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Formation of racemic crystals of transition metal complexes by grinding 1 : 1 mixtures of enantiomeric crystals†

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Grinding a 1 : 1 enantiomeric mixture of chiral transition metal complex crystals and subsequent annealing afforded crystals of a racemic compound by diffusion and rearrangement of component molecules, without melting and without racemization of each enantiomeric species.

Solvent-free organic reactions have attained increasing interest in recent years.[1] They are expected to provide alternative methods for chemical industries in which a large quantity of environmentally unfriendly solvents is consumed. Solvent-free reactions should be stereoselective if this becomes a practical method in the chemical industries. However, chirality control for solvent-free reactions has not been extensively investigated.

Toda *et al.* demonstrated that the grinding of a 1 : 1 enantiomeric mixture of chiral organic compound crystals in the solid state gave crystalline powders of racemic compounds.[2] Such an enantioselective interaction in the solid state leading to the formation of a new crystal is of great interest as a basic process for achieving enantioselective reactions in the solid state. However, the precise mechanism for the formation of the racemic compounds is not known.

Several mechanisms have been proposed for solid–solid reactions. Local melting may result in crystallization *via* a melt phase. Diffusion of a volatile component through a vapour phase was also suspected for the mechanism of crystal transformation.[3] The effect of a small amount of solvent on the solid-state crystallization (kneading effect) is also known.[4] For example, even water in the crystals or adsorbed from the atmosphere might act as a solvent which locally dissolves the crystals.

Crystals of chiral metal complexes are unique substrates for investigating the mechanism of the formation of racemic crystals by co-grinding enantiomeric crystals. Some metal complexes exhibit chirality due to the chiral coordination geometry of achiral ligands. For example, tris(diimine) complexes of a transition metal exhibit chirality with D_3 symmetry and their crystal structures were systematically analyzed.[5,6] For the crystals of the metal complexes that decompose at a higher temperature without melting, crystallization by local melting is not probable. For the metal complexes with lower vapour pressures than low molecular-weight organic compounds, reactions by diffusion through the vapour phase is less probable. Then, it will be an interesting question whether heavy and bulky molecules like those of the metal complexes can diffuse in the solid state or not.

Here, we report an interesting chirality-recognizing solid-state crystallization of a hexafluorophosphate salt of a Ru(II) tris(1,10-phenanthroline) complex ($[Ru(phen)_3](PF_6)_2$, **1**). Salts of the resolved enantiomers were obtained using the modified procedure of Dwyer and Gyarfas,[7] and were recrystallized from their respective aqueous solutions. Crystals of the racemic compound were obtained from an aqueous solution of a racemic mixture of the salt. Although freshly prepared single crystals contained water in the lattices, the water was lost within a few hours.[8]‡

In order to avoid the effect of water either included in the crystal lattice, adsorbed on the surfaces, or as atmospheric humidity, the crystals were ground and dried before use in a vacuum at 70 °C overnight and the co-grinding and heating experiments were performed in a dry box under a flow of dry nitrogen.

The grinding of a 1 : 1 mixture of the enantiomeric crystals of **1** in an agate mortar at room temperature resulted in powders which were quite amorphous with small broad peaks in the PXRD pattern (Fig. 1).§ Upon heating of the ground microcrystallines at 250 °C for 30 min, these small diffraction peaks grew substantially. During heating, the mixture kept its powder form. The formed crystals were proved to be the crystals of the racemic compound, as compared with the simulated diffraction pattern (Fig. 1).

The transformation of the crystals was monitored by thermogravimetry (TG) and differential thermal analyses (DTA) (Fig. 2). Transformation of the crystals was observed as an exothermal peak at 205–220 °C. No discontinuous change in gravity was observed at the transformation temperature. A slow continuous loss in gravity was observed over the wide range of temperatures. However, this seems not to be due to the loss of water, because the TG curves

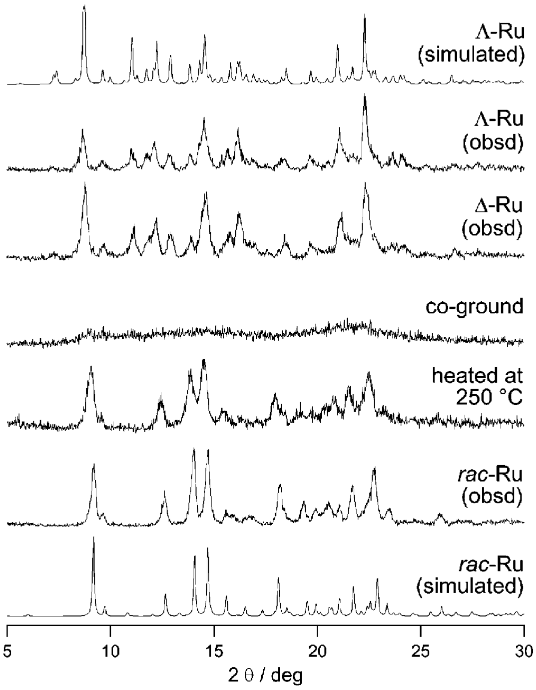

Fig. 1 X-Ray diffraction patterns for the crystalline powders of Λ-**1** and Δ-**1** and their co-ground mixture before and after annealing. Simulated diffraction patterns based on the single crystal structures are also shown at the top and bottom.[8]

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† Electronic supplementary information (ESI) available: experimental details, structural data for the crystals of $[Ru(phen)_3](PF_6)_2$ and $[Os(phen)_3](PF_6)_2$, and powder X-ray diffraction patterns for the mixture of Δ-$[Ru(phen)_3](PF_6)_2$ and Λ-$[Os(phen)_3](PF_6)_2$. See http://www.rsc.org/suppdata/cc/b4/b409006c/

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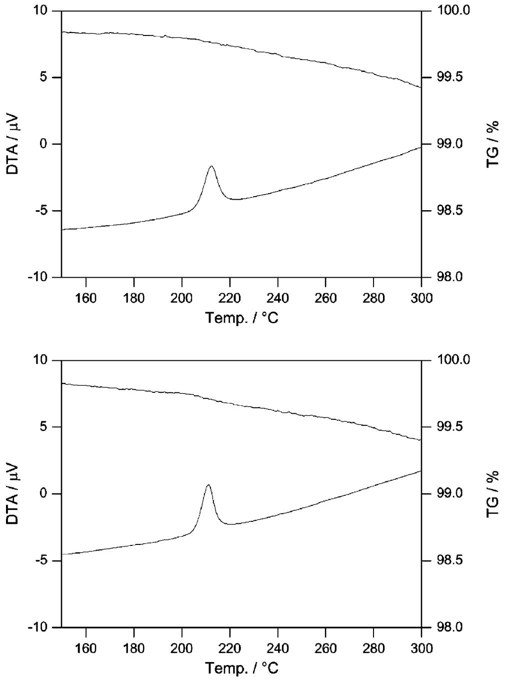

Fig. 2 TG and DTA curves for the ground 1 : 1 mixture of the crystalline powders of Λ-**1** and Δ-**1**. The upper curve in each figure is for TG. The lower curve is for DTA. The experiments were performed under a flow of dry nitrogen and heated at a rate of 10 °C min^{-1}. Top: the co-grinding was performed in a dry box under a flow of dry nitrogen. Bottom: the co-grinding was performed in air.

were nearly identical for the experiments under dry and atmospheric conditions.[9]

The transformation of the crystals was also followed by differential scanning calorimetry (DSC). At temperatures between 205 and 220 °C, the co-ground mixture of the Λ-**1** and Δ-**1** crystals showed an exothermic peak (Fig. 3a). This process was irreversible. The heat of transition was estimated to be 12.1 kJ mol^{-1}. The DSC peak was not very broad, which indicates that the crystallization proceeded at a considerably high rate.

When the DSC was measured for a mixture prepared by shaking separately ground powders of the Λ-**1** and Δ-**1** crystals, no exothermic peak was observed (Fig. 3b). This indicates that co-grinding was necessary to initiate the crystallization. Without heating, the PXRD pattern for the co-ground mixture did not change even after several hours and even days. Thus, heating was necessary to grow the crystals.

The formation of the racemic compound is not due to the racemization of molecules in each enantiomeric component crystal, but is a result of molecular rearrangement in the solid state to form new racemic crystals. This was proved by a similar grinding–annealing experiment using a mixture of Λ-[Os(phen)$_2$](PF$_6$)$_2$ (**2**) and Δ-**1** crystals, which produced pseudo-racemic compound crystals showing nearly the same X-ray diffraction pattern as the racemic compound crystals of **1**.[10] A HPLC analysis using a chiral stationary phase indicated that both species did not racemize at all upon heating at 250 °C. The product mixture contains only Δ-**1** and Λ-**2**. Thus, the product was a pseudo-racemic compound of Δ-**1** and Λ-**2**, but not a mixture of the racemic compounds of the Ru and Os complexes (see ESI†).

Two important properties of the crystals of the hexafluorophosphate salts of the tris(1,10-phenanthroline) transition metal complexes became clear based on the above results. Firstly, simply by grinding and annealing, co-crystals of the complexes with different metals can be obtained.[11] Secondly, pseudo-racemic compound crystals are preferred over the chiral crystals. Based on these properties, we may expect that the other type of reactions, *e.g.* the chirality transfer between different kinds of metal complexes, may also be possible in the solid state, if one of the complexes is optically labile. Experiments with this objective are now underway, and their results will soon be published elsewhere.

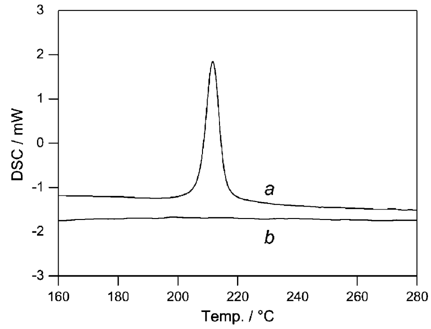

Fig. 3 DSC curve for the ground (a) and gently-shaken (b) 1 : 1 mixture of the dried crystalline powders of Λ-**1** and Δ-**1**. The experiments were performed under a flow of dry nitrogen and heated at a rate of 10 °C min^{-1}.

Notes and references

‡ X-Ray data for the single crystals were collected at 100 K or 298 K on a Bruker SMART APEX diffractometer with Mo–Kα radiation. Crystal data are summarized in Table S1 in the Electronic Supplementary Information.† SHELXS-97 and SHELXL-97[12] were used for structure solution. Mercury[13] and PyMOL[14] were used for graphical representation. CCDC 242567–249786. See http://www.rsc.org/suppdata/cc/b4/b409006c/ for crystallographic data in .cif or other electronic format.

§ Powder data for all samples were collected at rt on a Rigaku MultiFlex diffractometer with Cu–Kα radiation. For calculating the X-ray diffraction patterns based on the single crystal structural data, the Mercury program was used.

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8 The single-crystal structures are discussed in detail in Electronic Supplementary Information†.

9 For the powder co-ground in air, a significant weight loss was observed while the temperature was kept at 50 °C prior to heating. The constant weight obtained at 50 °C was set at 100%.

10 Both chiral and racemic crystals of **2** were isomorphous with the corresponding crystals of **1**. See Electronic Supplementary Information for details†.

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