# Self-association of analgesics in aqueous solution: micellar properties of dextropropoxyphene hydrochloride and methadone hydrochloride

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The solution properties of several analgesics including dextropropoxyphene hydrochloride, methadone hydrochloride, dextromoramide acid tartrate and dipipanone hydrochloride have been examined using light scattering, conductivity, vapour pressure osmometry and surface tension techniques. A micellar pattern of association was established for dextropropoxyphene hydrochloride and methadone hydrochloride and critical micelle concentrations and aggregation numbers are reported. The hydrophobic contribution to the free energy of micellization of dextropropoxyphene was determined from measurements of the critical micelle concentration in the presence of added electrolyte.

Previous studies have shown that amphiphilic drugs with hydrophobic regions based on the diphenylmethane moiety aggregate in solution by a micellar process. Such drugs have included compounds with antiacetylcholine (Attwood 1976) and antihistaminic (Attwood 1972; Attwood & Udeala 1974, 1975a, b) activity.

In this present investigation, the physicochemical properties of several diphenylmethane analgesics is examined. Of those compounds reported here, only dextropropoxyphene has previously been reported to form aggregates in aqueous solution. Conine (1965) has demonstrated the ability of this drug to solubilize sparingly water-soluble organic acids and has reported a critical micelle concentration (cmc) of $0.14 \ mol \ kg^{-1}$ from freezing point depression measurements. Thakkar et al (1970) using n.m.r. techniques have shown evidence of hydrophobic interactions in aqueous solutions of dextropropoxyphene at high concentration.

## MATERIALS AND METHODS

*Materials.* The following drugs were sufficiently well characterized and purified by the manufacturers to be used without further purification; methadone hydrochloride B.P. ($\pm$)-6-dimethylamino-4,4-diphenylheptan-3-one hydrochloride (Wellcome); dextropropoxyphene hydrochloride B.P. ($+$)-α-4-dimethylamino-3-methyl-1,2-diphenylbut-2-yl propionate hydrochloride (Lilly Research Centre),

dipipanone hydrochloride B.P. ($\pm$)-4,4-diphenyl-6-piperidinoheptan-3-one hydrochloride monohydrate (Wellcome) and dextromoramide acid tartrate ($+$)-1-(3-methyl-4-morpholino-2,2-diphenylbutyryl) pyrrolidone acid tartrate (M.C.P. Pharmaceuticals).

Sodium chloride was Analar grade and water for surface tension and conductivity measurements was distilled from alkaline permanganate in an all-glass still.

*Light scattering measurements.* Measurements were made at 303K using a Fica 42000 photogoniodiffusometer (A.R.L. Ltd) at a wavelength of 546 nm. Solutions were clarified by ultrafiltration through $0.1 \ \mu m$ Millipore filters until the ratio of the light scattering at angles of 30° and 150° did not exceed 1·10. The refractive index increments of the micellar species, $(dn/dm_2)$ determined at 546 nm using a differential refractometer were methadone hydrochloride, 0·064; dextropropoxyphene hydrochloride, 0·069; dipipanone hydrochloride, 0·070 and dextromoramide acid tartrate, $0.095 \ kg \ mol^{-1}$. Addition of electrolyte to solutions of dextropropoxyphene had no significant effect on the refractive index increment.

*Conductivity measurements.* Measurements were made at $303 \pm 0.01K$ using a Wayne Kerr Autobalance Universal Bridge Model B641.

*Surface tension measurements.* The drop-volume method of determining surface tension was used. An Agla micrometer syringe fitted with a carefully ground brass tip was immersed in a thermostat bath at $303 \pm 0.05K$. The tip was surrounded by an atmosphere saturated with solvent vapour.

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*Vapour pressure osmometry.* A Hewlett Packard 302B vapour pressure osmometer calibrated with mannitol solutions of known activity was used at 303K.

## RESULTS AND DISCUSSION

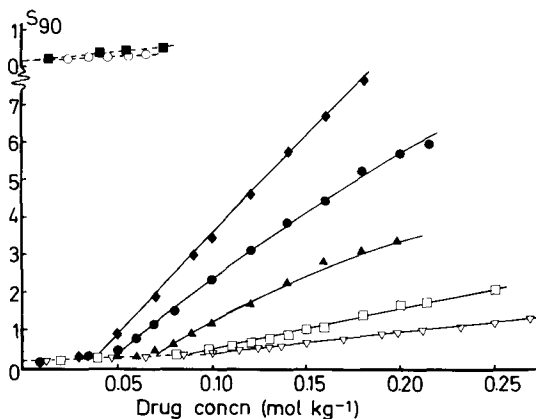Fig. 1 shows clear inflection points in plots of light scattering intensity at a scattering angle of 90°, $S_{90}$,



FIG. 1. Variation of the light scattering ratio, $S_{90}$ with concentration for □, dextropropoxyphene HCl; ▽, methadone HCl; ■, dextromoramide acid tartrate and ○, dipipanone HCl in $H_2O$ and dextropropoxyphene HCl in the presence of ▲, 0·1, ●, 0·3 and ◆, 0·5 mol $dm^{-3}$ sodium chloride. (– – –) theoretical light scattering from unassociated monomers.

against concentration for dextropropoxyphene hydrochloride and methadone hydrochloride in water and dextropropoxyphene hydrochloride in the presence of added electrolyte. The effective thermodynamic charge, p, and the micellar aggregation number, N, were evaluated using equations proposed by Anacker & Westwell (1964).

$$p = [2fm_3B \pm (8m_3B)^{\frac{1}{2}}]A^{-1}(2 - fA)^{-1} \quad .. \quad (1)$$

$$N = p(p + 1)A(2m_3B + pA^2)^{-1} \quad .. \quad (2)$$

A and B are the intercept and slope respectively of plots of $Km_2/\Delta R_{90}$ against the molal concentration of micelles, $m_2$. $\Delta R_{90}$ is the Rayleigh ratio of the solution in excess of that of a solution at the cmc; $K = 2\pi^2 n_0^2 (dn/dm_2)^2_{m_3} V^0/L\lambda^4$; $n_0$ is the refractive index of the solvent, $V^0$ is the volume of solution containing 1 kg of water, L is the Avogadro constant; $\lambda$ is the wavelength of the incident light, $m_3$ is the molality of supporting electrolyte and f = $(dn/dm_3)_{m2}/(dn/dm_2)_{m3}$. In the derivation of equations 1 and 2, unassociated monomers are considered to be part of the supporting electrolyte and hence

in the absence of added salt, $m_3$ may be equated with the cmc and the ratio f becomes unity. Micellar properties are summarized in Table 1.

Table 1. Micellar properties of methadone hydrochloride and dextropropoxyphene hydrochloride.

| Salt concn mol $kg^{-1}$) | p | N | α | cmc (mol $kg^{-1}$) | | | |
|---|---|---|---|---|---|---|---|
| | | | | Light scatt. | Sur. tens. | Conduc. | V. press |
| Methadone HCl | | | | | | | |
| 0 | — | 3 | — | 0·098 | 0·110 | 0·099 | 0·096 |
| Dextropropoxyphene HCl | | | | | | | |
| 0 | 1·9 | 7·3 | 0·26 | 0·100 | 0·100 | 0·102 | 0·102 |
| 0·1 | 3·3 | 12·7 | 0·26 | 0·070 | — | — | — |
| 0·3 | 3·8 | 16·5 | 0·23 | 0·046 | — | — | — |
| 0·5 | 8·6 | 29 | 0·30 | 0·037 | — | — | — |

Measurements on dipipanone hydrochloride and dextromoramide tartrate were limited by their low solubilities. Fig. 1 shows that the light scattering data for solutions of these compounds could be represented up to their solubility limits by the theoretical light scattering lines calculated assuming ideality, for unassociated monomers.

Cmc values of dextropropoxyphene hydrochloride and methadone hydrochloride from conductivity (Fig. 2), surface tension (Fig. 3) and vapour pressure osmometry (Fig. 4) were in reasonable agreement with those from the light scattering method (see
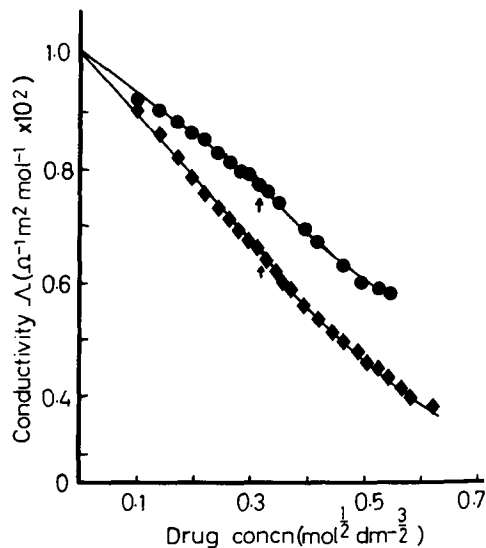


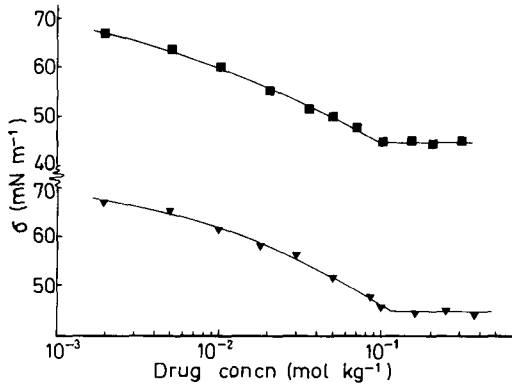FIG. 2. Molar conductivity, $\Lambda$ of aqueous solutions of ◆, dextropropoxyphene HCl; and ●, methadone HCl.

FIG. 3. Surface tension, $\sigma$ as a function of log molal concentration for aqueous solutions of ■, dextropropoxyphene HCl and ▼, methadone HCl.



FIG. 5. Log cmc against log counterion concentration for dextropropoxyphene HCl in the presence of sodium chloride. Concentrations are expressed as mole fractions.

Table 1). Limiting areas per molecule were determined from the surface tension data using the Gibb's adsorption equation.

$$\Gamma = -\frac{1}{(x2{\cdot}303RT)}\left[\frac{d\sigma}{d\log m}\right] \quad .. \quad .. \quad (3)$$

$x$ has a numerical value varying from 1 for ionic surfactants in dilute electrolyte-free solution to 2 in concentrated electrolyte-free solution (Pethica 1954). Limiting areas per molecule of 0·52 and 0·54 nm² were calculated for methadone and dextropropoxyphene respectively assuming $x = 1$. In view of the uncertainty in the value of $x$ it is possible that these surface areas represent an underestimation of the true values. The limiting areas per molecule
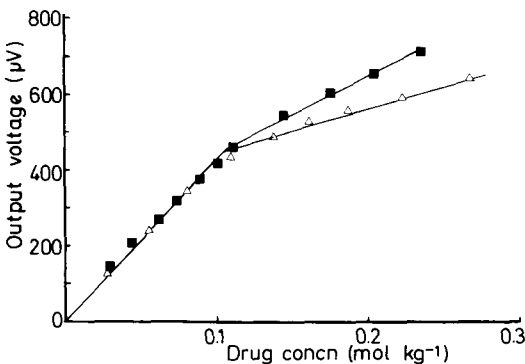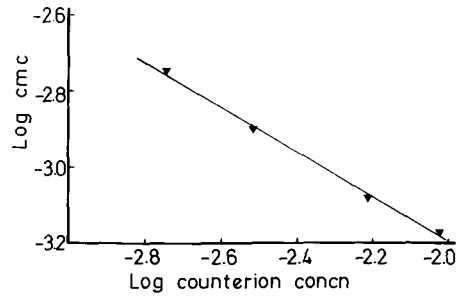


FIG. 4. Output voltage of vapour pressure osmometer against concentration for aqueous solutions of △, dextropropoxyphene HCl and ■, methadone HCl.

agree well with the value of 0·53 nm² which is the area of the diphenylmethane hydrophobic region estimated from Catalin models (Florence 1970).

The agreement between cmc values from this wide variety of techniques and the effect of added electrolyte on the aggregation number and cmc suggests that, in common with other diphenylmethane derivatives, dextropropoxyphene and methadone associate in a micellar manner. According to equation (4) which is derived by the application of the law of mass action to the micellization process (Anacker 1970), plots of log cmc against log counterion concentration, X⁻, should be linear.

$$\log \text{cmc} = -(1 - \alpha)\log X^- + \Delta G_h^{\circ}/$$
$$2{\cdot}303RT + 1/N \log F (M^{+p}) \quad .. \quad (4)$$

$\Delta G_h^{\circ}$ is the hydrophobic contribution to the standard free energy of micellization (per mole of monomeric drug), $M^{+p}$ is the mole fraction of micelles and F is a term involving the activity coefficients of all species present in solution. Fig. 5 shows the cmc values obtained by light scattering for dextropropoxyphene plotted in accordance with equation 4. A degree of dissociation, $\alpha$, of 0·4 was calculated from the slope of this linear plot which is in reasonable agreement with the values derived from light scattering. Assuming the concentration of micelles at the cmc to be negligible, the intercept obtained on extrapolation to log X⁻ = 0 may be equated with $\Delta G_h^{\circ}/2{\cdot}303$ RT thus enabling $\Delta G_h^{\circ}$ to be estimated. The value of −25·4 kJ mol⁻¹ obtained in this manner may be compared with $\Delta G_h^{\circ}$ values previously determined by this method for other diphenylmethane derivatives which, like dextropropoxyphene, have no halide substituents on the phenyl rings of the hydrophobic moiety. Attwood & Udeala (1975a) determined $\Delta G_h^{\circ}$ values of −26·6

and $-28 \cdot 8$ kJ mol$^{-1}$ for diphenhydramine hydrochloride and diphenylpyraline hydrochloride respectively, which are of the same order as the value for dextropropoxyphene. In making the comparison it should however be noted that the extra $-CH_2$ group in the hydrophobic moiety of dextropropoxyphene will probably contribute about $-3 \cdot 5$ kJ mol$^{-1}$ to the total $\Delta G_h^\circ$ value (Tanford 1973).

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