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A Few Molecules Can Control the Enantiomeric Outcome. Evidence Supporting Absolute Asymmetric Synthesis Using the Soai Asymmetric Autocatalysis

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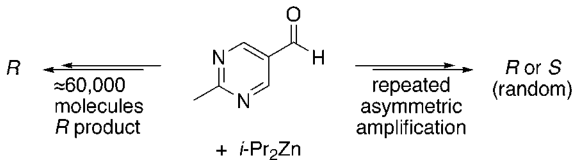
ABSTRACT



Experiments were carried out to investigate whether the Soai asymmetric autocatalysis can accomplish true absolute asymmetric synthesis. In 54 reactions, *R* and *S* enantiomeric products were obtained 27 times each. Of 25 pairs of side-by-side identical reactions, 12 afforded opposite enantiomers. In a test of the mechanistic viability of a random-chance process, it was found that a very few molecules (approximately 60 000) were sufficient to control the enantiomeric outcome of these reactions. These observations appear most consistent with asymmetric synthesis originating from the chance enantiomeric excess in a racemate.

Under limited circumstances, optically active material may be prepared from achiral starting materials in the absence of optically active catalysts or reagents. One way is through processes involving crystallizations, taking advantage of chance seeding events.[1,2] Another approach is the use of asymmetric external physical forces, such as circularly polarized light.[3−5] Such processes are described as "spontaneous" or "absolute" asymmetric synthesis.[6−8]

For over a century, there has been discussion of whether simple chemical reactions in solution could afford optically active products in the absence of external forces or crystallization processes.[9,10] Any normal "racemic mixture" will have an unequal mixture of enantiomers, deviating from 50:50 with a standard deviation of $(n^{1/2})/2$ for n molecules. However, such undetectable enantiomeric excesses (ee's) are in practice equivalent to achirality,[11] and experimentally observable absolute asymmetric synthesis is often considered impossible in a homogeneous closed system.

Soai has recently reported landmark results suggesting that optically active material can be produced by simple reaction

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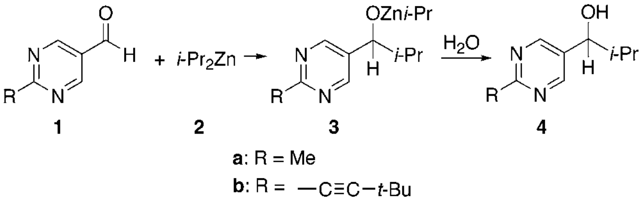
chemistry, involving asymmetric amplification of the random-chance ee in a racemate.[12] The process generating optical activity employs Soai's extraordinary asymmetric autocatalysis reactions.[13] In these reactions, the chiral product **3** from the addition of diisopropyl zinc (**2**) to pyrimidines **1** is a catalyst for its own formation, and the kinetics are such that the ee in **3** can increase greatly as the reaction proceeds. In this way, small ee's in **3** are amplified, and repeated amplifications can transform ee's as low as 10^{-5}% up to high ee's.[14] In the absence of any discrete optically active additives, Soai carried out 37 reactions of **1b** with **2** in a ~80:20 ether/toluene solvent mixture with "new and clean equipment," for which 19 of the reactions afforded the *S* enantiomer of **4b** and 18 afforded the *R* enantiomer. Soai concluded carefully, "The stochastic behavior ... reported here constitutes one of the conditions necessary for spontaneous asymmetric synthesis."



In our earlier attempts to apply this procedure to absolute asymmetric synthesis, the outcome had been dominated by trace optically active impurities.[14] If the optical activity had arisen by amplification of an initial random-chance ee, the enantiomer obtained should have varied randomly from reaction to reaction. We found that reactions in benzene or toluene afforded a decidedly nonrandom distribution of enantiomers.

For reactions using diethyl ether as solvent, our observations were different. In three cases, side-by-side pairs of reactions using identical batches of solvent and reagent afforded opposite enantiomers![14a]

However, we felt that there were at least two reasons to doubt that the reactions in ether or ether/toluene are true examples of absolute asymmetric synthesis. First, there is no way to exclude the possibility that optically active impurities are present in all of these reactions.[15] Since we were unable to purify materials for reactions in toluene or benzene sufficiently, there was no reason to expect absolute purity for reactions in ether.[16] Second, high ee in these reactions is observed surprisingly quickly. Our reactions in ether here afford discernible ee in at most four amplifications, and the Soai system affords high ee's within two. This would seem to require exceptionally large asymmetric amplifications in ether. The amplification of 10^{-5}% ee to high ee is still very far from amplifying 0% ee to high ee. By what mechanism could high ee ensue so quickly without a chiral influence playing a role?

In a total of 54 reactions employing only **1a** and **2** in ether, we have obtained the *R* enantiomer of **4a** 27 times and the *S* enantiomer 27 times.[17] If it is hoped to distinguish a random process (which must give a 1:1 ratio) from control by impurities (which may not give a 1:1 ratio), the significance of the necessarily limited number of results should not be overestimated. With 95% confidence, the "true" ratio of *R*:*S* for this experiment (the ratio obtained with infinite repetitions) is between 1:1.7 and 1.7:1. This does not convincingly exclude control by random impurities. Somewhat more swaying is the observation that out of 25 pairs of side-by-side reactions using identical reagents, 12 afforded opposite enantiomers and 13 afforded the same enantiomer. If impurities were the ultimate source of the optical activity, it would seem unusual for the paired reactions to not show a propensity to afford the same enantiomer.[18]

Mechanistically, for asymmetric autocatalysis to lead to high ee's so quickly, it must be proposed that the asymmetric amplification in the initial reaction is exceptionally large. This could occur only under special mechanistic circumstances: (1) The uncatalyzed (or achirally catalyzed) reaction of **1** with **2** would have to be much faster than reactions catalyzed by optically active impurities or surfaces. (2) The uncatalyzed reaction has to be much slower than the reaction catalyzed by optically active product.

The effect of these conditions would be to allow the reaction, during its apparent induction period,[19] to generate a random mixture of a few product molecules. These few could then dominate further product production. For example, a typical outcome when 10 000 product molecules are formed by a random uncatalyzed process would be the formation of 4950 *R* molecules and 5050 *S* molecules (1% ee). If reaction catalyzed by these few product molecules outpaced the uncatalyzed process, high ee could rapidly ensue.

This mechanism critically hinges on the ability of a very few optically active product molecules to dominate the outcome of these reactions. To test this, solutions of optically active **4a** at extremely low concentrations in ether were prepared by serial dilution.[20] Reactions of **1a** with **2** initiated in these solutions were then subjected to repeated amplifica-

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(15) In our view, absolute asymmetric synthesis is not automatically precluded by the (likely unavoidable) presence of optically active impurities, so long as the optical activity arises as a first cause from random chance rather than the impurities or other asymmetric influences.

(16) In the Soai work, the same reactions that afforded a stochastic mixture of enantiomers in ether/toluene led to nonrandom results in toluene alone.

(17) In chronological order, the enantiomer obtained from ether reactions containing no additives has been: *R*,*S*,(*R*,*S*),(*R*,*S*),*R*,(*R*,*S*),(*R*,*S*),(*S*,*S*),(*R*,*R*),(*R*,*R*),(*R*,*S*),(*R*,*S*),(*R*,*R*),(*R*,*R*), (*R*,*R*),(*R*,*S*),*S*,*S*,(*S*,*S*),(*S*,*S*),(*R*,*S*),(*S*,*S*),(*R*,*S*),(*S*,*S*),(*R*,*S*),(*S*,*S*),(*R*,*S*),*R*, (*R*,*R*),(*R*,*S*). Sets of reactions in parentheses were carried out side-by-side using identical batches of starting materials.

(18) A plausible alternative to random chance was that the product enantiomer could be controlled by the surface of the flask having a net optical activity. However, records kept of the enantiomer obtained from particular flasks show no sign of a "memory effect", that is, the same initial flask may afford either enantiomer in an apparently random pattern.

(19) Sato, I.; Omiya, D.; Tsukiyama, K.; Ogi, Y. Soai, K. *Tetrahedron: Asymmetry* **2001**, *12*, 1965.

Table 1. Results from Replicative Asymmetric Amplifications in Ether, with or without Optically Active Product **4a** as Additive[a]

trial	additive[b]	result[c]	trial	additive[b]	result[c]	trial	additive[b]	result[c]
1	none	$S^{f,h}$	28	none	R^{f}	55	none	S^{f}
2	none	R^{f}	29	10^{-16} M *R*	$R^{f,h}$	56	10^{-22} M *S*	$S^{f,h}$
3	10^{-2} M *S*	S^{d}	30	10^{-16} M *R*	R^{f}	57	10^{-22} M *S*	S^{f}
4	10^{-4} M *S*	S^{d}	31	none	S^{f}	58	none	R^{f}
5	10^{-6} M *S*	$S^{e,h}$	32	none	S^{f}	59	none	S^{f}
6	10^{-8} M *S*	S^{f}	33	10^{-16} M *R*	$R^{e,h}$	60	10^{-22} M *R*	$R^{g,h,i}$
7	10^{-10} M *S*	$S^{f,h}$	34	10^{-16} M *R*	R^{e}	61	10^{-22} M *R*	$S^{g,i}$
8	10^{-12} M *S*	S^{f}	35	none	R^{e}	62	none	$S^{g,i}$
9	10^{-14} M *S*	S^{f}	36	10^{-16} M *R*	$R^{f,h}$	63	10^{-22} M *R*	$S^{f,h}$
10	none	$S^{f,h}$	37	10^{-16} M *R*	R^{f}	64	10^{-22} M *R*	S^{f}
11	none	S^{g}	38	none	S^{f}	65	none	R^{f}
12	10^{-16} M *S*	$S^{e,h}$	39	none	S^{f}	66	none	S^{f}
13	none	R^{f}	40	10^{-22} M *S*	$R^{g,h}$	67	10^{-22} M *R*	$S^{e,h,i}$
14	none	R^{g}	41	10^{-22} M *S*	R^{g}	68	10^{-22} M *R*	$R^{f,i}$
15	10^{-16} M *S*	$S^{e,h}$	42	none	R^{g}	69	none	$S^{e,i}$
16	none	R^{f}	43	none	R^{g}	70	none	$R^{g,h}$
17	none	R^{g}	44	10^{-22} M *S*	$S^{e,h}$	71	none	R^{g}
18	10^{-16} M *S*	$S^{e,h}$	45	10^{-22} M *S*	S^{e}	72	none	$S^{f,h}$
19	none	R^{g}	46	none	S^{e}	73	none	S^{f}
20	none	S^{f}	47	none	R^{e}	74	none	$R^{f,h}$
21	10^{-16} M *R*	$R^{f,h}$	48	10^{-22} M *S*	$R^{f,h}$	75	none	R^{f}
22	10^{-16} M *R*	R^{f}	49	10^{-22} M *S*	S^{e}	76	none	$S^{f,h}$
23	none	S^{f}	50	none	S^{f}	77	none	R^{f}
24	none	S^{f}	51	none	R^{f}	78	none	$R^{f,h}$
25	10^{-16} M *R*	$R^{f,h}$	52	10^{-22} M *S*	$S^{f,h}$	79	none	S^{g}
26	10^{-16} M *R*	R^{f}	53	10^{-22} M *S*	S^{f}	80	none	$R^{f,h}$
27	none	S^{f}	54	none	S^{f}	81	none	R^{f}

[a] Trials employed the procedure of ref 21. The trials are not listed in chronological order. See ref 17. [b] *R* or *S* refer to solutions containing 88% ee of the *R* enantiomer of **4a** or 90% ee of the *S* enantiomer of **4a**, respectively. Concentrations of **4a** are approximate theoretical values (see ref 20) in the initial reaction mixture. [c] Major enantiomer of **4a** obtained after amplifications. [d] Enantiomeric excess observed after 1st amplification. [e] Enantiomeric excess observed after 2nd amplification. [f] Enantiomeric excess observed after 3rd amplification. [g] Enantiomeric excess observed after 4th amplification. [h] Sets of trials 1−4, 5/6, 7−9, 10/11, 12−14, 15−17, 18−20, 21−24, 25−28, 29−32, 33−35, 36−39, 40−43, 44−47, 48−51, 52−55, 56−59, 60−62, 63−66, 67−69, 70/71, 72/73, 74/75, 76/77, 78/79, 80/81 were carried out side-by-side using identical batches of starting materials. [i] Reaction in Teflon flask.

tion until measurable enantiomeric excess was observed.[21] To guard against the impact of catalytically significant optically active impurities, side-by-side sets of reactions in the presence and absence of **4a** were carried out using otherwise identical reagents and solvent. The results are summarized in Table 1.

In 13 out of 13 reactions carried out in the presence of 10^{-16} M optically active **4a** (∼60,000 molecules in a ∼1 mL reaction, theoretically[20]), the major enantiomer observed after two to four amplifications was the same as that of the initial **4a**. Simultaneous reactions lacking **4a** afforded a mixture of enantiomers. In an important control study, the solutions of **4a** were diluted to a theoretical 10^{-22} M, so that a ∼1 mL reaction volume would contain on average 0.06 molecules of **4a**. These reactions also afforded a mixture of enantiomers.

The significance of this set of experiments is that it places severe limitations on alternative hypotheses. If random chance is not the ultimate source of the observed optical activity, then the optical activity must arise from either optically active agents within the reaction (e.g., impurities or the surface of the flask) or external chiral forces. Whatever the nature of such a hypothetical “chiral influence” on these reactions, it would have to be overwhelmed by 10^{-16} M **4a** and yet afford a random distribution of enantiomeric products in the absence of **4a**. This is not inconceivable, but in our view the most economical explanation at this time is that both our reactions in ether and the Soai reactions in ether/toluene are affording optical activity based on amplification of the random-chance excess of one enantiomer in the initial “racemic” product.

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(20) (a) It should be noted that the solution concentrations obtained by serial dilution are, at very low concentrations, *theoretical*, that is, not experimentally verified (or readily verifiable). It would be quite possible for adsorption of the solute to the surface of the flasks to result in concentrations that are much lower than theoretically expected. However, the results obtained are consistent with the theoretical concentrations. (b) Procedure for dilutions: A series of prewashed and oven-dried vials were rinsed with purified diethyl ether. In the first vial, a 10^{-2} M solution of **4** in ether was prepared using 8.7 mg (0.05 mmol) of **4** in 5 mL of ether. Sequential dilutions were then prepared in new vials adding 100 μL of solution and 9.9 mL of purified ether by syringe. After each use, syringes were rinsed at least 10 times.

(21) In a typical procedure, a 25-mL flask was charged sequentially with 0.1 mmol of **1**, 1.0 mL of ether, and 10 μL of 10^{-14} M **4** (90% ee of the *S* enantiomer) and cooled to 0 °C, and 0.2 mL of 1.14 M **2** in ether was added. The reaction was stirred at 0 °C for 4 h and allowed to warm slowly to 25 °C. A 100-μL aliquot of this solution was then added to a new flask containing 0.1 mmol of **1** and 1.0 mL of ether at 0 °C, and 0.2 mL of 1.14 M **2** in ether was added. After 4 h at 0 °C and 2 h at 25 °C, the mixture was subjected to a standard aqueous workup, and the ee of the *S* enantiomer in the crude product was 24% (NMR, Eu(hfc)$_3$).