Selective Functionalisation. Part 4.† ^{1}H Nuclear Magnetic Resonance Studies of the Orientation of Aromatic Molecules by Surfactant Micelles

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The ^{1}H n.m.r. spectra of phenol and anisole in the presence of anionic and cationic detergents are described. The spectra are characterised by differential upfield shifts of the protons of the solubilisate as the detergent concentration is increased. Evidence is presented to show that, although the upfield shifts are sensitive to pH and to the head group of the detergent, the major cause of the differential upfield shift is a time-averaged orientation of the solubilisate in the micellar environment. The significance of these results with respect to micellar control of regioselectivity in aromatic substitution is discussed.

THE success of simple selective oxidation systems for aromatic compounds requires that the attacking reagent and the substrate be precisely positioned with respect to each other. To develop such systems efficiently, it is necessary to have a probe technique which can define the orientation of the aromatic substrate with respect to the oxidising agent. We [1,2] and others [3,4] have found that amphiphilic molecules can influence the course of chlorination,[1,3] bromination,[3] hydroxylation,[2] and nitration [4] substitution reactions of monofunctional aromatic compounds. In no case was it possible to adduce experimental evidence relating to the orientation of the substrate although micelle formation was clearly important in each case. ^{1}H N.m.r. studies have been used to detect the dynamic solubilisation sites of aromatic molecules in micelles,[5-10] but spectra have not been run under conditions closely relating to the conditions of chemical reactions in micelles. In some studies, saturating concentrations of solubilisate made it difficult to interpret the effects observed. In others, resolution was insufficient to deduce anything concerning orientation. In this paper, we present the effects of anionic and cationic detergents upon the ^{1}H n.m.r. spectra of some phenols and their ethers under conditions closely comparable to those in chemical reactions.

RESULTS AND DISCUSSION

Monofunctional Compounds.—At 360 MHz, the ^{1}H n.m.r. spectra of phenol and anisole are sufficiently well resolved to distinguish clearly each type of aromatic proton (Figure 1). Thus, if a non-uniform change in the spectra results on solubilisation of a compound in a micelle, the change will be detectable for each type of proton independently. Spectra have been determined for three detergents, sodium dodecylsulphate (SDS), cetyltrimethylammonium bromide (CTAB), and cetylpyridinium chloride (CPC) in mixed aqueous–organic solvents. The organic component (methanol or acetonitrile) of the solvent mixtures assists solubilisation of water-immiscible compounds and, most importantly, provides a deuterium lock signal and a sharp internal reference peak from the residual protons for measurement of chemical shifts. Micelles are readily formed in all the solvent mixtures used as the n.m.r. data itself, conductivity, or e.s.r. spin probe experiments show.[2] The addition of an organic solvent raises the critical micelle concentration (c.m.c.) with respect to the c.m.c. in water alone.[11] Figure 2 shows the change in chemical

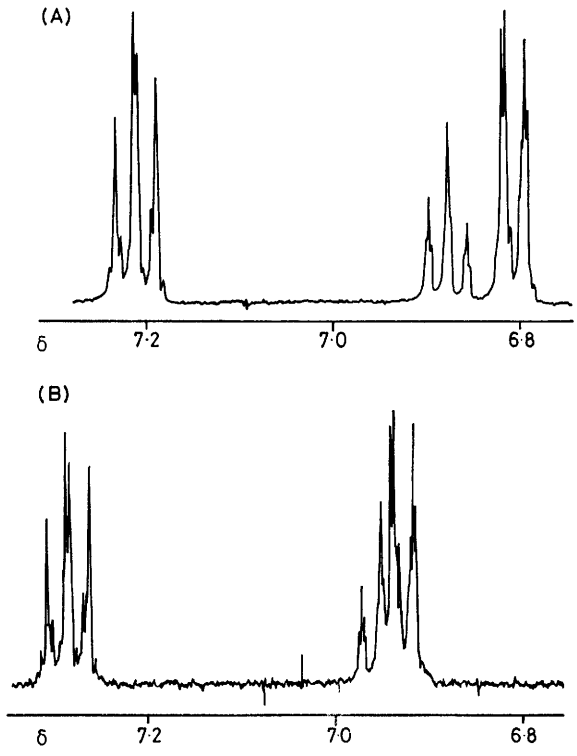

FIGURE 1 360 MHz ^{1}H N.m.r. spectra of (A) phenol and (B) anisole, both 30mM in 1 : 9 v/v CD_3CN–D_2O

shift for each type of proton of phenol in the presence of (a) SDS, (b) CTAB, and (c) CPC and Figure 3 gives the analogous results for anisole. It is immediately apparent that on increasing the detergent concentration, all resonances initially move upfield as expected for the increase in the non-polar character of the medium.[5] However, within each series, the upfield shifts were not uniform; always the *para*-proton resonance moved upfield most, and *ortho* least. Small uniform upfield shifts

† Part 3, see ref. 15.

occurred at detergent concentrations below the c.m.c. but only at concentrations above the c.m.c. was a differential between *ortho*-, *meta*-, and *para*-proton references observed. Therefore changes in n.m.r. spectra are a property of the micellar state.

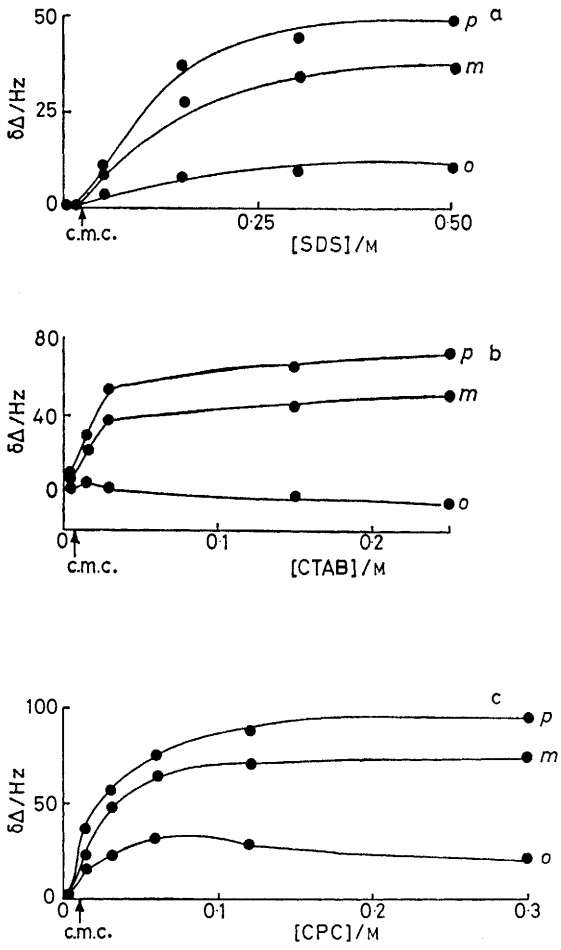

FIGURE 2 Chemical shift changes for phenol as a function of [detergent]. [Phenol] = 30 mM in 1:9 v/v CD_3CN–D_2O

Another notable feature shown in Figures 2 and 3 is the trend to reach a maximum chemical shift change at high detergent concentration, although in several cases the *ortho*-shift decreases, as has been observed previously.[10] From the saturation values of chemical shift changes a value for the association constant per molecule of detergent, K, can be obtained using equation (1)

$$K = \frac{1}{[\mathrm{D}] - \text{c.m.c.}} \times \frac{\Delta\delta_{\text{obs.}}}{(\Delta\delta_{\text{max.}} - \Delta\delta_{\text{obs.}})} \qquad (1)$$

where [D] is the total detergent concentration, $\Delta\delta_{\text{max.}}$ is the saturation chemical shift change, and $\Delta\delta_{\text{obs.}}$ is the chemical shift change at the detergent concentration in question.

This equation is derived assuming 1 : 1 association of substrate and micelle, a situation which is approached under the conditions of the n.m.r. experiments only at higher detergent concentrations. Reasonably self-consistent results (±10%) were obtained using data for *meta*- and *para*-protons, which do not decrease in chemical shift change at high concentration, and these are collected in Table 1. The values are comparable to those obtained by Bunton and Sepulveda for phenols and CTAB in aqueous solution by electronic spectroscopy.[12] Since

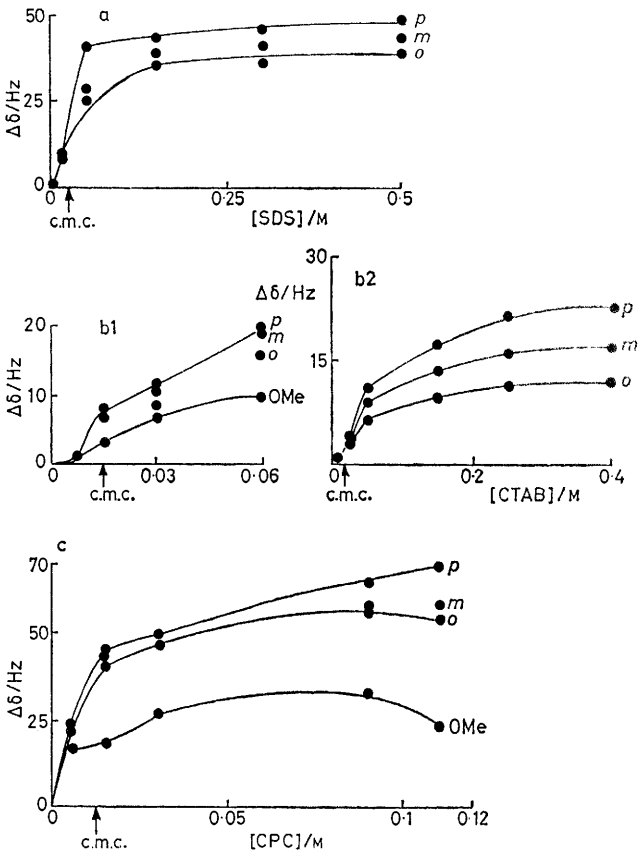

FIGURE 3. Chemical shift changes for anisole as a function of [detergent]. [Anisole] = 30 mM in 1:9 v/v CD_3CN–D_2O (a, b2, c) and 1:1 v/v CD_3OD–D_2O (b1)

TABLE 1

Equilibrium constants from n.m.r. data

Detergent	[Detergent]/mM	Solubilisate	K/l mol^{-1}
SDS	300	Phenol	33
CTAB	200	Phenol	62
CPC	300	Phenol	138
SDS	300	Anisole	62
CTAB	400	Anisole	70

the association constants are determined from environment-sensitive chemical shifts, they may depend upon the solubilisation site and the concentration of the solubilisate. A further significant feature of the spectroscopic changes is that for anisole, the difference between the *ortho*- and *para*-proton chemical shift changes is very much less than for phenol in all three detergents.

The general order of the chemical shift changes, *para* > *meta* > *ortho*, is not typical of an electronic effect within an aromatic molecule bearing a single electron-donating substituent but it is possible that the observations reflect

a combination of environmental and electronic effects. In any case, the observed spectra represent an average of the experiences of each type of proton in the aromatic molecules because the rate of exchange of solubilisate molecules between micellar and aqueous environments is fast on the n.m.r. time scale. For consideration of the origins of the spectroscopic shifts, three general environments of the solubilisate are important, the non-polar micellar core, the hydrated region,[5,13] and the bulk aqueous solvent.

TABLE 2

Effect of pH(D) and anionic and cationic detergents on the n.m.r. spectra of *p*-n-octylphenol

		Δδ/Hz relative to δ for [detergent] = O			
	[Detergent]/	Neutral		Alkaline	
Detergent	mM	H(2)	H(3)	H(2)	H(3)
SDS	200	1.67	6.51	1.08	2.59
CTAB	200	0.76	7.63	3.51	8.54

Neutral solutions contained 30mM-n-octylphenol. Alkaline solutions contained 20mM-n-octylphenol and 67mM-Na_2CO_3–$NaHCO_3$ (5 : 4 w/w). Solvent = 1 : 1 v/v CD_3CN–D_2O

Electronic Interactions.—The possibility that a pK_a change of phenol when bound to a micelle contributes to the observed chemical shift behaviour will be considered first. A cursory inspection of the data (Figures 2 and 3) indicates that it is most unlikely for a pK_a change alone to be responsible for the effects observed for the following reasons. (1) Similar trends are found with anisole, which cannot ionise under these conditions. (2) Anionic and cationic detergents both cause upfield shifts in the order *para* > *meta* > *ortho*.

Nevertheless, we have investigated the phenomenon of pK_a changes of phenols with respect to their n.m.r. spectra using *p*-n-octylphenol, which, having some of the properties of detergents, incorporates into micelles in an unambiguous orientation (see below). The aromatic protons of this compound are resolved at 100 MHz and the data in Table 2 shows the effect of pH(D) and anionic and cationic detergents upon the n.m.r. spectra.

An anionic detergent should depress the ionisation of a phenol and, since the more electron-rich anion has a higher chemical shift, a net downfield shift should take place. Conversely, a cationic detergent should enhance the ionisation, raising the concentration of anion and hence the chemical shifts should move upfield. The data in Table 2 are in agreement with this expectation.

Orientation Effects.—Intermolecular anisotropic effects in n.m.r. spectra are known for large aromatic compounds such as porphyrins [14] at moderate concentrations in organic solvents such as chloroform. The aggregation behaviour responsible for these shifts can be related to the chemical shift changes observed through preferred orientation to minimise steric interactions between substituents. Such effects are, however, unlikely in dilute aqueous solutions of phenol and anisole which are extensively solvated by water. It is particularly hard to understand how the continuous trend of *para* > *meta* > *ortho* can be rationalised by intermolecular anisotropic effects especially at high detergent concentrations. Consequently the most probable major cause of the changes in the n.m.r. spectra that we have observed is an average preferred orientation of the solubilisate.

To establish orientation of solubilisate as the major mechanism causing n.m.r. changes, we have examined the spectra of *p*-n-octylphenol in CTAB and SDS micelles at 100 MHz. This solubilisate is itself an amphiphile and must orient itself in the micelle with the hydroxy-group in the region of the head groups. Figure 4 shows

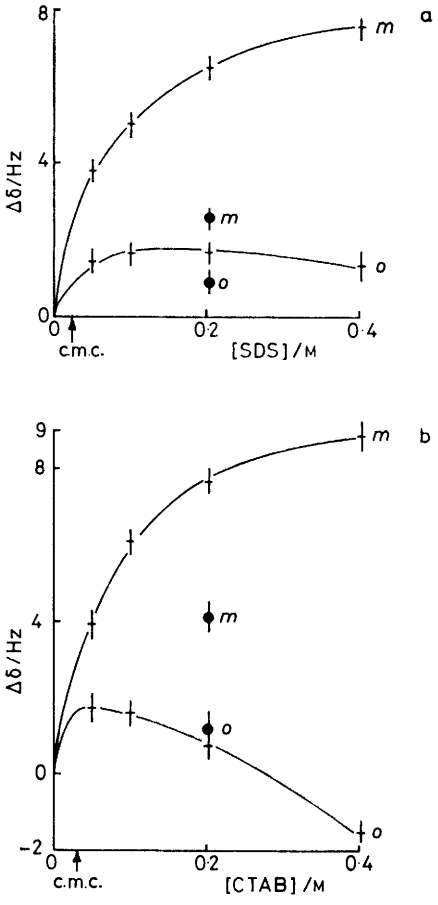

FIGURE 4 Chemical shift changes for 4-*p*-octylphenol as a function of [detergent]. [*p*-$C_8H_{17}C_6H_4CH$] = 30 mM in 1 : 1 v/v CD_3CN–D_2O

that the changes in chemical shift follow the pattern expected on the basis of the behaviour of phenol and anisole, namely the protons *ortho* to hydroxy showed a smaller upfield shift than the *meta*-protons. Since the orientation of this molecule in the micelle is defined by its structure, it is reasonable to ascribe the differential chemical shift changes to the different polarities of the average environments of the *ortho*- and *meta*-protons. That is the proton in the less polar average environment (*meta*) is shifted upfield more than the proton in the more polar average environment (*ortho*). Similar results have been obtained for other n-alkylphenols,[10] although at saturating concentrations of solubilisate.

If this explanation is correct, then a direct comparison of n-octylphenol can be made with the more mobile

solubilisate, *p*-cresol. Since the average environments of such a small molecule will be more varied than with the amphiphilic n-octylphenol, a smaller differential chemical shift change would be expected. Experiment agrees with these expectations as the data points (●) plotted on Figure 4 show. A further structural variation that would support the orientation explanation is to examine an n-

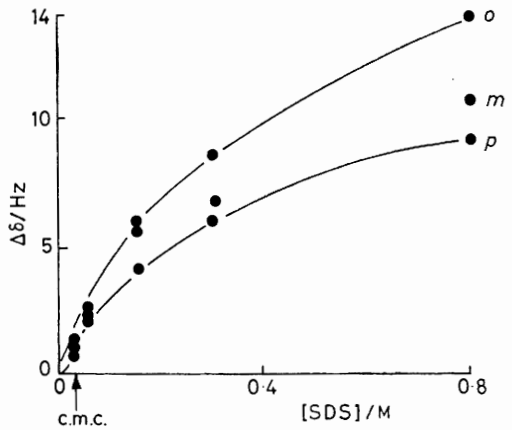

FIGURE 5 Chemical shift changes for hexyl phenyl ether as a function of [SDS]. [$C_6H_{13}OPh$ = 30 mM in 6:4 v/v CD_3CN–D_2O

alkyl ether of phenol with a sufficiently long alkyl group to encourage its preferential solubilisation by the micelle instead of the phenyl group, as is the case with anisole. In micelles of SDS, differential chemical shift changes can be observed for n-hexyl phenyl ether at 360 MHz and the chemical shift changes over a range of concentrations are plotted in Figure 5. Compared with phenol and anisole, the changes were smaller, due probably to the higher concentration of organic solvent, but most significantly, the *ortho*-proton now experienced a greater shift than either *meta*- or *para*-protons. This result indicates a preferred average orientation of n-hexyl phenyl ether in the opposite sense to phenol and anisole (Figure 6).

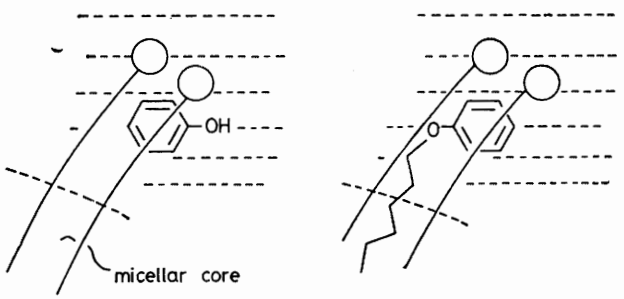

FIGURE 6 Schematic representation of average binding orientations of phenol (anisole) and hexyl phenyl ether in micellar solution

Effect of Head Groups.—The data plotted in Figures 2 and 3 reveal that the pyridinium head group had the largest effect on the n.m.r. spectra. To ascertain whether this was due to a head group–solubilisate interaction, we examined the n.m.r. spectra of phenol with isolated head group ions in methanolic solution. Methanol was chosen as a solvent to approximate to the polarity of the polar micellar groove. The results (Table 3) showed that only small changes were caused and then downfield, in the opposite sense to the effect of micelles. Possibly this simply reflects the increased ionic strength caused by salts.

TABLE 3

Effects of salts upon the n.m.r. spectra of phenol

		Δδ/Hz		
Salt	[Salt]/mM	*o*	*m*	*p*
N-Methylpyridinium iodide	30	0	0	0
	300	0	−3.2	−2.9
Tetramethylammonium bromide	30	−0.61	−0.49	0
	180	−2.9	−2.5	−1.9
	(satd.)			
Potassium methyl sulphate	30	0	0	0
	122	0	0	0
	(satd.)			

Solutions contained phenol (30mM).

Orientation and Selectivity.—It is significant that in some reactions of phenol and its ethers, selectivity changes in substitution have been caused by detergents.[1-3] We have found [1] that chlorination of phenol is promoted at the *ortho*-position by SDS micelles, and conversely, Jaeger and Robertson have shown that enhanced *para*-chlorination can be obtained for n-pentyl phenyl ether in the presence of SDS.[3] These results are readily understandable in terms of the average orientations illustrated in Figure 6. The protons showing the largest shift changes are in the less polar environments where the micellar polymethylene chain obstruct approach of the reagent. The effects are not large (2—5 fold), but it will be shown [15] that the higher selectivity that we have observed in hydroxylation reactions also correlates with orientation effects observed in n.m.r. spectra. Complications arise with changes in head group. Neither we [16] nor Jaeger and Robertson [3] observed significant chemical selectivity changes when cationic detergents were used. This may be due to repulsion between the electrophile and the cationic head group. For selective functionalisation purposes, it is clearly important for the approach of the reagent to be controlled.

The results discussed above illustrate the use of ^1H n.m.r. spectroscopy as a probe for average orientation and solubilisation of small aromatic molecules in micellar systems. Information obtained from such studies will be of great value in the development of novel selective functionalisation systems.

EXPERIMENTAL

SDS was obtained from Fisons (specially purified grade), CTAB was obtained from B.D.H., and CPC from Aldrich. CPC was recrystallised from ethyl acetate to analytical purity. Phenol and anisole were purified by distillation. n-Hexyl phenyl ether and *N*-methylpyridinium iodide were prepared by alkylation of the parent compound with hexyl bromide and methyl iodide respectively. *p*-n-Octylphenol was obtained from the late Dr. A. J. Hyde, Strathclyde. Tetramethylammonium bromide and potassium methyl sulphate were reagent grade chemicals from B.D.H.

100 MHz ^1H N.m.r. spectra were obtained on a JEOL PS100 spectrometer operating in the Fourier transform

mode. 360 MHz ^{1}H N.m.r. spectra were obtained on the Bruker WH 360 spectrometer at Edinburgh University with the assistance of Drs. I. Sadler and A. Boyd. CD_3CN or CD_3OD was used as internal lock and the residual protons as internal standard.

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