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The self-association in aqueous solutions of morphine sulphate and some related salts

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Conductivity and optical rotatory dispersion investigations suggest that morphine sulphate and some related salts aggregate in aqueous solution. This association is probably due to the stacking of the aromatic rings.

Recently optical rotation and ellipticity have been shown to depend upon the state of aggregation of optically active surfactants (Bonkoski & Perrin, 1968, 1969; Mukerjee, Perrin & Witzke, 1970; Perrin & Witzke, 1971). The change in optical properties was attributed to changes in degree of ionization (Bonkoski & Perrin, 1968, 1969; Perrin & Witzke, 1971) when the differently charged species have dissimilar optical rotatory dispersion (ORD) or circular dichroism (CD) curves and/or a "medium" effect arising from changes in refractive index at the micellar surface (Mukerjee, & others, 1970).

Concentrated solutions of morphine salts appeared to be surface-active (Perrin, unpublished observations), and it was decided to investigate the possible aggregation of some morphine related salts by conductivity and optical rotation. Anomalous ORD curves have been reported for morphine and related compounds (Bobbitt, Weiss & Hanessian, 1959), Cotton effects occurring at wavelengths near 300 nm; these are probably associated with the aromatic rings. Observations at lower wavelengths are complicated by the high absorbances of the compounds.

MATERIALS AND METHODS

Materials

The following salts were used as supplied by the manufacturer. Codeine phosphate U.S.P., codeine sulphate N.F., morphine sulphate U.S.P. (Mallinckrodt, St. Louis, Mo.); hydromorphone hydrochloride (Dilaudid, Knoll Pharmaceutical Co., Orange, N.J.). All solutions were prepared in deionized water.

Methods

The conductivities were measured using a Beckman RC 16B2 conductivity bridge (Beckman Instrument, Cedar Grove, N.J.) at $25 \pm 0{\cdot}01°$. ORD curves were obtained using a Cary Model 60 spectropolarimeter (Applied Physics Corporation, Monrovia, Calif.). The measurements were made at $25 \pm 0{\cdot}2°$ in 5 cm cells, taped to the cell carriage to aid reproducibility. The solutions were scanned at wavelengths between 450–410nm, a region far from any Cotton effect. This minimized absorption by the concentrated solutions necessary for these investigations and enabled a long path-length cell to be used, so increasing the precision of the experiment.

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RESULTS

Fig. 1 shows the plot of specific conductance versus concentration for the four salts investigated. All the curves show breaks which are usually associated with micelle or aggregate formation in ionic surfactants (Mukerjee, 1967). The critical micelle concentrations (cmc) obtained are shown in Table 1. A plot of observed rotation against concentration at a given wavelength also showed a break in all cases. To emphasize the break, a deviation plot was made as shown in Fig. 2. The theoretical rotation at a given concentration was found by multiplying the concentration by the slope of the straight line plot of observed rotation against concentration for concentrations well below the cmc. The deviation at a given concentration is this theoretical rotation minus the observed rotation. The cmc's estimated from these plots are shown in Table 1 together with the wavelength of measurement. The specific rotations [α] in Table 1 are calculated from the formula

$$[\alpha] = \frac{100}{l} \cdot \frac{\Delta \text{ rot.}}{\Delta c}$$

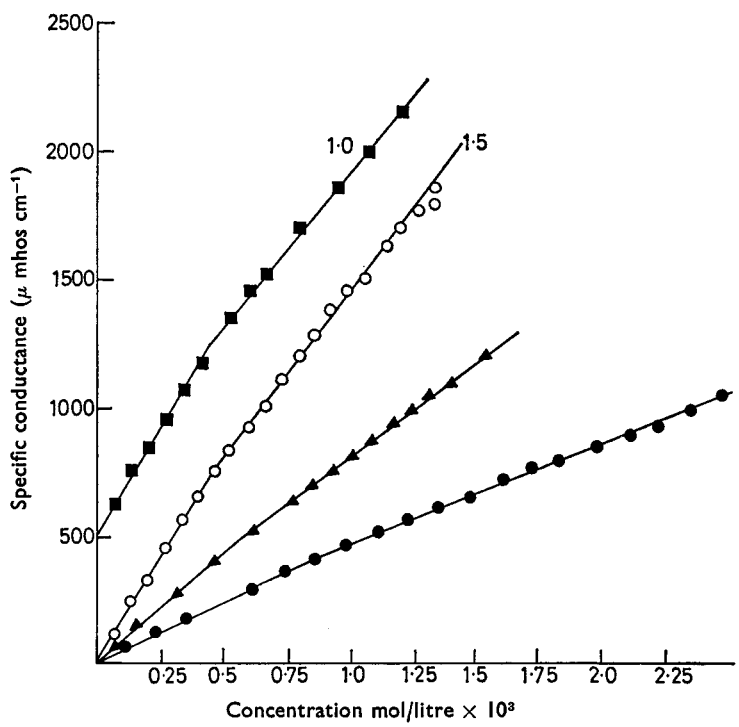

FIG. 1. Specific conductances for the salts of morphine related compounds as a function of concentration. ◆–◆–◆, codeine sulphate; ○–○–○, morphine sulphate; ◀–◀–◀, hydromorphine hydrochloride; ●–●–●, codeine phosphate.

where l = pathlength in decimeters and Δ rot. is the change in rotation in degrees for a change in concentration, Δc, in g/100 g of solution. The wavelengths reported in Table 1 are the lowest, and hence the rotations the highest, at which measurements could be accurately made with the system employed.

Table 1. *Summary of conductivity and ORD data.*

Drug	cmc mol/litre × 10_3		Specific rotations		
	Conductivity	ORD	Below cmc	Above cmc	Wave-length nm
Morphine sulphate U.S.P. $(C_{17}H_{19}NO_3)_2H_2SO_45H_2O$	4·35	4·35	224·0	218·0	420
Codeine phosphate U.S.P. $C_{18}H_{21}NO_3H_3PO_4\frac{1}{2}H_2O$	8·61	8·61	223·2	213·4	427·5
Codeine sulphate N.F. $(C_{18}H_{21}NO_3)_2H_2SO_43H_2O$	4·39	4·00	225·6	236·4	425·0
Hydromorphone hydrochloride $C_{17}H_{11}NO_3HCl$	5·59	4·97	438·6	444·6	415·0

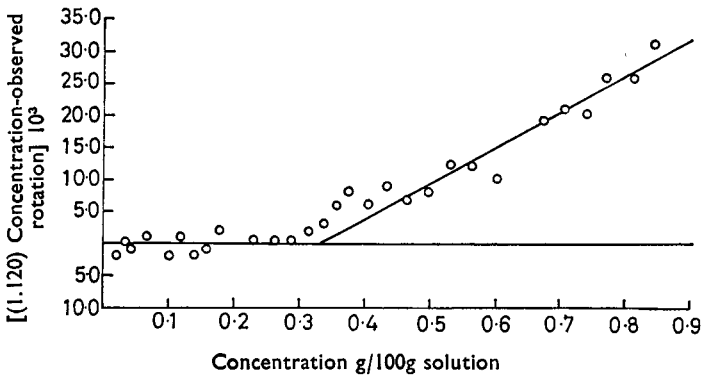

FIG. 2. Interpretation of ORD for morphine sulphate using a deviation plot. The theoretical rotation is calculated from concentration below the cmc (see text).

DISCUSSION

The break in the specific conductance versus concentration curves suggests that these molecules aggregate in large numbers at a well-defined concentration. This association is probably due to the stacking of the aromatic rings. The plots of observed optical rotatory dispersion at a given wavelength also show breaks at similar concentrations to the cmc's found by conductivity. The cmc's of the sulphates of morphine and codeine are very similar, suggesting the substitution of the methoxy for the hydroxy has little effect on the stacking of the molecules in the aggregate. From Table 1 it can be seen that a mole of codeine sulphate contains twice the number of equivalents of codeine as does the phosphate, and in terms of equivalents the cmc's of the two salts are similar and the cmc's appear to be independent of these counterions. The molecules are not planar and the packing could involve some sort of helical arrangement. The loss of the double bond and the substitution of the keto for the hydroxy group in hydromorphone does not seem from models to greatly alter the shape of the molecule as far as the proposed stacking is concerned. The cmc of hydromorphone (Table 1) is approximately 20% higher than the other drugs. The hydrochloride of hydromorphone is very much more soluble in water than are the hydrochlorides of codeine and morphine (Merck Index, 1968). This suggests that the base is more hydrophilic than the codeine and morphine, probably due to the keto group hydrogen bonding with the water molecules. It is also possible that

the hydromorphone molecules could associate by the interaction of the phenolic group of a second molecule. This type of interaction as well as the increased hydrophilicity of the hydromorphone are competitive reactions to the predominantly hydrophobic reaction envisioned for the aggregate formation, and so would result in the higher observed cmc. The reasons for the changes in the specific rotations on micelle formation are difficult to evaluate at these wavelengths so far from the absorption maximums, and as can be seen from the data in Table 1 no general trend is noticed. The rotation of codeine sulphate is enhanced on micelle formation. whereas codeine phosphate is not. This is possibly due to the different degrees of ionizations of the two salts in the micellar and non-micellar forms. The morphine sulphate, unlike codeine sulphate, shows a decrease in rotation, on aggregation yet both have similar basic pK_a's (Merck Index, 1968) and so differing degrees of ionization are unlikely to explain the observations. Interpretation of these changes involves investigation of the medium effect (Bonkoski & Perrin, 1969) and the changes in ionization on micelle formation (Bonkoski & Perrin, 1968, 1969; Perrin & Witzke, 1971). This is currently being attempted using circular dichroism to investigate the optical changes.

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REFERENCES

BOBBITT, J. M., WEISS, U. & HANESSIAN, D. D. (1959). *J. org. Chem.*, **24**, 1582–1585.
BONKOSKI, S. & PERRIN, J. H. (1968). *J. Pharm. Pharmac.*, **20**, 934–940.
BONKOSKI, S. & PERRIN, J. H. (1969). *J. pharm. Sci.*, **58**, 1428–1429.
MERCK INDEX (1968). 8th edn. Rahway, N. J.: Merck and Co.
MUKERJEE, P. (1967). *Adv. Colloid Inter. Sci.*, **1**, 241–175.
MUKERJEE, P., PERRIN, J. & WITZKE, E. (1970). *J. pharm. Sci.*, **59**, 1513–1515.
PERRIN, J. H. & WITZKE, E. (1971). *J. Pharm. Pharmac.*, **23**, 76–77.