p_1,n_1 Salts: self-assembled supramolecular structures sequestering racemates. Diastereomeric separation and enantiomeric enrichment of *trans*-chrysanthemic acid†

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The occurrence of p_1,n_1 salts can be exploited to sequester racemates; an application to technical mixtures of chrysanthemic acids (ChA) allowed the separation of *trans*- and *cis*-ChA and the recovery of the excess enantiomer of *trans*-ChA.

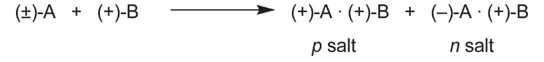
Since its original discovery by Pasteur in 1853,[1] the most widely used method for obtaining enantiomerically pure compounds still remains the formation and separation of crystalline diastereomeric salts between racemic substrates and optically pure resolving agents[2,3] (Scheme 1).[4]

Despite being widely used for such a long time, this technique is far from being fully understood and predictable. It is not exceptional to find that a well-crystallized and poorly soluble mixture invariably affords the racemic substrate upon work-up, even after several recrystallizations. This failure has been ascribed[6] to the formation of a 1 : 1 double salt, a third salt originating from a stable 1 : 1 combination of the diastereoisomeric *p* and *n* salts (p_1,n_1 salt).[7] Herein, we demonstrate the structural characterization of a p_1,n_1 salt through single-crystal X-ray diffraction analysis[8] that shows its supramolecular architecture[9] and qualifies the salts as functional materials.[10]

We present here the results obtained from the salts that form between racemic *trans*-chrysanthemic acid[11,12] (*trans*-ChA) and pure enantiomers of *threo*-2-dimethylamino-1-phenyl-1,3-propanediol[13] (DMPP) (Fig. 1).

We show an innovative methodology based on p_1,n_1 salt formation to achieve: (a) an efficient and practical separation of *cis*- and *trans*-ChA isomers, and (b) the recovery of the excess enantiomer of *trans*-ChA from scalemic mixtures.

We prepared separately the diastereomeric *p* and *n* salt‡[14] by treatment of (1*S*,2*S*)-(+)-DMPP with a stoichiometric amount of, respectively, (1*R*,3*R*)-(+)-*trans*-ChA and (1*S*,3*S*)-(−)-*trans*-ChA in refluxing *i*Pr$_2$O. When equimolar amounts of these two diastereoisomeric salts were suspended in *i*Pr$_2$O and refluxed for one hour, a third solid having a completely different DSC profile was quantitatively obtained.[15]



$$(\pm)\text{-A} + (+)\text{-B} \longrightarrow \underbrace{(+)\text{-A}\cdot(+)\text{-B}}_{p\ \text{salt}} + \underbrace{(-)\text{-A}\cdot(+)\text{-B}}_{n\ \text{salt}}$$

Scheme 1 Resolution of a racemic acid (A) with an enantiopure base (B).

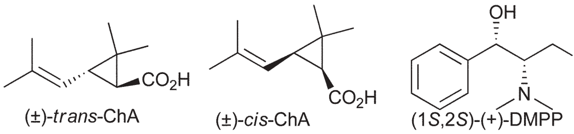


Fig. 1 (±)-*trans*-ChA, (±)-*cis*-ChA and (+)-DMPP structures.

Several recrystallizations of this salt failed to effect the enrichment in one of the diastereoisomeric *p* or *n* salts. From these crystals, racemic *trans*-ChA was always obtained, a result consistent with the p_1,n_1 salt.

Single-crystal X-ray diffraction analysis§[16] (Fig. 2) proved that this salt is not a mixture of the *p* and *n* salts. Rather, it is a new entity, the unit structure of which is made up of four components: one molecule of (+)-*trans*-ChA, one molecule of (−)-*trans*-ChA, and two molecules of (1*S*,2*S*)-(+)-DMPP, two molecules of the same base but with a different spatial disposition.

The unit cell of this crystal (Fig. 3) reveals its uniqueness. It hosts sixteen components: four (+)- and four (−)-*trans*-ChA units and eight (+)-DMPP regularly arranged in two compartments of the unit cell. The marked difference from the crystal structure of the *n* salt[15] is apparent from the hydrogen-bond network that keeps the crystal together. Here, each ChA unit is linked to two

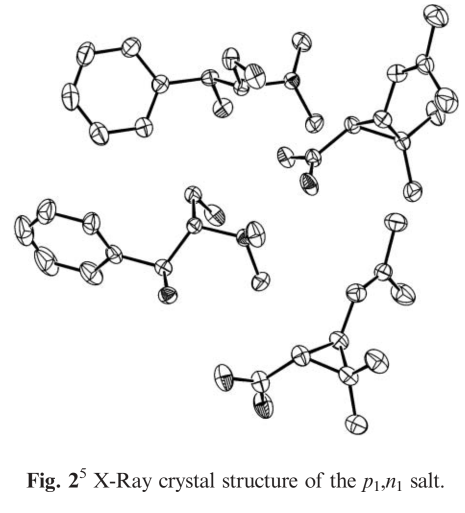


Fig. 2[5] X-Ray crystal structure of the p_1,n_1 salt.

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† Electronic supplementary information (ESI) available: Preparations, X-ray diffraction analysis data, characterization data, and DSC profiles of the three salts; procedures for the separation of racemic *trans*-ChA from *cis*-ChA and for the recovery of excess enantiomer of *trans*-ChA from scalemic mixtures. See DOI: 10.1039/b608405b

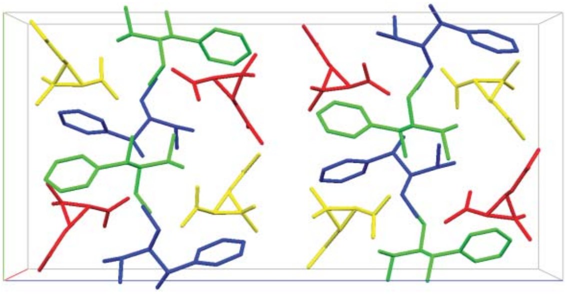

Fig. 3[17] Cell unit of the p_1,n_1 salt crystal.

DMPP units, while in the crystal structure of the *n* salt, each ChA unit is H-bonded to three DMPP units.

In the structure of the p_1,n_1 salt the hydrogen bonds act as the main glue among diastereoisomeric salts of the same species (*n* salts or *p* salts) driving a directional growth forming two different and diastereoisomeric H-bonded polymers (Fig. 4), the *n* and *p* tectons,[18] through H-bonds involving the secondary hydroxyl group of (1*S*,2*S*)-(+)-DMPP.

The two ribbon-like polymers stack on top of one another and are held in position by van der Waals type interactions (Fig. 5). Adjacent stacks of ribbons self-assemble in a "herring-bone" array through van der Waals forces.

van der Waals interactions and hydrogen-bonding play a crucial role in the supramolecular architecture of the p_1,n_1 salt crystalline structure. In fact, this structure could result either from the self-assembly of the *n* and *p* tectons, in a 1 : 1 ratio, or from the formation in solution of a "p_1,n_1 supermolecule" as the unit structure of the forming p_1,n_1 crystal. In both of these processes, similarity and complementarity are key features in determining the recognition and the self-assembly factors that determine the precipitation of p_1,n_1 salt crystals with a well defined and robust network of non covalent interactions. These kinds of interactions are known to be crucial in the formation and stability of inclusion complexes.[19]

p_1,n_1 Salt formation with (1*S*,2*S*)-(+)-DMPP is peculiar to the *trans* isomer of ChA. This turned out to be extremely useful, since most of the industrial syntheses of ChA produce mixtures of the *trans*- and *cis*-isomers. When (1*S*,2*S*)-(+)-DMPP (stoichiometric to *trans*-ChA) was added to industrial racemic mixtures of *trans*/*cis*-ChA, in refluxing *i*Pr$_2$O, all the (±)-*trans*-ChA immediately precipitated through the formation of the p_1,n_1 salt (86% yield, de > 96%), while (±)-*cis*-ChA remained in solution (Fig. 6).[15]

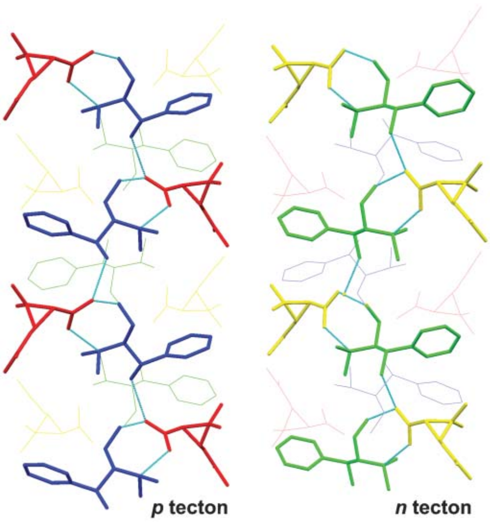

Fig. 4[17] The supramolecular ribbon-like polymers of the two diastereoisomeric *p* and *n* tectons in the p_1,n_1 salt viewed along the *a* axis. (H-bond network in cyan).

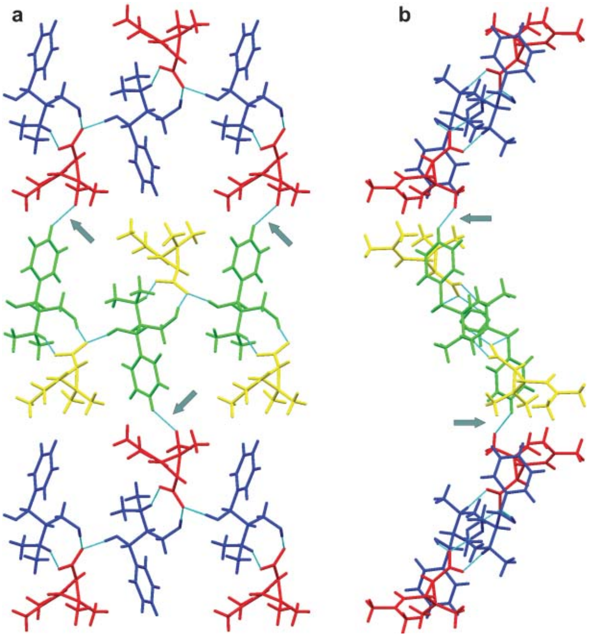

Fig. 5[17] Representation of a mono layer of alternating tectons along *a* and *b* axes. Arrows show shortest visible van der Waals interaction holding together adjacent stacks of ribbons, between the *p*-hydrogen atom of the aromatic ring (green) and one of the geminal methyls of (+)-ChA (red).

It is evident from the observations above that (1*S*,2*S*)-(+)-DMPP can be exploited as a "*sequestering agent*" of racemic *trans*-ChA through the formation of p_1,n_1 salts. So we addressed the question: what if, instead of racemic, we use enantiomerically enriched *trans*-ChA? Can the racemate be sequestered by formation of the p_1,n_1 salt, thus freeing the remaining pure enantiomer? (Fig. 7)

This would furnish an alternative solution in all those cases (academic and industrial) where asymmetric synthesis furnishes products that do not meet the required enantiomeric purity standards. One such case is *trans*-ChA which can be industrially

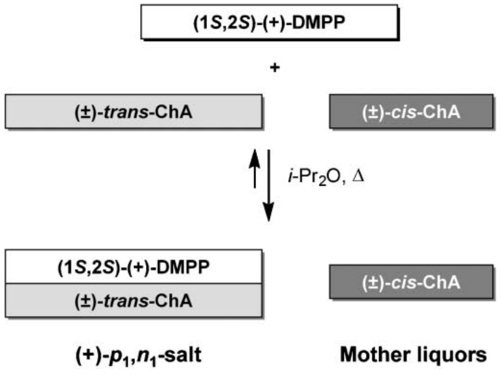

Fig. 6 Purification of racemic *trans*-ChA from a mixture of *trans*- and *cis*-ChA by selective p_1,n_1 salt formation with (1*S*,2*S*)-(+)-DMPP.

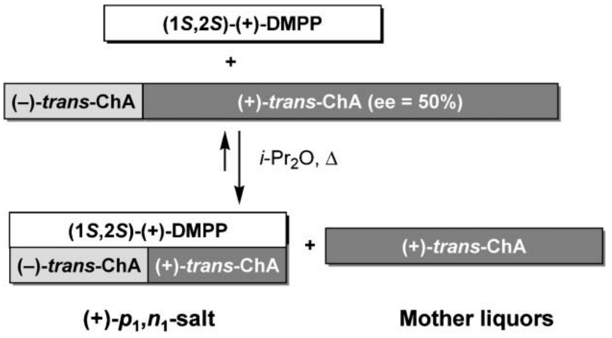

Fig. 7 Recovery of the excess enantiomer from an enantiomerically enriched mixture of *trans*-ChA through p_1,n_1 salt formation.

obtained by catalytic asymmetric synthesis through a variety of different procedures that afford the product with varying degrees of enantiomeric enrichments.[20]

In a set of experiments,[15] we treated samples having different enrichments in (+)-*trans*-ChA (ee's ranging from 50% to 90%) with (1*S*,2*S*)-(+)-DMPP, stoichiometric to the racemic *trans*-ChA present in the starting sample. The precipitation of p_1,n_1 salt occurred almost immediately. After filtration and standard work-up, the salt gave racemic *trans*-ChA, while mother liquors afforded (+)-*trans*-ChA in high ee's (96%). In all cases the enantiomerically pure base used can be recovered in nearly quantitative yields and reused.

In conclusion, we have reported the structural characterization of a p_1,n_1 salt that shows its unique supramolecular structure made up of four different components, two diastereoisomeric salts (*n* and *p*), built through self-recognition, self-assembly and replication processes.

Obtaining a racemate after several resolution attempts is always frustrating. However, the results reported here demonstrate that more attention should be paid to the occurrence of p_1,n_1 salts.[21] In fact, they could turn out to be extremely useful for the separation of stereoisomers: when starting from mixtures enriched in one enantiomer, their formation and precipitation allow the recovery from the solution of the excess enantiomer with highly improved ee values. These characteristics of p_1,n_1 salts demonstrate that they are functional materials.[10] We have revealed the p_1,n_1 structure of one particular system demonstrating: (i) that it is possible to obtain monocrystals of p_1,n_1 supramolecular compounds; (ii) that in our system, the two tectons (diastereoisomeric *n* and *p* salts) are arranged with very similar spatial dispositions; (iii) the importance of the flexibility of the linear chiral base, and its ability to assume two different conformations in the two different tectons in the p_1,n_1 salt crystal structure; (iv) the alternate disposition of the two tectonic ribbons *n* and *p* to demonstrate the importance of the similarity and the complementarity of the components of the supramolecular structure. Moreover, we have demonstrated the utility of the p_1,n_1 salt in a range of important separation applications, pointing out how very important it is to reflect upon many data reported in the literature, and to reassess several results that have been hastily depicted as failures.

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Notes and references

‡ CCDC 287292. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608405b

§ CCDC 276877. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608405b

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14 CCDC 287292 contains the supplementary crystallographic data for the *n* salt. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. $C_{11}H_{18}NO_2\cdots C_{10}H_{15}O_2$; M_r 363.48; orthorhombic, $P2_12_12_1$, a = 7.3883(8), b = 10.1582(11), c = 28.935(3) Å, V = 2171.6(4) Å^3, T = 293(2) K, Z = 4, $\mu(\mathrm{Mo_{K\alpha}})$ = 0.076 mm^{-1}, 27500 reflections collected; 6299 independent reflections; R_{int} = 0.046; $R[F^2 > 2\sigma(F^2)]$ = 0.056.

15 See Electronic Supplementary Information (ESI) for full details.

16 CCDC 276877 contains the supplementary crystallographic data for the p_1,n_1 salt. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. $C_{11}H_{18}NO_2\cdots C_{10}H_{15}O_2$; M_r 363.48; orthorhombic; $P2_12_12_1$; a = 11.1297(6), b = 13.4914(7), c = 28.0333(14) Å; V = 4209.3(4) Å^3; T = 293(2) K; Z = 8; $\mu(\mathrm{Mo_{K\alpha}})$ = 0.078 mm^{-1}; 45793 reflections collected; 9681 independent reflections; R_{int} = 0.045; $R[F^2 > 2\sigma(F^2)]$ = 0.042.

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