

¹H-NMR Analysis of Intra- and Intermolecular H-Bonds of Alcohols in DMSO: Chemical Shift of Hydroxy Groups and Aspects of Conformational Analysis of Selected Monosaccharides, Inositols, and Ginkgolides

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The interpretation of ¹H-NMR chemical shifts, coupling constants, and coefficients of temperature dependence ($\delta(\text{OH})$, $J(\text{H},\text{OH})$, and $\Delta\delta(\text{OH})/\Delta T$ values) evidences that, in (D₆)DMSO solution, the signal of an OH group involved as donor in an intramolecular H-bond to a hydroxy or alkoxy group is shifted upfield, whereas the signal of an OH group acting as acceptor of an intramolecular H-bond and as donor in an intermolecular H-bond to (D₆)DMSO is shifted downfield. The relative strength of the intramolecular H-bond depends on co-operativity and on the acidity of OH groups. The acidity of OH groups is enhanced when they are in an antiparallel orientation to a C–O bond. A comparison of the ¹H-NMR spectra of alcohols in CDCl₃ and (D₆)DMSO allows discrimination between weak and strong intramolecular H-bonds. Consideration of IR spectra (CHCl₃ or CH₂Cl₂) shows that the rule according to which the downfield shift of $\delta(\text{OH})$ for H-bonded alcohols in CDCl₃ parallels the strength of the H-bond is valid only for alcohols forming strong intramolecular H-bonds. The combined analysis of $J(\text{H},\text{OH})$ and $\delta(\text{OH})$ values is illustrated by the interpretation of the spectra of the epoxyalcohols **14** and **15** (Fig. 3). H-Bonding of hexopyranoses, hexulopyranoses, alkyl hexopyranosides, alkyl 4,6-*O*-benzylidenehexopyranosides, levoglucosans, and inositols in (D₆)DMSO was investigated. Fully solvated non-anomeric equatorial OH groups lacking a vicinal axial OR group (R=H or alkyl, or (alkoxy)alkyl) show characteristic $J(\text{H},\text{OH})$ values of 4.5–5.5 Hz and fully solvated non-anomeric axial OH groups lacking an axial OR group in β -position are characterized by $J(\text{H},\text{OH})$ values of 4.2–4.4 Hz (Figs. 4–6). Non-anomeric equatorial OH groups vicinal to an axial OR group are involved in a partial intramolecular H-bond ($J(\text{H},\text{OH})=5.4\text{--}7.4$ Hz), whereas non-anomeric equatorial OH groups vicinal to two axial OR form partial bifurcated H-bonds ($J(\text{H},\text{OH})=5.8\text{--}9.5$ Hz). Non-anomeric axial OH groups form partial intramolecular H-bonds to a *cis*-1,3-diaxial alkoxy group (as in **29** and **41**: $J(\text{H},\text{OH})=4.8\text{--}5.0$ Hz). The persistence of such a H-bond is enhanced when there is an additional H-bond acceptor, such as the ring *O*-atom (**43–47**: $J(\text{H},\text{OH})=5.6\text{--}7.6$ Hz; **32** and **33**: 10.5–11.3 Hz). The (partial) intramolecular H-bonds lead to an upfield shift (relative to the signal of a fully solvated OH in a similar surrounding) for the signal of the H-donor. The shift may also be related to the signal of the fully solvated, equatorial HO–C(2), HO–C(3), and HO–C(4) of β -D-glucopyranose (**16**: 4.81 ppm) by using the following increments: –0.3 ppm for an axial OH group, 0.2–0.25 ppm for replacing a vicinal OH by an OR group, *ca.* 0.1 ppm for replacing another OH by an OR group, 0.2 ppm for an antiperiplanar C–O bond, –0.3 ppm if a vicinal OH group is (partially) H-bonded to another OR group, and –0.4 to –0.6 for both OH groups of a vicinal diol moiety involved in (partial) divergent H-bonds. Flip-flop H-bonds are observed between the diaxial HO–C(2) and HO–C(4) of the inositol **40** ($J(\text{H},\text{OH})=6.4$ Hz, $\delta(\text{OH})=5.45$ ppm) and levoglucosan (**42**; $J(\text{H},\text{OH})=6.7\text{--}7.1$ Hz, $\delta(\text{OH})=4.76\text{--}4.83$ ppm; bifurcated H-bond); the former is completely persistent and the latter to *ca.* 40%. A persistent, unidirectional H-bond C(1)–OH \cdots O–C(10) is present in ginkgolide B and C, as evidenced by strongly different $\delta(\text{OH})$ and $\Delta\delta(\text{OH})/\Delta T$ values for HO–C(1) and HO–C(10) (Fig. 9). In the absence of this H-bond, HO–C(1) of **52** resonates 1.1–1.2 ppm downfield, while HO–C(10) of ginkgolide A and of **48–50** resonates 0.5–0.9 ppm upfield.

Introduction. – Hydrogen bonds have a strong influence upon the conformation of alcohols in the solid state and in solution. The solid state of alcohols is characterized by networks of intermolecular H-bonds. Intramolecular H-bonds are formed only when

they are particularly favourable [1]. In dilute solutions, there is competition between intra- and intermolecular H-bonds. The former dominate in apolar and the latter in polar solvents.

We have analysed the H-bonds of partially protected monosaccharides in apolar solvents by IR and $^1\text{H-NMR}$ spectroscopy, and correlated H-bonding with the reactivity of individual OH groups towards glycosylidene carbenes (for leading references, see [2–4]). Interest in cellulose analogues prompted us to also investigate the H-bonds of analogues of celooligomers in polar solvents (for leading references, see [5–7]). For this, IR spectroscopy proved insufficient. The rather weak bands for intramolecular H-bonds of the solute are, as a rule, obscured by strong bands for intermolecular H-bonds to, or of the solvent. The detection of OH signals in protic solvents (especially D_2O) by $^1\text{H-NMR}$ spectroscopy is hampered by a fast exchange of OH protons with H_2O . Individual OH signals of solutes in H_2O can be detected only under special conditions, *e.g.*, in the presence of cosolvents, at low temperature, and using special NMR techniques [8–10], while individual OH signals of solutes in $(\text{D}_6)\text{DMSO}$ are readily detected due to the slow exchange of OH protons in this solvent [11]. However, formation and cleavage of H-bonds in $(\text{D}_6)\text{DMSO}$ is still rapid relative to the NMR time scale (see below), so that chemical shifts and coupling constants of alcohols in DMSO reflect conformational equilibria.

For this reason, $(\text{D}_6)\text{DMSO}$ is widely used as solvent for NMR studies; yet surprisingly little is known about its interaction with alcohols. DMSO may be bound to one or two alcohol molecules depending on the concentration [12–15]. In dilute solutions, the 1:1 complex **1** between MeOH and DMSO is clearly favoured over the 2:1 complex **2** [12], in keeping with the semiempirically calculated 8.28 and 7 kcal/mol binding energy for the H-bonds in **1** and **2**, respectively [12] (*Fig. 1*). *Ab initio*

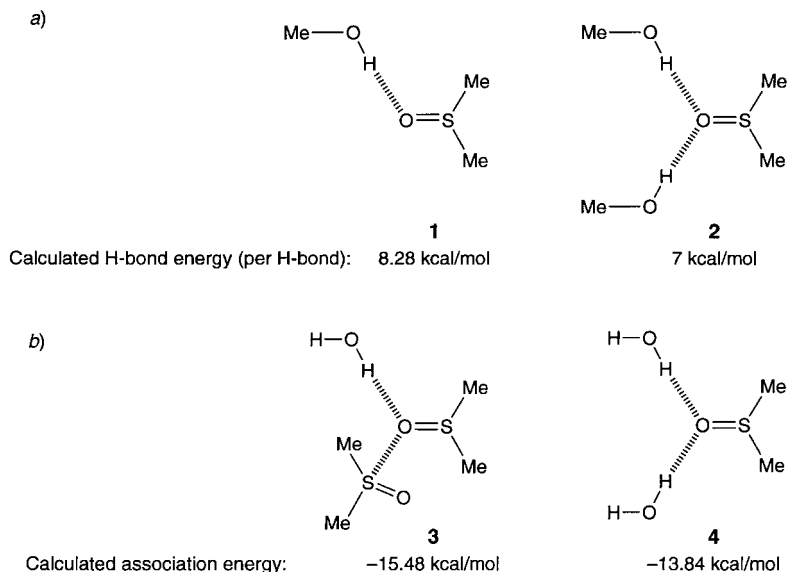


Fig. 1. a) *Ab initio* calculation of the H-bond energy of the $\text{DMSO}\cdot\text{MeOH}$ complexes **1** and **2** [12].
b) Semiempirical calculation (PM3) of the $\text{DMSO}\cdot\text{H}_2\text{O}$ complexes **3** and **4** [13].

calculations also show a higher stability of the DMSO \cdots DMSO \cdots H₂O complex **3** over the H₂O \cdots DMSO \cdots H₂O complex **4** ($\Delta E = 1.64$ kcal/mol [13]). This implies that – at least in dilute solutions – DMSO that is partially protonated by an alcohol prefers to interact with a second molecule of DMSO rather than with a second molecule of ROH. This conclusion differs from an early interpretation of the ¹H-NMR spectra of glucose and celooligomers in (D₆)DMSO by *Casu et al.* [16] (*cf.* also [17]). These authors proposed that two vicinal OH groups are bonded to one DMSO molecule, and that three vicinal OH groups are bonded to two DMSO molecules. This was claimed to be the case irrespective of the energetically unfavourable bending of the H-bonds implicit in the formation of seven-membered rings as implied by their proposition. We decided to reinvestigate H-bonding of alcohols in DMSO by using NMR spectroscopy.

¹H-NMR Spectroscopy provides at least six parameters [18] that can be used to study intra- and intermolecular H-bonding: the chemical shift δ of OH groups, the vicinal coupling constant ³*J*(H,OH), the temperature coefficient $\Delta\delta/\Delta T$, the isotopic effect (SIMPLE ¹H-NMR [19] [20]), the nuclear *Overhauser* effect (NOE), and the H/D exchange rate. Among them, chemical shifts and coupling constants are routinely accessible, whereas the other parameters require dedicated experiments. Yet, these two factors are often neglected in the analysis of H-bonding networks. This is surprising when one considers that vicinal ³*J*(CH,OH) and ³*J*(CH,CH) values show a similar dependence on the dihedral angle. *Fraser et al.* [21] have determined the pertinent parameters of the *Karplus* equation:

$${}^3J(\text{HO,CH}) = 10.4 \cos^2\theta - 1.5 \cos\theta + 0.2$$

Large coupling constants are observed for conformers with *anti*- and *syn*-periplanar arrangement of the C–H and O–H bonds and small couplings for conformers where these bonds are orthogonal. In DMSO, fully solvated equatorial OH groups show *J*(H,OH) values between 4.2 and 5.7 Hz, while fully solvated axial OH groups are characterized by *J*(H,OH) values of 3.0 to 4.2 Hz [22]. Coupling constants deviating from these values evidence restricted rotation around the C–O bonds and indicate that the OH group in question acts – completely or partially – as H-donor in an intramolecular H-bond¹⁾.

The fast H-bond formation and cleavage in DMSO leads to equilibria of H-bonded species. Some of the above mentioned parameters are not useful in assigning the position of these equilibria. The single best parameter for this purpose is the vicinal *J*(H,OH) coupling, provided that the conformers in question differ by their dihedral H–C–O–H angles. Molecular modeling may be employed to test the plausibility of the dihedral H–C–O–H angles derived from coupling constants. Obviously, the result of such an analysis should be in keeping with all other parameters that are indicative of H-bonding.

¹⁾ *A priori*, this could also be valid for H-bond-accepting OH groups. However, analysis of H-bonding in ginkgolides (see below) shows that the *J*(H,OH) value for H-bond-accepting OH groups differs little from the *J*(H,OH) value of fully solvated OH groups. This finding suggests that the rotational mobility of H-bond-accepting OH groups is less restricted than that of H-bond-donating OH groups.

It is generally assumed that OH groups involved as donors in strong H-bonds resonate at lower field than the same OH groups not involved in H-bonding, or acting as donors in weak H-bonds. Strong intramolecular H-bonds of alcohols in poorly H-bond accepting solvents, like CDCl_3 and C_6D_6 , have usually been assigned on the basis of their chemical shifts. In DMSO, however, OH groups may form strong intra- and strong intermolecular H-bonds. Still, the downfield shift of an OH group has most often been correlated with an intramolecular H-bond.

To the best of our knowledge, there have been no investigations of the relative chemical shifts for OH groups acting either as (intramolecular) H-donor to an OR group or as (intermolecular) H-donor to DMSO. This paper aims to examine the influence of intra- vs. intermolecular H-bonding of alcohols in DMSO solution on the chemical shift of the OH signals of monosaccharides. In the following paper [23], interresidue H-bonds of oligomeric saccharides will be investigated. Analysis of $^1\text{H-NMR}$ spectra in CDCl_3 , where even weak intramolecular H-bonds are formed, should yield coupling constants characteristic for intramolecularly H-bonded species.

Analysis. – 1. *Assignment of Weak Intramolecular H-Bonds of Alcohols in CDCl_3 Solution.* In apolar solvents, even weak intramolecular H-bonds are detected on the basis of characteristic $J(\text{H},\text{OH})$ values. This is illustrated by the data in Fig. 2 for the diols **5–12** and the triol **13** in CDCl_3 solution.

In the benzylidenated gluco- and galactopyranosides **5–8**, equatorial OH groups that are vicinal to an axial OR group ('1,2-*cis*-equatorial OH groups') are characterized by large $J(\text{H},\text{OH})$ values of 8–10.1 Hz, while equatorial OH groups vicinal to equatorial OR groups ('1,2-*trans*-equatorial OH groups') are characterized by small $J(\text{H},\text{OH})$ values (<2.5 Hz) [24]. These values correspond to dihedral H–O–C–H angles of 150–160° and of *ca.* 90°, respectively, in agreement with the intramolecular H-bonds depicted in Fig. 2.

In the fluorinated *myo*-inositol **9**, the equatorial OH group is vicinal to two *cis*-OR groups. There is a 1,3-diaxial arrangement of an OH and a F substituent. The $^1\text{H-NMR}$ spectrum of **9** exhibits large $J(\text{H},\text{OH})$ values; $J(2,\text{OH}) = 11.8$ Hz and $J(4,\text{OH}) = 8.3$ Hz correspond to dihedral H–O–C–H angles of 180 and 150°, respectively, and indicate a bifurcated $\text{OH}\cdots(\text{OR})_2$ and a weak $\text{OH}\cdots\text{F}$ H-bond [25] (see also [26]). The latter H-bond (in CDCl_3) is also evidenced by a J value of *ca.* 8.8 Hz between HO–C(4) and F that is observed only in apolar solvents. In the desfluoro analogue **10**, HO–C(2) is still involved in a bifurcated H-bond. The axial HO–C(4) lacks a neighbouring H-acceptor, and $J(4,\text{OH}) = 4.3$ Hz evidences that it rotates freely (*cf.* [22]).

$J(\text{H},\text{OH})$ may also be used to define equilibria between differently H-bonded isomers, as illustrated by the anomeric allopyranosides **11** and **12**. In the β -D-anomer **11**, $J(3,\text{OH}) < 1.5$ Hz evidences a H-bond to either O–C(4) or HO–C(2) (dihedral angles H–O–C(3)–H of *ca.* 90°), while the value of 6.0 Hz for $J(2,\text{OH})$ is in keeping with a 2 : 1 mixture of the tautomers **11a** and **11b** [27]. A comparison with the $J(2,\text{OH})$ values for the α -D-anomers **5** and **7** (10.1 and 8.0 Hz) shows that **11a** cannot be the only tautomer. There is, however, no other evidence for the presence of conformer **11b**.

The analysis of the spectrum of **12** is facilitated by first considering that of **13**. All $J(\text{H},\text{OH})$ of the tritylated α -D-altroside **13** are rather large, evidencing a system of cooperative H-bonds involving HO–C(4), HO–C(3), and the MeO group besides a

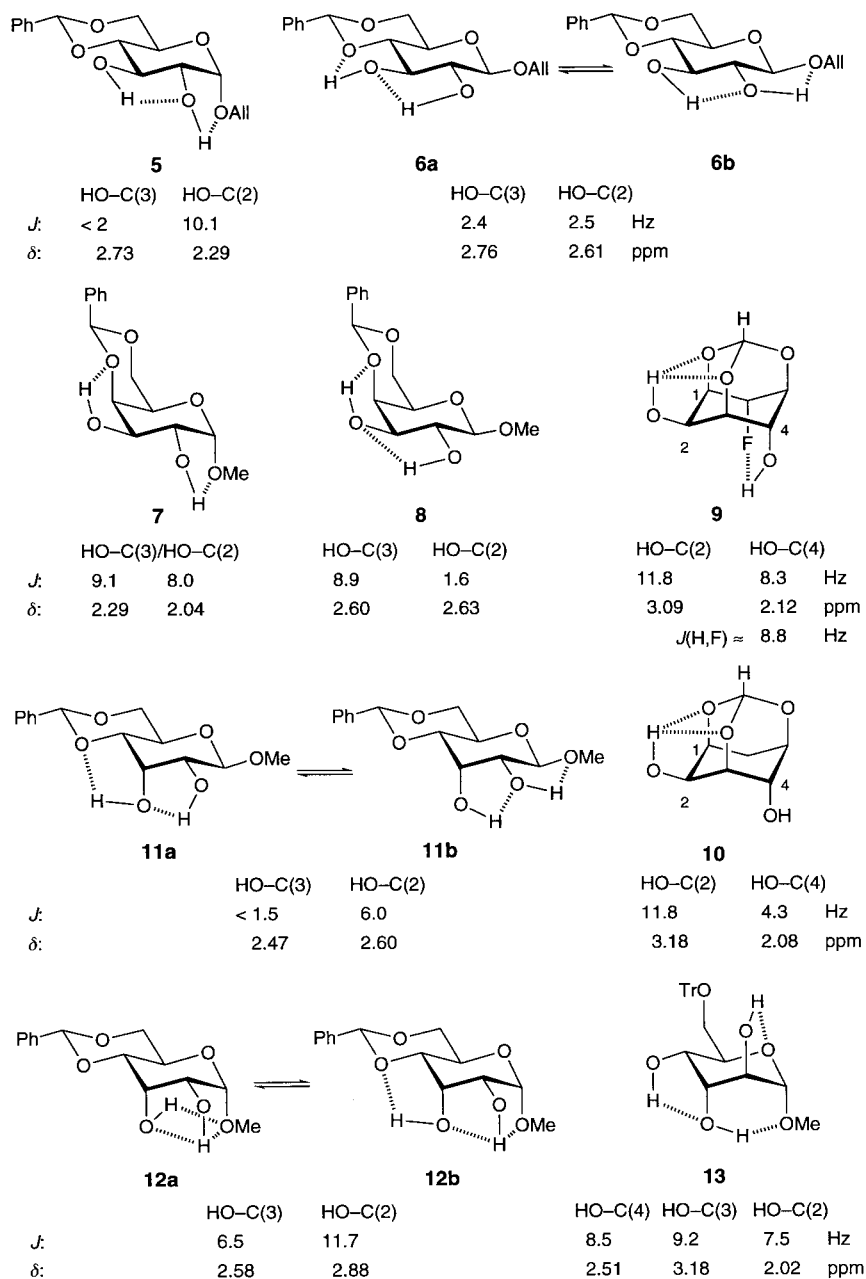


Fig. 2. $J(\text{H},\text{OH})$ and $\delta(\text{OH})$ values of **5–13** in CDCl_3 . Intramolecular H-bonds indicated by hashed bonds.

weak H-bond between HO-C(2) and the ring O-atom [28]. The α -D-allopyranoside **12** is characterised by a large $J(2,\text{OH})$ of 11.7 Hz and a smaller $J(3,\text{OH})$ of 6.5 Hz [27]. The value of $J(2,\text{OH})$ strongly suggests a bifurcated H-bond, while $J(3,\text{OH})$ is too small

for a H-bond of HO–C(3) to the anomeric MeO group (as in **12a**, compare with $J(3,\text{OH})=9.2$ Hz for **13**). The expected value for $J(3,\text{OH})$ of **12b** is *ca.* 1.5 Hz, as observed for $J(3,\text{OH})$ of the corresponding β -D-altropyranoside [24], *i.e.* the C(2)-epimer of **11**. Most probably then, **12** exists as a 2 : 1 mixture of **12a** and **12b** in CDCl_3 solution.

These observations show that $J(\text{H},\text{OH})$ of alcohols in CDCl_3 solution is indicative of even weak intramolecular H-bonds. However, $J(\text{H},\text{OH})$ does not allow to assess their relative H-bond strength, while IR spectroscopy provides a parameter for assessing the strength of the H-bond ($\tilde{\nu}$ or $\Delta\tilde{\nu}$ values²⁾ [29–32]). According to this parameter, intramolecular H-bonds in a six-membered ring, as for HO–C(3) of **13**, are stronger than H-bonds in five-membered rings. The strength of H-bonds forming five-membered rings decreases from bifurcated H-bonds, as in **9**, **10**, and **12** and H-bonds from an equatorial OH to a vicinal axial OR group, as in **7** and **13**³⁾, to H-bonds from an axial OH to a vicinal equatorial OR group, as in **11b** and **12b**, and further to H-bonds from an equatorial OH to a vicinal equatorial OR group, as in **6a** and **6b** [24] [27] [28] [31] [32]. The relative strength of the intramolecular H-bonds in **5**–**13** may be assigned on the basis of the $\Delta\tilde{\nu}$ values. The assignment is, however, contrary to the rule of thumb according to which the ¹H-NMR signal of an OH group is shifted downfield with increasing strength of its intramolecular H-bond. This rule appears to be only partly valid for alcohols in CDCl_3 solution. In keeping with it, the strong intramolecular H-bonds of HO–C(2) of **9** ($\tilde{\nu}(\text{CH}_2\text{Cl}_2)=3568\text{ cm}^{-1}$) and **10** ($\tilde{\nu}(\text{CH}_2\text{Cl}_2)=3573\text{ cm}^{-1}$) and of HO–C(3) of **13** ($\tilde{\nu}(\text{CH}_2\text{Cl}_2)=3520\text{ cm}^{-1}$) lead to a strong downfield shift of the corresponding OH signal, appearing at 3.09–3.18 ppm, whereas the fully solvated HO–C(4) of **10** ($\tilde{\nu}(\text{CH}_2\text{Cl}_2)=3604\text{ cm}^{-1}$) resonates at 2.08 ppm. However, the weakly H-bonded HO–C(2) and HO–C(3) of β -D-glucopyranoside **6** ($\tilde{\nu}(\text{CH}_2\text{Cl}_2)=3590\text{ cm}^{-1}$) resonate at lower field (2.61 and 2.76 ppm) than the more strongly H-bonded HO–C(2) and HO–C(3) of α -D-galactopyranoside **7** ($\tilde{\nu}(\text{CH}_2\text{Cl}_2)=3568\text{ cm}^{-1}$; 2.04 and 2.29 ppm). Although the co-operativity of the H-bonds in **6** may have some influence upon the chemical shift of the OH groups, it is hardly the dominating factor, since HO–C(3) of 2-*O*-glucosylated derivatives of **6** [24] ($\tilde{\nu}(\text{CHCl}_3)=3600\text{ cm}^{-1}$) also resonate at lower field (3.14–3.32 ppm) than HO–C(3) of 2-*O*-glucosylated derivatives of **7** [24] ($\tilde{\nu}(\text{CH}_2\text{Cl}_2)=3560\text{ cm}^{-1}$; 2.60–3.02 ppm) while their $J(\text{H},\text{OH})$ remain unchanged. Apparently, configurational and electronic factors have a strong influence upon the chemical shifts of OH signals in CDCl_3 solution.

These observations show that the validity of the above quoted rule is restricted to strong intramolecular H-bonds that result in strong downfield shifts. In spite of this restriction, the combination of the more reliable coupling constant $J(\text{H},\text{OH})$ and the chemical shift of OH groups is a powerful tool for the assignment of intramolecular H-bonds in apolar solvents. This is illustrated by the following example. *Pearce* and *Sanders* [33] have assigned structures **14b** and **15b**, respectively, to the diepoxy triols **14** and **15** that differ in the configuration of the 7,8-epoxy substituent (*Fig. 3*). Analysis of

²⁾ The difference between the experimental value and a standard value for non-H-bonded alcohols.

³⁾ The band at 3500 cm^{-1} corresponds to a stretching mode; for equatorial OH groups H-bonded to either one or two vicinal axial OH groups, one expects differences in the bending mode. To the best of our knowledge, this has not been investigated.

the coupling constants and the chemical shifts strongly evidences that the correct structures are **14a** and **15a**, respectively. The large $J(12,\text{OH}) = 12$ Hz of **14** corresponds to a dihedral angle $\text{H}-\text{O}-\text{C}(12)-\text{H}$ of 180° . It evidences a bifurcated H-bond as depicted in **14a** and is incompatible with **14b**, where the dihedral angle $\text{H}-\text{C}(12)-\text{O}-\text{H}$ is *ca.* 130° ⁴⁾ corresponding to $J(12,\text{OH})$ of *ca.* 5.5 Hz. The strong relative deshielding of $\text{HO}-\text{C}(12)$ agrees well with the bifurcated H-bond. The small $J(14,\text{OH}) = 0$ Hz is compatible with a H-bond to the 7,8-epoxy substituent (the calculated dihedral angle $\text{H}-\text{O}-\text{C}(14)-\text{H}$ of -66° ⁴⁾ corresponds to $J(14,\text{OH}) = 1.6$ Hz). The change of the configuration of the 7,8-epoxy substituent in **15** leads to a strong downfield shift for $\text{HO}-\text{C}(13)$ ($\Delta\delta = 1.55$ ppm) evidencing the H-bond between $\text{HO}-\text{C}(13)$ and this epoxy substituent. $J(12,\text{OH})$ and $J(14,\text{OH})$ of 10.7 Hz indicate anti- or synperiplanar O–H and C–H groups. The large $\Delta\delta$ value of 1.41 ppm for $\text{HO}-\text{C}(14)$ and $\text{HO}-\text{C}(12)$ of **15** reveals that $\text{HO}-\text{C}(14)$ resonating at 3.64 ppm is involved in a strong H-bond and $\text{HO}-\text{C}(12)$, resonating at 2.23 ppm – at best – in a weak one. The strong downfield shift of $\text{HO}-\text{C}(14)$ is clearly due to the bifurcated H-bond to the 9,11-epoxy substituent and to $\text{HO}-\text{C}(12)$, and this intramolecular H-bond is responsible for the synperiplanar arrangement of $\text{H}-\text{O}-\text{C}(12)-\text{H}$. These data are compatible only with structure **15a**.

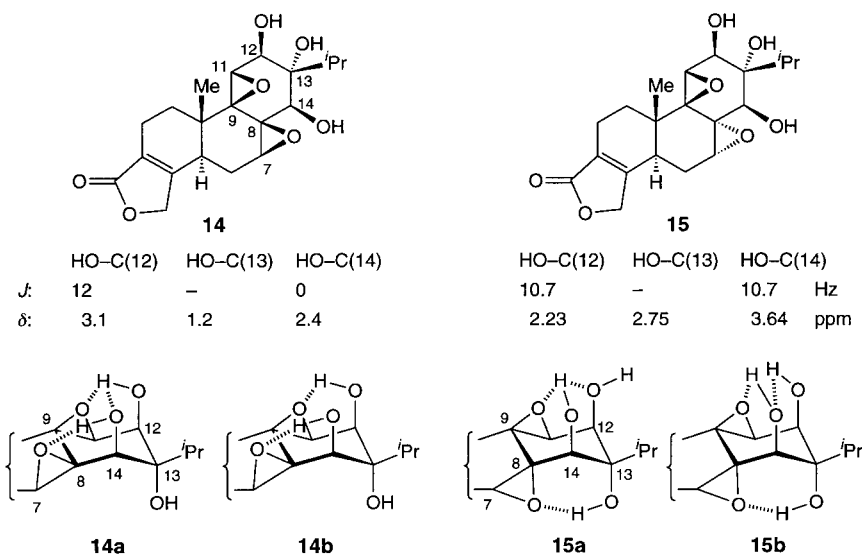


Fig. 3. $J(\text{H},\text{OH})$ and $\delta(\text{OH})$ values of the epimeric diepoxy triols **14** and **15** in CDCl_3 [33]. Assignment of intramolecular H-bonds (hashed bonds): **14a/15a** (this work) vs. **14b/15b** [33].

2. Comparison of the $^1\text{H-NMR}$ Spectra of CDCl_3 or $(D_6)\text{DMSO}$ Solutions of Selected Diols and Triols. The analysis in Sect. 1 showed the strong tendency of alcohols in CDCl_3 to form even weak intramolecular H-bonds. DMSO is a much better H-bond acceptor than chloroform; a comparison of the $^1\text{H-NMR}$ spectra of alcohols in CDCl_3

⁴⁾ From modeling with Macromodel V. 6.0 (MM3* force field, gas phase) [34].

and in (D_6)DMSO should allow differentiation between weak and strong intramolecular H-bonds. For this, $J(\text{H},\text{OH})$ coupling constants are a useful parameter.

Fully solvated equatorial and axial OH groups of dilute solutions of alcohols in (D_6)DMSO show characteristic coupling constants of 4.2–5.7 and 3.0–4.2 Hz, respectively [22]. The range of $J(\text{H},\text{OH})$ values shows that the directionality of intermolecular H-bonds to DMSO is not completely unbiased. Fortunately, the range is rather narrow, and most intramolecular H-bonds are characterized by dihedral H–C–O–H angles that give rise to $J(\text{H},\text{OH})$ values outside of it. OH Groups acting as H-donors in weak intramolecular H-bonds should survive only in CDCl_3 . Hence, they are expected to show (small or large) $J(\text{H},\text{OH})$ outside of the above mentioned range in CDCl_3 and $J(\text{H},\text{OH})$ in the range typical for fully solvated OH groups in (D_6)DMSO. OH Groups acting as H-donors in strong intramolecular H-bonds should show the same small or large $J(\text{H},\text{OH})$ values in both solvents. Finally, OH groups involved as H-donors in intramolecular H-bonds of intermediate strength that persist in CDCl_3 and are partially broken in (D_6)DMSO should show small or large $J(\text{H},\text{OH})$ in CDCl_3 and $J(\text{H},\text{OH})$ values intermediate between the one in CDCl_3 solution and the range typical for a completely solvated OH group. The limiting values should allow to assess the position of the equilibrium between intra- and intermolecularly H-bonded species.

We have thus compared the CDCl_3 and (D_6)DMSO ^1H -NMR data for the diols **9**–**12** and the triol **13** (Figs. 2 and 4). In CDCl_3 , **11**–**13** possess co-operative intramolecular H-bonds, while the cyclitols **9** and **10** [25] can form only isolated intramolecular H-bonds, which are more easily analysed. The HO–C(4) of **10** can not form an intramolecular H-bond. It is, indeed, completely solvated in both solvents as evidenced by $J(4,\text{OH})$ (4.3 Hz in CDCl_3 and 4.1 Hz in (D_6)DMSO). As expected, the weak OH...F H-bond of **9** in CDCl_3 ($J(4,\text{OH}) = 8.3$ Hz) is completely broken in (D_6)DMSO ($J(4,\text{OH}) = 3.8$ Hz). Also the weak HO–C(2) H-bond of **13** in CDCl_3 ($J(2,\text{OH}) = 7.5$ Hz) is completely broken in (D_6)DMSO ($J(2,\text{OH}) = 4.4$ Hz). The bifurcated H-bond of **9** and **10** persists to *ca.* 15–30% in (D_6)DMSO as deduced from the change of $J(2,\text{OH})$ from 11.8 Hz in CDCl_3 to 5.8 and 6.5 Hz, respectively.

The β -D-allopyranoside **11** [27] illustrates the H-bonding between vicinal equatorial and axial OH groups of a *cis*-1,2-diol and the equilibrium between two H-bonded isomers. In (D_6)DMSO, the axial HO–C(3) of **11** is completely solvated ($J(3,\text{OH}) = 3.9$ Hz). The slight increase of the $J(2,\text{OH})$ value from 6.0 Hz in CDCl_3 to 6.7 Hz in (D_6)DMSO indicates that conformer **11b** (Fig. 2) is no longer relevant, as will be elaborated below. The value of 6.7 Hz has to be compared to a limiting value of 8–10 Hz for an equatorial OH that is completely H-bonded to a vicinal axial OR group, as deduced from $J(2,\text{OH})$ of **5** and **7** and $J(3,\text{OH})$ of **7** and **8** in CDCl_3 . It evidences an equilibrium between intra- and intermolecularly H-bonded species of **11** in CDCl_3 , to which **11a** contributes to *ca.* 50%.

A comparison of the ^1H -NMR data of the α -D-allopyranoside **12** [27] and the α -D-altropyranoside **13** [28] in CDCl_3 and (D_6)DMSO should allow a comparison of the persistence of various intramolecular H-bonds in (D_6)DMSO solution with their relative strength, as deduced above from IR data. In (D_6)DMSO, the bifurcated H-bond of **12** is mostly retained, as evidenced by $J(2,\text{OH}) = 9.5$ Hz. $J(3,\text{OH}) = 5.1$ Hz is too large for a fully solvated axial OH group and indicates either a *ca.* 1:4 equilibrium

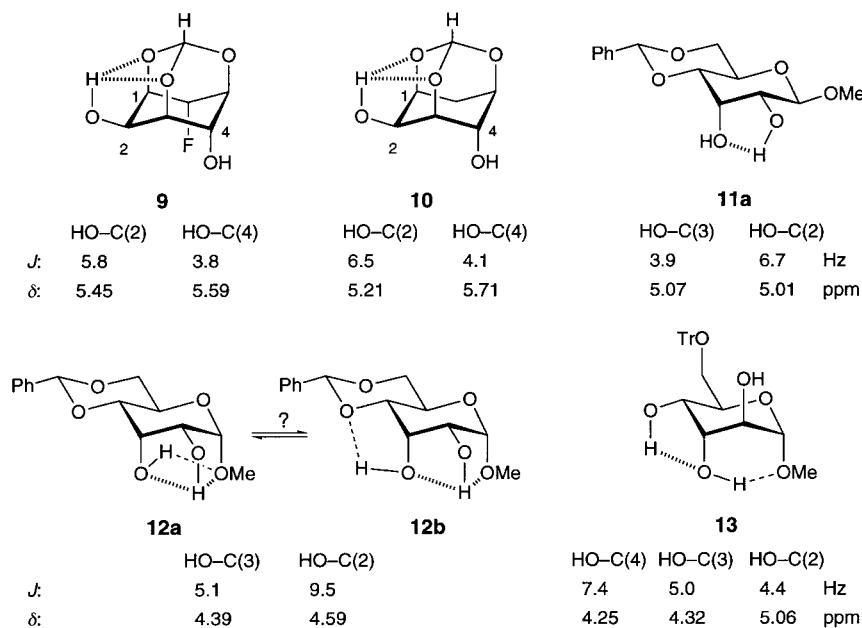


Fig. 4. $J(H,OH)$ and $\delta(OH)$ values of **9–13** in (D_6) DMSO. Hashed bonds indicate more strongly persistent intramolecular H-bonds than dashed bonds.

between **12a** and a species possessing a fully solvated HO-C(3) group, or an equilibrium between this species, **12a**, and **12b**. As mentioned above, HO-C(2) of **13** is completely solvated in (D_6) DMSO. Surprisingly, the stronger H-bond of HO-C(3) is mostly broken ($J(3,OH) = 5.0$ Hz), whereas the weaker H-bond of HO-C(4) is preserved to *ca.* 50% ($J(4,OH) = 7.4$ Hz).

These observations raise questions about the relative strength of intramolecular H-bonds: Why is the bifurcated H-bond of **12** more persistent than the bifurcated H-bond of the inositols **9** and **10**, and why, in **13**, is the H-bond of HO-C(4) (part of a five-membered ring!) more persistent than the H-bond of HO-C(3) that is part of a six-membered ring? Could this persistence be due to a co-operativity between the intra- and intermolecular H-bonds for HO-C(2) in **12** and for HO-C(4) in **13**, while such a co-operativity does not exist for the bifurcated H-bonds of **9** and **12**, nor for the ‘six-membered’ H-bond of **13**? We will discuss these issues in the following chapters.

Once the $J(H,OH)$ values have evidenced the (partial) intramolecular H-bonds of individual OH groups of **9–13** in (D_6) DMSO solution, it should be possible to analyse their effects on the chemical shift of the OH groups. The fully solvated axial HO-C(4) of **10** and **9**⁵⁾, HO-C(3) of **11**, and HO-C(2) of **13** resonates at 5.71, 5.59, 5.07, and 5.06 ppm, respectively. HO-C(2) of **9** and **10**, involved in a weakly persistent bifurcated H-bond, resonates at 5.45 and 5.21 ppm, respectively, whereas HO-C(2) of **12**, involved in a strongly persistent bifurcated H-bond, resonates at 4.59 ppm. The equatorial HO-C(2) of **11** and HO-C(4) of **13**, involved in a similarly persistent

⁵⁾ Related to the cyclohexane ring (HO-C(4) is equatorial with respect to the dioxane ring).

intramolecular H-bond to the vicinal axial OH group resonate at 5.01 and 4.25 ppm, respectively.

The chemical shifts for the OH groups of **9–13** suggest that the signal of a fully solvated OH group resonates at lower field than the signal of an intramolecularly H-bonded OH group. Obviously, there are a large range of chemical shifts for OH groups involved to a similar extent in intramolecular H-bonds of apparently the same type; the chemical shift of OH groups in (D_6)DMSO seems to strongly depend not only on H-bonding, but also on subtle structural effects that act directly and/or indirectly on the environment of the OH groups. A broader data basis is required to analyse such effects, and appropriate reference compounds are needed to determine the shifts due to H-bonding before chemical-shift values can be used to assign intramolecular H-bonds. Fortunately, $^1\text{H-NMR}$ data are available for closely related hexopyranoses, alkyl hexopyranosides, alkyl 4.6-*O*-benzylidene-hexopyranosides, levoglucosans, and inositols in (D_6)DMSO solution. Their $J(\text{H,OH})$ and $\delta(\text{OH})$ values will be analysed in *Sect. 3*.

3. *H-Bonding of Monosaccharides and Inositols in (D_6)DMSO*. Gillet *et al.* have analysed coupling constants and chemical shifts for the equatorial and axial OH groups of some hexopyranoses, methyl hexopyranosides, and hexulopyranoses in (D_6)DMSO as a function of their relative configurations, but without taking H-bonds into account [35]. They report $J(\text{H,OH})$ values of 4.5–5.5 Hz for non-anomeric equatorial OH groups⁶⁾ lacking a vicinal axial OR group ($\text{R} = \text{H}$ or Me) and of 4.2–4.4 Hz for non-anomeric axial OH groups lacking an axial OR group in β -position. These $J(\text{H,OH})$ values are typical of fully solvated OH groups [22]. The chemical shift values for fully solvated equatorial OH groups are 4.6–5.0 ppm, while the fully solvated axial OH groups resonate at 4.25–4.7 ppm, *i.e.*, upfield by 0.3 ppm. Both types of OH groups resonate *ca.* 0.5 ppm downfield of the OH signals for monoalkylated cyclohexanols (4.0–4.5 and 3.8–4.2 ppm [22]).

Gillet *et al.* have compared the $J(\text{H,OH})$ and $\delta(\text{OH})$ values for equatorial OH groups in *trans*, diequatorial and in *cis*, axial/equatorial 1,2-glycol moieties of the above mentioned pyranoses and pyranosides. The $J(\text{H,OH})$ value for a non-anomeric, equatorial OH group⁶⁾ in a *cis*-glycol moiety is larger (J of 5.7–6.8 Hz) than $J(\text{H,OH})$ in the *trans*-glycol moiety (J of 4.5–5.5 Hz)⁷⁾. This evidences that an equatorial OH is involved as donor in a partially persistent intramolecular H-bond to a vicinal axial OR group. The increase of $J(\text{H,OH})$ is quantified by comparing $J(\text{H,OH})$ for an equatorial OH in a *cis*-glycol moiety to $J(\text{H,OH})$ for an equatorial OH of an epimer in a *trans*-glycol moiety. A similar comparison should show the effect of the intramolecular H-bond on the chemical shift $\delta(\text{OH})$. It requires that $J(\text{H,OH})$ and $\delta(\text{OH})$ values for corresponding equatorial OH groups in *cis*- and *trans*-diol units are known. This is the case only for the pairs of compounds shown in *Fig. 5*, where the OH groups under consideration are outlined (*e.g.*, in **17** and **16**). The increase of $J(\text{H,OH})$ (ΔJ of 0.7–2 Hz) for an equatorial OH in passing from a *trans*- to a *cis* 1,2-diol unit is paralleled by an upfield shift $\Delta\delta$ of 0.2 to 0.5 ppm. A closer inspection reveals a semiquantitative

⁶⁾ $J(\text{H,OH})$ of fully solvated anomeric equatorial and axial OH groups (4.2–4.55 and 6.5–6.7 Hz, respectively) is influenced by the *exo*-anomeric effect (see, *e.g.*, [36]).

⁷⁾ A similar difference of the coupling constants is also observed for solutions in (D_6)acetone/ H_2O 2:1 at 250 K [37].

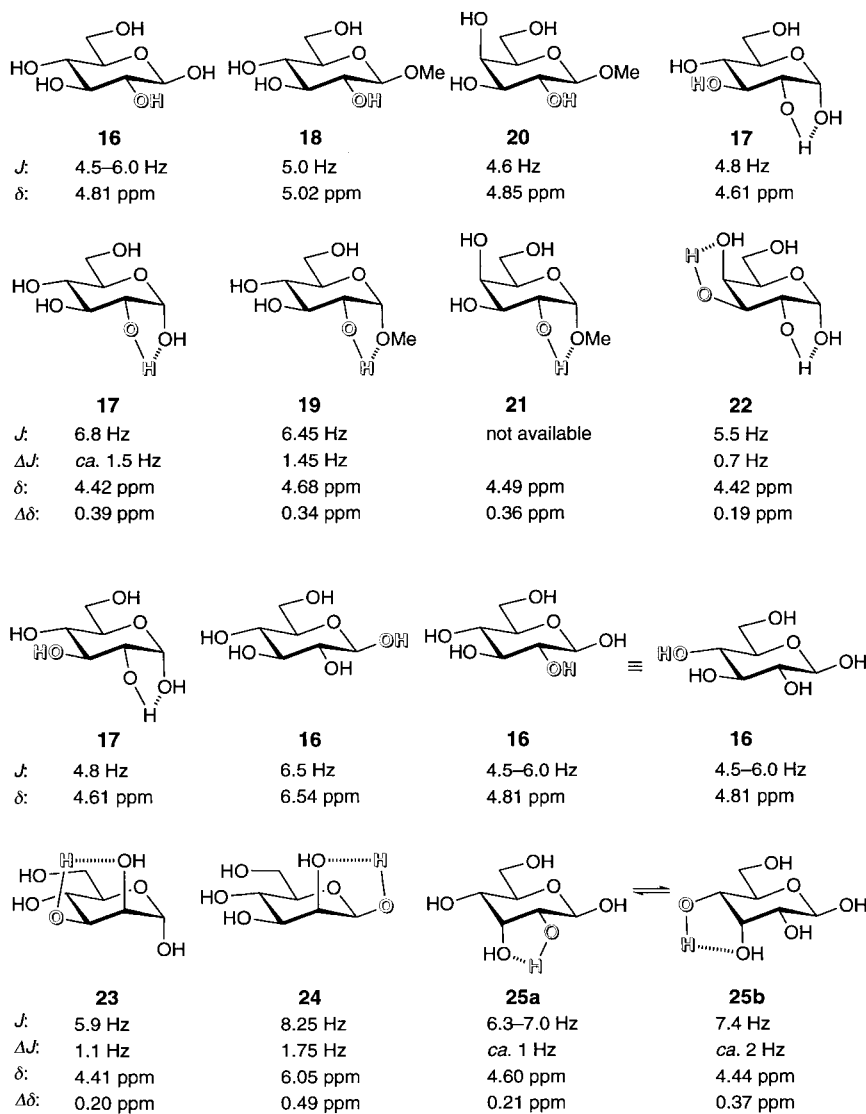


Fig. 5. Hexopyranoses and -pyranosides in (D_6)DMSO: Influence of an equatorial or axial OH group upon $J(H,OH)$ and $\delta(OH)$ of a vicinal equatorial OH group (marked by outlined letters, data from [35]) and assignment of the partially persistent intramolecular H-bonds (hashed bonds)

correlation between $\Delta J(H,OH)$ and $\Delta\delta(OH)$ values; larger ΔJ and $\Delta\delta$ values are observed for HO–C(2) of **16/17**, **18/19**, and **20/21**, for HO–C(1) of **24/16**, and for HO–C(4) of **25/16**, and smaller ΔJ and $\Delta\delta$ values for HO–C(3) of **22/17** and **23/17** and for HO–C(2) of **25/16**. The small ΔJ and $\Delta\delta$ values for HO–C(2) of **25/16** are presumably a consequence of the equilibrium between **25a** and **25b**, with HO–C(2) and HO–C(4) competing as H-bond donors and for HO–C(3) of **22/17** and **23/17** due

to the enhanced acidity of HO–C(2) (close to the anomeric centre and *anti*-periplanar to the C(1)–O(5) bond) and of HO–C(4) (*anti*-periplanar to the C(5)–O(5) bond; see below). Since HO–C(2), HO–C(3), and HO–C(4) of β -D-glucopyranose (**16**) resonate together at 4.81 ppm, this value is well-suited as reference for the chemical shift of equatorial OH groups in a *trans*-glycol moiety of hexopyranoses. It allows quantification of $\Delta\delta(\text{OH})$ for cases where only the values for the equatorial OH 1,2-*cis* to OR are known, as for HO–C(3) of the fructo- and sorbopyranoses ($J(\text{H},\text{OH}) = 6.7\text{--}6.8\text{ Hz}$ [35]), leading to $\Delta\delta(\text{OH}) = 0.45\text{--}0.6\text{ ppm}$.

Finally, Gillet *et al.* observed that the transformation of hexopyranoses into hexopyranosides leads to a downfield shift of HO–C(2) by 0.2–0.25 ppm and of all other OH groups by *ca.* 0.1 ppm, providing useful increments for this change.

These considerations lead to the conclusion that intramolecular OH \cdots OR H-bonds of 1,2-diols of pyranoses and pyranosides in (D₆)DMSO are associated with an upfield shift of the signal of the H-donating OH group. The upfield shift for an equatorial OH group acting partially as H-donor to a neighbouring axial OR group amounts to 0.2 to 0.4 ppm. Fully solvated axial OH resonate upfield from fully solvated equatorial OH groups; $\Delta\delta$ is typically 0.3 ppm. The transformation of a hexopyranose into a hexopyranoside leads to a downfield shift of 0.2 ppm for HO–C(2) and to a downfield shift of 0.1 ppm for all other OH groups.

To test the validity of these conclusions and to expand them to OH \cdots OR H-bonds between 1,3-diaxial substituents, we have analysed the (D₆)DMSO spectra of the epimeric 4,6-*O*-benzylidene-D-hexopyranosides **6**, **11**, **12**, and **26–33**⁸) (*Fig. 6*), the rigidity of the trioxadecalin ring system facilitating the analysis of intramolecular H-bonds of the C(2)–C(3) glycol moiety. A comparison of allyl β -D-glucopyranoside (**6**), methyl α -D-glucopyranoside (**26**), and methyl α -D-mannopyranoside (**27**) with the parent pyranoses **16**, **17**, and **23** shows a downfield shift for HO–C(2) and HO–C(3) of **6**, **26**, and **27** of *ca.* 0.5–0.6 ppm. Thus, (formal) alkylation of both the anomeric and non-anomeric OH groups induces a downfield shift of *ca.* 0.25 ppm for a vicinal OH group and of 0.1–0.15 ppm for the other OH groups.

The couplings and chemical shifts for equatorial OH groups of the 4,6-*O*-benzylidene-D-hexopyranosides will be analysed first. A comparison of the data for **6** and **30** shows the importance of the relative configuration, while the distance of the equatorial OH group from the anomeric centre has only a negligible influence on $J(\text{H},\text{OH})$ and $\delta(\text{OH})$. Both HO–C(2) and HO–C(3) of **6** are fully solvated ($J(\text{H},\text{OH}) = 5.2$ and 4.6 Hz, resp.). The same holds true for HO–C(3) of **26** (5.0 Hz) and HO–C(2) of **31** (4.2 Hz); the relatively wide range for $J(\text{H},\text{OH})$ of fully solvated OH groups has been noticed before. This is expected, as all these OH groups are characterized by an exclusive *trans*-relation to their neighbours.

Significantly larger $J(\text{H},\text{OH})$ values are observed for equatorial OH that have at least one axial neighbour. This is the case for HO–C(2) and HO–C(3) of **30**, HO–C(2) of **11** and **26**, and HO–C(3) of **27**, **28**, and **31** (5.6–6.75 Hz). $\Delta J(\text{H},\text{OH})$ is larger if both vicinal neighbours are axial, as for HO–C(2) of **12** (9.5 Hz) and

⁸) Me and allyl groups exert a similar influence on the chemical shifts of the OH groups; the $\delta(\text{OH})$ values for corresponding OH groups of methyl and allyl α -D-galactopyranoside [35] [40] differ by less than 0.02 ppm.

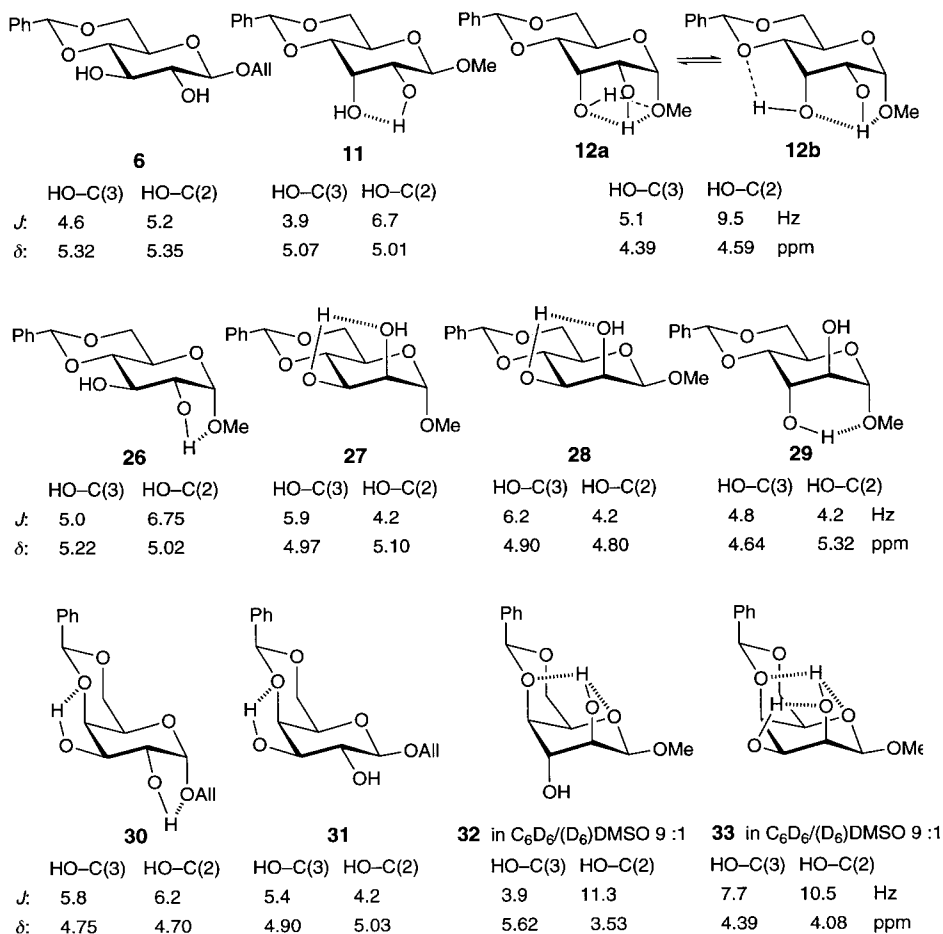


Fig. 6. $J(H,OH)$ and $\delta(OH)$ values of the 4,6-O-benzylidenehexopyranosides **6** [24], **11** [24], **12** [27], **26** [35], **27** [24], **28** [24], **29** [24] [38], **30**, and **31** in (*D*₆)DMSO, and of **32** [39] and **33** [39] in C₆D₆/(D₆)DMSO 9:1 and assignment of the (partial) intramolecular H-bonds. Hashed bonds indicate more strongly persistent intramolecular H-bonds than dashed bonds.

HO-C(3) of **33** in C₆D₆/(D₆)DMSO 9:1⁹⁾ (7.7 Hz). Such an increase of $J(H,OH)$ evidences a partially intramolecular H-bond of the equatorial OH group to the vicinal

⁹⁾ Perlin and co-workers [39] have published $J(H,OH)$ and $\delta(OH)$ values for solutions in C₆D₆/(D₆)DMSO 9:1 of methyl α -D-galactopyranoside (**7**; 4.69 (*d*, $J=6.3$, HO-C(3)); 4.64 (*d*, $J=6.3$, HO-C(2))), methyl β -D-galactopyranoside (**8**; 5.20 (*d*, $J=4.3$, HO-C(2)); 4.85 (*d*, $J=6.2$, HO-C(3))), methyl β -D-idopyranoside (**32**; see Fig. 6), and methyl β -D-talopyranoside (**33**; see Fig. 6). A comparison of the $J(H,OH)$ and $\delta(OH)$ values of **7** and **8** in C₆D₆/(D₆)DMSO 9:1 with the values of **30** and **31** in (D₆)DMSO (Fig. 6) shows that the addition of C₆D₆ leads to a slight increase of $J(2,OH)$ ($\Delta J=0.1$ Hz), a stronger increase of $J(3,OH)$ ($\Delta J=0.5$ to 0.8 Hz), a weak upfield shift ($\Delta\delta=0.05-0.06$ ppm) for the OH partially involved in intramolecular H-bonds to vicinal axial OR groups, and a stronger downfield shift ($\Delta\delta=0.17$ ppm) for the fully solvated HO-C(2) of **8**. One expects that the addition of 90% of C₆D₆ leads to similar weak upfield shifts for the partially intramolecularly H-bonded OH groups of **32** and **33** and to a stronger downfield shift for the fully solvated HO-C(3) of **32**.

OR group(s) (R = H, Me, allyl, or (alkyloxy)alkyl), as discussed above for hexopyranoses, hexulopyranoses, and hexopyranosides. Based on the observed $J(\text{H},\text{OH})$ values (5.4–6.75 Hz; Fig. 6), an upper limiting value of 8.0–10.1 Hz¹⁰), and a lower limiting value set to 4.5 Hz, we conclude that HO–C(2) of **11**, **26**, and **30**, and HO–C(3) of **27**, **28**, **30**, and **31**, are involved to ca. 35–50% in an intramolecular H-bond to the neighbouring axial OR group. Co-operativity of the intramolecular H-bonds in the β -D-talopyranoside **33** suggests that HO–C(2) acts exclusively as H-bond acceptor of HO–C(3). If so, $J(3,\text{OH}) = 7.7$ Hz and an assumed upper limiting value of 9.0 Hz indicate that the intramolecular H-bond between HO–C(3) and O–C(2) is formed to ca. 70%. $J(2,\text{OH}) = 9.5$ Hz of **12** in (D_6)DMSO, compared to 11.7 Hz in CDCl_3 , evidences that this bifurcated H-bond is also retained to ca. 70%.

The diequatorial, fully solvated and more or less freely rotating HO–C(2) and HO–C(3) of the β -D-glucopyranoside **6** resonate at a similar position (5.35 and 5.32 ppm) that must be typical of fully solvated equatorial OH groups in 4,6-*O*-benzylidenehexopyranosides. An interpretation of the upfield shift for the fully solvated, equatorial HO–C(3) of the α -D-glucopyranoside **26** ($\Delta\delta = 0.1$ ppm) and HO–C(2) of the β -D-galactopyranoside **31** ($\Delta\delta = 0.32$ ppm) is facilitated by first analysing the chemical shifts and coupling constants of the equatorial OH groups of the other compounds in Fig. 6. The equatorial OH groups that are involved to 35–50% in an intramolecular H-bond resonate at 4.70–5.02 ppm. This is the case for HO–C(2) of the β -D-allopyranoside **11**, the α -D-glucopyranoside **26**, and the α -D-galactopyranoside **30**, and HO–C(3) of the manno- and galactopyranosides **27**, **28**, **30**, and **31**, and corresponds to an upfield shift of 0.3–0.4 ppm for **11**, **26**, **27**, **28**, and **31** relative to $\delta(\text{OH})$ of a fully solvated equatorial OH group in 4,6-*O*-benzylidenehexopyranosides. A surprisingly large upfield shift of 0.6 ppm is observed for both OH groups of the α -D-galactopyranoside **30**. It is not readily explained, but may be correlated with the fact that the intramolecular H-bonds in **30** point in opposite directions. Indeed, similar strong upfield shifts of 0.4–0.6 ppm are observed for HO–C(2) and HO–C(3) of α -D-galactopyranose (**22**) and HO–C(3) and HO–C(4) of β -D-fructopyranose [35] that form similar divergent H-bonds. (Partially) divergent H-bonds of vicinal OH groups may thus also be responsible for the upfield shift of the fully solvated HO–C(2) of the β -D-galactopyranoside **31** (0.32 ppm) and HO–C(3) of the α -D-glucopyranoside **26** (0.1 ppm; a downfield shift of ca. 0.2 ppm due to the *anti*-periplanar C(1)–O bond must be included in the analysis). An upfield shift ($\Delta\delta(\text{OH}) = 0.93$ ppm relative to **6**) is also noticed for HO–C(3) of the β -D-talopyranoside **33** involved to 70% in an intramolecular H-bond. This shift is remarkably strong, even when considering that the spectrum of **33** has been recorded in $\text{C}_6\text{D}_6/(\text{D}_6)\text{DMSO } 9:1^9$; it should be compared to the shift for HO–C(2) ($\Delta\delta(\text{OH}) = 0.76$ ppm relative to **6**) of the α -D-allopyranoside **12** that is also involved to 70% in an intramolecular bifurcated H-bond.

¹⁰) Deduced from the couplings observed in the CDCl_3 spectra: 8.0 and 9.1 Hz for HO–C(2) and HO–C(3) of **7**, 8.9 Hz for HO–C(3) of **8**, and 10.1 Hz for HO–C(2) of **5** (Fig. 2). The $^1\text{H-NMR}$ spectra of **11**, **27**, and **28** in CDCl_3 show equilibria between species that possess co-operative intramolecular H-bonds pointing in opposite directions [24] so that $J(\text{H},\text{OH})$ of their equatorial OH groups cannot be used as limiting values; the upper limiting value for **11**, **27**, and **28** is set to 9.0 Hz.

Turning to the axial OH groups of the benzylidenated hexopyranosides (Fig. 6), one notes that HO–C(2) of **29** and HO–C(3) of **32** cannot form intramolecular H-bonds and are fully solvated, as shown by the characteristic $J(\text{H},\text{OH})$ values of 4.2 and 3.9 Hz, respectively. The same $J(\text{H},\text{OH})$ values are also observed for HO–C(2) of **27** and **28** and HO–C(3) of **11**. We may draw the conclusion that axial OH groups that function as H-bond acceptors in a partial intramolecular H-bond are fully solvated by DMSO. Their H-bonds to DMSO do not show a preferred direction.

In the absence of an axial alcohol that may serve as a reference for the chemical shift of a fully solvated axial OH group in 4,6-*O*-benzylidenehexopyranosides, we based the interpretation of the shift of axial OH groups on the shift difference of 0.3 ppm between fully solvated equatorial and axial OH groups. This upfield shift has been indicated by *Pretsch et al.* [22] for fully solvated axial OH groups in cyclohexanols. It is in agreement with the analysis, at the beginning of this section, of unprotected hexopyranoses and hexopyranosides. Based on the chemical shift for the equatorial OH groups of the β -D-glucopyranoside **6** (ca. 5.3 ppm), one expects a $\delta(\text{OH})$ value of ca. 5.0 ppm as typical for fully solvated axial OH groups of benzylidenated hexopyranosides. The observed $\delta(\text{OH})$ for the axial OH groups increases from 4.80 (HO–C(2) of **28**), to 5.07 (HO–C(3) of **11**), 5.10 (HO–C(2) of **27**), 5.32 (HO–C(2) of **29**), to a maximum of 5.62 ppm (HO–C(3) of **32** in $\text{C}_6\text{D}_6/(\text{D}_6)\text{DMSO}$ 9:1, some deshielding is due to C_6D_6^9). A strong deshielding has already been observed for the fully solvated axial HO–C(4) of the *myo*-inositols **9** and **10**⁵) (5.59 and 5.71 ppm, resp.; Fig. 4). The deshielding of these axial OH groups increases with the number of antiperiplanar C–O bonds; *i.e.*, from 0 (**28** and **11**), 1 (**27**), and 2 (**29** and **33**) to 3 bonds (**9** and **10**). The large range of the $\delta(\text{OH})$ values suggests the effect of an electronic interaction with an antiperiplanar OR group leading to a higher acidity of the OH group, hence to a stronger H-bond to $(\text{D}_6)\text{DMSO}$, and to a stronger deshielding. Indeed, AM1 calculations [41] for the alcohols **34**–**36** and the corresponding anions **37**–**39** (Fig. 7) evidence that the acidity increases from cyclohexanol **34** *via* the hydroxytetrahydropyran **35** to the hydroxydioxane **36**, with ΔE for deprotonation decreasing from 14.5 (**34/37**) *via* 9.1 (**35/38**) to 3.5 kcal/mol (**36/39**).

Axial OH groups may be involved in strong H-bonds forming six-membered rings to *cis*-oriented (axial) OR groups in β -position. Such H-bonds may be formed by HO–C(3) of the α -D-altropyranoside **29** and the α -D-allopyranoside **12**, and by

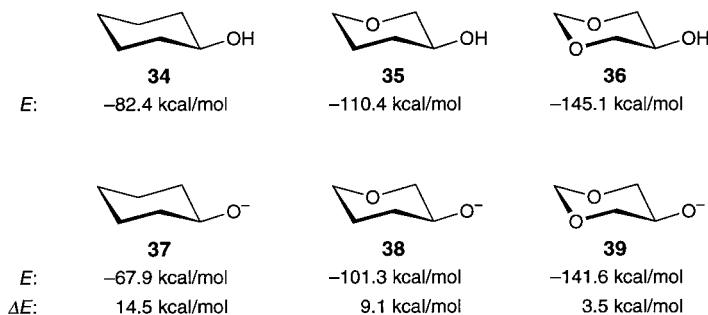


Fig. 7. AM1 Calculated (Ampac 6.0 [42]) enthalpies of the equatorial alcohols **34**–**36** and of the corresponding anions **37**–**39**.

HO–C(2) of the β -D-idopyranoside **32** and the β -D-talopyranoside **33** (Fig. 6). $J(3,\text{OH}) = 4.8$ Hz of **29** indicates that this intramolecular H-bond is formed only to a small extent. This is in keeping with the observation that anomeric OR groups are relatively weak H-bond acceptors [42], and that HO–C(3) of **29** in CDCl_3 also forms a (competing) H-bond to O–C(4) [24] [38]. To quantitatively interpret $J(3,\text{OH})$ of **29**, we have accepted an upper limiting value for $J(3,\text{OH})$ of 9 Hz, corresponding to a H–C(3)–O–H angle of *ca.* 150° (to be compared with $J(4,\text{OH}) = 8.3$ Hz of the 6-fluoro-*myo*-inositol **9** in CDCl_3 ; Fig. 2). This means that only *ca.* 10% of **29** form an intramolecular H-bond to the anomeric MeO group. The same limiting value allows us to interpret that $J(3,\text{OH}) = 5.1$ Hz for the α -D-allopyranoside **12** is compatible with either a 1:5 equilibrium between **12a** and the species possessing a fully solvated HO–C(3), or with an equilibrium between **12a**, **12b**, and to a minor extent, a species possessing a fully solvated HO–C(3). The large $J(2,\text{OH})$ values of **32** (11.3 Hz) and **33** (10.5 Hz) correspond to dihedral angles of nearly 180° and evidence persistent, bifurcated H-bonds to O–C(4) and O–C(5). The smaller value of **33** is probably due to the co-operativity of the H-bond of HO–C(3). The chemical shifts of these axial OH groups increase from 3.53 (HO–C(2) of **32**; including a weak effect of C_6D_6^9) to 4.08 (HO–C(2) of **33**; again including a weak effect of C_6D_6^9), to 4.39 (HO–C(3) of **12**), and to 4.64 (HO–C(3) of **29**) in parallel with the decreasing strength of the intramolecular H-bonds.

The 1,3-diaxial OH groups of 1,3,5-*O*-alkylidene-*myo*-inositols (such as **40**; Fig. 8) are involved in strong intramolecular H-bonds, while HO–C(2) and HO–C(4) of levoglucosan (**42**) form at best a weak intramolecular H-bond [43]. The 1,3,5-*O*-alkylidene-*myo*-inositols and levoglucosans are suitable model compounds for the investigation of the influence of strong and weak intramolecular H-bonds on the chemical shift of 1,3-diaxial OH groups. The C(4)–O \cdots O–C(6) distance of 2.768 Å in **40** (solid state [43]) corresponds to the optimal distance of 2.8 Å observed for intermolecular H-bonds in crystals [44]. In the absence of bulky protecting groups, the pyranose ring of levoglucosans prefers a (slightly distorted) ${}^1\text{C}_4$ conformation and a *cis*-1,3-diaxial orientation of the substituents at C(2) and C(4) (see [45] and refs. cit. therein). This is evidenced by small $J(2,3)$ and $J(3,4)$ couplings (≤ 4 Hz)¹¹). The *anti*-reflex effect [48] leads to a large C(2)–O \cdots O–C(4) distance of 3.299 Å in crystalline **42** [49] that is compatible with only a weak intramolecular H-bond. Conceivably, O–C(5) of **42** may act as an additional H-bond acceptor, as it does in the case of the bifurcated H-bond of HO–C(2) of the ido- and altropyranosides **32** and **33**, but it is hardly a single, strong acceptor in (D_6)DMSO, as suggested by the observation that HO–C(2) in the α -D-altropyranosides **13** and **29** (Figs. 4 and 6) is fully solvated.

At this stage, we also considered the temperature dependence of the chemical shifts of OH groups ($\Delta\delta/\Delta T$ values; see [24] and refs. cit. therein) to facilitate the analysis of H-bonds. Fully solvated OH groups show large $|\Delta\delta/\Delta T|$ values, while OH groups

¹¹) Sometimes only smaller $J(2,3)$ and $J(3,4)$ values (≤ 2 Hz) have been assigned to the ${}^1\text{C}_4$ conformer (see, e.g., [46]), whereas $J(2,3)$ and $J(3,4)$ values of 3–4 Hz should indicate an equilibrium between the ${}^1\text{C}_4$ and the $B_{3,0}$ conformer which shows typical $J(2,3)$ and $J(3,4)$ values of 8–10.5 Hz [45]. However, these small changes of $J(2,3)$ and $J(3,4)$ can be easily explained by a slight flattening of the ${}^1\text{C}_4$ chair influenced by the substituents and the solvent. According to the Karplus equation of Altona [47], values for coupling constants of 2 and 4 Hz correspond to H–C–C–H dihedral angles of 108° and 119° , respectively.

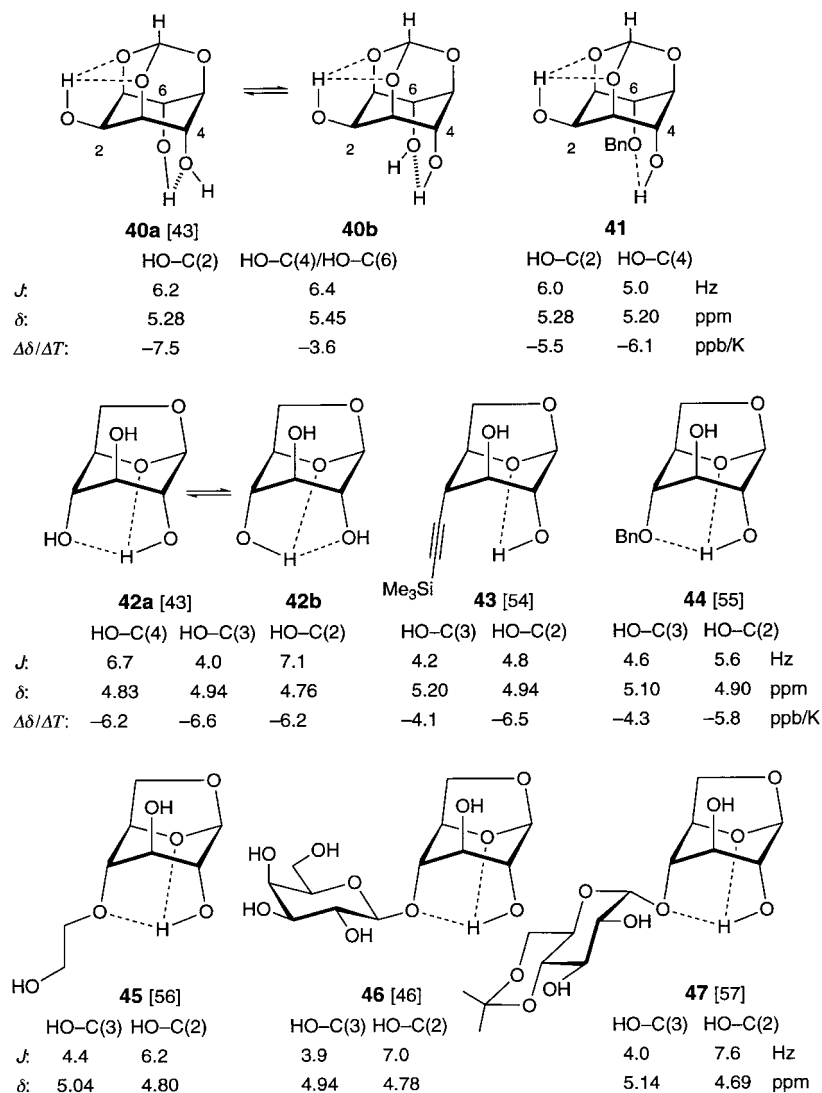


Fig. 8. $J(H,OH)$, $\delta(OH)$, and $\Delta\delta(OH)/\Delta T$ values of the myo-inositols **40** and **41**, and the levoglucosans **42–47** in $(D_6)DMSO$, and assignment of the intramolecular H-bonds. Hashed bonds indicate strongly persistent and dashed bonds weakly persistent intramolecular H-bonds.

acting as H-bond donors in intramolecular H-bonds are less well-solvated and show small $|\Delta\delta/\Delta T|$ values. $\Delta\delta/\Delta T$ Values of -5 to -8 ppb/K have been assigned to fully solvated OH groups of alcohols in $(D_6)DMSO$, and $\Delta\delta/\Delta T$ values of -1 to -2.5 ppb/K to OH groups acting as H-donors in strong intramolecular H-bonds [50].

According to the $\Delta\delta/\Delta T$ and $J(H,OH)$ values, the bifurcated H-bond of HO-C(2) in 1,3,5-*O*-methylidene-*myo*-inositols is mostly broken, as evidenced by $\Delta\delta/\Delta T$ of -7.5 (**40**) and -5.5 ppb/K (**41**) and by $J(2,OH)$ of 6.5 (**10**), 6.2 (**40**), 6.0 (**41**), and 5.8 Hz (**9**);

Figs. 4 and 8). The upper limiting value for $J(2,\text{OH})$ is given by 11.8 Hz for **8** and **9** in CDCl_3 , where this H-bond is formed to 100%; the lower limiting value is set to 4.5 Hz. This means that the extent to which $\text{HO}-\text{C}(2)$ of the methylidyne-*myo*-inositols forms an intramolecular H-bond in (D_6) DMSO decreases with increasing polarity of the $\text{C}(6)-\text{X}$ bond ($\text{X} = \text{H}, \text{OH}^{12}$), OBn, and F) from 27% for **10** to 18% for **9**. The $\delta(\text{OH})$ values for $\text{HO}-\text{C}(2)$ decrease from 5.45 (**9**) via 5.28 (**40** and **41**) to 5.21 ppm (**10**) in parallel with the increasing proportion of the intramolecularly H-bonded species with the exception of **40** (a consequence of the strong intramolecular H-bond between the axial OH groups?). $\text{HO}-\text{C}(2)$ in these *myo*-inositols is much better solvated by (D_6) DMSO than the OH groups of the 4,6-*O*-benzylidenehexopyranosides **12**, **32**, and **33** that are involved in bifurcated H-bonds. This is rationalized by two factors, the absence of an additional co-operative inter- or intramolecular H-bond in the *myo*-inositols and the poor H-accepting properties of the O-atoms of the orthoester moiety [51], as evidenced by the influence of the electronegativity of the *anti*-periplanar $\text{C}(6)-\text{X}$ substituent.

The ^1H -NMR spectrum of **40** in (D_6) DMSO exhibits a single, sharp signal for both $\text{HO}-\text{C}(4)$ and $\text{HO}-\text{C}(6)$. This is in keeping with either a symmetric, fully solvated molecule or a rapid equilibrium between **40a** and **40b** (flip-flop H-bond). Thus, $\Delta\delta/\Delta T$, $J(\text{H},\text{OH})$, and $\delta(\text{OH})$ values should either indicate completely solvated axial OH groups, or correspond to a value intermediate between that for an axial OH group acting as H-donor and that for a completely solvated axial OH group acting as H-acceptor⁵). $\Delta\delta/\Delta T = -3.6$ ppb/K and $J(\text{H},\text{OH}) = 6.4$ Hz evidence a flip-flop H-bond system. $J(\text{H},\text{OH}) = 6.4$ Hz is exactly average between *ca.* 9 Hz, derived from the dihedral angle $\text{H}-\text{C}-\text{O}-\text{H}$ of *ca.* 153° of crystalline **40** (compare with $J(4,\text{OH}) = 8.3$ Hz of **9** in CDCl_3 ; see Fig. 2), and 3.8–4.1 Hz observed for the fully solvated $\text{HO}-\text{C}(4)$ of **9** and **10**, establishing a 1:1 equilibrium between **40a** and **40b**. $\text{HO}-\text{C}(4)$ and $\text{HO}-\text{C}(6)$ of **40** resonate at 5.45 ppm, *ca.* 0.15–0.25 ppm upfield to the fully solvated $\text{HO}-\text{C}(4)$ of **9** and **10**. Derivatives of **40** that are protected at $\text{O}-\text{C}(2)$ show an analogous flip-flop H-bond, as evidenced by a characteristic $J(\text{H},\text{OH})$ of 6.6 Hz. The doublet for $\text{HO}-\text{C}(4)/\text{HO}-\text{C}(6)$ resonates at 5.22–5.23 ppm [52] [53]. Conceivably, the downfield shift for $\text{HO}-\text{C}(4)/\text{HO}-\text{C}(6)$ of **40** is conditioned by the partial intramolecular H-bond of $\text{HO}-\text{C}(2)$, equivalent to a partial protonation of the alkoxy groups *anti*-periplanar to $\text{HO}-\text{C}(4)/\text{HO}-\text{C}(6)$. Unfortunately, we do not know the limiting chemical-shift values for the H-donating and H-accepting OH groups in this flip-flop system; the analysis of the ginkgolides (see below) shows that the signal for a H-accepting, fully solvated OH group may be shifted downfield by *ca.* 0.75 ppm relative to the signal of an isolated, fully solvated OH group. Although the 6-*O*-protected *myo*-inositol **41** should possess a unidirectional $\text{C}(4)-\text{OH}\cdots\text{O}-\text{C}(6)$ H-bond, the large temperature dependence for $\text{HO}-\text{C}(4)$ (-6.1 ppb/K)¹³ and $J(4,\text{OH}) = 5.0$ Hz evidences that it is only formed to an extent of *ca.* 20% in (D_6) DMSO. The

¹²) This OH group is involved in a strong intramolecular H-bond, and is, thus, partially protonated.

¹³) With increasing temperature, the signal for $\text{HO}-\text{C}(2)$ shows a weak broadening and an unchanged coupling constant, whereas the signal for $\text{HO}-\text{C}(4)$ shows a stronger broadening and a more or less constant coupling constant up to 55° . At 65° , there is a poorly resolved *doublet* with a small coupling constant of 2.8 Hz. This is due to the enhanced H/H exchange for $\text{HO}-\text{C}(4)$ at higher temperature (*cf.* [11]).

intramolecular H-bond in **40** and **41** is thus formed to a very different extent. This is due to the co-operative effect of the intra- and intermolecular H-bonds in **40** (see next section).

The analysis of H-bonding in levoglucosan (**42**) is facilitated by first turning to the diol **43** [54], which should possess completely solvated OH groups in (D₆)DMSO. Indeed, HO–C(3) is completely and HO–C(2) almost completely solvated, as evidenced by $J(3,\text{OH})$ of 4.2 Hz and $J(2,\text{OH})$ of 4.8 Hz and by $\Delta\delta/\Delta T$ of -6.1 ppb/K for HO–C(2). That $J(2,\text{OH})$ is slightly larger than $J(3,\text{OH})$ of **42** and than $J(4,\text{OH}) = 3.8$ Hz of the fluoro-inositol **9** indicates some intramolecular H-bonding (bifurcated H-bond to O–C(5) and the acetylene moiety?). The low $\Delta\delta/\Delta T$ value of -4.1 and -4.3 ppb/K for the fully solvated HO–C(3) of **43** and **44** is surprising. A large $\Delta\delta/\Delta T$ value of -6.6 ppb/K is observed for HO–C(3) of levoglucosan (**42**). Together with $J(3,\text{OH}) = 4.0$ Hz, it evidences a completely solvated HO–C(3). Flip-flop H-bonds for HO–C(2) and HO–C(4) of **42** are evidenced by $J(\text{H},\text{OH})$ of 6.7–7.1 Hz and the same $\Delta\delta/\Delta T$ value of -6.2 ppb/K. The $\Delta\delta/\Delta T$ and $J(\text{H},\text{OH})$ values for HO–C(2) and HO–C(4) of **42** are averaged values for an axial OH group acting as H-donor and a completely solvated axial OH group acting as H-acceptor; this must also be so for the $\delta(\text{OH})$ values. $J(2,\text{OH})$ and $J(4,\text{OH})$ of **42** are larger than $J(4/6,\text{OH}) = 6.4$ Hz of **40** and suggest that also O–C(5) acts as H-bond acceptor of the intramolecular H-bond. This is supported by the above mentioned geometrical similarity of **42** with the idopyranoside **32**, which possesses a completely persistent bifurcated intramolecular H-bond. MM3* Modeling⁴) shows that the distortion of the pyranose ring of **42** due to the *anti*-reflex effect increases the C(2)–O⋯O–C(4) distance (**42**: 2.98 Å, **32**: 2.63 Å), but shortens the C(2)O⋯O–C(5) distance (**42**: 2.79 Å, **32**: 2.88 Å). The weaker H-bond of HO–C(2) to O–C(4) of **42** is thus partially compensated by a stronger H-bond of HO–C(2) to O–C(5). If one assumes a bifurcated H-bond in **42**, one may take the value for $J(2,\text{OH})$ of **32** (11.3 Hz) as an upper limit of $J(\text{H},\text{OH})$ for HO–C(2) and HO–C(4) of **42**, meaning that *ca.* 40% of **42** still possesses the intramolecular flip-flop H-bond in (D₆)DMSO. In agreement with this deduction, HO–C(2) and HO–C(4) of **42** resonate at similar positions (4.76 and 4.83 ppm, resp.) and slightly upfield to HO–C(3) (4.94 ppm).

The acetylene **43** and the 4-*O*-protected levoglucosans **44** [55], **45** [56], **46** [46], and **47** [57] can form only an unidirectional intramolecular H-bond¹⁴). An increasing proportion of the bifurcated H-bond in this series is indicated by $J(2,\text{OH})$ values that increase from 4.8 to 7.6 Hz and by upfield shifts for HO–C(2) from 4.94 ppm for **43** to 4.69 ppm for **47**. The $J(2,\text{OH})$ values indicate about 10% of the intramolecularly H-bonded species for **43**, 20% for **44**, 30% for **45**, 40% for **46**, and 50% for **47**. The high proportion of the intramolecularly H-bonded species for the disaccharides **46** and **47** is surprising considering that anomeric O-atoms are weak H-bond acceptors [42]. Conceivably, HO–C(2') of **45–47** is involved in stabilizing the bifurcated H-bond by forming a tetravalent H-bond¹⁵). It is also surprising that the benzylated inositol **41** and the benzylated levoglucosan **44** show the same proportion of intramolecularly

¹⁴) Considering that standard quality (D₆)DMSO is sufficient to obtain meaningful spectra, we have compared data of **44–47** taken from different sources.

¹⁵) Such H-bonds are often observed in solid-state structures [1], but we are not aware of an example in solution.

H-bonded species (20%), irrespective of the different strengths of the H-bonds. This suggests that additional (geometrical) factors favour the intramolecular H-bond in levoglucosans. The parallel increase of the ΔJ and $\Delta\delta(\text{OH})$ values of **43–47** demonstrates that the combined analysis of $J(\text{H},\text{OH})$, $\Delta\delta/\Delta T$, and $\delta(\text{OH})$ is a sensitive tool for the analysis of intramolecular H-bonds. It shows that a careful analysis on the basis of reliable and relevant references is required to correctly interpret changes in $J(\text{H},\text{OH})$ and $\delta(\text{OH})$ values.

Similar flip-flop H-bonds as between the 1,3-diaxial OH groups of **40** and **42** are also observed between HO–C(2) and HO–C(4) of *epi*-inositol [19], of talopyranoses and talopyranosides [19], and of ribopyranoses and ribopyranosides [19] [58]. They are evidenced by $J(2,\text{OH})$ and $J(4,\text{OH})$ of 5.3–7.0 Hz. The axial OH groups resonate at 4.75–5.11 ppm. As mentioned in the discussion of the *myo*-inositol derivatives, the interpretation of the $\delta(\text{OH})$ values of these flip-flop systems is hampered by our ignorance of the effect of the intramolecular H-bond on the chemical shift of a H-acceptor involved in an intermolecular H-bond to (D_6)DMSO, as it may be derived from unidirectional, fully persistent intramolecular H-bonds between two 1,3-diaxial OH groups. A case in point is discussed in Sect. 4.

4. *A Persistent, Unidirectional H-Bond between Two OH Groups: H-Bonding of Ginkgolides in (D_6)DMSO and (D_6)Acetone.* Ginkgolide B and C possess an intramolecular H-bond between HO–C(1) and HO–C(10) [59] (Fig. 9). According to the molecular geometry resulting from force-field calculations⁴⁾, no additional H-donors or H-acceptors can strongly interact with these OH groups. Thus, ginkgolides are ideally suited to analyse the effect of solvation on OH groups acting as H-donors in an intramolecular H-bond, and OH groups acting as H-acceptors. The tertiary hydroxy group of ginkgolide B and C and the secondary HO–C(7) of ginkgolide C can – at best – form weak intramolecular H-bonds. There had been some confusion concerning the correct configuration at C(1) of ginkgolide B and C [60] until *van Beek* and *Lankhorst* [61] confirmed the (1*R*)-configuration by ¹H-NMR spectroscopy.

The poor quality of the X-ray analyses of ginkgolide B and C [60d] [60e] does not allow us to locate the H-atoms of the OH groups or to unambiguously assign H-bonds. The O(1)⋯O(10) distances are in the range of 2.79–2.82 Å, ideal for an intramolecular H-bond (*cf.* [44]). In ginkgolide A, HO–C(1) is replaced by H, and there is no intramolecular H-bond. As a consequence, ring A of ginkgolide A adopts a different conformation leading to a larger distance (3.38 Å) between this H–C(1) and O–C(10) [60e].

In (D_6)DMSO solution, a H-bond interaction in ginkgolide B and C has been evidenced by selective ¹H-NMR saturation transfer between HO–C(1) and HO–C(10) [60c]. The direction of the H-bond is readily assigned on the basis of the $\Delta\delta/\Delta T$ data for the OH groups that have been reported by *Roumestand et al.* [60b,c] (Fig. 9). The $\Delta\delta/\Delta T$ values for HO–C(1) of ginkgolide B and C are small (B: –0.7, C: –1.1 ppb/K), whereas the values for HO–C(10) of ginkgolide B, C, and A are larger (–3.9 to –5.0 ppb/K) and similar to those for HO–C(3), suggesting that HO–C(1) acts exclusively as H-donor and HO–C(10) exclusively as H-acceptor¹⁶⁾.

¹⁶⁾ Surprisingly, the $\Delta\delta/\Delta T$ data have not been correlated with H-bonding; rather $\Delta\delta/\Delta T$ for HO–C(1) of ginkgolide B and C has been rationalised by assuming that HO–C(1) is (*S*)-configured and 'buried in the cage of the molecule' [60c].

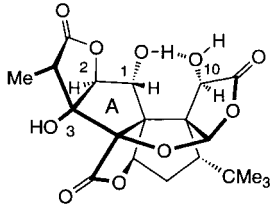
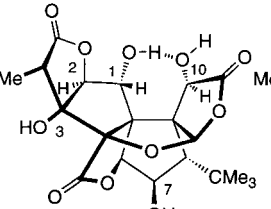
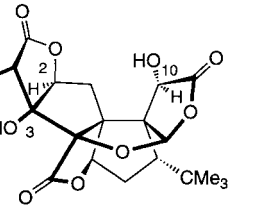
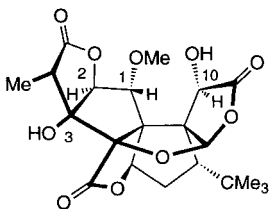
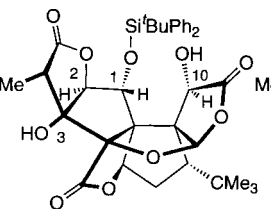
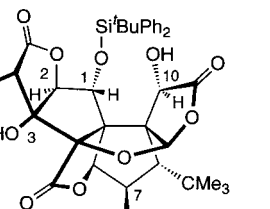
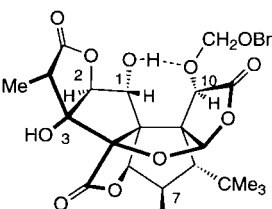
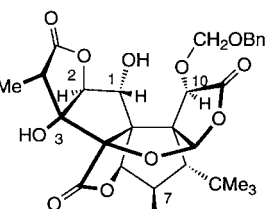
| | | |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|  |  |  |
| Ginkgolide B [59] | Ginkgolide C [62] | Ginkgolide A [62] |
| HO-C(3) HO-C(1) HO-C(10) | HO-C(3) HO-C(1) HO-C(10) | HO-C(3) HO-C(10) |
| $J(\text{H},\text{OH})$: – 3.5 5.5 | – not given not given | – 4.0 Hz |
| $\delta(\text{OH})$: 6.45 4.91 7.45 | 6.37 4.82 7.32 | 6.24 6.70 ppm |
| $\Delta\delta(\text{OH})/\Delta T$: -4.3 -0.7 -5.0 | -4.3 -1.1 -4.3 | -4.6 -3.9 ppb/K |
| $J(1,2)$: 7.5 | 7.0 | Hz |
|  |  |  |
| 48 [60c] | 49 [63] | 50 [63] |
| HO-C(3) HO-C(10) | HO-C(3) HO-C(10) | HO-C(3) HO-C(10) |
| $J(\text{H},\text{OH})$: – not given | – not given | – 5.9 Hz |
| $\delta(\text{OH})$: not given 6.8 | 6.20 6.51 | 6.40 6.81 ppm |
| $J(1,2)$: not given | not given | 5.3 Hz |
|  |  | |
| 51 [64] | 52 [64] | |
| HO-C(3) HO-C(1) | HO-C(3) HO-C(1) | |
| $J(\text{H},\text{OH})$: – 5.2 | – 5.7 Hz | |
| $\delta(\text{OH})$: 6.43 5.48 | 6.58 6.00 ppm | |
| $J(1,2)$: 6.7 | 5.8 Hz | |

Fig. 9. $J(\text{H},\text{OH})$, $\delta(\text{OH})$, $\Delta\delta(\text{OH})/\Delta T$, and $J(1,2)$ values of ginkgolide B, C, A, and their derivatives **48–52** in (D_6)DMSO solution, and assignment of the intramolecular H-bond. Hashed bonds indicate a more strongly persistent intramolecular H-bond than dashed bonds. $\Delta\delta(\text{OH})/\Delta T$ Values are deduced from the pictures in [60c].

In (D_6)DMSO solution, the OH groups at C(1), C(7) (only ginkgolide C), C(3), and C(10) of ginkgolide B and C are shifted to increasingly lower fields and resonate at 4.82–4.91 ppm, 5.52 ppm, 6.37–6.45 ppm, and 7.32–7.45 ppm (Fig. 9). The strong shift differences between HO–C(1) and HO–C(10) confirm that HO–C(1) acts as H-donor and HO–C(10) as H-acceptor. Molecular modeling⁴) shows that such H-bonded ginkgolides possess a completely rigid skeleton. According to the Karplus equation of Fraser, the calculated dihedral angle H–C(1)–O–H of 52° for ginkgolide B corresponds to $J(1,OH) = 3.2$ Hz, in agreement with the experimental value of 3.5 Hz. HO–C(10) of ginkgolide A [62] and HO–C(3) of all ginkgolides are completely solvated in (D_6)DMSO solution. Whereas HO–C(3) of ginkgolide A resonates at a similar position as HO–C(3) of ginkgolide B and C (6.24 ppm; $\Delta\delta$ 0.15–0.2 ppm), the signal for HO–C(10) of ginkgolide A is clearly shifted upfield to 6.70 ppm ($\Delta\delta$ 0.6–0.75 ppm). Similarly, HO–C(10) of the ginkgolides **48** [60c], **49**, and **50** [63]) that are methylated or silylated at O–C(1) resonates at a similar position as HO–C(10) of ginkgolide A, evidencing that HO–C(10) in these compounds is completely solvated and does not act as donor to O–C(1), although geometrically this would be possible, as suggested by molecular modeling. These results show that HO–C(10) of ginkgolide B and C acts as H-bond acceptor in a strong intramolecular H-bond and resonates downfield ($\Delta\delta$ ca. 0.5–0.9 ppm) from the fully solvated HO–C(10) of ginkgolide A and of **48–50**.

Benzoyloxymethylation of the H-accepting HO–C(10) of ginkgolide C and of a HO–C(7)-protected derivative of ginkgolide C leading to **51** and **52** [64] is accompanied by a strong deshielding of HO–C(1) of **51** (5.48 ppm; $\Delta\delta = 0.6$ ppm) and **52** (6.00 ppm; $\Delta\delta = 1.2$ ppm). This strong shift suggests that the intramolecular H-bond is partially broken in **51** (ca. 50%) and completely broken in **52**. This conclusion is supported by the increase of $J(1,OH)$ for ginkgolide B, **51** and **52** (3.5, 5.2, and 5.7 Hz, resp.; the value for ginkgolide C is missing). The downfield shift for HO–C(1) of **51** and **52** is incompatible with Braquet's assumption that HO–C(1) of ginkgolides B and C is buried in the cage of the molecule.

The weakening or the absence of the intramolecular H-bond in the partially protected ginkgolides **50–52** is further evidenced by the $J(1,2)$ values. Molecular modeling⁴) shows that the intramolecular H-bond in ginkgolide B (OH...OC(10) distance: 1.78 Å, O–H...OC(10) bond angle: 141°) forces the ring A to adopt an E_1 conformation (pseudoequatorial position of HO–C(1)). The H–C(1)–C(2)–H angle in this conformation is 159.8° and corresponds to a calculated $J(1,2)$ value [47] of 7.5 Hz, in agreement with the experimental $J(1,2)$ values for ginkgolide B and C of 7.0–7.5 Hz (Fig. 9). In the absence of this H-bond, ring A can adopt the E_1 or the 3E conformation. The latter (stabilised in the gas phase by an intramolecular H-bond between HO–C(1) and HO–C(3)) possesses a H–C(1)–C(2)–H angle of 95.1°. This corresponds to a calculated $J(1,2)$ value of 0.6 Hz. The experimental $J(1,2)$ values for ginkgolides B and C protected at O–C(1), such as **50** [63] are typically 5.3–5.8 Hz, and suggest a ca. 7:3 equilibrium between the E_1 and the 3E conformers. The correlation of conformation, H-bonding, and $J(1,2)$ values of **51** (6.7 Hz) and **52** (5.8 Hz) corroborates the conclusion that the intramolecular H-bond is broken to ca. 50% in **51** and more or less completely in **52**.

Weber and Vasella prepared glucosides of ginkgolide B by the reaction with glucosylidene diazirines [59]. The 1-*O*- and 10-*O*-glucosylated ginkgolides B **53**–**57** (Fig. 10) provide additional information about the intramolecular H-bond of ginkgolide B. Unfortunately, the $^1\text{H-NMR}$ spectra of the glucosides have been recorded only in (D_6)acetone. (D_6)Acetone is less polar than (D_6)DMSO and a weaker H-bond acceptor [65]. This is evidenced by an upfield shift of 0.55–0.7 ppm for corresponding OH signals of ginkgolide B in (D_6)acetone relative to (D_6)DMSO; the relative chemical shifts are affected to a minor extent only (Figs. 9 and 10). This evidences the complete persistence of the intramolecular C(1)OH...OC(10) H-bond of ginkgolide B in (D_6)acetone. Glucosylation at HO–C(1) interrupts the intramolecular H-bond and leads to an upfield shift of 0.8–1.1 ppm for HO–C(10) of **53** (Fig. 10), in excellent agreement with the corresponding upfield shift of *ca.* 0.8 ppm in (D_6)DMSO.

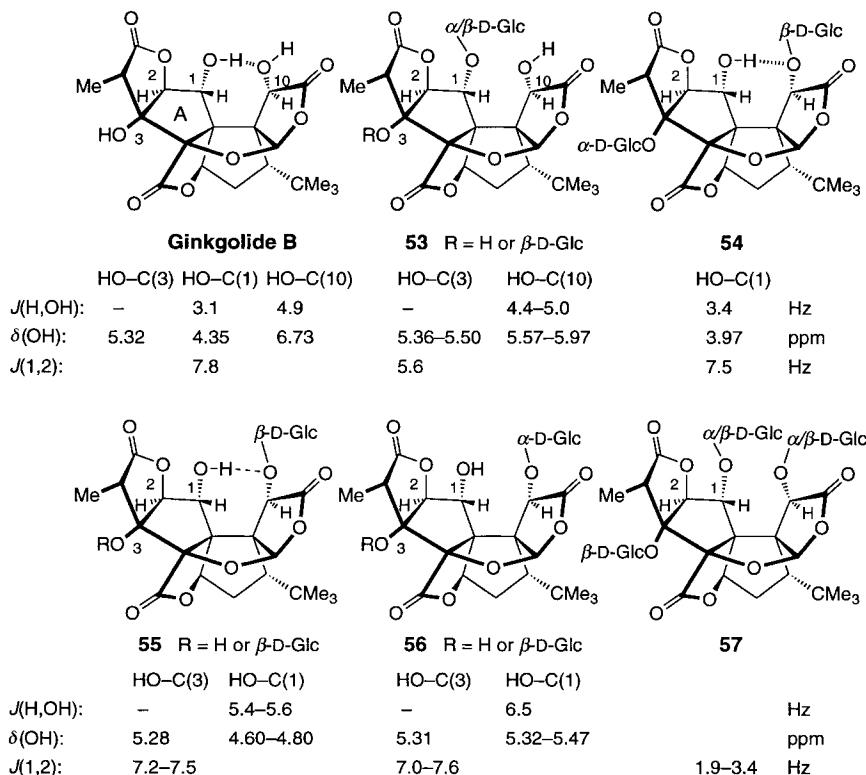


Fig. 10. $J(\text{H},\text{OH})$, $\delta(\text{OH})$, and $J(1,2)$ values of ginkgolide B and its glucosylated derivatives **53**–**57** (Glc = 2,3,4,6-tetra-*O*-benzyl-glucopyranosyl) in (D_6)acetone, and assignment of the intramolecular H-bond. Hashed bonds indicate a more strongly persistent intramolecular H-bond than dashed bonds.

The persistence of intramolecular H-bonds in the 10-*O*-glucosylated ginkgolides B is modulated by the steric demand of the glycosyl group at O–C(10) and of the substituent at O–C(3). The H-bond is hardly affected in **54** ($J(1,\text{OH}) = 3.4$ Hz, $\delta(\text{HO–C}(1)) = 3.97$ ppm) possessing a β -D-glucopyranosyl residue at O–C(10) and an α -D-glucopyranosyl residue at O–C(3). Replacing the latter substituent by H or the

sterically less demanding β -D-glucopyranosyl residue induces partial cleavage of the intramolecular H-bond in **55** ($J(1,\text{OH}) = 5.4\text{--}5.6$ Hz, $\delta(\text{HO}-\text{C}(1)) = 4.6\text{--}4.8$ ppm). The intramolecular H-bond is completely broken when a bulkier α -D-glucopyranosyl residue is attached at O-C(10) (**56**: $J(1,\text{OH}) = 6.5$ Hz, $\delta(\text{HO}-\text{C}(1)) = 5.32\text{--}5.47$ ppm). The different extent to which the intramolecular H-bond in the 10-*O*-glucopyranosylated derivatives **54–56** is affected does not lead to a conformational change for ring A; the same E_1 conformation is evidenced by $J(1,2)$ values of 7.0–7.6 Hz. However, the 1-*O*-glucosylated derivatives **53** ($J(1,2) = 5.6$ Hz) show a minor contribution of the 3E conformer, and the O-C(1) and O-C(10) diglucosylated derivatives **57** ($J(1,2) = 1.9\text{--}3.4$ Hz) a dominant one. The partial H-bond in **55** and in their debenzylated derivatives is also indicated in the ^{13}C -NMR spectra. These derivatives show an upfield shift for C(1) of the β -D-glucopyranosyl residue attached at O-C(10) resonating at 99.8–100.6 ppm ($\Delta\delta$ ca. 5 ppm, compare with 105.5 ppm for the 10-*O*- β -D-glucosylated **57**), while no upfield shift is observed for C(1) of the O-C(1)-glucosylated **53** (104.0–104.5 ppm) lacking an intramolecular H-bond (^{13}C -NMR data of **54** are not available).

The data of the glucosylated ginkgolides in (D_6)acetone confirm the completely persistent intramolecular H-bond C(1)–OH \cdots O–C(10) of ginkgolide B in aprotic polar solvents. The data show also that a completely persistent intramolecular H-bond leads to a strong upfield shift for the H-donating OH group ($\Delta\delta = 1.35\text{--}1.5$ ppm for HO–C(1) of **54** and **56**) and to a strong downfield shift for the H-accepting OH group ($\Delta\delta = 0.76\text{--}1.16$ ppm for HO–C(10) of ginkgolide B and **53**).

5. *Co-operative H-Bonding in (D_6)DMSO*. The proportion of the intramolecular H-bond between the 1,3-diaxial OH groups of the inositol **40** and the levoglucosan **42** (Fig. 8), and between HO–C(1) and HO–C(10) of ginkgolide B and C (Fig. 9) decreases when the H-accepting OH group is alkylated. This strongly evidences cooperativity between an intramolecular H-bond and an intermolecular H-bond to (D_6)DMSO [66]¹⁷). The larger $J(2,\text{OH})$ value for α -D-glucopyranose (**17**; 6.8 Hz) than for methyl α -D-glucopyranoside (**19**; 6.45 Hz [35]) similarly indicates that cooperativity with intermolecular H-bonds to (D_6)DMSO strengthens a rather weak intramolecular H-bond. That the intramolecular H-bond of HO–C(3) to the anomeric MeO group of the α -D-altropyranoside **13** – a H-bond in a six-membered ring – (Fig. 4) is cleaved more readily in (D_6)DMSO than the intramolecular H-bond of H–OC(3) to HO–C(4) – a H-bond in a five-membered ring – illustrates the stabilising effect of the co-operative intermolecular H-bond to (D_6)DMSO. This finding is in contradiction to conclusions of *Christofides* and *Davies* [20], who analyzed glucose and maltose by SIMPLE ^1H -NMR spectroscopy¹⁸). Based on weak SIMPLE ^1H -NMR effects, they postulated that α -D-glucopyranose (**17**) exists in (D_6)DMSO as the intramolecularly H-bonded species **17a** possessing a co-operative H-bond network beginning with

¹⁷) For co-operativity between intra- and intermolecular H-bonds in CDCl_3 , see [43] [67].

¹⁸) SIMPLE ^1H -NMR Spectroscopy (partial deuteration of polyols leads to additional OH signals) is a powerful method for detecting even weak intramolecular H-bonds, provided that the H-acceptor carries a H-atom (not applicable to H-bonds between OH and an alkoxy group). This method should only be used in combination with other NMR methods, since the sign of ^1H -NMR SIMPLE effects does not allow to unambiguously assign the H-donor and the H-acceptor (see [68]). Small SIMPLE ^1H -NMR effects must be supported by other experimental data.

HO–C(1) and ending with HO–C(6) (Fig. 11). This interpretation disagrees with our analysis of the $J(\text{H},\text{OH})$ and $\delta(\text{OH})$ values; **17** in (D_6)DMSO exhibits only a partial (ca. 50%) intramolecular C(2)O–H \cdots O–C(1) H-bond, as evidenced by $J(2,\text{OH}) = 6.8$ Hz as depicted for **17b** in Fig. 11. The contradiction illustrates the dangers inherent in the application of a single, complex parameter. The SIMPLE $^1\text{H-NMR}$ data [20] are difficult to interpret. On the one hand, one expects a positive SIMPLE effect for HO–C(1) of **17a**, on the other hand, the results of our analysis should lead to opposite SIMPLE $^1\text{H-NMR}$ effects for HO–C(1) and HO–C(2) and no effect for the other OH groups.

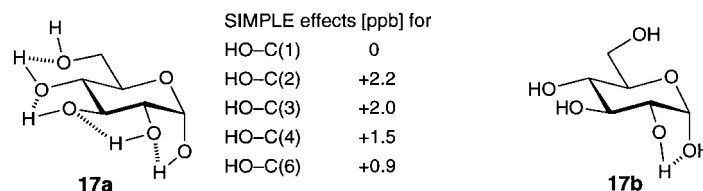


Fig. 11. Intramolecular H-bonds of α -D-glucopyranose (**17**) in (D_6)DMSO solution, as assigned from the interpretation of SIMPLE $^1\text{H-NMR}$ effects (**17a** [20]) and from the interpretation of $J(\text{H},\text{OH})$ and $\delta(\text{OH})$ values (**17b**, this work)

In (D_6)DMSO solution, co-operativity between two intramolecular H-bonds appears to be restricted to rather strong H-bonds. The only clear example here is given by the β -D-talopyranoside **33** (Fig. 6). Possibly, the α -D-allopyranoside **12** and the β -D-altropyranoside **13** (Fig. 4) also show co-operativity between intramolecular H-bonds, but co-operativity between an intra- and an intermolecular H-bond dominates.

The same proportion of the intramolecularly H-bonded species of the 4-*O*-benzyl-levoglucosan **44** and the 6-*O*-benzyl-*myo*-inositol **41** in (D_6)DMSO shows the strong influence of an additional H-bond acceptor leading to a bifurcated H-bond and stabilising a relatively weak intramolecular H-bond.

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Experimental Part

Standard $^1\text{H-NMR}$ spectra ((D_6)DMSO) of **6**, **28**, **30**, and **31** were measured at 298 K and of **41**, **43**, and **44** at 298, 308, 318, 328, and 338 K on a 300-MHz apparatus (*Varian-Gemini-300*). The assignment of HO–C(2) and HO–C(3) of **6** and **43** is based on selective homonuclear decoupling experiments.

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