

# Direct Assignment of the Relative Configuration in Acyclic 1,3-Diols by $^1\text{H}$ NMR Spectroscopy

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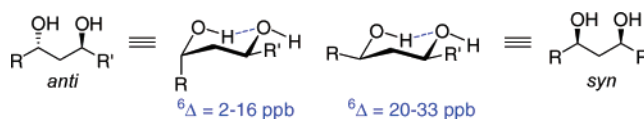
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Received October 20, 2005

## ABSTRACT

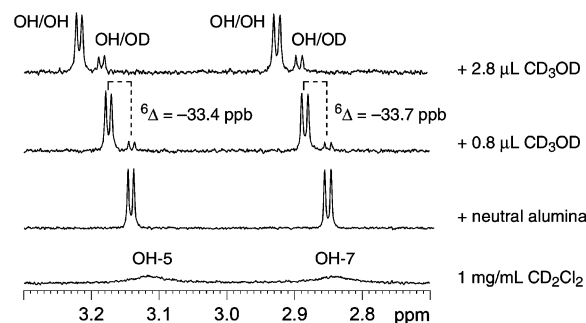


Using an operationally simple deuterium isotopic perturbation method, the relative configuration of 1,3-diols can be determined directly using  $^1\text{H}$  NMR spectroscopy. A comparison of the OH chemical shifts for OH/OH and OH/OD isotopomers provides a reliable assessment of the relative configuration 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  $^{13}\text{C}$ -acetone 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 acetone.<sup>1</sup> Another approach, using a systematic analysis of backbone  $^{13}\text{C}$  NMR resonances, can be used to determine relative and absolute configuration in underivatized polyhydroxylated systems.<sup>2</sup> Herein, we report an operationally simple  $^1\text{H}$  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  $\text{CD}_2\text{Cl}_2$ ).<sup>3</sup>

Using vapor pressure osmometry, we were able to show that *syn*- and *anti*-2,4-pentanediol are monomeric in  $\text{CH}_2\text{Cl}_2$  under



**Figure 1.**  $^1\text{H}$  NMR (400 MHz) spectra showing the OH resonances of diol **7** (2.2 mM in  $\text{CD}_2\text{Cl}_2$ ) resolving into sharp doublets ( $^3J_{\text{H-O-C-H}}$ ) after addition of neutral alumina. Upon addition of  $\text{CD}_3\text{OD}$ , new upfield OH doublets, due to OH/OD species, appear and all OH resonances shift downfield as a consequence of intermolecular hydrogen bonding between the diol and methanol.

(1) (a) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9–17. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100. (c) Rychnovsky, S. D.; Skaltzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948.

(2) Kishi, Y. *Tetrahedron* **2002**, *58*, 6239–6258.

conditions similar to the NMR studies reported here.<sup>4</sup> A dilute solution is also helpful in suppressing line broadening due to intermolecular proton exchange among 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<sub>3</sub>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<sup>5</sup> ( $^6\Delta$ ) equilibrium isotope shift.  $^6\Delta$  is assigned as a negative value because the isotope shift is upfield ( $^6\Delta = \delta_{\text{OH/OD}} - \delta_{\text{OH/OH}}$ ). In the case of *syn*-propionate **7**, the isotope shifts are on the order of –33 ppb for each hydroxyl group and are clearly visible on a 400 MHz <sup>1</sup>H NMR spectrum (Figure 1).

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.<sup>6,7</sup> 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  $^6\Delta$  allows unambiguous assignment of the relative configuration of 1,3-diols contained within these common motifs.<sup>8</sup> 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 alkyne-substituted diol **2**; something not easily achieved using the [<sup>13</sup>C]-acetanide method.<sup>1a</sup> It is also useful to note that primary 1,3-diol **10** resulted in equilibrium isotope shifts of a similar magnitude to *anti*-1,3-diols.

The origin of the NMR isotope effect is a heavy-atom perturbation of the intramolecular hydrogen bond equilibrium (Figure 2).<sup>8–12</sup> Such effects are well-known in the carbohy-

**Table 1.** Observed Equilibrium Isotope Shifts for Various 1,3-Diols

compound	1,3-diol	observed isotope shifts ( $^6\Delta$ , ppb)	
		downfield OH	upfield OH
1		–3.7	–3.5
2		–10.0	–3.6
3		–11.7	–2.8
4		–15.7	–10.4
5		–27.2	–30.7
6		–27.1	–23.4
7		–33.4	–33.7
8		–25.1	–20.7
9		–25.2	–25.1
10		–4.8	–4.0

<sup>a</sup> Conditions: 400 MHz <sup>1</sup>H NMR, 2.2–5.8 mM in CD<sub>2</sub>Cl<sub>2</sub>, 5–10 mg neutral alumina, 19 °C.

drate literature where the method is referred to as Secondary Isotope Multiplets of Partially Labeled Entities (SIMPLE) NMR.<sup>13,14</sup> In a nonpolar solvent such as CD<sub>2</sub>Cl<sub>2</sub>, 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

(3) 1 mg/mL = 2.2–5.8 mM depending on diol structure.

(4) Osmometry studies were performed at a concentration of 10–20 mM (CH<sub>2</sub>Cl<sub>2</sub>, 32 °C) using a Gonotec Osmomat 070 osmometer (MW<sub>obs</sub> = 110 ± 10 for *syn*-2,4-pentanediol; MW<sub>obs</sub> = 111 ± 10 for *anti*-2,4-pentanediol; formula weight = 104).

(5) Six covalent bonds separate the hydrogen and deuterium of the OH/OD pair.

(6) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177–2180.

(7) The relative configuration of each polypropionate diol was confirmed by comparison of the <sup>13</sup>C NMR spectrum in CD<sub>3</sub>OD to that reported in ref 6.

(8) The isotope shift for *anti*-2,4-pentanediol (–6 ppb, CD<sub>2</sub>Cl<sub>2</sub>; –8 ppb, benzene-*d*<sub>6</sub>) is also smaller than that for *syn*-2,4-pentanediol (–30 ppb, CD<sub>2</sub>Cl<sub>2</sub>; –38 ppb, benzene-*d*<sub>6</sub>), see: Vasquez, Jr., T. E.; Bergset, J. M.; Fierman, M. B.; Nelson, A.; Roth, J.; Khan, S. I.; O'Leary, D. J. *J. Am. Chem. Soc.* **2002**, *124*, 2931–2938.

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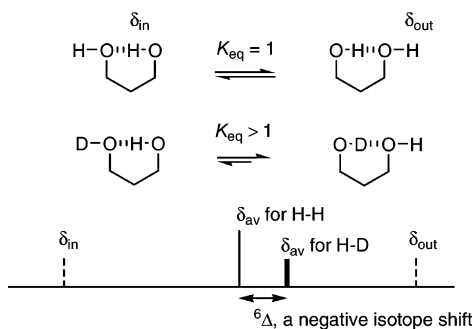
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(12) For a review, see: Bolvig, S.; Hansen, P. E. *Curr. Org. Chem.* **2000**, *4*, 19–54.

(13) For representative studies, see: (a) Lemieux, R. U.; Bock, K. *Jpn. J. Antibiot.* **1979**, *32*, S163–S177. (b) Christofides, J. C.; Davies, D. B. *J. Am. Chem. Soc.* **1983**, *105*, 5099–5105.

(14) SIMPLE NMR has been used to study intramolecular hydrogen bonding in the macrolide bafilomycin A<sub>1</sub> in CDCl<sub>3</sub>, see: Everett, J. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1878–1880.

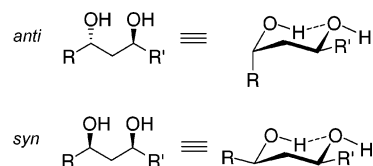


**Figure 2.** Theoretical model for negative equilibrium isotope effects.

outer OH torsional frequencies.<sup>11,15</sup> Perturbation of the equilibrium results in a new upfield  $^1\text{H}$  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 ( $\delta_{\text{in}}$  vs  $\delta_{\text{out}}$ ) 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).<sup>16</sup> 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  $\text{CD}_2\text{Cl}_2$ .<sup>8</sup> In our studies,  $\text{CD}_2\text{Cl}_2$  had the advantage of placing the hydroxyl group resonances



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

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.<sup>17</sup> In addition, sharp OH resonances were generally achieved more easily in  $\text{CD}_2\text{Cl}_2$ . 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  $^1\text{H}$  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.

**Acknowledgment.** Work at Pomona College was supported by the Camille and Henry Dreyfus Scholar/Fellow Program for Undergraduate Institutions and the National Science Foundation. A number of the diols were prepared at UC-Irvine with the support of the NIGMS (GM-43854). We thank Professor Yoshito Kishi (Harvard University) for providing a polypropionate sample and Tom Vasquez (Pomona College) for performing preliminary studies related to the work reported here.

**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>.

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(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.

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

(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  $\text{CD}_2\text{Cl}_2$ .