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Chirality Directed Self-Assembly . Resolution of 2,5-Diazabicyclo[2.2.2]octane-3,6-dione and Crystal Structures of its Racemic and (–) Enantiomeric Forms

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Abstract : The chiral bicyclic bis-lactam **1** has been resolved and the crystal structures of the racemate (±)-**1** and of enantiomerically pure (-)-**1** have been determined. They show that the chiral nature of the substance determines the supramolecular architecture generated by hydrogen bonding self-assembly, giving an infinite zig-zag chain for the racemate and a cyclic tetramer for the enantiomer.

The self-assembly of well-defined supramolecular architectures depends on suitably instructed components and on the interactions that hold them together. Thus, hydrogen bonding units comprizing a sequence of acceptor and donor sites have been used to direct the formation of a variety of organic supramolecular entities[1,2]. Of particular interest would be the control of the build-up of a defined superstructure by molecular chirality features. We herewith describe the self-assembly of the chiral bicyclic bis-lactam **1** and show that the resulting architecture depends on the enantiomeric purity of the substance. Indeed, if full use is made of the hydrogen bonding capabilities of **1**, one expects the formation of an infinite zig-zag chain (Fig. 1a) of alternating (+) and (-) units in the case of the racemate or of a hexameric supramolecular bracelet (Fig. 1b) in the case of the single enantiomer

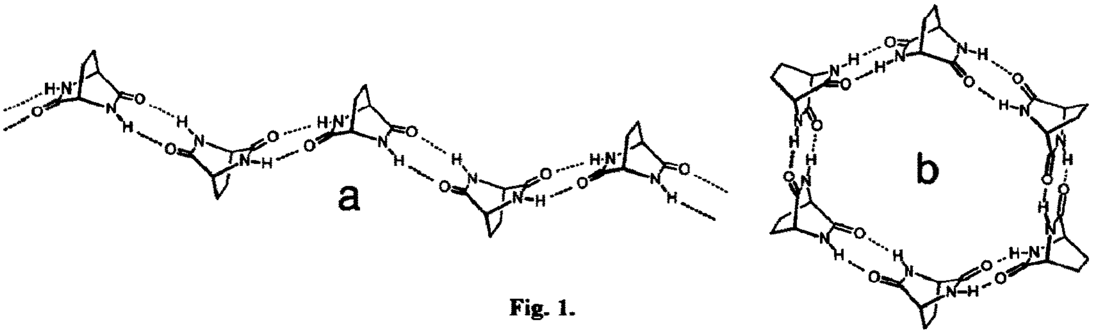
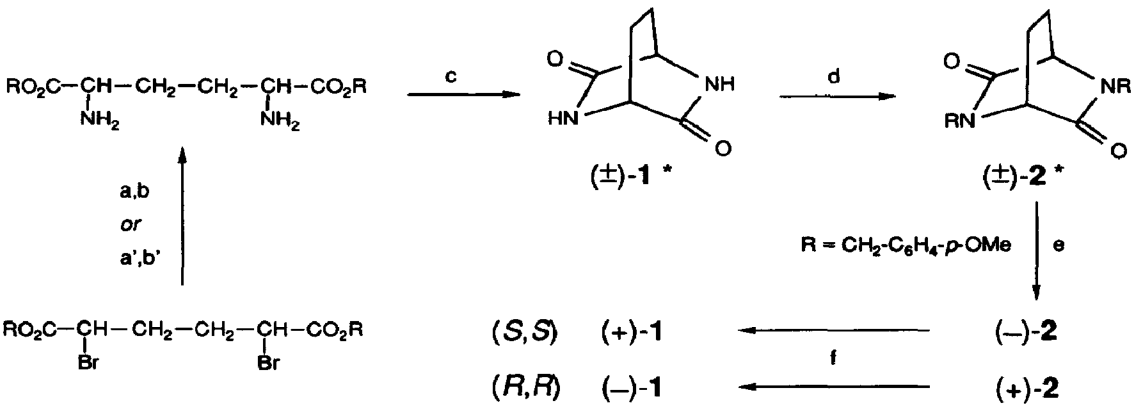


Fig. 1.

The known (±)-2,5-diazabicyclo[2.2.2]octane-3,6-dione **1** was obtained from *meso* or *dl* dialkyl α,α'-dibromoadipate (Scheme below) with minor modifications of previously described procedures[3]. The enantiomer



* Only the (*R,R*)-enantiomer is shown

a. NaN_3, EtOH, reflux 15 h.
b. H_2/Pt Adams, EtOH.
a'. K-phtalimide, DMF.
b'. H_2N-NH_2, EtOH, reflux 2 h , then HCl/MeOH.
c. MeONa, MeOH, reflux 5 h
d. HNa, DMF, *p*-MeO-$C_6H_4-CH_2Cl$
e. HPLC resolution on chiral phase.
f. CAN, MeCN-H_2O, 3 h , RT.

(*S,S*)-(+)-**1** was also previously prepared in 6 steps from L-homoserine[4]. The *p*-methoxybenzyl derivative (±)-**2**[5] could be efficiently resolved by preparative HPLC[6] on a chiral phase giving (+)- and (-)-**2** (e.e. ≥ 98 %, 80 %.). Cleavage of the *p*-methoxybenzyl groups of (+)-**2** was achieved by oxidation with cerium ammonium nitrate (CAN)[7] to provide (*R,R*)-(-)-**1** in 85% yield.

Racemic (±)-**1** and enantiomerically pure (-)-**1** were crystallized and their solid state structure determined[8,9].

In the *racemate structure* (Fig. 2) the molecules are, as anticipated (Fig. 1a), assembled into an infinite undulating chain of alternating (+) and (-) units through a centrosymmetric cyclic hydrogen-bonding network (Fig. 2a). Each molecule is located on the crystallographic diad axis passing through the ethylene bridge 5A-5B and involved in four hydrogen bonds (N-H···O 2.88 Å, <NHO 162°) linking two symmetrical donor (NH, 1A and 1B) and two symmetrical acceptor (O, 2A and 2B) groups. Three successive molecules (**I** - **III**) are related by crystallographic symmetry operations (**I** X, Y, Z ; **II** -X, 1-Y, 1-Z; **III** 1-X, 2-Y, 1-Z).

In the (-)-**1** *enantiomer structure* (Fig 3) the molecules are assembled into cyclic tetrameric arrays clearly different from the superstructure of racemic (±)-**1**, although being not the hexameric one (Fig. 1b) expected on the basis of internal hydrogen bonding through the formation of cyclic bidentate interaction units as found in (±)-**1**. As in the racemate structure, each molecule is located on the crystallographic diad axis passing through the ethylene bridge 5A-5B and is involved in four hydrogen bonds (N-H···O 2 88 Å, <NHO 156°). Here, however, four molecules (**I** - **IV**), related by crystallographic symmetry operations (**I** X, Y, Z ; **II** 0.5-X,

0.5+Y, 2-Z; **III** -1+X, Y, Z; **IV** 0.5-X, -0.5+Y, 2-Z) are linked together through a monodentate cyclic hydrogen bond scheme, repeated indefinitely in the space (Fig. 3a,b). The molecules are closely packed showing an alternation of polar layers and of hydrophobic layers due to the ethylene bridge (Fig. 3c). The anticipated structure shown in Fig. 1b is not favorable from the point of view of the crystal packing and it may be possible to find a substrate which could co-crystallize with **1** and enforce the crystallization in the expected way.

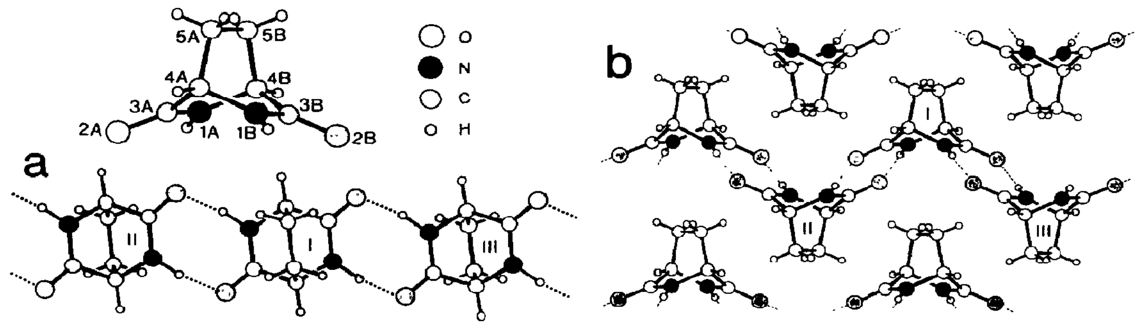


Fig. 2. X-ray crystal structure of (±)-**1**

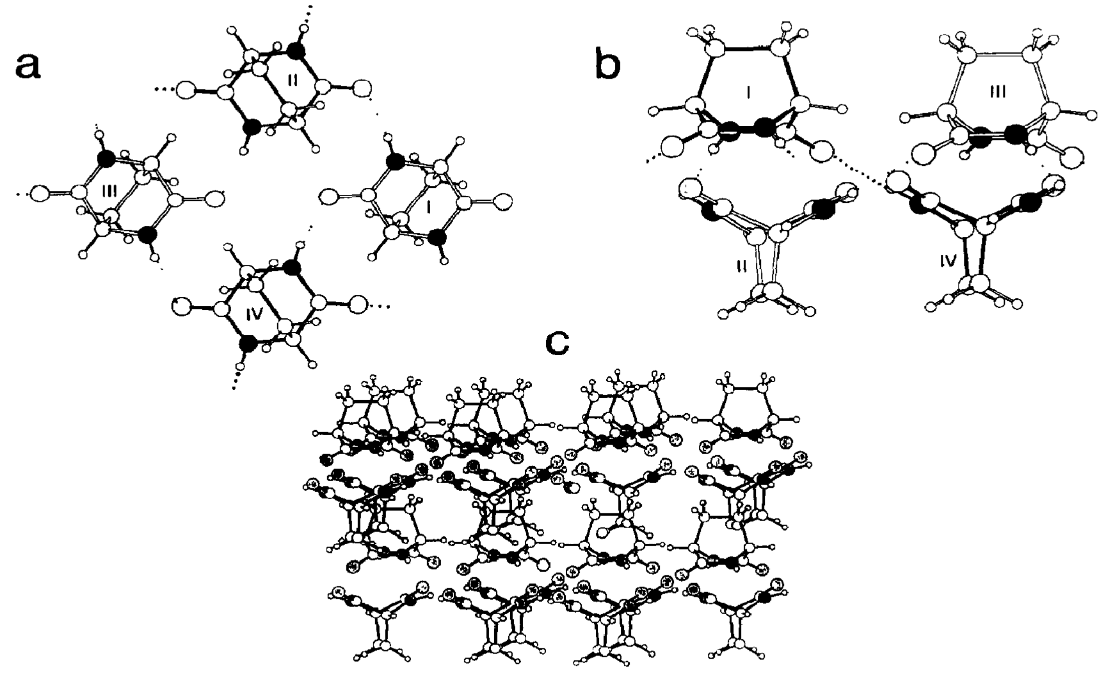


Fig. 3. X-ray crystal structure of (-)-**1**

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5. (±)-**2** was prepared according to the procedure described[3b] for the dibenzyl derivative of **1**, using (±)-**1** (700 mg, 5 mmol), HNa (50% suspension in oil, 480 mg, 10 mmol) and *p*-methoxybenzyl chloride (1.5 mL, 11 mmol) in DMF (15 mL). After the reaction, water was added, and the crystalline product was filtered off then recrystallized (MeOH) to give 1.45 g, 75% yield; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.7 (m, CH_2CH_2, 4H), 3.80 (s, OMe, 6H), 3.99 (m, 2H), 4.67, 4.27 (AB, J=14.5 Hz, CH_2-Ar, 4H), 6.85, 7.15, ($A'_2B'_2$, Ar, 8H); Anal. $C_{22}H_{24}N_2O_4$ Calcd C 69.46 H 6.36 N 7.36, Found C 69.5 H 6.5 N 7.2. DSC mp 126 °C, ΔH of fusion 8.6 kcal mol^{-1}; IR spectrum (KBr pellets) identical to that of the enantiomer; these data indicate that (±)-**2** should be a conglomerate[10]. We were unable however to resolve this compound by direct crystallization methods.
6. HPLC resolution : PROCHROM column (length 23 cm, diameter 6 cm, axial compression) packed with cellulose tris(3,5-dimethylphenylcarbamate) CHIRALCEL OD type (400 g), heptane - propanol-2 80:20 mixture as an eluent, flow rate 40 mL/min, UV detection at 254 nm Two charges (500 mg each) of (±)-**2** gave (+)-**2** (415 mg, 83 %); $[\alpha]_D^{20} = +105 \pm 3$ (*c* = 0.5, MeOH), e.e. ≥ 98% and (-)-**2** (405 mg, 81%, e.e ≥ 98%); DSC mp 151 °C, ΔH of fusion 9.3 kcal mol^{-1}.
7. The procedure described by Yamaura, M., Susuki, T : Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C. *Bull. Chem. Soc. Japan* **1985**, *58*, 1413-1420, was modified as follows. A solution of CAN (1.84 g, 6.6 mmol), in H_2O (6.6 mL), was added dropwise (40 min) to a solution of (+)-**2** (380 mg, 1 mmol) in acetonitrile (8 mL) with stirring. The reaction mixture was stirred for further 2 h and then $NaHCO_3$ (1 76 g, 21 mmol)) was added (pH ≈ 5 - 6) with formation of an abundant precipitate. The liquid phase was separated by centrifugation. The solid residue was rinced with water (3 × 20 mL) followed by centrifugation. The combined liquid phases were concentrated under reduced pressure at ≈ 50 °C. The residue was chromatographed twice on a silica gel column (50 g, then 25 g, Merck 9385) using $CHCl_3$ - MeOH - H_2O 10:5:1 as an eluent affording (-)-**1** (124 mg, 88%), mp 300-305 °C, $[\alpha]_D^{25}$ -79 ± 3 (*c* = 0.5, MeOH). In ref. 4, (+)-**1** is reported as an intermediate of e e. ≈ 90% with a rotation $[\alpha]_D$ +44 (*c* = 0 3, MeOH)
8. Crystal data for (±)-**1** . $C_6H_8N_2O_2$, M 140.14, orthorhombic, space group Pccn, a = 6.793(3), b = 8.362(6), c = 11.156(9) Å, V = 633.7(7) Å^3, Z = 4, d_x = 1.47, μ = 0.9 cm^{-1}. Colorless crystal of dimensions 0.3 × 0.3 × 0.5 mm (H_2O). Graphite monochromated 4-circle Nonius diffractometer, λ(CuKα) = 1.5418 Å, ω-2θ scan technique, ($2\theta<65°$), $-7<h<7$, $0<k<9$, $0<l<13$, 1138 measured reflections, 869 considered as observed [$I>3\sigma(I)$] and 484 unique reflections. Lorentz polarisation and empirical absorption corrections. The structure was solved by direct methods (program SHELXS86)[11a] and refined by full-matrix least squares, minimizing the function $\Sigma w(|Fo|-|Fc|)^2$ (program SHELX76)[11b]. Anisotropic refinement converged to R = 6.81% for 46 parameters. Hydrogen atoms, located on difference synthesis were included in the refinement with an isotropic thermal factor equivalent to 1.1 that of the bonded atom, weighting scheme $w = [\sigma^2(F) + 0.001F^2]^{-1}$, σ from counting statistics. Full data deposited at the Cambridge Crystallographic Data Centre.
9. Crystal data for (-)-**1** : orthorhombic, space group $P2_12_12$, a = 8.314(2), b = 6.864(2), c = 12.215(5) Å, V = 317.12 Å^3, Z = 2, d_x = 1.47, μ = 0.9 cm^{-1}. Colorless crystal of dimensions 0.2 × 0.3 × 0.8 mm (EtOH). Other details as above except for the following : ($2\theta<63°$), $-6<h<6$, $0<k<7$, $0<l<9$, 608 measured reflections, 326 considered as observed [$I>3\sigma(I)$] and 334 unique reflections. Lorentz polarisation and no absorption corrections. Anisotropic refinement converged to R = 4.12% for 46 parameters. Weighting scheme $w = [\sigma^2(F) + 0.001F^2]$, σ from counting statistics.
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