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Two-Dimensional NMR Spectral Study of the Tautomeric Equilibria of D-Fructose and Related Compounds

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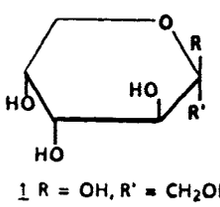
The use of two-dimensional NMR techniques and spin simulation afforded a detailed set of chemical shift and spin–spin coupling data for the main tautomeric forms of D-fructose in dimethyl sulfoxide and aqueous solutions. Differences in vicinal coupling parameters for β-D-fructofuranose in the two solvents are taken as evidence that this tautomer incorporates intramolecular hydrogen bonding in dimethyl sulfoxide, which helps to account for its exceptional prominence in this solvent. The enhanced proportion of α-D-fructofuranose in dimethyl sulfoxide over that in water also receives comment. Also described are corresponding data from NMR measurements on the tautomeric equilibria of disaccharides that contain a D-fructose reducing-end residue, and of the homomorphic ketose, L-*galacto*-2-heptulose, i.e. structurally related compounds that may entail different kinds of hydrogen-bonding possibilities. Evidence indicating the presence of extensive inter-residue hydrogen bonding within the individual tautomers of the disaccharide turanose is provided by the pattern of hydroxyl proton chemical shifts in dimethyl sulfoxide.

KEY WORDS 2D NMR Tautomeric equilibrium D-Fructose Lactulose Turanose, L-*galacto*-2-Heptulose

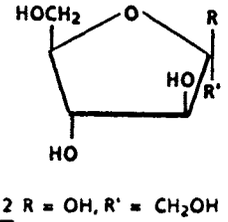
INTRODUCTION

As is well known, the tautomeric equilibria of sugars may vary considerably with the solvent. An exceptionally large variation of this kind is exhibited by D-fructose,[1–4] in that its β-pyranose form (**1**) is by far the major tautomer (*ca.* 75%) in water, whereas the β-furanose form (**2**) is the preponderant form (*ca.* 55%) in dimethyl sulfoxide (DMSO). Such characteristics as the temperature dependence of the chemical shifts and spacings of hydroxyl proton resonances[3,4] and ^{13}C T_1 values for the individual tautomers in the two solvents[4] appear to account for this marked change in composition. That is, they indicate that water is particularly effective as a solvent in preferentially stabilizing the β-pyranose[5,6] **1** and that, in contrast, the greater prominence of the β-furanose **2** in DMSO solution is associated with a facility to form hydrogen bonds intramolecularly.[3,4] It is also noteworthy that the α-furanose tautomer **3** is increased from *ca.* 4% in water to *ca.* 20% in dimethyl sulfoxide, whereas the α-pyranose tautomer **4** is a trace component in either solvent.

Through the application of two-dimensional (2D) NMR methodology, further observations on the tautomeric equilibrium of D-fructose are offered here. They are supplemented by comparable equilibrium data for several related compounds, namely, 1-*O*-methyl-D-fructose, 4-*O*-β-D-galactopyranosyl-D-fructose (lactulose), 3-*O*-α-D-glucopyranosyl-D-fructose (turanose) and the homomorphic 7-carbon ketose L-*galacto*-2-heptulose.



1 R = OH, R' = CH_2OH



2 R = OH, R' = CH_2OH

4 R = CH_2OH, R' = OH

3 R = CH_2OH, R' = OH

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EXPERIMENTAL

The NMR spectra were recorded with solutions of 25–50 mg of D-fructose, and the other sugars used in this study, in either D_2O or DMSO-d_6. In some instances, where indicated, the samples in the latter solvent were first deuterium-exchanged with D_2O (3–4 times) to ensure deuteriation of the hydroxyl groups. For equilibration of the tautomeric mixtures, the solutions were stored at room temperature for 4–8 weeks (a sample of D-fructose in DMSO-d_6, when kept at 70 °C, decomposed after 1 week).

One-dimensional high-resolution ^1H and ^1H-decoupled ^{13}C NMR experiments were performed on a

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Varian XL-300 and/or a Bruker WH-400 spectrometer. To enhance the resolution of ^{1}H Fourier transform NMR spectra, a double-exponential apodization function was applied to the free-induction decays prior to Fourier transformation. Whenever resolution enhancement was applied, FIDs were zero-filled to obtain acceptable digital resolution.

2D homonuclear-correlated experiments were carried out using Jeener's[7] two pulse sequence (90°–t_1–90°–acquire). Typical spectral parameters were as follows: 300 Hz in both dimensions; 32 transients for each FID; 256 t_1 increments; recycling delay 1.0 s; and data matrix for processing 1024 × 512. Free induction decays were subjected to 'pseudo-echo' processing and diagonal folding was applied to the final spectra.

For 2D J-resolved experiments a 90°–$t_{1/2}$–180°–$t_{1/2}$–acquire pulse sequence was employed,[8] using spectral widths of 300 Hz and 50 Hz in the F_2 and F_1 dimensions, respectively, a 2048 × 256 data matrix, 64 time increments and 32 transients for each FID, and the recycling delay time was 1.0 s. The time domain data were subjected to 'pseudo-echo' processing prior to 2D Fourier transformation, and the resulting frequency domain data were processed to remove tilt and also symmetrized.

The ^{1}H–^{1}H relayed coherence transfer was achieved using the sequence[9] 90°–t_1–90°–τ–180°–τ–90°–acquire with a τ delay of 45 ms, optimizing the second coherence transfer step for $J \approx 12.5$ Hz. Data processing and other acquisition parameters were similar to those used for the homonuclear-correlated experiments.

2D heteronuclear-correlated spectra were obtained using the sequence[10] (90°, ^{1}H)–$t_{1/2}$–(180°, ^{13}C)–$t_{1/2}$–τ_1–(90°, ^{1}H; 90°, ^{13}C)–τ_2–(BB, ^{1}H)–acquire. The fixed delays correspond to the coupling $J(^{13}C, ^1H) = 140$–150 Hz. Typical parameters were as follows: spectral widths of 3500 Hz in the F_1 and 300 Hz in the F_2 dimensions; 2048 × 512 data matrix; recycling delay 1.5 s; and 256 transients for each of the 128 t_1 increments.

Simulated 1D ^{1}H NMR spectra were obtained by an iterative spin-simulation program based on the Fortran program LAME, which was implemented in the Varian VXR 4000 data station. The RMS error of the calculated *vs.* experimental spectrum was found to be ±0.1 Hz.

RESULTS AND DISCUSSION

Recent improvements in spectral analysis, facilitated by 2D methodology, now allow for a fuller description than previously of the spectra of the tautomers of D-fructose in water and DMSO. This includes extensive data for the carbon-bonded protons, in DMSO, following deuterium exchange of the hydroxyl protons, which had been the major source of information in earlier studies.[2–4]

Many of the ^{1}H signal assignments for the three main tautomers of D-fructose (**1**, **2** and **3**), in DMSO-d_6 at 20 and 70 °C, listed in Table 1, were obtained from the heteronuclear shift correlation (HETCOR) spectrum (Fig. 1), which makes use of the already analysed ^{13}C NMR spectrum.[4] Ambiguities in resolving the methylene proton resonances were largely clarified by means of a multiple step ^{1}H–^{1}H relay experiment (Fig. 2), which afforded detailed information about most of the H-1,1′ and H-6,6′ coupling networks for each tautomer. The assignments given in the accompanying 1D NMR spectrum incorporate these details. Second-order effects and peak overlap, apparent for such resonances as those of H-3, -4 and -5 even at 500 MHz, were partly compensated for by spin simulation of the appropriate subspectra. Having combined the data from these various sources (Table 1), an extensive set of ^{1}H chemical shift parameters are now available for the three tautomers in DMSO, in addition to most of the associated ^{1}H–^{1}H couplings.

Analogously, most of the ^{1}H NMR spectrum of D-fructose in D_2O (Fig. 3) has been analysed affording, in particular, data for the β-furanose **2** (Table 2). The parameters obtained for the β-pyranose **1** are in full agreement with those reported[11] previously, and are wholly consistent with the $^2C_5$ conformation expected for this tautomer.

Especially noteworthy are the coupling data for β-fructofuranose at 20 °C, i.e. J(3,4) and J(4,5) are 6.4 and 1.4 Hz, respectively. In terms of dihedral angles, these values suggest that **2** is prominently represented by conformations in which H-3 and H-4 approach the antiperiplanar arrangement, and also wherein H-4 and H-5 subtend an angle between 60° and 90°. Considering the

Table 1. ^{1}H NMR chemical shifts[a] and coupling constants for the three main tautomers of D-fructose in dimethyl sulfoxide at 20 and 70 °C

	Chemical shift, δ (ppm)							J (Hz)		
	β-Pyranose		β-Furanose		α-Furanose[b]			β-Pyranose,	β-Furanose	
Proton	20 °C	70 °C	20 °C	70 °C	20 °C	70 °C		70 °C	20 °C	70 °C
H-1	3.39	3.44	3.40	3.44			^2J(H-1, H-1′)	11.32		11.05
H-1′	3.25	3.29	3.23	3.28			^3J(H-3, H-4)	10.1[c]	6.4[c]	7.1[c]
H-3	3.55	3.59	3.80	3.85	3.77	3.83	^3J(H-4, H-5)	4.0[c]	1.4[c]	5.9[c]
H-4	3.58	3.61	3.79	3.85	3.72	3.75	^3J(H-5, H-6)	1.91	5.79	2.30
H-5	3.62	3.68	3.53	3.58	3.69	3.76	^3J(H-5, H-6′)	1.56	3.27	3.58
H-6	3.77	3.82	3.48	3.53	3.52	3.57	^2J(H-6, H-6′)	12.05	11.15	11.32
H-6′	3.41	3.47	3.37	3.44	3.40	3.44				

[a] From TMS.
[b] Tentative values of ^3J(H-5, H-6′) = 3.0 Hz, ^2J(H-6, H-6′) = 11.6 Hz and ^3J(H-4, H-5) = 5 Hz from 2D J-resolved spectrum at 70 °C.
[c] Values obtained by spin simulation.

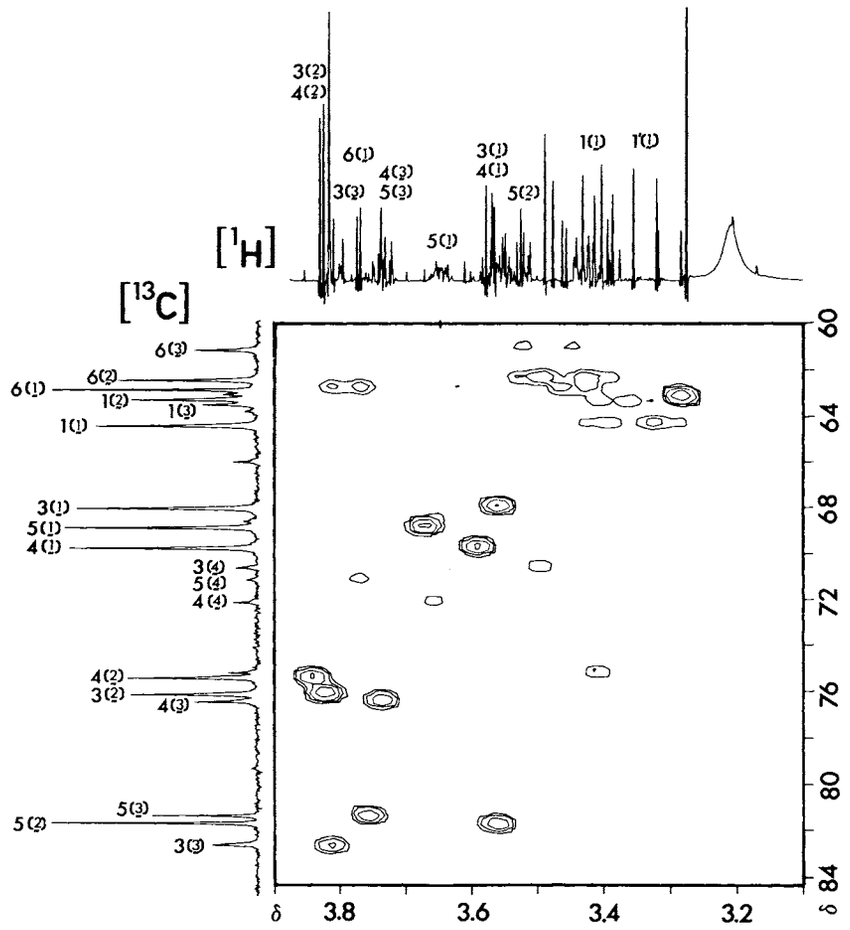


Figure 1. ^{13}C–^{1}H 2D shift correlation spectrum (300 MHz) of an equilibrated solution of the D-fructose tautomers in DMSO-d_6 at 70 °C.

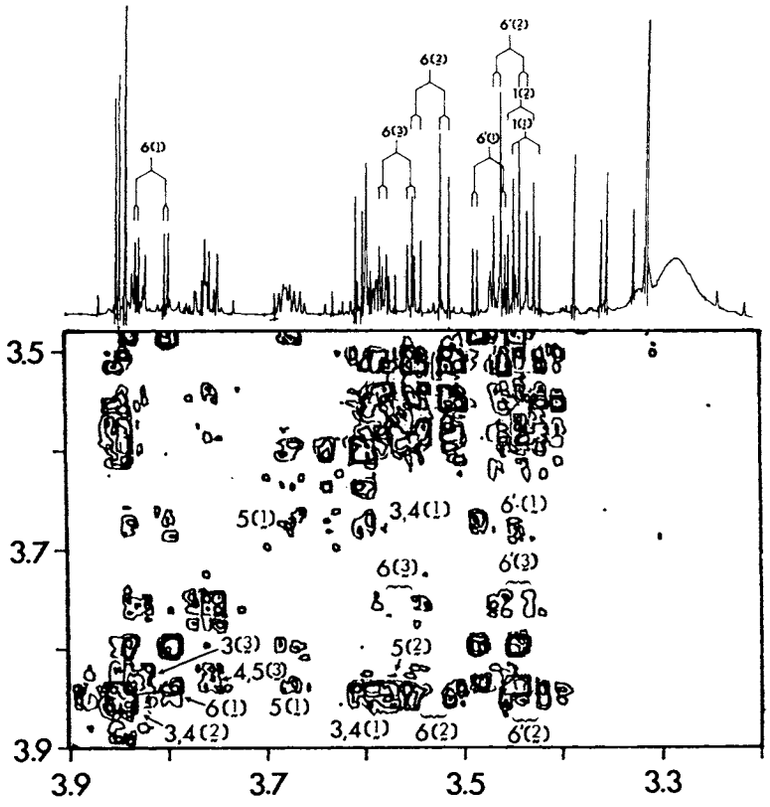


Figure 2. Relay ^{1}H 2D spectrum (300 MHz) of an equilibrated solution of the D-fructose tautomers in DMSO-d_6 at 70 °C.

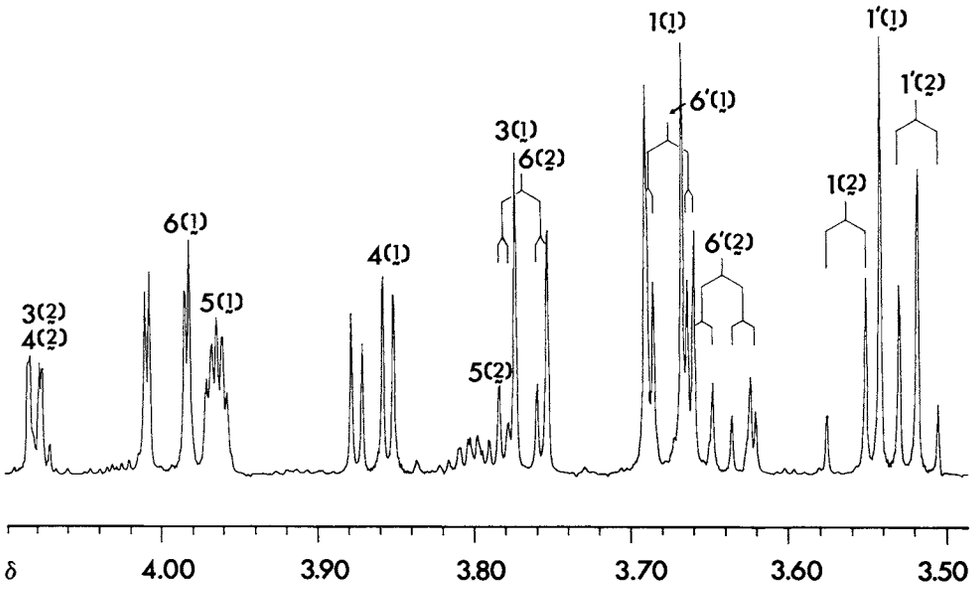


Figure 3. ^{1}H NMR spectrum (500 MHz) of an equilibrated mixture of the D-fructose tautomers in D_2O at 70 °C.

^2E conformation (C-2 is above the plane formed by C-3, C-4, C-5 and O-5), which broadly satisfies this geometry, it appears that intramolecular hydrogen bonding can readily take place between 2-OH and 6-OH (in addition to, vicinally, between 2-OH and 3-OH). Although this suggestion is consistent with the earlier proposal that hydrogen bonding helps to stabilize **2**, it shifts the emphasis away from those thought to involve 6-OH with 3-OH and/or 1-OH and 4-OH.

This information does not constitute direct evidence of a hydrogen bond within **2**. However, the conformation of this tautomer is altered when the temperature is raised, presumably with an increase in the distance between 2-OH and 6-OH. Hence, at 70 °C the chemical shifts of H-3, -4 and -5 are displaced downfield and, more particularly, J(3,4) and J(4,5) are 7.1 and 5.9 Hz, respectively (Table 1). Accordingly, these couplings indicate a shift towards conformations in which both pairs of protons, H-3, H-4 and H-4, H-5, are antiperiplanar. In the ^4E conformation (C-4 is above the plane formed by C-2, C-3, C-5 and O-5), for example, which could accommodate this arrangement of the secondary protons, 2-OH and 6-OH are no longer favorably disposed for intramolecular hydrogen bonding, as at 20 °C. The possibility that this is accompanied by a change in the (normally slow) equilibration of the tautomers could not be determined, because the sugar decomposed relatively rapidly at this elevated temperature.

It is worth noting that, in D_2O at 20 °C (Table 2), the larger values of 8.1 and 7.4 Hz for coupling between H-3, H-4 and H-4, H-5, respectively, are even more strongly indicative of such a conformation as ^4E. We proposed that this evidence for a substantial difference in the conformation of β-fructofuranose in DMSO and water at 20 °C is consistent with the fact that the relative proportion of the tautomer in the two solvents is different. It is also consistent with our suggestion[2–4] that intramolecular hydrogen bonding is a source of stabilization of the tautomer in DMSO.

Although the α-furanose form **3** is a relatively minor species, its presence is increased from *ca.* 4% in aqueous solution to *ca.* 20% in DMSO (Table 3), which partially accounts for the decrease in the percentage of β-fructopyranose.[3] However, the data available[4] have given no indication that **3** incorporates an intramolecular hydrogen bond, e.g. between 3-OH and 1-OH or 6-OH. In fact, the proportions of the α- and β-furanose forms both increase with increasing temperature in D_2O and DMSO (Table 3). Also, the relative proportions of the α- and β-form increase in D_2O (from 1 : 5 to

Table 2. ^{1}H NMR chemical shifts[a] and coupling constants for the two main tautomers of D-fructose in D_2O at 20 °C

				δ (ppm)			
Tautomer	H-1	H-1′	H-3	H-4	H-5	H-6	H-6′
β-Pyranose	3.68	3.53	3.76	3.86	3.96	4.00	3.68
β-Furanose	3.56	3.52	4.08	4.08	3.80	3.77	3.64
				J (Hz)			
	H-1, H-1′	H-3, H-4	H-4, H-5	H-5, H-6	H-5, H-6′	H-6, H-6′	
β-Pyranose	11.69	10.03	3.46	1.33	2.02	12.79	
β-Furanose	12.12	8.1[b]	7.4[b]	2.98	5.91	12.10	

[a] In ppm from sodium 4,4-dimethyl-4-silapentane-1-sulfonate.
[b] Obtained by spin simulation.

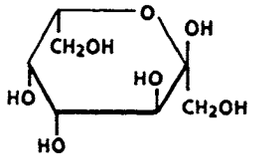
Table 3. Tautomeric composition[a] (%) of solutions of D-fructose, and related ketoses in deuterium oxide and dimethyl sulfoxide

Sugar	Temperature (°C)	Solvent	β-Pyranose	β-Furanose	α-Furanose	Ref.
D-Fructose	20	D_2O	75	21	4	This work
	27		66	28	6	12
	30		70	23	5	13
	31		65	25	6.5	14
	36		57	31	9	15
	80		53	32	10	16
	85		56	33	11	12
	20	DMSO	26	55	20	This work
	20		29	46	20	17
	30		26	48	21	17
	40		23	50	22.5	17
	50		21	51	23.5	17
1-*O*-Methyl-D-fructose	20	D_2O	61	30	9	This work
	30	DMSO	20	61	18	This work
3-*O*-Methyl-D-fructose	16.5	D_2O	37	34	11	18
Lactulose	25	D_2O	61.5	29	7.5	19
	58		55	32	11	19
	73		52	35.5	12.5	19
	20	DMSO	33	44	22	This work
	24		27	52	20	20
Turanose	36	D_2O	39	41	20	15
	20	DMSO	38	38	23	This work
D-galacto-Heptulose	22	D_2O	78	16	6	21
	20	DMSO	38	38	23	This work

[a] Only the three major tautomers are shown.

1 : 3) with increasing temperature. In DMSO, by contrast, in which intramolecular hydrogen bonding appears to be favorable, the relative proportions of the two forms are nearly constant over the whole temperature range. Such variations raise the possibility that factors in addition to those already considered merit attention. In this regard, it is worth noting that in the tautomerization of D-fructose-1-phosphate in water, the ratio of the β- to α-furanose forms were shown[22] to decrease with increasing temperature as a result of the exothermic nature of the conversion of β- to α-furanose ($\Delta H^{\circ}_{\beta\to\alpha} = 1$ kcal mol^{-1}).

α-L-*galacto*-Heptulopyranose (**5**), a seven-carbon homomorph of β-D-fructopyranose, affords ^{1}H- and ^{13}C NMR spectra closely analogous to those of the latter compound, when freshly dissolved in dimethyl sulfoxide-d_6. At equilibrium, a mixture of pyranose **5** and its α-furanose (**6**) and β-furanose (**7**) tautomers was found in a ratio of about 5 : 5 : 3 (Table 3). The ^{1}H and ^{13}C assignments for deuterium-exchanged **5**–**7** (Table 4), again obtained by a combination of HETCOR and COSY experiments, show the many analogies expected with those of the corresponding D-fructose tautomers **1**, **2** and **3**. However, coupling information obtained from the 2D *J*-resolved spectrum for mixture **5**–**7** (Fig. 4) shows that, in contrast to the small *J*(4,5) coupling for **2** at 20 °C, the corresponding value for its analog, **6**, is much larger, i.e. 6.8 Hz, although *J*(3,4) is approximately the same in both instances. Consequently, it appears that the room temperature conformation of **6** is akin to that of **2** at 70 °C (e.g. ^4E). As a hydrogen bond between 2-OH and 6-OH would be unlikely under such circumstances, the fact that **6** is a less prominent tautomer (38%) than its counterpart, **2** (55%), is consistent with the view that the latter receives enhanced stabilization through intramolecular hydrogen bonding in DMSO. As this difference may be expected to disappear in water, it is pertinent that the equilibrium compositions of L-*galacto*-heptulose and D-fructose in D_2O (see Table 3) are almost the same. Probably, pyranoses **1** and **5** are equally preponderant because they receive comparable stabilization by the solvent. In DMSO, however, wherein the furanose forms attain increased prominence, the proportion of β-fructofuranose (**2**) is relatively greater than that of α-galactoheptulofuranose (**6**), presumably because it alone gains added stability from intramolecular hydrogen bonding. Accepting that the latter entails an interaction between anomeric 2-OH and *primary* 6-OH in **2**, the absence of such an inter-



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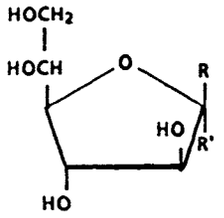


6 R = OH, R' = CH_2OH

7 R = CH_2OH, R' = OH

Table 4. ^1H and ^{13}C NMR chemical shifts (δ)[a] and ^1H coupling constants (in parentheses, Hz) for L-*galacto*-heptulose in dimethyl sulfoxide at 20 °C.

Proton	β-Pyranose	β-Furanose	α-Furanose	Carbon	β-Pyranose	β-Furanose
H-1[b]	3.45	3.39		C-1	64.63	62.99
H-1'[b]	3.20 (11.15; 1,1')	3.25 (11.15; 1,1')		C-2	97.75	101.98
H-3	3.51 (~2; 3,4)	3.81 (7.05; 3,4)	3.79 (7.00; 3,4)	C-3	69.17	75.85
H-4	3.74 (6.76; 4,5)	3.98 (6.8; 4,5)	3.94 (6.76; 4,5)	C-4	71.32	75.01
H-5	3.51	3.61 (2.90; 5,6)	3.74 (2.41; 5,6)	C-5	70.78	80.67
H-6	3.50	3.41	3.43	C-6	67.98	70.89
H-7				C-7	60.75	62.71

[a] In ppm from TMS.
[b] May be interchanged.

action in heptulofuranose **6** raises the possibility that its 6-OH group bonds less readily because it is *secondary* and hence more acidic in DMSO.[23] Another possibility, relating to conformational features of aldopentofuranoses and hexofuranoses, is that the two-carbon (C-6, C-7) exocyclic moiety of **6** is more likely[24] to be quasi-equatorial than is the one-carbon (C-6) exocyclic carbinol group of **2**. This would cause 6-OH to be more remote from 2-OH in **6** than in **2**.

Other modifications of the D-fructose structure entail additional variations in tautomeric equilibrium. With 4-OH substituted, as in the disaccharide lactulose (4-*O*-β-D-galactopyranosyl-D-fructose), there is less of the major β-pyranose form, **8**, in water and also less of the major, β-furanose form **9** in DMSO. [As shown earlier,[2,20] the crystalline disaccharide has the unusual property of being a mixed crystal consisting primarily of **9** in admixture with small proportions of the β-pyranose (**8**) and the α-furanose (**10**) forms.] This is not inconsistent with such possibilities as that the removal of 4-OH from β-D-fructopyranose interferes with selective stabilization of its pyranose structure by water, and/or that this hydroxyl group contributes to some extent in the stabilization of β-D-fructofuranose through intramolecular hydrogen bonding. The latter was presumed, earlier, also to involve interaction with 1-OH. If true, this could entail it only in the role of a proton donor, because the equilibrium composition of 1-*O*-methyl-D-fructose (Table 3) shows that the β-furanose form **11** is at least as prominent in DMSO as is β-D-fructofuranose itself. In any event, the overall indication from these data is that neither 1-OH nor 4-OH of β-D-fructofuranose makes a major contribution towards its selective stabilization in DMSO.

A unique solvation pattern is found with turanose, 3-*O*-α-D-glucopyranosyl-D-fructose, in that its equilibrium composition is virtually the same in water as in DMSO and also, in both of these solvents, is different

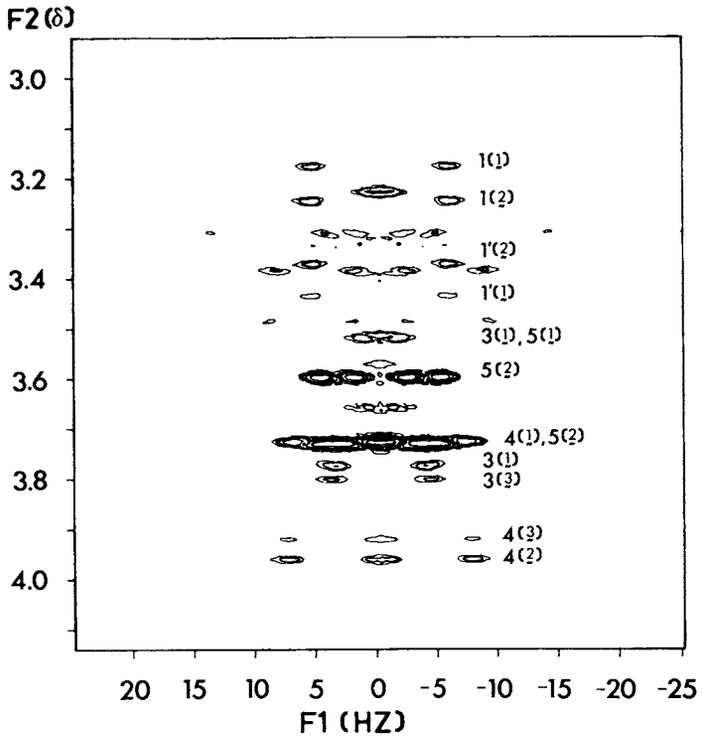
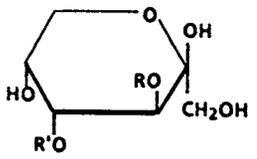


Figure 4. 2D *J*-resolved spectrum (300 MHz) of an equilibrated mixture of the tautomers of α-L-*galacto*-2-heptulose in DMSO-d_6 at 20 °C.

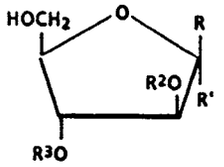
from that of the other ketoses. When freshly dissolved as the crystalline β-pyranose **12** in the latter solvent, it gives rise to two hydroxyl proton doublets, probably 2-OH of the glucose moiety and 4-OH of the fructose, that show marked deshielding characteristic of inter-residue hydrogen bonding. As additional OH doublets appear in this downfield region during equilibration, analogous inter-residue bonding also appears to occur in the newly formed β-furanose (**13**) and α-furanose (**14**) tautomers. Although we have no evidence that these inter-residue interactions persist in D_2O, the overall results suggest the possibility that the tautomeric equilibrium of turanose is dominated by such interactions rather than, as seen for the other compounds in the series, by the influence of solvent. Nevertheless, the equilibrium composition of this disaccharide is the same as that of 3-*O*-methyl-D-fructose (**15**–**17**) (Table 3), for which inter-residue hydrogen bonding cannot be invoked. Consequently, as proposed[25] for the methyl ether, steric interactions introduced by the substituent on O-3 may help to account for the distinctive tautomeric equilibrium of turanose.



8 R = H, R' = β-Galp

12 R = α-Glcp, R' = H

15 R = Me, R' = H



9 R = OH, R' = CH_2OH
R^2 = H, R^3 = β-Galp

10 R = CH_2OH, R' = OH
R^2 = H, R^3 = β-Galp

11 R = OH, R' = CH_2OMe,
R^2 = R^3 = H

13 R = OH, R' = CH_2OH
R^2 = α-Glcp, R^3 = H

14 R = CH_2OH, R' = OH
R^2 = α-Glcp, R^3 = H

16 R = OH, R' = CH_2OH
R^2 = Me, R^3 = H

17 R = CH_2OH, R' = OH,
R^2 = Me, R^3 = H

CONCLUSION

The NMR data presented here support the original suggestion that intramolecular hydrogen bonding is an important contributor to the stabilization of the β-furanose form of D-fructose in DMSO solutions, although it shifts the emphasis from the specific solvation pattern suggested earlier.[3,4]

Acknowledgements

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