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Polymorphism and isostructurality of cyclodextrins and their inclusion complexes

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Broad classification of the crystal structures and packing modes of cyclodextrins (CDs) and their inclusion complexes into channel and cage types is well known. An example of a more detailed classification is that for dimeric (-CD complexes [1] where channel-, intermediate channel-, screw channel- and chessboard arrangements were identified. A survey of available CD inclusion complexes of organic guests led to their systematic classification into ~17 isostructural series, each with a distinctive PXRD pattern [2]. These patterns have proven useful for definitive characterization of new inclusion complexes. More recently, several reports of polymorphs of CDs and their inclusion complexes have appeared, indicating yet wider structural diversity in this class of compounds. In this report, we review these aspects of CDs and their inclusion complexes, and present data for three crystalline forms of permethylated β-CD and several β-CD inclusion complexes of salts of the anti-inflammatory drug diclofenac and its structural isomer meclofenamic acid. The former series comprises a monohydrate (Form 1), a trihydrate (Form 2) and an anhydrate (Form 3), all crystallizing in the space group $P2_12_12_1$. The latter two phases are isostructural and were obtained during failed attempts to obtain inclusion complexes with the drugs bucetin and atenolol [3]. The most striking feature revealed here is the relatively round shape of the host molecule in Forms 2 and 3 that results from inclusion of two primary methoxyl groups of each host into the cavity of a neighbouring CD molecule. This contrasts strongly with the collapsed structure of the host in Form 1, where one of the seven methylated glucose rings was found to adopt the unusual $^1C_4$ conformation. The β-CD complexes of diclofenac prepared and characterized in our laboratory include those of the sodium, potassium and caesium salts of the drug. Although the mode of inclusion of the drug anion in the host cavity is essentially the same in this series, only the latter two complexes are isostructural, crystallizing in the space group $P2_12_12_1$, while the crystal of the sodium analogue is hexagonal, space group $P6_1$. We recently prepared the Ca^{2+} and Mg^{2+} salts of both diclofenac and meclofenamic acid, and attempted their inclusion in β-CD. Surprisingly, no complex formation was detected with either of the salts of diclofenac, but its isomer yielded isostructural crystals with compositions β-CD•(meclofenamate$^-$)$(M^{2+})_{0.5}$(17H_2O. These were found to be isostructural with the sodium analogue investigated earlier and in all three complexes a common mode of inclusion of the guest is observed. New instances of isostructurality among CD hosts and their inclusion complexes reported here have been incorporated into an updated library which includes their PXRD patterns.

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Past and present: the meaning of morphotropism

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Morphotropism, isostructurality and polymorphism form a magic triangle in structural chemistry. Since Groth used the *term* first [1], we wish to reveal how far his original morphological observations are from non crystallographic rotations described by the same word recently [2]. Groth revealed that the habit of crystals of 'chemically allied' substances changes upon H substitution by Cl, Br, I or small groups of atoms. He denoted the reckoned directional changes on the crystal shape as *morphotropy*. But his rules were based only on the 32 point groups and the reflecting goniometer.
The 2D-structure determinations by X-ray diffraction enabled Kitaigorodskii [3] to regard a rearrangement in a row of $Sn(C_6H_4R)_4$ molecules as *morphotropism*, which he attributed 'to the impossibility of maintaining a sufficiently high packing coefficient for *isomorphous* substitution'. To find a bridge between the virtual non-crystallographic rotations in related structures [2] and Groth's morphotropy, examples are studied: (a) In the structures of *o-, m-* and *p*-substituted $Sn(C_6H_4R)_4$ derivatives the achiral molecules are related to each other by different rotations, or the crystals remain isostructural [4], as predicted by Groth, if *R* is relatively small, or the site of the substitution is well isolated. (b) Between nitrophenols, studied also by Groth, a mononitro→dinitro substitution is found where both forms of morphotropy are observed, while the polymorphs of *m*-dinitrophenol exhibits morphotropism.
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