J|A|C|S
COMMUNICATIONS

Published on Web 08/06/2002

Enantioselective Synthesis without Discrete Optically Active Additives

Daniel A. Singleton* and Loan K. Vo

Department of Chemistry, Texas A&M University, PO Box 30012, College Station, Texas 77842

Received May 31, 2002

Absolute asymmetric synthesis is the formation of optically active materials from achiral starting materials in the absence of optically active reagents or catalysts.[1,2] All successful approaches to absolute asymmetric synthesis have either involved crystallization or have used the photons of circularly polarized light as chiral reagents. Chemists often believe that the formation of optically active materials from only achiral starting materials in a closed homogeneous reaction is impossible. It is not;[3] in fact, any synthesis of a racemic mixture will by random chance produce an average excess of $n^{1/2}$ molecules of one enantiomer out of an *n*-molecule "racemate."[3a] However, absolute asymmetric synthesis is only meaningful if the optical activity is observable, and this has never been achieved in a homogeneous closed system.

We have been attempting absolute asymmetric synthesis by the repeated asymmetric amplification of the small enantiomeric excess (ee) generated by chance in an initial racemate. These experiments have failed, thus far, but in a way that we did not anticipate. We are reporting our results because they provide focus for problems in absolute asymmetric synthesis, because they involve novel experimental challenges and probes, and because the results have implications toward both asymmetric amplification reactions and the origin of biological homochirality.

We have adapted the remarkable asymmetric autocatalysis reactions of Soai[4] to achieve replicative growth in enantiomeric excess. For the reaction of 2-methylpyrimidine-5-carboxaldehyde (**1**) with diisopropyl zinc (**2**), series of reactions on the same scale were carried out by taking either 2.5 or 10% of the product mixture containing **3** from each completed reaction and adding it to a new flask along with only **1**, **2**, and the solvent (toluene, benzene, or diethyl ether). Thus, the ee formed in an initial reaction (the "first generation") is used as catalyst for a second reaction, the ee formed in this second generation is used as catalyst for the third reaction, and so on (Figure 1). In this way, small enantiomeric excesses may be quickly multiplied to an arbitrary extent. For example, when 10 mol % of nearly racemic pyrimidylcarbinol **4**, prepared with an ee of the *R* enantiomer of only 0.00003%, was added to the initial reaction, the product ee grows to 71% of the *R* enantiomer by the end of the fourth generation.

We reasoned that the replicative process should ultimately lead to observable optical activity even when no additives are included. For the first nanomole ($n = 6 \times 10^{14}$) of "racemic" product formed from an uncatalyzed process at the beginning of a new reaction, there will by random chance be an average of 2×10^7 molecules ($n^{1/2}$) excess of one enantiomer (0.000004% ee). Due to the asymmetric autocatalysis, such excesses should increase with time and with each generation, just as in the experiment above where enantiomeric excess was added discretely.

Indeed, in 48 trials of this process, each one has ultimately afforded substantial optical activity in the product. For example,

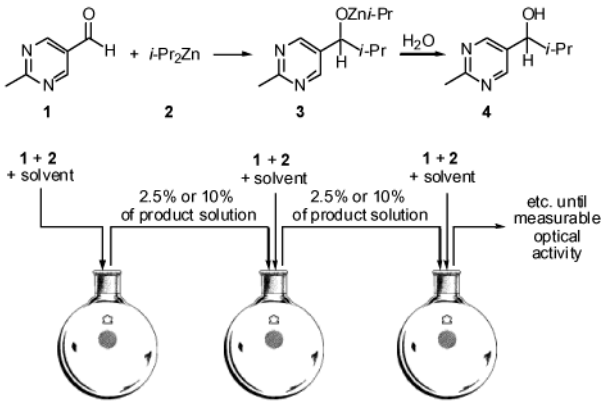

Figure 1. Process for replicative asymmetric amplification.

in an experiment where the process of Figure 1 was carried out at 0.1 M in toluene at 0 °C, an ee of 22% of the R enantiomer of **4** was observed at the end of the fourth generation. These trials afforded optical activity despite considerable effort to purify reagents and avoid experimental contamination with dust. The presence versus absence of ambient room light and the use of Teflon reaction vessels made no apparent difference in these reactions.

However, there is substantial evidence that most (and likely all) of these reactions are not true examples of absolute asymmetric synthesis. When series of reactions were carried out using the same batches of starting materials and solvent, they almost invariably afforded the same enantiomer. Indeed, the first nine trials all afforded the *S* enantiomer of **4**. These results strongly suggest that the ultimate optical activity arises from optically active impurities.

Although efforts to detect the optically active impurities in these reactions were not successful, their nature can be probed experimentally. For example, a key question was whether the major optically active impurities were homogeneous contaminants of the starting materials and solvent or else heterogeneous contaminants arising from dust or the reaction flask surfaces or introduced from syringes. This was tested repeatedly by running pairs of trials side by side using the same batches of reagents and solvent for the pair. In 12 out of 15 pairs of trials under various conditions (Table 1), the same enantiomer was formed at the same generation, usually with approximately the same ee. This suggests that the major source of optical activity is homogeneous in the starting materials. In other experiments, pairs of reactions used different batches of one reagent while leaving the others unchanged (e.g., trials 6/7). The general observation has been that changing the batch of solvent makes a difference between pairs of trials, while changing the batch of **1** or **2** makes little or no difference. This supports the conclusion that the major optically active impurities arise from the solvent.

Spiking reactions with trace amounts of terpenol or amino acid contaminants resulted in the rapid onset of product optical activity.

* Corresponding author. E-mail: singleton@mail.chem.tamu.edu.

10.1021/ja027129o CCC: $22.00

Table 1. Results from Trials of Replicative Asymmetric Amplification without Discrete Optically Active Additives

trial[a]	% ee[b]	trial[a]	% ee[b]	trial[a]	% ee[b]
1[c]	16 *S*[k]	17[g,i,u]	65 *S*[m]	33[e,s,u]	21 *S*[l]
2[c,t]	11 *S*[k], 78 *S*[l]	18[g,i,u]	70 *S*[m]	34[e,s,u]	81 *R*[l]
3[c,d]	18 *S*[k]	19[g,i,r,u]	85 *S*[l]	35[c,h,u]	29 *S*[l]
4[c,d]	16 *S*[k]	20[g,i,r,u]	86 *S*[l]	36[c,h,u]	29 *S*[l]
5[c,e,j]	32 *S*[l]	21[g,h,i]	48 *S*[l]	37[g,i,h,r,u]	18 *S*[l], 54 *S*[m]
6[c,f,j]	22 *S*[l]	22[g,h,i]	52 *S*[l]	38[g,i,u]	11 *S*[l], 42 *S*[n]
7[c,f,h,j]	30 *R*[m]	23[g,h,i,u]	48 *S*[l]	39[g,i,u]	5 *S*[k], 48 *S*[l]
8[c,e,h,j,t,u]	80 *S*[n]	24[g,i,u]	37 *S*[l]	40[g,i,u,v]	3 *S*[k], 43 *S*[l]
9[c,e,j,t,u]	75 *S*[n]	25[g,h,i]	32 *S*[l]	41[e,i,u]	18 *S*[n], 48 *S*[o]
10[c,h,u]	26 *R*[l]	26[s]	21 R[l]	42[e,i,u]	8 *S*[m], 32 *S*[n]
11[i,u]	54 *S*[l]	27[e,s]	67 *S*[m]	43[e,i,h,u]	4 *S*[p], 18 *S*[q]
12[c,h,u]	22 *R*[l]	28[e,j,s,u]	25 *R*[l]	44[e,i,u]	22 *S*[p], 45 *S*[q]
13[c,u]	23 *R*[l]	29[e,j,s,u]	32 *S*[l]	45[e,i,u]	5 *S*[n], 21 *S*[o]
14[c,h]	48 *R*[m]	30[e,j,s,u]	26 *R*[l]	46[e,i,u]	4 *S*[n], 24 *S*[o]
15[e,i]	21 *S*[n], 70 *S*[o]	31[e,j,s,u]	18 *S*[l]	47[e,h,i,u]	8 *S*[n], 26 *S*[o]
16[e,j]	13 *S*[l]	32[e,s,t]	34 *R*[l]	48[e,i,u]	13 *S*[n], 21 *S*[o]

[a] The trials employed the procedure of Figure 1, transferring 10% of the product solution at each generation unless otherwise noted. [b] Determined by NMR using $Eu(hfc)_3$. [c] Toluene solvent, reagent grade or purified as noted. [d] Solvent distilled from P_2O_5. [e] Solvent distilled from Na/benzophenone. [f] Solvent treated with H_2SO_4 followed by distillation. [g] Solvent purified by repeated crystallization. [h] New batch of solvent, relative to previous otherwise identical trials. [i] Benzene solvent, reagent grade or purified as noted. [j] Reaction in Teflon flask. [k] After second generation. [l] After third generation. [m] After fourth generation. [n] After fifth generation. [o] After sixth generation. [p] After seventh generation. [q] After eighth generation. [r] Transferring 2.5% of the product solution at each generation. [s] Ethyl ether solvent, reagent grade or purified as noted. [t] Reaction used a Teflon septum. [u] The pairs of trials 8/9, 12/13, 17/18, 19/20, 23/24, 28/29, 30/31, 33/34, 35/36, 37/38, 39/40, 41/42, 43/44, 45/46, and 47/48 were carried out side-by-side using identical reagents. [v] Absence of light.

The addition of 5 ppm of (−)- or (+)-menthol to the first generation resulted in 35% ee *R* and 41% ee *S* product, respectively, after the third generation. The addition of 10 ppm of (D)- or (L)-FMOC-phenylalanine to the first generation resulted in 42% ee *S* and 39% ee *R* product, respectively, after the third generation. If the unknown contaminants in the unspiked reactions are similarly effective in inducing optical activity, they are present in lower amounts. For trials such as 43 and 44 where optical activity was not observed until the seventh generation, the concentration of optically active contaminants must be extremely low.

Presumably, multiple optically active impurities are present in these reactions, with some favoring formation of one enantiomer of **4** and others favoring the opposite enantiomer. The ability of one enantiomer to "take over" was studied in the apparatus of Figure 2. A tube was filled with glass beads to elongate the path length between ends, and opposite ends of the tube were initialized with opposite enantiomers of FMOC-alanine (250 ppm). A series of reactions of **1** with **2** were then carried out in the tube, removing ~90% of the reaction mixture after each generation. For the example experiment shown, samples removed from opposite ends of the tube afforded opposite enantiomers of **4** for the first four generations. However, asymmetric autocatalysis makes the production of both enantiomers intrinsically unstable. The enantiomeric excess at one end by chance grows faster, and diffusional mixing is ultimately unavoidable. By the sixth generation, one enantiomer predominated throughout the tube.

It is an adage in chemistry that "purity is a matter of degree."[5] Thus, it is not clear to us how any macroscopic solution reaction may be carried out in the biosphere in the complete absence of optically active materials. The results here demonstrate that trace

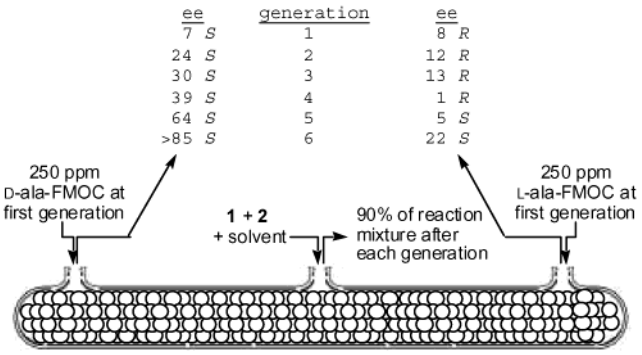

Figure 2. Competition between enantiomers in asymmetric autocatalysis.

amounts of optically active materials may dominate the outcome of reactions, and this suggests caution in interpreting reactions involving large asymmetric amplifications.

More generally, our results support Soai's suggestion that asymmetric autocatalysis may be relevant to biological homochirality.[4a] Many origins have been proposed for initial optical activity on a prebiotic Earth. Possibilities include asymmetric crystallizations,[6] circularly polarized light,[2,7] meteorites,[8] the weak nuclear force,[9] or just random chance in the formation of a racemic mixture, as described above. However, any complete theory on the origin of biological homochirality also requires a mechanism for asymmetric amplification, a mechanism for maintenance of optical activity despite decomposition and racemization, a mechanism for dispersal of optical activity from localized areas, and a mechanism by which one enantiomer can take over in areas where the opposite enantiomer is in excess. If, on a prebiotic Earth, appropriate achiral precursors were continually generated, then asymmetric autocatalysis could intrinsically provide both asymmetric amplification and maintenance of optical activity. The impact of trace optical activity here suggests that dispersal of optical activity would be inevitable.[3] Homochirality could then occur prior to any biological activity. We are currently exploring this hypothesis in both mathematical and experimental models.

Acknowledgment. We acknowledge NIH Grant No. GM-45617 and The Robert A. Welch Foundation for financial support.

References

(1) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418.
(2) (a) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Barron, L. D. *Chem. Rev.* **1998**, *98*, 2391. (b) Bonner, W. A. *Top. Stereochem.* **1988**, 18, 1. (c) Mason, S. R. *Chem. Soc. Rev.* **1988**, *17*, 347.
(3) (a) Siegel, J. S. *Chirality* **1998**, *10*, 24. (b) Frank, F. C. *Biophys. Acta* **1953**, *11*, 459. (c) Mislow, K.; Bickart, P. *Isr. J. Chem.* **1977**, *15*, 1.
(4) (a) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767. (b) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382. (c) Sato, I.; Kadowaki, K.; Soai, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1510.
(5) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press: New York; 1980; p 1.
(6) Kondepudi D. K.; Kaufman, R. J.; Singh, N. *Science* **1990**, *250*, 975.
(7) (a) Flores, J. J.; Bonner, W. A.; Massey, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 3622. (b) Norden, B. *Nature* **1977**, *266*, 567.
(8) (a) Rubenstein, E.; Bonner, W. A.; Noyes, H. P.; Brown, G. S. *Nature* **1983**, *306*, 118. (b) Pizzarello, S.; Cronin, J. R. *Nature* **1998**, *394*, 236. (c) Bailey, J.; Chrysostomou, A.; Hough, J. H.; Gledhill, T. M.; McCall, A.; Clark, S.; Menard, F.; Tamura, M. *Science* **1998**, *281*, 672. (d) Engel, M. H.; Nagy, B. *Nature* **1982**, *296*, 837.
(9) (a) Lee, T. D.; Yang, C. N. *Phys. Rev.* **1956**, *104*, 254. (b) Vester, F.; Ulbricht, T. L. V.; Krauch H. *Naturwiss* **1959**, *46*, 68. (c) Yamagata, Y. J. *Theor. Biol.* **1966**, *11*, 495. (d) Mason, S. F.; Tranter, G. E. *Chem. Phys. Lett.* **1983**, *94*, 34.

JA027129O