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Communication

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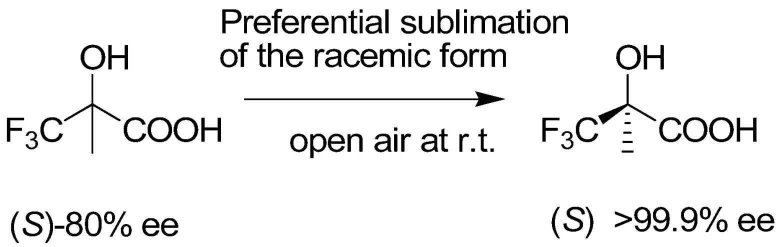

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Phenomenon of Optical Self-Purification of Chiral Non-Racemic Compounds

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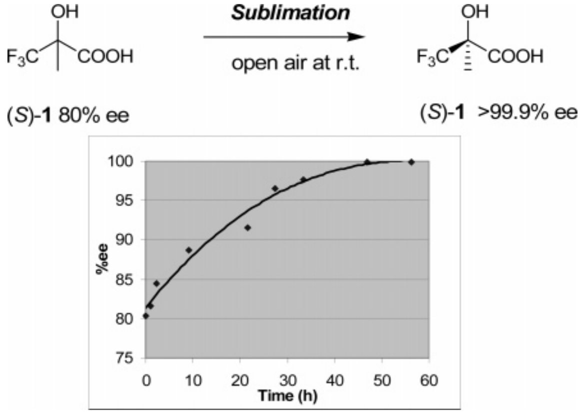
In the solid state, optically pure compounds and their racemates have significantly different crystallographic structures and therefore different physical properties, such as melting point and solubility.[1] On the other hand, the effect of these crystallographic differences on sublimation rates of optically pure compounds and their racemates has been overlooked and remains virtually unstudied, despite its potential importance as an ultimately economical optical purification technique as well as implications of broader scientific significance.

Only three papers in the literature deal with fractional sublimation of chiral, nonracemic compounds. In the first publication, appearing in 1959, Pracejus observed that the first fractions of enantiomerically enriched phenylalanine derivatives obtained via sublimation were of higher enantiomeric purity as compared to the starting material.[2] In 1967, Kwart and Hoster made a similar observation while drying in vacuum enantiomerically enriched samples of α-ethylbenzyl phenyl sulfide.[3] Finally, Garin et al. carried out more detailed study of fractional sublimation of enantiomerically enriched mandelic and camphoric acids.[4] There are also two papers describing the detection of preferential sublimation of an enantiomer relative to racemate via mass spectroscopy of the isotopically labeled hydrochloric salt of (phenyl)ethylamine and mandelic[5] and tartaric acids.[6] Two reports on the theoretical treatment of sublimation of enantiomerically pure compounds and their racemates should also be mentioned.[7] Therefore, it is not surprising that because of the lack of experimental data this phenomenon is poorly understood as one can find in the cited literature[1−7] truly incompatible, controversial statements and conclusions.[8]

Here we report the first example of an organic compound having racemic crystals which sublime[9] substantially faster than the corresponding enantiomerically pure crystals. This unusual order of sublimation gives rise to a phenomenon of optical self-purification when an enantiomerically enriched compound purifies itself to enantiomerically pure form without any external force, action, or special condition, except being exposed to open atmosphere. Various practical consequences of this phenomenon, in particular its possible application in the emergence of the prebiotic homochirality, are discussed.

Recently we have discovered that a trifluoromethyl group directly bonded to a stereogenic center can induce a remarkably strong enantiomer self-disproportionation effect resulting in separation of the racemate from the excess enantiomer during chromatographic purification of trifluoromethyl-containing chiral compounds under achiral conditions, that is, using an achiral stationary phase and achiral eluent.[10] In the course of our studies of this effect we noticed that the optical purity of a sample of (*S*)-α-(trifluoromethyl)lactic acid (**1**) (Scheme 1), originally of 74% ee, spontaneously increased to 81% ee simply by being stored in a sealed vial on a bench. Careful examination of the vial revealed that some acid **1** had sublimed onto the upper parts of the vial's walls and the lid. Enantiomeric purity of the sublimed acid **1** was found to be only 35% ee, indicating that a new type of phenomenon leading to separation of the original sample into enantiomerically enriched and depleted fractions took place at room temperature and at the normal pressure. To confirm that alteration of the enantiomeric purity of the original sample occurred via fractional sublimation, we conducted a regular sublimation experiment starting with a sample of 76% ee. After heating the sample of acid **1** at 60 °C for 3 h the enantiomeric composition of the sublimate and the remainder was examined. We found that enantiomeric purity of the sublimate was substantially lower (48% ee), while optical purity of the remainder increased (80% ee). Taking advantage of the relatively high volatility of acid **1**, we conducted a series of experiments at atmospheric pressure in the open air. First, we decided to examine the difference in the sublimation rates between racemic and optically pure samples of acid **1**. As is usually observed for evaporative sublimation,[11] the sublimation rates of **1** where found to depend on various physical factors such as temperature, wind currents in the lab, and particle size. However, for samples prepared identically, the sublimation rate of the racemate was always higher as compared with that of the enantiomerically pure sample. The sublimation of samples from open tubes cleanly followed zero-order kinetics, and the ratio of zero-order rate constants k(racemate)/k(enantiopure) based on regression analysis was 1.50 ± 0.02. This substantially greater rate for sublimation of the racemic crystals was reproducible by separate workers in independent laboratories.[12]

Scheme 1



On the basis of these data we decided to test the ultimate question, whether or not this fractional sublimation may result in qualitative transformation: a complete optical self-purification of an enantiomerically enriched sample to enantiomerically pure compound. To this end, the optical purity of an 80% ee sample in a Petri dish in the open air was monitored over time. The data are summarized in the graph of Scheme 1. Thus, after 21.5 h the

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enantiomeric purity of the sample had increased over 90% ee and reached the 98% ee after 33 h. The desired and complete ($>$99.9% ee) purification was observed after 56.5 h.

Next, we conducted crystallographic analyses of the racemic and optically pure crystals of acid **1** (see the corresponding CIF files in SI). In contrast to our expectations and in partial agreement with the Wallach's rule,[13] the density of the less stable racemic crystals was found to be 1753, while the enantiomerically pure crystals were less dense at 1719. Comparison of the melting points of the racemate and the optically pure compound (88 and 110 °C, respectively) also suggested that the racemic crystals are less stable.

While the detailed physicochemical description of this phenomenon remains to be clarified, we can suggest that a clue to the substantial difference in the sublimation rates can be found considering the molecular arrangements in the crystals of racemate and optically pure compound. First of all we would like to emphasize the striking difference in the hydrogen-bonding network in the crystals. Thus, in the case of the optically pure crystals the molecules of (*S*)-**1** acid are arranged in a zigzag form allowing for each molecule to form four hydrogen bonds to four other molecules. In sharp contrast, in the crystal structure of the racemate, one can clearly distinguish formation of heterochiral dimers with two hydrogen bonds between (*R*) and (*S*) enantiomers. Each enantiomer has two more hydrogen bonds to the neighboring dimers. Furthermore, as a result of this different crystallographic structure, in the racemic and denser crystals the trifluoromethyl groups between the crystal layers are found to be closer to each other as compared with that of the optically pure crystals. Thus, the shortest distances between fluorine atoms of the trifluoromethyl groups in the racemate (see the SI file) are 2.909 and 3.005 Å. In fact, this distance of 2.909 Å is shorter than the sum of van der Waals radii[14] (1.47 Å) of two fluorine atoms and strongly suggests that these trifluoromethyl groups are involved in destabilizing electrostatic repulsive interactions.[15,16] By contrast, the shortest distances between the fluorines in the enantiomerically pure crystals are 3.032 and 3.110 Å, which does not suggest any substantial interactions between the trifluoromethyl groups.

Thus, this striking difference in molecular packing (hydrogen-bonding network and close fluorine−fluorine contacts) may be a physical reason for the observed, quite unusual differences in the sublimation rates as well as the melting points of the racemic and optically pure compounds.

The results presented here have three implications of broader significance. First, great care should be taken in the interpretation of enantiomeric excesses measured on materials after drying in a vacuum because of the possibility of preferential sublimation of racemate or enantiomerically pure material. Second, related to the observation of enantiomerically enriched amino acids found in meteorites,[17] consideration should be given to the possibility that the enantiomeric composition can be significantly altered by sublimation over time in space or at very high temperatures during the meteorites impact with the Earth. Third, a possible role for the self-purification of enantiomerically enriched mixtures[18] should be considered for the prebiotic origin of optically pure materials.[19] The process described here has the advantage of occurring without any external action or special environmental condition, and we believe that it is worthy of further study.

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Supporting Information Available: Experimental procedure for the determination of enantiomeric purity of acid **1**; crystallographic data for (*S*)-**1** and racemic **1**; preliminary kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, John Wiley & Sons: 1995; pp 179−183. (b) Jacques, J.; Collet, A.; Wilen, S.; Krieger, H. *Enantiomers, Racemates, and Resolutions;* 1994, pp 162−165.

(2) Pracejus, G. *Liebigs Ann. Chem*. **1959**, *622*, 10.

(3) Kwart, H.; Hoster, D. P. *J. Org. Chem*. **1967**, *32*, 1867.

(4) Garin, D. L.; Greco, D. J. C.; Kelley, L. *J. Org. Chem*. **1977**, *42*, 1249.

(5) Zahorszky, U.-I.; Musso, H. *Chem. Ber*. **1973**, *106*, 3608.

(6) Fales, H. M.; Wright, G. J. *J. Am. Chem. Soc*. **1977**, *99*, 2339.

(7) (a) Farina, M. *J. Chem. Soc., Chem. Commun*. **1987**, 1121. (b) Perlovich, G. L.; Kurkov, S. V.; Hansen, L. K.; Bauer-Brandl, A. *J. Pharm. Sci*. **2004**, *93*, 654.

(8) Thus, in the refs 1b and 4 one can read that "the eutectic composition is predicted to preferentially sublime regardless of the initial composition", while in the authoritative review (ref 1a) and articles 7a,b one can find a conclusion that the "sublimation process for both the racemate and the enantiomer was found to be enthalpy driven." Furthermore, in refs 1b and 4 one can read that "the modification with the lowest melting point should exhibit the greater volatility and should sublime preferentially.", while in the authoritative review (ref 1a) one can find totally opposite statement: "It is important to note that it is not always the lowest melting form that sublimes preferentially.

(9) As suggested by one of the reviewers, the term "sublimation" used in the paper refers to a kinetic process of evaporative sublimation rather than a thermodynamic phase transition.

(10) (a) Soloshonok, V. A. *Angew. Chem., Int. Ed*. **2006**, *45*, 766. (b) Soloshonok, V. A.; Berbasov, D. O. *J. Fluor. Chem*. **2006**, *127*, 597. (c) Soloshonok, V. A.; Berbasov, D. O. *Chim. Oggi/Chem. Today* **2006**, *24*, 44.

(11) For a recent review, see: L'vov, B. V. *Thermochim. Acta* **2001**, *373*, 97.

(12) For details, see Supporting Information.

(13) (a) Wallach, O. *Liebigs Ann. Chem*. **1895**, *286*, 90−143. (b) Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811.

(14) Bondi, A. *J. Phys. Chem*. **1964**, *68*, 441.

(15) (a) Soloshonok, V. A.; Gerus, I. I.; Yagupolskii, Y. L.; Kukhar, V. P. *Zh. Org. Khim.* **1987**, *23*, 2308−2313; *Chem. Abstr. 109*, 55185. (b) Soloshonok, V. A.; Kukhar, V. P.; Galushko, S. V.; Svistunova, N. Y.; Avilov, D. V.; Kuzmina, N. A.; Raevski, N. I.; Struchkov, Y. T.; Pisarevsky, A. P.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3143. (c) Soloshonok, V. A.; Hayashi, T.; Ishikawa, K.; Nagashima, N. *Tetrahedron Lett.* **1994**, *35*, 1055. (d) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron* **1996**, *52*, 12433. (e) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 7845. (f) Soloshonok, V. A.; Kacharov, A. D.; Hayashi, T. *Tetrahedron* **1996**, *52*, 245. (g) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, N.; Hayashi, T. *J. Org. Chem*. **1997**, *62*, 3470. (h) Soloshonok, V. A.; Avilov, D. V.; Kukhar', V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Lett.* **1997**, *38*, 4903−4904. (i) Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. *Org. Lett.* **2003**, *5*, 1007. (j) Soloshonok, V. A. *Angew. Chem., In. Ed. Engl*. **2006**, *45*, 766. (k) Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc*. **2005**, *127*, 15296−15303.

(16) For a study on structure/volatility correlation of fluorinated compounds, see: (a) Samuels, J. A.; Folting, K.; Huffman, J. C.; Caulton, K. G. *Chem. Mater*. **1995**, *7*, 929. For a theoretical study on magnitude and orientation dependence of intermolecular interactions of perfluorinated organic compounds, see: (b) Tsuzuki, S.; Uchimaru, T.; Mikami, M. *J. Chem. Phys*. **2004**, *121*, 9917.

(17) Pizzarello, S.; Cronin, J. R. *Nature* **1998**, *394*, 236.

(18) (a) Flores, J. J.; Bonner, W. A.; Massey, G. A. *J. Am. Chem. Soc*. **1977**, *99*, 3622. (b) Norden, B. *Nature* **1977**, *266*, 567. (c) Kondepudi, D. K.; Kaufman, R. J.; Singh, N. *Science* **1990**, *250*, 975−977. (d) Lee, T. D.; Yang, C. N. *Phys. Rev*. **1956**, *104*, 254. (e) Singleton, D. A.; Vo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 10010.

(19) (a) Meiring, W. J. *Nature* **1987**, *329*, 712. (b) Kondepudi, D. K.; Nelson, G. W. *Nature* **1985**, *314*, 4381.

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