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Selectivity in Aromatic Substitution: Effects of Micellar 6-Hydroxystearate on the Chlorination of Phenol

SAMUEL O. ONYIRIUKA

Department of Chemistry, University of Nigeria, Nsukka, Nigeria

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High selectivity has been observed in the chlorination of phenol in aqueous and methanolic sodium dodecyl sulfate by a t-alkyl hypochlorite located remote from the detergent anionic head group. The location of the substituent electrophile suggests that the reaction should lead mainly to *para* chlorination. In fact, *ortho* chlorination predominates. The results obtained are attributed to the bifunctional nature of the detergent molecule and are discussed in relation to the structure of micelles.

INTRODUCTION

The design of systems aimed at improving the selectivity of chemical reactions have engaged, and will continue to engage, the attention of many. However, the achievement of the type of selectivity generally observed in enzyme reactions is an onerous task requiring a great deal of effort. What is perhaps easier to achieve is the design of simple systems for the conversation of otherwise nonselective reactions to those which can go overwhelmingly and more selectively in the desired direction. The use of detergent micelles to enhance selectivity has previously been utilized to modify selectivity of the substitution of bromobenzene (*1*) and pentyl phenyl ether (*2*). Although micellar systems are labile (*3–7*), they do possess binding pockets (much like the enzyme binding sites) which can be used to hold simple molecules in particular orientations. In addition reaction conditions are often mild and products clean. It is this their ability to impose an average orientation on a solubilized aromatic substrate which makes them attractive as media for selective functionalization reactions. The selectivity observed is often small but significant. To achieve greater control of selectivity, it has been found necessary to reduce further the degrees of freedom of motion of the system. A number of ways may be used to achieve this, one of which is to localize the reagent electrophile at a defined position in the detergent micelles (*8, 9*). We have shown that functionalized detergent micelles can be used to achieve a high degree of selectivity in electrophilic aromatic reactions, and by employing two tertiary alkyl hypochlorites functionalized at C-3 and C-12 positions of a stearate molecule, we studied the chlorination of phenol in sodium dodecyl sulfate (SDS)[1] solutions and achieved substantial enhancement of *ortho* chlorination (*8, 9*).

[1] Abbreviations used: SDS, sodium dodecyl sulfate; THF, tetrahydrofuran; FFAP,

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We have demonstrated from our study of 3- and 12-methoxystearates that in micellar SDS, the C-3 position enjoyed a more polar environment than the C-12 position (*9*). NMR experiments have also shown that in aqueous micellar SDS, phenol is principally solubilized in such a way that the *ortho* position occupies a more polar environment than the *para* (*10*). The detergent molecule functionalized at the C-3 position was therefore expected to lead mainly to *ortho* chlorination of phenol and that functionalized at C-12 to lead mainly to *para* chlorination. Although the former expectation was realized, we also found that the detergent functionalized at C-12 promoted *ortho* chlorination but not to the same extent as the C-3 substituted compound (*8*, *9*). The ambiguous behavior of the C-12 substituted compound has therefore prompted us to examine the reaction of the C-6 substituted isomer with phenol in order to ascertain if the behavior of the C-12 isomer was a result of any special features peculiar to it, or if it was general for similarly functionalized stearate molecules.

RESULTS AND DISCUSSION

We had surmised from the orientation of phenol in aqueous SDS that the C-12 substituted stearate should lead to *para* chlorination, but as the results have shown this was not the case. An examination of the classical model of the micelle (Fig. 1), however, shows that the C-12 position of the stearate molecule resides in the micellar core and may not be effective in the transfer of chlorine to the *para* position of phenol. The two positions are remote from each other. The C-6 substituted stearate molecule on the other hand would seem to be a better model because of its proximity to the *para* position of the substrate and can therefore be expected to lead to a more effective chlorine transfer to the *para* position. Sodium-6-hydroxy-6-methylstearate (1a, Scheme 1) was prepared from 6-ketostearic

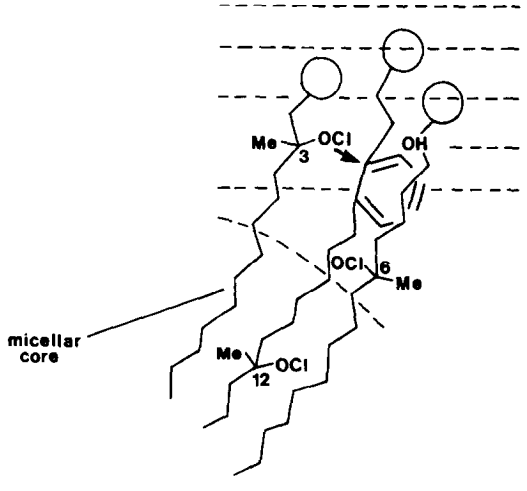
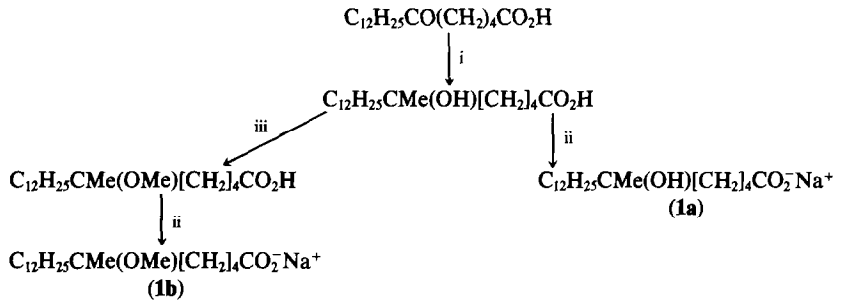


FIG. 1. Idealized location of hypochlorite group with respect to phenol in micellar SDS.



SCHEME 1. (i) MeMgI. (ii) 1 eq NaOH. (iii) MeI–NaH.

acid (*11*). As in our previous work (*8, 9*) t-butyl hypochlorite was used as the source of chlorine which was allowed to transfer to the detergent tertiary alcohol (**1a**) *in situ* (*12, 13*) to produce the tertiary alkyl hypochlorite. Mixtures of the functionalized stearate (**1a**) with SDS were then prepared in aqueous acetonitrile (CH_3CN–H_2O, 1/9 v/v) or in methanol at a total concentration of about 300 mM at which concentration micellar orientations are well established (*10*). t-Butyl hypochlorite, followed by phenol, was added to give concentrations of 15 and 30 mM, respectively. The products were then analyzed by GLC on a calibrated column (10% FFAP on Chromosorb G at 170°C) and the results are shown in Table 1.

TABLE 1

CHLORINATION OF PHENOL (30 mM) BY t-BUTYL HYPOCHLORITE (15 mM) IN THE PRESENCE OF ALCOHOL (**1a**) AND SDS

[SDS] (mM)	[**1a**] (mM)	2- (%)[a]	4- (%)[a]	2,4,6- (%)[a]	Yield (%)[b]
		In CH_3CN–H_2O (1/9, v/v)			
0	0	48	52	—	100[c]
510	0	62	38	—	54[c]
297	3	64	15	21	52
290	10	86	14	—	32
285	16	88	12	—	21
280	20	89	11	—	19
270	30	94	6	—	50
		In methanol			
0	0	28	72	—	100
279	3	83	17	—	27
290	10	49	16	35	59
285	15	70	19	10	47
280	20	62	11	27	17
270	30	68	2	30	50

[a] Normalized percentage of total chlorination products.

[b] Based upon t-BuOCl added.

[c] From Ref. (*9*).

The results (Table 1) clearly show that in aqueous solution *ortho* chlorination is strongly promoted in a concentration-dependent manner by the 6-hydroxystearate. In methanol solution, *ortho* chlorination is also promoted but to a lesser extent and in a less well defined manner, with polychlorination to give 2,4,6-trichlorophenol becoming significant. That the change in selectivity was due to the tertiary alcohol was demonstrated by the fact that the corresponding methyl ether (**1b**) when used in place of the alcohol (**1a**) annulled the additional *ortho* substitution. The significant yield of 2,4,6-trichlorophenol in methanolic solution probably reflects the extent to which exchange between t-butyl hypochlorite and the tertiary alcohol (**1a**) takes place in both solutions.

The high *ortho* chlorination observed in both aqueous and methanolic solutions of C-6 hydroxystearate once again demonstrates that high selectivity can be achieved in substitution reactions by the use of functionalized detergents. The fact, however, that *ortho* and not the expected *para* chlorination predominated as was the case with the C-12 substituted stearate may be significant with respect to the structure of micelles.

The design of our selectivity experiments has been based on the concept of a model of a substantial permanent hydrocarbon core made up of the hydrocarbon ends of the components of micelles (Fig. 1). From our results, this concept of the micelle as it pertains to these functionalized stearates appears to be in doubt. Micellar solubilization has been recognized as dynamic and Menger has established that in certain cases water can penetrate at least seven carbon atoms below the head group (*14*). If this situation applies in our case then it would make the reaction products of 6-hydroxystearate similar to those of the 3-hydroxy isomer. More recent work by Menger's group (*15, 16*) now suggests that even terminal hydrocarbon groups frequently make contact with the polar external medium. With the presence of a polar functional group such as alcohol or hypochlorite, it is even less surprising that the behavior of the 12- and 6-substituted stearates is similar to that of the 3-isomer. The bifunctional nature of our compounds thus appears to be crucial in interpreting the effects observed with the 12- and perhaps 6-substituted stearate. From the results obtained the 3-, 6-, and 12-substituted stearates all appear to enjoy about the same degree of polar environment as they all mediate *ortho* chlorination. It may be that the presence of a hydroxy or hypochlorite group causes the micellar structure to be even more open as the polar functional group in the hydrophobic alkyl chain could perturb the micellar structure in seeking a polar environment and thereby make more frequent contact with bulk solvent. These results therefore appear consistent with the current features of Menger's model of a micelle (*15, 16*) even though the special nature of our compounds in possessing polar functional groups also makes it possible for the results to be explained on the basis of the classical Hartley model.

CONCLUSION

The results obtained in this and other experiments show that with adequate control, even poorly ordered aggregates such as micelles can be used to influence

selectivity. The simplicity of construction of such systems as well as the ease with which products can be isolated and analyzed are added advantages. However, a clearer understanding of the structure of micelles especially as they are affected and modified by the various functional groups present at different locations of the detergent molecule will be required in order to make more accurate and meaningful predictions on the regiochemistry of solubilized substrates.

EXPERIMENTAL

NMR (90 MHz) spectra were recorded on a Perkin–Elmer R32 spectrometer.

6-Hydroxy-6-methylstearic acid. Magnesium turnings (0.9 g, dry) in sodium-dried ether (5 ml) were treated slowly with iodomethane (3 ml) in ether (15 ml). The reaction mixture was heated under reflux until most of the magnesium had dissolved. 6-Ketostearic acid (3.3 g) prepared using Robinson's procedure (*11*) and dissolved in the minimum amount of ether or ether/THF mixture was added slowly from a dropping funnel to a stirred solution of the methyl magnesium iodide. The resulting reaction mixture was further refluxed for 6 h. On cooling, the mixture was decomposed with a saturated solution of ammonium chloride (100 ml). The organic layer was extracted with ether, dried, and evaporated to give a thick oil which was purified by chromatography on silica gel to give the alcohol (3.1 g, 89%). Found: C, 72.8; H, 12.2%. *Anal.* Calcd for $C_{19}H_{38}O_3$: C, 72.6; H, 12.2%. $\delta(CDCl_3)$ 0.92 (3H,t) 1.19 (3H,s) 1.30 br (28H,s) 2.38 (2H,t) and 4.36 (1H, exch. with D_2O); ν_{max} (liquid film) 3420 and 1705 cm^{-1}.

6-Methoxy-6-methystearic acid. Eight-tenths gram was methylated with iodomethane and sodium hydride following the procedure used for the other long-chain tertiary alcohols (*9*) to give the ether (0.8 g, 96%). Found: C, 73.3; H 12.3%. *Anal.* Calcd for $C_{20}H_{40}O_3$: C, 73.1; H, 12.3%. $\delta(CDCl_3)$ 0.92 (3H,t) 1.17 (3H,s) 1.30 br (28H,s) 2.38 (2H,t) and 3.20 (3H,s); ν_{max} (liquid film 1705 and 1075 cm^{-1}. Sodium salts of acids were prepared by treatment of the corresponding acids with the calculated quantity of methanolic sodium hydroxide.

Chlorination experiment. t-Butyl hypochlorite was added to the solution of detergents (2 ml) which was then shaken together for 1 min before addition of a concentrated aqueous or methanolic solution of phenol (0.1 ml). Products were extracted and analyzed by GLC as described in our previous report (*9*) using a calibrated 1-m column of 10% FFAP on Chromosorb G at a flow rate of 20 ml min^{-1} and a temperature of 170°C.

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REFERENCES

1. MENGER, F. M., AND JERKUNICA, J. M. (1979) *J. Amer. Chem. Soc.* **101,** 1896.
2. (a) JAEGER, D. A., AND ROBERTSON, R. E. (1977) *J. Org. Chem.* **42,** 3298. (b) JAEGER, D. A., WYATT, J. R., AND ROBERTSON, R. E. (1985) *J. Org. Chem.* **50,** 1467.
3. MENGER, F. M. (1979) *Acc. Chem. Res.* **12,** 111.
4. MENGER, F. M., YOSHINAGA, H., VENKATASUBBAN, K. S., AND DAS, A. R. (1981) *J. Org. Chem.* **46,** 415.
5. ANIANSSON, G. E. A. (1978) *J. Phys. Chem.* **82,** 2805.
6. REED, W., POLITI, M. J., AND FENDLER, J. H. (1981) *J. Amer. Chem. Soc.* **103,** 4591.
7. FROMHERTZ, P. (1981) *Chem. Phys. Lett.* **77,** 460.
8. ONYIRIUKA, S. O., AND SUCKLING, C. J. (1982) *J. Chem. Soc. Chem. Commun.,* 833.
9. ONYIRIUKA, S. O., SUCKLING, C. J., AND WILSON, A. A. (1983) *J. Chem. Soc. Perkin Trans. 2,* 1103.
10. SUCKLING, C. J., AND WILSON, A. A. (1981) *J. Chem. Soc. Perkin Trans. 2,* 1616.
11. ROBINSON, G. M., AND ROBINSON, R. (1925) *J. Chem. Soc.,* 175.
12. BRESLOW, R., KOHN, H., AND SIEGEL, B. (1976) *Tetrahedron Lett.,* 1645.
13. BRESLOW, R., AND CAMPBELL, P. (1976) *J. Amer. Chem. Soc.* **91,** 3085.
14. MENGER, F. M., JERKUNICA, J. M., AND JOHNSTONE, J. C. (1978) *J. Amer. Chem. Soc.* **100,** 4679.
15. MENGER, F. M., AND CHOW, J. F. (1983) *J. Amer. Chem. Soc.* **105,** 550.
16. MENGER, F. M., AND DOLL, D. W. (1984) *J. Amer. Chem. Soc.* **106,** 1109.