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Asymmetric three-coordinated nitrogen compounds: spontaneous resolution and absolute asymmetric synthesis[†]

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The spontaneous resolution of conglomerates of a dibenzo analogue of Tröger's base 1 and aziridine 2, as well as the second-order asymmetric transformation of (±)-1 into a single enantiomer were carried out for the first time.

The Pasteur's discovery stimulated the search for homochiral systems with stereogenic heteroatoms. Even during Pasteur's lifetime, questions were raised[2] whether asymmetric four-coordinated (J. Wislicenus, 1877) or three-coordinated nitrogen (A. Hantzsch, A. Werner, 1890) can exist. The positive answer for the former was found by the Pasteur-like separation of racemates of chiral ammonium salts both *via* diastereomeric salts and by spontaneous resolution.[2] As for the three-coordinated asymmetric nitrogen, the separation of numerous racemates was performed only with the use of chiral agents.[3]

In this work, we aimed at the spontaneous resolution of racemic compounds containing three-coordinated asymmetric nitrogen.

In the search for conglomerates, we paid special attention to classical stereochemical objects, namely, the Tröger's base (TB) and its analogues, which were intensely studied in the last decade.[3(*f*)] As far as we know (Cambridge Crystallographic Database-2003), TB racemates studied by X-ray diffraction crystallise in achiral space groups.[3(*f*)] However, according to Tálas *et al.*,[4] the melting point of the enantiomer of TB dibenzo analogue **1** (Scheme 1) is 45 °C higher than that of the racemate. This is an indication of conglomerate formation;[5] therefore, we synthesised and studied compound (±)-**1**.[‡] In fact, the crystal grown from MeOH was found to have a chiral space group ($P2_12_12_1$, $Z = 4$),[§] similarly to that for previously studied authentic (*S*,*S*)-(+)-**1**.[4] It should be noted that a similar bis-acridine TB analogue crystallises in an achiral space group ($Pna2_1$, $Z = 4$).[6] Analysis of the crystal structure showed that molecules of **1** are united into helices directed along the crystallographic axis *a* (Figure 1) by C–H···π contacts.[7] We have recently found the similar crystallographic packing for 2,3,6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione, which also undergoes spontaneous resolution.[5]

It is known that (+)- and (–)-TBs racemise in acidic media,[3(*f*)] whereas a salt of (±)-TB with a chiral acid will undergo almost complete asymmetric conversion into a single diastereomer.[8] We succeeded in the almost complete conversion of (±)-**1** into a single enantiomer (absolute asymmetric synthesis[2]) by crystallisation under conditions of acid-catalysed enantiomerisation in solution (Scheme 1).

Table 1 Spontaneous resolution of (±)-**2** by stirred crystallisation from water.

Sample mass/mg	Precipitate mass/mg	Crystallisation temperature/°C	Stirring rate/rpm	$[\alpha]_D^{25}$	Concentration in MeOH, *c* (%)	*ee* (%)[a]
50.1	16.1	12	500	–4.8	1.2	10.1
50.2	16.6	14	600	–7.0	1.3	14.8
50.0	15.6	14	850	+23.6	1.3	50.0
50.1	16.3	8	1000	–17.3	1.2	38.0
50.0	15.5	20	1000	+25.1	1.3	52.9
50.3	15.0	40	1000	–28.9	1.3	61.0
50.2	16.0	60	1000	–34.3	1.2	72.5
50.1	16.3	80	1000	+45.5	1.3	96.0

[a] Assuming $[\alpha]_D^{25}$ 47.4° (*c* 1.0, MeOH) for enantiomerically pure (*R*)-(+)-**2**.[10(*b*)]

[†] Asymmetric nitrogen. Part 88, previous communication see ref. 1.

[‡] (±)-**1** was obtained[6] from β-napthylamine [a strong carcinogene (!)][4] and hexamethylene tetramine in MeOH in the presence of CF_3CO_2H; yield 76.5%; the ^{1}H and ^{13}C NMR spectra coincided with reported data[4] and are similar to those reported for the TB bis-quinoline analogue.[12] Crystallisation from MeOH with slow self-evaporation gave single crystals of 1.1, 1.5 and 2.3 mg. It was found that the melting point of the former is 258 °C, which is equal to that of (+)-**1** [mp 257–259 °C, in contrast to 213–215 °C for (±)-**1**].[4] The third crystal was found to have optical activity, $[\alpha]_D^{20}$ +1100° (*c* 0.05, $CHCl_3$) {*cf.*[4] for (+)-**1** $[\alpha]_D^{24}$ +1166° (*c* 0.1, $CHCl_3$); for the similar bis-acridine analogue,[5(*a*)] $[\alpha]_D$ +2600° (*c* 0.09, $CHCl_3$)}. The second crystal was studied by X-ray diffraction.[§]

Compound (±)-**2** was obtained by the amidation of diethyl 1-methoxyaziridine-2,2-dicarboxylate,[10(*a*)] yield 80%, mp 158 °C (EtOH). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 2.66 (d, 1H, H_b, ^2J –2.7 Hz), 3.11 (br. d, 1H, H_a, ^2J –2.7 Hz), 3.66 (s, 3H, MeO), 5.45, 5.69, 6.86 and 6.94 (br. s, 4H, HN). ^{13}C NMR (100.61 MHz, [$^2H_4$]methanol/D_2O, 5:1) δ: 41.92 (dd, CH_2, $^1J_{CH_a}$ 178.0 Hz, $^1J_{CH_b}$ 170.8 Hz), 52.58 (t, CN, ^2J 2.9 Hz), 61.23 (q, MeO, ^1J 143.9 Hz), 167.41 (dd, A-CO, $^3J_{CH_a}$ 4.4 Hz, $^3J_{CH_b}$ 3.6 Hz), 171.44 (t, B-CO, ^3J 3.6 Hz). A portion of (±)-**2** (100 mg) was dissolved on heating in 2 ml of an $Pr^iOH–H_2O$ mixture (1:1); the solution was cooled to 20 °C and kept for three days at 0 °C. The intergrown crystal (48.5 mg) was divided by the cleavages. For one of the parts (26.5 mg), $[\alpha]_D^{25}$ –14.6° (*c* 2.2, MeOH), *ee* 30.8%; for the other part (22 mg), $[\alpha]_D^{25}$ +22.8°, *ee* 48.2%. Crystallisation of (±)-**2** from 2 ml of H_2O was carried out at different temperatures and stirring rates; the results are shown in Table 1.

[§] *Crystallographic data*: crystals of **1** ($C_{23}H_{18}N_2$, $M = 322.39$) are orthorhombic, space group $P2_12_12_1$, at 110 K $a = 6.384(1)$ Å, $b = 9.411(1)$ Å, $c = 26.866(5)$ Å, $V = 1614.1(5)$ Å^3, $Z = 4$ ($Z' = 1$), $d_{calc} = 1.327$ g cm^{-3}, μ(MoKα) = 0.78 cm^{-1}, $F(000) = 680$. Intensities of 15298 reflections were measured with a Smart 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, $2\theta < 60°$]. 4643 independent reflections ($R_{int} = 0.0371$) were used in a further refinement.

Crystals of **2** ($C_5H_9N_3O_3$, $M = 159.15$) are orthorhombic, space group $P2_12_12_1$, at 190 K $a = 7.439(2)$ Å, $b = 7.522(2)$ Å, $c = 13.369(4)$ Å, $V = 748.0(4)$ Å^3, $Z = 4$ ($Z' = 1$), $d_{calc} = 1.413$ g cm^{-3}, μ(MoKα) = 1.17 cm^{-1}, $F(000) = 336$. Intensities of 1409 reflections were measured with a Syntex $P2_1$ diffractometer [λ(MoKα) = 0.71072 Å, θ/2θ-scans, $2\theta < 60°$] and 1107 independent reflections were used in a further refinement.

Both 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 $wR_2 = 0.1197$ and GOF = 1.045 for all independent reflections [$R_1 = 0.0505$ was calculated against F for 3750 observed reflections with $I > 2\sigma(I)$] for **1** and to $wR_2 = 0.1126$ and GOF = 1.098 for all independent reflections [$R_1 = 0.0423$ was calculated against F for 2810 observed reflections with $I > 2\sigma(I)$] for **2**. All calculations were performed using SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 213980 and 213981. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2003.

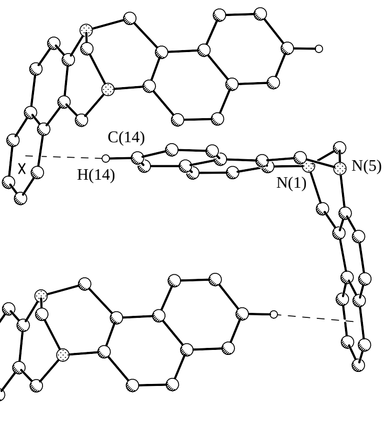
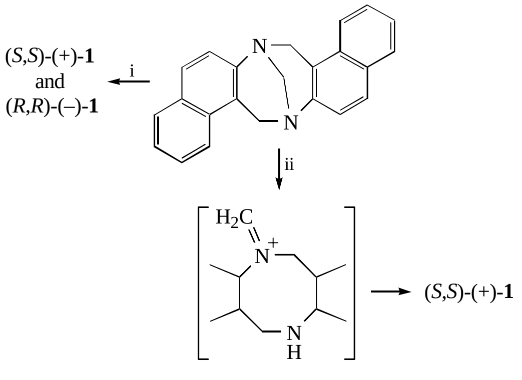


Figure 1 C–H···(π-system) contacts in the crystal structure of **1**. The C(14)–H(14)···X contact parameters are: H(14)···X 2.59 Å, C(14)···X 3.71(2) Å, C(14)H(14)X 172º.

In the series of three-membered nitrogen-containing heterocycles, examples of crystallisation in chiral space groups are known only for compounds that cannot be separated under ordinary conditions: 1-H-[9(*a*)] and 1-phenyl-2,2-dicarbamoylaziridines[9(*b*)] (two polymorphs have been found in each case) and two 3,3-dialkyldiaziridine complexes.[9(*c*)] It is also known that enantiomeric enrichment is observed for 1-methoxy-2,2-dicarbamoylaziridine (±)-**2**[10(*a*)] upon crystallisation from an optically active solvent (*l*-methyl lactate),[10(*b*)] which is used as a test for conglomerate formation. However, it was shown that noticeable enantiomeric enrichment of (±)-**2** also occurs upon simple heating in *l*-methyl lactate; this results from the asymmetric inversion of nitrogen, *i.e.*, a shift of inversion equilibrium towards the enantiomer that is more solvated by the chiral solvent.[10(*b*)] Thus, here we deal with a non-racemic separable sample; hence, the above test for conglomerate formation is ambiguous. In fact, although (±)-2-methoxy-3,3,5,5-tetracarbamoyl-1,2-oxazolidine is enriched, similarly to (±)-**2**, upon crystallisation from *l*-methyl lactate,[10(*c*)] it crystallises in an achiral space group.[10(*d*)]

Conglomerate formation in the case of (±)-**2** was unambiguously confirmed using X-ray diffraction (space group $P2_12_12_1$, $Z = 4$).§ The *trans*-amide group forms an intramolecular H-bond with the aziridine nitrogen, which results in a decrease in the C(5)C(2)N(1) angle in comparison with the C(4)C(2)N(1) angle (Figure 2). In a crystal, the molecules of **2** are combined into a 3D framework (3)N–H···O=C [N···O 2.881–2.906(2) Å], whereas the (2)NH(2NB) group participates in the weaker intermolecular H-bond with O(1) (N···O 3.086 Å), thus uniting molecules into helices directed along the crystallographic axis *c*.

Routine crystallisation gave crystals of (–)- and (+)-**2**, whereas stirred crystallisation resulted in the enantiomeric enrichment of the entire portion of crystals (Table 1)‡ obtained in 30–33% yields (Scheme 2).



Scheme 1 *Reagents and conditions*: i, routine crystallisation;† ii, CF_3CO_2H in MeOH (10%), total evaporation with stirring (500 rpm), 5 h; dissolution of the residue in methanolic NH_3, evaporation *in vacuo*, extraction with $CHCl_3$ and crystallisation from MeOH, (+)-**1** yield of 80%, *ee* 94.3%.

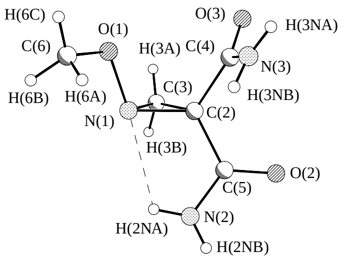
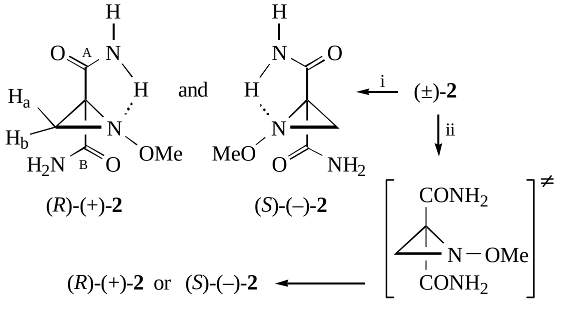


Figure 2 General view of **2**. Selected bond lengths (Å): O(1)–N(1) 1.443(2), N(1)–C(3) 1.468(3), N(1)–C(2) 1.502(2), C(2)–C(3) 1.490(3); bond angles (º): O(1)–N(1)–C(3) 107.1(1), O(1)–N(1)–C(2) 109.1(1), C(3)–N(1)–C(2) 60.2(1), C(3)–C(2)–N(1) 58.8(1), N(1)–C(3)–C(2) 61.0(1), N(1)–C(2)–C(4) 117.6(1), N(1)–C(2)–C(5) 116.3(1). The parameters of intramolecular H-bond: N(1)···H(2NA) 2.32 Å, N(1)···N(2) 2.764(2) Å, N(1)H(2NA)N(2) 114º.



Scheme 2 *Reagents and conditions*:† i, routine crystallisation; ii, stirred crystallisation at Δ.

On increasing the stirring rates and temperatures, the degree of enrichment increased up to *ee* 96%.‡ Despite the rather high inversion barrier of nitrogen in **2** ($\Delta G^{\#} = 31$ kcal mol^{-1} at 90 °C),[10(*a*)] these results can be explained by an autocatalytic effect upon formation of the solid phase.[11]

Thus, we found the conglomerates of racemic compounds containing stereogenic centres only at three-coordinated nitrogen atoms and performed their spontaneous crystallisation resolution.

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