# Chiral Recognition by Multicenter Single Proton Hydrogen Bonding of Trifluorolactates

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An X-ray crystallographic analysis of optically pure isopropyl trifluorolactate suggested possible seven centered hydrogen bondings with chirality. The hydroxy group was surrounded by three intra- and three intermolecular proton acceptors within reasonable hydrogen bonding distances.

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In the previous paper, we reported a phenomenon on discrimination of the enantiomeric excess by a simple distillation of isopropyl 3,3,3-trifluorolactate.[1] The boiling point of the compound varied in a certain extent depending on its enantiomeric excess. This change of boiling point suggested some energetic difference between a homo- and a hetero-chiral intermolecular interaction of the trifluorolactate. The extent of boiling point difference between isopropyl trifluorolactate of the highest boiling point (ca. 142 °C at 60% ee) and that of the lowest (ca. 92 °C at 0% ee) suggested that, the energetic difference of those two states would be ca. 1.1 kcal/mol, based on Trouton –Hildebrand's empirical estimation of latent heat of vaporization.[2] This difference of the discrimination energy is smaller than that of successful metal-catalyzed catalytic asymmetric reactions[3] or that of enzymatic enantiomeric discriminations,[4] and is, of course, smaller than that of usual hydrogen bonding (HB) interactions. Notably, a remarkable difference between IR spectra of the trifluorolactate having higher ee and that of lower ee suggested a possible contribution of HB as well as a participation of fluorine atom to this phenomenon.[1]

Chiral recognition needs enough inter- and intramolecular interactions to fix the molecule. However, the trifluorolactate has only one OH-donor group for HB. Thus the HB system of this molecule should have three, at least, intermolecular HBs, and some intramolecular HBs. Although three centered HBs have often been found in crystals of amino acids and sugars, four centered HBs are relatively rare, and more than five-centered HBs had been found very scarcely.[5]

Unfortunately, up to now, indisputable structural evidence and information for the HB system have been obtained from crystals. Thus, one has to imagine the HB structures of liquid and/or solution just on the basis of crystalline structures. The trifluorolactate is colorless needles at ambient temperature, although nonfluorinated lactates with aliphatic alcohol moieties are liquids. Therefore, the trifluorolactate was submitted to the X-ray crystallographic analysis to get a key to solve the riddle on enantiomeric discriminations in their liquid states.[1]

The ORTEP drawing and packing with HB system of the trifluorolactate are illustrated in Figure 1.[6a] Surprisingly, the illustrate reveals that each OH group of the trifluorolactate bears three inter- and three intramolecular HBs around it; the OH group seems to be the center of sextuple HB, seven centered HB. Moreover, this HB system constructs a spiral ladder HB network. The same seven centered HB system could also be seen in the crystals of methyl trifluorolactate,[6b] and hexamethylene ditrifluorolactate,[6c] commonly.

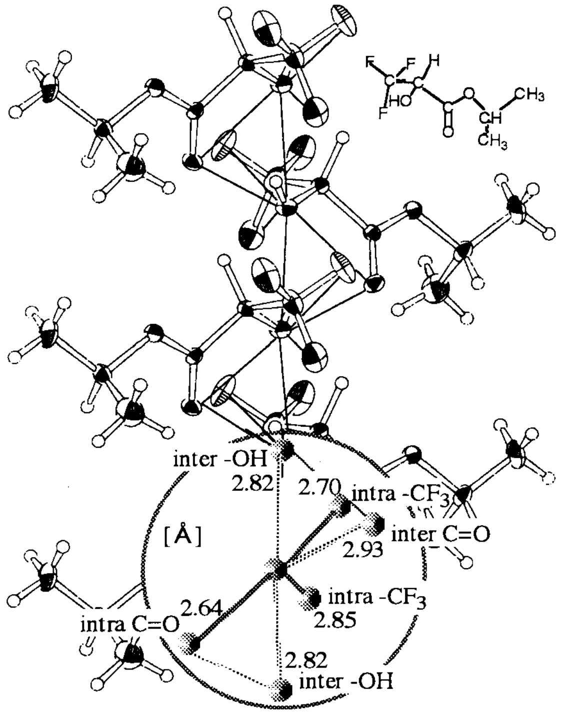

**Figure 1.** The ORTEP drawing of isopropyl (*S*)-trifluorolactate with illustration of the packed molecules with HBs.

There had been reported only two crystallographic reports on non-fluorinated lactates, due to low melting points of the compounds. The one example showed possible intermolecular interaction between hydroxy groups of neighboring molecules, while the distance between two OH oxygen atoms had been reported to be 3.56 Å, which is 0.74 Å longer than that of the trifluorolactate.[7] This comparison suggests that the fluorine atom in trifluorolactates would strengthen intermolecular HB to construct HB networks between hydrogen of OH group and fluorine of $CF_3$ group.[8]

This HB system seems to satisfy the demands for chiral recognition, locking of conformation by three intramolecular HBs and fixation of molecule by three intermolecular HBs around OH and additional HB to next molecule's OH by C=O were attained. There have been reported some examples on multi-center one proton HBs known as three-centered or bifurcated HB in crystal structures of amino acids.[5] In the present case, the HB acceptors seem to be arranged in a spherical way around the OH oxygen as illustrated in Figure 1. The intermolecular distance of O–O between two OH was found to be 2.82 Å and 2.93 Å for C=O to OH HB. It was reported that the neutron diffraction study on the cyclodextrin hydrates revealed that the possibility of HB with O–O distances shorter than 3.0

Å is 100%.[9] Thus, it is sure that one molecule is hydrogen-bonded to other molecules at least with four HBs in the crystal.

Existence of another possible two intramolecular HB between OH group and fluorine on $CF_3$ would be controversial. A classic criterion had been suggested that, a heavy atom distance less than the sum of their van der Waals radii is sufficient for HB.[5a] The present distances between oxygen atom of OH and two fluorine atoms were 2.85 and 2.70 Å, both of these distances are evidently smaller than the sum of van der Waals radii of an oxygen and a fluorine, 2.99 Å. An IR spectrum of liquid isopropyl trifluorolactate would be an another evidence for participation of fluorine atom to this HB system.[1] In our previous report, it was clarified that IR spectrum of the melted isopropyl trifluorolactate with a low boiling point had shown characteristic three bands attributable to the $CF_3$ group. Meanwhile, these three bands had been found to be broaden or shifted in the case of the melted trifluorolactates with higher boiling points. The remarkable change of these bands by $CF_3$ depending on the ee of the trifluorolactate implies a possible existence of F–H–O intramolecular HBs which cooperate with intermolecular HBs in making spherical HB system; the neighboring $CF_3$ group would act as a labile HB acceptor.[10] Also the strong electron withdrawing effect of $CF_3$ group would contribute to form this HB system to make the hydroxy group much acidic and let the proton free from hydroxy oxygen.

Optically active $\alpha$-$CF_3$-alcohols are a reliable class of fluorinated chiral compounds due to a variety of their preparations,[11] thus they would be finely tunable and highly utilizable class of compounds for a variety of molecular recognition. Utilization of this moiety for intra- and intermolecular chiral recognition is now in progress in our group as well as other groups.[12]

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