

¹H N.m.r. Studies of the Orientation of some Aromatic Compounds by Amphiphilic Molecules and its Relationship to Regioselectivity in Substitution

By COLIN J. SUCKLING and ALAN A. WILSON

(Department of Pure and Applied Chemistry, University of Strathclyde, Thomas Graham Building, Cathedral Street, Glasgow G1 1XL)

Summary ¹H N.m.r. spectroscopy of mono- and di-substituted phenols and their ethers in micellar solutions of anionic and cationic detergents reveals non-uniform upfield shifts of the different protons in the solubilisate; these shifts can be rationalised in terms of a preferred average orientation of the solubilisate in the micelle.

THE use of a micellar-based system to control the selectivity of an organic reaction is attractive because of the simple construction of the system, but practical difficulties in work-up and small changes in stereo- or regio-selectivity usually obtained are major drawbacks. In order to improve the performance of such systems it would be useful

to have a probe of the way in which an amphiphilic molecule orients a solubilisate. In none of the cases of regioselectivity in micellar-based systems so far described has pertinent evidence been presented.¹⁻³ ¹H N.m.r. spectroscopy has been used to detect the general solubilisation sites of aromatic molecules in micelles,^{4,5} but lack of resolution or the use of saturating solubilisate concentrations have prevented the detection of any orientation details.

We have found that mono- and di-substituted derivatives of phenols show significant changes in their ¹H n.m.r. spectra in micellar solution. Phenol in micellar sodium dodecyl sulphate (SDS) is typical. Thus, a 30 mM solution in CD₃CN-D₂O (1:9 v/v) in the presence of SDS (5 mM), a concentration well below the critical micellar concentra-

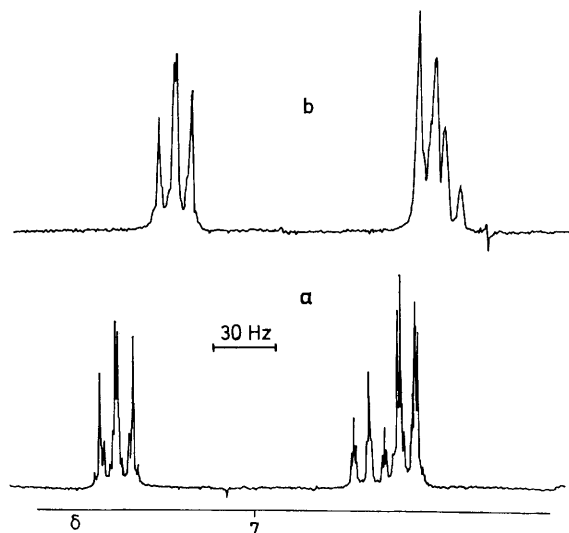


FIGURE 1. ^1H N.m.r. spectra of phenol: (a) 5 mM SDS; (b) 300 mM SDS.

tion (c.m.c.) (25 mM in this solvent system) at 360 MHz gave the spectrum shown in Figure 1a. In the presence of micellar SDS (300 mM) a substantial upfield movement in the chemical shifts of all protons was evident (Figure 1b).[†] As can be seen from Figure 2, the changes in chemical shift are concentration dependent and are non-uniform at concentrations above the c.m.c.

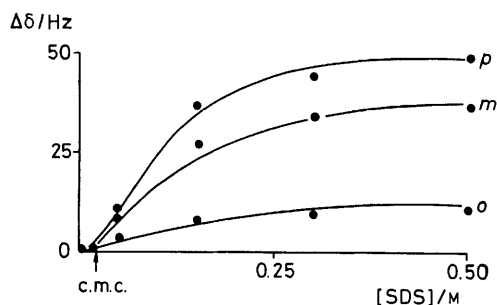


FIGURE 2. Graph of chemical shift changes ($\Delta\delta$) for the protons of phenol (30 mM) as a function of [SDS].

TABLE. ^1H N.m.r. data for aromatic solubilisates in micellar solution.

Solute (30 mM)	Detergent	Maximum [Detergent]		C.m.c. /mM	Maximum chemical shift change/Hz			K/N^b /dm ³ mol ⁻¹
		/mM	Solvent ^a		<i>o</i>	<i>m</i>	<i>p</i>	
Phenol	SDS	500	1	25	11.2	37.4	50.0	33
Phenol	CTAB	200	1	2.2	-7.72	43.02	71.33	62
Phenol	CPC	300	1	11	22.0	74.3	94.6	138
Anisole	SDS	500	1	25	39.6	43.6	48.4	62
Anisole	CTAB	400	2	5.8	11.98	16.94	22.5	70
Anisole	CPC	150	1	11	54.46	58.1	69.1	—
Anisole	<i>N</i> -dodecyl-2-hydroxybenzylamine	60	3	5	10.0	11.7	12.5	—

^a Solvents: 1, $\text{CD}_3\text{CN}-\text{D}_2\text{O}$ (1:9 v/v); 2, $\text{CD}_3\text{OD}-\text{D}_2\text{O}$ (1:1 v/v); 3, $\text{CD}_3\text{CN}-\text{D}_2\text{O}$ (1:2 v/v) containing 0.04 M NaD_2PO_4 (pD 5.8).

^b K/N = binding constant per micelle/aggregation number.

[†] ^1H N.m.r. spectra were recorded at 360 MHz on a Bruker WH-360 spectrometer at 25 °C. CD_3CN was used as an internal lock and the residual protons were used as the internal reference (1.93 p.p.m. from Me_4Si).

The same pattern of behaviour was observed with phenol in the presence of cationic detergents [cetyltrimethylammonium bromide (CTAB) and *N*-cetylpyridinium chloride (CPC)] (cetyl = hexadecyl), and with anisole in the presence SDS, CTAB, CPC, and *N*-dodecyl-2-hydroxybenzylamine. In all cases the *ortho* proton was shifted upfield the least and the *para* proton the most. However, the magnitude of the change in chemical shifts varied with the head group of the detergent (Table). For those cases in which a limiting chemical shift change was observed at concentrations of detergent below saturation, it was possible to calculate a binding constant for solubilisate and micelle. The values obtained are in the same range as those obtained for phenols by Bunton and Sepulveda⁶ by absorption spectroscopy.

Many effects might contribute to the production of differential chemical shifts in micellar solution. Electronic effects (such as those produced by $\text{p}K_a$ changes in phenol on micellar solution) are clearly inconsistent with the data in the Table since both anionic and cationic detergents produce the same gross effect with an ionisable and non-ionisable solubilisate. The head groups influence the observed spectroscopic properties and it is possible that anisotropic interactions of the head group and solubilisate contribute to the changes measured, especially in the case of the pyridinium group, which produced the greatest shifts. However, a possible general phenomenon that underlies all the trends observed is that the micelles solubilise aromatic compounds in a preferred average orientation. The observed spectra are, of course, time-averaged because the rate of exchange of solubilisate and micelle monomers with bulk solvent and micelles is rapid on the n.m.r. time scale. Consequently, a precise micellar-solubilisate structural relationship cannot be defined from n.m.r. data, especially since the detailed structure of micelles is still uncertain. If Menger's model of micellar structure⁷ is adopted, three environments for the solubilisates can be considered, *viz.* the micellar core, the hydrated micellar grooves, and the bulk aqueous phase. It is then conceivable that the major source of the observed chemical shift changes is an average orientation of the solubilisate such that the polar end of the molecule resides on average in the hydrated grooves and the non-polar end interacts with the polymethylene chains of the detergents. This average orientation would cause a greater upfield shift of the *para* protons than of the *ortho* ones as we observed, since the latter will have the less polar average environment.⁴

To test this concept we examined an amphiphilic phenol, *p*-n-octylphenol, in micellar solutions of SDS and CTAB. The structure of this solubilise predetermines the orientation. The results obtained at 100 MHz are shown in Figure 3 and the close similarity between the behaviour of *p*-n-octylphenol and phenol is obvious. Further support for

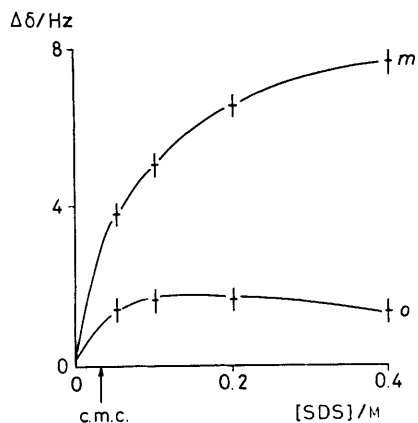


FIGURE 3. Graph of chemical shift changes ($\Delta\delta$) for the protons of *p*-n-octylphenol (30 mM) in micellar solution in $\text{CD}_3\text{CN}-\text{D}_2\text{O}$ (1:1 v/v).

the importance of orientation effects was obtained using *n*-hexyl phenyl ether, spectra of which were obtained at 360 MHz. In this case it might be anticipated that, on average, the *n*-hexyl chain will penetrate the micellar core more effectively than the rigid phenyl ring. If this is so, then the greatest shift on micellar solution should be observed for the *ortho* proton and this was observed (Figure 4).

On the basis of the above results it seems reasonable to suggest that the major effect producing differential chemical shifts is the average orientation of the solubilise in the micelle. If this is so, then such an orientation should be reflected in regioselectivity in aromatic substitution in micellar solution. For a reagent approaching from the aqueous phase or within the micellar groove, a solubilise such as phenol should undergo enhanced *ortho* substitution. Menger¹ has advanced this hypothesis for the nitration of bromobenzene in micellar solution. In a similar way, the enhanced *ortho* hydroxylation of anisole observed in our earlier work³ can be rationalised.⁸ We have also shown that, under conditions parallel to those of the n.m.r. experiments, *ortho* chlorination of phenol by *t*-butyl hypochlorite is

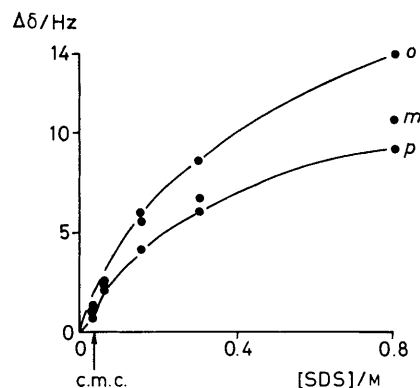


FIGURE 4. Graph of chemical shift changes ($\Delta\delta$) for the protons of *n*-hexyl phenyl ether (30 mM) in micellar solution in $\text{CD}_3\text{CN}-\text{D}_2\text{O}$ (6:4 v/v).

promoted (*o*:*p* ratio increases by a factor of about 2) in concentrated micellar solutions of SDS. Conversely, if a molecule adopts the opposite average orientation to that of phenol, the effect of micelles upon the regioselectivity should be reversed. Jaeger and Robertson² have shown that this is the case for chlorination of pentyl phenyl ether in micellar solutions of SDS: up to a 5-fold increase in *para* chlorination was observed.

In the examples outlined above, the average orientations of aromatic molecules probed by ¹H n.m.r. spectroscopy are reflected in the regioselectivity of aromatic substitution, and some limited insight into the origins of selectivity is provided. There are, of course, many other factors that influence selectivity; the location of the electrophile, for example, must be considered. Also, a detailed understanding of the n.m.r. observations depends greatly upon the poorly defined micellar structure. Nevertheless, the gross effects observed will be of assistance in the design of more efficient regioselective oxidation systems.

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