Discrimination of enantiomeric excess of optically active trifluorolactate by distillation: Evidence for a multi-center hydrogen bonding network in the liquid state

Toshimasa Katagiri [a,*], Satoshi Takahashi [a], Akio Tsuboi [b], Miki Suzaki [b], Kenji Uneyama [a]

[a] Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushimanaka 3-1-1, Kita-ku, Okayama 700-8530, Japan
[b] Science and Technology Research Center, INC, Mitsubishi Chemical Group, 3-10 Ushiodori, Kurashiki 712-8054, Japan

ABSTRACT

The paper provides evidence for the existence of a multi-center hydrogen bonding network of trifluorolactate, the structure of which was elucidated by single crystal X-ray diffraction analysis, in the liquid state. We reported that the trifluorolactate experienced discrimination of its enantiomeric excess by distillation. X-ray crystallographic analyses of the single crystals of the trifluorolactates suggested that the phenomenon could be caused by a homo-chiral recognizing hydrogen bonding system. Low-angle X-ray diffraction measurement of the trifluorolactate in the liquid state showed a ca. 5 Å repeated, which indicates the existence of the hydrogen bonding network in the liquid state. Here, the chiral recognition could be caused by the electrostatic repulsion of the negative charges on trifluoromethyl groups.

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1. Introduction

The discrimination of the enantiomeric excess of an optically active mixture of chiral compounds, which is ultimately a resolution of optically pure compound and racemate, is quite common during recrystallization and/or sublimation [1,2]. Recognition of the molecular chirality during these processes is achieved when the substrates are in their solid (crystal) states. Meanwhile, distillation would be an unusual and unpopular process for such resolution because it is believed that a strict recognition of the molecules is impossible in the liquid state. To date, so many reports on such discrimination have been reported but denied [1]. To the author's knowledge, there have been only two examples: trifluorolactate (**1**) [3] and N-trifluoroacetyl valine methyl ester (**2**) [4]. It is noteworthy that both of these compounds have β-trifluorinated proton donating groups. In the case of trifluorolactate, the alteration of the boiling point of the mixtures of the enantiomers depending on their enantiomeric excess could be attributed to this resolution phenomenon. Moreover, a contribution of hydrogen bonding in the liquid state was also suggested by an IR spectroscopic result [3].

trifluorolactate **1**   CF$_3$CO-Val-OMe **2**
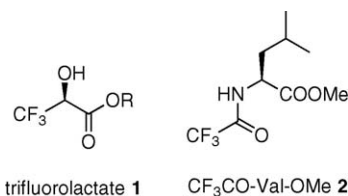
Publication [3] of the phenomenon by the distillation has led to controversy. A few review papers highlighted this phenomenon positively, as an extreme example of non-linear effects [5]. Due to the urgent need to identify the resolution mechanism, we performed single crystal X-ray crystallographic analyses and found an infinite hydrogen bonding network, which was constructed of successive multi-center hydrogen bonding systems of homo-chiral aggregate of trifluorolactates [6]. However, this result is just a structural aspect of the hydrogen bondings in the crystals of trifluorolactates. In this paper, we present evidence for a multi-center hydrogen bonding network in the liquid state and discuss an origin of the chiral recognition, energetically.
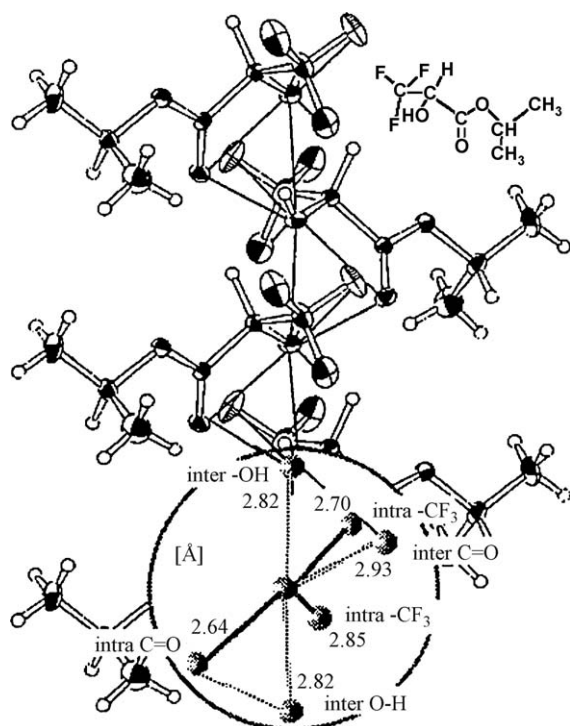
Fig. 1. ORTEP drawing of isopropyl (S)-trifluorolactate with an illustration of the hydrogen bonding system and the infinite one-dimensional network (CCDC 162589).

Fig. 3. Estimated bond energy between dimers of lactates by MO calculation by PM3: (a) S–S dimer of methyl trifluorolactate, (b) S–R dimer of methyl trifluorolactate, (c) S–S dimer of methyl lactate, and (d) S–R dimer of methyl lactate.

2. Results and discussion

2.1. Hydrogen bonding system and network in the liquid state

We have studied the structures of successive multi-center hydrogen bonding networks of trifluorolactates using X-ray crystallographic analyses [6,7]. A typical structure of the hydrogen bonding system and network is illustrated in Fig. 1.
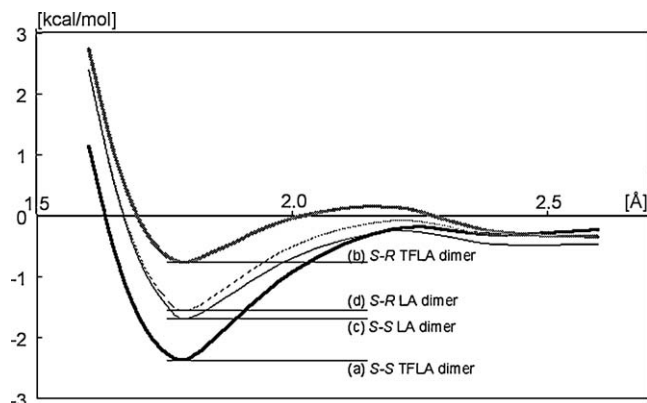
Every oxygen of the hydroxy group is surrounded by three intermolecular oxygens (2.82 Å × 2 for hydroxy oxygen and 2.93 Å for carbonyl oxygen), an intramolecular carbonyl oxygen (2.64 Å), and two intramolecular fluorine atoms (2.70 Å and 2.85 Å), within a distance of 3 Å. These hydrogen bondings could fix every trifluorolactate molecule enough to recognize the chirality of the next molecule.

The novel hydrogen bonding system and network are not enough evidence to explain the discrimination phenomena by distillation because this hydrogen bonding system had been only found in the crystal state, not in the liquid state. Thus, we need to confirm the existence of the hydrogen bonding networks in the liquid state (melt) of the trifluorolactates. The existence of the hydrogen bonding network in the liquid state was confirmed by low-angle X-ray diffraction measurement with hot stage. The result is shown in Fig. 2.

We found a very broad but evident diffraction peak (ca. 18°) above the melting point of the compound, as shown in Fig. 2(b)–(c). This result suggests a repeating structure with 5 Å intervals in the liquid state of the trifluorolactate. The lattice sizes of the mother
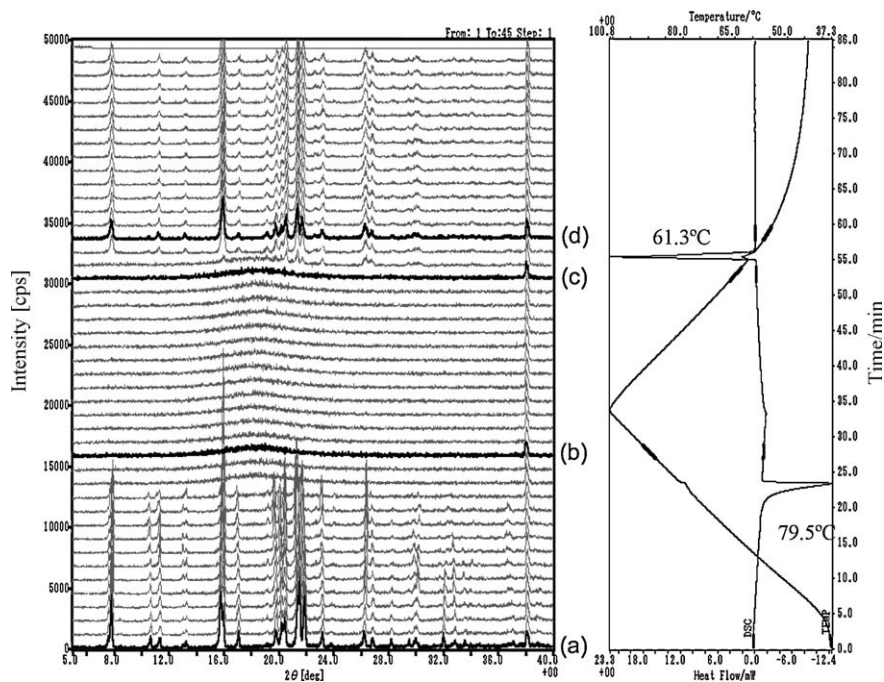

Fig. 2. Low-angle X-ray diffraction of the powdered **TFLA-d8** over a temperature range: (a) powder, (b) melt, (c) melt of the melting point, and (d) solid.

crystal (orthorhombic) are 5.2 Å, 8.0 Å, and 23.0 Å, respectively. Among them, the hydrogen bonding network is parallel to the 5.2 Å axis. Thus, the X-ray diffraction from 5 Å intervals implies that the hydrogen bonding network survived, even in the liquid state.

This hydrogen bonding system and network in the liquid state would promote the aggregation of the trifluorolactates, of which the extent and amount were varied by its enantiomeric excess. Thus, the boiling point of the trifluorolactate was changed depending on its enantiomeric excess. We may conclude that the discrimination of the enantiomeric excess of the trifluoro-lactate by distillation would be a thermodynamic process with a change in the intrinsic energy of the liquid state, depending on the extent of the hydrogen bonding network. The next question would be, "What is the origin of the difference of intrinsic energy?"

2.2. Electrostatic repulsion between negative charges on trifluoromethyl groups as a possible origin of chiral recognition

The Trouton-Hildebrand's empirical rule suggested that the 50 °C difference in the boiling points of trifluorolactate [3] could be converted to a ca. 1.1 kcal/mol energetic difference in the latent heat of vaporization. This value of the energy is comparable to the energetic differences of 80% de process [8]. That is, such extent of energetic difference could commonly be seen in moderate stereoselective reactions in solution.

At first, we estimated the differences of the hydrogen bonding energy between S–S pairs and S–R pairs of trifluorolactate and non-fluorinated lactate using a PM3 molecular orbital calculation method, as illustrated in Fig. 3.

As shown in Fig. 3, the hydrogen bonding energies of S–S lactate dimer and that of S–R lactate dimer were almost the same; the estimated difference of the energies was smaller than 0.1 kcal/mol. However, the hydrogen bonding energy of the S–S trifluorolactate dimer and that of S–R trifluorolactate dimer were obviously different. The difference was estimated to be 1.6 kcal/mol. This energetic difference is semi-quantitatively identical to that estimated from the max-difference range of the boiling point of isopropyl trifluorolactate depending on the enantiomeric excess (1.1 kcal/mol).

The structural information from the X-ray crystallographic analyses and a charge distribution analysis using MO calculations showed that the estimated energetic difference was attributed by the electrostatic repulsion between the two neighboring trifluor-omethyl groups in the supramolecular ribbon of trifluorolactates [9]. The negative charges on these trifluoromethyl groups were estimated to be 0.57e by PM3 MO calculation. The distance between the neighboring trifluoromethyl groups in the crystal of S-isopropyl trifluorolactate was 6.2 Å (Fig. 4(a)) [6]. Thus, the electrostatic repulsion between the trifluoromethyl groups was estimated to be 5.7 kcal/mol, while those of the irregular polymorph state of (S,R)-double head trifluorolactate were 5.1 Å and 4.9 Å (Fig. 4(b)) [7b]. Thus, the electrostatic repulsion was estimated to be 7.1 kcal/mol. Therefore, the energetic difference between the homo-chiral hydrogen bonding association and that of the hetero-chiral association was estimated to be 1.4 kcal/mol (the hetero-chiral association is relatively unstable), which again is
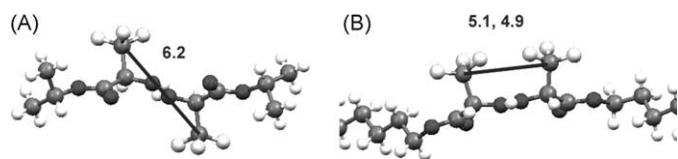
semi-quantitatively identical to that estimated from the boiling point range of isopropyl trifluorolactate while varying the enantiomeric excess.

3. Summary

In summary, the mechanism for the discrimination of the enantiomeric excess of the optically active trifluorolactate was explained by a structural study of their crystals and melted liquids. The energetic difference (1.1 kcal/mol from boiling points, 1.6 kcal/mol from MO calculation of hydrogen bonding energy, and 1.4 kcal/mol from charge distribution with X-ray crystallographic results) between homo-chiral and hetero-chiral recognition could be attributed to the differences in the electrostatic repulsion of negatively charged trifluoromethyl groups [10]. We are now eager to study the use of the hydrogen bonding network in crystal engineering to construct nano-architectures [7].

4. Experimental

Optically pure (S)-trifluorolactic acid was prepared according to methods described in the literature [11]. Trifluorolactates, isopropyl trifluorolactate (**1**) and **TFLA-d8** were prepared accord-ing to the literature methods [3,7c].

Single crystals of isopropyl trifluorolactate (**1**) and **TFLA-d8** were prepared by slow evaporation of the n-hexane/ether solutions. Single crystal X-ray diffraction data of these compounds were collected on a Rigaku R-AXIS IV imaging plate diffractometer using graphite-monochromated Mo-Kα radiation [λ = 0.71073 Å]. The structures were solved by direct and expanded using Fourier techniques. The structures were refined by full-matrix least-squares calculations using the teXsan program package.

Crystallographic data for the compounds was deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 162589 (isopropyl trifluorolactate (**1**)), CCDC 246922 (**TFLA-d8**), and CCDC 264877 (**TFLA-d9 SR**).

Low-angle X-ray diffraction analysis was measured using a Rigaku X-ray diffractometer, XRD-DSC(I).

The molecular orbital calculations were performed using the MacSpartan Pro package program.

Fig. 4. A cross-section view of the hydrogen bonding network: (a) The S–S network of isopropyl trifluorolactate (CCDC 162589) and (b) the S–R network of **TFLA-d9 SR** (CCDC 264877).

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