Selective Functionalisation. Part 6.† The Chlorination of Phenol in Micellar Solution

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The regioselectivity of chlorination of phenol by t-butyl hypochlorite in aqueous and methanolic sodium dodecyl sulphate (SDS) solution is shown to be related to the average orientation of the phenol molecule indicated by n.m.r. studies. Thus *ortho*-chlorination is promoted in micellar solution but in reduced yield. When chlorination is mediated by a functionalised detergent containing a tertiary alcohol close to the head group, reaction occurs exclusively at the *ortho*-position. In contrast, a tertiary alcohol located remote from the head group mediates chlorination with a small increase in *ortho*-substitution. The results are discussed with respect to the design of selective functionalisation systems and the structure of micelles.

In our studies aimed at the development of selective substitution systems we have always been mindful of the need to keep potential practical systems as simple as possible from the point of view of synthesis. The discovery that our selective hydroxylating system based upon *N*-alkyl-2-hydroxybenzylamines contained a micellar component [1] and the reports of modification of selectivity of substitution of bromobenzene [2] and pentyl phenyl ether [3] in micellar solution prompted us to investigate the origins of selectivity in such reactions. Micellar systems are attractively simple to construct and to manipulate. Our approach to understanding selectivity in micellar systems has been based upon the use of ^{1}H n.m.r. spectroscopy to probe the average orientation of the solubilised substrate [4] and, in the case of hydroxylation by *N*-alkyl-2-hydroxybenzylamineiron complexes,[5] a correlation between orientation shown by n.m.r. and selectivity was discernible. Phenol showed particularly clear changes in the n.m.r. spectrum in micellar solution [4] and its chlorination by t-butyl hypochlorite is a clean reaction. Both factors made the system suitable for investigating the origins of selectivity in substitution in micellar solution.

Results and Discussion

Chlorination by t-Butyl Hypochlorite in Aqueous Sodium Dodecyl Sulphate.—^{1}H N.m.r. studies of phenol in aqueous sodium dodecyl sulphate (SDS) solution [4] showed that above the critical micelle concentration (c.m.c.), the *ortho*-position occupied a more polar environment than the *para*. It would therefore be anticipated that a reagent approaching from the aqueous phase would preferentially attack the more exposed *ortho*-position and that the *para*-position would be protected by the polymethylene chains of the detergent. This expectation was substantiated by experiment (Table 1), the *ortho*/*para* ratio close to doubling in concentrated micellar solution. The decrease in yield observed suggests that the reaction rate is decreased in concentrated micellar solution because the chlorinating agent hydrolyses before it can attack the substrate. A reduced yield is common in micellar-based systems.[1] The origin of the enhanced selectivity for *ortho*-chlorination was supported by a quantitative correlation between the average orientation of phenol shown by n.m.r. and the selectivity (Figure 1). This plot of the orientation, measured by the difference in chemical shift change for *ortho*- and *para*-protons, and the selectivity, measured by the *ortho*/*para* ratio, against the SDS concentration suggests a close relationship between orientation and selectivity in agreement with the preliminary results.

Table 1. Selectivity in the chlorination of phenol (106mM) in aqueous SDS solution (1 : 9 v/v CH_3CN–H_2O) by 0.5 mol equiv. t-butyl hypochlorite

[SDS]/mM	2-Chloro (%) [a]	4-Chloro (%) [a]	Yield (%) [b]
0	48	52	93
1.7	48	52	96
6.8	50	50	95
17.0	50	50	90
51	52	48	94
170	56	44	76
510	62	38	68
1 700 (saturated)	67	33	58

[a] Normalised % of total chlorination products. [b] % yield based upon chlorinating agent used.

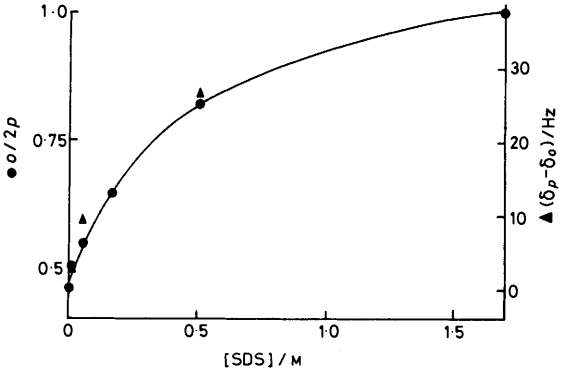
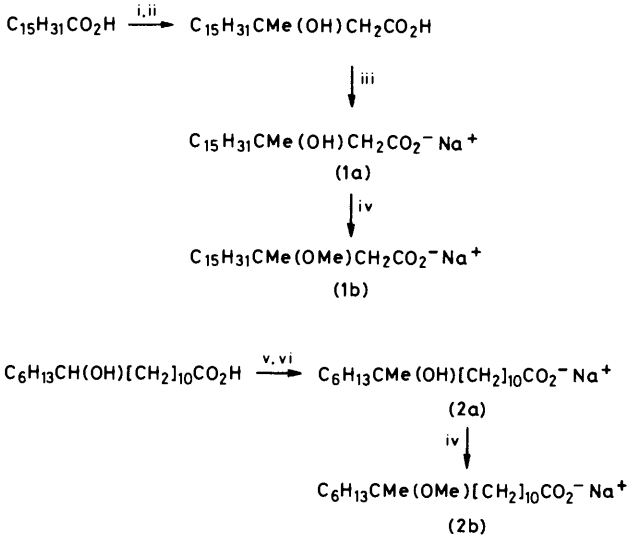


Figure 1. Comparison of orientation of phenol measured by n.m.r. (Δδ/Hz; ▲) and selectivity in chlorination (*o*/2*p*; ●) as a function of concentration of detergent (SDS)

Chlorination by Functionalised Detergents.—Although simple micellar systems are easily constructed, they are so labile that high selectivity can only be expected in fortuitously ideal situations.[1,6,7] To obtain greater control of selectivity, it is necessary to reduce the degrees of freedom of motion in the system. This can be done in principle in several ways. First, the

† Part 5, see ref. 8.



Scheme. *Reagents:* i, MeLi; ii, $BrCH_2CO_2CMe_3$–Zn; iii, 1 equiv. NaOH; iv, NaH–MeI; v, $Na_2Cr_2O_7$–H_2SO_4; vi, MeMgI

single detergent chains can be attached to each other either through a polymer [8] or in the form of a tentacle molecule.[9,10] Alternatively, the reagent can be localised at a defined position in the detergent molecule. The latter approach was adopted in the present study. Functionalised detergents have been widely employed in studies of micellar catalysis,[11,12] especially of enantiomeric specificity.[13,14] Some functionalised detergents capable of use as substitution reagents have been prepared [15,16] but do not appear to have been studied as such. We considered the use of several possible reagent types in functionalised detergents including *N*-chlorosulphonamides and *NN*-dichloroamides. Such reagents were capable of chlorinating phenol in micellar solution but the extensive synthesis required to locate such a group anywhere other than at the head group made these systems unsuitable for detailed investigation. We therefore chose to study detergents containing tertiary alcohols firstly because a direct comparison with t-butyl hypochlorite would be possible, and secondly because suitable compounds were readily synthesised (Scheme).

The choice of C-3 and C-12 for localisation of the tertiary alcohol was governed by two further factors. First, for the C-3 compound (1a), we wished to minimise the electronic effect of the head group upon the desired chlorinating agent whilst maintaining its position as close as possible to the head group. Second, for the C-12 analogue (2a), we wished to locate the reagent unambiguously within the expected hydrophobic core of the micelle. The detailed molecular structure of micelles is still a matter of active debate (see below) and the location of a reagent in the middle region between C-12 and C-3 would most probably have led to ambiguous results. Our expectation on the basis of the results described above was therefore that the C-3 substituted tertiary alcohol (1a) should lead to high *ortho*-substitution whereas the C-12 alcohol (2a) might show diminished yield because of its remoteness from the solubilisation site of phenol or might enhance *para*-substitution. As will be seen, the former expectation was substantiated by experiment. The latter, however, was not and the results obtained may have a bearing upon detailed molecular micellar structure.

We had hoped to prepare the pure hypochlorites derived from alcohols (1a) and (2a) but chlorination even under mild conditions led to products containing more than one atom of chlorine. Therefore transfer chlorination employed by Breslow [17,18] was used. A solution of SDS and the functionalised detergent (1a) or (2a) was prepared in the appropriate solvent (methanol or H_2O–CH_3CN 9 : 1 v/v; the small proportion of acetonitrile was present to provide an internal reference peak as in the n.m.r. experiments),[4] t-butyl hypochlorite was added, and the exchange of alkyl hypochlorites allowed to proceed. The substrate phenol was then added. This method inevitably led to reduced yields of chlorinated phenols since decomposition of t-butyl hypochlorite competes with exchange. At low concentrations of functionalised detergent, the yields were typically 2—10% based upon added chlorinating agent. Higher yields resulted when SDS was absent and only the functionalised detergent was used (13—37%). The results for the C-3 alcohol (1a) in methanol and aqueous acetonitrile are listed in Table 2.

Table 2. Chlorination of phenol (30mM) in the presence of alcohol (1a) and SDS with t-butyl hypochlorite (15mM)

[SDS]/mM	[(1a)]/mM	2-Chloro (%) [a]	4-Chloro (%) [a]	2,4,6-Trichloro (%) [b]	Yield (%) [a]
in CH_3CN–H_2O 1 : 9 v/v					
297	3	57	33	9	*c*
290	10	64	30	6	*c*
285	15	69	24	7	*c*
280	19	73	4	23	*c*
270	30	79	2	18	*c*
0	~100 (saturated)	100			17
in methanol					
0	0	28	72		100
464	0	26	74		*c*
296	3	55	10	15	*c*
290	10	64	26	10	*c*
285	15	64	24	12	*c*
280	20	72	17	11	*c*
269	30	76	17	7	*c*
0	100	75	25		25
0	317	100			13

[a] Normalised % of total chlorination products. [b] Based upon Bu^{t}OCl added. [c] Yield 2—10%, see text.

The results show that, as the concentration of alcohol (1a) was increased, the proportion of *ortho*-chlorination rose in both solvents. Under the constant total detergent concentration regime used, well above the c.m.c. in both solvents (25mM in aqueous CH_3CN and 110mM in methanol), this trend is consistent with chlorination being increasingly mediated by the tertiary hypochlorite derived from (1a). The interpretation is further supported by two observations. First, when the methyl ether (1b) corresponding to (1a) was included in place of (1a), the enhancement in selectivity due to the localised reagent was abolished and the proportions of products were those of simple micellar chlorination. Second, the use of the alcohol (1a) as sole detergent led to exclusive *ortho*-chlorination, no other product being detectable. This is the first time that virtually complete selectivity has been observed in a micellar-mediated electrophilic substitution reaction and it is consistent with the expectations outlined in the design of the system.

The significant yield of 2,4,6-trichlorophenol was not anticipated. This product was obtained frequently when chlorinations were carried out in the presence of polymers [8] or tentacle molecules [9] and in those cases seemed to be due to polychlorination of unbound phenol. In the present system, n.m.r. experiments [4] suggested that *ca.* 90% of phenol was

Table 3. Selectivity in chlorination of phenol (30mM) in the presence of alcohol (2a) and SDS with t-butyl hypochlorite (15mM)

[SDS]/mM	[(2a)]/mM	2-Chloro (%) [a]	4-Chloro (%) [a]	2,4,6-Trichloro (%) [a]	Yield (%) [b]
in CH_3CN–H_2O 1 : 9 v/v					
297	3	70	30		c
290	10	67	24	9	c
285	15	62	28	10	c
280	19	65	25	10	c
270	31	66	27	7	c
0	99	81	19		37
0	313	82	18		37
in methanol					
297	3	44	39	17	c
290	10	40	41	19	c
285	15	42	41	17	c
280	20	41	45	14	c
270	30	50	39	11	c
0	100	53	47		19
0	316	44	56		13

[a–c] As Table 2.

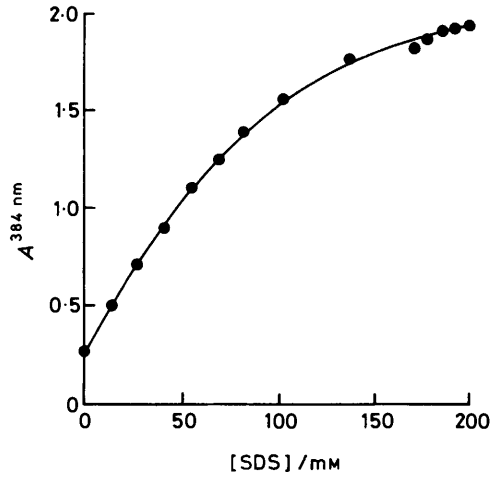


Figure 2. Association of SDS in methanol probed by *N*-methyl-3-nitropyridinium iodide (2×10^{-4}M) absorbance at 384 nm

bound by the micelles. Therefore polychlorination is probably due to multiple attack upon one molecule of free phenol as was found with the tentacle systems and polymers. This behaviour probably reflects the poor exchange between t-butyl hypochlorite and the tertiary alcohol (1a).

When the C-12 substituted alcohol (2a) was used under similar conditions, it was found that *ortho*-chlorination was again promoted, but not to the same extent as with the 3-substituted compound (1a) (Table 3). Although no significant concentration dependence was observed, the use of methyl ether (2b) once again returned the proportions of products to the simple micellar standard. The *ortho*-promotion can therefore be attributed to the transfer of chlorine to alcohol (2b). This observation is surprising and opposite to expectations. Clearly the 12-substituted alcohol (2a) was not adopting the anticipated position in the micelle relative to phenol.

The results described above show close parallels in behaviour between the aqueous and methanolic systems implying that micellar phenomena are attainable in methanol also.

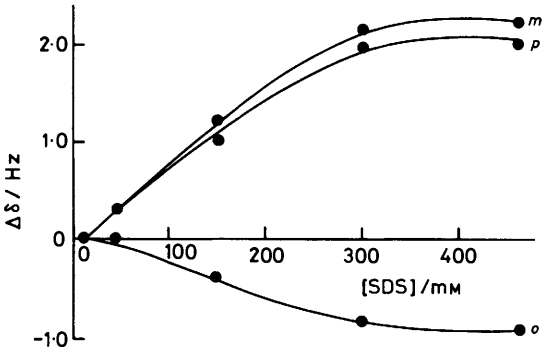


Figure 3. Effect of concentrated SDS solutions upon the chemical shifts of the protons of bound phenol

Table 4. Upfield chemical shifts (Hz) of specified protons in micellar solution. Spectra measured at 250 MHz. Shifts are with respect to the same compound in non-micellar solution

[SDS]/mM	[ether]/mM	δ(OMe)/Hz
in CD_3CN–D_2O (1 : 9 v/v)		
200	30 (Bu^{t}OMe)	3.5
270	30 (1b)	−0.5
270	30 (2b)	14.0
in CD_3OD		
460	51 (Bu^{t}OMe)	1.1
459	51 (1b)	−1.3
459	52 (2b)	2.1

Large micelles do not usually form in organic solvents but the key to selectivity in substitution is the ability of the aggregated state to control the average orientation of the substrate. To confirm micelle-like behaviour, an appropriate probe is a monocyclic aromatic compound of similar size to the substrate. We have used *N*-methyl-3-nitropyridinium iodide, a compound whose electronic spectrum is sensitive to its environment. Figure 2 shows that the change in absorbance at 384 nm is not linear with SDS concentration and indicates a c.m.c. of *ca.* 110mM. There is no sharp discontinuity in the curve which suggests that small aggregates are significant components of the system. Similar behaviour was found in our earlier work using aqueous acetonitrile as solvent.[1] It is also possible to probe aggregation using the differential chemical shifts of the substrates in micellar solution.[4] Although in the case of methanolic SDS, the shifts are very small (Figure 3) and are not of themselves convincing, the pattern of behaviour is similar to that found in aqueous solution [4] and the approximate c.m.c. derived from these data agrees with that obtained from u.v. studies (Figure 2).

We also used the n.m.r. technique to investigate the environments of the partners of these reactions in aqueous and methanolic solution. Because of the instability of the hypochlorites, the methyl ethers of the alcohols were used to monitor the environment as had been possible with anisole.[4,5] Table 4 lists the results. In aqueous acetonitrile solution, the upfield shift of the 12-methoxy-group in (2b) suggests that it resided in a relatively apolar region of the micelle whereas the 3-methoxy-compound (1b) and t-butyl methyl ether experienced substantially more polar environments. Parallel results were obtained in methanolic solution, although because of the smaller difference in polarity between the micelle and the solvent, very small chemical shift changes were observed.

In both solvents, the behaviour of the 12-methoxy-compound (2b) was indicative of a non-polar environment of this group, as had been planned. However, this result is inconsistent with the chlorination behaviour of the corresponding alcohol (2a) which indicated that the alcohol must enter the polar environment where the phenol is bound. In a model of a micelle in which an irregular but essentially radial pincushion array of detergent chains exists,[19,20] a 12-methoxy-substituent would be expected to reside in the micellar core, as the n.m.r. results suggest. The normal depth of penetration of water into such micelles has been estimated to be 6—7 carbon atoms from the head group.[19] If this is so, then the 12-hydroxy-compound (2a) would also be expected to occupy an apolar environment. It may be that the presence of a hydroxy-group causes the micellar structure to be even more open than the pincushion model usually suggests.[21] A more chaotic model of a micelle has been proposed in which clusters of ionic head groups on the surfaces are separated by oily areas.[22] If this model is a better description of micellar structure, the behaviour of alcohol (2a) might be interpreted as if the alcohol and carboxylate are found in different ionic pools spanned by the polyalkyl chain. Theoretical considerations [23] have emphasised both the rapid dynamic nature of micelles and also that the protrusion of monomer molecules is to be expected. This description suggests that the 3-position in our compounds would frequently interact with the bulk solvent but that the 12-position would contact it only rarely in the absence of the hydroxy-group. Perhaps the most attractive model consistent with our results is that of Fromhertz [24] which incorporates some features of several of the above models. The bifunctional nature of our compounds thus appears crucial in interpreting the effects observed with the 12-substituted stearate. Nevertheless, in any model the apolar environment of the methyl ether can be achieved simply by rotation of carbon–carbon bonds in the polymethylene chain without altering the overall micellar structure.

Conclusions.—The spectroscopic and selectivity results described above demonstrate clearly the importance of a localised reagent in optimising the performance of selective functionalisation systems. It is encouraging that such high selectivity can be obtained with simply constructed micellar systems. However, the ambiguous behaviour of the 12-substituted compounds once again emphasises the difficulty of basing systems upon such labile aggregated as micelles, especially when the structure is so ill defined.

Experimental

250 MHz ^{1}H N.m.r. spectra were obtained on a Bruker WH-250 spectrometer; 90 MHz spectra were recorded on a Perkin-Elmer R 32 spectrometer.

12-Hydroxy-12-methylstearic Acid.—Magnesium turnings (2 g; dry) in sodium-dried ether (10 ml) were treated slowly with methyl iodide (5 ml) in ether (30 ml). The mixture was heated under reflux until most of the magnesium had dissolved. 12-Oxostearic acid (8 g) dissolved in the minimum amount of ether or ether–THF was added slowly from a dropping funnel to the stirred solution of methylmagnesium iodide. The resulting mixture was further refluxed for 4 h. On cooling, the mixture was decomposed with a saturated solution of ammonium chloride (200 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 (8 g), b.p. 150 °C at 0.4 Torr (decomp.) (Found: C, 72.6; H, 12.2. $C_{19}H_{38}O_3$ requires C, 72.5; H, 12.1%); $\delta(CDCl_3)$ 0.89 (3 H, t), 1.15 (3 H, s), 1.29br (28 H, s), 2.33 (2 H, t), and 5.05 (1 H, s, exch. with D_2O); $\nu_{max.}$ (liquid film) 3 420 and 1 705 cm^{-1}. t-Butyl bromoacetate [25] and heptadecan-2-one [26] were prepared following published procedures.

3-Hydroxy-3-methylstearic Acid.—This was prepared following the published procedure [27] and was obtained in 90% yield as a waxy solid, m.p. 41—43 °C (Found: C, 72.4; H, 12.3%); $\delta(CDCl_3)$ 0.89 (3 H, t), 1.28br (32 H, s), 2.53 (2 H, s), and 6.55 (1 H, s, exch. with D_2O); $\nu_{max.}$ (liquid film) 3 420 and 1 705 cm^{-1}.

3-Methoxy-3-methyl- and 12-Methoxy-12-methyl-stearic Acids.—To a solution of the alcohols (1 g) in 1,2-dimethoxyethane (10 ml) and iodomethane (4 ml) was added sodium hydride (5 g) previously washed free of oil (using dry ether) with stirring at room temperature over 30 min. Stirring was continued for a further 1 h at room temperature before the mixture was set to reflux for 15 h. The cooled mixture was treated with ether (100 ml) and 10% HCl (50 ml) and shaken in a separating funnel. The aqueous layer was extracted twice with ether (50 ml) and the combined ether extracts dried (Na_2SO_4) and evaporated *in vacuo* to give the methoxy-derivative of the respective hydroxy-acids. Each was further purified by chromatography on silica gel. The *3-isomer*, b.p. 200 °C at 0.2 Torr, was obtained in 94% yield (Found: C, 73.3; H, 12.5. $C_{20}H_{40}O_3$ requires C, 73.1; H, 12.2%); $\nu_{max.}$ (liquid film) 1 705 and 1 075 cm^{-1}. The *12-isomer*, b.p. 170 °C at 0.1 Torr, was obtained in 90% yield (Found: C, 73.9; H, 12.5%); $\nu_{max.}$ (liquid film) 1 710 and 1 075 cm^{-1}.

Sodium salts of acids were prepared by treatment of the corresponding acids with the calculated quantity of methanolic sodium hydroxide.

Chlorination Experiments.—Where no transfer of chlorine was required, solutions of SDS and phenol were prepared in 2 or 10 ml of the appropriate solvent to give the concentrations stated in the Tables. t-Butyl hypochlorite was then added over 15 min beneath the surface of the liquid from a microsyringe. When the transfer reagents were used, t-butyl hypochlorite was added to the solution of detergents (2—3 ml) which were shaken together for 5 min before addition of a concentrated solution of phenol (0.1 ml). Products were extracted by diluting the aqueous reaction mixtures with five volumes of ether. To the stirred solution, 1 equiv. of calcium chloride calculated based upon the total detergent concentration was added (typically 0.1 ml of 33% aqueous solution) and stirring continued for 10 min. This removes most of the detergent which can otherwise interfere with g.l.c. analysis. Methanolic solutions were conveniently analysed as the solutions obtained after evaporation of methanol and resolution of the phenols in ether. G.l.c. analysis was carried out on a 1 m column of 5% FFAP on Chromosorb G at a flow rate of 25 ml min^{-1}. The system was calibrated with standard solutions of monochloro-, dichloro-, and trichloro-phenols at concentrations in the range obtained in chlorination experiments. Typical retention times (min) were 2-chlorophenol, 3.4; phenol, 4.9; 2,6-dichlorophenol, 7.0; 2,4-dichlorophenol, 8.6; 2,4,6-trichlorophenol, 9.2; and 4-chlorophenol, 13.2. All chlorination experiments were run using a 50% deficiency of chlorinating agent so that the residual phenol acted as an internal standard and measure of overall yield.

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