Carbohydrate Research, 194 (1989) 288–295
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

A ^{13}C spin–lattice relaxation study of solvent effects on the rotational dynamics of methyl glucosides

PHOTIS DAIS
Department of Chemistry, University of Crete, 71110 Iraklion, Crete (Greece)

AND ARTHUR S. PERLIN
Department of Chemistry, McGill University, Montreal, Quebec, H3A 2A7 (Canada)

(Received January 10th, 1989; accepted for publication, May 3rd, 1989)

Many instances are known of prominent solvent effects on the chemical and physical properties of carbohydrates. Familiar examples[1,2] are found in the tautomeric equilibria of sugars and the interconversions among conformational isomers. By contrast, relatively little is known about the influence of solvents on the rotational dynamics of carbohydrate molecules. As ^{13}C-relaxation measurements are highly sensitive to differences in the configurations and conformations of such molecules[3–8], they may also be expected to reflect alterations in dynamic behaviour associated with solvation. Accordingly, the present study utilizes ^{13}C-R_1 values in an attempt to evaluate possible effects on the motional behaviour of a pair of anomeric glycosides, *i.e.*, methyl α- (**1a**) and β-D-glucopyranoside (**1b**), in a group of solvents that represent an extended range of such properties as viscosity and dielectric constant.

The relaxation rates (R_1 values, see equation *1*) for ^{13}C obtained at 25° for all carbons of **1a** and **1b** in various protic and aprotic solvents are summarized in Tables I and II, respectively. Two reports[3,4] have presented T_1 values for glucose derivatives in D_2O and our results are in qualitative agreement with those values. The n.O.e. values for all carbons approached the asymptotic value of 2.988 to within ±5%, indicating that these carbons relax preponderantly *via* dipole–dipole interactions.

The R_1 values of the ring carbons (C-1–5) of **1a** in each solvent are similar within experimental error, suggesting isotropic overall motion for this molecule. For **1b**, the same isotropic overall motion is observed in methanol and acetic acid, whereas a slight anisotropicity in its overall motion is detectable in D_2O, *N,N*-dimethylformamide, pyridine, and methyl sulfoxide (Table II), from the fact that the R_1 values of the anomeric carbon differ from those of the other ring carbons by ~8%, which was highly reproducible and outside the experimental error. As such

0008-6215/89/$ 03.50

TABLE I

^{13}C-SPIN-LATTICE RELAXATION RATES (s^{-1}), ROTATIONAL CORRELATION TIMES (ps), AND COUPLING CONSTANTS (Hz) FOR METHYL α-D-GLUCOPYRANOSIDE[a] IN VARIOUS SOLVENTS AT 25°

Solvent	η^b	D^c	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	CH_3	τ_0	τ_{eff} (C-6)	$J_{H\text{-}1,H\text{-}2}$
MeOH	0.542	31.7	0.88	0.87	0.83	0.85	0.87	1.61	0.31	40.3	37.8	3.73
$HCONMe_2$	0.796	36.7	0.94	0.91	0.91	0.91	0.91	1.52	0.37	42.9	35.5	3.66
Pyridine	0.824	12.3	1.43	1.41	1.39	1.35	1.37	2.44	0.41	65.1	57.1	3.66
D_2O 0.5M	0.894	78.5	1.04	1.01	1.01	1.06	1.01	1.67	0.38	48.2	39.0	3.70
M			1.28	1.25	1.25	1.27	1.27	2.27	0.43	59.3	53.2	
AcOH 0.25M	1.232	6.2	2.08	2.08	2.17	2.13	2.08	3.57	0.60	100.7	83.6	3.70
Me_2SO 0.5M	1.960	46.4	1.89	1.85	1.85	1.82	1.82	3.13	0.69	87.3	73.2	3.60
M			2.44	2.38	2.38	2.38	2.38	4.17	0.76	113.2	97.6	

[a]0.5M Solutions, unless otherwise stated. [b]Solvent viscosities in cP at 25°. [c]Dielectric constants in Debye at 25°.

TABLE II

^{13}C-SPIN-LATTICE RELAXATION RATES (s^{-1}), ROTATIONAL CORRELATION TIMES (ps), AND COUPLING CONSTANTS (Hz) FOR METHYL β-D-GLUCOPYRANOSIDE[a] IN VARIOUS SOLVENTS AT 25°

Solvent	η^b	D^c	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	CH_3	τ_0	τ_{eff} (C-6)	$J_{H\text{-}1,H\text{-}2}$
MeOH	0.542	31.7	1.27	1.32	1.33	1.35	1.33	2.44	0.44	61.6	57.1	7.76
$HCONMe_2$	0.796	36.7	1.19	1.28	1.28	1.32	1.30	2.38	0.47	59.7	55.8	7.81
Pyridine	0.824	12.3	1.96	2.13	2.08	2.13	2.13	3.85	0.57	97.6	90.1	7.71
D_2O	0.894	78.5	1.14	1.18	1.25	1.27	1.27	2.27	0.42	57.1	53.2	8.00
AcOH	1.232	6.2	3.70	3.85	4.00	4.00	3.85	6.67	1.06	180.1	156.1	7.87
Me_2SO	1.960	46.4	2.56	2.78	2.78	2.78	2.78	5.00	0.83	126.6	117.1	7.81

[a]M solutions. [b]Solvent viscosity in cP at 25°. [c]Dielectric constants in Debye at 25°.

anisotropy is not exhibited by **1a** in any of the solvents, nor by **1b** in methanol or acetic acid, these atypically lower R_1 values of C-1 cannot be ascribed to an unexpected change in the stereochemistry of the anomeric carbon. This finds support in the constancy in the values of $J_{H\text{-}1,H\text{-}2}$ (Table I and II), which indicate that there is no substantial departure from the ideal $^4C_1$ conformation. An additional fact supporting this conclusion is the relative constancy (generally $\leq$3.5%) in the ^{13}C chemical shift data (Table III) on changing the solvent; presumably, the minor differences observed are caused by variation in the solvating ability of each solvent, and hence the electronegative character of the hydroxyl groups.

The anisotropicity in the overall motion of **1b** relative to that of **1a** in D_2O has been attributed[4] to an effect of the β-anomeric substituent on the inertial axes, sufficient to cause molecular diffusion about a preferential, but undefined, axis of rotation. Although the basic argument seems correct, *i.e.*, the presence of the β-anomeric substituent is the major cause of the anisotropic motion, especially in the light of higher anisotropicities observed for larger β-substituents[4], it is unlikely that this anisotropic motion can be described in terms of a preferential axis of rotation, as found with methyl β-D-galactopyranoside[4]. Moreover, such solvent effects as hydrogen bonding may alter the overall shape of the solvated entity, resulting not only in a further shift of the principal axes of the diffusion tensor, but also in a different type of overall motion, as observed for **1b** in the two classes of solvents. The asymmetric molecule **1b** contains four hydroxyl groups and two oxygen atoms that constitute strong solvating centers. Therefore, the assumption that the principal axes of the diffusion tensor coincide with the principal axes of the moment of inertia may not be justified for this highly polar molecule[9,10]. Rather, the three Euler angles defining the orientation of the diffusion tensor, in addition to the three diffusion coefficients, should be determined. In the context of Woessner's treatment[11,12], six linearly independent equations, and hence six unique C–H vectors, as well as the corresponding ^{13}C-R_1 values, are needed for the determination of these six parameters, which appears to be impractical at this stage.

In the following discussion, **1a** and **1b** are treated as approximate isotropic tumblers, and hence their overall motion is described by equation *1*,

$$R_1 = \frac{1}{T_1} = \frac{N_H \gamma_H^2 \gamma_C^2 \hbar}{r_{C\text{-}H}^6} \tau_0 \qquad (1)$$

which holds under the extreme narrowing condition and where N_H is the number of protons bonded to the carbon atom in question, γ_H and γ_C are the gyromagnetic ratios of the proton and carbon nuclei, respectively, $\hbar(=h/2\pi)$ is Planck's constant, $r_{C\text{-}H}$ is the C–H bond-length, and τ_0 is the rotational correlation time of the C–H vector under study. Tables I and II summarize the correlation times of **1a** and **1b** calculated by means of equation *1*.

Neither the solvent viscosity nor the dielectric constant bear a direct relationship to the correlation times found for the overall motions of **1a** and **1b**. This may

TABLE III

^{13}C CHEMICAL SHIFTS[a] OF **1a** AND **1b** IN VARIOUS SOLVENTS

	MeOH		*$HCONMe_2$*		*Pyridine*		*D_2O*		*AcOH*		*Me_2SO*	
	1a	**1b**	**1a**	**1b**	**1a**	**1b**	**1a**	**1b**	**1a**	**1b**	**1a**	**1b**
C-1	101.20	105.20	100.78	104.74	101.53	105.73	99.33	103.31	100.40	104.39	99.71	104.03
C-2	73.49	74.88	73.25	74.46	72.94	75.18	71.31	73.17	72.42	74.42	72.03	73.55
C-3	75.09	77.71	74.74	77.54	75.52	78.46	73.18	75.87	74.84	76.49	73.44	76.79
C-4	71.72	71.44	71.62	71.18	72.21	71.55	69.65	69.73	71.00	70.81	70.39	70.24
C-5	73.49	77.86	73.43	77.78	74.24	78.56	71.64	75.97	72.89	77.06	72.64	76.89
C-6	62.65	62.60	62.38	62.29	62.95	62.86	60.66	60.85	62.14	62.17	61.02	61.27
OMe	55.51	57.32	54.77	56.29	55.09	56.98	55.09	57.25	55.67	57.34	54.33	56.21

[a]In p.p.m. relative to Me_4Si.

not be surprising, because the simple hydrodynamic model[13] does not reflect such specific solvent effects as the strong hydrogen bonding that dominates solvation in some of the present systems. Nevertheless, viscosity cannot be excluded as a factor contributing to the rate of the overall and internal motions. For instance, a comparison of the rates of the overall motion of both compounds in the aprotic solvents *N,N*-dimethylformamide and methyl sulfoxide, which have approximately the same donor character[14,15], or of the rate of **1a** at two concentrations in D_2O and $(CD_3)_2SO$ (Table I) shows a decrease in the rate of motion with increasing solvent or solution viscosity.

No correlation was found between the relaxation data and the solvent dielectric constants, as might be expected. That is, the latter provide a measure of solvent polarity in terms of its ability to separate electrical charges and orient a dipolar molecule, whereas the total sum of the interaction of solute and solvent molecules is more extensive and complex. For carbohydrate molecules in particular, hydrogen bonding can play a critical role in determining the rate of motion and, in this respect, the most significant factor is whether the hydrogen bonding is internal or external. In polar media, the interaction of the solvent and a hydroxyl group is typically strong, and often favors external hydrogen bonding with the solvent over internal hydrogen bonding, whereas the latter is favored in a solvent of low dielectric constant, if structurally permitted. In addition, solute–solute intermolecular hydrogen bonding cannot be excluded in solvents of low dielectric constant. This may account for the very slow overall motion observed for both **1a** and **1b** (Tables I and II) in acetic acid relative to that in methyl sulfoxide, which has the lower viscosity. As acetic acid, a highly associated liquid at room temperature, has a low dielectric constant and low ionizing ability[16], its tendency to form strongly associated dimers makes it an inferior solvating agent relative to other protic solvents, despite its rather high electron-acceptor properties[15,17].

An attempt was made to correlate the relaxation data with parameters, other than dielectric constant, that reflect solvent polarity[18,19]. None of these empirical parameters [*e.g.*, Kosover Z-values, Winstein Y-values, Dimroth and Reichardt E_T-values, acceptor numbers (AN), donor numbers (DN), or P parameters][20] correlated well with the data, even when the protic and aprotic solvents were considered separately. The most satisfactory fit ($r = 0.859$) was obtained between the τ_0 values of **1b** and the (AN) parameters. Overall, these findings suggest that carbohydrate molecules, with many donor and acceptor centres, cannot be easily classified relative to the donor and/or acceptor properties of a solvent. Moreover, specific and non-specific interactions (*e.g.*, coulombic, directional, inductive, and dispersion interactions) of sugar and solvent molecules cannot be reflected together in a single empirical parameter. No attempt was made to fit the data with a multiparametric equation that has been proposed[19].

Each of the solvents used, except perhaps for pyridine, is associated to a greater or lesser extent in the liquid state. The introduction of **1a** or **1b** into the solvent breaks the clusters of solvent molecules which promote solvation through

interactions with the hydroxyl groups and other polar centres. The strength and the type of solvation depend on the solvent donor and/or acceptor properties. In studying the n.m.r. shifts of the resonances of the hydroxyl protons of several sugar molecules as a function of pH and temperature, Harvey and Symons[21] concluded that each hydroxyl group is hydrogen-bonded to two molecules of water and two of methanol. These finding, however, are at variance with hydration numbers of 3–5 for each sugar molecule, reported by Suggett *et al.*[22,23] on the basis of n.m.r. and dielectric relaxation data. Moreover, the possibility cannot be excluded[21,24] that certain OH groups in the *gauche* conformation could form bridged structures with water or methyl sulfoxide and that, once attached, these solvent molecules could remain with the sugar molecules for a relatively long time because of the chelate effect. Based on the maximum allowed error of ±13% in the τ_0 values in Tables I and II derived from the experimental error in the measured R_1 values, the rate of the overall motion for either **1a** or **1b** in these solvents follows the order methanol ≈ *N,N*-dimethylformamide ≈ D_2O < pyridine < methyl sulfoxide. Although the structures of the solvated species in *N,N*-dimethylformamide and pyridine are unknown, the above sequence appears to reflect both the viscosities and the molecular weights of the solvated entities. This is especially evident in the light of the Harvey and Symons' model[21] depicting each hydroxyl group as hydrogen-bonded to two molecules of solvent. On this basis, the molecular weights of the solvated species are: in methanol (256), *N,N*-dimethylformamide (364), water (144), pyridine (496), and methyl sulfoxide (312). Underlying such a proposal is the basic assumption that the lifetime of the solvated species is longer than, or at least comparable to, the time scale of the molecular motion ($\geq 10^{-12}$ s), which seems to hold for sugars in water solutions as deduced[22,23] from n.m.r. and dielectric relaxation studies.

As shown in Tables I and II, the correlation times for the motions of **1a** and **1b** in D_2O under the same conditions of concentration and temperature are comparable. Comparable rates of overall motion are also found[22,25] for α- and β-D-glucopyranose in D_2O. From these observations, it appears that any possible restriction to the rotational motion of β-D-glucopyranose (or **1b**) by the tridymite arrangement of water molecules, with which this compound is more compatible than is its anomer[26], is of minor importance relative to the rotational motion of the hydrated entity. Although, β-D-glucopyranose is more highly hydrated than α-D-glucopyranose[22,23], the molecular weights of their hydrated forms differ by only 18 ($OH:H_2O = 1:1$) or 36 ($OH:H_2O = 1:2$), which would not contribute significantly to differences in their relaxation rates.

Interpretation of the R_1 values of the hydroxymethyl group of these compounds is complicated additionally by the possibility of rotation about the C-5–C-6 bond. An effective correlation time (τ_{eff}) for C-6 can be calculated from equation *1*, and the values obtained in this manner are summarized in Tables I and II. Compared with the τ_0 values, for each solvent, they indicate a greater degree of motional freedom in **1a** than in **1b**. As there is no obvious basis for assuming large differences in the rotational conformation and solvation pattern at C-6 for these anomers, the

different degree of motional freedom indicated by these data can be attributed to variations in their principal rotation axes, as discussed previously.

EXPERIMENTAL

The ^{1}H- and ^{13}C-n.m.r. experiments were carried out on a Varian XL-200 spectrometer operating at 200.0 and 50.4 MHz, respectively. ^{13}C-T_1 experiments were conducted on the same spectrometer under conditions of full ^{1}H noise-decoupling. The temperature was controlled at 25.0° ±0.1°. The relaxation times were measured by the FIRFT method[27] and analyzed by a three-parameter non-linear procedure[28]. The pulse duration for a 180° flip angle, checked periodically, was 28–29 μs. Other details on relaxation experiments and ^{13}C-n.O.e. measurements are given elsewhere[5]. The r.m.s. error in the three-parameter fit and the reproducibility were both ±5%, or better. Solutions of the glucopyranosides in various deuterated solvents were degassed by saturation with dry nitrogen for 1–2 min before use. The concentrations were M for methyl β-D-glucopyranoside and 0.5M for methyl α-D-glucopyranoside (0.25M in acetic acid) due to its more limited solubility in most solvents.

A 2D heteronuclear shift-correlation experiment was performed for the assignment of the chemical shifts of the resonances of C-3 and C-5 of **1b** in D_2O, which are resolved at 50 MHz, in contrast to earlier reports[29] where the two signals appear to coincide.

ACKNOWLEDGMENTS

The authors thank McGill University and the Natural Sciences and Engineering Research Council of Canada, for generous support. One of us (P.D.) thanks University of Crete for a leave of absence.

REFERENCES

1 W. PIGMAN AND H. S. ISBELL, *Adv. Carbohydr. Chem.*, 23 (1968) 11–59.
2 H. S. ISBELL AND W. PIGMAN, *Adv. Carbohydr. Chem. Biochem.*, 24 (1969) 13–65.
3 K. BOCK AND L. D. HALL, *Carbohydr. Res.*, 40 (1975) c3–c5.
4 M. F. CZARNIECKI AND E. R. THORNTON, *J. Am. Chem. Soc.*, 99 (1977) 8279–8290.
5 P. DAIS AND A. S. PERLIN, *Can. J. Chem.*, 61 (1983) 1542–1548.
6 P. DAIS AND G. FAINOS, *Can. J. Chem.*, 64 (1986) 560–565.
7 P. DAIS, *Macromolecules*, 18 (1985) 1351–1354.
8 P. DAIS, *Carbohydr. Res.*, 160 (1987) 73–93.
9 W. T. HUNTRESS, JR., *J. Chem. Phys.*, 48 (1968) 3524–3533.
10 P. STILBS AND M. E. MOSELEY, *J. Magn. Reson.*, 33 (1979) 209–210.
11 D. E. WOESSNER, *J. Chem. Phys.*, 37 (1962) 647–654.
12 D. E. WOESSNER, B. S. SNOWDEN, JR., AND G. H. MEYER, *J. Chem. Phys.*, 50 (1969) 719–721.
13 G. K. ALMS, D. R. BAUER, J. L. BRAUMAN, AND R. PECORA, *J. Chem. Phys.*, 59 (1973) 5321–5328; D. R. BAUER, J. I. BRAUMAN, AND R. PECORA, *J. Am. Chem. Soc.*, 96 (1974) 6840–6843; D. HOEL AND D. KIVELSON, *J. Chem. Phys.*, 62 (1975) 4535–4544.
14 R. W. TAFT, JR., E. PRICE, I. R. FOX, I. C. LEWIS, K. K. ANDERSEN, AND G. T. DAVIS, *J. Am. Chem. Soc.*, 85 (1963) 3146–3156.

15 V. GUTMANN, *Electrochim. Acta,* 21 (1976) 661–670.
16 A. I. POPOV, in J. J. LAGOWSKI (Ed.), *The Chemistry of Nonaqueous Solvents,* Vol. III, Academic Press, New York, 1970, pp. 244–246.
17 V. MAYER, V. GUTMANN, AND W. GERGER, *Monatsh. Chem.*, 106 (1975) 1235–1257.
18 C. REICHARDT, *Angew. Chem. Int. Ed. Engl.*, 4 (1965) 29–40.
19 C. REICHARDT, *Angew. Chem. Int. Ed. Engl.*, 18 (1979) 98–110.
20 C. REICHARDT, *Solvent Effects in Organic Chemistry,* Verlag Chemie, Weinheim, 1979.
21 J. M. HARVEY AND M. C. R. SYMONS, *J. Solution Chem.*, 7 (1978) 571–586.
22 A. SUGGETT, S. ABLETT, AND P. J. LILLFORD, *J. Solution Chem.*, 5 (1976) 17–31.
23 A. SUGGETT, *J. Solution Chem.*, 5 (1976) 33–46.
24 Y. KONDO AND K. KITAMURA, *Can. J. Chem.*, 55 (1977) 141–150.
25 J. M. BERRY, L. D. HALL, AND K. F. WONG, *Carbohydr. Res.*, 56 (1977) c16–c20.
26 A. S. PERLIN, *Can. J. Chem.*, 44 (1966) 539–550.
27 D. CANET, G. C. LEVY, AND I. R. PEAT, *J. Magn. Reson.*, 18 (1975) 199–204.
28 M. SASS AND D. ZIESSOV, *J. Magn. Reson.*, 25 (1977) 263–276.
29 K. BOCK AND C. PEDERSEN, *Adv. Carbohydr. Chem. Biochem.*, 41 (1983) 27–66; and references therein.