Spontaneous resolution under supramolecular control†

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The spontaneous resolution of enantiomers is an intriguing and important phenomenon in a number of research areas. Non-covalent interactions can play a key role in the process which can now be observed not only in crystals, but in liquid crystals, self-assembled monolayers, self-assembled fibres, and supramolecules self-assembled in solution. The evidence gathered in all of these areas is important for explaining the transfer of chirality from molecule to bulk, and in particular the spontaneous resolution of enantiomers.

1 Introduction

The chirality of molecular components can have dramatic consequences in chemical systems, and presents great opportunities across a spectrum of disciplines: from medicinal chemistry to materials science in both industrial and academic sectors.[1,2] Commonly, the separation and study of mirror image molecules—enantiomers existent because of stereogenic centres, planes of chirality, or atropoisomerism—has been through condensation into crystals.[3] The segregation of enantiomers upon crystallisation is known as *spontaneous resolution*.[1]

When mixtures of mirror-image configurations or conformations of a compound—a racemate—condense they may do so in three general ways (Fig. 1):[3] (i) as a *racemic compound* in which both enantiomers are present in the same condensate; (ii) as a so-called *conglomerate* (in the scientific chemical sense), in which molecules form condensates comprised of only one enantiomer, but where the sample as a whole is racemic because it contains equal amounts of enantiomorphic condensates; (iii) as a *pseudoracemate,* in which the condensates contain the two enantiomers in a non-ordered arrangement. Only the second category, the conglomerate, implies spontaneous resolution.[3] The recent availability of a wider range of analytical techniques which delve down in scale has permitted the study of the chirality of microscopic and even nanometer-scale condensates, and thus the terms previously associated only with crystals become applicable to smaller chemical objects. Here, the term condensate embraces ordered crystals, two-dimensional monolayers, one-dimensional fibres and zero-dimensional aggregates, in which the chemical tools of supramolecular chemistry—non-covalent bonds—and particularly the phenomenon of self-assembly[4] are central.

This review concentrates on contemporary work concerning strict spontaneous resolution with emphasis on systems in which supramolecular chemistry plays a central and defined role. We do not cover 'external' influences used to effect optical resolution of these racemates (diastereomer formation, circularly polarised light, stirring, *etc*.) for which excellent reviews exist.[5,6] Since most of the concepts were first developed in crystalline systems, we discuss some of the new work in this area, followed by phenomena occurring in other media. The

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† *Abbreviations*. 0D: Zero-dimensional; 1D: One-dimensional; 2D: Two-dimensional; 3D: Three-dimensional; CD: Circular Dichroism; LC: Liquid Crystal ; ML: Monolayer; *M*: Minus (left-handed) helicity; *P*: Plus (right-handed) helicity; STM: Scanning Tunnelling Microscopy; UHV: Ultra-high vacuum.

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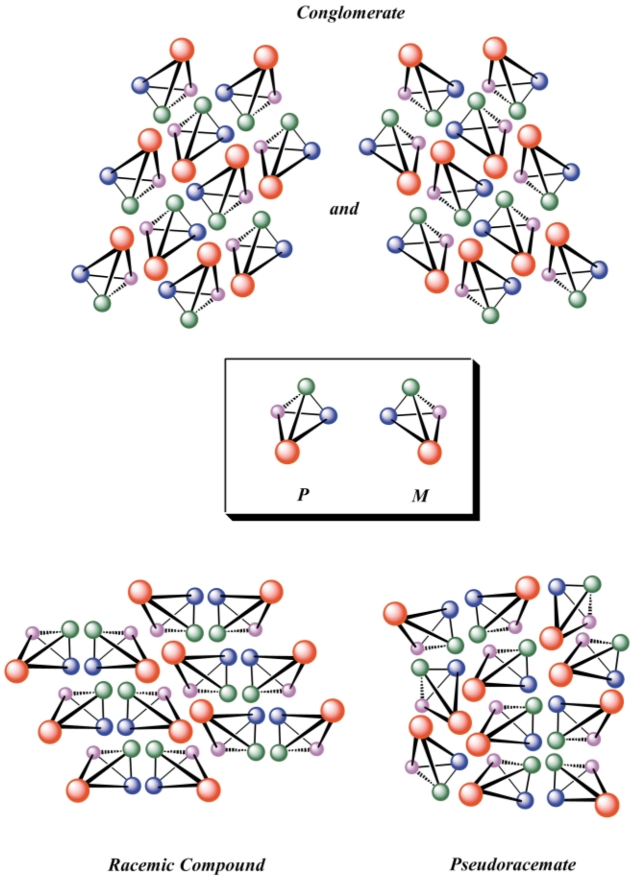


Fig. 1 Conglomerate, racemic compound and pseudoracemate condensates of an imaginary chiral chemical form.

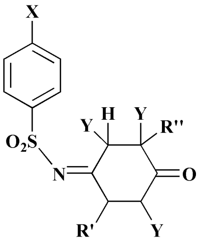
helix is one of the most attractive and evocative expressions of chirality, from the molecular to the supramolecular level, and will be a recurring theme in the review. Space limitations mean omission of some excellent work, and we strongly encourage the curious to read around the references cited in the examples given.

2 Spontaneous resolution in crystals

The classic *Enantiomers, Racemates and Resolutions* by Jacques, Collet and Wilen covers spontaneous resolution in crystals comprehensively;[3] here the essential fundamentals and more recent developments are presented. Crystallisation constitutes the most economical procedure to obtain enantiopure compounds, when separation of the crystals forming a conglomerate is feasible. However, in ordered three-dimensional crystals conglomerate formation is not very frequent (and is even less predictable), reflecting the tremendous preference (more than 90%) for compounds to crystallise in centrosymmetric space groups.[3,7,8]‡ The exact reasons for this preference are a matter of debate, but while it is clear that thermodynamic factors are critical in determining the packing of molecules in crystals [particularly the efficiency of packing, more dense packing being favoured, in which entropy ($T\Delta S$) and the enthalpy (ΔH) offset one another[7]], kinetics of crystallisation also play a role. After all, molecules in a crystal are kinetically confined in conformation and relative disposition.

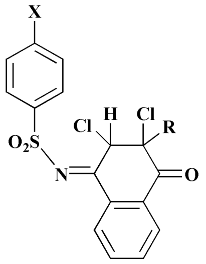
2.1 Which compounds will form conglomerates and how are conglomerates identified?

The first part of this question remains unanswerable today because of the unpredictability of crystal structures. Some 1D or even 2D aspects of crystals can be designed, but in most instances the 3D structure cannot owing to the weak forces acting between chains or sheets of molecules. Several isolated examples of conglomerates are known, and certain families of compounds apparently tend to crystallise in chiral space groups.[3] We find a recent example in a series of 4-arenesulfonyliminocyclohex-2-en-1-one derivatives (**1** and **2**) which produced eleven new conglomerates.[8] One of the compounds crystallizes as a 2:1 inclusion compound with CCl_4 (space group $P1$). This achiral solvent molecule is considered to act as a 'conglomerator', and preferential spontaneous resolution can be achieved by its use in substoichiometric amounts. In contrast, the structurally related O-benzenesulfonyl-oximes **3** are racemic compounds, demonstrating how a fine variation in the molecular structure can influence the nature of the racemate.



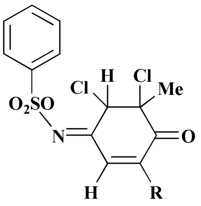
1a-f

	X	R'	R''	Y
a	H	Me	Cl	Cl
b	H	Cl	Cl	Cl
c	H	Me	Me	Br
d	Me	Me	Cl	Cl
e	Me	Cl	Cl	Cl
f	Cl	Cl	Cl	Cl



2a-e

	X	R
a	H	H
b	H	Cl
c	Me	H
d	Cl	H
e	Cl	Cl



3a,b

	R
a	Me
b	Cl

How do we know if a crystalline sample is a conglomerate? Today, the most immediate and conclusive method is determination of the crystal structure by diffraction techniques, generally X-ray, in combination with CD spectroscopy (of ground crystals or their solutions if the enantiomers are stable). Others methods are used,[3] for example: (i) Observation of enantiomorphic hemihedral crystals (showing half the faces required for full symmetry) which have hemihedral faces (hemihedry), but most crystals are not and do not! Among organic compounds, around 80% of chiral crystals belong to the space groups $P2_1$ and $P2_12_12_1$,§ and the probability of encountering hemihedral faces is only high in the former,[1] so observation proves positive, but the test cannot be conclusively negative. (ii) Melting point determination: if that of the enantiomer is greater than that of the racemate by more than 25 °C then the possibility of a conglomerate is high. (iii) Dissolution of a crystal in a nematic liquid crystal: formation of the cholesteric phase indicates an excess of one enantiomer. (iv) Dissolution of the sample in a saturated solution of the racemate: insolubility indicates a conglomerate.

While the observation of chiral space groups implies spontaneous resolution, the observation of a chiral space group

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‡ Of the 230 space groups, 65 are chiral, they being: cubic $P23$, $P2_13$, $I23$, $I2_13$, $F23$, $P432$, ($P4_132$, $P4_332$), $P4_232$, $I432$, $I4_132$, $F432$, $F4_132$, tetragonal $P4$, ($P4_1$, $P4_3$), $P4_2$, $I4$, $I4_1$, $P422$, $P42_12$, ($P4_122$, $P4_322$), ($P4_12_12$, $P4_32_12$), $P4_222$, $P4_22_12$, $I422$, $I4_122$, monoclinic $P2$, $P2_1$, $C2$, orthorhombic $P222$, $P222_1$, $P2_12_12$, $P2_12_12_1$, $C222$, $C222_1$, $I222$, $I2_12_12_1$, $F222$, triclinic $P1$, trigonal $P3$, ($P3_1$, $P3_2$), $P312$, $P321$, ($P3_112$, $P3_212$), ($P3_121$, $P3_221$), $R3$, $R32$, hexagonal $P6$, ($P6_1$, $P6_5$), ($P6_2$, $P6_4$), $P6_3$, $P622$, ($P6_122$, $P6_522$), $P6_322$, ($P6_222$, $P6_422$). The space groups between brackets are enantiomorphous pairs. Note that all *chiral* space groups are *noncentrosymmetric*, but the *reverse* is *not* true.

§ These space groups can contain non-covalent polymeric chains which while chiral are generally not *necessarily* helical, since the 2_1 screw axis can be operative equally in a clockwise or anticlockwise direction giving the same result, therefore the chain has no helical sense.

is no guarantee that crystals as an entity will be optically active, a result of either racemic crystal twinning or lamellar epitaxy (in which macroscopic layers of opposite enantiomers stack on top of each other). For example, (*RS*)-5-ethyl-5-methylhydantoin crystallises in a chiral space group ($P2_12_12_1$), in which homochiral supramolecular chains of molecules held together by hydrogen bonds (Fig. 2) unite through van der Waals interactions forming sheets which pile up through the same weak force. However, when no stirring is applied the crystals have virtually no enantiomeric excess.[9] Selective dissolution of the crystals in an undersaturated solution of one enantiomer leaves plates (Fig. 2) with high *ee* of the same chirality as those of the enantiomer used in the solvent, demonstrating that the crystals are actually composed of lamellae of enantiomers. The union of enantiomeric lamellae arises from epitaxial growth because of locally-oscillating supersaturation, which can be nulled by gentle stirring whereupon diffusion is aided and leads to the formation of a conglomerate of crystals each with high enantiomeric excess of one enantiomer or the other (this contrasts with effects of stirring leading to optical resolution in which nucleation of just *one* enantiomer is favoured[10]). Molecular modelling was used to generate hypothetical racemic structures with alternating layer chirality, and showed that the racemic compound lies only a few kJ above the conglomerate because of the weak interactions between the layers, thereby explaining the dramatic effects of local supersaturation in this system.

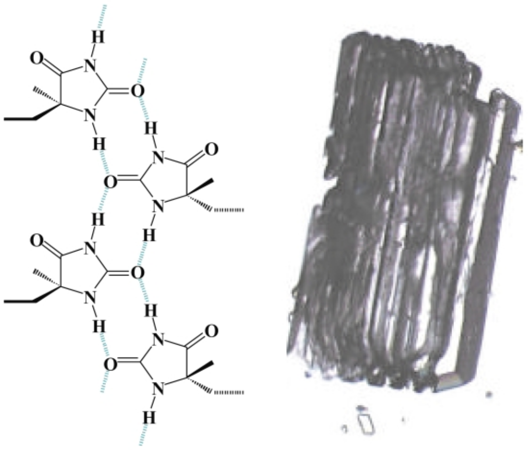


Fig. 2 Schematic representation of the homochiral supramolecular chains formed by 5-ethyl-5-methylhydantoin in its crystals and a partly-dissolved crystal showing the homochiral lamellae.[9]

2.2 Spontaneous resolution as an expression of the supramolecular structure

The previous example has already given a flavour of how expression of chirality in crystals is a function of the supramolecular structure. Consequently, minute structural changes at the molecular level can induce dramatic changes beyond the molecule and tip the balance between racemic compound and conglomerate. A simple example is 2,2′-dipyrrolylthioketone **4** and its ketone analogue **5**.[11] At the molecular level the geometries of the two compounds are almost identical. At the supramolecular level the thioketone **4** packs in antiparallel layers of opposing enantiomers (Fig. 3), comprised of cyclic dimers formed by very weak [N–H···S] interactions of adjacent but offset enantiomers. Instead, ketone **5** crystallises in a chiral space group in which single enantiomers form columnar chains through strong [N–H···O] hydrogen bonds reinforced by π–π stacking interactions (Fig. 3).

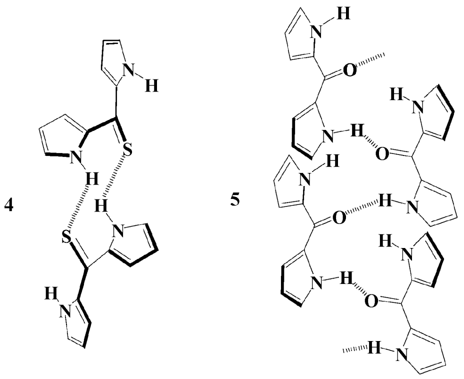
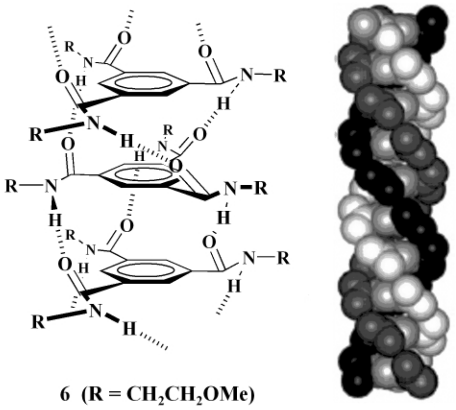


Fig. 3 Schematic representations of the crystal packing of the racemic compound formed by **4** and the conglomerate formed by **5**.[11]

Achiral amides such as *N*,*N*′,*N*″-tris(2-methoxyethyl)benzene-1,3,5-tricarboxamide (**6**, Fig. 4) are capable of spontaneous resolution, forming chiral supramolecular structures.[12] The driving non-covalent interactions responsible for the columnar disposition of the molecules in the crystal are π–π stacking aided and abetted by multiple amide-type hydrogen bonds. In this case, the molecular structure of **6** presents a tilted disposition for the three carboxamido groups, resulting in a triple helical arrangement of these moieties in the crystal (Fig. 4). In both this case and the previous one, an explanation as to why resolution of the chains is translated up to the whole crystal is awaited.



6 ($R = CH_2CH_2OMe$)

Fig. 4 Schematic representation of the packing of **6** in its crystals.[12]

Although coordination chemistry will be gathered in a specific section, we will provide a taste here reporting an interesting example where the metal coordination to a ligand can give a conglomerate but only when the supramolecular structure, which is governed by a hydrogen bonded network, is adequate.[13] The achiral ligand 5-(9-anthracenyl)pyrimidine (**7**, Fig. 5) when combined with cadmium nitrate in ethanolic water forms the complex $\mathbf{7}_2\cdot Cd(NO_3)_2\cdot H_2O\cdot EtOH$ (**8**). The hexacoordinate metal ion is in a chiral environment because of *cis*

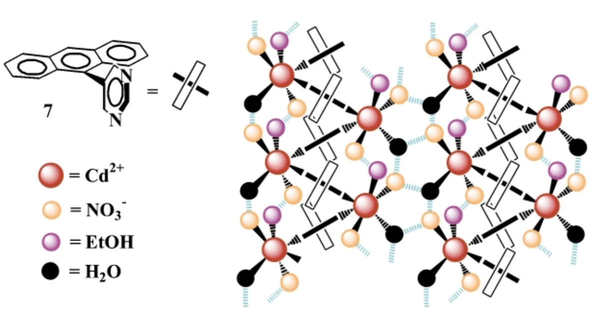


Fig. 5 A schematic view of the chiral helices and hydrogen bonds in the conglomerate $\mathbf{7}_2\cdot Cd(NO_3)_2\cdot H_2O\cdot EtOH$ (**8**).[13]

coordination by two pyrimidine rings, and forms an exclusively homochiral coordination polymer (Fig. 5). Intra- and inter-helical hydrogen bonds between water–nitrate and ethanol–nitrate apparently stabilise the structure. In a single batch homochiral crystals were formed, and different batches produced enantiomorphous crystals statistically. When ethanol is *not* present in the crystallisation, the achiral adduct 7_2·Cd(NO$_3$)$_2$·3H$_2$O (**9**) with zigzag chain disposition results, despite the fact that extensive intra- and inter-chain hydrogen bonds exist. Loss of ethanol from **8** and uptake of water converts it into achiral **9**. Exposure to ethanol vapours regenerates **8**. Interconversion between achiral and chiral arrangements is possible, indicating that chirality is an expression of supramolecular structure. A chirality memory effect seems to be involved, because the chiral-achiral-chiral cycle occurs with retention of absolute configuration, although the mechanism is not yet fully understood.

Urea frequently forms inclusion compounds with long chain alkanes which belong to the enantiomorphic space groups $P6_122$ and $P6_522$, thanks to spirals of hydrogen bonded helical chains of urea molecules which wind their way along the sides of the hexagonal channels, as reviewed extensively elsewhere.[14] The host structure can be altered and even made achiral by guests which interact relatively strongly with the lattice. We limit ourselves here to a recent example which demonstrates the existence of enantiomorphic domains in crystals of urea with 2,12-tridecanedione in the hexagonal channels.[15] Photomicrography of the crystals clearly showed dextrorotatory and levorotatory domains. The use of synchrotron white beam X-ray topography confirmed chiral twinning and also revealed sectoring but no strain of the domain boundaries. With the help of the X-ray topography the crystal was cleaved and two complementary fragments were used for X-ray collection. The crystallographic study allowed a correlation between the domains and the handedness of the urea helical supramolecular structure. Apparently, reversal of helicity between the domains is possible through an *n*-glide relation in which the enantiomeric sides of the still hexagonal channel are linked by a loop-like topology of hydrogen bonds.

2.3 Spontaneous resolution through complexation with achiral compounds

Habitually, resolution of racemates is achieved by the use of one enantiomer of a chiral reagent (a resolving agent), giving rise to the formation of diastereomers.[1–3] However, more recently achiral compounds have also been used to generate conglomerates from otherwise racemic compounds. This phenomenon arises from modification of the supramolecular structure of the compound by its interaction with the achiral guest, which presumably reduces symmetry possibilities of the host. Again, supramolecular structure of the host-guest complex directs conglomerate formation. As an example, the axially chiral 1,1′-binaphthyl-2,2′-dicarboxylic acid (**10**, Fig. 6) is a racemic compound and forms racemic complexes with a variety of guests.

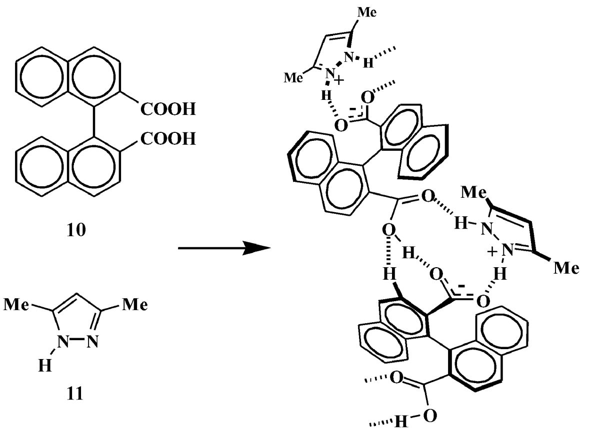


Fig. 6 Schematic representation of the chains of the mono-anion of **10** and protonated **11** which are present in the conglomerate crystals of the salt.[16]

However, the salt-type complex of **10** with 3,5-dimethylpyrazole (**11**) spontaneously resolves upon crystallisation.[16] The 1:1 complex is formed by a carboxylate anion and a pyrazolium cation linked by an $[^+N\text{–}H\cdots O^-]$, $[^+N\text{–}H\cdots O]$ and $[O\text{–}H\cdots O^-]$ hydrogen bonds as well as $[C\text{–}H\cdots O]$ interactions in a cyclic arrangement, leading to the formation of chains of the same configuration, *i.e.*, each crystal is formed by only on enantiomer of **10** (Fig. 6). The crystals showed hemihedrism and they were separated and their physical properties evaluated. The spontaneous resolution of the 1:1 complex of **10** with **11** into a conglomerate constitutes a unique example amongst many complexes reported for the bis-acid.[16]

Chiral crystals can also be formed by co-crystallisation of two achiral molecules. For example, self-assembly of an achiral molecule in a chiral conformation and another achiral molecule was achieved through a combination of hydrogen bonding and ionic interactions in a series of 12 carboxylic acids and achiral bases.[17] In the co-crystallisation of diphenylacetic acid and acridine (or phenanthridine) the molecular components are linked by $[O\text{–}H\cdots N]$ hydrogen bonds, inducing a chiral propeller-like conformation in the acid. Either configuration *M* or *P* is formed in each of the enantiomorphic crystals (Fig. 7).

Another group of chiral co-crystals was formed and analysed, where chirality arises from formation of helical-type chains.[17] For instance, in the co-crystal of 3-indolepropionic acid and phenanthridine (Fig. 8) two relevant hydrogen bonds can be accounted: (i) $[O\text{–}H\cdots N]$ between the acid and base molecular components, and (ii) $[N\text{–}H\cdots O{=}C]$ which connects the 3-indolepropionic acid through the lattice. These interactions are responsible for the adoption of a unidirectional helical chain, the origin of the chirality. It is thought that π–π interactions also play a role in the asymmetric packing. Additionally, in some of the co-crystals obtained from 3-indolepropionic acid and tryptamine, the $[N\text{–}H\cdots O]$ interaction is replaced by a $[^+NH_3\cdots{}^-O_2C]$ bond, giving also origin to helical structures. A remarkable feature of this work is the fact that enantiomer control in crystallisation can be induced by the pseudo-seeding with a crystal of desired chirality.

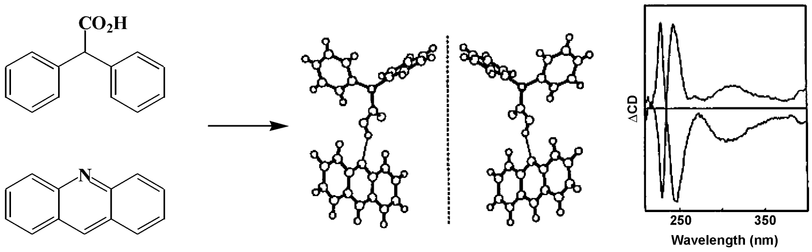


Fig. 7 The structures of the *M* and *P* complexes of diphenylacetic acid and acridine and their solid state CD spectra. Copyright 2000, with permission from Elsevier Science.[17]

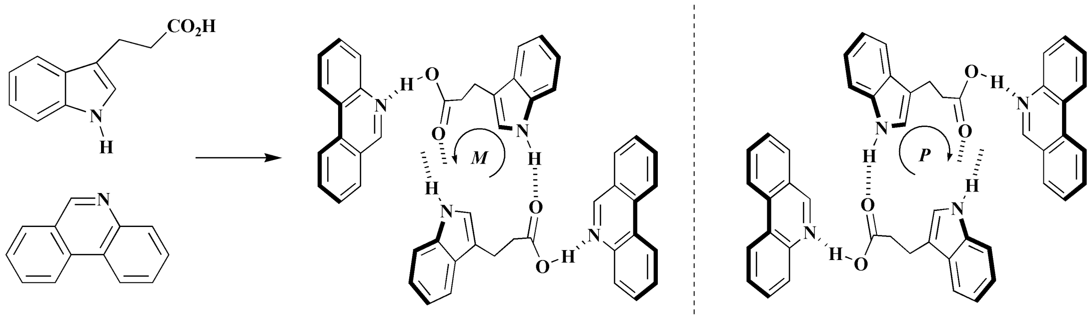


Fig. 8 The schematic structures of the *M* and *P* complexes of 3-indolepropionic acid and phenanthridine.[17]

The helical tubuland hosts are a family of aliphatic chiral dialcohols (*e.g.* **12–15**, Fig. 9) which exhibit almost predictable behaviour when co-crystallising with achiral guests of a compatible size, forming conglomerates.[18] The chiral crystals contain parallel helical tubes of the host molecules maintained and linked together through hydrogen bonds with guest molecules located in the cavities (Fig. 9). The helical structure is extremely tolerant to the spacer between the two alcohol groups. However, if the guest is of a non-compatible size, the spiral tube becomes disfavoured and centrosymmetric packing results. Resolution of the diols overcomes this obstacle.[19]

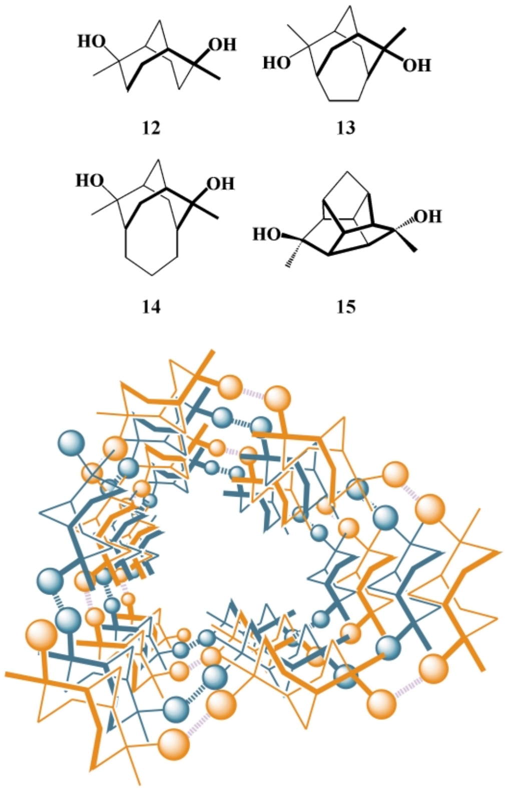


Fig. 9 The structural formulae of diols which form helical tubulands by spontaneous resolution and a schematic representation of the structure of the channels formed by **12**.[18,19]

A ‘rogue’ among the compounds is racemic dialcohol **13**. It crystallises as the helical tubular form in enantiomorphic space groups $P3_121$ and $P3_221$ with ethyl acetate, carbon tetrachloride or fluorocyclohexane, but with smaller guests such as dichloromethane, benzene or cyclohexane it forms an achiral ellipsoidal clathrate, in which the sub-lattices are formed with both enantiomers and connected by [O–H···O] hydrogen bond networks.[19] The larger guest *tert*-butylcyclohexane is not included at all by racemic **13**. However when enantiopure **13** is used the formation of a helical type chiral crystal ensues with both cyclohexane (host–guest stoichiometry 3:1.5) and *tert*-butylcyclohexane (host–guest stoichiometry 3:0.75). Helix formation is always associated to host chirality, either *via* pre-resolution or spontaneous resolution. The work is an elegant example of how spontaneous resolution controlled by supramolecular structure can be probed by using one enantiomer.

An interesting example where an achiral crystalline molecule is transformed to a chiral inclusion compound by treatment with vapours of an achiral guest is found in the system tetra(*p*-bromophenyl)ethylene-*p*-xylene.[20] After the finding that the host forms chiral inclusion compounds with many achiral guests, its racemic crystals obtained from *m*-xylene were exposed to a vapour of guest (for instance, *p*-xylene) and a chiral inclusion complex (Fig. 10) was formed which exhibited the same properties as the one obtained by direct crystallization. In some cases, the gas solid reaction induced chirality not observed by crystallization with some of the guests. Furthermore, after removal of the guest from the crystal lattice, the chiral disposition of the host persists in the crystal and the process can be reversed on exposure to the guest, recovering the original chirality. This finding may have important implications in the field of asymmetric synthesis.

2.4 Spontaneous resolution in coordination compounds

One the simplest chiral coordination compounds one could imagine involves a metal ion coordinated by three bidentate ligands in an octahedral environment, generating the helical right-handed Δ and left-handed Λ enantiomers. The hexafluorophosphate salts of this type of complexes of metal(II) cations with 2,2′-bipyridine can form racemic compounds or conglomerates (Fig. 11).[21] While the Fe(II) and Ru(II) are racemic compounds, the Zn(II) compound is a conglomerate and the Ni(II) compounds exhibits polymorphism with both chiral and non-chiral crystals in the sample. The subtlest of differences in packing energy appear to arise from the interaction between the homochiral layers present in both structures. In the racemic compounds [C–H···π] interactions are present between coordinated ligands, while in the conglomerates π–π stacking dominates. The energy differences between the two types of racemate appear to originate in tiny differences in bond lengths and geometry, rather than energy of interaction of the organic ligands. The dominant forces in these ionic compounds are presumably electrostatic.

Union of 2,2′-bipyridine units produces ligands capable of helicate formation with metal ions, complexes which normally crystallise as racemic compounds, with a very notable exception.[22] The ligand **16** when combined with Ni(II) forms a trinuclear triple helicate (Fig. 12) which upon crystallisation as its perchlorate salt forms a conglomerate, as proved by X-ray crystallography as well as dissolution of individual crystals and measurement of their CD spectra, which showed opposite Cotton effects. This example proved transmission of chirality not only within the supermolecule through the ligand strands, but also beyond into the crystal lattice, although *why* this helicate should resolve while others do not is unclear.

By using flexible *exo*-dentate ligands the pre-programmed information of building blocks is lower but still a high degree of

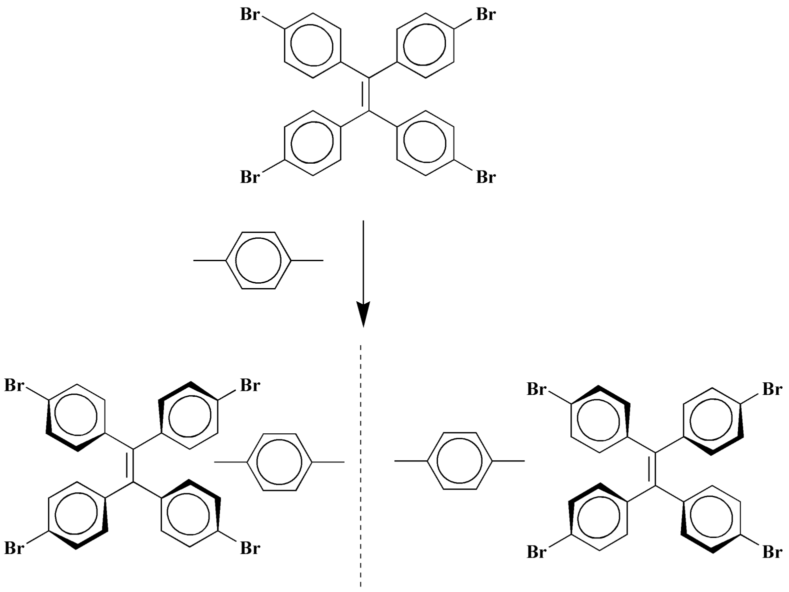


Fig. 10 The two atropoisomers of the host tetra(*p*-bromophenyl)ethylene-*p*-xylene present in different crystals of the conglomerate formed by vapour diffusion of the achiral guest *p*-xylene into racemic crystals of the host.[20]

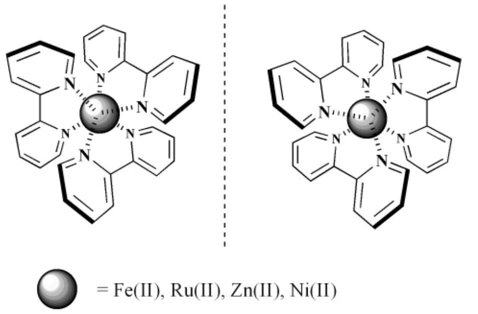


Fig. 11 The two chiral forms of metal(II) tris(2,2′-bipyridine) complexes which form either racemic compounds or conglomerates in their crystals as hexafluorophosphate salts.[21]

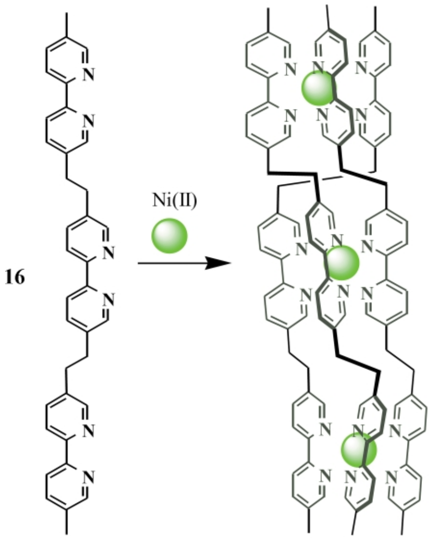


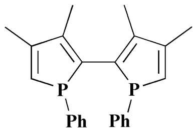
Fig. 12 The triple helicate formed by **16** and nickel(II) which form a conglomerate.[22]

control can be exercised in the design of chiral metal coordinated assemblies, and also the supramolecular control of chirality can be induced by guest or templates.[23] Thus, when 1,3-bis(4-pyridyl)propane was mixed with [Mn(hfac)$_2$(H$_2$O)$_3$], crystals grew that X-ray analysis indicated were formed by homochiral metal helicates (space group C_2), having undergone a spontaneous self-resolution into a conglomerate. The homochirality seems to be induced by the interlocking of adjacent helices. Co-crystallisation with achiral compounds can vary the chirality of the solid state structure of the complex. Thus, benzene acted as a template for the formation of an ‘2+2’ achiral cyclophane (space group $P1$), whereas by crystallization in the presence of 1,2-diphenylethane, reproducible helical structures were obtained in this case of achiral nature (space group $P2_1/n$) possibly because the guest precludes the interlocking of helices, and prevents homochirality.

2.5 Exploiting crystalline conglomerates

Perhaps the widest use of conglomerates is in the preparation of enantiopure materials by the process of *entrainment*, in which an enantiopure crystal acts as a seed for the growth of new crystals of the same chirality from a racemic solution.[3] Principally homochiral crystals can also be obtained by spontaneous resolution under racemising conditions. In this experiment, crystal growth of one enantiomer initiates, but rather than the concentration of this species depleting in the solution, the equilibrium re-establishes the $R:S$ ratio. Thus, crystals of one or other enantiomer can form uniquely, with random statistical formation of each in different experiments. Tri-*o*-thymotide, a macrocycle which exists as P and M enantiomers as a result of slow interconversion in solution and forms chlathrates with solvent molecules is an example of this phenomenon,[24] as is the spontaneous resolution of the cadmium complex mentioned earlier.[13]

Conglomerate formation is not only important for the separation of enantiomers, but also in chemical synthesis. The separation of the 1,1′-diphenyl-3,3′,4,4′-tetramethyl-2,2′-biphosphole ligand (**17**) as a conglomerate of large crystals (50 to 150 mg each) allowed the preparation of their enantiomerisation-stable palladium(II) complexes which were subsequently used for asymmetric allylic substitution in solution.[25]



17

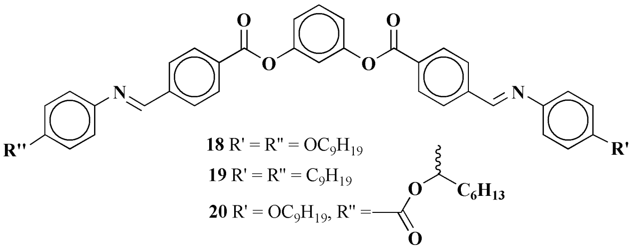
The main advantage of exploiting stereoselective reactions in the solid state is that, since the crystal packing is the source of chiral induction, there is no need for the use of chiral auxiliaries or chiral catalysts. A more direct generation of chiral compounds is by photochemical reactions of achiral compounds fixed in a chiral conformation in a crystal. A particular example for a group of aromatic *ortho*-keto thioesters has been reported,[26] which spontaneously resolved ($P2_12_12_1$), and for selected enantiopure crystals their photochemically induced transformation into phthalides has been studied from a mechanistic point of view. In addition to the stereospecificity observed (*P* configuration in the starting material leads to products of *R* configuration) good enantioselectivities were obtained, although these depended on the reaction conditions.

3 Spontaneous resolution in liquid crystals

Achiral and racemic compounds (mesogens) which form liquid crystalline phases normally generate non-chiral nematic (orientational order), smectic (orientational order in layers) or discotic (columnar order) liquid crystal phases. The most common chiral phases in LCs are the smectic and cholesteric (a phase equivalent to a nematic with homochiral twisting between the long axes of the molecules) types. These phases are generated only from samples with some degree of enantiomeric excess, the average degree of twisting between molecules following the enantiomeric purity. These sweeping generalisations held true until very recently.

An achiral mesogen can form a chiral LC phase. The ‘bent-core’ (or more colloquially ‘banana-shaped’) mesogens were the first compounds discovered with this remarkable property. A detailed analysis of the high temperature mesophase formed by the achiral compounds **18** and **19** revealed spontaneous resolution and rich stereochemical complexity of the systems at the supramolecular level.[27]

The compounds form tilted layers that organise amongst themselves to give either racemic or enantiopure stacks which are defined by three supramolecular factors (Fig. 13):[27] (i) the chirality (tilt angle) of each layer, *P* or *M* with respect to the normal to the layer plane; (ii) the relative interlayer clinicity *in the tilt plane*, either synclinic or anticlinic, and; (iii) The relative directions of the polar axes (P, defined by the C–H bond direction at the central 1,3-phenylene ring) of the layers, either ferroelectric (parallel axes) or antiferroelectric (antiparallel axes). Thus there are four possible phases.



In freely suspended thin films of the compounds **18** and **19** depolarised reflected light microscopy in conjunction with small applied electric fields confirmed chiral layers of molecules, which stack on top of each other with alternating chirality giving a racemic compound.[27] When the compounds were placed in electro-optic cells, two types of order were observed in the transmission polarised light micrographs:[27] the majority SmC_SP_A, a racemic compound, and the minority one a conglomerate SmC_AP_A. Proof of the enantiomeric domains came by switching an applied electric field in opposite directions, and noting opposite optical twisting of the extinction brushes depending on the domain and the field direction (electro-optic switching—applying a field induces the ferroelectric phase SmC_SP_F in which layer chirality is conserved). Interestingly, these metastable minority domains can be generated predominantly by warming up from the lower temperature phase. The origin of this remarkable discovery probably resides in the conformational chirality of the core of the molecule, arising from twisting of the aromatic rings joined by ester or imine units which can be *P* or *M*.

In a cunning design strategy based on the observations outlined above and precedents in other LCs, a molecule designed to favour anticlinic unions between the layers was prepared which is a ferroelectric liquid crystalline conglomerate.[27] In the *polar plane* the ferroelectric SmC_SP_F is anticlinic and the 1-methylheptyloxycarbonyl group promotes anticlinic interfaces in other mesogens. The racemate **20** forms the so-called B7 LC phase (SmC_SP_F Fig. 13), as confirmed by the characteristic behaviour of the phase in electric fields. Another very interesting observation in this material is that when the isotropic phase is cooled to the B7 phase left- and right-handed

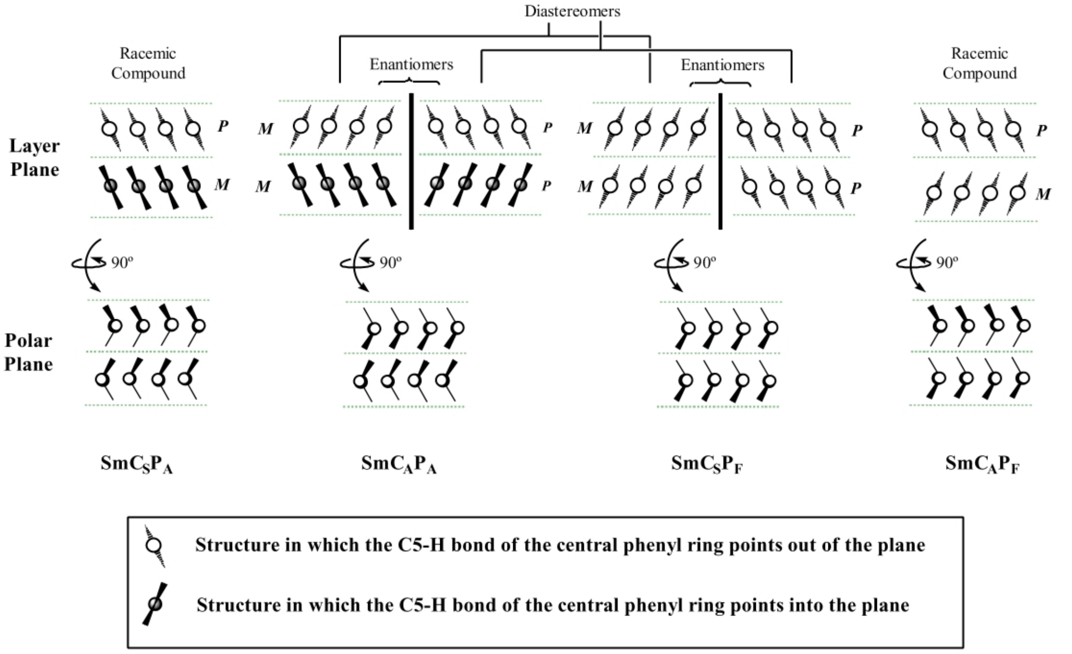
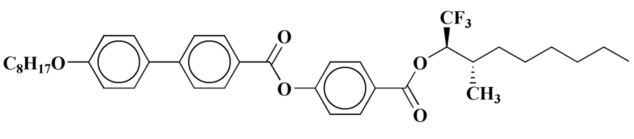


Fig. 13 Schematic representation of the supramolecular stereoisomers in the higher temperature mesophases of bent-core molecules **18** and **19**. Sm indicates smectic (layered), C clinicity—either all the same tilt (synclinic, S subscript) or alternating tilt (anticlinic, A subscript) in the layer plane—and P polarity, ferroelectric (F subscript) or antiferroelectric (A subscript).[27]

helical ribbons and tubes are observed with a polarised light microscope, another example of spontaneous resolution.

A conglomerate has also been observed in the smectic phase of a more classical calamitic (rod-shaped) mesogen with two stereogenic centres in its tail.[28] The *unlike* racemic mixture[1] (with two stereogenic centres with opposite configurations with respect to each other, which exist as *RS* or *SR*) of diastereomers (*R**,*S**)-**21** shows electro-optic switching of the mesophases akin to chiral compounds (racemates and achiral compounds normally show no switching because there is no net dipole). Evidence for conglomerate formation was also revealed in the textures of the smectic phase in a polarising micrscope. This spontaneous resolution, which was not observed in the corresponding homologues with just one chain substituent, was put down to the bending in the conformation of the alkyl chain with respect to the rigid core of the molecule, and its greater rigidity when two chain substituents are present.[29]



(*R**,*S**)-**21**

It should be pointed out that in the liquid crystals studied so far, while being referred to as 'conglomerates', they could in fact partially contain small amounts of the enantiomer which provides the opposite bulk behaviour. It remains to be seen, and is an interesting challenge, to evaluate the stereoselectivity of these phase-separating phenomena in the fluid state.

4 Self-assembled monolayers

The possible packing arrangements of molecules restricted to a 2D plane are considerably less than in a three-dimensional aggregate. Compared with 230 3D space groups, there are just 17 2D ones, and five of them are chiral when laid on a surface. Escher famously illustrated this idea for us in the form of lizards: those on the left side of Fig. 14 cannot be converted into those on the right without changing the way their body is twisted. Lizards aside, 2D structures which are chiral on a surface can be achiral in isolation, a hypothetical situation since the surface stabilises the monolayer and to superimpose the structures they must be removed from the plane. It is apparent, then, that should the adsorbates have any specific interaction with the surface then symmetry of the surface plays a fundamental role in the possible packing modes of a molecule upon it. Let us start with an example in which the surface imposes no symmetry restrictions, because it has no long-range order, a liquid.

Ordered monolayers (MLs) on liquids are invariably prepared using the Langmuir technique. Even now, the observation of spontaneous resolution in 2D ML systems is not at all trivial compared with 3D crystalline compounds. The use of the form of pressure–area isotherms of Langmuir MLs of racemic and enantiopure compounds to infer the type of domains is fraught with problems, partially because the amphiphiles can self-assemble into clusters even in the absence of surface pressures. In the following example, synchotron grazing incidence X-ray diffraction was used to determine the structure of the monolayers.

If we consider an assembly of amphiphilic molecules oriented perpendicularly to a structurally disordered surface, such as that of water, the inversion centre, the glide with its plane parallel to the surface and the related twofold screw symmetry (the most common symmetry elements in 3D) are ruled out, leaving merely the translation and a glide plane normal to the surface. The snag is that water is more often than not the subphase of choice, and the amphiphiles generally rely on lengthy alkyl chains, which have a penchant for herringbone-type packing with glide symmetry. Consequently, for spontaneous resolution to be achieved some feature which avoids this element, promoting translation-dominated packing (and precludes solid solutions) is necessary.[30]

An elegant demonstration of this argument was performed in the study of Langmuir films of enantiopure and racemic amphiphiles derived from glycine and lysine, the amphiphiles C_n-Gly and C_n-Lys (Fig. 15).[30] Synchotron grazing incidence X-ray diffraction was used to determine the structures. The results showed that while enantiopure (*S*)-C_n-Gly (n = 12 or 16) form crystalline domains with molecules related by translation only in an oblique unit cell (chiral in two dimensions), the equivalent racemates 'spontaneously assemble on water into heterochiral crystalline domains', with the expected symmetry elements of herringbone packing. In contrast, study of the Langmuir films formed by both the enantiopure forms and the racemates of the C_n-Lys (n = 17 or 21) lead to essentially isostructural monolayers with the same oblique unit cell, and thus are homochiral. In these monolayers the molecules are related by translation thanks to their union through hydrogen bonds between the amide units incorporated in the amphiphilic chains, in addition to the hydrogen bonds between ammonium and carboxylate groups in the head group. Judicious choice of hydrogen-bonding motif has therefore led to a system displaying spontaneous resolution.

The symmetry elements open to molecules which pack coplanar with a surface are quite different to that of amphiphiles at

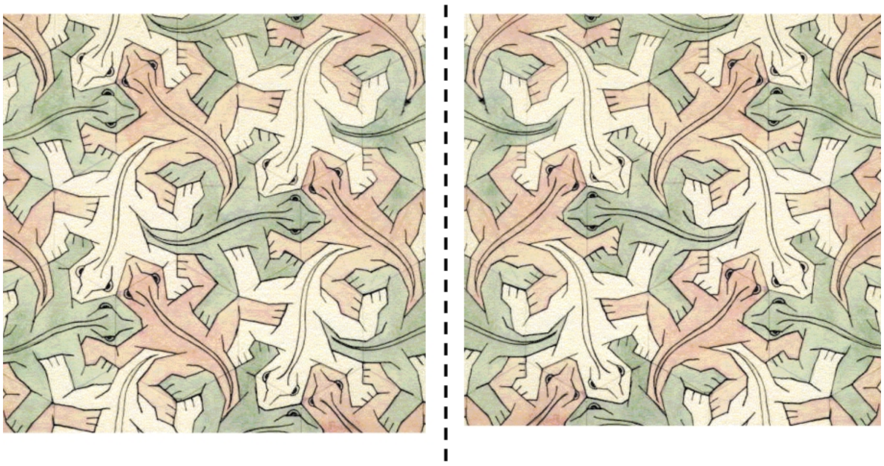


Fig. 14 A drawing by M. C. Escher (Lizards; Symmetry Drawing 25) and its enantiomer illustrating 2D chirality. Reproduced with permission. All M. C. Escher works © 2002 Cordon Art - Baarn - Holland. All rights reserved.

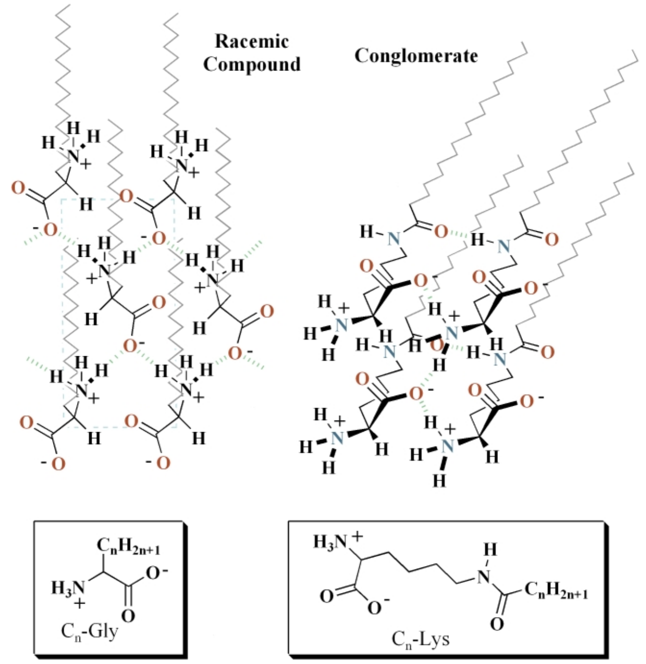


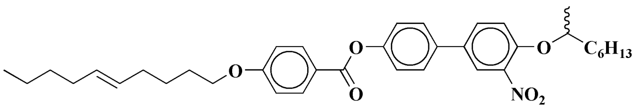
Fig. 15 The general formula of gycine and lysine-derived amphiphiles and a representation of the possible packing motifs in the assembled racemic compound and conglomerate MLs, viewed perpendicular to the layer plane.[30]

a water surface. In principle, the centre of inversion, glide plane, twofold screw axis and translation may all be possible, assuming that the surface does not impose any restrictions on these operations. When a molecule packs on a conducting surface in this manner, scanning tunnelling microscopy becomes a particularly potent instrument in order to observe it, and has proved a unique means for studies on chirality at the molecular level.[31,32]

The basal plane of graphite, comprised of the familiar hexagonal net of carbon–carbon bonds, *does* impose restrictions on the symmetry operations open to certain molecules which pack on top of it. The most frequently encountered structural feature of adsorbents to graphite is a long alkyl chain. The reason for this trait is that saturated *n*-alkyl chains form a series of [C–H···π] interactions between the methylene groups of the hydrocarbon and the aromatic rings of the graphite, which obliges these chains to lie parallel to the carbon surface.

STM has been used to directly observe enantiomorphous domains of molecules in an LC on the graphite surface. Although the LC phase exists above, the ML at the surface is in effect a 2D crystal and is imaged with the STM tip passing through the bulk fluid overlayer. The achiral smectic mesogens 4′-*n*-alkyl-4-cyanobiphenyl (*n* = 8, 10, 12) have been observed on both graphite and MoS_2.[32] Enantiomorphous domains arise because the orientation of the alkyl chain with respect to the coplanar biphenyl core is either *M* or *P* when viewed from above or below the surface (Fig. 16).

Incorporation of a stereogenic centre in the molecule gives thermodynamic preference to one of the two possible orientations at the surface since a diastereomeric relationship exists, defined by the orientation of the molecule with respect to the substrate and the position of the substituent groups. This case pertains to monolayers formed between the bulk LC phase formed by **22** and the graphite surface.[33] When samples with an enantiomeric excess greater than 99% were imaged by STM, the MLs were comprised of rows of molecules with a defined tilt angle which was always either clockwise (for *S*) or anticlockwise (for *R*) with respect to the row normal. The racemate produced MLs with domains in which the tilt angle was either all clockwise or all anticlockwise, and whose 2D cell dimensions coincide with those of the pure enantiomers, thus providing evidence for spontaneous resolution and formation of a conglomerate on the graphite.



(*RS*)-**22**

Monolayers at the graphite surface are not only formed by LCs, but also by lipophilic molecules dissolved in high boiling solvents,[31] and achiral molecules often separate into enantiomorphous domains.[34] For example, the disc-like molecules $\mathbf{23}_n$ (Fig. 17, n = 9,11) form ordered monolayers with hexagonal lattices of adsorbed molecules when applied in a tetradecane solution,[35] whose STM images imply a chiral structure, depicted schematically in Fig. 17, in which two ordered molecules are contained within the unit cell (observed as triangles with an elipse extending outwards) with a disordered molecule at each apex (observed as bright discs). It was surmised that the molecule which is disordered as a result of mobility which is fast on the STM timescale of the experiment because of frustration in the packing of these molecules. Since there is no source of asymmetry, both left- and right-handed ordering are observed equally in different domains on the surface.

Also, when a stereogenic centre is present in the adsorbate, spontaneous resolution can occur at the surface. Thus, when a solution of (*RS*)-2-bromohexadecanoic acid dissolved in 1-phenyloctane is applied to the graphite surface, domains of between 30 and 100 nm^2 are observed by STM which apparently contain just one enantiomer.[36] The structure of the domains consists of

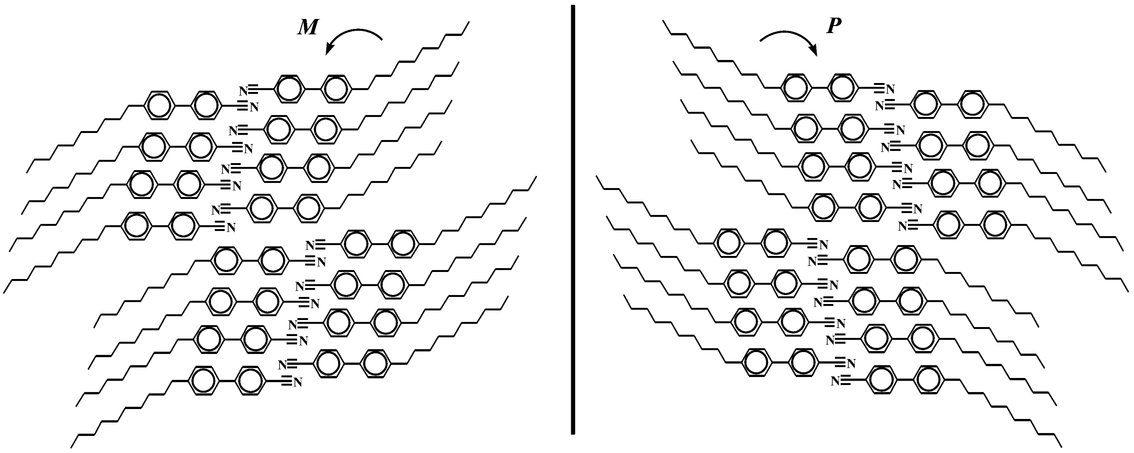
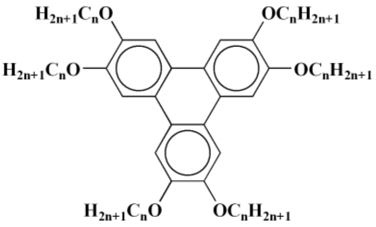


Fig. 16 Schematic representation of the two possible orientations (*M* or *P*) of 4′-decyl-4-cyanobiphenyl in their supramolecular tapes on an imaginary surface.[32]



23_n (n = 9,11)

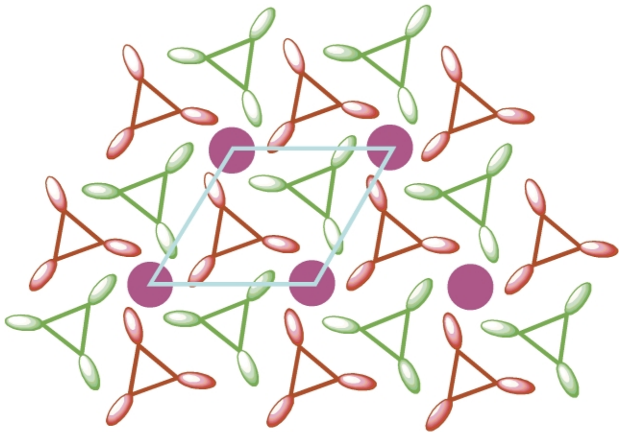


Fig. 17 The molecules **23_n** and a representation of the chiral structures observed at the graphite–tetradecane interface by STM (the green and red shapes represent independent molecules and the purple circles the disordered molecules, and the blue parallelogram the unit cell).[35]

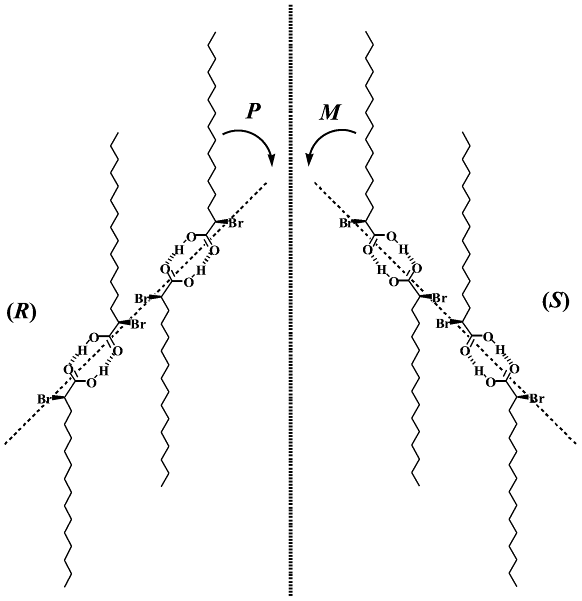


Fig. 18 Schematic representation of the possible orientations of (*R*)- and (*S*)-2-bromohexadecanoic acid in their supramolecular chains on graphite.[36]

non-covalent chains of molecules (Fig. 18) whose alkyl groups inter-digitate. The chain is comprised of hydrogen-bonded dimers, formed thanks to the self-complementarity of the carboxylic group, which aggregate with the bromine atoms on neighbouring molecules in the chain coming close to each other. The identification of the enantiomers was possible in this case not only because of the different angle formed by the alkyl group with respect to the supramolecular chain axis, but also because of the different contrast effects which the bromine (bright) and carboxylic (dark) groups present in the STM images. The (*R*) enantiomer form *P* domains (where P refers to the helicity with respect to an imaginary axis on the surface) and the (*S*) enantiomer forms *M* domains. In the crystal the racemate exists as a racemic compound in which the two enantiomers form the hydrogen-bonded pair with a centre of symmetry at its core. This situation is not possible on the graphite without forcing a bromine atom into the surface, a thermodynamically unfavourable situation.

A similar situation has been observed in a supramolecular system comprised of either (*S*)- or (*RS*)-16-methyloctadecanoic acid and bipyridine in which a 2:1 complex is formed.[37] Here again, spontaneous resolution takes place in the complex at the graphite surface, as witnessed by STM (Fig. 19). The supramolecule consists of two aliphatic acids hydrogen-bonded to the pyridine nitrogen atoms, and these aggregates come together to form tapes of homochiral molecules on the surface and the two halves of the tape are related by a C_2 axis (a particularly common situation in this type of ML). The assignment of the different domains, in this case, was done by comparing the images of the conglomerate with those of a sample prepared with enantiomerically pure aliphatic acid. An interesting aspect of this work is that the pure (*S*) enantiomer forms quasi-achiral domains, with the alkyl chains oriented perpendicular to the tape axis. This situation, which causes pseudo-centrosymmetry, is caused by the promiscuity of the chiral alkyl chain terminus, which apparently is ambivalent whether it has its methyl or ethyl group oriented towards the surface (a similar situation was seen in quasi-enantiomorphous domains formed by an enantiopure liquid crystal[33]). It seems that the complex formation with bipyridine resolves this problem by forcing the alkyl group to adopt an angle to the supramolecular tape axis. While spontaneous resolution is tremendously favoured over racemic

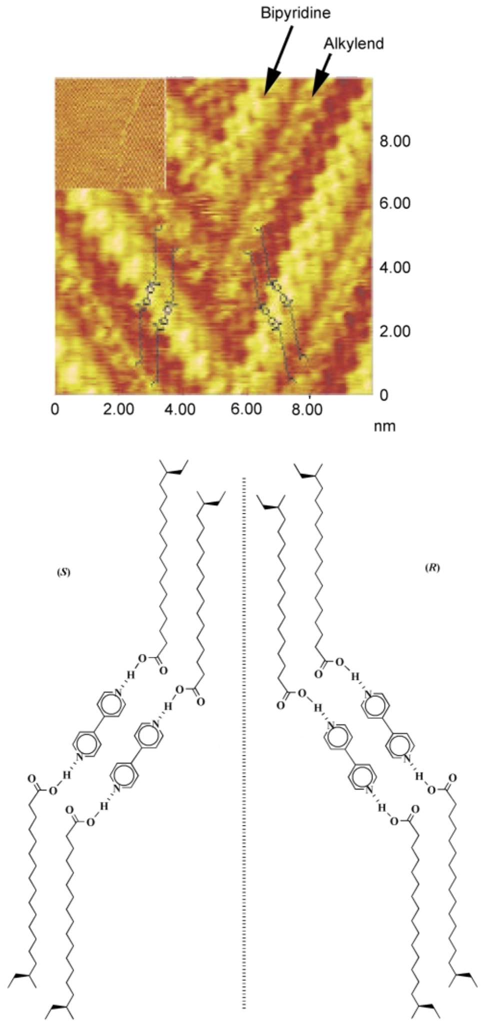


Fig. 19 STM image of a 2:1 mixtures of (*RS*)-16-methyloctadecanoic acid and bipyridine in phenyloctane at the graphite surface, and a representation of the possible supramolecular structure in the conglomerate.[37]

compound formation at the graphite surface, this phenomenon does not always preside[34] and is apparently strongly determined by the angle formed between the supramolecular tape axis and that of the carbon surface.

It should be taken into account that in many of the examples of spontaneous resolution observed using STM, the evidence for the phenomenon is based on the observation of an oblique lattice symmetry. In the cases where the images are not of sub-molecular resolution, a cautionary tale has been told in which chiral disorder was revealed in a report of Langmuir-Blodgett layer undergoing resolution of diastereomeric salts,[38] in which refinement of monolayer crystal structures complemented by lattice energy calculations were suggested to aid in this difficult problem.

5 Self-assembled fibres

The self-assembly of organic molecules often produces microscopic helical fibres, usually in a stereospecific way as a result of the presence of a stereogenic centre in the amphiphile.[39] Changes in morphology are often observed, from helical fibres for pure enantiomers to platelets for the racemates.[40] However, there are notable cases where helical aggregates are formed from achiral molecules, which constitutes the formation of enantiomorphic fibres. One of the most spectacular of these arises when achiral amphiphilic derivatives of the well-known melamine–barbituric acid supramolecular system are self-assembled in chloroform.[41]

When an equilibrated dispersion of the mixture of the two components (Fig. 20) in chloroform was evaporated and stained with an ethanol/water solution of uranyl acetate, supercoiled fibres were observed by tunnelling electron microscopy with dimensions of approximately 10 μm length by 300 nm diameter. Both left and right-handed supercoils were observed. A number of control experiments indicate that it is the polar solvent that causes the transformation. While the exact structure of the fibres is not clear, the alkene moiety in the barbituric acid derivative makes the hexamer non-centrosymmetric, and π–π stacking does seem to be involved in supporting the chiral arrangement which could arise from stacked discs or a helical chain.

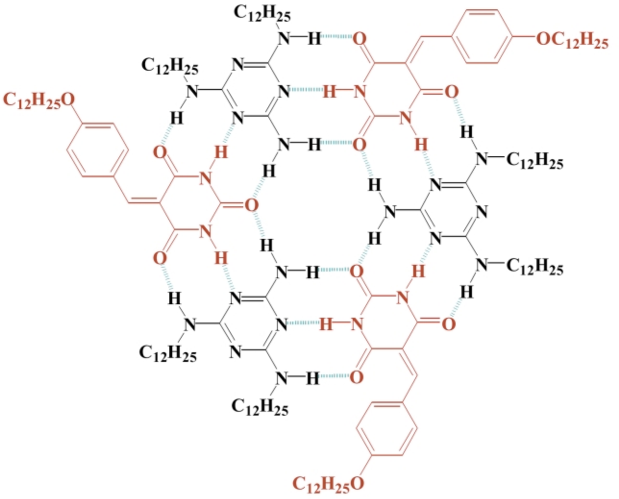
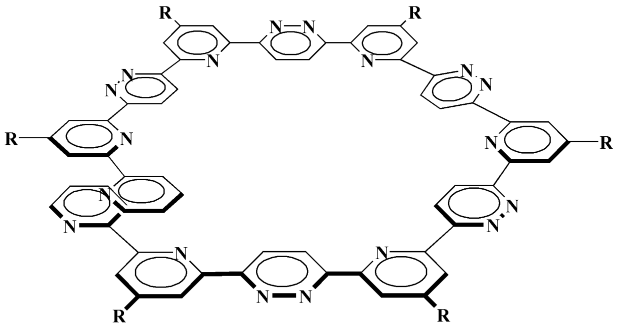


Fig. 20 The rosette aggregate proposed as a supramolecular component in helical supercoils of the mixture of the barbituric acid and melamine derivatives depicted.[41]

The molecule **24** exists in a helical conformation in solution, thanks to the preferential *transoid* conformation of the 2,2′-bipyridine subunit, and also expresses its helicity into the nanometre scale.[42] The molecules aggregate through π–π stacking interactions in dichloromethane and pyridine to give helical fibres, as observed by freeze fracture electron microscopy. The images reveal helical fibres of about 80 Å diameter, which are ‘probably composed of coiled-coil bundles of two or three single supramolecular stacks’.[42] In one image, produced from a dichloromethane solution, a predominance of fibres of one chirality was observed, which the authors hypothesised could arise from induction by seeds generated during the sonication process used in the preparation of the samples. More well-resolved helices, either right or left-handed, were observed when pyridine was used as solvent.



24 (R = S-*n*Pr)

Supramolecular sheets can also deform into helical ribbons if small distortions appear in the almost 2D structures. Such is the case for gels of achiral bisureas (such as **25**, Fig. 21), which form aggregates on account of strong bifurcated hydrogen bonds between the carbonyl oxygen atom and the NH hydrogen atoms.[43] The compounds form gels in tetralin in which helically twisted fibres are observed, either right or left-handed. In butyl acetate even stronger twisting is observed. It appears that this bending present in the supramolecular ribbons formed by the molecules within the sheets, which are tilted with respect to the normal to the sheet plane (as are the banana-shaped molecules in their smectic mesophase, *vide supra*), is at the root of the bending.

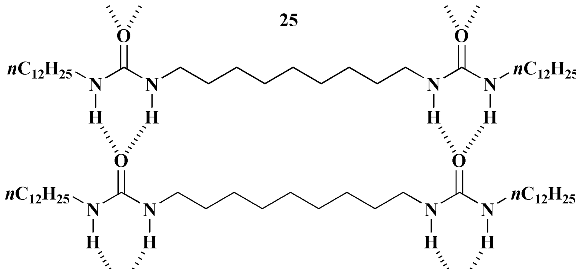
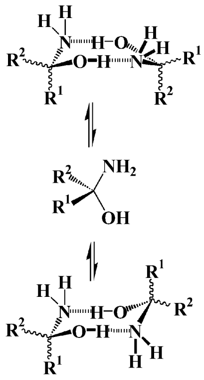


Fig. 21 Hydrogen bonding in the ribbons formed by **25**.[43]

6 Zero-dimensional aggregates

In principle, aggregation, or ‘self-assembly’, of molecules in any medium can give rise to achiral aggregates, or any of the three types of racemates. For example, racemic contacts of tartaric acid in aqueous solution are less favourable than those of the enantiopure compound. An interesting set of recent *ab initio* calculations on dimers of various α-amino alcohols (which exist in two possible conformations, see Fig. 22) has revealed the influence that media can have on the stereoselectivity of non-covalent interactions.[44] The results indicate that in the gas phase the racemic dimers are always favoured over their homochiral counterparts, independently of the substitution at the stereogenic carbon atom. However, when the dimers are immersed virtually in water the calculations predict



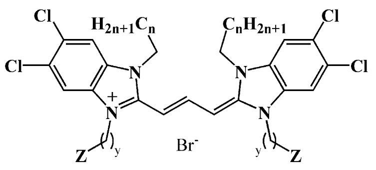
		Most Stable	
X	Y	Gas	Water
H	F	*RS*	*RS*
H	CH_3	*RS*	*RR SS*
H	CF_3	*RS*	*RR SS*
F	CH_3	*RS*	*RR SS*
CH_3	CF_3	*RS*	*RS*

Fig. 22 The possible structures of the α-amino alcohols with substituents R^1 and R^2, and the *ab initio* calculated most stable dimers.[44]

that for three of the five compounds the homochiral dimers become the thermodynamically preferred aggregate.

The conglomeration of enantiomers in solution is, however, not necessarily an indication that a crystalline conglomerate will be favoured. This is indeed the case for tartaric acid, for which the crystalline racemic compound is more stable than the conglomerate.

Aggregates of achiral molecules have been shown to spontaneously resolve *and* generate an enantiomeric excess of one of the chiral supramolecular assemblies. A family of benzimidocyanine dyes (**26**) shows spontaneous generation of chirality in dilute basic aqueous solutions.[45] The chirality is observed when measuring the CD spectra of the dyes *J*-aggregates (named after one of their discoverers, Jelley), which present optical activity in the two absorption bands (a Davydov-split band) shifted to long wavelength with respect to the longest wavelength band of the non-aggregated molecule. If the dyes are dissolved in ethanol in which they are isolated molecules, and dilute aqueous NaOH is added, the induction of chirality is optimum. Proof that the CD spectra observed were not artefacts (linear dichroism) was achieved by embedding the aggregates in a polymeric matrix and observing the spectrum at defined angles.[46]



26 (Z = COOH, SO_3Na, n>6, y =2,3)

The sign of chirality shows a statistical plus–minus distribution. The formation of the chiral aggregates is reversible by warming or cooling the sample, the effect of which is to form a different achiral aggregate. This effect bears witness to the equilibrium state of the system, and might point to a type of spontaneous resolution either as a result of multiple nucleation centres or under racemising conditions, where small chiral aggregate fragments break off a growing chiral supermolecule and initiates the growth of another larger supermolecule.

Mass spectrometry has also seen use in the determination of the stereoselectivity of aggregate formation.[47] For example, when serine is subject to electrospray ionisation mass spectrometry, octamers are observed. The stereoselectivity in the aggregate formation can be probed using mixtures of the ^{2}D analogue of one enantiomer and the ^{1}H form of the other, and these experiments indicate a preference for their homochiral diastereomer. Molecular modelling suggested a cubic type structure for the aggregate, which is maintained by a series of hydrogen bonds, and the cross sectional area of the calculated structure is very similar to that determined by ion mobility data.[47]

STM has provided evidence of spontaneous resolution of cysteine dimers on the Au(110) surface.[48] When deposited under UHV at low coverages the L and D isomers provide *M* and *P* dimers, respectively, with respect to the underlying chain of gold atoms. The racemic mixture generates dimers of both *M* and *P* type. While atomic resolution was not forthcoming, molecular modelling suggested that the cysteine is dimerised through its carboxylic acid groups and is stuck to the gold through its nitrogen and sulfur atoms. Once again, the enantiopure and racemic dimers correspond to diastereomers on the surface. A three-point model of enantioselectivity was implied to rationalise the stereoselectivity of dimer formation.

7 From 0D to 2D chirality

Along the length of this review we have whittled down dimensions, showing how spontaneous resolution can be observed at increasingly small scales, but perhaps one of the most intriguing and important questions in the area of stereochemistry in general with special relevance to spontaneous resolution is in the other direction: How is chiral preference at the molecular level passed from the molecule up to the macroscopic system? Surely the answer will be dependent on the nature of the media concerned, but STM studies reveal in a unique way this type of information, at least as far as the second dimension. A stunning example is that of STM experiments on 1-nitronaphthalene physisorbed onto the reconstructed Au(111) surface (which is built up of alternating fcc and hcp stacking uniaxial domains, with direction changes denoted as elbows).[49] When the 1-nitronaphthalene is adsorbed in UHV and the surface is cooled to 50 K at a coverage of 0.2 ML, 0D aggregates are formed at the fcc elbows which are approximately 85% decamers of either left (L) or right (R) handed nature, and thus spontaneous resolution has taken place at the aggregate level (Fig. 23). The decameric clusters represent a thermodynamic minimum, since the molecules are deposited near room temperature where diffusion is fast and then the system is cooled down. Hence the narrow distribution of aggregate size and location (although tetramers and undecamers are also observed, and the decamers sporadically appear in hcp domains).[49]

Not only can chiral decamers be observed, but they can also be sorted into areas of the surface, a molecular level triage with the STM tip![49] The decamers retain their chirality during the process (Fig. 23). High resolution images[50] aided by calculations do infer that while the aggregates are globally chiral, both enantiomers are present in an 8 : 2 ratio, on the outer ring and the core, respectively (Fig. 23). The non-covalent interactions holding the aggregate together appear to be hydrogen bonds between the oxygen atoms of the nitro-group and hydrogen atoms attached to the aromatic rings. Also, no less noteworthy is the fact that the tetramers are also chiral, each molecule being of the same stereochemistry (Fig 23).

When coverage is further increased (to 0.3 ML) STM implies that chains of molecules are formed which exist as a head-to-tail homochiral dimer, in a tape-type structure predominantly in the fcc domains of the gold.[49] At 0.4 ML coverage, kinks in the chains are observed (Fig. 24), and at full coverage, both these 1D tapes and extended 2D domains are formed. At the lower coverages in the homochiral tapes, occasionally R molecules are observed in an L chain (about 2% at low coverage), so that the terms ‘conglomerate’ or ‘pseudoracemate’ become a grey area! The molecules with opposite chirality to the majority of the chain are twisted by approximately 25° to the others, and permits hydrogen-bonding to the ‘back’ of a molecule in an adjacent chain. As coverage is increased, defects increase, and

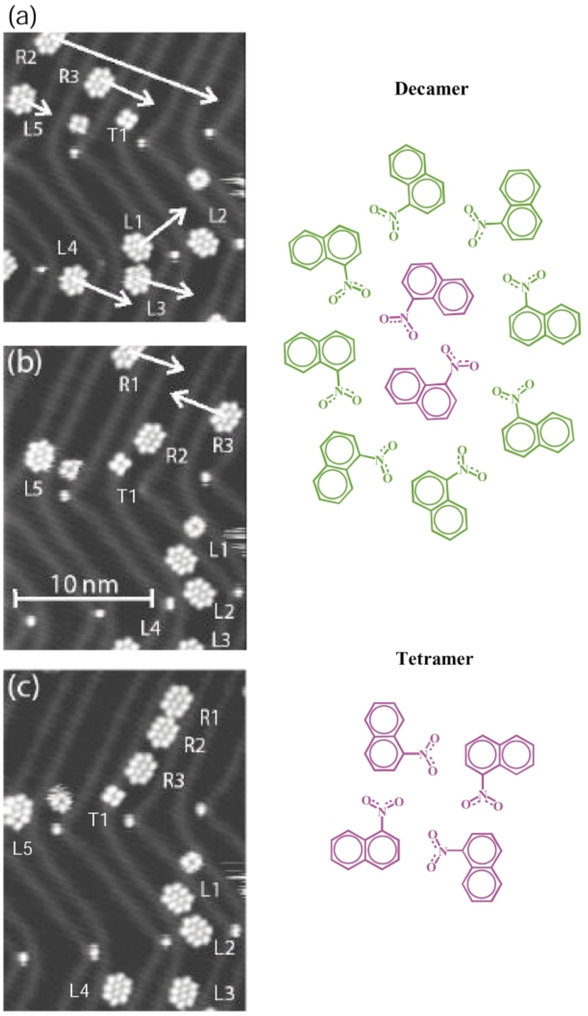


Fig. 23 Molecular triage! STM images of the decamers of 1-nitronaphthalene on the Au(111) surface and their sorting into left and right-handed aggregates using the STM tip, and a representation of the structure of the decamers and tetramers. (a) Before manipulation, the arrows indicate the movement of the supermolecules. (b) An intermediate stage of sorting. (c) The L decamers arranged at the bottom of the fcc domain and the right handed ones at the top! Note also the presence of a homochiral tetramer (T1).[49]

should these defects coincide, they cause a kink in the chain (mainly in fcc domains of the surface), as indicated in Fig. 24.

As coverage is increased to one ML, the compound forms principally a racemate in the fcc domains, and conglomerate in the hcp domains of the surface. Thus, there is imaging of the transition from conglomerate (at low coverage) to racemic compound (at high coverage). The phenomena were interpreted in terms of competing factors: (i) electrostatics which favour interactions amongst like enantiomers, and (ii) the stronger adsorption of the organic molecule to fcc domains. Another interesting observation is that the 2D racemic compound formed in the fcc domains of the gold are more dense than the double chains, and the hydrogen bond exists between the two surface enantiomers.

Transfer of chirality has also been observed under similar conditions (UHV on a noble metal surface) in the formation of homochiral twin chains of 4-[*trans*-2-(pyrid-4-yl-vinyl)]benzoic acid (Fig. 25).[51] The molecules are chiral on the surface as a result of the orientation of the central double bond with respect to the long axis of the molecule, and the chains are formed by hydrogen bonding between the acid and pyridine moieties. The twin chains are held together through weaker carbonyl oxygen atom to aromatic C–H groups. Remarkably, the homochiral chains form homochiral gratings over micrometer scales on the surfaces of gold(111) and silver(111), in the face of the large distances between the twin chains (2.5–5 nm) in the domains. The source of the transfer of chirality during the growth of the

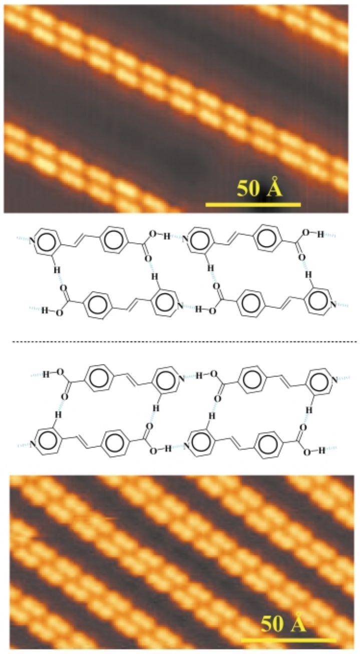


Fig. 25 Schematic representation of the surface stabilised enantiomeric twin chains of 4-(*trans*-2-(pyrid-4-yl-vinyl))benzoic acid and the observed STM images of the compound on Au(111) and Ag(111).[51]

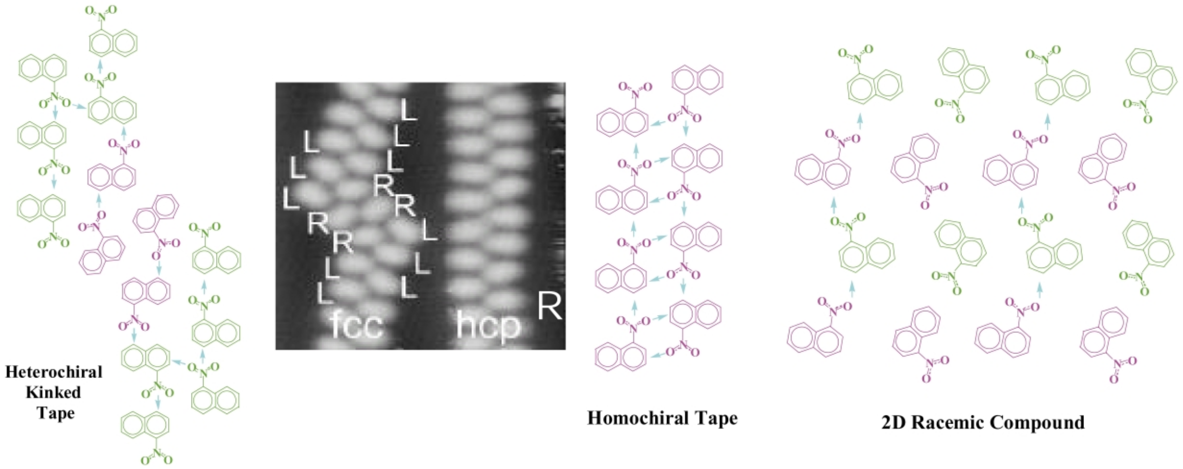


Fig. 24 An STM image of 1-nitronaphthalene on Au(111) (0.4 ML coverage) and representations of the kinked chains and the homochiral tapes, which at ML coverage convert into the 2D racemic compound in the fcc domain of the surface, whose packing is schematised.[49]

domains appears to be in the formation of metastable triple chains, which deviate away from the template chain, and initiate the growth of a new parallel one of like chirality to the original.

8 Conclusion and outlook

Spontaneous resolution can now be rationalised from the interactions between small aggregates of molecules up to macroscopic systems such as crystals in which studies were previously limited. It is tempting to speculate that if the pathways of chirality transfer in this hierarchy of scales can be mapped out using the powerful analytical and computational tools at the scientist’s disposal today, we may one day be able to answer reliably what is today an unanswerable question: Will a given compound form a conglomerate or a racemic compound? We are in a position where we are able to explain (at least partially) spontaneous resolution appealing to thermodynamic arguments, in which non-covalent bonds play such an important role. Progress is being made in crystal structure prediction.[52] Perhaps when this can be done, we will be able to use and control, rather than simply involve, supramolecular chemistry and particularly the “self-assembly paradigm (which) relies upon the mutual recognition that exists between complementary molecules and ions through non-covalent bonding interactions”[53] to effect spontaneous resolution.

Immediate challenges that remain to be addressed include the observation of conglomerates of racemic amphiphiles, and the evaluation of the stereospecificity of spontaneous resolution in LCs. As far as application of spontaneous resolution are concerned, crystals will remain important in both the purification of enantiomers as well as in the isolation of chiral catalysts, while liquid crystals displaying the phenomenon present interesting material properties, such as electro-optic switching. It is not so clear at present how one could make use of spontaneous resolution at a surface, where domains of *M* and *P* and *R* and *S* coexist in different but proximal domains: In the nano-age, with chemistries carried out at locally ever smaller scales using physical techniques, who is to predict what can or cannot be done?

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