Journal of Structural Chemistry. Vol. 60, No. 1, pp. 143-150, 2019.
Russian Text © 2019 M. S. Fonari, S. M. Pluzhnik-Gladyr, G. L. Kamalov, V. Kh. Kravtsov.

COCRYSTALLIZATION OF CHIRAL *N*7,*N*16-*bis* (*S*-1-PHENYLETHYL)-1,4,10,13-TETRAOXO-7,16-DIAZACYCLOOCTADECANE-7,16-DICARBOXAMIDE WITH HYDROCHLORIDES OF METHYL ETHERS OF LEUCINE AND VALINE ENANTIOMERS

M. S. Fonari[1], S. M. Pluzhnik-Gladyr[2], G. L. Kamalov[2], and V. Kh. Kravtsov[1]

An attempt to co-crystallize *N*7,*N*16-*bis*(*S*-1-phenylethyl)-1,4,10,13-tetraoxo-7,16-diazacyclooctadecane-7,16-dicarboxamide (**1**) with hydrochlorides of methyl ethers (HCMEs) of *L*- and *D*-valine and also *L*- and *D*-leucine results in separate crystallization of diazacrown-ether **1** (or its monohydrate **1**·H_2O) and HCMEs of respective α-amino acids. Crystal structures of *D*-leucine **1**·H_2O (**1)** and HCME (**2**) compounds, which were not described previously, are solved by single crystal X-ray diffraction.

DOI: 10.1134/S0022476619010207

Keywords: co-crystallization, crystal structure, enantiomer, crown-ether, amino acid, conformation, hydrogen bond.

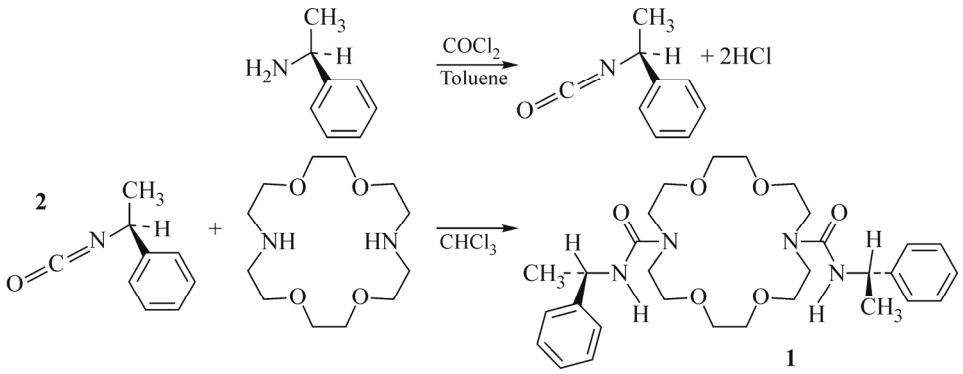
A search for the ways of effective separation of enantiomers is one of the most important problems of supramolecular chemistry [1]. Examples of the successful recognition of chiral amines and their salts by chiral macroheterocycles (in particular, derivatives of 18-crown-6 and diaza-18-crown-6) are given in reviews [2, 3]. One of the approaches to the solution of the problem being discussed is the use of solutions of chiral crown-ethers (CEs) as a liquid membrane in transporting α-amino acid racemates through it [4].

We have previously reported [5] the preparation of a series of substituted crown-ureas, including optically active *threo*-*N*7,*N*16-*bis*(*R*-1-phenylethyl)-1,4,10,13-tetraoxo-7,16-diazacyclooctadecane-7,16-dicarboxamide, by the counter synthesis.

In this work, we present data on the synthesis and structure of optically active *threo*-*N*7,*N*16-*bis*(*S*-1-phenylethyl)-1,4,10,13-tetraoxo-7,16-diazacyclooctadecane-7,16-dicarboxamidea (**1**) which we managed to obtain by the interaction of *S*-α-phenylethylisocyanate with 1,10-diaza-18-crown-6 (Scheme).

An attempt was made to consider the possibility of forming complexes of the host–guest type in the interaction (co-crystallization) of CE **1** with hydrochlorides of methyl ethers (HCMEs) of valine and leucine *R*- and *S*-enantiomers. To grow crystals suitable for the single crystal X-ray diffraction (XRD) analysis we applied a well-proven procedure (see, e.g., [6]) of diffusion of a replacing solvent carefully deposited on a solution of potential host and guest in the respective solvent.

[1]Institute of Applied Physics, Chisinau, Republic of Moldova; fonari.xray@phys.asm.md. [2]Bogatsky Physicochemical Institute, National Academy of Sciences of Ukraine, Odessa, Ukraine; sergey_pluzhnik@ukr.net. Translated from *Zhurnal Strukturnoi Khimii*, Vol. 60, No. 1, pp. 150-157, January, 2019. Original article submitted July 18, 2018; revised July 18, 2018; accepted September 07, 2018.



Scheme.

EXPERIMENTAL

The melting point was measured in an open capillary. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance DRX 500 spectrometer (499.95 MHz for ^{1}H and 125.74 MHz for ^{13}C); chemical shifts δ are given in ppm relative to TMS as the internal standard. SSI constants are given in Hz. Mass spectra (electron impact ionization) were measured on a MX 1321 apparatus using the direct sample input, ionization voltage 70 V, ionization chamber temperature 200 °C. The elemental analysis was carried out on a EuroVector EA3000 CHNS instrument. The optical rotation angle was measured on a Perkin-Elmer mc 241 polarimeter, 1 dm cuvette. Organic solvents were distilled before the use. Chloroform was dehydrated by distillation over phosphorus anhydride and diethyl ether was distilled over a sodium wire.

***S*-α-phenylethylisocyanate** was obtained by the modified procedure [7]. 40 g (147.38 mmol) of *L*-α-phenylethylamine tartrate (*S*-isomer) (TU 6-09-05-119-74) were treated with 60 ml of a 50% aqueous solution of potassium hydroxide. The released free base was extracted by toluene (40 ml×5); combined extracts were dried for 24 h with solid potassium hydroxide. At 0 °C the obtained solution was stirred for 15 min and treated with an intense flow of dry gaseous HCl. Then for 5 min an intense phosgene flow was passed through. Phosgene was obtained according to [8]. The reaction mixture was heated to boiling and treated with a phosgene flow for 3 h until the complete dissolution of the precipitate. The solvent was removed under reduced pressure (a water jet vacuum pump) and the residue was distilled. We obtained 11.77 g of *S*-α-phenylethylisocyanate (54.2%). B. p. 72-80 °C (5-10 mm), $[\alpha]_D^{20}$ + 2.24° (with 5.7 C_6H_6), –29.4° (with 2.5 *n*-C_7H_{16}), PMR δ, ppm in C_6D_6, 0.95 (MeC), 3.9 (CH), J_{MeCH} = 6.5 Hz.

Compound 1. To a solution of 2.54 g (9.68 mmol) 1,10-diaza-18-crown-6 (Pilot Plant, Physicochemical Institute, Academy of Sciences of Ukraine) in 30 ml of anhydrous chlorophorm at 0 °C a solution of 2.85 g (19.4 mmol) of S-α-phenylethylisocyanate in 20 ml of dry diethyl ether (DEE) cooled to 0 °C was added. In 24 h the solvent was distilled to dryness. The residue was washed with DEE (15 ml×3) and crystallized from a 1:5 ethanol–DEE mixture. Yield 4.79 g (89%); mp 126-127 °C. After the second crystallization from isopropanol m. p. was 133 °C (at a point).

^{1}H NMR. $CDCl_3$. 1.42-1.43, d, *J* = 6.59, 6H (Me); 3.41-3.64, m, 24H (CE); 4.88, q, *J* = 6.59, 2H (CH); 6.23-6.24, d, *J* = 5.76, 2H (NH); 7.19, t, *J* = 6.86, 2H (*n*-Ph) 7.30, m, 8H (*o*-, *m*-Ph).

^{13}C NMR. $CDCl_3$ 23.24, 2C; 50.21, 2C; 50.38, 4C; 70.71, 4C; 71.48, 4C; 126.07, 4C; 126.76, 2C; 128.39, 4C; 145.17, 2C; 158.74, 2C.

Mass: *m*/*z* (%): 556 ($[M]^+$, 2); 437($[M–MePhCHN]^+$, 3); 409 ($[M–MePhCHNHCO]^+$, 12); 263 ($[HN(C_2H_4OC_2H_4OC_2H_4)_2NH_2]^+$, 19); 132 ($[(C_2H_4O)_3]^+$, 100); 120 ($[MePhCHNH]^+$, 18); 105 ($[MePhCH]^+$ 26), 77 ($[Ph]^+$, 8).

Calculated for $C_{30}H_{44}N_4O_6$ (%): C 64.73, H 7.97, N 10.06.

Found C 64.69, H 8.01, N 10.04; $[\alpha]_D^{20}$ = +18.952 (with 2.1 $CHCl_3$).

HCMEs of *D*- and *L*-leucine and -valine were obtained similarly [9], by placing a portion of amino acid (8-12 mmol) at room temperature for 24 h in 90 ml of saturated methanol solution of chlorohydrogen. Then the solvent was removed to dryness on a rotary evaporator, the residue was washed with DEE (15 ml×3), and leucine HCME was crystallized from a 1:5 methanol–diisopropyl ether mixture (and valine from acetone) and dried in a vacuum desiccator over dry sodium hydroxide. HCME: *L*-leucine, yield 86%, m. p. 146 °C; *D*-leucine, yield 84%, m. p. 145-146 °C; *L*-valine, yield 81%, m. p. 167-168 °C; *D*-valine, yield 77%, m. p. 165-167 °C.

Co-crystallization of CE 1 with HCMEs of *D*- and *L*-leucine and -valine. A glass tube with an inner diameter of 8 mm constricted in the middle to an inner diameter of 1 mm was filled to the middle of the narrow part (by means of a pipette with a long capillary end) with a solution of an equimolar mixture of CE **1** and HCME of respective amino acid in isopropanol. *n*-Hexane was carefully deposited from above and the system was placed in a hermetic glass container. As hexane diffused into the solution of components, the crystal growth was observed.

X-ray crystallography. Structural data on the prepared compounds were obtained at room temperature in an Xcalibur CCD Oxford Diffraction diffractometer (MoK_α radiation, λ = 0.71073 Å, graphite monochromator, ω-scanning). Unit cell parameters were refined over the entire set of experimental data. Crystal structures were solved by a direct method and refined by the least squares technique in the anisotropic full-matrix variant for non-hydrogen atoms. Positions of hydrogen atoms of a water molecule in hydrate **1**·H_2O were found from the Fourier difference maps. Positions of the other hydrogen atoms were calculated geometrically and refined isotropically in the rigid body model. All calculations were performed in the SHELX-2014 program package [10]. The refinement was carried out using a set of F^2 values of the structural data.

In a molecule of CE **1** two fragments of oxyethylene chains are disordered over two positions and refined with occupancy multiplicities of 0.67(1) and 0.33(1) for the C3–O3–C4–C5–O4 fragment and 0.712(8) and 0.288(8) for the C9–O5 fragment. Crystallographic data and characteristics of the experiment for compounds **1**, **1**·H_2O, and **2** are summarized in Table 1; the parameters of hydrogen bonds are listed in Table 2; some torsion angles of a molecule of CE **1** are given in Table 3; geometric parameters for compound **2** are gathered in Table 4. Crystallographic data for compounds **1**, **1**·H_2O, and **2** have been deposited with the Cambridge Crystallographic Data Center (CCDC No CIF files CCDC No 1856189-1856191, deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

Four experiments on co-crystallization of CE **1** with HCME of *R*-enantiomer (**A**) and *S*-enantiomer (**B**) of valine and also with HCME of *S*-enantiomer (**C**) and *R*-enantiomer (**D**) of leucine were performed. For **A** two groups of crystals were successively isolated: monohydrate with the composition **1**·H_2O and initial HCME of *D*-valine whose parameters correspond to those deposited with CCDC (Refcode HABXAK [11], stereoisomer RAJKUK [12]). For **B** transparent crystals corresponding to CE **1** proved to be suitable for the measurement. In experiment **C** a mixture of crystals forms: blocks corresponding to CE **1** and thin needles (seems to be a guest) whose structure was not solved. Finally, for **D** also two types of crystals were found: bulk transparent crystals corresponding to CE **1** and needle-like crystals of better quality than those in sample **C**, identified as HCME of *D*-leucine. Data on the structure of the latter are absent in CCDC.

CE **1** crystallizes in the orthorhombic space group $P2_12_12_1$ (Table 1). Ordered fragments of the molecule are characterized by interatomic distances and bond angles similar to those of substituted diaza-CEs [13]. The molecule takes a general position in the cell and has an *S*-like shape (Fig. 1*a*). The macroheterocycle is elongated towards substituents, which is indicated by substantially different *trans*-annular distances between heteroatoms, namely, an increased distance N(3)…N(4) = 7.549(5) Å as compared to distances O(4)…O(6) = 6.40(2) Å and O(3)…O(5) = 4.11(2) Å.

Phenylcarbamide moieties of the CE **1** molecule are located on both sides of the middle plane of the 18-membered heterocycle and are differently oriented relative to it: the phenyl ring [C(15)–…–C(20)] is almost orthogonal to the

TABLE 1. Crystallographic Data and Characteristics of the Experiment for Compounds **1**, **1**·H_2O, and **2**

Parameter	Value		
	1	**1**·H_2O	**2**
CCDC number	1856189	1856191	1856190
Chemical formula	$C_{30}H_{44}N_4O_6$	$C_{30}H_{46}N_4O_7$	$C_7H_{16}ClNO_2$
M	556.69	574.71	181.66
Crystal symmetry	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a, Å	8.8073(6)	9.9593(5)	5.3194(5)
b, Å	16.8364(8)	10.1522(5)	9.2599(8)
c, Å	20.6508(11)	15.6925(10)	21.3073(18)
β, deg	90	99.618(5)	90
V, Å^3; Z	3062.2(3); 4	1564.35(15); 2	1049.53(16); 4
ρ(calc.), g/cm^3	1.208	1.220	1.150
μ, mm^{-1}	0.084	0.087	0.325
F(000)	1200	620	392
θ range, deg	3.122-25.250	3.068-25.047	3.615-25.038
Ranges of reflection indices	$-7 \le h \le 10$, $-18 \le k \le 19$, $-24 \le l \le 12$	$-11 \le h \le 10$, $-10 \le k \le 12$, $-9 \le l \le 18$	$-4 \le h \le 6$, $-5 \le k \le 11$, $-16 \le l \le 25$
Number of meas. / indep. reflections (R_{int})	7003 / 4870 (R_{int} = 0.0264)	5314 / 4272 (R_{int} = 0.0200)	2464 / 1733 (R_{int} = 0.0314)
Number of reflections with $I > 2\sigma(I)$	2972	2964	1080
Number of refined parameters	419	378	112
$GOOF$	1.019	0.998	0.983
R_1, wR_2 ($I > 2\sigma(I)$)	0.0611, 0.1170	0.0489, 0.0937	0.0550, 0.0719
R_1, wR_2 (entire set)	0.1128, 0.1416	0.0792, 0.1058	0.0965, 0.0824
$\Delta\rho_{max}$, $\Delta\rho_{min}$, e/Å^3	0.149, –0.171	0.127, –0.160	0.254, –0.149

TABLE 2. Hydrogen Bonds in Compounds **1**, **1**·H_2O, and **2**

Donor–H…Acceptor	d(H…A), Å	d(D…A), Å	∠(DHA), deg	Symmetry transformation for the acceptor
		1		
N(2)–H(2)…O(1)	2.21	3.043(5)	162.9	x+1/2, 1/2–y, 2–z
N(1)–H(1)…O(2)	2.25	3.066(5)	158.2	2–x, y+1/2, 3/2–z
		1·H_2O		
N(1)–H(1)…O(1W)	2.35	3.189(6)	165.2	x, y, z
N(2)–H(2)…O(4)	2.22	2.891(4)	135	x, y, z
O(1W)–H(1W)…O(6)	2.12(3)	2.907(5)	151(6)	x, y, z
O(1W)–H(2W)…O(2)	1.87(3)	2.735(5)	170(6)	x, y, z
		2		
N(1)–H(1N)…Cl(1)	2.13(2)	3.153(4)	178(3)	x+1/2, 3/2–y, 2–z
N(1)–H(2N)…Cl(1)	2.12(2)	3.121(5)	169(4)	x+1, y+1, z
N(1)–H(3N)…Cl(1)	2.16(2)	3.166(5)	172(3)	x, y+1, z
C(5)–H(5)…O(2)	2.48	3.453(6)	170	x+1, y, z

TABLE 3. Torsion Angles in the Heterocyclic Core of Macrocycle **1**

Parameter	**1**, deg	**1**·H_2O, deg
N3–C2–C3–O3	–178.3(9)	–61.8(4)
C2–C3–O3–C4	–178(2)	–179.6(4)
C3–O3–C4–C5	178(2)	–177.5(4)
O3–C4–C5–O4	–79(4)	72.5(5)
C4–C5–O4–C6	178(2)	–168.0(4)
C5–O4–C6–C7	–154(3)	–177.6(5)
O4–C6–C7–N4	–51(1)	–71.4(6)
C6–C7–N4–C8	71.0(6)	–99.1(5)
C7–N4–C8–C9	75(1)	77.7(6)
N4–C8–C9–O5	–169(1)	59.8(7)
C8–C9–O5–C10	–160(1)	150.7(4)
C9–O5–C10–C11	171(1)	167.0(4)
O5–C10–C11–O6	85.0(7)	62.5(5)
C10–C11–O6–C12	–169.9(5)	–138.7(4)
C11–O6–C12–C13	89.6(5)	76.1(5)
O6–C12–C13–N3	73.5(5)	168.7(3)
C12–C13–N3–C2	–81.1(6)	98.2(4)
C13–N3–C2–C3	–86.5(5)	88.3(5)

TABLE 4. Interatomic Distances and Bond Angles in Compound **2**

Parameter	*d*, Å	Parameter	ω, deg
O(1)–C(6)	1.332(6)	C(6)–O(1)–C(7)	114.9(5)
O(1)–C(7)	1.473(5)	C(2)–C(3)–C(1)	111.5(5)
O(2)–C(6)	1.187(6)	C(2)–C(3)–C(4)	113.3(5)
N(1)–C(5)	1.490(5)	C(1)–C(3)–C(4)	109.3(4)
C(1)–C(3)	1.523(6)	C(3)–C(4)–C(5)	117.1(4)
C(2)–C(3)	1.519(6)	N(1)–C(5)–C(6)	106.7(4)
C(3)–C(4)	1.521(6)	N(1)–C(5)–C(4)	108.5(4)
C(4)–C(5)	1.525(5)	C(6)–C(5)–C(4)	112.6(4)
C(5)–C(6)	1.526(6)	O(2)–C(6)–O(1)	127.1(6)
		O(2)–C(6)–C(5)	124.1(6)
		O(1)–C(6)–C(5)	108.8(5)

macrocycle, which is evidenced by a dihedral angle of 83.12° whereas the phenyl ring [C(24)–…–C(29)] is practically parallel to the middle plane of the heterocycle, which is evidenced by a dihedral angle of 5°. In the crystal of CE **1** each molecule is engaged in four hydrogen bonds NH…O through both amide moieties (Table 2) with four nearest molecules, generating a three-dimensional hydrogen-bonded motif (Fig. 1*b*).

Monohydrate **1**·H_2O crystallizes in the monoclinic space group $P2_1$ (Table 1, Fig. 2). In the complex the CE molecule takes a form completely different from that of **1**, which has an appreciably changed conformation of the heterocycle and the arrangement of substituents. This changes occurs due to the penetration of a water molecule involved in three intermolecular H bonds: by both hydrogen atoms into two OH…O bonds and one lone pair of the oxygen atom into the NH…O bond (Table 2). The second amide group is engaged into the intramolecular H bond N(2)…O(4) = 2.891(4) Å. Heteroatoms of the macrocycle are essentially non-coplanar; nitrogen atoms deviate to one side from the plane drawn through four oxygen atoms by 1.38 Å and 1.46 Å, and the heterocycle takes a saddle shape. Here the range of *trans*-annular O…O

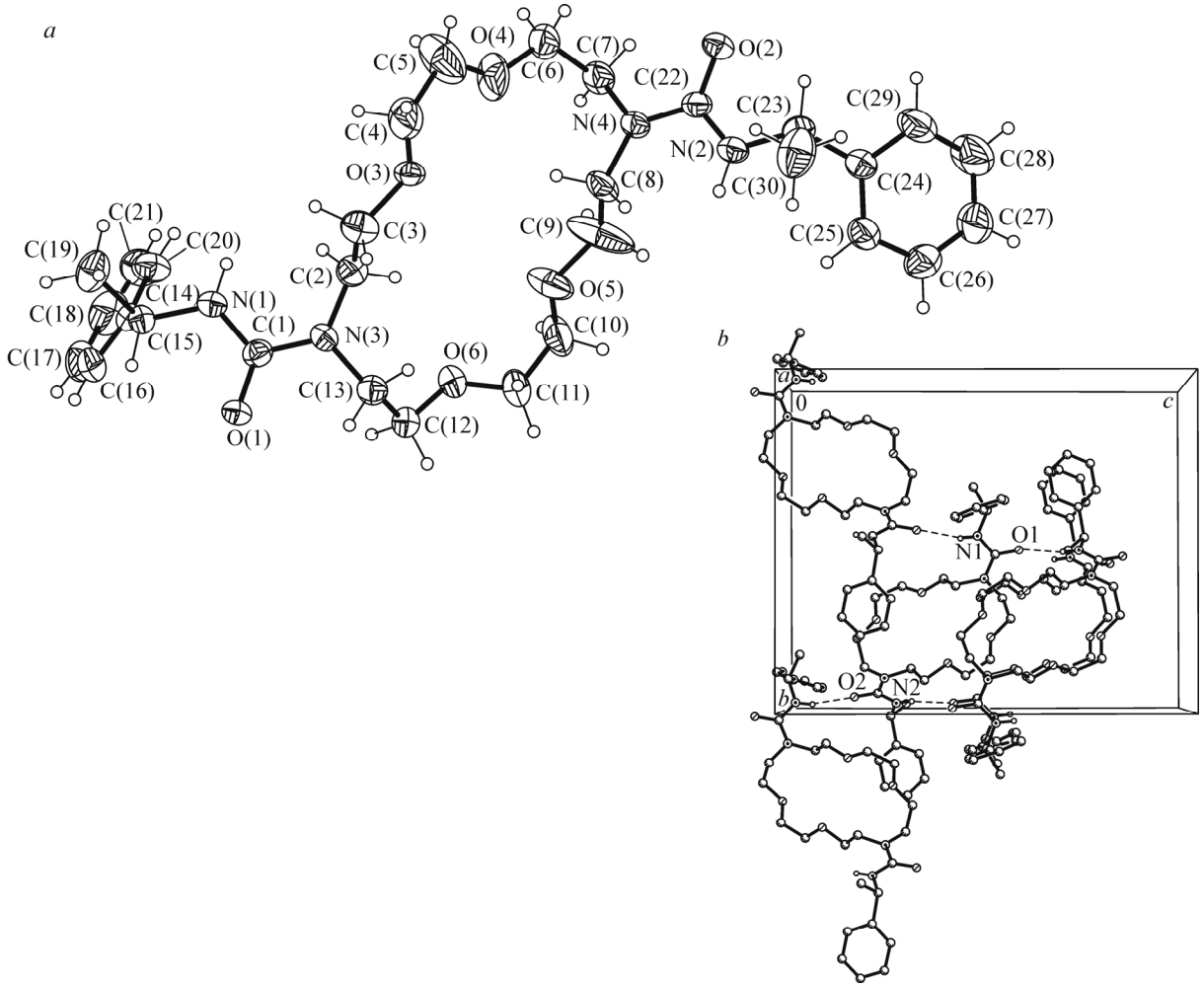


Fig. 1. ORTEP diagram of compound **1** with atom numbering (thermal ellipsoids are drawn at a 30% probability level; the second position for disordered fragments is not shown) (*a*); fragment of packing with showing atoms involved in hydrogen bonds (hydrogen atoms bonded to carbon atoms are omitted) (*b*).

and N…N distances narrows from 5.019(5) Å to 5.974(4) Å as compared with CE **1**, which indicates their equidistance. The macrocycle conformation is described by a sequence of torsion angles listed in Table 3.

In adduct **1**·H_2O both phenyl substituents are located on one side of the macrocyclic cavity and are turned to opposite sides, forming a dihedral angle between the planes of aromatic rings of 82.62°. Only van der Waals interactions exist between bulky molecular complexes **1**·H_2O in the crystal.

A comparison of the structures of CE **1** and its monohydrate **1**·H_2O gives evidence of a significant conformational rearrangement of the macrocycle molecule in the latter (which also follows from the comparison of the respective torsion angles (Table 3) in the macrocyclic fragment of **1**) It is accompanied by blocking active (for complexation with guests) centers of the molecule.

In conclusion, note that compound **2** (HCME of *D*-leucine) crystallizes in the orthorhombic space group $P2_12_12_1$ (Table 1, Fig. 3) and the C(5) atom reflects the *R*-absolute configuration. The molecular geometry of the cation is summarized in Table 4 and coincides with the data given in the recent publication for the cation coordinated to niobium pentachloride [14]. The tripod ammonia center is involved in three almost identical NH…Cl^- hydrogen bonds; the distances N…Cl = 3.121(5)-3.166(5) Å (Table 2). These H bonds in the form of two alternating supramolecular synthons R_4^2 (8) [15] and a short interaction C(5)H…O(2) organize the components into helical chains along the *a* axis in the crystal (Fig. 3*b*). Only van der Waals interactions occur between the chains.

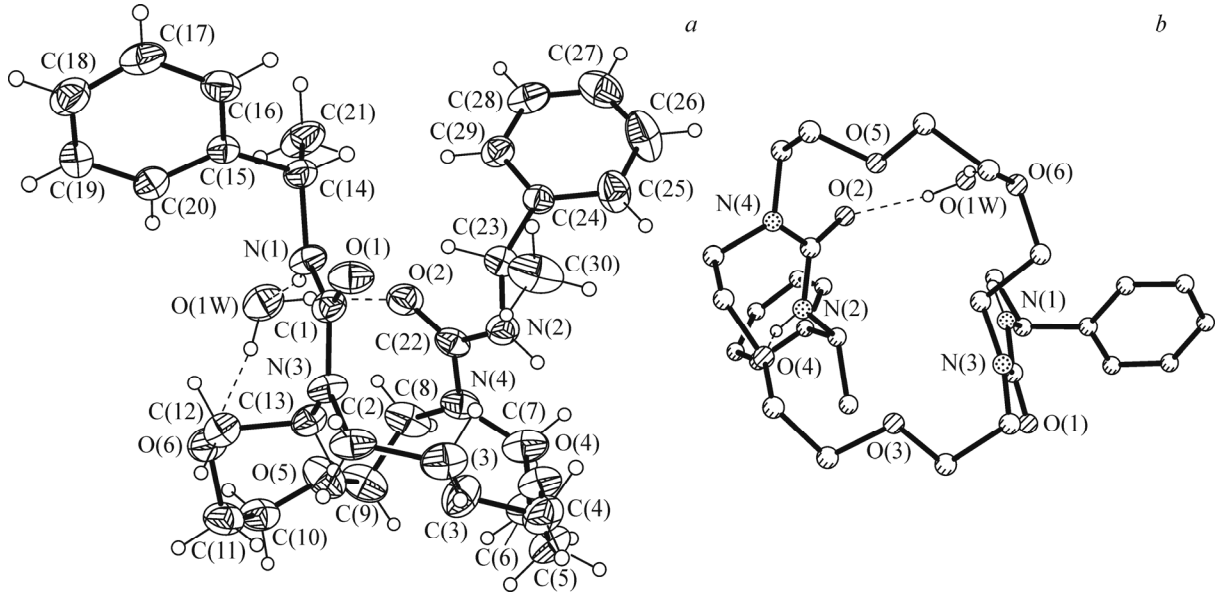


Fig. 2. ORTEP diagram of monohydrate **1**·H_2O with atom numbering (thermal ellipsoids are drawn at a 30% probability level) (*a*); conformation of the macrocycle in supramolecular complex **1**·H_2O, view of the heterocycle plane (hydrogen atoms bonded to carbon atoms are omitted) (*b*).

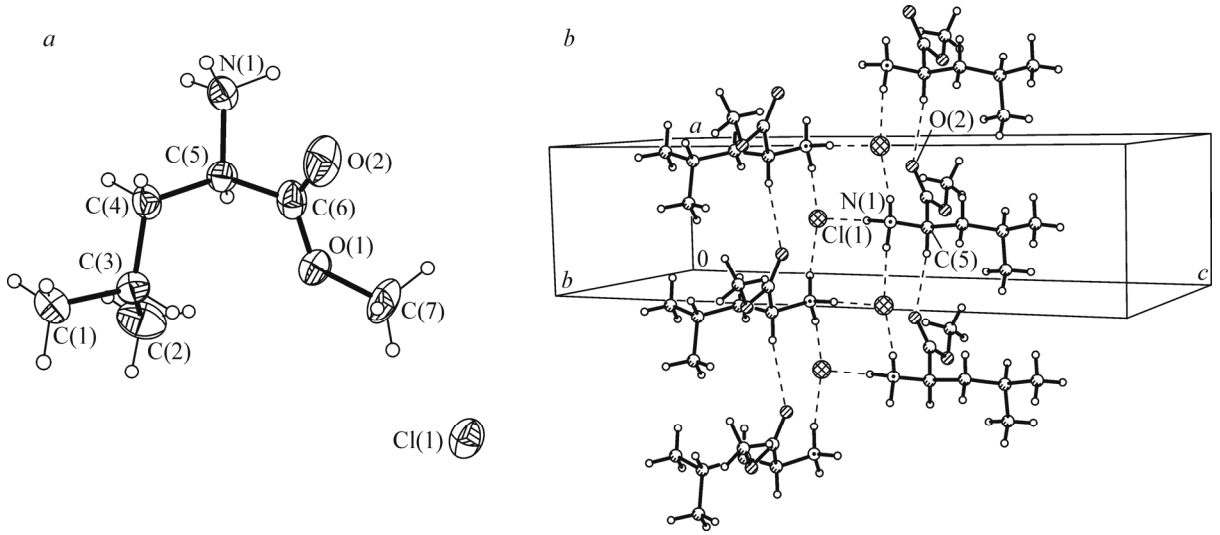


Fig. 3. ORTEP diagram of compound **2** with atom numbering (thermal ellipsoids are drawn at a 30% probability level) (*a*); hydrogen-bonded chain in the crystal structure of compound **2** (*b*).

It seems to us that the results presented can be useful for predicting the formation of host–guest complexes in the separation of enantiomers by chiral macrocyclic complexones such as CE **1**.

REFERENCES

1. Supramolecular Chemistry: Concepts and Perspectives. J.-M. Lehn (Ed.). Wiley-VCH, **1995**.
2. X. X. Zhang, J. S. Bradshaw, and R. M. Izatt. *Chem. Rev*., **1997**, *97*, 3313-3361.
3. G. W. Gokel, W. M. Leevy, and M. E. Weber. *Chem. Rev.*, **2004**, *104*, 2723-2750.
4. T. Yamaguchi, K. Nishimura, T. Shinbo, and M. Sugira. *Bioelectrochem. Bioenerg.,* **1988**, *20*, 109-123.
5. A. V. Bogatskii, S. M. Pluzhnik-Gladyr′, N. G. Luk′yanenko, S. A. Kotlyar, I. I. Chervin, and R. G. Kostyanovskii.

Chem. Heterocycl. Compd., **1985**, *21*, 832.
6. L. S. Kikot′, C. Yu. Kulygina, A. Yu. Lyapunov, S. V. Shishkina, R. I. Zubatyuk, T. Yu. Bogaschenko, and T. I. Kirichenko. *Beilstein J. Org. Chem.,* **2017**, *13*, 2056-2067.
7. A. E. Polyakov. Chiral Diaziridines. Dissertation … Cand. Chem. Sci., Chernogolovka, **1975**.
8. F. M. Rapoport and A. A. Ilyinskaya. Laboratornye Metody Polucheniya Chistykh Gazov. M.: GNTI Khimicheskoi Literatury, **1963**.
9. D. A. Rowlands and G. T. Young. *J. Chem. Soc*, **1952**, *74*, 3937-3940.
10. G. M. Sheldrick. *Acta Crystallogr.*, **2015**, *C71*, 3-8.
11. M. Jaeger, W. Steglich, and K. Polborn. CSD Communication (Private Communication), **2003**.
12. R. Betz, T. Gerber, H. Schalekamp, and E. Hosten. *Z. Kristallogr.-New Cryst.Struct*., **2011**, *226*, 637/638.
13. M. S. Fonari, E. V. Ganin, Y. M. Chumakov, M. M. Botoshansky, K. Suwinska, S. S. Basok, and Y. A. Simonov. *New J. Chem*., **2009**, *33*, 1646-1656.
14. L. Biancalana, M. Bortoluzzi, E. Ferretti, M. Hayatifar, F. Marchetti, G. Pampaloni, and S. Zacchini. *RSC Advances*, **2017**, *7*, 10158-10174.
15. J. Bernstein, R. E. Davies, L. Shimoni, and N.-L. Chang. *Angew. Chem. Int. Ed. Engl*., **1995**, *34*, 1555-1573.