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Lyotropic Mesophase Formation by Anti-Asthmatic Drugs

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The two lyotropic mesophases of the types previously thought to be unique to the disodium cromoglycate/water system have been found to occur also in aqueous systems of other anti-asthmatic drugs.

The molecular structural requirements for the formation of these mesophases and the reasons why anti-asthmatic activity might be correlated with this type of mesogenic behaviour are discussed.

INTRODUCTION

The anti-asthmatic drug disodium cromoglycate, SCG, (marketed by Fisons PLC 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, labelled the M and N phases. The extent of hydration of these mesophases is remarkable. The solid solution can hold up to 9 molecules of water per molecule of SCG, the M phase up to 43 molecules of water, and the N phase up to 260 molecules. These phases appear to be unlike those of conventional amphiphile/water systems in which the hydrophobic regions of the phase are composed of alkyl chains, and the molecular structure of SCG would appear, at first sight, to be totally unsuitable for mesophase formation of any kind.[1–5]

We have recently proposed models for the structures of these mesophases.[6] Both involve hollow columns of mesogen molecules. The spaces within the hollow columns and the continuum between the

columns are each filled with water. In the more concentrated M phase, the columns are arranged in a hexagonal array, whereas in the N phase they are pictured as separated by random distances, giving a nematic array.

The N phase usually shows the typical nematic *schlieren* texture (Figure 1) and the M phase exhibits a variety of textures including the characteristic pattern of herring-bone striations shown in Figure 2. The peritectic (rather than eutectic) form of the phase diagram leads to characteristic appearances of many of the two-phase regions. In particular, when the N phase is heated, islands of isotropic liquid appear within a mesophase continuum giving the reticulated appearance shown in Figure 3. Optical textures as characteristic as these give a way of identifying this type of mesogenic behaviour with some degree of certainty.

Many of the qualitative features of the phase diagram can be shown by a single preparation. If a little of the solid is placed on a slide, covered by a cover slip and water introduced so that it envelops the solid, a concentration gradient is set up and the regions corresponding to the isotropic liquid, N phase, M phase and hydrated solid appear simultaneously and can be easily distinguished. Heating and cooling give some indication of the variation of the phase boundaries with

FIGURE 1 The nematic *schlieren* texture of the N phase of SCG (room temperature, with crossed polars, 250×)

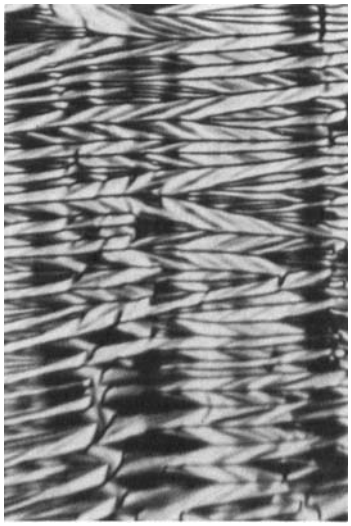

FIGURE 2 The typical herringbone texture of the M phase of SCG. (room temperature, with crossed polars, 500×)

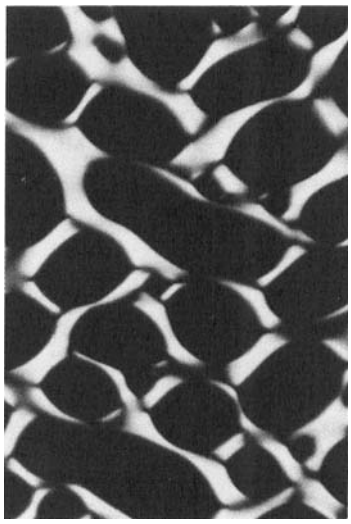

FIGURE 3 The two phase region produced when the N phase of SCG is heated. The continuous phase is the N phase and the circular islands are of isotropic liquid. (taken at 30 °C with crossed polars, 500×)

temperature and also tend to develop the characteristic textures, especially the herringbone texture of the M phase.

We have recently carried out an optical examination of the textures found when water is added to a number of anti-asthmatic drugs listed in Figure 4.[9-11] These are all drugs of a non-steroid type and are thought to act on the mast cells. To our surprise we found that *in every case* two lyotropic phases were formed and these showed the characteristic optical textures of the SCG N and M phases. Note that there is no apparent distinction in liquid crystal properties between

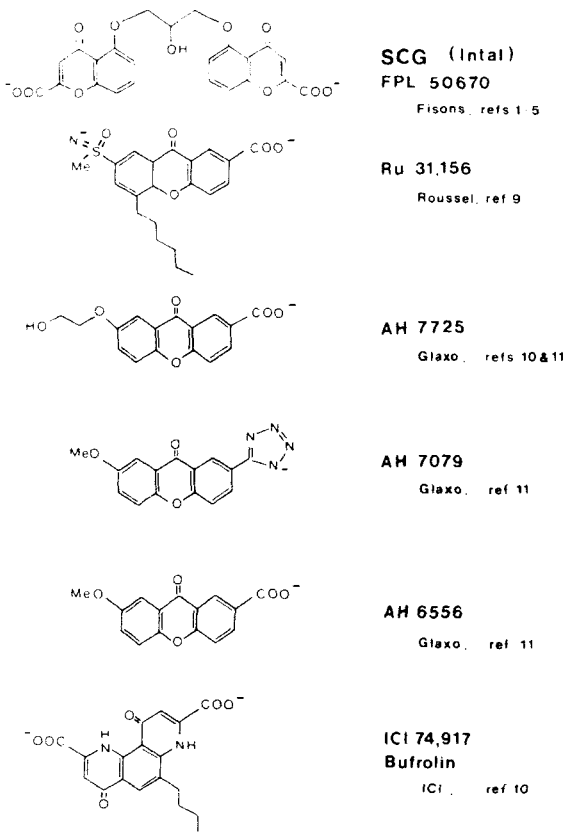

FIGURE 4 The molecular structures of the non-steroid anti-asthmatic drugs which we have investigated. They are all active as salts and only the anion species are shown here. The cation species are Na^+ ions for all cases except for Ru 31,156 where they are 'tris' ions.

SCG on the one hand (which is only effective when inhaled) and the other compounds which are effective when taken orally.

In similar experiments we attempted to study whether mesophases of the same type (i.e. N or M) of different compounds were miscible with each other. We found that although some pairs of corresponding mesophases were not miscible, it was possible to link every mesophase with all of the corresponding mesophases of the other compounds either directly or indirectly, by a scheme of miscibility.

In general, mesogenic molecules are of well-defined and clearly recognizable types. For example, conventional lyotropic molecules have clearly distinct hydrophobic and hydrophilic parts and discogenic molecules have a central rigid core surrounded by a ring of flexible alkyl chains. We had expected therefore, that there would be some obvious factor common to all of the molecules listed in Figure 4 and that this would indicate the structural requirements for both the mesogenic property and this type of anti-asthmatic activity. At first glance it is not easy to see exactly what this common factor can be.

Many of the features of the SCG molecule itself are not shared by the other active molecules. Some of the compounds are sodium salts of dicarboxylic acids but neither the presence of two acid groups, nor their precise nature, nor the presence of an Na^+ cation is a feature shared by all of the molecules and they cannot therefore be regarded as essential. Similarly, the butterfly-like structure of SCG with its central 'hinge' is not a common feature and hence this cannot be a structural requirement either.

There are, however, two features shared by all of these molecules:

(a) a rigid flat aromatic core which contains a benzpyrone or the iso–electronic benzpyridone group

(b) two hydrophilic groups at the opposite ends of the molecule, one of which is an acidic anion and the other either a second acidic anion or a group capable of hydrogen bonding.

Note that it does not appear to be necessary for these features to have a unique, precisely defined, geometrical relationship with each other; (in some cases, the hydrophilic carboxylic acid anion is joined directly to the pyrone ring and in other cases it is joined to an adjacent ring). The benzpyrone or benzpyridone group must confer an appreciable dipole on the molecule with the ring oxygen carrying a substantial positive charge. (This explains why this oxygen atom has been found not to take part in hydrogen bonding in crystal structures of a number of SCG analogues.[7]

Electrostatic interactions would be expected to dominate the way in which the molecules aggregate. Two obvious likely arrangements are

shown in Figure 5. The first is a head-to-tail packing of molecules directly on top of each other (Figure 5(a)) and the second is a tilted stacking pattern (Figure 5(b)). The latter type of stacking was found in crystals of SCG hydrate.[8] For molecules like AH7079 and AH6556 which have only one acid group, a modified tilted stack in which molecules point alternately right and left would appear likely as shown in 5(c). We suggest that structures of the types (b) or (c) are likely to occur in the crystalline solid phases and in both mesophases of all of the compounds listed.

These two structural requirements appear to be reasonable in terms of the type of model suggested for the N and M phases. The electrostatic interactions hold the molecules in tilted stacks and the hydrophilic interactions link a molecule in one stack with those in adjacent stacks by ionic or hydrogen bonding interactions. The hinged nature of SCG itself is not necessary and this particular molecule is to be regarded as a double mesogen (analogous in a sense to an $\alpha - \omega$ dicholesteryl ester). It is ironic that the first member of this new series of mesogens to be identified should be of a rather unrepresentative kind.

It is of course possible that this pattern of mesophase formation is widespread, that the requirements in terms of the molecular structure are rather lax and that it is purely fortuitous that it has so far been observed only in this series of anti-asthmatic compounds. To dismiss

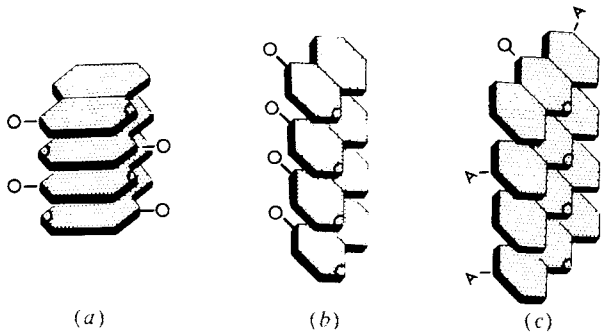

FIGURE 5 Possible patterns of packing of the rigid benzpyrone parts of the molecules as directed by the electrostatic interactions. The simple head to tail packing of molecules directly on top of each other is shown in (*a*) and the alternative way of accommodating the dipoles by tilting the molecules is shown in (*b*). This tilted arrangement has been found in the hydrated crystalline solid of SCG. A modified tilted stack where the molecules point alternately to the right and left, is shown in (*c*). We suggest that patterns of stacking of types (*b*) or (*c*) occur in both N and M mesophases.

this possibility we would have to examine a significant number of compounds with similar molecular structures and with proven *non* anti-asthmatic properties, which has not yet been done. At this stage, however, we tentatively hold the opinion that this type of hydrated mesophase formation is selective and goes hand-in-hand with anti-asthmatic property. If this is the case, there would appear to be three distinct ways in which the correlation could arise;

1. The drug actually works by creating a region of one or other of the mesophases somewhere in the patient (possibly at the lung surface or in the mast cells).
2. No actual mesophase region is formed, but there is a biologically active complex which is an assembly of drug molecules (possibly a ring or a hollow column) which also occurs in the mesophase.
3. There is no mesophase region or part of a mesophase assembly involved in the anti-asthmatic activity, but the structural requirements which give the molecule its mesogenic character also confer on it anti-asthmatic properties.

Very little is known with any certainty about the way in which SCG works and none of the three possible modes of action listed above can be discounted at this stage.

If the first alternative is correct, it may be relevant that the exposed surface of the lung is covered with a layer of fluid rich in mesogenic phospholipids. It is known that without these surfactants, the surface tension on the fluid-coated alveolar walls would be of sufficient magnitude to cause the collapse of the small alveoli at the end of expiration.[12] A major objection to any theory which postulates that entire regions of mesophase are created in the patient is that the effective dosage is very low—well below the level where the N phase occurs. This objection may be valid, but it is not necessarily insurmountable. It is possible that dynamic processes such as the continual loss of water from the lung surface, may serve to concentrate (rather than dissipate) the drug molecules in specific sites.

If the second option is correct, it may be that the assemblies form channels facilitating the passage of water or ions through a membrane or some otherwise impenetrable barrier (rather like the manner in which the cyclic oligopeptide or crown ether antibiotics operate).

If the third situation is correct, it may be that some particular feature of the molecular structure is responsible for its mesogenic character and also gives affinity for a specific receptor site. The pyrone ring oxygen atom would perhaps be the best candidate for this role.

In those general texts which have attempted to cover all significant aspects of the liquid crystalline state, the SCG/water mesophases, like the nocturnal barkings of Sherlock Holmes's dog,[13] are conspicuous by their absence. Obviously these phases were regarded as mere curiosities, out of the mainstream of liquid crystal studies, a glance at the molecular structure being sufficient to indicate that the molecules are totally unlike those of any 'respectable' lyotropic mesogen and therefore not likely to be capable of lyotropic mesophase formation.

This situation has now clearly changed. A new category of lyotropic mesophase can be defined which does not contain hydrophobic regions composed of alkyl chains. It will be convenient to have an adjective to describe the type of mesogenic behaviour where N and M phases of the SCG type are formed and we suggest the term 'chromonic' for this (derived from the bis-chromone structure in SCG).

To summarize:

1. Lyotropic mesomorphism of the N/M type is not unique to the SCG/water system;

2. All of the anti-asthmatic compounds which we have examined show mesomorphism similar to that of SCG and both N and M phases were found in every case;

3. The corresponding mesophases of all the compounds investigated could be linked, either directly or indirectly, by a scheme of miscibility.

4. The structure requirements for this type of mesophase formation appear to be two-fold:

(a) a rigid aromatic core which includes a benzpyrone or benzpyridone ring giving a large dipole in the plane of the ring system;

(b) a pair of hydrophilic groups situated at opposite ends of the molecule, one of these groups being the salt of an acid with a univalent cation;

5. We propose the term 'chromonic' to describe this type of mesogenic behaviour.

Acknowledgments

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