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Toward the Creation of NMR Databases in Chiral Solvents for Assignments of Relative and Absolute Stereochemistry: NMR Desymmetrization of Meso Compounds

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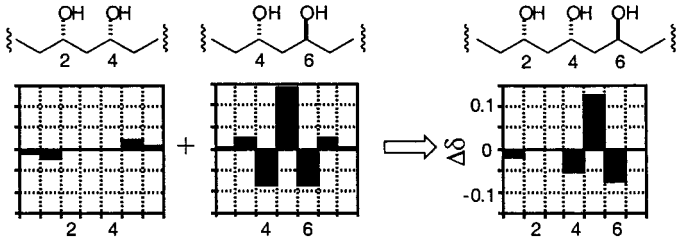
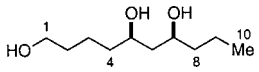
ABSTRACT



Examples of ^{13}C NMR desymmetrization of meso compounds are presented. On analysis of the NMR profiles of 1,3-diols, the additivity is recognized to predict the NMR profiles of 1,3,5-tirols.

During the studies of a 1,3-diol NMR database in a chiral solvent, we noticed that the C.4 and C.8 carbons of *syn*-1,3-diol **1** exhibited small but definite differences in chemical shift when collected in (*R*)- and (*S*)-DMBA (*N*,α-dimethylbenzylamine).[1] This is a remarkable and intriguing observation, particularly when one recognizes the meso nature of the C.4−C.8 moiety of **1**. To the best of our knowledge, there is only one known example of NMR desymmetrization of meso compounds in a chiral solvent.[2] In this Letter, we report examples of ^{13}C NMR desymmetrization of meso compounds. We also present examples of the additive nature of the NMR profiles of *syn*- and *anti*-1,3-diols, resulting in predictable NMR profiles of 1,3,5-triols.



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Considering the ^{13}C NMR desymmetrization observed for the meso portion of **1**, we first studied meso *syn*-1,3-diol **2a** and optically active *anti*-1,3-diol **2b** in (*R*)- and (*S*)-DMBA.[3] As shown in the graphs in Figure 1, *anti*-1,3-diol **2b** showed a ^{13}C NMR profile similar to that of the examples given in the preceding Letter.[1] As anticipated, meso *syn*-1,3-diol **2a** indeed exhibited clear NMR desymmetrization of the C.3 and C.2 carbons from the C.7 and C.8 carbons in (*R*)- and (*S*)-DMBA. We also tested meso *syn*-1,3-diol **3a** and optically active *anti*-1,3-diol **3b** (Figure 1). Once again, *anti*-1,3-diol **3b** gave the expected NMR profile for the central

(1) Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2249−2252.

(2) The methine protons of meso dimethyl 2,3-diaminosuccinate were observed as an AB system in chiral 2,2,2-trifluorophenylethanol: Kainosho, M.; Ajisaka, K.; Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1972**, *94*, 5924−5926.

(3) A Varian Mercury 400 spectrometer (100 MHz) was used to collect all the NMR database data in DMBA, with acetone-d_6 as an external reference (δ 29.8) and a lock-signal and with readout of NMR spectra being adjusted to 0.001 ppm/point (sw = 23980.8, fn = 524288).

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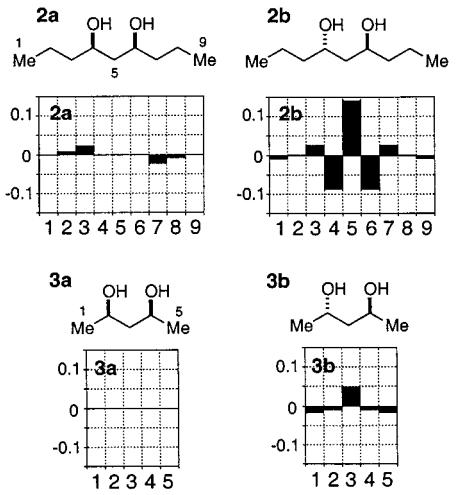

Figure 1. Carbon chemical shift differences of **2a**,**b** and **3a**,**b** between (*R*)- and (*S*)-DMBA. The *x*- and *y*-axes represent carbon number and $\delta_R - \delta_S$ in ppm, respectively, for all the charts in this Letter.

carbon, but the chemical shift difference ($\Delta\delta = \delta_R - \delta_S$) was significantly smaller than that observed for *anti*-1,3-diol **2b**. Interestingly, meso *syn*-1,3-diol **3a** showed no sign of ^{13}C NMR desymmetrization. The difference observed between **2a** and **3a**, as well as **2b** and **3b**, may be related to their conformational preference; the carbon backbone of **2a** is expected to adopt a more pronounced extended conformation than that of **3a**, and **2a** provides a better platform for desymmetrization by the chiral solvent.[4]

Naturally, we were interested in examining the NMR behaviors of other types of meso compounds and selected two additional types of substrates: (1) meso 1,2- and 1,4-diols and (2) meso 1,3,5-triols. On the basis of the difference observed between **2a** and **3a**, we chose **4** and **5** as representative of 1,2- and 1,4-diols, respectively. As shown in the graphs in Figure 2, a small but definite desymmetri-

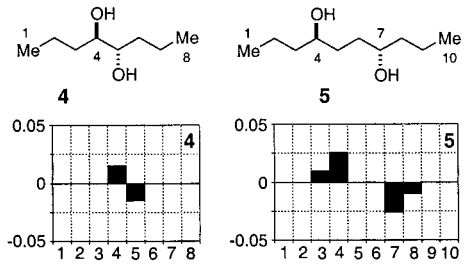

Figure 2. Carbon chemical shift differences of **4** and **5** between (*R*)- and (*S*)-DMBA.

zation was once again detected for both **4** and **5**.

Similarly, meso *syn*,*syn*-1,3,5-triol **6a** and meso *anti*,*anti*-1,3,5-triol **6b**, as well as optically active *syn*,*anti*-1,3,5-triol **6c**, were subjected to ^{13}C NMR studies in (*R*)- and (*S*)-DMBA, yielding the NMR profiles summarized in Figure 3. It was not surprising now to see desymmetrization of meso

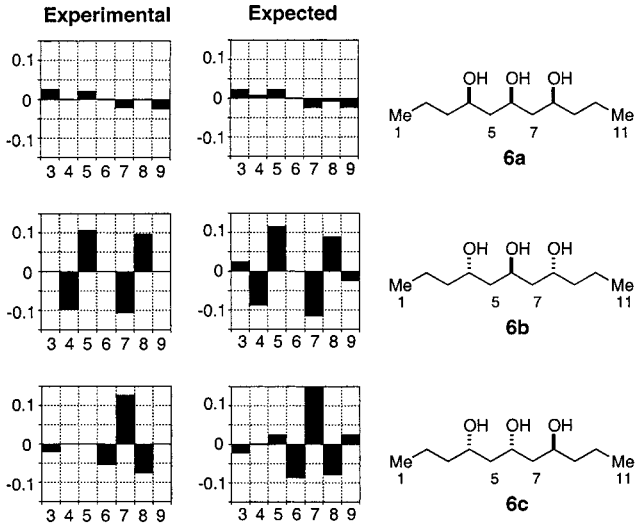

Figure 3. Experimental and expected carbon chemical shift differences of **6a**−**c** between (*R*)- and (*S*)-DMBA.

1,3,5-triols **6a** and **6b** by the chiral solvent. However, the magnitude of desymmetrization detected for meso *anti*,*anti*-1,3,5-triol **6b** seemed, at least at the first glance, to be unrealistically large.

Structurally, the meso 1,3,5-triol **6a** is composed of two *syn*-1,3-diol units, whereas the meso 1,3,5-triol **6b** is composed of two *anti*-1,3-diol units. If we assume that recognition by (*R*)- and (*S*)-DMBA primarily relies on the 1,3-diol substructure, the pattern of desymmetrization of **6a** and **6b** might be correlated with the NMR profile of meso *syn*-1,3-diol **2a** and optically active *anti*-1,3-diol **2b**. Figure 3 shows an exercise of adding the NMR profile of **2a** and/or **2b** to that of **2a** and/or **2b** and comparing the resultant composite profile with the profile experimentally obtained for **6a**−**c** in (*R*)- and (*S*)-DMBA. The resultant profiles undeniably demonstrate the presence of additivity.[5,6]

The remarkable additivity recognized suggests a possible mode for discrimination of the absolute configuration by (*R*)- or (*S*)-DMBA; the chiral solvent recognizes, at first approximation, one 1,3-diol structural motif separate from the adjacent 1,3-diol structural motif. The following experimental results indicate that the presence of a bidentate structural motif in a substrate is important for effective recognition. First, discrimination of enantiomers by (*R*)- or (*S*)-DMBA should, in principle, be possible for a substrate with a single stereogenic center, and we tested a variety of secondary

(4) Interestingly, the chemical shift differences were significantly amplified with the introduction of a methyl group with *anti*-orientation at the central carbon.[1]

(5) Additivity in increments was recognized for the chemical shifts of the central carbon of 1,3,5-triol in DMSO: Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562−2571.

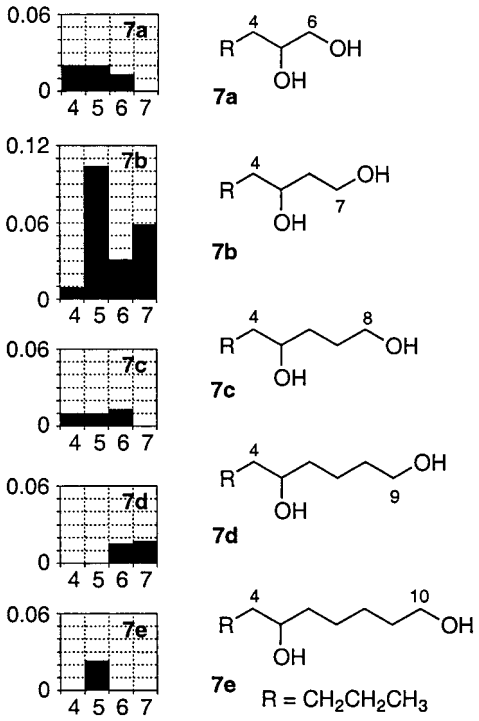

Figure 4. Carbon chemical shift differences ($|\Delta\delta|$) of **7a**−**e** between (*R*)- and (*S*)-DMBA.

alcohols but with a limited success.[7] Second, if a bidentate structural motif is involved in the recognition event, one would expect the effectiveness of discrimination to be a function of the proximity between the two functional groups. Figure 4 summarizes the chiral discrimination of primary/secondary diols **7a**−**e**, demonstrating the importance of the proximity between the two hydroxyl groups. In this context, we expect that a chiral NMR solvent with more than one functional group may offer unique and different potentials.[8]

In summary, examples of ^{13}C NMR desymmetrization of meso compounds have been presented. On comparison of the data of *syn*- and *anti*-1,3-diols **2a**,**b** with that of *syn*,*syn*-, *anti*,*anti*-, and *syn*,*anti*-triols **6a**−**c**, the additivity of NMR profiles was recognized. Through these studies, a possible mode was suggested for recognition by a chiral NMR solvent, in which a bidentate structural motif plays an important role in effective desymmetrization.

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Supporting Information Available: NMR databases of **2a**,**b**, **3a**,**b**, **4**, **5**, **6a**−**c**, and **7a**−**e** in (*R*)- and (*S*)-DMBA. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) In adding the NMR profile of **2a** to that of **2b** to predict the NMR profile of **6c**, there is another combination, i.e., addition of the opposite sign of $\Delta\delta$ ($\delta_R - \delta_S$) of **2a** to that of **2b**. Because of the meso nature of **2a**, the absolute NMR profile of **2a** in the chiral solvent is not established. However, taking account of the NMR profile observed for the *syn*-1,3-diol portion of **1**, we chose the combination shown in Figure 3.

(7) A number of substrates with only one stereogenic center, but no additional functional group, were tested. Chiral discrimination by (*R*)- and (*S*)-DMBA was observed for PhCH(OH)Me, PhCH(Me)CH_2OH, *t*-BuCH(OH)Me, and *n*-BuC(OH)(Me)Ph but not for *i*-BuCH(OH)Me and *n*-BuCH(OH)Me.

(8) Promising preliminary results were observed for several multidentate chiral solvents, including **i**−**v**.