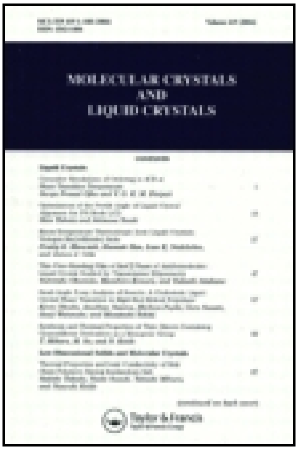

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New Models for the Mesophases of Disodium Cromoglycate (INTAL)

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NEW MODELS FOR THE MESOPHASES OF DISODIUM CROMOGLYCATE (INTAL)

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Abstract: New models are proposed for the two lyotropic liquid crystal phases of the anti-asthmatic drug, disodium cromoglycate (DSCG). It is suggested that the M phase consists of square hollow cylinders of DSCG packed in a hexagonal array in a water continuum. Each hollow cylinder consists of a stack of rings of four DSCG molecules and is filled with water. The N phase, which occurs at higher dilution, is pictured as a nematic array of the same hollow cylinders but separated by so much water that although the local parallelism is retained, the hexagonal ordering is lost.

Introduction: The anti-asthmatic drug disodium cromoglycate (DSCG) which is marketed by Fisons Limited under the trade name of INTAL, has a remarkable affinity for water. The anhydrous solid avidly absorbs water to form first an interstitial solid solution and then two lyotropic liquid crystal phases. Neither of these mesophases has a congruent melting point and a change of temperature results in a peritectic type of behaviour.[1]

The optical microscopy and X-ray diffraction of the two mesophases have been studied by Hartshorne and Woodard.[2] The mesophase formed at lower water concentrations showed some similarity to the lyotropic hexagonal (middle) phase and was therefore labelled the M phase. Hartshorne and Woodard described a model for this phase "... in which the DSCG is clustered into rods separated by a water continuum, and with the polar -COONa groups occupying the surfaces of the rods." The mesophase formed at higher water concentrations was identified as nematic and was labelled the N phase.

The extent of hydration of these mesophases is remarkable. The solid solution can hold up to nine molecules of water per molecule of DSCG, the M phase up to 43 molecules of water, and the N phase up to 260 molecules.[1]

The structure of the hydrated crystalline form

Cox, Woodard, and McCrone made a preliminary X-ray diffraction study of the hydrated crystalline form of DSCG.[1] They found the unit cell to be triclinic with space group P1 and with dimensions a = 11.5Å, b = 15.8Å, c = 3.92Å. All of the angles are close to 90°. There is one molecule per unit cell and the molecules are stacked one above the other with the short c axis corresponding to the needle axis of the crystal. They inferred that the molecule is flat and is shaped like a letter U.

A subsequent, full crystal structure determination by Hamodrakas, Geddes, and Sheldrick, confirmed the unit cell dimensions and the space group but showed that the molecule is appreciably non-planar.[3] It is shaped like a letter V with the planes of the two ring systems inclined at an angle of 53°. The crystal structure was complicated because one of the Na^+ ions is disordered. The other is clearly hydrated and lies in a site where it is next to the carboxylate ions of two molecules and the carbonyl group of a third. There is no clear division between hydrophobic and hydrophilic regions in the crystal and the general impression one gains is that the DSCG molecule is totally unsuitable for the formation of a conventional lyotropic liquid crystal phase.

The Hartshorne and Woodard models for the M and N phases

By comparing the dimensions of the hexagonal lattice of the M phase (as determined by X-ray diffraction) with the measured densities, Hartshorne and Woodard came to the conclusion that although the cylinders are separated by varying amounts of water, the actual cylinder diameter remains constant throughout the composition range of the phase. The value which they calculated for the cross-sectional area of the cylinders corresponds to a diameter of 16Å for a circular cross section.

For the N phase, Hartshorne and Woodard proposed a model "... in which planar molecules are arranged with their planes parallel, or approximately parallel to one another, and which is nematic in the sense that the distribution of the centres of the molecules is random and that they have freedom to move past each other in directions parallel to these planes." Such a structure would now be called discotic.

Criticisms of the Hartshorne and Woodard models.

(1) The DSCG molecule is not recognisably amphiphilic or discogenic and it is not easy to see why a compound of this type should form either an M_1 phase or a discotic phase.

(2) The column diameter of 16Å determined by Hartshorne and Woodard seems to be extremely small. There can only be three or four molecules lying in the cylinder section (their precise number depending on their orientation with respect to the cylinder axis). This situation is hardly comparable with that of a normal M_1 phase where the columns have well-defined hydrophobic cores and the cylinder cross-section accommodates some dozens of molecules.

(3) The amount of water between the M phase cylinders is very large. Even for this phase at its lowest water content, the cylinders are separated by 10Å of water, and it is not easy to see why the threshold condition for the formation of this phase should correspond to such a high degree of hydration.

(4) In addition to the sharp low angle reflections (corresponding to the inter-column hexagonal spacing), Hartshorne and Woodard found a diffuse high angle reflection corresponding to a spacing of 3.4Å. I take this to imply that there must be some common structural element larger than the molecule shared by the M and N phases - and this is not a feature of the models described above.

New models for the mesophases

In the light of the difficulties listed above, I propose modified models for the two mesophases. I suggest that in both cases the DSCG molecules form hollow, square cylinders filled with water. In the M phase these lie in a hexagonal array in a water continuum depicted in Figure 1(ii). (Such a structure would have more in common with a complex, hexagonal lyotropic phase than with an M_1 type.) In the N phase the DSCG columns are separated by so much water that although the local parallelism is retained, the hexagonal ordering is lost.

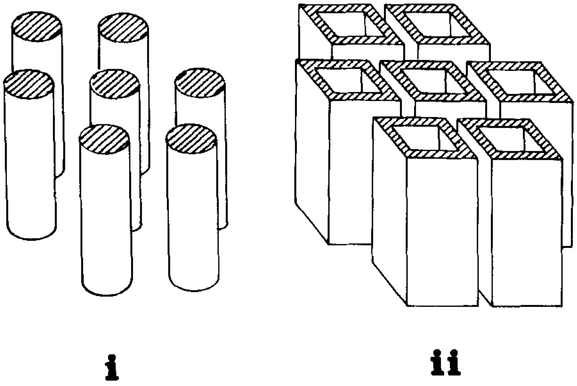

FIGURE 1: The contrasting models for the M phase of DSCG.

(i) The model of Hartshorne and Woodard with cylindrical columns of DSCG in a hexagonal array in a water continuum.

(ii) The modified model with hollow square columns of DSCG filled with water and also lying in a water continuum.

A consideration of the molecular geometry in the hydrated crystalline solid suggests that in a more dilute situation, a stable arrangement is given by rings of four molecules lying round the corners of a square and held together by electrostatic salt bridges as shown in Figure 2.

These models appear to offer satisfactory explanations for the very high degree of hydration of the mesophases and for the large value of the minimum spacing of the hexagonal lattice of the M phase. They are compatible with the uniaxial

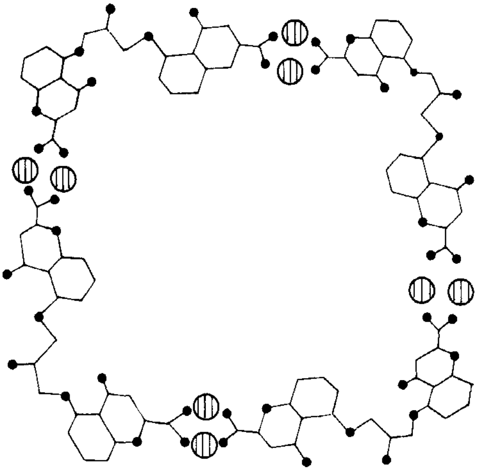

FIGURE 2: The proposed model for the hollow square columns of DSCG of the M and N phases viewed down the column axis, showing how the four molecules are linked by electrostatic salt bridges. In this figure each molecule has been drawn as it appears when viewed down the needle axis (the a axis) of the hydrated crystal.

The small solid circles represent oxygen atoms and the large hatched circles represent hydrated Na^+ ions.

optically negative nature of both mesophases and explain the presence of the high angle diffuse reflection in the X-ray diffraction patterns in both cases. The phase diagram of the DSCG/water system shows that 73^o is the maximum temperature at which the M phase can exist and this temperature must represent the upper temperature limit for the hollow square cylinders (a sort of Krafft point in reverse).

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