(1-Naphthyl)(trifluoromethyl) *O*-Carboxy Anhydride as a Chiral Derivatizing Agent: Eclipsed Conformation Enforced by Hydrogen Bonding

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ABSTRACT

The preparation of the (1-naphthyl)(trifluoromethyl) *O*-carboxy-anhydride 1 and its use as a chiral derivatizing agent with several α -chiral primary amines are reported. The very large $\Delta \delta^{RS}$ values observed in ¹H NMR have been correlated with a marked preference of the corresponding α -hydroxy-amides for the *eclipsed conformation*. In comparison, the related *O*-methylated amides are shown to adopt staggered conformations, which substantiates the critical role of intramolecular hydrogen bonding in maximizing the anisotropic effect.

The growing interest for enantioselective synthesis in chemical and pharmaceutical fields has stimulated the development of simple and inexpensive methods for the determination of the enantiomeric excess of chiral compounds and the assignment of the absolute configuration of stereogenic centers. In this context, the use of chiral derivatizing agents (CDA) combined with multinuclear NMR analyses is one of the most efficient methods.¹ The MTPA and MPA derivatives introduced by Mosher² and Trost,³ respectively, (Figure 1) have led to spectacular results especially with α -chiral primary amines and secondary alcohols. Further improvements have been possible exploiting the structural versatility of α -arylcarboxylic acids, as is nicely illustrated by the BPG⁴ and CFTA⁵ compounds.⁶

Current efforts focused on new CDA aim at increasing both their reactivity and resolution efficiency.⁷ In this regard,

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Figure 1. Structure of representative α -arylcarboxylic acid derivatives used as CDA (X = OH or Cl).

it is well-established that the eclipsed vs staggered conformations of the corresponding adducts have a major influence on the anisotropic effect induced by the aryl moiety.^{4,5,8,9} Riguera et al. reported an elegant illustration of this phenomenon in the derivatization of α -chiral primary amines with MPA. The addition of barium(II) salts was demonstrated to shift the conformation of the ensuing amides from staggered to eclipsed, resulting in a significant increase of the anisotropic effect (Figure 2, compounds **A** and **B**).^{8a} In



Figure 2. Control of the amide conformation by complexation to Ba^{2+} (**A**/**B**) or by intramolecular hydrogen bonding (**C** and **D**).

principle, the conformational equilibrium may also be controlled by replacing the methoxy group of the MTPA/ MPA models by a hydroxyl group, thanks to the formation of a hydrogen bond between the proximal OH and C=O moieties (Figure 2, compound C). Note that a somewhat related approach has been recently studied by Choi et al.

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(9) The situation may be further complicated if different rotamers with opposite anisotropic effects coexist in solution.

using *N*-(nitroaryl)prolines (NPP) as CDA.¹⁰ As the result of intramolecular hydrogen bonding between the amide hydrogen and proline nitrogen atoms (Figure 2, adduct **D**), significantly larger chemical shift differences ($\Delta \delta^{\text{RS}}$) values were obtained than with MPA and MTPA derivatives.

From a synthetic viewpoint, α -hydroxy-amides C can be readily accessed by reacting α -chiral primary amines with O-carboxy anhydrides (OCA).¹¹⁻¹³ The (1-naphthyl)(trifluoromethyl) OCA 1 was thus considered a promising CDA. Here we report its synthesis (in both racemic and enantiomerically pure forms) and its derivatization with several α -chiral primary amines. The very large $\Delta \delta^{RS}$ values observed in ¹H NMR have been correlated with a marked preference of the α -hydroxy-amides for the *eclipsed conformation*, as deduced from detailed spectroscopic analyses performed on the α -methylbenzylamine adducts 2a/2b. In comparison, the related O-methylated adducts 4a/4b (obtained from the MTPA analog 3) are shown to adopt a staggered conformation, which substantiates the critical role of intramolecular hydrogen bonding in enforcing the eclipsed conformation.

The OCA **1** was readily prepared in racemic form from the corresponding α -hydroxy-acid and isolated in 68% yield after recrystallization.¹⁴ Reaction of **1** with (*R*)- α -methylbenzylamine¹⁵ afforded an equimolar mixture of α -hydroxyamides **2a** and **2b** that were separated by silica-gel chromatography and fully characterized (Scheme 1). Notably, the

Scheme 1. Reaction of *rac*-1 with (R)- α -Methylbenzylamine



two diastereomers are readily distinguishable in the ¹H NMR spectrum, with differences in chemical shifts up to 0.26 ppm

(12) O-carboxy-anhydrides have also been involved recently for the dynamic kinetic resolution of monosubstituted α -hydroxy carboxylic acids: Tang, T.; Deng, L. J. Am. Chem. Soc. **2002**, 124, 2870.

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for the methyl group and 0.58 ppm for the H_{ortho} of the phenyl ring. These values are markedly larger than those usually observed, with previous CDA typically leading to $\Delta \delta^{\text{RS}} < 0.21$ ppm for the methyl group of ArCH(Me)NH₂ (Ar = phenyl, para-tolyl, 1-naphthyl).^{2-5,8d,16} To rationalize the large $\Delta \delta^{\text{RS}}$ values obtained with **1**, we sought to determine the conformations of **2a** and **2b**.

The absolute configuration (*S*,*R*) of **2b** was first deduced from an X-ray diffraction analysis (Figure 3), suitable crystals



Figure 3. Molecular structure of 2b.

being obtained from pentane solution at 0 °C. This study also provided the first indication of the conformation of the α -hydroxy-amide. As expected, the C-C(=O)-NH-C_{α} skeleton is almost perfectly planar, the amide fragment adopts a Z conformation and the vicinal N-H/C-H bonds are approximately antiperiplanar (HNCH torsion angle 152.4°). In addition, the O-C-C=O fragment adopts a synperiplanar (*sp*) conformation (OCCO torsion angle 13.6°), indicating the presence of an intramolecular hydrogen bond.¹⁷ As a result of this *eclipsed conformation*, the 1-naphthyl and trifluoromethyl groups eclipse the methyl and phenyl groups, respectively.

According to multinuclear NMR and IR analyses, the sp-Z conformation observed for 2b in the solid state is also favored in CDCl₃ solution for both diastereomers 2a and 2b. Indeed, the ${}^{3}J_{\rm HH}$ coupling constants (8.0 Hz) are diagnostic for an antiperiplanar arrangement of the vicinal N–H and C–H bonds (${}^{3}J_{\rm HH} = 7.0-9.0$ Hz).^{4,16,18} In addition, NOESY and ¹⁹F{¹H} HOESY experiments unambiguously supported the eclipsed sp conformation, cross-relaxation peaks being observed for the CF3 group and Hperi atom of the naphthyl on the one hand, and the CH₃ group and H_{ortho} of the phenyl on the other hand (Figure 4). Lastly, the presence of an intramolecular hydrogen bond between the OH and C=O groups is supported by the sharp signals observed for the hydroxyl group both in ¹H NMR ($\delta_{OH} = 5.28$ ppm for **2a** and 5.37 ppm for **2b**) and in IR ($\nu_{OH} = 3421 \text{ cm}^{-1}$ for **2a** and 2b), no noticeable displacements being detected upon dilution.



Figure 4. NOE interactions observed for 2a and 2b in NOESY and ${}^{19}F{}^{1}H$ HOESY experiments.

This hydrogen bond, which enforces the eclipsed conformation, is likely to explain the large $\Delta \delta^{RS}$ observed between **2a** and **2b** by maximizing the anisotropic effect of the naphthyl group (Figure 5). In this regard, the OCA **1** markedly differs from other CDA that usually favor the staggered conformation. The situation encountered in **2a/2b** is reminiscent of the eclipsed conformation induced by Riguera et al. upon complexation of both oxygen atoms of MPA-derived amides with barium(II) salts.^{8a}



Figure 5. Extended Newman projections of **2a/2b** and ¹H NMR spectra (aromatic and methyl regions) of **2a/2b** illustrating the eclipsed conformation and the resulting strong anisotropic effect of the naphthyl ring.

At this stage, one may argue that the larger anisotropic effect of the naphthyl versus the phenyl ring¹⁹ could also have a significant effect. This prompted us to investigate the 1-naphthyl analogue **3** of MTPA (Scheme 2).¹⁴ The spectroscopic study performed on the corresponding *O*-methylated amides derived from the (*R*)- α -methylbenzylamine **4a**/**4b**, revealed a preference for a *staggered conformation* with the MeO-C-C=O fragment adopting an antiperiplanar

⁽¹⁵⁾ The α -methylbenzylamine was chosen as a representative α -chiral primary amine available in enantiopure form and presenting diagnostic signals ¹H NMR.

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conformation. As a result, very low $\Delta \delta^{\text{RS}}$ are observed in the ¹H NMR spectra (0.01 ppm for the methyl group), confirming thus the critical role played by the hydrogen bond in **2a** and **2b**.

To further substantiate the utility of OCA-1, enantiomerically pure forms (S)-1 and (R)-1 were prepared after resolution of the α -hydroxy-acid precursor with α -methylbenzylamine (ee >99.6% after three recrystallizations in 2-propanol).^{14,20} A range of α -chiral primary amines with diverse structures were then reacted with both rac-1 and (S)-1, and the resulting $\Delta \delta^{RS}$ values were determined (Figure 6). The proton chemical shift differences follow the same trend for all the prepared α -hydroxy-amides, and are all consistent with the eclipsed hydrogen-bonded conformation established with α -methylbenzylamine. This includes the amino-alcohol adduct 11, illustrating (i) the complete selectivity of OCA 1 for amines vs alcohols in the absence of coupling reagents and (ii) its applicability to substrates featuring hydroxyl groups also susceptible to hydrogenbonding toward the amide moiety. Moreover, all the obtained $\Delta \delta^{\rm RS}$ values are significantly larger than those reported with classical CDA such as MTPA, MPA and even surpass those achieved with NPP.10

In conclusion, the (1-naphthyl)(trifluoromethyl) *O*-carboxyanhydride **1** was found to induce considerable ¹H NMR differentiation with a wide range of α -chiral primary amines. In marked contrast to related CDA such as MTPA and MPA, the use of **1** leads to *O*-unprotected adducts in which *eclipsed*



Figure 6. $\Delta \delta^{\text{RS}}$ values obtained for diastereomeric amides 5–11 [R = COC(OH)CF₃(1-naphthyl)] derived from the corresponding α -chiral primary amines. (¹H NMR spectra were recorded at 25 °C, in CDCl₃)].

conformations are enforced by *intramolecular hydrogen bonding*. As a result, the anisotropic effect of the naphthyl group is much larger than in the related *O*-methylated amides for which the staggered conformation is classically favored. Accordingly, this OCA may be considered as a promising CDA and further improvements may be expected in both reactivity and resolution efficiency by varying the substitution pattern.

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Supporting Information Available: Experimental details, spectroscopic characterization for all new compounds, and crystallographic data for **2a** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽²⁰⁾ The absolute configuration of enantiomerically pure **1** was determined by derivatization with (*R*)- α -methylbenzylamine and comparison with the known adducts **2a**/**2b** by ¹H NMR.