Absolute Asymmetric Synthesis

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Doctoral Thesis

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The Chymists are a strange class of mortals impelled by an almost insane impulse to seek their pleasure among smoke and vapor, soot and flame poisons and poverty, yet among all these evils I seem to live so sweetly, that may I die if I would change places with the Persian king.

J. J. Becher, 1669

Abstract

Absolute asymmetric synthesis is the synthesis of optically active products from achiral or racemic precursors only. This has generally been regarded as impossible and is relevant in the discussion of the origins of biomolecular homochirality. A possible route to absolute asymmetric synthesis involves total spontaneous resolution, which is possible for stereochemically labile substances which crystallise as conglomerates (*i.e.* the enantiomers crystallise in separate crystals).

Using total spontaneous resolution it was, for the first time, possible to prepare bulk-quantities of configurationally labile five-, seven-, and nine-coordinate enantiomers, containing only achiral ligands. Previously, only four- and six-coordinate complexes have been prepared enantiomerically pure in bulk quantities. Spontaneous resolution of eight-coordinate complexes has also been reported. It was also possible to perform total spontaneous resolution of a diaryl sulphide, an octanuclear organo(oxo)zinc complex, and a diindenylzinc complex. In the case of a helical coordination polymer based on copper(I) chloride and triallylamine, it was found that repeated synthesis always yielded an excess of the same enantiomer, possibly due to the influence of cryptochirality.

It has previously been practically impossible to measure enantiomeric excesses in stereochemically labile microcrystalline samples. A method utilising quantitative solid-state CD spectroscopy has been introduced to solve this problem.

In the case of the chiral organometallic reagent di(3-picoline)di(1-indenyl)zinc, it was possible to perform reactions with *N*-chlorosuccinimide in the presence of methanol and *p*-benzoquinone yielding optically active stereochemically inert 1-chloroindene in high yield and high enantiomeric excess (up to 89% ee).

During the cause of theses studies, three cases of concomitant crystallisation of racemic and chiral phases have been discovered. This is a rare phenomenon of considerable interest *e.g.* in structure prediction.

The first synthetic route to well-defined hydridoalkylzincates is also reported.

Keywords: absolute asymmetric synthesis, enantioselective synthesis, chirality, optical resolution, spontaneous resolution, conglomerate, organozinc reagents, organometallic chemistry, coordination chemistry, supramolecular chemistry, intermolecular interactions

Publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. Reprints were made with permission from the publishers.

Paper I: *Resolution of Seven-Coordinate Complexes*
A. Lennartson, M. Vestergren, M. Håkansson, *Chem. Eur. J.* **2005**, *11*, 1757.

Paper II: *Total Spontaneous Resolution of Five-Coordinate Complexes*
A. Lennartson, M. Håkansson, *Angew. Chem. Int. Ed.* **2009**, *48*, 5869.

Paper III: *cis- and trans-Bis(benzoylacetonato)pyridinecopper(II): co-crystallisation of isomers and reversible pyridine loss with retention of crystallinity*
A. Lennartson, M. Håkansson, S. Jagner, *N. J. Chem.* **2007**, *31*, 344.

Paper IV: *Total spontaneous resolution of nine-coordinate complexes*
A. Lennartson, M. Håkansson, *CrystEngComm* **2009**, *11*, 1979.

Paper V: *Non-stochastic homochiral helix crystallization: cryptochirality in control?*
M. Vestergren, A. Johansson, A. Lennartson, M. Håkansson, *Mendeleev Commun.* **2004**, 258.

Paper VI: *Synthesis and Total Spontaneous Resolution of an Octanuclear Organo(oxo)zinc Complex*
A. Pettersen, A. Lennartson, M. Håkansson, *Organometallics* **2009**, *28*, 3567.

Paper VII: *Dipyridinium dichromate: an achiral compound forming chiral crystals*
A. Lennartson, M. Håkansson, *Acta Cryst.* **2009**, *C65*, m182.

Paper VIII: *Facile Synthesis of Well-Defined Sodium Hydridoalkylzincates(II)*
A. Lennartson, M. Håkansson, S. Jagner, *Angew. Chem. Int. Ed.* **2007**, *46*, 6678.

Paper IX: *Concomitant formation of chiral and racemic crystals of a diaryl sulfide*
A. Lennartson, T. Wiklund, M. Håkansson, *CrystEngComm* **2007**, *9*, 856.

Paper X: *Concomitant polymorphism: Crystallising dichloro-bis(2,4-lutidine)-zinc as both chiral and racemic phases*
A. Lennartson, S. Olsson, J. Sundberg, M. Håkansson, *Inorg. Chim. Acta* **2009**, DOI: 10.1016/j.ica.2009.08.008.

Paper XI: *A Different Approach to Enantioselective Organic Synthesis: Absolute Asymmetric Synthesis of Organometallic Reagents*
A. Lennartson, S. Olsson, J. Sundberg, M. Håkansson, *Angew. Chem. Int. Ed.* **2009**, *48*, 3137.

Paper XII: *Towards Total Spontaneous Resolution of sec-Butylzinc Complexes*
A. Lennartson, A. Hedström, M. Håkansson, *submitted.*

Paper XIII: *Spontaneous Resolution and Carbonation of Chiral Benzyllithium Complexes*
A. Lennartson, J. Sundberg, T. Wiklund, G. Hilmersson, M. Håkansson, *submitted*.

Abbreviations

2,4-lut	2,4-lutidine; 2,4-dimethylpyridine
2,6-lut	2,6-lutidine; 2,6-dimethylpyridine
3,5-lut	3,5-lutidine; 3,5-dimethylpyridine
2-pic	2-picoline; 2-methylpyridine
3-pic	3-picoline; 3-methylpyridine
acac	acetylacetonate
ally	triallylamin
Bn	benzyl
bzac	benzoylacetonate
bpy	2,2'-bipyridine
CD	circular dichroism
CPL	circularly polarised light
CSD	Cambridge Structural Database
ee	enatiomeric excess
en	ethylenediamine
Et	ethyl
dbm	dibenzoylmethanate
de	diastereomeric excess
dme	dimethoxyethane
dmeda	*N,N′*-dimethylethylenediamine
ind	1-indenyl
i-Pr	*iso*-propyl
IR	infra red
Ph	phenyl
phet	1-phenylethyl
Ln	lanthanide atom
n-Bu	*n*-butyl
NCS	*N*-chlorosuccinimide
oda	oxodiacetate
pmdta	*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine
py	pyridine
s-Bu	*sek*-butyl
thf/THF	tetrahydrofuran
teeda	*N*,*N*,*N*',*N*'-tetraethylethylenediamine
tmeda	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
tmpda	*N*,*N*,*N*',*N*'-tetramethylpropylenediamine
UV	ultra violet
vinim	1-vinylimidazol

Contents

Chapter 1

Introduction

Dieses hade ich allerdings vorher zu erinnern nöthig gefunden, indem diese Sachen zuvor wohl bekannt seyn müssen, ehe man die Operation anfänget. Ich schreite nunmehr unter göttlichem Beystande zum Wercke.

Hermann Boerhaave, Anfangsgründe der Chymie, vol I, 1762.

Absolute asymmetric synthesis is the synthesis of optically active products from achiral or racemic precursors without the use of optically active catalysts or auxiliaries.[1, 2] To most organic chemists, well accustomed to the problems of ordinary asymmetric synthesis, it may sound as obscure as alchemy. Modern organic textbooks contain statements like "*A reaction that uses optically inactive reactants and catalysts cannot produce a product that is optically active. Any chiral product must be formed as a racemic mixture.*"[3] or "*Reaction between two optically inactive (achiral) partners always leads to an optically inactive product– either racemic or meso. Put another way, optical activity can't come from nowhere; optically active products can't be produced from optically inactive reactants.*"[4] Pasteur originally held the opinion that chiral molecules could not be synthesised in the laboratory, not even as racemates. This was soon disproved by the synthesis of *i.e.* malic and lactic acids followed by optical resolution using optically active bases. In 1894 Fisher reported the first asymmetric synthesis: transformation of hexoses to heptoses without the formation of diastereomers.[5] A vague idea that circularly polarised light (CPL) may induce an enantiomeric excess during a chemical reaction was introduced by Le Bel in 1874.[6, 7] Although several unsuccessful attempts were made over the years, it was not until 1929 that the goal was reached.[8-10] Numerous enantioselective reactions based on CPL have been reported over the years, but these reactions suffer from the fact that the handedness of the CPL is deliberately chosen by man.

In the late 1930's Havinga found that configurationally labile *N*-allyl-*N*-ethyl-*N*-methyl-*N*-phenyl ammonium iodide gave rise to an enantiomeric excess on slow crystallisation.[11] *N*-allyl-*N*-ethyl-*N*-methyl-*N*-phenyl ammonium iodide undergoes spontaneous resolution on crystallisation,[12, 13] *i.e.* the two enantiomers appear in separate crystals; since the salt is configurationally labile, the solution remained racemic during the crystallisation and since all crystals occasionally grew from a single nucleus, an enantiomeric excess could be obtained. This was the first example of total spontaneous resolution. Total spontaneous resolution of prochiral reactive substrates or chiral chemical reagents has since been performed and such substances have been used in enantioselective synthesis, as well as inter- and intramolecular photochemical reactions. Absolute asymmetric synthesis may prove to be a valuable method in enantioselective synthesis, in the optical resolution of stereochemically labile compounds and may also give a hint about the processes that led to the almost exclusive occurrence of *e.g. L*-amino acids and *D*-sugars in nature. In this thesis, total spontaneous resolution is used for absolute asymmetric synthesis of labile coordination compounds, organometallic reagents and chiral supramolecular materials.

Chapter 2

Chiral and racemic crystals

…the whole doctrine of crystallization will still continue to be, as it has been heretofore, a perfect chaos ; and those who undertake the description of methodical distribution of crystallized bodies, will inevitably lose their labour.

Torbern Bergman, Of the forms of crystals, Physical and chemical essays vol. II, 1788.

There is in principle three different ways for a racemate to crystallise: as a racemic phase, as a conglomerate of chiral crystals, or as a solid solution. In the case of a racemic phase ("racemic compound" in older literature) each crystal will contain equal amounts of the two enantiomers. In a conglomerate, however, the two enantiomers will crystallise in separate crystals, and the formation of a conglomerate is therefore called spontaneous resolution. Usually, the whole collection of crystals is still racemic, since there will be an equal amount of (+)- and (-)-crystals. Whether a substance crystallises as a conglomerate or not can be decided from its space group symmetry. Space groups can be divided in two main groups: centrosymmetric and non-centrosymmetric space groups (sometimes inadequately referred to as centric or acentric, but these terms should be reserved for intensity probability distributions).[14] Among the non-centrosymmetric space groups, there are 65 space groups (Table 2-1) that lack both reflection and inversion symmetry and those space groups are the only ones in which enantiopure substances can crystallise. These space groups have generally been called "chiral", but this is improper (except for the 11 pairs of enantiomorphous space groups, see below) since the space groups themselves are not chiral.[15] The term Sohncke space group has been proposed by Flack,[15] since these 65 space groups were first derived by Leonard Sohncke in 1874. Achiral molecules may also crystallise in Sohncke space groups and in these cases the chirality of the crystal structure arises from chiral packing of the molecules, *e.g.* formation of supramolecular helices. A special subgroup of the Sohncke space groups is the 22

enantiomorphous space groups. If one enantiomer crystallises in an enantiomorphous space group, the opposite enantiomer will crystallise in the other space group of that pair. An example of an enantiomorphous pair is $P3_1$ and $P3_2$; the effect arises since equivalent points generated by a 3_1-axis will form a helix, and points generated by a 3_2-axis will form an enantiomorphous helix.

Table 2-1. The 65 Sohncke space groups.

Crystal system	**Space groups**
triclinic	*P*1
monoclinic	*P*2, *P*2$_1$, *C*2
orthorhombic	*P*222, *P*222$_1$, *P*2$_1$2$_1$2, *P*2$_1$2$_1$2$_1$, *C*222$_1$, *C*222, *F*222, *I*222, *I*2$_1$2$_1$2$_1$
tetragonal	*P*4, *P*4$_1$*, *P*4$_3$*, *P*4$_2$, *I*4, *I*4$_1$, *P*422, *P*42$_1$2, *P*4$_1$22*, *P*4$_3$22*, *P*4$_2$22, *P*4$_2$2$_1$2, *P*4$_3$2$_1$2*, *P*4$_1$2$_1$2*, *I*422, *I*4$_1$22
trigonal	*P*3, *P*3$_1$*, *P*3$_2$*, *R*3, *R*32, *P*312, *P*321, *P*3$_1$21*, *P*3$_2$21*, *P*3$_2$12*, *P*3$_1$12*
hexagonal	*P*6, *P*6$_1$*, *P*6$_5$*, *P*6$_2$*, *P*6$_4$*, *P*6$_3$, *P*622, *P*6$_1$22*, *P*6$_5$22*, *P*6$_2$22*, *P*6$_4$22*, *P*6$_3$22
cubic	*P*23, *P*2$_1$3, *F*23, *I*23, *I*2$_1$3, *P*432, *P*4$_2$32, *P*4$_3$32*, *P*4$_1$32*, *F*432, *F*4$_1$32, *I*432, *I*4$_1$32

*enantiomorphous space groups

The crystallisation of a chiral substance in a Sohncke space group does not necessarily imply that the crystals are enantiopure, there are two exceptions. First, the asymmetric unit may consist of two molecules of opposite configuration. This is extremely rare.[15] A far more common phenomenon is twinning by inversion ("racemic twinning"). Twinning is a phenomenon where two components of a crystal are related by a symmetry element not described by the space group. It should not be confused with crystals that simply have grown together in a random way during crystallisation. In space group $P2_1$ for instance, inversion-twinning has the effect of cancelling any electric dipole moments of the crystal components. Twins may consist of two large domains and in such a case it may be possible to separate the two domains by cleaving the crystal. Twinning may also appear on a sub-microscopical level.

Chapter 3

Crystallisation and spontaneous resolution

Every species of salt cristallizes in a peculiar form, and even each salt varies in the form of its cristals according to circumstances, which take place during cristallization. We must not from thence conclude that the saline particles of each species are indetermiate in their figures : The primative particles of all bodies, especially of salts, are perfectly constant in their specific forms ; but the cristals which form in our experiments are composed of congeries of minute particles, which, though perfectly equal in size and shape, may assume very dissimilar arrangements, and consequently produce a vast variety of regular forms…

Lavoisier, Elements of Chemistry, 1790.

3.1. Formation of crystals

Crystallisation is believed to start with the formation of a so-called embryo, which consists of a number of molecules associated to each other. These embryos are unstable with respect to dissociation unless they reach a critical size represented by the critical radius, r_c (Fig. 3-1). The critical radius is not a constant, but depends on temperature; the higher the temperature, the larger is r_c.[16] The structure of the embryos is not known with certainty; they might be well ordered structures, or more diffuse aggregates. Aggregates of critical size are called nuclei and may perhaps consist of 10^1 to 10^3 molecules.[16] They are microscopically small crystal fragments that may grow into crystals. The formation of the first nucleus (in the absence of previous crystals) in the solution or melt is called primary nucleation. Primary nucleation may be divided in two categories, homogenous and heterogeneous nucleation. Homogeneous nucleation is a spontaneous process, while heterogeneous nucleation is induced by foreign particles, such as dust. Since it is practically impossible to eliminate particles from solutions, homogeneous nucleation is believed to be rare.[16] The most active "heteronuclei" are believed to be approximately 0.1-1 μm.[16]

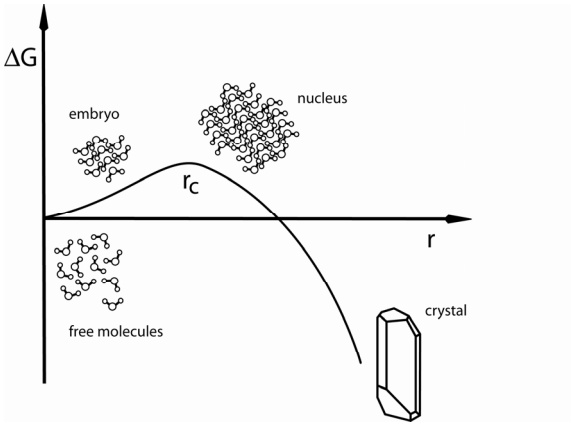


Figure 3-1. The formation of a crystal is believed to start with a so-called embryo, which may grow into a crystal nucleus. Crystal nuclei are thermodynamically stable and will grow into crystals in a supersaturated solution.

Once a crystal (or a crystal nucleus) has formed, it may induce formation of more crystals, a phenomenon known as secondary nucleation. The initial crystal emits small fragments, secondary nuclei, each of which may grow into a new crystal. Crystals formed this way are clones of the original crystal; they are always of the same phase. It has been shown, in the case of sucrose, that a supersaturated solution flowing around a crystal gives rise to a large number of secondary nuclei and new crystals deposit downstream.[17]

If crystals are present in a saturated solution the system is at equilibrium and the rate of crystallisation equals the rate of dissolution. At a slight degree of supersaturation, sometimes referred to as metastable supersaturation (Fig. 3-2),[16, 18, 19] new crystals will not form but if a crystal is present it will grow until the solution is saturated. At a higher degree of supersaturation, known as labile supersaturation, primary nucleation will occur. The boundary between labile and metastable supersaturation (*i.e.* the highest concentration at a given temperature where spontaneous nucleation cannot be prevented) is not, however, a sharp line. The metastable zone will be more narrow in an agitated solution.

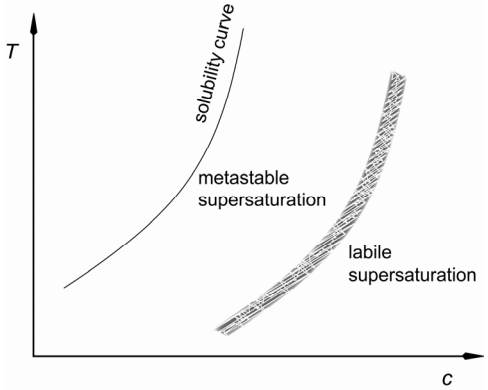


Figure 3-2. The idea of metastable and labile supersaturation was introduced by Ostwald in the late 19th century. In the metastable region a crystal may grow, but no spontaneous nucleation occurs.

3.2. Spontaneous resolution

A fused mixture of two enantiomers may, as pointed out earlier, crystallise as a conglomerate of enantiomerically pure crystals, as a racemic phase or as a solid solution.[20] In the first case (spontaneous resolution), the melting point phase diagram will have the characteristics displayed in Fig. 3-3.[20] The phase diagram will display a single eutectic point at the racemic composition and a racemic mixture of the two enantiomers will melt at a specific temperature, as if it was a pure substance. The melting point of the racemic mixture is always lower than the melting points of the pure enantiomers. At point *U* in Fig. 3-3, a sample will consist of crystals of the two enantiomers. The sample will be unaffected by heating until it reaches point *V* at the eutectic temperature (the melting point of the racemic mixture). At this temperature melting will start and the melt will have the eutectic composition, *i.e.* it will be racemic and the temperature will remain constant until the solid phase consists of pure *D*-enantiomer. As heating is continued, the composition of the melt will follow the line *EX* and the last crystals will disappear at temperature *T(X)*.

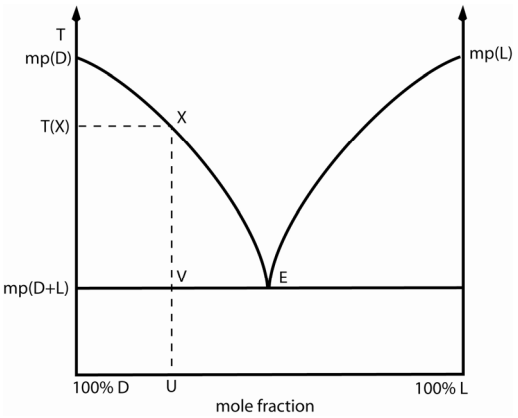


Figure 3-3. melting point phase diagram for a conglomerate, where mp(D) and mp(L) are the melting points of the pure enantiomers *D* and *L*, respectively. mp(D+L) is the melting point of the racemic mixture.

Formation of conglomerates is rare, the most recent estimation based on entries in the Cambridge Structural Database[21] estimates that approximately 8% of organic and metal-organic racemates form conglomerates on average.[22] However, spontaneous resolution appears to be more common in certain categories of compounds than in other. For example, spontaneous resolution in salts appears to be more common than in neutral compounds.[23]

In the case where a racemic mixture crystallises as a racemic phase, the melting point phase diagram will have the appearance displayed in Fig. 3-4.[20] It should be noted that the melting point of the pure enantiomers may be either higher or lower than the melting point of the racemate. The solid phase at a eutectic point will be a well defined mixture of the racemic phase and the major enantiomer; this mixture will have a sharp melting point.

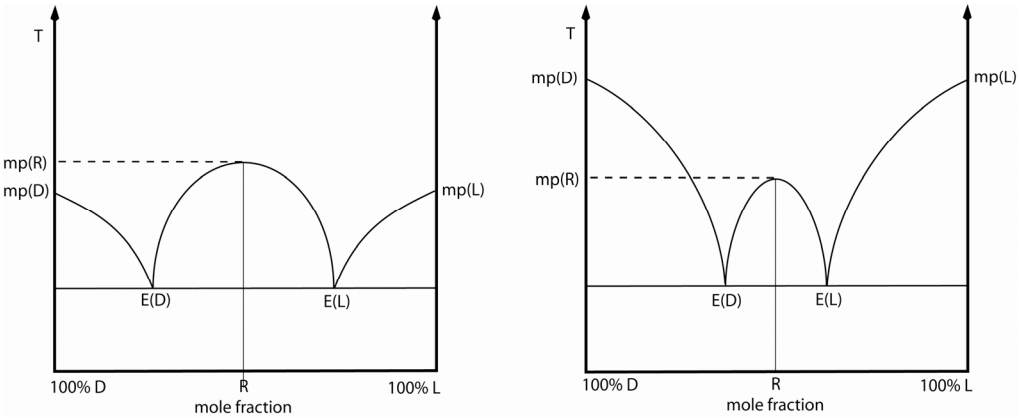


Figure 3-4. The melting point of a racemic phase may be either higher or lower than the melting points of the pure enantiomers, as shown in the melting point phase diagrams. An example of a compound forming a racemic phase with a higher melting point than the pure enantiomers is hyoscyamine. Pure (-)-hyoscyamine melts at 108.5 ºC, while the racemate (atropine) melts at 118-119 ºC.[24] In the case of mandelic acid, on the other hand, the racemate melts at 121.3 ºC and the pure *D*-enantiomer at 133-135 ºC.[24]

If a sample enriched in one enantiomer is fused, there are two possible outcomes (Fig. 3-5). If the mixture has composition *U*, the sample will start to melt at the eutectic temperature, where the temperature will remain constant until pure crystalline *D*-enantiomer remains. The last crystal will disappear at temperature *T(U)*. In the other case, a sample of composition *V* will consist of the pure racemic phase above the eutectic temperature, and fusion will be terminated at temperature *T(V)*.

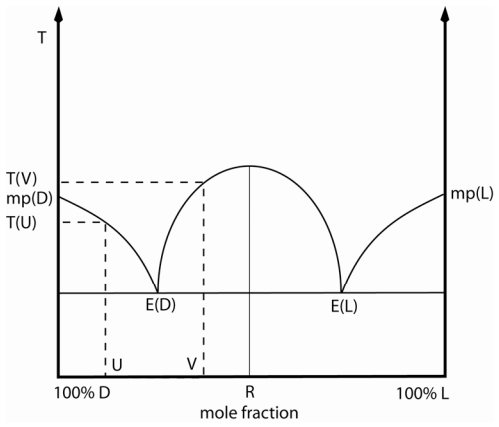


Figure 3-5. A mixture of an enantiomer and the corresponding racemic phase may give the pure enantiomer or the pure racemic phase on partial fusion, depending on the initial composition relative to the eutectic composition.

Solid solutions form when the enantiomers are miscible in various proportions in the solid state. An ideal solid solution is obtained when the melting points of the pure enantiomers and the racemate are equal (Fig. 3-6), but the racemate may also have a higher or lower melting point compared to the pure enantiomers.[20] An example of a substance forming an almost ideal solid solution is camphor. The melting point of the racemate is 178.8 ºC and the melting point of (-)-camphor is 178.6 ºC.[24]

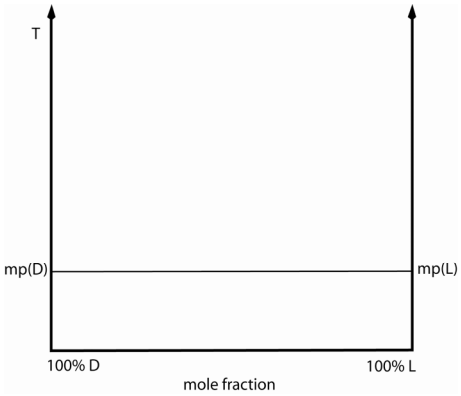


Figure 3-6. An ideal solid solution arises when the enantiomers and the racemate have equal melting points. The figure displays a system where a solid solution is formed over the entire range of enantiomeric composition.

Crystallisation from solution is more complicated and must be explained using ternary phase diagrams. Ternary diagrams are difficult to visualise, and are usually replaced by isothermal triangular sections. Fig. 3-7 represents the case of a conglomerate, where the solvent (*S*) does not form any solvate with the enantiomers (*D* and *L*).

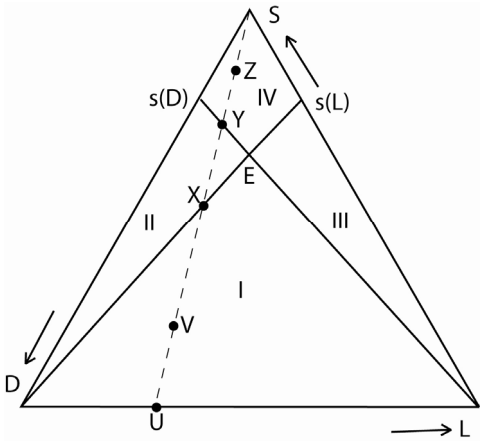


Figure 3-7. A triangular isothermal representation of a ternary phase diagram corresponding to spontaneous resolution. D and L are the two enantiomers, respectively, and S is the solvent. The enantiomers do not form any solvates with the solvent.

The points *s(D)* and *s(L)* are the solubilities of the pure enantiomers; in area II the pure *D*-enantiomer is in equilibrium with the saturated solution, and in area III, the pure *L*-enantiomer is in equilibrium with the saturated solution. In area I, the two solid enantiomers and the saturated solution are in equilibrium. Area IV represents unsaturated solutions. When a sample of composition *U* is mixed with a small amount of solvent, it will reach a point *V* on the line *SU*. All points on *SU* have the same enantiomeric composition, but varying proportions of the solvent. At point X, the last crystals of the *L*-enantiomer dissolve and pure *D*-enantiomer remains in the solid state. At point *Y* the last crystals dissolve and at point *Z* an unsaturated solution remains. Consequently, on evaporation of a solution of composition *Z*, there will first be a separation of pure *D*-crystals until point *X* is reached, the point corresponding to the highest possible yield of the *D*-enantiomer. Further evaporation will give a solid of lower enantiomeric purity. The composition of the deposited crystals will change from *D* to *U* during a complete evaporation.

A change in the temperature will simply result in a displacement of the solubility curve, as shown in Fig. 3-8. This can be used to describe crystallisation by cooling. A mixture of composition *U* will be an unsaturated solution at temperature *T2*, but will deposit crystals of the *D*-enantiomer at the lower temperature *T1*.

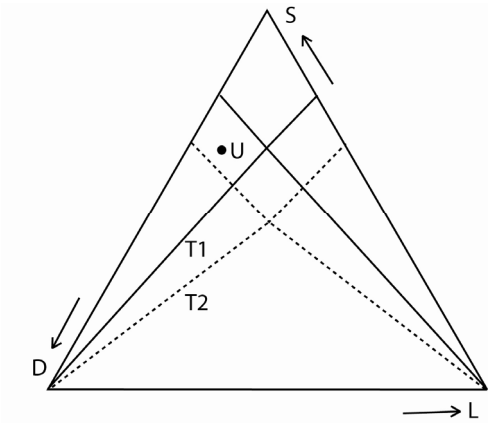


Figure 3-8. A change in temperature will cause a displacement in the solubility curves in the isothermal triangular phase diagrams. Two diagrams representing two temperatures, *T*1 (solid line) and *T*2 (dashed line) are superimposed in the figure.

A ternary phase diagram involving a racemic phase looks somewhat more complicated (Fig. 3-9). When solvent is added to a crystalline sample of composition *U*, it will first enter the area where the *D*-enantiomer, the racemic phase (*R*) and the saturated solution are in equilibrium. At point *V*, the solid sample will consist of the pure *D*-enantiomer, the last traces of the racemic phase being dissolved after crossing the line *DE*. At point *X*, an unsaturated solution remains. If the original composition of the sample is *U2*, the system will reach point *V2* on dilution. In this case the solid remaining will be composed of the racemic phase. On further dilution (*e.g. X2*) an unsaturated solution is obtained.

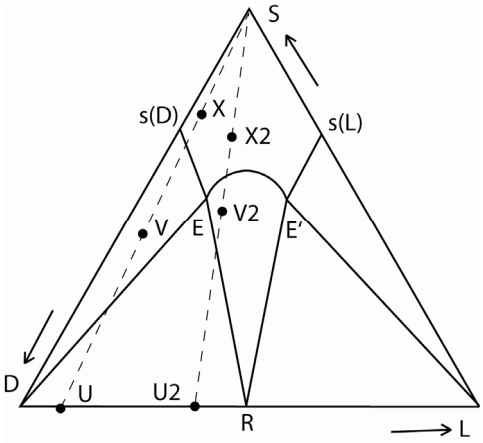


Figure 3-9. A triangular isothermal representation of a ternary phase diagram composed of the pure enantiomers (D and L respectively), a racemic phase (R) and a solvent (S). None of the phases form solvates with the solvent.

3.3. Separation of enantiomers: preferential crystallisation

If a substance crystallises as a conglomerate, the enantiomers will appear in different crystals that can be separated manually from each other.[25] It is sometimes possible to seed a racemic solution with two seeds, physically separated, which will both grow simultaneously. In practice, a racemic solution is usually allowed to flow through two different vessels containing the seeds and the method may be used on a relatively large scale.[26] A more convenient way is to use preferential crystallisation (also known as resolution by entrainment).[19] If the solution is crystallised slowly, seeding may give rise to selective crystallisation of one enantiomer exclusively. The problem is that the degree of supersaturation of the opposite enantiomer will increase during crystallisation; a point will be reached where spontaneous nucleation of this enantiomer will occur and only a small amount of pure enantiomer can be preferentially crystallised at a time.[12] In practice, the amount of solute is restored by addition of racemate, the mixture is heated to dissolution, cooled and seeded with the opposite enantiomer. This procedure is repeated, and *D* and *L*-enantiomer is crystallised alternately.

3.4. Total spontaneous resolution

Spontaneous resolution coupled with preferential crystallisation and stereochemical lability in solution or melt gives rise to a phenomenon called total spontaneous resolution or crystallisation-induced asymmetric transformation.[12] If a stereochemically labile compound that crystallises in a Sohncke space group is crystallised slowly enough, crystallisation may be induced by one single nucleus. With a fast interconversion of enantiomers in solution, the 1:1 ratio of enantiomers in solution will not be affected during crystallisation. If the rate of enantiomerisation is greater than the rate of crystal growth, and the rates of secondary nucleation and crystal growth are much greater than the rate of primary nucleation, the whole amount of solute may be crystallised as one single enantiomer (Fig. 3-10).

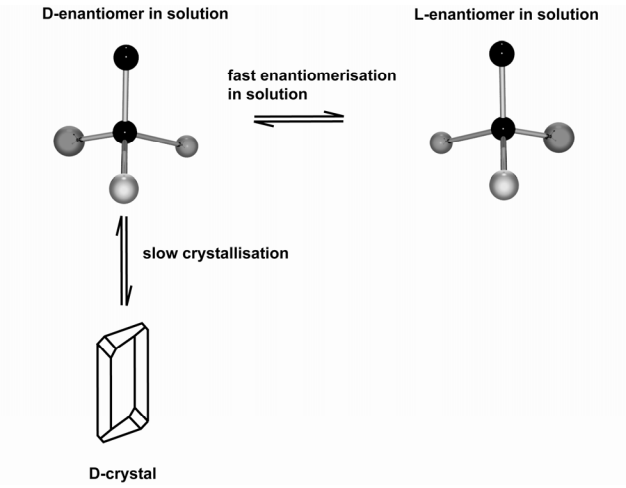


Figure 3-10. An equilibrium between the two enantiomers in solution may give rise to total spontaneous resolution, since equal amounts of *D* and *L*-crystals are not necessarily formed. If primary nucleation starts with *e.g.* a *D*-nucleus, *D*-crystals will start to grow and the entire amount of solute may successively be converted to the *D*-enantiomer and no *L*-crystals are obtained.

Due to secondary nucleation, it is not necessary to grow only one single-crystal since crystals formed by secondary nucleation will be of the same enantiomorph as the original crystal. It has been shown that some substances, *e.g.* $NaClO_3$ give racemic mixtures of crystals from an undisturbed solution, but only one enantiomorph is formed when crystallisation is performed under slow stirring.[27] The effect of stirring is probably to induce secondary nucleation.[28]

Recently, a new strategy for conversion of a racemate to a pure enantiomer involving abrasion/grinding technique has been introduced.[29, 30] Stirring a racemic mixture of chiral crystals in a saturated solution with glass beads leads to slow grinding of the crystals. Small fragments have a larger surface to volume ratio and are therefore less stable than larger crystals; small fragments will dissolve and larger fragments will grow (Ostwald ripening).[31] Alternatively, abrasion may cause the formation of small fragments which merge into larger crystals on contact with crystals of the same handedness. A small excess of one enantiomorph makes the merging of fragments of that enantiomorph more probable than for the other enantiomorph, which will dissolve.[32] This may result in the conversion of a racemic mixture of crystals into a sample enriched in one enantiomorph.

Chapter 4

Absolute asymmetric synthesis

Bei der Synthese einer organischen Verbindung aus inaktivem Ausgangsmaterial werden, wenn die Synthese zu Verbindungen mit asymmetrischen Kohlenstoffatomen führt, immer inaktive Verbindungen erhalten, weil die beiden möglichen asymmetrischen Konfigurationen in gleicher Menge entstehen.

Alfred Werner, Lehrbuch der Stereochemie, 1904.

The main approaches to absolute asymmetric synthesis over the years have been the utilisation of circularly polarised light (CPL) and total spontaneous resolution. The possible use of CPL in an asymmetric reaction was first introduced in 1874 by Le Bel.[6, 7] The ideas were justified by the discovery of circular dichroism, *i.e.* that absorption of CPL may be different for the two enantiomers. There are in principle three different ways CPL can bee used: in asymmetric photodestruction, photoresolution and asymmetric synthesis, [33] and the first positive results were reported in a partial photodestruction by Kuhn in 1929.[10] The first example of absolute asymmetric photosynthesis was reported in 1933.[34] However, CPL is asymmetric and the handedness of the CPL is deliberately chosen by man; one can therefore question if this is absolute asymmetric synthesis at all.

The first successful experiments on total spontaneous resolution were carried out during 1938 and 1939 by Havinga.[11] He performed slow crystallisation of *N*-allyl-*N*-ethyl-*N*-methyl-*N*-phenyl-ammonium iodide from water at elevated temperature and obtained optically active samples. The experiments by Havinga may be regarded as the first true absolute asymmetric synthesis, as it did not involve CPL. In 1971, Pincock *et al.* reported that crystallisation of 1,1'-binaphtyl from the melt gave rise to optically active samples,[35] and the probability of obtaining a certain enantiomer in excess was found to be stochastic.[36] Both *N*-allyl-*N*-ethyl-*N*-methyl-*N*-phenyl-ammonium iodide and 1,1'-binaphtyl racemise readily at elevated temperature, but racemisation is slow at ambient temperature.

It was therefore possible to measure optical rotation in solution at ambient temperature in order to analyse the products. Measurements of the enantiomeric purity in samples that racemise rapidly at ambient temperature must be carried out in the solid state; this is of course more complicated, and only a few examples have been reported. In 1990 Feng and McBride[37] reported that all 11 crystals of (11-bromoundecanoyl) peroxide obtained in a crystallisation experiment were of the same enantiomorph, and Kondepudi *et al.*[27] found that all crystals in a batch of sodium chlorate were of the same enantiomorph when crystallisation was performed under slow stirring. The power of total spontaneous resolution for the synthesis of novel, highly labile chiral structures has thus not been fully explored.

Due to the difficulties of analysing stereochemically labile substances, most research has been focused on reactions that transform a stereochemically labile substrate into a stereochemically inert product. The first example of such a reaction was reported in 1969 when enantiomeric excesses of 6-25% were obtained in a reaction between crystalline 4,4'-dimethylchalcone and bromine vapour.[38, 39] Another example appeared in 1999: it was found that tri-*o*-thymotide forms a clathrate with 3,4-epoxycyclopentanone that undergoes total spontaneous resolution. Treating the chiral crystals with gaseous hydrogen chloride gave a mixture of 4-hydroxy-cyclopent-2-en-1-one and 4-chloro-cyclopent-2-en-1-one. The enantiomeric excesses of the two products in the reaction mixture were estimated to be 9±3% and 22±2%, respectively.[40] In 2004, Sakamoto *et al*. reported up to 84% ee in the reactions with *n*-BuLi of certain prochiral ketones crystallising in Sohncke space groups.[41] Among the other examples, the vast majority involves intramolecular photochemical rearrangements in chiral crystals, and a few cases of intermolecular photochemical reactions within a chiral crystal. Unfortunately, in most cases reactions have been performed on individual single-crystals or bulk samples obtained by seeding. Such reactions cannot be considered as absolute asymmetric synthesis. Although enantioselectivities in these photochemical rearrangements are excellent, they are limited to peculiar compounds of very limited synthetic interest. Total spontaneous resolution of chemical reagents that may give rise to a wider variety of chiral products is actually very rare: Håkansson *et al.*[42] reported the first examples of absolute asymmetric synthesis of organometallic reagents in 2003. Up to 22% ee was reported in reactions between the "chiral-at-metal" Grignard reagents *cis*-[(*p*-$CH_3C_6H_4$)MgBr(dme)$_2$] or *cis*-[Mg(CH_3)(thf)(dme)$_2$]I and prochiral aldehydes. By complexation of simple prochiral aldehydes as chiral metal complexes, Johansson and Håkansson obtained enantiomeric excesses of up to 16% on reaction with methyl lithium in 2005.[43]

Other, more recent approaches to absolute asymmetric synthesis involve the Soai autocatalytic reaction[44] which may be utilised in absolute asymmetric synthesis,[45-47] and the spectacular report that rotary evaporation of dilute solutions of certain achiral porphyrins gives rise to chiral J-aggregates displaying circular dichroism.[48-50] The sign of the circular dichroism was found to depend on the direction of rotation during evaporation.

A considerably more detailed account for the history of absolute asymmetric synthesis is given in the Appendix.

Chapter 5

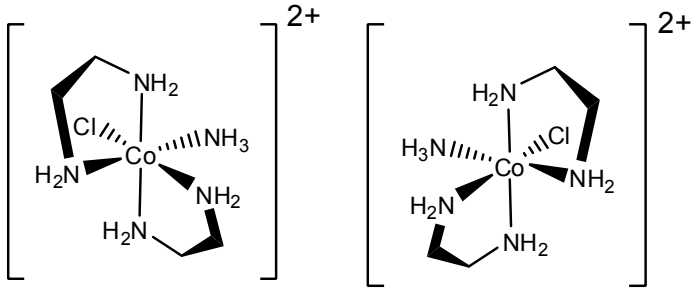
Total spontaneous resolution of seven-coordinate complexes

Nun komme ich auf eine andere noch wunderlichere Ercheinung…Solte ich wohl so glücklich seyn, die wahre Ursache dieses Phenomens entdecket zu haben ?

Carl Wilhelm Scheele, Chemische Abhandlung von der Luft und dem Feuer, 1777.

5.1. Introduction

The chirogenic[51] carbon atom is the most well-known element of chirality, but in the late 19th century it was realised that atoms with higher coordination numbers could become chirogenic centres. The idea that octahedral coordination compounds could give rise to optical isomerism was introduced by Werner in 1899.[52] It took many years of hard work[53] before he and his American Ph.D. student Victor L. King were able to resolve pure enantiomers of $[Co(en)_2NH_3Cl]Cl_2$ (Scheme 5-1) in 1911.[54]

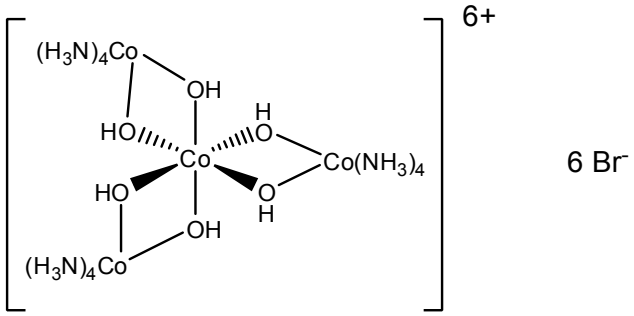


Λ Δ

Scheme 5-1.

According to King,[55] Werner had been working on the resolution of coordination compounds for some nine years before King finally succeeded. "*I shall never forget the day that the optically active isomers were first attained",* King

wrote[55] *"...so when the day came and I walked into his [Werner's] office with the information, he leaned back in his chair, smiled, and said not a single word."* That day Werner cancelled his 5 p.m. lecture and together with King he spent the whole night in the laboratory, carrying out analyses and preparing derivatives in fear that the optically active substance might racemise over night.[53] Some scientists argued that the optical activity arose from the organic ligands and that, after all, only organic compounds could be optically active. This led Werner in 1914 to prepare pure enantiomers of the complex $[Co\{(OH)_2Co(NH_3)_4\}_3]Br_6$ (Scheme 5-2), which displayed a specific rotation of over 4,000°.[56] This was the first observation of a carbon-free substance displaying optical activity in solution.



Scheme 5-2.

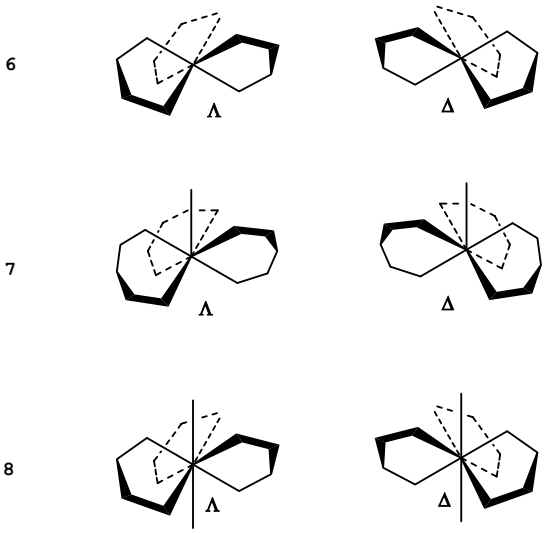
It is possible to form chirogenic centres for all coordination numbers higher than 3, nevertheless it took 88 years until the possibility of optical resolution of a complex displaying achiral mono- or bidentate ligands with a coordination number other than four or six was demonstrated.[57] Werner's success was due to the fact that some ions, *e.g.* Cr^{3+}, Co^{3+} and Ir^{3+} form stereochemically inert octahedral complexes, while *e.g.* five-, seven- and eight-coordinate complexes will racemise rapidly in solution. Classical methods for optical resolution, such as enantioselective chromatography or crystallisation of diastereomeric salts using optically active resolving agents, will fail. Stereochemical lability can, on the other hand, be turned into an advantage, and the possibility of total spontaneous resolution of eight-coordinate $[SmI_2(dme)_3]$ was demonstrated by Håkansson *et al.* in 1999.[57]

Due to the fast racemisation on dissolution, the optical purity must be determined in the solid state. Until recently, such determinations have been heavily dependent on the quality of the crystals. Hand-sorting of crystals displaying hemihedrism is very demanding, since crystals of very high quality are essential, and the operation requires much experience. If the crystals belong to the cubic crystal system, the two enantiomorphs may be distinguished by the sign of their optical rotation (most easily observed using a polarising microscope). This method was used by Kondepudi *et al*. in the examination of the product obtained on crystallisation of sodium chlorate.[27] Coordination compounds and organic molecules rarely form cubic crystals and only about 0.5% of the structures in the CSD belong to the cubic crystal system.[21] Crystals belonging to the other six crystal systems will display optical birefringence, which is a complicating factor. Optically uniaxial crystals (crystals belonging to the tetragonal, trigonal and hexagonal systems) will only display optical activity along the optic axis, and the crystal must therefore be properly oriented during the measurement. For optically

biaxial crystals, the situation is even more complicated, since the two optic axes may display different signs of optical rotation. Sucrose is such an example, the optical rotation is -22 ºcm^{-1} along one of the two optic axes, and +64 ºcm^{-1} along the other axis.[58] In crystals lacking inversion symmetry, it is even possible for achiral crystals to display optical activity if the two optic axes are related by reflection symmetry; the optical rotation about the two axes will have the same magnitude but different signs.[58] A useful strategy to determine optical purity in the solid state, not relying on optical activity, is to subject a random selection of crystals to single-crystal X-ray diffraction. This will work for high quality crystals that contain heavy atoms in order to display anomalous dispersion. The method is time consuming (and expensive) since many crystals must be analysed. Unless all crystals in the sample are analysed, the method will only give an estimate of the enantiomeric purity. None of the methods described so far are useful for microcrystalline samples.

5.2. Total spontaneous resolution of seven-coordinate complexes (Paper I)

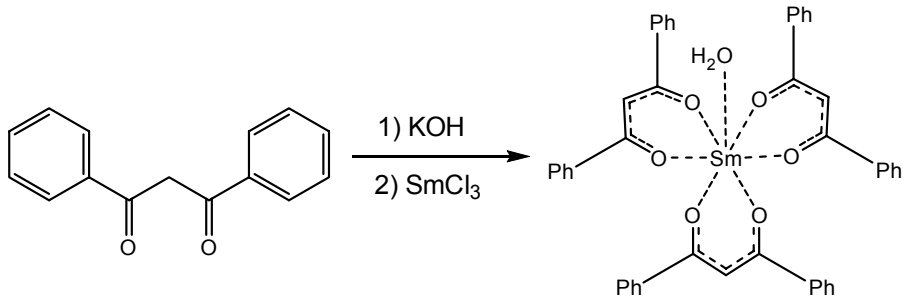
Eight-coordinate [$SmI_2(dme)_3$] can be thought of as an octahedral complex where two monodentate ligands have been added along the C_3-axis. If only one monodentate ligand is added, a chiral, seven-coordinate complex displaying monocapped octahedral coordination geometry (Scheme 5-3) is obtained. The two enantiomers of such complexes are designated Δ and Λ, respectively.[59]



Scheme 5-3.

A number of complexes of the type [$Ln(dbm)_3H_2O$] were prepared, since at least two members of this group of compounds, [$Ho(dbm)_3H_2O$][60] and [$Nd(dbm)_3H_2O$][61] have been reported to crystallise in Sohncke space group *R*3. [$Sm(dbm)_3H_2O$] (**1**) is obtained in high yield by deprotonation of dibenzoylmethane by potassium hydroxide in aqueous acetone, and subsequent addition of aqueous samarium(III) chloride solution to the refluxing reaction mixture (Scheme 5-4). On cooling to ambient temperature, a microcrystalline solid is obtained. High quality single-crystals may be grown by layering an

acetone solution of **1** on top of water. The isomorphous complexes $[Er(dbm)_3H_2O]$ (**2**) and $[Pr(dbm)_3H_2O]$ (**3**) were obtained in a similar manner.



Scheme 5-4

Single-crystal X-ray analysis revealed that the crystals indeed were composed of a seven-coordinate monocapped octahedral complex (Figure 5-1) and that the crystals belonged to space group *R*3. The heavy Sm atom allowed determination of the absolute configuration with no indications of twinning by inversion, since a low Flack parameter[62, 63] was always obtained. From a batch consisting of *c.* 100 crystals, 10 crystals were analysed by single-crystal X-ray diffraction, and all were found to be of the same enantiomer (Δ). This means that there is an even probability that the enantiomeric purity is higher than 93%, since $0.93^{10} = 0.48$. The probability for such a sample to be racemic is negligible. This proved that enantiomerically enriched samples could be prepared, and that total spontaneous resolution had been performed. However, the enantiomeric purity of the microcrystalline product obtained before recrystallisation was still unknown.

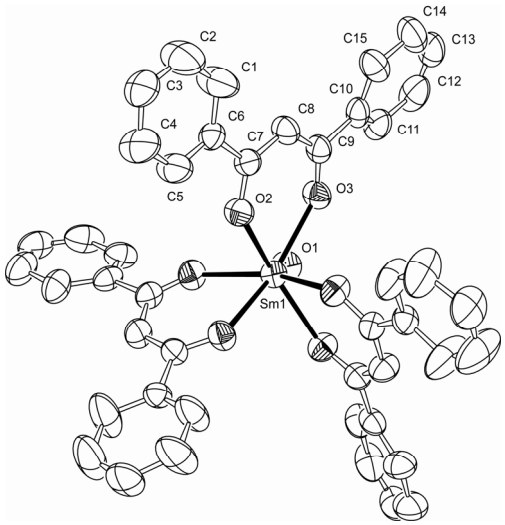


Figure 5-1. Molecular structure of Δ-**1**, displaying the crystallographic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and all H atoms are omitted for clarity.

It was discovered that crystals of **1** displayed circular dichroism in the solid state (Fig. 5-2). The acquisition of CD-spectra on solid samples has been performed since the 1970's, and is now a fairly common and useful technique among chemists.[64, 65] It is typically performed by very careful grinding of a small

amount of sample with potassium bromide, the mixture being pressed into a thin disc, in a similar manner as samples for IR-spectroscopy.

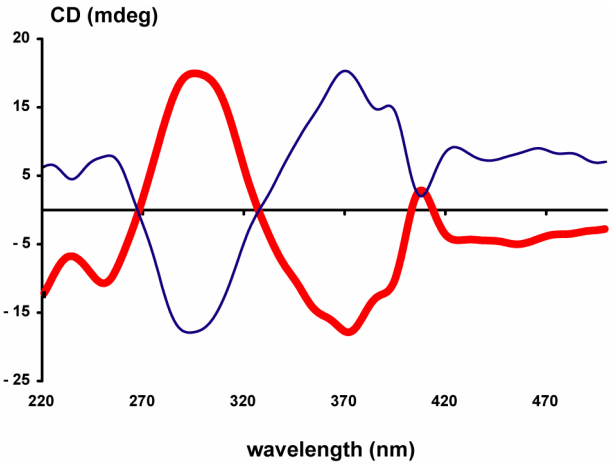


Figure 5-2. Solid-state CD-spectrum (KBr-matrix) of Δ-**1** (bold) and Λ-**1**. A. Lennartson, M. Vestergren, M. Håkansson, *Chem. Eur. J.* **2005**, *11*, 1757. - Reproduced by permission of Wiley-WCH.

The possibility to use solid-state CD-spectroscopy as a quantitative method for the determination of enantiomeric excess was studied: carefully weighted enantiopure single-crystals were ground with potassium bromide, pressed into discs and the circular dichroism from a selected peak was measured relative to the baseline. It was found, using crystals of different mass, that there was a linear dependence of the circular dichroism on the mass (Fig. 5-3).

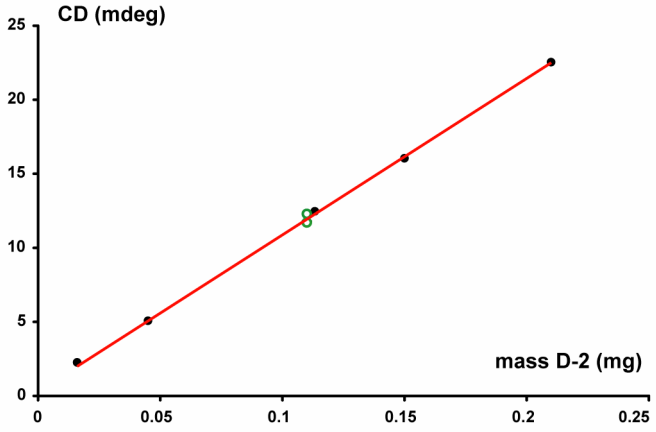


Figure 5-3. Graph showing the linear dependence of the circular dichroism of Δ-**1** on the mass. Dots represent single-crystals, circles represent bulk samples. A. Lennartson, M. Vestergren, M. Håkansson, *Chem. Eur. J.* **2005**, *11*, 1757. - Reproduced by permission of Wiley-WCH.

By mixing the two enantiomers, samples of known enantiomeric purity were obtained, and it was found that the enantiomeric excess in these samples could be determined from the circular dichroism, the margin of error being approximately ±3%. Finally, the enantiomeric excess of microcrystalline bulk-samples was measured, and these samples were found to be enantiomerically pure. A similar

careful investigation has been carried out in the case of the coordination polymer $[Cu(NO_3)_2(dmeda)]_n$, which also showed a linear relationship between circular dichroism and mass.[66] Thus, from the qualitative method of solid-state CD-spectroscopy, a powerful method for direct measurement of enantiomeric excess in microcrystalline bulk samples of stereochemically labile compounds has been developed.

One question has not been discussed so far, namely if a series of crystallisations will give an equal probability of obtaining an excess of the Δ- and Λ-enantiomers, respectively. Initially, only the Δ-enantiomer of **1** could be obtained on crystallisation. Neither the Λ-enantiomer, nor racemic samples were observed. Numerous crystallisation experiments were performed in order to isolate the Λ-form, but without success. Spiking the solutions with optically active $[Co(acac)_3]$ finally made it possible to obtain the missing Λ-enantiomer. There was no correlation, however, between the configuration of the $[Co(acac)_3]$-additive and the obtained enantiomer of **1**. Optically active additives have previously been reported to selectively suppress growth of particular enantiomorphs.[67, 68] The $[Co(acac)_3]$ additive may perhaps act as a nucleation inhibitor, either by deactivating nuclei of **1** present as a contamination since the first synthesis, or by deactivating chiral heteronuclei. It is known that certain impurities may influence nucleation.[16] For example, small amounts of colloidal substances or certain surface-active agents can act as nucleation inhibitors in aqueous solution.[16] Traces of foreign ions (especially Cr^{3+} and Fe^{3+}) can also suppress nucleation in solutions of inorganic salts, and the suppressing power appears to increase with ionic charge.[16] High molecular weight inhibitors are believed to inactivate heteronuclei, while cations are believed to act as structure-breakers in solution.[16]

Chapter 6

Total spontaneous resolution of five-coordinate complexes

Verbindungen ohne asymmetrische Kohlenstoffatome konnten nicht in aktiver Form erhalten werden.

Alfred Werner, Lehrbuch der Stereochemie, 1904.

6.1. Introduction

Five-coordinate complexes may adopt two different coordination geometries, trigonal bipyramidal and square pyramidal. Under which conditions may such complexes be chiral? The following analysis is limited to complexes containing only monodentate ligands (a-e) and bidentate ligands, which may be symmetrical (a^a) or non-symmetrical (a^b). Under these conditions, complexes with 16 different chemical compositions are possible: [Ma_5], [Ma_4b], [Ma_3b_2], [Ma_3bc], [Ma_2b_2c], [Ma_2bcd], [Mabcde], [M(a^a)c_3], [M(a^a)c_2d], [M(a^a)cde], [M(a^b)c_3], [M(a^b)c_2d], [M(a^b)cde], [M(a^a)$_2$c], [M(a^b)$_2$c], and [M(a^a)(a^b)c]. For trigonal bipyramidal geometry, one enantiomeric pair arises for each of [Ma_2b_2c], [Ma_2bcd], and [Mabcde]. In the case of square pyramidal geometries, the same is true for [Ma_3bc], [Ma_2b_2c], and [Mabcde], but two enantiomeric pairs are possible for [Ma_2bcd] (Fig. 6-1).

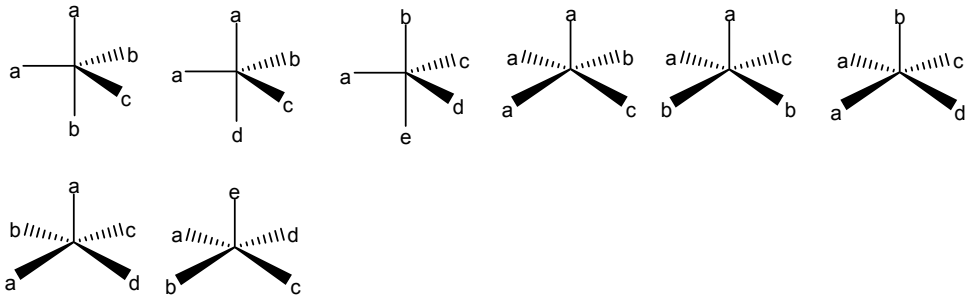


Figure 6-1. Eight pairs of enantiomers are possible for five-coordinate complexes containing only monodentate ligands. Only one of the enantiomers of each pair is depicted in the figure.

The trigonal bipyramidal geometry gives rise to six enantiomeric pairs in the case of one bidentate ligand, whereas square pyramidal geometry gives rise to ten different enantiomeric pairs (Fig. 6-2).

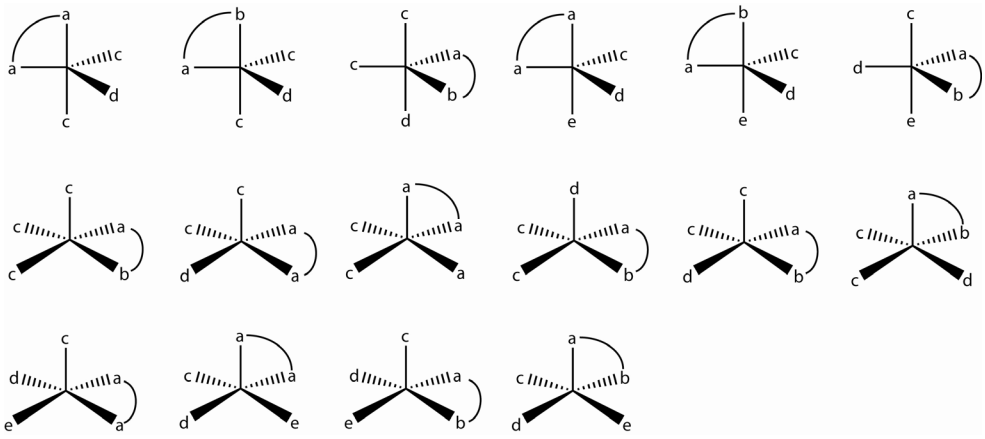


Figure 6-2. 16 pairs of enantiomers are possible for five-coordinate complexes containing one bidentate and three monodentate ligands. Only one of the enantiomers of each pair is depicted in the figure.

When complexes displaying two bidentate ligands are considered, five and six enantiomeric pairs result for trigonal bipyramidal and square pyramidal geometries, respectively (Fig 6-3).

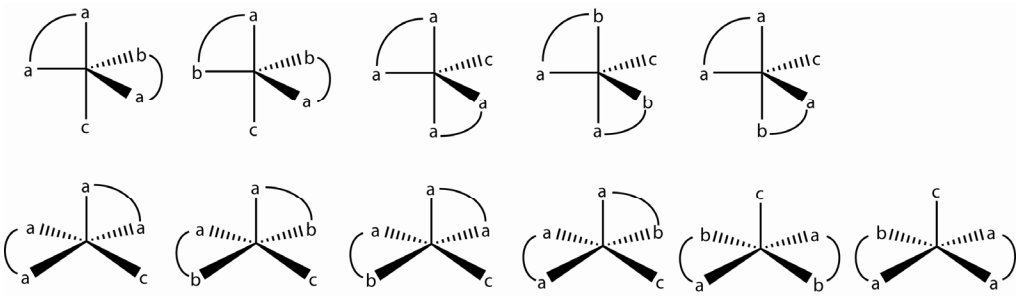


Figure 6-3. 11 pairs of enantiomers are possible for five-coordinate complexes containing two bidentate and one monodentate ligands. Only one of the enantiomers of each pair is depicted in the figure.

When Pope and Peachy resolved the first compound (*N*-allyl-*N*-benzyl-*N*-methyl-*N*-phenyl-ammonium iodide) displaying a chirogenic nitrogen atom in 1899,[69] quaternary ammonium salts were believed to be five-coordinate. van 't Hoff proposed a trigonal bipyramidal geometry, while Bischoff proposed a distorted square pyramidal geometry.[70] More recently, the chirality of five-coordinate complexes has been described by von Zelevsky, including a discussion on the difficulties of their resolution.[71] Although the possibility of five-coordinate chirogenic centres has been discussed for over 100 years, the optical resolution of five-coordinate complexes displaying achiral mono- or bidentate ligands has remained an unanswered challenge.

6.2. Total spontaneous resolution of five-coordinate enantiomers (Paper II)

A large number of complexes were synthesised in the search for a five-coordinate conglomerate. Initially, β-diketonate complexes of zinc and copper were studied, leading to either racemic or achiral five-coordinate complexes, or to six-coordinate complexes. The synthetic efforts were then directed towards *N*,*N*-diethyldithiocarbamates of zinc. After characterisation of a number of complexes forming racemic crystals, it was found that $[Zn(S_2CNEt_2)_2(vinim)]$ (**4**) crystallises in space group $P2_1$. Complex **4** is best described as a trigonal bipyramidal complex, displaying two bidentate and one monodentate ligand (Fig. 6-4).

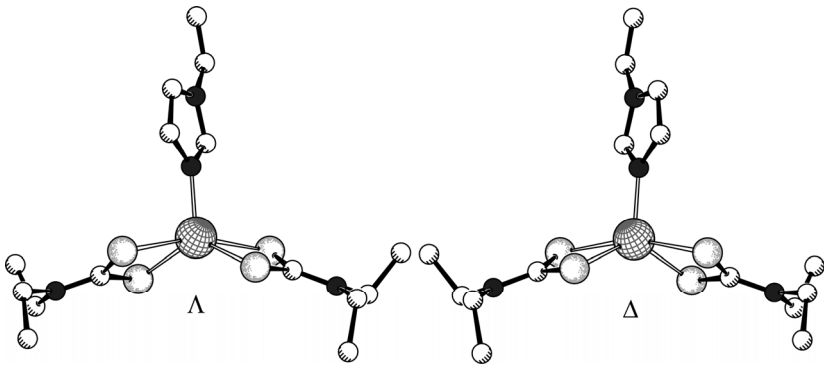


Figure 6-4. The molecular structure of the two enantiomers of **4**.

Crystals of **4** never showed any tendencies for twinning by inversion, and were always found to be enantiomerically pure. The complex formed large crystals, and sometimes the whole batch could be obtained as one large crystal. Individual crystals of **4** were found to give reproducible solid-state CD-spectra (Fig. 6-5) and both enantiomers could be obtained with similar ease.

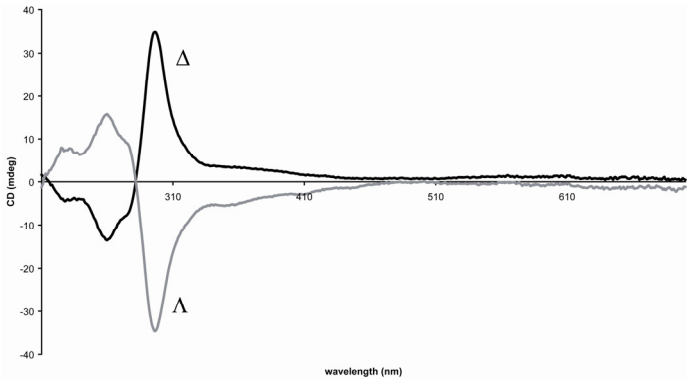


Figure 6-5. Solid-state CD-spectra (KBr-matrix) for both enantiomers of **4**.

Quantitative solid-state CD-spectroscopy[72] was performed on a representative sample, indicating an enantiomeric excess of approximately 90%. This is the first report of optically active five-coordinate compounds, and fills up the gap between the classic tetrahedral carbon compounds and the eight-coordinate $[SmI_2(dme)_3]$.

One additional five-coordinate complex, [Cd(S_2CNEt)$_2$(2,6-lut)] (**5**, Fig. 6-6) was found to crystallise as a conglomerate (space group $P2_1$), although no optically active bulk samples have been obtained so far.

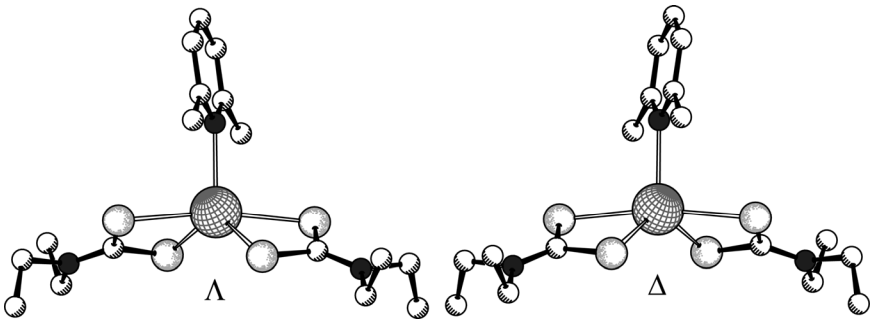


Figure 6-6. The molecular structure of the two enantiomers of **5**.

6.3. Co-crystallisation of five-coordinate diastereomers (Paper III)

The complex [Cu(bzac)$_2$(py)] (**6**) was prepared during the search for a five-coordinate conglomerate. This compound was found to occur in two stereoisomers, which co-crystallised. Both molecules displayed square pyramidal coordination geometries with the pyridine ligand in the apical position, but one of the molecules is *cis* and the other *trans* with respect to the benzoylacetonato ligands (Fig. 6-7).

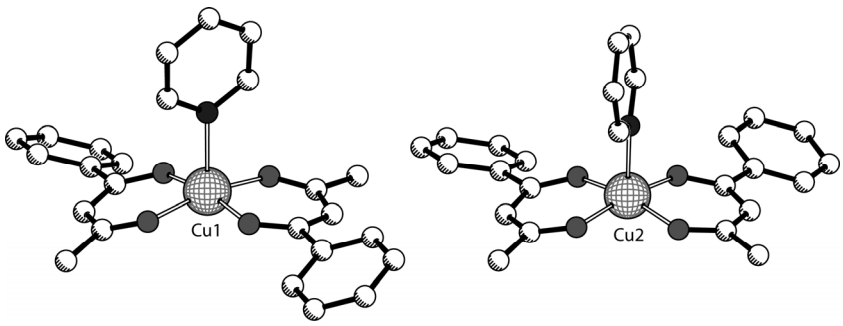


Figure 6-7. Complex **6** forms crystals with two co-crystallised diastereomers.

cis-benzoylacetonate complexes appear to be rare, and have previously not been reported for copper(II). *cis*-[Cu(bzac)$_2$(py)] is achiral, while *trans*-[Cu(bzac)$_2$(py)] is chiral, but since **6** crystallises in the centrosymmetric space group $P2_1/c$, the crystal structure is racemic. Co-crystallisation of distinct, well-ordered geometrical isomers with the same coordination figure is very rare, and only a few examples have been reported previously.[73, 74] The synthesis of **6** is perfectly reproducible, and the isolated *cis*-[Cu(bzac)$_2$(py)] or *trans*-[Cu(bzac)$_2$(py)] complexes have not been observed.

When exposed to air, crystals of **6** readily lose pyridine and the crystals turn grey. The outer shape of the original crystal is retained, but the desolvated product is microcrystalline, as indicated by powder X-ray diffraction. When the desolvated product is exposed to pyridine vapour, the colour changes back to green, and a powder pattern corresponding to **6** is obtained.

Chapter 7

Total spontaneous resolution of nine-coordinate complexes

…and I am further inclined to think, that when our views are sufficiently extended, to enable us to reason with precision concerning the proportions of elementary atoms, we shall find the arithmetical relation alone will not be sufficient to explain their mutual action, and we shall be obliged to acquire a geometrical conception of their relative arrangement in all the three dimensions of solid extension.

William Hyde Wollaston, Phil. Trans. Roy, Soc. vol. 98, 1808.

7.1. Introduction

Investigation and description of structures which undergo spontaneous resolution is important since it might, in a distant future, reveal factors promoting spontaneous resolution. A useful strategy to describe spontaneous resolution is the concept of transfer of stereochemical information.[72, 75-79] Breu *et al*. has examined complexes of the type $[M(bpy)](PF_6)_2$, where homochiral layers of $[M(bpy)]^{2+}$ are formed.[77] Depending on M (Ni, Zn or Ru), either a conglomerate or a racemate may be obtained. In another case, the presence of hydrogen bonds between homochiral layers of thiosemicarbazone metal complexes was discussed.[78] It has also been shown that chiral cationic cobalt(III) complexes crystallising in homochiral layers separated by anions, could be obtained either as conglomerates or racemates depending on the size of the anions.[79]

7.2. Total spontaneous resolution of nine-coordinate complexes (Paper IV)

Mixing the achiral starting materials $Dy(OH)_3$, $O(CH_2COOH)_2$, $NaHCO_3$ and $NaBF_4$ in aqueous solution followed by slow evaporation gives crystals of $Na_5[Dy(oda)_3](H_2O)_6(BF_4)_2$ (**7a**, Fig. 7-1). This compound crystallises in the Sohncke space group *R*32, and undergoes spontaneous resolution on crystallisation.

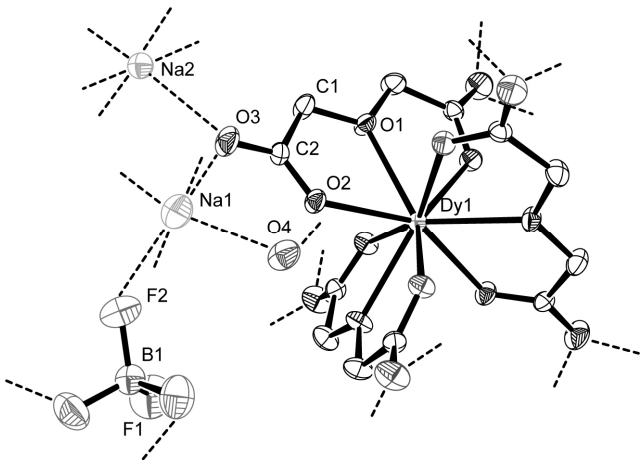


Figure 7-1. Molecular structure of **7a** displaying the crystallographic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. All H atoms have been omitted. A. Lennartson, M. Håkansson, *CrystEngComm* **2009**, *11*, 1979-1986 - Reproduced by permission of The Royal Society of Chemistry (RCS).

Dy1 coordinates three oxodiacetate anions to form a nine-coordinate complex anion, $[Dy(oda)_3]^{3-}$. The oxodiacetate ligands are virtually planar, and are oriented as the blades in a propeller. $[Dy(oda)_3]^{3-}$ may therefore be described as a nine-coordinate analogue of the chiral octahedral Werner complexes. The coordination geometry around Dy1 may be described as distorted three-face centred trigonal prismatic. Analogous structures have previously been described for the corresponding Gd, Sm, Nd[80] and Eu[81] complexes.

Na1 and Na2 both exhibit distorted octahedral coordination geometries. Na2 coordinates three water molecules and three carbonyl O atoms, resulting in three four-membered chelate rings (Fig.7-2). This means that Na2 displays a type of chirality analogous to that found in $[Co\{(OH)_2Co(NH_3)_4\}_3]X_6$.[56] Na1 coordinates two carbonyl O atoms, two water molecules and two BF_4^- ions, which results in two chelate rings and gives Na1 a chiral ligand environment (Fig. 7-2). Given Λ configuration at Dy1, the configurations at Na1 and Na2 are Λ and Δ, respectively.

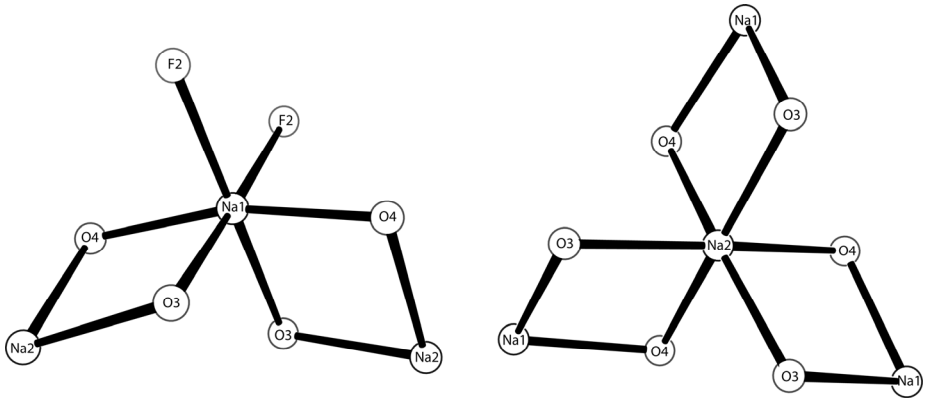


Figure 7-2. Illustration of the chiral environments around Na1and Na2, respectively.

The BF_4^- ions form pairs interconnected by three Na1 atoms back-to-back in a staggered conformation (Fig. 7-3). These motifs have a screw-like sense of chirality. Given Λ-configuration at Dy1, the motifs adopt a right-handed conformation that can be described in terms of a *P*-helix. All F atoms participate in hydrogen bonding: F1 forms hydrogen bonds to three H2b-atoms from three different $[Dy(oda)_3]^{3-}$ ions. F2 forms only one hydrogen bond to H2a in an adjacent $[Dy(oda)_3]^{3-}$ ion.

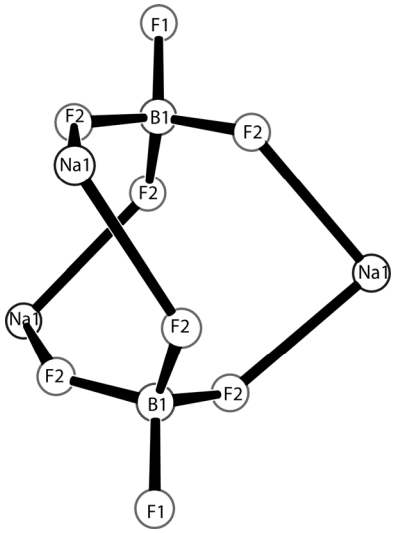


Figure 7-3. Two BF_4^- ions are connected by Na1 atoms in a screw-like chiral structural motif.

The central atom of the H_2O molecule, O4, could perhaps be described as a chirogenic centre, since it coordinates two non-equivalent Na atoms and forms a short contact with an O2 atom (Fig. 7-4). This short contact is indicative of hydrogen bonding, although the H atoms were not located. O4 exhibits (*R*)-configuration when Dy1 has Λ-configuration.

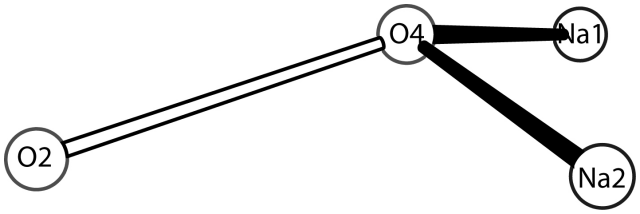


Figure 7-4. Illustration of the chiral environment around O4.

The complete crystal structure of **7a** is thus composed of chiral building blocks. These building blocks are associated to form layers (Fig. 7-5) interconnected by carbonyl O atoms from interstitial $[Dy(oda)_3]^{3-}$ anions (Fig. 7-6). There are no interactions within van der Waals contact between the $[Dy(oda)_3]^{3-}$ anions.

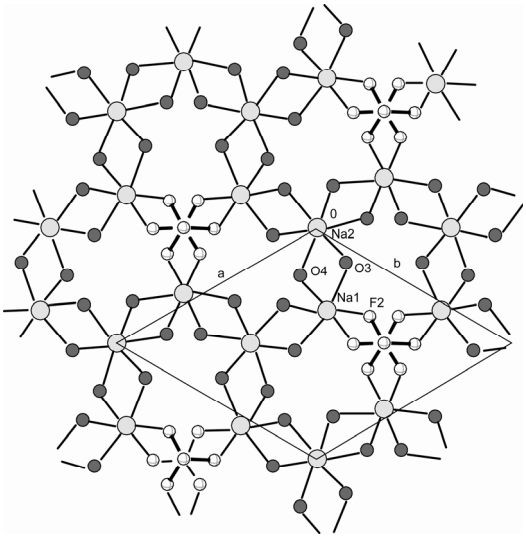


Figure 7-5. A layer in the crystal structure of **7a**, consisting of the building blocks Na^+, BF_4^-, H_2O, and carbonyl O atoms from $[Dy(oda)_3]^{3-}$ anions, viewed along the *c*-axis. All H atoms are omitted. A. Lennartson, M. Håkansson, *CrystEngComm* **2009**, *11*, 1979-1986 - Reproduced by permission of The Royal Society of Chemistry (RCS).

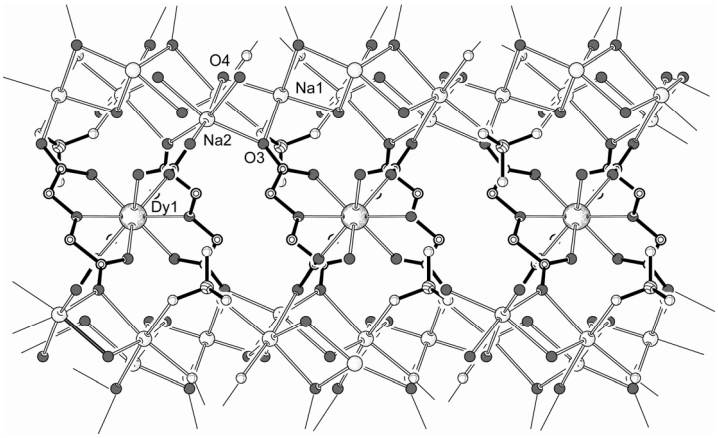


Figure 7-6. Stacking of layers viewed along the *a*-axis. $[Dy(oda)_3]^{3-}$ ions run horizontally in the figure between two layers consisting of Na^+, BF_4^-, and H_2O. All H atoms are omitted.
A. Lennartson, M. Håkansson, *CrystEngComm* **2009**, *11*, 1979-1986 - Reproduced by permission of The Royal Society of Chemistry (RCS).

Since there are no direct contacts between the chiral $[Dy(oda)_3]^{3-}$ ions in **1a,** the other constituents of the crystal structure will play an important role in the spontaneous resolution. Na2 connects three $[Dy(oda)_3]^{3-}$ ions by forming bonds to O3, O3(-y, x-y, z) and O3(-x+y, -x, z). These three $[Dy(oda)_3]^{3-}$ ions also form hydrogen bonds to F1(-2/3+y, -1/3-x, 5/3-z) in the other adjacent layer, effectively locking the three molecules into triads with the same configuration. A linkage between different triads is obtained by the F2 – H2a hydrogen bonds. The homochirality of adjacent $[Dy(oda)_3]^{3-}$ ions can thus be ascribed to the Na2, F1 and F2 atoms. The H_2O molecule forms a hydrogen bond with $[Dy(oda)_3]^{3-}$, but has also another important effect on the crystal structure since it is (along with the O3 atom) one of the links between Na1 and Na2. Homochiral layers are formed this way, but for spontaneous resolution to occur, adjacent layers must adopt the same chiral sense. The Na1 ion plays two important roles; first of all as a direct link between $[Dy(oda)_3]^{3-}$ ions *via* bonding to O3 atoms. Secondly, Na1 links the BF_4^- ions into pairs having their F1 atoms pointing in opposite directions, where hydrogen bonding to the $[Dy(oda)_3]^{3-}$ ions occurs.

Attempts were made to substitute the different components of the crystal structure; $Na_5[Er(oda)_3](H_2O)_6(BF_4)_2$, **7b**, and $Na_5[Pr(oda)_3](H_2O)_6(BF_4)_2$, **7c**, were synthesised, and were found to be isomorphous with **7a** and the Gd, Sm, Nd[80] and Eu[81] complexes previously reported. Attempts to prepare the K and Li analogues of **7c** were unsuccessful, as well as attempts to substitute Na for alkaline earth metals. Attempts to replace $NaBF_4$ with different salts generally resulted in compounds of the composition $Na_3[Ln(oda)_3](H_2O)_6$, except for NH_4SCN. These complexes are exemplified here by $Na_3[Gd(oda)_3](H_2O)_6$, **8** and $Na_3NH_4[Pr(oda)_3](SCN)(H_2O)_4$, **9**. Finally, crystallisation of **7b** was studied at different temperatures, and the same phase was obtained by slow evaporation both at depressed temperature (6 ºC) and elevated temperature (40 ºC). Since there is no sign of polymorphism (no racemic phase of $Na_5[Ln(oda)_3](H_2O)_6(BF_4)_2$ has been isolated), spontaneous resolution is obviously highly favoured for $Na_5[Ln(oda)_3](H_2O)_6(BF_4)_2$.

Complex **8** forms a racemic crystal structure in the polar space group *Cc* (Fig. 7-7). The $[Ln(oda)_3]^{3-}$ anion is similar to the anion found in **7a-c**, although the chelate rings show larger deviations from planarity. The crystal structure contains three independent Na^+ ions, all of which coordinate O atoms in achiral coordination figures. Like the structures of **7a-c,** the structure of **8** is built up by layers, but in **8** the Na^+ ions and H_2O molecules form clusters where carbonyl O atoms from the $[Gd(oda)_3]^{3-}$ anions take part. This is different from **7a-c**, where the $Na^+/H_2O/BF_4^-$ layers form an infinite chiral matrix fixing the $[Ln(oda)_3]^{3-}$ anions in the same configuration. A difference, worth noticing, is that the interactions between the $[Gd(oda)_3]^{3-}$ anions in **8** rely on Na^+ ions with achiral coordination figures in contrast to **7a-c**.

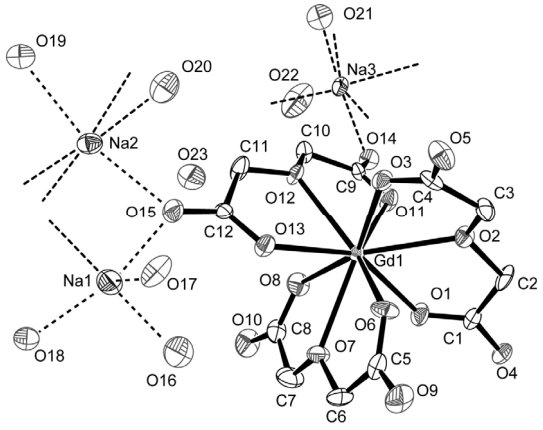


Figure 7-7. Molecular structure of **8** displaying the crystallographic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. All H atoms have been omitted. A. Lennartson, M. Håkansson, *CrystEngComm* **2009**, *11*, 1979-1986 - Reproduced by permission of The Royal Society of Chemistry (RCS).

Compound **9** (Fig. 7-8) forms a racemic crystal structure in the centrosymmetric space group *P*-1. The structure is built up from $[Pr(oda)_3]^{3-}$ anions, three independent Na^+ ions, four H_2O molecules, SCN^- and NH_4^+ ions. The coordination figures of Na1 and Na2 are achiral, while Na3 deviates considerably from any ideal coordination geometry, mainly since a carboxyl group acts as a chelating ligand with a small bite angle.

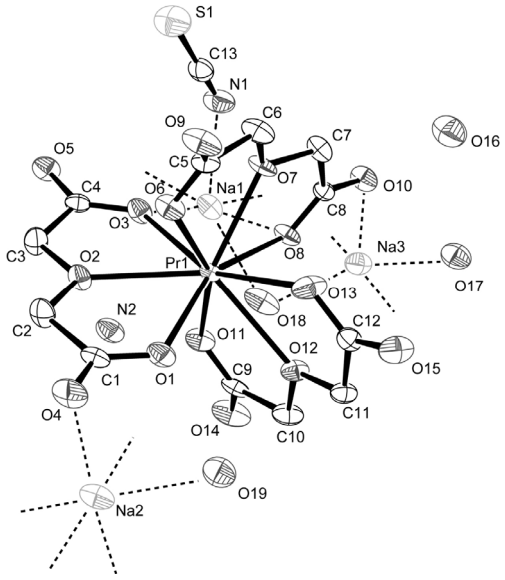


Figure 7-8. Molecular structure of **9** displaying the crystallographic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. All H atoms have been omitted. A. Lennartson, M. Håkansson, *CrystEngComm* **2009**, *11*, 1979-1986 - Reproduced by permission of The Royal Society of Chemistry (RCS).

The SCN^- ion forms a bridge between two Na^+ ions; compared to BF_4^-, SCN^- fails to support the formation of chiral layers like those in **7a-c**, and spontaneous resolution does not occur for **9**. The crystal structure of **9** is similar to the structure of **8**, since Na^+, NH_4^+, SCN^- and H_2O form clusters rather than the continuous 2D coordination polymers found in **7a-c**. Thus, the BF_4^- ions appear to have an important role in the spontaneous resolution of **7a-c**, since they will give rise to

continuous layers and promote favourable interactions between $[Ln(oda)_3]^{3-}$ anions.

No circular dichroism has been observed neither for KBr-discs of **7b-c,** nor for suspensions of **7a-c** in silicone oil. Circular dichroism has been observed for individual single-crystals of the Eu-analogue[81] but since the crystals are uniaxial, the CD-spectra will be obscured by birefringence. To investigate the enantiomeric homogeneity of samples of **7a-c**, single-crystal X-ray diffraction appeared to be the only useful method. During one crystallisation experiment with **7b**, all of the solute crystallised as one large crystal. Four fragments from different parts of this crystal were analysed by single-crystal X-ray diffraction, and were found to display the same absolute structure, proving that the sample had undergone total spontaneous resolution with a high enantiomeric excess. This represents the first example of optical resolution and absolute asymmetric synthesis of a nine-coordinate complex displaying no chiral ligands.

Chapter 8

Cryptochirality in control?

Die Eigenschaft unsrer Sinne , wenn sie auch durch die Kunst unterstüßet und verstärket werden , wird uns doch nicht weiter bringen können , als bis zu einem gewissen Punkte. Die Feinheit unsrer Instrumente ist auch nicht zureichend , und werden selbst die besten am Ende unbrauchbar.

Torbern Bergman, preface to Scheele's "Luft und Feuer"1777.

8.1. Introduction

Addition of an achiral nucleophile to a non-symmetric ketone, for instance, is well known to result in a racemic product, since there is an equal probability for an attacking nucleophile to approach the carbonyl from one side or the other. However, the probability that *exactly* 50% of the nucleophiles would attack on one side and *exactly* 50% on the other side becomes extremely small, as the number of molecules in the sample increases. Starting with 10^{20} molecules, there will be an even chance of obtaining an excess of some 6.7×10^{9} molecules of one enantiomer.[2, 82] Such small, non-measurable enantiomeric excesses have been termed cryptochirality.[2] In addition, one could expect any laboratory reagent to contain traces of optically active biomolecules, far below the limits of detection. The question is if such low levels of optical activity are of any significance?

In 1995 Soai *et al.* discovered the first case of asymmetric autocatalysis with amplification of the enantiomeric excess, *i.e.* an autocatalytic reaction where the product has a higher enantiomeric excess than the catalyst.[44] Soai's reaction involves the addition of diisopropylzinc to substituted pyrimidinyl carboxaldehydes to generate alkoxides. A small amount of the alkoxide is used as a catalyst. In a 1997 patent Soai *et al.* reported that optically active product could be obtained without addition of optically active catalyst.[45] The idea that the small statistical bias in racemic samples could be amplified was further studied by

Singleton and Vo. They reported that substantial optical activity was created with a non-random distribution of the enantiomers in toluene and benzene,[83] while ether afforded a random distribution of enantiomers.[47] Thus, optical activity far below the limit of detection can control the stereochemical outcome of an autocatalytic reaction.

8.1. Non-stochastic homochiral helix crystallisation: cryptochirality in control? (Paper V)

The early stages in crystallisation are poorly understood,[16] and cryptochirality could perhaps influence the nucleation of a conglomerate. Cryptochiral impurities could either favour the nucleation of one enantiomorph over the other, or selectively inhibit the nucleation of one enantiomorph. The problem is that one has to make sure that no nuclei of the investigated substance are present prior to the experiment; otherwise the first crystallisation may affect all forthcoming crystallisations and obscure any influence from other sources of cryptochirality. A possible way to prevent such a situation is to study the crystallisation of an air-sensitive substance, which is unlikely to survive in the ambient atmosphere over prolonged periods of time.

Dissolving CuCl in neat refluxing triallylamine and subsequent cooling to ambient temperature gives rise to crystals of a coordination polymer, $[CuCl(ally)]_n$ (**10**). The formation of a coordination polymer is due to the fact that triallylamine coordinates to Cu both through Cu-N σ-bonds and Cu-C π-bonds. The polymeric chain is folded into a helix (Fig. 8-1).

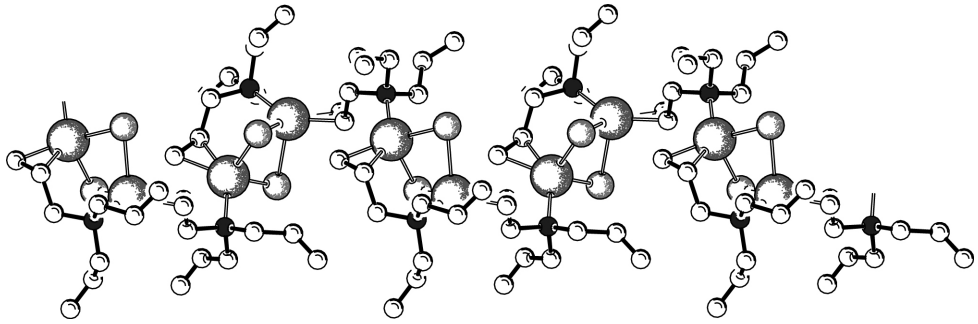


Figure 8-1. A helix of *P*-**10** with all H atoms omitted for clarity.

Compound **10** crystallises in space group $P2_1$, which means that it undergoes spontaneous resolution. The formation of a crystal of **10** can be described as a first level of homochirality, since all helices in the unit cell are of the same handedness. Allyl-groups from adjacent helices in **10** intercalate, which may be an important factor explaining the spontaneous resolution of **10**. There is a second level of homochirality in **10**, since essentially all crystals in a sample were of the same enantiomorph, *i.e.* **10** undergoes total spontaneous resolution. This was indicated by solid-state CD-spectroscopy, which showed that approximately equal amounts of powdered bulk sample and selected single-crystals gave CD of approximately the same magnitude. CD-spectra of both enantiomers are displayed in Fig. 8-2.

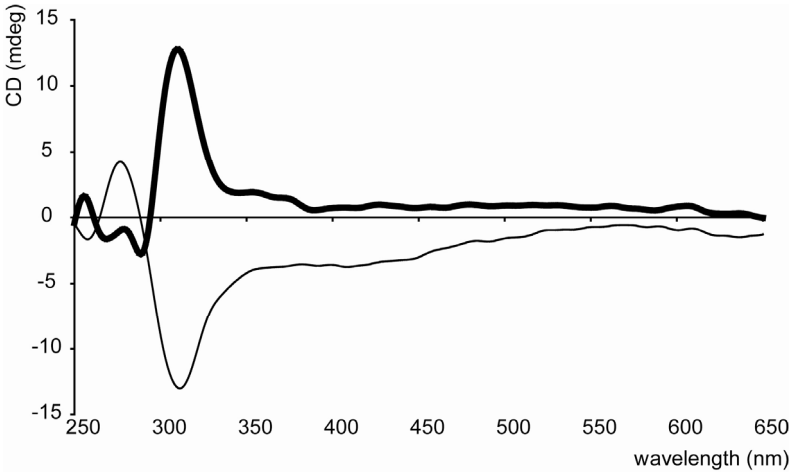


Figure 8-2. Solid-state CD-spectra (KBr-matrix) of *P*-**10** (thick line) and *M*-**10** (thin line).

In the case of **10** there is also a third level of homochirality, since all batches of **10** were found to be of the same enantiomer. Crystals of **10** readily decompose in the ambient atmosphere within a few minutes, and it is not likely that nuclei of **10** could survive attached to glassware or equipment. The triallylamine did not display optical activity, nor did solutions of CuCl in triallylamine. Distillation of the amine prior to use had no effect. A likely explanation to this phenomenon is the influence of small amounts of a foreign, optically active substance in minute amounts.

When an excess of CuCl was added to triallylamine at ambient temperature, crystals of **10** grew from the CuCl powder. Samples formed this way were different from those crystallised from solution, since it was possible to obtain an excess of either the *M*- or the *P*-enantiomer.

Chapter 9

Total spontaneous resolution of an octanuclear organo(oxo)zinc complex.

Die Angaben, daß Stoffe, welche keinen asymmetrischen Kohlenstoff enthalten, in aktiver Form vorkommen, sind sämtlich wiederlegt und haben deshalb nur noch einen historischen Wert;

J. H. Van't Hoff, Die Lagerung der Atome im Raume, 1908.

9.1. Total spontaneous resolution of an octanuclear organo(oxo)zinc complex (Paper VI)

Addition of water to diethylzinc in hexane results in a fast and vigorous reaction; ethane is evolved, and a white precipitate forms. In the presence of pyridine, however, the reaction proceeds much smoother. Gas is slowly evolved, and only minute amounts of precipitate are observed. An oil usually separates, and within two days large colourless needles start to grow. These needles were found to be an octanuclear ethyl(oxo)zinc complex, $[Zn_8Et_8O_4(py)_8] \cdot 2py$, **11** (Fig. 9-1). Alkyl(amido)zinc complexes have previously been reported to form oxo aggregates on reaction with water,[84] but there does not appear to be any similar structures of alkyl(oxo)zinc complexes reported previously.

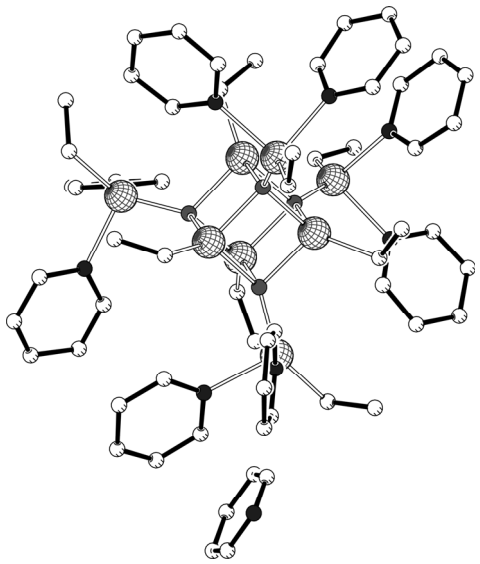


Figure 9-1. The core of **11** is cubane shaped, with the oxo groups capped by zinc atoms. All H atoms are omitted for clarity.

The core of the complex is cubane shaped, and is assembled from four oxide ions and four ZnEt groups. The core of the complex is similar to octanuclear alkyl(alkoxy) complexes; the aggregation of such complexes has been shown to be affected by the presence of water.[85] Each oxide ion is capped by a zinc atom coordinating one ethyl group and two pyridine ligands. The crystals also contain non-coordinated pyridine molecules, which are located in channels in the crystal structure (Fig. 9-2).

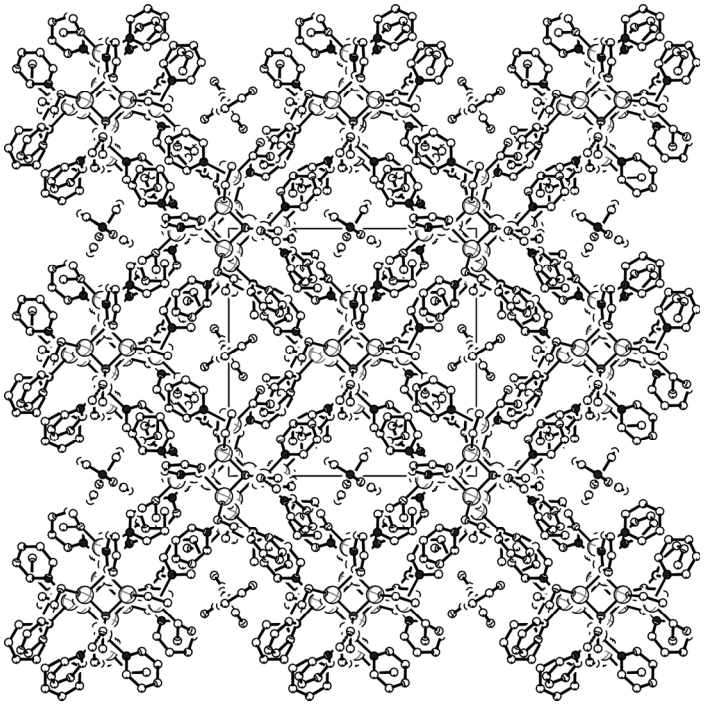


Figure 9-2. The co-crystallised pyridine is located in channels running through the crystal structure parallel to the *c*-axis. All H atoms are omitted for clarity.

Compound **11** crystallises in the enantiomorphous space group $P4_12_12$ (or $P4_32_12$). Several crystals were picked from one and the same batch, and all of these crystals were found to be of the same enantiomorph, thus indicating total spontaneous resolution. So, what has been resolved? The complex is centred on a crossing point between a two-fold axis and a 2_1-axis; with regard to the conformation of the pyridine rings, it may be described as a *meso*-complex. The co-crystallised pyridine molecules, however, are located at 4_1-axes, and will therefore be distributed in a helical manner through the channels. In the other enantiomorph, pyridine molecules will be located at 4_3-axes corresponding to helices of opposite sense of chirality (Fig. 9-3).

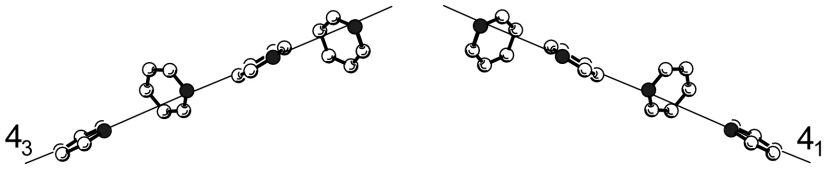


Figure 9-3. Distribution of pyridine molecules along a 4_3- and a 4_1-axis, respectively.

The perfectly reproducible synthesis of **11** demonstrates the possibility to create chiral materials with full stereoselectivity through self assembly. Gentle heating of **11** under reduced pressure converts the needles into a powder, most probably by loss of pyridine from the channels. The nature of this powder is unknown, but if the channels are retained, it may be possible to replace the pyridine molecules by prochiral aldehyde molecules (*e.g.* benzaldehyde) followed by an enantioselective ethylation reaction.

Chapter 10

Achiral compounds forming chiral crystals

Kromsyran har en djupt röd färg, och en skarpt sur samt efteråt sträf metallisk smak.

J. Jac. Berzelius, Lärbok i kemien, vol 2, 1812.

10.1. Introduction

When a chiral substance crystallises in a Sohncke space group, the two enantiomers will appear in separate crystals, and the substance will undergo spontaneous resolution. However, achiral substances may also crystallise in Sohncke space groups. This is not spontaneous resolution, since there is no racemate to resolve, but merely a spontaneous generation of chirality.[22] Several achiral inorganic compounds form chiral crystals *e.g.* α-quartz, magnesium sulphate heptahydrate, strontium formate and sodium chlorate.[86] The crystals will appear as two enantiomorphs, and crystallisation-induced asymmetric transformation is possible. Such chiral crystals may be used in separation of enantiomers or in enantioselective synthesis. It has, for example, been shown that alanine hydrochloride may be enantioselectively adsorbed on quartz crystals[87] and both quartz[88] and sodium chlorate[89] induce high enantioselectivity in Soai's asymmetric autocatalytic reaction.[44]

10.2. Dipyridinium dichromate: an achiral compound forming chiral crystals (Paper VII)

It was found that commercial dipyridinium dichromate, **12** (Fig. 10-1), known as PDC in organic synthesis, forms chiral crystals, crystallising in the Sohncke space group $P2_12_12_1$ with a low Flack parameter.

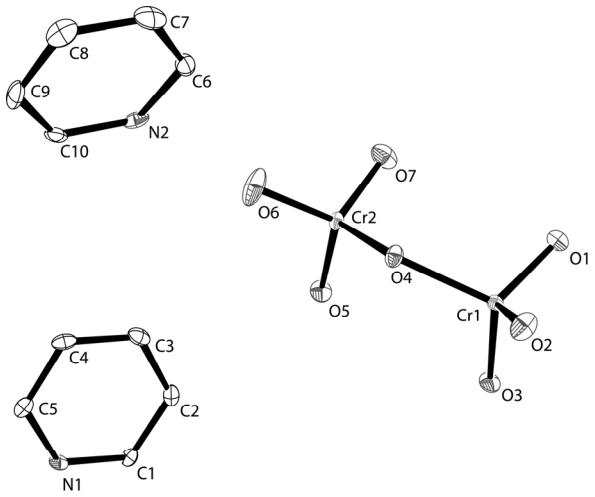


Figure 10-1. Molecular structure of **12** showing the crystallographic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. All H atoms are omitted.

Two phases of pyridinium dichromate have previously been reported,[90] but they do not correspond to **12**. Both appear to be triclinic but no space group has been reported. In addition, only a limited number of dichromates displaying substituted pyridinium counter ions are found in the CSD. Among the previously reported substituted pyridinium dichromates there is one example, di(2,6-dimethylpyridinium) dichromate, which crystallises in a Sohncke space group.[91] The dichromate ion in **12** adopts an eclipsed conformation and is therefore virtually achiral. This is similar to *e.g.* di(4,4'-dipyridinium) dichromate,[92] but different from *e.g.* bis(2,6-dimethylpyridinium) dichromate, where the dichromate ion adopts a staggered conformation.[91]

The assembly of the crystal structure appears to rely largely on CH-O and NH-O interactions between anions and cations. All H atoms appear to be involved in hydrogen bonding except for H2 and H3. As a result, **12** forms a layered structure, in which alternating layers of dichromate anions and pyridinium cations are stacked along the *c*-axis (Fig. 10-2). On inspecting the crystal structure it is not obvious where the chirality originates from, the anion being locked in an achiral conformation; the chirality is therefore to be traced to the orientation of the ions in the unit cell.

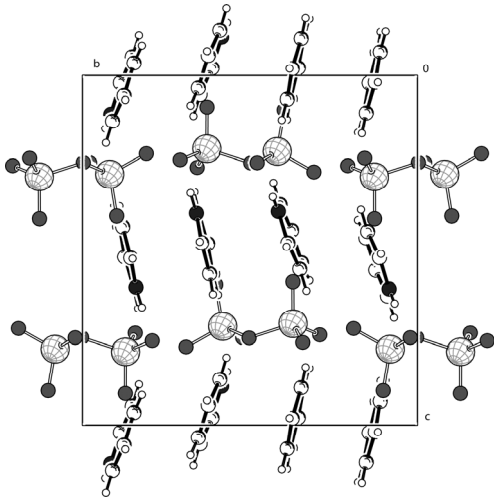


Figure 10-2. The crystal structure of **12** is built up by layers stacked along the *c*-axis.

The formation of chiral crystals is interesting, since pyridinium dichromate is a useful oxidising agent in organic synthesis. A suspension of **12** in methylene chloride is a mild oxidising agent that converts both saturated and unsaturated alcohols to aldehydes or ketones.[93] The reaction is accelerated by the presence of molecular sieves,[94] and oxidation of alcohols can also be carried out catalytically using bis(trimethylsilyl)peroxide as bulk-oxidant.[95] A solution of an aliphatic aldehyde and methanol in dry dimethylformamide gives a methyl ester,[96] cyclic alkenes give α-iodo-ketones when treated with **12** and iodine in dry methylene chloride,[97] and trisubstituted alkenes can be transformed into iodohydrins or (with longer reaction time) to epoxides.[98] Cyanohydrins give carboxylic acids with **12** in dimethylformamide[99] and Brown has converted organoboranes to carbonyl compounds using **12**.[100] It is perhaps unlikely, however, that the rather diffuse chirality of **12** would induce any substantial enantiomeric excess during *e.g.* a partial degradation of a racemic alcohol.

It is not trivial to determine if all crystals in a batch of **12** are of the same enantiomorph or not; we have not been able to observe any circular dichroism, not even for single-crystals. To establish the enantiomeric purity of a sample of **12**, one would probably have to subject a large number of crystals to single-crystal X-ray diffraction.

Chapter 11

Facile synthesis of well-defined sodium hydridoalkylzincates(II)

...and consequently all attempts to produce hydride of zinc by the action of the metal upon the hydrogen acids have failed. These considerations, taken in connexion with Mr. Wanklyn's mode of forming sodium-ethyl and potassium-ethyl, afford a clue to the nature of the reactions by which we shall probably eventually succeed in forming the hydrogen compounds of the highly positive metals.

E. Frankland, Proc. Roy. Soc. London, 1857-1859.

11.1. Introduction

In 1858 Alfred Wanklyn discovered that sodium slowly dissolves in diethylzinc, giving rise to a white crystalline compound and metallic zinc.[101, 102] These crystals were believed to be ethylsodium, but analysis revealed that the crystals contained diethylzinc. Thus, the composition of the crystals was reported as $NaEt{\cdot}ZnEt_2$ *i.e.* ethylsodium solvated by diethylzinc. Wanklyn soon discovered that his compound was useful in the synthesis of carboxylic acids by carbonylation.[103-105] Most organic textbooks from the late 19th century contain a comment on Wanklyn's compound, never the less it took nearly 100 years before it was realised that "$NaEt{\cdot}ZnEt_2$" actually is a zincate, $NaZnEt_3$[106, 107] and there is still no crystal structure in the CSD.

11.2. Facile synthesis of well-defined sodium hydridoalkyl-zincates(II) (Paper VIII)

Wanklyn's synthesis of $NaZnEt_3$ was reinvestigated, and it was found that gentle heating of a mixture of sodium and diethylzinc gave rise to a violent reaction with evolution of gas and precipitation of metallic zinc. When the reaction mixture

reached ambient temperature, colourless crystal plates were obtained. These crystals were identified as a dinuclear hydridoalkyl zincate, $Na[Zn_2Et_4H_2]$, **13**. Apparently, an initially formed sodium trialkylzincate undergoes β-elimination on heating, giving rise to a hydridozincate species (Fig. 11-1).

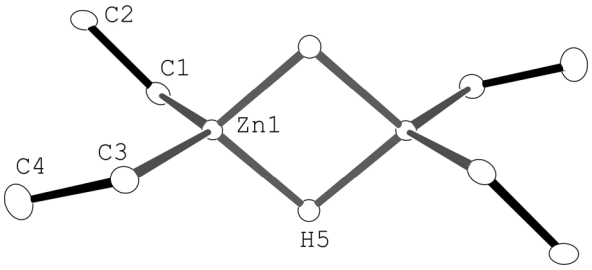


Figure 11-1. The hydride bridged dinuclear anion in **13**.

These results were surprising, since well-defined hydridoalkylzincates have not been isolated previously, in spite of considerable efforts.[108-110] These early attempts were performed by mixing alkali metal hydrides and dialkylzinc in ethereal solvents, and such solutions have been found to be useful reagents in organic synthesis.[111] The yields of **13** were essentially quantitative, and no impurities were detected by powder X-ray diffraction or careful microscopic investigation.

Performing the reaction using diisopropylzinc, instead of diethylzinc, afforded crystals of $Na_3[Zn_2(i\text{Pr})_6(H)]$, **14** (Fig. 11-2).

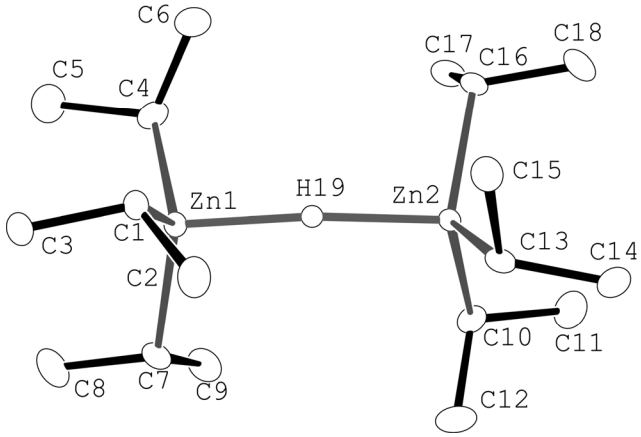


Figure 11-2. The hydride bridged dinuclear anion in **14**.

Unfortunately, both **13** and **14** crystallises in centrosymmetric space groups ($P2_1/c$ and $P\text{-}1$, respectively). In both compounds, Na-H and Na-C interactions give rise to network structures. In **13**, each hydrido ligand coordinates two Na^+ ions, each Na^+ ion coordinates hydrido ligands from two adjacent anions and an ethyl group from a third anion. In **14** the central hydrido ligand is surrounded by three Na^+ ions, and each Na^+ ion forms short contacts to an isopropyl group in an adjacent anion. The $[Zn_2Et_4H_2]^{2-}$ ions are located on inversion centres and are achiral, while the $[Zn_2(i\text{Pr})_6(H)]^{3-}$ ions are chiral due to the orientation of the isopropyl groups.

Chapter 12

Concomitant crystallisation of conglomerates and racemates

Phlogiston, förenadt med vitriols-syra til mättning, utgör hvad vanligen kallas Svafvel.

Torbern Bergman, Framledne directeuren herr H. T. Scheffers chemiske föreläsningar..., 1779.

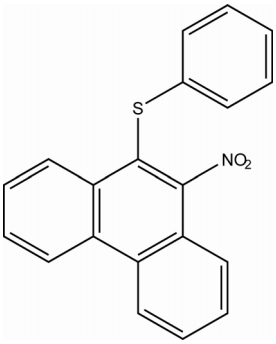
12.1. Introduction

Concomitant polymorphism is the formation of two or more polymorphs within the same crystal batch.[112] The concomitant crystallisation of polymorphs is controlled by both kinetic and thermodynamic factors. Two phases can only coexist in equilibrium at the transition point, where the two phases have the same free energy. It is unlikely, however, that a certain crystallisation experiment is carried out exactly at this point and kinetic factors will play at least some role in the overall explanation of concomitant polymorphism. Kinetic factors include the rate of nucleation and the composition of the crystal batch will only reflect the ratio of the corresponding free energies if the nucleation rates are the same for all polymorphs. Initial crystallisation of a metastable phase will relieve the supersaturation of the solution and may be followed by a phase transition, giving rise to the thermodynamically favoured phase. This is known as the rule of stages introduced by Ostwald.[18] A special case is the concomitant crystallisation of racemic phases and conglomerates. At least if there is a fast interconversion between the two enantiomers in solution, or if the molecules are achiral, this could be regarded as a form of polymorphism. This phenomenon is considered to be rather rare; a list of examples extracted from the CSD was published in 2004.[113] Information from such cases may be used *e.g.* for structure predictions.[112] One example of concomitant formation of a chiral and a racemic phase is 2,6-dimethylfuchsone.[114] This compound is packed into homochiral layers, which are almost identical in the two polymorphs. The

difference between the conglomerate and the racemic phase is the relationship between the layers. 9-(2-Hydroxyethyl)-adenine[115] appears in three polymorphs and is also packed into layers related in different ways in the three structures. One of the most well-known examples of concomitant polymorphism is *m*-nitrophenol, which was reinvestigated recently at several temperatures.[116] This is an example of an achiral compound which can form either a chiral or an achiral crystal structure. Also in this case, the structural differences are small between the two polymorphs. On crystallisation from acetone, 3,4-bis(phenylmethylene)-*N*-methylsuccinimide crystallises as three polymorphs in an approximate 1:1:1 ratio.[117] Two of these polymorphs are centrosymmetric; the third one crystallises in space group $P2_1$.

12.2. Concomitant formation of chiral and racemic crystals of a diaryl sulphide (Paper IX)

When a solution of 10-nitro-phenanthren-9-yl phenyl sulphide (**15**, Scheme 12-1) in methylene chloride was layered with hexane, needle shaped crystals were obtained.



Scheme 12-1.

Needles of α-**15** belong to space group $P2_12_12_1$, which is one of the Sohncke space groups. During one crystallisation experiment, however, two types of crystals were formed: a few small regular block-shaped crystals along with the needles of α-**15**. The block shaped crystals turned out to be a racemic phase, β-**15**, crystallising in space group $P2_1/c$. The molecules of **15** are conformationally chiral (Fig. 12-1), and the conformations of the molecules are very similar in α-**15** and β-**15**. During several crystallisations, performed under similar conditions, β-**15** was obtained only once. Erratic appearance of polymorphs is well-known.[118]

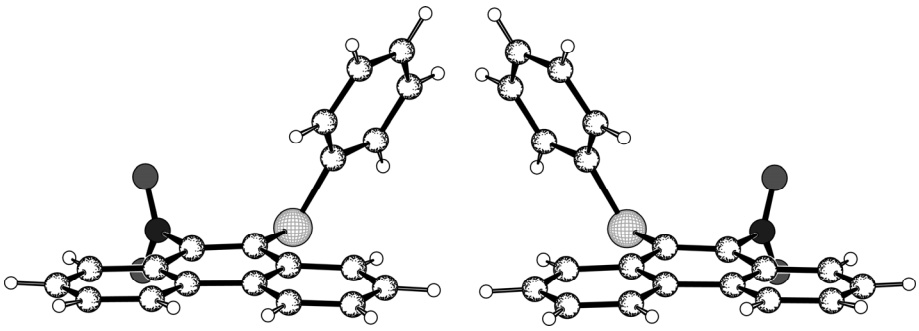


Figure 12-1. The two enantiomers of α-**15**.

Since **15** is stereochemically labile in solution, it may undergo total spontaneous resolution, and it was found that bulk samples of α-**15** displayed pronounced circular dichroism in the solid state (Fig. 12-2), indicating a significant enantiomeric excess. During several recrystallisations, the same enantiomer was obtained every time.

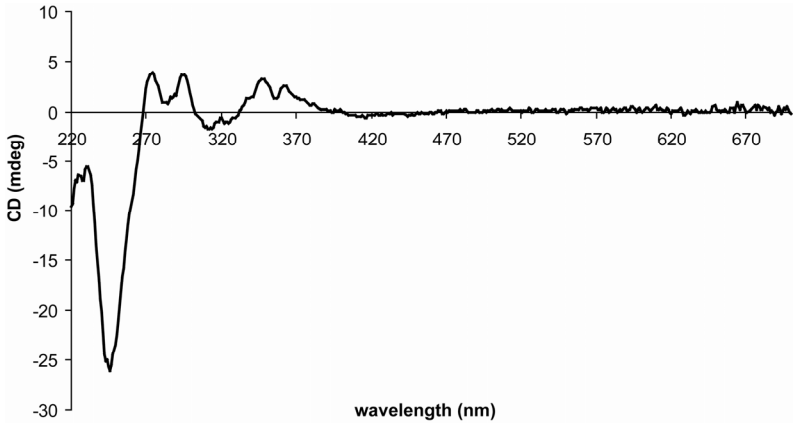


Figure 12-2. Solid-state CD-spectrum (KBr-matrix) of α-**15**. Reproduced by permission of The Royal Society of Chemistry (RCS).

Compared to several other cases of concomitantly crystallising racemic phases/conglomerates, the structural differences between β-**15** and α-**15** are rather striking. The molecules in β-**15** are associated into chains by CH-O interactions and the molecules in the chains exhibit the same sense of chirality. The chains are associated two and two by face to face π-π interactions, and each molecule is paired with its enantiomer. The molecules in α-**15** also form chains (parallel to the *b*-axis) through CH-O interactions, and these chains are further stabilised by CH/π interactions.[119] The chains resemble those found in β-**15**, which facilitates a comparison between the two structures. The difference between the chains found in the two phases is that every second molecule is rotated 180° around the axis of propagation of the chains in α-**15** compared to those in β-**15**, a necessary consequence of the extra two 2_1 axes in $P2_12_12_1$ compared to $P2_1/c$. The second shortest contact in α-**15** is another set of CH-O interactions; these interactions give rise to a helix that propagates parallel to the *a*-axis. A helix is interesting in this case, since it is a chiral structural motif, and perhaps capable of transferring chiral information between different molecules. Expansion of these two types of interactions gives the complete crystal structure, which is a network assembled by CH-O interactions, where the helices are an integrate part. This may be the most important difference between the two polymorphs: both polymorphs assemble into homochiral chains, but in α-**15** the interactions between the chains give rise to helices that stimulate adjacent chains to adopt the same sense of chirality, leading to the formation of a conglomerate.

The calculated densities of α-**15** and β-**15** are 1.38 and 1.39 gcm^{-3}, respectively, which indicates that the efficiency in packing is almost the same in both phases. Since ΔG for the crystallisation process in general depends on the density of the

crystal structure,[120] it is not surprising that both types of crystals can form concurrently.

The possibility of obtaining enantiomerically enriched samples of α-**15** may be utilised in a subsequent trapping reaction, since α-**15** could be transferred to a stereochemically inert sulphoxide on oxidation. It is reasonable to believe that the nitro-group would favour one of the enantiomers over the other, since it shields one side of the sulphur atom, protecting it from an incoming oxidising reagent (Fig. 12-3).

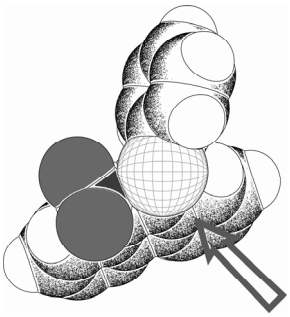


Figure 12-3. One side of the sulphur atom in α-**15** is more accessible for an incoming oxidising agent. A. Lennartson, T. Wiklund, M. Håkansson, *CrystEngComm* **2007**, *9*, 856.- Reproduced by permission of The Royal Society of Chemistry (RCS).

12.3. Concomitant polymorphism in coordination compounds (Paper X)

Following the discovery of concomitant crystallisation of a conglomerate and a racemate in the case of **15**, it was discovered that a diindenylzinc complex behaved in a similar fashion (see Chapter 13). In that case it was found possible to control the outcome of the crystallisation by varying the concentration. A different behaviour was observed for the conformationally chiral coordination compound $[ZnCl_2(2,4\text{-lut})_2]$, **16**. Crystallisation from ethanol gave crystals of either a racemic phase (α-**16**) crystallising in space group $P2_1/c$, or a conglomerate (β-**16**) crystallising in the enantiomorphous space group $P4_12_12$. Crystallisation could afford pure α-**16**, pure β-**16** or a mixture of the two phases under the same conditions, and reproducible routes to pure α-**16** or pure β-**16** were not found. Crystallisation from ethanol, methanol, THF, toluene, benzene acetonitrile, dichloromethane, acetone, ethyl acetate and neat 2,4-lutidine was investigated to reveal any preference for a particular phase, or to in order to find a third phase *e.g.* containing co-crystallised solvent. No new phases were found, and a slight preference for β-**16**, the phase of highest density, was indicated. No crystal structure of **16** has been reported previously, but **16** has been characterised by elemental analysis.[121, 122] The fact that **16** may appear as two polymorphs has not been reported previously, and perhaps the concomitant crystallisation of polymorphs is more common than generally believed. This is of importance, since apparently pure samples may consist of two (or more) different compounds with very different properties and reactivities (see Chapter 13).

Chapter 13

Absolute asymmetric synthesis of organometallic reagents displaying chirogenic α-carbon atoms

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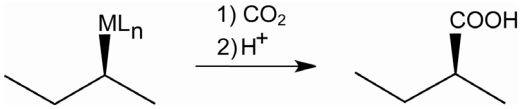
Nachdem also jede aktive, in den zwei eigentümlichen Isomeren auftretende Verbindung ein asymmetrisches Kohlenstoffatom enthält, gibt es anderseits viele Körper, die diese Konstitutionseigentümlichkeit besitzen und dennoch keine Aktivität zeigen; ja, es steht sogar fest, daß bei der Darstellung derartiger Derivate im Laboratorium aus inaktiven Verbindungen dieselben niemals in aktivem Zustande erhalten werden.

J. H. van 't Hoff, Die Lagerung der Atome im Raume, 1908.

13.1. Introduction

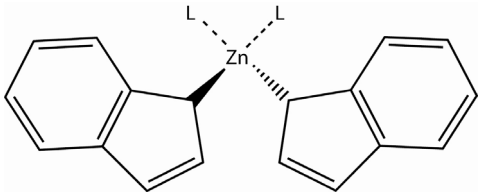
The first example of absolute asymmetric synthesis of an organometallic reagent was the synthesis of octahedral "chiral-at-magnesium" Grignard reagents.[123] Two such reagents, *cis*-[(*p*-$CH_3C_6H_4$)MgBr$(dme)_2$] and *cis*-[Mg$(CH_3)(thf)(dme)_2$]I, were found to crystallise in the Sohncke space group $P2_12_12_1$.[42] Crystalline samples of *cis*-[(*p*-$CH_3C_6H_4$)MgBr$(dme)_2$] and *cis*-[Mg$(CH_3)(thf)(dme)_2$]I gave optically active 1-*p*-tolyl-butan-1-ol and 2-pentanol, respectively, on reaction with butyraldehyde.[42] The low enantioselectivity (5-22%) may be due to incomplete resolution of the reagent or decomposition of the crystals during the course of reaction, but an important factor is probably the enantioselectivity of the nucleophilic attack. The reaction of a Grignard reagent displaying helical chirality with an aldehyde will most probably not be 100% enantioselective. Therefore, it was argued that a higher enantioselectivity could be attained using organometallic reagents displaying chirogenic α-carbon atoms. A reaction with an achiral electrophile, such as CO_2 or Br_2, could trap the configuration of the reactive chirogenic carbon centre (Scheme 13-1), without the need to form a new chirogenic centre. Such reactions may proceed with a high degree of stereochemical retention (or inversion).



Scheme 13-1.

13.2. Absolute asymmetric synthesis of 1-chloroindene *via* diindenylzinc (Paper XI)

A study of diindenylzinc complexes revealed that zinc coordinates the indenyl anions in a η^1-mode, the α-carbon atom being a chirogenic centre (Scheme 13-2). A number of complexes were prepared, and all of those displayed the same configuration at the two chirogenic carbon atoms (no *meso*-complexes were observed). Enantiomerisation of diindenylzinc in solution was believed to be fairly fast, since even diindenylmercury is known to be stereochemically labile in chloroform solution at room temperature.[124] Enantiomerisation of diindenylmercury is believed to occur through an intramolecular mechanism.[124] It thus appeared that diindenylzinc would be a promising system for absolute asymmetric synthesis.



Scheme 13-2.

It was found that $[Zn(ind)_2(3\text{-pic})_2]$ (**17**, Fig. 13-2) formed two polymorphs, α-**17** crystallising in space group $P2_12_12_1$ and β-**17** crystallising in the centrosymmetric space group $P2_1/c$. The most convenient crystallisation method appears to be layering a THF solution of **17** with a hydrocarbon. More dilute solutions tend to give β-**17**, while more concentrated solutions give pure α-**17**. At intermediate concentrations, concomitant crystallisation of the two phases was observed. Addition of a small amount of indenylpotassium before crystallisation was found to improve the crystal quality.

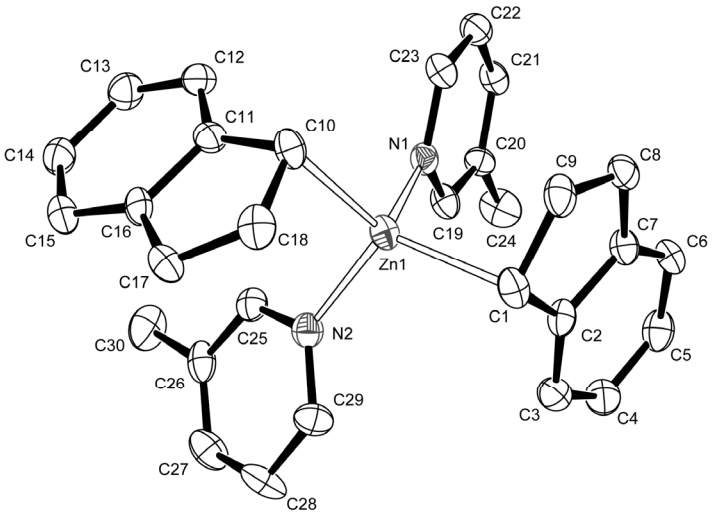
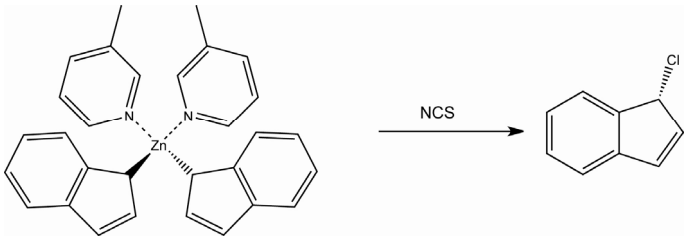


Figure 13-1. Molecular structure of (*R,R*)-α-**17** displaying the crystallographic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and all H atoms have been omitted for clarity.

Reaction of α-**17** with CO_2 was found to give an achiral product (indene-1-carboxylic acid is known to rearrange to indene-3-carboxylic acid[125]) and reaction with bromine gave a complex mixture of polybromination products. Reaction with solid *N*-chlorosuccinimide (NCS), on the other hand, gave the desired 1-chloroindene in reasonable yields and measurable enantiomeric excesses (Scheme 13-3; Table 13-1, entry 1). Even if no enantiomeric excess would have been obtained, this reaction is a more convenient route to racemic 1-chloroindene than those published previously.[125]



Scheme 13-3.

The reactions were performed by grinding a selected single-crystal with NCS under N_2 atmosphere at -196 ºC in a phial, sealing the phial with a rubber septum and allowing it to reach ambient temperature. The reaction mixture was quenched with water and extracted with hexane. It was found that quenching the reaction mixture with water directly after grinding gave a higher yield, but a slightly lower enantiomeric excess (Table 13-1 entry 2). These results indicated that the reaction was faster in the presence of water, than in the solid state. The lower yields observed in the solid-state reactions may be explained by slow quenching due to air. It was found that the addition of a solvent to the cooled reaction mixture and grinding until the mixture reached ambient temperature had a profound effect on the enantiomeric excess (Table 13-1, entries 3-7). THF gave essentially racemic product, while the enantiomeric excess increased dramatically on addition of

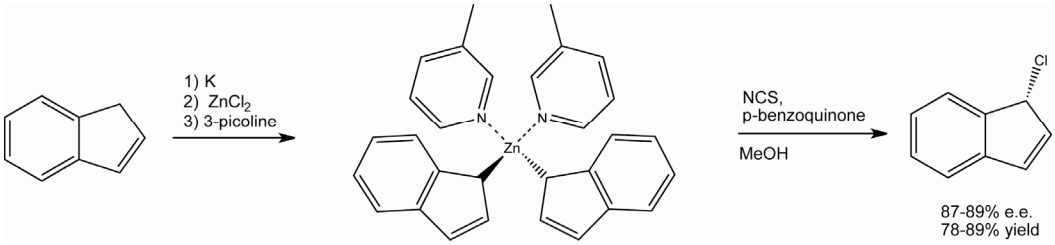
methanol. It was finally discovered that the addition of a radical inhibitor, such as *p*-benzoquinone, increased the enantiomeric excess even further, the highest enantiomeric excess observed being 89%. These high enantiomeric excesses are remarkable, since it could be feared that the second indenyl group would give rise to a considerably lower selectivity *e.g.* due to rearrangement to a η^5 coordinated species. The sporadic appearance of racemic twins unfortunately made some crystal samples essentially useless.

Table 13-1. Reaction between α-**17** and NCS.

entry	reagent configuration	solvent	product rotation	yield[a] (%)	ee (%)
1[b]	*S*	none	(+)	60-70	17-22
2[b]	*R*	H_2O	(-)	86-91	13-14
3[b]	*S*	CH_3OH	(+)	89-95	26-29
4[b]	*S*	CH_3OH[d]	(+)	85-99	82-83
5[b]	*R*	CH_3OH[d]	(-)	78-99	87-89
6[b]	*S*	CH_3CN	(+)	97-98	19-23
7[b]	*S*	THF	(+)	91-97	0-3
8[c]	*S*	CH_3OH[d]	(+)	70-80[e]	0-71
9[c]	*R*	CH_3OH[d]	(-)	60-80[e]	0-56

[a] Determined by HPLC; NMR showed no other products. [b] Selected single-crystals. [c] Full batch. [d] Addition of *p*-benzoquinone. [e] The presence of indenylpotassium (which does not give 1-chloroindene under the reaction conditions employed) lead to a lower apparent yield.

The overall synthesis of 1-chloroindene is visualised in Scheme 13-4. α-**17** is prepared by metallation of indene by potassium followed by transmetallation with zinc chloride.[126] Addition of equivalent amounts of 3-picoline and subsequent crystallisation affords α-**17**. In other words, chiral crystals of α-**17** were prepared solely from achiral starting materials. It is important to note that the reaction of single-crystals of α-**17** with NCS is not absolute asymmetric synthesis, since the starting material is a chiral crystal. Absolute asymmetric synthesis is achieved if the yield of one enantiomer of α-**17** is higher than 50% during crystallisation. Crystallisation of α-**17** gave yields higher than 90%, and absolute asymmetric synthesis would be demonstrated if a whole crystal batch of α-**17** gives an enantiomeric excess on reaction with NCS. Without full optimisation of the crystallisation conditions, enantiomeric excesses of up to 71% were observed. There was no strong preference for any enantiomer but 50 reactions gave an excess of (-)-1-chloroindene and 70 reactions gave an excess of (+)-1-chloroindene.



Scheme 13-4.

13.3. Further studies of organometallic reagents displaying chirogenic α-carbon atoms (Papers XII-XIII)

Before the successful isolation of **17**, several other groups of organometallic reagents were investigated. The simplest chiral alkyl group is the *sec*-butyl group, and complexes of di-*sec*-butylzinc were investigated. Di-*sec*-butylzinc was prepared according to published procedures[127], and a number of complexes were prepared including [Zn(*s*-Bu)$_2$(py)$_2$], **18**, [Zn(*s*-Bu)$_2$(2-pic)$_2$], **19**, [Zn(*s*-Bu)$_2$(3-pic)$_2$], **20**, [Zn(*s*-Bu)$_2$(tmeda)], **21**, and [Zn(*s*-Bu)$_2$(teeda)], **22**. Most other ligands gave microcrystalline or oily products on reaction with di-*sec*-butylzinc. All characterised complexes were chiral, and no *meso*-complexes were isolated, except in the case of binuclear complexes *i.e.* [Zn(*s*-Bu)(Me$_2$N(CH$_2$)$_2$NH)]$_2$, **23**. None of the complexes crystallises in Sohncke space groups, however. There are no previously reported crystal structures of *sec*-butylzinc complexes in the CSD. The possibility to obtain new phases containing co-crystallised solvent molecules was demonstrated by the preparation of two toluene clathrates, [Zn(*s*-Bu)$_2$(3-pic)$_2$] · C$_7$H$_7$, **24** and [Zn(*s*-Bu)$_2$(3,5-lut)$_2$] · C$_7$H$_7$, **25**.

Appendix

Absolute Asymmetric Synthesis 1874-2009

Es ist nicht leicht, sich eine Vorstellung über den Umfang des chemischen Wissens in der gegenwärtigen Zeit zu machen, ohne den Blick rückwärts auf vergangene Jahrhunderte zu lenken. Die Geschichte einer Wissenschaft ist eine Seite in der Geschichte des menschlichen Geistes; in Beziehung auf ihre Entstehung und Entwicklung gibt es keine, welche merkwürdiger und lehrreicher ist, wie die Geschichte der Chemie.

Justus Liebig, Chemische Briefe 1851.

This chapter collects a number of examples of absolute asymmetric synthesis and related topics.

1874: The idea that CPL might induce an enantiomeric excess in a reaction was first put forward by Le Bel,[6, 7] and the idea was further developed by van 't Hoff in 1894.[128]

1894: Pierre Curie discussed asymmetric synthesis under influence of physical forces. He concluded that a magnetic field would not suffice to obtain an enantiomeric excess, unless an electric field was applied in a certain direction.

1896: Cotton discovered the phenomenon of circular dichroism. He tried to degrade an alkaline aqueous solution of racemic copper tartrate using CPL, but the solution remained racemic.

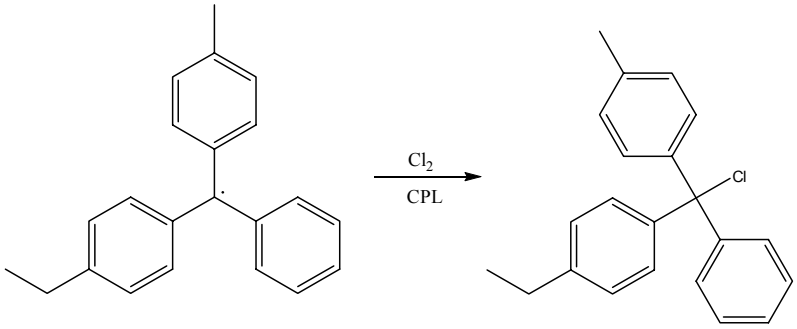
1898: Experiments on total spontaneous resolution by Kipping and Pope.[129] They found that crystallisation of sodium chlorate gave a 1:1 mixture of enantiomorphous crystals.

1904-1908: Further (unsuccessful) attempts to use CPL were made by Byk[130] and by Henle and Haakh.[131] Henle and Haakh used the term total asymmetric syntheses (totale asymmetrische Synthese) for such phenomena.

1923: Bredig introduces the term absolute asymmetric syntheses („absolute" asymmetrische Synthese).[132] Experiments were performed on degradation of mandelic nitrile, diazocamphor and ethylidene lactic acid as well as chiral coordination compounds with CPL, but the experiments were unsuccessful, and had to be cancelled as World War I broke out.

1929-1930: Kuhn *et al.* reported the first reaction where CPL gave rise to an enantiomeric excess. Low optical rotations (0.05º) were obtained by irradiation of ethyl α-bromopropionate with circularly polarised UV light leading to partial degradation.[8-10] In 1930 they reported a similar degradation of α-azidopropionic acid dimethylamide with optical rotations of 1º.[133] In the same year a third example of enantioselective degradation using CPL was reported by Mitchell.[134]

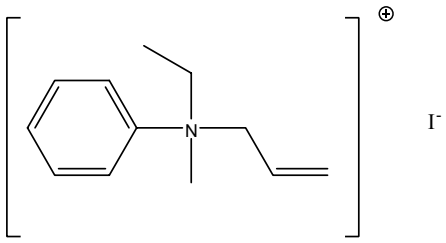
1933: An example of absolute asymmetric photosynthesis was reported: an optical rotation of 0.2º was observed for the phenyl-(4-methyl-phenyl)-(4-ethylphenyl)-chloro-methane prepared by irradiation of a solution of the phenyl-(4-methyl-phenyl)-(4-ethylphenyl)-methyl radical with CPL in the presence of cold chlorine gas (scheme A-1).[34]



Scheme A-1.

1935: Davis and Heggie obtained enantiomeric excesses in the addition of bromine[135] and chlorine[136] to 2,4,6-trinitrostilbene using CPL.

1938-1939: The first successful experiments on total spontaneous resolution were carried out by Havinga. The results were published in Dutch in 1941-1942, and an account in English appeared in 1954.[11] Havinga was able to resolve *N*-allyl-*N*-ethyl-*N*-methyl-*N*-phenyl-ammonium iodide (Scheme A-2) by crystallisation from water at elevated temperature. At room temperature the racemisation of aqueous solutions is slow. This salt had been shown by Fock to form hemihedral crystals, but the crystal structure was not published until 2001.[137] The experiments by Havinga may be regarded as the first true absolute asymmetric synthesis, as it did not involve CPL.



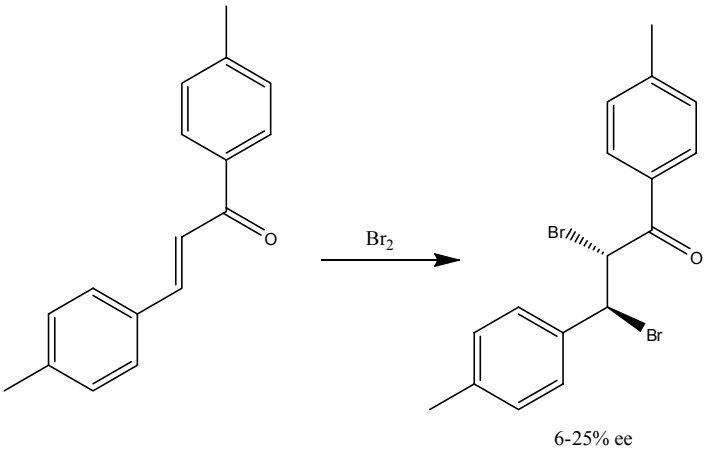
Scheme A-2.

1944: Mitchell and Dawson[138] reported asymmetric photolysis of β-chloro-β-nitroso-α,δ-diphenylbutane using CPL.

1945: Davis and Ackerman reported small enantiomeric excesses in diethyltartrate formed in the reaction between diethylfumarate and hydrogen peroxide using CPL.[139]

1955: Berson and Brown[140] reported a low optical rotation in a 4-aryl-1,4-dihydropyridine derivative obtained by a degradation induced by CPL.

1969: The first example of total spontaneous resolution followed by a transformation to a configurationally inert product was reported by Penzien. Crystalline 4,4'-dimethylchalcone was treated with bromine vapour, and the product was obtained with an enantiomeric excess of 6-25% (Scheme A-3).[38, 39]



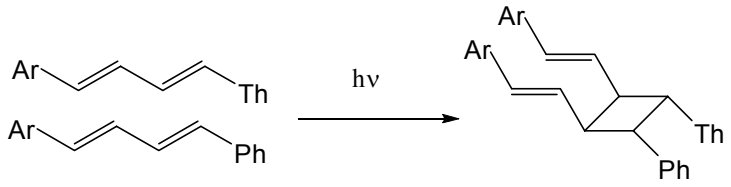
Scheme A-3.

The same year Stevenson reported an example of photoresolution: he irradiated an aqueous solution of a tris(oxalato)chromate(III) with CPL.[141] This resulted in excitation and enantiomerisation, giving rise to an enantiomeric excess in the product. Similar results were reported by Nordén.[142]

1971: Pincock *et al.* investigated the crystallisation of 1,1'-binaphtyl, which readily enantiomerises above the melting point and crystallises as a conglomerate. At room temperature the crystals may be dissolved and the optical rotation measured.[35] The crystal batches were found to be optically active, and the probability of obtaining a certain enantiomer was found to be stochastic.[36] The same year Kagan *et al.* reported an enantiomeric excess (≤0.2%) obtained by CPL

induced synthesis of hexahelicene[33] and in 1972 Calvin *et al.* independently reported similar results.[143]

1973: Green *et al*. reported an enantiomeric excess on irradiation of individual chiral single-crystals composed of two co-crystallising dienes, which undergo an intermolecular [2+2] cycloaddition on irradiation (Scheme A-4).[144] Only a few examples of such intermolecular reactions within a single-crystal have been reported. To qualify as absolute asymmetric synthesis reactions would have to be performed on bulk samples. This was, however, the first example of an enantioselective photochemical transformation in a chiral crystal.



Ar = 2,6-dichlorophenyl
Th = 2-thienyl

Scheme A-4.

1975-1976: Bonner reported an enantiomeric excess of 1.4% obtained by degradation of racemic leucine by longitudinally polarised electrons from an accelerator[145] and the following year he reported enantioselective adsorption of *DL*-alanine hydrochloride on chiral quartz crystals.[87] Both these results are relevant to the question of the origins of biomolecular homochirality.

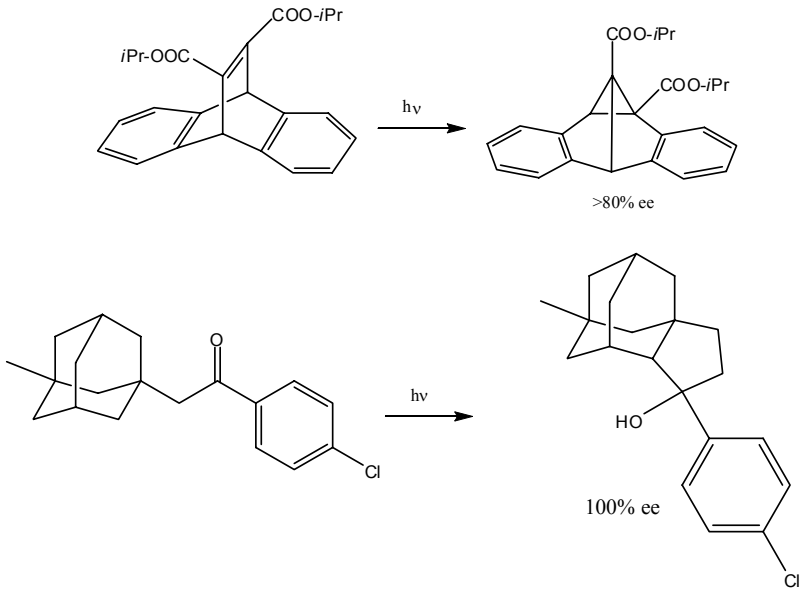
1981: It was found that selected chiral single-crystals of *p*-bromobenzoic anhydride reacted with racemic 1-phenylethylamine to give a chiral amide with at least 20% ee.[146]

1982: Addadi, van Mil and Lahav reported that large chiral single-crystals of achiral, substituted divinyl benzenes gave “quantitative enantiomeric yield" in a [2+2] photopolymerisation reaction.[147] Due to the use of selected single-crystals, this is not absolute asymmetric synthesis in the strict sense.

1983: Total spontaneous resolution of an oxazolobenzodiazepinone was reported.[148, 149]

1984: A low enantiomeric excess was observed in a photooxidation reaction of an alkene forming a clathrate with tri-*o*-thymotide.[150] More successful experiments using tri-*o*-thymotide were reported in 1999 (see below).

1986-1987: Two cases of photochemical rearrangements in chiral single-crystals were reported in 1986, giving >80 and 100% ee, respectively (Scheme A-5).[151]



Scheme A-5.

In 1987 Toda *et al.*[152] obtained 93% ee and 75% yield of a β-lactam by irradiation of chiral single-crystals (or bulk samples obtained by seeding) of an oxo amide. These cases do not qualify as absolute asymmetric synthesis, since reactions were performed on individual single-crystals, although it might be possible to perform total spontaneous resolution in these cases. Richardson *et al.* reported that *achiral* crystals of crotonic acid and tiglic acid gave up to 30% ee on dihydroxylation with OsO_4 or dibromination with Br_2-vapour, when the reagent was allowed to attack the crystal on a specified crystal face. This is only possible when the molecules are aligned in a special way relative to the selected face.[153]

1988: Large crystals of dibenzobarrelene gave an enantiomeric excess of 8% on bromination.[154]

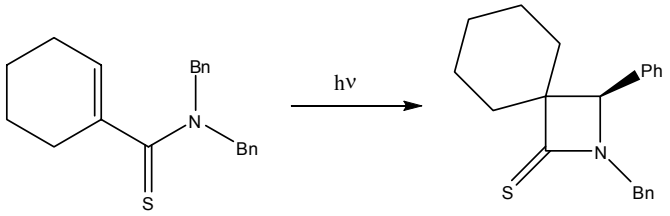
1990: Feng and McBride[37] reported that all 11 crystals of (11-bromoundecanoyl) peroxide obtained in a crystallisation experiment were of the same enantiomorph. In the same year Kondepudi *et al.*[27] reinvestigated sodium chlorate and found that all crystals in a batch were of the same enantiomorph when crystallisation was performed under slow stirring. Repeating the crystallisation gave a stochastic distribution of the optical rotation in different batches.

1991: Chiral crystals *containing both enantiomers* of a cobalt complex were irradiated by X-rays, which led to selective racemisation of one enantiomer. Thus, the 1:1 ratio of enantiomers shifted to a 2:1 ratio on irradiation.[155]

1994: Total spontaneous resolution of narwedine, a precursor of the alkaloid galanthamine was reported to be possible in alkaline solution at elevated temperature.[156] Optical resolution was performed by seeding (no absolute asymmetric synthesis) but the method is of practical interest. The method was developed at the pharmaceutical division of Ciba-Geigy Corporation, perhaps the only industrial contribution to the field.

The same year, an enantiomeric excess of 95% was obtained by a photoinduced [2+2] cycloaddition in chiral single-crystals of co-crystallised bis[1,2,5]thiadiazolotetracyanoquinodimethane and *o*-divinylbenzene.[157] The product obtained by irradiation was amorphous.

1993-1996: A number of photochemical reactions in chiral crystals were reported by Sakamoto *et al.* in the mid 90's.[158-161] An example from 1996[162] is the photochemical transformation of achiral *N*,*N*-dibenzyl-1-cyclohexenecarbothioamide to a chiral β-thiolactam (Scheme A-6). The β-thiolactam was obtained in a crystalline state, as indicated by X-ray powder diffraction. The X-ray powder diffractogram was different from that obtained after recrystallisation of the product, indicating that the photolysis product was obtained as a metastable phase.



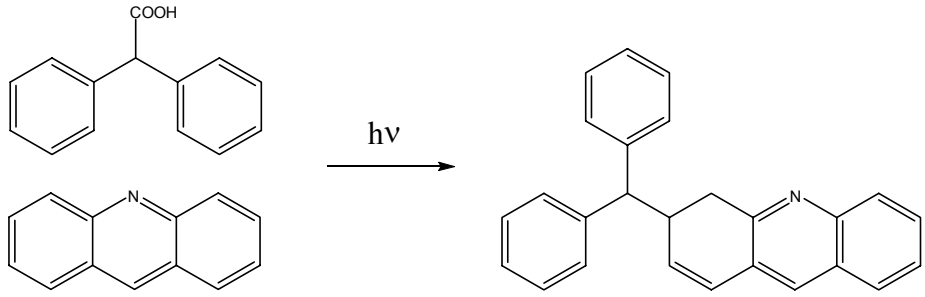
87-91%ee

Scheme A-6.

1995: Toda *et al.* reported that 3,4-bis(diphenylmethylene)-*N*-methylsuccinimide crystallises as three polymorphs form acetone, one of the phases belonging to space group $P2_1$. On UV irradiation of the chiral crystals, *N*-metyl-1,1,4-triphenyl-1,2-dihydronaphtalene-2,3-dicarboximide is formed with 64% enantiomeric excess.[117]

Reversible photoresolution for application in molecular switches was reported by Suarez and Shuster.[163] Feringa published experiments on chiroptical switches the following year.[164]

1996: Koshima *et al.* reported a reaction between two components in a chiral crystal (Scheme A-7).[165] It was found that the two achiral substances acridine and diphenylacetic acid co-crystallised and that the crystals belonged to the Sohncke space group $P2_12_12_1$. On irradiation, the two components reacted to give a chiral product with an enantiomeric excess of 35%. Samples were obtained by seeding, however, and the process does therefore not qualify as absolute asymmetric synthesis.

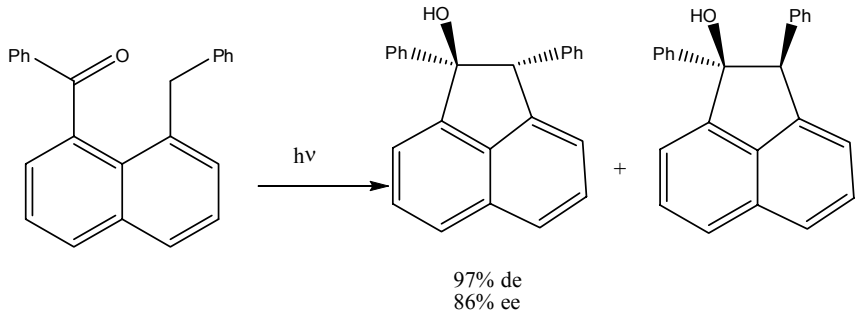


Scheme A-7.

In the field of chemical transformations initiated by circularly polarised radiation, a new approach was successfully tested in 1996, when circularly polarised synchrotron radiation was used in the photoresolution of (*E*)-cyclooctene.[166] A similar resolution of *DL*-leucine was reported a few years later.[167]

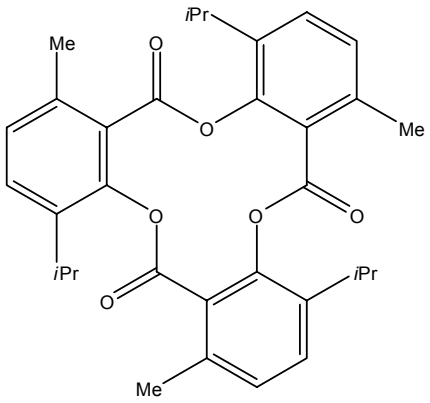
1997: Soai indicated the possibility to use asymmetric autocatalysis for absolute asymmetric synthesis in a 1997 patent.[45] More extensive studies appeared in 2002-2003. Enantioselective photocyclisation of 2-pyridones was reported by Wu and Cheer,[168] but only single-crystals were used. The authors utilised the reported tendency for *meta*-substituted aryls to form conglomerates.[169]

1998: A photochemical reaction was reported, where chiral crystals gave rise to both a high diastereomeric and a high enantiomeric excess at the same time (Scheme A-8).[170]



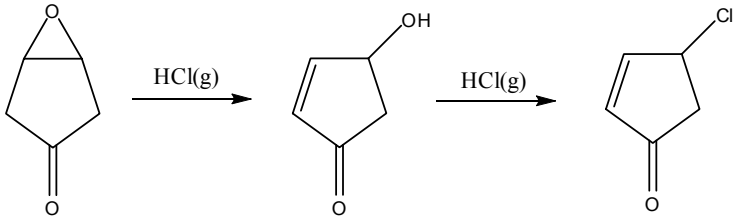
Scheme A-8.

1999: The main strategy for utilising chiral crystals in absolute asymmetric synthesis this far had been photochemical reactions, with the bromination of dimethylchalcone as one exception. Another exception appeared in 1999. The compound tri-*o*-thymotide (Scheme A-9) had been synthesised in the 1950's and was found to form clathrates with a variety of solvents such as *n*-hexane, ethanol, methanol, *m*-xylene and *p*-xylene.[171] Most clathrates crystallise in the Sohncke space group $P3_121$ or ($P3_221$) and tri-*o*-thymotide was found to display chiral recognition when crystallised with chiral guests.[172]



Scheme A-9.

It was found that the clathrate with 3,4-epoxycyclopentanone crystallised as chiral crystals, which reacted with gaseous hydrogen chloride to give a mixture of 4-hydroxy-cyclopent-2-en-1-one and 4-chloro-cyclopent-2-en-1-one (Scheme A-10). By measuring the optical rotation and performing least-squares analysis, the enantiomeric excesses of the two products in the reaction mixture were estimated to be 9±3% and 22±2%, respectively.[40]



Scheme A-10.

Total spontaneous resolution of a conformationally chiral cyanoguanidine derivative was also reported in 1999.[173] The enantiomeric excess was very close to 100%, since slow crystallisation could give rise to one large single-crystal in 89% yield. A low Flack parameter indicated an enantiomerically pure crystal.

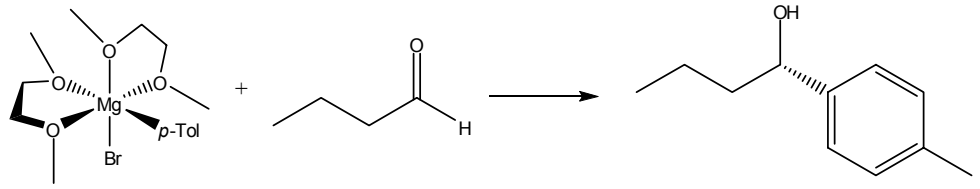
2001: Important results were reported in 2001, *i.e.* the first absolute asymmetric synthesis of a catalyst.[174] 1,1'-diphenyl-3,3',4,4'-tetramethyl-2,2'-diphosphole (BIPHOS) crystallises as a conglomerate, and it was possible to grow very large single-crystals. These crystals could be dissolved in dichloromethane at -78 ºC, and reacted with $[PdCl_2(CH_3CN)_2]$ to give $[PdCl_2(biphos)]$ which is stereochemically inert. This complex catalyses allylic substitutions, and an enantiomeric excess of 80% was observed in such a reaction.

Ribó *et al.* reported that rotary evaporation of dilute solutions of certain achiral porphyrins gave rise to solutions of chiral J-aggregates displaying circular dichroism.[48-50] The sign of the circular dichroism was found to depend on the direction of rotation during evaporation. According to the authors, this is not a process on the molecular level. Individual molecules are first assembled into aggregates which, under influence of the stirring, assemble into chiral fibres. Similar results had been reported in 1976 by Honda and Hada,[175] however,

Nordén showed that the detection of circular dichroism most probably was due to an artefact in this case.[176]

2002-2003: Using the Soai autocatalytic reaction,[44] Singleton and Vo[47, 83] and Soai[46] found that an enantiomeric excess could be obtained without any chiral additive. Another example of absolute asymmetric synthesis using the Soai reaction in the presence of silica gel was reported by Soai *et al.* in 2006.[177]

2003: Håkansson *et al.*[42] reported the first examples of absolute asymmetric synthesis of organometallic reagents. Enantiomeric excesses up to 22% were reported in reactions between "chiral-at-metal" Grignard reagents with prochiral butyraldehyde or benzaldehyde (Scheme A-11).

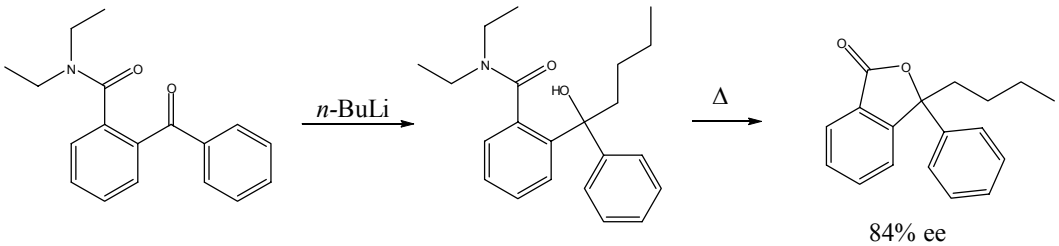


30-45% yield
5-21% ee

Scheme A-11.

Sakamoto *et al*. reported that chiral crystals of an aromatic amide could either undergo a photochemical rearrangement (>99% ee) or enantioselective addition of *n*-BuLi to give a mixture of two chiral products with up to 83% ee.[178]

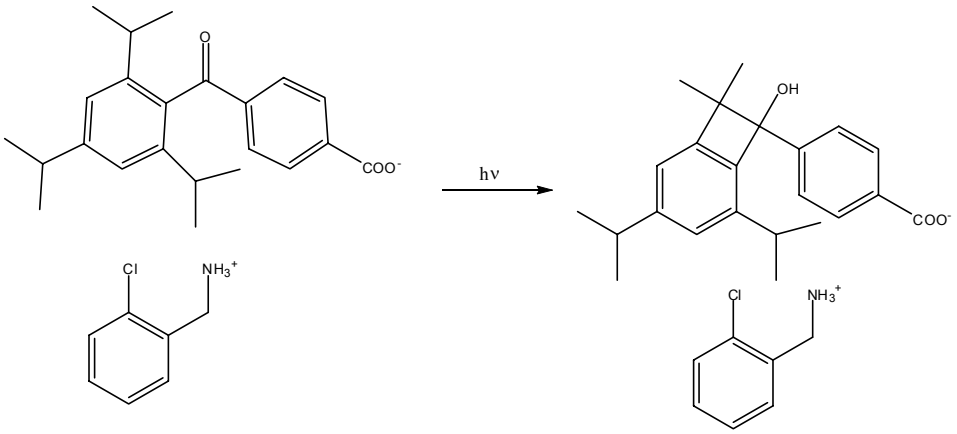
2004: Sakamoto *et al*. reported remarkably high enantiomeric excesses (17-84%) in the reactions of prochiral ketones crystallising in Sohncke space groups and *n*-BuLi (Scheme A-12).[41]



84% ee

Scheme A-12.

2005: By complexation of prochiral aldehydes as chiral metal complexes, Johansson and Håkansson obtained enantiomeric excesses of up to 16% on reaction with methyl lithium.[43] Total spontaneous resolution of a coordination network, $[Cu(NO_3)_2(dmeda)]_n$, was reported in the same year.[66] Symmetry breaking by abrasion/grinding of sodium chlorate was reported by Viedma.[29] Returning to photochemical rearrangements in chiral crystals, a remarkable example was given in 2005.[179] In this case photocyclisation of a triisopropyl benzophenone derivative resulted in single-crystal-to-single-crystal transformation, where the same crystal could be analysed by single-crystal X-ray diffraction before and after the irradiation (Scheme A-13).



Scheme A-13.

2006: A gaseous mixture of carbon monoxide, ammonia and water (known to exist in the interstellar medium) was irradiated with 3.0 MeV protons followed by CPL. The reaction produced several chiral amino acids *e.g.* alanine, with enantiomeric excesses up to 0.65%.[180]

2007: Spontaneous resolution of labile helical bimetallic complexes[181] and 1D helical coordination chains were reported.[182]

2008: Photocyclisation of a diarylethene derivative co-crystallising with octafluoronaphthalene with an enantiomeric excess >99% was reported.[183] By radiation with visible light, the reaction was reversed. In the same year, an aromatic amide was crystallised from different solvents, and 13 different phases were reported.[184] One of these crystallised in a Sohncke space group, although total spontaneous resolution was not proved. Spontaneous resolution of labile cyclic gold(I) complexes was reported the same year.[185]

2009: Total spontaneous resolution and absolute asymmetric synthesis of an octahedral nickel complex was reported.[186] The enantiomeric purity was estimated by single-crystal CD spectroscopy on ten crystals from each batch. A new report appeared where a reagent was applied on a selected surface of an achiral crystal, giving rise to an enantiomeric excess.[187] Achiral single-crystals of the prochiral ketone 3-acetyl-6-bromocoumarin gave up to 26% ee on reduction with sodium borohydride. Reaction from one end of the crystal gave the (+)-enantiomer, while reaction from the opposite side gave the (-)-enantiomer.

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[51] *The term "chirogenic centre" will be used through out this text. The terms "asymmetric centre" or "chiral centre" appear to be inappropriate since a centre is a point in space which can neither be asymmetric nor chiral. The term "stereogenic centre" is not useful in this thesis, since stereogenic centres with coordination numbers higher than four may generate diastereomers rather than enantiomers. Achiral octahedral complexes displaying stereogenic centres are common.*
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