Structure Elucidation

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The CFTA Method: A Reliable Procedure for the Determination of the Absolute Configuration of Chiral Primary Amines by ^{1}H NMR Spectroscopic Analysis**

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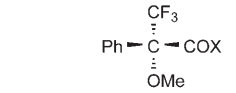
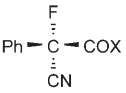
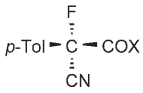
Methods for the determination of the absolute configuration of chiral molecules are indispensable in modern organic chemistry, especially in asymmetric synthesis and in studies of the structures of complex natural products.[1] Although the modified Mosher method[2] with α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, **1**)[3] is often employed for this



(*S*)-**1**: X = OH, (*S*)-MTPA
(*R*)-**2**: X = Cl, (*R*)-MTPA-Cl



(*S*)-**3**: X = OH, (*S*)-CFPA
(*S*)-**4**: X = Cl, (*S*)-CFPA-Cl



(*S*)-**5**: X = OH, (*S*)-CFTA
(*S*)-**6**: X = Cl, (*S*)-CFTA-Cl

purpose, many cases have been identified in which the MTPA procedure can not be applied, either because of the low reactivity of MTPA chloride (**2**)[4] or because of the number of complex conformers observed in the MTPA derivatives.[5] To overcome these limitations, we developed α-cyano-α-fluorophenylacetic acid (CFPA, **3**), in which the fluorine atom is

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located on the stereogenic center. We found that CFPA chloride (**4**) reacts with nucleophiles 500 times faster than MTPA chloride (**2**), and even undergoes condensation with hindered nucleophiles, such as pinacolyl alcohol.[6]

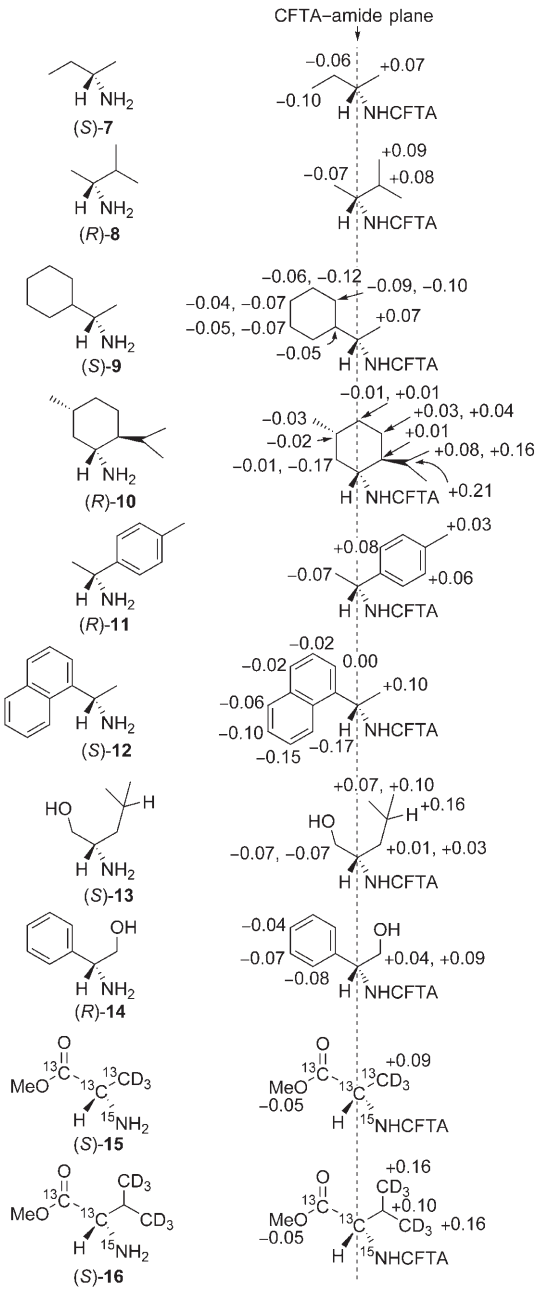
The phenyl hydrogen atoms of CFPA give rise to a complex multiplet in the ^{1}H NMR spectrum, which can often complicate the analysis of the ^{1}H NMR spectra of substrates with aromatic substituents. We therefore decided to search for a derivatizing agent with more readily distinguishable aromatic proton signals to simplify the assignment of proton signals to the derivatized diastereomers.[7] This approach led to our development of α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA, **5**; Tol = tolyl),[8] a reagent that can be used in the determination of the absolute configuration of chiral carbinols,[9] even those with two essentially identical substituents.[10] Herein, we report that the CFTA method is also reliably applicable to the determination of the absolute configuration of various chiral amine compounds.

We measured the chemical-shift difference, $\Delta\delta_H$ ($\delta_S-\delta_R$),[11] for corresponding protons of the diastereomeric (*S*)- and (*R*)-CFTA amides of chiral primary amines **7**–**14** of known absolute configuration (Scheme 1).[2] All proton signals for the amine residue were assigned for both the (*S*)- and (*R*)-CFTA diastereomers by means of COSY and other NMR spectroscopic techniques. Thus, a $\Delta\delta_H$ value was readily obtained for each hydrogen atom of the diastereomers.

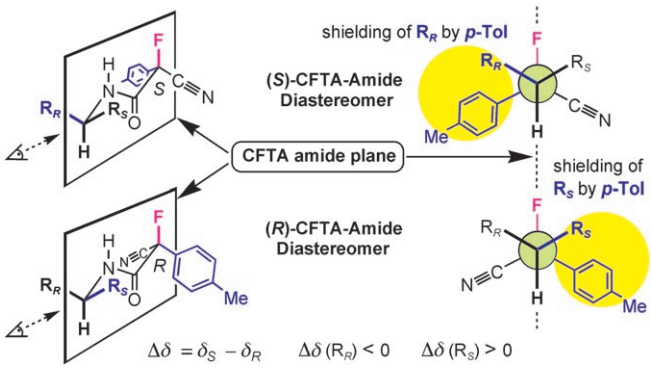
The CFTA–amide plane is defined as the plane with an all-*anti* (F–C)–(C=O)–(N–H)–(C–H) conformation[12] (Scheme 2). When the CFTA amides are depicted in a manner such that the two substituents at the stereogenic center adjacent to the N atom are in the plane of the page (which is perpendicular to the CFTA–amide plane) and the α hydrogen atom is coming out of the plane of the page, the hydrogen atoms with negative $\Delta\delta_H$ values are invariably on the left-hand side of the CFTA–amide plane and those with positive $\Delta\delta_H$ values are on the right-hand side of the CFTA–amide plane (Scheme 1). In general, greater $\Delta\delta_H$ values were observed for the CFTA amides than for the MTPA amides. Thus, the CFTA method enables the determination of the absolute configuration of chiral amines by ^{1}H NMR spectroscopy much more readily and accurately than the method with MTPA.

To investigate the scope and limitations of the CFTA method, we applied our procedure to the multiply labeled amino acid derivatives **15** and **16**. From the $\Delta\delta$ values obtained by ^{1}H and ^{2}H NMR spectroscopy, we found that both **15** and **16** have the *S* absolute configuration, as was expected from the synthetic route used for their preparation.[13] X-ray analysis of the CFTA amide of **15** confirmed the *S* configuration for this derivative.[14]

The signs of $\Delta\delta$ on each side of the CFTA–amide plane were opposite for the CFTA amides to those observed for the CFTA esters[9] and also opposite to those observed with MTPA amides. Therefore, we propose that the stable conformation for the amides is that in which the C–F bond occupies an anti-periplanar position with respect to the C=O bond (Scheme 2), in contrast to the syn-periplanar conformation that is favored in the case of the CFTA esters. The amides of the chiral amines $R_SR_RCHNH_2$ can be viewed from the left-hand side in an extended Newman projection, in which the amide linkage is omitted for convenience. Conformational arguments can be used to explain the algebraic signs of the $\Delta\delta$ values. In the case of the (*S*)-CFTA diastereomer, the signals for the hydrogen atoms of the R_R group should always be shifted upfield as a result of the anisotropic shielding of the aromatic ring. In contrast, for the *R* diastereomer, the hydrogen atoms of the R_S group are shielded, and these signals should therefore appear upfield. Thus, the $\Delta\delta$ values for the protons on the left-hand side of the CFTA–amide plane should be negative and those for the protons on the right-hand side of the plane should be positive. This conformation was supported by X-ray crystallographic analysis of the CFTA



Scheme 1. $\Delta\delta_H$ or $\Delta\delta_D$ values for CFTA amide diastereomers of chiral amines **7**–**16**.



Scheme 2. Conformations of (*S*)- and (*R*)-CFTA amides of chiral primary amines $R_SR_RCHNH_2$.

amide of 1-phenylethylamine[8a] and ab initio calculations (GAUSSIAN 98, RHF/6-31 + G*) of the CFPA amide of Val-OMe as a similar molecule.[8b]

In summary, we have presented the CFTA method as a new and reliable procedure for the determination of the absolute configuration of chiral amines. This method has important advantages over other conceptually similar procedures available because of the very high reactivity of the agent[6] and because the C–F bond at the stereocenter exerts strong conformational control on the amides.[12b] For these reasons we feel this method should be widely applicable.

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[1] J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17, and references therein.
[2] a) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Org. Chem.* **1991**, *56*, 1296; b) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.
[3] a) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543; b) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512; c) G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143.
[4] a) J. S. Dutcher, J. G. Macmillan, C. H. Heathcock, *J. Org. Chem.* **1976**, *41*, 2663; b) L. Hietaniemi, E. Pohjala, P. Malkonen, M. L. Riekkola, *Finn. Chem. Lett.* **1989**, *16*, 67; c) A. Svatos, I. Valterova, D. Samon, J. Vrkoc, *Collect. Czech. Chem. Commun.* **1990**, *55*, 485; d) Y. Takeuchi, N. Itoh, S. Kawahara, T. Koizumi, *Tetrahedron* **1993**, *49*, 1861.
[5] J. M. Seco, S. K. Latypov, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1997**, *62*, 7569.
[6] Y. Takeuchi, M. Itoh, T. Koizumi, *J. Chem. Soc. Chem. Commun.* **1992**, 1514; see also: Y. Takeuchi, M. Itoh, T. Koizumi, *Chem. Ind.* **1992**, 874.
[7] The assignment of the AB-quartet-like proton signals for the *p*-Tol group is much easier than that of the complex multiplet signals for the Ph group, especially for those chiral amines with aromatic residues.
[8] a) Y. Takeuchi, M. Konishi, H. Hori, T. Takahashi, T. Kometani, K. L. Kirk, *Chem. Commun.* **1998**, 365; b) T. Fujiwara, K. Omata, K. Kabuto, C. Kabuto, T. Takahashi, M. Segawa, Y. Takeuchi, *Chem. Commun.* **2001**, 2694; c) T. Fujiwara, M. Sasaki, K. Omata, C. Kabuto, K. Kabuto, Y. Takeuchi, *Tetrahedron: Asymmetry* **2004**, *15*, 555; d) (*S*)- and (*R*)-CFTA-Cl are both commercially available from Kanto Denka Kogyo Co., Ltd.
[9] T. Takahashi, A. Fukushima, Y. Tanaka, Y. Takeuchi, K. Kabuto, C. Kabuto, *Chem. Commun.* **2000**, 787.
[10] Y. Takeuchi, H. Fujisawa, R. Noyori, *Org. Lett.* **2004**, *6*, 4607.
[11] The $\Delta\delta$ values are defined as $\delta_S - \delta_R$, in which δ_S and δ_R are the chemical shifts of the corresponding protons in the (*S*)- and (*R*)-CFTA amides, respectively.
[12] a) S. K. Latypov, J. M. Seco, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1995**, *60*, 1538; b) C. R. S. Briggs, D. O'Hagan, J. A. K. Howard, D. S. Yufit, *J. Fluorine Chem.* **2003**, *119*, 9.
[13] S. N. Lodwig, C. J. Unkefer, *J. Labelled Compd. Radiopharm.* **1998**, *XLI*, 983; see also the Supporting Information.
[14] CCDC-291185 and CCDC-291186 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

