VIP Chirality

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Chiral Symmetry Breaking by Chemically Manipulating Statistical Fluctuation in Crystallization**

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Naturally occurring amino acids and sugars are building blocks of the biological world. They are distinctly left- and right-handed, respectively, with all members of one class possessing the same sense of chirality.[1] Chemically and statistically, however, there should be the same number of such molecules in both forms, because each enantiomer should be produced with equal probability if no external physical field or chiral reagent is introduced.[2] The origin of this homochirality remains a subject of much debate in biology, despite extensive research and various hypotheses.[1–9]

The problem of homochirality also represents a grand challenge with significant ramifications in modern physical and materials sciences,[10–14] as homochiral materials are useful for such important applications as enantioselective separation, nonlinear optics, catalysis, and sensor technology.[15,16] Abiotic mechanisms based upon asymmetry induction by external fields or forces have been investigated.[17] Experimentally more conclusive, however, is asymmetric resolution by chiral autocatalysis in crystallization.[18] A state of nonzero enantiomeric excess can arise spontaneously from an achiral or a racemic state through a chiral symmetry breaking transition. An elegant example by Kondepudi et al. demonstrated that secondary crystal nuclei of the same structure as the parent crystal (the primary nucleus) are rapidly cloned (chiral autocatalysis) under stirring, while competitive crystallization of the opposite enantiomer is suppressed, thus leading to chiral amplification and eventual production of enantiopure crystals.[19] Although this particular autocatalytic formation of crystals has subsequently been verified experimentally, secondary nucleation in general is a rather complex process,[20] and the explanation for the resulting chiral symmetry breaking remains unclear.[21]

Herein, we present a distinctly different approach to chiral symmetry breaking by manipulating the statistical fluctuation inherent to the crystallization of helical coordination polymers; this class of substances has attracted much recent interest owing to their potentially useful applications.[13,14] In the absence of any chiral influence, such as a chiral catalyst, template, or chiral starting materials, these intrinsically chiral materials are generally obtained as optically inactive conglomerates because of the stochastic nature of crystallization.[22]

Our approach may be compared to coin flipping. If a coin is flipped a sufficient number of times, it will come to rest on either side with equal probability. However, if the flipping is limited to just a small number of events, from a statistical point of view, the situation can differ significantly. Under such circumstances, the chance of getting just one particular side up becomes much higher than it would be otherwise. In the extreme case of just one toss, the chance of getting only a head or only a tail is 100%. When this statistical argument is applied to the nucleation of a targeted helical coordination polymer, the otherwise equal probability of forming the left- and right-handed primary nuclei is significantly skewed toward one particular enantiomeric form. Once the stochastic formation of the primary nucleus is limited, the ensuing generation of secondary crystal nuclei of the same structure on the surface of the primary nucleus is made possible by controlling the concentration of the reactants, eventually leading to a cluster of crystals of the same chirality.

The key to manipulating such statistical fluctuation lies in the control of the number of crystallization events and, more specifically, the number of primary crystal nuclei. We propose that the crystallization kinetics of helical coordination polymers may be controlled by the presence of a judiciously chosen reagent that competes with the polymer-forming ligands for the metal ions. As such, the availability of the metal ion for polymer formation is controlled by the concentration of the competing reagent, which in turn determines how facilely the product crystallizes.

The synthesis of the reported $[\{Cu(succinate)(4,4'\text{-bipyridine})\}_n]\cdot(4H_2O)_n$ (**1**)[23] was used to validate our hypothesis. This coordination polymer has been shown to possess a three-dimensional network structure in the solid state with the helical polymeric chains of copper succinate bridged by 4,4′-bipyridine. Our initial efforts to reproduce **1** according to the reported procedure yielded an optically inactive conglomerate, which can be rationalized in terms of the equally probable nucleation of both helical forms owing to the fast kinetics typical of coordination polymer synthesis.

Ammonia was then added as a competing reagent in a subsequent, modified synthesis of **1**. By forming the tetraammine complex $[Cu(NH_3)_4]^{2+}$, ammonia competes with succi-

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nate and 4,4′-bipyridine for Cu^{2+}. The higher the concentration of ammonia, the more likely the formation of $[Cu(NH_3)_4]^{2+}$ and the less likely the crystallization of the polymer product. In other words, how easily the coordination polymer crystallizes can be modulated by the amount of ammonia present in the reaction mixture.

Formally, these competitive processes can be summarized into two interdependent equilibria: the formation of the polymer product **1** [Eq. (1)] and the formation of $[Cu(NH_3)_4]^{2+}$ [Eq. (2)]. In the absence of ammonia, the rate of

$$Cu^{2+} + L_S + L_b \rightleftharpoons [\{Cu(L_S)(L_b)\}_n] \quad (1)$$

$$Cu^{2+} + 4\,NH_3 \rightleftharpoons [Cu(NH_3)_4]^{2+} \quad (L_S = \text{succinate}, L_b = 4,4'\text{-bipyridine}) \quad (2)$$

formation of **1** (r_f) is directly proportional to the concentrations of Cu^{2+} ($[Cu^{2+}]$), succinate ($[L_s]$), and 4,4′-bipyridine ($[L_b]$), that is, $r_f = k[Cu^{2+}][L_s][L_b]$. In the presence of ammonia, on the other hand, the rate law becomes $r_f = k[[Cu(NH_3)_4]^{2+}][L_s][L_b]/K[NH_3]^4$, where k is the rate constant for the formation of **1**, $K = [[Cu(NH_3)_4]^{2+}]/[Cu^{2+}][NH_3]^4$ is the equilibrium constant of Equation (2), and $[NH_3]$ and $[[Cu(NH_3)_4]^{2+}]$ are the concentrations of ammonia and the tetraammine complex, respectively. Considering $[[Cu(NH_3)_4]^{2+}] = [Cu^{2+}]_0 - [Cu^{2+}]$, where $[Cu^{2+}]_0$ is the initial concentration of Cu^{2+}, r_f can be expressed as $r_f = k[Cu^{2+}]_0[L_s][L_b]/\{K[NH_3]^4 + 1\}$, which can be approximated as $r_f = k[Cu^{2+}]_0[L_s][L_b]/K[NH_3]^4$, because $K[NH_3]^4 \gg 1$. The critical importance of $[NH_3]$ is clear, because for given amounts of Cu^{2+}, succinate, and 4,4′-bipyridine, the rate of formation of the coordination polymer is inversely proportional to $[NH_3]^4$. A high concentration of ammonia greatly impedes the formation of the polymer, while lowering ammonia concentration does the opposite. It follows that crystallization of the coordination polymer from a homogeneous solution containing the ligands (succinate and 4,4′-bipyridine) and Cu^{2+} can be controlled by modulating the concentration of ammonia. A low ammonia concentration is expected to result in quick crystallization and a large number of nuclei in the initial stage of metal–ligand coordination. This situation will ultimately lead to a racemic mixture or a product of a low enantiomeric excess, because the left- and right-handed helical structures are produced with equal probability. In contrast, when the concentration of ammonia is high, only a limited number of nuclei may be formed prior to crystal growth. The probability of establishing one particular isomeric form, left- or right-handed, in these nuclei is greatly enhanced as a consequence of the inherent statistical fluctuation discussed above. As a result of such a significantly skewed distribution of the two possible helical forms, the chiral symmetry is broken, and a product with a high enantiomeric excess, possibly a homochiral product, is formed.

The concentration of ammonia may be modulated by varying the pH value of the initial reaction mixture, as a high pH values favor NH_3 in the equilibrium $NH_3 + H_2O \rightleftarrows NH_4^+ + OH^-$. It can also be moderated by control of the evaporation rate of the solution or by a combination of these two methods. To verify our conjecture, reaction mixtures with three different starting pH values were prepared. Furthermore, solutions of the same initial pH value were allowed to evaporate at different rates (see the Supporting Information for details).

Our experimental observations were consistent with the above analysis. Regardless of the evaporation rate, crystallization of **1** from solutions with an initial pH of 8.3 was always rapid, affording a large number of small crystals (Figure 1 a). Careful crystallographic analysis established the optical purity of individual crystals. Left- and right-handed helices were found to coexist; their structures are shown in Figure 2 together with the overall structure in which individual helices are bridged by 4,4′-bypridine. Investigation using circular dichroism (CD) spectroscopy[24] showed that each of

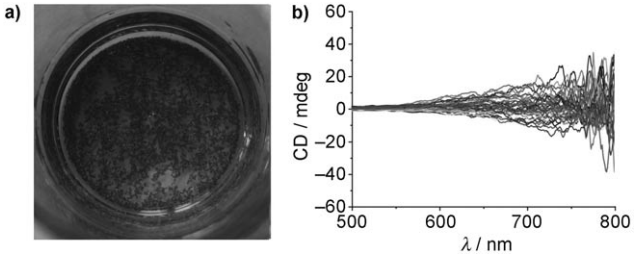

Figure 1. Crystallization using pH 8.3 solutions. a) A rapid crystallization of **1** yielding a large number of small crystals. b) The solid-state CD spectra of bulk samples of 30 different crystallizations.

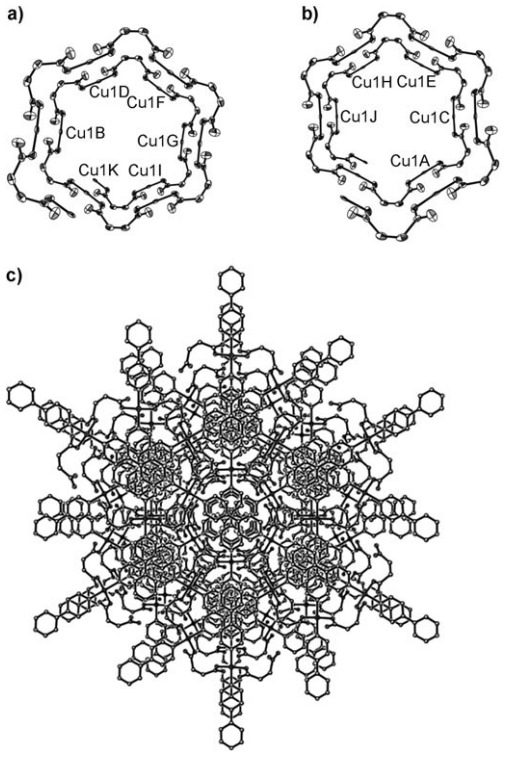

Figure 2. ORTEP plots with thermal ellipsoids set at the 30% probability level showing a) the right-handed helix of polymeric $[\{Cu(succinate)\}_n]$, b) the left-handed helix of polymeric $[\{Cu(succinate)\}_n]$, and c) the overall structure of $[\{Cu(succinate)(4,4'\text{-bipyridine})\}_n]\cdot(4\,H_2O)_n$ (**1**) viewed along the *c* axis.

the 30 bulk samples was CD-silent (Figure 1b). Together, these results indicate that **1** crystallizes as a racemic conglomerate—a mechanical mixture of enantiomerically pure crystals of one enantiomeric form and its opposite.

When the synthesis was carried out using pH 9.2 solutions, the outcome of crystallization was found to be profoundly influenced by how rapidly ammonia evaporated. Specifically, when the solution was more tightly capped to prevent fast evaporation, only a limited number of clusters of crystals were produced (Figure 3a). Out of 30 crystallizations investigated, 12 samples featured a single cluster of crystals, while the rest produced no more than five clusters. The CD spectra of these 30 samples reveal that each bulk sample was CD active (Figure 3b), suggesting chiral symmetry breaking. Further crystallographic analysis revealed that every single crystal in one particular cluster is of the same space group (see the Supporting Information, Table S1). In other words, the enantiomeric excess in that crystal cluster is 100%, and the cluster is homochiral. Our results represent a rare experimental verification of a crystallization event during which every single crystal within the cluster crystallizes in the same enantiomeric form.[25] It should be noted that the specific handedness of the crystals in any of the clusters cannot be predicted, as there is no systematic bias in favor of one particular enantiomer over the other. Because it is difficult to separate the left-handed crystals from their right-handed counterparts in a racemic mixture or to calculate the enantiomeric excess value based on the solid-state CD spectra, the ability to cultivate individual enantiopure crystals and to calculate the enantiomeric excess, as in the present case, becomes significant. Such a feat is possible only when the number of crystals and their clusters is limited, as demonstrated in our controlled crystallization. Carefully measuring the CD spectra for each of the crystal clusters and weighing the crystals revealed that half of the samples are homochiral, while an enantiomeric excess of at least 40% was achieved for each of the remaining half of the 30 crystallizations. In this case, it is possible that the achiral starting materials can give 100% homochiral materials, unlike when racemic compounds are crystallized; then, the maximum yield is 50% of the total material.[22]

When the pH 9.2 solutions underwent faster evaporation, a large number of relatively small crystals were produced (Figure 3c). Out of 30 crystallizations, only a few bulk samples were CD active (Figure 3d). This result can be understood as a consequence of an equilibrium shift toward the dissociation of $[Cu(NH_3)_4]^{2+}$; a higher concentration of Cu^{2+} facilitates crystallization under otherwise identical conditions.

Additional evidence in support of the above analysis is provided by analogous experiments using solutions of an initial pH 8.7. The 30 crystallizations with fast ammonia evaporation invariably resulted in crystals of **1** displaying very similar crystallization behavior and CD spectra to those prepared using the pH 8.3 mixture. Slow evaporation under otherwise identical conditions led to a number of crystal clusters (Figure 4a), some of which are CD active in the bulk (Figure 4b). The crystallization behavior and optical properties of the bulk material are qualitatively comparable to those observed for fast-evaporating pH 9.2 solutions.

On the basis of the above observations, it can be concluded that both the pH value of the reaction mixture and the ammonia evaporation rate are indeed critical for the crystallization behavior of **1**, with a high initial pH value and slow evaporation of ammonia favoring products of high enantiomeric excess values. On the other hand, the absolute configuration of the crystals in a particular cluster cannot be

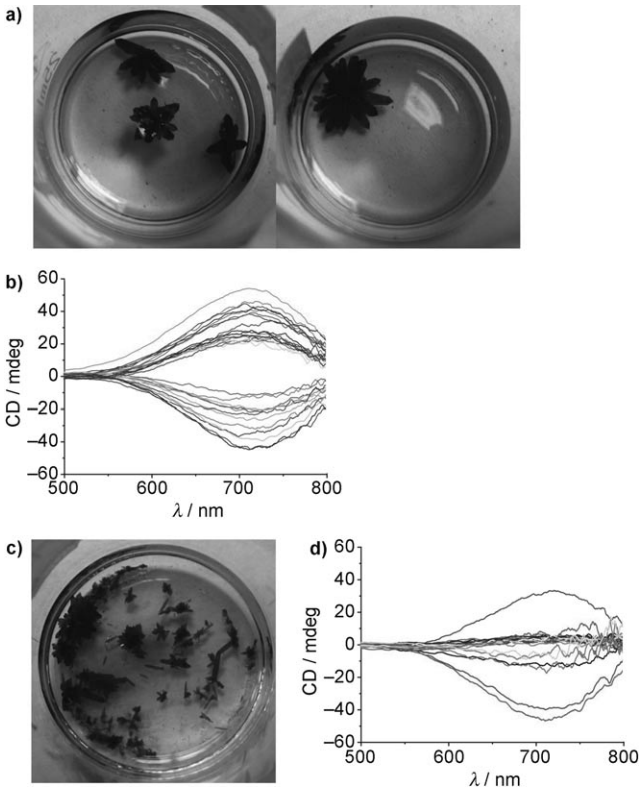

Figure 3. Crystallization using pH 9.2 solutions. a) The production of a small number of crystal clusters of **1** with slow evaporation of the reaction mixture. b) The solid-state CD spectra of bulk samples from 30 different slow crystallizations. The positive and negative values correspond to the right- and left-handed helices, respectively. c) The production of a large number of crystals (the majority not being in cluster form) of **1** with faster evaporation of the reaction mixture. d) The solid-state CD spectra of bulk samples from 30 different fast crystallizations.

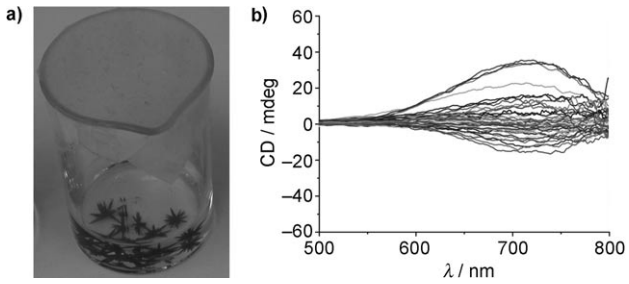

Figure 4. Crystallization using pH 8.7 solutions. a) The production of a relatively small number of crystal clusters of **1** with slow evaporation of the reaction mixture. b) The solid-state CD spectra of bulk samples from 30 different crystallizations.

known a priori. A high ammonia content is believed to be necessary to limit the number of primary nuclei, while slow evaporation ensures that subsequent crystallization is sluggish and that the handedness that has already been established in the primary nuclei is maintained with the growth of the polymer.

The validity of this strategy is further demonstrated by our successful preparation of two additional coordination polymers, $[\{Cu(nitrilotriacetate)Na(H_2O)\}_n]$[26] (Supporting Information, Figure S1a,b) and $[\{Cu(glycolate)\}_n]$[27] (Figure S1c,d,e) in their respective homochiral forms.

To summarize, we have synthesized homochiral coordination polymers by chemically manipulating the statistical fluctuation inherent to the formation of enantiomeric pairs of such materials. This synthesis was accomplished by moderating the concentration of a competing ligand in the reaction mixture to control the kinetics of product crystallization. By limiting the number of crystallization events to just a few, the probability of attaining only the left- or right-handed helical structure is significantly skewed, and in an ideal case, only one enantiomeric form is obtained. Our successful syntheses of three different coordination polymers in their homochiral forms suggest the general applicability of this statistically controlled nucleation and crystallization approach to chiral symmetry breaking. In a broader perspective, any new approaches to obtain enantiomerically pure materials are of fundamental importance to the application of such materials in chemical and pharmaceutical industries and, more importantly, may contribute to the ultimate understanding of the origin of life. Thus, further development and application of this straightforward strategy to chiral symmetry breaking warrant an optimistic outlook.

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[26] [{Cu(nitrilotriacetate)Na(H_2O)}$_n$] (**2**) was reported: S. H. Whitlow, *Inorg. Chem.* **1973**, *12*, 2286 – 2289. The key difference in our synthesis is the use of ammonia in competition for Cu^{II} with the nitrilotriacetate ligand. The pH value of the reaction is 6.0.
[27] [{Cu(glycolate)}$_n$] (**3**) is a new compound. Synthetic details and crystallographic information on both the left- and right-handed helices of **3** can be found in the Supporting Information; CCDC-653395–653423 (**1**) and CCDC-655352–655353 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

