$^2J_{COC}$ Spin−Spin Coupling Constants Across Glycosidic Linkages Exhibit a Valence Bond-Angle Dependence

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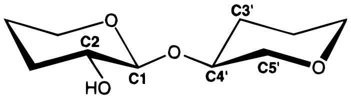
The recent intense interest in the biological functions and biomedical applications of oligosaccharides has stimulated renewed efforts to improve experimental tools for the determination of their conformational properties. NMR spectroscopy provides the most detailed structural information in solution derived mainly from $^1H-^1H$ NOEs and more recently from $^3J_{COCH}$ values across their constituent *O*-glycosidic linkages.[1] However, in many cases, these linkages are not conformationally rigid, and identifying those that exhibit flexibility[2] requires the use of multiple NMR parameters which provide the needed redundancy to make such determinations with confidence. In our ongoing efforts to develop trans-*O*-glycosidic $^2J_{COC}$ and $^3J_{COCC}$ values as conformational constraints,[3] we showed recently that $^2J_{COC}$ across an *O*-glycosidic linkage depends mainly on the ϕ torsion angle (Scheme 1) and considerably less so on ψ, using an experimentally derived projection resultant rule.[3a] This rule predicts that more negative projection resultants translate into more negative $^2J_{CCC}$ and, by analogy, into more negative $^2J_{COC}$. We show herein that the COC bond angle also influences $^2J_{COC}$ magnitude, with increasing angle producing more negative coupling.

Density functional theory (DFT) calculations[4] have been shown recently to yield computed J_{CC} within ∼10% of experiment without the need for scaling,[5] and thus $^2J_{COC}$ values can be computed to within 0.2−0.3 Hz of the true couplings. This degree of accuracy encouraged us to apply this method to determine whether other structural factors influence trans-*O*-glycosidic $^2J_{COC}$ values. Ab initio molecular orbital calculations were, therefore, conducted on the disaccharide mimics **1**−**4** with a modified[6] version of the Gaussian 94 suite of programs.[7] Electron correlation effects were treated by means of DFT. The standard B3LYP functional, due to Becke,[8] was used; this functional comprises both local[9] and nonlocal[10] exchange contributions and contains terms accounting for local[11] and nonlocal[12] correlation corrections. Geometric optimizations were conducted with this functional and the standard split-valence 6-31G* basis set.[13] $^{13}C-^{13}C$ spin-coupling constants were obtained by finite-field (Fermi-contact) double perturbation theory[14] calculations at the B3LYP level using a basis set previously constructed for similar systems.[6] In the initial treatment only the Fermi contact component was recovered since it is the main contributor to J_{CC} in saturated systems.



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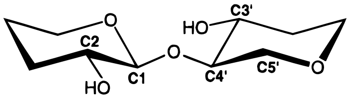

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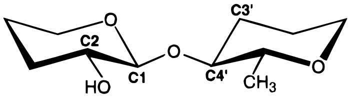

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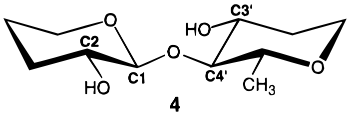

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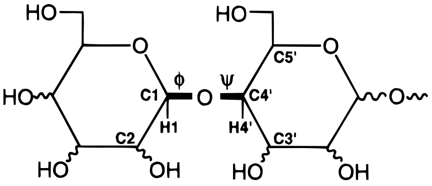
Scheme 1



Two sets of calculations were performed. In the first, geometrically optimized structures of **1**−**4** were obtained for the three staggered rotamers about ψ. The *initial* ϕ was the same in all calculations (H1−C1−O1−C4′ = 60°; Scheme 1) to optimize the exoanomeric effect.[15] For **1**, three fully optimized geometries were obtained (**1** 60R, **1** 60S, **1** AP), whereas for **2**−**4** only two resulted (**2**−**4** 60S and **2**−**4** AP); a more detailed discussion of these structures has appeared elsewhere.[16] $^2J_{C1,C4'}$ values were computed in all nine structures. Projection resultants of ∼0 for the C1−O1−C4′ coupling pathway in **1**−**4** yield predicted couplings of ∼ −2 Hz,[3a] in agreement with the DFT-computed average value of −2.2 ± 0.3 Hz. The negative sign has been verified experimentally.[3b,c]

The DFT-determined $^2J_{COC}$ values in the geometrically optimized **1**−**4** ranged from −1.9 to −2.8 Hz, with the most negative value observed in **3** AP, suggesting that factors in addition to ϕ influence $^2J_{COC}$. To examine this possibility, $^2J_{C1,C4'}$ were computed in **1** at defined ψ (60°, 80°, 110°, 130°, 150°; all other structural parameters were optimized). Computed $^2J_{C1,C4'}$, C1−O1−C4′ bond

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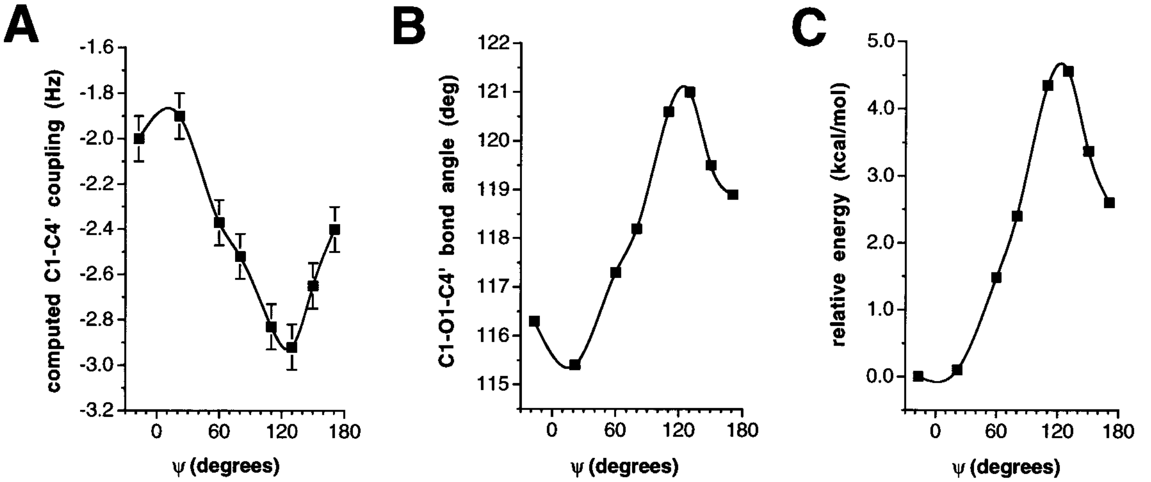


Figure 1. Computed ${}^2J_{C1,C4'}$ (A), C1−O1−C4′ bond angles (B), and conformational energies (C) in **1** as a function of the glycosidic torsion angle ψ (defined as C1−O1−C4′−H4′). Data taken from Tables 1 and 2 of the Supporting Information.

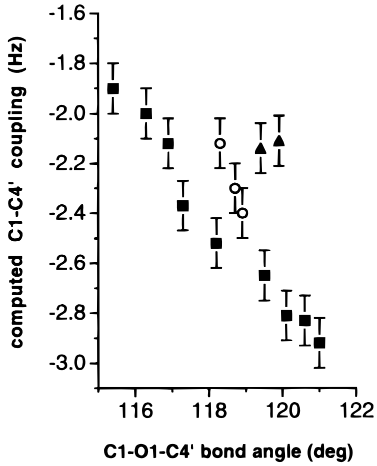
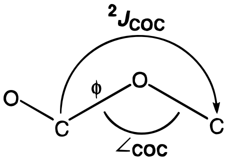


Figure 2. Computed ${}^2J_{C1,C4'}$ values as a function of the C1−O1−C4′ bond angle in **1**−**4**. The effect of ϕ (defined as H1−C1−O1−C4′) on the computed couplings is also illustrated. Data taken from Tables 1 and 2 of Supporting Information. Closed squares, ϕ = 38−58°; open circles, ϕ = 31−32°; closed triangles, ϕ = 16−18°.

angles and conformational energies as a function of ψ in **1** (8 structures) are shown in Figure 1. The least stable geometry (ψ = 130°) contains the maximum glycosidic bond angle (121.0°); in this structure, unfavorable eclipsing of C1 and C5′ is apparently relieved by the enhanced COC bond angle. Interestingly, ${}^2J_{C1,C4'}$ values in **1**−**4** (14 structures) exhibit a systematic dependence on C4′−O1−C1 valence bond angle (Figure 2). The observed scattering is attributed to variations in ϕ (16.5−58.1°).[3a] However, changes in ϕ cannot account for the observed changes in ${}^2J_{C1,C4'}$, since maximum *and* minimum couplings are found at essentially identical ϕ (43.4° and 43.8°, respectively).

Trans-*O*-glycosidic COC bond angles obtained from crystal structures of disaccharides containing β-(1→4) linkages have mean values of ~116.4°,[17] which is consistent with the 116.3° bond angle found in the lowest energy geometry of **1** (60S). Since bond angles as large as 121° are rare in crystal structures, extreme ${}^2J_{COC}$ values (−2.6−2.9 Hz) are not expected in solution. The present results show that, although ${}^2J_{COC}$ is largely determined by ϕ, ${}^2J_{COC}$ also depends on the trans-*O*-glycosidic bond angle, with larger bond angles yielding more negative couplings. A similar bond-angle dependence was also found for ${}^2J_{COC}$ in dimethyl ether, where the calculated ${}^2J_{COC}$ at the B3LYP/6-31G* optimized geometry is −1.9 Hz and the change per degree is −0.1 Hz for angles within ±5° of the equilibrium structure. Interestingly, these correlations differ from that observed for ${}^2J_{HH}$, where increasing bond angle translates into more positive couplings.[18]

Scheme 2



Since the computed Fermi contact coupling constants were small in magnitude, the non-Fermi contact contributions to the ${}^2J_{COC}$ interaction were investigated. These terms are less sensitive to the inclusion of electron correlation effects and were recovered at the Hartree−Fock level using the Dalton program.[19] For dimethyl ether, the non-Fermi contact term was −0.4 Hz for the equilibrium structure, dominated by the paramagnetic spin−orbit contribution. Opening or closing the COC bond angle gave less negative non-Fermi contact terms but the changes were very small (~0.01 Hz). The non-Fermi contact contributions to ${}^2J_{COC}$ in **3** were also small (for **3** 60S, ∠COC = 116.9° and ${}^2J_{COC}$ = −0.3 Hz) and were essentially unaffected by bond angle (for **3** AP, ∠COC = 120.1° and ${}^2J_{COC}$ = −0.3 Hz).

These results have important implications for ${}^2J_{COC}$ as conformational constraints in oligosaccharides. ${}^2J_{COC}$ across *O*-glycosidic linkages is subject to a first-order effect from ϕ and a second-order effect from the COC bond angle (Scheme 2). These couplings can be used to constrain the ϕ torsion angle, since no coupling is expected in one ϕ rotamer whereas negative values of similar magnitude and sign (~ −2 Hz) are expected in the remaining two.[3a,d] One of the latter two is expected to be preferred based on the exoanomeric effect,[15] and this assignment can be established independently via ${}^3J_{COCC}$ and ${}^3J_{COCH}$ analysis.[3d] Efforts are underway to test experimentally these predicted dependencies of ${}^2J_{COC}$ on molecular structure in oligosaccharides.

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Supporting Information Available: Two tables containing calculated ${}^2J_{COC}$ in geometrically optimized **1**−**4** and in ψ-constrained **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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