Confirmation by IR of the preferred conformations of CFTA esters in solution: a highly reliable criterion for the stereochemistry assignment of chiral alcohols†

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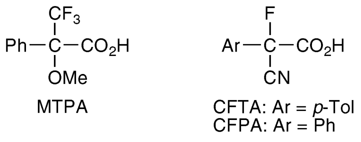
Direct confirmation of the preferred conformation of diastereomeric esters derived from a chiral secondary alcohol and a chiral derivatizing agent in solution, which is crucial for reliable NMR-based assignment of absolute stereochemistry of the alcohol, has been attained for the first time by examination of IR spectra of the CFTA esters.

Methods to determine absolute configurations are indispensable in research on the chemistry and applications of chiral molecules. Currently, ^{1}H NMR-based procedures using chiral derivatizing agents (CDAs) such as MTPA (α-methoxy-α-trifluoromethylphenylacetic acid, Fig. 1) are widely employed for this purpose.[1] In the CDA methods, distributions of the signs of chemical shift differences between diastereomers ($\Delta\delta$) are correlated to the absolute configuration of alcohols using an empirical correlation model. Thus the determination is made by extrapolation and therefore the reliability of the determination strongly depends on whether the model actually represents a preferred conformation in solution.

A practical procedure to assess the validity of a correlation model of Mosher's method[2] was reported by Kusumi *et al.*[3] They introduced the following criteria: (a) The signs of $\Delta\delta$ values for all assignable protons should be consistent at each side of the MTPA ester plane. (b) The signs for protons on one side should be opposite to those on the other side of the plane (Fig. 2).[2] If these two criteria are satisfied, the correlation model would be applicable.

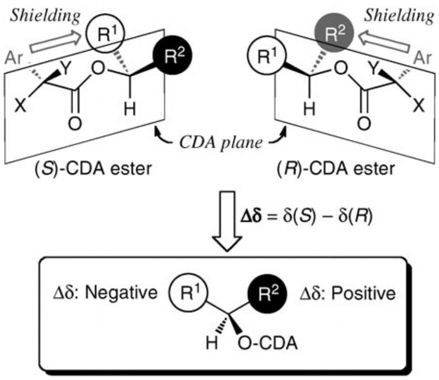
It is now common practice to use this type of analysis even for other CDA methods. However, it must be noted that this type of procedure is insufficient for strict judgement of applicability because an observed regular arrangement of the signs of $\Delta\delta$ values does not guarantee that the preferred conformation is actually the expected one. It has been known that each ester derivative of a common CDA exists as an equilibrium mixture of two or more conformers including those that give the opposite arrangement of signs to the observed ones. The energy differences among major conformers are small (<1 kcal mol^{-1}) and vary with the structures of alcohol moieties.[4] Therefore, the possibility cannot be excluded that the observed signs of $\Delta\delta$ values might be due to a different conformation from the one in the model and the adoption of the model might lead to the reversed configuration, especially in the case of the CDA esters of sterically hindered alcohols.


$\mathrm{Ph{-}C(CF_3)(OMe){-}CO_2H}$ $\mathrm{Ar{-}C(F)(CN){-}CO_2H}$

MTPA

CFTA: Ar = *p*-Tol
CFPA: Ar = Ph

Fig. 1 Structures of MTPA, CFTA, and CFPA.



MTPA: X = CF_3, Y = OMe, Ar = Ph
CFTA: X = F, Y = CN, Ar = *p*-Tol

Fig. 2 A correlation model for MTPA and CFTA methods.

In addition, the procedure has a limitation in practical use. It becomes less reliable for those esters that have only a few protons in the alcohol moiety.[5]

We present here a simple and direct elucidation of the preferred conformations for CFTA (α-cyano-α-fluoro-*p*-tolylacetic acid, Fig. 1) esters in solution by IR spectroscopy. CFTA has a unique structure with a fluorine and a cyano group at the stereogenic center.[6,7] For CFTA esters of various chiral secondary alcohols, a consistent distribution of the signs of $\Delta\delta$ values has so far been observed (Fig. 2).[7]

Ab initio calculations on the methyl and menthyl esters of CFPA (CFPA esters were used as simplified models of CFTA esters) found only two types of conformers with respect to the rotation around C_α–$C_{C=O}$.[7,8] One is the conformation with the C–F bond *synperiplanar* (*sp*) to the C=O bond and the other is *antiperiplanar* (*ap*). The *sp* conformers are more stable than the *ap* conformers by 0.6–0.9 kcal mol^{-1}. The aromatic plane in each conformer is facing either the R^1 or R^2 group of

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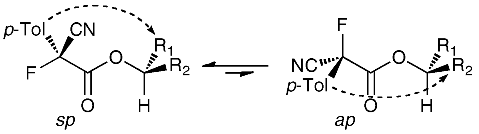

Fig. 3 The predicted conformational equilibrium in CFTA esters.

the alcohol moiety. In the case of the menthyl esters, the C–H bond on the carbinyl carbon is *syn* to the C=O bond in each diastereomer, as is well known for esters of secondary alcohols. The simple conformational preference (Fig. 3) suggested by the calculations is consistent with the correlation model for the CFTA method.

In order to examine the preferred conformers, we attempted to detect the individual conformers of twelve diastereomeric pairs of CFTA esters by IR spectroscopy[9] in $CHCl_3$, taking into consideration the solvent ($CDCl_3$) that was used for NMR measurement. The absolute configurations of the alcohol moieties of all these CFTA esters are in good agreement with those expected from the signs of $\Delta\delta$ values using the correlation model based on the *sp* conformation. In a typical example, the C=O stretching band for the (*R*)-CFTA ester of (1*R*,2*S*,5*R*)-menthol has a strong absorption around 1765 cm^{-1} with a weaker one as a shoulder around 1750 cm^{-1} (Fig. 4).

The carbonyl absorption with a distinct shoulder represents a marked difference from the absorption of the MTPA ester which does not show an apparent shoulder.[10] Curve-fitting of the C=O stretching band for all of the CFTA esters examined revealed absorptions around 1770 cm^{-1} (band I) and around 1750 cm^{-1} (band II) (Table 1).

It should be noted that the band I absorptions are consistently stronger than the band II absorptions. The band I and II absorptions were assigned to the *sp* and *ap* conformers, respectively, of three diastereomeric pairs of the CFTA esters by vibrational analysis.[11] The observed and calculated frequencies are summarized in Table 2. The calculated frequencies $\nu_{C=O}$ for the *sp* conformers were 1773–1783 cm^{-1}, while those for the *ap* conformers were 1749–1755 cm^{-1}. These calculated frequencies for the *sp* and *ap* conformers were in fair agreement with those of the observed bands I and II, respectively. The calculated intensities of the two absorptions were quite similar, indicating that they have similar molar extinction coefficients. Therefore, if one absorption band is clearly stronger than the other, the preferential conformer of the CFTA ester becomes clear. In the present cases, predominance of the *sp* conformers over the corresponding *ap* conformers in the equilibrium in chloroform solutions was ensured without the curve-fitting.

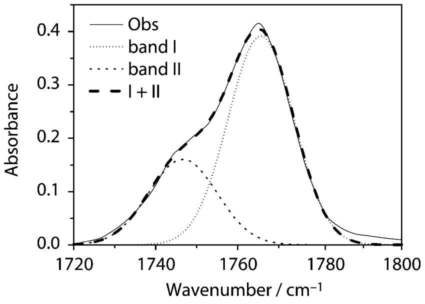

Fig. 4 $\nu_{C=O}$ band for (*S*)-CFTA ester of (1*R*,2*S*,5*R*)-menthol.

Table 1 Absorptions of C=O stretching bands observed for CFTA esters of chiral secondary alcohols (CFTA-OR*) in $CHCl_3$ solutions

			$\nu_{C=O}/cm^{-1}$		
entry	alcohol moiety (R*)	*R*/*S*[a]	band I	band II	A_I/A_{II}[b]
1	(*R*)-1-phenylethyl	*S*	1772	1752	2.3
2		*R*	1771	1751	2.3
3	(*S*)-1-phenylpropyl	*S*	1771	1750	4.8
4		*R*	1771	1749	6.6
5	(*R*)-2-(4-methylpentyl)	*S*	1766	1748	3.5
6		*R*	1755	1746	4.0
7	(*R*)-2-octyl	*S*	1772	1754	6.6
8		*R*	1771	1751	2.2
9	(*R*)-1-(2-methyl-1-phenylpropyl)	*S*	1765	1747	3.5
10		*R*	1772	1752	2.8
11	(1*R*,2*S*,5*R*)-menthyl	*S*	1766	1748	2.2
12		*R*	1766	1747	2.3
13	(1*S*,2*R*,5*R*)-isomenthyl	*S*	1768	1750	1.6
14		*R*	1768	1748	1.9
15	(1*S*,2*S*,5*R*)-neomenthyl	*S*	1766	1756	3.7
16		*R*	1766	1748	3.4
17	(1*R*,2*R*)-2-*exo*-bornyl	*S*	1767	1751	1.8
18		*R*	1768	1751	1.6
19	(1*S*,2*R*)-2-*endo*-bornyl	*S*	1767	1749	3.3
20		*R*	1767	1746	3.5
21	3β-5,6-dihydrocholesteryl	*S*	1767	1747	2.4
22		*R*	1767	1748	1.8

[a] Absolute configuration of CFTA moiety. [b] Ratio of areas of band I and band II absorptions.

Table 2 Observed and calculated absorption of C=O stretching for CFTA esters (CFTA-OR*) in $CHCl_3$ solutions[a]

			$\nu_{C=O}/cm^{-1}$			
entry	alcohol moiety (R*)	*R*/*S*[b]	band I (obsd)	*sp* (calcd)	band II (obsd)	*ap* (calcd)
1	(*R*)-1-phenylethyl	*S*	1772	1783	1752	1749
2		*R*	1771	1777	1751	1755
3	(1*R*,2*R*)-2-*exo*-bornyl	*S*	1767	1775	1749	1750
4		*R*	1767	1775	1746	1751
5	(1*S*,2*R*)-2-*endo*-bornyl	*S*	1767	1774	1751	1749
6		*R*	1768	1773	1751	1750

[a] Vibrational analysis was conducted on the *sp* and *ap* conformers calculated at the B3YLP/6-31G(d) level using the Gaussian 03 program.[11] Scaling factor 0.9613. [b] Absolute configuration of CFTA moiety.

Thus, we have developed a facile confirmation of the preferred conformer of individual CFTA esters. This is the first direct solution to the ambiguity of the stereochemistry assignment using CDAs. This confirmation makes the CFTA method an even more reliable one than any other conventional CDA procedures.

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