High Selectivity in the Chlorination of Phenol in the Presence of Functionalised Micelles

Samuel O. Onyiriuka and Colin J. Suckling*

Department of Pure and Applied Chemistry, University of Strathclyde, 295, Cathedral Street, Glasgow G1 1XL, U.K.

ortho-Chlorination of phenol by t-alkyl hypochlorites in methanolic and aqueous solution is markedly enhanced by the inclusion of a tertiary alcohol in a detergent chain β to the ionic head group.

The ability of detergent micelles to impose an average orientation upon small aromatic solubilisates has been demonstrated by studies of selectivity in substitution reactions[1] and of ^{1}H n.m.r. spectroscopy.[2] However, the effect of this orientation upon selectivity in substitution reactions is not large. To improve the selectivity and to assist the development of more complex selective functionalisation systems,[3] we chose to study reactions in which the electrophile was located at a defined position in the micelle. Functionalised detergents have been widely employed in studies of micellar catalysis,[4] especially of enantiomeric selectivity,[5] and although functionalised detergents capable of use as reagents have been prepared,[6] they have not to our knowledge been used to investigate selectivity in aromatic substitution. In this paper, we describe the effects of localising a tertiary hypochlorite upon the chlorination of phenol in micellar solution, a system which gives clean behaviour in both chemical and spectroscopic studies.

If phenol is principally solubilised in micelles close to the head group so that the polar substituent is in the more polar environment as ^{1}H n.m.r. studies suggest,[2] it would be anticipated that a tertiary hypochlorite located close to the anionic head group would further promote *ortho*-chlorination whereas one in the micellar core would not. To test this

Table 1. Chlorination of phenol in aqueous acetonitrile (9 : 1 v/v).

[SDS]/ mM		[Stearate]/ mM	% [a] 2-	4-	2,4,6-	Yield [c]/ %
0 [b]		0	48	52	—	100
170 [b]		0	56	43	—	
510 [b]		0	62	38	—	54
297	(1a)	3	57	33	9	[d]
290	"	10	64	30	6	[d]
285	"	15	69	24	7	[d]
280	"	19	73	4	23	[d]
270	"	30	79	2	18	[d]
0	"	*ca.* 100 (satd.)	100	—	—	17
270	(1b)	29	59	41	—	[d]
297	(2a)	3	70	30	—	[d]
290	"	10	67	24	9	[d]
285	"	15	62	28	10	[d]
280	"	19	65	25	10	[d]
270	"	31	66	27	7	[d]
0	"	99	81	19	—	37
0	"	313	82	18	—	37
270	(2b)	30	66	34	—	[d]

[a] Normalised % of total chlorination products. [b] Results obtained by Dr. A. A. Wilson.[2] [c] Based upon Bu^{t}OCl consumed. [d] Overall yield for transfer and aromatic substitution steps was low (2—10%).

$$C_{15}H_{31}CO_2H \xrightarrow{i,ii} C_{15}H_{31}CH(OH)CH_2CO_2H$$
$$\downarrow iii$$
$$C_{15}H_{31}CMe(OH)CH_2CO_2^-Na^+ \quad \textbf{(1a)}$$
$$\downarrow iv$$
$$C_{15}H_{31}CMe(OMe)CH_2CO_2^-Na^+ \quad \textbf{(1b)}$$

$$C_6H_{13}CH(OH)[CH_2]_{10}CO_2H$$
$$\downarrow v, vi$$
$$C_6H_{13}CMe(OH)[CH_2]_{10}CO_2^-Na^+ \quad \textbf{(2a)}$$
$$\downarrow iv$$
$$C_6H_{13}CMe(OMe)[CH_2]_{10}CO_2^-Na^+ \quad \textbf{(2b)}$$

Scheme 1. *Reagents:* i, MeLi; ii, $BrCH_2CO_2CMe_3$–Zn;[7] iii, 1 equiv. NaOH; iv, NaH–MeI; v, $Na_2Cr_2O_7$–H_2SO_4; vi, MeMgI.

hypothesis, we prepared derivatives of stearic acid with tertiary alcohols located at C-3 (**1a**) and C-12 (**2a**), and the corresponding methyl ethers (**1b**) and (**2b**) (Scheme 1).[7] We had hoped to convert the tertiary alcohols (**1**) into the corresponding hypochlorites but we were unable to obtain satisfactorily pure samples for test. Therefore t-butyl hypochlorite was used as the source of chlorine which was allowed to transfer to the detergent tertiary alcohol *in situ*,[8] although this procedure inevitably reduced the yield of chlorinated products. Mixtures of the functionalised stearates (**1a**) and (**2a**) with sodium dodecyl sulphate (SDS) were prepared at a total concentration of about 300 mM. Our previous studies[2] have shown that micellar orientation effects are well established at this concentration in aqueous solution. t-Butyl hypochlorite followed by phenol were added to give concentrations of 15 and 30 mM respectively. The products were analysed by g.l.c. on a calibrated column (5% FFAP on Chromosorb G at 210 °C) and the results are shown in Tables 1 and 2.

In aqueous solution (Table 1), the orientation of phenol by SDS caused enhanced *ortho*-chlorination but detergent (**1a**) bearing a tertiary alcohol close to the anionic head group further increased the *ortho*-chlorination in a concentration-dependent manner. That the change in selectivity was due to the added tertiary alcohol was demonstrated by the fact that the corresponding methyl ether (**1b**) annulled the additional *ortho*-substitution. When the functionalised detergent (**1a**) was used alone in saturated aqueous solution {[(**1a**)] = 100 mM}, chlorination proceeded almost exclusively at the *ortho*-position. This remarkably high selectivity is consistent with the hypothesis outlined above.

The hypothesis further suggested that the functionalised detergent (**2a**), in which the tertiary alcohol would be expected to be buried in the micellar core, would promote enhanced *para*-chlorination but this was not found. With respect to SDS alone, the 12-hydroxystearate (**2a**) also enhanced *ortho*-substitution, although in lower yield. The reason for this effect is not obvious but it may indicate that the 12-hydroxy-group approaches the aqueous phase much more than usual for a substituent at this position; this result has implications for the structure of micelles.[9]

The reactions in methanol showed analogous trends. The 3-substituted stearate (**1a**) induced a substantial *ortho* enhancement up to almost complete exclusion of *para* attack and the 12-substituted compound (**2a**) unexpectedly promoted *ortho*-chlorination as in aqueous solution. The use of the methyl ethers blocked the effects of the tertiary alcohols.

Table 2. Chlorination of phenol in methanol.

[SDS]/ mM		[Stearate]/ mM	%[a] 2-	4-	2,4,6-	Yield[b]/ %
0		0	28	72	—	100
464		0	26	74	—	—
296	(**1a**)	3	55	30	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
460	(**1b**)	51	27	73	—	[c]
297	(**2a**)	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
455	(**2b**)	53	22	78	—	[c]

[a] Normalised % of total chlorination products. [b] Based upon Bu^tOCl consumed. [c] Overall yield for transfer and aromatic substitution steps was low (2—10%).

Although the formation of micelles is inhibited by organic solvents such as methanol, n.m.r. studies of the solubilisation of phenol in methanolic SDS solution showed similar effects to those we have described for aqueous micellar solutions.[2] Analysis of the data indicated that aggregation phenomena occurred above a concentration of 130 mM.

To gain some insight into the environments in which the functional detergents were operating, we examined the effect of solubilisation in a micelle upon the chemical shift of the methoxy-group of the ethers of the tertiary alcohols used. The stable methoxy-group was in this experiment used to model the reactive hypochlorite. The upfield shifts of the 12-methoxy-proton resonances of stearate (**2b**) (14.0 and 2.1 Hz at 250 MHz in CD_3CN–D_2O and CD_3OD respectively) were larger than those of the 3-methoxy-protons of (**1b**) (−0.5 and −1.3 Hz) in both solvents and this result confirms that the latter is in the more polar environment. Indeed the chemical shift change for the 3-methoxy-protons was similar to that observed for the *ortho* proton of phenol under similar conditions suggesting that the two enjoy essentially the same polar environments, in agreement with the chemical results. However, the non-polar environment indicated by the n.m.r. data for the 12-methoxystearate (**2b**) is not consistent with the *ortho* promotion observed. It is possible that the more polar hypochlorite might have a significantly different environment from the methyl ether or alternatively, a model of micellar structure in which continuous areas of non-polar polymethylene chain made contact with the solvent[9] could account for the *ortho* promotion by (**2a**) and the upfield shift of the methoxy-group in (**2b**) by simple carbon–carbon bond rotation.

Taken together, chemical and spectroscopic results argue strongly that localisation of a reagent in a simply constructed system can have a profound influence upon the course of the reaction. The selectivity observed when the reagent is located near the head group is the highest yet obtained in an aromatic substitution reaction in micellar solution. Clearly it is possible to exert control on reactions of polar substrates close to the ionic head group, but the ambivalent behaviour of the 12-substituted compound shows that a better understanding of the structure of the micellar core is required before it can be used to control selectivity.

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