Spontaneous resolution, whence and whither: from enantiomorphic solids to chiral liquid crystals, monolayers and macro- and supra-molecular polymers and assemblies†

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One of the great challenges in stereochemistry is the explanation of why some molecules resolve spontaneously while others do not. In this *critical review* the recent advances in the creation of chiral systems from achiral and racemic compounds in three-, two- and one-dimensional systems are discussed. There are some groups of molecules in some systems that do tend to display conglomerates, which may suggest that there are *enantiophobic* and *enantiophilic* molecules whose assembly is guided by the structural and thermodynamic properties of the systems in question.

1 Introduction

When molecules associate, their enantiomers can condense either together or separately, and in the latter case we call the process *spontaneous resolution*.[1] This generally unplanned separation of enantiomers when they form aggregates – large or small – continues to be an intriguing phenomenon whose explanation is often elusive, more than 150 years after Pasteur's historic observation[2,3] of enantiomorphic hemihedral crystals[4] (showing half the faces required for full symmetry) of sodium ammonium tartrate tetrahydrate (Fig. 1). However, the modern tools for the characterisation of crystals and nanometre scale structures are giving great insight into the processes that lead to symmetry breaking. A spectacular example is that of the formation of chiral supramolecular decamers of 1-nitronaphthalene on the Au(111) surface and the achievement of a nanometre scale triage with a scanning tunnelling microscope (STM) tip (Fig. 1).[5] Since our last review covering this subject matter which appeared here four years ago,[6] a number of significant and enlightening contributions have been published, which we summarise in this text.

The phenomenon of spontaneous resolution is often associated with the resolution of enantiomers for exploitation in the pharmaceutical industries, is of increasing interest in materials science, as we shall see, and has even been linked to the terrestrial abundances of enantiomers in the natural world.[7] However, one of the great challenges which underlies all the work in this area of research is the explanation of why some molecules resolve spontaneously while others do not. The reader will observe that there are some groups of

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† The HTML version of this article has been enhanced with additional colour images.

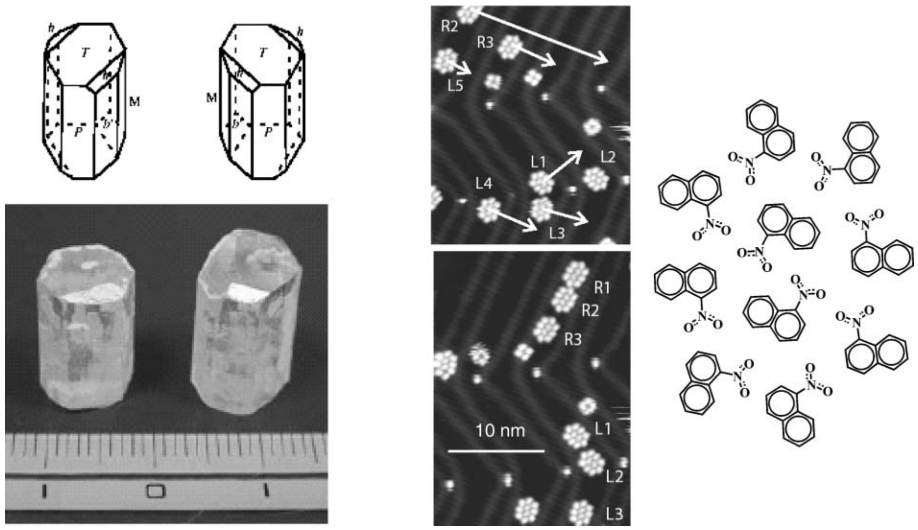

Fig. 1 Pasteur's simplified drawing of sodium ammonium tartrate (left) and a pair of crystals of the same grown by the seeding method,[4] alongside a modern day triage of a supramolecular decamer (right) using an STM tip (images centre).[5] (Reprinted with permission from ref. 4. Copyright 2003, Royal Society of Chemistry.)

molecules in some systems that do tend to display conglomerates. Are there, then, *enantiophobic* and *enantiophilic* molecules?‡ Or are packing forces responsible for conglomerate formation? In the works we have chosen to review, we have tried to take the most representative articles and those in which the passage of chiral conformations is discussed, more or less, in the hope that the work presented will act as a springboard to further reading and research. As in our previous review, we start in the bulk ordered situation of crystals, and then treat systems with smaller dimensions, being conscious of the fact that the phenomenon works from the bottom-up.

2 Spontaneous resolution in crystalline solids

2.1 Data mining

Ordered (periodic) 3D crystals conglomerate formation cannot be predicted and is not frequent. The first statistically significant studies of propensities of organic compounds for certain space groups were published many years ago,[1] and there has not been such a wide-ranging reappraisal since. This data implies that over 90% of compounds crystallise in centrosymmetric space groups. A recent structural database screening of achiral and purely organic compounds which crystallise in chiral space groups suggests that the flexibility of the molecules plays an important role in determining whether spontaneous resolution will occur, or not.[8] One of the most important observations from this work was that chiral conformationally flexible molecules are 7.9 times more likely to crystallise in $P2_1/c$ rather than $P2_12_12_1$, while the same preference is shown by more rigid molecules but "only" 5.9 times. Furthermore, if the rigid molecule has mirror symmetry, the preference is cut to 4.3 times. It is clear that apparently, when an achiral molecule crystallises in a chiral space group, some of its features make it prefer packing with the formation of a screw axis rather than an inversion centre and glide plane. This study – which has its limitations and was recognised as the first step towards a deeper understanding – suggests a role of flexibility in determining separation and packing of organic molecules. It is interesting to put these observations in the context of spontaneous resolution in crystals and other systems.

2.2 Conglomerate spotting

The most immediate and conclusive method for determining if spontaneous resolution has taken place remains the crystal structure determination by diffraction techniques, generally X-ray, in combination with CD spectroscopy (of ground crystals or their solutions if the enantiomers are stable), as we summarised before.[6] In addition, NMR spectroscopy can be used to determine stereoselective aggregation (as we shall point out in examples later), and EPR spectroscopy has been used recently to show the differences between magnetic interactions in the conglomerate and racemate of a nitroxide radical.[9]

An X-ray structure on its own does not necessarily prove that spontaneous resolution has taken place because the bulk of the crystal can be racemic.[10] In relation to this difficulty, recent developments in optical microscopy now allow the observation of circular birefringence and CD from crystals.[11] Thus, this technique constitutes a very interesting tool for the study of crystal chirality, and in particular spontaneous resolution. CD imaging spectroscopy was used to show the enantiomorphic twinning present in crystals of 1,8-dihydroxyanthraquinone.[12] This compound forms spirals of the flat molecules down the crystallographic *c* axis in the enantiomorphic space groups $P4_1$ and $P4_3$, and lamellae form in the plane with π-stacking interactions present. It has been suggested that the strongest interactions between the molecules are of the dipole–dipole type, with little intermolecular

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‡ Enantiophobic molecules would aggregate leading to a conglomerate, while enantiophilic molecules would give a racemic compound.

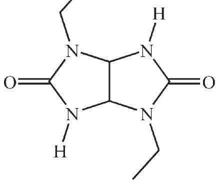
distance between oxygen atoms. The CD imaging microscope shows enantiomorphic areas in the crystals as red and blue (Fig. 2), and the CD spectra in each domain can be recorded.

Another very appealing microscopy technique which has been developed recently is based on optically active sum-frequency generation, and allows three-dimensional chiral imaging.[13] Here, sub-micron resolution observation of chiral objects on achiral backgrounds can de realised. It is to be expected that these optical methods will improve further in the coming years.

2.3 Spontaneous resolution in organic compounds

Non-covalent bonds, as well as molecular shape, influence strongly the packing of molecules in crystals. In organic compounds, where the interactions are relatively weak, hydrogen bonds and different types of association of aromatic residues can sometimes be invoked in the explanation of symmetry breaking, especially where series of compounds show a tendency for the phenomenon.

There are several examples of spontaneous resolution occurring on a series of dialkylglycolurils such as **1**,[14] as well as their synthetic precursor *trans*-4,5-dihydroxyimidazolidin-2-one (**2** and aminoguanidinium derivatives (**3**,[15] in contrast to diphenylglucoluril analogs.[16]



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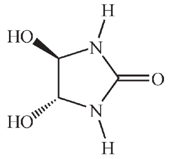

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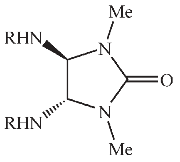

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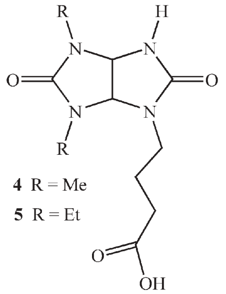

4 R = Me
5 R = Et

The formation of homochiral chains, as a consequence of the supramolecular structure within the crystal, is dictated by the network established by the different hydrogen bonding groups in the molecules, including some of the N-substituents when present (for instance propyl carboxylic acid). However, this hydrogen bonded network is not sufficient to determine whether the compound will crystallize as a conglomerate. Despite minor structural differences between compounds, all form homochiral layers but not all spontaneously resolve. For instance, the carboxylic acid glycoluril derivative **4** spontaneously resolves while **5** does not.[14]

For most of the examples reported there is a noticeable twist for the bridgehead positions or their equivalent, although the induction of spontaneous resolution has not been systematized.

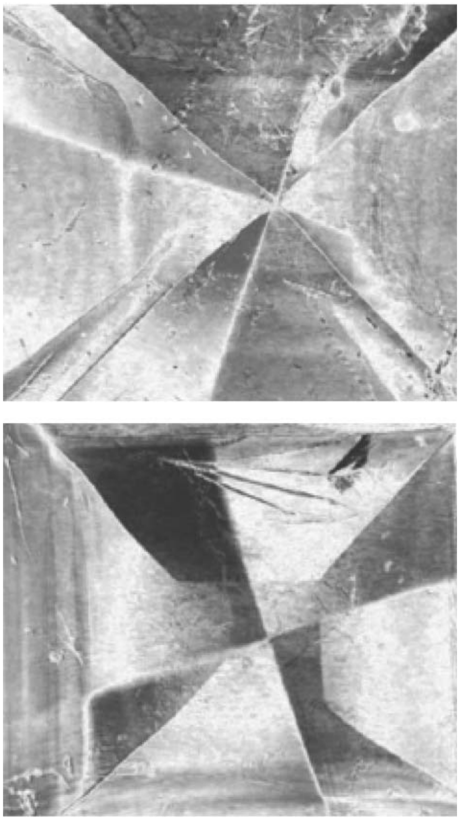

Fig. 2 Images of 1,8-dihydroxyanthraquinone crystals recorded with a CD imaging microscope. (Reprinted with permission from ref. 11. Copyright 2004, Royal Society of Chemistry.)

A series of *syn*-*N*,*N*-disubstituted glycolurils with aromatic substituents at the bridgehead carbon atoms has been reported[17] to form hydrogen bonded assembled chiral ribbons in the solid state. Each ribbon is comprised of a sequence of alternating face glycolurils, wherein each glycoluril monomer is linked to two adjacent monomers by two amide N–H···O=C bonds (Fig. 3). The chirality on the monomers arises from the twisted conformation adopted in order to maximize separation of the aromatic rings located at the bridgehead position, which reflects on the dihedral angle between the bridgehead carbon atoms of 26 and 29°. The chirality of the ribbons emerges from the fact that each ribbon contains only one of the enantiomers. Additionally, for one of the cases spontaneous resolution

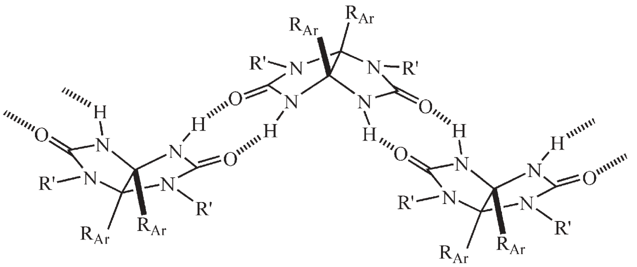

Fig. 3 Enantiomerically pure hydrogen bonded ribbon formed in the solid state by *syn*-*N*,*N*-disubstituted glycolurils with aromatic substituents.[17]

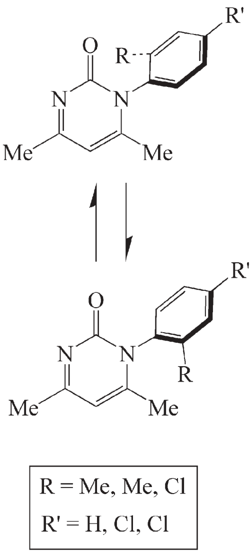

Fig. 4 Atropoisomeric 1*H*-pirimidon-2-ones which form conglomerates.[18]

operates, although the absolute configuration of the enantiomer that crystallizes is not known.

Spontaneous resolution has also been accounted for a series of atropoisomeric 1*H*-pyrimidon-2-ones (Fig. 4), and their rate of racemisation was examined in different solvents. Furthermore, asymmetric desequilibration was achieved by crystallizing at high temperatures with stirring. Moderate to high enantiomeric excess values were obtained, especially when seeding was used.[18]

Another example of chiral discrimination in crystals for atropoisomers is accounted for 4,4′-binicotinic acid, which crystallizes as a racemic compound in both its neutral and monohydrochloride salt forms, but as a conglomerate as its dihydrochloride salt.[19] The solid structure of this conglomerate shows a homochiral network held by –COOH···Cl···HN– hydrogen bonds, which are responsible for the homochiral association (Fig. 5). Furthermore, the homochiral layers interpenetrate, forming a 2D network based on C–H···O interactions.

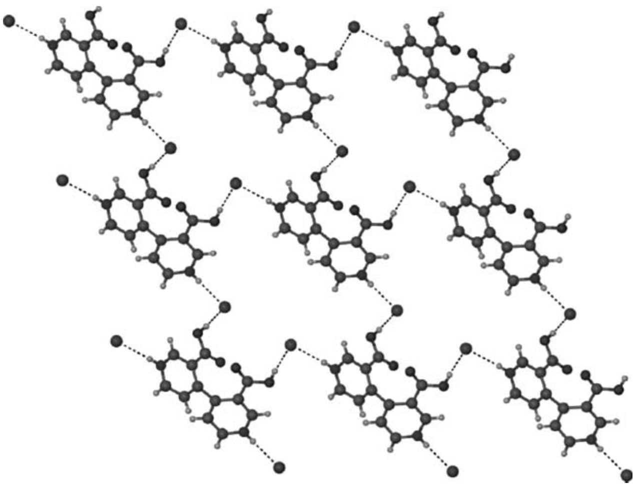

Fig. 5 Homochiral hydrogen-bonded network present in crystals of 4,4′-binicotinic acid bishydrochloride.[19]

The formation of salts is by no means a general way of generating conglomerates, though. By way of example, 2,6-diphenylbenzoic acid crystallises in a chiral space group, while its 4,4′-bipyridinium (and metal ion) salt(s) are all achiral,[20] and (±)-*trans*-diaminocyclohexane crystallises as a conglomerate, while its hydrosulphate salt (and others) are racemic compounds.[21] In this case it was inferred that appropriate choice of salt filler capable of maintaining the same type of layer packing as the neutral compound might also lead to a conglomerate. The counterion in the salts of the drug propranolol can be used to prepare rationally a conglomerate,[22] which crystallises for the fluoride salt where the hydrogen bonded homochiral chains can interact strongly because of the small size of the anion. The iodide salt is a racemic compound.

An achiral zwitterionic molecule (7-(*N*,*N*-dimethylpiperazinium)-7-oxo-8,8-dicyanoquinodimethane) is conformationally chiral, due to the twist between the benzene ring and the amide group, spontaneously resolves in the crystals obtained with and without crystallization water molecules.[23] Multiple electrostatic interactions and hydrogen bonds lead to the formation of helical structures along the orthogonal crystallographic axes. Another achiral molecule which forms a chiral solid with a remarkable crystal structure is tris(2-hydroxyethyl)-1,3,5-benzenetricarboxylate (Fig. 6).[24] The crystals belong to one of the enantiomorphic space groups $P6_1$ or $P6_5$, in which the helical chains are maintained by O–H···O=C hydrogen bonds and offset π–π stacking between the aromatic cores. The arrangement of these rings and the torsion formed by the hydroxyl groups lead to the chiral structure, which was confirmed by performing solid state CD spectroscopy on the enantiomers. In common with related one-dimensional chiral stacks, no interpretation of the interaction between these helical was made, and an explanation of the enantiophobic nature of the strands is awaited.

A chiral four-connected three-dimensional framework based on a twisted bimesityl core is formed on crystallisation of a tetraphenol derivative (Fig. 7).[25] The framework, which contains voids where solvent molecules are incorporated, is held together by phenolic O–H···O hydrogen bonds which generate supramolecular double helices along two crystallographic directions. The corresponding tetraacid does not form a conglomerate as a single crystal, at least (partially because of solvation of the acid groups), unlike simpler mesitylene-derived acids which form helical strands in conglomerates.[26]

Spontaneous resolution in a family of donor–acceptor [2]catenanes containing proton-ionisable 1*H*-1,2,4-triazole subunits has been proven not to be a curiosity, but a structure-based property within these catenanes. Two donor–acceptor [2]catenanes incorporating one 3,5-bis(methylene)-1*H*-1,2,4-triazole unit and either one 1,4-dihydroxybenzene or 1,5-dioxynaphthalene unit in the macrocyclic polyether component (Fig. 8) undergo spontaneous resolution upon crystallisation, providing evidence that the inclusion of this triazole unit in the neutral component favours the phenomenon. The formation of homochiral crystals under isomerising conditions

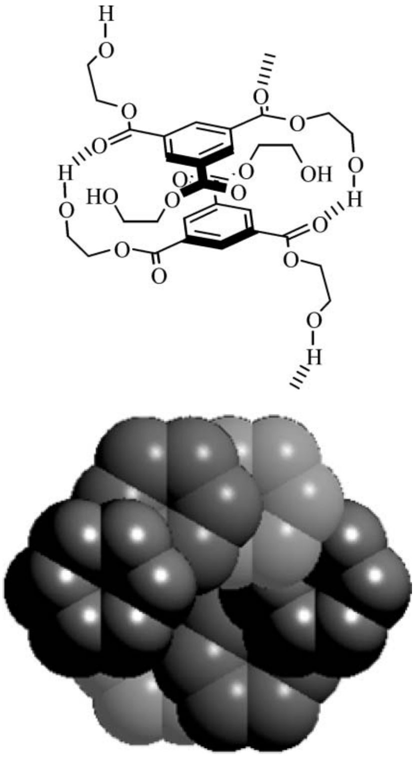

Fig. 6 A schematic drawing of the non-covalent interactions in the crystals of tris(2-hydroxyethyl)-1,3,5-benzenetricarboxylate, and a schematic view showing the aromatic cores in the 6_1 helices in the structure.[24]

–one amongst four possible isomers – was proved by X-ray crystallography[27] and CD experiments.[28]

Another chiral interlocked system is shown by the unusual crystal structure of methylmethanetriacetic acid.[29] The supramolecular structure in the solid state is based on the formation

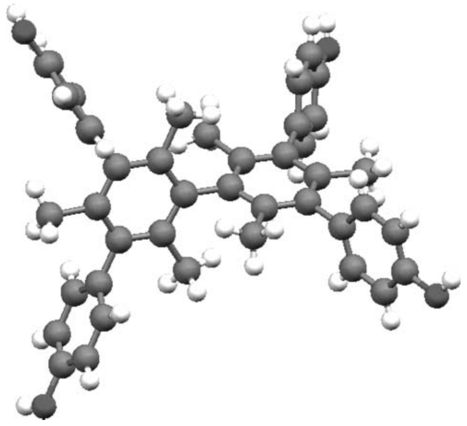

Fig. 7 The conformation of a tetraphenolic bimesityl derivative in its crystal.[25]

of intermolecular hydrogen bonds between the carboxylic groups, and shows the formation of a homochiral polycatenane based on interpenetrating layers of the hydrogen bonded triacid.

A number of cocrystals of achiral organic compounds have been shown to undergo spontaneous resolution. One framework-type crystal complex formed between an aromatic disulfonate and guanidinium ions is a conglomerate – very much the exception to the rule for the compounds studied up to now.[30] Sixteen (16) different framework compounds were prepared using the different biphenyl and binaphthyl disulfonates **6–10** shown in Fig. 9. The authors concluded that these results imply that in the one-dimensional guanidinium sulfonate ribbons the close packing interactions can lead to homochiral or heterochiral superstructures while big and permanent electric dipoles in the biphenyl spacers are important for the chirality transmission over large distances.

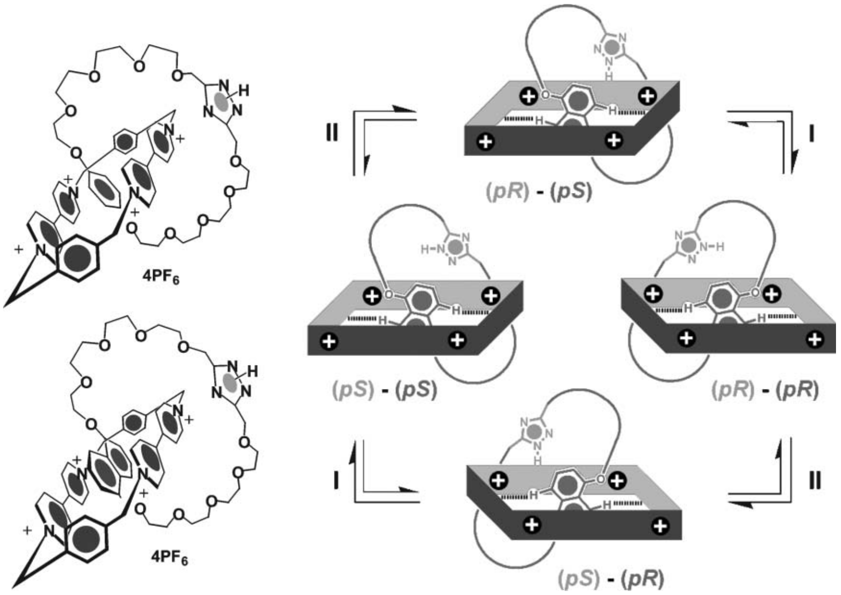

Fig. 8 Co-conformational diastereomers of triazole-containing [2]catenanes. (Reprinted with permission from refs. 27 and 28. Copyright 2004 and 2003, Royal Society of Chemistry.)

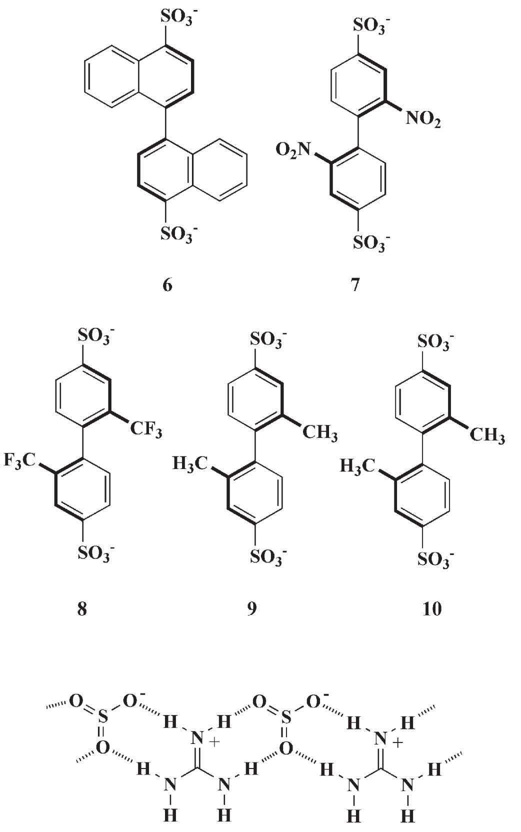

Fig. 9 The series of disulfonate ligands co-crystallised with guanidinium ions, and the one-dimensional ribbons that the two ions form in the solid state.[30]

N,*N*,*N*′,*N*′-Tetramethyl-*p*-phenylenediamine experiments spontaneous resolution due to conformational chirality originated by the twist in the dimethylamino groups present in the molecule. Through the formation of co-crystals with different halogenated electron acceptors only the co-crystals formed with 1,8-diiodoperfluorooctane are chiral.[31] The crystals consist of chains, wherein the components alternate: *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine is always conformationally chiral, and for 1,8-diiodoperfluorooctane disordered enantiomeric conformers occupy adjacent chains. Different factors can contribute to the phenomenon: The unusual *gauche* arrangement adopted by the perfluoroalkyl chains, the poor segregation and also H···F and F···F interactions in the crystal network. A spectacular example of a supramolecular chiral system formed from achiral components thanks to halogen bonding between iodide ions and the iodine atoms of the same diiodoperfluoroalkane is that which involves as counterion a calixarene–Ba(II) complex.[32] The crystals, which belong to the *I*422 space group, are comprised of segregated areas of twisted fluorocarbon–iodide alternating strands – which intertwine to give a double helix – and columns of the barium–calix complex. In this example, the *gauche* conformation of the fluorocarbon results in a homochiral arch which is ordered crystallographically.

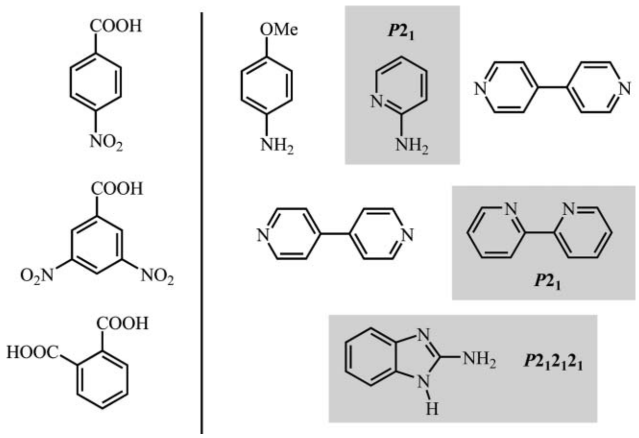

Fig. 10 Complexes formed between achiral carboxylic acids and pyridine-type bases with the conglomerates shaded.[33]

A number of co-crystals of benzoic acid derivatives and organic bases have been prepared (Fig. 10), all of which have 2_1 screw axes in their structures, and three of them pertain to chiral space groups.[33] All the complexes have hydrogen bonds between the acid and pyridine type basic heterocycles, although beyond this level the connectivities are quite different. The complex of 4-nitrobenzoic acid with 2-aminopyridine reveals a structure where clear heterodimers are formed between the components, then N–H···O hydrogen bonds between the "free" amine hydrogen atom and one of the carboxyl oxygen atoms generates the 2_1 chain. The 2 : 1 complex of 3,5-dinitrobenzoic acid and 2,2′-bipyridine is comprised of spiralling supramolecular chains of the acid pillared together by the transoid bipyridine, leaving voids which are filled by another network. On the other hand, the complex of phthalic acid and 2-aminobenzimidazole is comprised of sheets of supramolecular rings arising from the strong hydrogen bonds between the components. It is not clear, then, if there is a relation between the structures that explains the occurrence of chirality, but in any case they reaffirm the ease with which chiral cocrystals are generated from achiral components.

2.4 Spontaneous resolution in coordination compounds

Conglomerates have been observed from the simplest to most complex structures of coordination compounds, where each crystal shows only the helical right-handed Δ or left-handed Λ enantiomers,[34] although the kind of rationalisation of their propensity to crystallise as such has not been performed. "Zero dimensional" complexes, with no coordination bonds between the units, can show the phenomenon, as is seen for the hexafluorophosphate salt of the ruthenium(II) complex with two 2,2′-bipyridine molecules and one phenenthroline ligand.[35] In the crystals of the complex a stack of phenanthroline ligands is generated (π–π separation 3.52 Å) giving a homochiral column, which is surrounded by like ones (Fig. 11). The tetrafluoroborate salt of the same complex, on the other hand, is a racemic compound even though π-stacking interactions are present (though the stacking distance is longer than in the hexafluorophosphate salt). The Ru(II) tris(2,2′-bipyridine) complex as its hexafluorophosphate salt is also a racemic compound.[36] Very subtle differences in packing tip the balance between conglomerate and racemate in these systems.

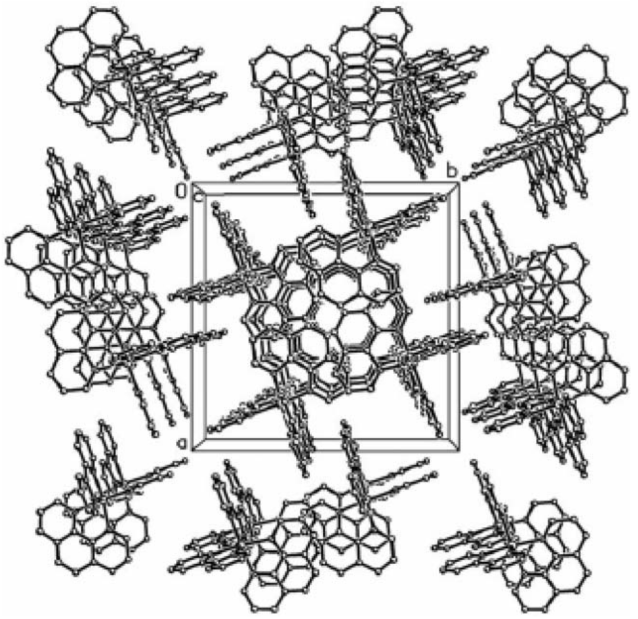

Fig. 11 A view down the stacks of a ruthenium(II) complex showing the π overlap of the phenanthroline ligands. (Reprinted with permission from ref. 35. Copyright 2006, Elsevier.)

Another octahedral complex which shows spontaneous resolution is that with formula [Pt^{IV}(pyrazine-1,2-diselenolene)$_3$]$Na_2 \cdot 6H_2O$, which crystallises in the $P2_12_12_1$ space group.[37] Face-to-face π–π stacking of the phenyl rings in the ligand at the core of a spiral superstructure lead to a formal 8_2 helix. A nitrogen atom of the pyrazine rings coordinate to sodium ions which is in turn solvated by water molecules, and it is these interactions which presumably join the helices together and result in the homochiral crystal, although a direct pathway was not identified.

A series of mononuclear seven-coordinate complexes has been resolved thanks to the spontaneous resolution of the compound.[38] Three lanthanide complexes of dibenzoylmethane (dbm) with the general formula [Ln(dbm)$_3$(H_2O)] have a molecular structure best described as a capped octahedron and crystallise as conglomerates (for Pr, Sm and Er) thanks to the formation of a "quadruple helix" and a series of C–H···π interactions. Because the complexes are labile in solution, spontaneous resolution under racemising conditions takes place (where nucleation is slower than crystal growth) and essentially enantiopure samples can be recovered.

Dinuclear silver(I) double helicates, in which achiral ligands **11** and **12** (which are twisted about the central C–C bond) bind the metal, crystallise in the enantiomorphic space groups $P3_121$ and $P3_221$, and have been proven optically active by recording their solid state CD spectra.[39] In the imidazole derivative **11**, two C–H···π contacts propagate down the supramolecular chains that are formed in the crystal (the NH groups are directed towards the disordered nitrate anions), while in the pyridine analogue (where perchlorate is the anion) these C–H···π interactions are also present, along with π–π stacking between phenyl and pyridine rings which leads to efficient packing of the supramolecular helices to form hexagonal channels in which the anions are located. In the latter case, significant enantiomeric excesses were observed in separate crystallisations, and therefore symmetry breaking takes place (the average over 50 independent experiments being zero and a bimodal distribution was reported).

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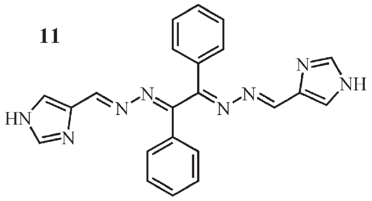

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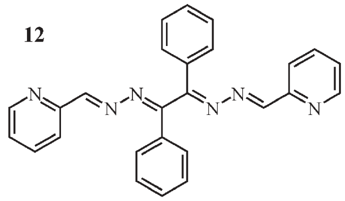

The nature of the metal ion used to assemble ferrocene-containing bisthiosemicarbazone clips was shown to play a critical role on the packing in general, and therefore on the formation of chiral structure or not.[40] The cobalt(II) complex forms one dimensional chiral channels, although the crystal is racemic, while the copper(I) complex forms a conglomerate. This example highlights the complexities of analysis of chiral interactions in three dimensions, since it is very challenging to explain the differences in packing.

Coordination polymers also reveal conglomerates, frequently starting from achiral ligands, and very often helical secondary structures are present.[41] The ligand **13**, with a bent cyclopentadienone core and lateral pyridine groups, forms helical coordination polymers with both zinc(II) and mercury(II) chlorides.[42] The pyridine–metal–pyridine unit forms an essentially linear rod and the ligand backbone provides the twist. It is π–π stacking of the phenyl rings on the "back" of a ligand in one strand with the cyclopentadienone core of a ligand in a neighbouring one, a path which is the relay of stereochemical information. At the macroscopic level, bunches of crystals form which have predominantly one enantiomer, leading to homochiral "colonies". The bispyridine triazolate ligand **14** can form a variety of supramolecular isomers when complexed with copper(I), one of which resolves spontaneously thanks to the formation of a 4_1 helical structure.[43] The conglomerate formation was explained by the π–π stacking, C–H···π and C–H···N interactions between chains, and the fact that an analysis of the packing of heterochiral helices did not yield efficient space filling or favourable interactions. It is interesting to note that the zigzag isomeric form crystallises as a racemic compound. This pattern of racemic compound in a 2_1 structure and spontaneous resolution in the 4_1 helical structure was also seen for the polymorphic silver complexes of ligand **15**, where argentophilicity (interchain silver–silver contact) was inferred to justify conglomerate formation.[44]

Non-stochastic homochiral helix crystallization of a copper(I) chloride triallylamine complex was observed from the neat components, where the crystals grow off particles of

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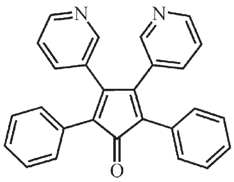

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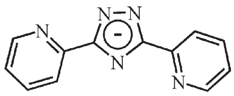

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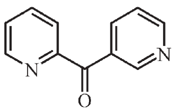


the metal salt.[45] The complex crystallises in the $P2_1$ space group (with one enantiomer in the unit cell) and the structure is comprised of alternating copper chloride dimers coordinated to nitrogen and allyl groups. Allyl groups from different helices intercalate. The conglomerate nature was proved by obtaining mirror image CD spectra of samples from initial experiments. However, consequent experiments only produced the *P* helical complex. The absence of any observable impurity led to the proposal of cryptochirality control in the system, that is a chiral impurity below detection levels whose presence induces chirality in the bulk.

The achiral ligand α,α′-bis(pyrazolyl)-*m*-xylylene forms a homochiral 1D-helical metal–organic framework in combination with zinc(II) chloride.[46] Each transition metal ion is coordinated to two chloride anions and two pyrazolyl nitrogen atoms, leading to a topologically linear and topographically helical chain. Both enantiomorphs were characterised by X-ray crystallography. A chiral channel is present in the structure: It is formed *via* C–H···Cl interactions between the helices.

A complex formed between 1,4-bis(2-pyrimidinesulfanylmethyl)benzene and copper(I) iodide results in a coordination polymer in which helical copper iodide chains interweave in three different directions.[47] The ligands serve to link these chains in different lamellae by interacting with the metal ion through sulphur and nitrogen atoms, which are coordinated to distinct copper ions. The ligand is twisted, and must surely play a role in the transmission of chirality in the network.

The homochiral crystallization of helical coordination chains bridged by achiral ligands can be influenced by the constitution of the organic component. The position of substitution of the pyridyl rings attached to a 1,3,4-oxadiazol-2-yl ring can lead to achiral or chiral coordination polymers with CdI_2 when either methanol or DMF is used as the solvent.[48] We saw how phthalic acid can form a purely organic conglomerate by co-crystallisation with a base, and a homochiral 3D covalent framework can be assembled using it, cadmium(II), and 4,4′-bipyridine bridging ligands.[49] The complex $[Cd(Hphthalate)_2(4,4'\text{-bipy})]_n$ crystallises in the space group $I4_122$ and is comprised of the distorted octahedral metal ion coordinated by four monodentate carboxyl groups and two nitrogen atoms. The phthalate–metal polymeric chain forms a helical secondary structure, with the chains propagating in two directions (the *b* and *c* crystallographic axes) and they are linked by the bipyridine units and lead to a two dimensional homochiral sheet. The authors hypothesise that the bipyridine does not only link the chains, but is central to the transfer of chirality in the system. The three dimensional array is generated through Cd ions. A dimeric phthalic acid ligand also forms conglomerates in combination with cadmium(II) or zinc(II) and 4,4′-bipyridine.[50] In the latter, the zinc(II) ions are complexed by one carboxyl group, a nitrogen atom and three waters of hydration, and packs to give a lamellar structure comprised of two helices, which arise because of (i) the torsion angles between the rings in the ligand and (ii) the angle the carboxyl groups form with respect to the plane of the phenyl rings (Fig. 12). Both have the same helical sense in a given crystal, and the helices are linked by the oxygen atoms between the phthalate groups and bipyridine ligand. The authors recognised that in the third dimension the sheets come together to form the conglomerate by chance. The corresponding cadmium(II) complex, on the other hand, forms a 3D homochiral structure, and again the twist in the

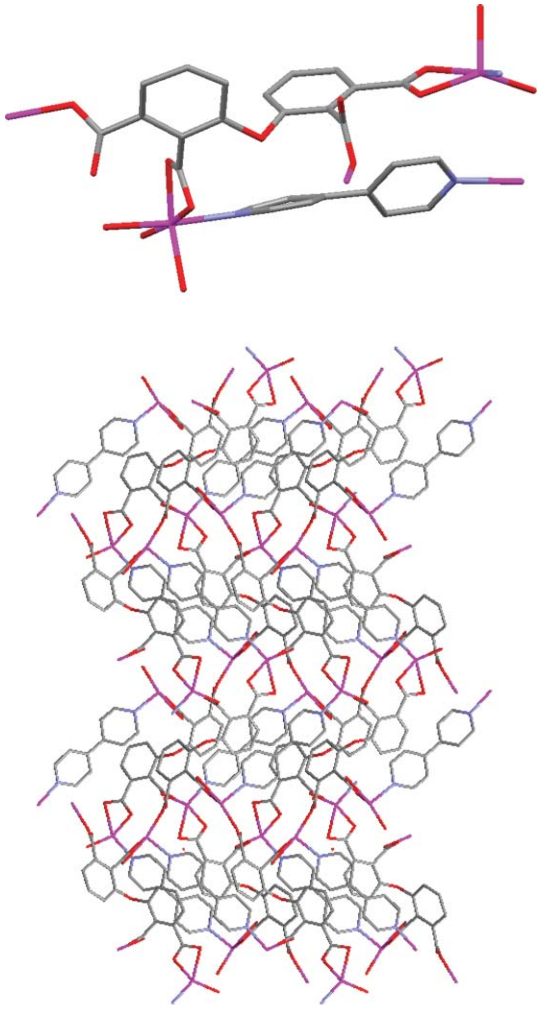


Fig. 12 The asymmetric unit of $Zn_2(2,2',3,3'\text{-oxydiphthalate})(4,4'\text{-bipyridine})(H_2O)_3(H_2O)$ (top) and the packing in the sheets formed by the complex (bottom) (water molecules and hydrogen atoms are not shown).[50]

tetracarboxylate ligand was identified as an important player in the transmission of chirality in the system. Both complexes show frequency doubling of light, on a par with the efficiency of urea.

In a related example, the complex [Co(pyridine-2,5-dicarboxylate)$(H_2O)_2$]$\cdot H_2O$ forms a layered structure where two helical chains are interconnected thanks to the coordination of the metal ion through nitrogen and carboxyl oxygen atoms.[51] In this case, the coordinated water molecules help to link the sheets through hydrogen bonds. The conglomerate was proven by performing vibrational circular dichroism which show a series of bands in the mid-IR region corresponding to carboxyl and aromatic ring vibrations. In common with other examples cited here, the mysterious appearance of just one enantiomer from the achiral components was observed, possibly as a result of seeding.

Chiral metal–organic framework compounds derived from chiral units can be interesting as sorbents for chiral species,[52] and an example of a spontaneously resolved complex derived from achiral components has been used in this way.[53] The coordination polymer, which was prepared under solvothermal conditions, has the formula $[Cu(PPh_3)(N,N'\text{-(2-pyridyl(4-pyridylmethyl)amine)})_{1.5}]ClO_4$ and crystallises in the trigonal *R*3 space group. The framework has a triangular shape cavity can host small guest molecules, such as 2-butanol. Mechanical separation of the enantiomorphs and CD spectroscopy of the complexes allowed the authors to conclude that the framework successfully resolved the cited alcohol.

2.5 Conglomerate and racemate in the balance

In certain cases, the difference in energy between crystalline solids which contain single or opposite enantiomers is sufficiently small that it can be observed experimentally, either by their isolation under different conditions (for example the solvent of crystallisation), in the coexistence of the two phases, or even by their interconversion, as shown in the following examples. For instance, the formation of Pasteur's salt is in competition with a metastable racemic compound which limits entrainment,[54] a situation which is also true for other racemates,[55] such as the diastereoisomerism displayed by rhenium(V) complexes can lead to conglomerates or racemic compounds.[56]

The transition between a conglomerate and a true racemate has been observed in the compound $[\{H_3N(CH_2)_2S\text{–}S(CH_2)_2NH_3\}PbI_5]H_3O$.[57] The conglomerate – which was crystallised by slow cooling under solvothermal conditions – is comprised of zigzag chains of lead iodide octahedra (which share corners) with the organic dication in between, packed in the space group $P2_1$. The disulfide bridge plays an important role in the structure, because the kinked conformation they have transmits chirality between equivalent all-alkyl lamellae. The ammonium ions interact with the inorganic part of the structure through hydrogen bonds. There is only one conformational enantiomer of the disulfide in this structure, but when the sample is warmed above 75 °C another crystalline phase is formed which belongs to the $P2_1/n$. In this structural transition two of the four molecules in the unit cell appear to undergo a conformational change to their opposite enantiomers. Cooling results in a twinned crystal which has no memory of its original chirality. The change originates in modification of the hydrogen bonding at the organic-inorganic interface.

Formation of polymorphs differing in their intrinsic chirality can be obtained under different crystallization conditions. Thus, for the *meso* compound myoinositol hexabenzoate, a chiral true polymorph forms under kinetically controlled conditions, giving raise to a helical supramolecular structure, with the molecules held by C–H···O intermolecular interactions. A more stable achiral polymorph is generated under thermodynamic conditions, its supramolecular structure consisting of centrosymmetric dimers linked by multiple C–H···O interactions.[58] The complexes formed between cobalt(II) and oxydiacetic acid under hydro- or solvo-thermal conditions show either achiral forms or chiral network, respectively, depending on the hydration at the metal centre.[59] The chiral complex can be obtained from the achiral one (which has a higher degree of hydration) by heating under solvothermal conditions. Both structures have a network of hydrogen bonds involving the coordinated water molecules and ligands.

The purely organic compound 2,3:6,7-dibenzobicyclo[3.3.1]-nona-2,6-diene-4,8-dione can be converted from its racemic compound into a conglomerate by heating up to around 130 °C.[60] The two phases have very different appearance when crystallised separately (Fig. 13) and in addition one or the other can be prepared preferentially depending on the temperature.[61] Both contain a series of C–H···O hydrogen bonds between the V-shaped molecules but only the homochiral compounds count on C–H···π interactions (a similar situation has been observed for diphenyl ether[62]). Heating of the racemic compound results in opaque crystals above 130 °C, while the conglomerate crystals remain clear above this

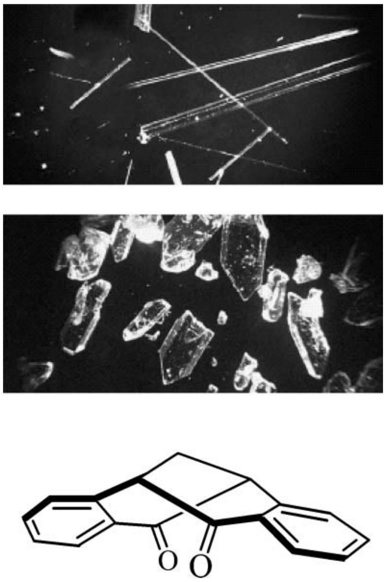


Fig. 13 Crystals of the racemic compound (top) and conglomerate (middle) of 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione (bottom). (Reprinted with permission from ref. 60. Copyright 2004, Elsevier.)

temperature. The transition of the racemic compound to the conglomerate was followed by X-ray diffraction as well as by differential scanning calorimetry, which showed an endothermic peak. The reverse process can be achieved by suspending the conglomerate in *n*-octane at room temperature and stirring with a seed of the racemic compound.

2.6 Exploiting crystalline conglomerates

Perhaps the most useful application of spontaneously resolved crystals is in the process of entrainment for the isolation of enantiopure compounds. For compounds or complexes incorporating a stereogenic centre this can lead to chiral catalysts, as in the spontaneous resolution of an optically active rhodium(III) complex in which the metal ion is coordinated by a chiral phosphate ligand as the source of asymmetry.[63] If an achiral compound crystallises in a chiral structure, or a chiral complex forms from achiral components, then there is the opportunity to perform what has been referred to as "*absolute asymmetric synthesis*".[64] This term is justified because at the start of the process, there are no chiral components, although obviously the chirality comes from the symmetry breaking in the crystal formation which can then be exploited for preparation of optically active compounds.

A nice example of this approach started with the spontaneous resolution of Grignard reagents.[65] The complex *cis*-$[(4\text{-}MeC_6H_4)MgBr(dme)_2]$ crystallises as a conglomerate, and an essentially enantiopure sample was obtained under racemising conditions: The compound interconverts rapidly in solution and provided the crystallisation is performed under conditions in which nucleation is slower than crystal growth (in this case at −20 °C) one enantiomer or the other is isolated. The complex *cis*-$[MeMg(thf)(dme)_2]I$ also resolves spontaneously (while the chloride does not). The reaction of these complexes with butyraldehyde or benzaldehyde at low temperatures provides the corresponding secondary alcohols in an enantiomeric excess of up to 22%. Interestingly, when the aforementioned Grignard reagents were crystallised at low temperatures the racemic compounds were obtained, perhaps an explanation for the relatively low enantiomeric excesses observed.

The complexes that benzaldehyde derivatives form with aluminium tris(2,6-diphenylphenoxide) show a quite remarkable preference to form crystalline conglomerates.[66] They form helical type conformations thanks to the relative orientations of the phenoxy ligands, and these chiral arrangements are propagated in the solid state thanks to a series of $C–H\cdots\pi$ interactions (Fig. 14) in three dimensions. Because the enantiomers interconvert rapidly in solution, high yields of one or the other can be obtained by slow crystallisation. Once the samples had been characterised by solid-state CD spectroscopy, the ground crystals were used in solid-state (solvent free) reactions with organometallic compounds, affording secondary alcohols in up to 16% ee.

Chiral cocrystals formed from achiral molecules have been used as the source of asymmetry in an autocatalytic reaction.[67] Reaction of a pyrimidine-5-carbaldehyde derivative **16** with diisopropyl zinc in the presence of powdered enantiomorphic cocrystals shown in Fig. 15 leads to the corresponding alcohols (*S*)- and (*R*)-**17** in very high enantiomeric excesses. The moles

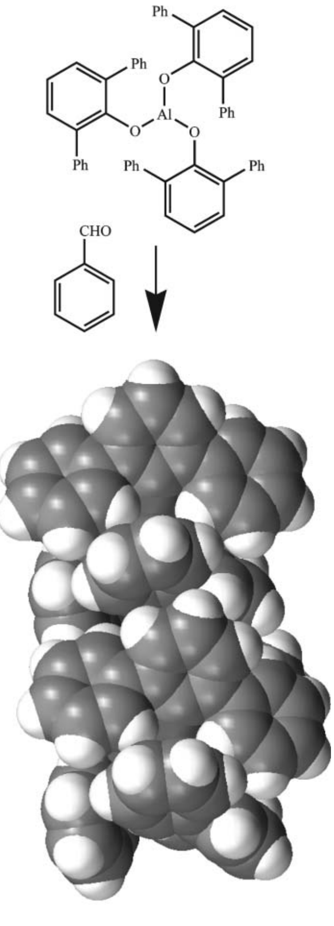


Fig. 14 The formation of the complex between benzaldehyde and aluminium tris(2,6-diphenylphenoxide), with the asymmetric unit of the crystal structure showing two complex molecules where the close edge-to-face contacts can be appreciated.[66]

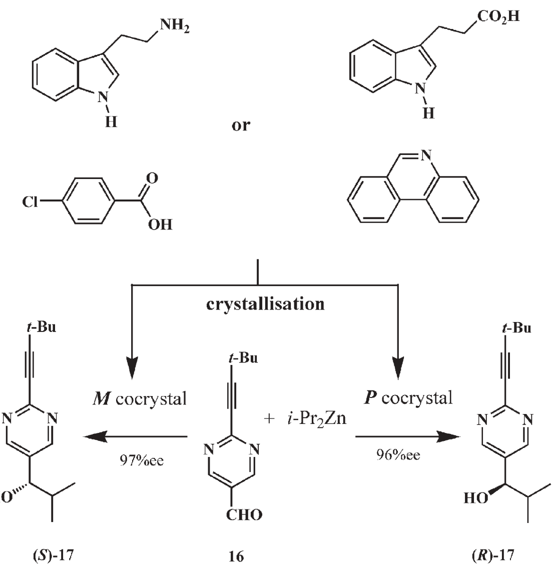
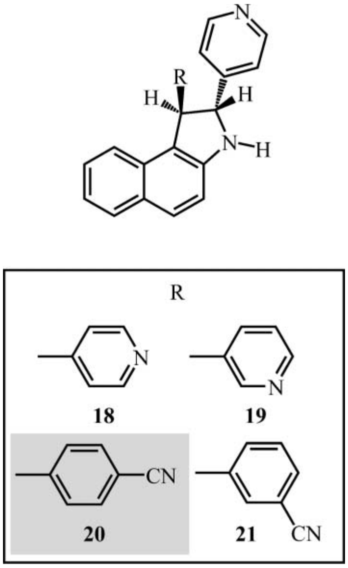


Fig. 15 Chiral cocrystals from achiral components, and the use of these conglomerates in an asymmetric autocatalytic system.[67]

of chiral compound prepared was approximately 30 times that of the chiral co-crystal. The origin of the induction, which is then amplified by the autocatalytic reaction as established previously,[68] appears to be the initiation of the reaction on the surface of the chiral crystals. In addition, chiral crystals of the achiral hippuric acid (naturally occurring *N*-benzoyl glycine) perform a similar function, proving the generality of the method.[69]

The presence of chirality in molecular materials can have great influence and benefits on their properties.[70] The spontaneous resolution of molecular materials can prove a convenient way to explore their properties. Of a series of four dihydrobenzo[*e*]indoles bearing a 4-pyridyl ring and either another pyridyl ring or a cyanophenyl group **18–21**, only compound **20** spontaneously resolves.[71] Compound **20** bears a 4-cyanophenyl group, and it is precisely the cyano moiety that brings the molecules together into hydrogen bonded chains by interaction with the amine's hydrogen atom. The material has an impressive magnitude of frequency doubling of light, showing second harmonic generation ability 12 times that of urea. Interestingly, a related coordination compound, which uses the molecule **18**, with two 4-pyridyl groups, as a ligand for cadmium(II), also showed spontaneous resolution.[72]



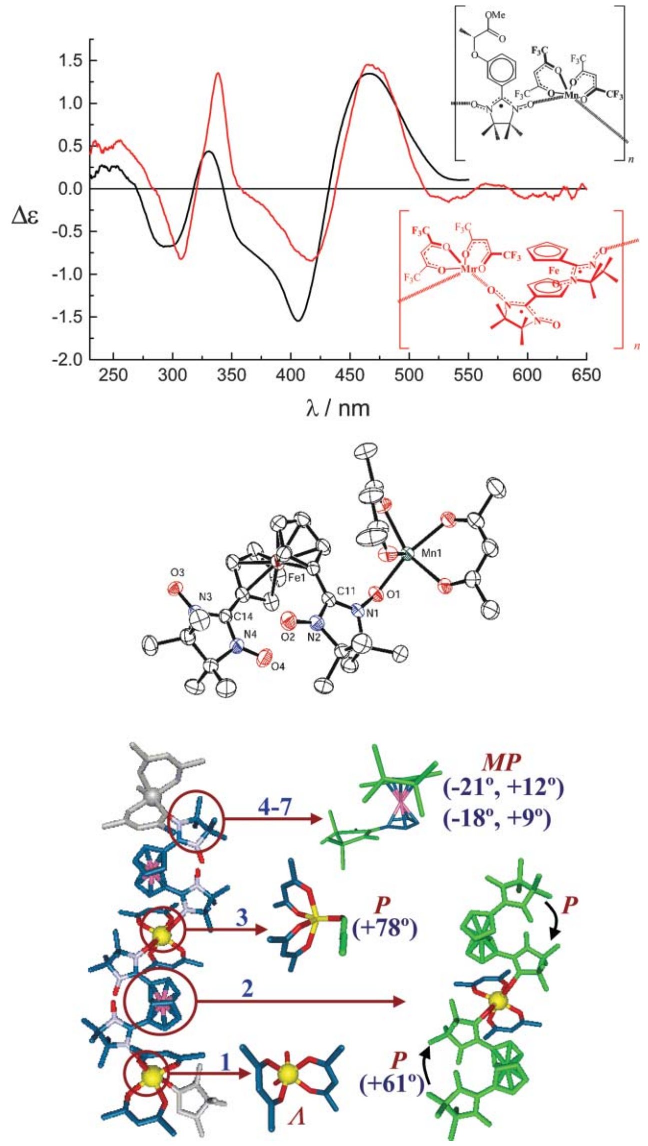


Fig. 16 CD Spectra of the spontaneously resolved a ferrocenyl nitronyl nitroxide and the crystal structure of one of the enantiomers showing the different elements of chirality. (Reprinted with permission from ref. 73. Copyright 2002, Royal Society of Chemistry.)

The formation of chiral coordination polymers that show magnetic properties are of particular interest currently, mainly as a result of the synergies that are hoped to arise from bulk magnetic order in a chiral environment. Some of these compounds are formed by spontaneous resolution, a frequent player being the coordination complexes of nitronyl nitroxides. For example, the coordination of a ferrocene bisnitronyl nitroxide to manganese(II) hexafluoroacteylacetonate leads to a 1 : 1 complex in the form of a coordination polymer (Fig. 16).[73]

A remarkable structure involving a radical of the type in the previous examples is the 1 : 1 complex formed between phenyl nitronyl nitroxide and the cyclic trimer perfluoro-*o*-phenylene mercury, which crystallises in a spectacular organization belonging to the space group $P6_1$.[74] The oxygen atoms of the radical are directed towards the centre of the mercury containing ring, and are virtually equidistant to the three metal ions. Weak and apparently non-directional van der Waals interactions bring the parallel chains together. A bis-iminonitroxide pyrazolato-silver(I) complex crystallises in the $P2_12_12_1$ space group with a zigzag chain of silver ions and pyrazolato units is formed.[75] Both nitrogen atoms of the pyrazolato ligand as well as the nitrogen atoms of the imino nitroxide are coordinated to the metal ion. No interpretation regarding the interchain non-covalent interactions has been made to date.

Purely organic radicals with magnetic properties have been shown to undergo spontaneous resolution. Especially interesting is a series of chiral nitroxides that show the phenomenon.[76] Despite their structural diversity, they all crystallise in the $P2_12_12_1$ space group. The non-covalent interactions that lead to the conglomerate formation are hypothesised as being strong intermolecular O–H···O–N hydrogen bonds and weaker O–H···O–N interactions, as well as dipole-dipole interactions between the nitroxide groups.

The electrocrystallisation of tetrathiafulvalene (TTF) in the presence of mellitate anions[77] provides a quite extraordinary case of spontaneous resolution in a magnetic system. Hexagonal plates of the salt $[TTF^{+}]_2[C_6(COO)_6H_4^{2-}]$ form in the process which have a crystal structure which belongs to the space groups $P6_222$ or $P6_422$ depending on the enantiomer. The crystals contain helical stacks of TTF radical cations along the 6_2 screw axis, with the metillate anions in a double helical hydrogen bonded chain around this stack (Fig. 17), although there is disorder in the structure.[78] This kind of regular stacking in flat π-functional materials is virtually without precedent. The preparation of the corresponding tetramethyl-TTF[79] and ethylenedithio-TTF[78] salts has already been achieved, although here the packing is achiral in either sheets or channels with different topology and topography to the chiral salt.

Coordination polymers often show interesting magnetic properties, the azide-linked manganese(II) complexes involving twisted diazine ligands to complete the coordination sphere being a particularly nice example.[80,81] Partial spontaneous resolution takes place for the complex formed by 2-pyridylmethylketazine and the manganese azide, because the racemic compound is also formed along with the chiral one. The chirality is forced by the twist in the ligand (Fig. 18) which is transmitted into layers which contain 2_1 chains of manganese ions linked by the diazine unit, in both compounds. However, the racemic compound contains an inversion centre between the layers, while a 3_1 axis runs perpendicular to the layers for the conglomerate (Fig. 18). Both racemic compound and conglomerate are weak ferromagnets. The spontaneous resolution process is sensitive to the ligand which is employed (changing the substituent at the imine carbon atom): slight changes result in the formation of racemic compounds or conglomerate.

A chiral system which displays temperature dependent magnetic properties is the spin crossover compound formed between a tris(imidazole) tripod ligand complexed to iron(II) and its oxidised deprotonated form.[82] The two components form a honeycomb network formed by supramolecular hexamers, held together by imidazole to imidazolate hydrogen bonds (Fig. 19), with the nitrate counterions located at the centre of the voids. These sheets stack on top of each other to

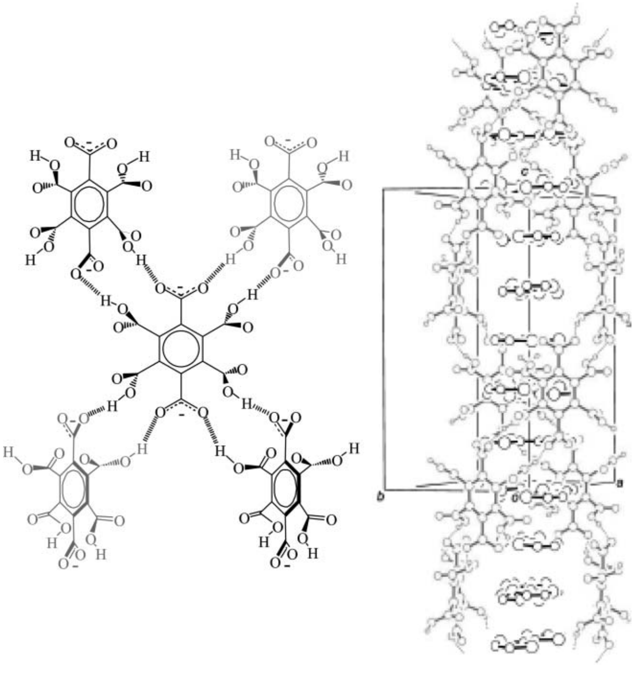


Fig. 17 The mellitate ion network (left) in the crystal structure of $[TTF^{+}]_2[C_6(COO)_6H_4^{2-}]$, and the double helix of mellitate anions which surrounds the helically-arranged TTF cation radicals. (Reprinted with permission from ref. 78. Copyright 2005, Royal Society of Chemistry.)

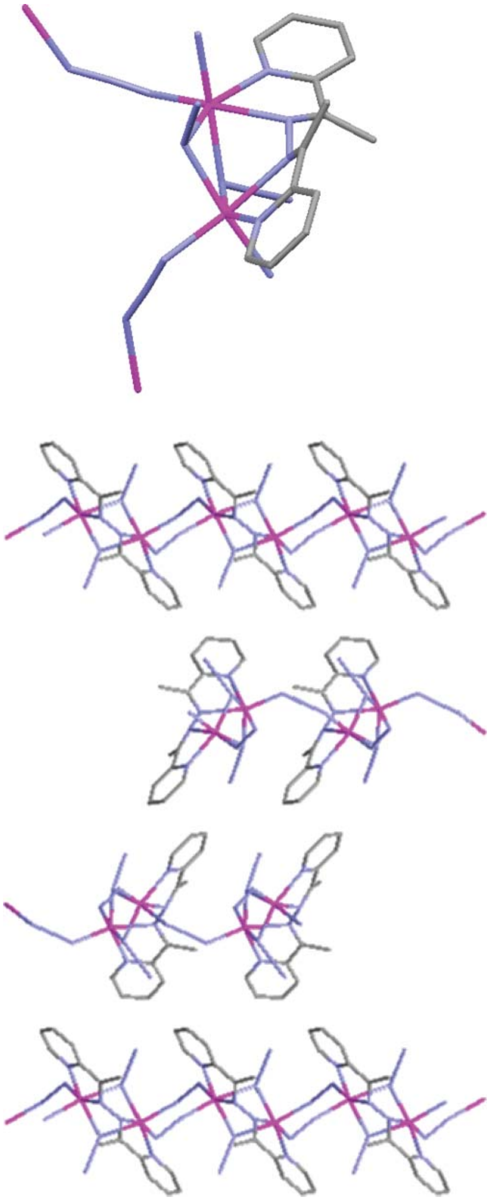


Fig. 18 The asymmetric unit of the complex $[Mn_2(\text{2-pyridylmethylketazine})(N_3)_4]_n{\cdot}n(MeOH)$ (top) and a view of the packing of the layers, perpendicular to the 3_1 axis.[80,81]

give a homochiral three-dimensional structure. Enantiomeric crystals were analysed by solid state CD spectroscopy, proving their opposite configuration. The spin state can be switched with light at low temperatures, and the authors propose that the system present s several advantages over related ones because optical rotation can be used to monitor the spin state at wavelengths which do not destroy the data. It is therefore a potential magnetochiral switch.

3 Spontaneous resolution in liquid crystals

One of the fastest moving areas of research involving systems which spontaneously resolve is that of compounds which display liquid crystalline (LC) phases. The separation of enantiomers in these (viscous) fluid states is remarkably probable if a bent shape is endowed on the molecules, as reviewed comprehensively very recently.[83] They have aroused great interest principally because of the switching behaviour that they display in electric fields.[84] Here we summarise the (to us) most relevant aspects of the research for this Review.

The bent core molecules in their fluid phases (often denoted Bn phases) are (with the exception of B1) smectic C (SmC, tilted layered) structures in which the point of the bend can be organised in a polar (P) manner to give ferroelectric (F) or antiferroelectric (A) phases (Fig. 20). The unions between the layers can be synclinic (S) or anticlinic (A), and of the four combinations that exist, two of them are conglomerates. The vast majority of bent core molecules that exist as conglomerates have the general form shown in Fig. 20, in which an angular centre (such as 1,3-phenylene, 3,4′-biphenylene, and odd-numbered methylene chains, amongst others) are flanked by promesogenic units (such as phenyl benzoate or imines) and terminated on either side with longish alkyl chains (octyl and, on the whole, longer: typically dodecyl).

The mesophases are characterised by their appearance under a polarising optical microscope, their switching behaviour under electric fields when viewed through it, and their characteristic X-ray diffraction patterns. Under the microscope, they can show domains with opposite handedness, and can even exhibit visible helices on cooling from the isotropic phase. In all cases, the most accepted models for propagation of the chirality propose a segregation of chiral conformers,[85] or superstructural chirality of the layers.[86]

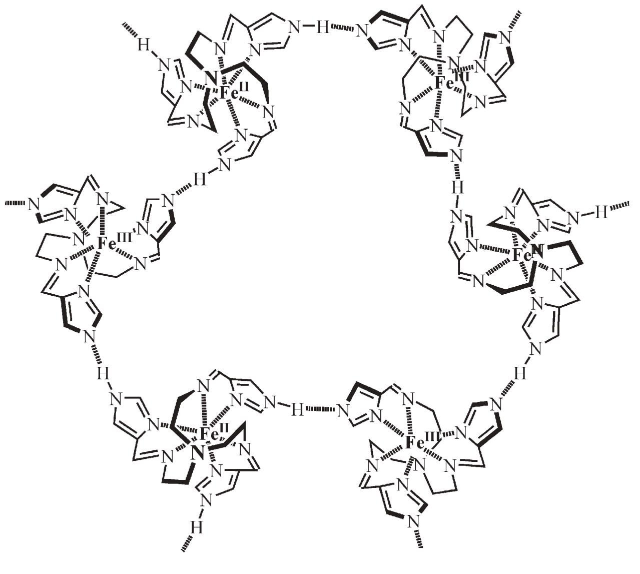


Fig. 19 A representation of the supramolecular cyclic hexamers present in the sheets of a mixed valence spin crossover molecular material.[82]

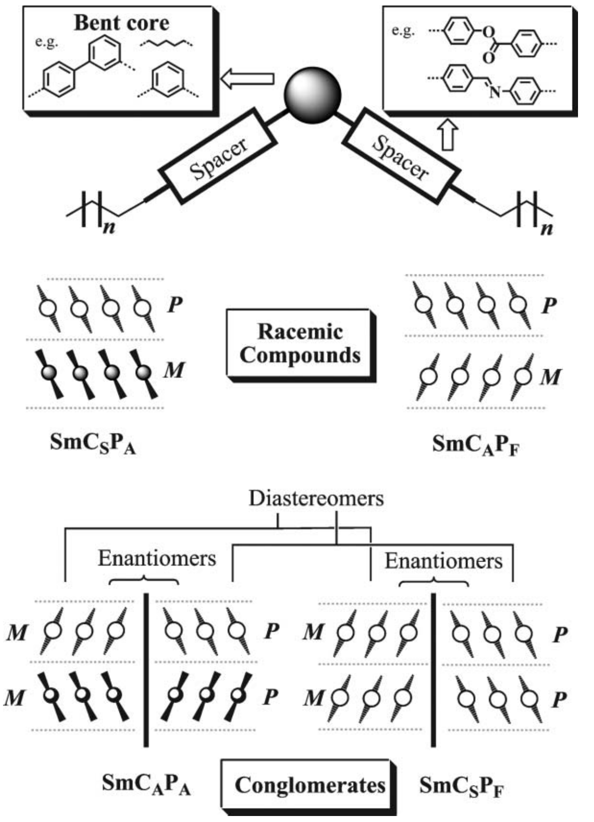
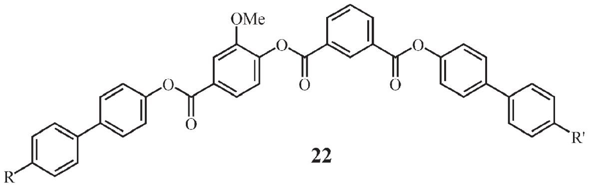


Fig. 20 A general structure of a bent core mesogen with examples of the different components and cartoon representations of the different smectic phases that they display: the lower ones exhibit spontaneous resolution.

The B2 phase is comprised of layered and tilted molecules, with an in-layer polar order.[87] A very recent example is that of the achiral and dissymmetric bent-core molecule **22** with a range of R groups (*e.g.* OC_8H_{17}, $OC_{11}H_{23}$, $OC_9H_{18}CH{=}CH_2$) which all reveal the B2 phase, and large optically active domains were observed under a polarising optical microscope when samples were cooled very slowly from the isotropic phase to the liquid crystal state.[88] These large domains were apparently caused by a twisted in-plane structure generated under the influence of the surfaces in contact with the layered fluid.



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The B4 phase is one of the most mysterious and chirally rich forms of these materials, which has been described as a glasslike state, and may be a soft crystal or liquid crystal,[89] but in any case shows no molecular reorientation in an electric field. The technique of second harmonic generation CD followed by a numerical analysis showed that the B4 phase has a twist-grain-boundary structure, in which a helix is formed between nanometre thick domains with the axis coinciding with the C_2 axis of the molecules which are organised in a polar manner.[90] In the experiments an achiral molecule was used with a chiral dopant to increase the proportion of domains of a determined handedness, and the sample was brought into the B4 phase from the B2 by cooling in an electric field in order to get large domains. Domains of opposite chiralities show huge nonlinear optical effects – dominated by the chiral contribution – in this system comprised principally of achiral molecules. The spontaneously resolved B4 phase is interesting in its conversion to the B2 by heating, because it apparently shows memory of chirality, and the system can be cycled.[91] The conformational chirality of the core was proposed as the source of this effect.

Mixtures of bent-core molecules which display the B4 phase with more habitual rod-like molecules give the chiral phase which exhibits very large chiral domains, several tens of mm^2, allowing their characterisation by CD spectroscopy as a function of the content of the achiral "conglomerator".[92] The sizes of the domains were much larger than when the bent-core molecule in question was studied on its own. The size of the domain increased two orders of magnitude in the same phase for a 20% increase in the quantity of the rod-like component (see also ref. 91).

The B7 phase and the similar B7′ are perhaps the most visually spectacular phases because they exhibit beautiful textures and include the appearance of helical ribbons. The mesophases are formed by layers of molecules which splay out with respect to each other, and as a result deformations of the layers are incurred.[93] They are very complex systems which do not show long range order, as exhibited in their X-ray diffraction patterns and their poorly defined electro-optic responses.[94]

The length of the alkyl chains can make the difference between antiferro- and ferro-electric phases, and on the occurrence of helical filaments and chirality switching under electric fields.[95] The directionality of the ester linkages in the promesogenic wings of the bent-core molecules has a profound effect on the type of mesophases observed, a much stronger effect than might be expected for such a small change in dipole moment.[96] Theoretical studies on the molecules confirm the change in dipole moment according to the directionality of the ester linkages, and that the flexibility of the wings also influences.[97]

A supramolecular approach to the bent-cores can also lead to spontaneous resolution of the chiral domains. The complementarity between derivatives of pyridine and benzoic acid leads to the enantiomorphic SmC_AP_A phase.[98] This phase was identified because of its texture under a polarised optical microscope as well as its electro-optic switching behaviour. The switching usually takes place between two chiral states or non-chiral states, highlighting the role of the molecular chirality on the resulting superstructures.

Silicon-containing segments have been introduced at the terminus of one of the alkyl chains in achiral bent core molecules to provide "polyphilic" character to the compounds.[99] These bent-core molecules show the ferroelectric chiral SmC_SP_F phase, whereas the phase is antiferroelectric for the non-silylated analogue. The authors proposed that the siloxane sublayers stabilise the synclinic structures. Chiral domains with opposite handedness were evident from polarised optical micrographs. Temperature dependence of chirality associated with changes in the tilt angles in the phases was observed in two cases, giving foundation to the idea of layer optical activity in supramolecular systems.[100] The siloxane segment can also form part of a polymer, and in this case an example of spontaneous symmetry breaking in an achiral polymer was proven (Fig. 21).[101] The bent-core moieties form part of the side-chains of the polysiloxane, which reduce viscosity in this random copolymer. In the $SmCP_F$ mesophase there is nanophase separation, with the siloxane, aliphatic, and aromatic groups occupying different spaces. Relatively large chiral domains were observed in this conglomerate using rotation of the polarisers in an optical microscope. The ratio in length of the siloxane to terminal alkyl chain is very important for the layer formation, because when the chains are very long columnar phases are formed.[102] It is remarkable that the chirality of the layers is transmitted through the polysiloxane layer which is a little over 3.5 nm thick in the mesophase.

Bent core molecules do not only show chiral smectic phases, it has also been shown that achiral liquid crystals exhibit the characteristics of a conglomerate in their nematic phase.[103] When compound **23** is warmed and then cooled into its nematic phase clear areas of opposite chirality were observed under the polarising microscope, as in the previous example.[104]

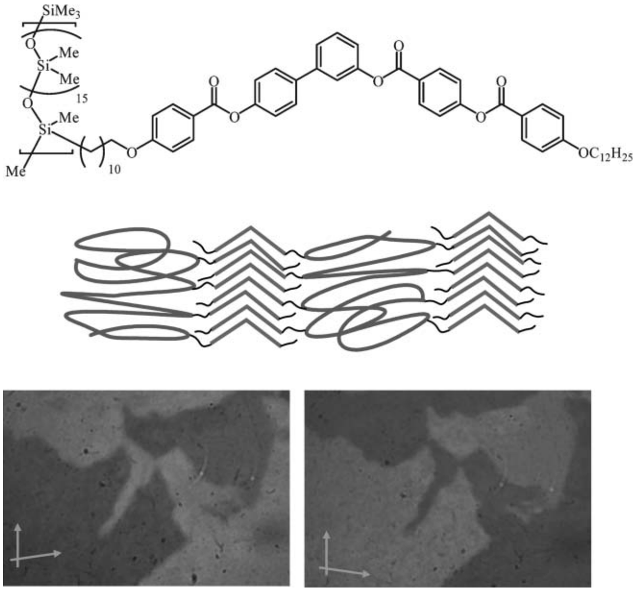
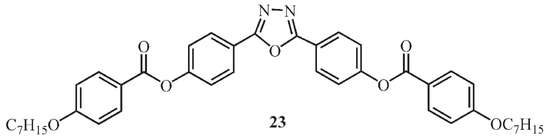


Fig. 21 A polymer with bent-core sidechains which exhibits spontaneous resolution in its liquid crystalline state, which has an approximate structure shown in the cartoon, and optical micrographs of the chiral domains revealed by placing the polarisers in the directions indicated.[101]

In related compounds to this oxadiazole (with different alkyl chains) also show traits of chiral structure in their mesophases. The dramatic history dependence of the samples and the dynamics in the uncovered mesophases indicated the importance of kinetics in the formation of the chiral structure. A helical supramolecular organisation implying polar assembly of the molecules was suggested.



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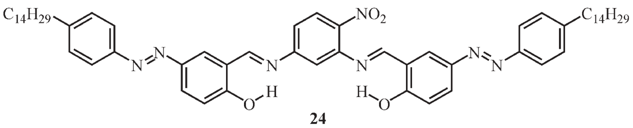
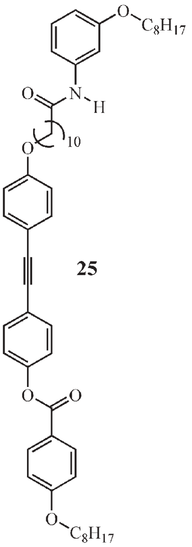


24

Chiral filaments have been observed in bent-core molecules with an extra bend, the W-shaped liquid crystalline compounds.[105] The compound **24** displays a novel type of mesophase, in which chiral domains big enough to be characterised by CD spectroscopy have been evidenced using this technique. The chiral filaments which apparently form these domains have a proposed structure – based on the microscopy and X-ray diffraction studies – in which the molecules form concentric chiral layers.

However, spontaneous resolution is not limited to the bent core molecules in the B phases. Spontaneous resolution in the cubic phase of the achiral bent tail mesogen **25** has been inferred.[106] The monotropic phase (it is only observed on cooling from the smectic C phase) was studied by polarised optical microscopy, which showed domains with different behaviour upon rotation of the polarisers, indicating enantiomorphism. Further evidence for the phenomenon was given by the CD spectra of the mesophase, which showed random positive or negative Cotton effects. The chiral induction in the phase was implied to have its origin in the rigidity of the amide-phenyl part of the molecule, and the fact that a straight non-chiral arrangement cannot be maintained while keeping an intermolecular hydrogen bond, because of the position of the 3-position of the alkoxy chain which forces a twist in between molecules.

The biphenyl derivative **26** shows helical structures under the polarising optical microscope in its smectic C phase (Fig. 22), as do other homologues with longer spacers between the biphenyl and phenyl moieties,[107] as well as the compound in which the terminal phenyl ring has no substituent at all.[108] However, the carboxylic acid group is essential for observation of the helical structures. Computer simulations indicate that the structures arise from a twisted (rather than a bent core) structure in which carboxylic acid dimers give rise to axially chiral conformers. The helices were explained using a physical argument, supported by wide-angle X-ray diffraction, which implied tilting of the dimers on cooling of the smectic A phase which compresses when turning into the smectic C phase.



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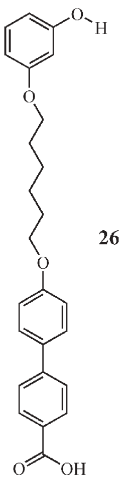


26

Even an extremely simple molecule can exhibit conglomerate formation: 4-octyloxyphenyl-4-octyloxybenzoate exhibits a smectic C phase in which chiral domains can be discerned in the homeotropically aligned material.[109] The chiral domains were observed by optical microscopy, again, as well as by CD

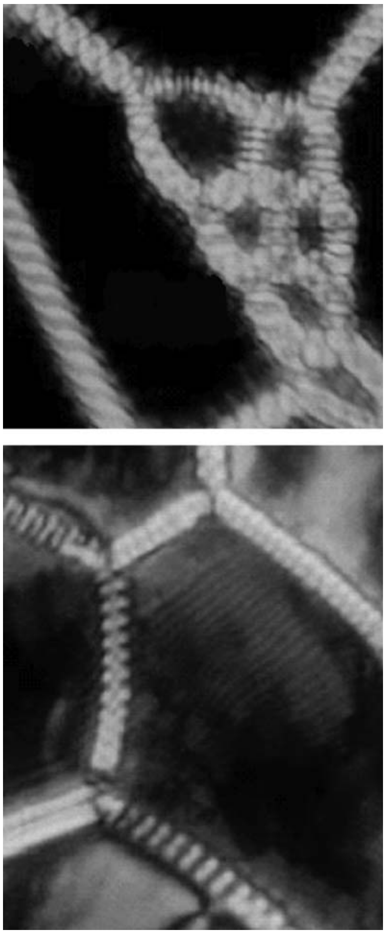


Fig. 22 Helical morphologies seen in the smectic C phases of **26** (top) and its homologue with no OH group (bottom) seen under a polarising optical microscope. The horizontal scale is approximately 20 μm.[107]

spectroscopy which revealed a random formation of the domains of opposite twist. The source of the chirality in this system appears to arise from the enantiomeric conformations that the phenyl benzoate moiety can adopt, and that the dipole-dipole interaction may play an important part. In a racemic rod-like molecule, also containing the phenyl benzoate moiety, an electro-optic response characteristic of a chiral phase has been observed.[110] These intriguing results await a full explanation. Exciting times for liquid crystal stereochemistry, indeed!

4 Self-assembled monolayers

The spontaneous separation of enantiomers of both chiral and achiral molecules at ordered surfaces is commonplace,[111] and was even predicted to be so,[112,113] even though the proportion of chiral space groups in 2D (5 chiral space groups of the 17 available, 29.4%) is roughly equal to that in 3D (65 space groups of the 230 available, 28.3%). This reality arises because of the mutual symmetry relations that adsorbate and surface must satisfy. A molecule confined in a monolayer on a surface cannot be related to another by inversion symmetry, and the glide plane parallel to the surface is similarly precluded. Specific restrictions depend on the nature of the surface, because of symmetry, molecular orientation, and strength of the molecule–surface and molecule–molecule interactions. The examples below are divided into three groups with these differences in mind.

4.1 Spontaneous resolution of organic molecules on metals

The evaporation of a racemic mixture of tartaric acid onto the copper(110) surface leads to enantiosegregation with a coverage dependence.[114] At low coverages, a LEED pattern is observed which is consistent with the formation of two enantiomorphic domains, and therefore spontaneous resolution of the enantiomers. In this state, as in the pure enantiomers,[115] the two carboxylates interact with the surface. However, at higher coverage, the molecules are forced together such that just one carboxylate per molecule is chemisorbed. Here, the substrate symmetry determines the two-dimensional packing, and a racemic crystal packing was inferred. This racemate has higher density than the corresponding chiral compound when it forms a similar packing, in contrast to the three-dimensional crystals of tartaric acid.

When the achiral *meso*-tartaric[116] or succinic acids[117] (in which the hydroxyl groups are absent) are adsorbed onto the achiral copper(110) surface in UHV conditions spontaneous resolution is observed. The origin of the effect in both instances appears to be the twist in the ethylene link between the two carboxylate groups (the hydrogen atoms are "lost" upon chemisorption), a situation which ensures that the oxygen atoms of the adsorbate interact comfortably with the metal (Fig. 23). In the case of the succinic acid it is clear that either enantiomer can be formed upon adsorption, but once the kink is formed on the surface – either because of the molecular distortion or metal reconstruction – it is propagated through the domains, which are enantiomorphous as shown by LEED and STM. When either enantiomer of tartaric acid land and are chemisorbed, the hydroxyl groups favour a twist of the organic framework, one way or the other, which is propagated over the surface. The case of *meso*-tartaric acid is an interesting one from the chiral induction point of view, because addition of small amounts of either (*R*,*R*)- or (*S*,*S*)-tartaric acid to the surface results in suppression of one of the enantiomorphs and the monolayer becomes homochiral.

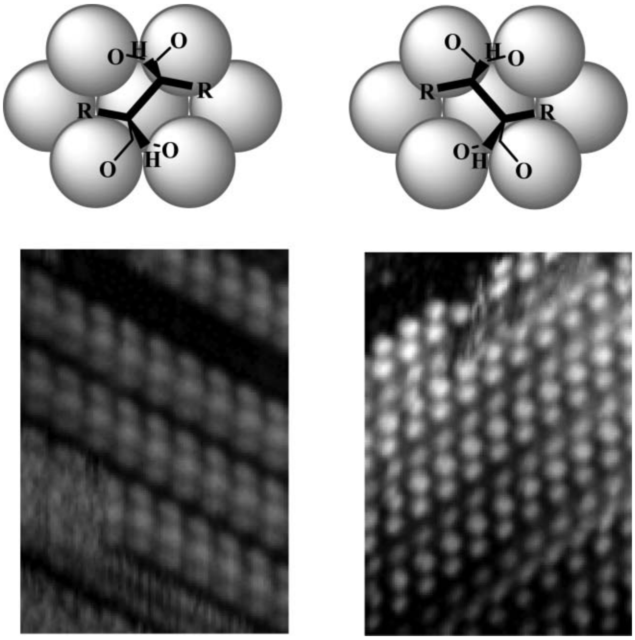


Fig. 23 A representation of the enantiomorphic twists generated in the carbon skeleton of succinic acid (R = H) and tartaric acid (R = OH) upon chemisorption on Cu(110) and STM images of domains of the two for succinic acid.[117]

Under quite different conditions, tyrosine has been shown to resolve spontaneously on the Cu(111) surface.[118] The molecule – in its enantiopure and racemic forms – was deposited from aqueous perchloric acid and was imaged using an electrochemical STM experiment. On the basis of the microscopy results and precedents of monolayers of the same compound on different metals, a model packing was proposed in which the carboxyl group and π-ring interact with the surface, with a kink in the molecule whose direction is determined by the configuration of the stereocentre. The images and the comparison between the electrochemical behaviour of the enantiopure and racemic monolayers show strong evidence for the formation of enantiomorphic domains.

The aromatic hydrocarbon naphtha[2,3-*a*]pyrene is prochiral (its shape is reminiscent of the letter P) and when it is deposited onto the gold(111) surface under UHV conditions the molecule forms polymorphic domains, both of which demonstrate spontaneous resolution.[119] In the dense packed structure, the molecules form dimers in a *ying-yang* arrangement, with spaces between the molecules which have been lauded as potential sites for stereoselective adsorption. The looser packed structure is comprised of dimer rows of the adsorbate.

Adenine is also prochiral and when it adsorbs on Cu(110) under UHV conditions rows of dimers of the molecule are formed at positive or negative angles to the 001 axis of the metal depending on which enantiotopic face is adsorbed.[120] The spontaneous resolution of these fibres is driven by the dimerisation of the bases, hydrogen bonding between them to form the regular chains, and the fact that the nitrogen atom in the amino group in adenine resides preferentially on top of a copper atom in the surface. Because of this situation, the copper atoms in the $(\pm 1,2)$ directions act as a template for the resolution. In turn, these resolved strips can act as templates for the subsequent adsorption of phenyl glycine molecules, an observation that confirms the homochirality of the strips.[121] When (*S*)-phenylglycine was evaporated onto the mixture of *M* and *P* adenine strips, STM showed that only the *M* strips acted as the templates for the adsorption of two rows of phenylglycine. It is a nice demonstration of how chirality can be propagated from a spontaneously resolved superstructure.

The symmetry of molecules can be used to favour spontaneous resolution or avoid it. For example, 4,4′-biphenyldicarboxylic acid has no kink in its structure, and when it is deposited on the Cu(100) surface under UHV conditions, (in which the protons of the acids are "lost") a single achiral phase is formed which has C_4 symmetry (Fig. 24).[122] However, 4,4″-*trans*-ethene-1,2-diylbisbenzoic acid (stilbene dicarboxylic acid) has two enantiotropic faces, and thus can form two configurations on the surface. STM experiments revealed that these enantiomers resolve spontaneously, with the packing patterns shown in Fig. 24, which have *p*4 symmetry. These observations led the authors to conclude that the structures of these dicarboxylate systems can be "programmed" by suitable choice of building blocks and substrate. Conceptually similar cases of spontaneous resolution are exhibited for 4-[*trans*-2-(pyrid-4-ylvinyl)]benzoic acid – which shows coverage dependent conglomerate to racemic compound transition[123] – and a bis-2-formylphenol derivative on gold(111) – which also shows a change in chirality switching induced by thermal stimulus.[124]

The spontaneous resolution of an iron complex of trimesitylate deposited on the (100) surface of copper leads to a hierarchichal assembly of chiral cavities.[125] Sequential evaporation of trimesic acid and iron under UHV conditions with the substrate held at 300 K lead first to the formation of cloverleaf-like 4 : 1 ligand to iron complexes which are chiral on the surface (Fig. 25). The chirality has its source in the monodentate complexation of the iron by the ligands. On the surface there is a random mixture of enantiomers of these complexes. Annealing of the sample to 350 K leads to

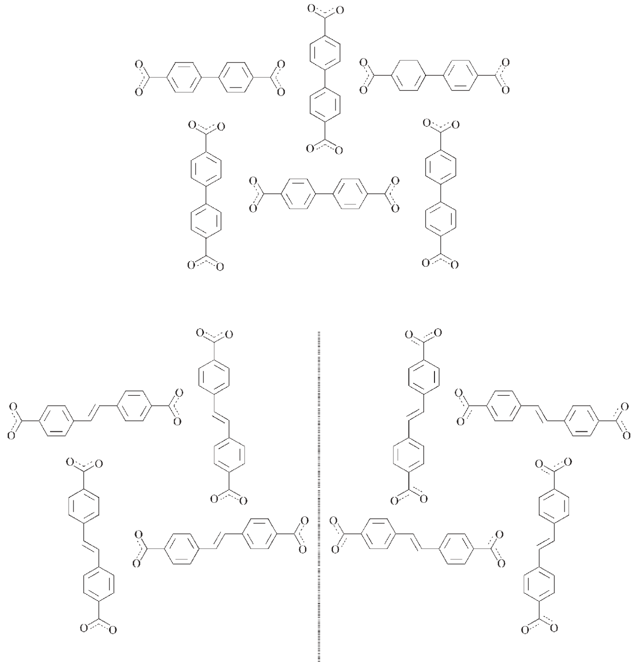


Fig. 24 Schematic representation of achiral and chiral two dimensional organisations of dibenzoate type molecules.[122]

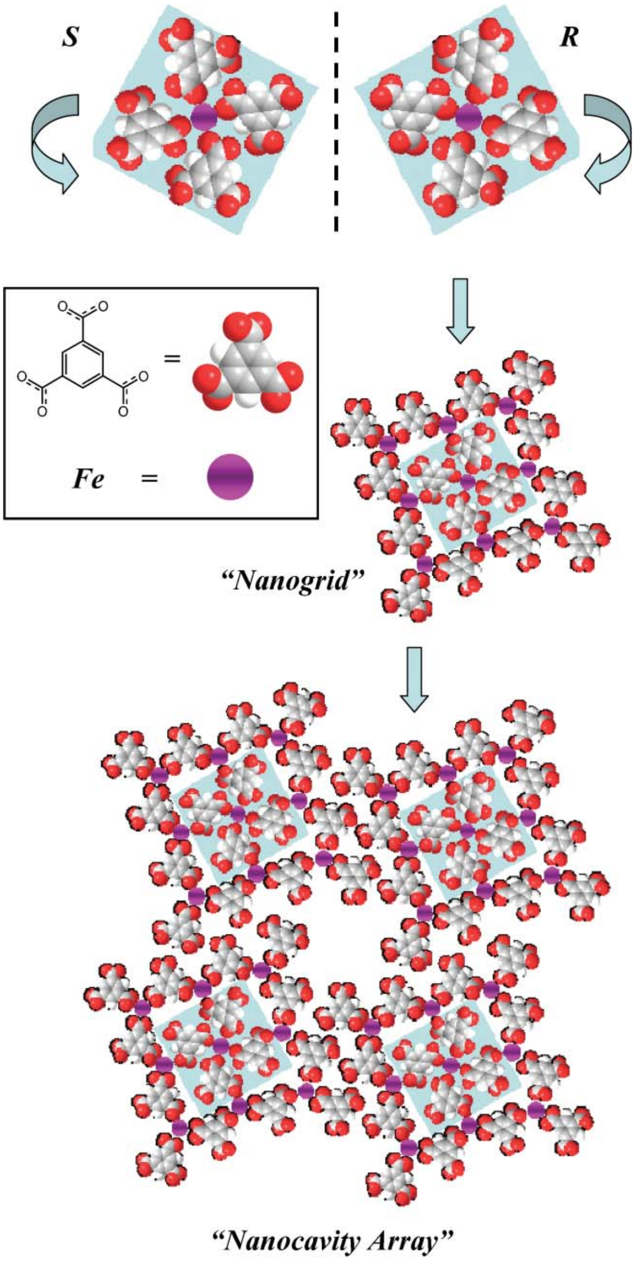


Fig. 25 Schematic representation of the hierarchichal self-assembly of a chiral nanocavity array that takes place on the copper (100) surface.[125]

the formation of nanogrids incorporating sixteen organic molecules, based on the formation of four Y-shaped complexes around the cloverleaf core. The attachment of the outer shell results in a rotation of the core with respect to the substrate to allow the peripheral iron atoms to locate at hollow sites in the substrate. Again, these grids form a racemic compound on the surface. However, spontaneous resolution manifests itself when the sample is annealed at 400 K. The nanogrids condense to form cavity-containing uniformly packed domains which belong to the *p*4 symmetry group and which are tilted with respect to the substrate axis. Thus, enantiomorphous domains are observed. The nanogrids are the unit which forms these grids.

The combination of molecules of different symmetries can lead to spontaneous resolution. The co-adsorption of the C_{2v} symmetric acridine-9-carboxylic acid and the I_h symmetric C_{60} onto silver(111) under UHV conditions yields a chiral superstructure which was observed by STM.[126] In this superstructure the acridine derivative lies in contact with the silver, and forms chiral cyclic trimers with opposite chiralities in all the domains. However, in any given domain, the C_{60} molecules which reside atop the centre of these trimers only do so in ones of a given direction. The proposed mechanism for resolution is that a C_{60} molecule lands on a given trimer and induces a local ordering of this grouping, which then orients with respect to the silver substrate. The carboxylic acids supposedly form dimers between the trimeric species, and the hydrogen bonding interactions between trimers are capable of transmitting the chirality. There is thus a delicate interplay of silver–acridine, acridine–acridine, and C_{60}–acridine interactions which act concertedly to produce the chiral domains.

A spectacular example of resolution of conformers at submonolayer coverage is that of the aromatic hydrocarbon rubrene.[127] This molecule exists as chiral conformers because of the non-planar structure forced by intramolecular contacts between atoms (Fig. 26). On the gold(111) surface in UHV conditions and at 5 K, STM images of the isolated molecules show three distinguishable lobes that define a directionality and therefore chirality to each molecule, acting as a tracer for the stereochemistry. The molecules form pentamers with a regular shape that can be assigned as *M* or *P*, and these structures can then aggregate further to form chains or rings of pentagons, all of the same chirality for a given object. This enantioselective assembly has been suggested to be a result of C–H–π interactions and van der Waals interactions, since the structures are incommensurate with the surface.

Importantly, the observation of enantiomorphous space groups is not necessarily an indication of spontaneous resolution, a situation revealed by the amplification of chirality in monolayers of heptahelicene on Cu(111).[128] When equal proportions of the enantiomers are deposited, equal proportions of enantiomorphous domains are observed, but a small enantiomeric excess leads to the formation of domains of a single enantiomorph predominantly. The explanation for this phenomenon lies in the energy of the boundaries between domains which contain both enantiomers, the domains between mirror image space groups being unfavourable.

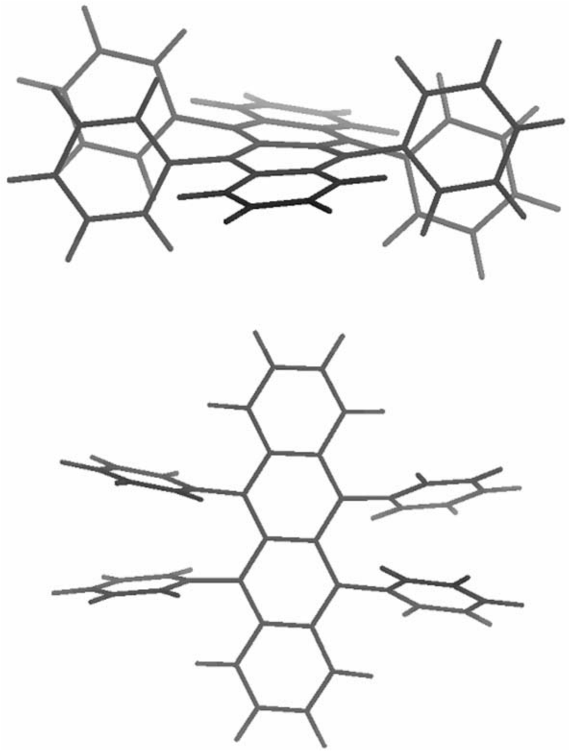


Fig. 26 Views of the structure of rubrene.

4.2 Spontaneous resolution of physisorbed organic molecules on graphite

The adsorption of molecules on graphite is observed more often than not by STM at the surfaces' interface with a high boiling organic solvent.[129] The interactions that are common to most examples are the alkyl chain–graphite ones. However, the cores which are attached to the alkyl chains in physisorbed systems play a definite role in the packing and on the stereochemistry of the monolayers: 2-octyl terminated aromatic formamides form either pseudoracemates or conglomerates at the graphite surface according to the spacer between the two.[130] Even tiny changes in molecular structure can tip the balance between racemic compound formation and spontaneous resolution in these physisorbed systems. Under some circumstances the expression of molecular chirality in self-assembled physisorbed monolayers is even lost completely.[131]

The anthracene derivatives shown in Fig. 27 are prochiral with respect to absorption on the surface, and they differ only in the length of the alkyl chains that act as substituents but also are largely responsible for their adsorption onto graphite.[132] The compound with undecanethiol chains forms rows of molecules on graphite, with the anthracene units within van der Waals contact, in which all are adsorbed on one enantiotopic face. These rows come together by interdigitation of the alkyl chains in such a way that consecutive rows have opposite chirality, and thus this achiral compound forms monolayer domains which are a racemic compound. In contrast, the compound with dodecanethiol chains spontaneously resolves on the surface, as evidenced in the STM images which show a similar row structure to the previous example, but in which each row has identical chirality. In both cases, the terminal CH_2–CH_3 bond is parallel

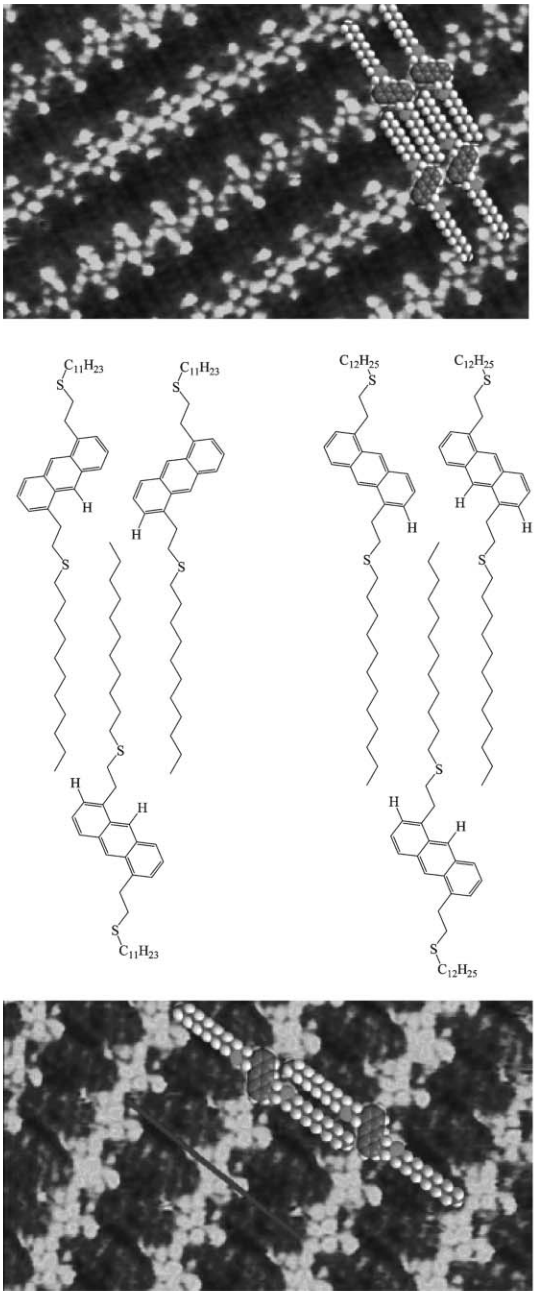


Fig. 27 STM images of the racemic and conglomerate domains formed by the prochiral anthracene derivatives which differ by only one carbon atom in the length of the alkyl chains. (Reproduced with permission from ref. 132. Copyright 2004, American Chemical Society).

to the S–CH_2 bond in the next row, which it is in registry with along the row direction. It is this packing requirement which seems to drive the formation of racemic compound or conglomerate, and is similar in origin to the odd–even racemic compound–conglomerate formation in the adsorption of fatty acid dimers on the same substrate.[133] In addition, formally C_3 symmetric molecules can show spontaneous resolution or racemate formation according to the number of carbon atoms in the alkyl chains.[134]

The study of a series of quinacridone derivatives substituted at the nitrogen atom with alkyl chains of different lengths and their complexes with stearic and palmitic acids (which interact with the dyes by hydrogen bonding to the carbonyl groups) shows an interesting variety of two-dimensional packing.[135] When methyl groups are incorporated onto the rigid core of the molecules spontaneous resolution is not observed, and the structures can even appear achiral. The reason for the latter observation is that the rigid cores tend to align their long axes because efficient packing cannot be attained with an angle and overlap between them (which would result in angle formation and chirality). Therefore the compound is potentially prochiral, but sometimes does not express its stereochemistry. The compound in which all positions have hydrogen atoms appears to behave prochirally, and has a conglomerate type packing.

An excellent example revealing the packing requirements in two dimensions on graphite and in crystals is that of the relatively complex achiral octyl-decorated dendrons which form trimers that then assemble into cyclic superstructures thanks to interdigitation of the alkyl chains on graphite (Fig. 28).[136] Over time, the STM experiments which revealed this organisation show that it evolves into a (also chiral) dimer structure. The crystal structure of one of the compounds also reveals interdigitation of the aliphatic chains in a back-to-back way, but the crystals belong to the achiral $P\bar{1}$ space group: there is a centre of inversion in between the molecules, a situation which is very improbable on the graphite surface.

The separation of the enantiomers of self-assembled rosette-type nanostructures has been observed on graphite using AFM, after evaporation of the solvent in which the enantiomers are formed.[137] The two achiral components – a quadruple melamine and barbiturate derivative – form stacked structure in which four hydrogen bonded hexamers, and it is the twist between these layers that generates the chirality of the assemblies. When chloroform solutions of the racemate are deposited on graphite by slow evaporation of the solvent, rods are formed in which the rosettes are stacked, and AFM reveals domains of these rods which have oblique unit cells with opposite chiralities. Although direct assignment of *P* or *M* rosette to each domain could not be made, the evidence suggests strongly that each occupies one of the domains.

While these results are spectacular, we would like to finish this section with an example in which the molecules which resolve on the graphite surface are extremely simple. STM images of 1-octadecanol suggested to the authors that it has a bent chiral conformation imposed on it by the packing into hydrogen bonded dimers and the registry that the methylene groups have with the six-membered rings of the substrate.[138] Hydrogen bonding is not essential either. Arachidic anhydride – two C_{19} chains joined by an anhydride group – resolves spontaneously on graphite.[139] The origin of the chirality lies in the kink in the anhydride group, which when it adsorbs can do so by either enantiotopic face. The chirality of the domains is identified most straightforwardly by observation of their unit cell in the STM images.

4.3 Spontaneous resolution in Langmuir films

The symmetry restrictions imposed by the geometry of amphiphiles at the air–water interface in Langmuir layers – where the inversion centre, the glide with its plane parallel to

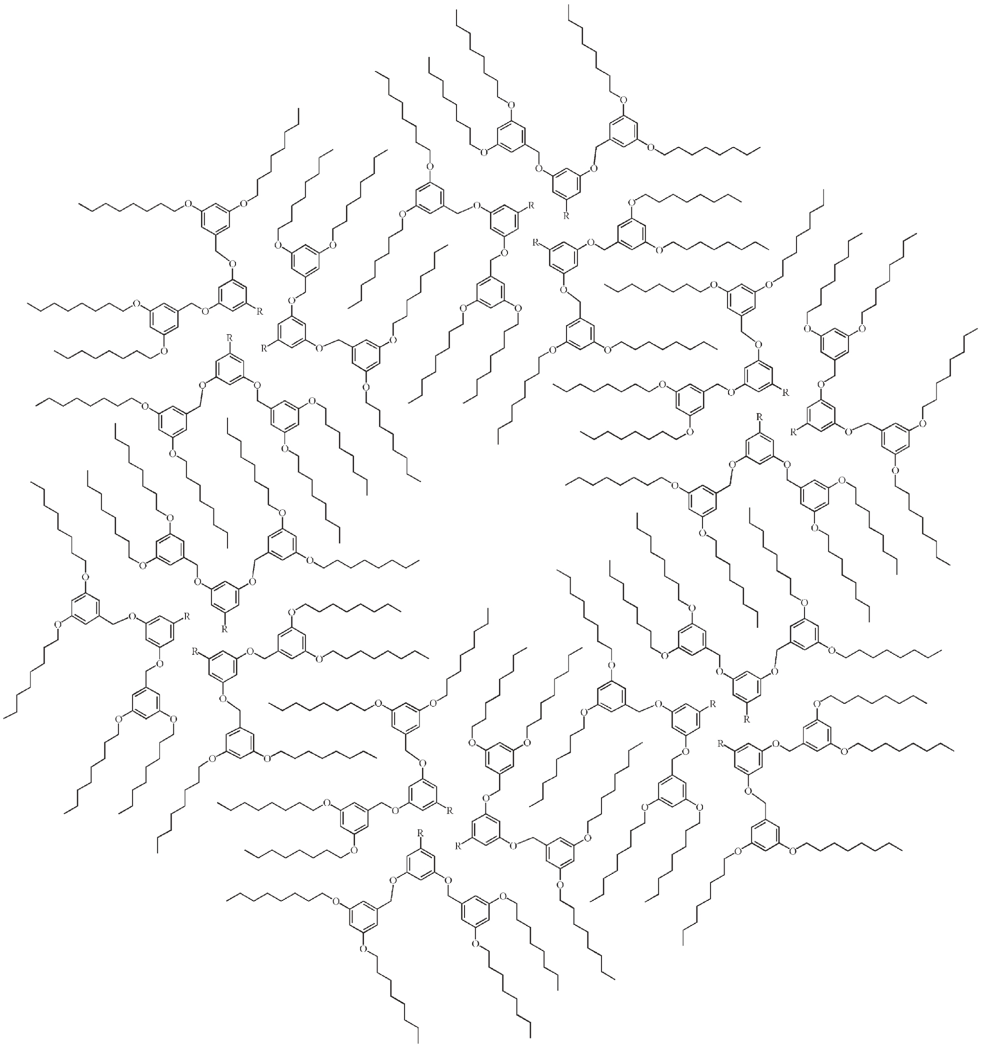


Fig. 28 The packing of trimers of dendrons (R = CHO, CH_2OH) which takes place on graphite.[136]

the surface and the related two-fold screw symmetry (the most common symmetry elements in 3D) are ruled out – offers great opportunity for the formation of chiral monolayers (only the translation and a glide plane normal to the surface remain), despite the fact that the subphase imposes no orientational restrictions in the plane. Perhaps the greatest challenge in these samples is the identification of the chiral domains, as the following example shows.

The formation of enantiomorphous domains of racemic mixtures of fatty amide derivatives that are reagents for the synthesis of oligopeptides can be used for the preparation of homochiral sequences.[140] While the standard polymerisation of racemic peptides might be expected to produce a random mixture of oligomeric products, if the reaction is carried out in areas of a sample rich in one enantiomer, then oligomers containing mainly one enantiomer could be expected. With this premise in mind, racemic stearoyl thiolysine can be employed as a monomer for the formation of these oligomers. However, unlike the structurally related stearoyl lysine, it is a racemic compound at the air-water interface, with a pseudo-glide plane in the 2D crystal, as revealed by synchrotron grazing incidence X-ray diffraction. Consequently, MALDI-TOF mass spectrometry showed that oligomerisation of racemic stearoyl thiolysine yields only a slightly higher than expected proportion of homochiral products. On the other hand, when stearoyl thiolysine is spread with a small amount of stearoyl lysine (10%), enantiomorphous layers are formed – that is, spontaneous resolution is induced by the second racemate. Now, the oligomerisation leads to a significantly higher proportion of the homochiral oligomers. Oligomerisation of the racemic carboxyanhydride of stearoyl-lysine – which spontaneously resolves on the water surface – also shows high proportions of homochiral oligomers up to the hexapeptide. There are also sequences containing both enantiomers, which can arise from poorly ordered areas of the film, but the concept that small enantiomeric clusters can lead to homochiral oligopeptides was proven. The formation of homochiral sequences is not limited to spontaneously resolved domains, even racemic compounds which contain homochiral supramolecular hydrogen bonded strands – resolved at the single chain level – in the domains can give rise to mirror symmetry breaking.[141,142]

An achiral aliphatic barbituric acid derivative has been shown to form spiral structures in Langmuir monolayers, of both clockwise and anticlockwise direction (Fig. 29), and in addition the layers reveal Cotton effects which have mirror symmetry, depending on the film.[143] This behaviour was associated with the formation of H-aggregates, with the formation of hydrogen bonds (confirmed by IR spectroscopy), and it appears that the assembly could involve the formation of a bent-core supramolecular structure (Fig. 29, bottom). The emergence of chirality in this system was extremely sensitive to temperature and surface pressure applied during formation of the film. The chirality of the pure compound is nulled by the addition of other achiral molecules to the aliphatic barbituric acid,[144] therefore it is not possible for the chirality to be transferred from the monolayers for the moment.

Coordination of an achiral aliphatic imidazole derivative to silver(I) has been used as a way to generate optical activity in a Langmuir–Blodgett film,[145] and exposure of an achiral 2-thiazolylazophenol derivative in a Langmuir–Schaefer film (generated by lift-off from the air–water interface) to hydrogen chloride gives rise to a change in the optical activity, so that the system acts as a chiroptical switch.[146] In both these cases a twisted supramolecular arrangement was inferred to explain the results, where addition of the complexing agent alters the relative orientation of the chromophores.

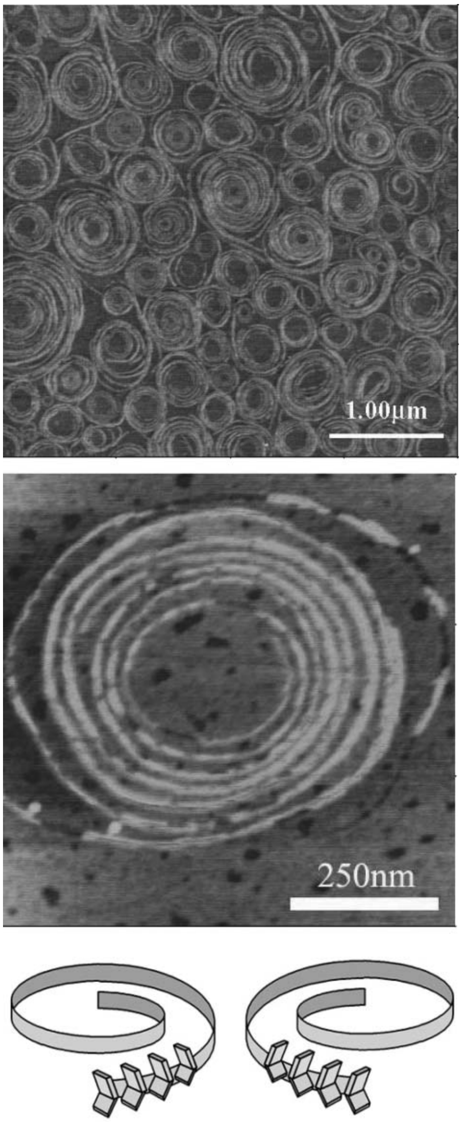


Fig. 29 AFM images of spiral structures formed in Langmuir layers of amphiphilic barbituric acids and a cartoon of the proposed aggregation mode.[143]

5 Self-assembled fibres

Helical superstructures are often formed when organic molecules form fibres, but actual observation of spontaneous resolution is not too commonplace.[147] When a helical superstructure is formed in a one dimensional system, provided the objects have perfect tacticity, we can consider that spontaneous resolution occurs. The microscopies able to resolve structure at the nanometre scale can reveal this phenomenon.

Circular dichroism has been used to show that achiral cyanine dye derivatives form chiral J-aggregates. Although optical activity is observed, the magnitude is increased by a factor of around 100 when a chiral inducer (enantiomeric 2-octanol) is added.[148] Diprotonated phenyl and 4-sulfonatophenyl *meso*-tetrasubstituted porphyrins gives a spontaneous chiral symmetry breaking, as observed by the formation of helicoidal colloidal particles by AFM.[149] It is important to point out that although CD spectroscopy is often used as a proof of spontaneous resolution in nanoscopic systems, the experiments have to be performed very carefully and the possibility of linear dichroism has to be ruled out.[150,151] A very interesting study of this kind of apparent circular dichroic effect was reported recently for the case of thiacyanine J aggregates formed in brine solutions.[152] Fitting of the apparent CD spectra to sums of different spectra resulting from different anisotropic objects in the solution shows a remarkably good correlation.

The achiral phthalocyanine **27**, which bears four macrocycles incorporating tetrathiafulvalene residues, forms left- and right-handed helical fibres from dioxane-chloroform solvent mixture (Fig. 30).[153] Here, the resolution into the different chiral fibres is driven by the supramolecular arrangement adopted between the molecules in which the two different π systems overlap.

An achiral porphyrin derivative has been shown to form helical fibres of left and right handedness (as observed by TEM) and whose twisted form can be changed by including different metal ions in the core of the macrocycle.[154] The porphyrin core was substituted at one *meso* position with a pyridine group and at the diametrically opposite one with a benzoic acid group (spaced from the porphyrin core by an aniline group), and with the other two positions bearing a dialkoxyphenyl group, a combination which affords hydrogen bond donor–acceptor groups as well as the possibility of van der Waals contacts between the alkyl chains. This balance is affected in a subtle way as a function of the core metal.

The racemic cyclic dipeptide **28** displays "homochiral supramolecular polymerisation", leading to a one-dimensional conglomerate in solution.[155] The aggregates are probably formed thanks to the interaction of all four amide groups in one molecule with the two neighbouring ones, since a derivative which does not have the solubilising groups crystallises in this manner. The stereoselectivity in the

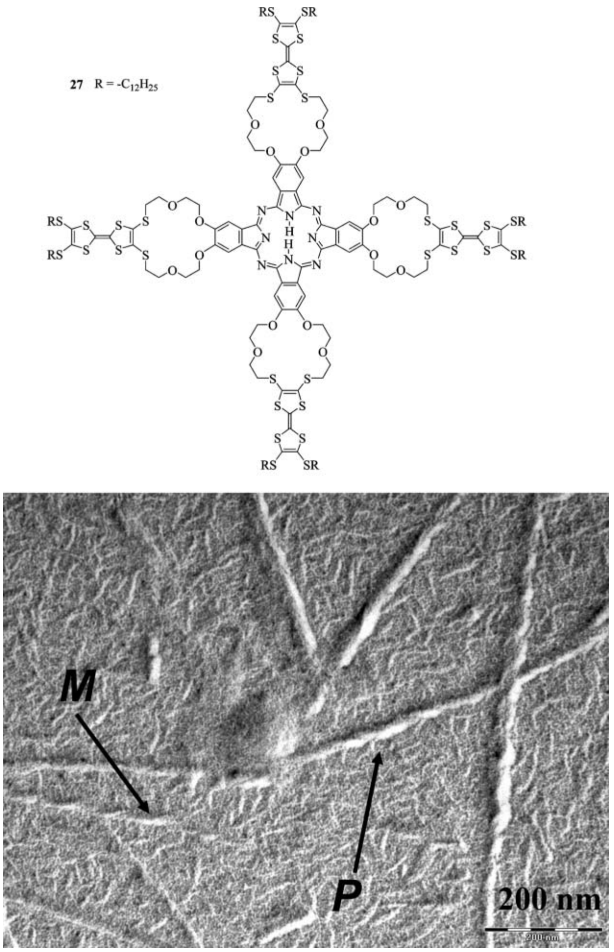
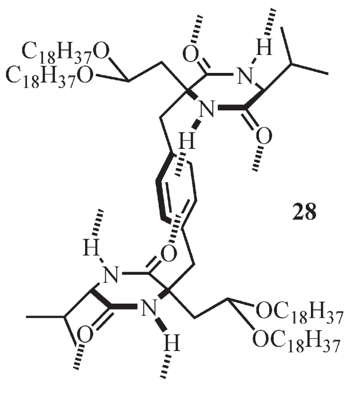


Fig. 30 The achiral tetrakis(tetrathiafulvalene-crown)phthalocyanine derivative that forms helical fibres that can be observed by TEM.[153]

aggregation was shown by size exclusion chromatography coupled with CD spectroscopy for different mixtures of the D and L enantiomers. It was proposed that the S (Z) shape of the molecule favours homochiral association – the molecules are enantiophobic – a hypothesis which was backed up by NMR experiments of molecules in which half-protected (half the amide groups) analogues formed a dimer which was much more stable for the homochiral pair.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Covalent polymeric systems have been shown to form helical superstructures with distinguishable chiralities. Two of these are not strictly spontaneously resolved, because the polymer backbones contain stereogenic carbon atoms, albeit in an essentially random distribution. We include them here because the local chirality is essentially overpowered by the symmetry breaking of the large groups attached to the polymer skeleton. In the first, poly[2-(acetoacetoxy)ethyl methacrylate] **29** forms a double stranded helix of ribbons which in turn are generated by sheet-like aggregation of antiparallel strands in which the acetoacetoxy groups form hydrogen bonds between each other.[156] The oppositely handed helices were observed by AFM of cast films of the polymers of different molecular weights onto graphite, where rodlike superstructures were evident. The pitch and turning angles inferred a helical tube formed by two strands. The other case is a dendronised poly(styrene) derivative **30** coated with ammonium groups on the exterior.[157] An aqueous solution of this material when studied by cryo-TEM reveals a complex structure which is comprised of interlinked double helical strands with a diameter of approximately 7.4 nm. It was believed that hydrophobic interactions gave rise to the formation of this superstructure, which was not apparent in very dilute solutions or on surfaces.

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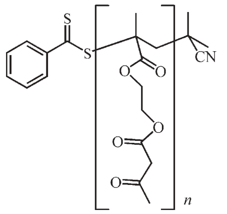

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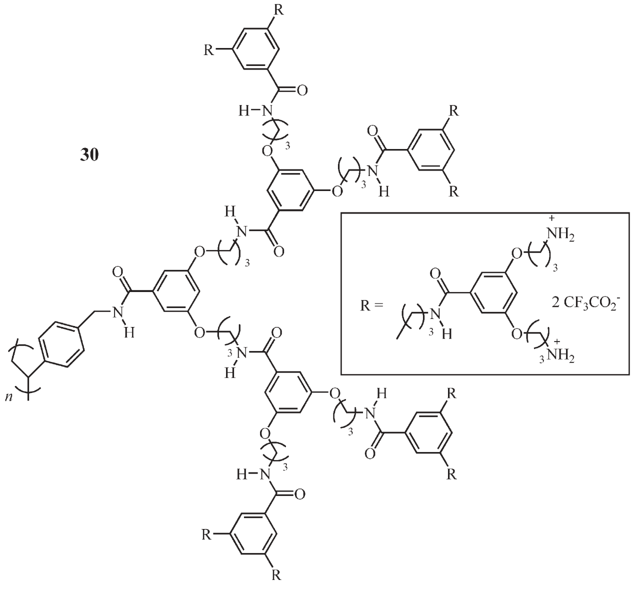


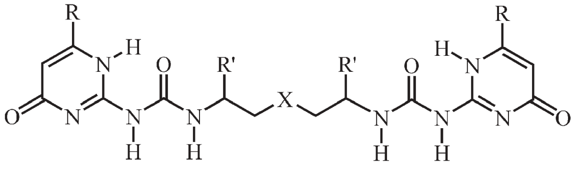
6 Zero-dimensional aggregates

The formation of chiral entities is an area of great interest for a number of reasons.[158] The association of molecules in any medium can give rise to achiral aggregates, or any of the three types of racemates. Theory has predicted that for the dimer of CHFClBr, which as just two points of contact, a clear (if small) thermodynamic difference exists between homochiral and heterochiral situations.[159] Different *ab initio* basis sets give different results regarding preference, but the important principle is that the smallest of interactions can lead to homochiral dimers preferentially, and the chiral distinction does not necessarily correlate with stabilisation energy.[160]

Apart from theory, the simplest aggregates can actually be observed under special experimental conditions, giving insight into the subtleties of how chiral molecules recognise each other in practice. Methyl lactate clusters, in enantiopure and racemic form, generated by jet cooling have been studied by mass spectrometry and FT-IR spectroscopy (and backed up by theory), and show an interesting dependence of stability of homochiral clusters depending on their size.[161] For the trimer structure, held together by O–H···O–H hydrogen bonds, the homochiral structure appears most stable, while for the tetramer O–H···O=C hydrogen bonds were invoked to stabilise the heterochiral aggregate.

Mass spectrometric experiments have been used to probe the association of serine non-covalent oligomers, which for the octamers show a preference for a homochiral aggregate for the singly protonated specie.[162] On the other hand, the doubly protonated complex and the decamer show a preference for heterochiral clusters.[163] As the oligomers become longer chiral preferences are smaller than for the octamer and decamer, although periodic trends are seen. Calculations suggest that entropy may act as a barrier to the homochiral aggregate formation in the racemic solutions.[164]

Cyclic supramolecular dimers formed by enantiomers of the di-2-ureido-4[1*H*]pyrimidone (UPy) homochiral compounds **31** and **32** exhibit spontaneous resolution at this level of assembly.[165] The dimers are formed in a certain concentration range in solution thanks to the formation of four hydrogen bonds between the self-complementary UPy groups, which favour the formation of supramolecular polymers at higher concentrations. A series of elegant NMR and chromatographic experiments proved the spontaneous resolution of enantiomers in solution for the dimers. The expression of chirality in the solid state, on the other hand, does not go beyond these dimers, at least for compound **31**, which crystallises as a racemic compound.



31 R' = Me; X = CH_2 **a** R = Me
32 R' = CO_2Me; X = S-S **b** R = $C_{13}H_{27}$

However, the reasoning that C_2 symmetrical units should prefer homochiral dimers is not general even for this class of compounds. Under conditions in which the *meso* compound of the disulfide **32b** can be formed with the two enantiopure isomers under equilibrium conditions, it is the former that is favoured.[166]

In a coordination chemistry system, an "artificial" racemate of bis-2,2′-bipyridine pinene derivatives shows "chiral self-recognition".[167] The enantiopure ligands were synthesised and were mixed with an equimolar amount of copper(I) hexafluorophosphate tetra-acetonitrile produced a cyclic hexamer, which was characterised by X-ray crystallography and ^1H NMR, which showed the perfect symmetry of the system on the timescale of the experiment. This same spectrum was obtained when a racemic mixture of the ligands was mixed with the metal ion, showing that the enantiomeric complexes are formed exclusively, and that each enantiomer can only form the cyclic hexamer with itself. The use of different proportions of the enantiomers of the ligands and copper(I) yielded CD spectra which had Cotton effects whose intensity were in accord with the formation of homochiral hexamers. Attempts to crystallise the racemic mixture yielded only poor quality crystals, but unit cell parameters were obtained and indicated to the authors that a conglomerate had been formed. Dinuclear cobalt(II) complexes of chiral tetradentate pyridylimine ligands also exhibit self-sorting on the basis of NMR experiements.[168]

The self-assembly of a chiral ball was achieved by the complexation of achiral bent-core diimine ligands to copper(I), and self-assembly of the resulting circular trimers (Fig. 31).[169] These trimers are slightly bowl shaped so that C–H···π interactions can take place between the ligands. Not only that but the trimers tetramerise to give a chiral "ball" in the solid state, and the whole crystal belongs to the chiral space group $P4_232$. Again, it is the C–H···π interactions (12 in all) that are responsible for this remarkable assembly. The chiral induction was accounted for by the pyridyl blades around the triangle.

7 Conclusion and outlook

Analytical tools are able to reveal with great precision many of the processes taking place during spontaneous resolution. From the synthetic point of view, it would be foolish to state that one can design or predict the occurrence of spontaneous resolution, especially in crystals, although there are certain groups of compounds which do seem to favour the phenomenon. There are now many examples of spontaneous resolution and qualitatively there seem to be lots in coordination compounds, whose comparison and correlation awaits an in depth study as that done for organic compounds, where it was pointed out that spontaneous resolution of salts seems to be more probable than for neutral compounds.[1] There lies the gauntlet!

In 2D, chemisorbed and physisorbed layers on surfaces with some element of symmetry are comparatively well understood. The scanning probe techniques, especially, offer unique insight into how molecules come together at interphases, and theoretically the challenges are fewer than in 3D. How one can harness this control to give useful chemical systems for applications in different sectors is an interesting question.

In 3D and 2D, it is (at least qualitatively) clear that certain features favour conglomerate formation. There are, apparently, *enantiophobic* and *enantiophilic* molecules. It is certainly true that in liquid crystals the bent-core compounds enantiomorphic domains form with remarkable frequency. In small aggregates or 1- and 2-D aggregates the supramolecular structures inherently favour a homochiral assembly, and a kink in the molecule favours this situation because the

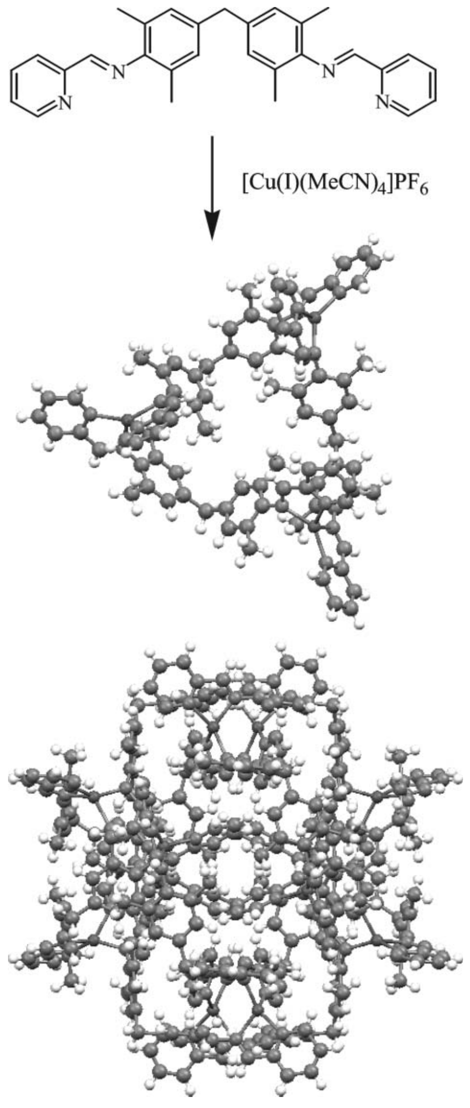


Fig. 31 An achiral ligand which forms a chiral cyclic trimer with copper(I), and the chiral ball that is observed in the solid state when four of these trimers pack together.[169]

symmetry elements that give rise to non-chiral superstructures are not feasible. So, molecules containing a bend and a kink are qualitatively more enantiophobic than others. But what about 3D crystals? It is interesting that designs for bent-core liquid crystals have such a high hit rate in terms of obtaining conglomerates. The question arises, are there analogous layered crystalline compounds which might show such a propensity to resolve spontaneously? There are examples of ligands containing the 1,3-phenylene spacer that form coordination polymers which form chiral structures in crystals.

The transfer of stereochemical information from points up into superstructures is essential for the generation of homochiral systems. But structure is not everything. While a great deal of thermodynamic data regarding the balance between racemates and conglomerates in crystals has been gathered in some cases, presently these analyses are less common, and in the case of liquid crystals and self-assembled monolayers this type of information is bound to deepen comprehension. In this sense, the understanding and prediction of spontaneous resolution – an apparently modest goal when compared with other contemporary ends – remains one of the true challenges for science in the 21st century.

Abbreviations

0D	Zero-dimensional
1D	One-dimensional
2D	Two-dimensional
3D	Three-dimensional
AFM	Atomic force microscopy
DME	1,2-Dimethoxyethane
CD	Circular dichroism
LC	Liquid crystal
LEED	Low-energy electron diffraction
ML	Monolayer
M	Minus (left-handed) helicity
P	Plus (right-handed) helicity
STM	Scanning tunnelling microscopy
TTF	Tetrathiafulvalene
UHV	Ultra-high vacuum

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