Selective bromination of the aromatic ring in $\omega-\text{phenylpolyoxaalkanes}$ and alkanols in Micelles

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Abstract - The regioselectivity of bromination of ω -phenylpolyoxaalkanes and alkanols by bromine in aqueous solution of dodecyl sulfate (SDS) and aqueous solution of cetyltrimethylammonium bromide (CTAB) are shown to be related to the average orientation of substrate as indicated by ¹H NMR studies. Thus ortho-bromination is promoted at higher concentrations of the surfactant relative to pure water. In contrast, at an equal ratio of the surfactant and substrate para-bromination is promoted. The results are discussed with respect to the average orientation of substrate in a micellar microenvironment and the formation of an ether-bromine comples as possible bromination agent.

The directive effects of substituents in electrophilic aromatic substitution reactions have been for a long time the subject of extensive investigations.^{1,2} It is known that substituents bearing a lone electron pair (aniline, phenol and their alkyl derivatives) increase the amount of ortho products relative to para substitution. 3 This ratio is sensitive to external factors, for example the bromination of anisole can be changed by changing the solvent. 4 Breslow used lpha -cyclodextrine as an enzyme model in the chlorination of anisole and obtained almost exclusively the para-substituted products.⁵ The alternative approach uses micellar systems.⁶ The use of a micellar-based system to control the selectivity of an organic reaction is attractive because of the simple construction of the system, but practical difficulties in work-up and small changes in stereo- or regioselectivity usually obtained are major drawbacks. The ability of dynamic multimolecular surfactant aggregates to control the selectivity of organic reactions has been investigated for many systems including aromatic substitution $^{7-9}$ and addition to alkenes. Thus, a selective bromination of n-pentylphenyl ether was achieved in the presence of SDS.^{8a} However, by this method it was impossible to chlorinate phenols selectively.^{7a,11} A functionalized micellar system had to be used. By inserting a hydroxyl group into the monomeric unit of the surfactant, the reaction with chlorine yields in the first step the corresponding hypochlorite which can then halogenate the closest position in the aromatic ring.¹² By this modification phenol is chlorinated mainly in the para position.

¹H NMR spectroscopy is a convenient and simple technique which can give information on the structure of micelles and on interactions between the surfactant and the organic substrate. However, these studies have been hampered by the relatively low solubility of organic compounds in water and small concentrations of the surfactant present in systems under investigation.¹³ In most cases the ¹H NMR technique was used to study the influence of changes in the media on chemical shifts of aromatic compounds, phenols¹⁴ and ω -phenylalkanoates¹⁵ in particular. These compounds are to a certain degree soluble in water, and the aromatic protons are clearly discernible

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from the proton signals of the aliphatic chain of the surfactant. The ω -phenylpolyoxaalkanes and alkanols <u>1a</u>-<u>d</u> and <u>4a</u>-<u>d</u> were found to be suitable organic substrates for such studies. These compounds are quite soluble in water and behave similarly to nonionic surfactants.

RESULTS AND DISCUSSION

In this paper I would like to report on the bromination with elemental bromine of compounds $\underline{1a}-\underline{d}$ and $\underline{4a}-\underline{d}$ in water, aqueous solutions of SDS, and aqueous solutions of CTAB. respectively, and on the time average orientation of these compounds in the same solutions.



 $\frac{1a-d}{2a-d}; n = 1-4, R_1 = R_2 = H; R_3 = OH$ $\frac{2a-d}{2a}; n = 1-4, R_1 = H, R_2 = Br, R_3 = OH$ $\frac{3a-d}{2a}; n = 1-4, R_1 = Br, R_2 = H, R_3 = OH$

 $\frac{4a-d}{5a-d}; n = 1-4, R_1 = R_2 = H, R_3 = OCH_3$ $\frac{5a-d}{5a-d}; n = 1-4, R_1 = H, R_2 = Br, R_3 = OCH_3$ $\frac{6a-d}{5a-d}; n = 1-4, R_1 = Br, R_2 = H, R_3 = OCH_3$

It has been found that compounds $\underline{1a} - \underline{d}$ and $\underline{4a} - \underline{d}$ show significant changes in their ¹H NMR spectra in water and micellar solution. Compounds $\underline{1a} - \underline{d}$ and $\underline{4a} - \underline{d}$ are structurally similar to the nonionic surfactants containing hydrophylic tail and a hydrophobic head and could, in principle, also form a micelle.So it seemed of interest to see the influence of different concentrations of $\underline{1a} - \underline{d}$ and $\underline{4a} - \underline{d}$ in water on the chemical shifts. It was found (Figure 1) that by increasing the concentration of compound $\underline{4d}$, the chemical shifts of the aromatic signals are moving downfield until critical micellar concentration (CMC) is reached. Further increase of the concentration of compound 4<u>d</u> has no significant influence on chemical shifts (Figure 2). The influence



Figure 1. ¹H NMR spectra of aromatic protons of 0.01 M and 1 M solutions of polyether $\underline{4d}$ in D₂0.

Figure 2. Chemical shift changes (Å §) for the protons of polyether $\underline{1}$ as a function of its concentration

of different concentrations of SDS and CTAB on the chemical shifts of the protons bound to different parts of the aromatic ring of compound $\frac{4d}{4d}$ is presented in Table I. The changes in chemical shifts are concentration dependent and are non-uniform above the CMC. Many effects can contribute to the formation of different chemical shifts in micellar solution. Electronic effects are clearly inconsistent with the data in Table I, since both anionic and cationic detergents produce the same gross effect with an ionisable and nonionisable solubilisate. However, a possible general phenomenon that underlies all the trends observed is that the micelles solubilise aromatic compounds in a preferred average orientation. The observed spectra are, of course, time-averaged because the rate of exchange of solubilisate and micelle monomers with bulk solvent and micelles is rapid on the ¹H NMR scale. Using Menger's model of micellar structure ¹⁶ three environments for the solubilisates can be considered: the micelle core, the hydrate micellar grooves and the

Concentration of SDS or CTAB in D ₂ O		SDS		¢δ/ppm	CTAB			
mol dm^{-3}	Но	Hm	н р		Но	н mo	Р	
0	0.000	0.000	0.000		0.000	0.000	0.000	
0.001	0.005	0.010	0.017		0.006	0.008	0.015	
0.005	0.010	0.013	0.027		0.011	0.012	0.028	
0.01	0.025	0.032	0.040		0.024	0.033	0.041	
0.05	0.034	0.050	0.098		0.035	0.050	0.096	
0.1	0.064	0.090	0.140		0.066	0.090	0.143	
0.25	0.130	0.164	0.230		-	-		
0.5	0.164	0.208	0.280		-	-	-	

Table I. ¹H NMR Chemical Shift Changes of Compound $\underline{4d}^{a}$ in SDS and CTAB Solutions in $D_{2}0^{0}$

^aConcentration was 30 mmol; ^b $\hbar \delta = \delta_{D_2 0} - \delta_{micelle}$

bulk aqueous phase. It is then evident that the major source of the observed chemical shift changes is an average orientation of the solubilisate, such that the polar end of the molecule residues on average in the hydrated grooves, and the non-polar end interacts with the polymethylene chain of the detergent. This average orientation would cause a greater downfield shift of the para protons than ortho ones, since the latter have the most polar average environment.¹⁷ This result indicates a preferred average orientation of polyoxaalkyl chain outside core micelle and can be explained on the basis of the formation of a mixed micelle (Figure 3). This reasoning, which refers to compound $\frac{4d}{4d}$, can also pertain to all other compounds of both series $(\underline{1a} - \underline{d} \text{ and } \underline{4a} - \underline{d})$.

The results of bromination of compounds $\underline{1a} - \underline{d}$ and $\underline{4a} - \underline{d}$ with bromine are given in Table II. It can be seen that the product composition is critically dependent on the concentration of the surfactant (Figure 4). At intermediate concentrations, where the ratio surfactant/substrate is ap-





Figure 3. Schematic representation of average binding orientation of compound $\frac{4d}{4d}$ in SDS micellar solution.

Figure 4. para/ortho Bromination ratio of compound 4b as a function of CTAB concentration.

proximately 1, almost exclusively para bromination occurs. At higher concentrations of the surfactant, a greater proportion of ortho products is formed. It is known that in the bromination of phenol, anisole or toluene in the presence of dioxane-dibromide complex the solubilisation occurs selectively at the para position.¹⁸ The compounds investigated here have a large number of ethereal groups in the side chain which can similarly form a complex with bromine and thus attack preferentially the para position. On the other hand amino or ether groups as substituents prefer the ortho substitution.¹ The side chain substituent in $\underline{1a} - \underline{d}$ and $\underline{4a} - \underline{d}$ can therefore act in two different ways. The greater amount of ortho products at higher concentrations of the

Table II. Bromination of Compounds 1a - d and 4a - d by Bromine in the Presence of CTAB

	Molar Ratio Surfactant/ <u>1</u> or <u>4</u>	Polyoxaalkanes or Alcohols								
Concentration of Surfactant		<u>1a</u>	<u>1b</u>	1c	1d	<u>4a</u>	<u>4b</u>	<u>4c</u>	<u>4d</u>	
		ortho/para ratio								
		<u>2a/3a</u>	<u>2b/3b</u>	<u>2c/3c</u>	<u>2d/3d</u>	<u>5a/6a</u>	<u>5b/6b</u>	<u>5e/6e</u>	<u>5d/6d</u>	
0	_	26/74	21/79	22/78	24/76	27/73	25/75	15/85	17/83	
0.0001 M SDS	0.02	38/63	37/63	32/68	35/65	39/61	38/62	35/65	33/67	
0.001 M SDS	0.2	22/78	20/80	18/82	20/82	25/75	26/74	23/77	22/78	
0.005 M SDS	1	5/95	2/98	0/100	0/100	7/93	5/95	0/100	0/100	
0.01 M SDS	2	4/96	1/99	0/100	0/100	5/95	8/92	0/100	0/100	
0.1 M SDS	20	12/88	10/90	8/92	9/91	13/87	10/90	8/92	9/91	
0.5 M SDS	100	24/76	22/78	20/80	18/82	27/73	23/77	20/80	20/82	
0.0001 M CTAB	0.02	18/82	15/85	5/95	10/90	28/72	31/69	35/65	37/63	
0.001 M CTAB	0.2	12/88	5/95	0/100	2/98	17/83	18/82	18/82	20/80	
0.005 M CTAB	1	7/93	2/98	0/100	0/100	8/92	8/92	8/92	2/92	
0.01 M CTAB	2	9/91	10/90	9/91	9/91	11/89	12/88	18/82	15/85	
0.1 M CTAB	20	60/40	61/39	60/40	61/39	61/39	62/38	63/37	64/36	

surfactant were consistent with the time average orientation of these compounds in the micellar environment in which the ortho protons occupy the most polar environment, as shown above. These results are also in agreement with the literature data on the chlorination of anisole and phenol in micellar media.¹¹ Here the bromine atom, as evidenced by UV spectroscopy^{8a}, resides in the aqueous medium and the bromination occurs at the surface of the micelle resulting in more ortho products (Figure 5). With an equal ratio of the surfactant and substrate, para substitution occurs because of the formation of a mixed micelle,^{19,20} where the aromatic rings of polyethers <u>1a-d</u> or <u>4a-d</u> are close to each other (Figure 6).



Figure 5



Figure 6

With the polyether chain inside the micelle, the polarity of ether group changes, thus enabling the formation of a complex with bromine. This bromine can then brominate the neighbouring aromatic ring (Figure 6). Further increase of the surfactant concentration abolishes this interaction and the result is eventually an almost statistical distribution of isomers.

Spectroscopic and chemical results, taken together, argue strongly that localization of the reagent in a simply constructed system can have a profound influence upon the course of the reaction.

EXPERIMENTAL

Infrared spectra of neat samples were recorded on a Perkin-Elmer 257 spectrometer. ¹H NMR spectra of samples dissolved in chloroform- d_3 were recorded on JEOL 90 FXQ spectrometer. Signal positions are given in δ units, with tetramethylsilane as the internal standard. All new compounds were characterized by H NMR and IR spectroscopy and in some cases also by elemental analysis.

The alcohols $\underline{1a}^{21}$ and $\underline{1b}^{22}$, ethers $\underline{4a}^{23}$ and $\underline{4b}^{24}$, and chloride $\underline{7a}^{21}$ (Br is replaced with Cl) were prepared as previously described.



Scheme

General Procedure for the Preparation of ω -Phenylpolyoxaalkanols (<u>1</u>) Potassium hydroxide (5.6 g; 0.1 mol) was added to hot (115-102^oC) vigorously stirred ethylene glycol (35 mL; 0.6 mol). After one hour, the reaction mixture was cooled and distilled from water-ethylene glycol mixture (21 mL) under reduced pressure. Bromide $\frac{7}{2}$ (0.1 mol) was slowly added under stirring to hot (120°C)residual solution of the potassium derivative of ethylene glycol. As soon as the potassium bromide began to precipitate, further external heating was discon-tinued. The mixture was heated $(120^{\circ}C)$ and stirred for one hour after all bromide <u>7</u> was added. The mixture was cooled, the precipitate removed and the filtrate distilled through a packed column under reduced pressure.

9-Phenyl-3,6,9-trioxanonal (1c)

y-menyi-5,0,y-trioxanonal (10) Yield = 14.7 g (67%); b.p. $74-77^{\circ}$ C/0.05 mm Hg; IR 3440 (0-H), 3060 and 3040 (Ar-H), 1600 and 1500 (C=C), 1250 (Ph-O), 1130 (C=O-C), 1065 (C=OH), 760 and 700 cm⁻¹ (Ar-H). H NMR \circ 7.27 (2H, m, H -aromatic), 6.90 (3H, m, H and H -aromatic), 4.09 (2H, m, PhO<u>CH</u>₂), 3.82 (2H, m, <u>CH</u>₂OH), 3.68^m(8H, m) 2.94 (1H \circ OU) 3.68^m(8H, m), 2.94 (1H, s, OH).

12-Phenyl-3,6,9,12-tetraoxadodecanol (1d) Yield = 19.5 g,(72%); b.p. 83-85°C/0.05 mm Hg; IR 3470 (0-H), 3060 and 3040 (Ar-H), 1600 and 1500 (C=C), 1250 (Ph-O), 1135 (C-O-C), 1065 (C-OH), 760 and 700 cm⁻¹ (Ar-H); H NMR & 7.26 (2H, m, H_-aromatic), 6.92 (3H, m, H_ and H_-aromatic), 4.08 (2H, m, PhOCH₂), 3.84 (2H, m, CH₂OH), 3.84⁻¹ (2H, m, CH₂OH), 3.66 (12H, m), 2.8⁴ (1H, s, OH).

Anal. Calcd. (%) for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20 Found: C, 61.50; H, 8.07.

General Procedure for the Preparation of 1-Bromo- ω -phenylpolyoxaalkanes (7) Phosphorous tribromide (32.5 g; 0.12 mol) was slowly added to cold (0[°]C) stirred solution of phenylpolyoxaalkanol (0.3 mol) in pyridine (9.7 mL; 0.12 mol). The mixture was then heated to 50° C until solution was complete. The material was poured into an excess of cold dilute hydrochloric acid and extracted with chloroform. The extract was washed thoroughly with dilute hydrochloric acid, then with water, and dried over sodium sulphate. The solvent was removed and the residue distilled.

1-Bromo-6-phenyl-3,6-dioxahexane (<u>7b</u>) Yield = 45.4 g (62%); b.p. 84-87[°]C/0.05 mm Hg; IR 3060 and 3040 (Ar-H), 1600 and 1500 (C=C), 1250 (Ph-0) 1125 (C-O-C), 760 and 700 (Ar-H), 670 cm⁻¹ (C-Br); [']H NMR & 7.27 (2H, m, H_-aromatic), 6.93 (3H, m, H_o and H_p-aromatic), 4.11 (2H, m, PhO<u>CH</u>₂), 3.75 (4H, m, CH₂OCH₂), 3.48 (2H,^mm, CH₂Br).

1-Bromo-9-phenyl-3,6,9-trioxanonane (<u>7c</u>) Yield = 41.6 g (48%); b.p. 92-94°C/0.05 mm Hg; IR 3060 and 3040 (Ar-H), 1600 and 1500 (C=C), 1250 (Ph-O), 1135 (C-O-C), 760 and 700 (Ar-H) and 670 cm⁻¹ (C-Br); H NMR § 7.26 (2H, m, H_m-aro-matic), 6.91 (3H, m, H_o and H_p-aromatic), 4.09 (2H, m, PhO<u>CH₂</u>), 3.78 (8H, m), 3.44 (2H, m, CH₂Br).

General Procedure for the Preparation of ω -Phenylpolyoxaalkanes (4)

Sodium (2.3 g; 0.1 mol), cut into small pieces) was added in portions to vigorously stirred methanol (50 mL) at room temperature. Methanolic solution (20 mL) of bromide $\frac{7}{2}$ (0.1 mol) was slowly added with stirring to hot (60° C) solution of the sodium derivative. The mixture was heated under reflux and stirred for two hours, after all the bromine 7 was added. The mixture was cooled and the precipitate of sodium bromide was removed by filtration. Methanol was evaporated and the residue distilled.

1-Phenyl-1,4,7,10-tetraoxaundecane (4c) Yield = 19.7 g (82%); b.p. 95-98 C/0.1 mm Hg; IR 3070 and 3030 (Ar-H), 1600 and 1500 (C=C), 1250 (Ph-O), 1115 (C-O-C), 760 and 700 cm⁻¹ (Ar-H); H NMR & 7.26 (2H, m, H -aromatic), 6.92 (3H, m, H_o and H_p-aromatic), 4.12 (2H, m, PhOCH₂), 4.01 (2H, m, CH₃OCH₂), 3.70 (8H, m), 3,36 (3H, s, COH₃).

Bromination of ω -Phenylpolyoxaalkanols (1) and Alkanes (4)

To aqueous solution of SDS or CTAB (100 mL) and ω -phenylpolyoxaalkanol (1) or ω -phenyloxaalkane (4) bromine (0.5 mmol) was added. After two days the reaction mixture was saturated with sodium chloride and the aqueous layer separated by filtration. The aqueous solution was extracted with ether (3x20 mL) and dried over sodium sulphate. The solvent was removed under reduced

pressure to leave a semisolid mixture containing the surfactant, which was separated by filtration through a column of silica gel with ether-methanol mixture (1:1). The organic solution was evaporated and the oily or solid residue analyzed by 'H NMR on the basis of signal positions for aromatic protons and their integrals.

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