Self-disproportionation of enantiomers of 3,3,3-trifluorolactic acid amides via sublimation

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ABSTRACT

Preparation of racemic and enantiomerically enriched N-phenyl- and N-benzyl-3,3,3-trifluorolactic acid amides has been developed. These compounds were found to have substantial magnitude of the self-disproportionation of enantiomers (SDE) via sublimation. For example, when N-phenyl-3,3,3-trifluorolactic acid amide of 87% ee was sublimed (12 h) from a Petri dish at 80 °C open to the atmosphere, the enantiomeric excess of the remainder increased to 96% ee. On the other hand, when a sample of the same compound of 67% ee was subjected to SDE via sublimation under the same conditions, the enantiomeric excess has decreased to 18% ee. These preliminary results as well as excellent chemical and physico-chemical characteristics of these amide derivatives render them as readily available and very promising substrates for systematic study of SDE via sublimation.

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1. Introduction

Self-disproportionation of enantiomers (SDE) is a transformation of an enantiomerically enriched system resulting in the formation of fractions of a different, as compared with the original, proportion of the enantiomers. The phenomenon of SDE suggests that the physico-chemical behavior of an enantiomerically enriched system might be better described, not as a mixture of unevenly proportioned enantiomers, but rather as a mixture of a racemate [1] with an excess enantiomer. Thus, the ultimate outcome of SDE is a complete separation of racemate from the excess enantiomer. This separation is of fundamentally general nature and can be observed under any physical processes. The most known and widely used example of SDE is crystallization of enantiomerically enriched compound resulting, ideally, in racemic and optically pure fractions [2]. On the other hand, the SDE via other typical physical processes such as, e.g., distillation/evaporation [3,4], sublimation [5,6], achiral chromatography [7], gravitational field [8] are substantially less known and virtually

unstudied. One of the reasons of the current lack of knowledge in this area is that most of the chemistry practitioners are unaware of this phenomenon and therefore it goes unnoticed in routine everyday laboratory experiments.

While the SDE phenomenon always takes place under any physico-chemical transformation, its magnitude and therefore practical observation is dependent on the physical and chemical properties of a particular compound, such as crystallinity, solubility, volatility, etc. We believe that fluorinated molecules possess a significant potential of SDE phenomenon of high magnitude due to their unique properties, as compared with non-fluorinated counterparts, such as increased density and viscosity, dipole–dipole and hydrogen-bonding intermolecular interactions, and lowered surface tension, refractive index, and dielectric constants [9–11]. Of particular interest are compounds containing a trifluoromethyl group which additionally impacts the pattern of intermolecular interactions because of its strong steric [12] and electrostatic [13] demands. For instance, isopropyl 3,3,3-trifluorolactate shows a remarkable magnitude of SDE via distillation while non-fluorinated lactate did not show any measurable SDE phenomenon under the same conditions [4]. Recently, we have discovered that a trifluoromethyl group directly bonded to a stereogenic center can induce significant magnitude of SDE during chromatography on achiral silica-gel stationary phase using achiral eluent [7b–d]. Furthermore, we have found that racemic crystals of α-(trifluoromethyl)lactic acid sublime at

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substantially higher rates, as compared with the optically pure form, leading to appreciable magnitude of SDE via sublimation [6]. Thus, remarkably, optical purification of enantiomerically enriched samples of α-(trifluoromethyl)lactic acid can be achieved under ultimately simple conditions, just leaving the compound on a bench in open air [6]. This data strongly suggest that compounds containing a trifluoromethyl group directly bonded to a stereogenic center represent a privileged class of molecules most suitable for a systematic study of SDE. In particular, we decided to investigate a possible SDE of some new derivatives of 3,3,3-trifluorolactic acid. In this communication we report the synthesis of amide derivatives of 3,3,3-trifluorolactic acid in racemic and enantiomerically enriched form, as well as preliminary results on their SDE via sublimation.

2. Results and discussion

As representative examples of an aliphatic and an aromatic amide of 3,3,3-trifluorolactic acid, we prepared phenyl (2a) and benzyl (2b) derivatives. The racemate (R/S)-2b was prepared from compound 1 by the standard condition (Entry 1). On the other hand, the synthesis of optically pure 2b under the same conditions resulted in racemization (Entry 2), probably due to the substantially increased acidity of the α-hydrogen activated by the strong electron withdrawing effects of the –CF$_3$ group. We then attempted to prepare optically pure 2b using various other methods, but racemization was found to be a persistent problem. However, the activation of acid 1 under relatively mild conditions using SOCl$_2$ allowed us to obtain the target product 2b with an optical purity of 88% ee (Entry 3). While the unexpected problem of racemization is still waiting for more optimal synthetic solution, the prepared sample of relatively high enantiomeric purity was sufficient to continue with our preliminary SDE via sublimation experiments. For the aromatic amide 2a, Method A also worked quite efficiently for the synthesis of racemic (R/S)-2a (Entry 4). For the synthesis of (S)-2a, treatment of compound 1 with methane sulfonyl chloride resulted in racemization of the final product whilst with the use of thionyl chloride did not cause any undesired racemization (Entries 5 and 6) (Table 1).

As we always suggest doing for the initial study of SDE via sublimation [6], the racemic and optically pure samples of 2a were sublimed separately at 80 °C on a Petri dish under open air condition (Fig. 1). In sharp contrast to the results reported for of α-CF$_3$-lactic acid [6] and 3,3,3-trifluorolactic acid isopropyl ester [4], racemic crystals (R/S)-2a sublimed substantially more slowly than

Table 1
Synthesis of 3,3,3-trifluorolactic acid amides.

R = Ph (a); Bn (b).
Method A: MeSO$_2$Cl, N-methylimidazole, RNH$_2$. Method B: SOCl$_2$, RNH$_2$.

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| Entry	1	Method	Yield (%)	ee of 2[a] (%)
1	(R/S)-1	A	44	0 (b)
2	(S)-1	A	41	0 (b)
3	(S)-1	B	18	88 (b)
4	(R/S)-1	A	43	0 (a)
5	(S)-1	A	51	0 (a)
6	(S)-1	B	31	>99 (a)

[a] Enantiomeric excesses were determined by chiral HPLC.
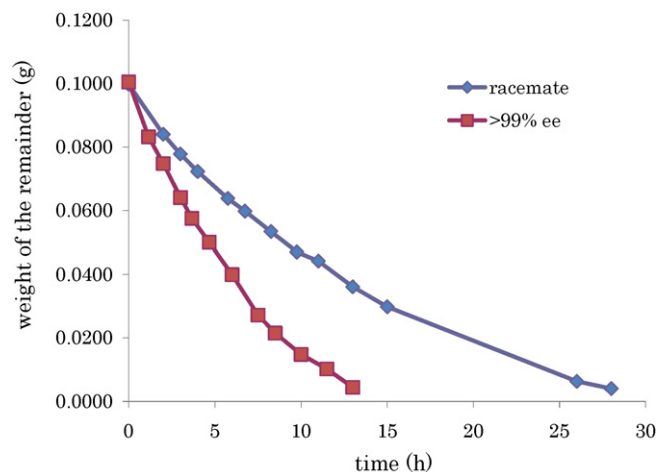
Fig. 1. Sublimation of racemate and >99% ee 2a at 80 °C.

the enantiomerically pure crystals (S)-2a. Thus, the initial rates of sublimation of (R/S)-2a and (S)-2a are 0.0062 and 0.0099 [g/h], respectively.

The obtained results of noticeably different sublimation rates of racemic 2a and enantiomerically pure 2a forms suggested that, first, in this case the SDE via sublimation should have a substantial, practically useful magnitude; and, second, in the range of samples of various enantiomeric purity, the sublimed material might undergo optical enrichment, while the remainder—optical depletion. Thus, when a sample of 2a of 67% ee was subjected to sublimation (Fig. 2), the optical purity of the remainder gradually decreased from 67 to 18% ee after 15.5 h. On the other hand, in the case of a sample of 89% ee, the enantiomeric purity of the remainder increased slowly up to 96% ee after 12 h of sublimation. All the samples were prepared from (R/S)-2a and (S)-2a by mixing and well grinding.

Similarly, when a sample of 67% ee benzyl amide 2b prepared by mixing racemate and 88% ee samples was subjected to sublimation under the same conditions (Petri dish, open air, at 50 °C) (Fig. 3), the optical purity of the remainder gradually decreased to 27% ee after 131 h.

These results clearly demonstrate that N-phenyl- and N-benzyl-3,3,3-trifluorolactic acid amides 2a and 2b are interesting and quite useful substrates for the systematic study of SDE via sublimation. Compounds 2a and 2b are easily available in racemic and enantiomerically enriched forms, highly crystalline, and reasonably volatile. Furthermore, compounds 2a and 2b are chemically and configurationally stable and can be readily monitored by TLC. All these important features render compounds
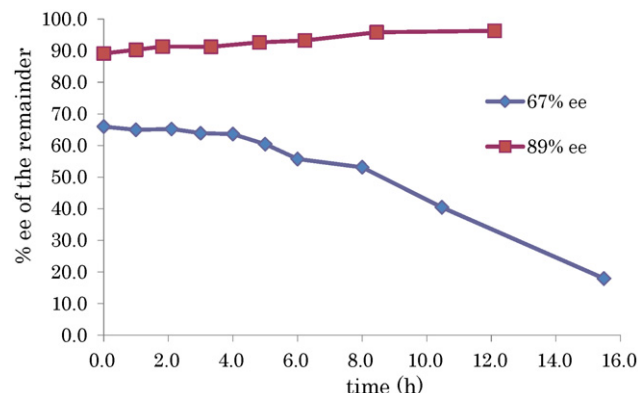
Fig. 2. SDE of 2a at 80 °C. Time dependent change of % ee of the remainder.
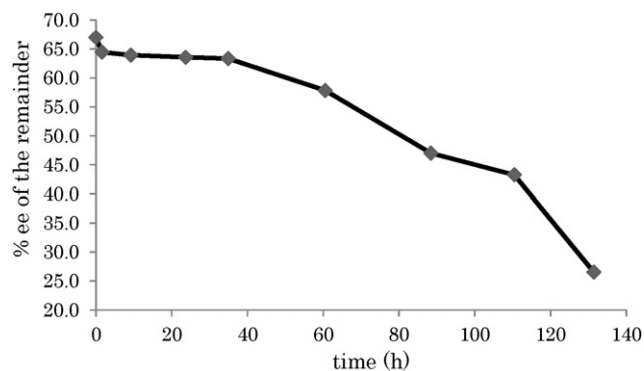
Fig. 3. SDE of **2b** at 50 °C. Time dependent change of % ee of the remainder.

2a and **2b**, and most probably other amide derivatives, as very promising structures for the systematic study of SDE via sublimation and its practical applications. These results also support the hypothesis that compounds containing –CF₃ group directly bonded to a stereogenic carbon center are prone to induce a SDE effect.

3. Experimental

3.1. General

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All of the reactions were carried out under N_2 atmospheric conditions. Unless indicated ^{1}H and ^{13}C NMR spectra, were taken in CDCl₃ solutions at 299.95 and 75.42 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C NMR refer to TMS as the internal standard. Chemical shifts for ^{19}F NMR refer to CFCl₃ as the internal standard. A Micromass Q-TOF was used to measure the time-of-flight electrospray mass spectra in positive ion mode (TOF-ESIMS⁺). All new compounds were characterized by ^{1}H, ^{13}C and ^{19}F NMR, high-resolution mass spectrometry (HRMS-ESI), and melting point, when applicable.

The optical purity of **2a** and **2b** was determined by HPLC (OD-H: 0.46 cm × 25 cm). The flow rate of solvent (*n*-hexane/*i*-PrOH = 90/10) was set at 1.0 mL/min. The retention times of compound **2b** were 8.9 and 10.7 min. The retention times of compound **2a** were 8.9 and 10.8 min.

3.2. General synthetic procedure

Method A: To a CH₂Cl₂ solution (3 mL) containing **1** (0.50 g, 3.47 mmol), was added methane sulfonyl chloride (0.40 g, 3.47 mmol), *N*-methylimidazole (0.85 g, 10.4 mmol), and amine (4.17 mmol) in this order at 0 °C under N₂ atmosphere. The reaction mixture was stirred overnight. Then, 3N HCl aq was added to the reaction mixture and the organic layer extracted with CH₂Cl₂ three times. The combined organic layers were dried over anhydrous MgSO₄. After filtration and crystallization from CH₂Cl₂/*n*-hexane, the desired compound **2** was obtained.

Method B: To a CH₂Cl₂ solution containing **1** (1.0 g, 6.94 mmol), was added thionyl chloride (8.26 g, 69.4 mmol) at rt under N₂ atmosphere. After stirring the solution for 1 d, the excess thionyl chloride was removed under vacuum. Then, the residue was dissolved in CH₂Cl₂ and amine (13.9 mmol) was added to the solution at 0 °C under N₂ atmosphere. The reaction mixture was for 4–5 h. Then, water was added to the reaction mixture, and the organic layer was extracted with CH₂Cl₂ three times. The combined organic layers were dried over anhydrous MgSO₄.

After filtration and silica-gel column, the desired compound **2** was obtained.

3.3. N-Phenyl-3,3,3-trifluorolactyl amide (2a)

^{1}H NMR in CDCl₃ δ 3.93 (1 H, s), 4.57 (1 H, q, J = 7.0 Hz), 7.18–7.23 (1 H, m), 7.35–7.41 (2 H, m), 7.53–7.56 (2 H, m), 7.90 (1 H, s). ^{19}F NMR δ −76.3 (s). ^{13}C NMR δ 70.3 (q, J = 32 Hz), 120.3, 122.8 (q, J = 283 Hz), 125.7, 129.3, 136.1, 162.4. HRMS (TOF) [M+H]⁺, calcd for [C₉H₈F₃NO₂+H]⁺: 220.0585, found: 220.0522. mp of racemate: 124 °C, mp of chiral isomer: 108 °C.

3.4. N-Benzyl-3,3,3-trifluorolactyl amide (2b)

^{1}H NMR in CDCl₃ δ 4.42 (1 H, q, J = 7.0 Hz), 4.56 (2 H, d, J = 5.6 Hz), 6.47 (1 H, s), 7.28–7.40 (5 H, m). ^{19}F NMR δ −76.6 (s). ^{13}C NMR δ 44.0, 69.9 (q, J = 32 Hz), 122.8 (q, J = 283 Hz), 127.6, 128.0, 128.9, 136.6, 164.6. HRMS (TOF) [M+H]⁺, calcd for [C₁₀H₁₀F₃NO₂+Na]⁺: 256.0561, found: 256.0593. mp of racemate: 92 °C.

3.5. Determination of rates of sublimation of (R/S)- and (S)-2a on a Petri dish

Sublimation experiment of (*R/S*)- and (*S*)-**2a** was conducted on a Petri dish (surface are 20.25π cm²) at 80 °C under atmospheric pressure. Since sublimation rates are affected by various physical factors such as temperature and wind, the experiments with racemate and optically pure compounds were conducted at the same time. As shown in Fig. 2, after a long time sublimation time dependent loss of the remainder started curving because the surface area became uneven. Therefore, as the determination of sublimation rates, initial rates (0–6 h) are used.

3.6. General SDE experiments procedure

Just prior to the start of the experiments, various optically enriched samples were prepared by simply mixing racemate and optically pure crystals in appropriate amounts and well grinding of the mixture, following which the optical purity was measured. The optically enriched sample was spread on a Petri dish as flat as possible, and sublimation experiments conducted under atmospheric pressure at 50 °C for **2b** and 80 °C for **2a**. After certain amount of time, the sample (0.01 g) of the remaining crystals on the Petri dish was taken for determination of its enantiomeric composition. Before the sampling, the remaining crystals on the Petri dish were carefully agitated with a spatula to provide for an even and homogeneous distribution of the remaining compound.

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[1] The term "racemate" as used in this paper refers to crystalline racemate in which the two enantiomers are present in equal quantities in the crystallographic unit. It does not refer the case of conglomerate that is a mechanical mixtures of two pure enantiomers.

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