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# (±)-*trans*-1,2-Diaminocyclohexane crystallises as a conglomerate

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**(±)-*trans*-1,2-Diaminocyclohexane has been found to crystallise from *n*-hexane at –10 °C as a conglomerate (space group $P2_12_12$, $Z = 2$), which offers a possibility of resolving (±)-1 by an entrainment procedure, whereas (±)-1·$H_2SO_4$ forms heterochiral crystals (space group *Pbca*, $Z = 8$).**

The enantiomers of *trans*-1,2-diaminocyclohexane **1**[1] are commonly used in the synthesis of polydentate ligands, and their metal complexes, in turn, make available many useful enantiomerically pure compounds.[2–7] Easily available $D_2$-symmetric macrocycles based on the enantiomers of **1** display a high enantioselectivity as the host molecules.[7(b)] Moreover, a platinum(II) complex containing enantiomerically pure **1** (*ee* > 99%) and tetronic acid as ligands was described as a chiral anticancer drug.[8] Thus, simple and efficient methods for preparing enantiomers of **1** are of great interest.

Racemate (±)-**1** can be resolved through diastereomeric tartrates.[1,2,9–18] The crystal structures of the diastereomeric salts,[12(b)] as well as diastereomeric complexes of (+)- and (–)-**1** with 1*S*,2*S*-cyclohexane-1,2-diol, have been studied.[12(a),(b)] Note that, in $^{13}$C NMR spectra of the complex of optically pure **1** with a partly enriched diol, the signals of its enantiomers are observed in the ratio of intensities correlated to the enantiomeric composition.[12(b)] Racemic diols (*trans*-cyclohexane-1,2-diol, butane-2,3-diol, 1,2-diphenylethane-1,2-diol and 2,2′-dihydroxy-1,1′-binaphtyl) have been resolved by the crystallization of their complexes with (+)- or (–)-**1**.[7,12(b),13] Obviously, it is possible to resolve (±)-**1** through its diastereomeric complexes with optically active diols. Asymmetric[14] and biocatalytic[15] syntheses of the enantiomers of **1** have also been reported.

In this work, a possibility for the spontaneous resolution of **1** and its derivatives, as well as the resolution by entrainment, are considered.[16,17] The necessary condition is crystallization in the form of a conglomerate, so the question reduces to seeking conglomerates. First of all, our attention was attracted to the melting point of the enantiomer **1**, which is 30 °C as high as that of the racemic mixture (mp 14–15 °C). However, without knowledge of the melting phase diagram (which is not reported as we know), it is not a sufficient indication of the conglomerate formation of (±)-**1**. For example, the melting point of the enantiomer of mandelic acid is 12 °C higher than that of the racemic mixture but the latter crystallises as a stable racemic compound. At the same time, it was reported that upon crystallization of the partly enriched samples of (±)-**1** from the melt at +9 °C and –3 °C the optical purity of the precipitate increased by factors of 2 and 2.7, respectively, up to *ee* 94 and 87.5%.[11]

The crystallization of (±)-**1** in the form of a conglomerate was unambiguously confirmed by X-ray diffraction analysis of the crystals grown from *n*-hexane at –10 °C.† It was established‡ that (±)-**1** crystallised in a chiral space group ($P2_12_12$, $Z = 2$), and the molecule in a crystal takes up a special position ($Z' = 1/2$), so that the crystallographic binary axis 2 passes through the middle of the bonds C(1)–C(1A) and C(3)–C(3A) (Figure 1). The six-membered ring has a chair conformation with $NH_2$ groups in equatorial positions. The nitrogen lone pairs (lp) are synclinal in relation to the C–C bonds with the pseudotorsion angles lpN(1)C(1)C(2) and lpN(1)C(1)C(1A) equal to –69.6° and 51.2°, respectively. This is probably caused by the weak H-bonds N–H···N, which combine the molecules into homochiral layers parallel to the crystallographic plane *ab* (Figure 2). It should be noted that only one proton of the amino group participates in the H-bonding, whereas another one does not form shortened contacts.

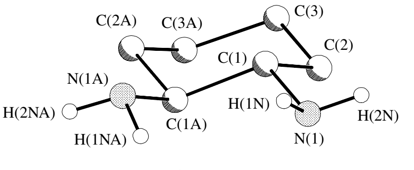

**Figure 1** The general view of **1** and the numbering of atoms. The bond lengths (Å): N(1)–C(1) 1.474(3), C(1)–C(2) 1.524(3), C(1)–C(1A) 1.534(4), C(2)–C(3) 1.524(4), C(3)–C(3A) 1.533(5); bond angles (°): N(1)–C(1)–C(2) 109.8(2), N(1)–C(1)–C(1A) 109.9(2), C(2)–C(1)–C(1A) 109.8(1), C(1)–C(2)–C(3) 111.3(2), C(2)–C(3)–C(3A) 111.0(2).

The data on the properties and X-ray analysis of the salts of (±)-**1** are limited. It is known that upon crystallization from $H_2O$ partly enriched (+)-**1**·2HCl forms a mixture of crystals; it con-

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† The NMR spectra were measured on a Bruker WH-400 spectrometer (400.13 MHz for $^1$H).

(±)-**1**: colourless transparent crystals suitable for X-ray analysis, obtained by crystallization from *n*-hexane at –10 °C. $^1$H NMR ($D_2O$) δ: 1.08 (m, 2H), 1.22 (m, 2H), 1.63 (m, 2H), 1.76 (m, 2H), 2.27 (m, 2H). $^{13}$C NMR {$^1$H} ($D_2O$ + $CD_3OD$) δ: 25.3 (β-$CH_2$), 33.6 (α-$CH_2$), 56.4 (CH).

(±)-**1**·$H_2SO_4$: bright transparent plates, mp > 350 °C, obtained by neutralization of (±)-**1** with $H_2SO_4$ in $H_2O$ followed by the slow cooling of the solution. $^1$H NMR ($D_2O$) δ: 1.35 (m, 2H), 1.51 (m, 2H), 1.81 (m, 2H), 2.15 (m, 2H), 3.38 (m, 2H). $^{13}$C NMR {$^1$H} ($D_2O$ + $CD_3OD$) δ: 23.8 (β-$CH_2$), 30.4 (α-$CH_2$), 53.2 (CH) [*cf.* $^1$H and $^{13}$C NMR spectra of **1**·HCl and tartrate, carbonate of **1** cited in refs. 4 and 12(*b*), respectively].

‡ *Crystallographic data for* (±)-**1** *and* (±)-**1**·$H_2SO_4$: at 110 K, the crystals of $C_6H_{14}N_2$ (±)-**1** are orthorhombic, space group $P2_12_12$, $a = 8.4382(8)$, $b = 5.2035(6)$ and $c = 7.7063(7)$ Å, $V = 338.37(6)$ Å$^3$, $Z = 2$, $M = 114.19$, $d_{\text{calc}} = 1.121$ g cm$^{-3}$, $\mu$(MoKα) = 0.69 cm$^{-1}$, $F(000) = 128$; the crystals of $C_6H_{16}N_2SO_4$ (±)-**1**·$H_2SO_4$ are orthorhombic, space group *Pbca*, $a = 9.6497(9)$, $b = 8.3133(8)$ and $c = 23.276(2)$ Å, $V = 1867.2(3)$ Å$^3$, $Z = 8$, $M = 212.27$, $d_{\text{calc}} = 1.510$ g cm$^{-3}$, $\mu$(MoKα) = 3.34 cm$^{-1}$, $F(000) = 912$. Intensities of 1757 and 20476 reflections were measured with a Smart 1000 CCD diffractometer at 110 K [$\lambda$(MoKα) = 0.71072 Å, ω-scans with 0.3° step in ω and 15 and 10 s per frame exposure, $2\theta < 58°$, $2\theta < 60°$ for (±)-**1** and (±)-**1**·$H_2SO_4$, respectively], and 832 and 2683 independent reflections ($R_{\text{int}} = 0.0503$ and 0.0396) were used in a further refinement. The structures were solved by a direct method and refined by the full-matrix least-squares technique against $F^2$ in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to $wR_2 = 0.1582$ and GOF = 0.917 for all independent reflections [$R_1 = 0.0644$ was calculated against $F$ for 620 observed reflections with $I > 2\sigma(I)$] for (±)-**1** and to $wR_2 = 0.1273$ and GOF = 1.049 for all independent reflections [$R_1 = 0.0553$ was calculated against $F$ for 2023 observed reflections with $I > 2\sigma(I)$] for (±)-**1**·$H_2SO_4$. All calculations were performed using SHELXTL PLUS 5.0 on an IBM PC AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2002. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/110.

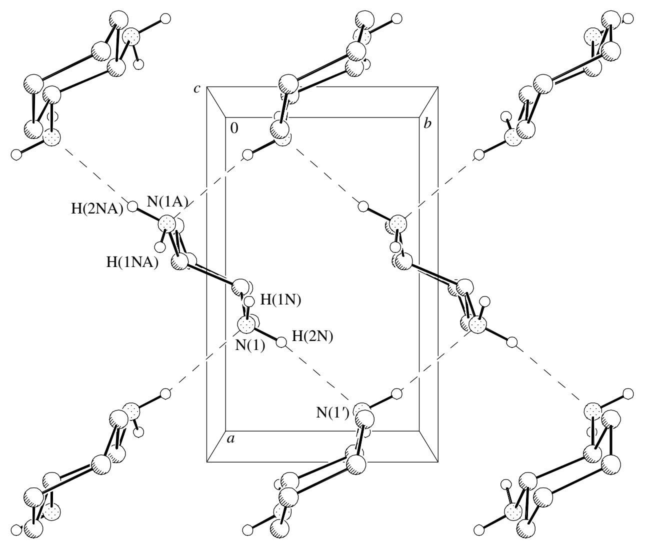

**Figure 2** H-bonded layers parallel to the crystallographic plane *ab*. Parameters of the H-bond: N(1)–H(2N)···N(1′) (–*x* + 3/2, *y* + 1/2, –*z* + 2): H(2N)···N(1) 2.39 Å, N(2)···N(1′) 3.257(3) Å, N(1)H(2N)N(1) 165°.

sists of the well-defined crystals of (+)-**1**·2HCl and feather-like crystals of (±)-**1**·2HCl.[10,11(*a*)] The salt of (±)-**1** with 3-(9-anthryl)-propionic acid contains solvate molecules of the solvent and crystallises in a centrosymmetric space group ($P\bar{1}$).[18] At present a systematic seeking for conglomerates among the higher melting salts of (±)-**1** with achiral acids (which are more suitable in terms of resolution) are being carried out.

Ethylenediamine sulfate is known to crystallise in a chiral space group;[19] therefore, an examination was performed with the monocrystal of (±)-**1**·$H_2SO_4$ obtained by crystallization from $H_2O$.[†] However, according to X-ray analysis,[‡] the above salt is a racemate (space group *Pbca*). Nevertheless, it is obvious that the crystallization of partly enriched **1**·$H_2SO_4$ is a simple way for increasing the optical activity (*cf.* ref. 8). Salt (±)-**1**·$H_2SO_4$ does not contain water molecules; its molecular structure is similar to the expected one (Figure 3). The protonation of $NH_2$ groups leads to a lengthening of N–C bonds up to 1.492(2) Å. Slight deviations in S–O bond lengths in the anion [1.468(1)–1.492(2) Å] may be caused by differences in the strength of the H-bonds formed by oxygen atoms.

The crystal structure of (±)-**1**·$H_2SO_4$ is built from H-bonded layers parallel to the crystallographic plane *ab*. Heterochiral layers have a cationic coat and anionic interlayer ($SO_4^{2-}$) connected by N–H···O bonds [N···O 2.755(2)–3.225(2) Å] (Figure 4). Apparently, the H-bonded layers are a sufficiently characteristic motive of the structure of **1**, which offers expectations of choosing the proper ‘filler’ for the layer in order to realise a homochiral self-assembling in a crystal.

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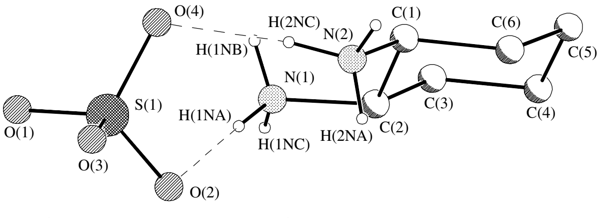

**Figure 3** The general view of (±)-**1**·$H_2SO_4$ and the numbering of atoms. The bond lengths (Å): S(1)–O(1) 1.468(1), S(1)–O(2) 1.477(1), S(1)–O(3) 1.481(1), S(1)–O(4) 1.491(1), N(1)–C(2) 1.493(3), N(2)–C(1) 1.496(2), C(1)–C(6) 1.530(3), C(1)–C(2) 1.530(3), C(2)–C(3) 1.531(3), C(3)–C(4) 1.530(3), C(4)–C(5) 1.524(3); bond angles (°): O(1)–S(1)–O(2) 110.20(9), O(1)–S(1)–O(3) 110.52(9), O(2)–S(1)–O(3) 109.62(8), O(1)–S(1)–O(4) 110.07(9), O(2)–S(1)–O(4) 108.31(8), O(3)–S(1)–O(4) 108.06(9), N(2)–C(1)–C(6) 108.2(2), N(2)–C(1)–C(2) 112.4(2), N(1)–C(2)–C(1) 113.0(2), N(1)–C(2)–C(3) 109.5(2).

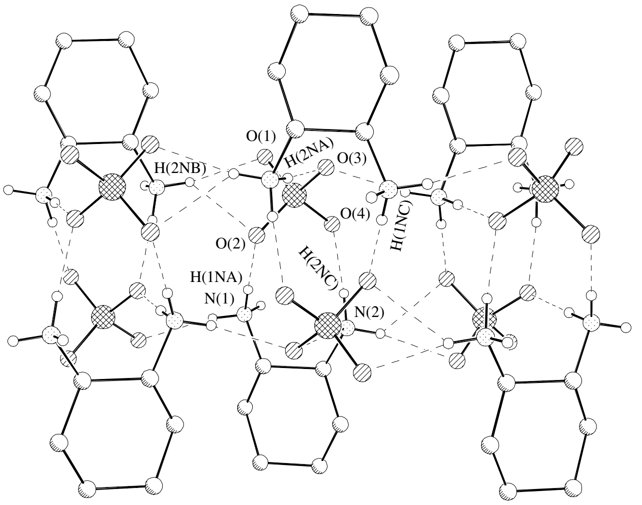

**Figure 4** H-bonded layers parallel to the crystallographic plane *ab* in (±)-**1**·$H_2SO_4$. Parameters of the H-bonds [N···H(Å), NHO(°), N···O(Å)]: N(2)–H(2NA)···O(3) (–*x* – 1, –*y* + 1, –*z* + 1) [1.92, 174, 2.792(2)], N(2)–H(2NA)···O(2) (–*x* – 1, –*y* + 1, –*z* + 1) [2.66, 124, 3.225(2)]; N(2)–H(2NB)···O(1) (*x* – 1/2, –*y* + 1/2, –*z* + 1) [2.02, 170, 2.856(2)]; N(2)–H(2NB)···O(2) (*x* – 1/2, –*y* + 1/2, –*z* + 1) [2.56, 123, 3.099(2)]; N(2)–H(2NC)···O(4) [1.89, 173, 2.818(2)]; N(1)–H(1NA)···O(2) [1.93, 178, 2.810(2)]; N(1)–H(1NB)···O(4) (–*x* – 1, –*y*, –*z* + 1) [1.89, 176, 2.755(2)]; N(1)–H(1NC)···O(3) (*x* + 1/2, –*y* + 1/2, –*z* + 1) [2.02, 168, 2.863(2)].

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