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Self-disproportionation of enantiomers of isopropyl 3,3,3-(trifluoro)lactate via sublimation: Sublimation rates vs. enantiomeric composition

Manabu Yasumoto [b], Hisanori Ueki [c], Taizo Ono [d],
Toshimasa Katagiri [e], Vadim A. Soloshonok [a,f,*]

[a] Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of the Ukraine, Murmanska Street, Kyiv 94 02660, Ukraine
[b] Central Glass Co., 2805 Imafuku-nakadai Kawagoe-shi, Saitama 350-1151 Japan
[c] National Institute for Materials Science, 1-1, Namiki, Tsukuba, Ibaraki 305-0044, Japan
[d] National Institute of Advanced Industrial Science and Technology (AIST), 2266-98 Anagahora, Shimoshidami, Moriyama-ku, Nagoya, Aichi Prefecture 463-8560, Japan
[e] Okayama University, Tsushimanaka 3-1-1, Okayama 700-8530, Japan
[f] Department of Chemistry and Biochemistry, The University of Oklahoma, Norman, OK 73019, United States

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ABSTRACT

The presented results convincingly demonstrate that self-disproportionation of enantiomers via sublimation is substantially more complex phenomenon then was previously believed. We demonstrate that the racemic form of isopropyl 3,3,3-trifluoro-2-hydroxypropanoate (**1**) sublimed faster regardless of the starting enantiomeric composition of the enantiomerically enriched mixtures studied in the range from 20.8, 36.8, 58.7 to 79.4% ee. This preferential sublimation of the racemic form allowed for, the most possibly simple, preparation of optically pure samples of compound **1**. In this work we also suggest some general experimental procedures, which may be easily used to facilitate the interpretation of the data collected in different laboratories.

1. Introduction

The book "*Enantiomers*, *Racemates and Resolution*" by Jacques et al. [1] has been a "bible" for several generations of chemists dealing with experimental stereochemistry. Providing the readers with the most comprehensive, yet detailed description of physico-chemical phenomena involving racemic, enantiomerically pure and enantiomerically enriched compounds, this book is deservingly continue to be the most creditable reference in this area. On the other hand, some subjects in the book, due to the lack, or insufficient amount of experimental data, received mostly theoretical treatment, based on the consideration of some ideal thermodynamic situations. While the applied principles of physical chemistry are unquestionably correct, the generalized conclusions made by the authors are erroneous and therefore dangerously misleading, considering the authoritative status of this book.

One of the most glaring mistakes in the book is the conclusion that the enantiomeric composition of enantiomerically enriched mixture *cannot* be changed via distillation [2]. While the early examples [3], discussed in the book, reported insignificant magnitude of self-disproportionation of enantiomers (SDE) [4] via distillation, and were disputed [5], the paper by Koppenhoefer et al. [6], describing distillation of *N*-(trifluoroacetyl)-Val-OMe of 91% ee to give fractions of 88.0 and 97.6% ee, presented the first undeniable fact that enantiomeric composition of enantiomerically enriched mixture *can* be changed via distillation. Even more powerful example was reported by Katagiri et al. [7]. This group of authors studied the distillation of (*S*)-isopropyl 3,3,3-trifluoro-2-hydroxypropanoate (**1**) (Fig. 1), its racemate as well as a series of the enantiomerically enriched mixtures of various % ee. The observed magnitude of SDE (Δee = 15.6%) [8] is truly remarkable rendering, in this case, a simple distillation procedure as a practically feasible method for optical purification. For instance,

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* Corresponding author at: Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of the Ukraine, Murmanska Street, Kyiv 94 02660, Ukraine.
E-mail address: vadim@ou.edu (V.A. Soloshonok).

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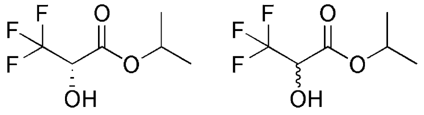

(*S*)-**1** (*R*/*S*)-**1**

Fig. 1. (*S*)-Isopropyl 3,3,3-(trifluoro)lactate (**1**) and its racemate.

the sample of 20% ee has a boiling point of 115 °C, that is well above of that for racemate **1** (93 °C) and well below for the enantiomerically pure compound **1** (136 °C).

Another point of concern in the book [9] is the treatment of sublimation of enantiomerically enriched compounds [10]. Thus, based on some theoretic considerations and a single set of experimental data available for sublimation of Mandelic acid [11,12,14], the authors suggest three sublimation scenarios with a general prediction that “initial sublimate always possesses the (enantiomeric) composition of the vapor eutectic” [15,16]. As it becomes more and more evident, the physico-chemical meaning of “enantiomeric composition of the vapor eutectic” has not been clearly defined and awaits an appropriate discussion and study. Furthermore, sublimation of enantiomerically enriched compounds is very complex phenomenon where vapor eutectic may play a role of merely one of numerous factors influencing the observed stereochemical outcome.

Sublimation of enantiomerically enriched compounds, the SDE via sublimation, has a multi-disciplinary importance [17,18] ranging from possible routine problems associated with accurate evaluation of stereochemical outcome of asymmetric transformations, development of conceptually new approaches for optical purifications and emergence of pre-biotic homochirality. Therefore, we believe that the discussions on commonly agreeable sublimation procedures/techniques [19], accumulation of new experimental data as well as different approaches in interpretation of the phenomenon, should be fundamentally welcomed [20].

Here we would like to report an example of SDE via sublimation, which contradicts the discussed above theoretical conclusions [9], as well as to suggest some experimental procedures, which may be used to facilitate the interpretation of the data collected in different laboratories.

2. Results and discussion

Among the numerous experimental results available in our laboratories, we chose to discuss the sublimation of isopropyl 3,3,3-(trifluoro)lactate [21] (**1**) because of the following major reasons: Compound **1** is perfectly chemically and configurationally stable in the open air and sublimation of both enantiomerically pure and racemic forms readily occurs at ambient temperature (23–25 °C) and normal (1 atmosphere) pressure. Therefore, any undesirable complications associated with long sublimation time [22], crystals melting, chemical decomposition or racemization are completely eliminated in this case.

First, we decided to examine the difference in the sublimation rates between enantiomerically pure and racemic compound **1**. As we demonstrated before [20a], the relative sublimation rates of racemic and optically pure samples can be accurately measured only under the conditions of zero-order kinetics. Therefore, the experiments were conducted in test-tubes (5 mm diameter) providing constant sublimation surface during the duration of the experiment. In this case, due to the relatively small sublimation surface and slow rate, the effect of wind currents in the lab is very insignificant. On the other hand, to eliminate the effect of particle (crystal) size, the samples of (*S*)-**1** and (*R*/*S*)-**1** were melted in the test-tubes and allowed to slow crystallize at ambient temperature, thus providing the samples of (*S*)-**1** and (*R*/*S*)-**1** with the same sublimation surface. The sublimation of samples from open test-tubes cleanly followed zero-order kinetics (Fig. 2). The observed substantially greater rate for sublimation of the racemic crystals was reproducible by separate workers in independent laboratories.

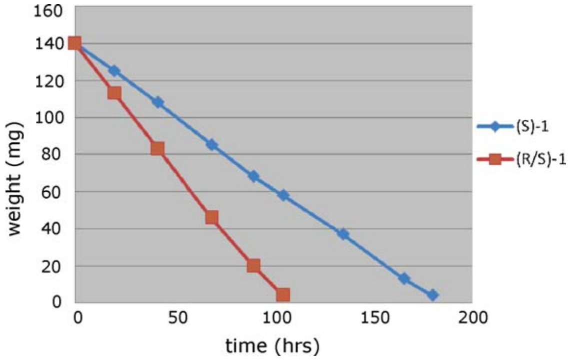

Fig. 2. Sublimation of (*S*)- and (*R*/*S*)-**1** from test-tube; zero-order kinetics.

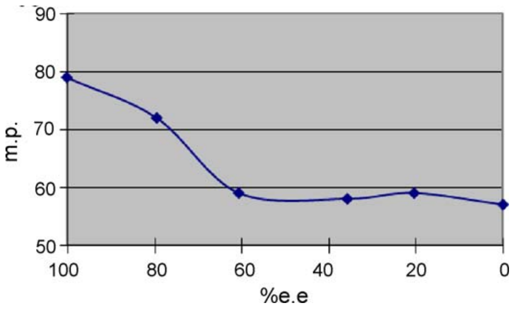

Fig. 3. Melting point vs. enantiomeric composition plot.

Before we proceeded with SDE experiments, we prepared melting point vs. enantiomeric composition plot shown in Fig. 3, to estimate the corresponding melting eutectic % ee. According to the curve, the melting eutectic composition of the compound under study is of ca. 40% ee.

All SDE experiments were conducted under the same conditions: at ambient temperature (23–25 °C) and regular atmospheric pressure. The samples of different enantiomeric composition were prepared by mixing (*S*)-**1** and (*R*/*S*)-**1**, in the corresponding proportions, and grinding. To provide for maximum possible [23] magnitude of SDE, samples (about 100 mg) were spread over the surface of a regular Petri dish (90 mm diameter) and weights of the samples were followed versus time in the open air. In this case, the sublimation from Petri dish follows the first-order kinetics as the surface of sublimation is shrinking over the time. As it follows form Fig. 4, racemic sample sublimed substantially faster, suggesting, in accord with the zero-order kinetics experiments, potentially high magnitude of the SDE for this compound.

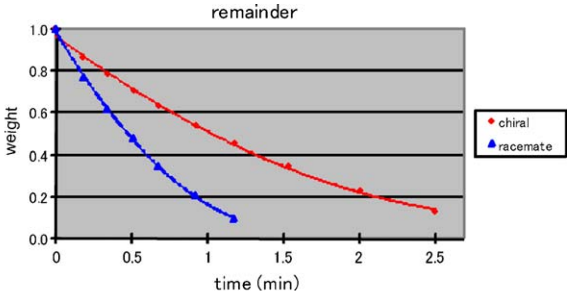

Fig. 4. Sublimation of (*S*)- and (*R*/*S*)-**1** from Petri dish; first-order kinetics.

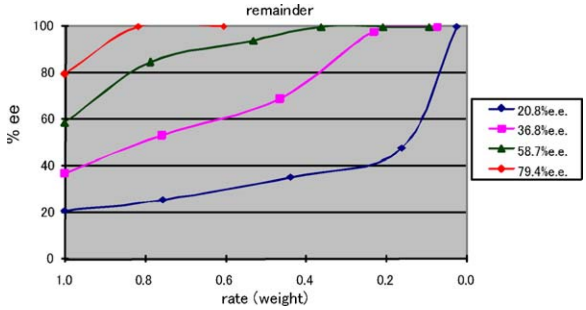

Fig. 5. Sublimation of samples of **1** of various enantiomeric composition (Petri dish).

The results or sublimation (% ee vs. time) of samples of different enantiomeric composition are presented in Fig. 5. Thus, regardless of the starting enantiomeric composition more racemic fractions sublimed faster, eventually leaving behind enantiomerically pure remainder. As one may see these results disagree with the theoretical predictions made in the book [9]. For instance, if, according to the predictions, the melting eutectic composition of the compound of ca. 40% should sublime preferentially, then in the case of samples of 36.8 and 58.7% ee (most close to 40% ee) the SDE should be barely observed. Furthermore, in the case of samples of 20.8 and 79.4% ee the order of SDE should be opposite, leaving behind the racemic remainder in the former (20.8% ee) case.

From the practical stand point, these data demonstrate the greater potential of simple sublimation technique for preparation of optically pure compounds. For instance, purification of an enantiomerically enriched sample of **1** of 75% ee to optically pure (*S*)-**1** form via conventional crystallization technique, requires several consecutive re-crystallizations furnishing an enantiomerically pure compound in about 60% yield [7]. On the other hand sublimation of sample of **1** of 79.4% ee over 25 min resulted in optically pure (*S*)-**1**, which was collected with 81.7% yield. In this case no solvents, labor, heating or cooling devises, filtration apparatus were used, as the optical purification via sublimation was accomplished simply by spreading the starting mixture over a Petri dish in the open air on the laboratory bench. Sublimation of the samples of lower % ees were less efficient in terms of the yield of enantiomerically pure compound **1**, however again, overall simplicity of the sublimation approach over conventional crystallization was obvious. Furthermore, one may assume that for practical reasons, the sublimed material can be collected and recycled via several sublimation experiments furnishing the racemic and enantiomerically pure fractions in virtually quantitative yield.

It should be emphasized that while the presence of fluoroalkyl [24] or fluoroaryl [25] groups in organic compounds significantly influences their physical properties, the difference in sublimation rates between racemic and optically pure compounds is irrelevant to the presence of fluorine-containing groups. Thus, in the same order as well-known differences in melting points and solubility between racemic and enantiomerically pure compounds, the differences in sublimation rates is a physico-chemical consequence of differences in the crystallographic structures of racemic and optically pure crystals. Therefore separation of racemate from the excess enantiomer via sublimation is ultimately general phenomenon and can be used as an alternative approach for optical purifications of *any* chiral organic or inorganic compound which forms racemic and enantiomerically pure crystals.

3. Conclusion

In summary, we believe that the data presented here and the recent literature results [20] clearly suggest a glaring gap in our knowledge of SDE via sublimation, which is clearly not as simple as one may assume [9–12,14–19]. For instance, besides the basic thermodynamic factors as energy/stability of crystals, kinetic features, such a minute nuance as shape of crystals [13], and therefore the sublimation surface, should be expected to have a dramatic effect on the difference in the sublimation rates of racemic and enantiomerically pure forms. We hope this paper will stimulate discussions and raise an additional interest in this new, fascinating and practically important area of research.

Acknowledgments

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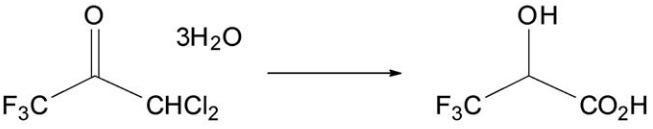
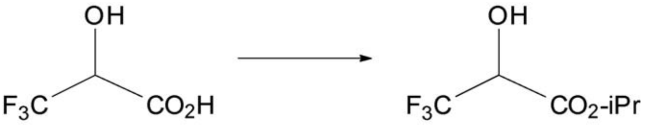
Experimental part

A.1. Large-scale preparation of 3,3,3-trifluoro-2-hydroxypropionic acid



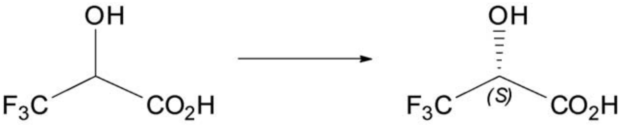
To the solution of 30 wt% aqueous sodium hydroxide (227 g, 1.70 mol), 1,1-dichloro-3,3,3-trifluoroacetone hydrate (100 g, 0.43 mol) was added drop-wise, keeping the solution temperature under 30 °C. After the addition, the mixture was stirred for 12 h at room temperature. 18% aqueous hydrochloric acid (172 g, 0.85 mol) and ethyl acetate (200 mL) were added to the solution. After separation, the organic layer was washed with brine (100 mL). The organic layer was evaporate to obtain the 3,3,3-trifluoro-2-hydroxypropionic acid (55 g). The crude product was used for the next step without any purification.

A.2. Preparation of isopropyl 3,3,3-trifluoro-2-hydroxypropanoate



To the solution of 2-propanol (69 mL), the crude 3,3,3-trifluoro-2-hydroxypropionic acid (10 g, 69 mmol) and sulfuric acid (0.07 g, 0.7 mmol) were added. The mixture was refluxed for 24 h and the solution was distilled. The main fraction was purified by sublimation to obtain the racemic isopropyl 3,3,3-trifluoro-2-hydroxypropanoate.

A.3. Preparation of (S)-3,3,3-trifluoro-2-hydroxypropionic acid



To the solution of the crude 3,3,3-trifluoro-2-hydroxypropionic acid (40 g, 0.28 mol) in ethyl acetate (120 mL) and *n*-heptane (12 mL), (*S*)-α-(methyl)benzylamine (33 g, 0.28 mol) was added. The mixture was heated at 60 °C for 30 min, then cooled to room temperature to crystallize 3,3,3-trifluoro-2-hydroxypropionic acid salt (26 g, 68%ee). The crystal was purified by further recrystallization (total three times) to give >99.0%ee salt (13 g, 0.05 mol). The salt was neutralized by 10% aqueous hydrochloric acid (36 g, 0.1 mol), and extracted by ethyl acetate (50 mL). The organic layer was evaporated and purified by distillation (81 °C/2.7 kPa).

A.4. Procedure for determination of % ee of (S)-isopropyl 3,3,3-trifluoro-2-hydroxypropanoate

(*S*)-isopropyl 3,3,3-trifluoro-2-hydroxypropanoate was analyzed by gas chromatography [column: CHIRASIL-DX CB (25 m, I.D. 0.25 mm, 0.25 μm)].

A.5. Sublimation of racemic and optically pure samples of 1 from test-tubes (Fig. 2)

Samples of racemic or enantiomerically pure **1** (5 g) were placed in test-tubes and melted to a transparent solution and allowed to slow crystallize at ambient temperature, thus providing the samples of (*S*)-**1** and (*R*/*S*)-**1** with the same sublimation surface. The sublimation, loss of weight vs. time was followed.

Time (h)	Weight, (*S*)-**1**	*rac.* **1**
0	140	140
20	125	113
41.94	108	83
68.94	85	46
90	68	20
104.94	58	4
135	37	
165.6	13	
180	4	

A.6. Sublimation of racemic and optically pure samples of 1 from Petri dishes (Fig. 4)

Crystals of racemic or enantiomerically pure compound **1**, or their mixtures (about 100 mg) were spread over the surface of Petri dish (90 mm diameter) and weights of the samples were followed versus time in the open air.

Racemic sample **1**:

Time (h)	Weight (g)
0.0	107.6
0.17	82.9
0.33	66.9
0.50	51.8
0.67	37.3
0.92	22.2
1.17	10.4

Enantiomerically pure sample **1**:

Time (h)	Weight (g)
0.0	104.9
0.18	91.0
0.34	82.2
0.51	73.9
0.68	66.1
0.93	56.7
1.18	47.6
1.54	36.7
2.01	24.3
2.50	13.4

A.7. Sublimation of enantiomerically enriched samples (Fig. 5)

Time (h)	Weight (mg)	% ee
0.00	79.7	20.8
0.25	60.3	25.4
0.50	34.9	35.2
0.75	12.9	47.6
0.92	2.0	99.9
0.00	83.5	36.8
0.25	63.4	53.0
0.50	38.8	68.5
0.75	19.3	97.9
1.00	6.3	99.9
0.00	87.0	58.7
0.25	68.7	84.3
0.50	46.3	94.0
0.75	31.6	99.9
1.00	18.2	99.9
1.25	8.1	99.9
0.00	84.7	79.4
0.25	69.2	99.9
0.50	51.3	99.9
0.75	38.5	
1.00	23.5	
1.25	11.9	

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[8] Δee is a difference between the highest and the lowest % ee obtained as a result of the SDE. In this case, distillation of 1 of 74.1% ee, allowed obtaining fractions of 81.7 and 66.1% ee.

[9] See Ref. [1], pp. 162–165.

[10] The discussion in the book (see Ref. [9]) on the sublimation is presented under the title "Separation of Enantiomers by Sublimation". This is a very misleading mistake, as enantiomers cannot be separated by any physical method not-involving external chirality. The correct title should be: "Separation of Racemate from the Excess Enantiomer by Sublimation," or SDE via sublimation.

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[18] The general unawareness and confusion in this area is manifested by the editorial choice of a misleading catch-phrase: ''Resolution by Sublimation'' for the highlight of emerging research in this area (Ref. [17]); ''Resolution'' means separation of enantiomers, which cannot be achieved by sublimation (see also comment in Ref. [10].). Once again the correct phrase should be ''Separation of Racemate from the Excess Enantiomer by Sublimation,'' or SDE via sublimation.

[19] Virtually all literature data on sublimation are dealing with zero-order kinetic process conducted in a typical sublimation apparatus and therefore simply irrelevant to the SDE. Therefore there is a need for development of mutually agreeable sublimation procedures resembling as closely as possible natural conditions of first-order kinetics (highest magnitude of the SDE), with as least as possible external action or special conditions. For example, as emphasized by Professor D.G. Blackmond [15], such simple procedural issue as how to mix crystals for sublimation experiment can dramatically complicate the interpretation of the results.

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[22] When experiment are conducted in the open air, shorter sublimation time is more desirable for quantitative description, minimizing such environmental effects as fluctuating temperature, pressure and wind currents in the lab.

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