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Application of chiral bidentate NMR solvents for assignment of the absolute configuration of alcohols: scope and limitation

Yoshihisa Kobayashi, Nobuyuki Hayashi and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, MA 02138, USA

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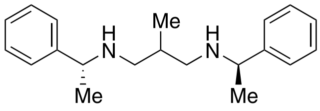
Abstract—The ^{13}C NMR behaviors of several cyclic and biaryl secondary alcohols as well as acyclic tertiary alcohols have been studied in the chiral bidentate NMR solvent BMBA-*p*-Me (**1**). An empirical rule has been advanced to correlate the absolute configuration of each type of alcohols with the ^{13}C chemical shift behaviors in (*R*,*R*)- and (*S*,*S*)-BMBA-*p*-Me.

As recently reported from our laboratory,[1–4] the absolute configuration of acyclic secondary alcohols can be determined from analysis of their ^{13}C NMR behaviors in chiral bidentate solvents such as BMBA-*p*-Me (**1**). The ^{13}C chemical shifts observed for various acyclic secondary alcohols in (*R*,*R*)-**1** and (*S*,*S*)-**1** exhibited a consistent relationship between their absolute configuration and the sign of $\Delta\delta_{RR-SS}$ ($\delta_{(R,R)\text{-}\mathbf{1}}-\delta_{(S,S)\text{-}\mathbf{1}}$) for the α carbons adjacent to the hydroxymethine unit as formulated in Figure 1A. It is worth noting that: (1) an assignment of the absolute configuration by this approach is accomplished without any derivatization/degradation work; (2) an analysis of two or more hydroxymethine units present in one substrate can be performed not only simultaneously, but also independently. To further explore the scope and limitation of this new approach, we have studied the ^{13}C NMR behaviors of additional types of alcohols, including cyclic and biaryl secondary alcohols, as well as tertiary alcohols.

First, the optically active cyclic secondary alcohols **2**–**5** were investigated (Fig. 2).[5] Primarily due to their conformational rigidity, NMR information, i.e. vicinal spin-coupling constants and NOE, is usually sufficient to deduce the relative stereochemistry of such cyclic alcohols. However, conventional NMR studies on intact substrates do not yield the information to assign their absolute configuration. For this purpose, it is required to perform additional experiments; one of the commonly used methods involves NMR analyses of



1: (*R*,*R*)-BMBA-*p*-Me

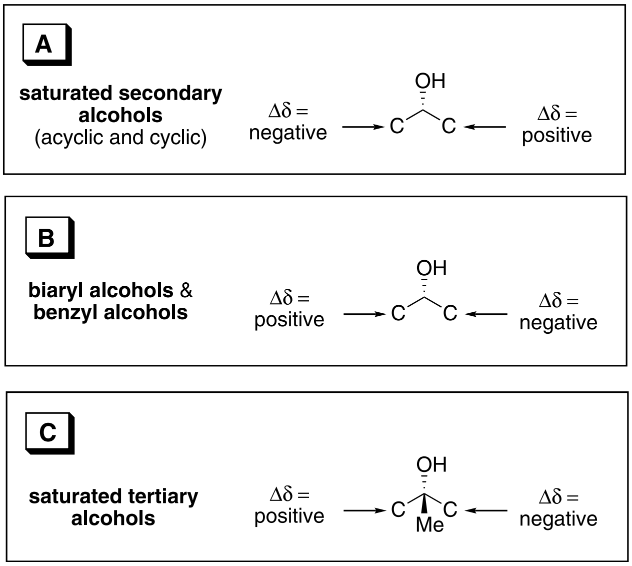


Figure 1. Relationship between the absolute configuration of alcohols and the sign of Δδ in the chiral bidentate NMR solvent BMBA-*p*-Me (**1**): $\Delta\delta=\delta_{(R,R)\text{-}\mathbf{1}}-\delta_{(S,S)\text{-}\mathbf{1}}$.

Keywords: absolute configuration; chiral NMR solvent; NMR database.

* Corresponding author. Tel.: +1-617-495-4679; fax: +1-617-495-5150; e-mail: kishi@chemistry.harvard.edu

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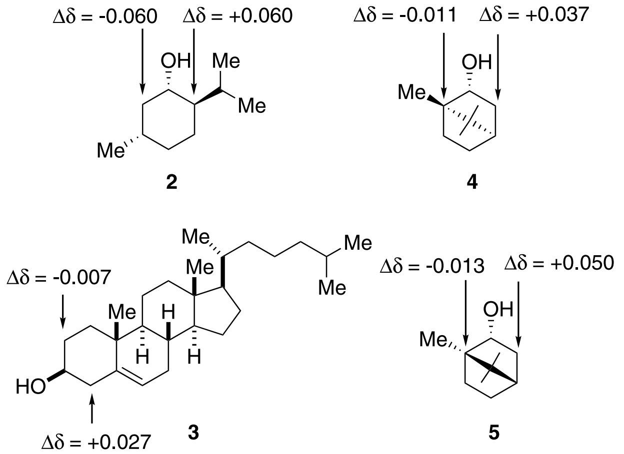

Figure 2. The behavior of the ^{13}C NMR chemical shifts of the cyclic secondary alcohols **2**–**5** in the chiral NMR solvent BMBA-*p*-Me (**1**): $\Delta\delta = \delta_{(R,R)\text{-}\mathbf{1}} - \delta_{(S,S)\text{-}\mathbf{1}}$, in ppm.

suitable chiral derivatives such as Mosher esters.[6–8] In this connection, we were interested in extending the chiral-NMR-solvent approach to cyclic secondary alcohols and first studied (+)-menthol (**2**) and cholesterol (**3**), both incorporating an equatorial hydroxyl group in a six-membered ring. The differences (Δδ) for the α carbons adjacent to the hydroxymethine unit of **2** and **3** exhibited the same behavior as the Δδ's of acyclic secondary alcohols. Interestingly, even the bicyclic *exo*- and *endo*-alcohols (−)-isoborneol[9] (**4**) and (−)-borneol (**5**) showed the same behavior, thereby demonstrating that the empirical rule formulated for acyclic secondary alcohols (Fig. 1A) can directly be extended to cyclic secondary alcohols.

Subsequently, we studied biaryl alcohols.[10–12] The desymmetrization of the enantiotopic carbons of benzhydrol (**6**) in BMBA-*p*-Me (**1**) encouraged us to synthesize and examine the optically active biaryl compounds **7**–**10** (Fig. 3).[13–16] The magnitudes of Δδ for the α carbons of **7**–**10** were found to be similar to those for isolated acyclic secondary alcohols, but, surprisingly, their signs were found to be opposite. This trend was consistently observed for biaryl alcohols bearing an electron-donating or -withdrawing substituent. Furthermore, the same trend was observed for the optically active secondary benzyl alcohol **11**. Based on these examples, we suggest an empirical rule (Fig. 1B) to correlate the signs of Δδ's in BMBA-*p*-Me (**1**) with the absolute configuration of biaryl and benzyl alcohols.

Lastly, we focused on the ^{13}C NMR behaviors of tertiary alcohols in (*R*,*R*)-**1** and (*S*,*S*)-**1**, with the hope that the current approach can be extended for determination of their absolute configuration.[17,18] Promise of this approach was immediately seen from the desymmetrization experiment on the tertiary alcohol **12**; the enantiotopic α carbons of **12** exhibited a Δδ of 0.026 ppm in BMBA-*p*-Me (**1**) (Fig. 4). Encouraged by this observation, we synthesized and studied the three optically active alcohols **13**–**15**.[19–23] Again, the magnitudes of Δδ for the α carbons of **13**–**15** were found to be similar to those for isolated acyclic secondary alcohols, but their signs were found to be opposite. Based on the three examples, we suggest an empirical rule (Fig. 1C) to correlate the signs of Δδ's in BMBA-*p*-Me (**1**) with the absolute configuration of tertiary alcohols.

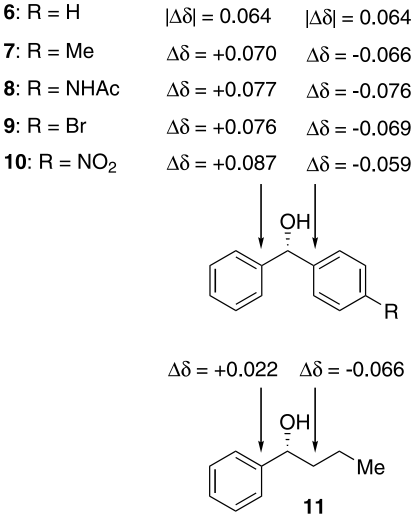

Figure 3. The behavior of the ^{13}C NMR chemical shifts of the biaryl alcohols **6**–**10** and the benzyl alcohol **11** in the chiral NMR solvent BMBA-*p*-Me (**1**): $\Delta\delta = \delta_{(R,R)\text{-}\mathbf{1}} - \delta_{(S,S)\text{-}\mathbf{1}}$, in ppm.

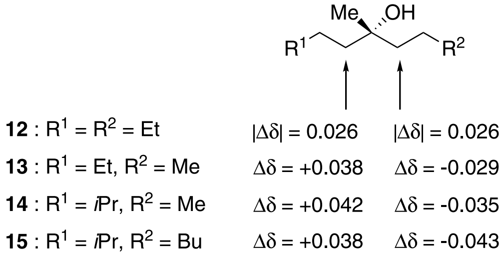

Figure 4. The behavior of the ^{13}C NMR chemical shifts of the acyclic tertiary alcohols **12**–**15** in the chiral NMR solvent BMBA-*p*-Me (**1**): $\Delta\delta = \delta_{(R,R)\text{-}\mathbf{1}} - \delta_{(S,S)\text{-}\mathbf{1}}$, in ppm.

In conclusion, we have studied the ^{13}C NMR behaviors of cyclic and biaryl secondary alcohols as well as acyclic tertiary alcohols in (*R*,*R*)-**1** and (*S*,*S*)-**1**. For each series of alcohols, a consistent relationship between the absolute configuration of the alcohol and the sign of Δδ was observed, which can be formulated as the empirical rule summarized in Fig. 1A–C. In our view, this empirical rule should be useful for determination of the absolute configuration of these types of alcohols without derivatization and/or degradation.

Acknowledgements

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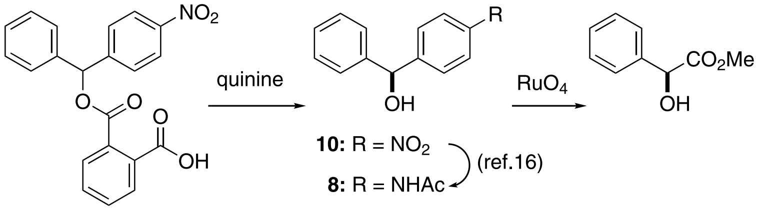

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