from Merck and Co. (Rahway, New Jersey, U.S.A.) and Regis Chemical Co. (Chicago, Illinois, U.S.A.), respectively.

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REFERENCES

ANDÉN, N. E., BUTCHER, S. G., CORRODI, H., FUXE, K. & UNGERSTEDT, U. (1970). *Eur. J. Pharmac.*, **11**, 303–314.

AZZARO, A. J., WENGER, G. R., CRAIG, C. R. & STITZEL, R. E. (1972). *J. Pharmac. exp. Ther.*, **180**, 558–568.

BILLIET, M., BERNARD, P., DELAUNOIS, A. & DE SCHAEPDRYVER, A. (1970a). *Archs int. Pharmacodyn. Thér.*, **186**, 179–181.

BILLIET, M., BERNARD, P., DELAUNOIS, A. & DE SCHAEPDRYVER, A. (1970b). *Ibid.*, **188**, 396–400.

DE LA TORRE & MULLAN, S. (1970). *J. Pharm. Pharmac.*, **22**, 858–859.

DE SCHAEPDRYVER, A. F., PIETTE, Y. & DELAUNOIS, A. L. (1962). *Archs int. Pharmacodyn. Thér.*, **140**, 358–367.

ERNST, A. M. (1967). *Psychopharmacologia*, **10**, 316–323.

GRUNDEN, L. R. & LINBURN, G. E. (1969). *J. pharm. Sci.*, **58**, 1147–1148.

JOBE, P. C., PICCHIONI, A. L. & CHIN, L. (1973). *J. Pharmac. exp. Ther.*, **184**, 1–10.

PROCKOP, D. J., SHORE, P. A. & BRODIE, B. B. (1959). *Ann. N.Y. Acad. Sci.*, **80**, 643–650.

SWINYARD, E. A. (1963). *Psychophysiologie, Neuropharmacologie, et Biochemie de la Crise Audiogene*, pp. 405–421, Editions du Centre National de la Recherche Scientifique, Paris, France.

WOODBURY, D. M. & ESPLIN, D. W. (1959). *Proc. Ass. Res. nerv. ment. Dis.*, **37**, 24–56.

Nuclear magnetic resonance studies of cetomacrogol 1000 - benzaldehyde - propyl gallate interactions

The system cetomacrogol 1000–benzaldehyde–propyl gallate–water has been examined by nuclear magnetic resonance spectroscopy.

The work was confined to aqueous systems containing 10% cetomacrogol and propyl gallate and benzaldehyde in concentrations which give clear solutions. These solutions contain spherical micelles and correspond to the L1 systems discussed by Nixon, Ul Haque & Carless (1971).

Spectra were obtained using a Varian T-60 high resolution spectrometer equipped with Perma-lock, T-6055, operating temperature of the probe was 35°.

Chemical shifts were measured by expanding the field to 50 Hz per chart width and are quoted with respect to the positions of the corresponding signals of 10% cetomacrogol 1000 in water.

Details of the experimental techniques, susceptibility corrections and accuracy were described previously (Jacobs Anderson & Watson, 1971).

Nixon & others (1971), from their studies of a series of phase diagrams of the cetomacrogol 1000–water–benzaldehyde–propyl gallate system, found that the solubilization of benzaldehyde by the cetomacrogol micelles was decreased by the addition of propyl gallate. These workers postulated that the decrease in solubility may be the result of competition by the benzaldehyde and propyl gallate for the same binding sites.

Fig. 1 (a) shows that both the polyethylene oxide proton signal and the alkyl methylene proton signal shift to higher fields upon the addition of propyl gallate to solutions of 10% cetamacrogol in water. The shift for the alkyl methylene protons is initially slightly greater than that for the polyethylene oxide protons. The shift

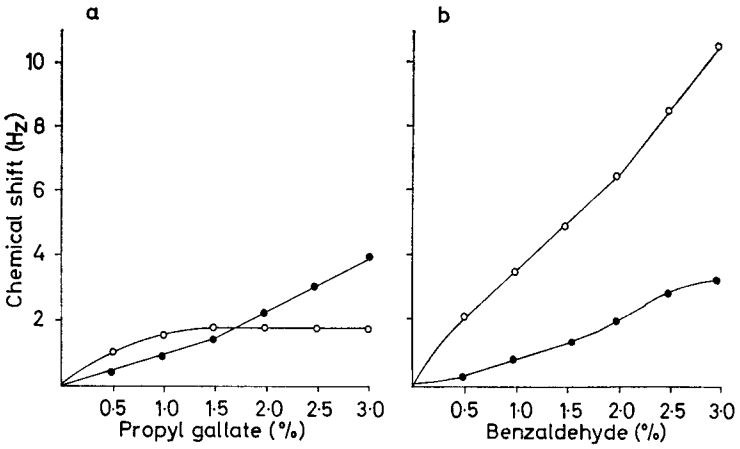

FIG. 1. Changes in chemical shift of cetomacrogol (10%) in the presence of varying concentrations of (a) propyl gallate; (b) benzaldehyde (measured with respect to the peak positions of 10% cetomacrogol in water). ● polyethylene oxide protons; ○ alkyl methylene protons.

increments for the alkyl protons decrease and the shift is arrested at about 1·5% of propyl gallate. The polyethylene oxide signal continues to shift upfield. These results suggest that initially the propyl gallate is present in both regions in approximately the same concentrations, or that the propyl gallate is predominantly located at the alkyl-polyethylene oxide interface. The latter is a more acceptable arrangement since the hydroxyl functions would be hydrogen bonded to the ethereal oxygen atoms of the polyethylene oxide chains with the less hydrophilic part of the molecule extending into the interior of the micelle. As this region approaches saturation, relatively more propyl gallate enters the polyethylene oxide region. This is indicated by the fact that the shift for the alkyl methylene protons is arrested while the signal for the polyethylene oxide protons continues to shift. The low solubility of propyl gallate in non-polar hydrocarbons and its much greater solubility in diethyl ether is consistent with this observation. Increasing the concentration of propyl gallate above 3% causes the separation of a second phase. This effect is also observed in aqueous systems containing 10% cetomacrogol 1000 and phenol in concentrations above 3%. The phenolic hydroxyl functions form hydrogen bonds with the ethereal oxygens of the polyethylene oxide units, leading to loss of bonded water hence making the micelles less hydrophilic.

Fig. 1 (b) shows the shifts for the cetomacrogol protons on addition of benzaldehyde. The much greater shift for the alkyl methylene protons is consistent with a higher concentration of benzaldehyde in the inner region of the micelle. Since no hydrogen bonding is envisaged in this system, the distribution of benzaldehyde between the alkyl and the polyethylene oxide regions of the micelles is considered merely a partition process rather than one of binding. The absence of sharp breaks in the curves of Fig. 1b indicates a gradual increase of the benzaldehyde concentration in both regions, which is consistent with partitioning.

On the other hand, the saturation of the alkyl-polyethylene oxide interface with respect to propyl gallate before saturation of the polyethylene oxide region must be explained in terms of specific binding or adsorption. Fig. 1 indicates therefore that the maximum concentrations of each species occur in different regions with some overlap taking place. This was further demonstrated by obtaining spectra of samples containing cetomacrogol and both benzaldehyde and propyl gallate.

Fig. 2 a shows the chemical shifts of the cetomacrogol signals in the presence of 2% propyl gallate and varying concentrations of benzaldehyde. The observed shifts

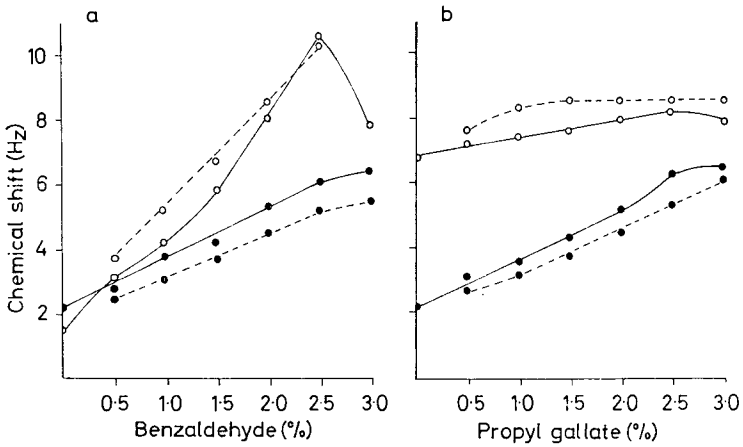

FIG. 2. Changes in chemical shift of cetomacrogol (10%) in the presence of (a) 2% propyl gallate and varying concentrations of benzaldehyde; (b) 2% benzaldehyde and varying concentrations of propyl gallate, (measured with respect to the peak positions of 10% cetomacrogol in water). ● polyethylene oxide protons. ○ alkyl methylene protons. (Broken lines represent shifts calculated by summation of the corresponding shifts of Fig. 1).

are compared with the shift calculated by summing the shifts in Fig. 1 b and the shifts obtained in presence of 2% propyl gallate alone. The decrease in shift at 3% benzaldehyde is due to the formation of a small amount of a benzaldehyde-rich phase. This leads to the loss of relatively large quantities of benzaldehyde from the micelles.

Fig. 2 b shows the chemical shifts of the cetomacrogol signals in the presence of 2% benzaldehyde and varying concentrations of propyl gallate. These shifts are compared with the shifts calculated by summing the shifts in Fig. 1 a and the shifts obtained in presence of 2% benzaldehyde alone. Both figures show that the shifts observed for the alkyl methylene protons are slightly less than those obtained by summation. On the other hand the observed shifts for the polyethylene oxide protons are slightly greater than those calculated. The presumably strongly bonded propyl gallate at the alkyl–polyethylene oxide interface may displace a small fraction of the benzaldehyde from the inner regions of the micelles. The benzaldehyde then preferentially enters the polyethylene oxide region, giving rise to an increased shift for the polyethylene oxide proton signals and a decreased shift for the alkyl methylene proton signals.

The above results indicate only a minor degree of competition at the concentrations used, but this would be sufficient to explain the only slight lowering of the benzaldehyde solubility observed by Nixon and co-workers.

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REFERENCES

JACOBS, J. J., ANDERSON, R. A. & WATSON, T. R. (1971). *J. Pharm. Pharmac.*, **23**, 786–793.
NIXON, J. R., UL HAQUE, R. S. & CARLESS, J. E. (1971). *Ibid.*, **23**, 1–7.