a rotating anode (50 kV, 200 mA), with use of graphite monochromated Mo Kα radiation (λ = 0.71069 Å). Crystal data are as follows: molecular formula, $C_{28}H_{40}NO_8SCl$; molecular weight, 586.1; orthorhombic space group, $P2_12_12_1$, a = 13.494 (4) Å, b = 18.833 (4) Å, c = 11.323 (8) Å, V = 2877.5 (10) Å^3, Z = 4, D_c = 1.35 g/cm^3; μ(Mo K); 2.48 cm^{-1}. A total of 2808 reflections within 2θ = 52°. The structure was solved by the direct method with a RANTAN81 program with some modification.[23] After the block-diagonal least-squares refinement for non-hydrogen atoms with anisotropic temperature factors, the hydrogen atoms were calculated geometrically and also verified from the difference Fourier map and then included in the refinement with isotropic temperature factors. The final R factor was 0.089 (R_w = 0.087) for 1789 reflections with $|F_o| > 3\sigma(|F_o|)$.

X-ray Crystallographic Study of the Racemate of 34. A colorless crystal,[10] mp 172-173 °C (from Et_2O-hexane), with dimensions of 0.20 × 0.20 × 0.25 mm was used for data collection on the above diffractometer. Crystal data are as follows: $C_{23}H_{33}NO_5$, molecular weight, 403.5; monoclinic space group, $P2_1/c$, a = 18.991 (1) Å, b = 7.651 (1) Å, c = 14.707 (1) Å, β = 93.71 (1)°, V = 2132.4 (3) Å^3, Z = 4, D_c = 1.26 g/cm^3; μ(Mo K), 0.82 cm^{-1}. A total of 4055 reflections within 2θ = 55°. The structure was solved as above, and the final R factor was 0.059 (R_w = 0.051) for 3370 reflections with $|F_o| > 3\sigma(|F_o|)$.

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Registry No. 1, 466-43-3; **2**, 124022-25-9; **5**, 113161-21-0; **6**, 25928-05-6; **7**, 113161-22-1; **8**, 113161-31-2; **9**, 124022-28-2; **10**, 124022-29-3; **11**, 124022-30-6; **12**, 124097-07-0; **13**, 124097-08-1; **14**, 124022-31-7; **15**, 124022-32-8; **15** (*S*)-MTPA ester, 124022-41-9; **16**, 124022-26-0; **16**·$HClO_4$, 124022-27-1; **17**, 124022-33-9; **18**, 124097-09-2; **19**, 124022-34-0; **20**, 124097-10-5; **21**, 124097-11-6; **22**, 124097-12-7; **22** (*S*)-MTPA ester, 124097-20-7; **23**, 124097-13-8; **24**, 124097-14-9; **25**, 124022-35-1; **26**, 124097-15-0; **27**, 124097-16-1; **28**, 124150-10-3; **29**, 124022-36-2; **30**, 124097-17-2; **30** aldehyde, 124022-42-0; **31**, 124097-18-3; **32**, 124022-37-3; **31** (R = CHO), 124022-43-1; **33**, 124022-38-4; **34**, 124097-19-4; **35**, 124022-39-5; **36**, 124022-40-8; $PhCH_2NH_2$, 100-46-9.

Supplementary Material Available: Listing of final atomic coordinates, temperature factors, and bond lengths and angles for the perchlorate of **16** and for the racemate of **34** (14 pages). Ordering information is given on any current masthead page.

Monohalogenation of Alkyl Phenyl Ethers in Micellar and Vesicular Media

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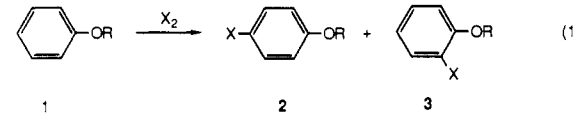
Abstract: The rates and regioselectivities of monohalogenation of C_6H_5OR (**1**: **a**, R = C_5H_{11}; **b**, R = C_9H_{19}; **c**, R = $C_{12}H_{25}$) by chlorine water and bromine water to give 4-XC_6H_4OR (**2**) and 2-XC_6H_4OR (**3**) (X = Cl, Br) have been determined in micellar sodium dodecyl sulfate (**4**) and vesicular sodium 3-[(2,2-diheptadecyl-1,3-dioxolan-4-yl)methoxy]-1-propanesulfonate (**5**) and *dl*-α-dipalmitoylphosphatidylcholine (**6**) in a pH 7.30 phosphate buffer. The **2**/**3** ratios for **1a** were greater in the surfactant media than in buffer/water alone and increased in the order **1a** < **1b** < **1c**. In general the second-order rate constants, k_2, for **1a** were less in the surfactant media than in buffer alone and decreased in the order **1a** > **1b** ≥ **1c**. The combination of kinetic and regioselectivity data indicated that the three ethers, which differ in hydrophilic/hydrophobic character, have different solubilization sites in the surfactant aggregates and react at these sites. The quantitative isolation of products and unreacted starting material from vesicular **5**, a cleavable surfactant, involved acid-catalyzed hydrolysis of **5**, followed by straightforward extractive workup.

There have been numerous studies of organic reactions in surfactant-based organized media.[2] Generally, the focus has been either regio/stereoselectivity or, more often, kinetics. Both factors have been investigated in relatively few systems.[3] But the combination of the two allows a determination of the relationship between solubilization and reaction sites within a surfactant aggregate. We and others have previously reported that micelles can influence the regioselectivity of electrophilic aromatic substitution reactions, including the halogenation and nitration of alkyl phenyl ethers,[4] phenol,[4c,5] and bromobenzene.[6] Herein we report a study of the relative abilities of aqueous micelles and vesicles to control *both* the regioselectivities and rates of monochlorination and monobromination of alkyl phenyl ethers **1** to give para (**2**) and ortho products (**3**) (eq 1).



(1)

1 2 3

1a, R = *n*-C_5H_{11}
b, R = *n*-C_9H_{19}
c, R = *n*-$C_{12}H_{25}$

X = Cl, Br

Results

Halogenations were performed with chlorine water and bromine water in micellar sodium dodecyl sulfate (**4**) and vesicular sodium 3-[(2,2-diheptadecyl-1,3-dioxolan-4-yl)methoxy]-1-propane-

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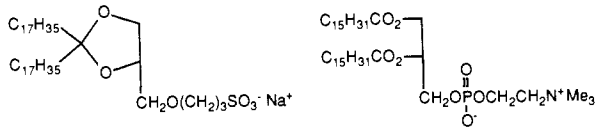
Table I. Monochlorination Regioselectivity at 25 ± 2 °C[a]

entry	medium[b]	ether	reaction time, min	% yield 2 + 3[c]	2/3 ratio[c]
1	pH 6.85 phosphate buffer	**1a**	25	49.5 ± 1.0	1.3 ± 0.1
			30	57.1 ± 1.0	1.3 ± 0.1
2	95:5 (v/v) H_2O–MeCN	**1a**	4	78 ± 2	1.3 ± 0.2
			6	90 ± 2	1.2 ± 0.2
3	0.20 M **4**	**1a**	15	31.0 ± 0.9	4.6 ± 0.2
			45	69.4 ± 1.0	4.7 ± 0.2
4	0.20 M **4**	**1b**	15	14.8 ± 0.9	5.3 ± 0.3
			75	40.9 ± 1.0	5.2 ± 0.3
5	0.20 M **4**	**1c**	30	26.8 ± 1.0	6.6 ± 0.3
			90	63.1 ± 1.0	6.8 ± 0.3
6	0.020 M **5**	**1a**	180	43.7 ± 0.1	4.0 ± 0.1
			300	80.9 ± 0.2	4.1 ± 0.2
7	0.020 M **5**	**1b**	180	23.9 ± 0.2	4.8 ± 0.1
8	0.020 M **5**	**1c**	180	19.2 ± 0.2	5.7 ± 0.3
9	0.020 M **6**	**1a**	60	16.3 ± 0.1	4.0 ± 0.2
10	0.020 M **6**	**1b**	150	22.9 ± 0.1	7.5 ± 0.1
11	0.020 M **6**	**1c**	120	15.2 ± 0.1	8.8 ± 0.2
			240	23.5 ± 0.2	8.9 ± 0.2

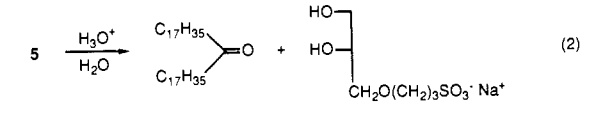
[a] [**1**] = 1.1 × 10^{-4} M; [active chlorine] = 3.2 × 10^{-3} M in entries 1 and 3–11, and 4.8 × 10^{-4} M in entry 2. [b] The surfactant solutions of entries 3–11 were prepared in the pH 7.30 phosphate buffer. Entries 1 and 3–11 contained 0.2 vol% MeCN. [c] By HPLC analysis. The limits of error are average deviations for duplicate analyses of at least two runs.

sulfonate (**5**)[7] and *dl*-α-dipalmitoylphosphatidylcholine (**6**). As appropriate, the reaction time of a halogenation was limited so that **2** and **3** were formed to the exclusion of any 2,4-$X_2C_6H_3OR$ (**7**) and/or 2,6-$X_2C_6H_3OR$ (**8**) in order to yield a meaningful para/ortho ratio (**2**/**3**), the measure of regioselectivity. Surfactant **5** is a cleavable system that is especially suited for the isolation of neutral organic reaction products from vesicular media since it undergoes acid-catalyzed hydrolysis to give nonsurfactant compounds **9** and **10** (eq 2),[7] which do not complicate straightforward extractive workup procedures as normal surfactants often do.



5

6



(2)

9 10

Chlorinations and brominations of individual ethers and ether pairs were performed in pH 7.30 phosphate buffer solutions of **4**, **5**, and **6**. In each run, the **2**/**3** ratio was determined, and with an excess of halogenating agent in the ether pair runs, a plot of the percentage of unreacted **1** vs time gave the pseudo-first-order rate constant, which was converted into the second-order rate constant k_2. For comparison, halogenations were also carried out in a phosphate buffer alone and in 95:5 (v/v) H_2O–MeCN.

Reactions in micellar **4** were performed as follows. An aliquot of **1** in MeCN was added to a buffer solution of 0.20 M **4**, and the system was sonicated at 50–55 °C and allowed to cool to 25 °C. Then an aliquot of excess chlorine or bromine water was added, and at appropriate times samples of the reaction mixture were treated with $Na_2S_2O_3$, diluted with an equal volume of MeCN, filtered, and analyzed directly for **1**, **2**, and **3** by calibrated reversed-phase high-performance liquid chromatography (HPLC) with UV detection at 210 nm.

Reactions in vesicular **5** were performed as follows. To a thin film of **5** were added aliquots of the pH 7.30 buffer and **1** in MeCN. The system was sonicated as above to give a solution containing 0.020 M **5**. Then an aliquot of excess chlorine or bromine water was added, and at the appropriate time the reaction mixture was treated with $Na_2S_2O_3$, acidified with hydrochloric acid, and held at 50 °C for 30 min to hydrolyze **5** (eq 2). The resultant system was basified with aqueous NaOH, diluted with an equal volume of MeCN, and filtered to remove precipitated **9**. The filtrate contained a salted-out MeCN layer that was analyzed for **1**, **2**, and **3** by HPLC.

The procedure for reactions in vesicular **6** was essentially the same as for **5** through the addition of $Na_2S_2O_3$. The remaining workup included the addition of an equal volume of MeCN to precipitate **6**, filtration, and analysis as above. Controls verified that the analytical results for each surfactant medium accurately represent the ether compositions of the reaction mixtures.

The regioselectivity results for the monochlorination of individual ethers are given in Table I. In these reactions the maximum percent conversion of **1** to **2** and **3** without the formation of **7** and/or **8** varied with the medium and, in vesicular **6**, also with the ether. In both micellar **4** and vesicular **5**, the value was ca. 70% for **1a**, **1b**, and **1c**, whereas in **6** the values were 15, 25, and ≥35%, respectively. In a pH 6.85 phosphate buffer and in 95:5 (v/v) H_2O–MeCN, the value was 90% for **1a**. The kinetic results for the monochlorination of ether pairs are summarized in Table II. The **2**/**3** ratios in these reactions (not shown) were the same as those in the individual runs of Table I. Monophasic kinetics were uniformly observed.

In both entries 1 and 2 of Table I and in H_2O alone (pH 3.4),[4b] **2**/**3** = 1.3 ± 0.1 for **1a**. Thus in homogeneous aqueous media the regioselectivity for monochlorination of **1a**, and presumably of **1b** and **1c** also, is insensitive to a change in pH from 3.4 to 6.85 and the accompanying phosphate salts, and to 5 vol % MeCN. In each of the surfactant media the **2**/**3** ratio for **1a** is greater

Table II. Monochlorination Kinetics at 25 ± 2 °C[a]

entry	medium[b]	ether/ether pair	10^2k_2,[c,d] M^{-1} s^{-1} LH	10^2k_2,[c,d] M^{-1} s^{-1} HH	k_2^{LH}/k_2^{HH}
12	pH 6.85 phosphate buffer	**1a**	15		
13	0.20 M **4**	**1a**, **1b**	13	6.9	1.9
14	0.20 M **4**	**1b**, **1c**	6.6	6.6	1.0
15	0.020 M **5**	**1a**, **1b**	1.0	0.56	1.8
16	0.020 M **5**	**1b**, **1c**	0.56	0.56	1.0
17	0.020 M **6**	**1a**, **1b**	2.2	1.0	2.2
18	0.020 M **6**	**1b**, **1c**	0.97	0.50	1.9

[a] [LH] = [HH] = 5.5 × 10^{-5} M in entries 13–18, and [**1a**] = 1.1 × 10^{-4} M in entry 12; [active chlorine] = 3.2 × 10^{-3} M. [b] The surfactant solutions of entries 13–18 were prepared in the pH 7.30 phosphate buffer; all entries contained 0.2 vol% MeCN. [c] LH and HH = lower and higher homologue, respectively. [d] The values for entries 13–18 are averages for duplicate runs with three to five points, and that for entry 12 is the average of two one-point k_2s derived from entry 1 of Table I. The estimated limits of error are ±10%.

Table III. Monobromination Regioselectivity at 25 ± 2 °C[a]

entry	medium[b]	ether	reaction time, s	% yield 2 + 3[c]	2/3 ratio[c]
19	pH 7.30 phosphate buffer	**1a**	60	92.3 ± 0.2	17.8 ± 0.4
20	0.20 M **4**	**1a**	<60	83.0 ± 0.2	>200
21	0.20 M **4**	**1b**	60	59.6 ± 0.3	>200
22	0.20 M **4**	**1c**	60	48.0 ± 0.3	>200
23	0.020 M **5**	**1a**	300	98.5 ± 0.3	36.3 ± 1.4
24	0.020 M **5**	**1b**	300	93.7 ± 0.3	>100
25	0.020 M **5**	**1c**	300	82.3 ± 0.4	>100
26	0.020 M **6**	**1a**	60	95.1 ± 0.2	22.8 ± 0.8
27	0.020 M **6**	**1b**	300	98.0 ± 0.2	50.6 ± 0.9
28	0.020 M **6**	**1c**	300	59.5 ± 0.3	54.8 ± 0.7

[a] [**1**] = 1.1 × 10^{-4} M; [active bromine] = 4.5 × 10^{-4} M in entry 19, 9.0 × 10^{-4} M in entries 20–22, 1.4 × 10^{-3} M in entries 23–26, and 2.7 × 10^{-3} M in entries 27 and 28. [b] The surfactant solutions of entries 20–28 were prepared in the pH 7.30 phosphate buffer; all entries contained 0.2 vol% MeCN. [c] By HPLC analysis. The limits of error are average deviations for duplicate analyses of at least two runs.

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Table IV. Monobromination Kinetics at 25 ± 2 °C[a]

entry	medium[b]	ether/ether pair	k_2,[c,d] M^{-1} s^{-1} LH	HH	k_2^{LH}/k_2^{HH}
29	pH 7.30 phosphate buffer	**1a**	95		
30	0.20 M **4**	**1a, 1b**	37	18	2.1
31	0.20 M **4**	**1b, 1c**	18	12	1.5
32	0.020 M **5**	**1a, 1b**	16	3.2	5.0
33	0.020 M **5**	**1b, 1c**	3.2	1.6	2.0
34	0.020 M **6**	**1a, 1b**	129	5.8	22
35	0.020 M **6**	**1b, 1c**	5.7	2.9	2.0

[a] [LH] = [HH] = 5.5×10^{-5} M in entries 30–35, and [**1a**] = 1.1×10^{-4} M in entry 29; [active bromine] = 4.5×10^{-4} M in entry 29, 9.0×10^{-4} M in entries 30–33, 1.4×10^{-3} M in entry 34, and 2.7×10^{-3} M in entry 35. [b] The surfactant solutions of entries 30–35 were prepared in the pH 7.30 phosphate buffer; all entries contained 0.2 vol% MeCN. [c] LH and HH = lower and higher homologue, respectively. [d] The values for entries 30–35 are averages for duplicate runs with ≥3 points, and that for entry 29 is the average of two one-point k_2s derived from entry 19 of Table III. The estimated limits of error are ±10%.

than 1.3, and it increases on going to **1b** and **1c**. In Table II, k_2 for **1a** in micellar **4** (entry 13) is comparable to that in the pH 6.85 buffer (entry 12), and the k_2s for **1b** and **1c** are the same and one-half that for **1a** (entries 13 and 14). The k_2s for **1a**, **1b**, and **1c** in vesicular **5** are less than those in micellar **4** by a factor of ca. 10, but the relative rates are the same. In vesicular **6**, k_2 is different for each ether.

The regioselectivity results for monobromination of individual ethers are given in Table III. In no run was **7** and/or **8** observed. The kinetic results for monobromination of ether pairs are summarized in Table IV. The **2**/**3** ratios in these reactions (not shown) were the same as those in the individual runs of Table III. Monophasic kinetics were uniformly observed.

The **2**/**3** ratio is 17.8 in entry 19 of Table III and 20 in H_2O alone (pH 4.8).[4a] Thus in homogeneous aqueous media the regioselectivity for monobromination of **1a**, and presumably of **1b** and **1c** also, is insensitive to a change in pH from 4.8 to 7.30 and the accompanying phosphate salts. The **2**/**3** ratio was >200 for each ether in micellar **4** (entries 20–22), 36.3 for **1a** and >100 for both **1b** and **1c** in vesicular **5** (entries 23–25), and 22.8 for **1a** and ca. 50 for both **1b** and **1c** in vesicular **6** (entries 26–28). In Table IV, the k_2s for the three ethers in each surfactant medium decrease in the order **1a** > **1b** > **1c**. Except for **1a** in vesicular **6** (entry 34), all of the k_2s in the surfactant media are less than that for **1a** in the pH 7.30 buffer (entry 29).

The solubilization of 1.1×10^{-4} M **1** at the molecular level in the pH 7.30 phosphate buffer containing 0.020 M vesicular **5** was demonstrated by UV spectroscopy. Molar extinction coefficients (ϵ) were calculated for λ_{max} = 220, 270, and 278 nm in each of the spectra of 5.5×10^{-5} M **1a**, **1b**, and **1c** solutions. Then the spectra of 1.1×10^{-4} M ether solutions were obtained. The absorbances at the λ_{max} values and the corresponding ϵ values verified that **1** was completely dissolved in each case. Complete solubilization of 1.1×10^{-4} M **1** in the pH 7.30 phosphate buffer containing 0.020 M **6** was assumed. Since the solubility limit of **1c** in aqueous 0.20 M **4** is 3.5×10^{-3} M,[4b] it is almost certain that 1.1×10^{-4} M **1** was completely solubilized in the pH 7.30 buffer containing 0.20 M **4**.

A combination of ultrafiltration and UV spectroscopy demonstrated that 1.1×10^{-4} M **1** was completely vesicular bound in the 0.020 M **5** and 0.020 M **6** solutions in the pH 7.30 buffer. A given surfactant solution was filtered through an ultrafiltration membrane (10000 MW cutoff) and the UV spectrum of the filtrate recorded. No ether absorption was detected. Complete micellar binding was assumed for **1** in 0.20 M **4**.

Dynamic laser light scattering (DLLS) measurements were made of sonicated vesicular **5** with and without solubilized **1a** and **1c**, and the results are summarized in Table V. In each case, a predominant small unilamellar and a minor multilamellar vesicle population (SUV and MLV, respectively)[2a] were detected, and the size and weight percent distributions were stable for at least 6 h. With **1a** and **1c** the hydrodynamic diameters of the SUV

Table V. DLLS Measurements of Vesicular **5** with and without Added **1**[a]

system[b]	SUV population diam, nm	SUV population wt %	MLV population diam, nm	MLV population wt %
5	35 ± 5	90 ± 6	100 ± 15	10 ± 6
5 + **1a**	26 ± 5	ca. 100	100 ± 20	<1
5 + **1c**	27 ± 5	ca. 100	81 ± 30	<1

[a] The values are the averages of five runs on the same sample. The analysis of a second sample gave comparable results. [b] See the Experimental Section for sample preparation.

population were the same and slightly less than that without **1**. Therefore, the rate and regioselectivity variations observed in the halogenations of **1a**, **1b**, and **1c** cannot be attributed simply to different substrate-induced effects on vesicle morphology.

Discussion

There are several possible halogenating agents in both chlorine and bromine water. Both Cl_2 and Br_2 disproportionate according to eq 3 with $K = 3.35 \times 10^{-4}$ and 7.2×10^{-9}, respectively.[8,9] Even in H_2O alone there is a significant amount of HOCl. For example, with [total active chlorine] = 0.0197 M, [Cl_2] = 0.0060 M and [HOCl] = [H^+] = 0.0137 M.[8] In a pH 7.30 buffer, with [total active chlorine] = 3.2×10^{-3} M, [Cl_2] = 2×10^{-9} M. Other pertinent equilibria are listed in eq 4–6, each of which generates another active chlorine species. Overall, the possible chlorinating agents are Cl_2, Cl_3^-, HOCl, $^-$OCl, and Cl_2O. Cl_2 is more reactive than HOCl in electrophilic aromatic substitution, and $^-$OCl should be less reactive than HOCl.[10] Chlorination of C_6H_5OMe by aqueous HOCl without acid catalysis proceeds by the formation of Cl_2O in the rate-determining step (eq 5), followed by its reaction

$$X_2 + H_2O \rightleftharpoons HOX + H^+ + X^- \quad (3)$$

$$HOX \rightleftharpoons H^+ + OX^- \quad (4)$$

$$HOX + HOX \rightleftharpoons X_2O + H_2O \quad (5)$$

$$X_2 + X^- \rightleftharpoons X_3^- \quad (6)$$

with C_6H_5OMe.[10a] Thus the reaction is zero order in C_6H_5OMe. Since pseudo-first-order kinetics were observed for the chlorinations of **1** as noted above, HOCl is probably not a significant chlorinating agent. Both Cl_3^- and $^-$OCl will be electrostatically repelled from the negatively charged interfaces of micellar **4** and vesicular **5**, but the sorption of relatively large, polarizable anions like Cl_3^- at such interfaces cannot be discounted.[11] In any event, it is impossible to state with certainty which one or combination of agents is involved in the electrophilic aromatic chlorination of **1** in the present study. However, if Cl_2 is the primary chlorinating agent, the path to the transition state, regardless of the detailed mechanism, should involve a separation of charge,[12] and the reaction rate will increase as the polarity of the reaction microenvironment increases. The reaction of 4-ClC_6H_4OMe with Cl_2 in 99:1 (v/v) $MeCO_2H$–H_2O is first-order each in ether and Cl_2.[13]

In H_2O alone there is little disproportionation of Br_2. For example, with [total active bromine] = 0.21 M, [HOBr] = [H^+] = 1.2×10^{-3} M.[9] However, in a pH 7.30 buffer with [total active bromine] = 9×10^{-4} M, there is substantial conversion to HOBr, since [Br_2] = 6×10^{-6} M. Other pertinent equilibria are eq 4 and 6, and overall, the possible brominating agents are Br_2, Br_3^-, HOBr, and $^-$OBr.[14] Without acid catalysis Br_2 is more reactive than HOBr in electrophilic aromatic substitution, and $^-$OBr should

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be even less reactive than the latter.[10b,c,15] Both Br_3^- and ^-OBr will be electrostatically repelled from the negatively charged interfaces of micellar **4** and vesicular **5**. Nevertheless, there may be a finite $[Br_3^-]$ at these interfaces since it is a large, polarizable anion.[11] Cerichelli, Bunton, and co-workers concluded that Br_3^- participates in the bromination of alkenes in micellar solutions containing Br_2 and Br^- with nonionic poly(oxyethylene) (23) lauryl ether (Brij 35), cationic $C_{16}H_{33}N^+Me_3Br^-$, and perhaps even anionic **4**.[11] However, Bell and Rawlinson found no evidence for Br_3^- reactivity in the bromination of C_6H_5OMe in bromine water at pH 3.0 with added Br^-.[16] In a study of the bromination of C_6H_5OH and $C_6H_5O^-$ in aqueous solution, Tee and co-workers determined that Br_3^- reacts with the latter but not significantly with the former.[17] Overall, as with chlorination, it is impossible to specify accurately the one or combination of agents actually involved. However, if Br_2 is the primary brominating agent, the path to the transition state, regardless of the detailed mechanism, should involve a separation of charge.[12,18] As a result, the reaction rate will increase as the polarity of the reaction microenvironment increases. The reaction of C_6H_5OMe with Br_2 in H_2O is first-order each in ether and Br_2 with $k_2 = 4 \times 10^4$ M^{-1} s^{-1} at 25 °C.[16]

Since the possible halogenating agents at pH 7.30 for both chlorination and bromination include neutral and anionic species, detailed comparisons of the kinetic and regiochemical results obtained in zwitterionic **6** with those in anionic **4** and **5** cannot be made. The different values noted above for the maximum percent conversion of **1** to **2** and **3** without dichlorination in **6** compared to **4** and **5** support this statement and in fact suggest the involvement of dissimilar combinations of chlorinating agents.

The critical micelle concentration (cmc) of **4** at 25 °C in H_2O is 8.1×10^{-3} M[19] and will be less in the buffered halogenation reaction mixtures since cmc's decrease with the addition of salts.[20] Vesicles derived from **6** by sonication are polydisperse with a lower diameter limit of ca. 25 nm, corresponding to SUVs,[2a] and they undergo fusion below the phase transition temperature (T_c) of 37 °C.[21,22] Sonicated vesicular **5** displays at least two phase transitions at ca. 29 °C and one at 44.2 °C, perhaps corresponding to different vesicle sizes.[7] Vesicles of both **5** and **6** prepared by sonication are closed bilayer systems.[7,23] Also, within 5 s after its addition, bromine water reacts with sodium ascorbate entrapped in vesicular **6** in a pH 7.4 phosphate buffer.[23] Thus the diffusion of active bromine across the bilayers of vesicular **6** occurs very rapidly, and the same is assumed for vesicular **5**. It is also expected that the diffusion of active chlorine across the bilayers of both vesicular **5** and **6** is rapid. The observation of monophasic kinetics for halogenation in the vesicular media is consistent in each case with both rapid diffusion of halogenating agent and essentially equal reactivities for an ether in the inner and outer leaflets of a bilayer.

On a time-averaged basis, an ether will align itself within a surfactant aggregate with the relatively hydrophilic phenoxy group toward the aggregate–water interface and the hydrocarbon tail toward the hydrocarbon core. In this orientation the ortho positions are sterically shielded to a greater degree than the para position by the aggregate superstructure, and enhanced para selectivity is anticipated relative to reaction occurring in the aqueous pseudophase. Furthermore, as the length of the alkyl chain and the relative hydrophobic character increase going from **1a** to **1b** to **1c**, the solubilization site of an ether should move radially inward from the interface, with a resultant enhancement of the differential-shielding effect. Support for this orientation of **1** is found in a ^1H NMR study of micellar solubilization by Suckling and co-workers.[24] For $C_6H_5OC_6H_{13}$, on going from a homogeneous aqueous solution to aqueous micellar **4**, the ortho protons underwent a greater upfield shift than the para proton, consistent with the former residing within a micelle in a less polar microenvironment than the latter. The opposite orientation is expected for C_6H_5OH with the hydroxyl group at the interface, and indeed, inverse chemical shift trends were found for its ortho and para protons.[24]

Another factor most likely contributing to the enhanced **2/3** ratio for chlorination within a surfactant aggregate is the polarity of the reaction site. The interface of an aggregate has an effective polarity less than that of H_2O and about that of MeOH/EtOH.[25] Earlier we reported[4b] **2/3** ratios of ca. 3.5 for the chlorination by chlorine water of **1a**, **1b**, and **1c** in 40:60 (v/v) H_2O–1,4-dioxane. Also, for the chlorination of C_6H_5OMe with Cl_2 in aprotic media with high dielectric constants, Seguchi and co-workers reported[26] that the para/ortho ratio increased with a decrease in dielectric constant.

The **2/3** ratios obtained for the chlorination of **1a**, **1b**, and **1c** in 0.20 M **4** in the pH 7.30 buffer (Table I) are uniformly greater than those in unbuffered 0.20 M **4**, 3.9, 4.1, and 4.8, respectively.[4b] These differences, as noted above, are not due to the pH difference or to an intrinsic effect of the buffer components. Also, at least for **1b** and **1c**, they do not result from a salt-induced enhancement of micellar substrate binding, since these ethers are completely insoluble in H_2O alone.[4b] Furthermore, a salt-induced sphere to rod transition for micellar **4** is probably not involved, since it occurs only at concentrations of Na^+ higher than that used in the buffer.[27] The greater **2/3** ratios in the buffer may derive from the polarity effect[26] noted above if the added salt causes a decrease in the effective polarity of the micellar interface. But Zachariasse and co-workers have found that up to 0.2 M NaCl has little effect on the polarity of the interface of micellar **4**.[28] An alternate or complimentary cause could be a salt-induced inward movement of the time-averaged ether solubilization sites to less polar microenvironments.

Ethers **1a**, **1b**, and **1c** are expected to have comparable, if not identical, intrinsic reactivities with respect to halogenation in homogeneous aqueous media. In chlorinations by chlorine water, the reactivities of **1a** and C_6H_5OMe were the same in 95:5 (v/v) H_2O–MeCN,[29] and **1a**, **1b**, and **1c** gave the same **2/3** ratio in 40:60 (v/v) H_2O–1,4-dioxane as noted above.[4b] Also, Bradfield and Jones reported[30] that the rate of ortho chlorination by Cl_2 in $MeCO_2H$–H_2O is almost invariant for 4-$ClC_6H_4OC_nH_{2n+1}$-n with n = 2–16. Therefore, the differences in the rates and regioselectivities for **1a**, **1b**, and **1c** in the surfactant media can be ascribed to microenvironmental effects.

For the chlorination and bromination of **1a**, the k_2s in micellar **4** are comparable to those in the phosphate buffers. Also, for both halogenations the k_2s for **1** are greater in micellar **4** than in vesicular **5**, which indicates that in the latter **1** resides in less polar microenvironments. The **2/3** ratios for both halogenations in micellar **4** were greater than those in vesicular **5**, whereas the

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opposite might have been expected since vesicles in general are more ordered than micelles.[2a] Also, greater para selectivities would be anticipated for the chlorinations in **5** compared to those in **4** based on the lesser polarities in the former as reflected by the smaller k_2s. However, the T_c for the major population of vesicular **5** is likely only ca. 29 °C,[7] so at 25 °C, the reaction temperature, the bilayers are undergoing a change from the gel to the less ordered liquid crystalline state.

The **2**/**3** and k_2 values for the chlorination of **1a** in vesicular **6** in the pH 7.30 buffer are greater than and less than, respectively, the values in the phosphate buffer alone as expected on the basis of the above discussion. Surprisingly, these values for the bromination of **1a** in the same medium are comparable to those in the buffer alone, even though the T_c for **6** (37 °C)[22] is well above the reaction temperature and **1a** is completely vesicular bound, as indicated by the ultrafiltration experiments. The k_2 values for **1b** and **1c** were much less than that for **1a**, but their **2**/**3** values were also relatively small.

The kinetic data alone demonstrate that vesicles, and to a lesser extent micelles, offer a variety of solubilization sites to the ethers, but they do not, by themselves, disclose the nature of the reaction sites. The obtainment of different halogenation rates for **1a**, **1b**, and **1c** in a given organized medium is consistent with at least two limiting possibilities. In the first, the ethers have different time-averaged solubilization sites as a result of their varying hydrophobic/hydrophilic characters. The time-averaged distance of the phenoxy group from the aggregate-water interface increases in the order **1a** < **1b** < **1c**, corresponding to the increasing relative hydrophobic nature. However, each ether reacts only at the interface, where it spends a fraction of the time that decreases in the order **1a** > **1b** > **1c**. The interface is the most polar microenvironment available to the phenoxy group of **1** solubilized within an aggregate. In the second limiting possibility, **1a**, **1b**, and **1c** have different solubilization sites as above and react at these solubilization sites. Overall, the combination of different rates and regioselectivities is consistent only with the latter possibility. The former would give different rates but the same **2**/**3** ratio for the three ethers in a given surfactant medium. The reactivity order **1a** > **1b** ≥ **1c** observed in each surfactant-based medium is consistent with inward radial movement of an ether to a less polar microenvironment as the chain length increases. In a study of the bromination of a series of surfactant and hydrophobic trans-stilbenes in aqueous micelles and vesicles, Mizutani and Whitten[23] found a wide spectrum of solubilization sites only in the latter.

The results obtained with **5** represent an impressive example of the isolation of neutral organic compounds from a vesicular solution based on a cleavable surfactant. Controls (see Experimental Section) demonstrated that the isolation of products and unreacted starting material from vesicular **5** was quantitative. Thus, for example, 0.024 mg of **1b** was isolated quantitatively from 1.00 mL of a 0.020 M solution of vesicular **5**. As noted above, the isolation procedure for reactions in vesicular **6** involved simply the precipitation of **6**, with the ethers remaining in the MeCN solution. Although a control indicated that the recovery of ethers was quantitative, this procedure almost certainly cannot be applied generally to the isolation of a broad range of neutral organic compounds from vesicular **6**. Its success in this case depended on fortuitous differences in the physical properties of **6** and the ethers. On the other hand, the procedure for product isolation from vesicular **5** is much more general.

Summary

The **2**/**3** ratios for **1a** were greater in micellar **4** and vesicular **5** and **6** than in buffer/water alone and increased in the order **1a** < **1b** < **1c**. In general the k_2 values for **1a** were less in the surfactant media than in buffer alone and decreased in the order **1a** > **1b** ≥ **1c**. The combination of kinetic and regioselectivity data indicated that the three ethers reside at different solubilization sites within the surfactant aggregates and react at these sites. The isolation of neutral organic products from vesicular **5** has been demonstrated.

Table VI. Physical Properties and Elemental Analyses for Ethers

		calcd		found	
ether	bp, °C (mmHg)	C	H	C	H
2b	125–127 (0.05)	60.21	7.75	59.98	7.54
2c	34–35[a]	63.34	8.56	63.23	8.69
3b	112–114 (0.1)	60.21	7.75	60.41	7.74
4b	145–147 (0.01)	47.64	5.86	47.60	5.83
4c	179–181 (0.01)	51.45	6.72	51.61	6.58

[a] Melting point.

Experimental Section

General Procedures and Materials. UV spectra were recorded on a Cary 2300 UV–vis–near-IR spectrophotometer with 1-cm quartz cuvettes. A Branson Model 3200 ultrasonic cleaner (150 W) was used for vesicle preparation with a bath temperature of 50–55 °C. Compounds **2b**, **2c**, **3b**, **7b**, and **7c** (X = Br) were prepared by a Williamson procedure with the appropriate combination of *n*-alkyl bromide/chloride and phenol.[31] Table VI summarizes their physical properties and elemental analyses. Of the ethers **8**, only **8a** (X = Cl) was prepared[4b] since **7a** and **8a** were indistinguishable by HPLC. All of the other ethers been reported previously.[4a,b,32] Compound **4** (BDH, specially pure) was purified as before,[4b,33] **5** was prepared by the literature procedure,[7] and **6** (Sigma) was used as received. The pH 6.85 buffer contained 0.010 M Na_2HPO_4 and 0.010 M KH_2PO_4 (both Aldrich Gold Label) in HPLC-grade H_2O, and the pH 7.30 buffer, 0.030 M Na_2HPO_4 and 0.0090 M KH_2PO_4. The following chlorine water and bromine water solutions were standardized by iodometry[34] and stored at 8–10 °C. Cl_2 (J. T. Baker) was bubbled through HPLC-grade H_2O at ca. 5 °C in a gas-washing bottle until chlorine hydrate began to precipitate. The resulting mixture was diluted with H_2O to give a stock solution of chlorine water (ca. 0.04 M). A stock solution of bromine water (ca. 0.09 M) was prepared with freshly distilled Br_2 (Mallinckrodt) and HPLC-grade H_2O.

Chlorination and Bromination of 1 in Homogeneous Media. Chlorination and bromination of **1a** in the pH 6.85 and 7.30 phosphate buffers were performed as follows. To 5.00 mL of the buffer was added 10 μL of 0.055 M **1a** in MeCN, and after the solution was sonicated for 1 h and cooled to 25 °C, 400 μL of 0.040 M chlorine water or 75 μL of 0.030 M bromine water was added. The reaction mixture was stirred for the appropriate time, followed by the addition of 10 mg of $Na_2S_2O_3$ and HPLC analysis (eluant = 75:25 (v/v) MeCN–H_2O; flow rate = 0.50 mL/min). The results for chlorination and bromination are summarized in Tables I and III, respectively. Chlorination of **1a** in H_2O–MeCN was performed as follows. To 5.00 mL of 95:5 (v/v) H_2O–MeCN was added 10 μL of 0.055 M **1a** in MeCN, followed by 150 μL of 0.040 M chlorine water. The reaction mixture was stirred for 15 min at 25 °C and then analyzed by HPLC as above. The results are summarized in Table I.

Chlorination and Bromination of 1 in Surfactant Media. Reaction mixtures were prepared and reactions carried out in 3-mL V-vials fitted with Teflon-faced septa (Wheaton, Aldrich Z11,514-2). Reactions in micellar **4** were performed as follows. To 2.00 mL of the pH 7.30 phosphate buffer were added 0.115 g (0.400 mmol) of **4** and 4.0 μL of 0.055 M **1** in MeCN or 2.0 μL each of two 0.055 M solutions of **1** in MeCN, and the system was sonicated for 1 h and allowed to cool to 25 °C during 2 h. Then 160 μL of 0.040 M chlorine water or 30 μL of 0.030 M bromine water was added. At appropriate times 0.6-mL samples of the reaction mixture were treated with 1.0 mg of $Na_2S_2O_3$, diluted with 0.6 mL of HPLC-grade MeCN, filtered (0.45 μm Nylon, Rainin 38-112), and analyzed for **1**, **2**, and **3** by HPLC. The results are summarized in Tables I–IV.

Reactions in vesicular **5** were performed as follows. A solution of 14.5 mg (0.020 mmol) of **5** in 0.50 mL of $CHCl_3$ (stored over Na_2CO_3) was rotary evaporated. Then 1.00 mL of the pH 7.30 phosphate buffer and 2.0 μL of 0.055 M **1** in MeCN or 1.0 μL each of two 0.055 M solutions of **1** in MeCN were added, and the system was sonicated for 1 h and allowed to cool to 25 °C during 1 h. Then 80 μL of 0.040 M chlorine water or 30 μL of 0.030 M bromine water was added, and at the appropriate time, 5.0 mg of $Na_2S_2O_3$ was added, followed by 25 μL of concentrated hydrochloric acid. The resultant mixture was held at 50 °C for 30 min and cooled to 25 °C, followed by the addition of 50 μL of aqueous 40% NaOH and 1.0 mL of HPLC-grade MeCN. The system was shaken vigorously for 1 min and filtered as above to give a filtrate containing a lower aqueous and an upper MeCN layer. The MeCN layer

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was analyzed by HPLC; the results are summarized in Tables I–IV.

Reactions in vesicular **6** were performed as follows. To 1.00 mL of the pH 7.30 buffer was added 14.7 mg (0.020 mmol) of **6** and 2.0 μL of 0.055 M **1** in MeCN or 1.0 μL each of two 0.055 M solutions of **1** in MeCN, and the system was sonicated for 1 h and allowed to cool to 25 °C during 30 min. Then 80 μL of 0.040 M chlorine water or 30 μL of 0.030 M bromine water was added, and at the appropriate time, 5.0 mg of $Na_2S_2O_3$ was added, followed by 1.0 mL of HPLC-grade MeCN, which precipitated **6**. The mixture was filtered and analyzed by HPLC as above. The results are summarized in Tables I–IV.

HPLC Analyses. All HPLC analyses were performed on a 25 cm × 4.6 mm (i.d.) column of 10-μm C-18 (Alltech 60086) with a Beckman Model 344 gradient liquid chromatograph equipped with an Altex Model 210 injector. A Beckman Model 165 variable-wavelength detector and a Hewlett-Packard Model 3390A reporting integrator were used for detection and quantitation at 210 nm. A 2-μm filter was inserted between the injector and column, and a back-pressure regulator was attached to the outflow line of the detector. HPLC-grade (J. T. Baker) H_2O and MeCN were used as eluants; the flow rate was 0.7 mL/min unless noted otherwise. For analysis of the individual runs, the following eluants were used: **1a**, 75:25 (v/v) MeCN–H_2O; **1b**, 86:14 MeCN–H_2O; **1c**, 92:8 MeCN–H_2O. For the ether pair runs, the following were used: **1a**, **1b**, 75:25 at time (t) = 0 and 88:12 MeCN–H_2O at t = 30 min; **1b**, **1c**, 88:12 at t = 0 and 94:6 MeCN–H_2O at t = 30 min. Retention times were as follows for the individual chlorination runs: **1a**, 18.5, **2a**, 26.2, **3a**, 22.2, **4a**, 36.0 min; **1b**, 26.5, **2b**, 35.1, **3b**, 30.3, **4b**, 46.0 min; **1c**, 35.2, **2c**, 42.8, **3c**, 38.3, **4c**, 51.3 min. Retention times were as follows for the ether pair chlorination runs: **1a–1b**, **1a**, 18.3, **2a**, 26.4, **3a**, 22.4, **4a**, 36.0, **1b**, 56.4, **2b**, 68.2, **3b** 61.5, **4b**, 87.5 min; **1b–1c**, **1b**, 30.4, **2b**, 41.2, **3b**, 34.9, **4b**, 54.5, **1c**, 70.8, **2c**, 79.6, **3c**, 74.5, **4c**, 86.0 min. Similar retention times were obtained in the brominations. Calibration factors for differences in detector response were as follows for the chlorination analyses: **1a**, 1.00, **2a**, 1.28, **3a**, 0.54; **1b**, 1.00, **2b**, 1.29, **3b**, 0.53; **1c**, 1.00, **2c**, 1.33, **3c**, 0.54. Calibration factors were as follows for the bromination analyses: **1a**, 1.00, **2a**, 0.98, **3a**, 0.41; **1b**, 1.00, **2b**, 0.97, **3b**, 0.42; **1c**, 1.00, **2c**, 1.05, **3c**, 0.44. Also, **1a**, **1b**, and **1c** have the same detector response.

Solubilization and Binding of 1 in Surfactant Solutions. Solutions of vesicular **5** with and without 5.5 × 10^{-5} M **1** were prepared by the procedure above with simultaneous sonication. The UV spectrum of the solution with **1** was recorded with the solution without **1** as the reference. The λ_{max} values are as follows: **1a**, 220 nm (ε 12000), 270 (2400), 278 (2100); **1b**, 220 (11000), 270 (2100), 278 (1600); **1c**, 220 (11000), 270 (1700), 278 (1800). Then the spectrum of vesicular **5** containing 1.1 × 10^{-5} M **1** was obtained, and complete solubilization was verified for each ether as described in the text.

Solutions of vesicular **5** and **6** with and without 1.1 × 10^{-4} M **1a**, **1b**, and **1c** were prepared by the procedures above. Each surfactant solution was filtered through an ultrafiltration membrane (Amicon PM10, 10000 MW cutoff) in a stirred ultrafiltration cell (Amicon 8010), and the UV spectrum of each solution prepared with **1** was recorded with the corresponding solution without **1** as the reference. No ether absorption was detected in any of the vesicular solutions.

DLLS. DLLS measurements were performed at 25 °C on a Coulter Model N4MD submicron particle analyzer at a scattering angle of 90°. Solutions of vesicular **5** with and without added **1a** and **1c** were prepared as above, diluted with 5 volumes of the pH 7.30 phosphate buffer, and filtered through a 0.45-μm membrane to yield solutions that gave 1–1.5 × 10^6 counts/s. Over 5–6 h, four to five runs were made for each solution. This procedure was performed twice for each system, and the results are summarized in Table V.

Controls on the Analysis Procedures. According to the standard procedure, a reaction mixture of **1a** in vesicular **5** was prepared with the substitution of H_2O for chlorine water, followed by the hydrolysis of **5**. Then an aliquot of **1b**–MeCN was added as an internal standard, and the mixture was worked up and analyzed as above. The **1a**:**1b** molar ratio by HPLC analysis was equal to the molar ratio of the amounts used. Therefore, **1a** was not lost during preparation of the reaction mixture, and **1a** and **1b** did not fractionate in the isolation procedure.

According to the standard procedure, the chlorination of **1b** in vesicular **5** was performed through the hydrolysis of surfactant **5**. Then an aliquot of **1c**–MeCN was added, and the mixture was worked up and analyzed as above. The (**1b** + **2b** + **3b**):**1c** molar ratio by HPLC analysis was equal to the molar ratio of the amounts of **1b** and **1c** used. Therefore, the ethers, including the monochloro products, did not fractionate in the isolation procedure.

According to the standard procedure, a reaction mixture of **1b** in vesicular **5** was prepared with the substitution of H_2O for chlorine water, followed by the remainder of the isolation scheme. After the addition of an aliquot of **1c**–MeCN, the MeCN extract was analyzed by HPLC to give a **1b**:**1c** molar ratio equal to the molar ratio of the amounts of **1b** and **1c** used. Therefore, the recovery of **1b** by the isolation procedure was quantitative.

According to the standard procedure, a reaction mixture of **1a** in vesicular **6** was prepared with the substitution of H_2O for chlorine water, followed by the addition of $Na_2S_2O_3$, the precipitation of **6** by MeCN, and filtration. After an aliquot of **1b**–MeCN was added, the filtrate was analyzed by HPLC to give a **1a**:**1b** ratio equal to the molar ratio of the amounts of **1a** and **1b** used. Therefore, the recovery of **1a** in the analysis procedure is quantitative. The same control was repeated with the substitution of **1c** for **1a** with an analogous result.

Control on the Stability of Active Chlorine. Reaction mixtures of vesicular **5** and **6** were prepared according to the standard procedures above with the substitution of MeCN for **1**–MeCN. Then 80 μL of 0.040 M chlorine water was added, and immediately thereafter an aliquot was removed from each solution and analyzed by iodometry. For the former solution, aliquots were withdrawn and analyzed at 6 and 24 h, and for the latter, at 1 and 24 h. The three aliquots for each solution contained the same amount of active chlorine. Therefore, active chlorine is not lost by a pathway other than chlorination during the course of a reaction.

Control on the Sonication Time. The effect of varying the sonication time from 2 min to 60 min in the preparation of vesicular **5** was evaluated in chlorinations of **1a**. The length of the sonication period had no effect on the rate and only a small effect on the **2**/**3** ratio, even though the system obtained with 2 min of sonication was opaque, as opposed to translucent solutions obtained with ≥15 min of sonication.

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Registry No. **1a**, 2050-04-6; **1b**, 36588-31-5; **1c**, 35021-68-2; **2a** (X = Cl), 51241-40-8; **2a** (X = Br), 30752-18-2; **2b** (X = Cl), 95248-98-9; **2b** (X = Br), 105100-90-1; **2c** (X = Cl), 95248-99-0; **2c** (X = Br), 123883-51-2; **3a** (X = Cl), 51241-39-5; **3a** (X = Br), 63076-60-8; **3b** (X = Cl), 95249-00-6; **3b** (X = Br), 101355-16-2; **3c** (X = Cl), 95249-01-7; **3c** (X = Br), 26910-11-2; **4**, 151-21-3; **5**, 119296-59-2; **6**, 2797-68-4.