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Crystal-Structure Prediction

Insight into Solid-State Entropy from Diffraction Data**

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The prediction of crystal structures of molecular compounds from first principles remains one of the challenges in chemistry. Despite significant computational efforts invested to solve this problem it is still not possible to predict the most stable polymorphic form of a simple organic molecule.[1] One of the reasons is that most of the present crystal-structure prediction programs do not take the entropy term into account. X-ray diffraction still maintains its position as a powerful method to determine crystal structures, in which the atomic positional parameters are derived from the thermally averaged electron distribution in the unit cell calculated from the X-ray diffraction data. With accurate, high-resolution X-ray diffraction data it is possible to deconvolute the thermal vibrations of the atoms and obtain static electron densities. Over the last ten years, topological analysis developed for theoretical electron densities[2] has demonstrated its usefulness in describing interatomic interactions in crystals based on analyses of experimental static crystal electron densities[3,4] and in this way provide information on the interaction energy in the crystal. Herein we show that unique information on crystal entropies can also be obtained from accurate X-ray diffraction data through an analysis of the atomic thermal-displacement parameters. The combined knowledge on enthalpy and entropy have enabled us to verify that the unusual difference in physicochemical properties between the two closely related pentoses, ribitol and xylitol (Figure 1)—the less dense one having the higher melting point—is related to a difference in their entropies and not in their enthalpies. Furthermore the difference in a particular molecular librational mode could be identified as the origin of the entropy difference.

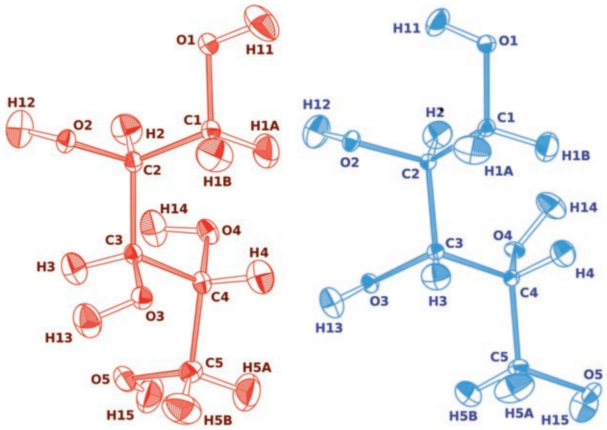

Figure 1. The molecular structures of ribitol (red) and xylitol (blue) showing the atomic labeling and displacement parameters, with thermal ellipsoids set at 50% probability.[29]

Ribitol and xylitol are epimers; they differ only in the chirality of their central carbon atom. Furthermore they are both meso forms. The crystal-structure determinations carried out almost 40 years ago by Jeffrey et al.[5,6] revealed that they both adopt bent conformations in the crystal structure leading to a conformational chirality in the solid state. Both compounds crystallize in common space groups, with four molecules in the unit cell. Ribitol crystallizes in the monoclinic space group $P2_1/c$ and is the less dense of the two compounds. Nevertheless, it has a melting point about 10° higher than xylitol (Table 1), which crystallizes in the acentric space group $P2_12_12_1$. Ribitol and xylitol display very similar hydrogen-bonding interactions, and were therefore expected to have very similar interaction energies. As the liquid phases of the two epimers do not differ in their physicochemical properties,[7] simple thermodynamic arguments show that the higher melting point represents the crystal form with the lowest free energy, which contains contributions from the crystal enthalpy and entropy. It is sometimes naively assumed that a more dense structure originates from stronger intermolecular interactions, which stabilize the crystal lattice and lead to a corresponding lower enthalpy. The results of the crystal-structure determinations of ribitol and xylitol are clearly at variance with this interpretation. Further support is

Table 1: Crystal data, sublimation enthalpy and entropy,[a] and calculated interaction energies.

	Ribitol	Xylitol
Unit cell volume [Å^3]	679.1(4)	656.1(4)
Calculated density [g cm^{-3}]	1.488	1.540
Experimental temperature [K]	122.4(5)	122.4(5)
Melting point [K][7]	374.7(2)	365.7(1)
ΔS_{sub} (298 K) [J mol^{-1} K^{-1}][7]	302	309
ΔH_{sub} (298 K) [kJ mol^{-1}][7]	161	161
Interaction energy (Espinosa approach[17]) [kJ mol^{-1}]	221(25)	228 (26)
Interaction energy (periodic DFT calculations) [kJ mol^{-1}]	171/180	172/179

[a] determined from calorimetric and vapor pressure measurements.[7]

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given by the fact that they have almost identical sublimation enthalpies, whereas their sublimation entropies are different (Table 1).[7] We found that these two chemically equivalent pentoses with their physicochemical differences are a suitable system to investigate the relation between crystal structures, intermolecular interactions, and thermodynamic properties.

High-resolution X-ray diffraction data were collected for both compounds on crystals cooled to 122.4 K.[8] To ensure that reliable parameters were available for the hydrogen atoms, this study was complemented with a neutron-diffraction experiment on xylitol, for which it was possible to grow crystals of a sufficient size for a neutron experiment.[9] An electron-density model, using the multipole formalism, was refined against the X-ray diffraction data.[10] As shown in a study of naphthalene,[11] it is possible to deconvolute thermal motion from the experimental electron densities to get static (0 K) densities that are in good agreement with electron densities from theoretical calculations.

The hydrogen atoms in the two structures play a central role in the intermolecular interactions, and it is essential to use physically realistic positional and thermal parameters of the hydrogen atoms in the description of the crystal electron density.[12] The parameters obtained from the refinement of the neutron diffraction data were used in the description of the hydrogen atoms in xylitol. In the absence of neutron diffraction data for ribitol we have used the SHADE server[13] to obtain anisotropic displacement parameters for the hydrogen atoms. The static-crystal electron densities calculated for ribitol and xylitol[12] were subjected to a topological analysis. This approach showed that the intramolecular atom–atom interactions are identical in the two molecules, as is expected from the chemical similarity between the two pentoses.[14]

The hydrogen-bond interactions (Figure 2 a,b) are expected to be the most significant contribution to the intermolecular interaction energies of ribitol and xylitol. Indeed, both compounds exploit their full potential for hydrogen-bond formation, with each of the five hydroxy groups in ribitol and xylitol acting as a donor and an acceptor in hydrogen bonds. However the resulting hydrogen-bond patterns are quite different. The sum of the O···O distances in the five OH···O hydrogen bonds are the same (to within 1 pm) for both ribitol and xylitol, but they involve nine other

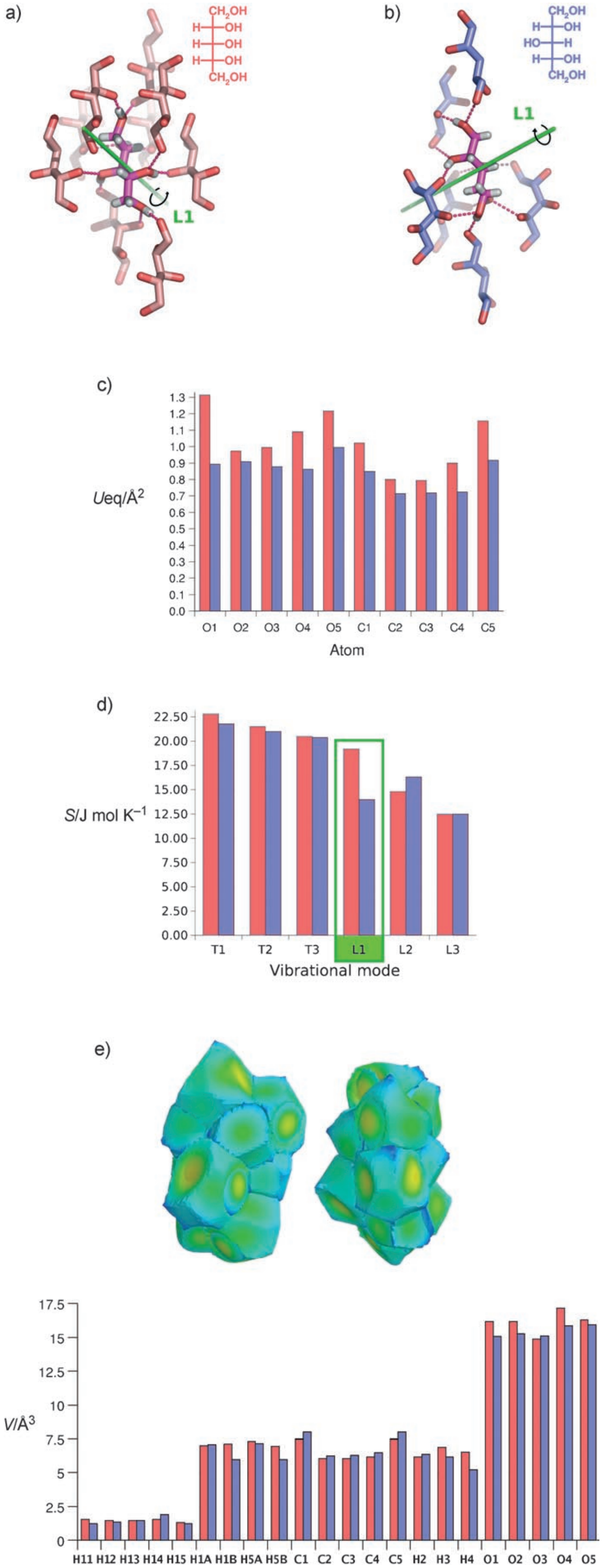

Figure 2. The surroundings of a) a ribitol and b) a xylitol molecule (crimson in (a) and (b), red O, white H) in their crystalline environment (light red in (a), blue in (b)). The Fischer projections show the difference in stereochemistry. The hydrogen-bond interactions are shown as dotted lines, and the green rods show the axis of the L1 libration. c) Differences in atomic motion of the non-hydrogen atoms between ribitol (red) and xylitol (blue). The equivalent isotropic displacement parameters U_{eq} of the non-hydrogen atoms are compared. d) The rigid-body analysis gave the three translational and three librational frequencies, 37, 42, 48, 56, 95, and 127 cm^{-1} for ribitol, and 45, 48, 41, 105, 80, and 127 cm^{-1} for xylitol, which were used to calculate their entropies using Equation (2). The histogram shows the solid-state entropies related to the librations and translations in the crystal. The mode with most significant differences, L1, is highlighted. e) The ribitol and xylitol molecular zero-flux surfaces showing the divisions into atomic basins. The volumes [Å^3] of the atomic basins defined by the zero-flux surfaces[28] are shown in the histogram.

molecules in the crystal structure of ribitol, whereas a xylitol molecule only interacts with six other molecules in the crystal. (Figure 2a,b). The topological analysis of the static crystal electron densities of ribitol and xylitol revealed distinct bond critical points for all OH⋯O hydrogen-bond interactions in both compounds.[14] A comparison of the properties (electron density and curvature (Laplacian)) of the bond critical points showed that the isomers are virtually identical; however, ribitol shows the slightly larger electron densities in the H⋯O critical points, which indicates that these interactions are slightly stronger in ribitol than in xylitol. The OH⋯O hydrogen bonds are not the only source of stabilization of crystal packing, and the crystal electron densities for both ribitol and xylitol contain additional bond critical points corresponding to weaker CH⋯O interactions. A significantly larger number of these interactions could be identified in xylitol with matching short H⋯O distances (9 compared to 5 in ribitol).[14]

The properties of the intermolecular bond critical points in crystal electron densities reflect the intermolecular interactions, and several attempts have been made to derive interaction energies from the static electron-density models.[15–17] We have used the method proposed by Espinosa and co-workers[17] that relies on the local kinetic-energy density derived from the properties of the bond critical points.[18] The results from the application of this model on the OH⋯O and CH⋯O interactions in ribitol and xylitol are shown in Table 1. The results differ significantly from the observed sublimation enthalpies and the slightly higher interaction energy of xylitol can hardly be considered significant if the standard uncertainties associated with the calculation of the interaction energies by this model are taken into account. To obtain more reliable information on the differences in interaction energies, a range of periodic HF and DFT calculations were performed[19] using the Crystal 2003 program.[20] The computed crystal energies and thus the calculated energy difference between ribitol and xylitol are sensitive to the DFT functional used. We selected the functional PW91, which Tsuzuki and Lüthi[21] have demonstrated to be a good choice for deriving intermolecular interaction energies, because it recovers most of the dispersion energy and gives results close to MP2 and coupled-cluster methods which include electron correlation explicitly. In agreement with their observations,[21] we find the PW91/6-311G(d,p) method for both compounds gives an interaction energy that with the appropriate kinetic-energy contribution and the $P\Delta V$ term[22] gives 166 kJ mol^{-1}, which is comparable to the experimental value of 161 kJ mol^{-1}. Overall, the DFT calculations performed with the three largest basis sets confirm the results from the analysis of the static crystal electron density and the thermodynamic measurements, namely that the difference in physicochemical properties is not due to a difference in the solid-state enthalpies (Table 1).

This result drew our attention to possible differences in the atomic motion of the two pentoses. We realized that there was a systematic difference in the magnitude of their atomic displacement parameters, which are more than 20% larger for some atoms in ribitol. This difference is most pronounced for atoms further away from the centre of mass of the molecules (Figure 1 and Figure 2c), indicating that the difference can be described as a collective librational motion of all the atoms in the molecule. We have analyzed the atomic motion of ribitol and xylitol in terms of a TLS model (translation, libration, screw; correlation of translation and libration)[23] in which the molecules are considered as rigid bodies translating and librating in a harmonic mean field of the surrounding molecules in the crystal.[24] This analysis revealed significant difference between ribitol and xylitol in the rigid-body libration (L1) illustrated in Figure 2a and b. The larger frequency of the xylitol L1 libration corresponds to smaller displacements compared to ribitol.

Assuming that a simple-harmonic-oscillator model can be applied to describe the rigid-body vibrations, we can use the T and L rigid-body mean-square displacements $\langle u^2\rangle$ to calculate the associated frequency through the relation in Equation (1).[25]

$$\langle u^2\rangle = \frac{h}{8\pi^2\mu\nu}\coth\left(\frac{h\nu}{2kT}\right) \tag{1}$$

From the frequencies ν obtained this way, the vibrational entropy of the crystals as a function of temperature can be calculated as a sum of the contributions from each oscillator [Eq. (2)].[25]

$$S_{\mathrm{vib}}(T) = nR\left(\frac{h\nu}{kT}\left[\exp\left(\frac{h\nu}{kT}\right)-1\right]^{-1} - \ln\left[1-\exp\left(-\frac{h\nu}{kT}\right)\right]\right) \tag{2}$$

The sum of contributions to the entropy from the three translational and three librational rigid-body motions to the total entropy is S_{rigid} (298 K) = 111 J mol^{-1} K^{-1} for ribitol and S_{rigid} (298 K) = 106 J mol^{-1} K^{-1} for xylitol.

The close structural similarity of the two compounds makes it reasonable to assume that they have identical gas-phase rotation and translation entropies, which allows[26] for a comparison (Figure 3) of the entropy difference, with the difference between the standard sublimation entropies derived from vapor pressure and calorimetric measurements,[7] namely ΔS_{sub}(298 K) = 302 J mol^{-1} K^{-1} for ribitol and 309 J mol^{-1} K^{-1} for xylitol. The difference of 7 J mol^{-1} K^{-1} is in quantitative agreement with the entropy

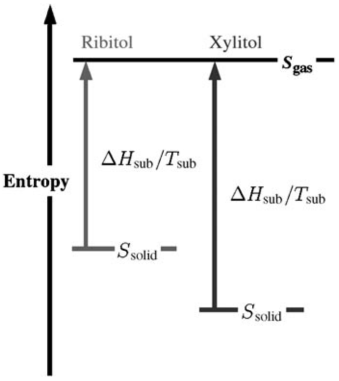

Figure 3. The solid-state entropy S_{solid} of ribitol must be larger than that of xylitol in order to explain the higher melting point. It is assumed that both have identical entropies in the gas phase (S_{gas}).

difference calculated from the rigid-body vibrations of ribitol and xylitol in the solid state. It is a considerable difference, corresponding to about 10% of the average melting entropy for organic compounds.[27]

It is the rigid-body libration (L1) about an axis perpendicular to the long axis of the molecules (Figure 2d) that gives the major contribution to the difference between the solid-state vibrational entropies of ribitol and xylitol. This mode is visualized in Figure 2a,b as a libration around the green vectors. The larger libration in ribitol seems to correlate with the larger volume of the unit cell. The atomic volumes defined by the atomic zero-flux surfaces[28] have been calculated from the electron density (Figure 2e). The additional space in the unit cell of ribitol is located close to the oxygen atoms O1, O2, O4, and O5, all atoms in the perimeter of the molecule, and those most affected by its larger L1 libration. This vibration can thus be correlated with the larger unit-cell volume and corresponding lower density for ribitol. At temperatures close to the melting point of ribitol and xylitol, the difference between their solid-state entropies would lead to a difference of about 3 $\mathrm{kJ\,mol^{-1}}$ in their Gibbs free energies. It should be noted that in the prediction of crystal structures for organic compounds, the different polymorphic forms that are the most likely candidates for a crystal structure are found within an energy gap of a few $\mathrm{kJ\,mol^{-1}}$.[27]

The atomic displacement parameters derived from refinement of accurate diffraction data and normally only used to illustrate atomic probability distributions (Figure 1) contain information on atomic vibrational movements that can be used in the calculation of crystal entropies. Through an analysis of the atomic displacement parameters, we were able to show that the higher melting point of the less dense ribitol is due to its higher solid-state entropy caused by a lower frequency of one of the librational movements in the crystal. We hope that these results may stimulate development of crystal prediction methods that not only focus on the enthalpy but also include the entropy term.

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