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Self-association of disodium cromoglycate in dilute aqueous solution

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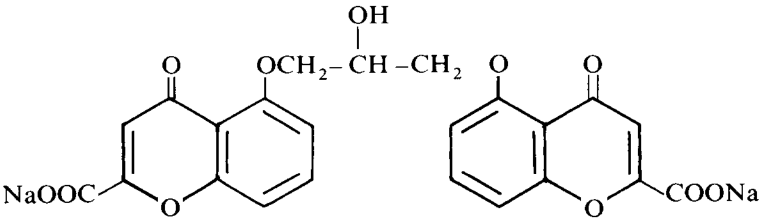
Summary

The association characteristics of isotropic solutions of disodium cromoglycate in water and aqueous electrolyte solutions have been examined using light-scattering techniques. The association in these solutions may be satisfactorily described using anti-cooperative stepwise association models in which successive association constants decrease with increasing aggregate size. Size distribution curves show that the extent of association is limited mainly to dimers and trimers.

Introduction

Previous studies on the anti-asthmatic drug, disodium cromoglycate (DSCG) I



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have been mainly concerned with the structure of its crystalline form and of the mesomorphic liquid crystalline phases formed in concentrated solution (Cox et al., 1971; Hartshorne and Woodard, 1973; Hamodrakas et al., 1974; Lydon, 1980; Goldfarb et al., 1982). Depolarized light scattering and magnetic birefrigence studies (Champion and Meeten, 1973) have demonstrated that the DSCG molecules exist in a planar conformation in dilute solution. It is interesting to note that these authors also report evidence of some association or strong solute–solute interaction at concentrations in excess of 1 g/100 ml. A transition point at 0.13 $\text{mol} \cdot \text{dm}^{-3}$ between isotropic solution and a mixed solution containing nematic mesophase was reported at 25 °C by Gonda and Groom (1983) from an examination of both water activity and surface tension. In the present study we have investigated the association characteristics of DSCG in water and electrolyte solution, restricting our measurements to the isotropic solution region before any such phase transition point.

Materials and Methods

Materials

Disodium cromoglycate (sodium cromolyn) was kindly supplied by Fisons Pharmaceuticals. It was dried under vacuum at 170 °C for 12 h and stored over phosphorous pentoxide. Sodium chloride was of AnalaR grade.

Methods

Light scattering measurements were performed at 303K using a FICA 42,000 photogoniodiffusometer at a wavelength of 546 nm. Solutions were freshly prepared and clarified by ultrafiltration through 0.1 μm Millipore filters. Refractive index increments, dn/dm, were measured at 546 nm by differential refractometry. A mean dn/dm value of $0.111 \pm 0.001\ \text{dm}^{-3} \cdot \text{mol}^{-1}$ was determined for DSCG over the range of electrolyte concentration used.

Results and Discussion

Fig. 1 shows the light scattering intensity at an angle of 90 °, S_{90}, plotted as a function of the concentration of DSCG. At concentrations exceeding those shown in Fig. 1 for each system, there were very pronounced increases in scattering intensity corresponding to a phase change from isotropic solution to mixed (solution + nematic mesophase). The limiting concentration noted for the DSCG–water system is similar to that reported by Gonda and Groom (1983). The scattering curves for all systems deviate significantly from that calculated for unassociated monomers indicating self-association of the DSCG molecules. With the exception of the solutions in 0.2 $\text{mol} \cdot \text{dm}^{-3}$ NaCl, the concentration dependence of S_{90} is linear and in none of the systems is there any evidence for a critical micelle concentration.

Methods of computer simulation of light scattering data using stepwise association models have been described previously (Attwood, 1982). Such models assume growth of aggregates by the stepwise addition of monomers according to:

$$b_1 + b_n \rightleftharpoons b_{n+1} \quad n = 1, 2, 3\ldots \tag{1}$$

The relationships between association constants for the formation of dimer (K_2), trimer (K_3), tetramer (K_4) and higher oligomers are expressed in terms of a parameter K and the aggregation number n. The following association models were considered.

Model 1. The equality of all association constants is assumed:

i.e. $K_2 = K_3 = K_4 = K_n = K$.

Model 2. Association constants increase sequentially with aggregation number according to the relationship: $K_n = K(n-1)/n$

i.e. $K_2 = K/2$, $K_3 = 2K/3$ etc.

Model 3. Association constants decrease in a mild sequence with increase aggregate size according to: $K_n = Kn/(n-1)$

i.e. $K_2 = 2K$, $K_3 = 3K/2$ etc

Model 4. Association constants decrease markedly with increasing aggregate size according to: $K_n = K/n$

i.e. $K_2 = K/2$, $K_3 = K/3$ etc.

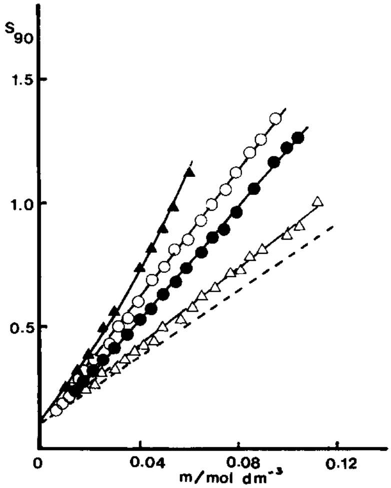

Fig. 1. Variation of light scattering ratio, S_{90}, with concentration, m, for disodium cromoglycate in △, H_2O; ●, 0.05 mol·dm^{-3} NaCl; ○, 0.10 mol·dm^{-3} NaCl; and ▲, 0.20 mol·dm^{-3} NaCl. - - - - - -, scattering intensity calculated for unassociated monomers.

The data are analyzed in order to determine the set of concentrations $(b_1 \ldots b_n \ldots)$ which is consistent with the overall concentration B given by:

$$B = \sum_{n}^{\infty} n b_n \tag{2}$$

and also consistent with the experimental light scattering data of Fig. 1. The computational technique determines for each model the concentration dependence of the light scattering intensity for a wide range of values of K and expresses the relationship between computed and experimental curves in terms of a goodness-of-fit parameter. In this way the optimum K value giving the best fit of data is determined for each model considered. Fig. 2 shows the best fit curves for each of the 4 models for DSCG in 0.2 $\mathrm{mol \cdot dm^{-3}}$ NaCl. The most satisfactory representation of the experimental data is achieved by the anti-cooperative model: $K_n = K/n$. This model also gave the closest fit for the other systems studied. K values, given in Table 1, show the expected increase in magnitude with increasing electrolyte concentration. The accuracy of these values is subject to the assumed ideality of the solutions.

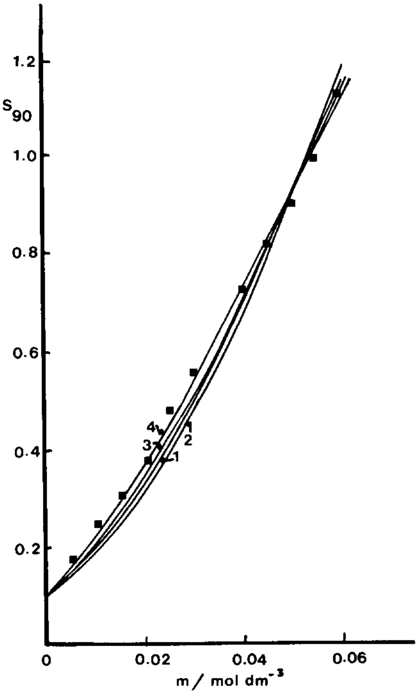

Fig. 2. Curves representing the best fit of experimental light scattering data (■) for disodium cromoglycate in 0.20 $\mathrm{mol \cdot dm^{-3}}$ NaCl as derived from stepwise association models with: (1) $K_n = K = 22.0\ \mathrm{dm^3 \cdot mol^{-1}}$; (2) $K_n = K(n-1)/n$ with $K = 26.0\ \mathrm{dm^3 \cdot mol^{-1}}$; (3) $Kn/(n-1)$ with $K = 17.9\ \mathrm{dm^3 \cdot mol^{-1}}$; (4) $K_n = K/n$ with $K = 101.2\ \mathrm{dm^3 \cdot mol^{-1}}$.

TABLE 1

STEPWISE ASSOCIATION CONSTANTS ($dm^3 \cdot mol^{-1}$) FOR DISODIUM CROMOGLYCATE IN WATER AND ELECTROLYTE SOLUTIONS AS GENERATED BY MODEL 4

[NaCl] ($mol \cdot dm^{-3}$)	K_2	K_3	K_4
0.00	0.90	0.60	0.45
0.05	6.53	4.35	3.26
0.10	15.45	10.30	7.73
0.20	50.58	33.72	25.29

The concentration of any aggregated species, b_n, can be obtained in terms of the concentration of the free monomer, b_1, and the stepwise association constants, using the relationship:

$$b_n = b_1^n \prod_{i=2}^{n} K_i \tag{3}$$

This information is shown in the form of the aggregate size distribution curves in Fig. 3. Association, even in the presence of 0.2 mol · dm^{-3} electrolyte, is clearly of a limited nature, the predominant species in solution being monomers, dimers and trimers.

The DSCG molecule is composed of two rigid chromones linked by a glycerol bridge. Rotation about the bonds of this bridge allows numerous possible conforma-

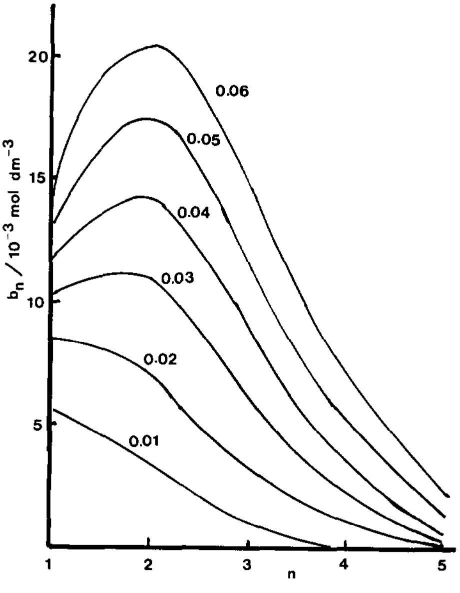

Fig. 3. Aggregate size distribution curves deduced from association model 4 for concentrations of disodium cromoglycate ranging from 0.01 to 0.06 mol·dm^{-3} in 0.20 mol·dm^{-3} NaCl.

tions, many with low energy barriers. Champion and Meeten (1973) have, however, produced convincing evidence of a planar configuration of the molecules in dilute solution. The limited, non-micellar association demonstrated in this present investigation is most probably a consequence of the stacking of these planar units, a mode of association noted with other planar drug molecules (Gormally et al., 1984).

Acknowledgements

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