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"Mix and Shake" Method for Configurational Assignment by NMR: Application to Chiral Amines and Alcohols

Silvia Porto, Juan Durán, José Manuel Seco, Emilio Quiñoá, and Ricardo Riguera*

Departamento de Química Orgánica and Unidad de RMN de Biomoléculas asociada al CSIC, Universidad de Santiago de Compostela, E-15782 Santiago de Compostela, Spain

ricardo@usc.es

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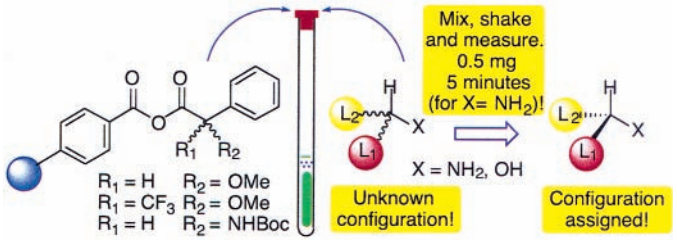
ABSTRACT



A new methodology for determining absolute configurations by NMR in just a few minutes is presented. The required derivatives are obtained by mixing a solid matrix-bound auxiliary reagent (MPA, MTPA, or BPG) with the chiral substrate (primary amines or secondary alcohols) directly in the NMR tube. The NMR spectra of the derivatives are obtained without any type of separation, workup, or manipulation. The use of a 1:2 (*R*)/(*S*)-MPA resin permits the configurational assignment to be carried out with just one spectrum.

NMR methods for the assignment of absolute configurations have undergone remarkable advances in recent years. Besides the classical reagents methoxytrifluoromethylphenylacetic acid (MTPA) and methoxyphenylacetic acid (MPA) originally proposed by Mosher[1] and Trost,[2] a wide variety of new and efficient auxiliaries have been developed that can be applied to diverse monofunctional compounds such as secondary and primary alcohols, amines or carboxylic acids,[3] and polyfunctional compounds (i.e., diols).[4] The commonly used method involves derivatization reactions between the substrate and the two enantiomers of the chiral auxiliary. However, the formation of two derivatives is no longer a prerequisite. Indeed, new methodologies that are applicable to alcohols and amines are based on the modification of the NMR spectra of relevant conformational species in equilibrium by means of modifying the temperature[5] or inducing selective complexation with metal cations.[6] The availability of such methods has simplified the procedures by requiring just one derivatizing reaction with only one enantiomer of the reagent. Automation has also been introduced in the analysis of enantiomeric mixtures and the assignment of

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(2) Trost, B. M.; Belletire, J. L.; Goldleski, P. G.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

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configuration on a microscale level by means of tandem HPLC NMR of 9-anthrylmethoxyacetic acid (9-AMA) esters of chiral alcohols.[7] This approach is an example of a recent major goal that is representative of the maturity reached in this field of chemistry and is of interest to all those involved in structural analysis, organic synthesis, or natural products.

In the pursuit of new tools to facilitate the use of this methodology, we now present a novel approach that allows the required derivatives to be obtained by simply mixing a solid matrix-bound auxiliary reagent with the substrate directly in the NMR tube and obtaining the NMR spectra without any type of separation, workup or manipulation being needed.

In this communication, we describe the application of this method to the assignment of configuration of chiral primary amines and secondary alcohols with MPA, MTPA, or BPG as auxiliary reagents (Figure 1).

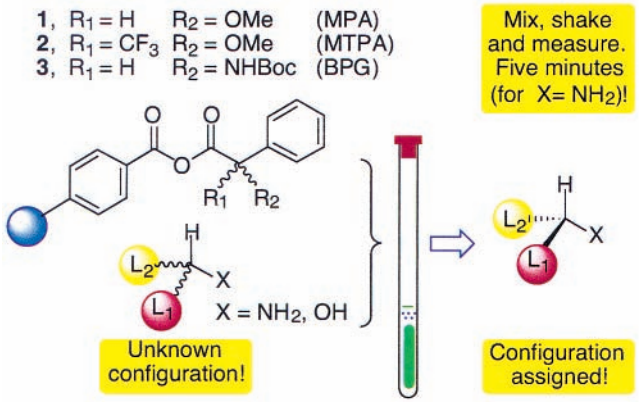

Figure 1. MPA, MTPA, and BPG resins employed in this new methodology.

The procedure is based on the binding of the auxiliary reagent (i.e., MPA) to a resin in such a way that, when attacked by the chiral nucleophile (amine or alcohol), the reagent part acts as an electrophile and liberates the corresponding amide or ester derivative into the solution while the solid matrix behaves as the leaving group.

Resins **1**−**3** were found to fulfill our expectations. These materials are easily prepared[9] from a commercial carboxypolystyrene resin,[10] present good swelling properties in $CDCl_3$, and possess a mixed carboxylic anhydride function that provides the appropriate reactivity and regioselectivity upon attack by an amine or alcohol. Furthermore, the resins also show remarkable stability.[11]

Resin **1** samples bearing a single enantiomer or different enantiomeric ratios of MPA [such as 1:2 (*R*)/(*S*)-MPA] were prepared and reacted in the NMR tube with amines **4**−**15** (Figure 2) as follows. The resin (2 equiv) was placed in the

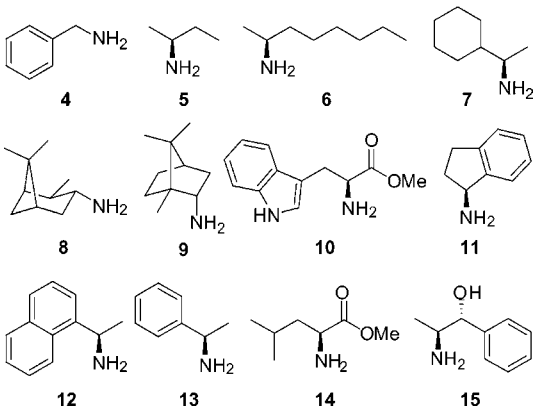

Figure 2. Amines of diverse structural characteristics selected for this study.[8]

NMR tube. The amine (1 equiv) was then added, followed by 300 μL of $CDCl_3$. The heterogeneous mixture in the tube was gently shaken for a few minutes (usually from 5 to 10 min), and then 300 μL of $CDCl_3$ was added (600 μL in total).[12]

Without any further manipulation, the ^{1}H NMR spectrum was recorded in the usual way immediately after sample preparation.[13] The solid resin floats on top of the $CDCl_3$ in the tube without causing interference of any kind in the spectrum of the resulting MPA-amide. In all cases tested, the transformations were shown to be quantitative.[14]

(7) Seco, J. M.; Tseng, L.; Godejohann, M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2149.

(8) It is worth noting the complete selectivity obtained in the case of *L*-norephedrine (**15**) when using the conditions developed for amines (absence of DMAP): only the amino group was derivatized, leaving the alcohol group free.

(9) Resins are prepared by transformation of the carboxylic groups to the acid chlorides with oxalyl chloride (or thionyl chloride) followed by treatment with MPA (idem for MTPA or BPG). **Standard Preparation Procedure for MPA Resins.** After 15 min of soaking, the resin (1 g, 1.4 mmol) in dry CH_2Cl_2 (10 mL) is treated with oxalyl chloride (20 mL, 233 mmol) (or with 20 mL of thionyl chloride) and the resulting mixture is heated under reflux (6 h; 4 h in the case of thionyl chloride) under an argon atmosphere. The polymer is filtered off, washed with dry CH_2Cl_2 (3 × 10 mL), and dried under vacuum. MPA (930 mg, 5.6 mmol) and dry pyridine (300 μL, 5.6 mmol) are added to a suspension of the acid chloride resin (1 g) in dry CH_2Cl_2 (10 mL), and the resulting mixture is shaken at room temperature (7 h) under an argon atmosphere. The polymer is filtered off under vacuum, washed with dry CH_2Cl_2 (6 × 10 mL), dried, and kept under vacuum. The formation of the anhydride was monitored by on-bead IR (characteristic bands at ν = 1802, 1730, 1087 cm^{-1}; 87% calculated yield). Analogous procedures were employed with the other auxiliary reagents.

(10) Carboxypolystyrene HL resin (100−200 mesh; loading = 1.4 mmol/g) was employed. The polymer matrix was copoly(styrene−1% DVB).

(11) Resins **1**−**3** are stable at room temperature for reasonable periods of time when kept dry under vacuum. In fact, in the case of **1**, less than 4% cleavage of MPA was detected after a 4 month period (monitored by ^{1}H NMR in $CDCl_3$ using toluene as an internal control).

(12) In a typical experiment, 9.8 mg (13.7 μmol) of resin **1** were reacted with 0.7 μL (6.8 μmol) of amine **5**.

(13) Reaction takes place so quickly that it can only be monitored by NMR if the order of addition to the tube is altered as follows: (1) amine is dissolved in $CDCl_3$; (2) MPA resin is added and the solution shaken; (3) the spectrum is recorded. In this way the evolution of the reaction can be monitored by observing the disappearance of the amine signals and the appearance of those corresponding to the amide [See in Supporting Information the monitoring of the transformation of **12** when reacted with 1:2 (*R*)/(*S*)-MPA resin].

(14) Measured as recovered amide and by complete disappearance of the amine signals in the ^{1}H NMR spectra.

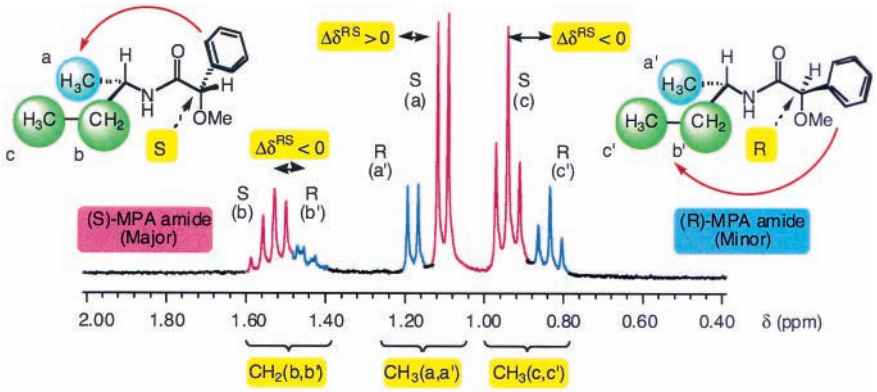

Figure 3. Straightforward assignment of the (*S*)-configuration of butyl-2-amine (**5**) from a single spectrum using the 1:2 (*R*)/(*S*)-MPA resin **1.**

The resulting spectrum is sufficiently clean to allow assignment of the absolute stereochemistry at the microscale level (less than 0.5 mg of substrate), in a single operation and requiring just one spectrum, if a 1:2 (*R*)/(*S*)-MPA resin **1** is used.

In this approach, the different ratios of the NMR signals of the two diasteromeric amides [those of the (*R*)-MPA amide are half the size of those for the (*S*)-amide] allow the upfield/downfield shifts ($\Delta\delta^{RS}$) of the amine substituents to be determined easily on the same spectrum. This situation makes it unnecessary to perform the usual double derivatization [with (*R*)-MPA and (*S*)-MPA] and recording of two spectra. Although integration of the signals of the diastereomers always showed values very close to the expected 1:2 ratio, researchers should be aware that, in other cases, kinetic resolution could be in operation.

The assignment of absolute configuration is, in both, cases straightforward from the $\Delta\delta^{RS}$ signs by use of the configurational models.[3b,15] Figure 3 represents the application of this method in the case of (*S*)-butyl-2-amine (**5**).

In a similar way to the MPA resins (**1**), MTPA (**2**) and BPG resins (**3**) were prepared and assayed with amines. However, in the case of **2** and although the derivatization was shown to take place successfully, the quality of the spectra was not as good as with **1**, probably due to the different swelling and floating properties of the MTPA resin.

Further applications of this methodology are based on the single derivatization procedures developed for amines and alcohols in which complexation with Ba^{2+} allows assignment of the configuration from just one derivative.[6,3b] This requires the recording of a first NMR spectrum (CD_3CN as the solvent),[16] followed by addition of $BaClO_4$ directly into the NMR tube until saturation and recording of the second spectrum. Comparison of both spectra allows the configuration to be inferred (Figure 4).

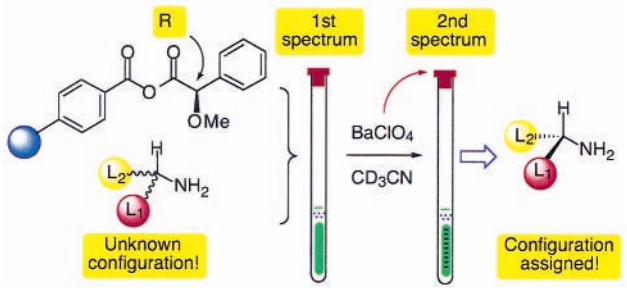

Figure 4. Application of the single derivatization method (complexation with Ba^{2+}) to amines.

MPA resins (**1**) also gave excellent results when employed to derivatize chiral secondary alcohols **16**−**21** (Figure 5). The transformations into esters were quantitative in $CDCl_3$, in the presence of DMAP,[17] and the configurational assignment only requires recording of the NMR spectra and interpretation of the $\Delta\delta^{RS}$ signs in the usual way.[2,3b,18]

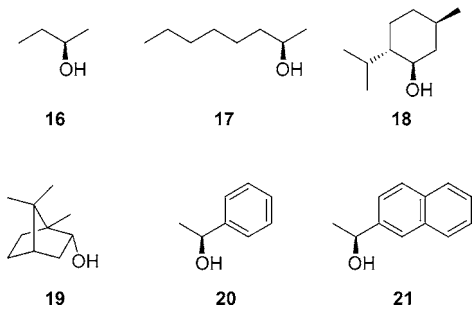

Figure 5. Alcohols of diverse structural characteristics selected for this study.

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(16) Resin **1**, derivatized with only one MPA enantiomer (i.e., (*R*)-MPA) was employed in the usual way. Formation of the derivative takes longer (90 min approximately) than when the reaction is carried out in $CDCl_3$, due to the different swelling properties of the resin in both solvents.

In conclusion, the use of solid matrix-bound auxiliary reagents has opened up new possibilities for the assignment of configuration by NMR and these are illustrated in this paper with its application to chiral amines and alcohols. The advantages of this method, when compared to the usual procedures, are its simplicity and convenience: external reaction flasks or manipulations are not necessary, coupling reagents (such as DCC) are not needed, undesired side products (such as dicyclohexylurea) are not generated, no filtration or purification of any kind is required, the reaction solvent ($CDCl_3$, CD_3CN) is also the NMR solvent, and the transformation of the substrate amines/alcohols into amides/esters takes place in 5 min (in the case of amines) at room temperature in a quantitative yield and on a microscale level.

Work is in progress to expand the scope of this new methodology to other chiral substrates.

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Supporting Information Available: ^{1}H NMR monitoring of the transformation of 1 equivalent of (*R*)-1-(1-naphthyl)-ethylamine (**12**) with 2 equivalents of 1:2 (*R*)/(*S*)-MPA resin according to ref 13 (1 page).

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(17) DMAP is added into the NMR tube with the other reagents. The procedures of the experiments are analogous to those with amines. A relationship alcohol/resin/DMAP 1/5/2 (equiv) was usually maintained. Longer reaction times than those of amines were necessary (5 h) for complete consumption of the starting alcohol. Strictly dry conditions are required. One or two beads of molecular sieves (4 Å) can be added into the NMR tube without causing any interference with the recording of the spectrum.

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