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^{13}C–^{13}C Spin–Spin Coupling Constants in Structural Studies: XXXVII. Rotational Conformations of Hydroxy Groups in Pyranose, Furanose, and Septanose Rings

V. A. Danilova, N. V. Istomina, and L. B. Krivdin

Angarsk State Technical Academy, ul. Chaikovskogo 60, Angarsk, 665835 Russia
e-mail: krivdin@irk.ru

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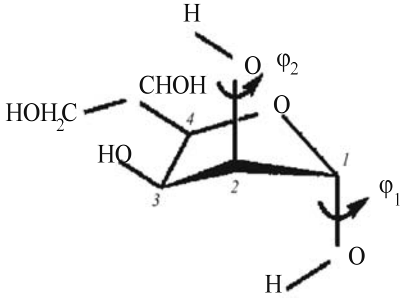
Abstract—Rotational surfaces for ^{13}C–^{13}C coupling constants with respect to two dihedral angles at C^1 and C^2 in model structures of aldopyranoses, aldofuranoses, and aldoseptanoses of the D-series were calculated in terms of the self-consistent finite perturbation theory. Internal rotation of the hydroxy groups exerts an appreciable effect (within 2.5 Hz) on the ^{13}C–^{13}C coupling constants of all cyclic forms of monosaccharides, which provides the possibility for performing conformational analysis of carbohydrates and their metabolites containing pyranose, furanose, and septanose fragments.

NMR spectroscopy is widely used for determination of configuration of the anomeric center and conformational analysis of biologically active molecules containing carbohydrate fragments [1]. Here, useful parameters are spin–spin coupling constants between carbon nuclei which exhibit clearly pronounced stereochemical effects, depending on spatial arrangement of the adjacent atoms and groups and molecular conformation [2, 3]. The available experimental data on ^{13}C–^{13}C coupling constants in cyclic forms of carbohydrates [4, 5] and the results of our previous stereochemical studies on pyranose [6], furanose [7], and septanose [8] monosaccharide rings unambiguously indicate that these constants are sensitive to stereochemical effects. They depend on both configuration of the anomeric center and conformational structure. It is also obvious that stereochemical behavior of the $^1J_{1,2}$ constant in cyclic carbohydrate species, apart from the configurational and conformational factors, is largely determined by rotation of hydroxy and hydroxymethyl groups, as was noted previously in some publications [9–11] concerning coupling constants of other types.

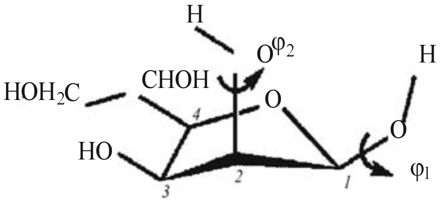
Recent fundamental studies performed by Serianni and co-workers [12, 13] revealed a relation between the direct ($^1J_{CH}$), geminal ($^2J_{HH}$), and vicinal coupling constants ($^3J_{HH}$), on the one hand, and rotational conformations of the hydroxy and hydroxymethyl groups on C^1 and C^5 in oligosaccharides, on the other. The authors also calculated the rotational surface for the $^2J_{HH}$ constant against two dihedral angles at the C^1 and C^5 atoms in oligosaccharides [13]. Malkin and co-workers [14, 15] studied in detail the dependences of the direct ($^1J_{CH}$), geminal ($^2J_{CH}$, $^2J_{HH}$), and vicinal coupling constants ($^3J_{CH}$, $^3J_{HH}$) upon rotational conformation of the hydroxymethyl group at the anomeric center in methyl D-xylopyranoside anomers. In addition, the results of numerous studies [16–18] showed that lone electron pairs (LEP) of heteroatoms also affect ^{13}C–^{13}C coupling constants for carbon atoms at the nearby bonds. It is known that the effect of LEP on ^{13}C–^{13}C coupling constants arises from intramolecular interaction between lone electron pair of a heteroatom and spatially close bonding or antibonding molecular orbitals. The effect of nitrogen LEP on the coupling constant $^1J_{1,2}$ between the adjacent carbon nuclei in oximes and their derivatives was studied in detail in [16, 17]. Cramer *et al.* [18] analyzed the influence of LEP on the oxygen atom at the anomeric center on the geometric parameters of different conformations of α-D-glucopyranose and its derivatives [18]. The results of these studies showed that *cis* orientation of lone electron pair on the heteroatom with respect to the neighboring carbon–carbon bond gives rise to an additional positive contribution to $^1J_{1,2}$ and that their *trans* orientation provides a negative contribution whose magnitude depends on the nature and hybridization of the heteroatom. These contributions originate from through-space interaction between the LEP and bonding (positive) or antibonding (negative) orbitals of the carbon–carbon bond [19].

Specific interest in ^{13}C–^{13}C coupling constants in carbohydrates arises from extensive use in biochemical studies of carbohydrates and their derivatives selectively labeled with ^{13}C isotope, where experimental measurement of ^{13}C–^{13}C coupling constants is a routine task: they can be determined directly from standard ^{13}C NMR spectrum with broad-band decoupling from protons [1].

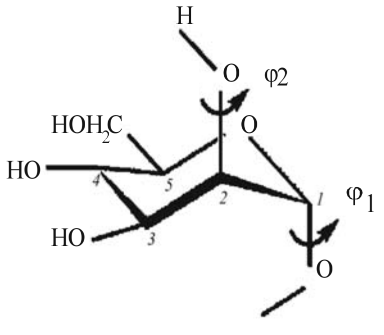
The present study was aimed primarily at estimating the effect of rotation of the hydroxy groups on C^1 and C^2 on the coupling constants $^1J_{1,2}$ of model furanose, pyranose, and septanose cyclic forms of α- and β-anomers of D-mannose. Table contains the most important equilibrium geometric parameters which will be referred to as natural in the further treatment. The geometric parameters were optimized in terms of the density functional theory (DFT) using the Becke three-parameter hybrid functional [20] in combination with the Lee–Yang–Parr correlation functional (B3LYP) [21]. The calculations were performed with the standard Pople 6-31G** polarizational basis set [22] which includes polarizational *p*-functions on hydrogen atoms and



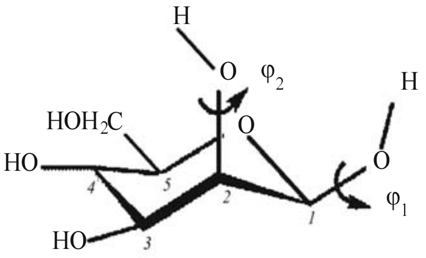
α-D-Mannofuranose E_4(**Ia**)



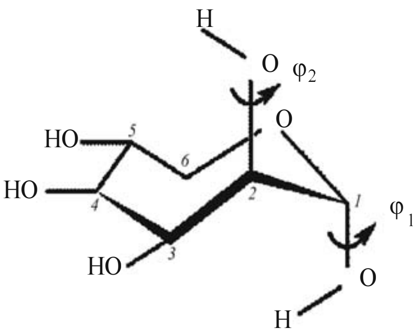
β-D-Mannofuranose E_4(**Ib**)



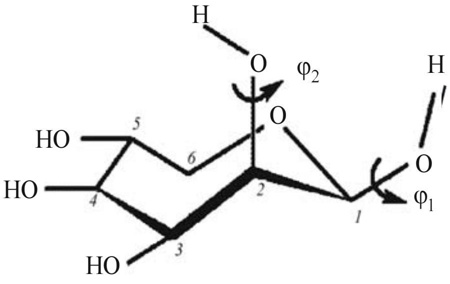
α-D-Mannopyranose C1 (**IIa**)



β-D-Mannopyranose C1 (**IIb**)



α-D-Mannoseptanose C1 (**IIIa**)



β-D-Mannoseptanose C1 (**IIIb**)

Geometric parameters of cyclic D-mannose anomers, optimized by the B3LYP/6-31G** method

Compound no.	C^1–C^2 bond length, Å	Dihedral angle, deg		Dihedral angle, deg	
		C^1OH	C^2OH	C^2C^1OH (φ_1)	C^1C^2OH (φ_2)
α-D-Mannose					
Ia	1.556	107.5	105.5	172.3	102.5
IIa	1.539	110.1	106.7	040.8	038.3
IIIa	1.530	108.2	106.9	014.0	041.6
β-D-Mannose					
Ib	1.578	105.1	104.8	005.9	105.9
IIb	1.538	106.8	106.1	038.0	048.8
IIIb	1.533	106.4	105.3	040.8	048.5

polarizational *d*-functions on carbon and oxygen atoms. The calculated C^1–C^2 bond lengths vary from 1.530 to 1.578 E. Regardless of the ring size of the monosaccharide, the bond angles are similar for the α-anomers of D-mannose with axial orientation of both hydroxy groups on C^1 and C^2, on the one hand, and for the β-anomers with equatorial and axial orientations of these groups.

We calculated the rotational surfaces for $^1J_{1,2}$ against two dihedral angles φ_1 and φ_2 in all cyclic forms of carbohydrates: furanoses, pyranoses, and septanoses using D-mannose as an example. The range of variation of $^1J_{1,2}$ for all the above compounds is, on the average, 2.5 Hz. Let us discuss the effect of rotation of the anomeric hydroxy group (which is characterized by the angle φ_1) on $^1J_{1,2}$ in the α- and β-anomers of D-mannofuranose E_4 (Fig. 1, a) at fixed natural (i.e., optimized) angle at C^2 (φ_2). Figure 1 shows that, depending on φ_1, $^1J_{1,2}$ changes within 1.5 Hz for α-D-mannofuranose and 2.5 Hz for its β-anomer. In each case, two minima and two maxima are observed. The first minimum is located at $\varphi_1 = 0°$ (or 360°). It corresponds to a rotamer in which both LEPs on the anomeric oxygen atom are arranged at an angle of 120° with respect to the C^1–C^2; therefore, there is no positive contribution to the coupling constant $^1J_{1,2}$.

The first maximum is observed at $\varphi_1 \approx 105°$. Here, one LEP on the anomeric oxygen atom is located *cis* with

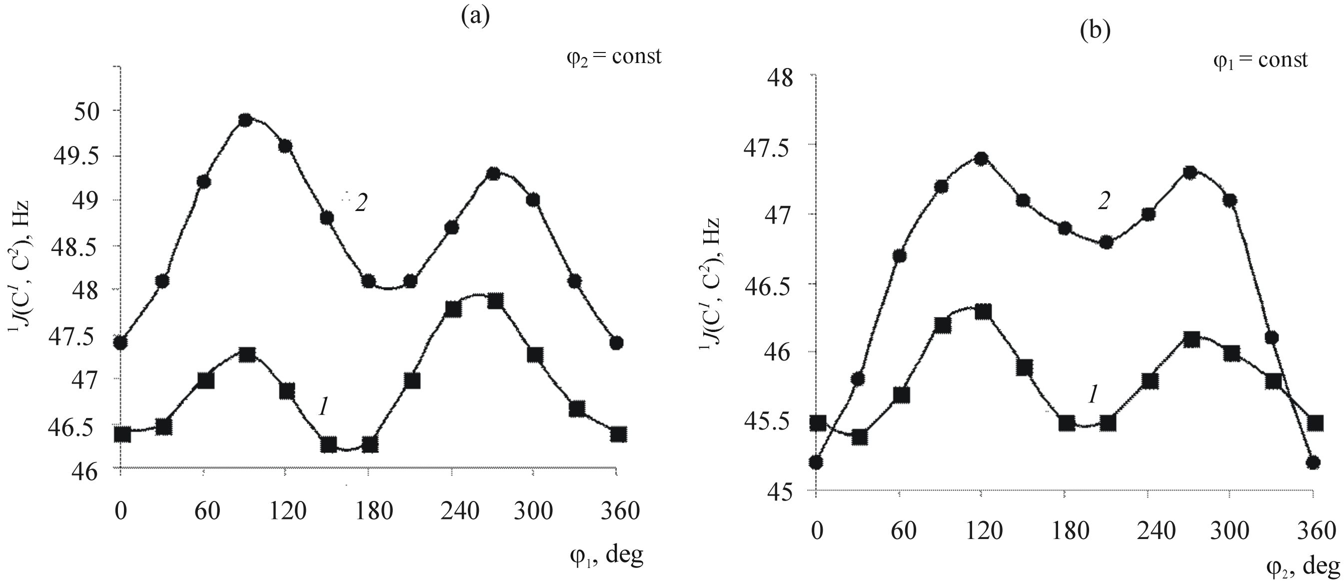


Fig. 1. Variation of the coupling constant $^1J_{1,2}$ in α- and β-D-mannofuranose E_4 (curves *1* and *2*, ewspectively), depending on the angle of rotation of the hydroxy groups on C^1 and C^2; (a) φ_2 = const, (b) φ_1 = const.

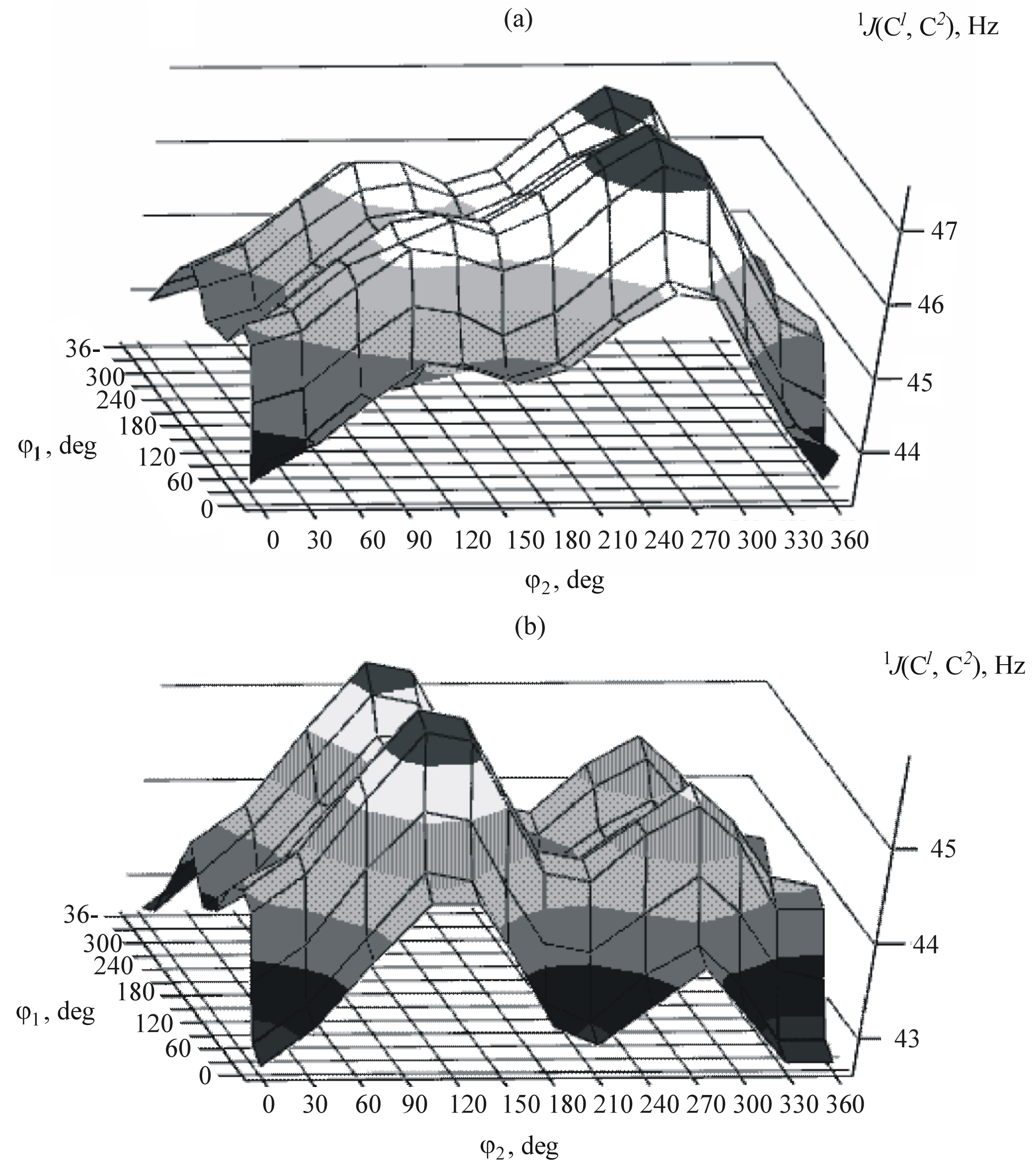


Fig. 2. Rotational surface for the coupling constant $^1J_{1,2}$ against dihedal angles φ_1 and φ_2 which characterize orientation of the hydroxy groups on C^1 and C^2 with respect to the $C^1–C^2$ bond: (a) α-D-mannopyranose C1 and (b) β-D-mannopyranose C1.

respect to the neighboring $C^1–C^2$ bond, giving rise to the maximal positive contribution to the coupling constant. It should be emphasized that the positive contribution of the oxygen LEP to $^1J_{1,2}$ in the β-anomer is considerably greater than in the α-anomer (2.5 and 0.9 Hz, respectively).

The second minimum corresponds to $\varphi_1 = 180°$. It results from reduction of the positive contribution to $^1J_{1,2}$ of the first oxygen LEP, while the contribution of the second LEP still remains insufficient. Finally, the second maximum is located at $\varphi_1 = 270°$. In this case, the second LEP on the anomeric oxygen atom is arranged *cis* with respect to the neighboring carbon–carbon bond, thus contributing most to $^1J_{1,2}$ value. The positive contribution of the oxygen LEP to $^1J_{1,2}$ is greater for α-D-mannofuranose (1.7 Hz) as compared to the β-anomer (1.2 Hz).

A similar pattern was observed when the angle φ_2 was varied at a fixed (natural) value of φ_1 (Fig. 1, b). The range of variation of $^1J_{1,2}$ is 0.8 Hz for α-D-mannofuranose and 2.2 Hz for β-D-mannofuranose. For each D-mannofuranose anomer, two minima and two maxima are observed. It seems exceptionally interesting that the contributions of the two oxygen LEPs are not equal, which indirectly indicates their nonequivalence from the viewpoints of energy and symmetry. The shapes of the rotational surfaces for the coupling constant $^1J_{1,2}$ of the examined pyranoses, furanoses, and septanoses against the φ_1 and φ_2 angles are similar: they differ by insignificant shift (about 15°) of the maxima and their intensity. We can conclude that (1) the effect of the anomeric oxygen atom on $^1J_{1,2}$ includes contributions of two rather than one lone electron pairs and (2) only positive constituent of the LEP effect is operative.

In order to examine the observed stereochemical effects in more detail, we analyzed variation of the coupling constant $^1J_{1,2}$ induced by simultaneous rotation of both hydroxy groups on C^1 and C^2. For this purpose, the corresponding surfaces were plotted with respect to the dihedral angles φ_1 and φ_2 for all cyclic forms of monosaccharides: pyranoses, furanoses, and septanoses.

Let us consider the rotational surfaces for $^1J_{1,2}$ versus φ_1 and φ_2 for α- and β-D-mannopyranose C1 (Fig. 2). As might be expected, the surfaces are characterized by the presence of four maxima and four minima. Cross sections of the surfaces at a fixed value of one of the dihedral angles (φ_1 or φ_2) almost coincide with the plots shown in Fig. 1; therefore, a conclusion can be drawn that the effect of rotation of the hydroxy groups on $^1J_{1,2}$ is additive. Analogous surfaces calculated for the furanose and septanose cyclic forms of α- and β-D-mannose are available from the authors (by e-mail).

Thus, rotation of the hydroxy groups on C^1 and C^2 exerts an appreciable effect on the direct C^1–C^2 coupling constant in pyranose, furanose, and septanose forms of carbohydrates. The observed effect originates from two rather than one lone electron pairs on the hydroxy oxygen atom, whose contributions to $^1J_{1,2}$ are different. The effect of oxygen LEP includes positive and negative constituents, but only the positive one is operative. We believe that the effect of rotation of the hydroxy groups on $^1J_{1,2}$ should be taken into account while analyzing conformations of cyclic monosaccharides and their derivatives in terms of the previously developed approaches which utilize stereospecificity of ^{13}C–^{13}C coupling constants involving the anomeric carbon atom [6–8].

Quantum-chemical calculations were performed using SCPT INDO [23], MOPAC [24], and GAMESS software packages [25] operating under Linux Red Hat 7.2. In the SCPT INDO calculation of ^{13}C–^{13}C coupling constants, the following parameters for carbon atoms were taken: *s*-electron density $s^2_{C(0)} = 3.2328$ and size of 2*p* orbitals $\langle r^{-3} \rangle = 2.8256$.

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