Synthesis and Evaluation of FICA Derivatives as Chiral Derivatizing Agents

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1-Fluoroindan-1-carboxylic acid (FICA) derivatives containing a monosubstituted benzene ring (1b–e) were synthesized as their methyl esters and their potential as chiral derivatizing agents (CDAs) were assessed by both 19F- and 1H-NMR spectroscopy. Introduction of a substituent at the 4-position in the benzene ring caused a 1.2–2 fold increase in ΔδF values when compared with that of FICA. This increase was investigated using a correlation model for 19F-NMR and by the order of the stability of the synperiplanar (sp) and anti-periplanar (ap) conformers of the (R, S) and (S, S) diastereomers from the Gibbs’ free energy at 298.15K.

Key words chiral derivatizing agent; 4-bromo-1-fluoroindan-1-carboxylic acid; 19F-NMR; correlation model; Gibbs’ free energy

Introduction

A convenient and reliable method for assigning the absolute configuration of chiral molecules is 1H-NMR analysis of diastereomers obtained by reacting these substrates with chiral derivatizing agents (CDAs).<sup>1,2</sup> Among the various CDAs developed, fluorine-containing CDAs are attractive because 19F-NMR can be used as an additional analytical probe, and the chemical shift differences of 19F signals are larger than those of 1H signals and 19F-NMR spectra are straightforward to analyze.<sup>3</sup> CDAs, such as α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA),<sup>1,2,4</sup> α-cyano-α-fluoro-p-tolylacetic acid (CFTA),<sup>5</sup> 1-fluoroindan-1-carboxylic acid (FICA),<sup>6,7</sup> and 8-fluoro-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid (F-THENA)<sup>8</sup> have been used systematically to determine the absolute configuration of chiral secondary alcohols using both 19F- and 1H-NMR spectroscopy (Fig. 1). However, 19F chemical shifts observed with MTPA cannot be used for configuration assignments because the signs of the ΔδF values of MTPA esters do not correlate with the absolute stereochemistry of the alcohols.<sup>6,7</sup> In contrast, CFTA,<sup>5</sup> FICA,<sup>7</sup> and F-THENA<sup>8</sup> can be reliably used to determine the absolute configuration by both 19F- and 1H-NMR spectroscopy. The source of chemical shift differences of CFTA and FICA are explained by an anisotropic effect change from the preferred conformational change in equilibrium.<sup>5,7</sup> F-THENA is a unique CDA where the F atom senses the shielding effect of the aromatic ring of the alcohol and is therefore used for configuration assignments of only chiral secondary aromatic alcohols in 19F-NMR spectroscopy.<sup>8</sup>

Recently, we prepared FICA and revealed that it can be a more reliable CDA than commercially available MTPA for determining the absolute configurations of secondary alcohols (Fig. 1). For all 14 alcohols examined including the nabumetone metabolite (+)-4-(6-methoxy-2-naphthyl)butan-2-ol, the signs of the ΔδF values for the FICA esters correlated with their absolute configurations.<sup>6,7,9</sup>

For 1H-NMR, when applied to cyclic alcohols, FICA was superior to MTPA, however, the ΔδH values of the FICA esters were similar to those of MTPA.<sup>7</sup> On the one hand, the comparatively small ΔδH values were attributed to the small amount of the synperiplanar (sp) rotamer, which is likely to be the 1H-NMR significant conformer.<sup>3</sup> On the other hand, conformational studies of methoxyphenylacetic acid (MPA) as a CDA showed that the introduction of substituents on the benzene ring shifted the equilibrium between the sp and anti-periplanar (ap) conformers.<sup>2</sup> The larger ΔδH and ΔδF values make the method very reliable for assigning the absolute stereochemistry of the chiral secondary alcohols. In this research setting, we selected commercially available indanes bearing a bromine atom at the 4-, 5-, or 6-position of the benzene ring and examined the positional effect of the substituent with rac-FICA derivatives (1c–e) and a rac-4-Me-FICA derivative (1b)<sup>10</sup> to obtain larger ΔδH and ΔδF values than those of FICA (Fig. 2).

Fig. 1. The Structures of Fluorine-Containing CDAs

Fig. 2. FICA Derivatives

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Results and Discussion

Methyl esters of FICA derivatives (2c–e) (Chart 1) were prepared in 74–79% overall yield starting from commercially available 1-indanone derivatives according to a reported method, \(^\text{10}\) except for methyl esterification of \(\alpha\)-hydroxycarboxylic acids. Esterification of the acids was improved by using trimethylsilyl-diazomethane\(^{11}\) instead of Blanchfield’s method\(^{10}\) to give the methyl esters in high yields within 15 min.

Each methyl ester (2b–e) was converted to the esters of secondary alcohols (3–7) by an ester exchange reaction (Chart 1). These esters (3–7) were examined by \(^1\)H- and \(^19\)F-NMR to determine their suitability as CDAs.

\(\Delta\delta\) values of selected methyl protons of each aliphatic and cyclic ester were obtained from the \(^1\)H-NMR spectra of the diastereomeric mixtures of the esters. The example of 2-butyl esters is shown in Table 1, and other results are listed in Tables 4–7 (Supplementary Materials). For 2-butyl esters, the \(\Delta\delta\) values of 1'-Me and 4'-Me groups of substituted FICAs esters (3b–e) were similar to those of 3a. The same results were obtained from 2-hexyl, 1-phenylethyl, l-methyl, and (-)-bornyl esters of the mono-substituted FICAs (4–7) (Tables 4–7 in Supplementary Materials). These data indicated that introducing a substituent on the benzene ring did not generally improve the capability of FICA to separate the signals of diastereomers.

\(\Delta\delta\) values were obtained from \(^19\)F-NMR spectra of the diastereomeric mixtures of the esters (3–7), and the results are shown in Table 2. \(\Delta\delta\) values of the corresponding CFTA esters are also provided in the last row of Table 2 for comparison. \(\Delta\delta\) values of FICA esters were smaller than those of CFTA esters for phenylethyl (5) and bornyl esters (7) but larger for 2-butyl (3) and menthyl esters (6).

In contrast to the \(^1\)H-NMR data, introducing a substituent on the benzene ring improved the capability of FICA to separate the \(^19\)F signals of diastereomers. The position of a substituent affected the \(\Delta\delta\) values. Apart from 3b, 3c and 5c, the \(\Delta\delta\) values of 4-substituted FICAs increased by 1.2–2 fold when compared with that of FICA, whereas 5- or 6-substituted FICAs gave \(\Delta\delta\) values that were smaller than that of FICA.

Contrary to our expectations, introducing a substituent on the benzene ring did not increase \(\Delta\delta\) values but improved \(\Delta\delta\) values. The reason for this result was then investigated by a correlation model of 4-Br-FICA (5)-2-hexyl ester for \(^19\)F-NMR that gave a 1.4-fold larger \(\Delta\delta\) value than that of the corresponding FICA ester\(^{12,13}\) (Fig. 3). We have reported that the non-equivalence in the measured \(^19\)F-NMR shifts can be rationalized by the bias associated with the existence of the \(sp\) and \(ap\) rotamers.\(^{7,14}\) The observed NMR signals report a population weighted average between the \(sp\) and \(ap\) rotamers due to conformational exchange. In the \(sp\) rotamers (8, 10), the F atom is affected by an anisotropic deshielding of the ester carbonyl, which is absent in the \(ap\) rotamers (9, 11). The conformational equilibrium is less biased to \(sp\)- (10) in the (S, S) pair (10 and 11) of the 4-Br-FICA ester when compared with that of the original FICA esters because of a repulsion between the 4-Br group on the benzene ring of the agent and the larger substituent (‘Bu) on the alcohol. Consequently, the \(\Delta\delta\) values of 4-Br-FICA esters are larger than those of the original FICA esters. Since the distance between the ester carbonyl and F atom is shorter than that between the benzene ring and alkoxy group, the influence of increasing or decreasing the ratio of the \(sp\) rotamer might have a larger effect on the \(\Delta\delta\) values than on \(\Delta\delta\) values.

To support the correlation model of 4-Br-FICA (5)-2-hexyl ester for \(^19\)F-NMR, we performed density functional theory (DFT) calculations on the corresponding four conformations of 4-Br-FICA (5)-2-hexyl ester (8–11; Fig. 4). All calculations including geometry optimization were performed at the B3LYP/6-31G(d, p) level.\(^{15}\) The vibrational frequency analyses were successively performed, and it was confirmed that there were no imaginary frequencies and that these four geometries were local minima of the potential energy surface.

The total energies, relative energies, and differences of Gibb’s free energy (\(\Delta G\)) of 8–11 at 298.15 K are shown in Table 3. From the total energy, the order of the stability of the conformations was \(10 > 11 > 9 > 8\); however, from the Gibb’s free energy at 298.15 K, the order of the stability was...
Conclusion

The magnitudes of $\Delta \delta_H$ values of FICA derivatives containing a monosubstituted benzene ring were similar to that of FICA. Therefore, FICA derivatives can be used as CDAs in the same way as FICA by $^1$H-NMR. However, the aim of improving the capability of FICA derivatives as CDAs for $^{19}$F-NMR to separate the signals of diastereomers was achieved by using the 4-Me- and 4-Br-FICA compounds. The 4-position of the substituent affected the $\Delta \delta_F$ values. A correlation model explained the increase in $\Delta \delta_F$ values, which showed that the repulsion between the 4-substituent on the FICA derivatives provided a good model for $^{19}$F-NMR.

Table 3. B3LYP/6-31G(d, p) Total Energies, Relative Energies, and Differences of Gibbs’ Free Energy ($\Delta G$) at 298.15 K of the Four Models of the 4-Br-FICA (S)-2-Hexyl Ester (8–11)

| Model          | Total energy [a.u.] | Relative energy [kcal/mol] | $\Delta G$ [kcal/mol] |
|----------------|---------------------|---------------------------|-----------------------|
| (R,S)-sp (8)   | −3443.805707        | 1.68                      | −0.17                 |
| (R,S)-ap (9)   | −3443.805330        | 1.20                      | −0.64                 |
| (S,S)-sp (10)  | −3443.803027        | 0.00                      | 0.00                  |
| (S,S)-ap (11)  | −3443.803797        | 0.23                      | −1.64                 |

11 > 9 > 8 > 10. The latter supports the model shown in Fig. 3.

Fig. 3. A Correlation Model of 4-Br-FICA (S)-2-Hexyl Ester for $^{19}$F-NMR

Fig. 4. DFT Calculation Models (8–11)
benzene ring of the CDA and the larger substituent on the alcohol changed a bias because of the existence of the sp and ap rotamers in each diastereomer. This was supported by the order of the stability of the corresponding four models from the Gibbs’ free energy at 298.15 K. The readily available substituted FICA CDAs offer greater sensitivity for determining the absolute stereochemistry of chiral secondary alcohols by $^{19}$F- and $^1$H-NMR spectroscopy and should be promising and popular reagents in organic synthesis and medicinal chemistry. We are currently preparing both enantiomers of 4-Br-FICA Me ester by asymmetric synthesis and/or optical resolution for application to the FICA-based method in assigning the absolute configuration of secondary alcohols based on $^{19}$F- and $^1$H-NMR.7,9)

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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12) The esters of (R)-acids with (S)-alcohols are designated (R,S), and those of (S)-acids with (S)-alcohols are denoted (S,S).
13) A correlation model is explained with (R,S) and (S,S) diastereomers because each of the enantiomer pairs, the (R,S) and (S,R) pair or the (S,S) and (R,R) pair, are identical in NMR properties.
14) These rotamers arise upon rotation about the C$\alpha$–CO bond: synperiplanar (sp), with the C–F and C=O bonds oriented in the same direction, and antiperiplanar (ap), with these same bonds oriented in opposing directions.
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