DL-Ribose Crystal Structures: the Glass–Crystal Transformation

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Dedicated to Professor Dr. *Dieter Seebach* on the occasion of his 75th birthday for his inspiration and example

'*In the past few years the glass transition phenomenon has won general recognition as one of the most outstanding unsolved problems in condensed matter physics*' [1].

We present two crystal structures of DL-ribose and a first glimpse into the mechanism of the glass–crystal transformation of sugars.

Introduction. – Following our belated crystal structure analysis and ^{13}C-MAS-NMR study of D-ribose [2], it seemed appropriate to complement this work by a similar study of the racemate, the properties of which have attracted attention on account of its possible role in a prebiotic world [3][4]. Here, we describe two crystal structures of DL-ribose, compare them with those of D-ribose, and examine by NMR methods the transformation of the glass obtained by cooling the melted sugar back into the crystalline form. Our new results point the way towards the recognition of possible catalytic processes in the ribose glass–crystal transition.

Crystal Structures. – We have found two polymorphs (*Table*), both obtained by evaporation of a solution of a 1:1 mixture of D- and L-ribose in dioxane. Form I, melting at 125 °C, is monoclinic, space group $P2_1/c$, $Z = 4$. Although the crystals were of poor quality, X-ray structure analysis showed that the molecules are exclusively in the β-pyranose form, in contrast to the D-ribose structure, which contains β- and α-pyranose anomers in an approximate proportion of 2:1.

In spite of this difference, the crystal structures of Form I of DL-ribose and D-ribose are remarkably similar, as suggested by the close resemblance of the unit cell dimensions (*Table*), and as seen by inspection of the structures viewed in projection down the short crystal axis of each (*Fig. 1*). The main difference is that molecules related by an approximate non-crystallographic screw axis in the chiral crystal are related by a center of symmetry in the racemate. Similar relationships exist between the chiral and racemic crystals of several amino acids, for example, L- and DL-leucine [5].

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Table. *Unit Cell Dimensions at 100 K of the Crystal Structures of* D-*Ribose* (Form I) *and the Two Polymorphs of* DL-*Ribose* (Forms I and II)[a])

	D-Ribose (Form I)	DL-Ribose (Form I)	DL-Ribose (Form II)
Space group	$P2_1$	$P2_1/c$	$Pbca$
Z	4	4	8
a [Å]	4.786(2)	4.801(2)	11.5507(4)
b [Å]	21.463(5)	21.692(7)	8.8422(3)
c [Å]	6.487(2)	6.280(2)	11.9350(4)
β [°]	110.82(1)	107.40(1)	
V [Å^3]	622.9(3)	624.1(3)	1218.96(7)
ρ_c [g cm^{-3}]	1.601	1.598	1.636
Reflections $I > 2\sigma(I)$	1497/1142	848/597	1403/1205
R [$I > 2\sigma(I)$]	0.061	0.129	0.032

[a]) Numbers in parentheses are estimated standard uncertainties in units of the last decimal place as calculated by least-squares fitting to the measured diffraction angles. They need not be taken too seriously. Detailed information for DL-ribose crystal structures is given in the *Supporting Information*[2]).

Later, a second Form II, melting at 133 °C, was obtained: orthorhombic, space group $Pbca$, $Z = 8$ (*Table* and *Fig. 2*). Again, the molecules are in the β-pyranose structure, but the H-bonding pattern and hence the molecular arrangement are different [2].

Breslow and *Cheng* [3] reported that D- and DL-ribose have the same melting point and concluded that the latter consists of a solid solution of the enantiomers. Our crystalline samples of DL-ribose melt at 125 °C and 133 °C compared with 88 – 92 °C for the pure enantiomer and have quite distinct structures.

NMR Experiments. – In our earlier work on D-ribose, ^{13}C-MAS-NMR spectroscopy was used to show that the liquid obtained by melting the crystal contained α- and β-furanose as well as the α- and β-pyranose molecules present in the crystal. On cooling the melt, broad signals indicative of a glassy state were obtained. After a month at 4 °C, the glass had transformed back to the crystalline state. It seemed important to observe the corresponding behaviour of the racemate. In contrast to the ten signals in the ^{13}C-NMR spectrum of the chiral crystal, the spectra of the two racemic crystal forms contain only the five signals of β-pyranose. The spectra of the two polymorphs are similar but clearly distinguishable (*Fig. 3*).

On crystal melting, the spectra of both crystal forms become identical and are indistinguishable from that of the liquid obtained by melting the chiral crystal, with signals from α- and β-furanose as well as from α- and β-pyranose (*Fig. 4,b*), as observed many years ago by *Lemieux* and *Stevens* for D-ribose in aqueous solution [6]. As for D-ribose, cooling the melt leads to a glassy state with broad NMR signals (*Fig. 4,c*). Again, as for D-ribose, the glass was found to show the characteristic spectrum of the original crystal polymorph after a few weeks at 4 °C (*Fig. 4,d*).

The Glass–Crystal Transformation. – We can find very little information concerning the mechanism of the glass–crystal transformation in organic compounds. Even for

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[2]) *Supporting Information* may be obtained upon request from the authors.

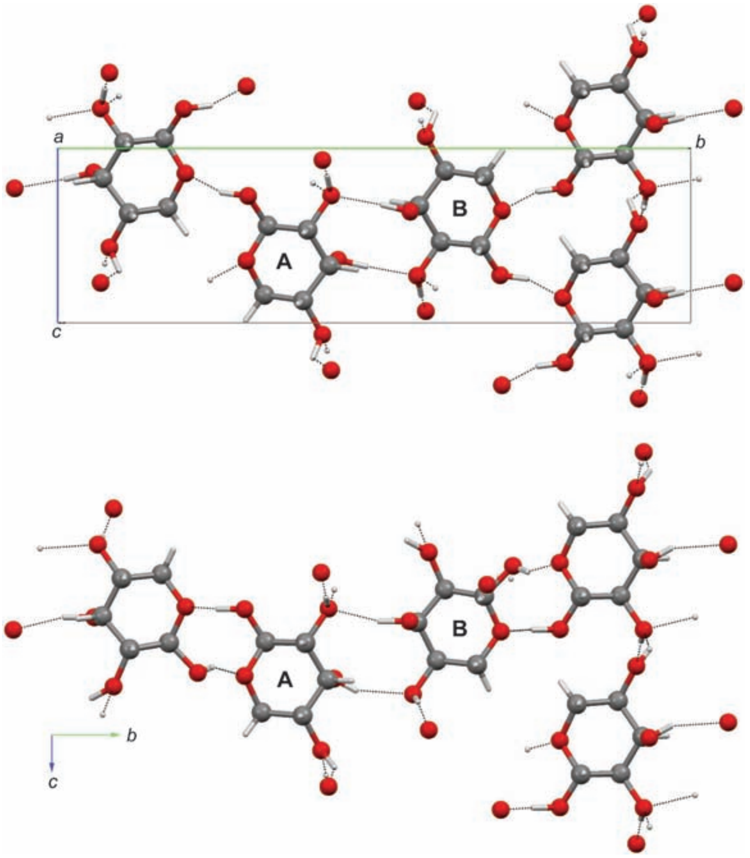

Fig. 1. *Crystal structure of* DL-*ribose* (Form I) *in projection down the* a *axis* (upper). Analogous view of D-ribose (Form I, lower). The similarity is striking, the main difference being that pairs of molecules **A** and **B** related by a center of symmetry in the racemate are related by a non-crystallographic screw axis in the chiral structure.

sugars, where the existence (and persistence) of the glassy state is of practical importance, very little seems to be known about the details of the process at the molecular level. In particular, we are not aware of any previous application of MAS-NMR methods to the problem, apart from our recent exploratory study of the glass–crystal transition of D-ribose [2]. The glassy state covers a wide range from frozen liquid to disordered crystal. In the present example, the glass resembles the liquid in that, as indicated by the NMR spectrum in *Fig. 4,c*, it contains a mixture of isomers, whereas the crystal is built from the single β-pyranose isomer.

We have now taken up the glass–crystal transition of DL-ribose in somewhat more detail and have been able to show that the process is catalyzed by H_2O. We found that while some samples of the cooled material remained in the glassy state indefinitely, other samples showed the characteristic five-line ^{13}C-MAS-NMR spectra of crystalline racemate after a few days at 4 °C. The difference was found to depend on the absence or

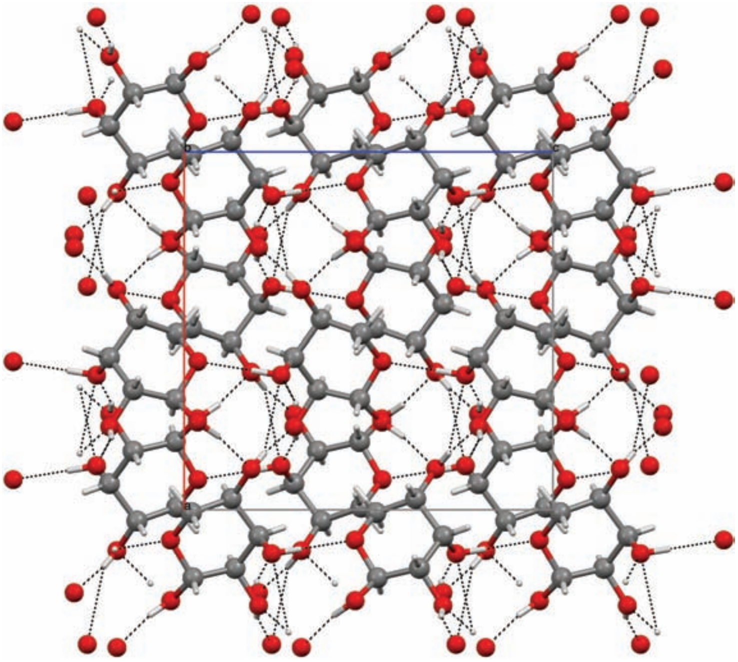

Fig. 2. *Crystal structure of* DL-*ribose* (Form II) *in projection down the* b *axis*

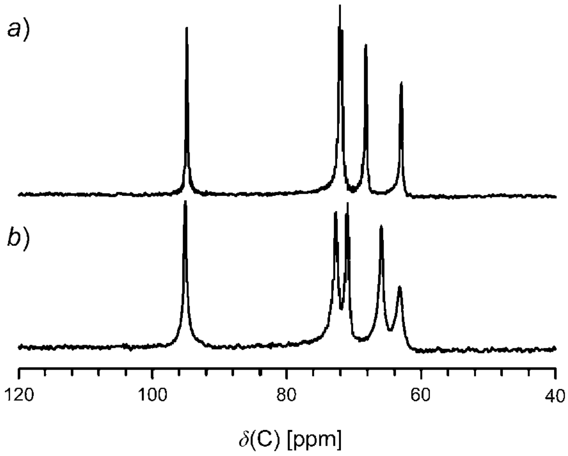

Fig. 3. *^{13}C-MAS-NMR Spectra of the two forms of crystalline* DL-*ribose. a*) Form I, *b*) Form II.

presence of traces of H_2O absorbed from the atmosphere. Closed samples showed no change, whereas samples stored in open containers adsorbed traces of H_2O (*ca.* 1 mg for a sample of 40 mg) and showed, by applying the appropriate NMR experiment (namely, a ^{13}C cross-polarization experiment which selects the species with slow

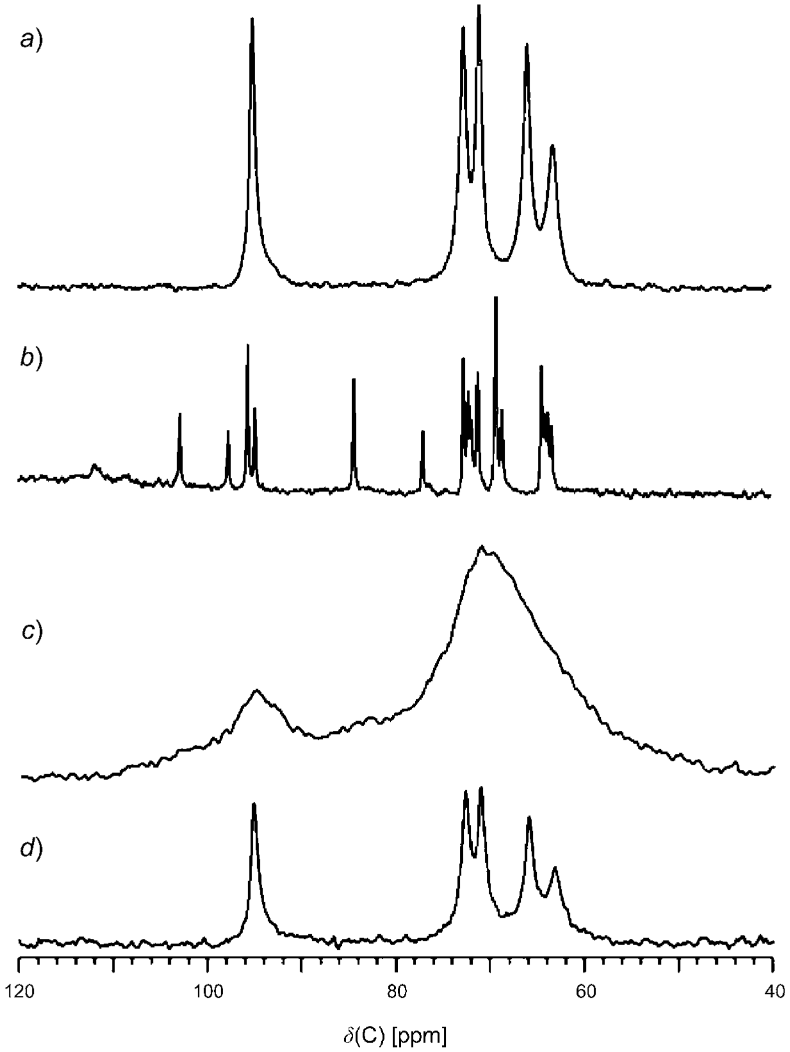

Fig. 4. *^{13}C-MAS-NMR Spectra of* DL*-ribose, Form II.* Spectrum *a* was recorded at 20 °C, the initial polarization was generated by cross polarization (CP; contact time was 1 ms), the number of scans was 144. Spectrum *b* was recorded at 135 °C by direct excitation of ^{13}C spins and is the sum of 800 acquisitions. Then, the sample was cooled to 20 °C, and after *ca.* 1 h the CP spectrum in *c* was acquired with contact time of 0.1 ms and 1000 scans. A shorter contact time (0.1 ms) proved to maximize the intensity in the non-crystalline phase, while a contact time of 1.0 ms was optimal for the crystalline phase. Spectrum *d* was recorded on the same sample after having been stored *ca.* one month without cap at 4 °C. The spectrum *d*) was generated by CP under similar conditions as in *a*.

dynamics, see *Supporting Information*[2])) the characteristic sharp five-line ^{13}C-MAS-NMR spectrum of the crystal, presumably superimposed on the broad-peak spectrum of the glassy state. In addition, the ^{13}C-INEPT spectrum (which selects species with fast isotropic dynamics) recorded of the same sample showed a complex many-line spectrum closely similar to that of the melted state and attributable here to the aqueous solution (see Fig. S1 in *Supporting Information*[2])). A quantitative assay of the various phases was not attempted[3]).

However, we may conclude that the glass–crystal transformation of DL-ribose is catalyzed by the presence of small amounts of H_2O absorbed from the atmosphere. Material from the glass surface is first dissolved in the absorbed H_2O and then transformed to the thermodynamically more stable crystalline state. Since a mixture of isomers is present in the dissolving glass and in the aqueous solution, continuous re-equilibration must take place in solution as β-pyranose isomers are removed from it by attachment to the growing crystal. Of course, the recognition of an essential role for H_2O, even in trace amounts, in chemical and physico-chemical processes is nothing new, and it may appear obvious that the glass–crystal transformation of sugars (and other classes of strongly H-bonded substances) can take place only in the presence of at least traces of H_2O (or other solvents). However, we are unaware of any previous experimental demonstration that this is actually the case[4]). Note that, once the intermediacy of H_2O in the glass-crystal transformation is recognized, the process should not, strictly speaking, be classified as a high-order phase transition of the sugar because it requires the presence of the additional component.

We hope that the experiments described here may point the way towards the recognition of possible catalytic processes in other glass–crystal transformations.

Experimental Part

Sample Preparation. A sat. soln. of DL-ribose was prepared by dissolving a 1:1 mixture of D- and L-ribose in hot 1,4-dioxane. The soln. was cooled to r.t. and evaporated under reduced pressure. During this process, a white solid precipitated providing crystals that were suitable for X-ray analysis.

Crystal-Diffraction Experiments. X-Ray diffraction data were obtained at 100 K with MoK_α radiation (λ 0.71073 Å) on a *Bruker Nonius APEX-II* system equipped with a graphite monochromator. Poor crystal quality of Form I gave only a limited data set. The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* with deposition numbers CCDC-876306 (Form I) and CCDC-876305 (Form II). These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_rwquest/cif.

NMR Experiments. ^{13}C-NMR Spectra were recorded with a *Varian Infinity + 500* spectrometer operating at a ^{13}C *Larmor* frequency of 125.67 MHz with a 4-mm *Varian T3* double-resonance MAS probe. Spectra were collected at a MAS frequency of 10 kHz and, when not specified otherwise, at 20 °C. Cross-polarization (CP) ^{13}C spectra were acquired where the protons were excited with a 5.5-μs pulse, and the polarization was subsequently transferred to ^{13}C using an adiabatic CP step with a spin-lock field centered at 50 kHz. During acquisition, 60-kHz TPPM (two pulse phase modulation) decoupling was applied with a 30° phase shift. The spectral width was 20 kHz, the acquisition time was 25.6 ms, and a line

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[3]) At time of writing, we are unable to prepare new samples of Form I. Moreover, although the sample of melted Form I had recrystallized back to Form I on cooling (see *Fig. 3*), in a later experiment the liquid melt was held at the higher temperature of 135 °C for several hours, it yielded Form II after cooling and storage at *ca.* 5 °C. Could this turn out to be another example of the phenomenon of 'disappearing polymorphs'? See [7].

[4]) The hygroscopic properties of sugars such as sucrose and glucose in the amorphous state, their tendency to form a hard cake ('caking effect'), and their transformation under certain conditions to a crystalline state are well-known in the food industry [8].

broadening of 30 Hz was applied before *Fourier* transform. The recycle delay was 240 s. The ^{13}C-NMR spectra in the melt were acquired using direct excitation. The 90° ^{13}C pulse was 5.5 μs, the spectral width was 20 kHz, and, during the 60-ms acquisition time, a 10-kHz TPPM ^{1}H decoupling was applied. The recycle delay was 3 s. ^{13}C-NMR Spectra were externally referenced to the peak of adamantane at 38.48 ppm rel. to TMS.

REFERENCES

[1] C. Alba-Simionesco, J. Fan, C. A. Angell, *J. Chem. Phys.* **1999**, *110*, 5262, cited in A. Gavezzotti, ‘Molecular Aggregation’, IUCr Monographs on Crystallography 19, Oxford Science Publications, Oxford, 2007.

[2] D. Šišak, L. B. McCusker, G. Zandomeneghi, B. H. Meier, D. Bläser, R. Boese, W. B. Schweizer, R. Gilmour, J. D. Dunitz, *Angew. Chem.* **2010**, *122*, 4605; *Angew. Chem., Int. Ed.* **2010**, *49*, 4503.

[3] R. Breslow, Z.-L. Cheng, *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 9144.

[4] G. Springsteen, G. F. Joyce, *J. Am. Chem. Soc.* **2004**, *126*, 9578.

[5] J. D. Dunitz, A. Gavezzotti, *J. Phys. Chem. B.* **2012**, *116*, 6740.

[6] R. U. Lemieux, J. D. Stevens, *Can. J. Chem.* **1966**, *44*, 249.

[7] J. D. Dunitz, J. Bernstein, *Acc. Chem. Res.* **1995**, *28*, 193.

[8] B. Makower, W. B. Dye, *J. Agric. Food Chem.* **1956**, *4*, 72.

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