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Rational application of self-disproportionation of enantiomers via sublimation—a novel methodological dimension for enantiomeric purifications

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The preliminary results presented in this work show that an enantiomer purification approach based on SDE via sublimation can be extended to non-volatile liquid compounds such as α-(phenyl)ethylamine and its β-fluoro-derivatives by way of their rational modification with a sublimation enabling tag. 3,3,3-Trifluoro-2-(trifluoromethyl)-2-methyl-propanoic acid was found to perfectly serve the role of such a modifying tag. Thus, the corresponding amides derived from the amines and the fluorinated propanoic acid were highly crystalline and reasonably volatile compounds allowing for their sublimation at room temperature under normal pressure. All of these derivatives showed substantial self-disproportionation of enantiomers (SDEs) via sublimation under kinetic conditions (on a Petri dish in the open air). These preliminary results serve as a proof of a new principle that may extend the generality of enantiomer purification via sublimation to various organic compounds with physico-chemical properties of which render them otherwise unsuitable for a sublimation procedure. In particular, the very attractive cost structure of sublimation procedure renders this approach of potentially high practical and economic efficiency.

1. Introduction

The preparation of enantiomerically pure compounds, driven by human health-related industries, is unarguably one of the major fields of research in organic chemistry.[1] During the last three decades asymmetric synthesis and biocatalysis have been developed with unprecedented pace, offering an amazing wealth of methodological choices to address virtually any structural and stereochemical complexity of the target molecules.[1] On the other hand, enantiomer purification, despite being an inherent step in the production of enantiomerically pure compounds, has received substantially lesser development. In enantiomer purification science there are only two conceptually different approaches: separation of enantiomers and separation of a racemate from the excess enantiomer. The former is based on application of an external source of chirality, while the latter makes use of the internal chirality present in enantiomerically enriched compounds. In terms of the theoretical chemical yield of the desired enantiomer, the separation of enantiomers approach is generally more efficient and has enjoyed an overwhelming portion of innovative developments in this area.[2,3] In particular, biocatalytic methods[4] as well as chromatography on chiral stationary phases[5] have been perfected to the level of effective industrial performance. In sharp contrast, the second conceptual option for enantiomer purification via separation of a racemate from the excess enantiomer using the internal chirality of enantiomerically enriched compounds, termed as self-disproportionation of enantiomers (SDEs),[6] has been grossly unappreciated, still, from the practical application standpoint, being limited to the age-old recrystallization technique.

From 1980s, several scattered reports in the literature[7] have demonstrated that separation of a racemate from the excess enantiomer of various enantiomerically enriched organic compounds can be generally observed under totally achiral HPLC conditions. In 1994 Professor Kagan's group conducted the first systematic study in this area and showed the enantiomer purification of chiral sulfoxides using achiral flash chromatography.[8] Subsequent reports from other research groups[9] have clearly demonstrated that SDE via achiral chromatography is a potentially general new enantiomer purification method which can be conveniently conducted using routine, gravity driven column chromatography on silica gel.[10]

Similarly, another example of unconventional separation of a racemate from the excess enantiomer via sublimation of enantiomerically enriched compounds[11] remained, until very recently,[12] virtually completely overlooked. However, recent interest in this area[12] clearly underscores its obvious potential as a generalized

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method for enantiomer purifications. In particular, the very attractive cost structure of sublimation procedure as compared, for instance, to that of recrystallization renders this approach of potentially high practicality and economical efficiency. On the other hand, the successful application of SDE via sublimation might be limited to compounds of high crystallinity, volatility, and differences in physical properties (crystallographic structure) between the corresponding enantiomerically pure and racemic forms.[13] However, this limitation can be overcome by thoughtful modification of the target compound to provide the required physico-chemical characteristics. Herein we report a first example of a successful rational application of SDE via sublimation to a series of α-(phenyl)ethylamines. We believe that our data serve as a proof of a new principle that may extend the generality of enantiomer purification via sublimation to various organic compounds with physico-chemical properties of which render them otherwise unsuitable for a sublimation procedure.

2. Results and discussion

Rational application of SDE via sublimation can be realized in a way illustrated in Figure 1. In the first step, an enantiomerically enriched compound in a liquid or crystalline state but with little to no volatility is being modified via covalent bond formation with an achiral molecule which serves as sublimation enabling tag, rendering the corresponding product of high crystallinity and also easy to sublime. The next step is the SDE via sublimation leading ideally to complete separation of the racemic form from the excess enantiomer. Finally the separated products can be disassembled to recover the sublimation enabling tag molecule and the target compound in enantiomerically pure and/or racemic form. While this design is technically very simple, its successful implementation will depend on the correct choice of the achiral sublimation enabling tag. In this regard it would be highly desirable to identify such molecules which can be of general use in application of SDE via sublimation as an enantiomer purification method.

We believe that fluorine-containing compounds possess significant potential to be used as the achiral sublimation enabling tags. It is well documented that fluorinated organic compounds have a lower intermolecular interactions when compared with fluorine-free molecules.[14] As a result fluorine-containing derivatives, when compared to non-fluorinated counterparts, have prominent properties such as high volatility, low viscosity, small coefficient of friction, increased density, dipole–dipole and hydrogen-bonding intermolecular interactions, and lowered surface tension, refractive index, and dielectric constants.[15] Of particular interest are compounds containing a pentafluorophenyl[16] or trifluoromethyl group which additionally impacts the pattern of intermolecular interactions because of their strong steric[17] and electrostatic[18] demands.

After consideration of several readily available fluorine-containing molecules as candidates to be used as achiral sublimation enabling tags, we decided to explore the potential of 3,3,3-trifluoro-2-(trifluoromethyl)-2-methyl-propanoic acid **1** (Fig. 2). The presence of two trifluoromethyl groups in acid **1** was expected to provide high crystallinity[19] and volatility of the corresponding amide derivatives **3** (Table 1), prepared from a series of liquid α-(phenyl)ethylamines **2**, which were thus used as the enantiomerically enriched compounds to study their SDE via sublimation.

Figure 2.

Racemic and enantiomerically pure pivalic acid amide derivatives **3a**–**c** were prepared from acid **1** and (*R*/*S*)- or (*R*)-**2** (Table 1) under standard conditions usually used for the formation of amide bond. It should be noted that no racemization was detected under the reaction conditions used. As anticipated, all of the amide derivatives **3a**–**c** possessed relatively high volatility, allowing us to conduct the corresponding SDE via sublimation experiments at room temperature (rt) and under atmospheric pressure. It should be emphasized that compounds **3a**–**c** have also possessed substantial thermal and chemical stability, therefore the corresponding SDE experiments by sublimation were not contaminated by any sort of chemical decomposition.

As we usually do for the initial study of SDE via sublimation,[12] the racemic and enantiomerically pure samples of **3a**–**c** were sublimed separately at room temperature on a Petri dish under open air conditions. The initial rates of sublimation of racemate and enantiomerically pure amides **3a**–**c** are summarized in Table 2. We found that enantiomerically pure samples sublimed faster for the derivatives **3a** and **3c**, while in the case of compound **3b** the sublimation rate of the racemic form was higher. Another noticeable point is that the compound with more fluorine substituents had the larger difference between the rates of (*R*/*S*)-**3** and (*R*)-**3**. Thus, in the case of compound **3a**, the enantiomerically pure isomer sublimed 2.2 times faster than the corresponding racemate, which is the largest difference reported in the literature so far. In the case of the amide **3c**, derived from non-fluorinated α-(phenyl)ethylamine **2c**, the difference in the initial sublimation rates was quite small.

As one might expect, the largest difference in the rates of (*R*/*S*)- and (*R*)-**3a** suggested that this compound might have more efficient separation of the corresponding racemic and enantiomerically pure forms by SDE via sublimation, however, in sharp contrast to this expectation, quite poor separation was observed (Figure 3). Thus in the case of samples of 51.0% and 80.8% ee, a gradual decrease in the enantiomeric purity of the remainder was observed. In the former the decrease in enantiomeric purity of the remainder was substantially more pronounced allowing us to reach in, about 6 h, a racemic form in the remainder. On the

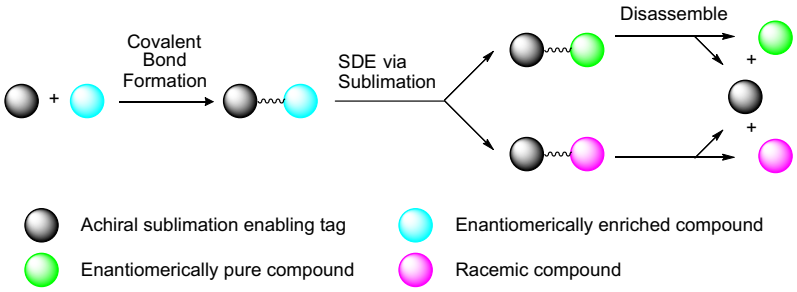
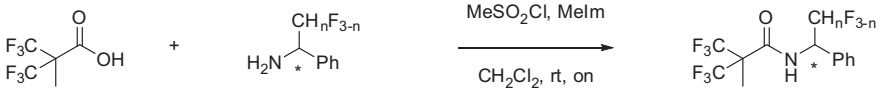


Figure 1.

Table 1
Synthesis of F_6-pivalic acid amide derivatives **3a–c**



1 **2a** (n=0), **b** (n-=1), **c** (n=3) **3a** (n=0), **b** (n-=1), **c** (n=3)

Entry	Compound **2**	Yield (%)	Product **3**
1	(*R*/*S*)-**2a**	78	(*R*/*S*)-**3a**
2	(*R*)-**2a**	78	(*R*)-**3a**
3	(*R*/*S*)-**2b**	82	(*R*/*S*)-**3b**
4	(*R*)-**2b**	87	(*R*)-**3b**
5	(*R*/*S*)-**2c**	83	(*R*/*S*)-**3c**
6	(*R*)-**2c**	85	(*R*)-**3c**

Table 2
Initial rates of sublimation of (*R*/*S*)- and (*R*)-**3**

Entry	Compound **3**	Rates of (*R*/*S*)-**3** (g/h)	Rates of (*R*)-**3** (g/h)
1	**3a**	0.0013	0.0029
2	**3b**	0.0025	0.0021
3	**3c**	0.0012	0.0013

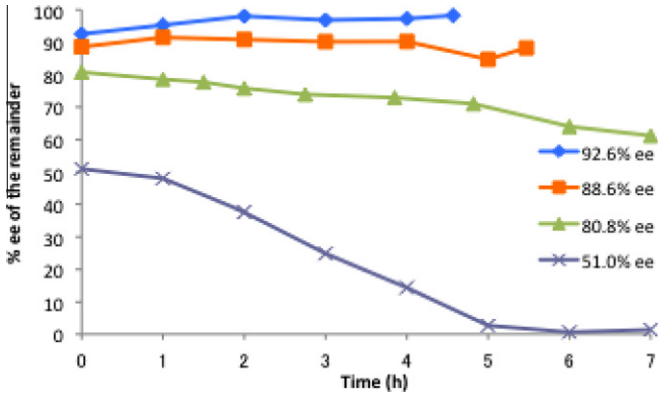


Figure 3. SDE of **3a** at rt. Time-dependent change of %ee of the remainder.

other hand, in the experiment starting with the sample of 88.6% ee, the enantiomeric excess was not noticeably altered by sublimation. Consequently, sublimation of the sample of 92.6% ee showed a gradual increase in the enantiomeric purity of the remainder allowing us to obtain an enantiomerically pure state in about 2 h.

Differences in sublimation rates of compounds **3b** and **3c** were substantially smaller as compared with that of **3a**. However, in both cases the sublimation of samples of about 70% ee resulted in a gradual increase in enantiomeric purity of the remainder (Figs. 4 and 5). This enantiomeric purification effect was more pronounced in the former case. Therefore we chose compound **3b** as an example to demonstrate the practical preparation of enantiomerically pure samples using SDE via a sublimation method. In a typical experiment, 145 mg of compound **3b** of 70.4% ee was evenly spread on a Petri dish and left on a bench in open air for 47.5 h. After this time, 43 mg of the remaining sample was collected from the Petri dish and its enantiomeric purity was found to be >99.5% ee. While the obtained yield of 42.4% of the enantiomerically pure compound is not remarkable, one may agree that operational simplicity, convenience, and therefore potential economical practicality of this enantiomer purification approach render it very attractive as compared to the existing conventional methods.

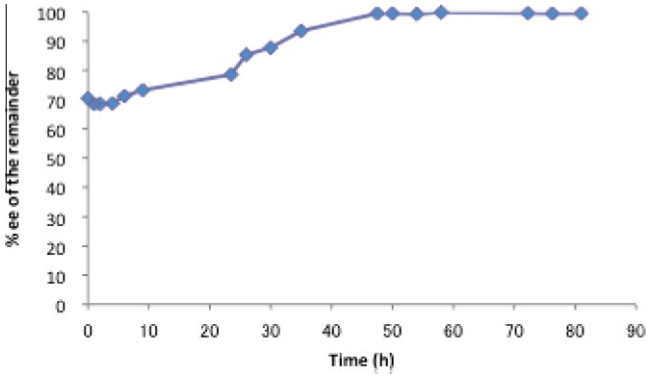


Figure 4. SDE of **3b** at rt. Time-dependent change of %ee of the remainder.

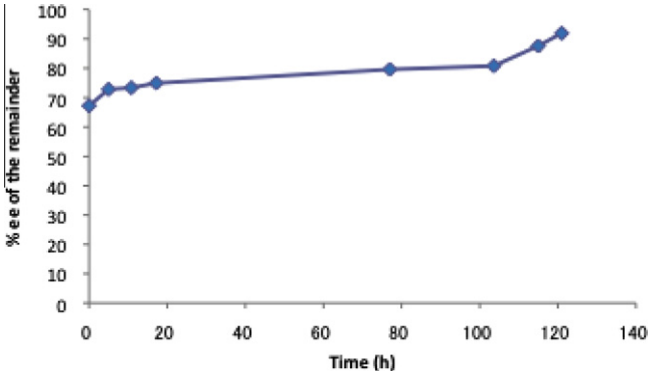


Figure 5. SDE of **3c** at rt. Time-dependent change of %ee of the remainder.

3. Conclusions

The preliminary results presented here show that an enantiomeric purification approach based on SDE via sublimation can be extended to non-volatile liquid compounds such as α-(phenyl)ethylamine and its β-fluoro-derivatives by the way of their rational modification with a sublimation enabling tag. We demonstrate that 3,3,3-trifluoro-2-(trifluoromethyl)-2-methyl-propanoic acid can serve the role of such modifying tag for these and, probably, for other non-volatile compounds due to its exceptional physico-chemical characteristics. The concept of rational application of self-disproportionation of enantiomers, via sublimation, presented here is operationally simple and should be applicable for chiral compounds of virtually any physico-chemical properties. While

in each particular case of optical purifications using this approach, the individual tune-up would be necessary, SDE via sublimation offers a generalized alternative to the conventional recrystallization procedure thus adding new dimension in methodological flexibility of current separation techniques.

4. Experimental part

4.1. General

Unless otherwise stated, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out under N_2 atmospheric conditions. Unless indicated ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ solutions at 299.95 and 75.42 MHz, respectively. Chemical shifts for ^1H and ^{13}C NMR refer to TMS as the internal standard. Chemical shifts for ^{19}F NMR refers to C_6F_6 as the internal standard. A Micromass Q-TOF was used to measure the time-of-flight electro-spray mass spectra in positive ion mode (TOF-ESIMS$^+$). All new compounds were characterized by ^1H, ^{13}C, and ^{19}F NMR, high-resolution mass spectrometry (HRMS-ESI) and melting point, when applicable.

4.2. General synthetic procedure of (hexafluoro)pivalic acid amides 3a–c

To a CH_2Cl_2 solution (10 mL) containing 3,3,3-trifluoro-2-(trifluoromethyl)-2-methyl-propanoic acid **1** (2.00 g, 9.52 mmol) were added methanesulfonyl chloride (0.74 mL, 9.52 mmol), *N*-methylimidazole (2.28 mL, 28.6 mmol), and phenylethyl amine (11.4 mmol) in this order at 0 °C under N_2 atmosphere, and the reaction mixture was stirred overnight. Then, 3 N HCl aq was added to the reaction mixture, and the organic layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous $MgSO_4$. After filtration, evaporation of solvents and purification by silica gel column chromatography, the desired compound **3** was obtained in good yield.

4.2.1. 2,2-Ditrifluoromethyl-*N*-(2,2,2-trifluoro-1-phenylehtyl)-propamide 3a

^1H NMR in $CDCl_3$ δ 1.69 (3H, m), 5.72 (1H, dq, J = 9.08, 7.62 Hz), 6.75 (1H, b), 7.30–7.48 (5H, m). ^{19}F NMR δ 87.5 (3F, d, J = 7.92 Hz), 92.8 (3F, q, J = 9.91 Hz), 93.1 (3F, q, J = 9.91 Hz). ^{13}C NMR δ 13.0 (quint, J = 2.3 Hz), 59.1 (quint, J = 26.5 Hz), 65.5 (q, J = 28.5 Hz), 130.7 (t, J = 280.6 Hz), 142.3 (q, J = 276.4 Hz), 124.9, 127.9, 129.3, 144.5, 163.3. HRMS (TOF) [M + Na]$^+$, calcd for $[C_{13}H_{10}F_9NNaO]^+$: 390.0516, found: 390.0466. Mp of racemate: 59 °C, mp of chiral isomer: 37 °C. $[\alpha]_D^{23} = -68.1$ (c 0.73, $CHCl_3$).

4.2.2. 2,2-Ditrifluoromethyl-*N*-(2,2-difluoro-1-phenylehtyl)propamide 3b

^1H NMR in $CDCl_3$ δ 1.68 (3H, m), 5.43 (1H, m), 6.03 (1H, td, J = 54.8, 2.05 Hz), 6.78 (1H, b), 7.20–7.48 (5H, m). ^{19}F NMR δ 32.2 (1F, ddd, J = 81.4, 55.4, 15.9 Hz), 37.6 (1F, ddd, J = 81.4, 55.5, 13.9 Hz), 92.8 (3F, q, J = 9.91 Hz), 93.1 (3F, q, J = 9.91 Hz). ^{13}C NMR δ 13.0 (quint, J = 2.3 Hz), 57.2 (quint, J = 26.5 Hz), 58.9 (t, J = 34.5 Hz), 123.4 (q, J = 284.4 Hz), 130.7 (t, J = 250.6 Hz), 126.5, 127.7, 128.6, 143.3, 161.2. HRMS (TOF) [M+Na]$^+$, calcd for $[C_{13}H_{11}F_8NNaO]^+$: 372.0611, found: 372.0545. Mp of racemate: 60.9 °C, mp of chiral isomer: 72.5 °C. $[\alpha]_D^{23} = -60.9$ (c 0.99, $CHCl_3$).

4.2.3. 2,2-Ditrifluoromethyl-*N*-(1-phenylehtyl)propamide 3c[19]

^1H NMR in $CDCl_3$ δ 1.51 (3H, d, J = 7.03 Hz), 1.64 (3H, m), 5.16 (1H, dq, J = 14.1, 7.03 Hz), 6.36 (1H, b), 7.10–7.44 (5H, m). ^{19}F NMR δ 93.0 (3F, q, J = 9.91 Hz), 93.2 (3F, q, J = 9.91 Hz). ^{13}C NMR δ 12.9 (quint, J = 2.31 Hz), 21.3, 50.3, 57.2 (quint, J = 26.5 Hz), 123.4 (q, J = 284.4 Hz), 125.7, 127.7, 128.8, 141.8, 159.2. HRMS (TOF) [M+Na]$^+$, calcd for $[C_{13}H_{13}F_6NNaO]^+$: 336.0799, found: 336.0793. Mp of racemate: 89.4 °C, mp of chiral isomer: 102.4 °C. $[\alpha]_D^{23} = +56.1$ (c 0.05, $CHCl_3$).

4.3. Determination of enantiomeric purity of 3a–c

The enantiomeric purity of **3a** and **3b** was determined by GC (HP-CHIRAL column: 30 m × 0.25 mm × 0.25 μm). The initial temperature was set at 50 °C for 5 min, then increased at a rate of 10 °C/min. The final temperature was set at 150 °C for 5 min. The total time for a single measurement was set as 20 min. The retention times of compound **3a** were 24.1 and 24.3 min. The retention times of compound **3b** were 30.0 and 30.3 min. The enantiomeric excess of the compound **3c** was determined by HPLC (OD-H: 25 cm × 0.46 cm). The flow rate of solvent (*n*-hexane/*i*-PrOH = 90:10) was set at 1.0 mL/min. The retention times of compound **3c** were 4.0 and 4.4 min.

4.4. Determination of rates of sublimation of (*R*/*S*)- and (*S*)-3 on a Petri dish

A sublimation experiment of (*R*/*S*)- and (*S*)-**3** was conducted on a Petri dish (surface area: 20.25π cm^2) at room temperature under atmospheric pressure. Since sublimation rates are affected by various physical factors such as temperature and wind, the experiments with racemate and enantiomerically pure compounds were conducted at the same time. After a long period of sublimation, time-dependent loss of the remainder started curving because the surface area became uneven. Therefore, for the determination of sublimation rates (weight vs time) in Table 2 initial rates were used.

4.5. General SDE via sublimation experimental procedure

Just prior to the start of the experiments, various enantiomerically enriched samples were prepared by simply mixing racemate and enantiomerically pure crystals in the appropriate amounts and thoroughly grinding the mixture, following this, the enantiomeric purity was measured. The optically enriched sample was spread on a Petri dish as flat as possible, and sublimation experiments were conducted under atmospheric pressure at rt. After a certain amount of time, the sample (ca. 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 in order to provide an even and homogeneous distribution of the remaining compound.

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