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A CRYSTALLISATION / CRYSTAL ENGINEERING APPROACH TO AID SALT SELECTION - ANIONS

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Salt selection is critical in the drug development process as selection of an appropriate form can reduce significantly the time to market of a new pharmaceutical entity. Salt formation is often employed to modify the final drug product. It is a simple chemical modification that can change to advantage the physiochemical, formulation, biopharmaceutical and therapeutic properties of a drug without varying the basic chemical structure. Crystal engineering is the understanding of intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design of new solids with desirable physical and chemical properties.[1] The aim being to establish reliable connections between molecular and supramolecular structure on the basis of intermolecular interactions.[2] Taking the known synthesis and structure of the hydrochloride salt as a starting point, novel salt forms of the pharmaceutical base ephedrine have been crystallised and the crystal structures subsequently solved.[3] The hydrogen bonding networks have been described and the relationship between structure and crystal morphology evaluated.

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Keywords: SALTS, CRYSTAL ENGINEERING, HYDROGEN BONDING

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RACEMIC AND ENANTIOMERIC 2-HYDROXY-2-METHYLBUTANEDIOIC ACID

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Citramalic acid, 2-hydroxy-2-methylbutanedioic acid (CMA) posesses one chiral center and is well characterized chemically in its enantiomeric form. It was unknown whether a racemate of the CMA resolves spontaneously or forms a racemic compound. We have investigated the crystal structures and thermodynamic properties of the enantiomer, (S)-CMA, and racemate, rac-CMA, of CMA. We have shown that the latter is a racemic compound, that is higher melting and less dense than the pure enantiomer. The enantiomeric forms of CMA crystallize in $P2_12_12_1$ and the racemic compound in $P2_1/c$, both with one molecule per asymmetric unit. Differential Scanning Calorimetry (DSC) has been employed to investigate the thermodynamic properties of rac-CMA and (S)-CMA. Though their hydrogen bonding patterns display some similarities to the ones observed in the related tartaric and malic acids, they also reveal some distinct differences. Attempts are made to rationalize these differences in crystal packing in terms of differences in the thermodynamic properties. A binary phase diagram for (R)-CMA and (S)-CMA was constructed from thermodynamic data. To examine the many ways enigmatic melting behavior observed for a racemate that is made as a mechanical mixture of the two enantiomers, we performed DSC experiments to elucidate how the variation in crystal size influences the melting curves.

Keywords: CRYSTAL PACKING, PHYSICO CHEMICAL PROPERTIES,CRYSTAL SIZE

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THE HALOGEN BOND I···O, I···N, Br···N AS A TEMPERATURE FUNCTION

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The X···B interaction, or halogen bond, between a halogen atom (X = I, Br) in perfluoro derivatives and a neutral or charged base (B = amines, pyridines, N-oxides, iodide etc.), is a useful synthon we have extensively used to produce a variety of supra-molecular structures. The goal of the present study is the temperature dependence of the halogen bond length. Three model systems were investigated, namely I···O in di-(4-pyridyl-N-oxide) 1,4-diiodotetrafluorobenzene (1), I···N in 4,4-dipyridine 1,4-diiodotetrafluorobenzene (2), and Br···N in trans-1,2-(4-pyridyl)ethylene 1,4-dibromotetrafluorobenzene (3). We chose these structures on the basis of their space group and Z at room temperature [*P*-1 and 1 for all the structures] assuring that no phase transition would happen in the temperature range under investigation. Data at 90, 145, 200 and 291 K were collected for all three structures taking care to minimize the effects of systematic errors (same crystal, collection strategy, instrument, etc.). The cell volume expansion, from 90 K to room temperature, is 3.09%, 5.05% and 4.75% for (1), (2) and (3) respectively. In the same temparature range, there is an I···O contraction from 2.753(2) to 2.723(2) Å in (1), I···N changes from 2.820(2) to 2.768(2) Å in (2) and Br···N shortens from 2.873(2) to 2.814(1) Å in (3). The thermal expansion and the variation of X···B distance is then quite high in (2) and (3), while is rather smaller in (1). We explain this difference with the fact that in (1) an O···H hydrogen bond between di-(4-pyridyl-N-oxide) molecules increases the packing energy and reduces the thermal expansion coefficient.

Keywords: HALOGEN BOND, INTERMOLECULAR INTERACTIONS, THERMAL EXPANSION

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SYNTHESIS AND CRYSTAL STRUCTURE OF THE COMPLEX OF AZA-BRIDGED INDIUM(III) PHTHALOCYANINE AND 4-METHYLPYRIDINE

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The metallophthalocyaninato (MPc) complexes are an important class of compounds extensively used in the industry of colorants and high technologies, including among others, display devices, sensing elements, photochemical redox agents and markers in photodynamic therapy of cancer. The oxidation state of the metal cation and its location relative to the phthalocyaninato ring determine the chemical and thermal stability as well as the colour and spectral features of the complexes. The new complex, which is stable up to about 483 K, was obtained as a result of intermolecular reaction of the triple decker indium phthalocyanine with 4 methylpyridine (4-Mepy). The crystal is triclinic, space group *P*1, with two independent formula units in the elementary cell. Each molecule consists of dimeric indium phthalocyanine (PcIn) bridged by a pair of the In - N - In bonds and one molecule of non bonded 4-Mepy, trapped into the area between two Pc rings of the dimer. The In ions are coordinated by four isoindole N atoms and two bridging nitrogens. The averaged distance between the In ions and the plane passing the isoindole N atoms is 0.8 Å. The In - N - In units are bent, forming the angles ranging from 105.3 to 112°. This type of double linked PcM(III)[N,N]M(III)Pc moiety, has been observed for the first time among the phthalocyaninato complexes.

Keywords: PHTHALOCYANINE, DIMER, N BRIDGED