The assignment of absolute configuration of cyanohydrins by NMR†

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Derivatization of aldehyde cyanohydrins as (*R*)- and (*S*)-MPA esters and comparison of the corresponding ^{1}H- and ^{13}C-NMR spectra allows the assignment of their absolute configuration.

The use of ^{1}H-NMR as a tool for the assignment of absolute configuration has been described for several classes of organic compounds derivatized with selected chiral derivatizing agents (CDAs).[1] Chiral cyanohydrins are well known natural products and versatile synthetic intermediates. They can be easily produced by addition of cyanide to the parent carbonyl compound in the presence of chiral catalysts or by enzymatic methods[2] and readily transformed into a variety of compounds such as α-hydroxyacids, α-aminoacids, α-hydroxyaldehydes, α-hydroxyketones or β-aminoalcohols, among others. Therefore, easy and cheap procedures for the reliable assignment of the absolute configuration of cyanohydrins should be very useful.

In this communication, we will describe such a simple procedure for aldehyde derived cyanohydrins, that simply requires derivatization of the cyanohydrin with the two enantiomers of the auxiliary agent (*R*)- and (*S*)-2-methoxy-2-phenylacetic acid (MPA) and comparison of the ^{1}H- and ^{13}C-NMR spectra of the corresponding cyanohydrin MPA ester derivatives.

Even though cyanohydrins derived from aldehydes [R_1CH(OH)CN] keep, at a first glance, some resemblance with the structure of secondary alcohols [R_1CH(OH)R_2; R_1, R_2 = alkyl, aryl…], the presence of the strongly polar[3] CN substituent makes the geminal hydroxynitrile moiety a wholly novel situation from the structural point of view to which the NMR procedures previously described for secondary alcohols cannot be applied without a previous and rigorous validation. Consequently, we decided to examine the NMR behaviour of the (*R*)- and the (*S*)-MPA ester derivatives of a series of aldehyde cyanohydrins of known absolute configuration and see if—just like in the case of secondary alcohols and other functional groups—a correlation between the absolute configuration and the NMR chemical shifts were present.

Fig. 1 shows the ^{1}H-NMR spectra of the MPA derivatives† of (*R*)-2-hydroxy-3-methylbutanenitrile (**1**). It is easily observable that the signals corresponding to methine CH(3), and to methyls Me(4) and Me(5) are more shielded in the (*S*)-MPA than in the (*R*)-MPA ester. These differences in chemical shifts expressed as $\Delta\delta^{RS}$‡ show a positive sign for all the protons of the isopropyl group ($\Delta\delta^{RS}_{CH(3)}$ = +0.18 ppm; $\Delta\delta^{RS}_{Me(4,5)}$ = +0.18/+0.19 ppm).

The nitrile group, lacking protons, could not be analyzed by ^{1}H-NMR. So, we decided to study its behaviour by ^{13}C-NMR. In this way, the characteristic and easy to identify carbon resonance for the CN group was also found to have a diagnostic value showing different chemical shifts in each derivative.§ In compound **1**, the CN carbon is more shielded in the (*R*)-MPA ester derivative than in the (*S*)-MPA ester derivative leading to a negative sign for the difference between chemical shifts ($\Delta\delta^{RS}_{CN}$ = −0.3 ppm).

Similarly, the ^{1}H- and ^{13}C-NMR spectra of the (*R*)- and the (*S*)-MPA derivatives of the structurally diverse cyanohydrins **2–11** (Fig. 2), with the same spatial relationship as **1**, showed signs of $\Delta\delta^{RS}$ for the side chain protons and for the CN groups (^{13}C-NMR) identical to those of **1** (positive for the side chain protons and negative for the CN group).

For their part, when cyanohydrins **12** and **13**, together with the enantiomers of **1**, **2**, **5**, **6**, **7**, **8**, **9** and **10**, were derivatized with (*R*)- and (*S*)-MPA and their NMR spectra examined, the opposite distribution of signs resulted in all cases: a negative $\Delta\delta^{RS}$ was obtained for the side chain protons and a positive one for the CN groups. In consequence, the distribution of $\Delta\delta^{RS}$ signs is characteristic for each enantiomeric series and can be used to determine the absolute stereochemistry of the cyanohydrins. As an example we show in Fig. 3 the partial ^{1}H- and ^{13}C-NMR spectra of sugar cyanohydrin **13**. Comparison of the (*R*)- and the (*S*)-MPA derivatives shows that all the protons that belong to the ring moiety undergo noticeable deshielding when going from the (*R*)- to the (*S*)-MPA ester producing negative $\Delta\delta^{RS}$ values, while the CN group experiments shielding (positive $\Delta\delta^{RS}$ value).

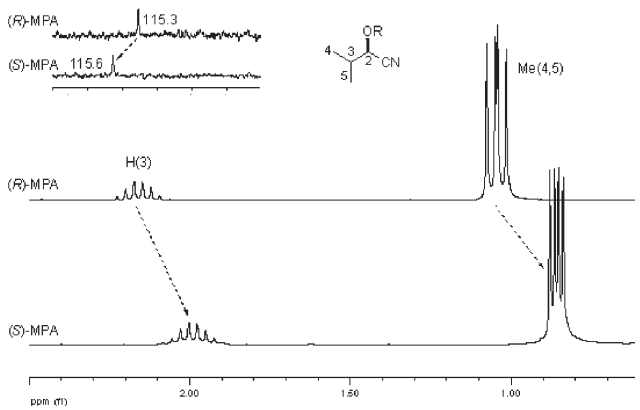

Fig. 1 Partial ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$, 250.13 MHz and 75.46 MHz respectively) of (*R*)- and (*S*)-MPA esters of (*R*)-2-hydroxy-3-methylbutanenitrile (**1**).

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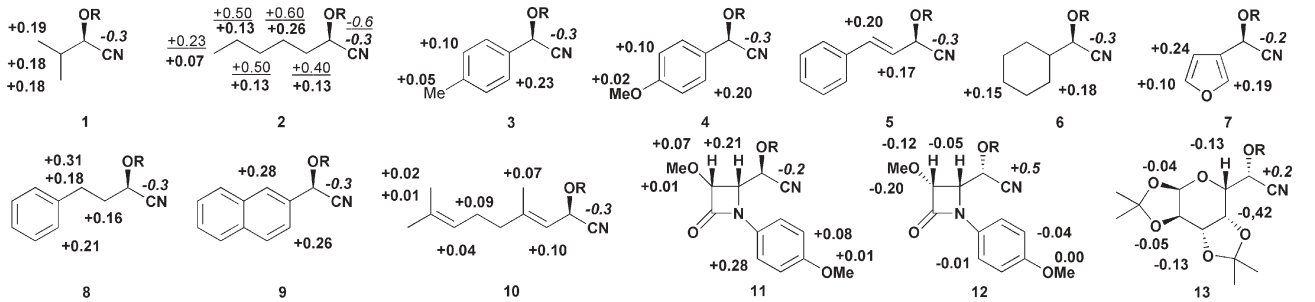

Fig. 2 $\Delta\delta^{RS}$ values and sign distribution for the MPA ester derivatives of the cyanohydrins **1–13** (in bold). Compounds **12** and **13** belong to the opposite stereochemical series than **1–11**. The opposite set of $\Delta\delta^{RS}$ signs was obtained for the enantiomers of **1**, **2**, **5**, **6**, **7**, **8**, **9** and **10**. The $\Delta\delta^{RS}$ values and sign distribution obtained from the ^{13}C spectra for the CN groups are shown in italic ($CDCl_3$). Underlined values correspond to 9-AMA esters (compound **2**).

These results can be easily explained on the basis of an NMR representative conformer similar to the one described for the MPA esters of secondary alcohols,[4] where the shielding effect produced by the phenyl ring of the auxiliary on the substituent of the alcohol—located in front of it—serves to connect the configuration of the auxiliary part with that of the alcohol.

It is known that, in esters, the MPA auxiliary moieties present two main forms in the equilibrium: an antiperiplanar (*ap*) conformer (minor) and a synperiplanar (*sp*) conformer (major and NMR relevant).[4] In our case, when the cyanohydrin is derivatized with the (*S*)-enantiomer of MPA, one of the substituents of the asymmetric carbon (*i.e.* L) faces the phenyl ring in the main conformer, experiencing a measurable shielding effect. When the (*R*)-MPA is used instead, the shielding affects the other substituent (*i.e.* CN) (Fig. 4).

Thus, in the (*S*)-MPA derivative of (*R*)-2-hydroxy-3-methyl-butanenitrile (**1**), the alkyl chain (isopropyl group) is subjected to the aromatic shielding effect of the phenyl ring of the auxiliary while in the (*R*)-MPA derivative it is not (Fig. 4). The difference in chemical shifts, expressed as $\Delta\delta^{RS}$, is in this case positive and this sign is therefore associated with that particular spatial location of the chain with respect to the phenyl ring of the auxiliary. For its part, the CN group is in front of the phenyl ring in the NMR relevant conformer (*sp*) of the (*R*)-MPA derivative but it is not in the (*S*)-MPA derivative. Accordingly, it presents a negative $\Delta\delta^{RS}$ sign, also associated with the stereochemistry of the chiral center. Exactly the same signs are obtained for all the cyanohydrins **1–11** that present the same configuration. Naturally, in the other stereochemical series, (**12**, **13**, and the enantiomers of **1**, **2**, **5–10**) the anisotropic effect acts in the same way but, as the two substituents around the asymmetric carbon are placed the other way around, the opposite set of $\Delta\delta^{RS}$ signs are obtained.

Derivatization of cyanohydrin **2** with (*R*)- and (*S*)-2-(9-anthryl)-2-methoxyacetic acid (9-AMA) gave the same set of $\Delta\delta^{RS}$ signs as MPA and larger absolute values, according to the stronger anisotropic effect produced by the anthryl group and to the presence of similar conformational equilibria.[4]

Thus, this correlation between the absolute configuration and the NMR spectra holds for all the compounds of Fig. 2, with acyclic and cyclic saturated chains as well as aromatic, olefinic and cyclic substituents, it can therefore be considered to be widely general for aldehyde cyanohydrins and be used for their configurational assignment in much the same way as for secondary alcohols. To sum up, in this procedure the aromatic shielding effect is being used to link the unknown configuration of the cyanohydrin (spatial location of L and CN around the asymmetric carbon) with the known absolute configuration of the auxiliary moiety (spatial location of the phenyl group in the (*R*) and (*S*)-MPA, Fig. 4).

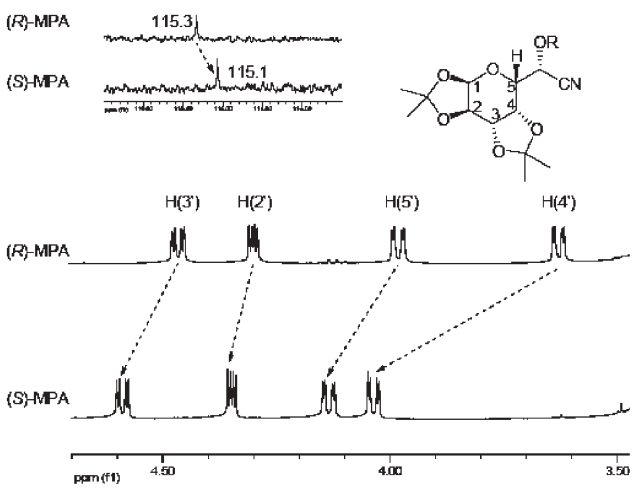

Fig. 3 Partial ^1H and ^{13}C-NMR spectra of the (*R*)- and (*S*)-MPA esters of (6*R*)-1,2-3,4-di-*O*-isopropilidene-α-D-*galacto*-heptopyranurononitrile (**13**) ($CDCl_3$, 399.97 and 100.58 MHz respectively).

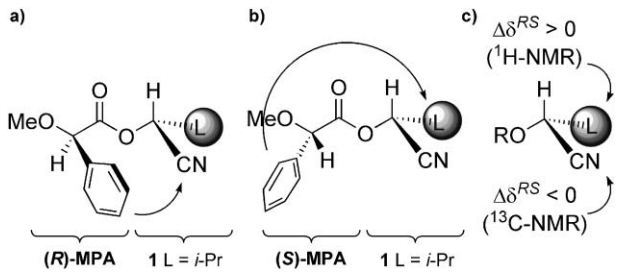

Fig. 4 (a) NMR representative conformer (*sp*) of the (*R*)-MPA ester of an aldehyde cyanohydrin. Shielding effect is shown by a curved arrow.(b) Idem for the (*S*)-MPA ester. (c) Model for users in order to place in space the L and CN substituents of the chiral center according to their $\Delta\delta^{RS}$ signs. The configuration is the opposite if the signs obtained are reversed to those shown.

Experimental (low temperature 1D and 2D-NMR and CD spectroscopy; selective formation of metal complexes) and theoretical (energy calculations) data corroborate the certainty of the conformations presented in Fig. 4 and will be presented in due course.

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Notes and references

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

§ Experimental evidence based on the decrease of the shielding experienced by the CN carbons in 2-cyclohexyl-2-methoxyacetic acid derivatives suggests that through space interactions can be a major cause of the observed ^{13}C shifts (unpublished results).

1 For recent reviews see: J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17–117; J. M. Seco, E. Quiñoá and R. Riguera, *Tetrahedron: Asymmetry*, 2001, **12**, 2915–2925.

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