Direct Assignment of the Relative Configuration in Acyclic 1,3-Diols by $^1$H NMR Spectroscopy

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ABSTRACT

Using an operationally simple deuterium isotopic perturbation method, the relative configuration of 1,3-diols can be determined directly using $^1$H NMR spectroscopy. A comparison of the OH chemical shifts for OH/OH and OH/OD isotopomers provides a reliable assessment of the relative configuration of the diol; anti-1,3-diols within polyacetate and polypropionate frameworks have upfield isotope shifts of 2−16 ppb, whereas syn-1,3-diols show upfield isotope shifts of 20−33 ppb.

Elucidation of the relative configuration of 1,3-diols is of particular interest due to the prominence of this motif within many classes of natural products. The commonly used [13C]-acetonide method allows the relative configuration of such 1,3-diols to be assigned reliably, albeit indirectly, as the diol must first be transformed into the corresponding acetonide. Another approach, using a systematic analysis of backbone 13C NMR resonances, can be used to determine relative and absolute configuration in underivatized polyhydroxylated systems. Herein, we report an operationally simple $^1$H NMR method for assigning the relative configuration of 1,3-diols within polyacetate and polypropionate frameworks without the need for derivatization.

A typical experiment is shown in Figure 1. For the method to work, nonaggregated diol species with sharp OH NMR resonances are required. Both conditions are readily met by using a dilute solution of 1,3-diol (1 mg/mL in CD2Cl2). Using vapor pressure osmometry, we were able to show that syn- and anti-2,4-pentanediol are monomeric in CH2Cl2 under...
conditions similar to the NMR studies reported here. A dilute solution is also helpful in suppressing line broadening due to intermolecular proton exchange of diols and residual water. However, OH line broadening can still be a problem in dilute solutions if adventitious acids catalyze proton exchange. By adding a small quantity of neutral alumina directly to the NMR tube, these exchange catalysts can be conveniently sequestered, resulting in the observation of sharp OH resonances. Partial deuteration of the hydroxyl groups with sub-microliter quantities of CD$_3$OD then causes new upfield OH resonances to emerge. These new peaks arise from the monodeuterated (OH/OD) diol species. The difference in chemical shift between the original OH/OH signal and the new OH/OD resonance is measured in parts per billion (ppb) and reported as the six-bond isotope shift. Isotope shifts within acyclic systems of variable relative configuration are listed in Table 1 and were found to correlate well with the relative configuration of 1,3-diols contained within these common motifs.

In an attempt to establish a trend in the observed isotope shifts within acyclic systems of variable relative configuration, a series of polypropionate diols were synthesized utilizing a variation of Kishi’s protocol. These compounds, along with several polyacetate diols, were subjected to isotopic perturbation experiments. The observed isotope shifts are listed in Table 1 and were found to correlate well with diol relative configuration. In the case of anti-1,3-diols, small isotope shifts, on the order of 2–16 ppb, were observed (compounds 1–4). Conversely, large isotope shifts, 20–33 ppb, were observed for syn-1,3-diols (compounds 5–9). The large difference in $\delta$ allows unambiguous assignment of the relative configuration of 1,3-diols contained within these common motifs. In general, different substitution patterns are well-tolerated by this method, although the relative configuration of the 2-methyl group of polypropionates cannot be distinguished (compare compounds 6 and 8). In addition, this method correctly predicts the relative configuration of alkyn-substituted diol 2; something not easily achieved using the $^{13}$C-acetonide method.

The origin of the NMR isotope effect is a heavy-atom perturbation of the intramolecular hydrogen bond equilibrium (Figure 2). Such effects are well-known in the carbohydrate literature where the method is referred to as Secondary Isotope Multiplets of Partially Labeled Entities (SIMPLE) NMR. In a nonpolar solvent such as CD$_2$Cl$_2$, the OD group of an OH/OD pair has a slight preference for the bridging position of the intramolecular hydrogen bond. This preference derives from the zero-point vibrational energy stabilization associated with the difference in the inner versus

<table>
<thead>
<tr>
<th>compound</th>
<th>1,3-diol</th>
<th>observed isotope shifts (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Hex</td>
<td>-3.7</td>
</tr>
<tr>
<td>2</td>
<td>n-Hex</td>
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<td>3</td>
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<td>5</td>
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<tr>
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<td>7</td>
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<td>8</td>
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<td>-25.2</td>
</tr>
<tr>
<td>10</td>
<td>n-Hex</td>
<td>-4.8</td>
</tr>
</tbody>
</table>

*Conditions: 400 MHz $^1$H NMR, 2.2–5.8 mM in CD$_2$Cl$_2$, 5–10 mg neutral alumina, 19 °C.

(6) SIMPLE NMR has been used to study intramolecular hydrogen bonding in the macrocyclic bafilomycin A1 in CD$_2$Cl$_2$, see: Everett, J. R. J. Am. Chem. Soc., Chem. Commun. 1987, 1878–1880.
outer OH torsional frequencies.\textsuperscript{11,15} Perturbation of the equilibrium results in a new upfield $^1$H signal for the OH group of the OH/OD isotopomer, which favors the exterior and more shielded position.

In general, differences in $^6 \Delta$ between stereoisomers likely arise from a combination of effects, including: the limiting chemical shifts ($\delta_{in}$ vs $\delta_{out}$) of each species, the intrinsic strength of the intramolecular hydrogen bond in each conformer, and the percentage of intramolecular hydrogen bonded species present. The substituents of syn-1,3-diols are expected to reinforce a hydrogen bonding conformation more than the corresponding anti isomer (Figure 3).\textsuperscript{16} As these factors are variable, the $^6 \Delta$ of the two OH groups in a given diol can differ. However, the $^6 \Delta$ ranges for syn and anti-diols are sufficiently differentiated to allow reliable stereochemical assignments to be made by inspection.

For this method to work reliably, some attention to sample preparation is required. For example, if the sample is too concentrated, intermolecular hydrogen bonding can cause downfield isotope shifts to occur when the sample is partially deuterated. In addition, the magnitude of the isotope shifts are strongly solvent dependent, with aromatic solvents such as benzene-$d_6$ tending to magnify the observed isotope shifts relative to a solvent like CD$_2$Cl$_2$.\textsuperscript{17} In our studies, CD$_2$Cl$_2$ had the advantage of placing the hydroxyl group resonances downfield of those arising from saturated alkyl groups. In benzene-$d_6$ the hydroxyl signals were observed to shift to higher field and overlap with saturated C–H resonances.\textsuperscript{17}

In addition, sharp OH resonances were generally achieved more easily in CD$_2$Cl$_2$. One other complicating factor is the presence of proximal hydrogen bond donor or acceptor groups. Such groups can bias the equilibrium or affect the limiting chemical shifts shown in Figure 2. Although the ramifications of these proximity effects remain to be explored, we feel that the method is of predictive value for isolated diol units in natural products and synthetic intermediates.

Using this isotopic perturbation method, the relative configuration of isolated 1,3-diols can be determined directly using conventional $^1$H NMR spectroscopy. This method has the advantage that no chemical modification is required prior to analysis, only a small amount of material ($<1$ mg) is necessary to achieve useful data, and the compound can be recovered unchanged at the completion of the experiments.

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**Supporting Information Available:** Experimental procedure and spectra for NMR measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

\textsuperscript{15} For a theoretical study of this effect in the water dimer, see: Scheiner, S.; Cuma, M. J. Am. Chem. Soc. 1996, 118, 1511–1521.

\textsuperscript{16} The amount of intramolecular hydrogen bonding is thought to be greater in syn-2,4-pentanediol than in the anti-isomer in CD$_2$Cl$_2$ at 40 °C; see: Fukuroi, T.; Fujiwara, Y.; Fujiwara, S.; Fujii, K. Anal. Chem. 1968, 40, 879–889.

\textsuperscript{17} The hydroxyl resonances of diol 1 were observed at 1.62 and 1.88 ppm in benzene-$d_6$ and 2.09 and 2.17 ppm in CD$_2$Cl$_2$. 

Figure 2. Theoretical model for negative equilibrium isotope effects.

Figure 3. Hydrogen bonding conformations for syn- and anti-1,3-diols.