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First principle lattice energy calculations for enantiopure and racemic crystals of α-(trifluoromethyl)lactic acid: Is self-disproportionation of enantiomers controlled by thermodynamic stability of crystals?

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ABSTRACT

The lattice energies for the enantiopure and racemic crystals of α-(trifluoromethyl)lactic acid were calculated by a combination of the DFT calculations with the periodic boundary condition and the MP2 calculations of the interactions with neighboring molecules. The lattice energies calculated for the two crystals (−16.56 and −17.35 kcal/mol, respectively) show that the racemic crystals are thermodynamically more stable, although the racemic crystals sublime faster than the enantiopure crystals. The calculations suggest that the relative thermodynamic stability is not the cause of the faster sublimation rate of the racemic crystals compared with the enantiopure crystals. Although the crystals have hydrogen-bonding networks, the dispersion interactions contribute to the lattice energies significantly. The MP2 calculations for the evaluation of the dispersion interactions with the neighboring molecules are important for an accurate evaluation of the lattice energies. The relative thermodynamic stability of the two crystals is not determined solely by the hydrogen bonds. The interactions with other neighboring molecules also play important roles in determining the relative stability. We demonstrate that the geometry optimization is essential for an accurate evaluation of the lattice energy by the first principle calculation. The interaction energies calculated using the structure by X-ray diffraction often have large errors.

1. Introduction

The purification of enantiomers is one of the most important stages in drug discovery and manufacturing of pharmaceuticals on the large-scale [1–3]. The current methodological choice of optical purification procedure is limited to either chromatography on chiral stationary phase or fractional crystallization. Therefore the discovery and development of novel optical purification methods would be of significant scientific and technological impact. In this regard the recently highlighted Self-Disproportionation of Enantiomers (SDE), describing spontaneous separation of racemate from the excess enantiomer [4] suggests that any physico-chemical process can disproportionate the original enantiomeric composition of any enantiomerically enriched mixture. For example, the practical potential of distillation [5], sublimation [6,7], gravitational field [8] and achiral-phase chromatography [9] for optical purifications, still remain virtually completely unknown and unexplored. In particular, recently the first example of optical self-purification by sublimation of the mixture of optically pure and racemic crystals was reported [7]. The racemic crystals of α-(trifluoromethyl)lactic acid (1) sublime about 1.5 times faster than the optically pure crystals. The almost complete (>99.9% ee) purification was observed from the sublimation of the optical purity of 80% ee sample. An enantiomerically enriched compound purifies itself to enantiomerically pure form only by being exposed to open atmosphere. The self-purification by the sublimation can potentially be one of the efficient enantioselective separation methods.

The thermodynamic stability of the two crystals is important for understanding the cause of the different sublimation rate constants [7]. The sublimation rate constants depend on the activation energies for the sublimation processes. If the activation energies for the sublimation are proportional to the lattice energies of the crystals, the lattice energies of the two crystals can explain the difference of sublimation rates. But the lattice energies for the two crystals were still unclear. Some experimental measurements were reported for understanding the relative stability of the two crystals. The density of the

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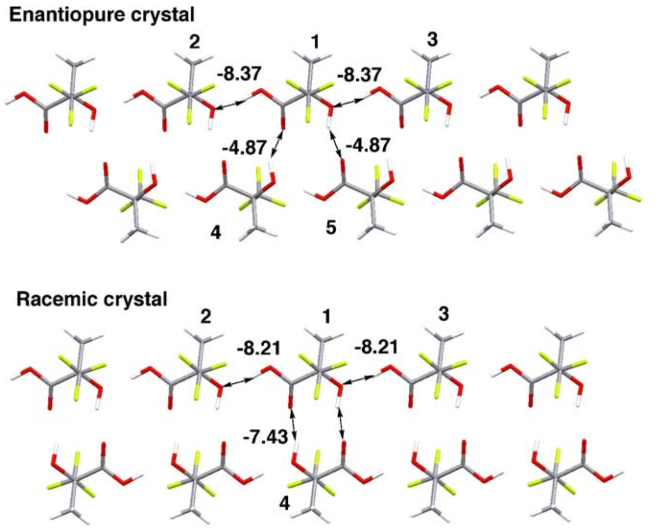

Fig. 1. The hydrogen bond networks in the two crystals. The interaction energies with the hydrogen-bonded neighboring molecules calculated by the MP2 method (kcal/mol).

racemic crystals is slightly larger than that of enantiopure crystals, which suggests that the racemic crystal is thermodynamically more stable. It is expected that the attractive intermolecular interactions in the dense crystals are stronger due to the shorter intermolecular distance. On the other hand the melting points of the two crystals suggest that the enantiopure crystal is thermodynamically more stable. The melting points of enantiopure and racemic compounds are 110 °C and 88 °C, respectively. The higher melting point shows that enantiopure crystal is more stable, if the energy of the enantiopure liquid and that of racemic liquid are identical. Unfortunately, the relative stability of the two liquids is not known. The crystallographic analyses showed that the hydrogen-bonding networks in the two crystals are completely different (Fig. 1). Molecules are arranged in a zigzag form allowing each molecule to form four hydrogen bonds to four other molecules in the enantiopure crystal. On the other hand heterochiral dimers form with two hydrogen bonds between (*R*) and (*S*) enantiomers in the racemic crystal. Each enantiomer has two more hydrogen bonds to neighboring dimers. Although the different hydrogen-bonding networks in the two crystals suggest that the thermodynamic stability of the two crystals is different, the relative stability of the two crystals is unclear. Therefore we evaluate the lattice energies for the two crystals by theoretical calculations in this work.

The lattice energies for the two crystals were calculated by a combination of the DFT calculations with the periodic boundary condition and the MP2 calculations [10] for evaluating the interactions with neighboring molecules in this work. We used this method for an accurate evaluation of the hydrogen bond cooperativity effects [11] and the dispersion interactions with neighboring molecules. The hydrogen bond cooperativity is the enhancement of hydrogen bonds by a formation of a hydrogen bond network. An accurate evaluation of the hydrogen bond cooperativity effects is essential for evaluating the relative stability of the two crystals, which have different types of hydrogen bond networks. The first principle calculation with the periodic boundary condition is necessary for an accurate evaluation of the hydrogen bond cooperativity effects. The cooperativity has its origin in molecular polarization by the formation of a hydrogen bond network. Commonly used force fields cannot accurately evaluate the effects of polarization. Pair wise additive first principle calculations cannot evaluate the cooperativity. Therefore we used the DFT calculations with the periodic boundary condition for the evaluation of the lattice energy [12]. Unfortunately, however, DFT calculations cannot accurately evaluate the dispersion interactions [13], which contribute to the lattice energies of molecular crystals significantly [14]. The dispersion interactions with neighboring molecules in the crystals were evaluated by the MP2 method, since the dispersion energy decreases rapidly with separation [15]. We will also discuss the details of the interactions with neighboring molecules in the two crystals for understanding which interactions play important roles in determining the stability of the crystals. In addition the effects of geometry optimizations on the interaction energy calculations will be discussed.

2. Computational method

DFT calculations were performed with the program package DMOL^3 in Material Studio of Accelrys Inc. In the DMOL^3 method [16], the physical wave functions are expanded in terms of accurate numerical basis sets. We used the double-numerical quality basis set with polarization functions (DNP). The size of the DNP basis set is comparable to Gaussian 6-31G** but DNP is more accurate [16]. The PW91 functionals were used for the DFT calculation [17]. The positions of atoms in the crystals were optimized with the periodic boundary condition. The experimental lattice parameters were fixed during the optimization. The energies of the crystals (E_{crystal}) were calculated using the refined geometries of the crystals. The geometry for an isolated molecule was optimized. The energy for an isolated molecule (E_{mol}) was calculated using the optimized geometry. The lattice energy per 1 mol molecule ($E_{\mathrm{lattice(DFT)}}$) was calculated from the E_{crystal} and E_{mol} as Eq. (1)

$$E_{\mathrm{lattice(DFT)}} = \frac{1}{n}E_{\mathrm{crystal}} - E_{\mathrm{mol}}, \tag{1}$$

where n is the number of molecules in an unit cell ($n = 4$ for the crystal of pure enantiomers and $n = 2$ for the racemic crystal). The lattice energy for the crystal of pure enantiomers relative to that for the racemic crystal ($\Delta E_{\mathrm{lattice(DFT)}}$) was calculated from the energies of the two crystals obtained by the DFT calculations (E_{crystal}). The Gaussian program [18] was used for the MP2 calculations [19]. The MP2 calculations were used for the evaluation of the intermolecular interactions with neighboring molecules. The aug(df, pd)-6-311G** basis set [20] was used for the MP2 calculations. This basis set is the 6-311G** basis set augmented with diffuse d and f functions on heavy atoms and diffuse p and d functions on hydrogen atoms. The basis set superposition error (BSSE) [21] was corrected by the counterpoise method [22]. The lattice energies of the two crystals were also evaluated using the interaction energies with neighboring molecules calculated at the MP2 level. The dispersion interactions between neighboring molecules in organic crystals are significant. The dispersion interactions decrease rapidly with distance, since the dispersion energy is approximately proportional to the inverse sixth power of the distance [15]. Therefore the interactions with neighboring molecules [$E_{\mathrm{short(MP2)}}$], where the shortest atom–atom distance is less than 6.0 Å, were evaluated by the MP2 calculations (Fig. 2). The lattice energy ($E_{\mathrm{lattice(MP2+DFT)}}$) was calculated as the sum of the $E_{\mathrm{lattice(DFT)}}$ and the MP2 correction term ($E_{\mathrm{short(MP2-cor)}}$) for the interaction energies with neighboring molecules as Eq. (2)

$$E_{\mathrm{lattice(MP2+DFT)}} = E_{\mathrm{lattice(DFT)}} + E_{\mathrm{short(MP2-cor)}}. \tag{2}$$

The $E_{\mathrm{short(MP2-cor)}}$ was obtained by subtracting the interaction energies with the neighboring molecules calculated by the DFT

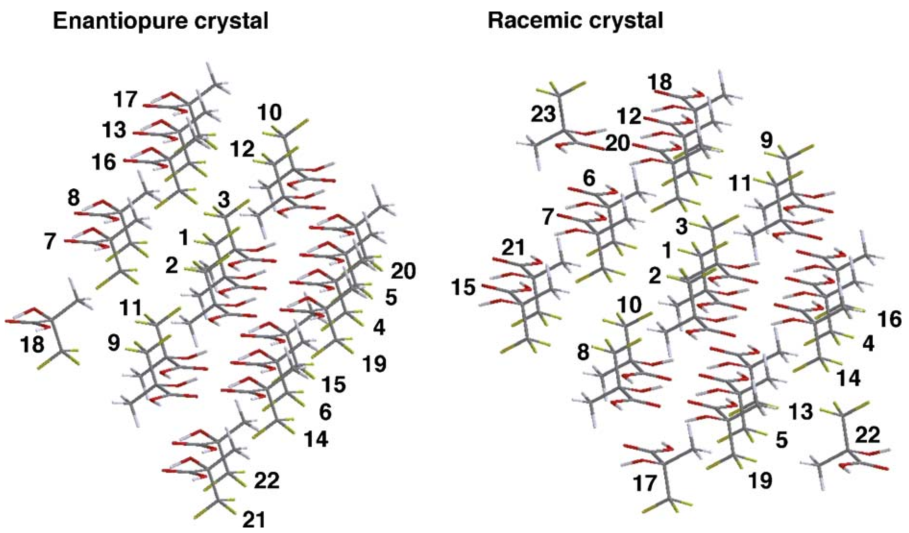

Fig. 2. The structures for enantiopure and racemic crystals of α-(trifluoromethyl)lactic acid. The central molecule (1) and neighboring molecules are shown. The shortest atom–atom distance between the central molecule and neighboring molecule is less than 6 Å.

method ($E_{\mathrm{short(DFT)}}$) from the interaction energies with the neighboring molecules calculated by the MP2 method ($E_{\mathrm{short(MP2)}}$) as Eq. (3)

$$E_{\mathrm{short(MP2-cor)}} = E_{\mathrm{short(MP2)}} - E_{\mathrm{short(DFT)}}. \tag{3}$$

The interaction energies with the neighboring molecules (E_{short}) was calculated as the sum of the pair interaction energies of a molecule with the neighboring molecules (E_{i}) as Eq. (4)

$$E_{\mathrm{short}} = \frac{1}{2}\Sigma E_{\mathrm{i}}. \tag{4}$$

The neighboring molecules considered in this work are shown in Fig. 2.

3. Results and discussion

3.1. Lattice energy calculations by DFT method

The energies for the enantiopure and racemic crystals (E_{crystal}) were calculated by the DFT method with the periodic boundary condition. The E_{crystal} for the two crystals were −2723.18893 and −1361.59408 AU, respectively. The energy for an isolated molecule was −680.77652 AU. The $E_{\mathrm{lattice(DFT)}}$ calculated for the two crystals are −12.99 and −12.87 kcal/mol, respectively. The lattice energies for the two crystals are very close, although the calculations show that the crystal of pure enantiomers is slightly more stable (0.12 kcal/mol).

3.2. Lattice energy calculations with MP2 correction for interactions with neighboring molecules

The lattice energies ($E_{\mathrm{lattice(MP2+DFT)}}$) calculated for the enantiopure and racemic crystals with the MP2 correction (Eq. (2)) show that the racemic crystal is more stable, which agrees with the expectation form the comparison of the densities for the two crystals. The $E_{\mathrm{lattice(MP2+DFT)}}$ calculated for the two crystals were −16.56 and −17.35 kcal/mol, respectively. The $E_{\mathrm{lattice(MP2+DFT)}}$ for the enantiopure crystal relative to the racemic crystal ($\Delta E_{\mathrm{lattice(MP2+DFT)}}$) is 0.78 kcal/mol. Although the two crystals have significantly different hydrogen bond networks [7], the lattice energy difference of the two crystals is not very large. The $E_{\mathrm{lattice(MP2+DFT)}}$ calculated for the two crystals are substantially larger (more negative) than the $E_{\mathrm{lattice(DFT)}}$. The DFT calculations ($E_{\mathrm{lattice(DFT)}}$) fail to reproduce the larger thermodynamic stability of the racemic crystal derived from the $E_{\mathrm{lattice(MP2+DFT)}}$. These results show that the evaluation of the dispersion interactions with neighboring molecules by the MP2 method is essential for accurate lattice energy calculations.

Although the $E_{\mathrm{lattice(MP2+DFT)}}$ values for the two crystals were also calculated by changing the range of neighboring molecules, the changes do not affect the preference of the two crystals. The shortest atom–atom distance for the neighboring molecules was changed for 3.0, 3.5, 4.0 and 5.0 Å, respectively [23]. The $E_{\mathrm{lattice(MP2+DFT)}}$ values calculated for the two crystals summarized in Table 1 show that the racemic crystal is always more stable.

3.3. Interactions with neighboring molecules

The pair interaction energies with the neighboring molecules in the two crystals (Figs. 1 and 2) calculated by the DFT, HF and MP2 methods are summarized in Table 2. The interactions with hydrogen-bonded neighboring molecules (1–2, 1–3, 1–4 and 1–5 pairs in the enantiopure crystal and 1–2, 1–3 and 1–4 pairs in the racemic crystal) are stronger than the interactions with other neighboring molecules. The interactions in the 1–4 and 1–5 pairs in the enantiopure crystal calculated by the MP2 method (−4.87 kcal/mol) are significantly weaker than the interactions in the 1–2 and 1–3 pairs (−8.37 kcal/mol), although each pair has a single

Table 1
Lattice energies calculated for optically pure and racemic crystals by changing the range of neighboring molecules.[a]

Method[b]	Range of neighbors[c]	E_{lattice}		$\Delta E_{\mathrm{lattice}}$[d]
		Pure	Racemic	
$E_{\mathrm{lattice(DFT)}}$		−12.99	−12.87	−0.12
$E_{\mathrm{lattice(MP2+DFT)}}$	3.0	−16.35	−16.50	0.15
$E_{\mathrm{lattice(MP2+DFT)}}$	3.5	−16.63	−16.70	0.07
$E_{\mathrm{lattice(MP2+DFT)}}$	4.0	−16.58	−16.66	0.08
$E_{\mathrm{lattice(MP2+DFT)}}$	5.0	−16.64	−17.06	0.42
$E_{\mathrm{lattice(MP2+DFT)}}$	6.0	−16.56	−17.35	0.78

[a] Energy in kcal/mol. See text.

[b] $E_{\mathrm{lattice(DFT)}}$ was obtained by DFT calculations with the periodic boundary condition. $E_{\mathrm{lattice(MP2+DFT)}}$ was the sum of $E_{\mathrm{lattice(DFT)}}$ and MP2 correction for the interaction energies with neighboring molecules. See text.

[c] The distance (Å) between the nearest atoms is less than this value. See text.

[d] E_{lattice} for pure crystal relative to that for racemic crystal ($=E_{\mathrm{lattice(pure)}} - E_{\mathrm{lattice(racemic)}}$). See text.

Table 2
Pair interaction energies in the two crystals calculated by DFT, HF and MP2 methods.[a]

	E_{DFT}[b]	E_{HF}[c]	E_{MP2}[d]	E_{corr}[e]
Enantiopure				
1–2	−8.39	−4.40	−8.37	−3.97
1–3	−8.39	−4.40	−8.37	−3.97
1–4	−4.46	−2.84	−4.87	−2.02
1–5	−4.47	−2.85	−4.87	−2.02
1–6	−1.05	0.84	−2.99	−3.83
1–7	−0.99	0.19	−1.61	−1.80
1–8	−0.99	0.19	−1.61	−1.80
1–9	−0.71	0.61	−1.32	−1.94
1–10	−0.71	0.61	−1.32	−1.94
1–11	−0.07	1.20	−0.85	−2.05
1–12	−0.07	1.20	−0.85	−2.05
1–13	0.10	1.15	−0.47	−1.62
1–14	−0.89	−0.57	−0.83	−0.26
1–15	−0.89	−0.57	−0.83	−0.26
1–16	−0.11	−0.02	−0.12	−0.10
1–17	−0.06	−0.02	−0.12	−0.10
1–18	−0.04	0.11	−0.10	−0.21
1–19	−0.08	0.01	−0.03	−0.04
1–20	−0.08	0.01	−0.03	−0.04
1–21	−0.01	0.08	0.01	−0.07
1–22	−0.02	0.08	0.01	−0.07
Sum	−32.40	−9.41	−39.55	−30.14
Racemic				
1–2	−8.15	−4.12	−8.21	−4.10
1–3	−8.14	−4.11	−8.21	−4.10
1–4	−6.58	−3.59	−7.43	−3.84
1–5	−4.38	−2.36	−5.98	−3.62
1–6	−1.13	0.05	−1.91	−1.96
1–7	−1.10	0.01	−1.76	−1.77
1–8	−0.57	0.96	−1.28	−2.24
1–9	−0.57	0.96	−1.27	−2.24
1–10	−0.23	0.98	−0.88	−1.87
1–11	−0.23	0.99	−0.88	−1.87
1–12	−0.13	0.88	−0.63	−1.52
1–13	0.12	1.04	−0.29	−1.33
1–14	−2.26	−2.00	−2.16	−0.16
1–15	0.00	−0.02	−0.23	−0.20
1–16	−0.05	−0.05	−0.22	−0.17
1–17	−0.11	−0.11	−0.22	−0.11
1–18	0.20	0.19	0.02	−0.16
1–19	0.27	0.23	0.14	−0.08
1–20	−0.19	−0.27	−0.33	−0.06
1–21	0.06	−0.08	−0.10	−0.02
1–22	0.19	0.16	0.06	−0.10
1–23	0.20	0.16	0.06	−0.10
Sum	−32.76	−10.10	−41.71	−31.61

[a] Energy in kcal/mol. Pair interaction energies were calculated using the optimized geometries by the DFT method. See Fig. 2 and text.

[b] Interaction energy calculated by the DFT method.

[c] Interaction energy calculated by the HF method.

[d] Interaction energy calculated by the MP2 method.

[e] Electron correlation contribution in interaction energy calculated by the MP2 method (=$E_{\mathrm{MP2}} - E_{\mathrm{HF}}$). E_{corr} is mainly dispersion energy. See text.

hydrogen bond. The interaction in the 1–4 pair in the racemic crystal (−7.43 kcal/mol) is weaker than the interactions in the 1–2 and 1–3 pairs (−8.21 kcal/mol), although the 1–4 pair has two hydrogen bonds. The H···O and O···O distances in the 1–4 and 1–5 pairs in the enantiopure crystal (1.831 Å and 2.722 Å, respectively) are substantially shorter than the H···O and O···O distances in the 1–2 and 1–3 pairs (1.627 Å and 2.630 Å, respectively). The O–H···O angles in the 1–2 and 1–3 pairs (168.0°) are close to 180°, while the O–H···O angles in the 1–4 and 1–5 pairs are 148.2°. The distances and angles show that the hydrogen bonds in the 1–4 and 1–5 pairs are substantially distorted. Probably the distortion is the cause of the weak hydrogen-bonding energy in the 1–4 and 1–5 pairs in the enantiopure crystal. Similar distortion was found in the hydrogen bonds in the 1–4 pair in the racemic crystal. The H···O and O···O distances and O–H···O angles in the 1–4 pair in the racemic crystal are 1.788 Å, 2.734 Å and 158.8°. The H···O and O···O distances and O–H···O angles in the 1–2 and 1–3 pairs in the racemic crystal (1.640 Å, 2.646 Å and 169.6°). These values are close to those in the 1–2 and 1–3 pairs in the enantiopure crystal. The interactions in the 1–2 and 1–3 pairs in the two crystals are substantially stronger than the interaction in the water dimer (about −5 kcal/mol) [13c], which is a typical hydrogen bond. The E_{corr} (=$E_{\mathrm{MP2}} - E_{\mathrm{HF}}$) for the 1–2 and 1–3 pairs are significant (−3.97 to −4.10 kcal/mol). The large E_{corr} values show that the dispersion interactions enhance the attraction in these pairs substantially. The E_{corr} is mainly dispersion energy, since the dispersion interaction has its origin in electron correlation and therefore the HF method cannot evaluate the dispersion energy.

Substantial attraction exists in the 1–5 and 1–14 pairs in the racemic crystal (−5.98 and −2.16 kcal/mol), although these pairs do not have hydrogen bonds. The negative E_{HF} values for these pairs (−2.36 and −2.00 kcal/mol) indicate that the electrostatic interaction, which is one of the long-range interactions, is an important source of the attraction in these pairs. Substantial attraction also exists in the 1–6, 1–7, 1–8, 1–9 and 1–10 pairs in the pure crystal and in the 1–6, 1–7, 1–8 and 1–9 pairs in the racemic crystal (−1.27 to −2.99 kcal/mol). The E_{HF} values for these pairs are positive, which shows that the dispersion interaction is the major source of the attraction.

The sum of E_{HF} with the neighboring molecules (within 6 Å) and that of E_{corr} were calculated for the two crystals as shown in Table 2. The E_{HF} is mainly the sum of the electrostatic and repulsion interactions. The E_{corr} values for the enantiopure and racemic crystals (−30.14 and −31.61 kcal/mol) are significantly larger than the E_{HF} for the two crystals (−9.41 and −10.10 kcal/mol). The large E_{corr} values show that the contributions of the dispersion interactions to the lattice energies of the two crystals are significant, although one may consider that the hydrogen-bonding energy (electrostatic energy) is mainly responsible for the lattice energies of the two crystals. The large contributions of the dispersion interactions show the importance of an accurate evaluation of the dispersion energy for the analysis of the lattice energies of the crystals.

Each molecule has four hydrogen bonds in the two crystals (Fig. 1). The pair interaction energies calculated for the four hydrogen-bonded pairs in the enantiopure crystal are −8.37, −8.37, −4.87 and −4.87 kcal/mol, respectively. The sum of the interaction energies with the four hydrogen-bonded molecules is −26.48 kcal/mol. Each molecule has two hydrogen bonds with an enantiomer and additional two hydrogen bonds with two other molecules in the racemic crystal. The interaction energy with the hydrogen-bonded enantiomer is −7.43 kcal/mol. The interaction energies with other two hydrogen-bonded molecules are −8.21 and −8.21 kcal/mol, respectively. The sum of the interaction energies with the three hydrogen-bonded molecules is −23.85 kcal/mol. The sum of the interactions with the hydrogen-bonded molecules in the enantiopure crystal is substantially (2.63 kcal/mol) larger than that in the racemic crystal. On the other hand the lattice energies ($E_{\mathrm{lattice(MP2+DFT)}}$) calculated for the two crystals show that the racemic crystal is more stable (0.78 kcal/mol). These results show that the relative stability of the two crystals are not determined solely by the hydrogen bonds and interactions with other neighboring molecules also play important roles in determining the relative stability of the crystals.

3.4. Effects of geometry optimization

Starting from XRD structures, geometry optimizations do not significantly change the positions of heavy atoms, while the positions of hydrogen atoms substantially change [10]. The

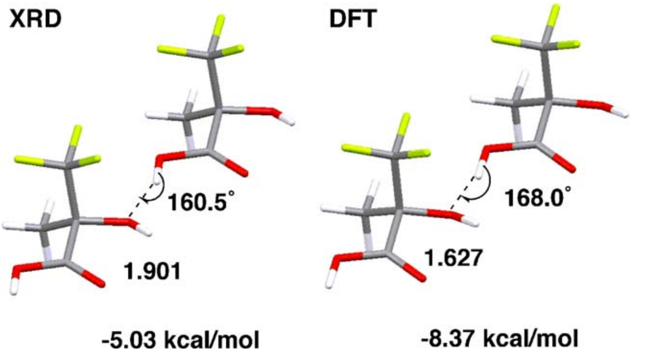

Fig. 3. The interaction energies calculated for the 1–2 pair in the enantiopure crystal by the MP2 method using the XRD structure and the optimized structure by the DFT method. The O···H distances and O···H–O angles in the two structures are shown.

geometry of the 1–2 pair in the enantiopure crystal is shown in Fig. 3. The hydrogen atom in the hydrogen bond moved substantially by the geometry optimization. The O···H distance in the optimized structure (1.627 Å) is substantially shorter than that in the structure by the X-ray diffraction (XRD) measurement (1.901 Å). The O···H–O angle in the optimized structure (168.0°) is closer to 180° compared with that by XRD (160.5°). The intermolecular interaction energy calculated for this pair using the optimized geometry (−8.37 kcal/mol) is more than 3 kcal/mol larger than that using the structure by XRD (−5.03 kcal/mol). The large difference clearly shows the importance of the geometry optimization. Apparently the position of the hydrogen atom in the optimized geometry is more appropriate for the stabilization by the hydrogen bond than that in the structure by XRD. It is well known that accurate determination of the positions of hydrogen nuclei by XRD is extremely difficult, and consequently, the positions of the hydrogen atoms in an XRD structure often have large error, which is probably the cause of the deviations when using the XRD structures for calculations. Our calculations show that the geometry of crystal must be optimized with great care, if one wants to evaluate the lattice energy of the crystal accurately.

3.5. Causes of different rate constants of sublimation

The lattice energies calculated for the two crystals suggest that the racemic crystal is more stable than the enantiopure crystal, while the experimental measurements of sublimation under followed zero-order kinetics, gave 1.50 ± 0.02 ratio of zero-order rate constants k(racemic)/k(enantiopure) [7]. These results suggest that the sublimation rates are not controlled by the thermodynamic stability of the crystals, which means that the activation energies for the sublimation of the two crystals are not proportional to the lattice energies. Although details of the sublimation processes of the two crystals are still unclear, the smaller sublimation rate constant for the thermodynamically less stable enantiopure crystals suggests that the sublimation mechanisms of the two crystals are different. It is quite probable that the α-(trifluoromethyl)lactic acid sublimates as dimers, since carboxylic acid molecules often form dimers in the gas phase. The structure of enantiopure crystal suggests that hydrogen bond recombination is necessary in the sublimation process provided that the molecules sublimate as dimers. On the other hand the recombination may not be necessary for the sublimation of racemic crystals. This difference is one of the possible reasons of the different sublimation rates.

4. Conclusion

The first principle lattice energy calculations of the enantiopure and racemic crystals of α-(trifluoromethyl)lactic acid show that the racemic crystal is thermodynamically more stable, although the racemic crystals sublime faster than the enantiopure crystals. The calculations suggest that the sublimation rates are not controlled by the thermodynamic stability of the crystals. Although the crystals have hydrogen-bonding networks, the interaction energy calculations show that the contributions of the dispersion interactions to the lattice energies are significant. The accurate evaluation of the dispersion interactions with neighboring molecules by the MP2 method is important for lattice energy calculations. Although the two crystals have significantly different hydrogen-bonding networks, which suggest that the hydrogen-bonding energies in the two crystals are different, the lattice energy difference of the two crystals is small. This shows that the relative stability of the two crystals is not determined solely by the hydrogen bonds and the interactions with other neighboring molecules also play important roles in determining the relative stability. The geometry optimization is essential for an accurate evaluation of the lattice energy by the first principle calculation. The positions of hydrogen atoms in the structure by the X-ray diffraction often have large errors, which largely change the interaction energies calculated for hydrogen-bonded pairs.

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