High-Pressure (+)-Sucrose Polymorph**

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Dedicated to Professor Joel Bernstein on the occasion of his 70th birthday

With the exponential rise in interest in the fundamental, commercial, and intellectual-property importance of crystal forms,[1] the late Walter McCrone's provocative statement regarding the propensity for the formation of polymorphs[2] is often cited: "It is at least this author's opinion that *every compound* has different polymorphic forms and that, in general, the number of forms known for each compound is proportional to the time and money spent in research on that compound." (italics in original). In response to McCrone, the lack of evidence for more than one crystal form of two very common, indeed paradigmatic and often crystallized compounds, sucrose and naphthalene, has been frequently cited.[3]

Sucrose (saccharose, (+)-$C_{12}H_{22}O_{11}$), common table sugar, is a particularly poignant example because of the well-known difficulty in inducing industrial-scale crystallizations[1] and the countless variety of conditions and number of times it has been crystallized merely for human consumption. Virtually all of these crystallizations have been carried out under ambient pressure, which represents but a small region of phase space. About ten years ago, with the development of relatively straightforward techniques to explore phase space at pressures above ambient,[4] we undertook a search for a high-pressure form of sucrose. A second form was elusive for a number of years, and although the search eventually proved successful, as reported herein, the preparation and characterization of the high-pressure form of sucrose required overcoming a number of experimental difficulties and in the end proved to be remarkably different from the ubiquitous common form sucrose I. Although unstable at ambient conditions, sucrose II provides new information about this compound and all sugars in general.

Sugars, in their variety of mono-, di-, and polysaccharides, are the main carriers for energy transport and storage in biological systems and the primary building blocks in living tissue. World-wide production of the disaccharide (+)-sucrose exceeds that of all other manufactured organic compounds. The molecule has considerable conformational freedom and many hydrogen-bonding functionalities (Figure 1), which might suggest the possibility or even tendency for the existence of multiple crystal forms, although there are no
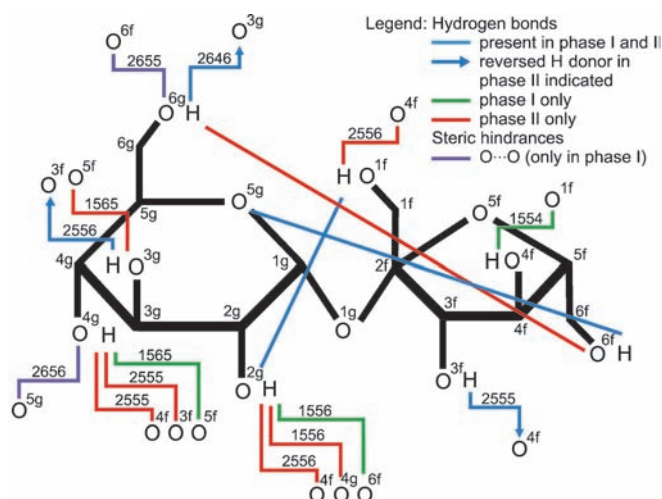
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Figure 1. Structural formula of sucrose, with hydrogen bonds and their transformations coded in colors described in the legend. A four-digit ORTEP code of symmetry transformations[20] has been used for specifying intermolecular H bonds; the explicit transformation codes have been listed in Table S7 in the Supporting Information. For clarity, only the hydrogen bonds involving the H-donor atom in the molecule have been indicated. All O···O contacts and OH···O bonds, separately in phase I and II, are shown in Figure S5 in the Supporting Information. Letters "g" and "f" in atomic labels denote the glucose and fructose moieties, respectively.

published statistics on such correlations between hydrogen-bonding functionality, molecular flexibility, and the tendency to crystallize in multiple crystal forms. Nevertheless, as for many other widely studied mono- and disaccharides,[5] only a few cases of polymorphs were reported, for example for β-D-allose.[6] Cellulose, the most abundant polymer on Earth, and starch are also known for structural transformations and polymorphs.[7] However, their macromolecular amorphous and microcrystalline composition allows for the determination of only average structural features. The structures of ribose anomers were revealed only recently.[8] The sucrose crystals were shown to be stable between 20 K[9] and 373 K, when sucrose starts to decompose.[10] So, there are scarcely any data on the polymorphism of sugars, and no direct observation of their phase transitions have been reported. This information is essential for understanding the interplay between properties of sugars with the conformational flexibility and intermolecular interactions. Sucrose is uniquely suitable for investigating the structure–property relations at varied thermodynamic conditions. Our study reveals an extraordinary molecular flexibility combined with transforming hydrogen-bond types and patterns in sucrose I and II. The types and patterns of hydrogen bonds are characteristic

features of all sugars and responsible for their properties, such as taste and solubility. Furthermore, the structure of sucrose II sheds new light on the extent of changes in structural dimensions commonly derived from crystallographic determinations: the balance between the main types of interactions in crystals, transformations of molecular association and properties of all sorts of molecular crystals.

We have used a modified high-pressure Merrill-Bassett diamond-anvil cell (DAC)[4,11] to perform in situ isochoric and isothermal crystallizations and X-ray diffraction studies on powder and aligned single crystals. We have found that sucrose is monotonically compressed up to a first-order isostructural phase transition at the critical pressure P_c of 4.80 GPa at 295 K. This transformation is manifested by discontinuities in the unit-cell dimensions and its volume collapse by -18 Å^3 (Figure 2).
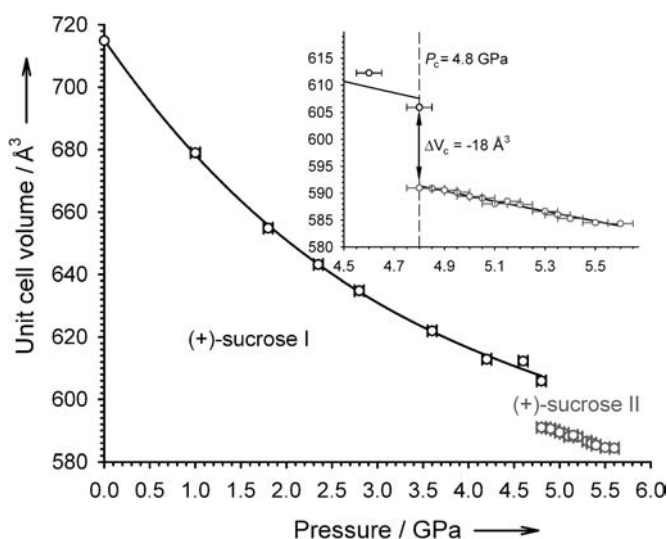

Figure 2. Pressure dependence of the unit-cell volume of (+)-sucrose. Black and gray circles represent the values measured by X-ray diffraction for sucrose I and II, respectively. The inset shows a magnification of the transition region and the volume collapse ΔV_c between the phases.

It is characteristic of isostructural phase transitions that the space-group symmetry remains the same and the unit-cell dimensions of both phases are similar. However, the sucrose crystal changes its structure to such an extent that it could be determined only after collecting the diffraction data of phase II for three differently oriented crystals in the DAC (Figure 3). The experiments were hampered by the very high solubility of sucrose and its notoriously difficult crystallization, common to very many sugars. On releasing the pressure, phase II transforms back to phase I, as evidenced by X-ray diffraction measurements performed for the crystals recovered from the DAC.

In sucrose there are eight hydroxy (OH) groups, which act both as H donors and H acceptors, and three ether (C–O–C) H acceptors. Structural determinations of phase I[12] revealed eight OH···O hydrogen bonds with the O···O distance shorter than 2.80 Å, each involving one OH group.
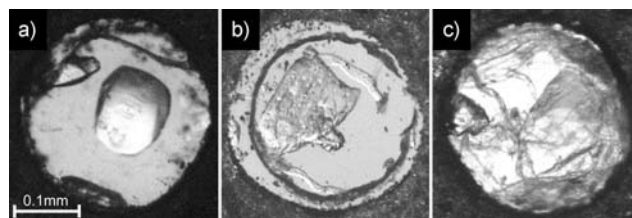

Figure 3. Crystal samples of sucrose II in three different orientations at: a) 4.85 GPa, b) 4.95 GPa, and c) 5.00 GPa, all at 295 K.

A general and rather dramatic reconstruction is required for the transformation to phase II. All the intermolecular hydrogen bonds in phase I are transformed in such a way that they are broken, new hydrogen bonds are formed, and the polarity of three OH···O bonds is reversed to O···HO; two intramolecular OH···O bonds are preserved and a third one is formed. This reshuffle of OH···O bonds is shown schematically in Figure 1. Generally, the structural transformations between phases I and II increase the number of OH···O bonds in high-pressure phase II, albeit of different types, and increase the number of short CH···O contacts compensating for the deficiency of H donors in the crystal structure. Moreover, short electrostatically repulsing O···O contacts, two per molecule and involving atoms $O6g···O6f^{2655}$ and $O4g···O5g^{2656}$ in phase I (the upper indices are symmetry codes: see Figure 1 and Table S7 in the Supporting Information), have been eliminated in phase II. The molecular conformation also changes, most significantly in the fructose ring and the glucose hydroxymethyl group (Figure 4).

As expected, phase I has a lower density, 1.674–1.857 g cm^{-3}, than phase II, 1.924–1.945 g cm^{-3} (Table S1 in the Supporting Information). Phase I is compressed in a very non-uniform manner: mainly the voids around O···O contacts (about the center of the unit cell in Figure S3 in the Supporting Information) are squeezed and eliminated,
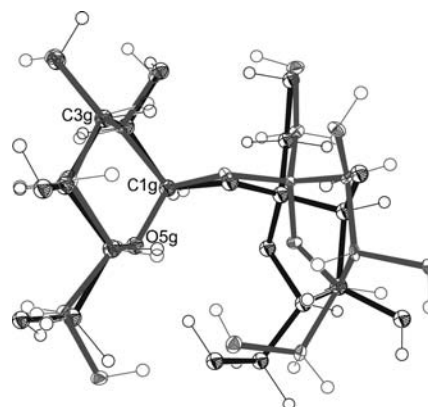

Figure 4. Crystal structures of phase I (black) and II (gray) sucrose with atoms C1g, C3g, and O5g of the glucose ring superimposed. Thermal ellipsoids are set at the 20% probability level. The largest bond-angle change between phase I at 0.1 MPa and phase II at 5.5 GPa is C6f-C5f-O5f from 109.75° to the Gmore strained 104.04°; the torsion angles change most in C4g-C5g-C6g-O6g from 64.4° at 0.1 MPa to $-168.9(5)°$ at 5.5 GPa (see Table S4 in the Supporting Information).

whereas the voids along OH···O bonds remain voluminous. Consequently, a considerable strain builds up in the structure. Moreover, the repulsing O···O contacts (Figure 1, as well as Figure S6 and Table S3 in the Supporting Information) are compressed much below the sum of the van der Waals radii (3.1 Å[13]) to 2.71(5) Å at 4.6 GPa. These O···O atoms are moved apart and the strain gradient is released when sucrose transforms to phase II. In this high-density sucrose phase the voids are smaller and evenly distributed (Figure S3 in the Supporting Information), and all nonbonding O···O distances are longer than 3.4 Å (Table S3 in the Supporting Information).

The transition to phase II is structurally characterized by the formation of twelve OH···O bonds with O···O distances shorter than 3.0 Å, which can be achieved only by sharing the hydroxy H atoms in so-called bifurcated, or three-centered, hydrogen bonds:[14] O1fH···O2g/O4f, O2gH···O4g/O4f, O3gH···O5f/O6g, and O4gH···O3f/O4f (the slash indicates two H-acceptor oxygen atoms; see Figures 1 and 5a as well as Figures S4 and S6 and Tables S3, S6, and S7 in the Supporting Information). The shortest H bond in phase I is O4fH···O1f^{1554} of 2.716(5) Å at 0.1 MPa. In phase II, atom O4f exhibits the highest, threefold H-accepting capacity. Despite the high H-accepting capacity, this hydroxy group hardly lengthens its only H-donor contact O4fH···O3f^{2546} to 2.743(6) Å (distances O···O are plotted in Figure S6 and listed in Table S3 in the supporting Information). This threefold H-accepting capacity of atom O4f is consistent with another characteristic transformation in phase II: the number of CH···O contacts, which complement the unbalanced H acceptors, is more than doubled. There are 18 CH···O contacts shorter than 2.8 Å at 4.8 GPa, compared to 7 at 0.1 MPa (Figure 5b). Pressure increases the directional character of the CH···O contacts, observed as a correlation of the C−H···O angles becoming more linear as the H···O distances decrease (see Table S6 and Figure S8 in the Supporting Information); also, above 4.8 GPa the H···O contacts are either shorter than 2.8 or longer than 3.22 Å.

Figure 5. Pressure dependence of a) OH···O and b) CH···O bond lengths in (+)-sucrose I and II. Lines joining the points are for guiding the eye only; the dashed horizontal line marks the sums of van der Waals radii for H and O atoms.[13] The explicit transformation codes given in parentheses have been listed in Table S7 in the Supporting Information. Letters "h" in atomic labels indicate the hydroxy hydrogen atoms (see Figure S7 in the Supporting Information).

In phase I, there was not such a clear gap distinguishing the shortest CH···O contacts. It is also characteristic that the shortest OH···O bonds are longer in phase II than in phase I. The shortest CH···O contacts are shorter in phase II. Previous spectroscopic and structural studies showed that pressure promotes the formation of CH···O hydrogen bonds.[15]

Jeffrey and Takagi[5a] classified OH···O bonds in sugars into five types, I–V, gradually increasing in H···O distances. In sucrose I, type I (hydroxy···hydroxy) is represented by six hydrogen bonds and type II (hydroxy···acetal O) by two bonds. These systematics of H bonds have been reversed in sucrose II, where the unsymmetrical bifurcated H bon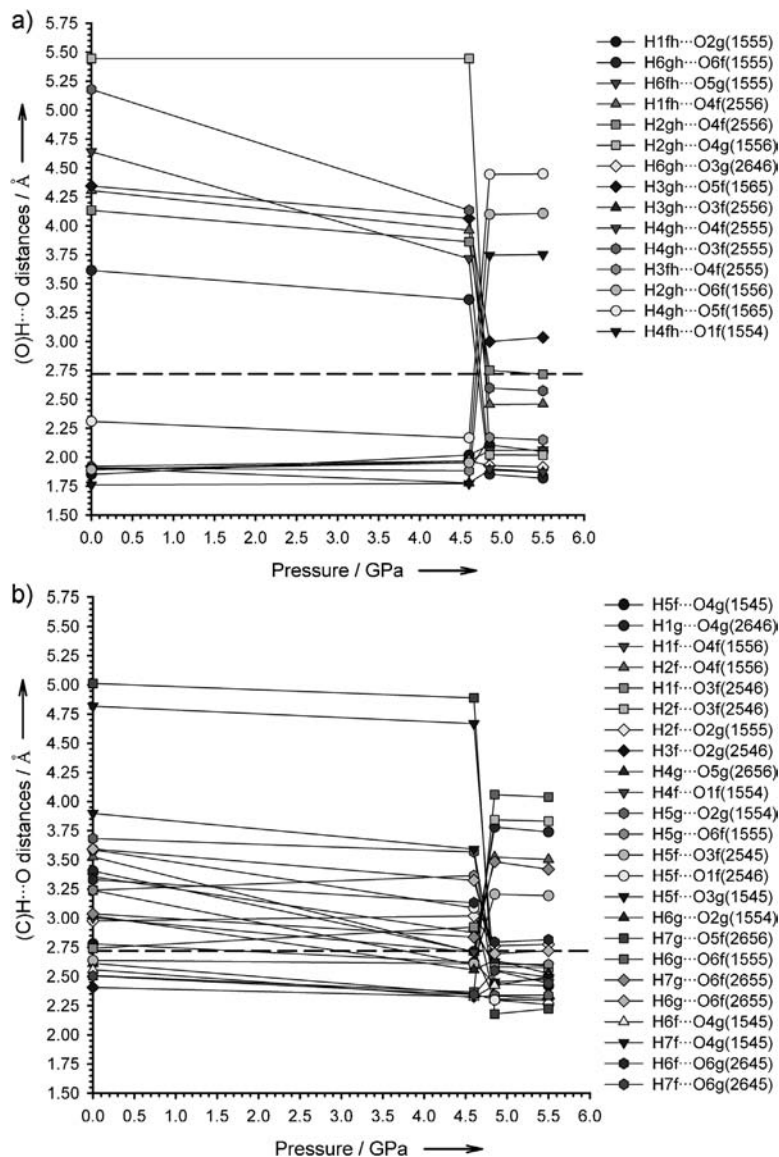ds (type IV) prevail, and the H-bond lengths are no longer correlated to the suggested types sequence. Table 1 compares the O···O distances and the H-bond types in sucrose phase I and II. The two bonds with the shortest O···O distances in sucrose II are still of the type I, however, the number of type I bonds has been halved and the third- and fourth-shortest H bonds are bifurcated (type IV).

This study on sucrose shows that the role of CH···O contacts, now commonly accepted in biological systems,[16] increases under high-pressure conditions. It can be attributed to the competition of CH···O contacts that the shortest of O···O distances in phase II above 4.8 GPa are longer than in phase I at 4.6 GPa, before the transformation (Figure 5a, Table S3 in the Supporting Information). Moreover, the

Table 1: Hydrogen-bond O···O distances (Å) and Jeffrey and Takagi's types[5a] in sucrose crystal phases I (0.1 MPa)[12c] and II (5.5 GPa). Letter A in the type descriptor indicates the simultaneous H-donor and acceptor role of the H-donor group and letter B only its H-donor role. Slashes separate the O···O contacts in bifurcated H bonds.

H-bond type		Phase I 0.1 MPa	Phase II 5.5 GPa
I	A	2.716(2)	2.635(7)
		2.781(2)	2.678(7)
		2.855(2)	2.743(6)
		2.862(2)	
		2.864(2)	
	B	2.848(2)	
II	A	2.850(2)	2.811(6)
	B	2.838(2)	
IV	A		2.681(7)/2.900(7)
			2.728(7)/2.884(6)
			2.808(6)/2.916(6)
	B		2.805(7)/2.973(6)

molecular association in phase II clearly depends on the CH···O contacts (Figure 5b, Table S6 in the Supporting Information), compressed to distances even by 0.5 Å shorter than the sum of van der Waals radii[13] of H and O (i.e. 2.75 Å). Thus the phase transition in sucrose originates from a combined effect of the collapse of voids in its structure above 4.80 GPa, and a rearrangement of the molecules into better positions for forming more hydrogen bonds. The sucrose structure shows that the characteristics of hydrogen bonds change under high pressure, and new types of hydrogen bonds can be favored. On the other hand, the OH···O bond breaking and polarity reversal can equally take place in the living tissue and in a transforming molecular environment in solution:[17] the free-energy change per one H bond at 4.8 GPa in sucrose I, assessed as the work component $\int V(p) \mathrm{d}p$, where $V(p)$ is the isothermally compressed molecular volume and p is pressure, is only 7 kJ mol^{-1}. In this respect, the observed results are consistent with the preferential formation of sucrose syrup, as small H_2O molecules can easily approach sucrose molecules and form hydrogen bonds of various types, depending on instantaneous molecular arrangements. The observed conformational flexibility of the molecule combined with the large number of H-bonding configurations hampers the sucrose crystallization. This property of all sugars is essential for the existence of honey bees and survival of plants and animals in extreme temperature conditions, from desert heat to arctic freezing, because sugars inhibit the formation of crystals, which damage living cells, for example, in the wood frog.[18] The molecule flexibility and variability of H bonding facilitate the docking of molecules in taste receptors and are likely to affect the sweetness of sucrose in different environments, too.[19] The variability is a distinctive feature of all sugars, desired by living organisms because of their high energetic value and favored solubility. The conformational flexibility of the pentose moiety is one main hinge element of

mechanisms governing the conversions of polysaccharides. In this respect our study on sucrose provides new information on the extent of structural transformations of molecules, which, in general, can change their interactions, conformation, and properties in varying molecular environments and thermodynamical conditions.

Experimental Section

High-pressure powder X-ray diffraction (PXRD) measurements were carried out on sucrose powder obtained by grinding analytical-grade sucrose (Polskie Odczynniki Chemiczne) and mounted in a modified diamond-anvil Merrill-Bassett cell (DAC).[4, 11] The methanol/ethanol/water 16:3:1 mixture saturated with sucrose, in order to prevent dissolution of the crystalline sample, was used as the hydrostatic medium. The powder-diffraction patterns were recorded by using a single-crystal Kuma KM4-CCD diffractometer equipped with a sealed Mo X-ray tube and graphite monochromator. A narrow, 0.3 mm in diameter, collimator was used to avoid the diffraction from the gasket, and the sample was rotated in $\omega \pm 7°$ scans at three χ-angle orientations at 0, 45, and 90°. After removing the diamond reflections from the recorded images, they were integrated radially for the constant 2θ angles, and the background scattering of the empty DAC was subtracted. So obtained powder diffraction patterns were analyzed by using the PowderCell package,[21] and above 4.80 GPa a new phase of sucrose II was detected, markedly different in diffraction than the ambient-pressure sucrose I.

Single crystals grown from water and glycerin/water (1:1) solutions were selected and mounted in the DAC. The samples were fixed in the chamber by a cellulose fiber; a methanol/ethanol/water 16:3:1 mixture with different concentrations of sucrose was used as the hydrostatic fluid; the concentration of sucrose was employed for controlling the size of the sample when changing the pressure (connected with the changing size of high-pressure chamber). The pressure was calibrated by the ruby-fluorescence method[22] using a Betsa PRL spectrometer with the accuracy of 50 MPa. The same Kuma KM4-CCD diffractometer equipped with a sealed Mo X-ray tube and graphite monochromator was used for the samples' centering and single-crystal diffraction measurements, according to the procedures described earlier.[23]

The high-pressure diffraction measurements on all accessible reflections were performed at 1.00, 1.80, 2.35, 2.80, 3.60, 4.60, 4.80, 4.85, 4.90, 4.95, 5.00, 5.05, 5.10, 5.15, 5.20, 5.30, 5.35, 5.50, and 5.60 GPa. The diffraction reflection intensities were compensated for the effects of the DAC absorption, gasket shadowing, and for the absorption of the sample itself.[24] To facilitate the solution of the new phase, detected in the powder-diffraction patterns and then to increase accuracy of structural refinements, the single crystal was mounted in the DAC in two, and then in three different orientations. Then the datasets were brought to one scale based on the intensities of common reflections. The structure of sucrose II was solved by direct methods and refined by full-matrix least squares.[25] The hydrogen atoms bound to carbon atoms were located from the geometry, and the hydrogen atoms of hydroxy groups either from difference Fourier maps, or refined occupancy, as a free variable in two reverse-polarity sites constrained by SHELXL instruction AFIX 83. The crystal data and experimental details are listed in Table S1 in the Supporting Information.

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