

Chiral Symmetry Breaking in Stirred Crystallization of 1,1'-Binaphthyl Melt

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Abstract: As a supercooled melt at 150 °C, the chiral compound 1,1'-binaphthyl racemizes rapidly. The melt solidifies as a conglomerate of crystals, each consisting exclusively of either *R*-(-) or *S*-(+)-enantiomer. We find that crystallization performed with a 2.00 g sample with *constant stirring* produces a large enantiomeric excess (mean 77%) in almost every crystallization. The predominance of *R*-(-) or *S*-(+) was random. Unstirred 2.00 g samples of binaphthyl produce a much lower enantiomeric excess (mean 20%) with optical activity centered around zero similar to an earlier report.¹ Thus, chiral symmetry breaking can be realized in crystallization from a melt by the mere act of stirring, as it can be in crystallization from a solution.

Introduction

Physical and chemical processes that do not have a preference for the production of one or the other enantiomer can yet spontaneously produce a large excess of one of the two enantiomers.^{2–5} Such *chiral symmetry breaking processes* are characterized by a bimodal or two-peak distribution of optical activity, the two peaks in the case of NaClO₃ crystallization being close to 100% enantiomeric excess (ee). Stirred crystallization reveals the powerful effect of chiral autocatalysis in kinetic resolution of enantiomers. In general, chiral autocatalysis in simple chemical reactions is rare (though it is ubiquitous in the complex chemistry of life), but it can be easily realized through stirring in not only crystallization from a solution^{4,5} but also in crystallization of a melt, as we report in this brief, article. The key process here is *secondary nucleation*: the formation of new crystal nuclei in the vicinity of an existing “parent” crystal. Apparently these secondary nuclei are dispersed by stirring. This process is autocatalytic because the crystal nuclei thus generated have the same crystal structure as the parent crystal. The fidelity with which the secondary nucleation “clones” the parent crystal can be quite high: in the case of NaClO₃ our estimates show that only one in about two thousand secondary nuclei does not have the same structure as the parent crystal.

What exactly happens in the vicinity of the parent crystal remains unclear. The collision between the stirbar and the parent crystal does generate secondary nuclei,^{6,7} but such solid–solid

contact is not the only mechanism that generates secondary nuclei. Fluid shear alone can generate secondary nuclei from a crystal suspended in a solution. Indeed by suspending an *l*- or *d*-NaBrO₃ crystal in a stirred solution of NaClO₃ we could generate secondary NaClO₃ nuclei that have the same handedness as the suspended crystal.⁸ Similar experiments conducted by Qian and Botsaris⁹ have led them to propose a theory¹⁰ of secondary nucleation in which enhanced cluster formation and subsequent nucleation in the vicinity of a crystal is the source of secondary nuclei. Whatever the mechanism, stirred crystallization is an autocatalytic process that can result in chiral symmetry breaking with its characteristic bimodal distribution of crystal ee.

Nearly three decades ago, Pincock et al.¹ studied the optical activity of 200, 0.20 g samples of 1,1'-binaphthyl crystallized at 150 °C. The distribution of optical activity was found to be Gaussian-like, centered around zero. They noted, “From this distribution it is apparent that obtaining binaphthyl with optical purity above 90% by this method would be a very exceptional event (observable in about one in 150 tries)” (ref 1, p 1019). Our study shows that crystallization of the melt with constant stirring dramatically changes the distribution of optical activity, producing nearly 80% enantiomeric excess in almost all tries. (Large ee's can be obtained in binaphthyl¹¹ and other compounds by appropriate seeding, but spontaneous production of large ee in every try is rare.) As described in more detail below, the main difference between the crystallization studied by Pincock et al. and ours is that, in our process, stirring introduces chirally autocatalytic secondary nucleation that is able to amplify small initial asymmetry in the number of *R*-(-) and *S*-(+) crystals, whereas in their process the crystals were generated independently of each other (through primary nucleation), resulting in a statistically equal number of *R*-(-) and *S*-(+) crystals.

For chiral symmetry breaking, characterized by a bimodal distribution of optical activity, chiral autocatalysis is essential

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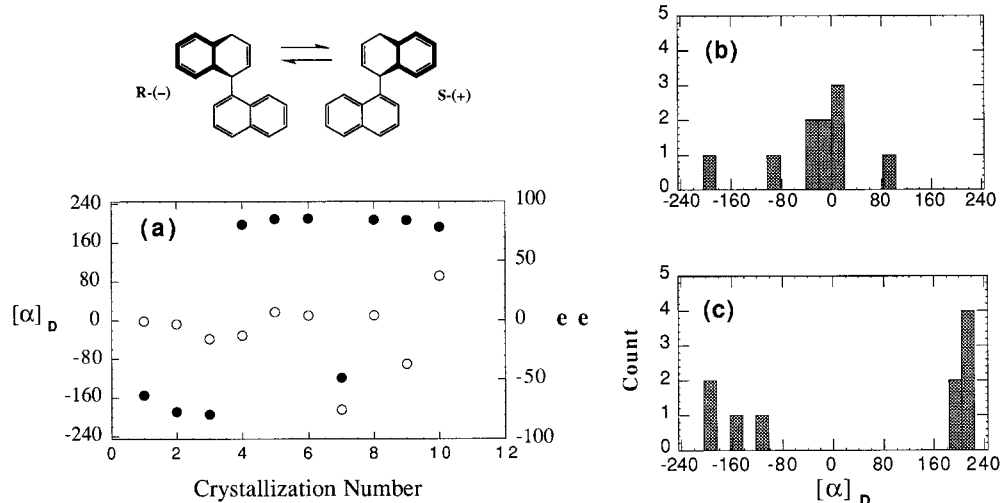


Figure 1. Specific rotation $[\alpha]_D$ and enantiomeric excess (ee), obtained in crystallizations of 2.00 g samples of binaphthyl melt at 150 °C. The crystals were dissolved in benzene and the optical rotation of the solution was measured. (a) The specific rotation of 10 stirred (filled circles) and 10 unstirred crystallizations (open circles) of binaphthyl. 100% optical purity corresponds to $[\alpha]_D$ 245°. (b) Histogram of $[\alpha]_D$ for unstirred samples. (c) Histograms of $[\alpha]_D$ for the stirred samples.

though not sufficient. Recently, chirally autocatalytic reactions have been reported in both inorganic¹² and organic reactions,¹³ but unambiguous spontaneous chiral symmetry breaking is yet to be achieved in these reactions. Autocatalysis generated through stirred crystallization, however, does have the ingredients necessary for chiral symmetry breaking, as was observed in the crystallization of NaClO_3 from solution.^{4,5} The results reported here show that similar chiral symmetry breaking crystallization could also occur in the crystallization of chiral organic compounds from their melt, thus establishing the generality of the phenomenon of symmetry breaking in stirred crystallizations.

Experimental Section

The crystallizations were performed along the lines of Pincock et al. A pair of 2.00 g samples of 1,1'-binaphthyl (Acros) in a 10.0 mL flask are placed in a bath of silicone oil and heated to 180 °C, which is well above the melting point (158 °C) of the most stable crystalline form, and maintained at this temperature for at least 20 min. Both flasks were sealed to avoid extraneous seeding during the crystallization. (1,1'-Binaphthyl has two crystal structures: one a conglomerate containing exclusively *R*(-) or exclusively *S*(+) enantiomers in a particular crystal, and the other a racemic form containing both *R*(-) and *S*(+) enantiomers in the same crystal. The conglomerate is more stable with a melting point of 158 °C; the racemic form has a melting point of 145 °C.) At a temperature of 180 °C, 1,1'-binaphthyl racemizes completely in less than a second,^{1,14} and this ensures that the starting material has no optical activity. The melt in one of the 10 mL flasks was stirred throughout the experiment with a Teflon stir-bar (1.2 cm × 5 mm × 5 mm) at about 60 rpm, while the other was not stirred. The melt is then cooled from 180 °C to 150 °C and allowed to crystallize. Once crystallized, the enantiomeric form of the molecule is essentially frozen, i.e., the racemization rate is extremely slow. Unlike Pincock, et al.¹ we did not initiate the crystallization by touching the flask with dry ice, but allowed the crystallization process to occur without any intervention. The time for the complete crystallization of the 2.00 g sample varied widely from run to run, ranging from 12 min to 2 days. In the stirred system, we noticed that once crystallization began, the entire melt solidified within 10 min (the solidifying melt encapsulates and arrests the stir-bar). In the unstirred melt, crystals grew much more slowly, often taking several hours from the onset of

crystallization to complete solidification of the melt. When the crystallization was complete, the entire 2.00 g of the solid from the stirred and unstirred flasks were cooled to room temperature and dissolved in 150 mL of benzene, and the optical rotation (at $\lambda = 598$ nm) was measured with a Rudolph Autopol IV polarimeter. At room temperature the racemization half-life of 1,1'-binaphthyl in benzene is about 10 h, so that the optical activity could easily be measured.

Results and Discussion

The observed specific rotation and ee for 10 stirred and 10 unstirred crystallizations of the melt are shown in Figure 1a in which an optical rotation of 245° corresponds to 100% ee. The corresponding histograms, shown in parts b and c of Figure 1, show the one-peak distribution centered around zero for the unstirred samples while stirred samples show symmetry breaking with the characteristic bimodal distribution, each peak being close to 80% ee. One out of 10 unstirred crystallizations gave nearly 80% ee while 7 of the 10 had an ee close to zero.

The key feature in the generation of chiral asymmetry in stirred crystallization from a solution or melt is the process of *secondary nucleation*. Though the exact nature of this process is not well understood, empirical rate laws have been widely used^{15–17} for crystallization from a solution. The rapidity of this process compared to the regular or primary nucleation makes it possible for one crystal of *R* or *S* enantiomer, created randomly, to become the parent crystal that generates a large number of secondary crystals with the same enantiomeric form resulting in a large ee. In addition, due to rapid secondary nucleation, the heat released may increase the temperature a little and decrease the primary nucleation rate thus decreasing the probability of generating new crystals through primary nucleation. (Indeed, even in a thermostated beaker, during the crystallization of NaClO_3 from solution we did observe a small increase of about 1 °C rise in temperature.) Such suppression of primary nucleation by autocatalytic secondary nucleation will enhance the chances for a single crystal and its secondary nuclei to dominate the system and result in a large ee.

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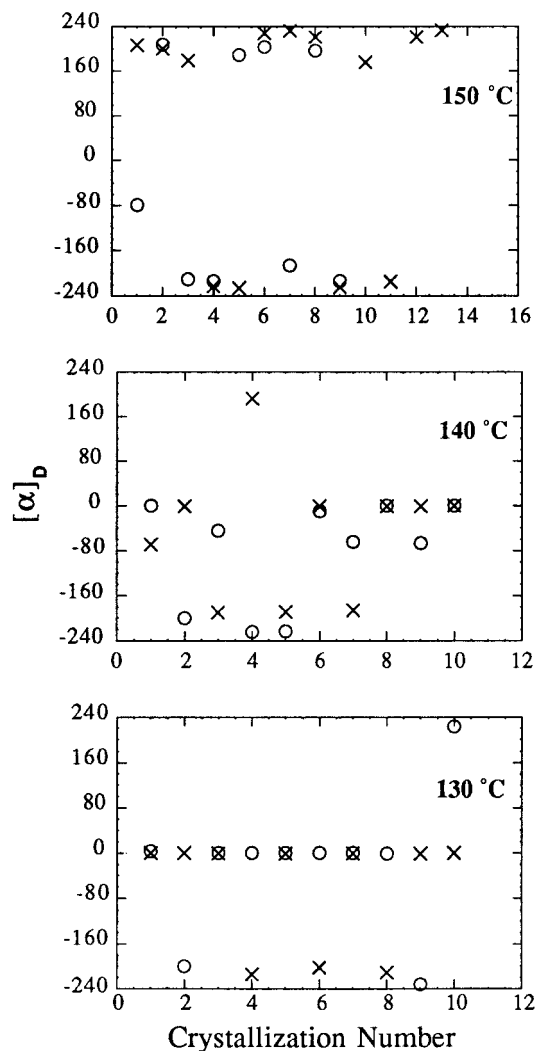


Figure 2. Specific rotation obtained in the crystallization of stirred (crosses) and unstirred (open circles) 0.20 g samples of binaphthyl at 150, 140, and 130 °C. The data show that at 150 °C the relatively slow nucleation rate gives large enantiomeric excess (ee) in small samples for both unstirred and stirred crystallizations, but as the nucleation rate increases due to an increase in supercooling, the probability of obtaining a large ee decreases. As shown in Figure 1, when the sample size is larger (2.00 g), only the stirred crystallization produces large ee.

For smaller samples, if the primary nucleation rate is low enough, large ee's can be generated even in unstirred samples because most of the solid phase could result from the growth of a single crystal. As the sample size increases, however, since the number of randomly generated nuclei increase with the volume, ee's will decrease. Even in the case of stirred systems, if the primary nucleation rate is comparable to the secondary nucleation rate, large enantiomeric excess will *not* be generated. The primary nucleation rate can be increased by simply increasing the supercooling of the melt below 150 °C. The lower the temperature of the crystallizing melt, the higher the primary nucleation rate, which is more likely to generate both *R*(-) and *S*(+) crystals in equal amounts. Such a decrease in ee with the lowering of the melt temperature can be seen in the crystallization of stirred and unstirred 0.20 g samples. The ee generated as a function of temperature of the melt is shown in Figure 2. As the temperature decreases from 150 °C to 130 °C, due to the increase in primary nucleation rate, the probability of obtaining a large ee decreases significantly. (Note

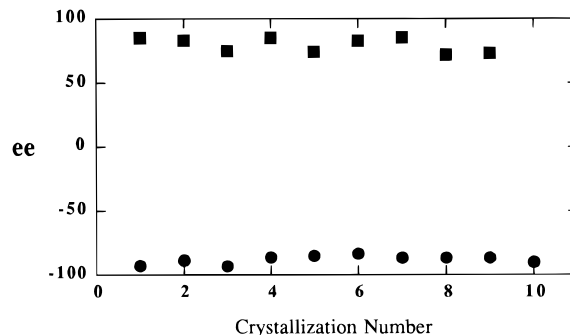


Figure 3. Enantiomeric excess (%) obtained in the stirred crystallization of 1,1'-binaphthyl melt by seeding it with *R*(+)- and *S*(-)-1,1'-bi-2-naphthol crystals. Squares are the ee obtained with *S*(-) seeds and circles are the ee obtained with *R*(+) seeds.

that below 145 °C both the conglomerate and the racemic form of the solid phase can crystallize.) In the experiments of Pincock et al.,¹ nucleation was initiated by touching the vial containing the melt with dry ice. This supercooling must have generated a large number of nuclei of both *R*(-) and *S*(+) enantiomers. As a result, only one in about 150 crystallizations produced an ee in excess of 90%. The 62 crystallizations whose specific rotation is summarized in Figure 2 involved no such intervention to initiate the nucleation. In the data shown, after initial heating to 180 °C, melt was cooled to, and maintained at, 150, 140, and 130 °C, respectively, until it crystallized completely—which took anywhere from 30 min to 2 days.

In their later work,¹¹ Wilson and Pincock showed that, if a specially prepared polycrystalline solid with a small excess of *R*- or *S*-binaphthyl was maintained in the temperature range 76–145 °C, an initial ee of about 1–10% was amplified to about 80% in the solid phase. The process we studied produces large ee spontaneously, without any special preparation of the initial state.

Crystallization with 1,1'-Bi-2-naphthol Seeds. We have also studied the effect of seeding 1,1'-binaphthyl melts with *R*(+)- or *S*(-)-1,1'-bi-2-naphthol. *R*(-)-1,1'-Binaphthyl is isomorphous with *R*(+)-1,1'-bi-2-naphthol. Since 1,1'-bi-2-naphthol has a higher melting point (208 °C) we in effect studied the influence of the surface of 1,1'-bi-2-naphthol crystals on the crystallization of racemic 1,1'-binaphthyl. The experiments were conducted as follows. 1,1'-Binaphthyl (0.25 g) was placed in a test tube, heated to 180 °C in an oil bath, and stirred for 30 min. This ensured that the initial 1,1'-binaphthyl sample was racemic. The sample was then cooled to 150 °C and 0.025 g of *R*(+)-1,1'-bi-2-naphthol or *S*(-)-1,1'-bi-2-naphthol were added to each test tube. The 1,1'-bi-2-naphthol was ground up to a powder to increase the surface area. The melt was continuously stirred till all of it crystallized. The crystallized 1,1'-binaphthyl was then cooled to room temperature and dissolved in benzene, and the specific rotation was measured. We found strong chiral influence due to the added seed. All of the 10 samples seeded with *R*(+)-1,1'-bi-2-naphthol had a high value of specific rotation. The mean specific rotation for these 10 samples was found to be -210° with a standard deviation of 8° . Similarly, for the nine samples seeded with *S*(-)-1,1'-bi-2-naphthol, the mean specific rotation was 191° with a standard deviation of 14° . Since the specific rotation for 100% optically pure 1,1'-binaphthyl is 245° , we see the strong influence of the seed. Thus we found that 1,1'-bi-2-naphthol is a chirally selective nucleating agent for 1,1'-binaphthyl.

Concluding Remarks

From our results it is clear that the effects of stirring become more significant for larger samples of 1,1'-binaphthyl. If a larger sample is melted and crystallized without stirring, slow primary nucleation is likely to generate many crystals, some being *R*-(-) and the others *S*-(+). This will result in a small ee. But if this sample is vigorously stirred then, since the rate of autocatalytic secondary nucleation is much higher than that of primary nucleation, a large number of either *R*-(+) or *S*-(-) crystals will be produced, resulting in a large ee.

Chiral selectivity near a solid surface, as seen in secondary nucleation, seems quite prevalent. In our recent studies^{12,18} of a reaction that produces a chiral cobalt complex, we found that if the reaction was performed under conditions in which the

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product crystallizes, chiral autocatalysis was observed (with random generation of large ee). From this work, the ability of NaBrO₃ crystals to catalyze the production of NaClO₃ crystals in a chirally selective way,⁸ and from the results presented in this article, a general picture seems to emerge. The surface of some chiral crystals provides a chiral environment that acts as chiral selectors for nucleation or formation of a chiral complex; this together with autocatalytic secondary nucleation that rapidly increases the surface area of crystals has the potential of generating large ee. Thus, the chiral environment provided by the solid phase of a chiral compound may result in chiral autocatalysis, which generates significant ee randomly.

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