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# Chiral Thiols: The Assignment of Their Absolute Configuration by $^{1}$H NMR

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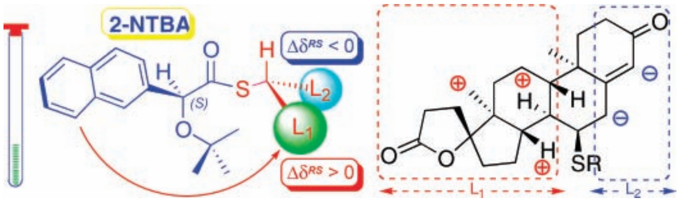
## ABSTRACT



**A general NMR spectroscopy protocol for determination of absolute configuration of thiols, that includes the introduction of new aryl-*tert*-butoxyacetic acids as chiral derivatizing agents (CDAs), is described.**

$^{1}$H NMR has become a very convenient tool for the assignment of absolute configuration of a variety of organic compounds. Derivatization of the substrate with selected chiral derivatizing agents (CDAs) and interpretation of the $\Delta\delta$ parameters ($\Delta\delta^{RS}$, $\Delta\delta^{T1T2}$, $\Delta\delta^{Ba}$...) obtained by comparison of two NMR spectra (either from two diastereomeric derivatives or from a single derivative at different temperatures or before/after formation of a metal complex) allow one to infer the configuration. Chiral substrates that are amenable to treatment with these methods include primary and secondary alcohols, primary amines, carboxylic acids, cyanohydrins, diols, triols, and amino alcohols.[1]

Thiols, the simplest organic compounds of sulfur, are relevant not only for their presence as natural products and their roles in biochemistry but also for their applications in the preparation of other organosulfur compounds[2] and for their uses as catalysts in asymmetric synthesis.[3] Hence, easy and cheap procedures for the reliable assignment of the absolute configuration of thiols should be very useful.

In this communication, we describe a procedure for chiral secondary thiols that requires derivatization of the thiol with the two enantiomers of 2-methoxy-2-phenylacetic acid (MPA) and comparison of the $^{1}$H NMR spectra of the corresponding diastereomeric thioesters.[4] In addition, the new and more efficient reagent 2-*tert*-butoxy-2-(2-naphthyl)acetic acid (2-NTBA) is presented.

To establish a general and validated methodology for the assignment of configuration of thiols and to know which one yielded the largest $\Delta\delta^{RS}$ values,[5] we derivatized the *R* enantiomers of 2-methoxy-2-phenylacetic acid (MPA, **1**), 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (MTPA, **2**), Boc-phenylglycine (BPG, **3**), and 2-(9-anthryl)-2-meth-

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(1) For review, see: (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. For polyfunctional compounds, see: (b) Lallana, E.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2006**, *8*, 4449 and references therein.

(2) (a) Patai, S. *The Chemistry of the Thiol Group: Parts I&II*; John Wiley & Sons: New York, 1974; Vol. 2. (b) Barret, G. C. Thiols. In *Comprehensive Organic Chemistry*; Jones, D. N. Ed.; Pergamon Press: Oxford, 1979: Vol. 3, Chapter 11.1.

(3) (a) Tseng, S. L.; Yang, T. K. *Tetrahedron: Asymmetry* **2005**, *16*, 773. (b) Haque, M. B.; Roberts, B. P. *Tetrahedron Lett.* **1996**, *37*, 9123.

(4) Two previous reports dealing with the use of NMR for this purpose consisted of empirical methods using acetic acid derivatives tested with a small number of thiols (three and two, respectively). See: (a) Helmchen, G.; Schmierer, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 703. (b) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, *46*, 3239.

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oxyacetic acid (9-AMA, **4**) with racemic pentane-2-thiol (chosen as model compound for the screening, Figure 1a).

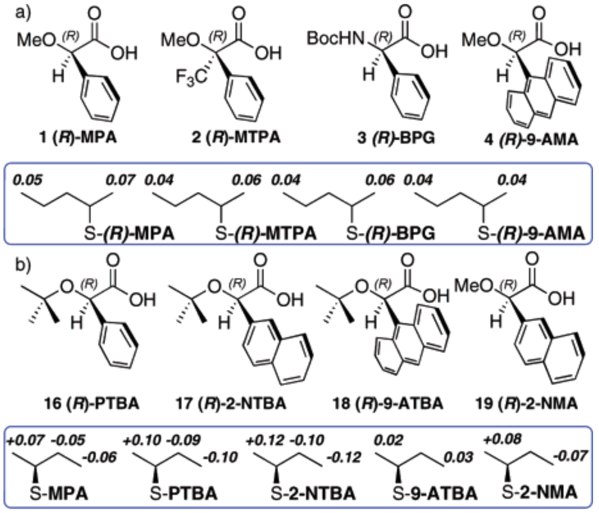

**Figure 1.** (a) CDAs **1**−**4** selected for this study and $\Delta\delta^{RS}$ absolute values (ppm, Me groups, *italic*) of their thioesters with pentane-2-thiol ($CDCl_3$, 250.13 MHz). (b) CDAs **16**−**19** and $\Delta\delta^{RS}$ values (ppm, *itali*c) of butane-2-thiol thioesters ($CDCl_3$, 250.13 MHz).

MPA (**1**) generated the largest separation of chemical shifts between diastereomeric thioesters, and as a result, it was selected to continue the studies.

Next, we decided to examine the NMR behavior of the (*R*)- and the (*S*)-MPA thioester derivatives of a series of thiols of known absolute configuration and see if—just as in the case of secondary alcohols, primary amines, and other functional groups—a correlation between the absolute configuration and the NMR chemical shifts was present.

Figure 2 shows the $^1$H NMR spectra of the MPA derivatives of (*S*)-butane-2-thiol (**5**). It is easily observable that the signal corresponding to $CH_3(1)$ is more shielded in the (*S*)- than in the (*R*)-MPA thioester. The opposite situation holds for $CH_2(3)$ and $CH_3(4)$, which are more shielded in the (*R*)- than in the (*S*)-MPA thioester. These differences of chemical shifts expressed as $\Delta\delta^{RS}$ show a positive sign for $CH_3(1)$ ($\Delta\delta^{RS} = +0.07$ ppm) and a negative sign for $CH_2(3)$ and $CH_3(4)$ ($\Delta\delta^{RS} = -0.05$ and $-0.06$ ppm, respectively).

Likewise, the $^1$H NMR spectra of the (*R*)- and the (*S*)-MPA thioesters of the structurally diverse thiols **6**−**15** of known configuration (Figure 3) showed signs of $\Delta\delta^{RS}$ for protons of the side chains ($L_1$ and $L_2$) identical to those with the same spatial relationship in **5** (positive for $L_1$ and negative for $L_2$).

This distribution of $\Delta\delta^{RS}$ signs is coherent for all the thiols studied and correlates with the configuration; therefore, it can be used to determine the absolute stereochemistry of the thiol. Figure 3 shows the spatial arrangement of $L_1$/$L_2$ and the corresponding $\Delta\delta^{RS}$ signs. These results can be explained on the basis of the presence, in each diastereomeric thioester, of NMR relevant conformer/s in equilibria where the shielding effect produced by the phenyl ring of the auxiliary affects mainly one of the substituents ($L_1$ or $L_2$) of the thiol—the one located closer to it—thus serving to connect the configuration of the auxiliary part with that of the thiol.

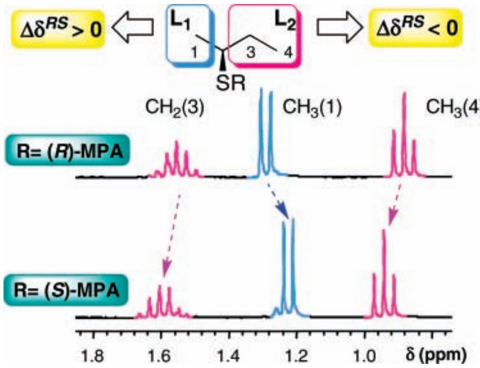

**Figure 2.** Partial $^1$H NMR spectra of the (*R*)- and (*S*)-MPA thioesters of (*S*)-butane-2-thiol (**5**) ($CDCl_3$, 250.13 MHz).

A combination of theoretical studies and experimental evidence led to the identification of the significant conformers. A short account follows.

We performed geometry and energy calculations[6] on dihedral angles $\Phi_1$ [$O-C_\alpha-C_{Ph}-C_{Ph}$], $\Phi_2$ [$O-C_\alpha-C=O$], $\Phi_3$ [$O=C-S-C_{\alpha'}$],[7] and $\Phi_4$ [$(O)C-S-C_{\alpha'}-H$] belonging to the MPA thioesters of methanethiol and butane-2-thiol (both taken as model compounds).

The resulting scenario shows equilibria between two predominant species of conformers that are named, according to the geometry of $\Phi_2$ at the MPA moiety, synperiplanar (*sp*, minor) and antiperiplanar (*ap*, major and NMR relevant). The situation depicted resembles that of the MPA derivatives of amines (Figure 4a).[8]

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[5] A value of $\Delta\delta^{RS}$ for a given substituent is the difference between its chemical shift in the (*R*)-CDA derivative minus that in the (*S*)-CDA derivative.

[6] DFT (B3LYP/6-31G*) both in gas and solution (PCM) with Gaussian03. See: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

[7] Conformational analysis on simple thioesters had previously shown that the *cis* planar form around the $\Phi_3$ angle was the prevailing conformation in a variety of solvents. See: (a) Nagy, P. I.; Tejada, F. R.; Sarver, J. G.; Messer, W. S., Jr. *J. Phys. Chem. A* **2004**, *108*, 10173. (b) Deerfield, D. W., II; Pedersen, L. G. *J. Mol. Struct. (THEOCHEM)* **1995**, *358*, 99. (c) Revén, M. F.; Boese, R.; Védova, C. O. D.; Oberhammer, H.; Willner, H. *J. Org. Chem.* **2006**, *71*, 616.

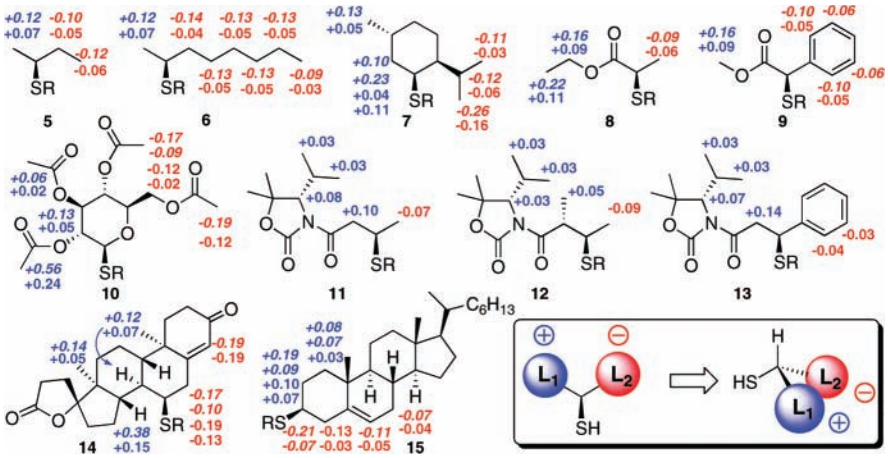

**Figure 3.** Values of $\Delta\delta^{RS}$ (ppm) and sign distribution for the MPA (plain) and 2-NTBA (*italic*) thioesters of thiols **5**−**15** ($CDCl_3$, 250.13 and 500.13 MHz). The 3-D model and the $\Delta\delta^{RS}$ signs obtained from those data are shown in the frame.

Subsequently, when the thiol is derivatized with the *R* enantiomer of MPA, one of the substituents of the asymmetric carbon ($L_2$, Figure 4a) faces the phenyl ring in the main conformer (*ap*), experiencing a measurable shielding effect. The other substituent ($L_1$) is shielded in the least populated conformer (*sp*). Overall, the shielding affects mainly to $L_2$ in this thioester. When the (*S*)-MPA is used instead, a similar analysis shows that the shielding affects largely to the other substituent ($L_1$, Figure 4a).

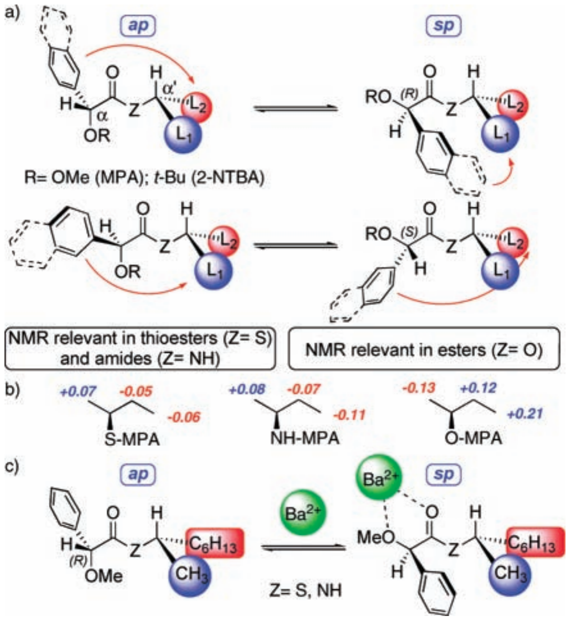

**Figure 4.** (a) Antiperiplanar (*ap*) and synperiplanar (*sp*) conformers in the equilibria of (*R*)- and (*S*)-MPA (and 2-NTBA) derivatives of thiols, amines, and alcohols. (b) Values and signs of $\Delta\delta^{RS}$ for MPA thioesters, amides, and esters with the same *sec*-butyl skeleton. (c) Complexation of the (*R*)-MPA thioester of (*S*)-octane-2-thiol and (*S*)-octan-2-amine with barium(II).

These theoretical results justify the experimental $\Delta\delta^{RS}$ signs found in thioesters **5**−**15**. For instance, in the (*R*)-MPA derivative of (*S*)-butane-2-thiol (**5**), the ethyl group is subjected to the aromatic shielding effect of the phenyl ring of the auxiliary in the most populated form (*ap*), while in the (*S*)-MPA derivative, it is not (Figure 2). The difference of chemical shifts, expressed as $\Delta\delta^{RS}$, is in this case negative, and this sign is therefore associated with that particular spatial location of the chain with respect to the phenyl ring of the auxiliary (corresponding to $L_2$ in Figure 4a). For its part, the methyl group is in front of the phenyl ring in the NMR relevant conformer (*ap*) of the (*S*)-MPA derivative, but it is not in the (*R*)-MPA derivative. Accordingly, it presents a positive $\Delta\delta^{RS}$ sign, also associated with the stereochemistry of the chiral center (corresponding to $L_1$ in Figure 4a). Exactly the same correlations are obtained for thioesters **6**−**15**.

The existence of these *ap*/*sp* equilibria and the spatial arrangement between $L_1$/$L_2$ and the phenyl group were experimentally confirmed from several sources of evidence: (a) Replacement of the MPA moieties by an acetate group and evaluation of the anisotropic effects of the phenyl groups on $L_1$/$L_2$. (b) Comparison of $\Delta\delta^{RS}$ signs of MPA thioesters with those of MPA amides and esters presenting identical carbon skeletons (Figure 4c) reinforce the analogy between thioesters and amides (*ap* predominant conformer) as opposed to esters (*ap* minor conformer). (c) Low-temperature NMR experiments with (*R*)- and (*S*)-MPA thioesters (from 298 to 183 K; $CS_2/CD_2Cl_2$ 4:1) showed no significant changes, indicating that the equilibria are already shifted toward the most populated conformers (*ap*) at the highest temperature. (d) Complexation of MPA thioesters with barium(II) [$Ba(ClO_4)_2$; $CD_3CN$] induced an NMR response analogous to the well-established behavior of MPA amides in the same circumstances: a redistribution of the *ap*/*sp*

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(8) In MPA amides, *ap* forms are the most populated and NMR relevant. In MPA esters, where the *ap*/*sp* forms are also present, the equilibria are shifted in the opposite way and *sp* conformers are major and NMR relevant (Figure 4a).

equilibria toward the *sp* conformer.[9] The experiments were performed with the (*R*)- and (*S*)-MPA thioesters of (*S*)-octane-2-thiol and the (*R*)- and (*S*)-MPA amides of (*S*)-octan-2-amine (Figure 4c).

The above results are fully coherent with the presence of a predominant form in solution where the spatial location of the phenyl group with respect the $L_1/L_2$ substituents is similar to the one depicted in the *ap* forms.

The *ap* conformation is also present in the solid state, as shown in the diffraction X-ray spectroscopy of a crystal of the (*S*)-MPA thioester of 1-thio-$\beta$-D-glucose tetraacetate (**10**).[10] It is noteworthy that the proximity shown in the crystal (see Supporting Information) between the phenyl group and the acetate at C(2) could also be detected in solution throughout a NOESY experiment.

Although the $\Delta\delta^{RS}$ values obtained with MPA are good enough to assign the configuration, we decided to explore the possibility of obtaining higher $\Delta\delta^{RS}$ values by replacement of the methoxy and phenyl groups present in MPA by *tert*-butoxy and naphthyl/anthryl groups. In this way, we expected to increase the predominance of the *ap* conformers, a more intense anisotropic effect and a more favorable orientation of the aryl rings toward $L_1/L_2$. Three CDAs [2-*tert*-butoxy-2-phenylacetic acid (**16**, PTBA),[11] 2-*tert*-butoxy-2-(2-naphthyl)acetic acid (**17**, 2-NTBA), and 2-(9-anthryl)-2-*tert*-butoxyacetic acid (**18**, 9-ATBA); **17** and **18** are new reagents] were synthesized and tested. Figure 1b compares the $\Delta\delta^{RS}$ values and signs of the butane-2-thiol (**5**) thioesters of MPA and these new agents. 2-NTBA (**17**) yielded the best values (virtually the double of those of MPA), and these excellent results were further confirmed when it was applied to thiols **6**−**10** and **14** and **15** (Figure 3). It is the combination of both the 2-naphthyl moiety and the *tert*-butoxy group that makes this reagent so effective, as shown by the fact that the introduction of only the 2-naphthyl group (derivatization of butane-2-thiol with 2-NMA **19**, Figure 1b) is not enough to increase significantly the $\Delta\delta^{RS}$ values.

Geometry and energy calculations analogous to those described above for MPA confirmed the similarity between the conformational equilibria of the MPA and 2-NTBA thioester derivatives: the *ap* conformers are the predominant forms in both cases (Figure 4a).

To sum up, a correlation between the absolute configuration and the NMR spectra of their MPA and aryl-*tert*-butoxyacetic acid derivatives holds for all the compounds of Figure 3 that possess substituents that are acyclic, cyclic, saturated, unsaturated, oxygenated, etc. It can therefore be considered to be widely general for thiols and be used for their configurational assignment. Experimental (chemical shifts analysis, low-temperature NMR, selective formation of metal complexes) and theoretical (energy calculations) data corroborate the certainty of the conformations presented in Figure 4a and substantiate the model for users (in order to place in space $L_1$ and $L_2$ according to their $\Delta\delta^{RS}$ signs) shown in Figure 3.

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**Supporting Information Available:** General experimental procedures and full spectroscopic data (including $^1$H NMR spectra) for all new compounds; crystal data and X-ray figure of the (*S*)-MPA thioester of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2006**, *71*, 1119 and references therein.

[10] Colorless prisms of the (*S*)-MPA thioester of 1-thio-$\beta$-D-glucose tetraacetate (**10**) were recrystallized from diethyl ether/hexane. Crystallographic data have been deposited with the Cambridge Crystallographic data center and allocated the deposition number CCDC 650882.

[11] Chataigner, I.; Lebreton, J.; Durand, D.; Guingant, A.; Villiéras, J. *Tetrahedron Lett.* **1998**, *39*, 1759.