Pergamon

Tetrahedron 57 (2001) 2231–2236

TETRAHEDRON

Determination of the absolute stereochemistry of alcohols and amines by NMR of the group directly linked to the chiral derivatizing reagent

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Received 27 October 2000; revised 13 December 2000; accepted 4 January 2001

Abstract—NMR experiments and calculations (PM3) indicate that the asymmetry of the substrate (alcohol or amine) leads to the redistribution of the conformer populations of their methoxyphenylacetic acid (MPA) or methoxytrifluoromethylphenylacetic acid (MTPA) derivatives rather than to the distortion of the conformer geometry as was postulated by Mosher. An absolute configuration of secondary alcohols and primary amines can be determined according to the chemical shifts of the $C_\alpha H$ protons in NMR spectra of their MPA derivatives. The $C_\alpha H$ proton of the diastereomer having a greater relative population of the *sp* form should resonate at a lower field.

1. Introduction

A survey of the recent chemical literature reveals an explosion of an interest in design of chiral derivatizing reagents (CDR) to access an enantiomeric purity and in the determination of the absolute configuration of organic compounds by NMR (^1H, ^{19}F, ^{13}C, ^{31}P, ^{77}Se).[1] The differentiation of the NMR signals of the diastereomers[2] or diastereotopic complexes[3] obtained by the reaction of the CDR (with the known absolute configuration) with the substrate molecule is used to determine the absolute configuration of the latter. Theories that correlate an absolute configuration and NMR chemical shifts of the substrate fragment have been developed.[4] These models exploit the selective shielding effect of the aryl group of the CDR on the nuclei of the substrate part of the obtained diastereomer. The relative chemical shifts of the substrate protons would depend on the relative spatial arrangement of the substrate fragment and the aryl group of the CDR part of the diastereomer as well as on the absolute configuration of both chiral centers.

At the same time, attempts to find an empirical correlation between NMR parameters of the CDR moiety of the diastereomer and the configuration of the substrate are known.[4a,5] For example, in the case of alcohols, the idea of using NMR of the acid moiety of a derived ester is very attractive due to the fact that usually the NMR signals do not overlap with other resonances. Only Mosher, however, gave a reasonable interpretation of the ^{19}F NMR chemical shifts of methoxytrifluoromethylphenylacetic acid (MTPA) derivatives of secondary alcohols and primary amines and proposed the model to determine an absolute configuration by ^{19}F NMR of the CF_3 group in the case of MTPA.[4a,5]

According to Mosher, the MTPA-esters in solution exist in a single form, where the C_α–CF_3 bond is, approximately, *syn-periplanar* to the C=O bond. Due to the difference of steric interactions between bulky substituents of alcohol and acid moieties in (*R*)- and (*S*)-esters that leads to distortion of the 'classical' conformation (Fig. 1) there is some difference of the CF_3–C_α–C=O angles. Therefore, the observed difference between the ^{19}F NMR chemical shifts of the (*R*)- and (*S*)-MTPA esters was explained as a result of different anisotropic deshielding effects of the C=O bond on the CF_3 group in these diastereomers.

This model has been used to explain the difference of ^{19}F NMR chemical shifts of the (*S*)- and (*R*)-MTPA-esters. It was found that in the series of similar derivatives when the interactions of MTPA and alcohol moieties do not vary, the differentiation of their ^{19}F NMR chemical shifts should also be very similar. Thus, provided the stereochemistry of one compound is known, the stereochemistry in a whole series

Keywords: absolute stereochemistry; NMR; chiral derivatizing reagents; methoxyphenylacetic acid; methoxytrifluoromethylphenylacetic acid.
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0040–4020/01/$ - see front matter
PII: S0040-4020(01)00056-4

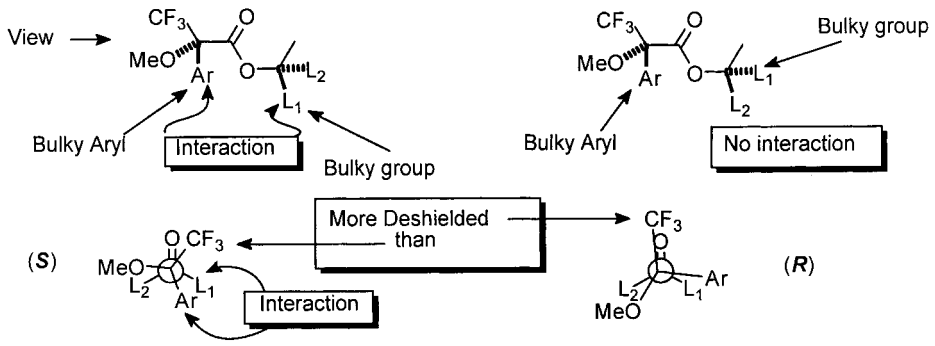

Figure 1. Mosher's model for the correlation of the ^{19}F NMR chemical shifts of MTPA-esters with their absolute configurations.

can be deduced by the comparison of the chemical shifts of the acid fragment. However, for the molecules that have no pattern with known stereochemistry this approach is very risky and can lead to erroneous assignment.[6]

Recent investigations of the conformational structure and dynamics of arylmethoxyacetic acid- (AMAA)- and MTPA-esters and amides in solution[7] and the progress in NMR theory of carbonyl anisotropy effects[8] has put Mosher's model in doubt. First, torsion interactions are quite expensive (in terms of energy), therefore, it is unlikely that additional interactions will lead to the distortion of the conformer structure. We think that a reasonable explanation can be found in the framework of conformationally mobile model, where additional interactions can redistribute equilibrium populations. Second, DNMR and theoretical investigation of the carbonyl shielding cone demonstrated that the model used by Mosher should be revised.[8] The authors pointed out that the influence of the carbonyl group on the neighboring nucleus can not be explained only by magnetic anisotropy effects, but the polar effects of the C═O bond also play a remarkable role. The modified model predicts the reverse effect: the C═O group near to the bond has essentially shielding character, and therefore, the NMR chemical shift of the nuclei should be high field shifted rather than low field shifted as was proposed by Mosher.

A good knowledge of the conformational parameters of AMAA-esters/amides and anisotropic properties of the C═O bond may serve as a basis for the method to determine an absolute configuration of alcohols/amines by NMR of the acid moiety. In this paper, an origin of the difference between the $C_\alpha H$ (^1H NMR) and the CF_3 (^{19}F NMR) chemical shifts in the diastereomers of the AMAA- and MTPA-esters/amides, respectively, is explained. The relationship between the NMR parameters of the $C_\alpha H$ protons and the configuration of the alcohol/amine are derived in the case of AMAA-esters/amides. The scope and limitations of the method are discussed.

2. Results and discussion

Let us consider the origin of the difference between the $C_\alpha H$ proton chemical shift for the diastereomers in the case of the AMAA esters since the conformational equilibrium of these esters is simpler and well established. Then the differentiation of MTPA esters in ^{19}F NMR spectra will be discussed.

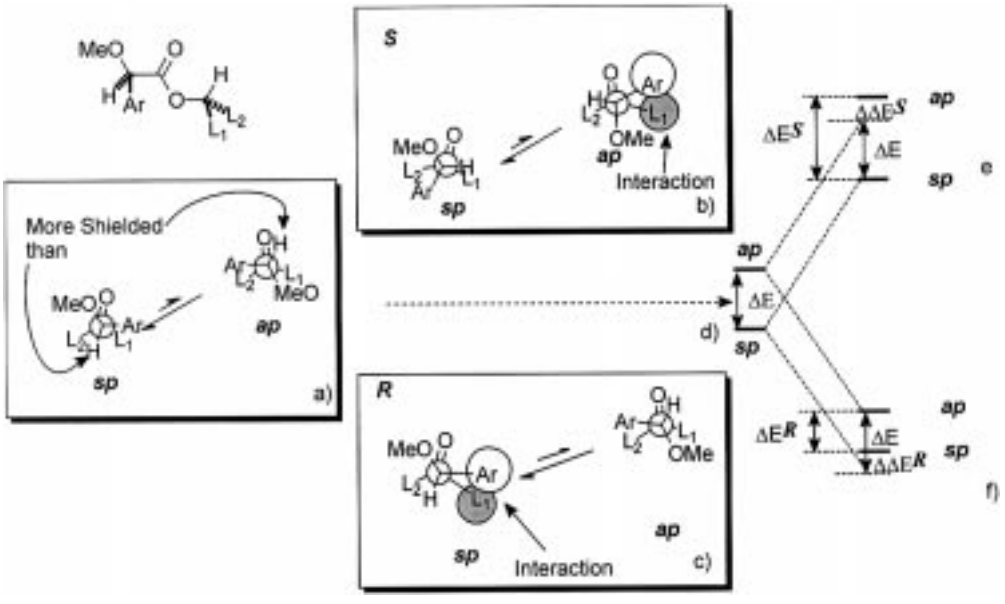

Figure 2. The origin of the energy difference in AMAA-esters (see the text).

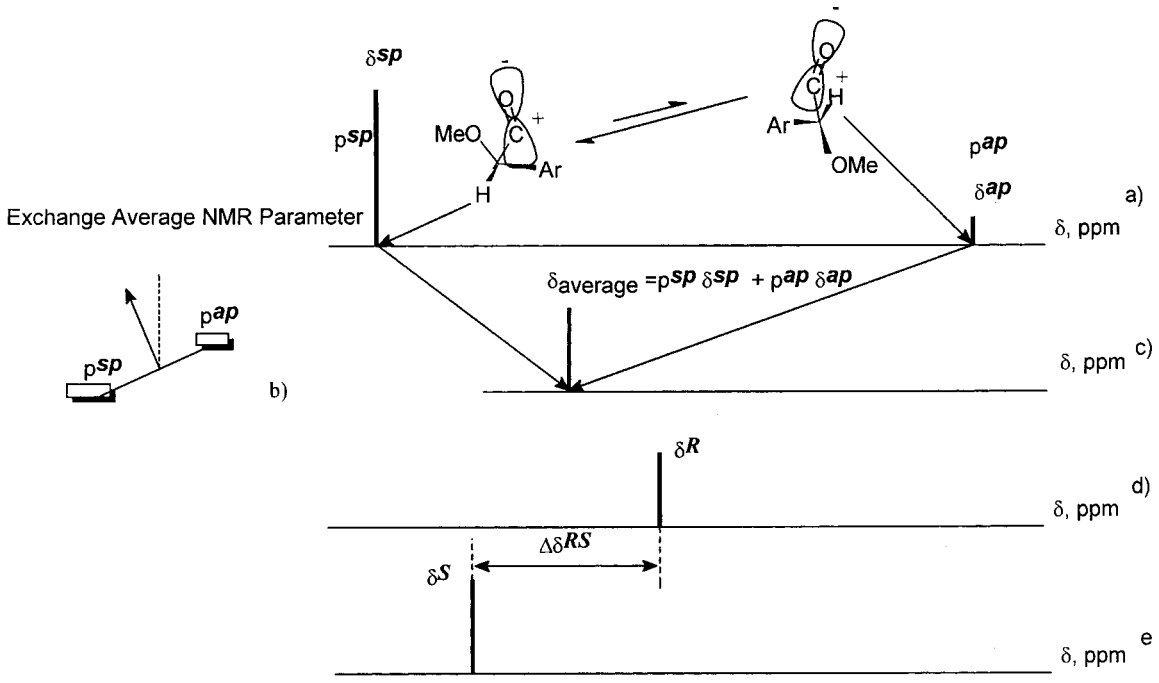

Figure 3. The $C_\alpha H$ proton chemical shift (see the text): (a) intrinsic values in the main forms; (b) balance; (c) exchange average; (d), (e) in (*R*)- and (*S*)-esters, respectively.

The AMAA esters exist in an equilibrium of two forms in solution: the C_α–OMe bond is ca. *syn-periplanar* (*sp*) and *anti-periplanar* (*ap*) to the C=O, the *sp* form being more stable than the *ap* one (Fig. 2a and d).[7]

The geometry of the *sp* and *ap* rotamers (acid fragments) depends slightly on the alcohol fragment and its chirality. Hence, keeping in mind that the through-space influence of the alcohol fragment on intrinsic chemical shift of the $C_\alpha H$ is negligible in both conformations, the chemical shifts of the $C_\alpha H$ protons are determined mainly by their local magnetic environment: in the *sp* form the $C_\alpha H$ proton is beyond the shielding influence of the C=O group while in the *ap* form it is ca. coplanar and therefore should be upfield shifted (Fig. 3a). Therefore, the average chemical shift of the $C_\alpha H$ proton (Fig. 3c) is determined mainly by the intrinsic chemical shifts in the conformers and by their populations. Thus, average chemical shift can serve as 'a balance' to measure the relative populations of the conformers (Fig. 3b).

In the case of chiral alcohol ($L_1 \neq L_2$) (Fig. 2b and c), the

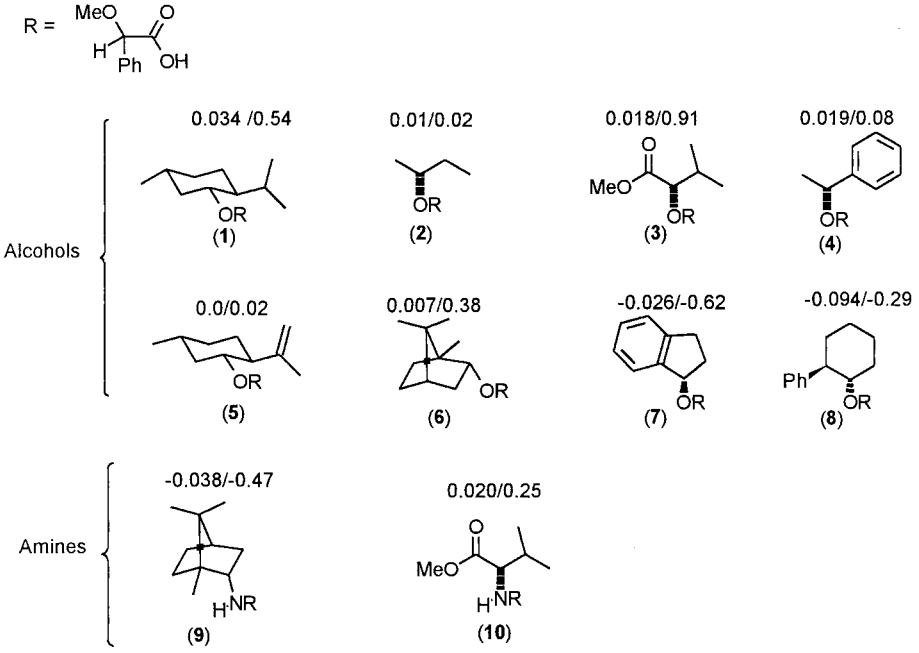

Figure 4. MPA-esters and amides with respective values of $\Delta\delta^{RS}/\Delta\Delta E^{RS}$ (ppm/kcal/mol).

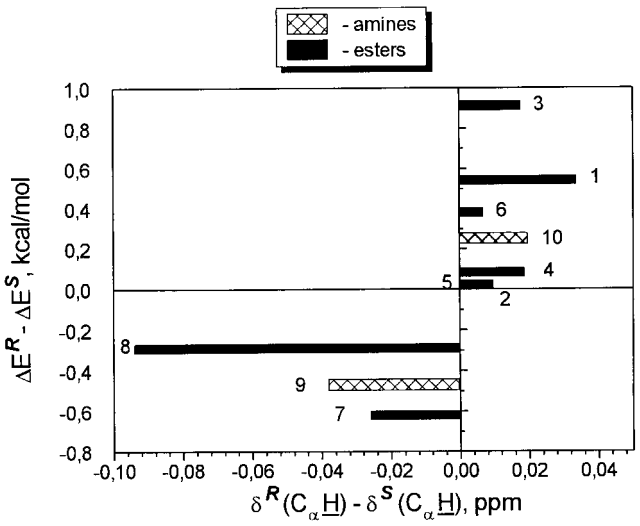

Figure 5. The diagram of relative chemical shifts of the $C_\alpha H$ protons in respective diastereomers vs. relative energies of the main conformers of the compounds **1–10** (chemical shifts are measured at room temperature in CD_2Cl_2/CS_2, the energies were calculated by PM3).

situation is changed and the interactions between OMe/Ar and L_1/L_2 are different in (*R*)- and (*S*)-AMAA esters. This is one of the points upon which Mosher's model was based: it was suggested that the geometries around the C_α–CO bond in respective diastereomers are different since these interactions distort the postulated conformers of MTPA-esters (Fig. 1).[4a,5]

However, unlike the Mosher's model, those interactions lead not only to the distortion of the geometry but rather to the redistribution of the conformational energy of the AMAA ester array (see energy diagrams on Fig. 2e and f) due to the asymmetry of the interactions (i.e. between L_1 and OMe or Ar if the L_1 is more bulky than L_2, Fig. 2b and c). Naturally, different populations of the main conformers (*sp* and *ap*) in the *S* and the *R*-esters would be expected and, as a result, different average chemical shifts of the $C_\alpha H$ protons are observed (Fig. 3c and d).

Thus relationship between chemical shift of the $C_\alpha H$ proton and the absolute configuration is to be considered in terms of energy. The higher the energy difference between the main forms, the larger should be the population of the *sp* conformer, and the $C_\alpha H$ proton has to resonate at lower field. Thus, the correlation between the energy differences of the main forms and the $C_\alpha H$ protons chemical shifts in the diastereomers allows us to make an assignment of the absolute configuration of alcohols.

A variety of secondary alcohols of known absolute stereochemistry and methoxyphenylacetic acid (MPA) as CDR (Fig. 4) have been used to check the model experimentally. The values of the $\Delta\delta^{RS}$ ($=\delta^R-\delta^S$) vs. $\Delta\Delta E^{RS}$ ($=\Delta E^R-\Delta E^S$) are presented in Fig. 5. In almost in all cases, the sign of $\Delta\delta^{RS}$ correlates with the sign of $\Delta\Delta E^{RS}$. The right/up quadrant corresponds to the positive values of the $\Delta\delta^{RS}$ and $\Delta\Delta E^{RS}$, and the low/left quadrant to negative ones. In full agreement with the model, if the energy gap (*sp*/*ap*) in the (*R*)-ester is higher than in the (*S*)-ester (positive $\Delta\Delta E^{RS}$ values), the $C_\alpha H$ proton in the (*R*) resonates at lower field than in the (*S*) (positive $\Delta\delta^{RS}$ values). In contrast, if the *sp*/*ap* energy difference in the (*R*)-ester is lower than the one in the (*S*) ester, its $C_\alpha H$ proton will resonate at a higher field than in the (*S*)-ester (negative quadrant, Fig. 5).

Thus, there is a direct relation between the energy differences of the main forms in the diastereomers and their $C_\alpha H$ chemical shifts. This allows the use of these NMR parameters to determine an absolute stereochemistry of secondary alcohol. A simplified rule can be formulated as follows: 'the more the *sp*-form is preferable, the lower the field at which the $C_\alpha H$ proton will resonate'. So, if one is to determine the absolute stereochemistry of a novel alcohol, the first step is to prepare two diastereomers from the (*R*)- and (*S*)-MPA and to determine chemical shifts of their $C_\alpha H$ protons. The next step is to assume the stereochemistry of the alcohol and to analyze the energy difference of the main forms in these diastereomers. If the assumed configuration is correct, the $\Delta\delta^{RS}$ and the $\Delta\Delta^{RS}$ values have to be of the same sign. Otherwise the assumption was not correct and the configuration has to be reversed.

Let us now consider the factor that determines an efficiency of the method and reagents. In the simplest case, i.e. steric interactions between the aryl ring in the acid moiety (Ar group is more bulkier than OMe) and bulky L_1 groups in alcohol fragment (Fig. 2b and c), an analytical expression can be derived. In this case, it can be assumed that the additional energies of these interactions are ca. equal in *R* (*sp*) and *S* (*ap*) esters ($\Delta\Delta E^R=\Delta\Delta E^S=\Delta\Delta E$) (Fig. 2e and f). Therefore, taking into account that the direct through-space influence of these group on the NMR parameters of the $C_\alpha H$ is negligible (except the aromatic systems) ($\delta^{sp}(R)\approx\delta^{sp}(S)$ and $\delta^{ap}(R)\approx\delta^{ap}(S)$), the $C_\alpha H$ chemical shifts difference is modulated by the energy distribution in each ester (*R* and *S*), and one can obtain the following relationship:

$$\Delta\delta^{RS} = \delta^R - \delta^S = (\delta(sp) - \delta(ap)) \times F(\Delta E, \Delta\Delta E)$$

$$= \Delta\delta^{\text{intr}} \times F(\Delta E, \Delta\Delta E), \quad (1)$$

where ΔE is the energy difference between *sp* and *ap* forms, $\Delta\Delta E$ an additional energy (see Fig. 2e and f), $\Delta\delta^{\text{intr}}=\delta(sp)-\delta(ap)$ the intrinsic difference between the chemical shifts of the $C_\alpha H$ proton in the *sp* and *ap* forms. According to the DNMR, data and equilibrium in AMAA esters depends only slightly on the exact structure and configuration of the alcohol. In other words, additional interactions ($\Delta\Delta E$) are smaller than the intrinsic energy difference of the two main forms (ΔE), $\Delta\Delta E<\Delta E$ and, therefore, $\Delta\delta^{RS}$ can be expressed as:

$$\Delta\delta^{RS} \approx \Delta\delta^{\text{intr}} \times 2 \times \Delta\Delta E/\exp(\Delta E). \quad (2)$$

Thus the NMR difference between the diastereomers ($C_\alpha H$) depends on intrinsic NMR chemical shifts in the *sp* and *ap* forms, on the magnitude of the energy gap between them (ΔE) and on additional terms ($\Delta\Delta E$) due to the interactions between acid and alcohol moieties.

It can be seen that an increase of the energy gap (ΔE) between the conformers leads to a decrease in the sensitivity of the $C_\alpha H$ chemical shift because the conformational equilibrium is essentially biased in favor of the *sp* form and,

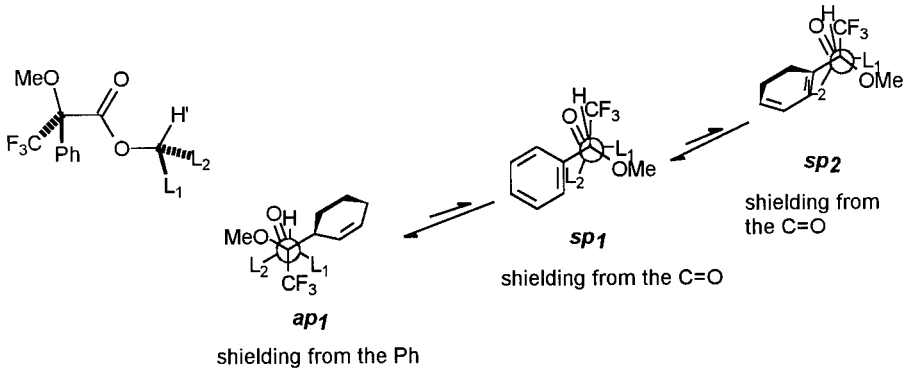

Figure 6. Main conformers of MTPA-esters and NMR effects expected on the CF_3 group.

therefore, no remarkable influence of the additional interactions on conformational equilibrium in both esters can be expected. For instance, in the 9-anthryl-methoxy-acid esters there are no differences for the $C_\alpha H$ chemical shifts in most cases.[7a]

MPA-amides of primary chiral amines obey a similar model. These amides are in equilibrium of the same two main forms in solution, namely, the *sp* and the *ap*. But in this case, the equilibrium is biased in favor of the *ap* form, and therefore, the $C_\alpha H$ protons resonate at higher field than in corresponding esters.

Although in MPA-amides the conformational preference is quite different from the MPA-esters, the source of the difference between the $C_\alpha H$ protons in the diastereomers is practically the same. In the case of the esters, the $C_\alpha H$ chemical shift is determined by intrinsic chemical shifts in the *sp* and *ap* forms and by their populations. Therefore, the proton resonating at lower field corresponds to the diastereomer in which the *sp* form is more populated (Figs. 4 and 5). In terms of energy, this means that the $C_\alpha H$ protons having lower chemical shift belong to the diastereomer with the smaller energy gap between the main forms.

2.1. Mosher (MTPA) esters

In the case of MTPA-esters, the situation is ambiguous. In one hand, these esters have more complex equilibrium in solution, and the average NMR chemical shift of the CF_3 group is determined by the structure and the populations of three conformers. Therefore, it is hardly possible to properly evaluate the redistribution of conformer populations due to additional interactions. On the other hand, the chemical shift of the CF_3 group is determined not only by the anisotropy of the carbonyl bond but also by the different anisotropy effects of the vicinal aryl ring because its orientation is different in these forms (Fig. 6).

Low temperature ^{19}F NMR experiments were carried out to prove the hypothesis. The (*R*)- and (*S*)-MTPA esters of (−)-menthol were used as a suitable model because the conformational parameters of these systems in solution are well established.[7d]

At room temperature the ^{19}F NMR spectrum of MTPA-ester consists of two singlets: the more intense line at −70.205 ppm corresponds to the (*R*)-ester, while the less intense one at −70.116 ppm is due to the (*S*)-ester. When the temperatures were decreased, a high-field shift was observed at first, following by the broadening of the lines, and at −60°C coalescence was seen.

In this case, both the difference between the ^{19}F chemical shifts of the diastereomers and their variations with the temperature mainly reflect the influence of the strong anisotropy of the aromatic rings. Namely, in the major ap_1 form, the aryl ring produces a shielding effect on the CF_3 group, therefore, its contribution to the average chemical shift is increased as temperature decreases. Some extra preference of this form in the (*R*)-ester vs the (*S*)-ester (0.43 kcal/mol vs 0.41 kcal/mol, respectively) is also the reason why the (*R*)-form resonates at a higher field.

As a whole, ^{19}F NMR chemical shifts of MTPA esters depend essentially on the variety of factors due to complexity of the equilibrium and the presence of several anisotropy groups showing different effects. Thus, there is no simple relation between NMR parameters and the structure, and therefore, the determination of the absolute configuration by ^{19}F NMR is in general impossible.

3. Conclusion

The absolute configuration of secondary alcohols and primary amines can be determined by NMR of CDR in the framework of a conformationally mobile model. The asymmetry of the substrate leads not to a distortion of the geometry of the main form as was postulated by Mosher but to the redistribution of the population of the main two forms.

Non-equivalence of the $C_\alpha H$ protons in NMR spectra of AMAA diastereomers was determined by the difference of interactions between acid and alcohol/amine substituents in the two main conformers. Therefore, the relative shifts of the $C_\alpha H$ can be used to measure the relative energy differences in the diastereomers.

To assign the absolute configuration of an alcohol or amine, interactions between the reagent and substrate moieties of the derived diastereomeric esters or amides have to be estimated in the two main forms and be compared with chemical shifts of the $C_\alpha H$ protons—the diastereomer

(enantiomer) having the higher relative population of the *sp* form should resonate at lower field.

4. Experimental

^{1}H NMR spectra were measured at 500.13 MHz in a Bruker AMX 500 spectrometer in 4:1 CS_2/CD_2Cl_2 containing TMS as internal standard. ^{19}F NMR spectra were measured on a Varian AMX 300 spectrometer. MM calculations (employing the MMX force field) were performed by the PCmodel program. The conformational space of each compound was scanned by MM optimization of the sterically allowed conformations around key single bonds. The energies of conformations were minimized in Cartesian coordinate space by the block diagonal Newton–Raphson method; minima corresponded to rms energy gradients <0.001 kcal/mol Å. The ground state energies of the geometries were then calculated by PM3 method by the VAMP program (version 4.56) on a IBM Pentium MMX 166 Computer. The program was kindly presented by T. Clark and B. Wiedel (Friedrich–Alexander University of Erlangen, Nurnberg, Germany). For all compounds full geometry optimization using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) method and the PRECISE option was carried out.

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