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Stereoregular self-assembling of diastereomeric bicyclic bis-lactam diesters

Remir G. Kostyanovsky,*[a] Oleg N. Krutius,[a] Irina A. Bronzova,[a] Denis A. Lenev,[b] Konstantin A. Lyssenko[c] and Boris B. Averkiev[c]

[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] *Higher Chemical College, Russian Academy of Sciences, 125047 Moscow, Russian Federation.*
E-mail: lenev@hotmail.com
[c] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813 Moscow, Russian Federation.*
Fax: +7 095 135 5085; e-mail: kostya@xrlab.ineos.ac.ru

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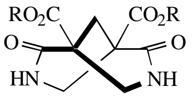
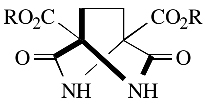
Unprecedented self-assembling of diastereomers has been found in (*S*)-2-methylbutyl-bis-lactam dicarboxylates 1 and 2, which were not resolved into diastereomers by crystallization but formed optically active H-bonded supramolecular structures of the diastereomeric ratio 1:1.

As we have observed earlier, the basic features of H-bonded heterochiral self-assembling of the molecules of bicyclic bis-lactam diesters **A** and **B** in crystals remained surprisingly constant regardless of the type of R in CO_2R groups,[1–4] and the tight-packed infinite tapes of diagonal (for **A**)[1,2] and linear (for **B**)[3,4] zigzag types were formed, *i.e.*, co-crystallization of enantiomers essentially occurred.



A, R = Et,[1] dodecyl[2]



B, R = Me,[4] Et,[3] Pr[4]

Is it possible to carry out a self-assembling of similar molecules to form optically active supramolecular structures, which are of potential interest as liquid crystals and non-linear optics materials? In principle, the presence of functional substituents like CO_2R groups makes it possible to introduce homochiral alcohol or amine residues into these molecules. However, this results in formation of diastereomer mixtures, which are well known to be resolved by crystallization. The main task of this work is to determine which way takes place in case of **1** and **2**, either resolution of the diastereomers by crystallization or their co-crystallization. The recently found co-crystallization rather than resolution of various configurationally opposite bis-lactam diesters like **B** (R = Et and Me, R = Et and Pr)[4] serves as a premise for the latter way.

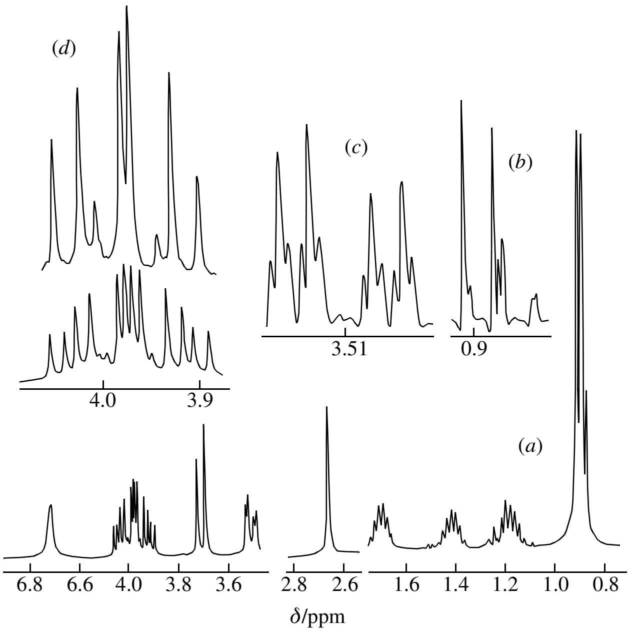
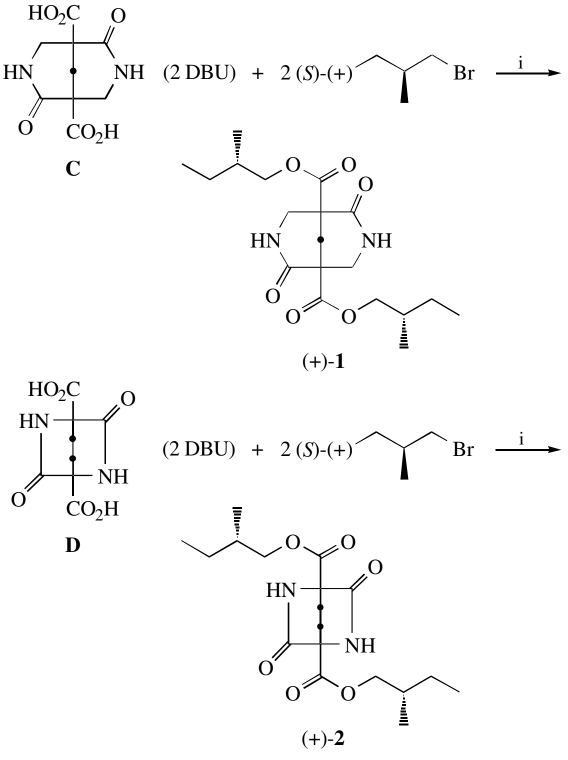


Figure 1 ^{1}H NMR spectrum (CD_3CN) of bis-(*S*)-2-methylbutyl 3,7-diazabicyclo[3.3.1]nonane-2,6-dione-1,5-dicarboxylate: (*a*) general view of the spectrum, (*b*) signals of *Me*CH_2 of the diastereomers, (*c*) *Me*CH signals of 4,8-H_e by which the virtual spin-coupling constants with 9-CH_2 protons are observed ($^4J_{obs}$ 1.3 Hz) and (*d*) signals of $OCH_aH_bCH_x$ of the diastereomers **a**, **b** [spectra ABX (below) and AB{H_x} (above)].

The synthesis[†] of bis-lactam diesters **1** and **2** containing homochiral groups R = (*S*)-Et(Me)$CHCH_2$ was affected *via* esterification of bis-lactam diacids **C**[2] and **D**[5] by alkylation of their salts with 1,8-diazabicyclo[5.1.0]undec-7-ene (DBU) using a known method.[6] (*S*)-(+)-2-Methylbutyl bromide was obtained from (*S*)-(–)-2-methylbutan-1-ol using a known method.[7]

The structure and diastereomeric composition (1:1) of both products (+)-**1** and (+)-**2** were confirmed by ^{1}H and ^{13}C NMR spectra[†] (Figure 1), the parameters of which corresponded to those of analogues **A**, **B** and related co-crystals.[4] It should be noted that diastereomers **a** and **b** for both **1** and **2** differ distinctively in the ^{1}H NMR signals of diastereotopic protons of CH_2O groups nearest to a chiral skeleton of diastereomers of



Scheme 1 *Reagents and conditions*: i, the salts were obtained from diacids **C**, **D** and DBU in MeOH; after removing the solvent the salt of **C** was kept with an alkyl bromide in MeCN (14 h at 20 °C), and the salt of **D** was boiled in MeCN (6 h). Compound (+)-**1** was isolated by gradient chromatography on silica (40×100, eluent: light petroleum ether–ethyl acetate, 0 → 30%), and (+)-**2**, by chromatography on silica (eluent: ethyl acetate–MeCN, 1:1).

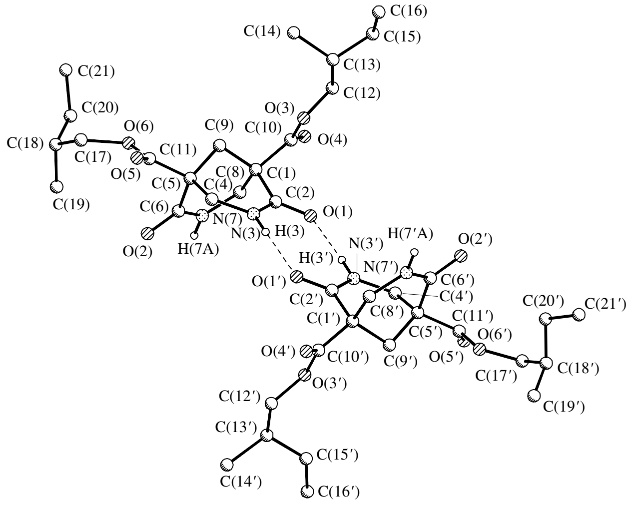


Figure 2 General view of two independent molecules of (+)-**1**. Disordered ester groups are omitted for clarity.

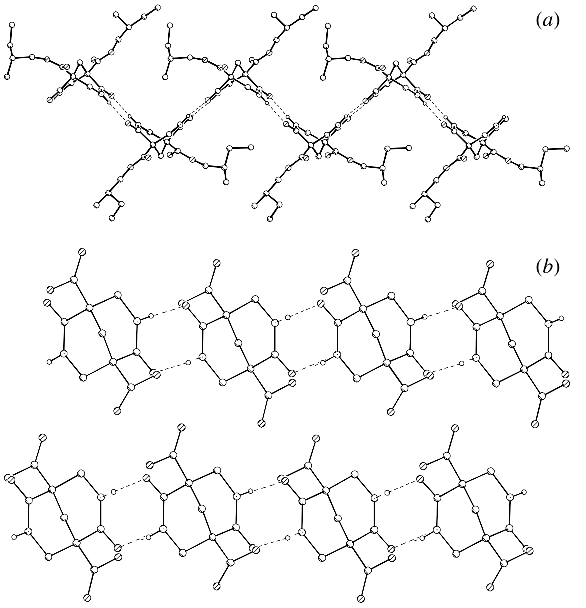


Figure 3 Diagonal zigzag (*a*) tapes and (*b*) layers (2-methylbutyl groups are omitted for clarity). Parameters of the N–H···O bonds: N···O, 2.795–2.908(3) Å; H···O, 1.81–2.12 Å; ∠NHO, 170–178°. Parameters of the C–H···O bonds: C···O, 3.490–3.539(3) Å; H···O, 2.47–2.52 Å; ∠CHO, 158–159°.

opposite configuration [Figure 1(*d*)]. The concentration dependence of δ_{HN} is the evidence for molecular self-association in solution (*cf.* ref. 8).

The optical activity of (+)-**1** and (+)-**2** was measured by polarimetry and CD spectroscopy[†] (*cf.* ref. 4).

The structure and composition of (+)-**1** were determined by X-ray diffraction analysis.[‡] It was found that the unit cell contains two independent molecules, which are diastereomers (Figure 2). Thus crystal of (+)-**1** is a 1:1 co-crystal of diastereomers, which has non-centrosymmetrical space group *P*1.

The geometry of central bicyclic fragments of two independent molecules is practically identical to that of previously studied diethyl and didodecyl derivatives.[1,2] The angle between C(1)–C(7)–C(10) and CO_2 planes varies in the range 59.5–68.5°.

In spite of the presence of chiral groups, two independent molecules are arranged pseudocentrosymmetrically (Figure 2)

[†] *(S)-(+)-1-Bromo-2-methylbutane*: bp 55 °C (80 torr), $[\alpha]_D^{20}$ 4.5° (*c* 5.0, $CHCl_3$). ^{1}H NMR ([$^2H_6$]acetone) δ: 0.91 (t, 3H, *Me*CH_2, ^3J 7.4 Hz), 1.00 (d, 3H, *Me*CH, ^3J 6.4 Hz), 1.28 and 1.50 (m, 2H, CH_2Me), 3.45 (m, 2H, CH_2Br, ABX spectrum, $\Delta\nu_{AB}$ 10.5 Hz, $^2J_{AB}$ –9.6 Hz, $^3J_{AX}$ 6.0 Hz, $^3J_{BX}$ 5.2 Hz).

For **1**: yield 10%, mp 135–136 °C (from C_6H_6), $[\alpha]_{578}^{20}$ 4.1°, $[\alpha]_{546}^{20}$ 4.8°, $[\alpha]_{436}^{20}$ 9.3°, $[\alpha]_{406}^{20}$ 10.8° (*c* 1.3, MeCN); $[\alpha]_{578}^{20}$ 4.8°, $[\alpha]_{546}^{20}$ 6.0°, $[\alpha]_{436}^{20}$ 10.7°, $[\alpha]_{406}^{20}$ 14.3° (*c* 0.84, C_6H_6). ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 6H, 2*Me*CH_2, ^3J 7.5 Hz), 0.88 (d, 6H, 2*Me*CH, ^3J 6.7 Hz), 1.17 and 1.40 (m, 4H, 2CH_2Me), 1.75 (m, 2H, 2CH), 2.62 (br. s, 2H, 9-CH_2), 3.72 (m, 4H, 4,8-CH_2, ABX, diastereomer **a**: Δν 40 Hz, $^2J_{AB}$ –12.5 Hz, $^3J_{H_aCNH}$ 4.3 Hz, $^3J_{H_bCNH}$ 0 Hz), 4.02 (m, 4H, CH_2O, diastereomer **a**: ABX, Δν 40 Hz, $^2J_{AB}$ –10.9 Hz, $^3J_{AX}$ 4.8 Hz, $^3J_{BX}$ 4.4 Hz; diastereomer **b**: ABX, Δν 30 Hz, $^2J_{AB}$ –10.9 Hz, $^3J_{AX}$ 4.8 Hz, $^3J_{BX}$ 4.4 Hz), 7.93 (br. d, 2H, 3,7-NH, ^3J 4.3 Hz, diastereomer **a**), 7.94 (br. d, 2H, 3,7-NH, ^3J 4.3 Hz, diastereomer **b**). ^{1}H NMR (CD_3CN) δ: 0.890 and 0.893 (t, 6H, 2*Me*CH_2, diastereomers **a** and **b**, ^3J 7.1 Hz), 0.90 (d, 6H, 2*Me*CH, ^3J 6.7 Hz), 1.18 and 1.42 (m, 4H, 2CH_2Me), 1.70 (m, 2H, 2CH), 2.66 (t, 2H, 9-CH_2, $^4J_{obs}$ 1.3 Hz), 3.51 (ddt, 2H, 4,8-Me, ^2J –12.4 Hz, $^3J_{HCNH}$ 4.0 Hz, $^4J_{obs}$ 1.3 Hz), 3.70 (d, 2H, 4,8-H_a, ^2J –12.4 Hz), 3.97 (m, 4H, 2CH_2O, diastereomer **a**: ABX, Δν 46.8 Hz, $^2J_{AB}$ –10.8 Hz, $^3J_{AX}$ 6.4 Hz, $^3J_{BX}$ 6.0 Hz; diastereomer **b**: ABX, Δν 12.0 Hz, $^2J_{AB}$ –10.8 Hz, $^3J_{AX}$ 6.4 Hz, $^3J_{BX}$ 6.0 Hz), 6.67 (br. d, 2H, 3,7-NH, ^3J 4.0 Hz). At a five-fold increase of concentration (56.8 mg in 0.5 ml) δ_{HN} 6.92 ppm. ^{13}C NMR (CD_3CN) δ: 10.75 (q, *Me*CH_2, ^1J 125.1 Hz), 15.85 (q, *Me*CH, ^1J 125.1 Hz), 26.00 (t, *C*H_2Me, ^1J 125.1 Hz), 33.20 (t, 9-CH_2, ^1J 136.6 Hz), 34.37 (d, CH, ^1J 126.6 Hz), 47.90 (t, 4,8-CH_2, ^1J 147.2 Hz), 49.60 (s, 1,5-C), 70.0 (t, CH_2O, ^1J 147.2 Hz), 168.4 and 169.2 (s, CO). It was shown by ^{1}H NMR monitoring that **1** is not resolved under various conditions such as sublimation (140–160 °C, 1 torr), crystallization from C_6H_6 or MeOH, gradient chromatography (see Scheme 1), and TLC on silica gel 60F_{254} (‘Merck’, the thickness of a separating layer is 0.2 mm). In the latter method, an acetone solution of **1** (5%) was applied (exposure of 10 min, iodine vapour as a visualising agent); the only spot, $R_f = 0.55$, was observed. Similar results were obtained using other solvent systems.

For **2**: yield 39%, mp 195–197 °C, $[\alpha]_{578}^{20}$ 4.1°, $[\alpha]_{546}^{20}$ 4.7°, $[\alpha]_{436}^{20}$ 8.8°, $[\alpha]_{406}^{20}$ 10.0° (*c* 0.9, MeCN). CD spectrum in MeCN (*c* 3×10^{-3} M), Δε (λ_{max}/nm): –0.95 (214), +0.76 (208), –1.4 (203.2). ^{1}H NMR (C_6D_6) δ: 0.75 and 0.77 (t, 6H, 2*Me*CH_2, ^3J 7.5 Hz, diastereomers **a** and **b**), 0.79 and 0.81 (d, 6H, *Me*CH, ^3J 6.7 Hz, diastereomers **a** and **b**), 0.88, 1.00, and 1.27 (m, 4H, 2CH_2Me), 1.55 (m, 2H, CH), 1.50 and 1.96 [m, 4H, $(CH_2)_2$, AA′BB′], 3.97 (m, 2H, CH_2O, ABX, $\Delta\nu_{AB}$ 70.0 Hz, $^2J_{AB}$ –10.4 Hz, $^3J_{AX}$ 6.8 Hz, $^3J_{BX}$ 5.6 Hz, diastereomer **a**), 3.97 (m, 2H, CH_2O, AB, Δν ≈ ≈ 12.0, $^2J_{AB}$ –10.5 Hz, $^3J_{AX} = {}^3J_{BX} = 0$ Hz), 6.72 (s, 2H, HN). ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 6H, 2*Me*CH_2, ^3J 7.4 Hz), 0.94 (d, 6H, 2*Me*CH, ^3J 6.7 Hz), 1.21 and 1.44 (m, 4H, 2CH_2Me), 1.79 (m, 2H, 2CH), 2.27 and 2.46 [m, 4H, $(CH_2)_2$, AA′BB′], 4.15 (m, 2H, CH_2O, ABX, Δν 40.0 Hz, $^2J_{AB}$ –10.6 Hz, $^3J_{AX}$ 8.0 Hz, $^3J_{BX}$ 6.0 Hz, diastereomer **a**), 4.15 (m, 2H, CH_2O, ABX, Δν 20.0 Hz, $^2J_{AB}$ –10.5 Hz, $^3J_{AX}$ 6.8 Hz, $^3J_{BX}$ 6.0 Hz, diastereomer **b**), 6.96 (br. s, 2H, HN). ^{13}C NMR ($CDCl_3$) δ: 10.60 (q, *Me*CH_2, ^1J 124.7 Hz), 16.16 (q, *Me*CH, ^1J 126.0 Hz), 25.76 (t, *C*H_2Me, ^1J 127.5 Hz), 27.99 [t, $(CH_2)_2$, ^1J 134.3 Hz], 33.91 (d, CH, ^1J 129.3 Hz), 64.74 (s, 4,7-C), 71.35 (t, CH_2O, ^1J 141.6 Hz), 165.60 and 167.20 (s and t, O=*C*OCH_2, ^3J 6.6 Hz).

[‡] *Crystallographic data for* **1**: at 110 K, crystals of $C_{19}H_{30}N_2O_6$ are triclinic, space group *P*1, $a = 9.752(3)$, $b = 10.888(3)$, $c = 11.310(3)$ Å, $\alpha = 103.236(5)°$, $\beta = 115.168(4)°$, $\gamma = 100.874(5)°$, $V = 1000.7(5)$ Å^3, $Z = 2$, $M = 382.45$, $d_{calc} = 1.269$ g cm^{-3}, μ(MoKα) = 0.094 mm^{-1}, $F(000) = 412$. Intensities of 11915 reflections were measured with a SMART 1000 CCD diffractometer at 110 K [λ(MoKα) = 0.710712 Å, ω-scans with a 0.4° step and 10 s per frame exposure, $2\theta < 60°$], and 10496 independent reflections (R_{int} = 0.0168) were used in the further refinement. The structure was solved by a direct method and refined by full-matrix least-squares against F^2 in the anisotropic approximation for non-hydrogen atoms using the SHELXTL-97 package. All hydrogen atoms (with the exception of ester hydrogens) were located from the electron density difference synthesis and included in the refinement in an isotropic approximation. The real parameters of the unit cell are twice higher than the parameters used for the refinement procedure. While molecules in the latter unit cell appeared to be disodered, the twinned unit cell contains four independent molecules without disordering. Unfortunately, the correlation between identical central fragments of these four molecules does not allow us to carry out a correct refinement. The positions of hydrogen atoms of disodered ester were calculated from the geometrical point of view. The refinement converged to $wR_2 = 0.1608$ and GOF = 1.061 for all independent reflections [$R_1 = 0.0549$ was calculated against *F* for 8822 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using the SHELXTL PLUS 5.0 program 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.*, Issue 1, 2001. Any request to the CCDC should quote the full literature citation and the reference number 1135/77.

and assembled by NH···O bonds into H-bonded diagonal zigzag tapes [Figure 3(*a*)]. The above tapes are drawn out along the [1 0 1] crystallographic direction and, in turn, are combined into layers parallel to the crystallographic plane ($\bar{1}$ 0 1) by C–H···O contacts [Figure 3(*b*)].

Thus, zigzag tapes observed in the crystals of bis-lactam derivatives are rather stable supramolecular units. They are unaffected by the introduction of chiral substituents. Therefore, the impossibility to resolve (+)-**1** and (+)-**2** into diastereomers by crystallization is an unprecedented phenomenon. Resolution did not also occur under conditions of sublimation or chromatography.[†]

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