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Selectivity in Aromatic Substitution: Effects of Functionalized Detergents on the Chlorination of Phenol

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The regioselectivity of chlorination of phenol in aqueous solution of an anionic detergent functionalized at its head group is shown to be similar to chlorination effects by *t*-butyl hypochlorite in aqueous sodium dodecyl sulfate (SDS) solution. *ortho* Chlorination is promoted in both micellar solutions. However, when chlorination is mediated by detergents carrying no charge at their functionalized head groups, selectivity depends on micellar concentration with *para* chlorination predominating at high detergent concentrations. The problems and advantages inherent in head group functionalization are discussed.

INTRODUCTION

The very high degree of selectivity achieved in enzymatic reactions has encouraged interest in efforts aimed at constructing chemical systems capable of imposing greater control in ordinary chemical reactions. Detergent micelles have been used to enhance selectivity in a number of substitution reactions (*1–3*). Although micellar systems are simple to construct and manipulate, they are poorly ordered and labile and are thus unsuitable for highly selective reactions. A system designed to impose greater control upon a micelle-like system would require that the attacking reagent and the substrate be precisely positioned with respect to each other. One way of achieving this control has been the attachment of the detergent chains to each other either through a polymer (*4*) or in the form of tentacle molecules (*5, 6*). Another way has been to localize the reagent at a definite position in the detergent molecule. This approach was adopted in the present study which parallels our previous efforts on selective functionalization (*7*). Functionalized detergents have been widely employed in studies of micellar catalysis (*8, 9*), especially of enantiomeric specificity (*10, 11*) and, although prior to our studies functionalized detergents capable of use as substitution reagents had been prepared (*12, 13*), they did not appear to have been used as such. Our studies with functionalized stearates have shown that high selectivity in the chlorination of phenol by *t*-alkyl hypochlorites in methanolic and aqueous solutions can be achieved by the inclusion of a tertiary alcohol in the detergent chain β to the ionic head group (*7*). The present study considers the chlorination of phenol with detergent molecules functionalized at their head groups.

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RESULTS AND DISCUSSION

Chlorination by Functionalized Detergents

In micelles phenol is principally solubilized close to the head group (see Fig. 1) in such a way that the polar substituent is in the more polar environment (*14–16*). ^{1}H NMR studies of phenol in aqueous sodium dodecyl sulfate (SDS) solution have shown that above the critical micelle concentration (CMC), the *ortho* position occupied a more polar environment than the *para* position (*14*). A reagent approaching from the aqueous phase would therefore preferentially attack the more exposed *ortho* position, while the *para* position would be protected by the polymethylene chains of the detergent. It then follows that a detergent functionalized at or close to the head group would reasonably be expected to promote *ortho* reaction. In agreement with this hypothesis, our previous work has demonstrated that when chlorination of phenol in SDS was mediated by a functionalized detergent containing a tertiary alcohol β to the head group, reaction occurred almost exclusively at the *ortho* position. The effect on the chlorination of phenol by a detergent functionalized at the head group has, however, not been studied. This paper examines the chlorination of phenol using aqueous or methanolic solutions of SDS in the presence of three functionalized detergents, **1a, 2,** and **3** (Scheme 1).

The tertiary alcohol **1a** provides a good comparison with *t*-butyl hypochlorite (since **1a** does not carry any charge at the head group) as well as with the tertiary stearates used in our previous investigation (*7*). Owing to the difficulties in the preparation of pure hypochlorite from 2-methyl-nonadecan-2-ol (**1a**), a problem we also encountered with other long-chain tertiary alcohols (*7*), transfer chlorination employed by Breslow (*17, 18*) was used. A solution of SDS and the tertiary alcohol **1a** was prepared in methanol (the alcohol is not soluble in aqueous aceto-

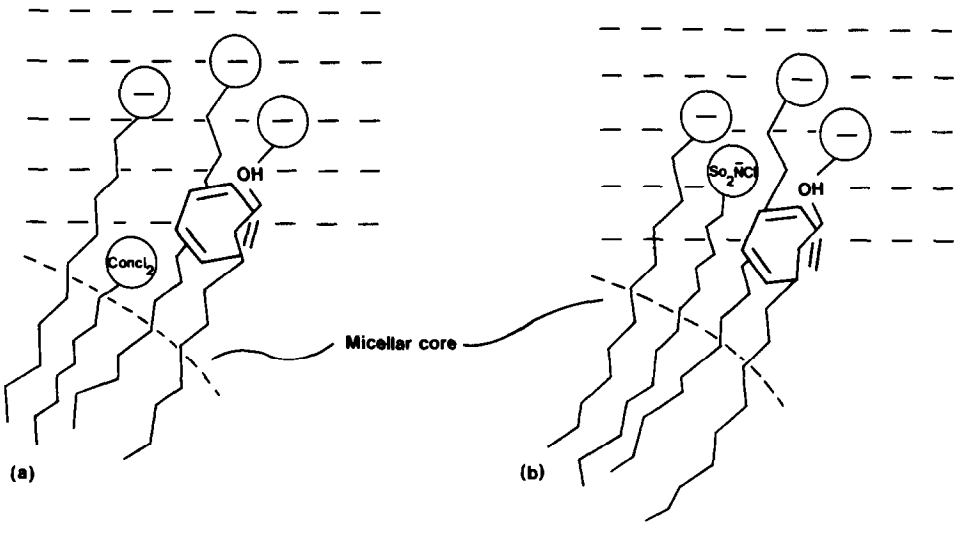
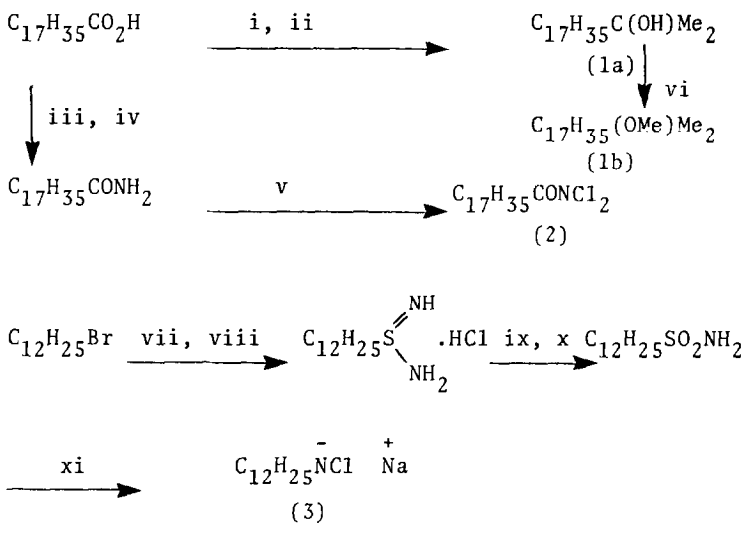


FIG. 1. Schematic representation of the position of the head group with respect to substrate molecule in micellar SDS. (a) Nonionic chlorinating agent; (b) ionic chlorinating agent.



Reagents: i, MeOH-HCl;
ii, Me MgI; iii, $SOCl_2$; iv, aq. NH_3; v, t.BuOCl;
vi, NaH - MeI; vii, $CS(NH_2)_2$; viii, HCl;
ix, Cl_2 - H_2O; x, aq.NH_3; xi, HOCl-NaOH.

SCHEME 1

nitrile, the solvent of choice in our previous investigations), *t*-butyl hypochlorite was added, and the exchange of alkyl hypochlorite was allowed to proceed. The substrate phenol was then added. Micellar phenomena are attainable in methanol (*7*). Although large micelles do not usually form in organic solvents, the key to selectivity in substitution is the ability of the aggregated state to control the average orientation of the substrate. Altogether this reaction method inevitably led to a reduced yield of chlorinated phenol since decomposition of *t*-butyl hypochlorite competes with exchange, the yields being typically 2–10% based upon added chlorinating agent.

The results (Table 1) show that as the concentration of the alcohol (**1a**) was increased, the proportion of *ortho* chlorination gradually but significantly rose. Under the constant total detergent concentration regime used, well above the CMC (110 mM), this result is consistent with chlorination being increasingly mediated by tertiary hypochlorite derived from the alcohol. Support for this view comes from the observation that when the methyl ether **1b** corresponding to **1a** was included in place of **1a** the enhancement in selectivity due to the localized reagent was abolished and the proportions of products were those of simple micellar chlorination. Compared with the stearate alcohols in our previous study (*7*), this selectivity is low. This may be due to the ability of the uncharged alcohol **1a** to penetrate deeper into the micellar core. If this is so, then the head group would

TABLE 1

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

[SDS] (mM)	[**1a**] (mM)	2- (%)[a]	4- (%)[a]	2,4- (%)[a]	Yield (%)[b]
0	0	28	72	—	100[d]
464	0	26	74	—	[c]
298	3	37	—	63	[c]
290	10	44	—	56	[c]
285	15	53	—	47	[c]
280	20	47	—	53	[c]
270	30	47	—	53	[c]

[a] Normalized percentage of total chlorination products.
[b] Based upon t-BuOCl added.
[c] Yield, 2–10%.
[d] Results obtained using t-BuOCl as chlorinating agent.

suffer considerable loss of proximity to the phenol *ortho* position (see Fig. 1), resulting in loss of selectivity with respect to the *ortho* position.

The significant yield of 2,4-dichlorophenol could be due to multiple attack upon one molecule of free phenol as was found with tentacle systems (*5*) and polymers (*4*) and probably reflects the poor exchange between *t*-butyl hypochlorite and the tertiary alcohol **1a**.

The use of *N,N*-dichlorooctadecanamide (**2**) and *N*-chloro-*N*-sodiododecanesulfonamide (**3**) for chlorination of phenol was also examined. Varying amounts of functionalized detergents (0–51 mM) and different quantities of SDS (0–510 mM) in aqueous acetonitrile (H_2O–CH_3CN, 9 : 1, v/v) or in methanol were reacted with phenol. The effect of each detergent molecule on the chlorination of phenol was then observed for different total detergent concentration.

In aqueous acetonitrile, *N,N*-dichlorooctadecanamide (**2**) is not soluble, but its solubility is very much enhanced at increased micellar concentrations of SDS (Table 2). At low total detergent concentrations very little reaction takes place presumably because of the insolubility of the chloramide. At higher detergent concentrations and when the chlorinating agent has become soluble, *ortho* chlorination is favored, and at still high concentrations *para* chlorination predominates. Increased *para* chlorination is probably a result of deeper penetration into the micellar core of the *N,N*-dichlorooctadecanamide (**2**) molecule with increasing detergent concentration, a situation arising from the fact that the chlorinating agent bears no charge at the head group (Fig. 1a). In methanolic solution the pattern is the same. At low SDS concentration there is exclusive *ortho* chlorination, but in very low yields, again because of low solubility of the chlorinating agent in methanol. At higher total detergent concentration, *para* chlorination is enhanced to an even greater extent since penetration of the chloramide into the micellar core in methanol would predictably be deeper than in aqueous SDS.

TABLE 2

SELECTIVITY IN THE CHLORINATION OF PHENOL (100 mM) BY *N,N*-DICHLOROOCTADECANAMIDE (**2**) IN THE PRESENCE OF SDS

[SDS] (mM)	[**2**] (mM)	[Total Det] (mM)	2- (%)[a]	4- (%)[a]	Yield (%)[b]
CH_3CN–H_2O (1:9, v/v)					
0	0	0	48	52	93[d]
0	1	1	—	—	0
6	1	7	—	—	0
45	5	50	50	50	[c]
152	18	170	44	56	[c]
459	50	509	26	74	[c]
510	0	510	62	38	68[d]
Methanol					
0	1	1	100	0	[e]
6	1	7	100	0	[e]
47	5	52	36	64	[d]
157	17	174	31	69	[c]
312	34	345	22	78	[c]
470	51	521	20	80	[c]
0	0	0	28	72	100[d]
464	0	464	26	74	[c]

[a] Normalized percentage of total chlorination products.
[b] Based upon chlorinating agent.
[c] Yield 2–10%.
[d] Results obtained using t-BuOCl as chlorinating agent (*7*).
[e] Yield, less than 2%.

N-Chloro-*N*-sodiododecanesulfonamide (**3**) is different from the other two chlorinating agents as it is an anionic detergent. Its chlorinating action is enhanced by the addition of one or two drops of methanesulfonic acid. The results (Table 3) show that at low detergent concentrations, there is very little reaction. However, above the CMC (25 mM in aqueous acetonitrile) an increase in total detergent concentration leads to a small increase in *ortho* chlorination. The *ortho* enhancement mediated by the chlorosulfonamide (**3**) is, however, very close to the selectivity observed in aqueous SDS alone when phenol is chlorinated with *t*-butyl hypochlorite.

The introduction of the chlorosulfonamide into SDS solution is not expected to alter the overall structure or nature of the binding "pockets," and phenol will essentially maintain its average orientation in the micellar solution. Significant changes with respect to the disposition of the electrophile toward the substrate molecule are therefore not expected. This is understandable if one considers that anionic chlorosulfonamide (Fig. 1b) will tend to align itself with SDS at both the head group region and in the micellar core, leaving the electrophile in the aqueous phase, essentially in the same type of position that *t*-butyl hypochlorite might reasonably be expected to take up in aqueous SDS.

TABLE 3

SELECTIVITY IN THE CHLORINATION OF PHENOL (100 mM) IN AQUEOUS SDS SOLUTION (1:9, v/v, CH_3CN–H_2O) BY *N*-CHLORO-*N*-SODIODODECANESULFONAMIDE (3)

[SDS] (mM)	[3] (mM)	[Total Det] (mM)	2- (%)[a]	4- (%)[a]	Yield (%)[b]
0	0	0	48	52	93[c]
0	3	3	—	—	0
4	3	7	—	—	0
46	5	51	63	37	85
148	20	168	67	33	81
155	18	173	66	34	80
458	52	510	66	34	75
510	0	510	62	38	68[c]

[a] Normalized percentage of total chlorination products.
[b] Percentage yield based upon chlorinating agent.
[c] Results obtained using t-BuOCl as chlorinating agent (*7*).

Conclusion

The results obtained from these head group functionalized detergents underscore the potentialities that exist in the use of functionalized detergents for selective substitution reactions. The ease with which the reacting system can be constructed is important, but caution must be employed in the selection of the actual position for localizing the reagent. Although functionalization at the head group may place the reagent close to a particular position of the substrate, it is obvious that other factors are also crucial for high selectivity. Apart from the fundamental disadvantage of basing systems upon such labile aggregates as micelles, the interference and interaction between head group and substituting reagent, especially when these are close to each other, can be an obvious disadvantage in head group functionalization. Also, as seen in two of the chlorinating agents under examination, the absence of charge at the head group can lead to the displacement of reacting agent, and indeed the entire molecule, away from the predicted or desired reaction site, into the micellar core. This can lead to poor selectivity and low reactivity at the particular site. This, however, need not be a disadvantage as decreased selectivity with respect to one position on the substrate can lead to improvement at another. Indeed this could make such detergent molecules more versatile for substitution reactions, since by a proper choice of conditions they could be manipulated to give selectively, different products at different times.

EXPERIMENTAL PROCEDURES

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

2-Methylnonadecan-2-ol. This compound was obtained in 95% yield by the reaction of methylmagnesium iodide and methyl stearate, following published procedure, as colorless crystals, mp 46°C [Lit. 45.5–47°C (*19*)].

2-Methoxy-2-methylnonadecane. 2-Methylnonadecan-2-ol was methylated with iodomethane and sodium hydride, following procedures used for the preparation of other long-chain tertiary alcohols (*7*), to give a colorless liquid, bp 150°C at 0.2 Torr in 90% yield. *Anal.* Calcd for $C_{21}H_{44}O$: C, 80.7; H, 14.2. Found: C, 81.2; H, 14.2.

N,N-dichlorooctadecanamide. Octadecanamide (3 g) was dissolved in methanol (20 ml) and treated with *t*-butyl hypochlorite (3 g). The reaction mixture was left to stand at room temperature for 30 min and the volume was reduced to one half on a water bath. On cooling, deposits of colorless crystals, recrystallized from methanol, were obtained in 93% yield, mp 55°C. *Anal.* Calcd. for $C_{18}H_{35}Cl_2NO$: C, 61.4; H, 10.0; N, 4.0; Cl, 20.1. Found: C, 61.5; H, 10.3; N, 4.2; Cl, 19.4. δ ($CDCl_3$) 0.88 (3H, *t*), 1.27*br* (30 H, *s*) 2.5 (2H, *t*).

N-Chloro-N-sodiododecanesulfonamide. This was prepared according to published procedure by Hardy (*20*).

Chlorination experiments. For reaction of the tertiary alcohol, *t*-butyl hypochlorite was added to the solution of SDS and alcohol (2 ml), which was shaken for 5 min before addition of a concentrated solution of phenol (0.1 ml). For the other chlorinating agents, solutions of SDS and the functionalized detergents (2 ml) were treated with concentrated phenol (0.1 ml) solution as above, and left to stand for 30 min. The solution containing *N*-chloro-*N*-sodiododecanesulfonamide had a drop of methanesulfonic acid added to it. Products were then extracted by diluting the aqueous reaction mixture with 5 vol of ether. To the stirred solution, 1 equivalent 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 GLC analysis. Methanolic solutions were conveniently analyzed as the solution obtained after evaporation of methanol and resolution of the phenols in ether. GLC 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 trichlorophenols 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% or more deficiency of chlorinating agent so that the residual phenol acted as an internal standard and measure of overall yield.

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