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# INTRAMOLECULAR HYDROGEN-BONDING AND SOLVATION CONTRIBUTIONS TO THE RELATIVE STABILITY OF THE β-FURANOSE FORM OF D-FRUCTOSE IN DIMETHYL SULFOXIDE*

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## ABSTRACT

Selective stabilization of the β-furanose form, among the tautomers of D-fructose in dimethyl sulfoxide, has been reexamined by extensive use of $^1$H- and $^{13}$C-n.m.r. spectroscopy. Although $^1$H-chemical shifts and coupling constants alone are not conclusive, their temperature dependence relative to those of the other major tautomers and of model compounds, as well as $^{13}C$–$T_1$ relaxation data, support our earlier suggestion that the β-furanose incorporates intramolecular hydrogen-bonds. Whereas this source of stabilization should contribute to the striking preponderance of the β-furanose among the three main tautomers in dimethyl sulfoxide, in contrast to water, an important associated factor is the influence of the medium on the free energy of the β-pyranose form. The changes in tautomeric composition observed for solutions in mixtures of dimethyl sulfoxide and water, indicate that specific solvation by water is crucial in stabilizing β-D-fructopyranose.

## INTRODUCTION

D-Fructose exists mainly as β-D-fructofuranose at equilibrium in dimethyl sulfoxide[1], in marked contrast to the fact[2] that the β-pyranose is by far the major tautomer in water. Based on $^1$H chemical-shift data in dimethyl sulfoxide-$d_6$, it has been suggested[3] that intramolecular hydrogen-bonding between OH-1 and OH-4 or/and OH-3 and OH-6 of β-D-fructofuranose contributes to its stabilization in this medium. Supplementary information, obtained by both $^1$H- and $^{13}$C-n.m.r. spectroscopy, is presented here on the influence of temperature on the chemical shift and coupling constants of the hydroxyl protons, the effect on isomer composition of mixtures of dimethyl sulfoxide with water, and $^{13}$C relaxation charac-

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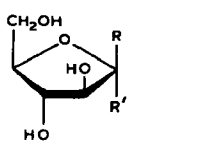
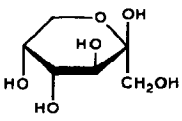
teristics. With this information, contributions of intramolecular hydrogen-bonding, and of solvation, to the tautomeric equilibrium of D-fructose are evaluated.

## EXPERIMENTAL

*Spectroscopy.* — $^1$H- and $^{13}$C-N.m.r. spectra were recorded with a Varian XL-300 or a Bruker WH-400 spectrometer. Equilibrated solutions of D-fructose in $(CD_3)_2SO$ or $D_2O$ were obtained by storage for several weeks. $^{13}$C-N.m.r. spin–lattice relaxation times were measured by the IRFT technique. The pulse duration for a 180° flip angle was 45 $\mu$s on the Varian XL-300 instrument. The waiting time between sequences was 5× the estimated value of the longest $T_1$ and a total of 200 scans was accumulated for each spectrum. Typically, 8–10 linearly spaced $\tau$ values were used. The probable error in the two-parameter fit in the $T_1$ calculations was ±5% and the reproducibility, ±10% or better. $^{13}$C-N.O.e. measurements were carried out with the same instrument. Additional details on the relaxation measurements and n.O.e. experiments are given elsewhere[4]. Quantitative $^{13}$C-n.m.r. data were obtained by the gated-decoupling method; the decoupler was gated on only during acquisition and gated off during a recovery time chosen to be 10× that of the longest $T_1$ required to re-establish equilibrium between 90° pulses. The Fourier-transformed spectra were integrated mechanically. The reproducibility of several measurements of the same peak was ±10%. Solutions of D-fructose in $(CD_3)_2SO$ or $D_2O$, or mixtures of them, were 0.2M for the $^1$H-n.m.r. experiments, whereas the $^{13}$C-n.m.r. measurements of chemical shifts and tautomeric equilibria were made with 4.0 and 1.0M solutions, respectively. For relaxation experiments, samples (1.5M) were deoxygenated with dry nitrogen before use. 2D Homonuclear-correlated experiments were carried out using spectral widths of 720 Hz in each domain, a 512 × 512 data matrix, 128 time increments, and 8 transients for each f.i.d. The 90° pulse was 23 $\mu$s and a relaxation time of 2.0 s was used. Free-induction decays were subjected to "pseudo-echo" processing, and diagonal folding was applied to the final spectrum.



1 R = OH, R′ = $CH_2OH$
2 R = $CH_2OH$, R′ = OH



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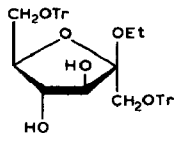

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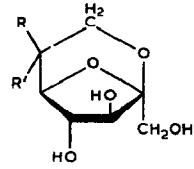
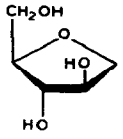


5 R = OH, R′ = H
6 R = H, R′ = OH



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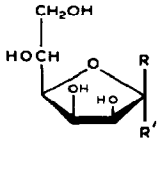
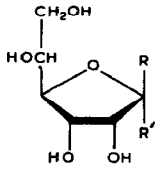
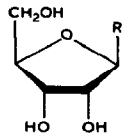


8 R = R′ = H
9 R = H, R′ = OMe



10 R = R′ = H
11 R = OMe, R′ = H



12 R = adenine
13 R = uracil

RESULTS

The assignments of the various hydroxyl group signals of the β-furanose (β-*f*,**1**), α-furanose (α-*f*,**2**), and β-pyranose (β-*p*,**3**) forms of D-fructose in $(CD_3)_2SO$ solutions were made by: (*a*) comparing hydroxyl resonances for a fresh solution of the crystalline ketose (in the β-*p* form) with those of equilibrating mixtures, (*b*) recording spectra at various temperatures, in which most of the OH-resonances are resolved (Fig. 1), and (*c*) integration measurements with reference to the well resolved OH-2 resonances of these three tautomers. Table I summarizes the temperature-dependence of the $^1$H-n.m.r. coupling constants and chemical shifts for the various OH-resonances determined in the range 293–343K. The superiority of the present procedure for assigning hydroxyl group signals is apparent from the data in Table I, which indicate that the primary hydroxyl groups of the β-furanose absorb at δ 4.68 and 4.54, a correction of previous assignments[1]. Table I also contains

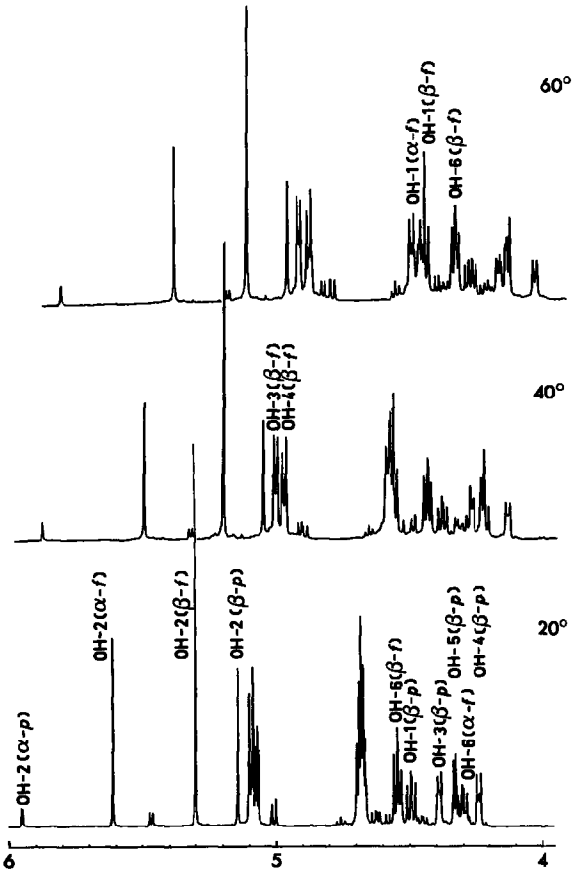



Fig. 1. $^1$H-N.m.r. spectra of the hydroxyl protons of D-fructose (0.2M) in $(CD_3)_2SO$ solution, recorded at 20, 40, and 60°.

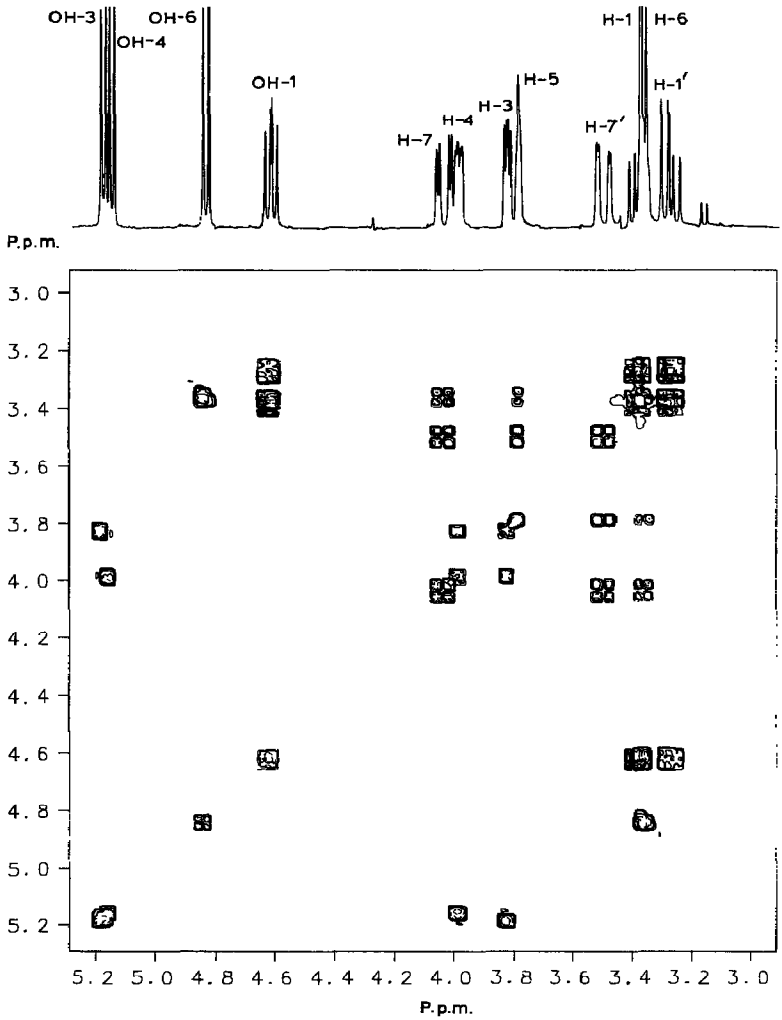



Fig. 2. Contour plot of the 2D-COSY spectrum of **6**, obtained at 300 MHz in $(CD_3)_2SO$, at 40°.

comparable data for model compounds, ethyl 1,6-di-*O*-trityl-β-D-fructofuranoside[5] (**4**), 2,7-anhydro-α-L-galactoheptulofuranose (**5**), and 2,7-anhydro-β-D-altroheptulofuranose (**6**). Chemical shifts and spacings are given in Table II for hydroxyl protons of another group of model compounds, comprised of 1,4-anhydro-D-arabinitol (**7**), 1,4-anhydro-D-mannitol (**8**), 1,4-anhydro-D-allitol (**10**), methyl α-D-mannofuranoside (**9**), methyl β-D-allofuranoside (**11**), adenosine (**12**), and uridine (**13**). The ring hydroxyl groups are *cis* in **8**–**13**, whereas they are *trans* in the other model compounds. The assignment of hydroxyl resonances of the model compounds was facilitated by 1D-homonuclear decoupling, and also by 2D-homonuclear correlation experiments as depicted in Fig. 2 for compound **6**.

Assignments of the $^{13}C$-n.m.r. resonances of the four tautomers (and the

TABLE I

TEMPERATURE-DEPENDENCE[a] OF THE $^1H$-CHEMICAL SHIFTS ($\delta$, 20°) AND COUPLING CONSTANTS ($^3J$, Hz) OF THE HYDROXYL PROTONS OF D-FRUCTOSE TAUTOMERS AND MODEL COMPOUNDS IN $(CD_3)_2SO$

| *Compound* | *δ OH-1* | *OH-2* | *OH-3* | *OH-4* | *OH-5* | *OH-6* |
|---|---|---|---|---|---|---|
| **1** | 4.68[b] | 5.30 | 5.09 | 5.07 | | 4.54[b] |
| | (−5.86) | (−4.60) | (−4.40) | (−4.86) | | (−5.23) |
| **2** | 4.30 | 5.61 | | | | |
| | (−4.05) | (−5.63) | | | | |
| **3** | 4.49 | 5.14 | 4.39 | 4.24 | 4.33 | |
| | (−5.63) | (−4.46) | (−5.37) | (−5.23) | (−4.86) | |
| **4** | | | 5.36 | 5.15 | | |
| | | | (−7.57) | (−6.10) | | |
| **5** | 4.76 | | 5.24 | 5.16 | | 5.24 |
| | (−7.22) | | (−4.69) | (−6.70) | | (−5.36 |
| **6** | 4.72 | | 5.24 | 5.24 | | 4.91 |
| | (−7.51) | | (−4.45) | (−6.40) | | (−5.80) |
| | *JOH-1,H-1* | *OH-1,H-1'* | *OH-3,H-3* | *OH-4,H-4* | *OH-6,H-6* | *OH-6,H-6'* |
| **1** | 6.24 | 6.24 | 5.40 | 4.84 | 4.74 | 6.11 |
| | (−0.20) | (−0.20) | (−0.08) | (+0.02) | (+0.10) | (−0.10) |
| **2** | 5.25 | 7.22 | 6.95 | | 4.85 | 5.95 |
| | | | (−0.14) | | | |
| **3** | 5.40 | 7.39 | 5.85 | 6.71 | 3.70[c] | |
| | (+0.04) | (−0.34) | (−0.55) | (−0.69) | | |
| **4** | | | 5.37 | 5.86 | | |
| | | | (−0.22) | (−0.57) | | |
| **5** | 5.38 | 7.33 | 4.40 | 4.39 | 4.40 | |
| | (+0.10) | (−0.38) | (+0.17) | (+0.28) | (−0.34) | |
| **6** | 5.46 | 7.14 | 4.13 | 3.77 | 5.65 | |
| | (−0.05) | (−0.13) | (−0.32) | (−0.57) | (−0.12) | |

[a]Expressed, by the values in parentheses, as temperature coefficients (p.p.m./°C × $10^3$) determined over the range 20–70° for D-fructose (**1–3**) and 20–90° for model compounds (**4–6**), or as $\Delta J_{OH,H}$ over the range 40–70°. [b]Resonances that may be interchanged. [c]$^3J_{OH\text{-}5,H\text{-}5}$.

TABLE II

$^1H$-CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF THE HYDROXYL PROTONS OF MODEL COMPOUNDS **7–13**

| *Compound* | *OH-2* | *OH-3* | *OH-5* | *OH-6* |
|---|---|---|---|---|
| **7** | 5.08 | 4.99 | 4.76 | |
| | (4.15) | (4.45) | (5.28) | |
| **8** | 4.65 | 4.79 | 4.49 | 4.43 |
| | (4.15) | (6.83) | (5.37) | (5.75) |
| **9** | 5.01 | 4.74 | 4.57 | 4.36 |
| | (6.65) | (4.09) | | (5.44) |
| **10** | 4.67[c] | 4.61[c] | 4.68 | 4.45 |
| | (4.26) | (5.08) | (4.63) | (5.50) |
| **11** | 4.92 | 4.67 | 4.58 | 4.41 |
| | (4.94) | (6.11) | (5.01) | (5.37) |
| **12** | 5.43 | 5.17 | 5.41 | |
| | (6.46) | (4.17) | (5.72) | |
| **13** | 5.34 | 5.05 | 5.07 | |
| | (5.67) | (4.47) | (5.24) | |

[a]$\delta$, 20°. [b]$^3J_{OH,H}$, Hz, in parentheses. [c]Resonances that may be interchanged.

TABLE III

$^{13}C$ CHEMICAL SHIFTS[a] FOR SOLUTIONS OF D-FRUCTOSE IN $D_2O$[b,c] AND $(CD_3)_2SO$[c] AT 40°

| *Carbon* | *α*-f | | *β*-f | | *α*-p | | *β*-p | | *Open chain* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *$D_2O$* | *$(CD_3)_2SO$* | *$D_2O$* | *$(CD_3)_2SO$* | *$D_2O$* | *$(CD_3)_2SO$* | *$D_2O$* | *$(CD_3)_2SO$* | *$D_2O$* | *$(CD_3)_2SO$* |
| C-1 | 63.01 | 64.15 | 63.12 | 64.03 | 61.59 | 64.36 | 64.08 | 65.12 | 65.88 | [d] |
| C-2 | 104.26 | 104.80 | 101.35 | 102.32 | 97.56 | 97.48 | 97.75 | 98.21 | 212.92 | 213.05 |
| C-3 | 81.97 | 83.16 | 75.87 | 76.88 | 70.41 | 71.71 | 67.80 | 68.75 | 74.93 | 75.81 |
| C-4 | 76.31 | 77.20 | 74.14 | 76.05 | 70.55 | 71.33 | 69.65 | 70.49 | 71.39[e] | 72.68[e] |
| C-5 | 81.43 | 82.13 | 80.65 | 82.19 | 64.88 | 66.68 | 69.03 | 69.58 | 70.11[e] | 69.43[e] |
| C-6 | 61.19 | 61.86 | 62.25 | 63.10 | 60.84 | 63.71 | 63.21 | 63.56 | 62.79[e] | 63.90[e] |

[a]P.p.m. downfield from $Me_4Si$. [b]Assignments according to ref. 6. [c]Solutions of 4.0M. [d]Signal not seen. [e]Uncertain assignments.

TABLE IV

$^{13}C$ SPIN–LATTICE RELAXATION TIMES (S) FOR THE PROTONATED CARBON ATOMS OF THE THREE MAJOR COMPONENTS OF D-FRUCTOSE IN $D_2O$ AND $(CD_3)_2SO$ SOLUTIONS[a]

| *Carbon* | α-f | | β-f | | β-p | |
|---|---|---|---|---|---|---|
| | *$D_2O$* | *$(CD_3)_2SO$* | *$D_2O$* | *$(CD_3)_2SO$* | *$D_2O$* | *$(CD_3)_2SO$* |
| C-1 | 0.88 | 0.33 | 0.88 | 0.28 | 0.93 | 0.34 |
| C-3 | 1.73 | 0.55 | 1.50 | 0.53 | 1.60 | 0.53 |
| C-4 | 1.74 | 0.53 | 1.61 | 0.51 | 1.53 | 0.52 |
| C-5 | 1.69 | 0.55 | 1.68 | 0.54 | 1.50 | 0.52 |
| C-6 | 0.95 | 0.31 | 0.94 | 0.29 | 0.81 | 0.33 |

[a]1.5M at 40°.

acyclic form) of D-fructose in $D_2O$ were made on the basis of earlier reports[6], whereas those in $(CD_3)_2SO$, reported here for the first time, were assigned by "titration" experiments, namely, by recording spectra while adding progressively increasing amounts of $(CD_3)_2SO$ to the $D_2O$ solution (see later). These data are listed in Table III. The $^{13}C$–$T_1$ values for the protonated carbons of the three major tautomers (*α-f*, *β-f*, and *β-p*) in both $D_2O$ and $(CD_3)_2SO$ are summarized in Table IV. Figure 3 lists the proportions of these tautomers as a function of the mol

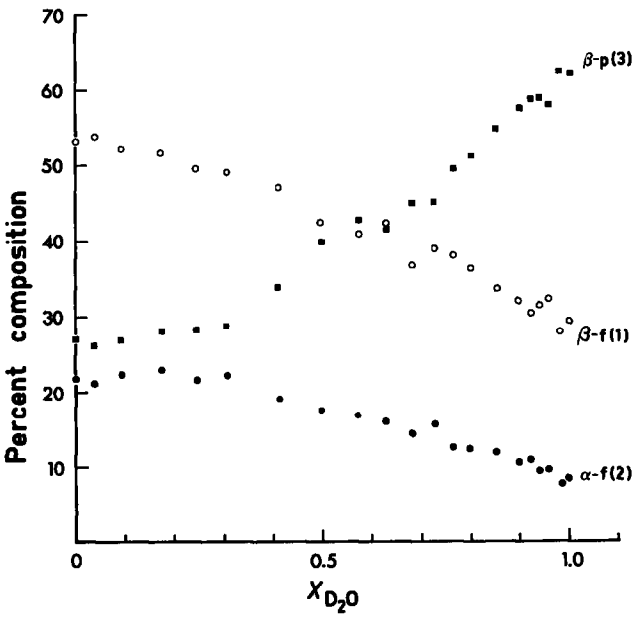



Fig. 3. Plot of changes in the relative proportion (% composition) of the three major components of D-fructose (M) in $D_2O$–$(CD_3)_2SO$ mixtures as a function of the mol fraction of water; **1** β-furanose, **2** α-furanose, and **3** β-pyranose.

fraction of $D_2O$, $x_{D_2O}$, in $D_2O$–$(CD_3)SO$ mixtures. These values constitute an average of those obtained for each protonated carbon.

## DISCUSSION

Our previous[3] interpretation of the enhanced stabilization of the β-fructofuranose in $(CD_3)_2SO$ was based on the assumption that the $^1H$-chemical shifts of hydroxyl protons engaged in intramolecular hydrogen-bonding appear at relatively low fields as compared to those of non-hydrogen-bonded hydroxyl groups. However, this assumption is not supported by the data for the other compounds (Table I). Thus, although OH-3 and OH-4 of **4** absorb at even lower field ($\delta$ 5.36 and 5.15, respectively) their *trans*-configuration, and the absence of neighboring primary hydroxyl groups, make an intramolecular hydrogen-bonding network impossible. Similarly, intramolecular hydrogen-bonding between pairs of secondary and primary hydroxyl groups is not expected to occur in compounds **5** and **6** mainly because of the large distance between the aforementioned groups. Nevertheless, resonances for the primary OH-1 and secondary OH-3 and OH-4 appear at low fields. Another example is compound **7** (Table II) in which a hydrogen bond between OH-2 and OH-5 appears to be feasible. Nevertheless, both OH-2 and OH-3 absorb at close to the same, low-field, position.

From these observations we conclude that chemical-shift assignments alone cannot distinguish intramolecularly hydrogen-bonded hydroxyl groups from those bonded to solvent and/or to solute molecules, and that the low field absorptions characterizing these secondary hydroxyl groups may also reflect their configurational arrangement as well as the overall conformation of the furanose ring. Support for this conclusion is offered (Table II) by several model compounds (**8–13**) in which the secondary (2,3) hydroxyl groups on the 5-membered ring are *cis*. Thus, the proton resonances of these hydroxyl groups show no obvious pattern of upfield or downfield shifts, despite the likelihood that they represent intramolecularly hydrogen-bonded species.

Another n.m.r. procedure, for distinguishing between protons that are inaccessible to the solvent as compared to those that are exposed to solvent, is the temperature-dependence of proton chemical-shifts. The resonances of protons hydrogen-bonded to the solvent migrate upfield with increasing temperature and show a substantial temperature coefficient ($d\delta/dT$) whereas, ideally, intramolecular association should be manifested by a relative insensitivity of the proton chemical-shift to temperature. When $d\delta/dT \sim 0$, the proton in question is said to form an intramolecular hydrogen bond, although there are problems of interpretation when $d\delta/dT$ is negative or greater than a reference value. For the latter situation, it has been suggested[7,8] that differentiation may be made on the basis that intramolecularly hydrogen-bonded protons are the least temperature-dependent. The data in Table I show that the temperature coefficients for the primary and secondary hydroxyl protons of β-*f* (**1**) are smaller than those of model compounds **4–6**, that

appear unlikely to form intramolecular hydrogen-bonds. Also noteworthy is the fact that OH-2 of **1** shows an upfield migration with temperature, comparable to that of the secondary, OH-3 and OH-4, groups (Table I) even though OH-2 is more likely to be intermolecularly hydrogen-bonded. A possible explanation is that OH-2, being a tertiary hydroxyl group, has a smaller tendency[9] to form hydrogen bonds, in comparison with primary and secondary hydroxyl entities.

Analysis of expanded spectra of the D-fructose mixture recorded over the range 20–70°, shows that the vicinal $^3J_{HCOH}$ values for both secondary and primary hydroxyl groups of the *β-f* tautomer are independent of temperature within experimental error (±0.2 Hz). This observatin (Table I) is compatible with the preponderance of a particular local conformation for each primary and secondary hydroxyl group, characteristic of an intramolecular hydrogen bonding arrangement[7]. However, it does not distinguish between specific hydrogen-bonding arrangements, such as those represented by II and III in ref. 7 or by flip-flop bonds[10], nor imply that bonding between the OH-1/OH-4 and OH-6/OH-3 pairs in **1** occurs simultaneously (see footnote, p. 218 of ref. 3). By contrast, the vicinal coupling constants for compounds **4–6** show a marked dependence on temperature (Table I), which rules out the possibility of single, preponderant, local conformations for their primary and secondary hydroxyl groups. As pointed out by Casu and coworkers[11], however, the solvation of carbohydrates by $(CD_3)_2SO$ is probably too complex to permit a simple interpretation of the temperature-dependence of coupling constants, such as those of compounds **4–6**, in terms of local conformations.

From the $^{13}C$–$T_1$ relaxation data presented in Table IV, it is evident that the three major tautomers of D-fructose tumble isotropically in both $D_2O$ and $(CD_3)_2SO$ solutions. $T_1$ values for the secondary carbons of **1, 2,** and **3** respectively, are all within 1.64 ±0.08 s, 1.73 ±0.07 s, and 1.55 ±0.05 s in $D_2O$, and 0.53 ±0.03 s, 0.54 ±0.04 s, and 0.52 ±0.03 s in $(CD_3)_2SO$. In the absence of freedom of rotation about the C–C bonds, the $T_1$ value of a primary carbon atom would be expected to be one-half that of a secondary carbon. As may be seen in Table IV, these values for all isomers in $D_2O$ are greater than the relaxation times of the overall motion, which is indicative of relatively faster internal motions about the C-1–C-2 and C-5–C-6 bonds. Also, the corresponding values for **2** and **3** in $(CD_3)_2SO$ are greater than those of the ring carbon atoms, again indicative of fast internal rotations, as in $D_2O$. By contrast, the $T_1$ values for the primary carbon atoms of **1** are only slightly greater than those of the overall motion, suggesting that there is restricted motion about the exocyclic bonds. Consequently, these relative rates of internal motion are in accord with the formation of an intramolecular hydrogen-bonding network, as already concluded here on the basis of the temperature effects on proton chemical-shifts and coupling-constants.

A factor that may contribute to an ostensible increase in the stabilization of the β-furanose is a concomitant destabilization of the β-pyranose tautomer (**3**) as the medium is changed from $D_2O$ to $(CD_3)_2SO$, through specific solvent-effects. The possible influence of water on the stability of pyranose forms has been men-

tioned[12,13] earlier. According to this view, the relatively satisfactory way in which a pyranose chair conformation may be accommodated into the tridymite structure of water, particularly when the hydroxyl groups are equatorially oriented, may account for the higher proportion of **3** in water than in dimethyl sulfoxide. Although the latter solvent is also strongly hydrogen bonding, its chain-like structure[14,15] appears unlikely to favor stabilization of one form over another[13].

In an effort to assess specific solvation effects on the relative stabilization of the D-fructose tautomers, their relative proportions in $D_2O$–$(CD_3)_2SO$ binary mixtures were determined. These data, obtained by $^{13}C$-n.m.r. spectroscopy, are shown in Fig. 3 as a function of the mol fraction of water. They show that when the solvent is rich in water ($x_{D_2O}$ ~1.0–0.7) the relative proportion of β-pyranose (**3**) decreases sharply in favor of the furanose forms (**1** and **2**), whereas relatively small changes in composition occur at the opposite end of the scale ($x_{D_2O}$ ~0.0–0.4). These experimental facts may be explained as follows: as $(CD_3)_2SO$ is added to the $D_2O$ solution, the water molecules no longer form hydrogen bonds only among themselves and with the D-fructose molecules, but do so also with the sulfoxide. This causes an efficient rupture of the ordered clusters of water molecules which, presumably, stabilize the β-pyranose form preferentially. In contrast to this marked effect of even a small proportion of dimethyl sulfoxide on the aqueous system, water added to the dimethyl sulfoxide solution of the sugars makes little impact before its mol fraction reaches $x_{D_2O}$ ~0.4. Again, this suggests that a structured, aqueous-rich environment is necessary for the stabilization of β-D-fructopyranose. There appears to be a gentle discontinuity over the range $x_{D_2O}$ ~0.5–0.7 in the curves for **1** and **3**, which could be related to the fact[16,17] that complexes of water and dimethyl sulfoxide behave like a distinct compound in this region.

As the β-pyranose suffers destabilization and declines in prominence, its loss is accounted for mainly by its tautomerization into the β-furanose (**1**). According to the evidence presented here, the latter forms intramolecular hydrogen-bonds. These are expected to enhance its stability and to contribute additionally to the fact that **1** becomes by far the major species in a dimethyl sulfoxide-rich environment. It is noteworthy that the latter kind of medium also is conductive to an increase in the percentage of the α-furanose (**2**). Indeed, the ratio of **2** to **1** remains relatively constant at ~1:2.5–3 over the concentration range[1] of 0.2M (also see Fig. 1) to[18] 1.0M (see Fig. 3) in either $D_2O$ or $(CD_3)_2SO$. Hence, the proportions of both furanoses increase comparably at the expense of the β-pyranose. Unlike **1**, the α-furanose appears not to form intramolecular hydrogen-bonds. Alternatively, however, the α-furanose might be stabilized through hydrogen-bonding intermolecularly with dimethyl sulfoxide, in a more effective manner than is feasible for **1**. Accordingly, the free energies of both anomeric furanoses would be decreased correspondingly in relation to the free energy of β-D-fructopyranose.

In summary, on the basis of the present n.m.r. study of D-fructose undergoing complex tautomerization in solution, it is proposed that specific solvation-effects are important in stabilizing the β-pyranose form in water, and the α-furanose form

in dimethyl sulfoxide, and that the β-furanose form is stabilized in the latter solvent by intramolecular association between pairs of primary and secondary hydroxyl groups.

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