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A 13-Membered Crown Ether with an Azoxy Subunit in the Macrocycle: Synthesis and X-Ray Structure

JAN F. BIERNAT,* ANDRZEJ CYGAN and ELŻBIETA LUBOCH
Faculty of Chemistry, Technical University of Gdańsk, 80–952 Gdańsk, Poland.

and

YURIJ A. SIMONOV and ALEXANDR A. DVORKIN
Institute of Applied Physics, of the Moldovian Academy of Sciences, Kishiniev 277028, Moldova, CIS.

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Abstract. The presented azoxy compound is an example of a new crown ether analogue. It has been synthesized by the reduction of an open chain dinitro compound with stannite under strongly alkaline conditions. A method for the separation of the azo and azoxy compounds formed simultaneously has been proposed. The structures of two crystallographically independent molecules of compound **2** have been determined. In spite of the small size of the macroring in compound **2**, the phenyl residues around the azoxy group have a *trans* orientation.

Key words: Crown ethers, azoxy subunit, X-ray structure.

Supplementary Data relating to this article have been deposited with the British Library as Supplementary Publication No. 82157 (11 pages).

1. Introduction

Compounds containing the azo or azoxy group form *cis* and *trans* isomers. Azo groups as subunits of macrocycles show the same feature. Their complexing ability depend on the arrangement of substituents around the N=N double bond [1]. Similar differentiation of complex formation was observed for crown ethers bearing an ethylene subunit in the macrocycle [2]. The azoxy and azo compounds are valuable components of charge transfer complexes [3], the former exhibiting specific O. . .N→O nonvalent interactions [4]. The use of azo and azoxy electron donating groups as internal parts of macrocyclic systems should substantially modify the properties of the cavity. One of the expected effects is a change in the selectivity of complex formation with cations, including the ionophoric properties of these compounds in ion-selective membrane electrodes [5].

* Author for correspondence.

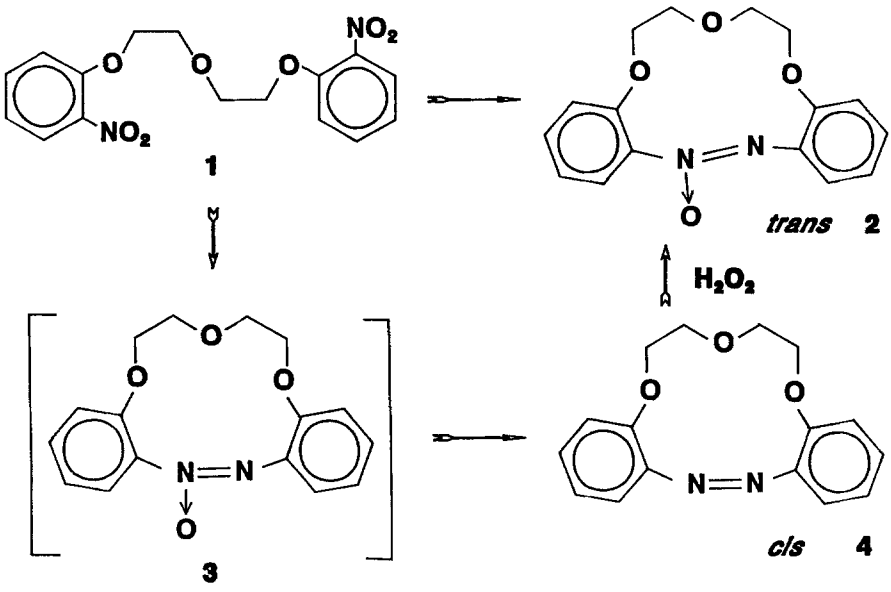


Fig. 1. Reduction of nitrocompound **1** with stannites.

In a previous paper [5] we described the synthesis of a 13-membered crown ether analogue bearing the azoxy group in the macrocycle. It is formed together with the respective azo compound **4** during the reaction of 1,5-bis-nitrophenoxy-3-oxapentane **1** [6] with alkali metal stannites as reducing agents [7]. In this paper the synthetic procedure has been improved, in particular the effective separation of both azo and azoxy macrocycles. The azoxy compound was also obtained by oxidation of the azo crown ether.

The X-ray structures of compounds **1** and **4** have been described previously [7]. The arrangement of substituents around the N(O)=N double bond in the azoxy crown ether was not established. Due to the small size of the macrocycle ring in **2**, the orientation of the phenyl residues of the internal azoxy group was expected to be *cis*.

The aim of this work was to correlate the stereochemistry of the 13-membered azoxy crown ether **2** with its azo analogue **4** by chemical and single crystal X-ray studies.

2. Experimental

All materials and solvents were of analytical reagent grade. Silica gel 5/40μ containing 13% gypsym (Chemapol, Czechoslovakia) was used for column chromatography. ^{1}H-NMR spectra were recorded on a Bruker (200 MHz) instrument. The m.p. are uncorrected.

2.1. THE SYNTHESIS OF THE AZOXY COMPOUND WITH STANNOUS CHLORIDE AND SODIUM IONS AS TEMPLATE

Water (25 mL) was carefully added in small portions to a vigorously stirred mixture of 1.74 g (5 mmole) of 1,5-bis(*o*-nitrophenoxy)-3-oxapentane, 4.1 g (21 mmole) of anhydrous stannous chloride, 6.5 g sodium hydroxide and 25 mL of acetone, until the strongly exothermic reaction ceased, bringing the mixture to the boil. Stirring and heating was continued for 4 h. The mixture was filtered, the solid washed with toluene until white and the filtrate separated. The organic layer was washed with water and evaporated. To remove polymers and diacetone alcohol, which is formed during the reaction, the crude material, dissolved in chloroform, was applied to a short silica gel column. Chloroform elutes both the azo and azoxy compounds. The azoxy compound crystallizes from the evaporated solution upon addition of ethyl ether. It is always deep orange colored and, as shown by NMR, it is always contaminated by about 20% of the azo compound. M.p. 114–116°C. Yield of the crude product: 1–1.3 g (60–80%).

2.2. SEPARATION OF AZO AND AZOXY COMPOUNDS ON NaCl IMPREGNATED SILICA GEL

A 50 g portion of silica gel was suspended in 100 mL of water containing 2 g of sodium chloride. The solvent was removed under reduced pressure and the residue dried at 105°C for several hours, sieved and used for separation.

A saturated solution of 2 g of the crude azoxy compound in chloroform was applied to a short column filled with approximately 5 g of impregnated silica gel. The separation of both compounds is indicated by different colors of the two zones formed: yellowish and red. The yellowish azoxy compound was eluted with chloroform, whereas the red azo compound remains on the column. After evaporation of the solvent the product crystallizes from the residue. The product was washed with ethyl ether and finally with hexane. The white or slightly yellowish azoxy compound (1.5 g; 75%) melts at 118–120°C. (*Analysis: Calc.* %C 63.99, %N 9.33, %H 5.37; *Found* %C 64.18, %N 9.37, %H 5.37). ^{1}H-NMR, CD_2Cl_2, δ [ppm]: CH_2–O–CH_2, 3.89 t, J = 8 Hz, 4H; ArOCH_2, 4.20 t, J = 7 Hz, 4H; ArH, 7.10 m, 4H; 7.30 t, J = 8 Hz, 1H; 7.45 t, J = 8 Hz, 1H; 7.50 d, J = 8 Hz, 1H; 7.64 d, J = 8 Hz, 1H. The red azo compound was removed from the column using ethyl acetate and ethyl acetate–acetone mixtures. The solution was washed with water to destroy the sodium chloride complex and evaporated. The residue (300–400 mg; 15–20%) was crystallized from a small amount of 2-propanol. M.p. 66–67°C.

When the separation was performed on sodium chloride impregnated silica gel using ethyl acetate as eluent the azoxy compound of lower purity was obtained whereas the azo compound, after decomposition of the complex and crystallization, melts at 70–72°C.

2.3. OXIDATION OF *cis*-AZO COMPOUND **4** WITH PERACETIC ACID

A 50 mg portion of azo compound **4** was dissolved in a mixture of 2 mL of acetic acid and 1 mL of 30% hydrogen peroxide. The mixture was heated at 60°C for 2 h and left overnight at room temperature. The solvent was then removed under reduced pressure, the residue dissolved in chloroform and the organic layer washed with water. The solvent was removed and the residue treated with ethyl ether. A crystalline product 50 mg (90%) was obtained (m.p. 118–120°C). It is identical with compound **2**.

The product obtained by oxidation of the starting azo compound with peracetic acid at room temperature in the dark was less pure and after crystallization from 2-propanol afforded 35 mg (66%) identical with compound **2**.

2.4. X-RAY ANALYSIS

The slightly yellowish prismatic monocrystals of **2** obtained by crystallization from ethylene chloride–hexane, exhibit cleavage of the oblong dimension of the crystal, along the *c* axis. There was serious trouble with the selection of a crystal suitable for X-ray analysis. Many of the selected samples had a mosaic-like structure, leading to the broadening of peaks and to a rapid decrease of intensity with the rise of $\sin\theta/\lambda$. Finally, a crystal of dimensions $0.25 \times 0.25 \times 0.50$ mm was isolated, giving acceptable diffraction data. The crystal was orthorhombic with the unit cell parameters (given in Table I) refined based on 12 reflections of the $h00$, $0k0$ and $00l$ type.

The experimental data were collected on a DAR-UMB diffractometer using the $\omega - \theta/2\theta$ scanning method and using CuK_α radiation (graphite monochromator). Collection was performed by layer slicing of the (hkl)-type, where $l = 0 - 8$. Variation of standard intensities was monitored every hour. The intensity differences did not exceed 2.5%. A mosaic-like structure of the crystal leads to a rapid decrease of reflection intensity, the maximum angle θ is equal to 48.3°. This is the reason for a limited number of 877 nonzero independent reflections used for calculations. The structure was solved by the direct method using the SHELX-76 [8] procedure.

It was found that two independent molecules of **2** are present in the unit cell. The limited number of experimental data have led to trouble with the refinement of the structure by the least squares method. Hence the aromatic residues were refined as for rigid groups with fixed and equal distances and internal angles. For nonhydrogen atoms the refinement was performed with the use of anisotropic approximation, whereas the positions of hydrogen atoms were found geometrically and were not refined. The final R-factor, as well as the additional crystallographic data, are given in Table I. Table II presents positional parameters and equivalent temperature factors.

TABLE I. Crystallographic data for $C_{16}H_{16}N_2O_4$ (compound **2**).

Parameter(s)	Value(s)
Formula	$C_{16}H_{16}N_2O_4$
Molecular weight	300.31
Space group	$P2_12_12_1$
a [Å]	20.340(2)
b [Å]	17.449(5)
c [Å]	8.381(2)
Cell volume [Å^3]	2975(2)
Unit cell mass (amu)	2402.72
$F(000)$ (electrons)	1264
Calculated density for $Z = 4$ [g.cm^{-3}]	1.341(1)
Absorption coefficient [1.cm^{-1}]	8.21
Radiation and wavelength [Å]	CuK_α 1.54178
Diffractometer	DAR-UMB
Restriction	$F(hkl) > 4.00\sigma(F)$
Weighting scheme	$1/[\sigma^2(F) + 0.0002(F_{obs})^2]$
Number of atoms in cell	304.0
Number of unique atoms	76
Measured reflections	917
Unique reflections	877
R, R_w	0.0732 0.0687
Goodness of fit	2.560

3. Results and Discussion

Reduction of nitro compounds with stannites under strongly alkaline conditions was originally used for the synthesis of azoxy compounds [9]. In the case of our substrate we always observed, besides polymers, the formation of both the macrocyclic azo and azoxy compounds, in spite of the fact that the amount of stannite used in the reaction was calculated to completely convert the nitro derivative into the azo product. The separation of azo and azoxy compounds was very difficult. Crystallization from all popular solvents was ineffective. Chromatography always gave one spot on different supports even when using different solvent systems. Our previous observations on the application of compounds **2** and **4** in ion-selective membrane electrodes indicate that the azo compound forms stronger complexes with sodium cations as compared to the azoxy derivative [5]. Previously we had found that the R_f values of crown ethers significantly change when chromatography was carried out on TLC plates with salt impregnated silica gel [10] or on columns filled with salt impregnated support and HPLC [11] (see for comparison the separation of crown ethers on cation exchangers [12]). Moreover, the changes correspond

TABLE II. Atomic parameters for $C_{16}H_{16}N_2O_4$ (compound **2**).

Atom	x/a	y/b	z/c	B_{eq}
O(a)	0.3472(7)	–0.4353(9)	0.3586(24)	16.4(8)
O(1a)	0.3554(5)	–0.3696(5)	0.6999(10)	7.3(4)
C(2a)	0.3451(7)	–0.3496(7)	0.8556(17)	7.8(6)
C(3a)	0.3096(7)	–0.4132(10)	0.9335(17)	10.(7)
O(4a)	0.3457(4)	–0.4828(5)	0.9409(11)	7.4(4)
C(5a)	0.3169(6)	–0.5474(8)	0.8845(19)	8.4(7)
C(6a)	0.3643(8)	–0.6108(8)	0.8602(16)	11.0(8)
O(7a)	0.4063(5)	–0.5920(6)	0.7307(9)	8.1(3)
C(8a)	0.3824(6)	–0.6142(8)	0.5844(13)	5.5(5)
C(9a)	0.3886(6)	–0.5641(8)	0.4556(13)	5.7(5)
N(10a)	0.4236(9)	–0.4920(7)	0.5052(17)	7.7(6)
N(11a)	0.3977(8)	–0.4424(10)	0.4385(18)	6.8(6)
C(12a)	0.4222(9)	–0.3652(7)	0.4779(20)	4.7(5)
C(13a)	0.3996(9)	–0.3301(7)	0.6171(20)	4.5(4)
C(14a)	0.4222(9)	–0.2573(7)	0.6586(20)	6.1(5)
C(15a)	0.4674(9)	–0.2196(7)	0.5609(20)	5.7(5)
C(16a)	0.4899(9)	–0.2547(7)	0.4217(20)	6.2(5)
C(17a)	0.4674(9)	–0.3275(7)	0.3803(20)	6.8(6)
C(18a)	0.3749(6)	–0.5894(8)	0.3013(13)	5.3(5)
C(19a)	0.3547(6)	–0.6649(8)	0.2758(13)	5.8(5)
C(20a)	0.3486(6)	–0.7150(8)	0.4045(13)	5.6(5)
C(21a)	0.3623(6)	–0.6897(8)	0.5588(13)	5.2(5)
O(b)	0.2583(5)	0.0039(6)	0.5956(13)	7.5(3)
O(1b)	0.3660(4)	0.0992(5)	0.7351(9)	6.6(3)
C(2b)	0.4027(6)	0.1255(7)	0.8693(13)	6.3(5)
C(3b)	0.3515(6)	0.1467(7)	0.9867(12)	6.0(5)
O(4b)	0.3163(4)	0.2106(4)	0.9334(10)	6.2(3)
C(5b)	0.2505(7)	0.2085(10)	0.9707(15)	9.5(8)
C(6b)	0.208(7)	0.1738(12)	0.8545(17)	14.2(11)
O(7b)	0.2186(4)	0.1945(6)	0.7036(10)	9.3(4)
C(8b)	0.1723(7)	0.1643(7)	0.6027(13)	5.3(4)
C(9b)	0.1942(7)	0.1164(7)	0.4806(13)	5.0(5)
N(10b)	0.2648(6)	0.1083(7)	0.4460(15)	6.0(5)
N(11b)	0.2858(7)	0.0543(8)	0.5145(16)	6.4(5)
C(12b)	0.3589(4)	0.0499(7)	0.4802(20)	4.7(4)
C(13b)	0.3995(4)	0.0697(7)	0.6080(20)	4.6(4)
C(14b)	0.4672(4)	0.0577(7)	0.5981(20)	4.7(4)
C(15b)	0.4943(4)	0.0259(7)	0.4603(20)	5.6(5)
C(16b)	0.4538(4)	0.0061(7)	0.3325(20)	5.1(5)
C(17b)	0.3861(4)	0.0181(7)	0.3424(20)	5.0(5)
C(18b)	0.1490(7)	0.0823(7)	0.3775(13)	5.4(5)
C(19b)	0.0819(7)	0.0961(7)	0.3965(13)	4.7(4)
C(20b)	0.0600(7)	0.1441(7)	0.5186(13)	5.8(4)
C(21b)	0.1052(7)	0.1782(7)	0.6217(13)	5.7(4)

* $B_{eq} = 4/3$ [B11 $A*2 + \ldots 2B23\ B^*\ C^*\ B\ C\ \cos\alpha$]

to the stability of complexes formed by the crown ethers with the respective salts. Thus, a procedure for chromatographic separation of azo and azoxy compounds was developed applying sodium chloride impregnated silica gel as a support [13].

The accepted mechanism of reduction of nitro compounds to azo derivatives involves the azoxy compounds as intermediates formed by condensation of nitroso and hydroxylamino derivatives. It was found that the isolated crystalline azo compound **4** is the *Z* isomer with *cis*-oriented substituents attached to the nitrogen to nitrogen double bond [4], hence the azoxy intermediate should also have a similar orientation of phenyl residues. However, attempts to reduce the pure azoxy compound with an excess of reducing agent under ordinary reaction conditions were, to a great extent, unsuccessful. Accordingly, the reduction of the dinitro compound **1** with an excess of stannous chloride only slightly increases the yield of the azo compound.

It suggests that two different azoxy compounds are probably formed under the reaction conditions: with *cis*-**3** or *trans*-**2** oriented phenyl residues, cf. [14]. The *trans* isomer **2**, as a rather stable compound under the reaction conditions, was isolated (see below Figures 2a and 2b) whereas the *cis*-13-membered azoxy compound **3** is probably easily converted into the *cis*-azo compound **4**. However, an alternative route to the *cis*-azo compound cannot be ruled out [1].

The azo compounds are easily convertible into the respective azoxy compounds [15]. Oxidation of azo compound **4** with peracetic acid at 60° leads to the azoxy compound **2**. At room temperature the yield of the pure crystalline azoxy compound is lower.

Figure 2 shows the structure of two crystallographically independent molecules of compound **2**. In contrast to the product **4** the phenyl–N=N–phenyl residue in **2** has a *trans* orientation. The torsional angle of the C(9)–N(10)–N(11)–C(12) fragment is equal to 176.6° for **2a** and –178.0° for **2b**. This is contrary to our expectations, as the *cis* orientation of phenyl residues was expected for the small macrocyclic system.

The oxygen atom in molecules **2a** and **2b** is located at corresponding nitrogen atoms in both molecules (N(11)). The geometric characteristic features of the azoxy group include the N=N distance which is equal to 1.15 and 1.18 Å for **2a** and **2b**, respectively; the average N–C distance is equal to 1.49 Å and N→O is equal to 1.23 for **2a** and 1.24 Å for **2b**. In the 3σ range these distances correspond to those found for azoxyanisole, where they are equal to 1.218, 1.496 and 1.279 Å, respectively. The N→O bond is practically located in the plane of the C–N=N–C chain and the sum of angles at N(11) is close to 360°.

The longer N–C bond for azoxy compounds as compared to azo analogues [16] can be attributed to the weaker conjugation of the nitrogen atom lone electron pair with the aromatic system.

Summarising data on the structure of the C–N=N–C residue of **2** and **4** and on the noncyclic analogues [4] one may state the following: (a) in the cyclic systems the oxygen atom in the –C–N(O)=N–C– residue is located at the same respective

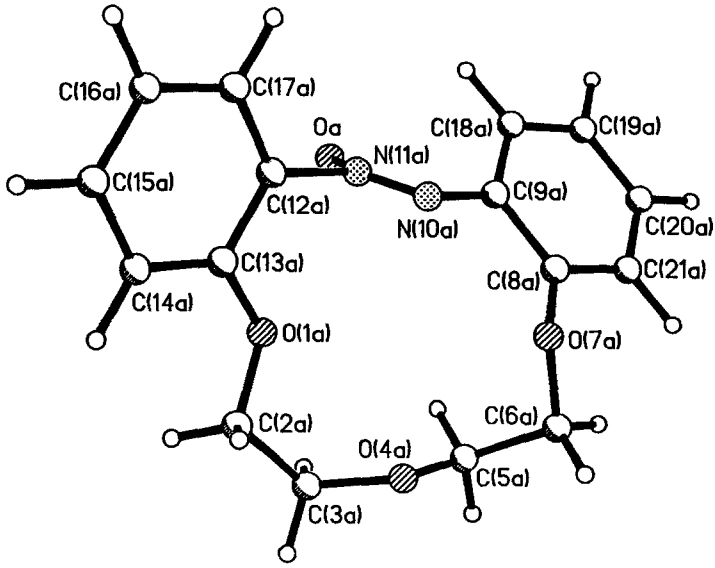


Fig. 2a. Designation of atoms and the conformation of compound **2a**.

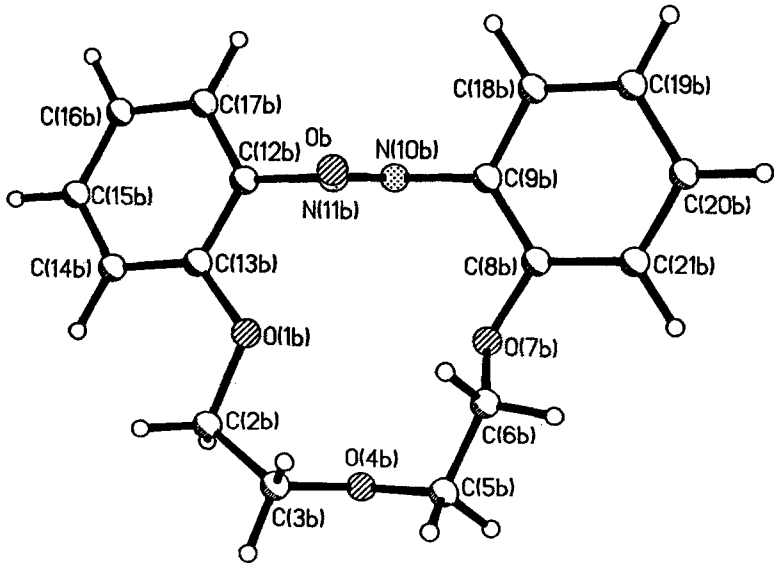
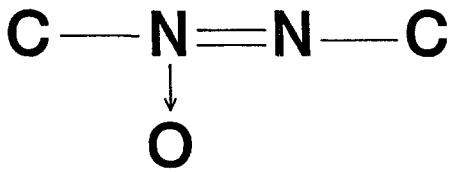


Fig. 2b. Designation of atoms and the conformation of compound **2b**.

nitrogen atom; (b) there is a tendency of a reduction of the –N=N– distance as compared to acyclic analogues; (c) in the oxygen possessing form **2** a tendency



gauche trans trans for **2a**

and *trans trans gauche* for **2b**

is observed to increase the C–N bond length, which suggests a lower degree of conjugation of the lone electron pair from the nitrogen atom to the aromatic system.

The macrocyclic molecule as a whole has a chair conformation with heteroatoms bent to opposite sides from the mean plane of the macrocycle; the deviations from the mean plane for molecule **2a** are: O(1) –0.0216, O(4) –0.0264, O(7) 0.0724, N(10) -0.0410, N(11) 0.011, O –1.505 Å; and for **2b** 0.053, 0.0548, –0.1414, 0.3868, –0.3541 and –1.597 Å. The dihedral angles between the mean plane of the macrocycle and the aromatic residues for **2a** are equal to –136.5 and 42.5° and for **2b** –26.0 and 26.5°, respectively. Hence, with the more planar core, macrocycle **2a** has larger dihedral angles with the aromatic groups, whereas molecule **b** is, as a whole, more planar.

The cyclic molecule can be divided into four fragments: two aromatic rings and two joining chains: the azoxy residue and the polyoxyethylene chain. Analysis of the geometry of the aromatic rings was abandoned as they were refined as rigid groups. The geometric and conformational parameters and the azoxy residue were discussed above. Analysis of the torsional angles of the polyoxyethylene chain shows some differences in their conformation. The corner fragment according to Dale [17] is at the C(6) atom in the **2a** molecule, whereas in **2b** it is at C(5). Thus the corner fragment is shifted by one oxyethylene fragment when comparing **2a** and **2b**. The remaining torsional angles on C–C bonds are in the *gauche* conformation; on C–O in *trans*, with the exception of C(6)–O(7) in **2a** and O(4)–C(5) in **2b**, which are *gauche*. It is worth adding that, as in **4**, there is a significant deviation of *trans* angles from the ideal 180°.

The conformation around –C–N– bonds is *gauche* and *trans* for both rings, according to the following scheme:

The interatomic distances do not differ from values of oxyethylene chains of other similar systems.

The strain of intramolecular contacts of the structure is worth mentioning. In both molecules, **2a** and **2b**, a shortening of N(11)...O(1) contacts is observed. They are equal to 2.68 for molecule **2a** and 2.59 Å for molecule **2b**. These contacts point to the interaction of the nitrogen lone electron pair with the oxygen atom.

The remaining intramolecular contacts are characteristic for cyclic molecules with polyoxyethylene chains.

The intermolecular contacts between the identical macrocycles of **2** are in the range of ordinary van der Waals contacts (~3.60 Å).

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