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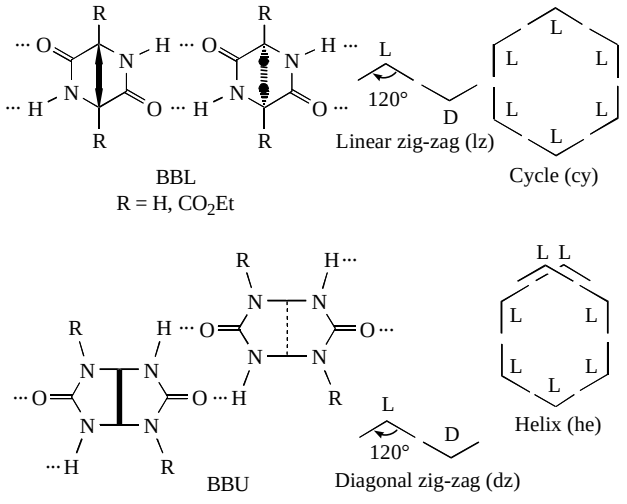
The title glycouril **1** was spontaneously resolved into enantiomers by crystallisation from H_2O and sorting of conglomerate crystals, then N-chlorination and N-aminomethylation to give **2**, **3** and **4**, respectively, were studied. The absolute configuration 1*R*,5*R*-(+) was determined by an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

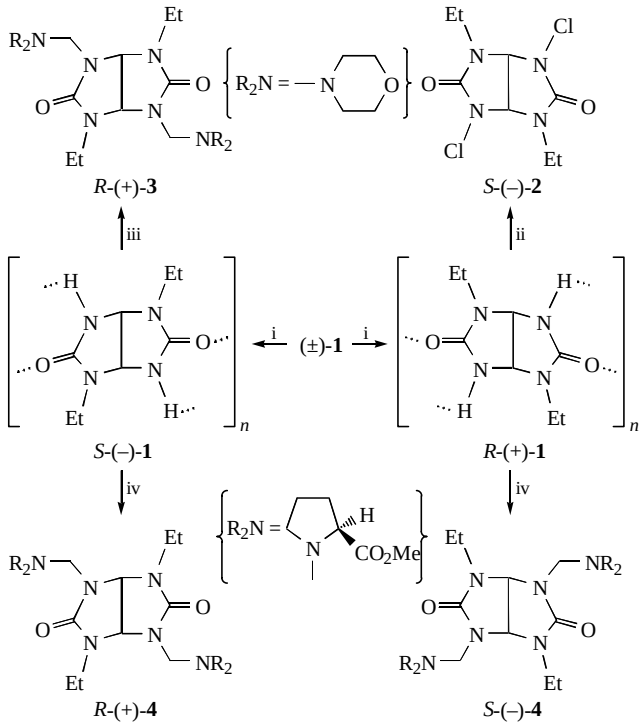
However, a similar self-assembling could be arranged along the diagonal line, for example, in the case of bicyclic bis-ureas (BBU) (Scheme 1) where two possibilities of hydrogen bonded polymerization without chain termination exist. One of them is a heterochiral diagonal zig-zag (dz) like BBL, and the 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^{t}OCl in CH_2Cl_2, 24 h, 20 °C; iii, $MeOCH_2N(CH_2CH_2)_2O$ and molecular sieves 4 Å in Pr^{i}OH, 1 week, 20 °C; iv, *S*-(–)-$MeOCH_2N(CH_2)_3CHCO_2Me$ and molecular sieves 4 Å in Pr^{i}OH, 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

† 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, $\Delta\nu$ 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), $\Delta\varepsilon$ = = +9.62 (λ_{max} 198 nm).

S-(–)-**1**: mp 330–331 °C (decomp.), $[\alpha]_D^{20}$ = –93.8° (*c* 0.19 MeOH), $\Delta\varepsilon$ = = –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 ($\Delta\nu$ = 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, $\Delta\nu$ 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, $\Delta\nu$ 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, $2(CH_2)_2CH$], 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, $\Delta\nu$ 168.0 Hz, ^2J –12.0 Hz, ^3J 7.0 Hz), 4.20 (m, 4H, $2NCH_2N$, AB spectrum, $\Delta\nu$ 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, $2(CH_2)_2CH$], 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, $\Delta\nu$ 196.0 Hz, ^2J –14.0 Hz, ^3J 7.0 Hz), 4.15 (m, 4H, $2NCH_2N$, AB spectrum, $\Delta\nu$ 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(MoKα) = = 0.94 cm^{-1}, F(000) = 516. Intensities of 2859 reflections were measured on a Siemens P3 diffractometer at 20 °C (λMoKα radiation, $\theta/2\theta$ scan technique, $2\theta < 52°$) 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.

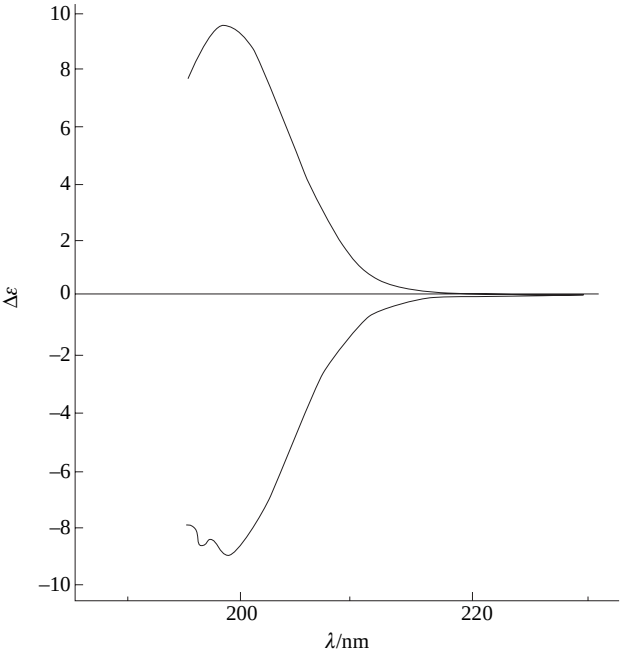


Figure 1 CD spectra of *R*-(+)-**1** (top) and *S*-(–)-**1** (bottom).

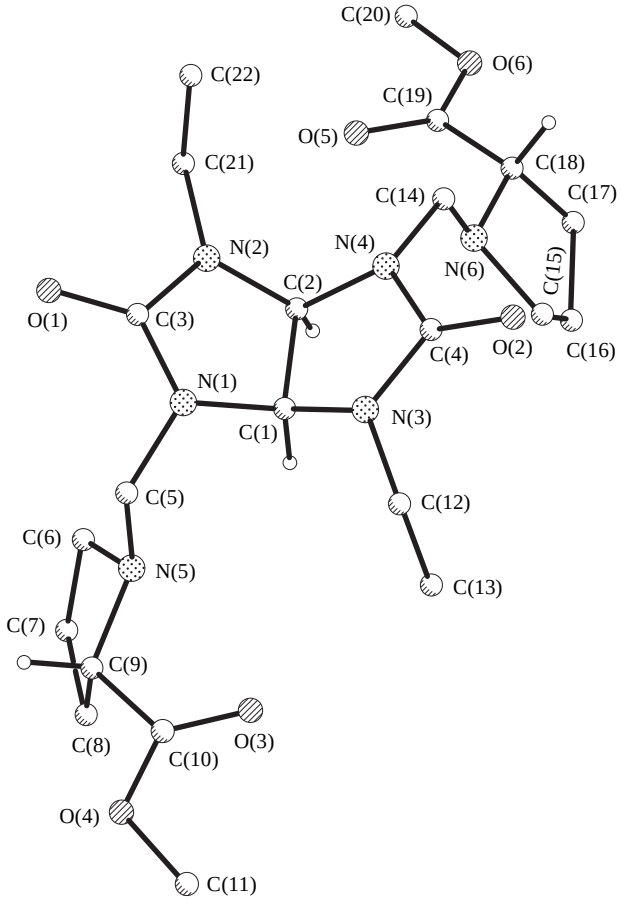


Figure 2 General view of the molecule (–)-4. Only hydrogens linked with asymmetric carbon atoms are shown. Selected bond lengths (Å): O(1)–C(3) 1.223(5), N(1)–C(1) 1.449(6), N(1)–C(3) 1.368(6), N(1)–C(5) 1.451(7), N(2)–C(2) 1.431(5), N(2)–C(3) 1.367(6), N(2)–C(21) 1.441(7), N(5)–C(5) 1.447(8), C(1)–C(2) 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).

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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References

1 M.-J. Brienne, J. Gabard, M. Leclercq, J.-M. Lehn, M. Cesario, C. Pascard, M. Cheve and G. Dutruc-Rosset, *Tetrahedron Lett.*, 1994, **35**, 8157.
2 R. G. Kostyanovsky, Yu. I. El'natanov, O. N. Krutius, I. I. Chervin and K. A. Lyssenko, *Mendeleev Commun*., 1998, 228.
3 M. G. Tsintsadze, A. Yu. Tsivadze, A. A. Dvorkin and T. B. Markova, *Soobshcheniya AN GSSR*, 1986, **121**, 553 (in Russian).
4 E. B. Shamuratov, A. S. Batsanov, Yu. T. Struchkov, A. Yu. Tsivadze, M. G. Tsintsadze, L. I. Khmel'nitskii, Yu. A. Simonov, A. A. Dvorkin, O. V. Lebedev and T. B. Markova, *Khim. Geterotsikl. Soedin*., 1991, 937 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1991, 745].
5 V. B. Rybakov, L. A. Aslanov, M. G. Tsintsadze and A. Yu. Tsivadze, *Zh. Strukt. Khim*., 1989, **30**, 175 [*J. Struct. Chem.* (*Engl. Transl.*), 1989, **30**, 151].
6 H. Petersen, *Synthesis*, 1973, 243.
7 P. H. Boyle and E. O'Brien, *Proc. Roy. Irish Acad*., 1983, **83B**, 13.
8 A. A. Bakibaev, A. Yu. Yagovkin and S. N. Vostretsov, *Usp. Khim*., 1998, **67**, 333 (*Russ. Chem. Rev.*, 1998, **67**, 295).
9 O. V. Lebedev, L. I. Khmel'nitskii, L. V. Epishina, L. I. Suvorova, I. V. Zaikonnikova, I. E. Zimakova, S. V. Kirshin, A. M. Karpov, V. S. Chudnovskii, M. V. Povstyanoi and V. A. Eres'ko, in *Tselenapravlennyi Poisk Novykh Neirotropnykh Preparatov* (*Purposeful Search for New Neurotropic Medicines*), Zinatne, Riga, 1983, p. 81 (in Russian).
10 (*a*) S. C. Stinson, *Chem. Eng. News*, 1992, **70**, 46; (*b*) S. C. Stinson, *Chem. Eng. News*, 1995, **73**, 44; (*c*) S. C. Stinson, *Chem. Eng. News*, 1997, **75**, 38.
11 R. Gompper, H. Nöth and P. Spes, *Tetrahedron Lett.*, 1988, **29**, 3639.
12 M. M. Conn and J. Rebek, Jr., *Chem. Rev*., 1997, **97**, 1647.
13 D. M. Rudkevich and J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl*., 1997, **36**, 846.
14 Y. Tokunaga, D. M. Rudkevich and J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl*., 1997, **36**, 2656.
15 Y. Tokunaga and J. Rebek, Jr., *J. Am. Chem. Soc*., 1998, **120**, 66.
16 J. M. Rivera, T. Martin and J. Rebek, Jr., *J. Am. Chem. Soc*., 1998, **120**, 819.
17 R. J. Jansen, A. E. Rowan, R. de Gelder, H. W. Scheeren and R. J. M. Nolte, *J. Chem. Soc., Chem. Commun*., 1998, 121.
18 D. Whang, Y.-M. Jeon, J. Neo and K. Kim, *J. Am. Chem. Soc*., 1996, **118**, 11333.
19 D. Whang and K. Kim, *J. Am. Chem. Soc*., 1997, **119**, 451.

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