^{13}C NMR as a general tool for the assignment of absolute configuration†

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^{13}C NMR, alone or in combination with ^{1}H NMR, allows the assignment of the absolute configuration of chiral alcohols, amines, carboxylic acids, thiols, cyanohydrins, *sec*,*sec*-diols and *sec*,*sec*-aminoalcohols, derivatized with appropriate chiral auxiliaries. This extends the assignment possibilities of NMR to fully deuterated and to nonproton containing compounds.

In its more general application, the assignment of the absolute configuration by NMR spectroscopy is based on the comparison of the ^{1}H NMR spectra of two derivatives of the substrate, prepared with the two enantiomers of an appropriate chiral derivatizing agent (CDA).[1] Those two derivatives show different chemical shifts for the protons on the substituents around the asymmetric carbon (L_1/L_2), and these differences, expressed as $\Delta\delta^{RS} = \delta^R - \delta^S$, show signs that correlate with the spatial location of L_1/L_2 that is the absolute configuration of the substrate.

This phenomenon is originated on the spatial location of L_1/L_2 with respect to the aromatic ring of the CDA: in each derivative the aromatic shielding effect acts mainly on one of the two substituents of the substrate (L_1 or L_2), allowing the identification of the one which is located on the same side of the aryl ring and therefore under its shielding cone. In summary, the through space aromatic shielding effect is being used to link the spatial information contained in the auxiliary moiety (known absolute configuration, position of the aryl ring) with the spatial location of substituents L_1/L_2 in the substrate (unknown absolute configuration).[1]

Although this methodology has proven to be successful for the assignment of the absolute configuration of a variety of mono and polyfunctional organic compounds, only very few reports have explored the use of ^{13}C instead of[2] or in addition to ^{1}H NMR[3-5] so that no general view about the possibilities of ^{13}C NMR as a tool for the stereochemical assignment has been established to date.

The reason for that neglect probably lies on: (a) the much longer time and amount of sample needed to obtain a good ^{13}C NMR spectrum, as compared with ^{1}H NMR, that were indeed difficult to assume in the old times, and (b) the smaller influence of the magnetic anisotropic term,[6] on the ^{13}C chemical shift, therefore producing small shifts frequently within the experimental error of the instrument. Both difficulties are nowadays clearly solved by the standard NMR instrumentation and therefore we decided to explore the use of ^{13}C NMR as a general tool for configurational assignment.

If that were possible with the very same auxiliary reagents used for the ^{1}H NMR based methodology, both the ^{1}H and the ^{13}C data could be obtained at the same time, with the same sample, and allowing a double checking assignment based on the shifts from the two nuclei. In addition, the absolute configuration of fully deuterated compounds and structures without protons not amenable to study by ^{1}H NMR could be assigned on the basis of the ^{13}C chemical shifts.

In this report we describe results indicating that there is a perfect correlation between the ^{13}C chemical shifts in the studied derivatives and the absolute configuration of the substrates and that therefore, the methodology developed for assignment of absolute configuration based on proton chemical shifts can equally well be applied to ^{13}C NMR.

Thus, we examined the ^{13}C NMR data of a collection of chiral samples, representative for the types of substrates that have previously been studied by the ^{1}H NMR method including monofunctional (α-chiral secondary alcohols,[7] α-chiral primary amines,[8] α-chiral carboxylic acids,[9] α-chiral secondary thiols,[10] α-chiral cyanohydrins)[11] and bifunctional (*sec*,*sec*-diols[12] and aminoalcohols)[13] compounds, derivatized with MPA, MTPA, BPG, 1-NMA, 2-NMA, 2-NTBA, 9-AMA, and 9-AHA as CDAs.

$\Delta\delta^{RS}$ was calculated for ^{13}C in the same way as for ^{1}H. A representative selection including the fully deuterated (*R*)-1-(pentadeuterophenyl)ethanol-2,2,2-d_3 is presented in Fig. 1.

The experimental data show that in all the cases there is a perfect correlation between the sign of $\Delta\delta^{RS}$ and the absolute configuration of the substrate: a positive $\Delta\delta^{RS}$ sign is obtained for all the carbon nuclei in one substituent (L_1/L_2) and a negative $\Delta\delta^{RS}$ sign for the carbon nuclei of the other substituent. The distribution of signs for all the compounds of the same class (*i.e.* secondary alcohols) and the same configuration is the opposite to that of their enantiomers. Also, the distribution of $\Delta\delta^{RS}$ signs in a given substrate–CDA couple is identical using ^{13}C and ^{1}H NMR chemical shifts.‡

The ^{13}C $\Delta\delta^{RS}$ data illustrate two other characteristics: (a) the absolute values of $\Delta\delta^{RS}$ along a chain (*i.e.* L_1 or L_2) diminish with the distance to the auxiliary, and (b) the change of the auxiliary produces greater $\Delta\delta^{RS}$ values in the order MPA < 1-NMA < 2-NMA < 9-AMA for the same substrate in those cases where the same phenomenon also occurs for ^{1}H $\Delta\delta^{RS}$ values.

In conclusion, the ^{13}C NMR chemical shifts of those derivatives follow the same pattern than the ^{1}H NMR shifts, the sign distributions for a substrate–CDA couple are identical with both nuclei, so ^{13}C NMR can be used as a general tool for the assignment of absolute configuration of those substrates in

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† Electronic supplementary information (ESI) available: Experimental section, characterization of new compounds, computational methods, ^{13}C $\Delta\delta^{RS}$ data of remaining chiral compounds. See DOI: 10.1039/c0cc02774j

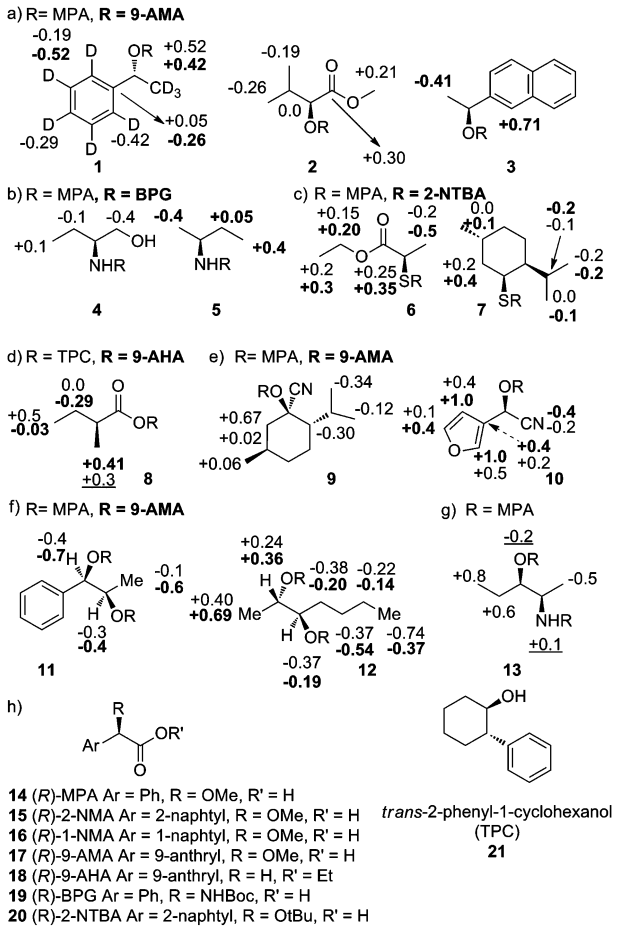

Fig. 1 Selection of chiral compounds among 76 examples examined, (see ESI†) including (a) α-chiral secondary alcohols, (b) α-chiral primary amines, (c) α-chiral secondary thiols, (d) α-chiral carboxylic acids, (e) cyanohydrins, (f) *sec*,*sec*-diols, (g) *sec*,*sec*-aminoalcohols, and (h) structures of CDAs **14–21** used in this study. Anomalous $\Delta\delta^{RS}$ signs are underlined.

exactly the same way as with ^{1}H, using the very same graphical models published for the ^{1}H NMR based methodology. In addition, the intensity of the shifts and their variations with the distance and the CDAs clearly suggest that the origin of the phenomenon is the same: the aromatic shielding effect produced selectively by the aryl ring of the auxiliary on L_1/L_2.

Trying to go further inside these results, particularly on the importance of the aromatic shielding effect on the ^{13}C NMR shifts, we selected as a model compound the secondary alcohol corynanthine, (Fig. 2a, **22a**) a rigid compound with well defined distances among atoms. Shielding tensor calculations were also carried out in this system.

Thus, if an aromatic shielding effect was in action, a clear relationship between the experimental chemical shifts of carbon nuclei in corynanthine derivatives and their positions with respect to the auxiliary should be found.

In addition, the theoretically calculated ^{13}C chemical shifts[4,14] and $\Delta\delta^{RS}$ signs should be coincident with the experimental ones.

So, the corynanthine ester derivatives with (*R*)- and (*S*)-MPA, 2-NMA, 1-NMA and 9-AMA, as CDAs, were prepared

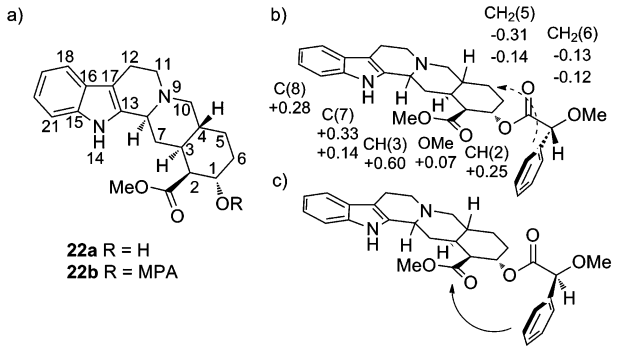

Fig. 2 (a) Structures of corynanthine and its (b) (*R*)- and (c) (*S*)-MPA derivatives in *sp* conformation. The ^{1}H $\Delta\delta^{RS}$ values are shown in (b) for comparison purposes.

(Fig. 2). For each derivative, the ^{1}H and ^{13}C NMR spectra were recorded, and the chemical shift differences $\Delta\delta^{RS}$ measured.

The results shown in Table 1 indicate that: (a) the shielding effects on ^{13}C go parallel to those experimented by ^{1}H nuclei located in the same spatial region; (b) $\Delta\delta^{RS}$ decrease with the distance to the chiral auxiliary; (c) the $\Delta\delta^{RS}$ values are higher with auxiliaries with higher ring current intensity. All this confirms that a shielding effect from the aryl ring of the auxiliary part is in operation on the skeleton of corynanthine.

Chemical shift calculations for the (*R*)- and (*S*)-MPA esters of corynanthine were carried out considering, for the auxiliary part, the two most representative conformers. Minimizations were performed in gas phase at DFT level using B3LYP functional and 6-31 + G(d) as basis set, followed by a single point calculation of the NMR parameters (GIAO) through polarizable continuum model (PCM) using $CHCl_3$ parameters as solvent and the same basis set and functional. Thus, the absolute isotropic shielding (σ) is obtained for each nucleus[15] (see ESI† for further details).

The theoretically calculated parameters relevant for the ^{13}C chemical shift are shown in Table 1 together with the final calculated $\Delta\delta^{RS}$ (considering either the lowest energy conformer *sp* or an estimated *sp*/*ap* distribution for MPA). As can be seen, a negative $\Delta\delta^{RS}$ sign is calculated for carbons C(6) and C(5) and a positive $\Delta\delta^{RS}$ sign for C(2), C(3), C(7) and C(8) in accordance with the experimental signs for those carbon nuclei. This sign distribution for carbons is identical to the one obtained for the protons located in the same spatial environment.

In addition, both the theoretical and the experimental $\Delta\delta^{RS}$ values diminish with the distance between the nuclei and the aromatic system of the CDA (Fig. 3).

In summary, our experimental and theoretical data demonstrate that ^{13}C NMR chemical shifts can be used, alone or in combination with ^{1}H NMR, for the assignment of absolute configuration. The foundations of the method are the same for both nuclei and reside on the aromatic shielding effect produced by the auxiliary on the protons and carbons of the substrate. In fact, the sign distribution obtained for a compound derivatized with a certain CDA is the same for both nuclei.

Thus, the graphical models that correlate the absolute configuration with the sign distribution are identical for both ^{13}C and ^{1}H.

Table 1 Experimental ^{13}C $\Delta\delta^{RS}$ (ppm) of the MPA, 1-NMA, 2-NMA and 9-AMA derivatives, and calculated[a] ^{13}C $\Delta\delta^{RS}$ (ppm) of the lowest energy conformers[b] of MPA esters of corynanthine

$\Delta\delta^{RS}$	C(6)	C(5)	C(2)	C(3)	C(7)	C(8)	CO	OMe
MPA[c]	−0.60	−1.03	−1.57	+0.67	+0.23	+0.49	+0.82	+0.34
MPA[d]	−0.45	−0.13	−0.45	+0.31	+0.24	+0.31	+0.41	+0.09
Exp. MPA	−0.17	−0.34	+0.74	+0.44	+0.19	+0.99	+0.10	+0.12
Exp. 2-NMA	−0.17	−0.41	+0.78	+0.52	+0.20	+0.65	+0.16	+0.12
Exp. 1-NMA	−0.31	−0.34	+1.21	+0.70	+0.67	+0.90	+0.21	+0.22
Exp. 9-AMA	−0.41	−1.05	+1.35	+0.96	+1.05	+0.59	+0.32	+0.14

[a] DFT-GIAO/B3LYP (PCM)/6-31+G(d) using $CHCl_3$ parameters. [b] $\Delta\delta^{RS}$ calcd (ppm) = $\sigma_S - \sigma_R$. [c] Considering only the lowest energy conformers *sp*. [d] An estimated relative population of 70/30 (*sp*/*ap*) was used for calculation.§

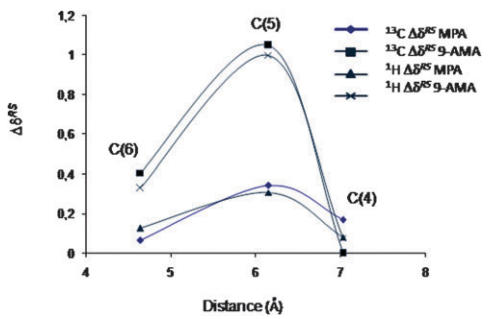

Fig. 3 ^{1}H and ^{13}C $\Delta\delta^{RS}$ superimposed values of corynanthine MPA and 9-AMA esters *vs.* distance measured from the auxiliary [C(1′) of phenyl ring] to C(6), C(5) and C(4) of corynanthine.

From a practical point of view, this means that the configurational assignment of compounds with no protons on L_1/L_2 can now be carried out using ^{13}C NMR. Naturally, if both ^{13}C and ^{1}H are present, the use of the two nuclei increases the number of data points and therefore the reliability of the assignment.

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Notes and references

‡ For the assignment of *sec*,*sec*-aminoalcohols, ^{13}C $\Delta\delta^{RS}$ data should be complemented with ^{1}H $\Delta\delta^{RS}$ data. Also, in the case of carboxylic acids, *trans*-2-phenylcyclohexanol (TPC) should be avoided as CDA. Other functional groups (*prim*,*sec*-1,2-amino alcohols,[16] *prim*,*sec*-diols[17] and *prim*,*sec*,*sec*-1,2,3-triols,[18] as well as β-chiral primary alcohols[19]) have also been investigated but unfortunately $\Delta\delta^{RS}$ values lower than 0.1 ppm, too close to the experimental error to allow a reliable assignment, are obtained.

§ The sign of C(2) is highly influenced by the acetyl group and gives variable signs depending on the conformer being considered. When the methyl ester is replaced by a methyl group, the calculated C(2) $\Delta\delta^{RS}$ is +0.55 ppm. Changing the carbonyl disposition in the *sp* conformation, the calculated value (for a 70/30 *sp*/*ap* ratio) is +0.34 ppm.

1 J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17; T. J. Wenzel, *Discrimination of Chiral Compounds Using NMR Spectroscopy*, Wiley, 2007.
2 M. Kobayashi, *Tetrahedron*, 2000, **56**, 1661; A. Arnone, R. Bernardi, F. Blasco, R. Cardillo, G. Resnati, I. I. Gerus and V. P. Kukhar, *Tetrahedron*, 1998, **54**, 2809.
3 Y. Fukushi, K. Shigematsu, J. Mizutani and S. Tahara, *Tetrahedron Lett.*, 1996, **37**, 4737; Y. Fukushi, C. Yajima and J. Mizutani, *Tetrahedron Lett.*, 1994, **35**, 599; T. Pehk, E. Lippmaa, M. Lopp, A. Paju, B. C. Borer and R. J. K. Taylor, *Tetrahedron: Asymmetry*, 1993, **4**, 1527.
4 M. A. Muñoz and P. Joseph-Nathan, *Magn. Reson. Chem.*, 2009, **47**, 578; K. W. Wiitala, C. J. Cramer and T. R. Hoye, *Magn. Reson. Chem.*, 2007, **45**, 819.
5 I. Louzao, J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Commun.*, 2006, 1422.
6 H.-O. Kalinovsky, S. Berger and S. Braun, *Carbon-13 NMR Spectroscopy*, John Wiley and Sons, Salisbury, 1986, p. 92.
7 Sh. K. Latypov, J. M. Seco, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 1996, **61**, 8569; B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal and J. M. Balkovec, *J. Org. Chem.*, 1986, **51**, 2370; A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.
8 J. M. Seco, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 1999, **64**, 4669; J. M. Seco, Sh. K. Latypov, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 1997, **62**, 7569; B. M. Trost, R. C. Bunt and S. R. Pulley, *J. Org. Chem.*, 1994, **59**, 4202.
9 M. J. Ferreiro, Sh. K. Latypov, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 2000, **65**, 2658; M. J. Ferreiro, Sh. K. Latypov, E. Quiñoá and R. Riguera, *Tetrahedron: Asymmetry*, 1997, **8**, 1015.
10 S. Porto, J. M. Seco, A. Ortiz, E. Quiñoá and R. Riguera, *Org. Lett.*, 2007, **9**, 5015.
11 I. Louzao, R. García, J. M. Seco, E. Quiñoá and R. Riguera, *Org. Lett.*, 2009, **11**, 53.
12 F. Freire, J. M. Seco, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 2005, **70**, 3778; J. M. Seco, M. Martino, E. Quiñoá and R. Riguera, *Org. Lett.*, 2000, **2**, 3261.
13 V. Leiro, F. Freire, E. Quiñoá and R. Riguera, *Chem. Commun.*, 2005, 5554.
14 M. J. Frisch, *et al.*, *Gaussian03, revision E.01*, Gaussian, Inc., Wallingford, CT, 2004. For full reference see ESI†.
15 J. Boyd and N. R. Skrynnikov, *J. Am. Chem. Soc.*, 2002, **124**, 1832.
16 V. Leiro, J. M. Seco, E. Quiñoá and R. Riguera, *Org. Lett.*, 2008, **10**, 2729.
17 F. Freire, J. M. Seco, E. Quiñoá and R. Riguera, *Chem.–Eur. J.*, 2005, **11**, 5509.
18 F. Freire, E. Lallana, E. Quiñoá and R. Riguera, *Chem.–Eur. J.*, 2009, **15**, 11963; E. Lallana, F. Freire, E. Quiñoá and R. Riguera, *Org. Lett.*, 2006, **8**, 4449.
19 F. Freire, J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Commun.*, 2007, 1456; Sh. K. Latypov, M. J. Ferreiro, E. Quiñoá and R. Riguera, *J. Am. Chem. Soc.*, 1998, **120**, 4741; M. J. Ferreiro, Sh. K. Latypov, E. Quiñoá and R. Riguera, *Tetrahedron: Asymmetry*, 1996, **7**, 2195.