In tube determination of the absolute configuration of α- and β-hydroxy acids by NMR *via* chiral BINOL borates†

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A simple NMR methodology, through the formation of chiral BINOL borates in the NMR tube, and that reunites the advantages of chiral derivatizing (CDAs) and chiral solvating agents (CSAs), is presented for the assignment of the absolute configuration of α- and β-hydroxy acids.

The assignment of absolute configuration of organic compounds by NMR [1] has been addressed by two main different approaches, each having its own advantages and disadvantages: the use of (a) chiral derivatizing agents (CDAs) or (b) chiral solvating agents (CSAs).

CDA methods involve the derivatization of the substrate with two enantiomers‡ of the appropriate chiral auxiliary (*i.e.* MPA, MTPA, BPG, 9-AMA, 9-AHA…) and examination of the NMR spectra of the resulting diastereomeric derivatives. This route, where the substrate and auxiliary moieties are linked through a covalent bond, has been successfully applied to some mono- (alcohols, amines, carboxylic acids, cyanohydrins, thiols…) and polyfunctional compounds (diols, triols and aminoalcohols).[1] In this approach, only one chemical species is present in the NMR tube, the shifts obtained (measured as $\Delta\delta^{RS}$) are usually large, and some kind of chemical manipulation (*i.e.* isolation/purification steps) of the sample is usually necessary.

When instead of CDAs, the choice are CSAs (*i.e.* Pirkle's alcohol, BPG…),[2] their use apparently presents greater advantages because no covalent bonds have to be formed between the substrate and the auxiliary reagents, that remain associated through weak interactions (electrostatic, dipole–dipole, hydrogen bonds…). As a result, no chemical manipulations—apart from mixing the CSA and substrate in the NMR tube or in a vial—are necessary.

Unfortunately, many different associations are usually present in that mixture and therefore, the NMR spectrum reflects the complexity of the equilibria among those species, rendering difficult to establish a correlation between NMR and stereochemistry. The addition of CSA in excess may increase the concentration of the desired CSA-substrate species but often the cost is an even more complex spectrum due to the overwhelming signals of the CSA. In addition, those weak interactions lead to distances between the CSA and the substrate longer than those obtained if the linkage were a covalent bond (like CDAs) and therefore smaller induced shifts are obtained.

Other relevant structural differences between those two systems (CDA–substrate or CSA–substrate) lie in the fact that while the CDA requires only one point of linkage with the substrate (*i.e.* the carboxylic group of MPA forms an ester bond with the OH of a chiral alcohol), and therefore can be applied to monofunctional substrates, the use of a CSA involves at least two sites of interaction with the substrate, (*i.e.* OH and F in Pirkle's alcohol;[2b] BocNH and OH in BPG[2c]) that should bear in its structure the complementary functionality, producing a "rigid" complex.

Thus, the efficiency of a CDA is favoured by the existence of a short covalent bond, but limited by the rotational freedom between the CDA and the substrate moieties, while the efficiency of a CSA is favoured by the experimental simplicity but limited by the long distance between the CSA and the substrate.

In this paper we present a simple one-pot procedure for the assignment of the absolute configuration of α- and β-hydroxy acids that combine the advantages of both approaches, using covalent bonds to link the substrate and the reagent (as CDAs), but with the experimental simplicity (just mixing) of CSA procedures.

It is based on the *in situ* formation of a mixed borate between the chiral auxiliary [(*R*) or (*S*)-1,1′-binaphthalene-2,2′-diol: BINOL] and the substrate (hydroxy acid of unknown configuration), where the boron atom acts as a bridge between both structures (Fig. 1). The C_2 symmetry of the auxiliary assures that the two possible orientations in the BINOL–substrate system will have identical NMR effects on the methine proton of the hydroxy acid. The intense ring current of the naphthyl ring compensates for the distance between the substrate and the auxiliary and the rigidity of

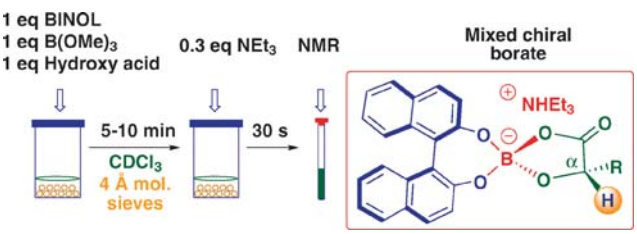

Fig. 1 Preparation of BINOL–borates of hydroxy acids for NMR spectroscopy.

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† Electronic supplementary information (ESI) available: Time evolution of borates; CD and ^3J studies; bases tested; NMR spectra. See DOI: 10.1039/b806529b

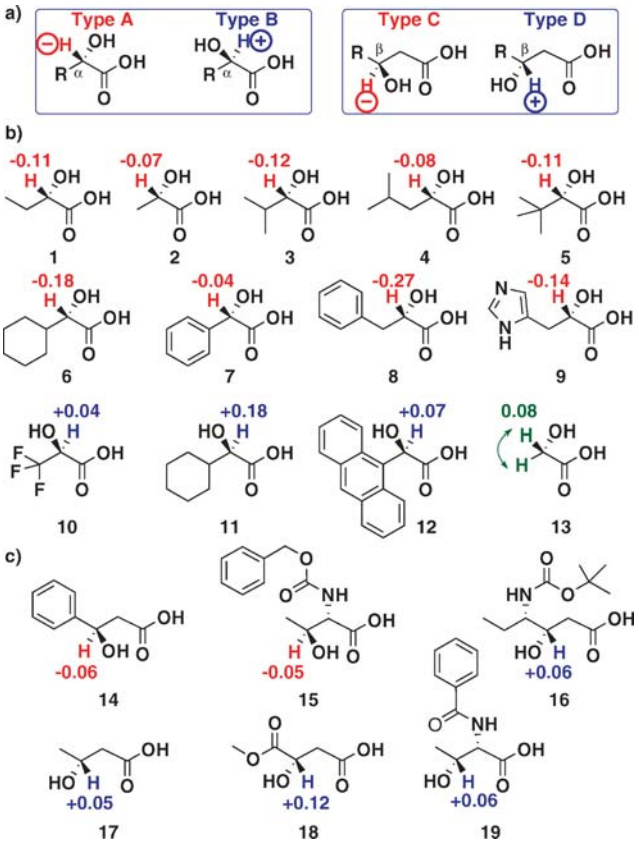

Fig. 2 (a) Types A, B, C and D hydroxy acids. (b) α-Hydroxy acids and (c) β-hydroxy acids studied in this work. $\Delta\delta^{RS}$ signs and values for diagnostic hydrogens are highlighted.

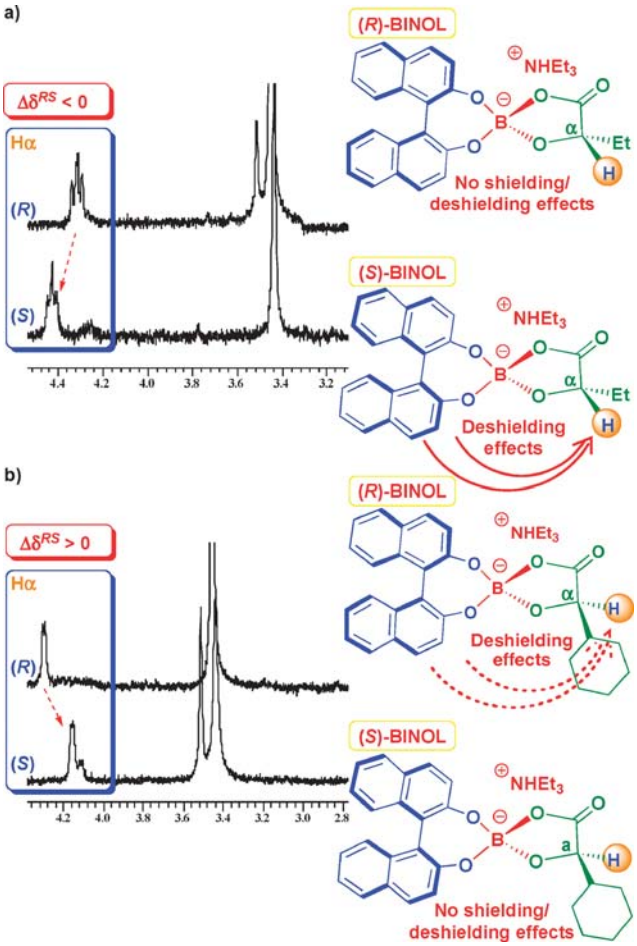

Fig. 3 (a) ^{1}H NMR spectra of (*R*)- and (*S*)-BINOL borates of (*S*)-2-hydroxybutanoic acid (**1**). (b) *Idem* for (*R*)-2-cyclohexyl-2-hydroxy-acetic acid (**11**). Hα shifts are highlighted.

the complex eliminates uncertainties about the spatial position of the auxiliary with respect to the substrate.

The experimental procedure consists of mixing—in a vial or NMR tube, $CDCl_3$ as solvent (*i.e.* 0.6 mL) and in the presence of 4 Å molecular sieves—equimolecular amounts of (*R*)-BINOL, trimethoxyborate and the chiral hydroxy acid (1 equiv. each; *i.e.* 2–5 mg of acid). After gentle shaking for 5–10 min, triethylamine (0.5 equiv.) is added and the ^{1}H NMR spectrum recorded without delay. The process is repeated with (*S*)-BINOL and the configurational assignment made by comparison of the chemical shifts of the methine hydrogen (Hα or Hβ for α- and β-hydroxy acids, respectively) bonded to the stereogenic carbon.§ Those chemical shifts are affected by the aromatic shielding/deshielding produced by the auxiliary, and therefore depend on the spatial location of that hydrogen with regard to the naphthyl rings. Thus, the sign of $\Delta\delta^{RS}$ correlates the absolute configuration in the auxiliary part (known) with that in the substrate part (unknown).¶

Examination of a series of α- and β-hydroxy acids validates this correlation between the sign of $\Delta\delta^{RS}$ and the absolute configuration (Fig. 2).

Thus, the mixed borate obtained from (*R*)-BINOL and (*S*)-2-hydroxybutanoic acid (**1**) presents the methine proton (Hα) unaffected by the aromatic influence of the naphthyl rings, while in the mixed borate obtained from the same substrate and (*S*)-BINOL, that proton lies under the influence of the deshielding cone of one of the naphthyl rings (Fig. 3(a)). Therefore, Hα is more shielded in the (*R*)-BINOL than in the (*S*)-BINOL complex for that configuration of the α-hydroxy acid and the difference of chemical shifts is negative ($\Delta\delta^{RS} = -0.11$). The same sign is obtained for compounds that belong to the same stereochemical series (**1–9**, Type A).

Similarly, hydroxy acids that belong to the opposite enantiomeric series (Type B), present the methine proton more deshielded in the (*R*)- than in the (*S*)-BINOL derivatives [*i.e.* (*R*)-2-cyclohexyl-2-hydroxyacetic acid (**11**), $\Delta\delta^{RS} = +0.18$, Fig. 3(b)) and this explains why a positive $\Delta\delta^{RS}$ sign is obtained for all the compounds with the same spatial disposition (**10–12**). In the case of β-hydroxy acids, a negative sign is obtained for the Type C series (**14**, **15**), and a positive sign in the Type D series (**16–19**).

The generality of this method is demonstrated by examining α- and β-hydroxy acids that present a variety of structures and substituents (aliphatic, heterocyclic, acyclic, cyclic, polar…). Even the presence of bulky groups (*i.e.* **5**) or aromatic rings (*i.e.* **12**) does not represent an obstacle for its application.

An especially interesting case is represented by glycolic acid (**13**). It lacks the stereogenic center, but the prochiral methylene protons are clearly distinguishable ($\Delta\delta = 0.08$ ppm) and assignable by this method: in the (*R*)-BINOL derivative, the pro-*R* proton is the one placed at high field and the pro-*S* at

lowfield, while in the (*S*)-BINOL derivative they are placed the other way around.

From a mechanistic point of view, the formation of the mixed borate entails several steps (Scheme 1S in ESI†) that can be observed.‖ Thus, ^{11}B NMR monitoring shows how after addition of the amine, the boron signal moves from the shift characteristic of a trialkoxyboron compound (15.7 ppm) to the shift of the more shielded tetrahedral borate (6.8 ppm).** CD monitoring shows that the binaphthyl ring remains in practically identical rotation angle after complexation. As a result, the sterochemistry of the substrate is fixed to that of the auxiliary and the $\Delta\delta^{RS}$ sign can be used to determine the absolute configuration of the chiral hydroxy acids. Models—that place the Hα close to the plane of a naphthyl ring in one of the two [(*R*) or (*S*)] derivatives—suggest that deshielding effects are the major cause of the differences in chemical shifts between the diastereomeric complexes. In this context, time evolution of these complexes is especially relevant. Detailed description of the species involved can be found in at ESI.†

Other 1,2-dihydroxy compounds have been assayed as potential auxiliaries (*i.e*. 1,2-diphenylethane-1,2-diols; 1,2-di-1-anthrylethane-1,2-diols) and although the stability of the cyclic mixed borates could be increased, the shifts induced were visibly lower. In addition, the advantage of using a commercially available reagent is obvious. Also, in order to optimize the process, a series of amines were tested and triethylamine was found to be the best suited one (see ESI†).

In summary, the preparation of the mixed borates is quite simple and fast just by mixing in the NMR tube the reagents and substrate, the auxiliaries are commercially available and do not interfere, the spectra are easy to interpret because only one signal (localized at 4–5 ppm) has to be analyzed and the absolute configuration is assigned just by comparison of the $\Delta\delta^{RS}$ sign with the models in Fig. 2(a). This correlation is validated by a series of representative molecules of known absolute configuration and can therefore be considered to be general for α and βacids and used for configurational assignment.

This is the first time a methodology comprising the advantages of a cyclic rigid complex (CSA type) with the presence of covalent bonds (CDA type) is used for the assignment of absolute configuration by NMR.

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Notes and references

‡ Simplified procedures using only one derivative or suppressing sample manipulation are known for CDAs, but not for CSAs. See ref. 1.

§ The signals due to protons of the R substituent at the stereogenic carbon are of no diagnostic value because free rotation of the chain places those protons under either shielding or deshielding influence of the naphthyl rings. Therefore, a confident and general correlation cannot be established for those protons.

¶ $\Delta\delta^{RS}$ for a substituent is the difference between its chemical shift in the (*R*)-CDA derivative minus its chemical shift in the (*S*)-CDA derivative.

‖ Other types of boron compounds have recently been used for enantiomeric excess measurement. See ref. 3.

** The addition of a ligand or base to the empty p-orbital on boron results in an upfield shift as compared to a tricoordinate borane. The chemical shift depends on the strength of the coordination complex: stronger complexes are shifted to higher field. See ref. 4.

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