CHLOROFLUOROACETIC ACID AS A HIGHLY VERSATILE DERIVATIZING AGENT: ASSIGNMENT OF STEREOCHEMISTRY TO ESTERS OF CHIRAL ALCOHOLS

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Stereochemistry of a series of diastereomeric esters obtained from chiral alcohols **1a**–**21a** by derivatization with (*S*)- or (*R*)-chlorofluoroacetic acid was correlated with their LC and GC separation (Δt_r) and NMR resolution ($\Delta\delta$). Both the chromatographic and NMR spectral behavior of respective diastereomers was found to follow systematic rules reflecting their steric arrangement. Moreover, identical conformations of the esters seem to be preferred in solution as well as in the chromatographic processes. Reasons underlying this behavior are discussed.
Key words: Chiral derivatizing agents; Enantiomers; Resolution; Absolute configuration; Secondary alcohols; Correlations; HPLC; NMR spectroscopy.

One of the most appealing methods for determining enantiomeric composition of chiral alcohols involves their derivatization with a pure chiral non-racemic reagent and the examination of the ratio of resulting diastereomers by chromatography or spectral techniques[1]. A variety of reagents have been designed for this purpose but only a few of them can be applied to a broad spectrum of compounds encountered in modern synthetic and analytical chemistry[2]. Among these reagents, 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (Mosher's acid, MTPA), although developed more then thirty years ago, still belongs to the most widely used[3,4]. There are examples known, however, where the use of MTPA fails either because of insufficient ability of some compounds to undergo the

derivatization due to sterical reasons or because of low volatility, low stability and insufficient separation of the MTPA esters[5,6]. Consequently, there is still a need for new chiral derivatizing agents (CDA) that might exceed the capability of, but still preserve the merits of MTPA. Although numerous derivatives have already been proposed[2,4,7] they still await a wide-scale acceptance. We have recently developed a new and efficient CDA, (*S*)- and (*R*)-chlorofluoroacetic acid (CFA) which, in our opinion, may serve as a very useful and attractive alternative to MTPA and to other known CDAs (ref.[6]).

In contrast to a large amount of papers dealing with the above mentioned topic only limited effort was devoted to correlation between the stereochemistry of derivatized chiral compounds and their chromatographic and/or spectral behavior[8]. For instance, Helmchen *et al.*[8a], as well as Pirkle[8b] or Hoyer[8c] compared the HPLC elution order of several acid amides and carbamates with their structures and have found good correlations. For similar purpose, TLC was used by Feltkamp[8d]. Feibush applied GC to analysis of diastereomeric esters[8e] while some dipeptides were determined by Wieland[8f] or Weygand[8g]. Consistent NMR (refs[3c,8h,8j]), capillary electrophoresis[8k] and circular dichroism[8m] differences in diastereomers data which correlate with stereochemistry and thereby suggest uniform configuration behavior for selected compound types, have also been described.

In this context, we have turned our attention to (*S*)- and (*R*)-chlorofluoroacetic acids (CFA). There are several reasons for being so, namely: (i) CFA with alcohols affords diastereomers relatively easily even if other derivatization means fails[6a], (ii) no racemization under the conditions of analysis was observed[6b], and (iii) chromatographic behavior of CFA esters appears to be superior to those obtained by, *e.g.*, Mosher's procedure[6b]. Furthermore, there are no other substituents present in the acetate moiety except of two halogen atoms of different size. Assuming, in the first approximation, that the interaction of these halogen atoms with the adsorbent is negligible (or relatively small) compared with the rest of the CFA molecule so it seems likely that the CFA esters coordinate with silica gel according to Helmchen's principle[8a] and, therefore, the steric hindrance determines the elution order of diastereomers.

In order to find out the scope and limitations of CFA stereochemical analysis, twenty-one diastereomeric esters **1b**–**21b** have been prepared and the configuration of esters obtained was correlated with their NMR, LC and GC data.

EXPERIMENTAL

NMR data were recorded on UNITY-200 and UNITY-500 spectrometers (^{1}H: 200.04 MHz, 499.8 MHz $CDCl_3$, TMS; ^{19}F: 470.29 MHz, $CDCl_3$, $CFCl_3$ (δ 0.0)). Chemical shifts are expressed in δ-scale, while *J* values are given in Hz. For IR (CCl_4) and mass recordings, a Perkin–Elmer spectrometer and ZAB EQ instrument (VG, Great Britain; EI 70 eV) were used. GC analyses were performed on Hewlett–Packard chromatograph (DB-5 column, 30 m × 0.25 mm i.d.) with helium as the carrier gas. For HPLC analyses, a Hewlett–Packard HP 1090 apparatus equipped with silica columns (2 × (150 mm × 3 mm i.d.), Tessek, Czech Republic, silica 5 μm, 8–50% diethyl ether in hexane, flow rate: 0.35 cm^3 min^{-1}, DAD UV detector, 220, 254 nm, controlled by HP-85B computer) was used. For preparation of CFA esters, the following alcohols were purchased from Aldrich: (*R*)-(–)-butan-2-ol (**1a**), (*R*)-(–)-octan-2-ol (**2a**), (*R*)-(+)-oct-1-yn-3-ol (**5a**), (*R*)-(+)-1-phenylethan-1-ol (**6a**), (*R*)-(+)-2-methyl-1-phenylpropan-1-ol (**7a**), (*S*)-(–)-1-(2-bromophenyl)ethan-1-ol (**8a**), (*S*)-(–)-1-phenyldecan-1-ol (**9a**), (*R*)-(–)-(9-anthryl)-2,2,2-trifluoroethan-1-ol (**10a**), (*S*)-(–)-1,1-diphenylpropane-1,2-diol (**11a**), (*S*)-(–)-benzoin (**13a**), methyl (*S*)-(–)-lactate (**14a**), (+)-isomenthol (**16a**) and (–)-menthol (**17a**). (*R*)-(+)-1,1,2-Triphenylethane-1,2-diol (**12a**) was from Fluka. All the alcohols were used without further purification. (*S*)-Octan-3-ol (**3a**) and (*R*)-oct-1-en-3-ol (**4a**) were prepared by partial and total hydrogenation of **5a**, respectively, over 5% $Pd/BaSO_4$; the analytical data of the products obtained were in an accordance with those already published[9]. Methyl (*R*)-2-hydroxybutanoate (**15a**) was synthesized according to ref.[10]. The data concerning the remaining alcohols as well as analytical data of their CFA esters can be found in our previous papers (ref.[6a]: **11b**, **12b**, **13b**; ref.[6b]: **2b**, **4b**, **6b**, **9b**, **10b**, **16b**; ref.[11]: **18b**, **19b**, **20b**, **21b**).

To identify particular isomers in diastereomers, we have compared all the data (^{1}H NMR, GC, HPLC) for esters with racemic CFA with those for esters prepared using (*S*)-CFA. The esterification was carried out using DCC method[12a] with three-fold molar excess of reagents[12b] the end of the reaction being monitored by TLC (30–180 min). Resolution of CFA has been described in ref.[6b]

The structures of **1b** and **6b** molecules, both in (*R*,*R*) as well as (*S*,*R*) configurations were optimized at the DFT (Density Functional Theory) B3LYP level[14] using a large triple zeta basis set[15] augmented with polarization functions on all atoms and diffuse functions on non-hydrogen atoms (6-311+G**). The total optimization of the structures has been done with the GAUSSIAN98 program package[16].

General Procedure for Esterification of Alcohols **1a**–**21a**

To a stirred and cooled (0 °C) solution of (*S*)-chlorofluoroacetic acid (0.34 g, 3 mmol), alcohol (1 mmol) and 4-dimethylaminopyridine (0.037 g, 0.3 mmol) in CH_2Cl_2 (1 ml) was under N_2 added dropwise the solution of dicyclohexylcarbodiimide (0.62 g, 3 mmol) in CH_2Cl_2 (0.5 ml). After warming up to room temperature, the reaction was checked in 15 min intervals using TLC. As soon as the starting alcohol disappeared (30–150 min), the solvent was evaporated off the reaction mixture and the rest covered three times by 2 ml of light petroleum–ether (2 : 1). The organic fractions were filtered through Cellite 545 (Pasteur pipet) and the solvent evaporated again. The residuum was re-chromatographed using ten-fold excess of silica gel (Merck, 40–60 μm) to give the products in quantitative yields.

(1R)-1-Methylpropyl (2S)-2-chloro-2-fluoroacetate [(1*R*,2*S*)-**1b**]. ^{1}H NMR: 0.94 (t, *J* = 7.4, 3 H, CH_3); 1.305 (d, *J* = 6.87, 3 H, CH_3); 1.59–1.75 (m, 2 H, CH_2); 4.97–5.04 (m, 1 H, CH); 6.255

(d, $J_{H,F}$ = 50.7, 1 H, CHF). ^{19}F NMR: –146.17 (d, $J_{H,F}$ = 50.2, CHF). MS, *m/z* (%): 168 [M^+] (1), 153 (6), 155 (2), 139 (25), 141 (8), 111 (8), 113 (3), 67 (50), 57 (100). IR: 1 770 (C=O), 1 291 (C–O), 1 200 (C–O), 1 110 (C–F), 656 (C–Cl). For $C_6H_{10}ClFO_2$ (168.6) calculated: 42.75% C, 5.98% H; found: 42.80% C, 6.00% H.

(1*R*,2*R*)-**1b**: ^{1}H NMR: 1.308 (d, *J* = 6.87, 3 H, CH_3); 6.252 (d, $J_{H,F}$ = 50.5, 1 H, CHF). ^{19}F NMR: –146.64 (d, $J_{H,F}$ = 50.6, CHF).

(1S)-1-Ethylhexyl (2S)-2-chloro-2-fluoroethacetate [(1*S*,2*S*)-**3b**]. ^{1}H NMR: 0.87–0.94 (m, 6 H, 2 × CH_3); 1.25–1.38 (m, 6 H, 3 × CH_2); 1.58–1.70 (m, 4 H, 2 × CH_2); 4.94–5.00 (m, 1 H, CH); 6.269 (d, $J_{H,F}$ = 50.7, 1 H, CHF). ^{19}F NMR: –145.83 (d, $J_{H,F}$ = 50.0, CHF). MS, *m/z* (%): 153 (15), 113 (6), 112 (16), 83 (80), 71 (62), 57 (90), 55 (100). IR: 1 770 (C=O), 1 292 (C–O), 1 201 (C–O), 1 110 (C–F), 657 (C–Cl). For $C_{10}H_{18}ClFO_2$ (224.7) calculated: 53.45% C, 8.07% H; found: 53.35% C, 8.01% H.

(1*S*,2*R*)-**3b**: ^{19}F NMR: –145.84 (d, $J_{H,F}$ = 50.5, CHF).

(1R)-1-Pentylprop-2-en-1-yl (2S)-2-chloro-2-fluoroacetate [(1R,2S)-**4b**]. ^{1}H NMR: 0.87–0.92 (m, 3 H, CH_3); 1.22–1.90 (m, 8 H, 4 × CH_2); 5.24–5.36 (m, 3 H, 3 × =CH); 5.76–5.84 (m, 1 H, CH); 6.271 (d, $J_{H,F}$ = 50.5, 1 H, CHF). ^{19}F NMR: –146.16 (d, $J_{H,F}$ = 50.7, CHF). MS, *m/z* (%): 151 (15), 153 (8), 123 (12), 111 (8), 110 (15), 95 (20), 81 (35), 82 (17), 69 (100), 67 (90), 54 (65), 55 (60). IR: 3 096 (=C–H), 1 767 (C=O), 1 650 (C=C), 1 253 (C–O), 1 107 (C–F). For $C_{10}H_{16}ClFO_2$ (222.7) calculated: 53.94% C, 7.24% H; found: 53.80% C, 7.24% H.

(1*R*,2*R*)-**4b**: ^{1}H NMR: 6.271 (d, $J_{H,F}$ = 50.5, 1 H, CHF). ^{19}F NMR: –146.10 (d, $J_{H,F}$ = 50.7, CHF).

(1R)-1-Pentylprop-2-yn-1-yl (2S)-2-chloro-2-fluoroacetate [(1*R*,2*S*)-**5b**]. ^{1}H NMR: 0.88–0.92 (m, 3 H, CH_3); 1.25–1.92 (m, 8 H, 4 × CH_2); 2.56 (d, *J* = 2.1, 1 H, ≡CH); 5.44–5.49 (m, 1 H, CH); 6.304 (d, $J_{H,F}$ = 50.3, 1 H, CHF). ^{19}F NMR: –146.96 (d, $J_{H,F}$ = 50.2, CHF). MS, *m/z* (%): 164 (10), 109 (3), 93 (30), 91 (15), 79 (50), 67 (100), 55 (35). IR: 3 312 (≡CH), 2 097 (C≡C), 1 761 (C=O), 1 282 (C–O), 1 188 (C–O), 1 109 (C–F). For $C_{10}H_{14}ClFO_2$ (220.7) calculated: 54.43% C, 6.39% H; found: 54.44% C, 6.30% H.

(1*R*,2*R*)-**5b**: ^{1}H NMR: 6.301 (d, $J_{H,F}$ = 50.3, 1 H, CHF). ^{19}F NMR: –146.70 (d, $J_{H,F}$ = 50.7, CHF).

(1R)-2-Methyl-1-phenylpropyl (2S)-2-chloro-2-fluoroacetate [(1*R*,2*S*)-**7b**]. ^{1}H NMR: 0.826 (d, *J* = 6.7, 3 H $(CH_3)_a$); 1.031 (d, *J* = 6.6, 3 H $(CH_3)_b$); 2.16–2.62 (m, 1 H, CH); 5.563 (d, *J* = 8.1, 1 H, CH–O); 6.275 (d, $J_{H,F}$ = 50.4, 1 H, CHF); 7.29–7.37 (m, 5 H, CH arom.). ^{19}F NMR: –145.94 (d, $J_{H,F}$ = 50.5, CHF). MS, *m/z* (%): 244 [M^+] (12), 201 (70), 173 (30), 133 (25), 107 (45), 91 (100), 77 (50). IR: 3 091 (C–H arom.), 3 068 (C–H arom.), 1 775 (C=O), 1 286 (C–O), 1 194 (C–O), 1 108 (C–F). For $C_{12}H_{14}ClFO_2$ (244.7) calculated: 58.90% C, 5.77% H; found: 58.81% C, 5.70% H.

(1*R*,2*R*)-**7b**: ^{1}H NMR: 0.837 (d, *J* = 6.9, 3 H $(CH_3)_a$); 1.022 (d, *J* = 6.7, 3 H $(CH_3)_b$); 5.560 (d, *J* = 7.9, 1 H, CH–O); 6.305 (d, $J_{H,F}$ = 50.5, 1 H, CHF). ^{19}F NMR: –146.25 (d, $J_{H,F}$ = 50.2, CHF).

(1S)-1-(2-Bromophenyl)ethyl (2S)-2-chloro-2-fluoroacetate [(1*S*,2*S*)-**8b**]. ^{1}H NMR: 1.621 (d, *J* = 6.7, 3 H, CH_3); 6.309 (q, *J* = 6.6, 1 H, CH–O); 6.331 (d, $J_{H,F}$ = 50.2, 1 H, CHF); 7.14–7.60 (m, 4 H, CH arom.). ^{19}F NMR: –146.45 (d, $J_{H,F}$ = 50.2, CHF). MS, *m/z* (%): 215 (70), 217 (12), 183 (50), 185 (50), 157 (8), 155 (7), 104 (100), 103 (70), 77 (65). IR: 3 073 (C–H arom.), 3 065 (C–H arom.), 1 779 (C=O), 1 290 (C–O), 1 191 (C–O), 1 110 (C–F). For $C_{10}H_9BrClFO_2$ (295.5) calculated: 40.64% C, 3.07% H; found: 40.75% C, 3.17% H.

(1*S*,2*R*)-**8b**: ^{1}H NMR: 1.631 (d, *J* = 6.4, 3 H, CH_3); 6.312 (d, $J_{H,F}$ = 50.4, 1 H, CHF); 6.317 (q, *J* = 6.6, 1 H, CH–O). ^{19}F NMR: –146.38 (d, $J_{H,F}$ = 50.2, CHF).

Methyl (2′S)-2-[(2S)-2-chloro-2-fluoroacetoxy]propanoate [(2′*S*,2*S*)-**14b**]. ^{1}H NMR: 1.600 (d, J = 7.2, 3 H, CH_3); 3.79 (s, 3 H, CH_3); 5.263 (q, J = 7.2, 1 H, CH); 6.363 (d, $J_{H,F}$ = 50.2, 1 H, CHF). ^{19}F NMR: –146.49 (d, $J_{H,F}$ = 50.0, CHF). MS, *m/z* (%): 167 (7), 139 (62), 131 (6), 111 (15), 87 (40), 67 (85), 59 (100). IR: 1 784 (C=O), 1 763 (C=O), 1 284 (C–O), 1 191 (C–O), 1 110 (C–F). For $C_6H_8ClFO_4$ (198.6) calculated: 36.29% C, 4.06% H; found: 36.20% C, 3.99% H.

(2′*S*,2*R*)-**14b**: ^{1}H NMR: 1.592 (d, J = 7, 3 H, CH_3); 5.253 (q, J = 7, 1 H, CH); 6.374 (d, $J_{H,F}$ = 50.5, 1 H, CHF). ^{19}F NMR: –146.19 (d, $J_{H,F}$ = 50.2, CHF).

Methyl (3R)-3-[(2S)-2-chloro-2-fluoroacetoxy]butanoate [(3*R*,2*S*)-**15b**]. ^{1}H NMR: 1.397 (d, J = 6.26, 3 H, CH_3); 2.58–3.68 (m, 2 H, CH_2); 3.702 (s, 3 H, CH_3); 5.41–5.47 (m, 1 H, CH); 6.246 (d, $J_{H,F}$ = 50.5, 1 H, CHF). ^{19}F NMR: –146.63 (d, $J_{H,F}$ = 50.2, CHF). MS, *m/z* (%): 183 (2), 181 (3), 117 (3), 101 (10), 69 (60), 67 (40), 59 (100). IR: 1 776 (C=O), 1 749 (C=O), 1 284 (C–O), 1 191 (C–O), 1107 (C–F). For $C_7H_{10}ClFO_4$ (212.6) calculated: 39.55% C, 4.74% H; found: 39.63% C, 4.81% H.

(3*R*,2*R*)-**14b**: ^{1}H NMR: 1.404 (d, J = 6.41, 3 H, CH_3); 3.698 (s, 3 H, CH_3); 6.248 (d, $J_{H,F}$ = 50.36, 1 H, CHF). ^{19}F NMR: –146.56 (d, $J_{H,F}$ = 50.5, CHF).

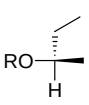
(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl (2S)-2-chloro-2-fluoroacetate [(1′*R*,2′*S*,5′*R*,2*S*)-**17b**]. ^{1}H NMR: 0.784 (d, J = 7 $(CH_3)_a$); 0.913 (d, J = 7 $(CH_3)_b$); 0.933 (d, J = 6.6 $(CH_3)_y$); 1.40–2.12 (m, 9 H, 3 × CH_2, 3 × CH); 4.74–4.88 (m, 1 H, CH–O); 6.257 (d, $J_{H,F}$ = 50.7, 1 H, CHF). ^{19}F NMR: –146.09 (d, $J_{H,F}$ = 50.8, CHF). MS, *m/z* (%): 139 (12), 138 (30), 123 (40), 109 (10), 95 (100), 81 (95), 67 (65). IR: 1 771 (C=O), 1 295 (C–O), 1 198 (C–O), 1 108 (C–F). For $C_{12}H_{20}ClFO_2$ (250.7) calculated: 57.48% C, 8.04% H; found: 57.37% C, 7.98% H.

(1′*R*,2′*S*,5′*R*,2*R*)-**17b**: ^{1}H NMR: 0.775 (d, J = 7 $(CH_3)_a$); 0.907 (d, J = 7 $(CH_3)_b$); 6.249 (d, $J_{H,F}$ = 50.7, 1 H, CHF). ^{19}F NMR: –145.85 (d, $J_{H,F}$ = 50.2, CHF).

RESULTS AND DISCUSSION

The chiral alcohols **1a**–**21a** were transformed to their CFA esters **1b**–**21b** both with (*S*)- and racemic-CFA. Following the strategy of DCC esterification[12], we have used three-fold excess of reagents in order to avoid incomplete conversion. Therefore, all esters were obtained in quantitative yields (it is to be noted that the esterification of alcohols **11a**–**13a** with MTPA completely fails for steric reasons[6a]). The presence of fluorine atom at the chiral center of acetate moiety results in separation of two doublets at about 6.2 ppm ($J_{H,F}$ = 50 Hz), not overlapped by other signals thus allowing their characterization. The relatively large non-equivalence ($\Delta\delta \approx 2$ Hz) of the hydrogens on the other hand, along with the sharpness of these doublets enabled an easy determination of particular diastereomers in the mixture. We have summarized all $\Delta\delta$ as well as the retention time differences (Δt_r) in Table I. The data demonstrate that the constitution and configuration of CFA esters influence both the properties (Δt_r, $\Delta\delta$) in a consistent manner.

As far as the chromatography is concerned, all the CFA esters included are well resolved except those **10b** and **13b** (under the described conditions). A good correlation between structure and the elution order suggests



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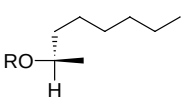

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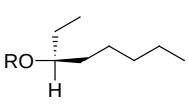

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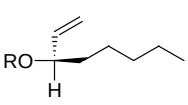

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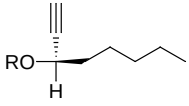

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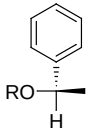

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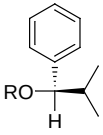

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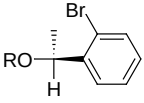

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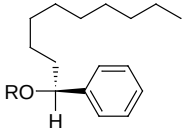

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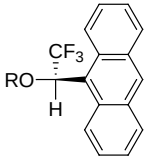

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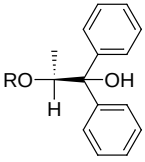

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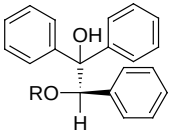

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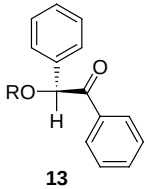

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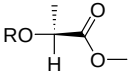

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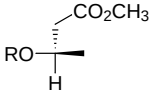

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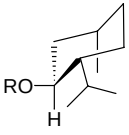

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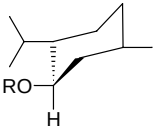

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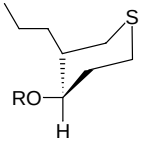

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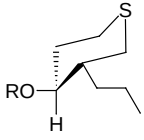

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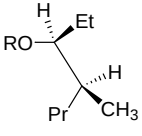

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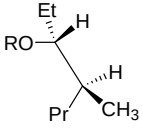

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1–21	
a	R = H
b	R = C(O)CHClF

TABLE I
Chromatographic and spectroscopic differences of CFA diastereomers

Ester **1b–21b**	GC		Δδ, Hz[a]			HPLC				
	t_r/min of diastereomers		Δt_r[b]	^{1}H	^{19}F	t_r/min of diastereomers				Δt_r[b]
	l	*u*				*l*	(conf.)[d]	*u*	(conf.)[d]	
1b	10.97	10.80	0.17	–1.2	–50.3	16.08	**A**	15.28	**A′**	0.80
2b	32.17	30.45	1.72	–1.5	–51.3	22.29	**A**	21.03	**A′**	1.29
3b	24.77	24.48	0.29	0.0	4.3	16.73	**A**	15.26	**A′**	1.47
4b	21.69	22.06	–0.37	4.5	–28.3	17.97	**B**	19.11	**B′**	–1.14
5b	21.96	22.16	–0.20	–1.2	6.9	37.21	**B**	38.26	**B′**	–1.05
6b	64.17	62.90	1.27	6.0	5.6	18.32	**B**	21.57	**B′**	–3.25
7b	109.35	110.11	–0.76	15.1	146.3	39.43	**B**	39.93	**B′**	–0.50
8b	36.29	35.43	0.86	9.3	–33.6	17.05	**B′**	16.24	**B**	0.80
9b	39.97	34.58	5.39	6.0[c]	39.5	16.97	**B**	17.20	**B′**	–0.23
10b	24.88	25.02	–0.14	–4.7	3.2	20.82	–	20.82	–	0.00
11b	16.77	16.33	0.44	19.4	91.3	22.17	**A**	16.90	**A′**	5.27
12b	30.81	30.81	0.00	16.3	171.9	27.70	**B′**	20.10	**B**	7.60
13b	17.50	17.14	0.36	–21.8	91.6	24.80	–	24.80	–	0.00
14b	8.69	8.47	0.22	–5.3	–91.5	45.11	**A**	44.07	**A′**	1.04
15b	29.96	29.82	0.14	0.9	33.7	31.63	**A**	30.51	**A′**	0.12
16b	31.80	30.47	1.33	–1.7	15.5	20.10	**A**	18.59	**A′**	1.51
17b	20.05	16.64	3.41	–4.0	112.1	15.41	**A**	15.00	**A′**	0.41
18b	25.99	25.88	0.10	–2.0[c]	–	16.36	**A**	14.12	**A′**	2.24
19b	26.36	26.25	0.11	–2.5[c]	–	16.14	**A**	14.38	**A′**	1.76
20b	79.88	82.59	–3.01	–	–	–		–		–
21b	82.47	84.53	–2.06	–	–	–		–		–

[a] Chemical shift nonequivalence (Δδ) was calculated by subtracting ^{1}H chemical shifts of CHFCl of (*R*,*S*)- or (*S*,*R*)-isomers (= *u* unlike) from those of corresponding (*S*,*S*)- or (*R*,*R*)-ones (= *l* like), respectively; [b] Δt_r obtained similarly by subtracting of retention times; [c] 200 MHz; [d] assumed conformer, see Fig. 2.

a prefered weighted time-averaged conformation in a non-polar solution as well as during the interaction with silica gel, which accounts for their chromatographic behavior.

Evidently, the ester group laying in the plane (coplanar with fluorine, methine carbon and hydrogen atoms, Fig. 1; see also refs[3a,8a]) is responsible for the interaction of CFA esters with silica gel surface[8b,13] while its approach to the silica gel depends on the bulkiness of substituents (chlorine atom *vs* larger alkyl group) and on their attachment to this plane (the same *vs* opposite side). This interpretation of chromatographic data (Table I) corresponds to Helmchen's model of steric approach[8a].

In order to explain the chromatographic behavior correctly, two groups of compounds may be recognized in Table I. The compounds of the first group must adopt predominantly conformation **A** during the chromatography (**1b**–**5b**, **11b**–**19b**) while conformation **B** (Fig. 2) suits the second group, *i.e.* compounds having α-phenyl group attached to the methine carbon atom (**6b**, **7b**, **9b**, **12b**).

Both predominant conformations differ in mutual position of substituents. While all substituents in structure **A** are almost in the eclipsed position, the torsion angle in conformer **B** must be little distorted due to the repulsion of chlorine atom and the α-phenyl group (similar effect was already described by Mosher[8h] and by other authors[1c,4a]). Consequently, one

FIG. 1
Spatial arrangement of CFA diastereomers

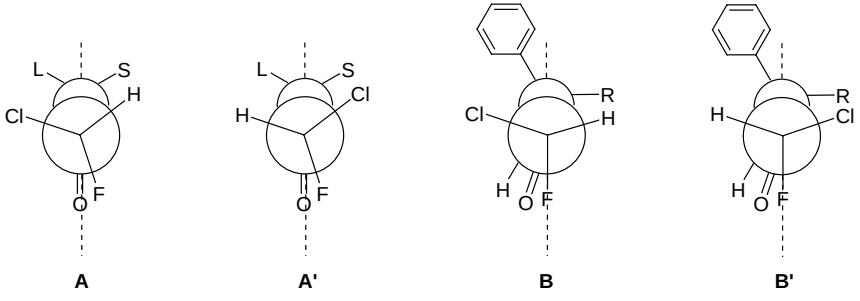

FIG. 2
Assumed conformations of diastereomers **1b**–**21b**

side of the above mentioned plane (dotted line, Fig. 2) is less hindered (**A**, **B′**), being occupied by the smaller substituents than the other one (**A′**, **B**). Therefore, its interaction with the adsorbent is less hindered and conformers **A** and **B′** are less mobile. In other words, equations $\Delta t_r = t_A - t_{A'} > 0$ and $\Delta t_r = t_B - t_{B'} < 0$ hold true for conformers **A** and **B**, respectively. A comment should be made concerning the behavior of **8b**. According to Δt_r, the conformation of diastereomers of **8b** corresponds to the model **A** rather than to **B**. The bulky 2-bromophenyl group is evidently responsible for this anomaly. On the other hand, the reversed elution order of esters **12b** is because of exchanged substitution in the alcohol moiety.

It is to be emphasized again that the planar C(O)O group[13] is responsible for the affinity of CFA compounds to the silica gel surface and that the discussed conformers are preferred. If other substituents with larger affinity to silica gel are present in the molecule, they most probably cause collapse of conformers **A**–**B′** with the change of chromatographic properties as a consequence. However, this is no the case of esters **11b** and **12b** even though they contain free hydroxy group with assumed large affinity to silica gel; the reason being the shielding by two adjacent aromatic rings[6a].

The summarized results are rather surprising because the compound–adsorbent interaction is generally believed to disrupt the preferred conformations in solution[8b]. However, the data obtained rationalize the above mentioned steric approach.

^{1}H NMR spectra also show the consistency of spectral differences with stereochemistry thus supporting the idea of uniform arrangement both in solution and during the interaction with silica gel. The doublet resonance of C**H**FCl in esters **1b**–**2b**, **14b**, **16b**–**19b** (Table I) occurs upfield in the conformer **A** while the opposite is valid for **B′** (ester **3b** was not resolved at 500 MHz; however, this could be certainly done using higher-frequency spectrometers). In esters having α-group with pronounced anisotropic effect (**4b**–**11b**, **13b**, **15b**), the chemical shift depends on the position of appropriate group with respect to the C**H**ClF (the same *vs* opposite sides) and its shielding/deshielding ability. Thus, in compounds **6b**–**11b**, the phenyl group located on the same side as C**H**FC causes upfield shift (**B′**) in comparison with the opposite diastereomer (**B**). Generally, those relationships can be described by the equations as follows: $\Delta\delta = \delta_{A'} - \delta_A > 0$ and $\Delta\delta = \delta_B - \delta_{B'} > 0$. The exceptional spectral behavior of **5b** can be attributed to the presence of triple bond in the molecule and its deshielding of the C**H**ClF group. A sort of anisotropy is also apparent in ester **11b** even though the aromatic rings are not in the α-position. This is nothing curious because the anisotropy of benzene ring is known to affect even more distant protons[4]. At least one of

the two β-phenyl groups in **11b** is oriented in such a way that it shields the appropriate hydrogen atom effectively. Similarly, C**H**ClF in **12b** is shielded by β-phenyl group rather than by the more closer α-phenyl one (*cf.* Δδ for both **11b** and **12b**).

^{19}F NMR spectral data are certainly affected by mutual position of fluorine atom and ester carbonyl group thus being deshielded to a different degree. As a such, fluorine adsorption can be hardly used for the purpose of chiral analysis because unreliably reflects its chemical environment. Similarly, GC values were also included in this paper in order to complete the set of data.

The results of structure optimization (compounds (*R*,*R*)-, (*S*,*R*)-**1b** and (*R*,*R*)-, (*S*,*R*)-**6b**)) well coincide with their chromatographic and spectral behavior thus supporting the assumed arrangement of **A** and **B** (Fig. 3). According to the DFT calculations the bonds F–C–C(=O)–O–C–H are approximately in plane (maximum deviation x^0) that clarify the sterical approach of esters to the surface of silica gel ((*R*,*R*)-**1b** is identical with **A** while (*S*,*R*)-**6b** with **B′**; both structures are less mobile on silica gel than the corresponding diastereomers). However, in compounds (*R*,*R*)-**6b** as well as in (*S*,*R*)-**6b**, there were two conformations found equal in energy, differing in mutual position of phenyl group and the substituents in the acetate moiety. Apparently, the lower conformers (*R*,*R*)-**6b** and (*S*,*R*)-**6b** in Fig. 3 more correspond to those derived from chromatographic data (Fig. 2).

The energy difference between the particular diastereomers is negligible. For instance, (*R*,*R*)-**1b** is by 0.2 kJ mol^{-1} more stable than the corresponding (*S*,*R*)-**6b** isomer.

In conclusion, the CFA esters were proven to be an effective tool in chiral analysis. Easily accessible (*S*)- or (*R*)-CFA undergoes esterification even with sterically hindered secondary alcohols where, *e.g.*, the Mosher's method fails. Chromatographic separations seem to be superior to the methods used so far. The chromatographic behavior as well as ^{1}H NMR data suggest that those compounds occupy the same preferred conformation in solution as well as during interaction with adsorbent. The determination of optical purity and relative and/or absolute configuration are very simple procedures; however, they are restricted to the methine carbon atom of secondary chiral alcohols. On the other hand, a combination of chromatographic and spectral investigation as well as a rational analysis of energy-minimized models gives an effective and highly reliable tool for determining the composition of chiral alcohols, especially when the classic CDAs fail. The method was already used in synthesis of chiral compounds with good results[11].

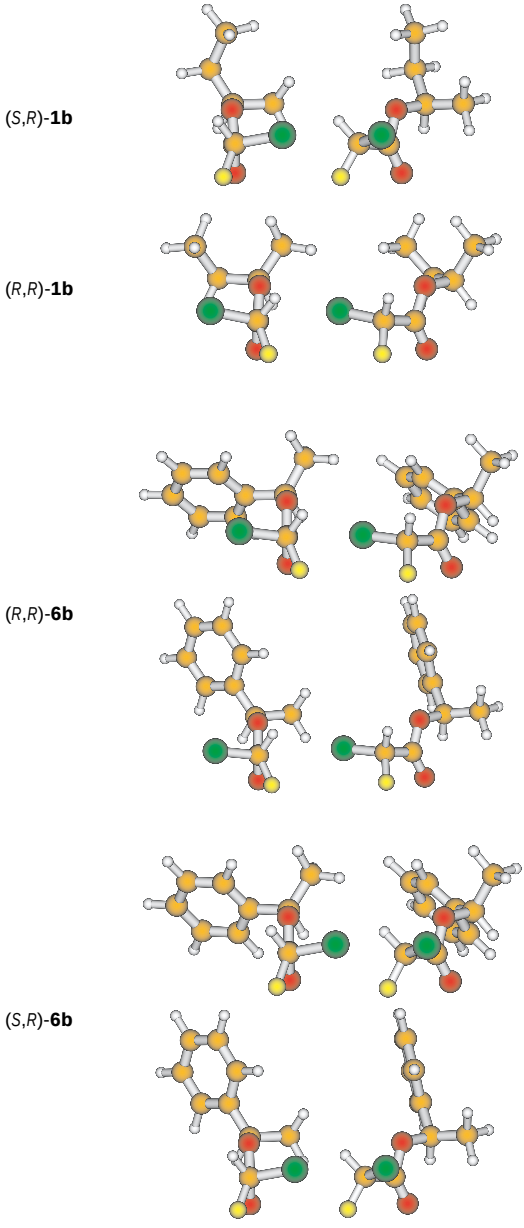

FIG. 3
Newman-like (left) and perspective projection (right) of energy-minimized sructures of esters **1b** and **6b** (H silver; O red; Cl green; F yellow)

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