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Asymmetric Induction by Retgersite, Nickel Sulfate Hexahydrate, in Conjunction with Asymmetric Autocatalysis

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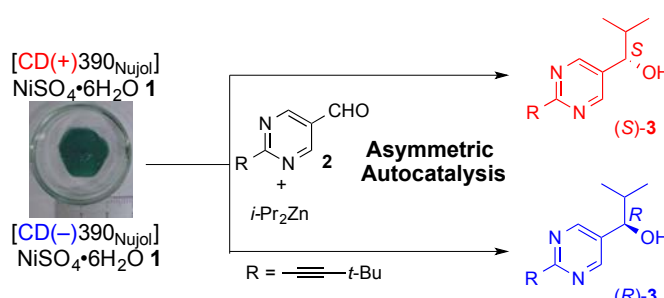
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Retgersite, nickel sulfate hexahydrate, forms a chiral crystal with space group $P4_12_12$ or $P4_32_12$. Chiral crystal of nickel sulfate hexahydrate was found to act as a chiral initiator of asymmetric autocatalysis, affording highly enantiomeric enriched pyrimidyl alkanols with the corresponding absolute configurations.

The origin of biological homochirality is of great interest to the scientific community and several possible origins for homochirality have been proposed.¹ Chiral inorganic crystals are considered to be one possible origin of homochirality because the inorganic minerals are considered to have existed widely on Earth before the emergence of life.^{2,3} Metal sulfates are one of the most abundant minerals on Earth, and the sulfate and metal ions are symmetric achiral ions.

Retgersite, nickel sulfate hexahydrate, is a naturally occurring mineral and exhibits enantiomorphism. Nickel sulfate forms various hydrate salts such as hexahydrate and heptahydrate depending on the crystallization conditions. The relatively stable α -form of hexahydrate has a chiral structure. The hexahydrate crystal **1**, crystallized at 31.5–53.3 °C,⁴ has a bright blue-green colour and has absorption bands in the visible light region; the optical properties of the crystal have been studied, including the chiral optical properties such as ORD and CD.⁵ The absolute structure, analyzed by X-ray and ORD spectra, of **1** was first reported in 1987 and detailed chiral optical properties of the crystal were measured recently by Asahi *et al.*⁶ The chiral optical properties of the chiral crystal of achiral nickel sulfate have thus attracted broad interest. However, to the best of our knowledge, usage of the chirality of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ in chemical reactions has not been realized. In this paper, we report asymmetric induction using chiral crystals of nickel sulfate hexahydrate in conjunction with asymmetric autocatalysis (Scheme 1).



Scheme 1. Asymmetric induction by chiral nickel sulfate hexahydrate and asymmetric autocatalysis.

Asymmetric autocatalysis is the reaction that the product act as an asymmetric catalyst for the reaction to form the product with the same structure and absolute configuration. We have been studying the asymmetric autocatalytic reaction of the pyrimidyl alkanol with amplification of enantiomeric excess.^{7–9} By using asymmetric autocatalyst, we have reported that various inorganic¹⁰ and organic¹¹ crystals act as chiral triggers for the asymmetric autocatalysis. Herein, we report chiral nickel sulfate hexahydrate crystal triggers asymmetric autocatalysis.

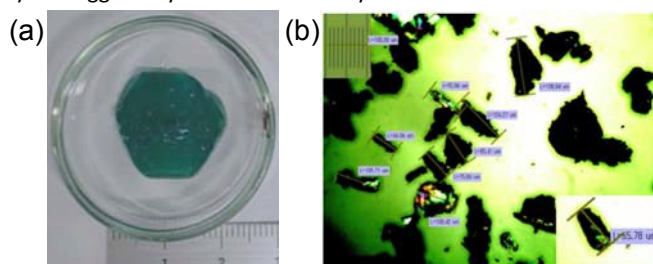


Figure 1. (a) Single crystal of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ **1** (b) ground powder-like crystal of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ **1**

The chiral single crystal of nickel sulfate hexahydrate was obtained by recrystallization. $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ **1** (25 g) was dissolved in distilled water (33 mL) at 70 °C and was kept for 12 h and the slow evaporation of water for 2–3 d at above 31.5 °C in a Petri dish to give a crystal of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ **1** of ca. 2 cm size (Figure 1). The solid state CD spectrum was measured with the powder crystal of **1** in Nujol. Although the base line of obtained CD spectrum was not flat

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due to the anisotropy of the crystal powders, the distinguishable signal was observed around 390 nm region (Figure 2b). The chirality of the crystal was determined by CD spectrum at 390 nm region and confirmed by the X-ray single crystal diffraction analysis using Flack parameter (Figure 2a).^{12,13} The $P4_12_12$ crystal exhibits the negative Cotton effect at 390 nm, and the $P4_32_12$ crystal exhibits the opposite positive Cotton effect at 390 nm.^{5,6}

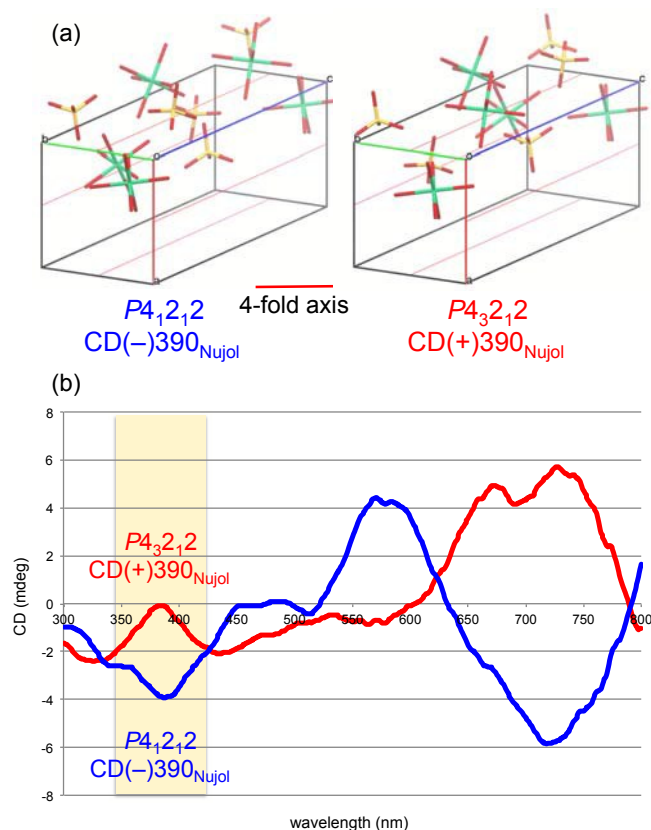


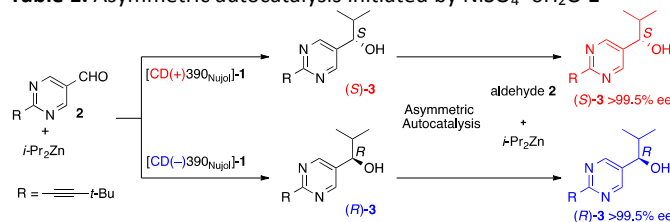
Figure 2. (a) Crystal structure of the $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ (b) CD spectrum of the $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ (powder, Nujol mull)

Using these chiral crystals of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ **1** as chiral initiator, asymmetric autocatalysis of diisopropylzinc ($i\text{-Pr}_2\text{Zn}$) and pyrimidine-5-carbaldehyde **2** was performed.¹⁴ Thus, chiral crystal of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ **1** was ground with agate and mortar, then was mixed immediately with pyrimidine-5-carbaldehyde **2** and used for the reaction before the progress of the dehydration of the crystal. By adding $i\text{-Pr}_2\text{Zn}$ slowly, addition reaction was performed in combination with asymmetric autocatalysis with amplification of enantiomeric excess (ee). After the purification, the enantiomeric excess of the formed pyrimidyl alkanol **3** was determined by HPLC using chiral column.

The results are summarized in Table 1. As shown in Entry 1, (*S*)-pyrimidyl alkanol **3** was obtained in the presence of a chiral crystal of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ with positive Cotton effect at 390 nm [$\text{CD}(+)390_{\text{Nujol}}$]. On the other hand, (*R*)-**3** was obtained in the presence of a chiral crystal of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ with negative Cotton effect [$\text{CD}(-)390_{\text{Nujol}}$] (entry 2). Although the yields and ees were not so high probably due to the heterogeneous conditions with the existence of crystallization water, the sense of enantioselectivity exhibits good

reproducibility for the several different crystal samples. It should be noted that the ee of the formed alkanol **3** was amplified to near enantiomerically pure (>99.5% ee) during the subsequent asymmetric autocatalysis (Entries 1 and 2).

Table 1. Asymmetric autocatalysis initiated by $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ **1**



Entry	Crystal 1 CD390 nm _{Nujol}	Pyrimidyl alkanol 3 yield (%)	ee (%) ^d	Amplification of asymmetric autocatalysis ^c yield (%)	ee (%) ^d	ee by asymmetric autocatalysis ^c Config.
1 ^a	(+)	27	3	77	50 (>99.5) ^e	<i>S</i>
2 ^a	(-)	28	3	72	37 (>99.5) ^e	<i>R</i>
3 ^a	(+)	81	9	72	28	<i>S</i>
4 ^a	(+)	27	2	78	76	<i>S</i>
5 ^a	(+)	27	5	74	95	<i>S</i>
6 ^a	(-)	37	6	80	91	<i>R</i>
7 ^b	(+)	14	4	85	53	<i>S</i>
8 ^b	(-)	30	4	73	68	<i>R</i>

^a Reaction conditions: Molar ratio, **1** : **2** : $i\text{-Pr}_2\text{Zn}$ = 16 : 1 : 3 in toluene at 0 °C, and additional **2** : $i\text{-Pr}_2\text{Zn}$ = 2 : 4 and 8 : 16 were added stepwise. ^b Reaction conditions: Molar ratio, **1** : **2** : $i\text{-Pr}_2\text{Zn}$ = 32 : 1 : 9 in toluene at 0 °C, and additional **2** : $i\text{-Pr}_2\text{Zn}$ = 2 : 12 and 8 : 48 were added stepwise. ^c Asymmetric autocatalytic reaction with obtained alkanol after removing the $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$. ^d The ee value was determined by HPLC on a chiral stationary phase. HPLC conditions: CHIRALPAK IB (4.6 mmφ×250 mm), 5% 2-propanol in hexane, 1.0 mL/min, 254 nm, r.t., retention time (min) 10.3 for (*S*)-**3**, 13.9 for (*R*)-**3**. ^e After additional **2** to 5 rounds of asymmetric autocatalytic reaction.

We have demonstrated, by using asymmetric autocatalysis of pyrimidyl alkanol, the chiral natural mineral of Retgersite $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ induces the chirality of the chiral organic compound with high ee. These results suggest that common inorganic sulfate minerals on Earth may have acted as the origin of chirality of the chiral organic compounds.

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- The Flack x determined using quotients [(+)-(I-)]/[+(+)+(I-)] method. For P4₂2₁ is 0.025(5) and 0.044(7) for P4₃2₁.
- Typical experimental procedure (Table 1, Entries 1-6): A crystal of nickel sulfate hexahydrate **1** was ground by a pestle and mortar (particle size estimated from microscope images = 66-140 μm). Toluene solution of *i*-Pr₂Zn (0.15 mL, 0.15 mmol) was added dropwise at 0 °C with stirring to a mixture of powder-like crystal **1** (0.21 g, 0.80 mmol) and aldehyde **2** (9.4 mg, 0.050 mmol) in the presence of toluene (0.50 mL). After stirring overnight at 0 °C, toluene (1.0 mL) was added to the mixture. Then toluene solution of *i*-Pr₂Zn (0.20 mL, 0.20 mmol) and toluene (0.5 mL) solution of aldehyde **2** (19 mg, 0.10 mmol) were added dropwise alternately over a period of 1 h. After stirring for 4 h at 0 °C, toluene (1.5 mL) was added, then toluene solution of *i*-Pr₂Zn (0.80 mL, 0.80 mmol) and toluene (1.0 mL) solution of **2** (75 mg, 0.40 mmol) were added dropwise alternately over a period of 2 h, and the mixture was stirred overnight. The reaction was quenched with a mixed solution (14 mL) of saturated aq. ammonium chloride and aq. ammonia (sat. NH₄Cl : 30% NH₄OH = 2 : 1 (v/v)). The resulting mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. Purification of the residue by silica gel column chromatography gave 5-pyrimidyl alkanol **3**. Further asymmetric autocatalysis using the obtained alkanol **3** was performed to amplify the enantiomeric excess.