Crystal properties of *N*-alkyl-substituted glycolurils as the precursors of chiral drugs

Remir G. Kostyanovsky,*[a] Konstantin A. Lyssenko,[b] Angelina N. Kravchenko,[c] Oleg V. Lebedev,[c] Gul'nara K. Kadorkina[a] and Vasilii R. Kostyanovsky[a]

[a] *N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 117977 Moscow, Russian Federation. Fax: +7 095 938 2156; e-mail: kost@center.chph.ras.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813 Moscow, Russian Federation. Fax: +7 095 135 5085; e-mail: kostya@xray.ineos.ac.ru*
[c] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5328*

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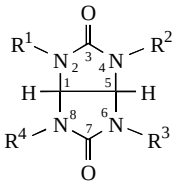
2,6-Dimethylglycoluril **1** crystallises to form a conglomerate (space group $P2_1$) and co-crystallises with isomeric 2,8-dimethylglycoluril **2**; 2,6-diethylglycoluril **A** is the best precursor in the synthesis of chiral drugs.

The chemistry of glycolurils is progressing in different directions including the construction of self-assembling molecular entities such as clips, capsules and supramolecular coordination-bonded systems based on cucurbiturils,[1,2] as well as the preparation of pharmaceuticals.[3–5] The psychotropic drugs Mebicar and Albicar are well-known tranquilizers and antidepressants[3–6] (Scheme 1). Albicar crystallises in a centrosymmetric space group ($P2_1/a$);[4] therefore, its resolution into enantiomers is difficult. However, its potential precursor, chiral 2,6-diethylglycoluril **A** (which can be easily separated from achiral isomer **B**), forms a conglomerate (space group $P4_12_12$)[5] and thus smoothly undergoes spontaneous resolution.[1] According to published data on the glycoluril structures,[1,4,5,9–11] there are two another examples of conglomerates, *i.e.*, 2,6-dinitro-4,8-diacetylglycoluril (space group $P2_12_12_1$)[9] and compound **3** (space group $P1$).[4] The latter can be considered as a synthetic drug precursor.



Mebicar: $R^1 = R^2 = R^3 = R^4 = Me$
Albicar: $R^1 = R^3 = Me$, $R^2 = R^4 = Et$
A: $R^1 = R^3 = Et$, $R^2 = R^4 = H$
B: $R^1 = R^4 = Et$, $R^2 = R^3 = H$
1: $R^1 = R^3 = Me$, $R^2 = R^4 = H$
2: $R^1 = R^4 = Me$, $R^2 = R^3 = H$
3: $R^1 = R^2 = Me$, $R^3 = Et$, $R^4 = H$

Scheme 1

In this work, we examined the spontaneous resolution of chiral glycolurils **1** and **3**. Using a known method,[12] the isomers of **1** and **2** were obtained in the ratio 1.8:1 (^{1}H NMR data); they were purified by repeated crystallization[12] and characterised.† An unambiguous structural ^{1}H NMR test is the non-equivalency of the 1-CH and 5-CH protons in **2**; the signal of the latter can be easily assigned by additional triplet splitting of the doublet on the HN-4 and HN-6 protons. Note that these protons are readily exchanged; therefore, the spin coupling constants ^3J can be observed in only dry aprotic solvents.

Difficulties in the resolution and purification[12] of isomers **1** and **2** are caused by easy co-crystallization. The composition of a co-crystal grown from H_2O under slow self-evaporation [1 (*R*)-**1** + 1 (*S*)-**1** + 2 **2** + 5 H_2O] was established by ^{1}H NMR† and X-ray‡ methods (Figures 1 and 2). Note that co-crystallization does not occur in the case of a mixture of **A** with **B**. The crystallization of this mixture from H_2O leads to the two groups of crystals[5], namely, large tetragonal **A** and thin lamellate monoclinic **B** (space group $P2_1/c$).[5] The separate crystallization from supersaturated aqueous solutions was also observed for the mixtures of **1** with **B** and **2** with **A** (2 days at 20 °C) to form the crystals of pure **B** and **2**, respectively (both compounds were identified by ^{1}H NMR spectra).†

By crystallization of pure isomer **1** from H_2O under slow self-evaporation (3–5 days), the fine needle-shaped crystals suitable for an X-ray study‡ were grown (Figure 3). They exhibit a chiral

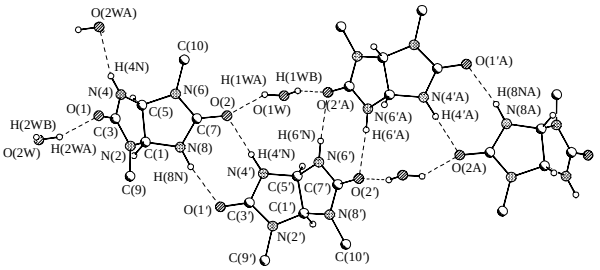


Figure 1 Tetramers in a co-crystal of **1** + **2**. The N··O distances are N(8)··O(1′) 2.940(2) Å, O(2)··N(4) 2.842(2) Å, N(6′)··O(2′A) 2.980(2) Å, O(1′A)··N(8A) 2.955(2) Å, N(4′A)··O(2A) 2.842(2) Å.

space group similarly to the analogue **A**.[1] Thus, the fourth conglomerate has been found in the series of glycolurils.[4,5,9] The optical activity was detected in individual crystals of **1** (up to 1.5 mg). The positive Cotton effect at 202 nm was observed in the CD spectrum of (+)-**1**; by analogy with diethyl analog **A**,[1] this fact permits assigning its absolute configuration *R*-(+)-**1**.

Many attempts to resolve glycoluril **3** spontaneously have failed. The crystallization from ethyl acetate (under conditions of mono-

† *Characteristics and spectroscopic data.*

1: mp 268–270 °C (H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.62 (s, 6H, 2Me), 5.05 (s, 2H, 2HC), 7.40 (br. s, 2H, 2HN); (CD_3OD): 2.76 (s, 6H, 2MeN), 5.25 (s, 2H, 2HC).

R-(+)-**1**: mp 335 °C (charred), $[\alpha]_{578}$ +49.5°, $[\alpha]_{546}$ +55.0° (*c* 0.1, H_2O). CD spectrum in H_2O, cell 1 mm (*c* 3.3×10^{-3} mol dm^{-3}), $\Delta\varepsilon$ (λ_{max}/nm): +2.04 (202).

2: mp 298–300 °C (H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.78 (s, 6H, 2Me), 5.11 (d, 1H, 1-CH, ^3J 8.2 Hz), 5.18 (dt, 1H, 5-CH, ^3J 8.2 Hz, $^3J_{HCNH}$ 1.8 Hz), 7.3 (br. s, 2H, 2HN); (CD_3OD): 2.93 (s, 6H, 2Me), 5.24 (d, 1H, HC, ^3J 8.4 Hz), 5.34 (d, 1H, HC, ^3J 8.4 Hz).

1 + **2**, co-crystal: mp 254 °C (H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.60 (s, 6H, 2Me), 2.80 (s, 6H, 2Me), 5.10 (s, 2H, 2HC), 5.11 (d, 1H, 1-CH, ^3J 8.2 Hz), 5.17 (br. s, 1H, 5-CH, ^3J 8.2 Hz), 7.35 (br. s, 2H, 2HN), 7.50 (br. s, 2H, 2HN); (CD_3OD): 2.76 (s, 6H, 2Me), 2.93 (s, 6H, 2Me), 5.24 (d, 1H, $1H_c$), 5.25 (s, 2H, $2H_c$), 5.34 (d, 1H, 1HC, ^3J 8.4 Hz).

3: mp 148–149 °C (AcOEt). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.13 (t, 3H, *Me*CH_2, ^3J 7.15 Hz), 2.68 (s, 3H, MeN), 2.82 (s, 3H, MeN), 3.25 (m, 2H, CH_2N, ABX_3 spectrum, $\Delta\nu$ 56.0 Hz, $^2J_{ab}$ –14.3 Hz, $^3J_{ax} = {}^3J_{bx} =$ = 7.15 Hz), 5.05 (dd, 1H, 1-CH, $^3J_{1,5}$ 8.2 Hz, $^3J_{1,8}$ 1.6 Hz), 5.16 (d, 1H, 5-CH, ^3J 8.2 Hz), 7.5 (br. s, 1H, HN); ($CDCl_3$): 1.17 (t, 3H, *Me*CH_2, ^3J 7.1 Hz), 2.79 (s, 3H, MeN), 2.94 (s, 3H, MeN), 3.34 (ddq, 2H, CH_2N, ABX_3 spectrum, $\Delta\nu$ 120.0 Hz, $^3J_{ax} = {}^3J_{bx}$ = 7.1 Hz, $^2J_{ab}$ –14.3 Hz), 5.00 (d, 1H, 1HC, ^3J 8.4 Hz), 5.05 (d, 1H, 1HC, ^3J 8.4 Hz), 7.23 (br. s, 1H, HN). ^{13}C NMR ($CDCl_3$) δ: 13.0 (qt, *Me*CH_2, ^1J 127.0 Hz, ^2J 3.1 Hz), 27.8 (q, MeN, ^1J 138.4 Hz), 30.3 (q, MeN, ^1J 138.0 Hz), 36.9 (tq, CH_2N, ^1J 138.0 Hz, ^2J 4.5 Hz), 66.0 (d, ^1J 167.0 Hz), 71.4 (d, CH, ^1J 166.0 Hz), 158.4 (sept, 7-CO, ^3J 3.0 Hz), 160.1 (br. s, 3-CO).

B: mp 240 °C (H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.06 (t, 6H, 2Me, ^3J 6.9 Hz), 3.20 (m, 4H, $2CH_2N$, ABX_3 spectrum, $\Delta\nu \approx 60$ Hz, $^2J_{ab}$ –14.0 Hz, $^3J_{ax} = {}^3J_{bx}$ = 6.9 Hz), 5.17 (dt, 1H, 5-CH, $^3J_{1,5}$ 8.4 Hz, $^3J_{HCNH}$ 2.2 Hz), 5.36 (d, 1H, 1-CH, ^3J 8.4 Hz), 7.38 (br. s, 2H, 2HN).

crystal growth for X-ray diffraction study of **3**[4]) gives large-sized crystals (up to 20–30 mg). However, no optical activity was detected for any individual crystal selected in several tens of our experiments. This can be explained by epitaxy phenomena (*cf.* refs. 13–18), and the fact that a piece of the crystal suitable for X-ray analysis was cut out from such a splice and used in the experiments.[4] Many of 2-mono-R- (R = Me, Et, Pr^n) and 2,4,6-tri-R-substituted (R = Me, Et) glycolurils do not give well-formed crystals.

Based on the results, we can state that the enantiomers of **A**[1] obtained by spontaneous resolution are the precursors of choice for the synthesis of chiral drugs such as Albicar and its analogues.

The basic geometric parameters of **1** and **1** + **2** do not depend on the type of isomer, and actually do not differ from those described earlier.[1–4,10–12] The angle between the root-mean-square planes of five-membered rings in **1** and **1** + **2** varies in a range of 118.7–120.3°.

Analysis of the crystal packing show that (similarly to **A**[1]) the molecules in **1** are combined with N–H··O=C bonds into a homochiral three-dimensional H-bonded framework formed by two helices of the molecules directed along the crystallographic axis *a* [H-bond N(4)–H(4N)··O(1′)] and along the axis *b* [H-bond N(8)–H(8N)··O(2′)] (Figure 3). It is interesting that in a molecule of 3,7-diazabicyclo[3.3.1]nonane-2,6-dione [which is similar to **1** in terms of potential donors and acceptors of protons, and

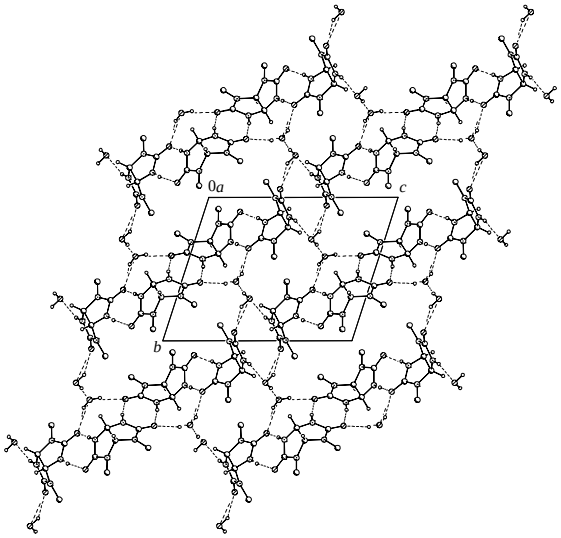


Figure 2 Projection of the crystal structure of **1** + **2** on the crystallographic plane *bc*.

‡ *Crystallographic data for* **1** *and* **1** + **2**: crystals of **1** ($C_6H_{10}N_4O_2$) are orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 4.421(2)$ Å, $b = 7.950(3)$ Å, $c = 22.473(7)$ Å, $V = 789.8(5)$ Å^3, $M = 170.18$, $d_{calc} = 1.431$ g cm^{-3}, μ(MoKα) = 1.11 cm^{-1}, $F(000) = 360$; crystals of **1** + **2** ($C_{12}H_{22}N_8O_6$) are triclinic, $Z = 2$, space group $P\bar{1}$, $a = 5.771(4)$ Å, $b = 11.114(7)$ Å, $c = 14.053(9)$ Å, $\alpha = 106.52(5)°$, $\beta = 98.51(5)°$, $\gamma = 96.16(5)°$, $V = 843.9(9)$ Å^3, $M = 376.39$, $d_{calc} = 1.481$ g cm^{-3}, μ(MoKα) = 1.21 cm^{-1}, $F(000) = 360$. Intensities of 1154 (for **1**) and 4767 (for **1** + **2**) reflections were measured on a Siemens P3 diffractometer [λ(MoKα) = 0.71072 Å, $\theta/2\theta$-scans, $2\theta < 56°$] at 298 and 153 K, respectively; 1154 and 3971 independent reflections were used in the 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 riding model was used for the methyl hydrogen atoms in **1**. The refinement converged to $wR_2 = 0.1029$ and GOF = 0.954 for all independent reflections [$R_1 = 0.0343$ was calculated against F for 679 observed reflections with $I > 2\sigma(I)$] for the structure of **1** and to $wR_2 = 0.1725$ and GOF = 1.080 for all independent reflections [$R_1 = 0.0562$ was calculated against F for 3484 observed reflections with $I > 2\sigma(I)$] for the structure of **1** + **2**. All calculations were performed using the SHELXTL PLUS 5.0 program. 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, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/91.

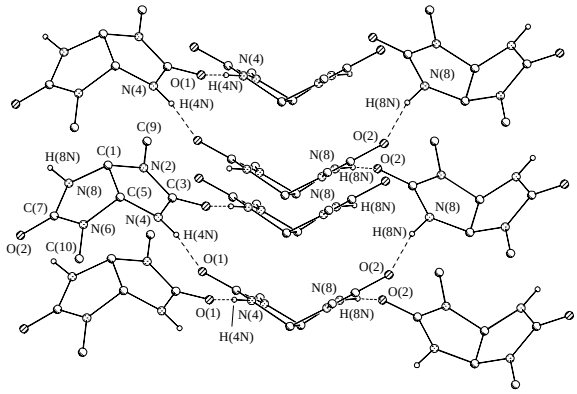


Figure 3 Three-dimensional H-bonded framework in the crystal structure of **1**. The N··O distances are N(4)··O(1′) 2.809(3) Å, N(8)··O(2) 2.848(3) Å.

for which the formation of a conglomerate (space group $P2_12_12_1$) is also observed] the two perpendicular H-bonded helices combine bicycles into a homochiral layer.[19]

Like **1**, achiral monohydrate **2** is crystallised in a chiral space group of $P2_12_12_1$;[10] however, the molecules of **2** are combined into a helix by an eight-membered H-ring rather than an H-bond, as it takes place in **1** and **A**. Thus, **1** and **2**, which crystallise individually in chiral space groups, form a centrosymmetric co-crystal. The principal distinction of its crystal packing is the absence of an infinite N–H··O bonded structure (Figure 1). The basic structure unit in **1** + **2** is an H-bonded heterochiral tetramer, in which the enantiomers of **1** are not connected (Figure 2).

Two solvate molecules of H_2O in the structure **1** + **2** play different roles. The molecule O(1w) links additionally **1** and **2**, whereas O(2w) combines tetramers into heterochiral zigzag chains similar to those observed, for example, in the racemic crystals of substituted diazabicyclo[3.3.1]nonanes.[19] The associated solvate molecules of H_2O combine these chains into a three-dimensional H-bonded framework (Figure 2).

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