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CONFORMATIONAL STUDIES ON ALDONOLACTONES BY N.M.R. SPECTROSCOPY. CONFORMATIONS OF D-PENTONO-1,4-LACTONES IN SOLUTION*†

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ABSTRACT

The conformations of D-pentono-1,4-lactones in solution were studied by ^{1}H- and ^{13}C-n.m.r. spectroscopy. Conformational equilibria between the ^3E and E_3 forms were found to favor, strongly, that having the OH-2 group quasiequatorially oriented. The exocyclic, CH_2OH groups in these lactones generally favor the *gauche–gauche* disposition around the C-4–C-5 bond, except for D-lyxono-1,4-lactone, which favors the *trans-gauche* arrangement.

INTRODUCTION

It is generally accepted that aldono-1,4-lactones adopt envelope conformations in the crystalline state; this has been demonstrated by X-ray diffraction for four D-hexono-1,4-lactones[2–4] and for D-glucaro-1,4-lactone[5]. Small deviations from planarity of the lactone group may be caused by intermolecular packing-forces in the crystal. Also, envelope conformations have been postulated for aldono-1,4-lactones in solution[6,7], but without experimental evidence. Chiroptical properties of aldono-1,4-lactones in relation to their conformations have been studied by several groups. Some authors interpreted their results in terms of a dynamic equilibrium between two twist conformers for any given 1,4-lactone[8], whereas others have taken envelope conformations into consideration[9–14]. The pseudorotation[7] typical of furanoid rings has been suggested[7] for aldono-1,4-lactone rings. However, as pointed out recently, partial double-bond character of the C-1–O-4 bond of the 1,4-lactone ring would restrict pseudorotation, and dictate envelope conformations as favored conformations of the 1,4-lactone ring in general[15,16] and of sugar lactone rings in particular[17].

Although n.m.r. spectroscopy provides a logical probe for the geometry of aldono-1,4-lactones in solution, no systematic n.m.r. studies have thus far been

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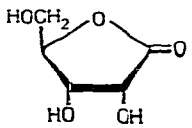
reported. For pentono-1,4-lactones, ^{1}H-n.m.r. spectra have been recorded for D-ribono-1,4-lactone[14,18] and its 2,3-*O*-isopropylidene derivative[18], and interpreted in terms of a non-planar conformation of the lactone ring. Some coupling constants have been determined for D-pentono-1,4-lactones and their 2-deoxy-2-*C*-methyl derivatives, and discussed in terms of deviations of C-3 from the plane of the lactone ring, which was assumed to have envelope geometry[13]. Our systematic studies, using ^{1}H-n.m.r. data supported by ^{13}C-n.m.r. studies, furnish more-precise conformational assignments for D-pentono-1,4-lactones in solution that might also be of interest in the conformational analysis of nucleosides and nucleotides.

^{1}H-N.m.r. spectra of D-ribono-1,4-lactone (**1**), D-arabinono-1,4-lactone (**2**), D-xylono-1,4-lactone (**3**), and D-lyxono-1,4-lactone (**4**) were measured at 100 MHz in various solvents, generally methanol-d_4, dimethyl sulfoxide-d_6, and pyridine-d_5; if first-order spectra were not obtained, either a lanthanide shift-reagent was used, or *O*-acetyl or *O*-methyl derivatives, or both, of the D-pentono-1,4-lactones were studied. Computer-simulated spectra were generated as a further test of the assigned, ^{1}H-n.m.r. chemical-shifts and coupling constants. The coupling constants and proton chemical-shifts were used to provide evidence that conformational equilibria between two envelope forms (^3E and E_3) exist for D-pentono-1,4-lactones in solution. It was also possible to determine the disposition of the exocyclic CH_2OH group on C-4 in relation to the lactone ring.



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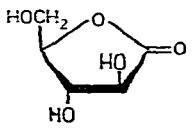

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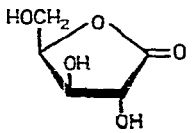

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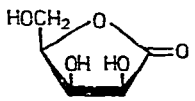

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Natural-abundance, ^{13}C, pulse, Fourier-transform, n.m.r. spectra were recorded in Me_2SO-d_6 and D_2O for freshly prepared and (with D_2O) for mutarotated solutions of the lactones. Analysis of the ^{13}C chemical-shifts of the lactones furnished additional support for conclusions reached from the ^{1}H-n.m.r. data. Furthermore, resonances of the D-pentonic acids were also observed in the ^{13}C-n.m.r. spectra of the mutarotated solutions, and ^{13}C shifts for D-ribonic, D-arabinonic, D-xylonic, and D-lyxonic acid were recorded.

TABLE I

100-MHz, ^{1}H-N.M.R.-SPECTRAL DATA FOR D-RIBONO-1,4-LACTONE (1), D-ARABINONO-1,4-LACTONE (2), D-XYLONO-1,4-LACTONE (3), D-LYXONO-1,4-LACTONE (4), AND VARIOUS DERIVATIVES

Compound	*Solvent*	*Chemical shifts in δ values*[a]					*Coupling constants in Hz*				
		H-2	*H-3*	*H-4*	*H-5*	*H-5'*	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{4,5'}$	$^2J_{5,5'}$
D-Ribono-1,4-lactone (1)	CD_3OD	4.61d	4.32q	4.39o	3.81q	3.73q	5.7	0.8	3.2	3.2	−13.0
	Me_2SO-d_6[b]	4.89d	4.59q	4.70q	4.09m	4.01m	5.3	0.8	3.6	3.6	−12.3
	C_5D_5N	5.78d	5.11q	5.09q	4.11q	4.04q	5.5	0.5	3.2	3.2	−12.3
D-Arabinono-1,4-lactone (2)	Me_2SO-d_6[b]	4.70d	4.47m	4.48m	4.17q	3.88q	8.7	8.0	1.8	4.0	−12.8
	C_5D_5N	4.92m	4.915m	4.58m	4.23q	4.07q	8.4	7.8	2.4	3.9	−12.8
2,3,5-triacetate[c]	$CDCl_3$	5.54d	5.40q	4.53o	4.43q	4.24q	6.8	6.3	2.6	5.1	−12.5
	Me_2SO-d_6	5.78d	5.48t	4.75o	4.42q	4.25q	7.5	7.5	2.6	5.1	−12.6
2,5-dimethyl ether[d]	$CDCl_3$	4.47d	3.98q	4.33o	3.71q	3.63q	6.7	7.2	2.7	3.9	−11.4
D-Xylono-1,4-lactone (3)	CD_3OD	4.41d	4.50q	4.55o	3.91q	3.83q	7.3	7.3	3.1	2.8	−12.5
	C_5D_5N	5.29d	5.02t	4.90q	4.44q	4.27q	7.2	6.7	3.0	3.0	−12.3
2,3,5-triacetate[e]	Me_2SO-d_6	5.67d	5.80t	5.12q	4.39q	4.30q	7.4	7.0	3.6	3.6	−13.0
D-Lyxono-1,4-lactone (4)	CD_3OD[f]	4.42d	4.27q	4.43o	3.88q	3.73q	4.8	3.2	6.4	5.2	−12.0
	Me_2SO-d_6[b]	4.92d	4.70q	4.81o	4.16q	4.11q	4.8	2.8	4.7	6.7	−12.2

[a]Signal multiplicities: d, doublet; m, complex multiplet; o, octet; q, quartet. [b]In the presence of CF_3CO_2H. [c]Chemical shifts of acetyl-group protons: δ 2.14, 2.09, and 2.07 in chloroform-*d*; and 2.14, 2.09, and 2.07 in dimethyl sulfoxide. [d]Chemical shifts of methoxyl-group protons: δ 3.53 and 3.43. [e]Chemical shifts of acetyl-group protons: δ 2.16, 2.10, and 2.10. [f]In the presence of 0.4 molar equivalent of $EuCl_3$.

RESULTS AND DISCUSSION

General features of the ^{1}H-n.m.r. spectra of D-*pentono-1,4-lactones. — Chemical shifts.* All resonances in the ^{1}H-n.m.r. spectra of D-pentono-1,4-lactones appear within very narrow ranges, usually as narrow as 0.9 p.p.m. The dispersion is scarcely greater for the *O*-acetyl or *O*-methyl derivatives of the lactones (see Table I). Nevertheless, by changing solvents or using lanthanide shift-reagents, it was possible to observe first-order spectra. Resonances of individual protons in unsubstituted lactones appear between δ 3.73 and 4.61 in methanol-d_4, between δ 3.88 and 4.92 in dimethyl sulfoxide-d_6, and between δ 4.01 and 5.78 in pyridine-d_5. Thus, all resonances are shifted, on average, ~0.3–0.5 p.p.m. to lower field in Me_2SO-d_6 and in pyridine-d_5. As regards substituted D-pentono-1,4-lactones, the resonances of individual protons are shifted either to lower field (for *O*-acetyl derivatives, an average of 0.3–1.3 p.p.m.), or to slightly higher field (*O*-methyl derivatives).

The most shielded protons are H-5 and H-5′, whereas H-4 and H-2, respectively being strongly affected by O-4 or a carbonyl group, are the most deshielded; hydroxyl groups in either *cis*-1,2- or *cis*-1,3 disposition, with respect to the aforementioned protons, cause their resonances to be shifted to slightly higher field.

Coupling constants. When interpreting the magnitudes of vicinal coupling in five-membered rings, it must be borne in mind that the observed values represent weighted averages of all conformations present, and that their magnitudes depend both on ring puckering and the disposition of electronegative substituents on the ring. Ring puckering in five-membered-ring compounds depends on pseudorotational tendencies[19], or (in some instances) simply on conformational equilibria (twist conformations are flatter than envelope ones[20]) and on the substituents on the ring[21,22]. Thus, the puckering of five-membered rings varies from one compound to another. For five-membered rings[23], it was recognized quite early that vicinal coupling-constants depend on the disposition of electronegative substituents with respect to coupled protons. The substituent-electronegativity effect has also been considered in the ^{1}H-n.m.r. spectroscopy of nucleosides and nucleotides[24–28]. For all of these reasons, quantitative interpretation of ^{1}H-n.m.r. data, in terms of any relationship between coupling constants and torsional angles, is difficult for five-membered systems[15,21]. However, the couplings experimentally determined offer a possibility for evaluating conformational tendencies. In particular, this is easier for cyclopentene derivatives and for 1,4-lactones, for which the conformational equilibrium is limited to two envelope conformations. It should be noted that several modifications of the Karplus equation have been applied in the conformational analysis of nucleosides and nucleotides[24–28]. A new, statistical method has also been applied in order to determine the values of the coupling constants for isomeric pentofuranosyl nucleosides[29,30] in their extreme conformational states, without any assumptions as to the geometry of the sugar ring. By use of self-consistent field, finite perturbation theory (SCF, FPT) methods, cisoidal coupling-constants for the furanosyl ring were found to depend on the conformation of the whole nucleoside, so

TABLE II

CARBON-13 CHEMICAL-SHIFTS FOR D-PENTONOLACTONES AND D-PENTONIC ACIDS IN D_2O AT ~30°

Compound	*Chemical shifts in p.p.m. downfield from Me_4Si*[a]				
	C-1	*C-2*	*C-3*	*C-4*	*C-5*
D-Ribono-1,4-lactone (1)	179.5	70.4[b]	69.9[b]	87.7	61.5
D-Ribonic acid	176.3	73.8[b]	72.8[b]	71.5[b]	64.0
D-Arabinono-1,4-lactone (2)	177.05	74.75[b]	73.4[b]	82.15	60.3
D-Arabinonic acid	177.6	72.7[b]	71.45[b]	71.3[b]	63.9
D-Xylono-1,4-lactone (3)	178.1	74.1[b]	73.1[b]	81.35	59.9
D-Xylono-1,5-lactone	175.7	72.1[b]	71.2[b]	70.3[b]	76.8
D-Xylonic acid	176.75	73.1[b]	72.8[b]	72.3[b]	65.3
D-Lyxono-1,4-lactone (4)	179.1	71.5[b]	70.5[b]	82.5[b]	60.7
D-Lyxonic acid	177.0	72.7[b]	72.4[b]	71.5	63.6

[a]Original data, referenced to the highest-field resonance of DSS, were converted according to the equation[17]: $\delta_{Me_4Si} = \delta_{DSS} - 1.6$. Assignments were made by following established principles for 1,4-lactones[15,16,34-36] and for furanoid sugars [37-39]. Comparisons of the pentonolactones and the pentonic acids with each other and with other, related compounds[17] were made. [b]These assignments may have to be reversed.

TABLE III

CARBON-13 CHEMICAL-SHIFTS IN Me_2SO-d_6

Compound	*Chemical shifts in p.p.m. downfield from Me_4Si, and solvent-induced shifts*[a] *$\Delta\delta$ (in parentheses)*[b]				
	C-1	*C-2*	*C-3*	*C-4*	*C-5*
D-Ribono-1,4-lactone (1)	176.6 (2.9)	69.4 (1.0)	68.7 (1.2)	85.5 (2.2)	60.5 (1.0)
D-Arabinono-1,4-lactone (2)	174.7 (2.35)	73.1 (1.05)	72.2 (1.2)	81.1 (1.05)	59.0 (1.3)
D-Arabinonic acid	175.4 (2.2)	72.2 (0.2)	70.5 (0.95)	69.9 (1.4)	63.1 (0.8)
D-Xylono-1,4-lactone (3)	175.5 (2.6)	73.0 (1.1)	72.2 (0.9)	79.8 (1.55)	58.5 (1.4)
D-Lyxono-1,4-lactone (4)	176.2 (2.9)	70.3 (1.2)	69.0 (1.5)	80.5 (2.0)	59.3 (1.4)

[a]$\Delta\delta = \delta$ in $D_2O - \delta$ in Me_2SO-d_6; see footnote [a] in Table II. [b]See footnote *b* in Table II regarding individual, signal assignments.

that there is no unique relationship between dihedral angle and the vicinal coupling-constant[29,30].

In general, the coupling constants found for pentono-1,4-lactones are similar to those observed for other 1,4-lactones[15,31] and for cyclopentene derivatives[21,32,33]. The values of $J_{2,3}$ (*cis*) were found to be usually larger, by ~2–3 Hz, than those of $J_{3,4}$, probably because of the inevitable *gauche* disposition of the carbonyl group with respect to H-2 in both the ^3E and the E_3 conformation of the 1,4-lactone ring; this feature seems to be common for 1,4-lactones[15,31].

General features of the ^{13}C-n.m.r. spectra of D-*pentono-1,4-lactones.* — Assignments (see Tables II and III) were made by following principles established for 1,4-lactones[15,34–36] and furanoid sugars[37–39]. In D_2O, the carbonyl carbon atoms of D-pentono-1,4-lactones resonate 177.05–179.5 p.p.m. downfield from Me_4Si. Their chemical shifts are slightly influenced by the configuration of the hydroxyl groups on C-2 and C-3; vicinal, *cis*-disposed, hydroxyl groups deshield the carbonyl carbon atom. Because of deshielding by the ring-oxygen atom, the C-4 resonances appear between 81.35 and 82.5 p.p.m., except for compound **1**, whose C-4 resonance is further deshielded to 87.7 p.p.m. The C-2 resonances appear within the range of 70.4–74.75 p.p.m., and those of C-3 within the range of 69.9–73.4 p.p.m. The positions of the C-2 and C-3 resonances depend on the configurations of the hydroxyl groups bonded to them: vicinal, *cis*-disposed, hydroxyl groups give rise to increased shielding. The most-shielded carbon atoms are those of C-5, resonating within the range of 59.9–61.5 p.p.m.

Spectra of the fully mutarotated lactones in D_2O showed signals of D-pentonic acids. The carboxylic carbon atoms resonated in the range of δ 176.3–177.6, and C-2, C-3, and C-4 resonated together, within the narrow range of 71.3–73.8 p.p.m.; the most-shielded carbon atoms were, again, C-5, resonating between 63.3 and 64.0 p.p.m. The carbonyl carbon atoms of D-pentono-1,4-lactones resonate at lower field than C-1 in the corresponding D-pentonic acids, except for D-arabinonic acid and its 1,4-lactone (**2**). If the C-2 and C-3 atoms of D-pentono-1,4-lactones have the same configuration, they are shielded in comparison with the corresponding carbon atoms in pentonic acids; otherwise, they are somewhat deshielded in the 1,4-lactone as compared with the pentonic acid. The C-5 resonances of D-pentono-1,4-lactones appear at higher field than the C-5 signals of the corresponding D-pentonic acids. The mutarotated solution of D-xylono-1,4-lactone (**3**) showed resonances of D-xylono-1,5-lactone, as well as resonances of the 1,4-lactone (**3**) and D-xylonic acid. The shielding/deshielding effects observed for D-pentono-1,4-lactones follow, to some extent, rules elaborated for tetra-*O*-acetyl-D-aldopentofuranoses[39].

All resonances of the pentonolactones and of the pentonic acids are shifted to higher fields in Me_2SO-d_6 (see Table III). As already pointed out, a notable feature of the ^{13}C-n.m.r. spectra of aldonolactones in D_2O is a relatively large deshielding (in comparison with solutions in Me_2SO-d_6) of carbonyl carbon atoms and of carbon atoms bonded to the ring-oxygen atom[17]. This type of deshielding might be explained in terms of protonation of the -C-O- group as a result of hydrogen bonding in a protic

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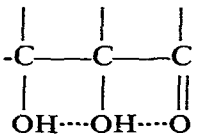
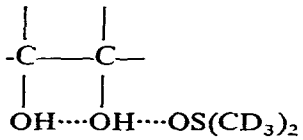
solvent. The magnitude of this deshielding depends on the disposition of the hydroxyl groups on C-2 and C-3, the *cis*-disposition giving rise to the larger deshielding. This deshielding seems to reflect not only protonation by H_2O molecules (or deuteration

by D_2O molecules) but also such intramolecular hydrogen-bonding as the following:

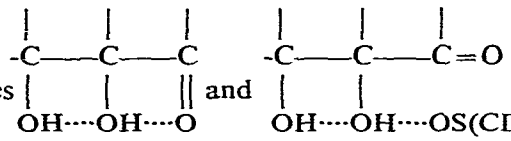


. The larger deshielding of carbonyl carbon atoms observed in such instances might be explained in terms of a hydrogen-bond, conjugation effect[40]. It is also noteworthy that vicinal *cis*-hydroxyl groups in glycosides, and especially in nucleosides, have been found to exhibit enhanced acidities[27,28] because of intramolecular hydrogen-bonding.

For the other carbon atoms, interpretation of solvent shifts is more complex, because of additional interactions between hydroxyl groups bonded to the carbon atoms and to Me_2SO-d_6 molecules. For dilute solutions of alcohols in Me_2SO-d_6, the equilibrium $ROH\cdots\underset{H}{O}R + 2\ (CD_3)_2SO \rightleftarrows 2\ ROH\cdots OS(CD_3)_2$ is strongly shifted to the right, and, in β-D-glucopyranose, for example, each hydroxyl group forms a hydrogen bond with the solvent. However, when a favorable, geometric arrangement for intramolecular hydrogen-bonding exists, such structures as

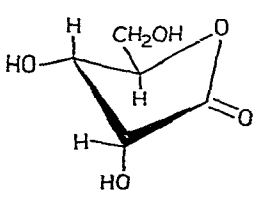


can exist at equilibrium[41]. With aldonolactones, such a favorable arrangement appears to exist in examples having *cis*-disposed hydroxyl groups on C-2 and C-3, and structures of the types

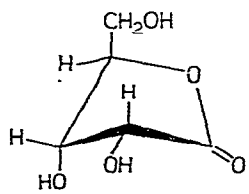


should exist at equilibrium in Me_2SO-d_6 solution, especially at the relatively high concentrations used in these ^{13}C-n.m.r. experiments.

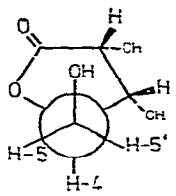
Conformational features of individual D-*pentono-1,4-lactones.* — D-*Ribono-1,4-lactone* (**1**). — A very small value of $^3J_{3,4}$ (0.8 Hz in methanol-d_4 and in dimethyl sulfoxide-d_6, and 0.5 Hz in pyridine-d_5), and also the small values of $^3J_{4,5}$ and $^3J_{4,5'}$ (see Table I) strongly support a conformational equilibrium in solution between the following conformations.



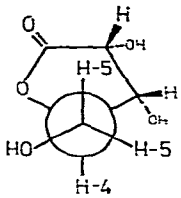
^3E(D)



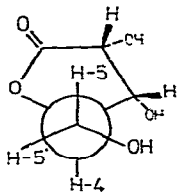
E_3(D)



1-*gg*



1-*gt*



1-*tg*

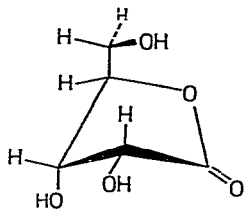
TABLE IV

CONFORMER POPULATIONS FOR D-RIBONO-1,4-LACTONE (1), D-ARABINONO-1,4-LACTONE (2), D-XYLONO-1,4-LACTONE (3), D-LYXONO-1,4-LACTONE (4), AND VARIOUS DERIVATIVES, IN SOLUTION

Compound	*Solvent*	*Lactone-ring conformational contributions (%)*[a]		*Exocyclic CH_2OH group conformation contributions (%)*[b,c]		
		^3E	E_3	gauche-gauche	gauche-trans	trans-gauche
D-Ribono-1,4-lactone (1)	CD_3OD	10	90	66	17	17
	Me_2SO-d_6	10	90	60	20	20
	C_5D_5N	5	95	66	17	17
D-Arabinono-1,4-lactone (2)	Me_2SO-d_6	90	10	70	25	5
	C_5D_5N	90	10	65	25	10
	$CDCl_3$	70	30	55	35	10
2,3,5-triacetate	Me_2SO-d_6	80	20	55	35	10
D-Xylono-1,4-lactone (3)	CD_3OD	25	75	70	15	15
	C_5D_5N	40	60	70	15	15
2,3,5-triacetate	Me_2SO-d_6	30	70	60	20	20
D-Lyxono-1,4-lactone (4)	CD_3OD	100	0	15	35	50
	Me_2SO-d_6	100	0	20	30	50

[a]Estimated for **1** from the experimentally observed interdependence of the ring-proton coupling-constants in ribonucleosides, which is consistent with a two-state equilibrium of the sugar ring in solution[42]. Estimated for **2** and its triacetate from the equation: percent of $^3E = (^3J_{2,3}/9.5) \times 100$, as for arabinonucleosides[42], and consistent with the experimentally observed interdependence of the ring-proton coupling-constants in arabinonucleosides[43]. Estimated for **3** and its triacetate from the coupling between the cisoidal protons (H-3 and H-4) as for xylonucleosides[27,28,44], where the values 3.64 and 8.55 Hz have been calculated as the theoretical $^3J_{3,4}$ values for the ^3E and E_3 conformations, respectively[30]. Estimated for **4** from the coupling constant between the cisoidal protons (H-3 and H-4), as for lyxonucleosides, for which the value 2.6–3.0 Hz has been calculated to be the theoretical $^3J_{3,4}$ value for the ^3E conformation[30]. The calculated contributions are consistent with the experimentally observed interdependence of the ring-proton coupling-constants in lyxonucleosides[45].
[b]Estimated from the Karplus relation, with $J_{60°} = 1.5$ and $J_{180°} = 11.5$ Hz, as for nucleosides[46].
[c]See corresponding Figs. for the assignment of H-5 and H-5'; the assignments are, to some extent, arbitrary, and may have to be reversed.

The conformational equilibrium is described quantitatively by data calculated as for ribonucleosides[42] (see Table IV). The E_3 conformation, which has OH-5 lying over the lactone ring, and the exocyclic, CH_2OH group in *gauche–gauche* disposition, appears to be the favored form in the equilibrium.



1-E_3(D),*gg*

A relatively large value of $^3J_{2,3}$ (5.7 Hz in methanol-d_4) may be explained in terms of the influence of electronegative substituents bonded to C-1, C-2, and C-3. It should be pointed out that almost the same coupling constants were found for 2,3-*O*-isopropylidene-D-ribono-1,4-lactone, which has a rigid, bicyclic structure[18]. For nucleosides and nucleotides[25–28,42], small ^3J values (0.5–0.8 Hz) were found to be very characteristic of vicinal protons having either the equatorial–quasiequatorial or the quasiequatorial–equatorial orientation. Therefore, the aforementioned equilibrium considered for **1** should thus be shifted far toward the E_3,*gg* conformation. Replacement of H-2 in **1** by a methyl group generates a large steric interference between the quasiaxial methyl group on C-2 and the quasiaxial CH_2OH group on C-4, and the conformational equilibrium is shifted toward the ^3E conformation in the *C*-methyl derivative of **1** (the value of $^3J_{3,4}$ reported[13] for this derivative is as large as 7.1 Hz). It may be deduced from the $^3J_{4,5}$ and $^3J_{4,5'}$ values reported[13] for the 2-*C*-methyl derivative of **1** that the 2-substitution causes a slight increase in the proportions of *gauche–trans* and *trans–gauche* rotamers of the exocyclic CH_2OH group.

A noteworthy feature of the ^{13}C-n.m.r. spectrum of **1** (see Tables II and III) is a strong deshielding of C-4, and also some deshielding of C-5, in comparison with other D-pentono-1,4-lactones. The deshielding of C-4 and C-5 might be explained in terms of the *trans*-disposition of substituents on C-3 and C-4 in **1**. In D_2O, a relatively large deshielding of C-1, in comparison with the solution in $(CD_3)_2SO$, may be explained in terms of protonation (or deuteration) of the -C-O- group. It seems probable that the favored conformation of **1** is further stabilized in aqueous solution by intramolecular hydrogen-bonding (see the preceding discussion). The hydrogen-bond system would decrease the electron density at C-1 and C-4, causing some deshielding of these carbon atoms. At the same time, the electron densities at C-2 and C-3 should increase, and so these atoms should undergo increased shielding.

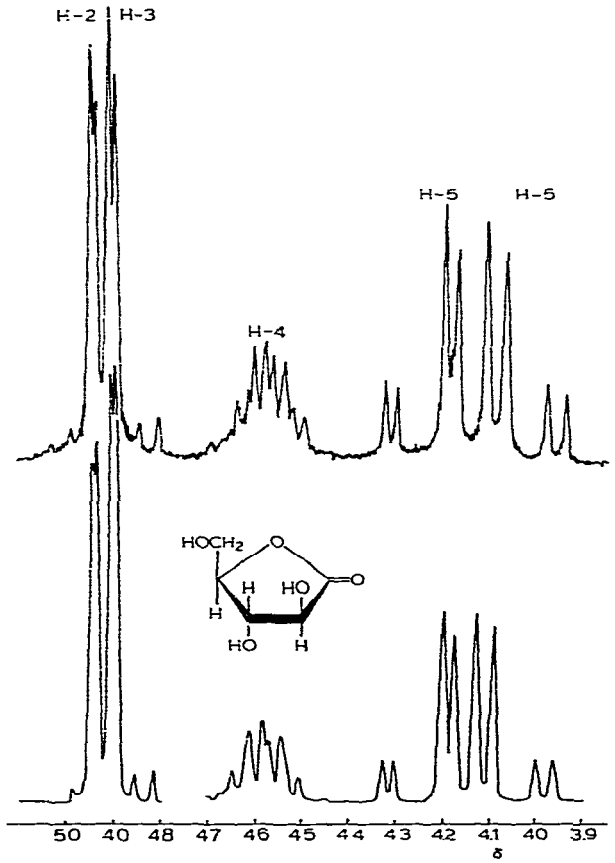
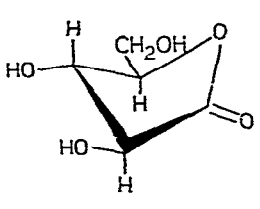


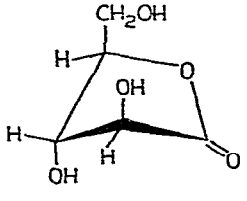
Fig. 1. The 100-MHz ^{1}H-n.m.r. spectrum of D-arabinono-1,4-lactone (**2**) in pyridine-d_5 (upper trace) and the simulated spectrum (lower trace).

Such increased shielding of C-2 and C-3 is, in fact, observed for **1** (even in comparison with compound **4**, which has all substituents in *cis*-disposition).

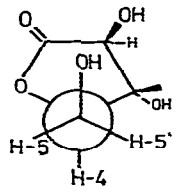
D-*Arabinono-1,4-lactone* (**2**). — The relative large values of $^3J_{2,3}$ and $^3J_{3,4}$ and the small values of $^3J_{4,5}$ and $^3J_{4,5'}$ (see Fig. 1 and Table I) give evidence that the conformational equilibrium between the envelope conformations of **2** in solution



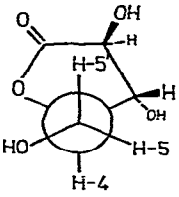
$2\text{-}^3E_{(D)}$



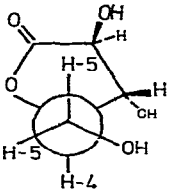
$2\text{-}E_{3(D)}$



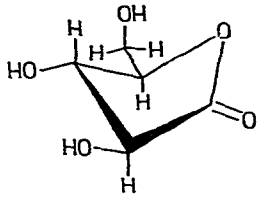
2-*gg*



2-*gt*



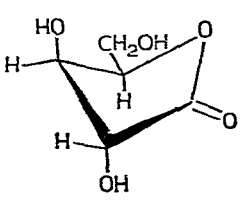
2-*tg*



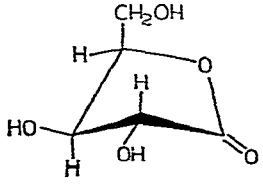
2-^3E(D),*gg*

lies strongly in favor of the E_3 conformer having the exocyclic, CH_2OH group oriented *gauche–gauche* (^3E,*gg*). Quantitative conformational data, calculated as for arabinonucleosides[42,43], are given in Table IV.

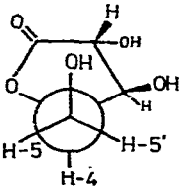
Coupling constants similar to the aforementioned $^3J_{2,3}$ and $^3J_{3,4}$ values have been observed for any pair of axial–quasiaxial, vicinal protons in various arabinonucleosides and arabinonucleotides[27,28,42,43]. Replacement of H-2 by the methyl group does not significantly affect this conformational equilibrium, as may be deduced from the values $^3J_{3,4}$ 7.5 Hz, $^3J_{4,5}$ 2.5 Hz, and $^3J_{4,5'}$ 4.8 Hz, reported[13] for the 2-*C*-methyl derivative of **2**.



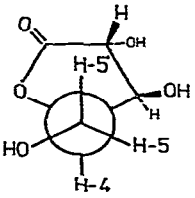
3-^3E(D)



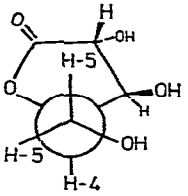
3-E_3(D)



3-*gg*



3-*gt*



3-*tg*

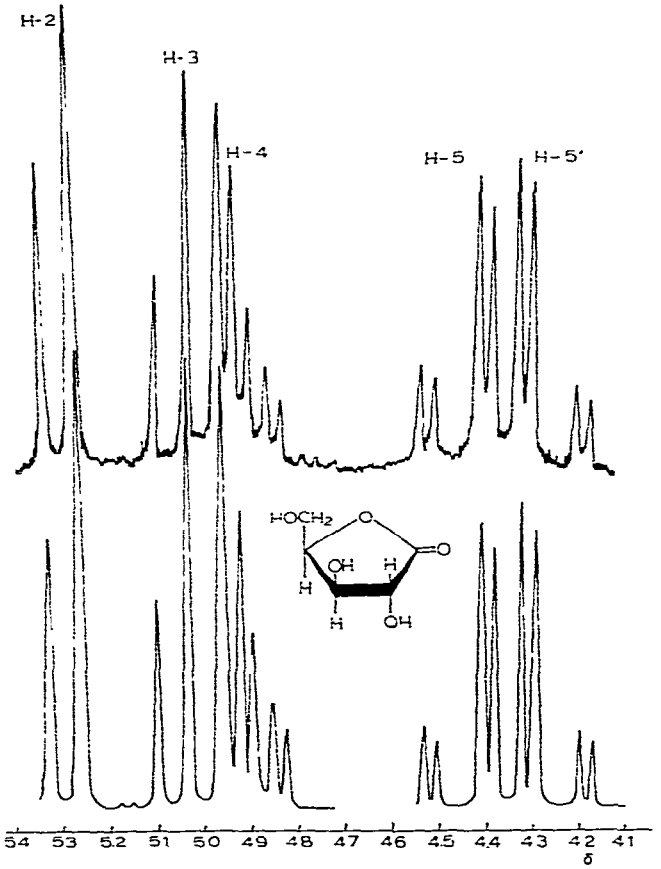
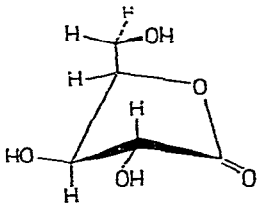


Fig. 2. The 100-MHz ^{1}H-n.m.r. spectrum of D-xylono-1,4-lactone (3) in pyridine-d_5 (upper trace) and the simulated spectrum (lower trace).



3-E_3(D),*gg*

D-*Xylono-1,4-lactone* (3). — The relatively large value (7.2 Hz in pyridine-d_5) of $^3J_{2,3}$, and the small values of $^3J_{4,5}$ and $^3J_{4,5'}$ (3 Hz in pyridine-d_5; see Fig. 2 and Table I), indicate that an equilibrium of the aforenoted conformations for 3 in solution is shifted far toward the E_3 conformation, which has OH-5 situated over the lactone ring; the side-chain rotamer having H-4, H-5, and H-5′ in *gauche–gauche* disposition (E_3, *gg*) is favored. Quantitative conformational data, calculated as for xylonucleosides[29,30], are shown in Table IV.

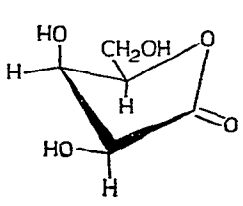
A relatively large magnitude of $^3J_{3,4}$ (6.7 Hz in pyridine-d_5) may be attributed to flattening of the lactone ring, as well as to synclinal dispositions of electronegative substituents on C-3 and C-4; similar behavior was observed with D-glucaro-1,4-lactone, which has identical configurations of the carbon atoms of the lactone ring, and the same conformational tendencies[17]. By application of the SCF, finite-perturbation theory in the intermediate neglect of differential overlap (INDO) molecular approximation for the calculation of ^{1}H-n.m.r., cisoidal, vicinal, coupling constants for the pentose rings of nucleosides, the values 3.64 and 8.55 Hz were respectively calculated as the theoretical magnitudes for the ^3E and E_3 conformations of xylonucleosides[29,30].

When H-2 in **3** is replaced by a methyl group, the conformational equilibrium is shifted toward the ^3E conformation, and the proportions of *gauche–trans* and *trans–gauche* rotamers of the CH_2OH group are increased, as may be deduced from the values $^3J_{3,4}$ 3.4, and $^3J_{4,5} = {}^3J_{4,5'} = 5.5$ Hz reported[13] for the 2-*C*-methyl derivative of **3**. It is significant that similar coupling-constants and conformational features were observed for *O*-methylated xylonucleosides[44]. It should also be pointed out that similar values of $^3J_{3,4}$ (3.4–3.6 Hz) were found[17] for D-glucaro-1,4:6,3-dilactone, which has a rather rigid, dienvelope conformation, with a similar disposition of H-3 and H-4.

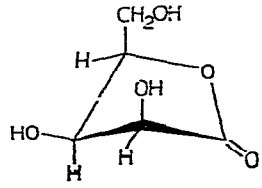
The C-4 and C-5 atoms in **3** are shielded even more than the corresponding carbon atoms in **4**, which has all substituents *cis*-disposed. The shielding of C-4 and C-5 in **3** may be explained in *terms* of the *cis*-disposition of the substituents on C-3 and C-4, and the quasiaxial orientation of the CH_2OH group on C-4.

D-*Lyxono-1,4-lactone* (**4**). — The values of $^3J_{2,3}$ (4.8 Hz) and $^3J_{3,4}$ (2.8 Hz) found for **4** (see Fig. 3 and Table I) are very similar to those for L-gularo-1,4-lactone[17], D-mannono-1,4-lactone, and D-gulono-1,4-lactone[47]. By use of the SCF, FPT method, the values of 4.5–4.6 Hz and 2.6–3.0 Hz were calculated for $^3J_{2,3}$ and $^3J_{3,4}$, respectively, for lyxonucleosides in the ^3E conformation[29].

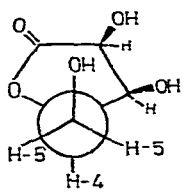
As the C-1, C-2, and C-3 resonances in the ^{13}C-n.m.r. spectra of **4** and the aforementioned three lactones appear at almost identical fields[17,47], it is very probable that they all favor the ^3E conformation. Also taking into account the $^3J_{4,5}$ and $^3J_{4,5'}$ values found for **4**, it seems clear that a conformational equilibrium between the following conformations exists in solutions of **4**, and that $^3E,tg$ is the favored conformation.



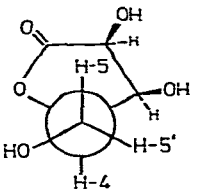
4-^3E(D)



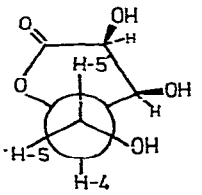
4-E_3(D)



4-*gg*



4-*gt*



4-*tg*

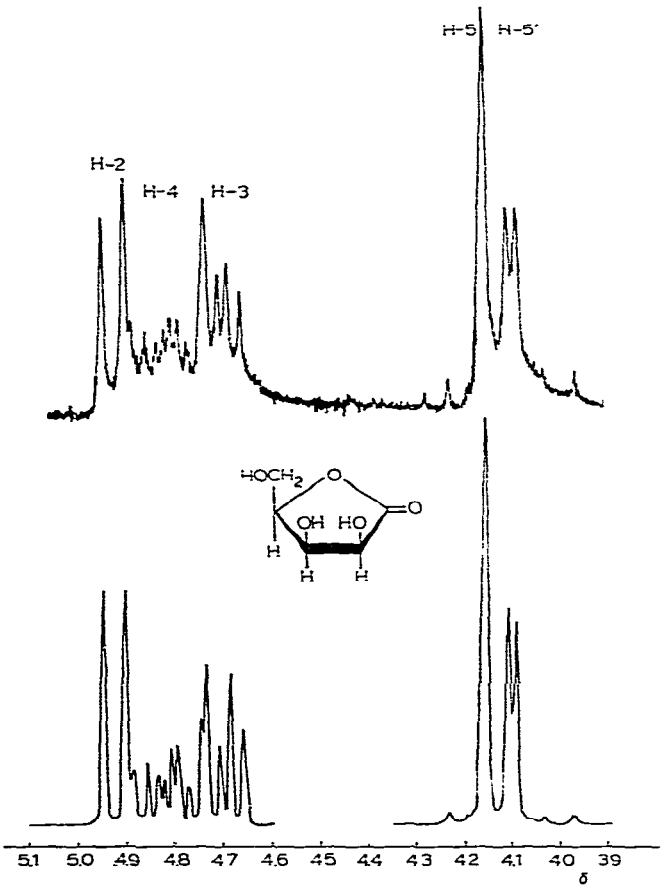
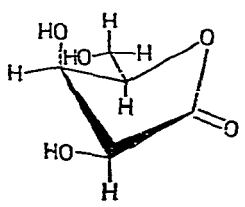


Fig. 3. The 100-MHz ^{1}H-n.m.r. spectrum of D-lyxono-1,4-lactone (4) in dimethyl sulfoxide-d_6 (upper trace) and the simulated spectrum (lower trace).



4-*E*(D),*tg*

TABLE V

100-MHz, ^{1}H-N.M.R.-SPECTRAL DATA FOR D-LYXONO-1,4-LACTONE (**4**) IN METHANOL-d_4 IN THE PRESENCE OF $EuCl_3$ AT ~30°

$EuCl_3$ added (equiv.)	*Chemical shifts in δ values[a] and lanthanide-induced shifts in Δδ (in parentheses)[b]*					*Coupling constants (Hz)*				
	H-2	*H-3*	*H-4*	*H-5*	*H-5'*	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{4,5'}$	$^3J_{5,5'}$
0.0	4.43m	4.43m	4.43m	3.85m	3.85m	[c]	[c]	[c]	[c]	[c]
0.4	4.42d (−0.01)	4.27q (−0.16)	4.43o (0.00)	3.88q (0.03)	3.73q (−0.12)	4.8	3.2	6.4	5.2	−12.0
0.6	4.40d (−0.03)	4.24q (−0.19)	4.43o (0.00)	3.87q (0.02)	3.71q (−0.14)	4.8	3.2	6.5	5.2	−12.1
0.8	4.38d (−0.05)	4.22q (−0.21)	4.43o (0.00)	3.86q (0.01)	3.70q (−0.15)	4.8	3.2	6.4	5.2	−12.1

[a]Signal multiplicities as in Table I. [b]Upfield shifts, negative. [c]Not obtainable by first-order analysis.

Quantitative, conformational data calculated as for lyxonucleosides[30,45] are shown in Table IV. It may be noted that, in comparison with **1–3**, increased proportions of *gauche–trans* and *trans–gauche* rotamers of the CH_2OH group exist for **4** at equilibrium; similar conformational tendencies were observed for lyxonucleosides[45]. It is also relevant that replacement of H-2 by a methyl group does not significantly affect this equilibrium, as may be deduced from n.m.r. data reported[13] for the 2-*C*-methyl derivative of **4**.

Coupling constants observed for **4** dissolved in methanol-d_4 are not changed during addition of $EuCl_3$ (see Table V), but the $^3J_{4,5}$ and $^3J_{4,5'}$ values measured in the presence of $EuCl_3$ differ from those measured in Me_2SO-d_6 (see Tables I and V), indicating that the geometry of **4** undergoes some modification on coordination of the Eu^{3+} ion, particularly the disposition about C-4–C-5. It should be noted that, to effect a significant change in chemical shifts of the aldono-1,4-lactone, ~10 times as much lanthanide shift-reagent had to be used as for an aldaro-1,4-lactone[17]; clearly, the CO_2H group in aldaromonolactones facilitates coordination of the lanthanide ion.

General correlations. — A characteristic feature of D-pentono-1,4-lactones in solution[14] appears to be the adoption of envelope conformations having the OH-2 group quasiequatorially disposed; all of the conformational equilibria described for **1–4** in the present study are shifted far toward conformations having OH-2 quasiequatorially oriented. X-Ray diffraction studies of certain sugar lactones in the solid state also support the conclusion that the OH-2 group favors the quasiequatorial rather than the quasiaxial disposition[2–5]. This trend may be ascribed to a tendency to minimize the total dipole moment of the sugar lactone molecule, possibly also supported by intramolecular hydrogen-bonding with OH-2 as the donor and the lactone-ring carbonyl group as the acceptor of the proton. The tendency of sugar lactones to favor envelope conformations having OH-2 quasiequatorially oriented

brings the CH_2OH groups in **1** and **3** into quasiaxial orientation. It is not clear why the OH-5 group favors a location above the lactone ring in **1** and in **3**. Generally, the exocyclic CH_2OH group in D-pentono-1,4-lactones seems to favor the *gauche–gauche* orientation about the C-4–C-5 bond. The only exception, occurring to some extent, seems to be D-lyxono-1,4-lactone, which favors *trans–gauche* and *gauche–trans* orientations, possibly because of repulsion between OH-5 and OH-3. Contributions of the *gauche–gauche*, *gauche–trans*, and *trans–gauche* arrangements were calculated according to a method that has been applied for nucleosides[46]. It has been pointed out that contributions of the *trans–gauche* rotamer, calculated according to this method, might be slightly overestimated[48].

Correlations between the puckering modes of the furanose ring and the exocyclic, C-4′–C-5′ rotamers have been found for purine and pyrimidine nucleosides in aqueous solution. For pyrimidine ribonucleosides[24] and for both purine and pyrimidine arabinonucleosides[43] and xylonucleosides[44], the ^3E conformation of the glycosyl group coexists to some extent with a *gauche–gauche* disposition of the exocyclic 4′-CH_2OH group. On the other hand, for pyrimidine lyxonucleosides, the ^3E conformation instead coexists with *gauche–trans* and *trans–gauche* rotamers of the exocyclic 4′-CH_2OH group[45]. Apparently, the hydroxymethyl group responds to the puckering of the ring.

It is difficult to assess the apparent interdependence of the puckering and the exocyclic-group disposition in terms of steric or electrostatic forces. It is possible that rotation around C-4′–C-5′ is a response to a change in the local dipole-moment of the molecule as a result of conformational ring-conversion, which would alter the local, solvation properties of the molecule[24]. It should be noted that neither a solvent change nor *O*-substitution significantly affects the conformational equilibria of D-pentono-1,4-lactones (see Table IV). Small changes observed in the conformational equilibria might reflect the effects of intramolecular hydrogen-bonding on the stabilization of favored conformations. It is noteworthy, however, that replacement of H-2 by a methyl group strongly affects the $^3E \rightleftarrows {}_3E$ conformational equilibrium if the replacement leads to a large steric interference between the CH_3 group and a *cis-*

TABLE VI

EQUILIBRIUM COMPOSITIONS[a] OF D-ALDOPENTONIC ACIDS AND THEIR LACTONES IN D_2O AT ~30°

Configuration	*Content of acid and lactones in percent*[b]		
	Acid	*1,5-Lactone*	*1,4-Lactone*
D-*ribo*	25	—	75
D-*arabino*	33	—	67
D-*xylo*	60	5	35
D-*lyxo*	20	—	80

[a]Calculated from total peak-areas of protonated carbon atoms in ^{13}C-n.m.r. spectra[49]. [b]±5%.

disposed CH_2OH group, as may be deduced from comparison of ^{1}H-n.m.r. data herein reported with those[13] for the 2-*C*-methyl derivatives of **1**–**4**.

Equilibrium compositions of D-*pentonolactones and* D-*pentonic acids in* D_2O. — Equilibrium compositions after mutarotation of D-pentonolactones and D-pentonic acids in D_2O were calculated from the total peak-areas of all protonated carbon atoms in the ^{13}C-n.m.r. spectra, according to a procedure described elsewhere[49]. It should be borne in mind, however, that the data given in Table VI were found for specific concentrations and temperatures, and that the equilibrium compositions vary with concentration and temperature. It is noteworthy that, in the equilibrated solutions, only one example of a 1,5-lactone, namely D-xylono-1,5-lactone, was observed. It is also of interest that the content of D-xylonic acid and the total content of D-xylonolactones at equilibrium is very close to the content of 2,3,5-tri-*O*-methyl-D-xylonic acid and 2,3,5-tri-*O*-methyl-D-xylono-1,4-lactone, respectively, in equilibrated solutions of the corresponding 2,3,5-tri-*O*-methyl derivatives[50].

EXPERIMENTAL

Materials. — D-Ribono-1,4-lactone (**1**) and D-arabinono-1,4-lactone (**2**) were respectively obtained from Sigma, St. Louis, Mo., and Koch–Light, Colnbrook, England. The literature methods indicated were used in order to prepare 2,3,5-tri-*O*-acetyl-D-arabinono-1,4-lactone[51], 2,5-di-*O*-methyl-D-arabinono-1,4-lactone[52], D-xylono-1,4-lactone[53] (**3**) and its 2,3,5-triacetate[54], and D-lyxono-1,4-lactone[55]. All of these compounds had physical constants in good agreement with published values, and were chromatographically homogeneous [t.l.c. being performed on Silica Gel G (E. Merck, Darmstadt, G.F.R.), and the solvent system and spray reagents the same as those used earlier for D-glucarolactones[17]].

^{1}*H-N.m.r. spectra.* — Spectra were recorded at 100 MHz with a Varian HA-100 n.m.r. spectrometer operating under conditions already described[17]. Solvents were obtained from Stohler Isotope Chemicals, Waltham, Mass. A solution of $EuCl_3$ in D_2O containing 30 μmol of $EuCl_3$ per drop (4 μL) was added dropwise with continual, spectral scanning to monitor the effect of each addition. The solution was prepared from $EuCl_3 \cdot 5\ H_2O$ (Alfa-Ventron) as described earlier[17] for solutions of $PrCl_3$. Computer-simulated spectra were generated as a confirmatory test of ^{1}H-n.m.r. chemical-shifts and coupling-constants. The spectra were simulated with the aid of the program LAOCOON III.

^{13}*C-N.m.r. spectra.* — Proton-decoupled, natural-abundance-carbon-13, pulse, Fourier-transform, n.m.r. spectra were recorded with a Bruker FX-90 multinuclear spectrometer, in part by Dr. C. Cottrell of The Ohio State University. Each compound (0.4 g) was dissolved in 1.5 mL of D_2O or Me_2SO-d_6. The internal reference [4,4-dimethyl-4-silapentane-1-sulfonate (DSS) or Me_4Si] was then added. Spectra were recorded at $\sim 30°$ by using the deuterium resonance of D_2O or Me_2SO-d_6 as the lock signal. Spectra in Me_2SO-d_6 were referenced directly to the internal Me_4Si. Spectra that were recorded for solutions in D_2O were referenced to the highest-field,

^{13}C resonance of DSS; by using internal 1,4-dioxane as an additional, internal reference, the aforementioned resonance of DSS was found[49] to be shifted upfield by 1.6 p.p.m. with respect to Me_4Si, so that chemical shifts measured in D_2O and referenced to DSS were recalculated according to the equation: $\delta_{Me_4Si} = \delta_{DSS} - 1.6$. Typical conditions for measurement were as follows: number of scans 1100–8000, data points 8k, repetition 0.8 or 3 s, and sweep width 5 kHz.

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