MS32-O4

Understanding selectivity in host-guest systems

luigi Nassimbeni[1]

1. Chemistry, Rondebosch, South Africa

email: luigi.nassimbeni@uct.ac.za

The formation of inclusion compounds, comprising host and guest molecules, depends on the phenomenon of molecular recognition. An important application of this process is the separation of compounds in a mixture, particularly when the individual components have similar physico-chemical properties as often occurs in isomers.

The techniques which may be used to understand the mechanism of separation are:

a) Competition experiments, b) Crystal Structure, c) Thermal Analysis; d) Packing coefficient; e) Hirshfeld Surface Analysis; f) Lattice Energy

Each of these methods will be outlined, and recent publications dealing with important aspects will be indicated. Recent experimental results of guest selectivity and the concomitant mechanisms will be presented.

Keywords: Host-Guest, Selectivity, Mechanism

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Finding polar crystal structures: molecular structures, intermolecular interactions and unit cell dipoles

Frank Blockhuys[1], Jasper Van de VeldeAlain Colla[2]

1. Department of Chemistry, University of Antwerp, Antwerp, Belgium
2. Crystallization Technology Unit, Johnson & Johnson , Beerse, Belgium

email: frank.blockhuys@uantwerpen.beT

The structure and electronic properties of one class of organic semiconductors, *i.e.*, 1,4-distyrylbenzene (1,4-DSB) and its derivatives, have been extensively studied, indicating the usefulness of the DSB template for electro-optical materials [1]. A number of their applications, such as non-linear optics and non-volatile organic memories, require materials with dipole moments, both at the molecular and the supramolecular levels. These two requirements, however, generally work against each other: 1,4-DSBs containing electron acceptor (A) and donor (D) fragments connected by a π-spacer (A–π–D structures) have large molecular dipoles and superior molecular properties, but will, in the majority of the cases, result in the energetically preferred anti-parallel dipolar stacking in the crystal leading to a centrosymmetric and, therefore, non-polar supramolecular structure. These observations have led to the development of a rational overall design strategy for polar molecular crystals of DSB-type oligomers, consisting of four parts. First, the formation of an anti-parallel stacking should be hampered by the introduction of steric hindrance between the molecules; this could be obtained by deviating as much as possible from rigid-rod molecular shapes. Second, the electronic-ground-state dipole moment of the molecules should be sufficiently small; this way, the energy barrier to stack two molecules with aligned dipoles is lowered and the probability to obtain a non-centrosymmetric arrangement in the resulting solid is increased. Third, the deviation from planarity of the constituent molecules should be increased through the incorporation of heteroatoms in the conjugated spacers between the rings; the introduction of (a) nitrogen atom(s) results in typical non-planar molecular shapes hampering the formation of π-stacks [2]. Fourth, the most favourable conformation of the molecule should have an energetic advantage with respect to its other conformations which is as high as possible; this results in greater control over which conformation is eventually found in the solid and, consequently, its shape and the size of its dipole moment. The results of a CSD analysis reveal that 1,4-DSBs are statistically far less prone to crystallization in polar space groups than 1,3-DSBs and our efforts are now focused on developing new materials using the latter template in an approach which combines synthetic and computational chemistry, and crystallography. Computational chemistry is used to great advantage, from the calculation of molecular properties such as conformational energies and dipole moments to full DFT treatments of the molecular crystal, and an elegant procedure has been developed for the calculation and visualization of unit cell dipoles.

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MS33 Prediction of molecular crystal structures

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MS33-O1

Computational screening for organic drug hydrates

Doris Braun[1]

1. University of Innsbruck / Institute of Pharmacy, Innsbruck, Austria

email: doris.braun@uibk.ac.at

Water has the ability to occupy regular positions in the crystal lattice of other substances and to form molecular compounds, named hydrates. As water is an ever present component of the environment such multi-component crystals can form during many steps of product manufacturing and can have profound effects on the performance of a (drug) product. [1] Hydrate formation is a widespread phenomenon and is known to occur for at least one third of drug molecules. [2] Nevertheless, we are still not able to predict hydrates, their stability and dehydration mechanisms based on the molecular diagram only. With computational crystal structure prediction (CSP) methods being successfully employed for predicting smaller pharmaceutical molecules and even multi-component systems, [3] we tested the potential of CSP for drug hydrates. Stoichiometric and nonstoichiometric hydrate systems were chosen as model compounds for experimental and computational studies.

The experimental screen of two dihydroxybenzoic acid (DHB) isomers indicated hydrate formation for one isomer but not the other. The computationally generated hydrate crystal energy landscapes correctly predicted hydrate formation for 2,4-DHB and its stoichiometric ratios and rationalised why no hydrate was found for 2,5-DHB [4].

For 4-aminoquinaldine (4-AQ) the computational hydrate screening suggested the existence of an unknown monohydrate polymorph, which was then produced and found to be the thermodynamically most stable hydrate form of 4-AQ. [5] Calculating the crystal energy landscapes for hydrates is very complex and computationally (time) demanding, as host and different guest molecules in different stoichiometric ratios have to be considered. Therefore, we tested whether it is possible to derive information about hydrate formation for a Z′=3 monohydrate and higher hydrates from their Z′=1 hydrate and anhydrate crystal energy landscapes, respectively. For *o*-phenanthroline the Z′=1 monohydrate the crystal energy landscape rationalised why the compound forms a very stable Z′=3 channel hydrate. [6] For the hydrate forming alkaloid brucine and the non-hydrate forming derivative strychnine the evaluation of the anhydrate crystal energy landscapes, in particular the close-packed crystal structures and high-energy open frameworks containing voids of molecular (water) dimensions, allowed us to unravel the diverse solid state behaviour of the two alkaloids at a molecular level. [7]

Thus, modelling at the electronic and atomistic level can provide vital support for unravelling the complexity of or-