On the spontaneous induction of chirality in the preparation of Werner's complex *cis*-[CoBr(NH_3)(en)$_2$]Br_2†

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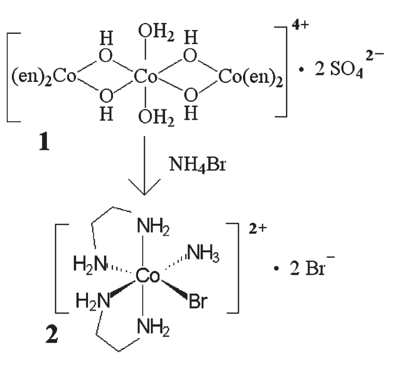
The product obtained directly from the standard reaction to produce Werner's complex *cis*-[CoBr(NH_3)(en)$_2$]Br_2 is shown, *via* structure determination from powder X-ray diffraction data, to be a racemic crystalline phase; implications of this observation in relation to previous reports that this reaction leads to significant enantiomeric excesses are discussed.

There is considerable interest in the phenomena of chiral symmetry breaking, spontaneous resolution and chiral amplification, as one or more of these processes may have been crucial in the development of homochirality among the building blocks of life.[1,2] A system that has been studied closely[3–7] in relation to these phenomena is the reaction (Scheme 1) of [Co(H_2O)$_2${(OH)$_2$Co(en)$_2$}$_2$](SO_4)$_2$ (denoted **1**) with NH_4Br to give the chiral complex *cis*-[CoBr(NH_3)(en)$_2$]Br_2 (denoted **2**). This reaction is of considerable historical interest[8] as **2** and its chlorine analogue were the first octahedral metal complexes to be resolved into Δ and Λ stereoisomers,[9] 12 years after Werner's original prediction[10] that octahedral ions of the type M(en)$_2$XY should exist as enantiomeric pairs. Thus, studies relating to the chirality of **2** have a direct bearing on the history of the stereochemistry of coordination compounds.

The reaction from **1** to **2** has been reported to be optimized[3,5,6] for spontaneous resolution by variation of experimental parameters such as the rate of stirring, temperature, concentration and molar ratio of reactants, and has been shown to lead to a high enantiomeric excess (of random sense). It has also been shown that, when the reaction system is seeded with a catalytic quantity of an optically active sample of the product, the reaction yields a high enantiomeric excess (of the same enantiomer) of the product, thus demonstrating chiral autocatalysis.[4]



Scheme 1

Studies of spectroscopic,[7] thermodynamic[5,6] and kinetic[6] properties of this reaction have provided insights into both the mechanism of the reaction and the mechanism of spontaneous resolution. Although the reaction is difficult to study directly by spectroscopic techniques, as **1** is highly insoluble in the reaction medium, the reaction is believed[7] (on the basis of results from absorption spectroscopy) to proceed *via* an intermediate [Co(H_2O)(OH)(en)$_2$]. The mechanism of chiral asymmetry generation has been explained[4,5] on the basis that the product is formed as a conglomerate crystalline phase. For a conglomerate, each individual crystal is homochiral, containing either the Δ form only or the Λ form only (and thus a racemic sample of this material would exist as a physical mixture of these homochiral crystals); clearly, it is obligatory that such crystals have a chiral space group. It is proposed that the product **2** crystallizes at an early stage of the reaction, and that the chirality of the first formed crystals is transmitted through secondary nucleation to promote further crystallization of the same chirality. When less than 50% of the product has crystallized, the enantiomeric excess can approach 100%.

As part of our interest in issues relating to chirality in crystallization processes, we have made extensive attempts to reproduce the spontaneous resolution experiments under the conditions described previously, but have consistently been unable to obtain an optically active product in spite of systematic variation of all the experimental conditions within our control (purity of reagents, solvents, temperature and concentration).[11] In light of this (initially surprising) observation, we have undertaken to determine the structure of the material produced directly in this reaction, employing powder X-ray diffraction (XRD) techniques (see below). In this regard, it is important to recognize that the two previous reported crystal structure determinations[12] of **2** (both from single-crystal XRD) were both carried out on samples obtained by re-crystallization of **2**, rather than studies of the solid product obtained directly in the reaction.

One of these previous structure determinations,[13] in the chiral space group $P2_12_12_1$ (with one molecule in the asymmetric unit), was on a single crystal grown from a homochiral sample ((+)$_{589}$-enantiomer) of **2**, with the aim of determining the absolute configuration (Λ). This structure is here denoted phase I. The other previous structure determination[14] of **2** (actually a dihydrate of **2**), on a single crystal prepared by crystallization from a racemic mixture of **2**, is a racemic structure in the achiral space group $C2/c$. This structure is here denoted phase II. We note that neither of

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these cases involved a conglomerate crystalline phase of **2** being obtained from a racemic system.

The procedure[3] for preparation of **2** (Scheme 1) involves treatment of **1** with an excess of NH_4Br in water, and precipitation of the product.[15] Our powder XRD studies of the product indicate that a new solid phase of **2** is produced that is different from the previously reported structures of phases I and II discussed above. This new phase is denoted phase III, and in the present context it is clearly important to establish the structural properties of this new phase. However, as the product is obtained as a microcrystalline powder that does not contain crystals of suitable size to carry out structure determination by single-crystal XRD, alternative approaches for structural characterization are required. Fortunately, there have been significant advances in recent years in the opportunities for carrying out complete structure determination of molecular solids directly from powder XRD data,[16] particularly through the development of the direct-space strategy for structure solution.[16a] Here we have exploited the opportunity provided by these techniques in order to determine the structure of the powder sample of **2** (phase III) obtained directly from the reaction.

The powder XRD pattern[17,18] of the sample of **2** obtained directly from the reaction was indexed using the program TREOR,[19] giving the following unit cell with monoclinic metric symmetry: a = 7.66 Å, b = 12.39 Å, c = 13.97 Å, β = 98.7°. The space group was assigned from systematic absences as $P2_1/n$. Unit cell and profile refinement were carried out for this unit cell and space group using the LeBail fitting procedure, leading to a good quality of fit (R_{wp} = 8.48%, R_p = 6.76%). With one independent formula unit $[Co(C_2H_8N_2)_2(NH_3)Br]Br_2$ in the asymmetric unit, and Z = 4 for space group $P2_1/n$, the calculated density is 2.202 g cm^{-3}, which lies within the anticipated density range for this material.

Structure determination was carried out directly from the powder XRD data using the direct-space genetic algorithm (GA) technique[20] (in the program EAGER[21]) for structure solution, followed by Rietveld refinement (using the program GSAS[22]). The structural model used in the GA structure solution calculation[23] involved three independent fragments and a total of 12 structural variables.[24] The best structure solution was used as the starting model for Rietveld refinement, in which standard restraints were applied to bond lengths and bond angles, and were relaxed gradually as the refinement progressed. Hydrogen atoms were inserted in calculated positions. The good agreement between calculated and experimental powder XRD patterns in the final Rietveld refinement[25] (Fig. 1), together with the fact (see below) that the structure obtained is chemically and structurally sensible, vindicates the correctness of the structure.

The crystal structure[26,27] is shown in Fig. 2 (fractional coordinates are given in Supplementary Information). The *cis*-$[CoBr(NH_3)(en)_2]^{2+}$ complexes are arranged in chains along the *a*-axis and in chains along the *b*-axis; in each type of chain, neighbouring complexes are linked by N–H···Br^-···H–N interactions. Along the *a*-axis, neighbouring repeat units in the chain are related by translation and the chain is relatively straight; along the *b*-axis, neighbouring repeat units in the chain are related by the 2_1 symmetry operation and the chain is helical. Within the context of the present work, however, the most important feature of the crystal structure is that it is a racemic structure in an achiral space group ($P2_1/n$). Thus, our observation (see above) that we have never observed any enantiomeric excesses in our experiments to prepare **2** is fully explained by the fact that the structure of the product (phase III) obtained directly from the reaction in our experiments is a racemic crystalline phase.

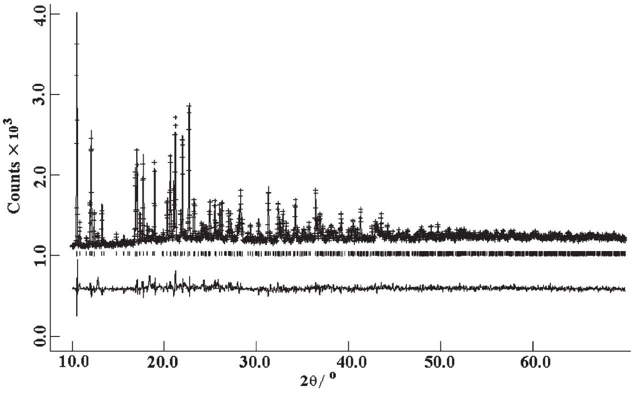

Fig. 1 Experimental (+ marks), calculated (solid line), and difference (lower line) powder XRD profiles for the final Rietveld refinement of phase III of **2**.

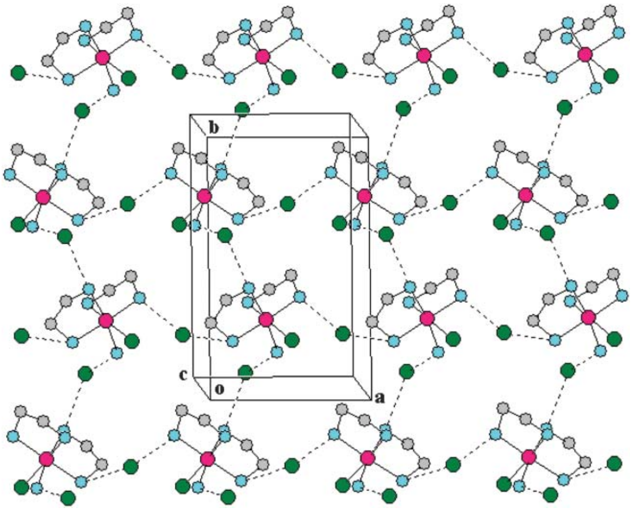

Fig. 2 Crystal structure of phase III of **2** viewed nearly along the *c*-axis, showing the straight and helical chains that run along the *a*-axis and *b*-axis respectively (Co – red; Br – green; N – blue; C – grey). Hydrogen atoms are omitted for clarity.

In conclusion, our studies of the solid product obtained directly from the reaction of **1** to **2** indicate that a new racemic crystalline phase (phase III) is consistently obtained. We have thus been unable to observe the production of **2** as a conglomerate crystalline phase from the reaction under any of the wide range of experimental conditions considered in our work.[11,28] As conglomerate crystallization is a pre-requisite for the spontaneous induction of chirality in this system, it is clear that our results are not in accord with previous reports of spontaneous resolution in the formation of **2** (recalling that, in these previous studies, no structure determination was actually carried out on the solid material obtained directly from the reaction). Although our experiments to prepare **2** have consistently yielded the racemic phase III, it would not be correct to infer that conglomerate crystallization of **2** *cannot* occur, and it is certainly not our intention to cast doubt on the veracity of the previously published work. Nevertheless, our results clearly demonstrate that there is an intrinsic irreproducibility between the results obtained by different groups on this system, even when experimental procedures are followed in a manner that is ostensibly a faithful replication of previously reported procedures. These observations may reflect the types of difficulties that can often be encountered in reproducibly obtaining specific crystalline forms of a compound, as manifested *inter alia* in cases of "disappearing polymorphs".[29]

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12 From a survey of the Cambridge Structural Database (Version 5.26, update August 2005).

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15 From the stoichiometry of the reaction from **1** to **2**, we note that the reaction must yield another (unknown) cobalt species in addition to **2**, and precipitation of **2** thus takes place from a solution containing this other cobalt species and excess NH_4Br.

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17 For structure determination, the powder XRD pattern was recorded at ambient temperature on Station 2.3 at the Synchrotron Radiation Source, Daresbury Laboratory [capillary, 0.7 mm; λ = 1.3034 Å (the maximum flux at this station is between 1.1 Å and 1.5 Å); 2θ range 10–70°; step size 0.02°; data collection time 7 h].

18 Powder XRD patterns of samples of **2** obtained directly from the reaction often contain low-intensity peaks at 2θ = 15.15° and 21.82° for $CuK_{\alpha1}$ radiation (12.79° and 18.39° in Fig. 1) that are not indexed by the unit cell determined here for **2**. These peaks are confidently assigned as impurity phases on the following basis: (i) these peaks usually have significantly different linewidths (broader) from other peaks (due to **2**) in the same 2θ region, and (ii) the intensities of these peaks relative to those due to **2** (and relative to each other) can vary substantially for different samples obtained on repeating the preparation procedure (in some cases, the peak at 12.79° is absent). The peak at 12.79° is assigned as Co(OH)Br ((*a*) A. Ludi, S. Locchi and Y. Iitaka, *Chimia*, 1961, **15**, 532) and the peak at 18.39° is assigned as NH_4Br ((*b*) H. A. Levy and S. W. Peterson, *J. Am. Chem. Soc.*, 1953, **75**, 1536), both of which are plausible impurity phases in the material recovered from the reaction.

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23 The GA calculation involved the evolution of 80 generations for a population of 100 trial structures, with 50 mating operations and 30 mutation operations carried out in each generation.

24 The three fragments were the *cis*-$[CoBr(NH_3)(en)_2]^{2+}$ complex and two Br^- anions. For the *cis*-$[CoBr(NH_3)(en)_2]^{2+}$ complex, 6 structural variables $\{x, y, z, \theta, \varphi, \psi\}$ are required to define the position and orientation in the unit cell; the intramolecular geometry, taken from the structure reported in ref. 13, was fixed in the structure solution calculation. For each Br^- anion, 3 structural variables $\{x, y, z\}$ are required to define the position in the unit cell.

25 Final Rietveld refinement: a = 7.6704(5) Å, b = 12.4028(7) Å, c = 13.9885(10) Å, β = 98.726(6)°, R_{wp} = 9.62%, R_p = 7.40%; 3000 profile points; 110 refined variables.

26 Refined Co–N distances for en ligands: 1.965 Å, 1.978 Å, 1.992 Å, 1.986 Å; Co–N distance for NH_3 ligand: 1.976 Å; Co–Br distance 2.408 Å; N–C–C–N torsion angles for en moieties: −48.48° and −49.78°.

27 Along the *a*-axis, the geometries of the $N–H\cdots Br^-\cdots H–N$ interactions within the chain are (N···Br distance, N–H···Br angle): 3.31 Å, 130°; 3.32 Å, 149° (in both cases, the N–H bonds are from NH_2 groups of the complexes). Along the *b*-axis, the geometries of the $N–H\cdots Br^-\cdots H–N$ interactions within the chain are: 3.28 Å, 169°; 3.37 Å, 152° (in the former, the N–H bond is from an NH_2 group; in the latter, the N–H bond is from the NH_3 group). On geometric criteria, it is reasonable to assign these contacts as N–H···Br hydrogen bonds. The bromide anions in these chains and the bromide ligand in the complex are also involved in other contacts with NH_2 and NH_3 groups in neighbouring complexes, but the N···Br distances are greater than 3.4 Å and in some cases the N–H···Br angles are far from linear; these contacts are more appropriately assigned as van der Waals interactions.

28 In order to further explore the possibility of obtaining a conglomerate crystalline phase from a racemic sample of **2**, re-crystallization of the sample of **2** obtained directly from the reaction was carried out using a variety of solvents and under a range of different concentration conditions. The samples obtained were either phase II or phase III or mixtures of phases II and III. We found no evidence for the formation of phase I in these re-crystallization experiments.

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