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Surprises in Crystal Chemistry of Sugars

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ABSTRACT: The supramolecular chemistry of polyhydroxylated compounds (called carbohydrates) is well established. It essentially comprises strong O−H···O and C−H···O H-bonds. The crystallization of these compounds has been carried out innumerable times and has resulted in the formation of a single polymorph only. But recent efforts directed toward the structure determination and observation of polymorphism in this class of compounds have led to the discovery of new forms of two well-known sugar molecules, namely ribose and sucrose. This perspective aims to highlight the significant features associated with this novel discovery, with subsequent implications in the biological function of these compounds.

The importance of polymorphism is of significance from both an academic and an industrial perspective.[1] This field has achieved tremendous development and growth in the pharmaceutical industry, wherein issues related to polymorphism are directly interlinked to intellectual property rights. In recent years, this physical feature has been observed in compounds of significance to the chemical, biological, physical, geological, and metallurgical sciences. The role of serendipity has played a crucial role in the discovery of different physical forms of a given molecule, but the element of design and systematic exploration of the phase space has also contributed toward the isolation of new crystalline phases. A well-documented statement by the late Walter McCrown[2] proves the fact that polymorph formation can accompany any molecule. This facet was not observed for commonly crystallized molecules, namely aspirin, naphthalene, and sucrose, which have been crystallised innumerable times. This statement has stood the test of time. The case of aspirin was of tremendous scientific and commercial interest, wherein Vishweshwar et al. reported the observation of a new form for aspirin.[3] The identity of the new form was questioned by Bond et al.[4a] The final conclusion reached is that the crystal of aspirin, as is the case for several other aspirin crystals, is an intergrowth of two "polymorphic domains".[4b] Observations on aspirin gave the scientific community an opportunity to look at polymorphism in compounds wherein new forms have not been known for a long time. A very recent example supports this observation, wherein Prof Katrusiak's group in Poland have used high pressure techniques to generate *in situ* a new form of the disaccharide (+)-sucrose.[5] The presence of O−H···O H-bonds, which are ubiquitous in nature, seems to be universally prevalent, in addition to the well documented C−H···O interactions (both intra- and intermolecular) in rigid molecular scaffolds of different mono- and disaccharide units, and these render stability to the crystal packing. An investigation of the Cambridge Structural Database for crystallographic investigations, with the search constraints being "molecules containing C, H, and O only" and the keyword "carbohydrates", revealed 1943 examples.[7] In recent times, scientists have been working on the origin of the possible formation of sugars on Earth.[6] In these investigations, scientists have performed chemical reactions under prebiotic conditions to form ribose, which constitutes the backbone of RNA. The surprising part is that the crystal structure of D-ribose (Figure 1a) had not been determined. On most occasions, the crystals obtained were of small size, generally twinned and of poor diffraction quality. Traditional techniques to crystallize D-ribose have failed, including a melt procedure for crystallization. It was only in 2010 that Prof J. Dunitz and co-workers utilized powder diffraction techniques along with advanced developments in structure solution algorithms (charge flipping methods), using high resolution powder X-ray data, which enabled a complete structure determination of this compound.[8] It was observed in the solid state that the asymmetric unit consisted of two independent molecules, and the anomeric carbon atom contains both a β-pyranose and α-pyranose form. Experiments performed on the single crystal grown using zone-melting techniques reveal the disordered arrangement of the hydroxyl group at the anomeric center, an important observation from single crystal data. The surprise observation was the isolation and characterization of another form of D-ribose containing three independent molecules in the asymmetric unit. *The questions of relevance are whether it is possible to obtain a third form with $Z' = 1$, are the hydrogen bonding patterns affected because of the disorder at the anomeric center, and third, what is the reproducibility in experimental procedures for the formation of the observed polymorphs.* The first question can be answered by predicting crystal structures using programs on theoretical crystal structure prediction, which is indeed an area of intense computational interest. The latter involves detailed experimentation with the available starting material (it has been observed that the source of the compound is important). This includes setting up of crystallization screens using different solvents (polar, nonpolar, and polar/nonpolar combinations at room and low temperature) and also melt crystallization. In addition, the role of additives and cocrystallisation procedures can also significantly influence the final outcome as regards the formation of a given form.

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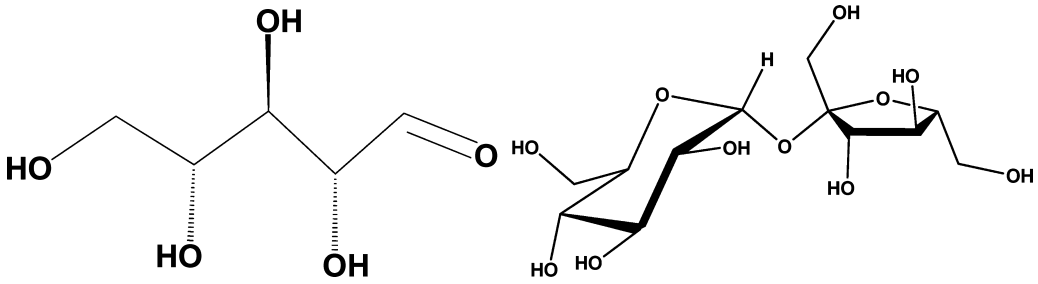

Figure 1. Molecular structures of (a) D-ribose and (b) sucrose.

Complementing these significant observations was a very recent report highlighting polymorphism in (+)-sucrose (Figure 1b) generated via *in situ* crystallization conditions, using the techniques of high pressure (>4.8 GPa), performed at constant volume and temperature.[5] Experimental inputs on polymorphism in sugars[9] and the observation of a phase transition in this class of compounds are rare.[10] In the last four decades, the crystallization of sucrose, a disaccharide, has resulted in the formation of the monoclinic form only [Form I].[11] The recently obtained high-pressure Form II also exists in monoclinic form but with the unit cell volume reduced by 18 Å^3 and with different lattice parameters when compared to Form I. It is of interest to note that sucrose is a conformationally flexible molecule with potential H-bond donors and any alteration in the torsion angles with respect to the glycosidic linkage can modify the H-bonding patterns with concomitant changes in crystal packing. It is of interest to compare the salient structural features (in terms of associated intra- and intermolecular H-bonds), which are characteristic of both the forms of sucrose. Subsequent variations in these are reflected in the associated physical properties, such as taste and solubility. X-ray diffraction studies were performed on both powder samples, and for enhanced accuracy in structure refinement, data was also collected on aligned single crystals. It has been observed that all the voids present in Form I of sucrose collapse in Form II, with subsequent rearrangement of the positions of the atoms in molecules into positions which are more conducive for hydrogen bonding. It is also to be noted that all the existing intermolecular hydrogen bonds in the old phase are broken and new ones are formed. The increase in pressure obviously results in the increase in the number of O–H···O H-bonds and also C–H···O interactions in the crystal lattice. In all the above-mentioned cases of investigation, the authors have taken advantage of the increased development in technology pertaining to detectors and advanced structure building and refinement software. Such inputs have contributed immensely toward the development of polymorphism. Subsequently this structural aspect is also related to the biological activity of the new form of sucrose (sweetener properties). "High-pressure" is an important external variable which needs to be seriously considered, if sucrose is an important ingredient which can transform during the stage of compaction in drug formulation. To summarise, the phenomenon of polymorphism can surpise any compound wherein new crystal forms have not been known, even for decades.

It is a challenge to generate and characterize unambiguously new forms for different compounds, particularly for those exhibiting potent biological function. The difficulty also lies in successfully reproducing the conditions for isolation and recovery of new polymorphs. In this regard, generation of theoretical crystal structures using crystal structure prediction packages wherein the energies vary between 0.5 and 2.0 kcal/mol can circumvent the problem wherein unusual forms may appear suddenly. Needless to say, the phenomenon of polymorphism can bring surprises by virtue of the existence of "disappearing polymorphs" wherein new forms have a transient existence only.[12]

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Notes

The authors declare no competing financial interest.

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