Non-stochastic homochiral helix crystallization: cryptochirality in control?

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A non-random distribution of handedness among homochiral batches, comprising air-sensitive CuCl/triallylamine coordination helices, was obtained during total spontaneous resolution from neat triallylamine.

Self-assembly of homochiral helical structures is an essential element of life, and the creation of artificial helical architectures, such as polynuclear metal complexes with multidentate ligands winding around the metal centres (so-called helicates), has attracted much attention.[1] If only achiral building blocks (*i.e.*, ligands) are used, the isolation of homochiral helices usually depends on spontaneous resolution.[2] An enantiopure

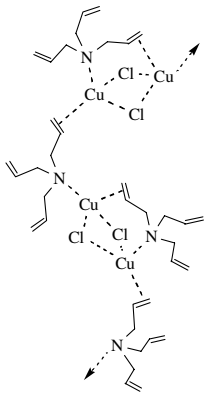

Figure 1 Asymmetric unit in compound **1**.

single crystal, obtained from spontaneous resolution, can be said to represent a first level of homochirality. A second level of homochirality is attained when total spontaneous resolution, assisted by single-colony crystallization, results in an enantiopure bulk product in a high yield.[3] We now report on a third level of homochirality: a non-stochastic distribution of handedness among the enantiopure batches.

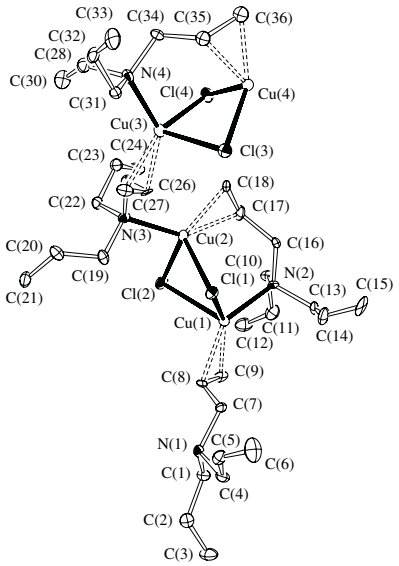

Figure 2 ORTEP drawing of **1**, showing the crystallographic numbering. Selected bond lengths (Å) and angles (°): N(3)–Cu(2) 2.084(5), N(2)–Cu(1) 2.098(5), Cl(1)–Cu(1) 2.2936(15), Cl(1)–Cu(2) 2.5489(16), Cl(2)–Cu(2) 2.3068(16), Cl(2)–Cu(1) 2.5827(17), C(8)–C(9) 1.335(9), C(8)–Cu(1) 2.079(5), C(9)–Cu(1) 2.045(6), C(17)–C(18) 1.364(8), C(17)–Cu(2) 2.079(6), C(18)–Cu(2) 2.053(6); N(2)–Cu(1)–Cl(1) 105.48(14), N(2)–Cu(1)–Cl(2) 98.67(14), Cl(1)–Cu(1)–Cl(2) 95.59(6), N(3)–Cu(2)–Cl(2) 101.72(14), N(3)–Cu(2)–Cl(1) 102.57(14), Cl(2)–Cu(2)–Cl(1) 96.18(5).

When neat triallylamine (ally) is added to copper(I) chloride at ambient temperature, colourless crystals of helical $[Cu_4Cl_4(ally)_4]_\infty$ **1** form.† As can be seen in Figures 1 and 2, the tetranuclear asymmetric unit corresponds to one turn of a helix, and both triallylamine and chloride ligands bridge the copper atoms. The helical coordination polymer in **1** is not a helicate, but rather an example of a less common helix type[4] where the metal is an integral part of the helix (Figure 3). The pitch height is 11.6 Å and the helix winds along the *a*-axis, perpendicular to the crystallographic screw axis of the $P2_1$ space group.‡ As can be seen in Figures 4 and 5, stereochemical information can be transferred between adjacent helices since they are intertwined, and it is apparent that these interactions can promote homochirality. Rational design of helices that prefer to crystallise as conglomerates requires detailed knowledge about how stereochemical information is transferred between helices in the crystal.[5,6] In **1**, only one of the allyl groups (in each ally ligand) is coordinated by copper, while the other two are free to intercalate neighbouring helices. This is in agreement with the IR spectrum of solid **1**, which shows absorption bands at 1638 (free allyl groups) and 1540 cm^{-1} (coordinated allyl groups). The shift in $\nu_{C=C}$ of 98 cm^{-1} upon coordination to Cu^I is normal compared to the shifts previously reported (71–141 cm^{-1}) for alkene complexes of CuCl.[7] A corresponding lengthening of coordinated C=C bond distances in **1** to 1.34 Å (mean value of the four coordinated C=C bonds), as compared to the free C=C bond distance of 1.31 Å (mean value of the eight free C=C bonds), is observed as a consequence of both π-donation to Cu^I and back-bonding from Cu^I.

Since **1** crystallises in the $P2_1$ space group (and since the asymmetric unit contains only one enantiomer), spontaneous

† All operations were carried out under nitrogen using Schlenk, glove box or low temperature[20] techniques. Commercial triallylamine (Aldrich) was dried with 4 Å molecular sieves, distilled and deoxygenated. Copper(I) chloride was purified according to published methods.[21] To eliminate the risk that crucial trace impurities were introduced during purification, commercial triallylamine and copper(I) chloride were used as delivered in control experiments.

Preparation of $[Cu_4Cl_4(ally)_4]_\infty$ **1**. *Method A*. Purified copper(I) chloride (1.0 g, 10 mmol) and 5.0 ml of triallylamine were allowed to react without stirring at ambient temperature. Colourless crystals of **1** deposited after a few days at ambient temperature. Crystallization started at the surface of the CuCl particles and exhibited single colony growth. Determination of yield is not trivial, since the product is initially mixed with unreacted CuCl. However, after several weeks at ambient temperature, CuCl is quantitatively transformed to **1**. *Method B*. A suspension of purified copper(I) chloride (0.12 g, 1.2 mmol) in 5.0 ml of triallylamine was heated until all CuCl dissolved. Colourless crystals of *P*-**1** deposited after a few hours at ambient temperature, and crystallization was continued at 4 °C. IR (KBr, ν/cm^{-1}): 3456 (b), 3076 (m), 2973 (m), 2833 (s), 1956 (w), 1858 (b), 1638 (m), 1540 (m), 1458 (s), 1438 (s), 1411 (s), 1356 (w), 1341 (w). Yield 0.41 g (65%).

Solid-state CD spectra were recorded on a Jasco J-175 spectropolarimeter using thin (100 mg) KBr disks or as a Nujol mull on a quartz plate. A strong positive CD peak (the signal was measured at several different disk positions) at 311 nm was observed for *P*-**1** and the corresponding negative signal for *M*-**1** could also be recorded. Crystals of **1** decompose slowly when excess triallylamine is removed (which is necessary in order to obtain translucent KBr disks), so it is difficult to obtain perfect solid-state spectra (see *e.g.*, the region 260–290 nm). IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer using 300 mg KBr disks or a Nujol mull on CaF_2 windows.

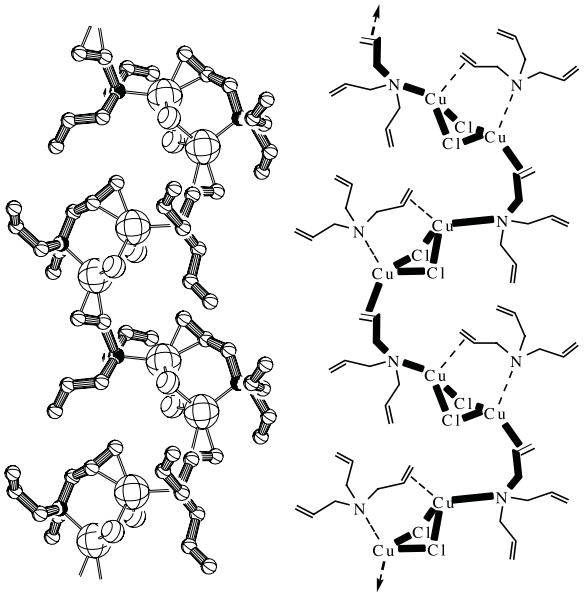

Figure 3 Copper atoms as an integral part of the helices in **1**.

resolution occurs on crystallization. If lability in solution is assumed, it should thus be possible to prepare enantiopure bulk samples of homochiral **1** in high yield, provided that racemic twinning can be avoided. The absolute value, as well as the standard uncertainty, of the Flack parameter[8,9] proved conclusively that the first crystals consisted of exclusively right-handed (clockwise) helices, which consequently may be denoted *P*-**1**. The use of solid-state CD spectroscopy has been demonstrated recently,[10] and we were able to record the solid-state CD spectrum of *P*-**1**, which is displayed in Figure 6. The identity of the crystals was proven by recording a CD spectrum of the same single crystal that had been used in an absolute structure determination (from X-ray data). It could also be shown that the CD signal from a measured quantity of a single crystal was of approximately the same magnitude as the signal from a bulk sample of the same quantity. Crystal batches of **1** should thus be essentially enantiopure. When an excess of CuCl was used during the synthesis (method A), crystals of *M*-**1** were obtained from a different batch. Out of five preparations, three resulted in predominantly *P*-**1** crystals and two in predominantly *M*-**1** crystals, which suggests that the distribution of *P*-**1** and *M*-**1** helicity among different preparations (batches) is, as would be expected, stochastic.

‡ *Crystallographic data*: at 123 K, crystals of **1** are monoclinic, space group $P2_1$, $a = 11.571(3)$, $b = 12.052(2)$ and $c = 14.723(2)$ Å, $\beta = 94.088(6)°$, $V = 2047.9(7)$ Å^3, $Z = 2$, $M = 944.84$, $d_{calc} = 1.532$ g cm^{-3}, μ(MoKα) = 2.340 mm^{-1}. For a typical crystal, intensities of 18247 reflections were measured with a Rigaku R-AXIS IIc image plate system (using graphite-monochromated MoKα radiation from a Rigaku RU200 rotating anode operated at 50 kV and 90 mA), and 8182 independent reflections were used during refinement. A multi-scan absorption correction was applied using the REQAB program under CrystalClear. The structure was solved using SHELXS-97[22] and refined using SHELXL-97[22] (full-matrix least-squares calculations on F^2) operating in the WinGX program package.[23] Anisotropic thermal displacement parameters were refined for all the non-hydrogen atoms. All hydrogen atoms were included in calculated positions and refined using a riding model. The refinement converged to $R_1 = 0.0589$ for 7132 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1306$ for all reflections. The Flack parameter was 0.008(15). Structural illustrations have been drawn with ORTEP-3 for Windows[24] and PLUTON[25] under WinGX.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 224003. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

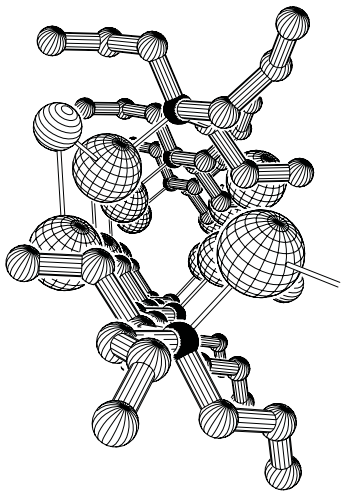

Figure 4 Top view (along the *a*-axis) of the clockwise helix in *P*-**1**. Chloride ions inside the helix and half of the ally ligands have been omitted for clarity.

However, when all CuCl was dissolved by heating before crystallization (method B), we obtained only *P*-**1** helices in all batches. The CD spectra of bulk samples from 15 consecutive preparations indicated enantiopure *P*-**1** batches and, as further confirmation, absolute structure determinations of nine crystals from different batches all exhibited *P*-**1** helices. Using preparative method B, we obtained a non-random distribution of enantiopure batches with regard to *P*-**1** or *M*-**1** helices. We refer to this phenomenon as non-stochastic homochiral crystallization. It is in contrast to the crystallizations of sodium chlorate conglomerates by Kondepudi,[11,12] in which stirring resulted in enantiopure crystal batches but a stochastic distribution (14 *levo* and 18 *dextro*) of optical activity among the batches.

A likely explanation to the non-stochastic distribution of handedness in these helix crystallizations is the presence of optically active impurities (probably of biological origin), which may either favour the formation of *P*-nuclei or disfavour the growth of *M*-crystals by selective surface adsorption.[13] Contamination by nuclei of *P*-**1** itself (from previous experiments) is unlikely since the helices are air-sensitive and decompose readily outside the Schlenk tube. Triallylamine could be a source of trace impurities, but optical activity could not be detected in neat triallylamine and purification by distillation had no effect, so the impurity concentration must be very low. Neither could any optical activity be detected when CuCl was added. Solutions that contain optically active impurities, present in concentrations well below the level of detection, may be referred to as cryptochiral.[14]

It is well-known that nuclei or seeds of a given phase may contaminate a laboratory (or even a factory) and predetermine

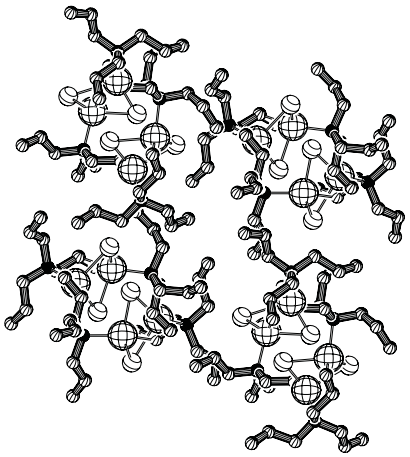

Figure 5 Top view of four helices, showing how allyl groups from different helices intercalate.

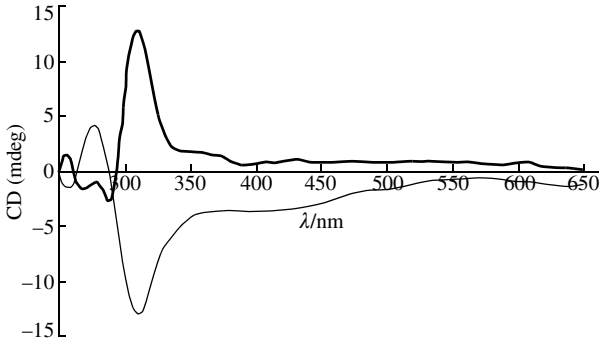

Figure 6 Solid-state CD spectra for *P*-**1** (thick line) and *M*-**1** (thin line).

all following crystallizations to yield the same phase, but if trace amounts of *foreign* molecules can control the chirality of a crystallizing helix, a pendant to the findings of Singleton and Vo[15,16] can be envisioned. They obtained a non-random distribution of (*R*)- and (*S*)-alcohol from the autocatalytic reaction of Soai[17–19] and suggested that chiral trace impurities in the solvent could be responsible. Both crystallization-induced asymmetric transformation (such as single-colony growth of *P*-**1**) and autocatalysis with amplification of chirality (such as the Soai reaction) are plausible mechanisms in a theory describing the origin of biomolecular homochirality. The possibility that both mechanisms are highly enantioselective, as well as sensitive to a cryptochiral environment, indicates how homochirality may propagate from one compound to another and from one location to another. More experiments are obviously needed to verify the existence of non-stochastic homochiral crystallizations, but if many compounds can be shown to exhibit this behaviour, the case for a prebiotic mechanism to the origin of homochirality is strengthened. Meanwhile, realising that many (all?) chemical reactions take place in a cryptochiral environment (as a result of three billion years of life) should be useful.

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References

1 C. Piguet, G. Bernardinelli and G. Hopfgartner, *Chem. Rev.*, 1997, **97**, 2005.
2 L. Perez-Garcia and D. B. Amabilino, *Chem. Soc. Rev.*, 2002, **31**, 342.
3 (*a*) B. L. Feringa and R. A. van Delden, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 3419; (*b*) M. Vestergren, J. Eriksson and M. Hakansson, *Chem. Eur. J.*, 2003, **9**, 4678.
4 U. Siemeling, I. Scheppelmann, B. Neumann, A. Stammler, H. G. Stammler and J. Frelek, *Chem. Commun.*, 2003, 2236.
5 K. Biradha, C. Seward and M. J. Zaworotko, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 492.
6 T. Ezuhara, K. Endo and Y. Aoyama, *J. Am. Chem. Soc.*, 1999, **121**, 3279.
7 M. Hakansson, K. Brantin and S. Jagner, *J. Organomet. Chem.*, 2000, **602**, 5.
8 H. D. Flack and G. Bernardinelli, *Acta Crystallogr., A*, 1999, **A55**, 908.
9 H. D. Flack and G. Bernardinelli, *J. Appl. Crystallogr.*, 2000, **33**, 1143.
10 (*a*) R. Kuroda and T. Honma, *Chirality*, 2000, **12**, 269; (*b*) S. Hirano, K. Yoshizawa, F. Toda and Z. Urbanczyk-Lipkowska, *Mendeleev Commun.*, 2003, 141.
11 D. K. Kondepudi, J. Laudadio and K. Asakura, *J. Am. Chem. Soc.*, 1999, **121**, 1448.
12 D. K. Kondepudi, R. J. Kaufman and N. Singh, *Science*, 1990, **250**, 975.
13 I. Weissbuch, M. Lahav and L. Leiserowitz, *Cryst. Growth Des.*, 2003, **3**, 125.
14 K. Mislow, *Collect. Czech. Chem. Commun.*, 2003, **68**, 849.
15 D. A. Singleton and L. K. Vo, *J. Am. Chem. Soc.*, 2002, **124**, 10010.
16 D. A. Singleton and L. K. Vo, *Org. Lett.*, 2003, **5**, 4337.
17 K. Soai, I. Sato, T. Shibata, S. Komiya, M. Hayashi, Y. Matsueda, H. Imamura, T. Hayase, H. Morioka, H. Tabira, J. Yamamoto and Y. Kowata, *Tetrahedron: Asymmetry*, 2003, **14**, 185.
18 K. Soai, T. Shibata, H. Morioka and K. Choji, *Nature*, 1995, **378**, 767.
19 K. Soai, T. Shibata and I. Sato, *Acc. Chem. Res.*, 2000, **33**, 382.
20 M. Hakansson, *Inorg. Synth.*, 1998, **32**, 222.
21 R. N. Keller and H. D. Wycoff, *Inorg. Synth.*, 1946, **2**, 1.
22 G. M. Sheldrick, *SHELX97 – Programs for Crystal Structure Analysis (Release 97-2)*, Institut für Anorganische Chemie der Universität, D-3400 Göttingen, Germany, 1998.
23 L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.
24 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.
25 A. L. Spek, *PLATON. A Multipurpose Crystallographic Tool*, Utrecht University, The Netherlands, 2002.

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