# Supramolecular chirons

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The most practical method for obtaining enantiomerically pure compounds on a laboratory and industrial scale is the optical resolution of racemates through diastereomeric salt[1]. However, the procedure is tedious and capricious. The number of steps involved is large, the maximum theoretical yield is only 50%, and the undesired enantiomer has to be either recycled or discarded. The exact experimental conditions have to be arrived at by trial-and-error because the chemical basis for the fractional crystallization of a particular diastereomer is not properly understood. The other method for obtaining enantiomers is mechanical separation of chiral crystals. Discovered by Pasteur[2] a century-and-a-half ago, success in this approach has been even slower. This article discusses developments on the former approach: how to obtain the enantiopure molecule from a racemic mixture of the compound? While there have been studies to design new chiral host compounds[3] to correlate the efficiency of resolution with crystal structures of less and more soluble salts[4] and to examine the role of the solvent[5], there are as yet no general and globally applicable criteria for the selection of a particular resolving agent, solvent, and crystallization conditions for a given substrate. The exact boundary conditions for the fractional crystallization of a particular diastereomer are guided by the experience of chemists. Even so, the empirical rules have limited applicability and are valid only within a family of structures. Many of the thumb rules for efficient resolution are part of the classified information with pharmaceutical companies and may never be disseminated in the public domain.

The recent paper of Hanessian *et al.*[6] disscusses the rationale for enantiodifferentiation during self-assembly through a detailed understanding of molecular recognition between chiral diamines and chiral diols. From an analysis of the dozen or so crystal structures of amine–alcohol complexes (supraminols, Figure 1), the authors are able to predict structures of the best-matched pairs of diamines and diols through the notion of *supramolecular chirons*. Thus, supramolecular chiron is 'the minimal homo- or heterochiral molecular unit or ensemble capable of generating ordered superstructures by self-assembly through hydrogen bonding or other noncovalent forces, and leading to topologically distinct enantio- or diastereopure architectures'.

In what way is the Hanessian approach superior to related papers published recently? Saigo *et al.*[4] have examined the resolution of 2-arylalkanoic acids with (1*R*,2*S*)-2-amino-1,2-diphenylethanol. Crystal structures of the less soluble salts have a chiral columnar hydrogen bond arrangement of O–H···O and N–H···O bonds formed by ammonium hydrogens and carboxylate oxygens, reinforced by electrostatic forces between the charged ions. The structure includes a water molecule which is bonded to the columnar structure through short O···O contacts. There are no strong interactions between the polar, hydrogen bond columns except weak hydrophobic, van der Waals inter-

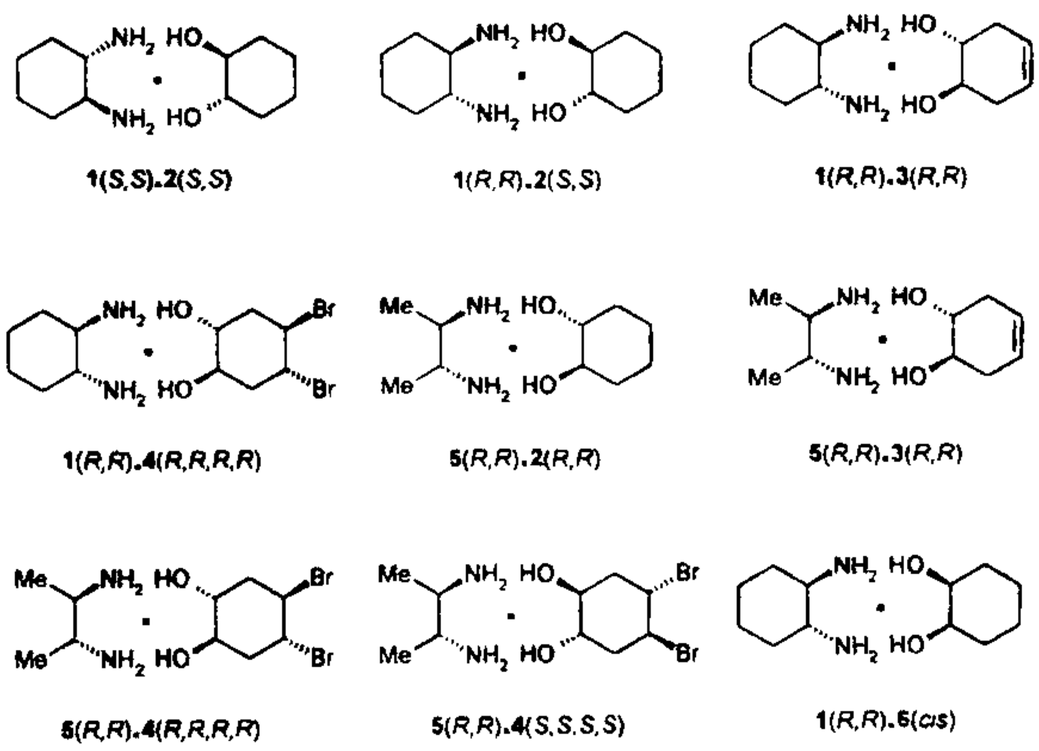


**Figure 1.** Some vicinal diamines and vicinal diols comprising carbocyclic and alicyclic structures and their adducts.

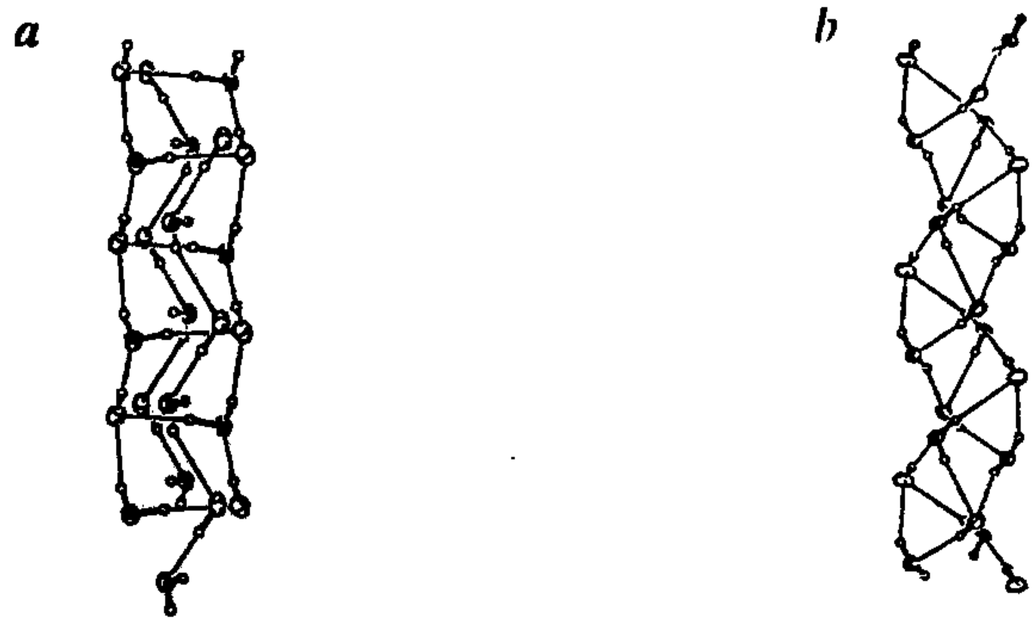


**Figure 2.** Two types of supramolecular chirons in the crystal structures of supraminol adducts. ***a***, 1(*R*,*R*)·2(*R*,*R*); ***b***, 1(*R*,*R*)·3(*R*,*R*). Motif ***a*** is pleated-sheet staircase and ***b*** is right-handed ribbon structure (Reproduced with permission of the author, ref. 6).

actions. The packing motif in the more soluble complex is similar with comparable O···O and N···O distances except that the water molecule is absent in the polar domain. While the authors ascribe the additional hydrogen bonding by the inclusion of water in the crystal as a reason for the lower solubility, this does not significantly improve our understanding of selective crystallization. The phenomenon of hydration in crystals is not properly understood in terms of when water is included, for what reasons, and its exact role on the solubility of the crystal. Moreover, comparison of the stability of a crystal and its hydrate is non-trival because the constituents are different. In another study, optical resolution of *trans*-chrysanthemic acid with (1*R*,2*R*)-1-(4-nitrophenyl)-2-dimethylamino-propane-1,3-diol[5] was found to be dramatically enhanced when either pure methanol is used for crystallization (93% optical purity) or when methanol is added to ether-type solvents ($Et_2O$, THF, MTBE, *i*-$Pr_2O$; 91–99%). The authors postulate that hydrogen bonding of the acid–diol complex with methanol promotes nucleation and crystallization of the less soluble diastereomer. It is not clear from the paper why methanol works and another alcoholic solvent, say ethanol or *iso*-propanol gives no crystals. This is a general problem in resolution chemistry – the results of one system cannot be extended to a related substrate.

In three papers during the last five years, Hanessian *et al.*[6–8] have analysed the crystal structures of 1:1 complexes of chiral, C2-symmetric, vicinal diamines and diols. In the crystalline adduct of (1*S*,2*S*)-1,2-diaminocyclohexane and (1*S*,2*S*)-1,2-cyclohexanediol (**1***SS*·**2***SS*), the cyclohexane rings align into four vertical columns and the polar hydrogen bonding groups face inward. The structure is a pleated sheet-like array of eight-membered, square planar hydrogen bonded units in which the oxygen and nitrogen atoms are tetracoordinated. The remaining hydroxy and amino functional groups are engaged in two symmetrical side rows of tricoordinated zigzag hydrogen bond patterns which flank opposite sides of the central octagonal staircase core. The crystal structure of the 1:1 adduct of (1*R*,2*R*)-diamine and (1*S*,2*S*)-diol (**1***RR*·**2***SS*) is gratifyingly predictable and virtually identical to the structure of the homochiral complex. Interestingly, chirality of the diol and diamine components controls the tertiary structure of the complex, that is the (*S*,*S*)-diamine and (*S*,*S*)-diol have a left-handed helicate while the (*R*,*R*)-diamine with the same diol produces a right-handed helicate. The crystal structures of other C2-symmetric vicinal diamines and diols in Figure 1 have pleated-sheet staircase-like or right-handed ribbon-helicate hydrogen bond architectures. A common theme in this family of enantiomorphous structures is the connection between molecular functional groups and their crystal packing motifs, thus opening avenues for future design and optimization. A high degree of predictability is ascribed to the supramolecular chirons displayed in Figure 2. These recurring hydrogen bond helicate motifs in supraminol adducts could provide the key to our understanding of enantio- and diastereodifferentiation during crystallization.

What is the origin of supraminol self-assembly? The ready formation of amine–alcohol adducts may be understood from the mutual recognition of complementary hydrogen bonding donor–acceptor groups in the components: $NH_2$ has 2 donors and 1 acceptor while OH has 1 donor and 2 acceptor groups. Thus, in a 1:1 supraminol the tetracoordinated network is saturated at both the heteroatoms through one O–H···N and two N–H···O hydrogen bonds[9]. The authors propose that enantiodifferentiating recognition between a diamine and a matching diol partner produces a thermodynamically stable architecture in a single step, or alternatively, matching diol (or diamine) molecules insert in the lattice of diamine (or diol) to produce the coordinatively saturated network. This was verified through competition experiments.

When (1*R*,2*R*)-cyclohexane diamine is heated with racemic *trans*-1,2-cyclohexane diol, the homochiral (*R*,*R*)·(*R*,*R*)-complex (**1***RR*·**2***RR*) crystallizes out while the heterochiral (*R*,*R*)·(*S*,*S*)-pair (**1***RR*·**2***SS*) remains in the mother liquor. In practice, the (*R*,*R*)-diol could be obtained from the racemic *trans*-diol in 98% enantiomeric excess. This and related experiments show that the homochiral adducts consist of the preferred (and therefore stable) chiron combination given the diol partner selected by a particular diamine during crystallization. Further, in the structure of achiral *cis*-1,2-cyclohexane diol and enantiopure *R*,*R*-diamine a markedly different hydrogen bonding network (or supramolecular chiron) is formed with two diamine and two diol moieties in the asymmetric unit. Notwithstanding the detailed analysis of many closely related crystal structures, it is not possible to say definitively whether the observed packing features are a result of kinetic factors or thermodynamic stability. A major limitation in making such predictions based on crystallization properties is that though melting point and crystal density generally correlate with solubility, connection between crystal energy and solubility can be tenuous.

Hanessian *et al.*'s study is notable for several reasons: (1) It is the first systematic analysis of closely related enantiomorphous crystal structures, their crystallization behaviour, and their hydrogen bonding patterns; (2) The stereochemical information encoded in the molecule is reflected in the recognition motifs of complementary functional groups; (3) Crystal structures of the matched homochiral supraminol adducts are analysed via the newly introduced concept of supramolecular chiron. In summary, the authors provide a rational and improved interpretation of a classical phenomenon using contemporary ideas. Applications of these ideas for enantiomer enrichment, resolution and design of chiral auxiliaries should be forthcoming in the near future.

The genesis of supramolecular chiron lies in its covalent sibling, chiron, a term introduced by Hanessian more than a decade ago to logically synthesize enantiomerically pure molecules from the chiral pool[10]. With a shift in paradigm from the molecule to the supermolecule in the nineties, the conceptual relationship between crystal engineering and organic synthesis has been proposed through another new term 'supramolecular synthon'[11]. Synthons are structure-directing motifs involving non-covalent bonds and contain the logic code for self-assembly in the solid state. In effect, supramolecular chirons are the chiral counterparts of supramolecular synthons. Thus, (supramolecular) synthons and chirons

play the same focusing role in the synthesis of target crystal structures (supermolecules) that (molecular) synthons and chirons have in the synthesis of complex natural products (molecules). All these exciting developments project that the challenge for organic chemists in the new millennium will lie in understanding and controlling another type of bond, the hydrogen bond.

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# Do our maternal and paternal genes pull us in different directions?

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In all diploid organisms such as ourselves, each individual inherits one set of chromosomes from the mother and another set from the father. It is generally assumed that once these chromosomes reach our bodies, they lose any 'memory' of where they came from. However there is evidence that chromosomes (and the genes they contain) sometimes get differentially imprinted as they pass through a male or female body and this imprint may be retained when the chromosomes are passed on to the next generation[1–6]. There is also evidence that DNA methylation is a mechanism by which chromosomes may acquire such male-specific or female-specific imprints. Differential patterns of DNA methylation are known to lead to different levels of gene expression[7–10]. What all this means then is that our paternally derived genes and maternally derived genes may behave differently in our bodies even though they may be otherwise identical. To the extent that genes influence our behaviour it may well be that our father's genes and mother's genes pull us in different directions.

In 1992, David Haig[11], then at the University of Oxford, pointed out that such a possibility has serious consequences for the standard predictions of sociobiological theory which is based on the assumption that paternal and maternal genes do not behave differently. Let us consider two examples. In insects that belong to the order Hymenoptera (ants, bees, wasps) females can lay both unfertilized, haploid eggs as well as fertilized, diploid eggs. The fertilized diploid eggs develop into diploid adult females whereas the unfertilized haploid eggs develop into haploid adult males. Since males are haploid, they produce sperm that are clones of each other. The females, being diploid, produce haploid eggs that receive a randomly chosen 50% of the maternal genome. In such haplodiploid insects, two sisters would be related to each other by a coefficient of genetic relatedness $r$ of 0.75 but a female would be related to her offspring by the usual 0.5 (as in diploid species) (Figure 1). In 1964 W. D. Hamilton[12,13] pointed out that such asymmetries in genetic relatedness should select for altruistic behaviour on the part of females to care for their sisters rather than to produce their own offspring. This is indeed what workers (who are females) in many social insect colonies do. In 1976 Trivers and Hare[14] pointed out that although workers are more closely related to their sisters ($r = 0.75$) they are much less related to their brothers ($r = 0.25$), as compared to their offsp ($r = 0.5$). They predicted there

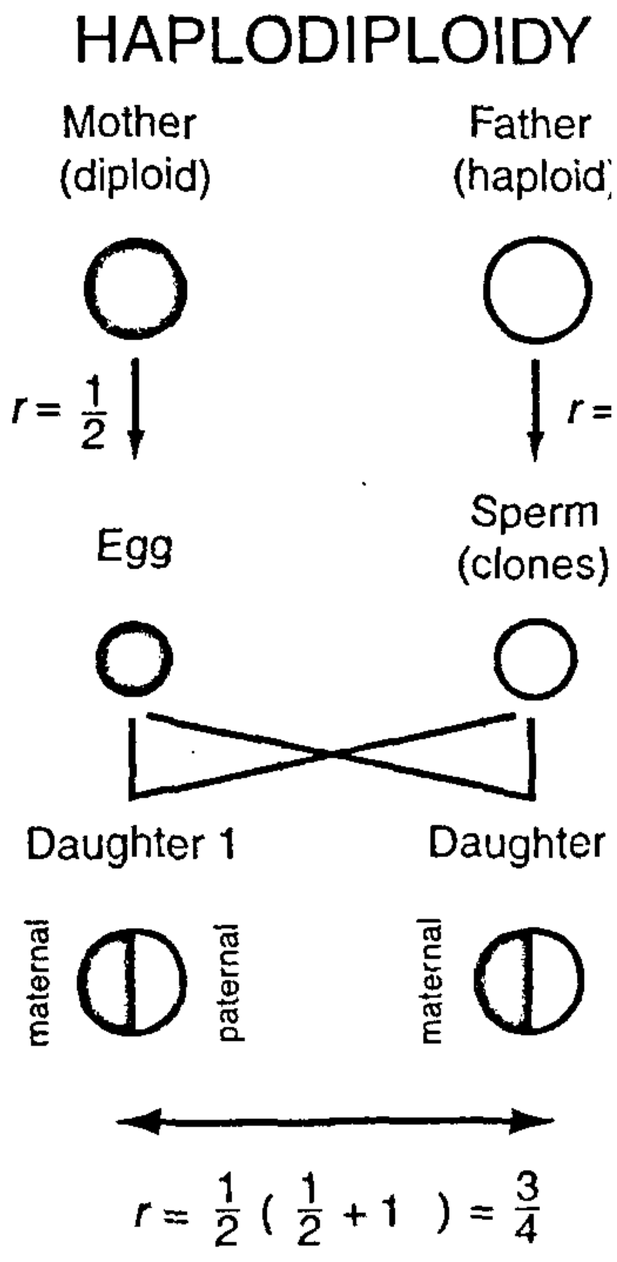


**Figure 1.** Genetic relatedness u haplodiploidy (see text for details).