Separation of an Enantiomorph and Its Racemate by Distillation: Strong Chiral Recognizing Ability of Trifluorolactates

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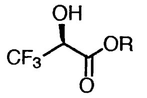
Trifluorolactate experienced modification of its enantiomeric excess by fractional distillation. Quantitative studies have shown that the separation of an enantiomorph and its racemate is due to a change in boiling points that depend on the enantiomeric excess of the compound. Such a change in the boiling point was not seen in the case of the non fluorinated lactate.

It is entirely logical to suppose that the energy of intermolecular homochiral interactions in the liquid state must be different from that of the corresponding heterochiral interactions. Thus, chiral recognition in the liquid state is, of course, possible. Yet, it has long been claimed that distillation of a partially resolved enantiomer is an operation that cannot lead to a modification of enantiomeric excess.[1]

Recently, we developed a nitric acid oxidation process for the preparation of optically active trifluorolactic acid ((S)-3,3,3-trifluoro-2-hydroxypropionic acid) having 75%ee[2] from (S)-3,3,3-trifluoropropene oxide with the corresponding enantiomeric excess.[3] Since then, we have been studying the properties of this compound as well as its derivatives. Trifluorolactates **1** have three functional groups around the methyne chiral center.



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These functional groups, a trifluoromethyl, a carbonyl, and a hydroxyl group are known to participate in hydrogen bonding. Thus, we expect this compound can be a chiral recognizing reagent.[4]

Interestingly, we did the modification of enantiomeric excess of the trifluorolactate by a simple distillation using a Claisen distillation apparatus. When we subject 2.0 g of isopropyl trifluorolactate of 74.1%ee to distillation, we found the enantiomeric excess of the distillate (1.0 g) to be 81.7%ee whereas that of the residue (1.0 g) was only 66.1%ee.[5] Contrary to our expectation, the distillation of another 2.0 g of the compound having 40.2%ee resulted in obtaining 0.9 g of the 33.2%ee distillate and 1.1 g of the 50.3%ee residue; that is, the way of discrimination of enantiomeric excess was up set down depending on the starting enantiomeric excess.[6]

Figure 1 is the boiling point diagram as a function of the enantiomeric excess of isopropyl trifluorolactate.[7] We have done three sets of measurements using different instruments by independent chemists.[8] The circles (●) denote the work done by Katagiri and Yoda, the squares (■) indicate the work done by Ueki, and the triangles (▲) are the measurements of Kubota.[9]

Surprisingly, we found that the boiling points of the racemate and pure enantiomer differ by 43 °C; the racemate boiled at 93 °C and the pure enantiomer at 136 °C. Every set of boiling point curve measured independently had a bell shape with its maximum value around 60%ee. We did observe small differences in the boiling points among the three sets of measurements, except for the point of 0%ee and 100%ee. We considered these differences due to the change of the inner surface size of vessel as well as cooler; a larger vessel holds a larger amount of distillate with lower boiling point on its surface, which resulted in the change in enantiomeric excess of the bottom liquid and a higher boiling point of that. The boiling point of 0%ee and 100%ee were authenticated by the trifluorolactate synthesized from 2,2,2-trifluoroacetaldehyde ethyl hemiacetal.[10]

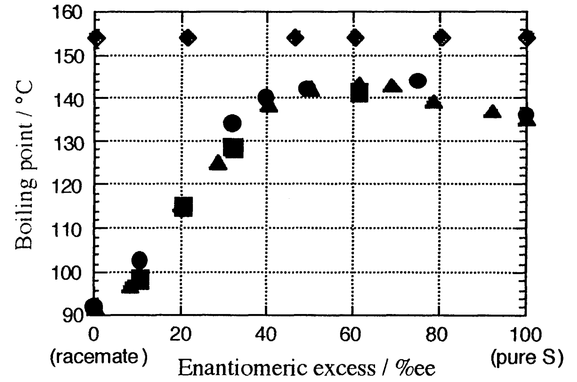

Figure 1. Boiling point (temperature of the liquid phase) of lactates at 1 atm as a function of enantiomeric excess. Isopropyl trifluorolactate(■, ●, ▲, see text) and non-fluorinated ethyl lactate (◆).

This boiling point diagram explains the results of the previously mentioned distillations, that is, distillation of 75%ee trifluorolactate would proceed down the right slope that gave a distillate of higher enantiomeric excess, while that of the 40%ee went down the left slope resulting in the formation of a lower enantiomeric excess distillate.

This bell shape as well as the large change in boiling points depending on enantiomeric excess could not be seen in the case of the non-fluorinated ethyl lactate (◆); the compound has a constant boiling point (154 °C) independent of its enantiomeric excess. This result suggests the contribution of fluorine being essential. The contribution of fluorine to influencing the boiling point was also confirmed by the infrared spectra of the compound. Figure 2 is the infrared spectra of the isopropyl trifluorolactates of (*a*) a lower enantiomeric excess (17%ee) with lower boiling points and (*b*) a higher enantiomeric excess (75%ee) with higher boiling points. When these two spectra are compared, we found some broadening of the absorption bands due to stretching of the carbonyl carbon - oxygen bond (1740 cm^{-1}) and the hydroxyl oxygen - hydrogen bond (3400 cm^{-1}), in the case of higher enantiomeric excess were found. The most striking change was seen in the three absorption bands (1120 cm^{-1}, 1200 cm^{-1},

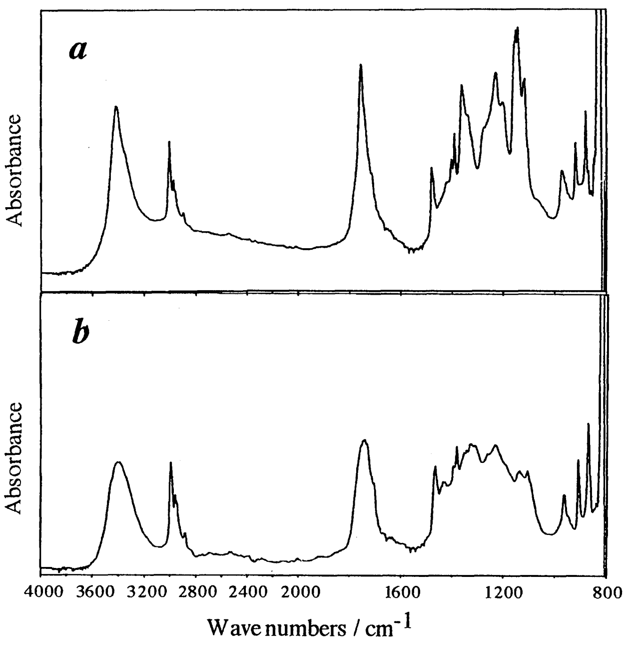

Figure 2. Infrared spectra of trifluorolactates (neat liquid) measured at 60 °C; *a* is trifluorolactate of 17%ee (lower boiling point) and *b* is 75%ee (higher boiling point).

and 1340 cm^{-1}) due to the stretching of the carbon - fluorine bond.[11] The absorption was very sharp in the case of lower enantiomeric excess (*a*), while they almost disappeared because of broadening in the 75%ee case (*b*). These changes also suggested the possible participation of fluorine in enantiomeric discrimination.

Discrimination of the enantiomeric excess by a simple distillation was once reported by Koppenhoefer and Trettin.[12] They distilled N-TFA-Val-OMe (91.0%ee), a protected amino acid, and obtained a compound having a lower enantiomeric excess (88.0%ee) as a distillate and the compound having the higher enantiomeric excess (97.6%ee) as a residue. They reported that there was no large change in boiling point between the racemate and highly enriched enantiomer (within 0.1 °C) in their case. With respect to this result, there is a very different result between our case and their case. They ascribed their result to a kinetic phenomenon.

It is common knowledge that boiling points of some azeotropic mixtures are some ten degrees lower than those of pure component compounds.[13] Thus, it is not so surprising that the boiling point of a racemate is some ten degrees lower than those of the pure enantiomer, so long as the chirality of each of the enantiomers are recognized even when the compound is going through a vaporization process.

Very recently, an experimental (liquid jet) study[14] and a molecular - dynamic simulation study[15] of hydrogen bonding compounds independently proposed the direct evaporation of hydrogen bonded dimers. Thus, we may consider that a chiral recognition on the vaporization process with participation of much larger cluster is possible.

We considered that our compound can be a good probe for the investigation and simulation of the detailed mechanism of the vaporization process of associated compounds. Further study on this phenomenon may affect the thermodynamic as well as molecular dynamic descriptions of the liquid gas interface of a chiral alcohol and perhaps more generally of hydrogen bonded liquids.

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References and Notes

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[5] The enantiomeric excess of these compounds was determined by gas chromatography using a CP-Cyclodex β 236M column (GL Science). V. Shurig and H P. Nowotny, *Angew. Chem., Int. Ed. Engl.*, **29**, 939 (1990).

[6] We cannot exclude a possible participation of sublimation in these discrimination processes. Especially in the later case, the way of discrimination is the same to that of sublimation process; when we put 1.0 g of the partially crystalline isopropyl trifluorolactate having 81.7%ee under reduced pressure (30 mmHg) for 1 h, 0.5 g of the crystalline trifluorolactate having 95.0%ee remained. Such separation of enantiomer and racemate has been previously reported; H. Kawart, D. P. Hoster, *J. Org. Chem.*, **32**, 1867 (1967).

[7] The temperature of the bubbling bottom liquid was observed. We defined the boiling point as the point when the temperature of the bottom liquid did not increase even though the temperature of the oil bath was 15 °C higher.

[8] For the first set of measurements (● of Fig. 1) and the measurements of ethyl lactate (◆), we used 20 ml three-necked flasks equipped with an air cooler and thermometer. Two grams of lactates were used for measurements. For the second set of measurements (■), we used a round-bottomed flask with side-arm equipped with an air cooler and thermometer. Lastly, for the third set of measurements (▲) we used a test tube as the vessel.

[9] We did elemental analysis of the iso-propyl trifluorolactates to assure the purity of the compounds. Iso-propyl trifluorolactate of 0%ee: elem.anal., found % (calcd for $C_6H_9F_3O_3$): C 38.74 (38.70); H 4.89 (4.88). Iso-propyl trifluorolactate of 42%ee: C 38.72 (38.70); H 4.85 (4.88). Iso-propyl trifluorolactate of 68%ee: C 38.67 (38.70); H 4.82 (4.88). Iso-propyl trifluorolactate of 99.5%ee: C 38.72 (38.70); H 4.86 (4.88).

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