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SELECTIVE BROMINATION OF THE AROMATIC RING IN ω-PHENYLPOLYOXAALKANES AND ALKANOLS IN MICELLES

BRANKO JURŠIĆ

Laboratory of Organic Chemistry, Faculty of Science,
University of Zagreb, Strossmayerov trg 14,
41000 Zagreb, Yugoslavia

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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 ^{1}H 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.

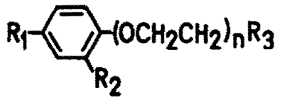
The directive effects of substituents in electrophilic aromatic substitution reactions have been for a long time the subject of extensive investigations.[1,2] It is known that substituents bearing a lone electron pair (aniline, phenol and their alkyl derivatives) increase the amount of ortho products 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 α-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.[10] 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.

^{1}H 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 ^{1}H NMR technique was used to study the influence of changes in the media on chemical shifts of aromatic compounds, phenols[14] and ω-phenylalkanoates[15] in particular. These compounds are to a certain degree soluble in water, and the aromatic protons are clearly discernible

from the proton signals of the aliphatic chain of the surfactant. The ω-phenylpolyoxaalkanes and alkanols 1a-d and 4a-d 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 1a-d and 4a-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.



1a-d; n = 1-4, $R_1 = R_2 = H$; $R_3 = OH$
2a-d; n = 1-4, $R_1 = H$, $R_2 = Br$, $R_3 = OH$
3a-d; n = 1-4, $R_1 = Br$, $R_2 = H$, $R_3 = OH$
4a-d; n = 1-4, $R_1 = R_2 = H$, $R_3 = OCH_3$
5a-d; n = 1-4, $R_1 = H$, $R_2 = Br$, $R_3 = OCH_3$
6a-d; n = 1-4, $R_1 = Br$, $R_2 = H$, $R_3 = OCH_3$

It has been found that compounds 1a-d and 4a-d show significant changes in their ^1H NMR spectra in water and micellar solution. Compounds 1a-d and 4a-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 1a-d and 4a-d in water on the chemical shifts. It was found (Figure 1) that by increasing the concentration of compound 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 4d has no significant influence on chemical shifts (Figure 2). The influence

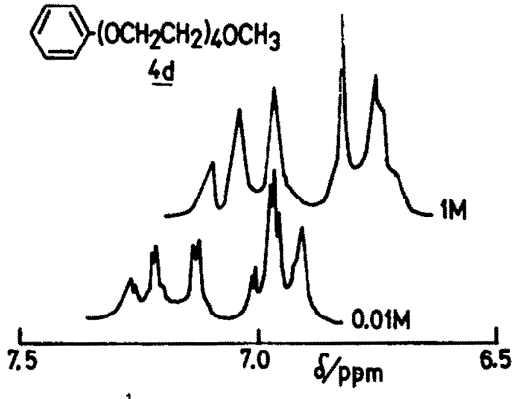


Figure 1. ^1H NMR spectra of aromatic protons of 0.01 M and 1 M solutions of polyether 4d in D_2O.

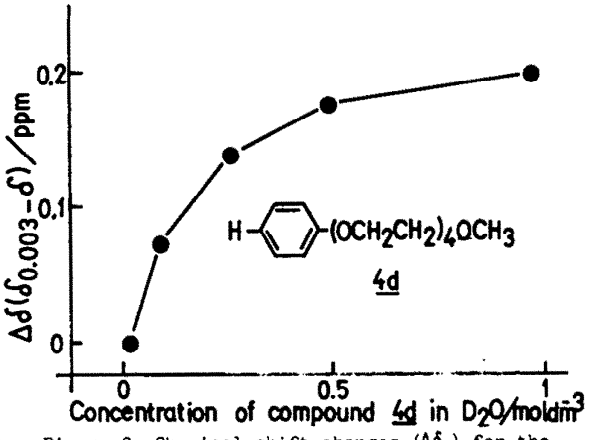


Figure 2. Chemical shift changes ($\Delta\delta$) for the protons of polyether 1 as a function of its concentration

of different concentrations of SDS and CTAB on the chemical shifts of the protons bound to different parts of the aromatic ring of compound 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

Table I. ^{1}H NMR Chemical Shift Changes of Compound 4d[a] in SDS and CTAB Solutions in D_2O[b]

Concentration of SDS or CTAB in D_2O mol dm^{-3}	$\Delta\delta$/ppm SDS H_o	SDS H_m	SDS H_p	CTAB H_o	CTAB H_m	CTAB H_p
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	-	-	-

[a]Concentration was 30 mmol; [b]$\Delta\delta = \delta_{D_2O} - \delta_{micelle}$

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 4d, can also pertain to all other compounds of both series (1a-d and 4a-d).

The results of bromination of compounds 1a-d and 4a-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 approximately 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 1a-d and 4a-d can therefore act in two different ways. The greater amount of ortho products at higher concentrations of the

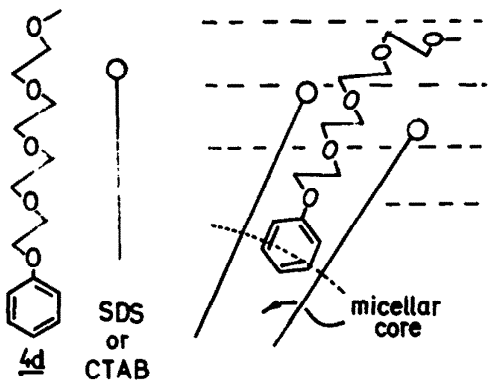


Figure 3. Schematic representation of average binding orientation of compound 4d in SDS micellar solution.

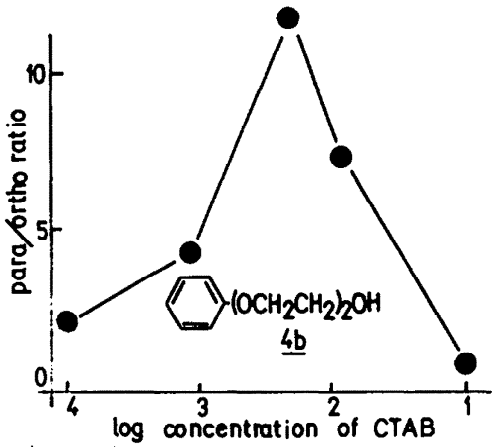
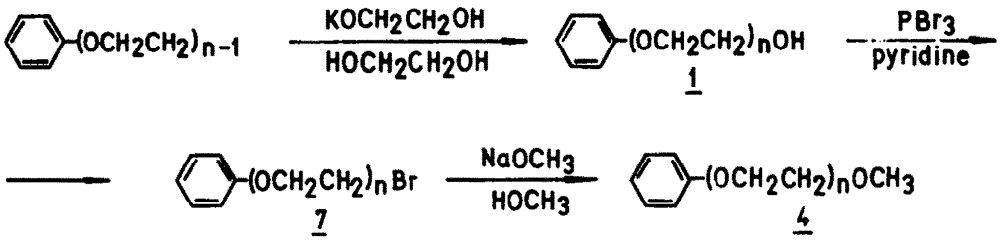


Figure 4. para/ortho Bromination ratio of compound 4b as a function of CTAB concentration.



Scheme

General Procedure for the Preparation of ω-Phenylpolyoxaalkanols (1)

Potassium hydroxide (5.6 g; 0.1 mol) was added to hot (115-102°C) 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 7 (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 discontinued. The mixture was heated (120°C) and stirred for one hour after all bromide 7 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)

Yield = 14.7 g (67%); b.p. 74-77°C/0.05 mm Hg; IR 3440 (O-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). ^{1}H NMR δ 7.27 (2H, m, H_m-aromatic), 6.90 (3H, m, H_o and H_p-aromatic), 4.09 (2H, m, $PhOCH_2$), 3.82 (2H, m, CH_2OH), 3.68 (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 (O-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); ^{1}H NMR δ 7.26 (2H, m, H_m-aromatic), 6.92 (3H, m, H_o and H_p-aromatic), 4.08 (2H, m, $PhOCH_2$), 3.84 (2H, m, CH_2OH), 3.84 (2H, m, CH_2OH), 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 ω-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 (7b)

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-O) 1125 (C-O-C), 760 and 700 (Ar-H), 670 cm^{-1} (C-Br); ^{1}H NMR δ 7.27 (2H, m, H_m-aromatic), 6.93 (3H, m, H_o and H_p-aromatic), 4.11 (2H, m, $PhOCH_2$), 3.75 (4H, m, CH_2OCH_2), 3.48 (2H, m, CH_2Br)

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); ^{1}H NMR δ 7.26 (2H, m, H_m-aromatic), 6.92 (3H, m, H_o and H_p-aromatic), 4.12 (2H, m, $PhOCH_2$), 4.01 (2H, m, CH_3OCH_2), 3.70 (8H, m), 3,36 (3H, s, COH_3).

1-Phenyl-1,4,7,10,13-pentaoxatetradecane (4d)

Yield = 23 g (81%); b.p. 116-118°C/0.1 mm Hg; IR 3070 and 3040 (Ar-H), 1600 and 1500 (C=C), 1250 (Ph-O), 1110 (C-O-C), 760 and 700 cm^{-1} (Ar-H); ^{1}H NMR δ 7.26 (2H, m, H_m-aromatic), 6.90 (3H, m, H_o and H_p-aromatic), 4.11 (2H, m, $PhOCH_2$), 3.82 (2H, m, CH_3OCH_2), 3.58 (12H, m), 3.35 (3H, s, OCH_3).

Anal. Calcd. (%) for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51
Found: C, 64.17; H, 8.32

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 (3 x 20 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 ^{1}H NMR on the basis of signal positions for aromatic protons and their integrals.

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REFERENCES

1. D.E. Pearson and C.A. Buehler, Synthesis, 455 (1971).
2. K.L. Nelson and H.C. Brown, J. Am. Chem. Soc., 73, 5605 (1951).
3. D.E. Pearson, R.D. Wysong, and C.V. Breder, J. Org. Chem., 23, 2358 (1967).
4. K. Geatharani, Indian J. Chem., 14B, 787 (1976).
5. a) R. Breslow and P. Campbell, J. Am. Chem. Soc., 91, 3085 (1969).
   b) R. Breslow and P. Campbell, Bioorganic. Chem., 1, 140 (1971)
   c) R. Breslow, H. Kohn, and B. Siegel, Tetrahedron Lett., 17, 1645 (1976).
6. C.J. Suckling, Ind. Eng. Chem. Prod. Res. Dev., 20, 434 (1981).
7. a) D.A.Robinson, D.C. Sherrifton, and C.J. Suchling, J. Chem. Res., Synop., 142 (1985); J. Chem. Res., Miniprint, 1701 (1985).
   b) F.M. Menger and J.M. Jerkunica, J. Am. Chem. Soc., 101, 1896 (1979).
8. a) D.A. Jaeger and R.E. Robertson, J. Org. Chem., 42, 3298 (1977).
   b) D.A. Jaeger, J.R. Wyatt, and R.E. Robertson, J. Org. Chem., 50, 1467 (1985).
9. a) P.A. Grieco, P. Gyrner, and Z. He, Tetrahedron Lett., 24, 1897 (1983).
   b) N.J. Turro, Pure and Appl. Chem., 53, 259 (1981).
   c) R. Breslow, S. Kitabatake, and J. Rothbard, J. Am. Chem. Soc., 100, 8156 (1978).
   d) P. de Mayo and K.L. Syndes, J. Chem. Soc., Chem. Commun., 994 (1980).
   e) D.A. Jaeger, M.D. Ward, and C.A. Martin Tetrahedron, 40, 2691 (1984).
10. a) C.M. Link, D.K. Jansen, and C.N. Sukenik, J. Am. Chem. Soc., 102, 7798 (1980).
    b) J.K. Sutler and C.N. Sukenik, J. AM. Chem. Soc., 49, 1295 (1984).
    c) M.T. Bianchi, G. Cerichelli, G. Marcini, and F. Morinelli, Tetrahedron Lett., 25, 5205 (1984).
    d) R.B. Lennox and R.A. McClelland, J. Am. Chem. Soc., 108, 3771 (1986).
11. S.O. Onyiriuka, C.J. Suckling, and A.A. Wilson, J. Chem. Soc., Perkin Trans. II, 1103 (1983).
12. a) S.O. Onyiriuka and C.J. Suckling, J. Chem. Soc., Chem. Commun., 833 (1982).
    b) S.O. Onyiriuka, Bioorg. Chem., 13, 179 (1985).
    c) S.O. Onyiriuka, Bioorg. Chem., 14, 97 (1986).
    d) S.O. Onyiriuka and C.J. Suckling, J. Org. Chem., 51, 1900 (1986).
13. a) J.C. Erikson, Acta Chem. Scand., 17, 1478 (1963).
    b) T. Nakagawa and K. Tori, Kolloid. Z. u Z. Polymere, 194, 143 (1964).
    c) P.D. Cration and B.K. Roberts, J. Phys. Chem., 69, 1087 (1964).
14. a) J.J. Jacobs, R.A. Anderson, and T.R. Walson, J. Pharm. Pharmac., 23, 148 (1971).
    b) F. Tokiwa and K. Rigami, Kolloid. Z. u Z. Polymere, 246, 688 (1971).
    c) C.J. Suckling, J. Chem. Soc., Chem. Commun., 661 (1982).
    d) C.J. Suckling and A.A. Wilson, J. Chem. Soc., Perkin Trans II, 1616 (1981).
15. R.E. Stark, R.W. Storrs, and M.L. Kasakevich, J. Phys. Chem., 89. 272 (1985).
16. F.M. Menger, Acc. Chem. Res., 12, 111 (1979).
17. B. Juršić and D.E. Sunko, Bioorg. Chem., 15, 000 (1987).
18. a) L.A. Yanovskaya, A.P. Terent'ev, and L.I. Belen'skij, Zh. Obshch. Khim. (J. Gen. Chem.), 22, 1594 (1952).
    b) A.P. Terent'ev, L.I. Belen'skij, and L.A. Yanovskaya, Zh. Obshch. Khim. (J. Gen. Chem.), 24, 1265 (1954).
19. B. Juršić, J. Chem. Soc., Chem. Commun., submitted for publication.
20. B. Juršić, H. Vančik, and K. Furić, J. Chem. Res., submitted for publication.
21. S. Foldeak, J. Czombos, B. Matkovics, and J. Porszasz, Acta Aniv. Szeged, Acta Phys. Chem., 9, 134 (1963); C.A. 61, 11964e (1964).
22. a) O. Bobleter, Monatsch. Chem., 87, 483 (1956).
    b) F. Patat, E. Cremer, and O. Bobleter, Monatsch. Chem., 83, 322 (1952).
23. A.A. Aroyan, Univ. Ser. Khim. Nauk, 44, 54 (1960); C.A. 369g (1960).
24. F. Drakowazahl and D. Klamann, Monatsch. Chem., 82, 588 (1951).