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Nuclear magnetic resonance studies of interactions between oxyethylene-oxypropylene polymer, macrogol and phenol

The interactions occurring between phenol and cetomacrogol have been examined using nuclear magnetic resonance (nmr) spectroscopy. The changes of chemical shift of the various protons have been interpreted in terms of the changes of environment which occur during solubilization (Jacobs, Anderson & Watson, 1971b). The investigation has been extended to include the interactions of phenol with an oxyethylene polymer macrogol ("Carbowax" 4000, Union Carbide) and an oxyethylene-oxypropylene block polymer POEPOP ("Pluronic F68", Wyandotte Chemicals). The phenol used was reagent grade; water was freshly distilled from an all-glass still. Spectra were obtained and treated as described previously (Jacobs, Anderson & Watson, 1971b).

Macrogol. Aqueous systems containing phenol and macrogol are clear if the ratio of macrogol to phenol is sufficiently high, but are turbid if this ratio is low. The turbidity is due to the separation of a phenol-macrogol-rich phase. The two phases occurring in the system containing 3% phenol and 6% macrogol were separated and the composition of the phenol-macrogol-rich phase determined from the integrated nmr spectrum; the molar ratio of phenol : ethylene oxide units : water was about 3 : 8 : 10.5.

The nmr signals from the phenol ring protons shift upfield with increasing macrogol concentration, but the magnitude of these shifts are small compared to those previously observed in corresponding cetomacrogol-phenol and sodium dodecyl sulphate-phenol systems (Table 1). The smaller shift is consistent with the absence of micelles from solutions of macrogol in water, so that most of the phenol molecules remain in an essentially aqueous environment; the small upfield shift would then be explained as interaction of some fraction of the phenol molecules with the macrogol chains.

Addition of phenol to aqueous macrogol also causes the signal from the macrogol

Table 1. *Changes of chemical shift of ring protons of phenol (2%) in the presence of other agents with respect to signals of 2% phenol in water (all systems clear).*

Concentration of agent		Upfield shift (Hz)
Macrogol	10%	0.5
	15%	0.8
	20%	1.0
		} (<i>ortho</i> , <i>meta</i> and <i>para</i> protons)
Cetomacrogol ¹	10%	3.7 (<i>ortho</i> protons)
		8.0 (<i>meta</i> and <i>para</i> protons)
Sodium dodecyl sulphate ²	10%	3.3 (<i>ortho</i> protons)
		7.4 (<i>para</i> protons)
		9.0 (<i>meta</i> protons)
	20%	3.5 (<i>ortho</i> protons)
		9.2 (<i>meta</i> protons)

¹ From Jacobs & others (1971b).

² From Jacobs & others (1971a).

protons to shift upfield (Fig. 1) but, in contrast to the corresponding cetomacrogol systems, the signal remains a singlet and no broadening was observed. In the presence of 2% phenol, concentrations of macrogol above about 10% give clear systems; as the macrogol concentration increases and the phenol to macrogol ratio falls, the upfield shift with respect to the signal from the corresponding macrogol solution in water is reduced. When the phenol concentration is increased to 3%, turbid systems are obtained with up to 20% macrogol and there are upfield shifts of macrogol protons in the aqueous phase of such systems. Upfield shifts become larger with increase in (overall) macrogol concentration suggesting some degree of aggregation of the macrogol molecules in the aqueous phase, perhaps because of interaction of some phenol molecules with some of the ether oxygens to give complexes that are less hydrophilic and are subject to aggregation. These aggregates could take a form similar to micelles, and the overall result would be that the macrogol protons are in a less-polar environment than in the corresponding macrogol-water system.

As with cetomacrogol systems previously studied, increasing macrogol concentration leads to upfield shifts of the water proton signals due to disruption of water structure.

POEPOP. Oxyethylene-oxypropylene block polymers exhibit surface activity and may form micelles. The polymer we used has polyoxyethylene chains making up 80% of the molecule, the remainder being a polyoxypropylene block of molecular weight 1750.

Aqueous systems containing POEPOP and phenol are clear if the ratio of polymer to phenol is sufficiently high, but are turbid if this ratio is low. For example, systems containing 10% POEPOP become turbid if more than 4% phenol is added, whereas 4% POEPOP is required to give clear solutions containing 2% phenol.

Fig. 2 shows the upfield changes of shift of the signals from the phenol ring protons in the presence of POEPOP. These are consistent with the changes observed in corresponding cetomacrogol systems, except that for increasing phenol concentration in 10% POEPOP the upfield shift increases (Fig. 2a) suggesting that the aromatic rings are randomly arranged (in contrast to the more ordered arrangement in cetomacrogol micelles).

There is a much greater initial shift of the methyl signal of the polyoxypropylene chains compared with the polyoxyethylene methylene signal (Fig. 2c), and this is consistent with phenol being "associated" mainly with the polyoxypropylene region

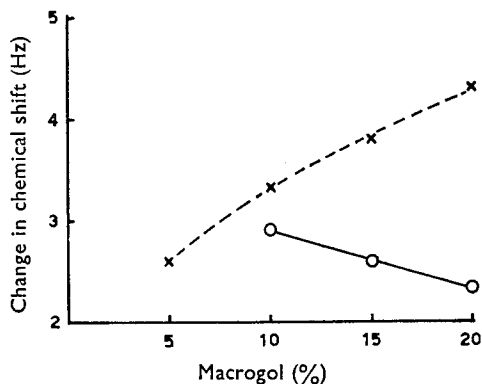


FIG. 1. Changes in chemical shift of macrogol protons in the presence of phenol (measured with respect to the peak positions of corresponding concentrations of macrogol in water). ○ 2% phenol (all systems clear), × 3% phenol (aqueous phase of two-phase system).

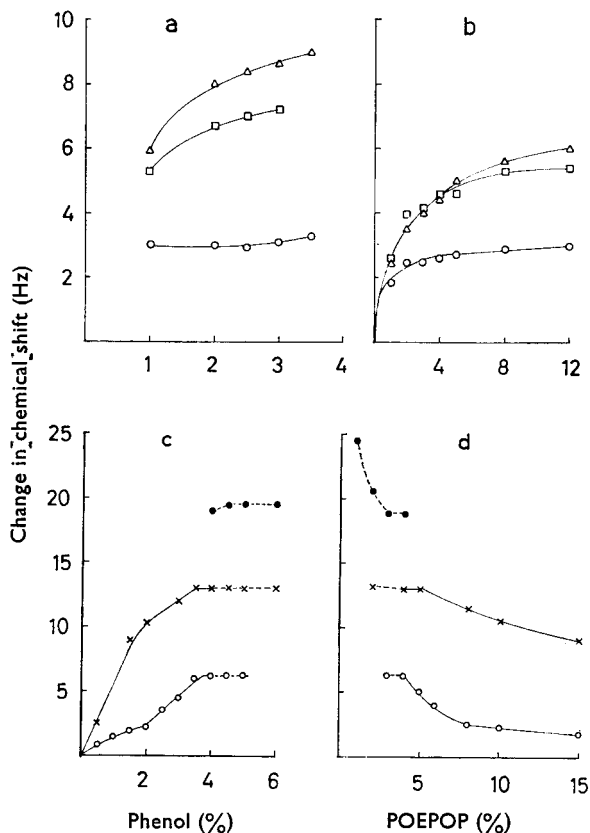


FIG. 2. Changes in chemical shift of: a, b ring protons of phenol; c, d, POEPOP protons. a, varying concentrations of phenol in the presence of 10% POEPOP (measured with respect to the peak positions of corresponding concentrations of phenol in water), b 1% phenol in the presence of varying concentrations of POEPOP (measured with respect to the peak positions of 1% phenol in water). Δ *meta* protons. \square *para* protons. \circ *ortho* protons.

c, 10% POEPOP in the presence of varying concentrations of phenol (measured with respect to the peak positions of 10% POEPOP in water); d, varying concentrations of POEPOP in the presence of 2% phenol (measured with respect to the peak positions of corresponding concentrations of POEPOP in water). \times methyl protons of polyoxypropylene block. \circ methylene protons in "aqueous" phase. \bullet methylene protons in "oily" phase. Broken lines link data from cloudy systems.

at low phenol to polymer ratios. Above about 2% phenol the upfield shift increments of the methyl signal decrease (i.e. the slope of the curve decreases) (Fig. 2c) and the shift increments of the polyoxyethylene methylene protons increase, indicating that as the polyoxypropylene region approaches saturation, relatively more phenol enters the polyoxyethylene region. This is consistent with the data for clear systems shown in Fig. 2d; the initially greater negative slope of the curve representing the methylene protons compared to that for the methyl protons shows that the phenol preferentially remains in the polyoxypropylene region as the polymer concentration is increased.

Fig. 2c also shows that when the system reaches the cloud point at about 4% phenol, both the methyl and the polyoxyethylene methylene shifts are arrested. However a new signal appears at higher field (as was observed in the corresponding phenol-cetomacrogol system) due to the polyoxyethylene protons in the phenol-POEPOP-rich phase. The polyoxypropylene methyl signal appears at the same position in both phases of the cloudy systems indicating that this region is already

completely saturated in the aqueous phase. The polyoxyethylene signal from the aqueous phase disappears at about 5% phenol, indicating that little POEPOP remains in the aqueous phase.

The relatively large shifts shown in Fig 2c and d indicate the presence of micelles in POEPOP-phenol-water systems. This is further supported by the magnitude of the shifts of the phenol ring-proton signals (Fig. 2a and b) which compares with that of the corresponding phenol-cetomacrogol systems, whereas in phenol-macrogol systems, where the aromatic rings are essentially in an aqueous environment, a very small shift is observed.

Significant broadening of both polyoxyethylene methylene and the polyoxypropylene methyl peaks upon the addition of phenol to POEPOP in water is also indicative of micelle formation; the polyoxyethylene peaks (but not polyoxypropylene) also split.

These micelles need not necessarily be aggregates of polymer molecules but could consist of one molecule with the polyoxyethylene chains rolled around the polyoxypropylene region.

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Apomorphine and its dopamine-like action

Observations published a few months ago (Pinder, Buxton & Green, 1971) demonstrating the low dopamine-like potency of aporphine, call for some comment on the problem that has arisen in the relation between apomorphine and dopamine effects. From molecular orbital calculations on dopamine using the extended Hückel theory (Kier & Truitt, 1970) it has been concluded that a *trans* conformation is absent and that only the two *gauche* conformers are significantly populated (Fig. 1A). In consequence Kier & Truitt postulated that an important part of the apomorphine molecule in its interaction with dopamine receptors is the tetrahydroisoquinoline moiety (the combination of *N* with phenyl ring *a* in Fig. 1B). Our calculations* and those of Bustard & Egan (1971) using the extended Hückel theory showed that, in contrast to Kier & Truitt's findings, the *trans* conformation was slightly preferred to the *gauche* conformers. Additional evidence was obtained by Bustard & Egan from potential energy functions and nmr spectroscopy.

In our opinion, it may now be readily assumed that Kier & Truitt's view is conformationally incorrect; hence Pinder, Buxton & Green rightly postulate that, when allowance is made for the low potency of aporphine, apomorphine in producing dopamine-like effects acts in a way which intimately involves the dihydroxytetrahydroaminonaphthalene moiety (the combination of *N* with phenyl ring *b* in Fig. 1B). Fig. 2 shows the Newman projections of the three low-energy dopamine conformers.

* To be published. We have found that rotation of 30° about the phenyl — C₁ axis in the $\theta_{e-e} = 300^\circ$ conformer did not reveal new conformations of low energy.