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Chiral glycouril, 2,6-diethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione: spontaneous resolution, reactivity and absolute configuration

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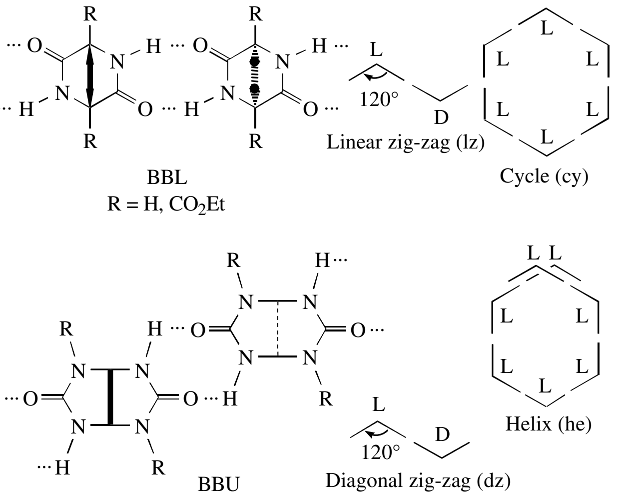
The title glycouril 1 was spontaneously resolved into enantiomers by crystallisation from H_2O and sorting of conglomerate crystals, then N-chlorination and N-aminomethylation to give 2, 3 and 4, respectively, were studied. The absolute configuration 1*R*,5*R*-(+) was determined by an X-ray diffraction study of diastereomeric *N*,*N*-bis-aminomethyl derivative (–)-4.

Racemic bicyclic bis-lactams (BBL) were observed to self-assemble into the hydrogen bonded heterochiral polymeric linear zig-zag (lz) chains in crystals (Scheme 1), with space groups *Pccn* (for R = H)[1] and $P2_1/n$ (for R = CO_2Et).[2] Therefore, these compounds cannot be spontaneously resolved by crystallisation. It can be assumed that chain termination of hydrogen bonded polymerisation takes place in the case of homochiral self-assembling. Indeed, in a crystal of (*R*,*R*)-(–)-BBL (R = H) (space group $P2_12_12$) a cyclic tetramer rather than the expected hexamer (cy) is formed.[1]



Scheme 1

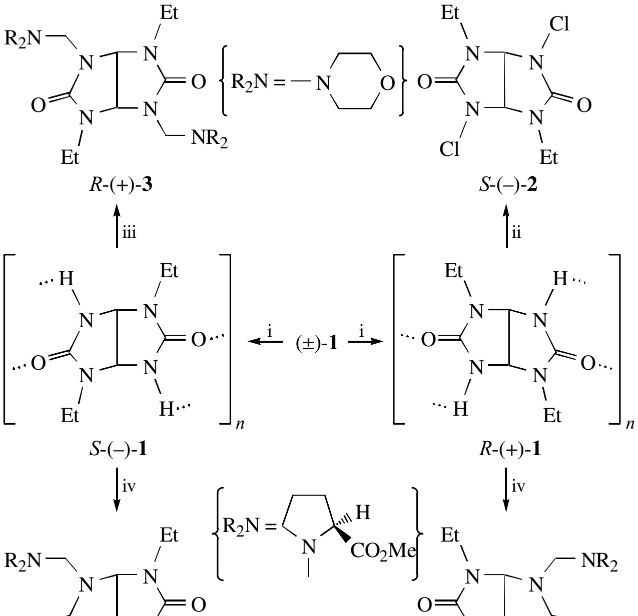
However, a similar self-assembling could be arranged along the diagonal line, for example, in the case of bicyclic bis-ureas (BBU) (Scheme 1) where two possibilities of hydrogen bonded polymerization without chain termination exist. One of them is a heterochiral diagonal zig-zag (dz) like BBL, and the other is a homochiral helical structure (he). Exactly the latter possibility, though in a more complicated form, is realised for BBU. According to an X-ray diffraction study the chiral BBU, 2,6-diethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **1** forms a conglomerate (space group $P4_12_12$)[3,4] whereas its complex **1**·$ZnCl_2(H_2O)$ has a centrosymmetric structure (space group $P2_1/c$).[5]

Thus, for the first time, spontaneous resolution of glycouril (±)-**1** was brought about successfully by routine crystallisation from H_2O followed by the sorting of levo- and dextro-rotatory crystals (Scheme 2).

Crystallisation of (±)-**1** in open vessels at slow self-evaporation gives large transparent sparkling crystals; the weight ranges from 10 to 50 mg and more and the size is up to 1 cm^3. Aggregations are also formed, and their fracture results in enantiomeric, levo- and dextro-rotatory samples. Repeated crystallisations lead to optical enrichment, and substantial amounts of optically pure crystals of (+)- and (–)-**1**, which show maximum optical rotation values and constant melting points, were obtained. They are characterised by NMR and CD spectra† (Figure 1).

Results of their study by X-ray diffraction are in agreement with the previous data.[4] It is noteworthy that enantiomers **1** are less soluble in H_2O and MeOH compared with racemic sample. After boiling of enantiomer **1** in concentrated HCl (1 h) complete decomposition of the sample (^{1}H NMR) and loss of the optical activity are observed.

In order to determine the absolute configuration of enantiomers **1** a search for suitable derivatives was carried out (Scheme 2). The heavy atom containing derivative, 2,6-dichloro-BBU (–)-**2** was prepared by N-chlorination of (+)-**1**; however, it is rather unstable and decomposes during crystallisation attempts from a benzene–hexane mixture. N-Aminomethylation of (–)-**1** gives the stable crystalline 2,6-bis-morpholinomethyl-BBU (+)-**3** and oily diastereoisomer (+)-**4** containing an *S*-(–)- proline residue. Crystalline diastereomer (–)-**4** was obtained from (+)-**1** and its



Scheme 2 *Reagents and conditions*: i, crystallisation from H_2O and sorting of crystals; ii, Bu^tOCl in CH_2Cl_2, 24 h, 20 °C; iii, $MeOCH_2N(CH_2CH_2)_2O$ and molecular sieves 4 Å in Pr^iOH, 1 week, 20 °C; iv, *S*-(–)-$MeOCH_2N(CH_2)_3CHCO_2Me$ and molecular sieves 4 Å in Pr^iOH, 1 week, 20 °C.

molecular structure (Figure 2) and the absolute configuration 1*S*,5*S* were determined by X-ray diffraction.‡

The results obtained are of importance for the chemistry of glycouril, which has been developing extensively during the last 120 years.[6–8] First of all 2,4,6,8-tetraalkyl-BBUs exhibit high psychotropic activity,[9] and glycouril **1** is a precursor of 2,6-diethyl-4,8-dimethyl-BBU known as the medicine Albicar. These results open up possibilities for synthesis of chiral drugs.[10]

Gompper's group has studied the rearrangement reactions of glycouril derivatives, and based on them new tricyclic *cis*-diaziridines and polyaza heterocycles were synthesised.[11] In

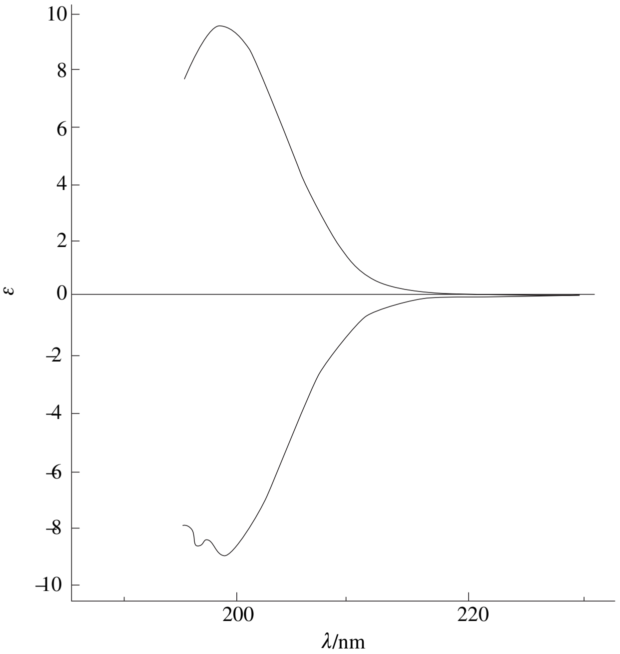


Figure 1 CD spectra of *R*-(+)-**1** (top) and *S*-(–)-**1** (bottom).

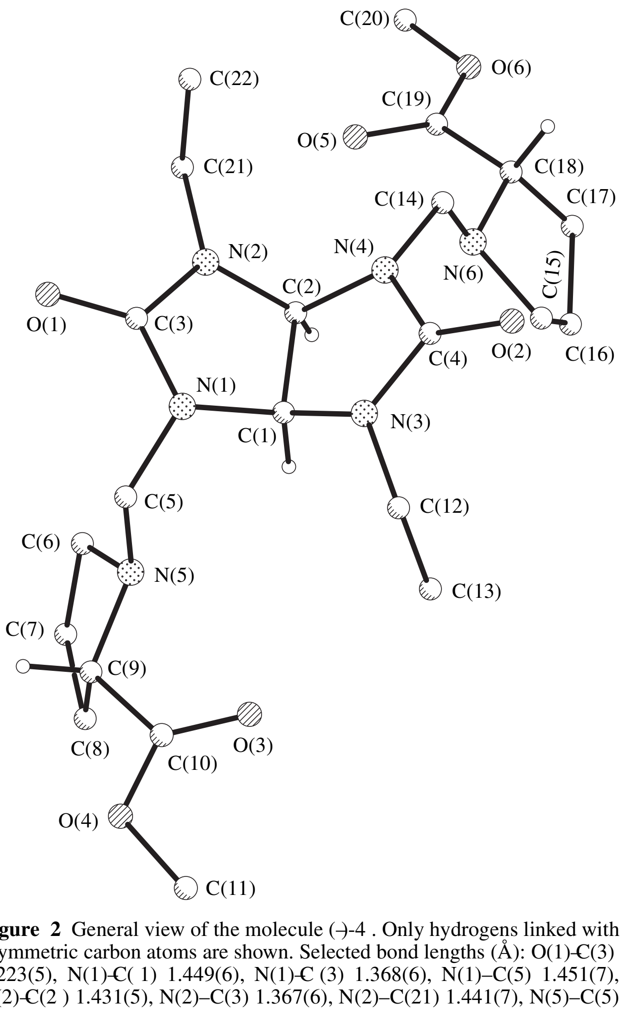


Figure 2 General view of the molecule (–)-4. Only hydrogens linked with asymmetric carbon atoms are shown. Selected bond lengths (Å): O(1)–C(3) 1.223(5), N(1)–C(1) 1.449(6), N(1)–C(3) 1.368(6), N(1)–C(5) 1.451(7), N(2)–C(2) 1.431(5), N(2)–C(3) 1.367(6), N(2)–C(21) 1.441(7), N(5)–C(5) 1.447(8), C(1)–C(2) 1.549(6); selected bond angles (°): C(3)–N(1)–C(1) 112.4(4), C(3)–N(1)–C(5) 122.3(4), C(1)–N(1)–C(5) 121.7(4), C(3)–N(2)–C(2) 112.5(4), C(3)–N(2)–C(21) 121.9(4), C(2)–N(2)–C(21) 125.2(4), N(3)–C(1)–N(1) 115.2(4), N(3)–C(1)–C(2) 103.4(4), N(1)–C(1)–C(2) 102.8(3), N(2)–C(2)–N(4) 115.9(4), N(2)–C(2)–C(1) 103.8(3), N(4)–C(2)–C(1) 103.4(3), O(1)–C(3)–N(2) 125.3(4), O(1)–C(3)–N(1) 126.7(4), N(2)–C(3)–N(1) 108.0(4), N(5)–C(5)–N(1) 112.1(4).

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† The NMR spectra were measured on a Bruker WM-400 spectrometer (at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C from TMS). Optical rotation was measured on a Polamat A polarimeter. The CD spectra were recorded on a JASCO J-500A instrument with a DP-500N data processor.

(±)-**1**: obtained by the method described in ref. 4, mp 286–288 °C. ^{1}H NMR (CD_3OD) δ: 1.14 (t, 6H, 2Me, ^3J 7.0 Hz), 3.25 (m, 4H, 2CH_2, ABX_3 spectrum, ν 84.0 Hz, ^2J –14.0 Hz, ^3J 7.0 Hz), 5.39 (s, 2H, 2CH). ^{13}C NMR (CD_3OD) δ: 13.25 (qt, Me, ^1J 126.4 Hz, ^2J 2.9 Hz), 36.56 (tq, CH_2, ^1J 138.1 Hz, ^2J 4.4 Hz), 67.49 (d, CH, ^1J 167.1 Hz), 161.64 (tt, CO, ^3J 2.9 Hz). λ_{max} 216.2 nm (MeOH).

R-(+)-**1**: mp 330–331 °C (decomp.), $[\alpha]_D^{20}$ = 101.4° (*c* 1.2 H_2O), ε = = +9.62 (λ_{max} 198 nm).

S-(–)-**1**: mp 330–331 °C (decomp.), $[\alpha]_D^{20}$ = –93.8° (*c* 0.19 MeOH), ε = = –9.3 (λ_{max} 198 nm).

R-(+)-**2**: obtained from *S*-(–)-**1** {$[\alpha]_D^{20}$ = –84.4° (*c* 0.58 MeOH)}, yield 96%, mp 122–129 °C, $[\alpha]_D^{20}$ = +46.1° (*c* 0.3 MeOH). ^{1}H NMR (C_6D_6) δ: 0.87 (t, 6H, 2Me, ^3J 7.5 Hz), 3.08 (br. q, 4H, 2CH_2, ^3J 7.5 Hz), 3.94 (s, 2H, 2CH).

S-(–)-**2**: obtained in a similar manner from *R*-(+)-**1** {$[\alpha]_D^{20}$ = +87.5° (*c* 0.37 MeOH)}, $[\alpha]_D^{20}$ = –53.2° (*c* 1.67 MeOH).

R-(+)-**3**: obtained from the partly enriched *S*-(–)-**1** and *N*-methoxymethylmorpholine [^{1}H NMR ($CDCl_3$) δ: 2.66 (m, 4H, 2CH_2N), 3.31 (s, 3H, MeO), 3.69 (m, 4H, 2CH_2O), 3.98 (s, 2H, OCH_2N)], yield 47%, mp 144–146 °C (benzene–*n*-hexane), $[\alpha]_D^{20}$ = +25.6° (*c* 0.2 MeOH), ee ≈ ≈ 15% [as found from ^{1}H NMR spectrum, in C_6D_6 with addition of Eu(tfc)$_3$, by displacement of the CH_2N signal (from 2.15 to 2.55 ppm) and its split (ν = 42 Hz) into two signals in a ratio of 1.35]. ^{1}H NMR (C_6D_6) δ: 0.96 (t, 6H, 2Me, ^3J 7.0 Hz), 2.15 (m, 8H, 4CH_2N), 3.39 (m, 2CH_2Me, ABX_3 spectrum, ν 256.0 Hz, ^2J –14.0 Hz, ^3J 7.0 Hz), 3.45 (m, 8H, 4CH_2O), 3.72 (m, 4H, 2NCH_2N, AB spectrum, ν 168.0 Hz, ^2J –12.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 12.42 (q, Me, ^1J 126.4 Hz), 37.02 (tq, CH_2Me, ^1J 138.1 Hz, ^2J 4.4 Hz), 50.57 (t, NCH_2C, ^1J 133.7 Hz), 65.16 (t, NCH_2N, ^1J 145.3 Hz), 66.14 (d, CH, ^1J 165.7 Hz), 66.38 (t, CH_2O, ^1J 142.4 Hz), 157.55 (s, CO).

S-(–)-**4**: obtained from *R*-(+)-**1** {$[\alpha]_D^{20}$ = +95.8° (*c* 0.24 MeOH)} and *S*-(–)-methyl 1-methoxymethylprolinate {$[\alpha]_D^{20}$ = –58.3° (*c* 1.3 MeOH)}, yield 34%, mp 98.5 °C (benzene–*n*-hexane), $[\alpha]_D^{20}$ = –122.5° (*c* 0.6 MeOH). ^{1}H NMR (C_6D_6) δ: 1.17 (t, 6H, 2Me, ^3J 7.0 Hz), 1.38, 1.56–1.72 and 1.80 [m, 8H, 2$(CH_2)_2$CH], 2.43 and 2.87 (m, 4H, 2CH_2N), 3.01 (dd, 2H, 2HCN, ^3J 6.3 and 8.9 Hz), 3.28 (s, 6H, 2MeO), 3.55 (m, 4H, 2CH_2Me, ABX_3 spectrum, ν 168.0 Hz, ^2J –12.0 Hz, ^3J 7.0 Hz), 4.20 (m, 4H, 2NCH_2N, AB spectrum, ν 252.0 Hz, ^2J –14.0 Hz), 5.36 (s, 2H, 2CH).

R-(+)-**4**: obtained from *S*-(–)-**1** {$[\alpha]_D^{20}$ = –89.5° (*c* 0.83 MeOH)} and *S*-(–)-methyl 1-methoxymethylprolinate, yield 82.6%, oil, $[\alpha]_D^{20}$ = +7.23° (*c* 1.9 MeOH). ^{1}H NMR (C_6D_6) δ: 1.14 (t, 6H, 2Me, ^3J 7.0 Hz), 1.28, 1.56 and 1.73 [m, 8H, 2$(CH_2)_2$CH], 2.19 and 2.82 (m, 4H, 2CH_2N), 3.30 (m, 2H, 2CHN), 3.36 (s, 6H, 2MeO), 3.50 (m, 4H, 2CH_2Me, ABX_3 spectrum, ν 196.0 Hz, ^2J –14.0 Hz, ^3J 7.0 Hz), 4.15 (m, 4H, 2NCH_2N, AB spectrum, ν 224.0 Hz, ^2J –12.0 Hz), 5.55 (s, 2H, 2CH).

‡ Crystallographic data for (–)-**4**: $C_{22}H_{36}N_6O_6$, *M* = 480.57, monoclinic crystals, space group $P2_1$, *a* = 9.616(3) Å, *b* = 8.952(3) Å, *c* = 14.783(5) Å, β = 98.14(3)°, *V* = 1259.6(7) Å^3, *Z* = 4, d_{calc} = 1.267 g cm^{-3}, μ(MoK) = = 0.94 cm^{-1}, *F*(000) = 516. Intensities of 2859 reflections were measured on a Siemens P3 diffractometer at 20 °C (λMoK radiation, θ/2θ scan technique, 2θ < 52°) and were used in further calculations and refinement. The absolute configuration 1*S*,5*S* for the molecule of (–)-4 was confirmed on the basis of the known configuration (*S*) of the proline moiety. The structure was solved by a direct method and refined by full-matrix least-squares against F^2 in the anisotropic–isotropic approximation. The positions of the hydrogen atoms were calculated. The refinement converged to wR_2 = 0.2123 and GOF = 1.043 for all 2698 independent reflections [R_1 = 0.0595 is calculated against *F* for the 1663 observed reflections with $I > 2\sigma(I)$]. The number of the refined parameters is 307. 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.*, 1998, Issue 1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/34.

the extensive studies of Rebek's group[12–16] and Nolte's group[17] achiral glycourils have been examined as structural units for the design of self-assembling molecular clips and capsules. A glycouril-based system (cucurbituril) was used by Kim's group in the elegant design of a coordination polymeric polyrotaxane[18] and polycatenated polyrotaxane.[19]

Readily accessible enantiomeric glycourils can give new, strong impetus to the synthesis of chiral supramolecular systems and can be used as new chiral reagents in asymmetric halogenation and aminomethylation reactions.

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