RECENT ADVANCES IN ^{1}H NMR DETERMINATION OF ABSOLUTE CONFIGURATION VIA CHIRAL DERIVATIZING AGENTS

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INTRODUCTION

NMR analysis of diastereomeric derivatives is one of the few methods capable of establishing the absolute configuration of chiral compounds. Reaction with a chiral derivatizing agent (CDA) that turns enantiomers into diastereomers correlates the distinct chemical shift changes of the diastereomeric derivatives to their absolute configuration. Although the nuclei used in NMR experiments include ^{2}H, ^{13}C, ^{31}P, ^{29}Si, ^{1}H NMR remains to be the most popular method.

Basics of ^{1}H-NMR Determination of Absolute Configuration

In the classical approach developed by Dale and Mosher,[1] a chiral molecule is reacted with *R*- and *S*-CDAs to form two diastereomers. Commonly used CDAs usually incorporate an aryl ring at their α-carbon. The different orientation of the aromatic shielding cone in *RR/SR, RS/SS* (Figure 1) leads to selective shielding or deshielding of R_1 or R_2 at the asymmetric center. Thus, the spatial relationship between R_1/R_2 and the aryl ring is correlated to the observed chemical shift change. Consequently the absolute configuration of the substrate would be established.

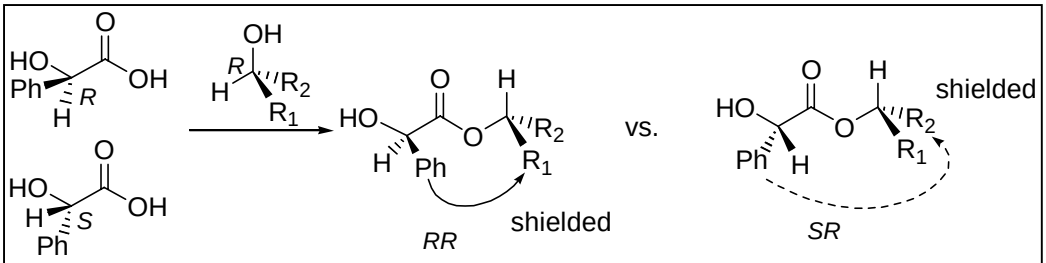

Figure 1. Derivatization of secondary alcohol by R-mandelic acid. R_2 is defined arbitrarily as the higher priority group compared with R_1.

R_1 of the *RR* derivative illustrated in Figure 1 is at higher field than R_2. Conversely, R_2 in the *SR* derivative shifts more upfield relative to R_1. For *R* and *S*-alcohol, the chemical shift changes $\Delta\delta^{RS}$ of their diastereomers behave oppositely (Table 1), $(\Delta\delta^{RS})_R R_1 \times (\Delta\delta^{RS})_S R_1 < 0$

$(\Delta\delta^{RS})_R R_1 = \delta$ (*RR*-*SR*) of R_1

$(\Delta\delta^{RS})_S R_1 = \delta$ (*RS*-*SS*) of R_1

The $\Delta\delta$ distribution pattern of the substituents in CDA derivatives illustrates the way to determine the absolute configuration. Empirical correlation between chemical shift and configuration was drawn from the NMR spectra of diastereomers derived from substrates with known configuration.[1,2] Once theoretical models[3-6] succeeded in rationalizing the empirical correlation, the "sense of nonequivalence" was applied to a broad spectrum of chiral compounds.

Table 1. NMR Chemical shift differences for diastereomeric mandelic esters.

R_2	R_1	$\Delta\delta^{RS}$ (R_2)	$\Delta\delta^{RS}$ (R_1)
t-Bu	Me	-0.15	+0.24
t-Bu	Et	-0.22	+0.37
Ph	*t*-Bu	---	+0.22

Conformation Model

In mandelic esters, the α–hydroxyl group eclipses the carbonyl group due to hydrogen bonding. For *O*-methylmandelate, even in the absence of hydrogen bonding the conformational model retains with the α-methoxy group near coplanar with the carbonyl (Figure 2). The shared model for both mandelate and MPA esters highlights the electron-withdrawing character of the methoxy group. Nevertheless, the larger $\Delta\delta^{RS}$ observed of mandelates suggests that hydrogen bonding assists to lock the conformation.[1] In MTPA esters, it is the CF_3 group that eclipses the carbonyl due to electronic factors (Figure 3).[1,7]

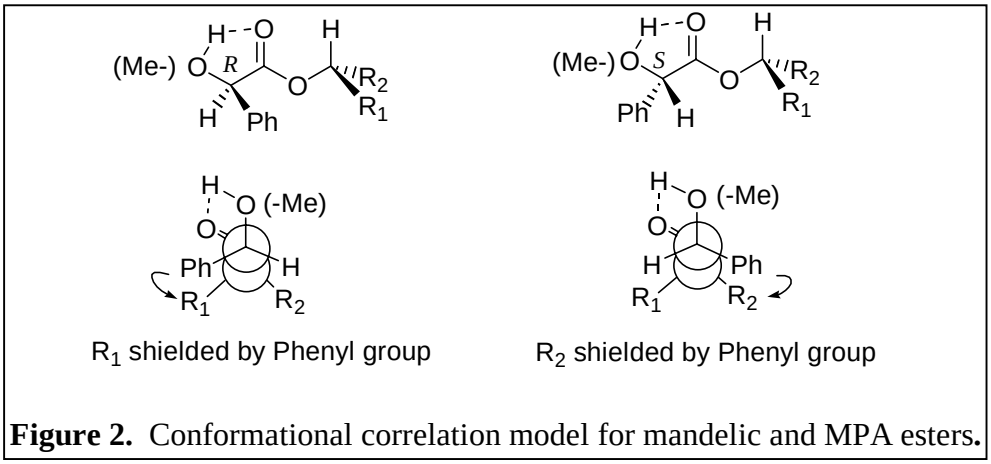

Figure 2. Conformational correlation model for mandelic and MPA esters.

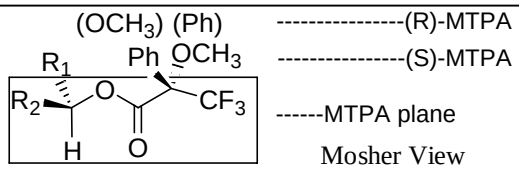

Figure 3. Conformational correlation models for MTPA esters.

ADVANCES IN MOSHER METHOD

Theoretical conformation study

Molecular mechanics (MM), semiempirical (AM1), and aromatic shielding calculations were carried out to study the conformations of MTPA and MPA derivatives.[5,8-10] Three factors are responsible for the chemical shift changes: the nature of the aromatic system, the geometry and orientation of the aryl group relative to the substrate part of the derivative and the population distribution of the conformers.

In MTPA esters, MM and AM1 calculations suggest that three major rotamers are close in energy: *ap1* (antiperiplanar), *sp1* (synperiplanar) and *sp2*, with *ap1* as the most stable conformation. The small energy gap results in the insignificant temperature dependence of $\Delta\delta^{RS}$ in MTPA esters according to Boltzmann distribution. The aromatic shielding and deshielding effects in *sp1* and *sp2* partially cancel each other. Hence the deshielding effect in the major conformer *ap1* becomes the key anisotropic contribution. Accordingly, it is reasonable to have observed rather small $\Delta\delta^{RS}$ in MTPA esters.[11] MPA esters differ from MTPA esters in that two major rotamers *ap* and *sp* are well separated in energy (Figure 4). The expected minimized cancellation of anisotropic shielding effects is supported by relatively large experimental $\Delta\delta^{RS}$ observed.

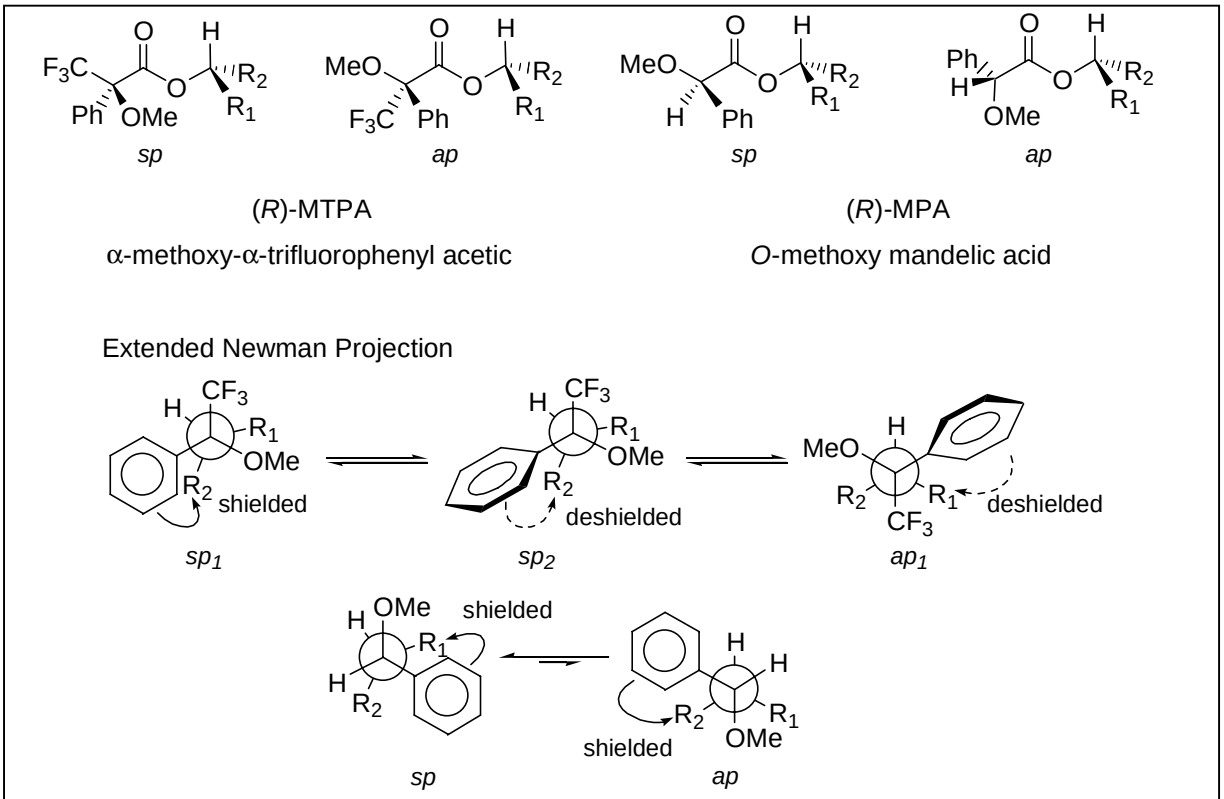

Figure 4. Low energy conformations of MTPA and MPA esters derived from MM and AM1.

Contrary to the ester case, MTPA induces larger $\Delta\delta^{RS}$ in its amide than MPA does. In the most populated rotamer, *sp*, the R_1 group is shielded by the α-phenyl ring. On the other hand, similar to MPA esters, MPA amides consist of two principal conformers but with *ap* more stable than *sp* due to hydrogen bonding (Figure 5).

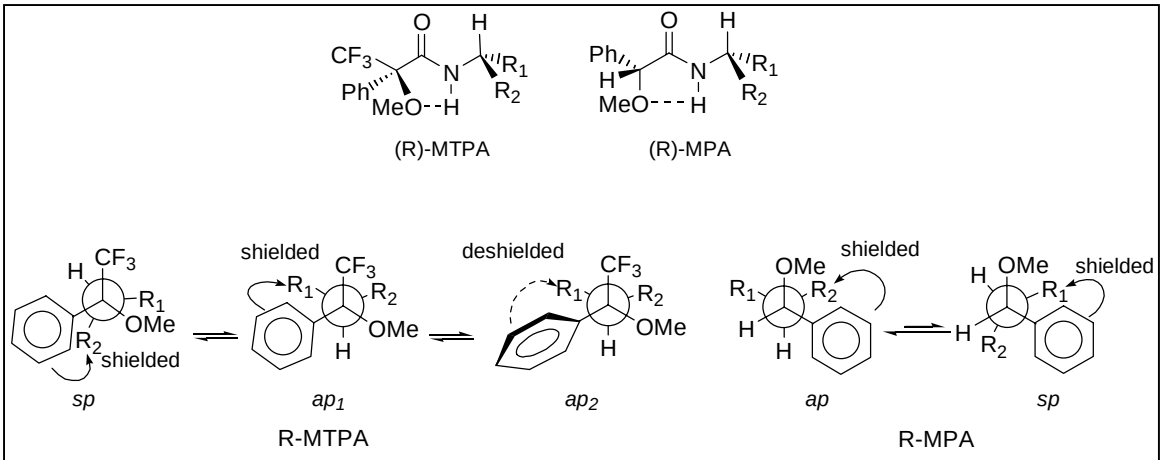

Figure 5. Low energy conformations of MTPA and MPA amides derived from MM and AM1.

MTPA vs. MPA

The popularity of MTPA as a CDA probably derives from its resistance to racemization at the α-carbinyl carbon and its potential for ^{19}F-NMR analysis. However, with new derivatization procedures that suppress racemization,[12] MPA is regarded as a more efficient chiral derivatizing agent especially in the case of alcohol configuration determination.

New Chiral Derivatizing Agents

The goal of creating new chiral derivatizing agents is to generate larger chemical shift change either by increasing the size and strength of aromatic shielding cone or by locking the conformations. Larger α-π systems were tested in order to achieve increased chemical shift changes and a remote anisotropic effect (Figure 6). Methoxy-(2-naphthyl)acetic acid (2-NMA) and 2-anthrylmethoxyacetic acid (2-AMA) proved to be particularly effective for linear alcohols, 1-NMA and 9-AMA cyclic alcohols (Figure 7). In certain cases,[13] Ba^{2+} proved to efficiently lock the *sp* conformation in MPA (Figure 6), although its generality is still under investigation.[14]

The scope of Mosher Method has been expanded to highly hindered secondary alcohols,[15,16] primary alcohols,[17] primary amines,[4,13,18] 1,n-diols,[19] β-amino alcohols,[20] and carboxylic acids.[21-23] Functional group manipulation can lead to even broader range of chiral substrates. For example,

carboxylic acids could be converted from aldehyde, alkene and glycol etc. New CDAs such as phenylglycine methyl ester (PMGE) were designed for carboxylic acids (Figure 8).[21]

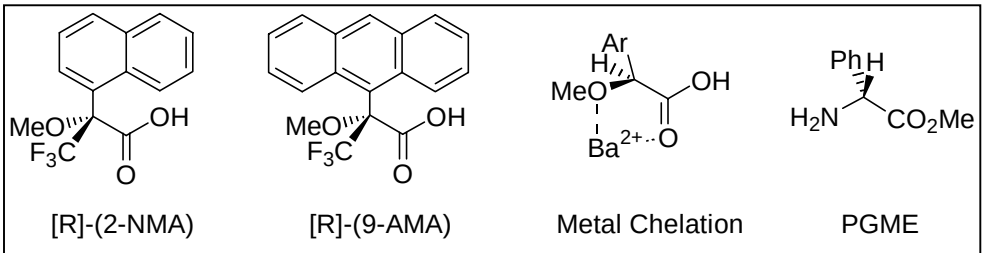

Figure 6. Newly developed chiral derivatizing agent.

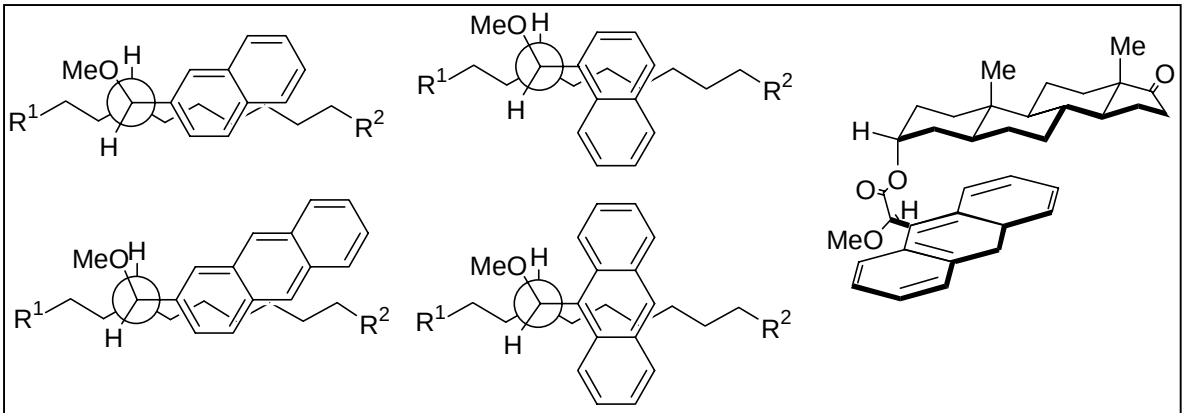

Figure 7. Remote and local anisotropic effect of larger aryl rings.

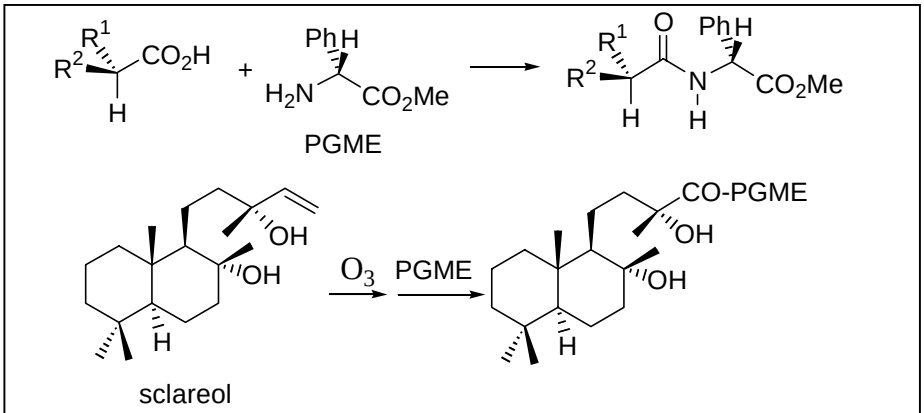

Figure 8. The determination of the absolute configuration of sclareol**.**

Simplification of Mosher Method

As addressed previously, the classical Mosher method necessitates the use of both *R* and *S*-CDAs. The possibility of preparing only one derivative has been investigated recently. Either *R* or *S*-MPA at two different NMR temperatures successfully determined the configuration of secondary alcohols.[24,25] The limit was soon pushed to one derivative at constant NMR temperature, albeit the scope is still confined to secondary alcohols.[26]

APPLICABILITY OF MOSHER METHOD

Mosher method cannot give accurate results if the derivative conformation deviates from the theoretical model because of steric hindrance,[15] molecular flexibility or the interference from other aryl rings present in a mobile side chain of the substrate moiety.[14] Valid application should fulfill the following requirements:

a. The signs of $\Delta\delta$ remain uniformly positive or larger on one side chain and negative or smaller on the other side.

b. The $\Delta\delta$ is sufficiently large relative to experimental error. The choice of CDA is thereby important.

c. Caution should be taken to apply the method outside the established scope, e.g. polyfunctional compounds.[27]

CONCLUSION

The mosher method is one of the classical methods for determining the absolute configuration of chiral compounds. The spatial relationship between R_1/R_2 and the α-aryl substituent in the acid moiety is reflected in chemical shift difference $\Delta\delta$ through the anisotropic time-weighted shielding effect of the aryl ring. The scope includes alcohols, amines, diols, and carboxylic acids. For secondary alcohols the procedure has been simplified to the use of one CDA enantiomer and constant NMR temperature. Work is in progress to test the idea that the absolute stereochemistry can be elucidated by comparison of calculated chemical shift change for one CDA derivative and its experimental NMR spectrum.

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(11) The degree of deshielding effect abates with distance dramatically.
(12) Synthetic routes that reduce racemization if not completely eliminate the possibility: a) dicyclohexylcarbodiimide and 4-dimethyl-aminopyridine; b) dicyclohexylcarbodiimide and hydroxybenzotriazole in pyridine; c) DMF and oxalyl chloride.
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