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Boc–phenylglycine: a chiral solvating agent for the assignment of the absolute configuration of amino alcohols and their ethers by NMR

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Abstract—The absolute configuration of β-amino alcohols and their ethers can easily be determined by comparison of the ^{1}H NMR spectra of the mixture formed by the substrate amino alcohol or amino ether plus one equivalent of (*R*)-Boc–α-phenylglycine (BPG) with that of the mixture formed by the substrate plus one equivalent of (*S*)-BPG. Several examples of known absolute configuration have been used to validate the results, which are explained in terms of the selective shielding experienced by protons of the substrate located on the complex on the same side of the phenyl group of BPG. A graphical model has been proposed in which the use of the $\Delta\delta^{RS}$ parameters for Cα–H, Cβ–H and the L group allow the direct configurational assignment from the NMR data.

1. Introduction

The assignment of the absolute configuration of mono and difunctional organic compounds, including alcohols, amines, carboxylic acids[1] and diols,[2,3] by NMR spectroscopy of their derivatives with selected auxiliary reagents is a well known and reliable procedure. This technique requires the covalent derivatization of the substrate of unknown absolute configuration with the two enantiomers of the auxiliary reagent and comparison of the NMR spectra of the resulting derivatives. In the cases of chiral secondary alcohols and primary amines, the assignment can be carried out using only one derivative with one enantiomer of the auxiliary α-methoxy-α-phenylacetic acid (MPA), either by modifying the temperature[4] or by inducing selective complexation with barium(II).[5,6] Advances have been made in this area that simplify the experimental procedures, which eliminate the need for isolation and purification steps[7] and allow the application of this methodology to the microscale level.[8] However, despite these improvements, it is clear that procedures based on the association between the substrate and a solvating agent through weak interactions, rather than covalent bonds, would represent a great breakthrough.

A practical expression of this idea was pioneered by Pirkle,[9,10] who used 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) as a chiral solvating agent (CSA) for the determination of enantiomeric purity. In a recent example,[11] TFAE was employed for the determination of the absolute configuration of α-acyloxyketones. A related methodology, which focused on the creation of NMR databases in chiral solvents, has been introduced by Kishi and co-workers. It is based on the use of bidentate solvents and the recording of ^{13}C NMR data and has recently been applied to secondary alcohols.[12,13]

In spite of these efforts, the most important limitation of this method still remains: The need to add a large excess of the expensive CSA to obtain very small chemical shift differences, makes it difficult to examine the NMR spectra as it is frequently dominated by the signals of the added agent.

Herein we report that Boc–phenylglycine[14] (BPG) is an excellent CSA[†] for the NMR assignment of the absolute configuration of β-amino alcohols and their carboethers because only one equivalent is needed to obtain a clean

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[†] Both enantiomers of Boc–phenylglycine are commercially available in pure form.

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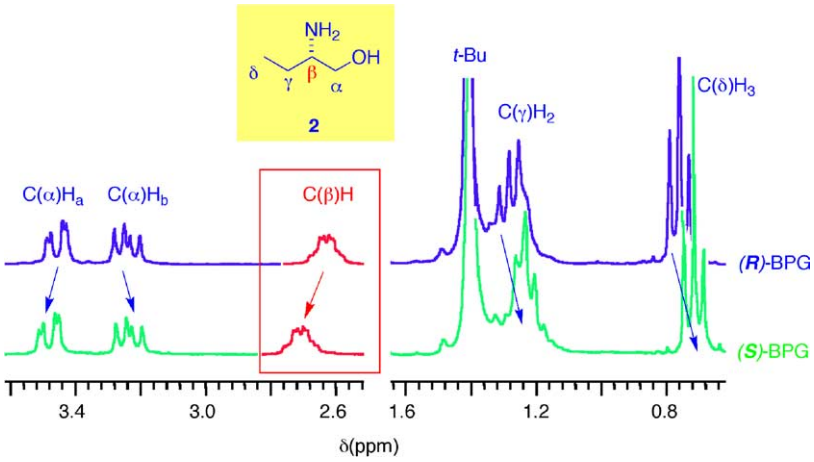

Figure 1. Partial ^{1}H NMR spectra (250 MHz) of (*S*)-2-aminobutanol **2** after the addition of 1 equiv of (*R*)-BPG and (*S*)-BPG in $CDCl_3$. The upfield and downfield shifts are highlighted.

spectrum and sufficient shift differences to distinguish between both enantiomers.

2. Results and discussion

We herein report a standard experiment that illustrates the use of this methodology: When one equivalent of (*R*)-BPG was added to an NMR tube containing (*S*)-2-aminobutanol **2** in $CDCl_3$, the resulting spectrum was compared with that obtained in a parallel experiment with (*S*)-BPG. It was observed that certain signals of substrate **2** were shifted upfield while other signals were shifted downfield. On comparing the spectrum of (*R*)-BPG/**2** to that of (*S*)-BPG/**2** (Fig. 1), it was found that the signals due to the ethyl group [$\Delta\delta^{RS} = +0.030$ and $+0.023$ for the $CH_2(\gamma)$ and $CH_3(\delta)$, respectively] and one of the diastereotopic hydrogens of the $CH_2(\alpha)$ [$\Delta\delta^{RS} = +0.010$] were shifted upfield in the latter spectrum. Signals for the other proton on the $CH_2(\alpha)$ group [$\Delta\delta^{RS} = -0.024$] and the proton at the stereogenic carbon [CH(β), $\Delta\delta^{RS} = -0.058$] shifted downfield.

This last signal (Cβ–H) is particularly important because: it is (a) easy to identify in the spectrum, (b) is generated by a hydrogen directly linked to the asymmetric carbon and (c) usually gives rise to the largest $\Delta\delta^{RS}$ values[‡] of all the protons in the substrate.

These shifts and the resulting distribution of the signs of $\Delta\delta^{RS}$ are fully consistent with an association between a substrate and a chiral solvating agent as shown in Figure 2. This involves an electrostatic interaction between the carboxylate anion and the ammonium cation, as well as hydrogen bonding between the carbamate and the hydroxyl group. In this arrangement, Cβ–H of **2** is located under the shielding cone of the BPG phenyl group when

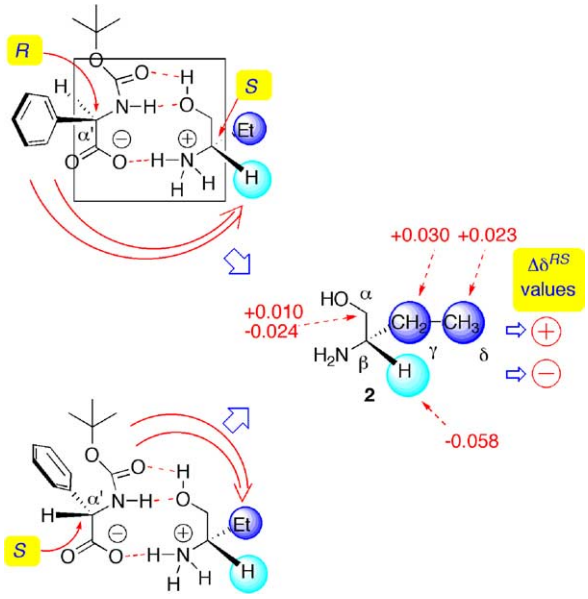

Figure 2. Association of (*R*)-BPG and (*S*)-BPG with (*S*)-2-aminobutanol **2** and experimental $\Delta\delta^{RS}$ values.

the association is formed with (*R*)-BPG, causing a measurable shielding effect on that atom. When the association takes place with the other enantiomer [(*S*)-BPG], the Cβ–H and the phenyl group are situated on opposite sides of the 'plane' defined by the interacting groups, with the shielding effect now only influencing the ethyl group.

In this way, Cβ–H of **2** resonates at a higher field in the presence of (*R*)-BPG than in the presence of (*S*)-BPG and, for the amino alcohol with this particular stereochemistry, $\Delta\delta^{RS}$ of Cβ–H has a negative value while the $\Delta\delta^{RS}$ corresponding to the ethyl group [$CH_2(\gamma)$ and $CH_3(\delta)$] are positive.

When the same experiment was carried out with (*R*)-2-aminobutanol **6**, the $\Delta\delta^{RS}$ signs were opposite to those described for the (*S*)-enantiomer. The general nature of this correlation between the NMR signals and the

[‡] $\Delta\delta^{RS}$ represents the difference between the chemical shift of a group of the amino alcohol in its spectra with (*R*)- and (*S*)-BPG $\{\Delta\delta^{RS} = \delta[(R)\text{-BPG/amino alcohol}]\text{-}\delta[(S)\text{-BPG/amino alcohol}]\}$.

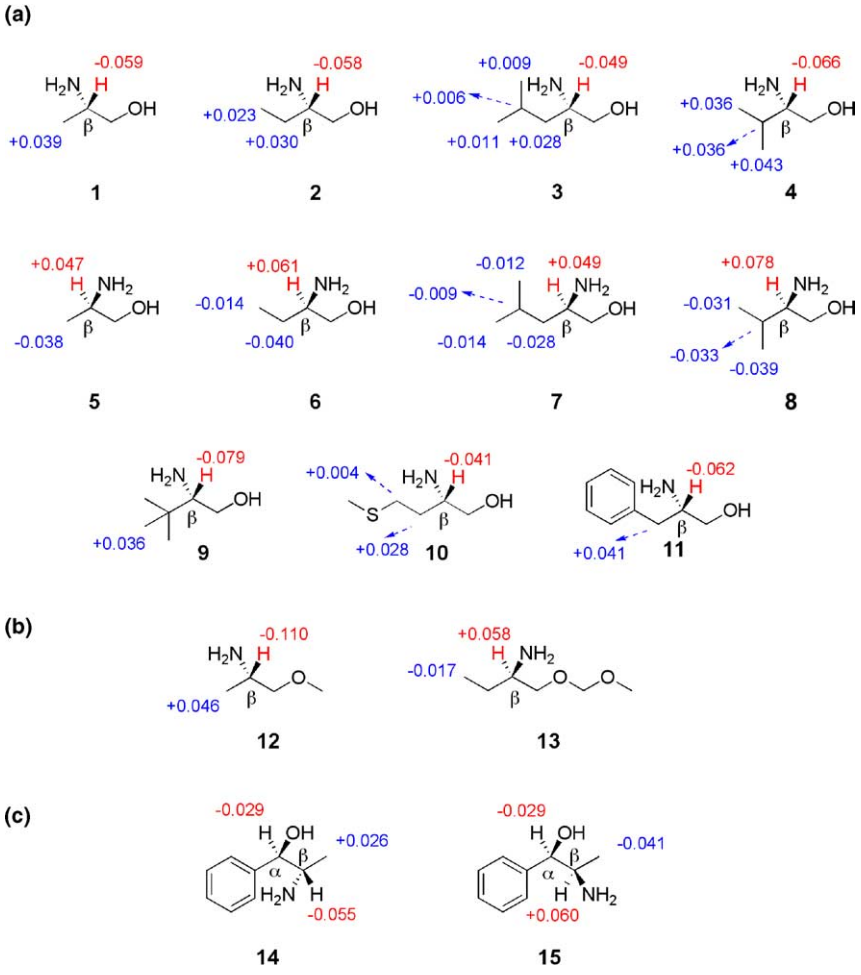

Figure 3. (a) β-Amino alcohols, (b) β-amino ethers and (c) β-amino alcohols containing two asymmetric carbons used in this study. The $\Delta\delta^{RS}$ values obtained from their spectra with (*R*)- and (*S*)-BPG are shown.[§]

absolute configuration for this class of substrates was demonstrated by studying a series of β-amino alcohols and ether derivatives of known absolute stereochemistry shown in Figure 3. This includes compounds containing a primary amino group linked to the asymmetric carbon, vicinal to a primary hydroxyl group **1**–**11** and compounds where the hydroxyl group has been replaced by its methyl and MOM ether **12** and **13**.

In all of the above cases, the addition of (*R*)- and (*S*)-BPG produced signs of $\Delta\delta^{RS}$ for the protons and groups located on the asymmetric carbons of the β-amino alcohols, (Cβ–H and L substituents), in parallel with those described for (*R*)- and (*S*)-2-aminobutanol and in accordance with the structural model shown in Figure 2. As a consequence, the signs of $\Delta\delta^{RS}$ for Cβ–H and L constitute a reliable indicator of their spatial location and can therefore be used for the determination of the absolute configuration of β-amino alcohols and their *O*-derivatives. Thus, for assignment purposes, the NMR spectra of 1:1 mixtures of (*R*-BPG/chiral amino alcohol and (*S*-BPG/chiral amino alcohol should be recorded in $CDCl_3$ with the chemical shifts of the signals due to Cβ–H and the L group measured and compared. The spatial location of the proton in question and the L group (and thus the absolute configuration) can then be deduced from the sign of $\Delta\delta^{RS}$ by application of the models shown in Figure 4a.[¶]

In order to obtain further insight into the characteristics and requirements of the association between BPG and the amino alcohols, a further set of experiments was carried out. The results of these investigations are described below.

Firstly, ^{1}H NMR titration of (*S*)-2-aminobutanol **2** with increasing amounts of (*R*)- and (*S*-BPG showed a steady increase in the magnitude of $\Delta\delta^{RS}$, which reached its maximum value when about 1 equiv of BPG was

[§] ^{1}H NMR spectra of samples **1**–**8** were recorded at 500 MHz. ^{1}H NMR spectra of samples **9**–**16** were recorded at 250 MHz. Chemical shifts (ppm) were internally referenced to the TMS signal (0 ppm) in all cases.

[¶] In a typical experiment, 19.3 mg of BPG (0.077 mmol) and 6.8 mg of (*S*)-2-aminobutanol **2** (0.077 mmol) were dissolved in 0.5 mL of $CDCl_3$ in an NMR tube.

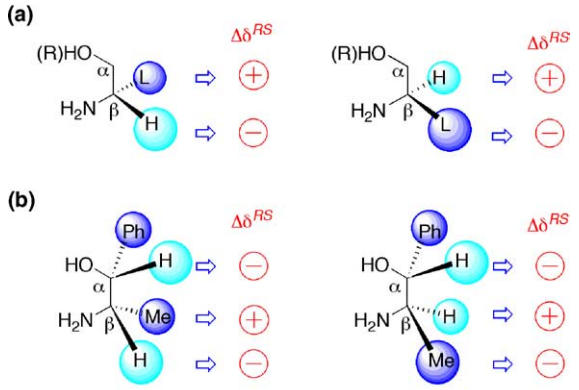

Figure 4. (a) Models for the assignment of the absolute configuration of β-amino alcohols and β-amino ethers from the $\Delta\delta^{RS}$ signs of their Cβ–H and L groups. (b) Idem for *erythro*/*threo* norephedrines, including the $\Delta\delta^{RS}$ signs for Cα–H.

added.[‖] This indicates that the stoichiometry of the association is 1:1 and that the binding constant is relatively large. Under these conditions, the resonances of Cα′–H and NH of BPG both appear as sharp doublets [$J = 6.4$ Hz in (*R*)-BPG/**2** and $J = 6.9$ Hz in (*S*)-BPG/**2**], while the same signals in BPG resonate as a doublet ($J = 5.3$ Hz, Cα′–H) and a broad doublet ($J = 5.0$ Hz, NH), indicating that BPG has adopted a different and more 'fixed' conformation in the mixture.

Further support for the participation of the carboxylic and amino groups in this association was obtained from the evolution of the ^{13}C NMR signals, which followed the expected pattern.[15,16] In this way, upon addition of the amino alcohol, the signal of the carboxylic group of BPG shifted to lower field (from 173.3, in the carboxylic acid, to 176.6 ppm, in the carboxylate anion). For its part, the carbon atoms of the amino alcohol moved upon addition of BPG, as expected from the protonation of the amino group (from 10.9 to 9.9/9.8 ppm for Cδ; from 27.4 to 23.1/22.6 ppm for Cγ; from 54.7 to 54.3/54.3 ppm for Cβ; from 66.6 to 61.7/61.3 ppm for Cα in the (*R*)/(*S*-BPG complexes, respectively).

Furthermore, in accordance with the formation of this complex, the addition of acids such as TFA to NMR samples containing either the (*R*)-BPG/**2** or the (*S*)-BPG/**2** mixtures breaks the association with the resulting spectra no longer useful for the purpose of configurational assignments.

In order to verify the application of this methodology to more complex structures, β-amino alcohols containing two asymmetric carbons (the pair of *erythro*/*threo* norephedrines **14**–**15**) were also tested. The $\Delta\delta^{RS}$ values obtained (Fig. 3c) suggest an analogous model of association to the one between BPG and the amino alcohols already shown in Figure 2. The summarized $\Delta\delta^{RS}$ signs for these systems can be found in Figure 4b.[**]

The role of other factors, such as steric effects in the formation of the association were also examined. Thus, TMS ether **16** (Fig. 5), which presents a high steric hindrance around the oxygen, did not show noticeable $\Delta\delta^{RS}$ magnitudes when submitted to the standard procedure, suggesting that the formation of the association is clearly impeded in these cases.[††]

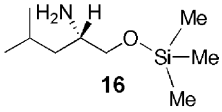

Figure 5. Sterically hindered ether employed in this study.

In conclusion, BPG is a superb CSA for the assignment of configuration by NMR of β-amino alcohols and their carboethers through complex formation in the NMR tube with $CDCl_3$ as solvent. The advantage of this method, when compared to other procedures, resides in its simplicity: derivatizations, purifications or manipulations are not necessary and only one equivalent of CSA is needed to obtain representative shifts. The solvating agent is commercially available, inexpensive and the spectrum of the resulting mixture is very clean.

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[‖] Increasing amounts of (*R*)-BPG were added to 0.077 mmol samples of (*S*)-2-aminobutanol **2** in 0.5 mL of $CDCl_3$·BPG/**2** ratios ranging from 0.25:1.00 to 3.00:1.00 were used in these experiments. The same procedure was carried out with (*S*)-BPG and the $\Delta\delta^{RS}$ values calculated.

[**] It is worth mentioning that this procedure allows us to distinguish between the four possible stereoisomers of these systems. When the enantiomers of the norephedrines **14** and **15** were examined, the opposite set of $\Delta\delta^{RS}$ signs resulted.

[††] In fact, the effect of the TMS group might be a combination of electronic and steric effects.

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