, k_2 for PNPDPP cleavage by 1:1 16-PhOH/CTABr at pH 9 is ~6 M^{-1} s^{-1} ([CTABr] = 4×10^{-3} M), whereas (e.g.) 2-pyridinecarboxaldoximate in 10^{-3} M CTABr at pH 10 has k_2 = 410 M^{-1} s^{-1}.[8b] Similarly, 5×10^{-4} M *p*-(hexyloxy)benzamidoximate ion in 3×10^{-3} M CTACl and 10^{-2} M NaOH shows k_ψ = 0.16 s^{-1} for cleavage of PNPDPP. However, this is only ~3 times the rate constant for OH^--mediated cleavage in CTACl and 10^{-2} M NaOH.[8c] The kinetic efficiency of long-chain hydroxamic acid/CTABr systems has also been established,[13] although comparisons with our reagents are not possible because of the different substrates employed.

Conclusion

The data show that 16-PhOH and 16-OH are moderately effective reagents for the cleavage of neutral phosphate esters in either micellar or vesicular phases. They are, however, inferior to hydrophobic oximate reagents solubilized in micellar CTA. More importantly, we find no intrinsic kinetic advantage to the use of hydroxyl-functionalized *vesicular* cleavage reagents, relative to the comparable *micellar* system, in the cleavage of PNPDPP, although the vesicular systems are more efficient toward the very tightly bound anionic phosphate substrate **6**. The enhanced binding elicited by vesicular, relative to analogous micellar, reagents does not immediately translate into enhanced catalytic properties, at least with the simple systems examined here.

Experimental Section

General Methods. Melting points are uncorrected. NMR spectra were measured with a Varian T-60 spectrometer, and chemical shifts are reported relative to internal Me_4Si. Microanalyses were performed by Robertson Laboratory, Florham Park, NJ.

Materials. Substrate **2**[14] and surfactants **4**[6b] and **5**[16] were prepared and purified by literature methods. CTABr was a commercial sample, purified by a standard method.[21] Details of the preparations of surfactant **3**[11] and substrate **6** are given here.

***N*,*N*-Di-*n*-hexadecyl-*N*-methyl-*N*-(β-hydroxyethyl)ammonium Bromide (3, 16_2OH).** To 15 g (49.2 mmol) of cetyl bromide (MCB) was added 30 g (405 mmol) of 2-(methylamino)ethanol (Aldrich); the materials were refluxed in 60 mL of acetone. After 3 h an oily layer had separated from the solution. The entire reaction mixture was transferred to a separatory funnel, and the lower layer was removed. The upper layer was stripped of acetone, dissolved in ether, and washed twice with warm (30 °C) aqueous sodium bicarbonate solution. The ethereal solution was dried over $MgSO_4$ and stripped of ether. The resultant viscous oil was recrystallized from anhydrous ether in the freezer, giving 12.2 g (83% yield) of white flakes (mp 31–32 °C) of *N*-methyl-*N*-(β-hydroxyethyl)-*n*-hexadecylamine. The NMR spectrum ($CDCl_3$) displayed signals at δ 0.94 and 1.26 (crude t and s, 31 H, $CH_3(CH_2)_{14}$), 2.26 (s, 3 H, N-CH_3), 2.40 (m, 4 H, $C_{15}H_{31}CH_2NCH_2$), 3.50 (s, 1 H, OH), and 3.61 (t, J = 5.4 Hz, 2 H, CH_2OH). Anal. Calcd for $C_{19}H_{41}NO$: C, 76.17; H, 13.81; N, 4.68. Found: C, 76.13; H, 13.98; N, 4.33.[22]

This tertiary amine (10.0 g, 33.4 mmol) and 15.3 g (50.1 mmol) of cetyl bromide (Sigma) were dissolved in 100 mL of absolute ethanol and refluxed for 21 h. The ethanol was removed under vacuum to give a white solid. This was triturated with anhydrous diethyl ether, recrystallized twice from ethyl acetate, and dried under high vacuum to give 16.2 g (26.8 mmol, 80%) of surfactant **3**: mp 76–78 °C (liquid crystal), 148–150 °C; ^1H NMR ($CDCl_3$) δ 0.87 (t, 6 H, $(CH_2CH_3)_2$), 1.26 (s, 56 H, $((CH_2)_{14})_2$), 3.3–3.8 (m, 9 H, $(-CH_2)_2N^+(CH_3)CH_2^-$), 4.10 ("t", 2 H, CH_2OH), 5.1 (s, 1 H, OH). Anal. Calcd for $C_{35}H_{74}BrNO$: C, 69.48; H, 12.34; N, 2.32. Found: C, 69.05; H, 12.20, N, 2.39.[23]

Lithium 2,4-Dinitrophenyl Ethyl Phosphate (6). 2,4-Dinitrophenol (1.84 g, 10 mmol), diethyl chlorophosphate (1.72 g, 10 mmol, Aldrich), and 1.11 g (11 mmol) of triethylamine were dissolved in 50 mL of benzene. The solution was refluxed overnight, and the precipitated triethylamine hydrochloride was filtered. The benzene filtrate was extracted with 5 × 100 mL of water and dried over $MgSO_4$, and the benzene was removed under

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(23) This synthesis is due to Mr. G.O. Bizzigotti and is outlined in ref 11.

reduced pressure to give 2.20 g (6.9 mmol, 69%) of 2,4-dinitrophenyl diethyl phosphate as a light yellow oil. This was dissolved in 100 mL of dry acetone and refluxed for 3 h with 0.61 g (7 mmol) of dry LiBr. The solution was then allowed to stand at 25 °C overnight, and the precipitate of **6** was collected and washed several times with dry ether. We thus obtained 1.05 g (3.5 mmol, 35%) of purified **6** after recrystallization from methanol/ether: mp 110–120 °C dec; ^{1}H NMR (D_2O, DSS) δ 1.3 (t, J = 7 Hz, 3 H, CH_3), 4.1 ("quintet", J = 8 Hz, 2 H, CH_2),[24] 7.6–9.0 (m, 3 H, aryl). Anal. Calcd for $C_8H_8LiN_2O_8P$: C, 32.21; H, 2.71; N, 9.40. Found: C, 31.95; H, 2.97; N, 8.85.[25]

Kinetic Studies. Reactions were followed on a Gilford Model 250 spectrophotometer coupled to a Gilford Model 6051 recorder. A constant-temperature circulating bath maintained the reaction temperature at 25.0 ± 0.02 °C. Rate constants were obtained from computer-generated correlations of log ($A_\infty - A_t$) with time in the standard way. Micellar reactions were generally followed to >90% completion (70–80% in the case of vesicular reactions) and showed good first-order kinetics ($r > 0.999$).

Vesicular solutions were typically prepared at 60–65 °C by sonication with a Bransonic Model 221 bath-type sonifier, operated at maximum power (225 W) for 30 min, or by the injection method.[11] Further details appear in the Results section.

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Registry No. 1 (Z = O; $R_1 = R_2$ = OEt; X = Cl), 814-49-3; 1 (Z = O; $R_1 = R_2$ = OEt; X = 2,4-dinitrophenoxy), 54436-53-2; **2**, 10359-36-1; **3**, 83710-46-7; **4**, 20317-32-2; **5**, 77551-97-4; **6**, 84175-82-6; 16_2, 70755-47-4; CTABr, 57-09-0; MCB, 112-82-3; 2-(methylamino)ethanol, 109-83-1; *N*-methyl-*N*-(β-hydroxyethyl)-*n*-hexadecylamine, 7089-36-3; 2,4-dinitrophenol, 51-28-5.

Supplementary Material Available: Tables I–IV containing (respectively) rate constants for cleavage of PNPDPP by 16-OH and 16_2OH, rate constants for the cleavage of **6** by CTABr, 16-OH, 16_2, and 16_2OH, rate constants for the cleavage of PNPDPP by 16-PhOH and 16-OH, and rate constants for the cleavage of PNPDPP by 16-PhOH/16_2 and 16-PhOH/CTABr (4 pages). Ordering information is given on any current masthead.

(24) This signal is actually an overlapping doublet of quartets, with the additional splitting due to $^{31}POCH_2$ coupling. The quoted "J" value is apparent.

(25) Complete hydrolysis of **6**, followed by spectrophotometric determination of 2,4-dinitrophenol, gave a purity of 95 ± 2$_4$%.

Friedel–Crafts Reactions of Some Conjugated Epoxides[1]

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The Friedel–Crafts (FC) reactions of (1,2-epoxyethyl)benzene, 1,2-epoxy-1-*p*-tolylethane, 1,2-epoxy-1-(*p*-methoxyphenyl)ethane, 1,2-epoxy-3-butene, and 1,2-epoxy-2-methyl-3-butene were examined under various conditions. Reaction time, temperature, Lewis acid, Lewis acid concentration, and solvent were varied. For (1,2-epoxyethyl)benzene (**1**), aromatic nucleophilicity was shown to be an important factor in promoting good FC yields. It was also shown that para carbocation stabilizing substituents on **1** did not improve FC yields. Vinyloxirane yielded primary products from direct ring opening (2-aryl-3-buten-1-ols) and conjugate addition (4-aryl-2-buten-1-ols) and secondary products (1,4-diaryl-2-butenes). Increased reaction time or catalyst concentration increases the proportion of secondary products. The primary and secondary FC pathways gave an excellent opportunity for study of the effects on product distributions of the use of aluminum chloride, boron trifluoride etherate, and stannic chloride Lewis acids. A significant FC reaction yield was not obtained with 1,2-epoxy-2-methyl-3-butene and toluene under the same conditions used for 1,2-epoxy-3-butene. Presumably this results from steric effects. All products can be explained by attack of the aromatic nucleophile on the epoxide position (or positions) most capable of stabilizing incipient positive character. The epoxide is also less electrophilic than other alkylating agents under similar conditions. An explanation for this is given.

Despite the abundance of studies on other classes of Friedel–Crafts (FC) alkylation reactions,[2] comparatively few studies have been done on the FC reactions of epoxides.[3-9] As with many other reactions of this type, complex product mixtures have been observed, but, atypically, complex epoxide FC alkylation mixtures generally do not appear to be the result of isomerization and disproportionation processes.[2,5,8] Instead they apparently result from multiple ring-opening pathways and from the formation of halohydrins resulting from ring opening by the Lewis acid alkylation promoter (LAAP).[4-8]

Recently, Japanese workers demonstrated a 100% stereospecific epoxide FC alkylation,[5] and our group reported a highly stereoselective one involving the transannular cyclization of a medium-ring epoxide.[10] These reactions suggested further investigations on epoxide FC reactions were of significant interest. However, most work prior to ours, other than polyene cyclizations (which are not intermolecular FC reactions[11]) dealt mainly with simple

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