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Absolute Configuration of Ketone Cyanohydrins by ^{1}H NMR: The Special Case of Polar Substituted Tertiary Alcohols

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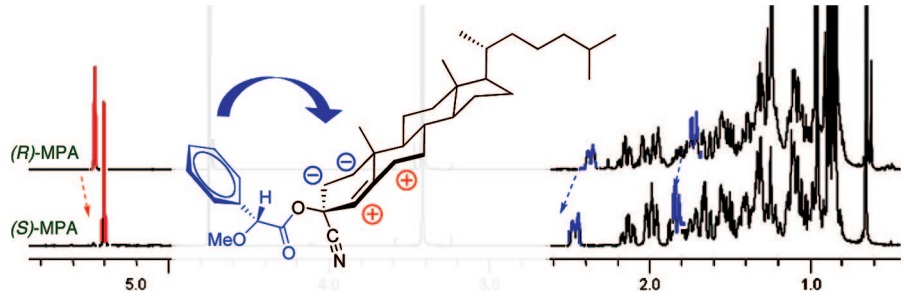
ABSTRACT



The absolute configuration of ketone cyanohydrins can be assigned from analysis of the ^{1}H NMR spectra of the corresponding (*R*)- and (*S*)-MPA ester derivatives and use of $\Delta\delta^{RS}$ signs. This is an application of the NMR methodology for stereochemical assignment to tertiary alcohols possessing polar groups as substituents.

Cyanohydrins are a versatile family of compounds that have always attracted the interest of chemists due to their importance both as industrial products and as reagents in organic chemistry. For instance, they are key building blocks for the synthesis of many biologically active compounds that are otherwise only obtained with difficulty, such as hydroxy aldehydes, amino alcohols, hydroxy amino acids and hydroxy acids.[1] Particularly, ketone cyanohydrins, are valuable intermediates in the preparation of compounds with a quaternary stereocenter.[2] Additionally, cyanohydrins are extensively found in nature (plants, insects) in the form of glycosides that are believed to play important biological roles (i.e., as antifeedants or insecticides).[3]

To date, only one attempt to disclose the absolute configuration of cyanohydrins using NMR[4] spectroscopy has been described.[5] It is useful only for aldehyde cyanohydrins and relies on the preparation of diastereomeric CDA (chiral derivatizing agent) derivatives and analysis of both ^{1}H and ^{13}C NMR data. 2-Methoxy-2-phenylacetic acid (MPA) was found to be the CDA of choice for those compounds.

Despite their importance, there is not a parallel procedure for ketone cyanohydrins. This is not surprising because these compounds present an extra challenge when compared to other hydroxylated compounds: they may be considered tertiary alcohols with a polar substituent (CN), and tertiary

(1) Kirsten, C. N.; Herm, M.; Schrader, T. H. *J. Org. Chem.* **1997**, *62*, 6882.
(2) Fessner, W.-D., Ed. *Biocatalysis*; Springer: Berlin, 1999.
(3) (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555. (b) Peterson, C. J.; Tsao, R.; Cotas, J. R. *Pest Manag. Sci.* **2000**, *56*, 615.
(4) For a recent review on NMR methods for configurational assignment, see: Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.
(5) Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Commun.* **2006**, 1422.

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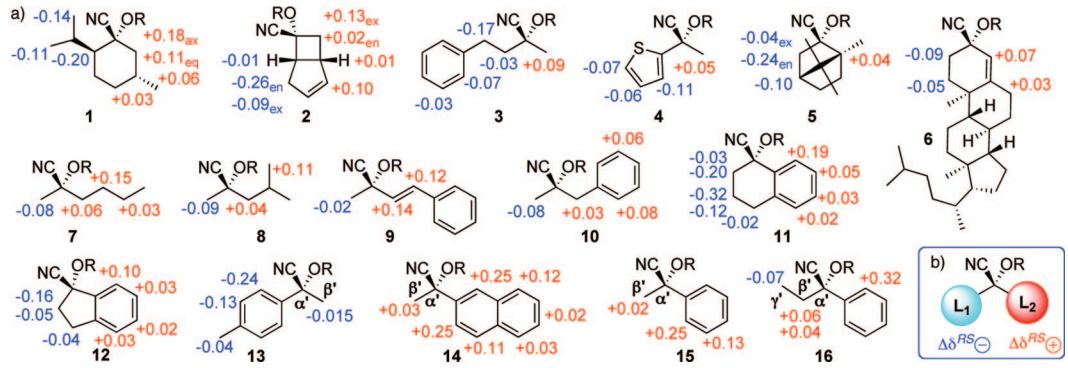

Figure 1. (a) $\Delta\delta^{RS}$ values and signs for the MPA ester derivatives of ketone cyanohydrins **1**−**16** ($CDCl_3$). (b) Spatial distribution of signs.

alcohols have been elusive in the past to stereochemical assignment by NMR methods, due to the unsuitable conformational characteristics of their CDA derivatives. Furthermore, they are notoriously difficult to derivatize. Few attempts are registered in the literature and the examples are limited to α-methyl-substituted tertiary alcohols.[6]

In this communication, we propose an NMR approach based on theoretical and experimental evidence that allows one to determine the absolute configuration of chiral ketone cyanohydrins by comparison of the NMR spectra of their (*R*) and (*S*)-MPA derivatives.

First, a representative collection of structurally varied ketone cyanohydrins (including cyclic and acyclic ones) of known absolute configuration (Figure 1) was selected for this study. Next, the corresponding (*R*)- and (*S*)-MPA derivatives were prepared, their NMR spectra analyzed with special attention to the shifts of the substituents on the asymmetric carbon, and the chemical shift differences ($\Delta\delta^{RS}$) for L_1/L_2 calculated. This parameter is obtained by subtracting the chemical shifts observed for L_1 and L_2 in the (*R*)-MPA ester minus the corresponding values in the (*S*)-MPA ester.

A homogeneous distribution of $\Delta\delta^{RS}$ signs was found in compounds **1**−**12**, as shown in Figure 1: both substituents of the stereogenic carbon (L_1/L_2) exhibit opposite signs. That is, protons located at the same substituent (i.e., L_1) present the same $\Delta\delta^{RS}$ sign and opposite to those of the other substituent (i.e., L_2). As a result, a correlation between the $\Delta\delta^{RS}$ signs for L_1 and for L_2 and the spatial position around the asymmetric carbon of these substituents is inferred, and thus allowing the assignment of the cyanohydrin absolute configuration.[7]

In order to understand the origin of this correlation we carried out studies to identify the most significant conformers, using theoretical calculations [DFT (B3LYP)],[8] circular dichroism (CD) and variable temperature NMR experiments.

The MPA esters of **7** were chosen as model compounds for theoretical calculations. Main conformations were generated around Cα-C(O) (MPA moiety) and O−Cα′ (cyanohydrin moiety). Rotation around the Cα-C(O) bond provided two conformers, *sp* and *ap*, while rotation around O−Cα′ gave rise to three: *g*+, *g*− and *a*, in which the dihedral angle formed by atoms C(O)−O-Cα′-CN is *ca.* +60, −60 and 180° respectively (see Figure 33S in the Supporting Information). As summary, the calculations show (Table 1) that the

Table 1. Relative Energies [B3LYP/6-31+G(d), kcal/mol] for Significant Conformers of (*R*)- and (*S*)-MPA Derivatives of **7**

	conformer					
ester	*spg*+	*spg*−	*spa*	*apg*+	*apg*−	*apa*
(*R*)-MPA	2.84	0.00	5.42	3.12	0.94	3.55
(*S*)-MPA	0.00	0.94	3.18	0.90	1.24	3.88

conformational equilibria are basically established by two main *sp* conformers (*spg*+ and *spg*−, Figure 2), both having

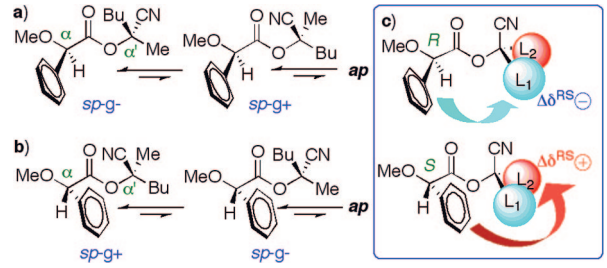

Figure 2. (a and b) Conformational equilibria for the (*R*)- and (*S*)-MPA esters of **7**; (c) NMR significant conformers.

similar energies. The CN group is preferably placed in the opposite side of phenyl group for both cases: so, in the equilibrium of the (*R*)-MPA derivative, *spg*− is the most

(6) (a) Izumi, S.; Moriyoshi, H.; Hirata, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2600. (b) Takahashi, H.; Kato, N.; Iwashima, M.; Iguchi, K. *Chem. Lett.* **1999**, 1181. (c) Kobayashi, M. *Tetrahedron* **1998**, *54*, 10987.

(7) The ^{13}C $\Delta\delta^{RS}$ parameters of the CN groups of ketone cyanohydrins **1**−**16** are not diagnostic: the absolute values are small and the signs cannot be correlated with the configurations. See Table 1S in the Supporting Information and ref 9.

stable conformer (Figure 2a), while the most stable one in the (*S*)-MPA derivative is *spg*+ (Figure 2b).[9]

According to this conformational scenario, the shielding and deshielding effect of the phenyl ring of the auxiliary on each conformation can now be analyzed. Thus, the butyl group is effectively shielded in the *spg*− conformer of the (*R*)-MPA ester, whereas the same group in the *spg*+ conformer is just slightly shielded (Figure 2a). Meanwhile in the (*S*)-MPA ester, the butyl group is slightly shielded only in *spg*+ conformer (Figure 2b). The neat result is that the butyl group is more shielded in the (*R*) than in the (*S*)-MPA derivative, leading to a $\Delta\delta^{RS}$ negative difference.

Simultaneously, in the (*S*)-MPA ester, the methyl group is strongly shielded in the *spg*+ conformation, and slightly shielded in the *spg*− conformation (Figure 2b), while it is slightly shielded only in *spg*− (Figure 2a) in the (*R*)-MPA derivative. Consequently, the methyl group is more shielded in the (*S*)- than in the (*R*)-MPA ester, leading to a $\Delta\delta^{RS}$ positive value.

The above conformational composition was experimentally supported by CD studies, low-temperature NMR experiments and exhaustive analyses of the collection of cyanohydrins of known absolute configuration shown in Figure 1. Thus, CD spectra (Figure 34S in Supporting Information) revealed the conformational preference in the MPA fragment. Cotton effects observed for the (*R*)- and (*S*)-MPA ester of (*S*)-2-hydroxy-2-methylhexanonitrile **7** at 226 nm are negative and positive respectively ($\Delta\epsilon = -2.42$ and 4.34 cm^{-2} mol^{-1}), indicating that the most abundant conformer in the MPA moiety is *sp*.[10]

Variable-temperature NMR experiments carried out on the MPA derivatives of (1*R*,2*S*,5*R*)-1-hydroxy-2-isopropyl-5-methylcyclohexanecarbonitrile (**1**), taken as model compounds, exhibit in both cases a deshielding of the CαH signal and a shielding of the OMe signal (Figure 3, MPA moiety), when lowering the temperature of the NMR probe. Both phenomena indicate an increase of the relative population of the *sp* conformer around Cα-C(O) bond,[11] in agreement with the theoretical calculations and CD experiments. As temperature drops, a gradual shielding of Me(8′) and Me(9′) signals (Figure 3a) is noticed in the NMR spectrum of the (*R*)-MPA ester, whereas the signals from Me(10′) and H(6′) are deshielded. These findings are due to the progressive increase of the number of molecules in the most stable conformations (*spg*− and *spg*+, according to the order of stability) characterized by the shielding of Me(8′) and Me(9′), along with a decrease in the number of molecules in the least stable conformation (*ap*), where Me(10′) and H(6′) are shielded.

The analysis of the spectrum of the (*S*)-MPA derivative (Figure 3b) leads to similar conclusions. It shows a progressive shielding of Me(10′) and H(6′) when lowering the temperature, meanwhile Me(8′) and Me(9′) get deshielded. This outcome can be explained on the basis of an increase of the population of the most stable conformers (*spg*+ and *spg*−, according to the order of stability), in which Me(10′) and H(6′) are shielded, and a decrease of least stable conformer (*ap*), that produces a shielding of Me(8′) and Me(9′) by the MPA phenyl group. These latter signals are deshielded due to disappearance of molecules in the *ap* conformation.

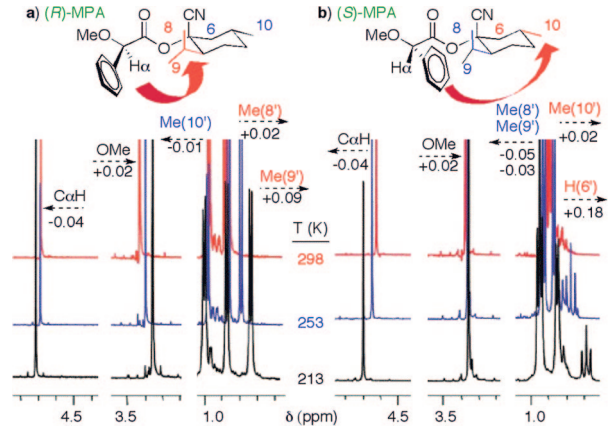

Figure 3. Temperature evolution of the ^{1}H NMR spectra of (*R*)- and (*S*)-MPA derivatives of **1** (a and b) and $\Delta\delta^{T1T2}$ values (ppm).

In practice, a simplified procedure for assignment relies on the interpretation of the NMR shifts as if the conformational equilibria were summarized in just a single conformer, the same for both MPA esters. This conformer is characterized by a synperiplanar situation between the CN and the C═O groups (Figure 2c), which causes the shielding on one of the substituents (L_1 or L_2, depending on the configuration). Therefore, L_1 substituent is clearly shielded in the (*R*)-MPA derivative, while L_2 is shielded in the (*S*)-MPA ester. This simplified and representative (NMR standpoint) conformation can be used in practice to rationalize the assignment of the absolute configuration of ketone cyanohydrins by means of their MPA derivatives: the substituent that presents a negative $\Delta\delta^{RS}$ should occupy the location of L_1 in Figure 1b, meanwhile the other substituent, with a positive $\Delta\delta^{RS}$, should be located in that of L_2.[12]

Attention was paid to the scope and limitations of the method. The $\Delta\delta^{RS}$ sign distributions in α-arylsubstituted cyanohydrins **13**-**16** showed anomalies at the protons placed at the β' position (methyl groups in **13**-**15** and methylene in **16**). In those cases, $\Delta\delta^{RS}$ presented very small values and

(8) Frisch, M. J.; et al. *Gaussian03*, revision E.01; Gaussian, Inc.: Wallingford, CT, 2004. For full reference see Supporting Information.

(9) In the most stable conformers, the CN group is not shielded by the Ph and probably this contributes to the phenomenon depicted in ref 7.

(10) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2006**, *71*, 1119.

(11) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504.

(12) The MPA esters of aldehyde cyanohydrins [$L_1CH(OH)CN$] adopt a different preferred conformation where the C−H and C═O bonds are synperiplanar, similar to the preferred form of the MPA derivatives of secondary alcohols, amines and thiols [$L_1CH(Z)L_2$, Z = OH, NH_2, SH]. In those cases, the presence of the hydrogen atom (small size and slight bond polarity) as substituent at the asymmetric carbon plays a major role in determining the main conformers. In ketone cyanohydrins, the asymmetric carbon is substituted by the CN group, L_1 and L_2. The equilibria are now more complex and the most favorable conformers (*spg*+, *spg*−, Figure 2) do not place any of those substituents synperiplanar to the C═O.

unexpected signs (i.e., +0.03 ppm, **14**). For every mentioned case, the aromatic system exhibited large values and the expected signs of $\Delta\delta^{RS}$ according to the model explained previously (i.e., +0.25 ppm, **14**).

In order to clarify these facts, theoretical calculations were performed, taking compound **15** as model. They revealed a similar conformational preference concerning the rotation around Cα-C(O) (MPA) and O−Cα′ (cyanohydrin) bonds as in previous studies: *spg*− and *spg*+ for (*R*)- and (*S*)-MPA derivatives respectively (see Figure 35S and Table 2S in Supporting Information).

Thus, CD analysis corroborated those conformational preferences (see Figure 36S in Supporting Information). Also, in low-temperature ^{1}H NMR experiments performed with the (*S*)-MPA derivative, a strong shielding effect was observed for the substrate phenyl protons (see Figure 37S in Supporting Information) as expected according to the increase in the number of molecules that adopt the most stable conformation (*spg*+). However, in an analogous set of experiments carried out with the (*R*)-MPA ester, the expected shielding of the methyl group (due to the increase in population of conformer *spg*−) did not take place.

The studies revealed that the observed behavior is due to a third conformational process related to the rotation around Ph-Cα′ bond at the cyanohydrin fragment that induces additional anisotropic effects on the methyl group in competition with those from MPA, and therefore resulting in an unpredictable $\Delta\delta^{RS}$ sign for that substituent. As expected, increasing the distance between the aryl group and the proton considered attenuates this overlapping effect, as observed in compound **16**, where the methyl group at γ' presents the expected sign.

The remainder of the studied cyanohydrins possessing aromatic rings behaves in agreement to the previous model, presenting opposite $\Delta\delta^{RS}$ signs for both L_1/L_2 substituents. The phenyl groups of compounds **3**, **9** and **10** are further from the asymmetric carbon and from the β'-methyls. In compounds **11** and **12**, the phenyl groups cannot rotate freely, and therefore, the third conformational process does not take place. In summary, when dealing with α-arylsubstituted cyanohydrins (such as **13**-**16**) the diagnostic signals are those from the aromatic systems, which present large $\Delta\delta^{RS}$ values and correct signs.

The experimental procedure that allows assigning the absolute configuration of a ketone cyanohydrin by NMR follows the steps that are applied to (*E*)-2-hydroxy-2-methyl-4-phenylbut-3-enenitrile in Figure 4.[13] Special attention has

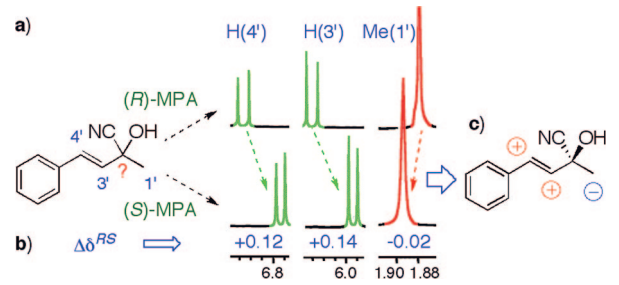

Figure 4. Steps to follow to assign the absolute configuration of ketone cyanohydrins using **9** as example.

to be paid to α-arylsubstituted cyanohydrins, where only the aryl signs must be considered for assignment purposes.

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Supporting Information Available: Experimental Section, Computational Methods, Spectroscopic Data, ^{1}H and ^{13}C NMR Spectra, ^{1}H NMR Assignments, Tables 1S−2S, Figures 33S−37S, Cartesian Coordinates and Total Energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (1) Preparation of the corresponding (*R*)- and (*S*)-MPA derivatives (Figure 4a). (2) Recording of their ^{1} NMR spectra and calculation of the chemical shifts differences ($\Delta\delta^{RS}$) for L_1/L_2 (Figure 4b). (3) Situate the substituent that presents negative signs in the position of L_1 according to Figure 1b [Me(1′)], and the substituent that shows positive signs in that of L_2 [H(3′) and H(4′)] (Figure 4c).