Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule

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THE homochirality of natural amino acids and sugars remains a puzzle for theories of the chemical origin of life[1–18]. In 1953 Frank[7] proposed a reaction scheme by which a combination of autocatalysis and inhibition in a system of replicating chiral molecules can allow small random fluctuations in an initially racemic mixture to tip the balance to yield almost exclusively one enantiomer. Here we show experimentally that autocatalysis in a chemical reaction can indeed enhance a small initial enantiomeric excess of a chiral molecule. When a 5-pyrimidyl alkanol with a small (2%) enantiomeric excess is treated with diisopropylzinc and pyrimidine-5-carboxaldehyde, it undergoes an autocatalytic reaction to generate more of the alkanol. Because the reaction involves a chiral catalyst generated from the initial alkanol, and because the catalytic step is enantioselective, the enantiomeric excess of the product is enhanced. This process provides a mechanism by which a small initial imbalance in chirality can become overwhelming.

In earlier studies of asymmetric autocatalytic reactions[19–21], the enantiomeric excess (e.e.) of chiral products has always been lower than that of the chiral catalysts. In our studies[22] of the enantioselective addition of dialkylzincs to aldehydes using chiral β-aminoalcohols[23,24] and piperazines[25], we have discovered that the pyrimidine-containing secondary alcohol, 2-methyl-1-(5-pyrimidyl)propan-1-ol (**1**), is an efficient asymmetric autocatalyst. We find that with only a small e.e., (*S*)-**1** catalyses the enantioselective addition of diisopropylzinc to pyrimidine-5-carboxaldehyde (**3**) (ref. 26) to yield (*S*)-**1** with significantly higher enantiomeric enrichment.

When a mixture with 5% e.e. of (*S*)-**1** (*S*-isomer: *R*-isomer = 52.5 : 47.5) was treated as an asymmetric autocatalyst (20 mol%) with aldehyde **3** and diisopropylzinc, pyrimidyl alcohol (*S*)-**1** was obtained with a 62% yield as a mixture of the newly formed product **1** and the catalyst (*S*)-**1** (run A1; Table 1). The amount of (*S*)-**1** in the catalyst increased by a factor of 4.1. It is surprising that the enantiomeric excess of the mixture of the newly formed product **1** and the catalyst **1** has increased to 39% (*S*-isomer: *R*-isomer = 69.5 : 30.5) (Fig. 1). This shows that (*S*)-**1** with 55% e.e. (note; >5% e.e.) was newly formed in 42% yield as a result of the asymmetric autocatalytic reaction of catalyst (*S*)-**1** (Table 1, run A1; Fig. 1). The reaction was performed successively, with the products of one round serving as the reactants for the next, resulting in an overwhelming imbalance between the two stereo isomers (Table 1).

In a similar manner, starting from the chiral catalyst (*S*)-**1** with even lower enantiomeric excess (2% e.e., *S*-isomer: *R*-isomer = 51 : 49) (20 mol%), asymmetric autocatalytic reaction of **1** and the amplification of the e.e. of **1** are also observed (series B in Table 1, runs 1–5). The e.e. of (*S*)-**1** has increased successively from 2% to 10%, 57%, 81% and 88% (runs 1–5). The amount of (*S*)-**1** of the initial catalyst (2% e.e., run B1) has increased by the factor of 942 times (run B5). When (*S*)-**1** with 88% e.e. was employed as asymmetric autocatalyst, the e.e. of the mixture of catalyst and the product was also 88% (run B5). Thus in series A and B, the low e.e. of (*S*)-**1** was autocatalytically amplified to 88–89%, and the amount of (*S*)-**1** was increased by a factor of 942 and 1,674.

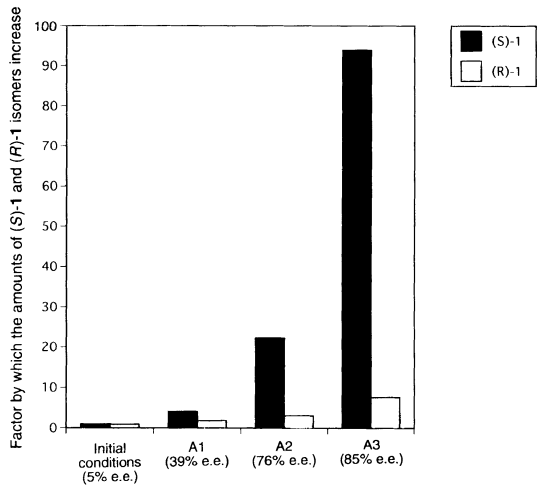

FIG 1. Asymmetric autocatalysis of chiral pyrimidyl alkanol (**1**). Runs A1–3 correspond to Table 1. The enantiomeric excess of (S)-**1** increases from 5 to 89% e.e. without the use of additional chiral auxiliaries. During the reactions (runs A1–3), the (S)-**1** increases by a factor of 94 times, while (*R*)-**1** increases by a factor of only eight times.

On the other hand, when the opposite enantiomer, (*R*)-**1**, with 10% e.e. was employed as an asymmetric autocatalyst, the *R*-enantiomer of the mixture of the catalyst and the newly formed **1** was obtained in comparable enantiomeric excess (53% e.e.) (run C1; Table 1). When the asymmetric autocatalyst was (*R*)-**1** with 30% e.e., (*R*)-**1** increased to yield a mixture of the catalyst and the product with 72% e.e. (run C2). In addition, the enantioselectivity of a racemic **1** as autocatalyst was below the detection level (run D; Table 1). These results show that the configurations of the asymmetric autocatalyst, (*S*)- or (*R*)-**1**, determine the configuration of the product, (*S*)- or (*R*)-**1**. In other words, (*S*)- or (*R*)-**1** do work as asymmetric autocatalysts.

We propose the following reaction scheme for asymmetric autocatalysis of (*S*)-**1** (Fig. 2). Pyrimidyl alcohol (*S*)-**1** reacts with an equimolar amount of diisopropylzinc to form *in situ* the chiral isopropylzinc alkoxide **2** (characterized by proton NMR). Compound **2** catalyses the enantioselective addition of diisopropylzinc to aldehyde **3** to yield **2** with increased e.e. Subsequent

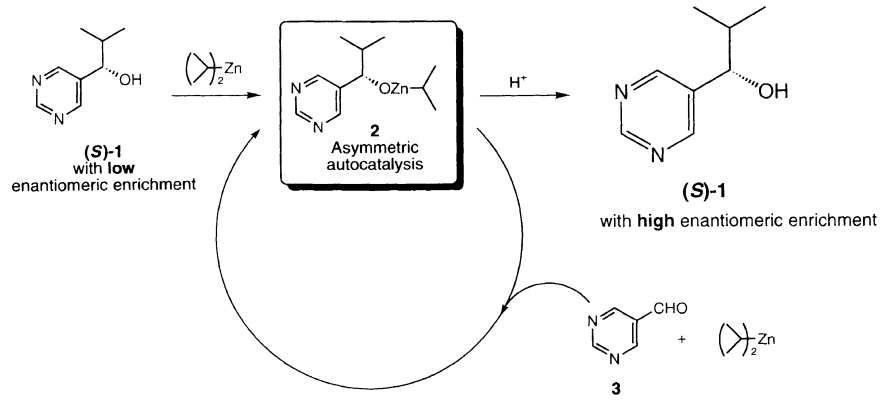

FIG. 2 Proposed reaction scheme of asymmetric autocatalysis of (S)-**1**.

TABLE 1 Asymmetric autocatalysis of chiral pyrimidyl alcohol **1**

Run*	Catalyst **1** (% e.e.)	Time (h)	Mixture of catalyst (**1**) and product **1** Yield (%)	Mixture of catalyst (**1**) and product **1** e.e. (%)	Factor by which the amount of (S)-**1** has increased	Newly formed product **1**† Yield (%)	Newly formed product **1**† e.e. (%)
Series A‡							
A1	5 (S)	74	62	39 (S)	4.1	42	55 (S)
A2	39 (S)	60	86	76 (S)	22	66	87 (S)
A3	76 (S)	68	80	85 (S)	94	60	88 (S)
A4	85 (S)	66	86	89 (S)	413	66	90 (S)
A5	89 (S)	60	81	89 (S)	1,674	61	90 (S)
Series B‡							
B1	2 (S)	74	46	10 (S)	2.5	26	16 (S)
B2	10 (S)	91	75	57 (S)	13	55	74 (S)
B3§	57 (S)	96	80	81 (S)	61	60	89 (S)
B4	81 (S)	70	75	88 (S)	239	55	90 (S)
B5	88 (S)	77	79	88 (S)	942	59	88 (S)
Series C							
C1	10 (*R*)	70	81	53 (*R*)		61	67 (*R*)
C2	30 (*R*)	65	79	72 (*R*)		59	86 (*R*)
Run D	Racemate	55	68	BDL‖		48	BDL‖

* Molar ratio. Pyrimidine-5-carboxaldehyde (**3**): diisopropylzinc: catalyst **1** = 1 : 1.2 : 0.2. All reactions were reproducible.

† The amount of pyrimidyl alcohol **1** after subtracting that of **1** used as a catalyst from that of total pyrimidyl alcohol.

‡ In each series, the mixture of catalyst and the newly formed product are used as a catalyst of the next run.

§ As an example, details of the experimental procedure, and of the calculation of yield and e.e. are given for run B3. Pyrimidyl alcohol **1** (31.7 mg (0.208 mmol), 57% e.e., containing (S)-**1** (24.9 mg) and (*R*)-**1** (6.8 mg) in toluene (49 ml) and diisopropylzinc (1.2 ml of 1 M toluene solution, 1.2 mmol) was stirred for 20 min at 0 °C, and then a toluene solution (1.8 ml) of pyrimidine-5-carboxaldehyde (**3**) (112.7 mg, 1.04 mmol) (ref. 26, purified by sublimation) was added at 0 °C. This reaction mixture was stirred for 96 h at 0 °C, and was then quenched by the addition of 1.0 M hydrochloric acid (5 ml) and saturated aqueous sodium hydrogen carbonate (15 ml) at 0 °C. The mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate and allowed to evaporate until dry. Purification of the crude product using thin-layer chromatography yielded pyrimidyl alcohol **1** (127.3 mg)—a mixture of the newly formed alcohol and the catalyst alcohol (31.7 mg). Analysis of the product by high-performance liquid chromatography using a chiral column (Daicel Chiralcel OD) showed it has 81% e.e. (see run B3); it therefore must consist of (S)-**1** (115.4 mg) and (*R*)-**1** (11.9 mg). The amount of newly formed alcohol **1** is 127.3 − 31.7 = 95.6 mg (0.628 mmol, 60% yield), which consists of (S)-**1** (115.4 − 24.9 = 90.5 mg) and (*R*)-**1** (11.9 − 6.8 = 5.1 mg). The newly formed alcohol thus has an enantiomeric purity of 89% e.e.

‖ Below the detection level.

hydrolysis of **2** gives (*S*)-**1** with amplified e.e. (Fig. 3). Even when the catalyst has an e.e. of just 5%, the newly formed product (that is, **1**) had enantiomeric excess of 55%.

It seems conceivable that the reaction reported here may be an example of the scheme proposed by Frank[7]. The symmetry breaking by spontaneous crystallization reported by Kondepudi[27], which involves indirect inhibition, is the only other possible experimental realization of this scheme so far, and that involved physical rather than chemical processes. But the detailed mechanism of the autocatalytic steps in our reaction, and in particular, whether an inhibitory mechanism is present, remains to be clarified. □

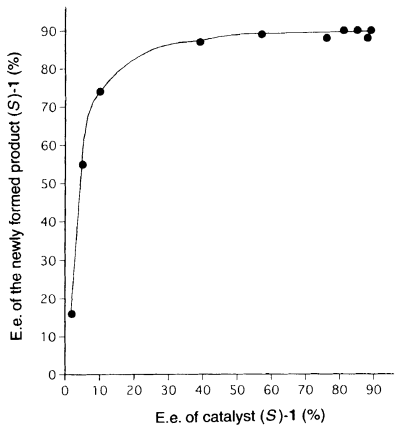

FIG. 3 Relation between the enantiomeric excess (e.e.) of catalyst (S)-**1** and that of the newly formed product (S)-**1** in asymmetric autocatalytic reaction of (S)-**1**.

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