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Synthesis and crystal structure of 1,4,10,13-tetraoxa-7,16-diazoniumcyclo-octadecane bis (4-chloro-2-methyl-phenoxyacetate)

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Abstract

The title compound was prepared by the reaction of 1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane with 4-chloro-2-methyl-phenoxyacetic acid in a ratio of 1:2. The structure has been proved by the data of elemental analysis, IR spectroscopy, NMR (^{1}H, ^{13}C) technique and by X-ray diffraction analysis. Intermolecular hydrogen bonds between the azonium protons and oxygen atoms of the carboxylate groups were found. Immunoactive properties of the title compound have been screened. The compound has the ability to suppress spontaneous and Con A-stimulated cell proliferation in vitro and therefore can be considered as immunodepressant.

Findings

Over many years the complexes of crown ethers (CE) with protonic acids and their metal salts attract the attention of scientific community due to both their peculiar molecular and stereoelectronic structure as well as the possibility of practical application [1,2]. The CE complexes enhance physiological activity of several chemical compounds. This fact is likely related to the ability of the complexes formed to overpass cellular and hematoorganic barriers. In particular, specific complex-forming properties of CE allow them to be used for the drug design [2].

Recently, we have shown that tris-(2-hydroxyethyl) ammonium salts of organylheteroacetic acids [$RYCH_2COO$]$^-$·[$NH(CH_2CH_2OH)]_3^+$, (R = Ar, Het; Y = O, S, SO_2), the cation of which has compact tricyclic atrane (2,8,9-trihydro-prototranic) structure [3], promoting to penetration of a matter through cellular membranes, represent a new class of biologically active compounds [4-9]. For example, tris(2-hydroxyethyl)ammonium salt of 4-chloro-2-methyl-phenoxyacetic acid exhibits adaptogenic, immunomodulating and antitumor properties. Besides, it effectively increases the resistance of animals to microwave electromagnetic radiation [7-9].

To search for new immunoactive congeners of this series, we have synthesized 1,4,10,13-tetraoxa-7,16-diazoniumcyclo-octadecane bis(4-chloro-2-methyl-phenoxyacetate) **1** and studied its immunoactive properties. Compound **1** was prepared in a yield of up to 98% by the reaction of 1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane (1,10-diaza-18-crown-6 ether) with 4-chloro-2-methyl-phenoxyacetic acid in a ratio of 1:2 (Figure 1).

Compound **1** forms colorless crystals with m.p. 128°C. The structure of **1** has been proved by the data of elemental analysis, IR spectroscopy and NMR (^{1}H, ^{13}C) technique. The IR spectra of **1** show broad vibration bands of $\nu(NH_2^+)$ in the region 2800-2200 cm^{-1}. The stretching vibration bands of the O-C-O fragments of starting CE are high-field shifted from 1120, 1100 and 1067 to 1150-1090 cm^{-1}. In the IR spectrum, the bands of symmetric and asymmetric stretching vibrations of the carboxylate-ion are observed at 1580-1350 cm^{-1}.

The structure of compound **1** was established by crystal structure analysis. Crystal and experimental data are summarized in Table 1. The molecular structure with the atom labeling scheme is given in Figure 2. The packing diagram is shown in Figure 3. Selected bond lengths (Å), bond angles (°) as well as torsion angles (°) are listed in Table 2.

The asymmetric unit of **1** contains a half of the diprotonated 1,10-diazatetraoxa-18-crown-6 moiety and 4-chloro-2-methylphenoxyacetate as anion. The crown ether is centrosymmetric and the second half of the

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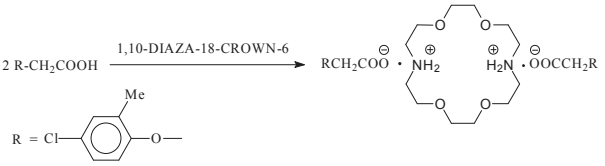

Figure 1 Synthesis of the title compound 1.

cation is generated by inversion. 4-Chloro-2-methylphenoxyacetic acid is known as herbicide. In this molecule, the benzene ring and the oxoacetic acid side-chain are almost coplanar (CSD-Code CMPHAA) [10]. In contrast to this, in **1** the acetate moiety is torsioned around O1-C7 forming a torsion angle of -79.7(2)°, whereas a torsion angle of only -8.0(1)° was found in the reference compound. Additionally, the distorsion of the exo-C1 ring angles is more pronounced **1**: 115.4(1), 124.3(2)°; CMPHAA: 115.8(12), 122.0(13)°). The molecular packing is characterized by hydrogen bonds forming a ribbon-like structure along the crystallographic *b* axis. The geometry of the hydrogen bonds are given in Table 3.

Immunoactive properties of **1** have been screened. For example, the ability to impact on spontaneous and mitogen-stimulated (Con A, Sigma, 2 mkg/ml) proliferation of splenocytes in mice in vitro (antiproliferative properties) have been studied. It has been found that compound **1** exerts a distinct influence on spontaneous and mitogen-stimulated proliferation of splenocytes. The ability to suppress spontaneous (up to 72%) and Con A-stimulated (up to 99%) cell proliferation of spleen in vitro in the dosage of 3-300 mkg/ml allows compound **1** to be considered as immunodepressant.

Table 1 Crystal data and details of the structure solution and refinement

Emirical formula	$C_{15}H_{22}ClNO_5$
Formula weight	331.79
Temperature	210(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, *P*
Unit cell dimensions	a = 7.5342(6) Å α = 97.624(7)° b = 9.1935(8) Å β = 93.340(6)° c = 12.8532(10) Å γ = 108.945(6)°
Volume	829.73(12) Å^3
Z, Calculated density	2, 1.328 g/cm^{-3}
Absorption coefficient	0.252 mm^{-1}
F(000)	352
Crystal size	1.5 × 0.6 × 0.15 mm
Θ range for data collection	1.61 to 25.0°
Reflections collected/unique	5361/2738
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2738/0/288
Goodness-of-fit on F^2	1.001
R indices [$I > 2\sigma(I)$; 2280]	*R*1 = 0.0423, *wR*2 = 0.1110
R indices (all data)	*R*1 = 0.0495, *wR*2 = 0.1147
Largest diff. Peak and hole	0.413 and -0.319 eÅ^{-3}

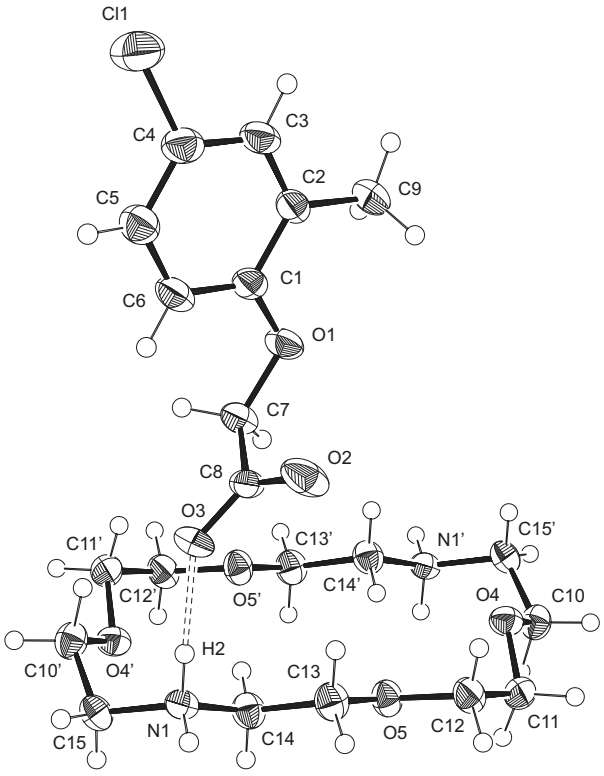

Figure 2 ORTEP plot of 1, drawn at a 50% probability level, with atom labeling. Symmetry operation: ^{i}2-x, 2-y, 2-z.

Experimental

IR spectra were recorded on a Varian 3100 FT- IR75 spectrophotometer. NMR spectra (ppm) were measured on a DPX 400 instrument (400,13 MHz for 1H and 101,62 MHz for 13C) in D_2O or methanol D4 at 25°C. Reflections were collected using a STOE Imaging Plate Diffraction System (IPDS-II) at 210 K. The structure was solved by direct methods as implemented in the program SHELXS-97 [11]. The refinement was carried out using SHELXL-97 [12]. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from the difference Fourier map and refined isotropically. For the visualisation of the structure the graphic programs DIAMOND [13] and ORTEP for Windows [14] were used. CIF data: Additional file 1. CCDC reference number: 812142.

Compound **1** was synthesized in the following manner. To a solution of 4-Cl-2-CH_3-$C_6H_3OCH_2COOH$ (4.01 g, 0.02 mol) in MeOH (10 ml), was added dropwise a methanol (10 ml) solution of (CE) (2.62 g, 0.01 mol). The mixture was stirred at 25°C for 12 h.

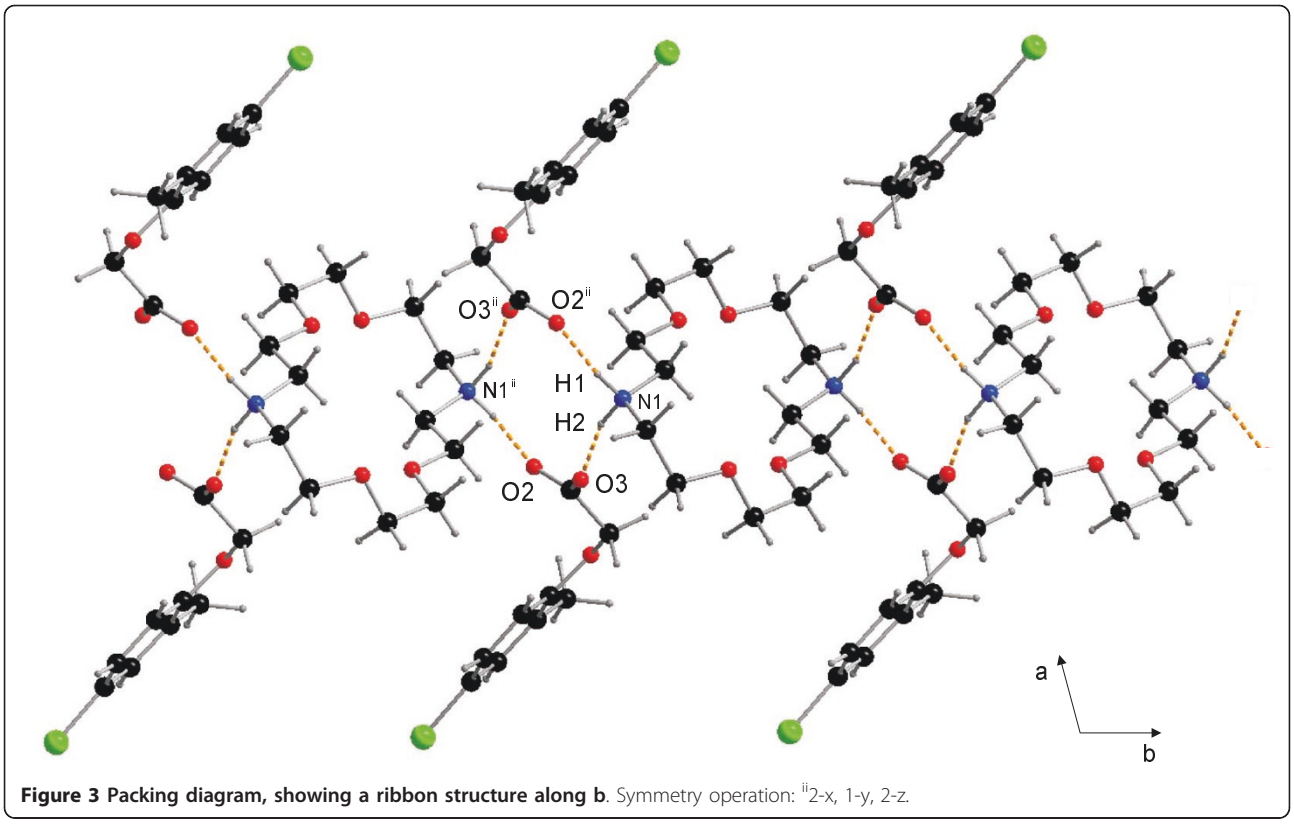

Figure 3 Packing diagram, showing a ribbon structure along b. Symmetry operation: [ii]2-x, 1-y, 2-z.

Table 2 Selected bond lengths (Å), bond angles (°), and torsion angles (°)

C1-O1	1.369(2)	C4-Cl1	1.744(2)
C2-C9	1.502(2)	C7-O1	1.423(2)
C7-C8	1.523(2)	C8-O2	1.237(2)
C8-O3	1.249(2)	C10-O4	1.420(2)
C11-O4	1.419(2)	C12-O5	1.425(2)
C13-O5	1.405(2)	C14-N1	1.490(2)
C15-N1	1.500(2)		
O1-C1-C6	124.33(15)	O1-C1-C2	115.40(13)
O1-C7-C8	115.00(14)	O2-C8-O3	126.33(16)
O2-C8-C7	119.17(14)	O3-C8-O7	114.48(15)
O4-C10-C15[i]	109.71(13)	O4-C11-C12	108.92(15)
O5-C12-C11	108.47(15)	O5-C13-C14	107.27(14)
N1-C14-C13	110.33(14)	N1-C15-C10[i]	113.09(14)
C14-N1-C15	115.90(13)	C1-O1-C7	117.34(12)
C11-O4-C1	112.78(13)	C13-O5-C12	111.91(13)
O1-C1-C2-C3	-178.46(15)	O1-C1-C2-C9	-1.0(3)
C2-C3-C4-Cl1	-177.68(14)	O1-C7-C8-O2	-15.4(2)
O1-C7-C8-O3	166.31(14)	O4-C11-C12-O5	67.19(19)
O5-C13-C14-N1	-173.03(15)	C13-C14-N1-C15	-179.80(15)
C10[i]-C15-N1-C14	-72.10(19)	C6-C1-O1-C7	5.5(2)
C2-C1-O1-C7	-174.16(16)	C8-C7-O1-C1	-79.74(19)
C12-C11-O4-C10	-167.40(15)	C15[i]-C10-O4-C11	167.28(14)
C14-C13-O5-C12	-175.94(15)	C11-C12-O5-C13	179.36(16)

Symmetry code: [i]2-x, 2-y, 2-z

The solvent was distilled in vacuum. The solid residue was repeatedly washed with ether and dried in vacuum to afford colorless powder (6.50 g, 98% yield), soluble in water and alcohol. Crystals suitable for X-ray diffraction were obtained by recrystallyzation of **1** from methanol (20°C). ^{1}H NMR (D_2O): 7.11-6.68 (m, 6H, C_6H_3O); 4.37 (s, 4H, CH_2COO); 3.63-3.56 (m, 16H, OCH_2, OCH_2-CH_2O); 3.15 (t, 8H, NCH_2); 2.13 (s, 6H, C_6H_3-CH_3). ^{13}C NMR (D_2O): 176.80 (C=O); 156.04 (C_6H_4O); 140.87-111.56 (C_6H_3); 69.42 (OCH_2); 66.99 (CH_2COO); 65.29 (OCH_2CH_2O); 47.31 (NCH_2); 15.53 (C_6H_3-CH_3). Anal. Calcd. for $C_{30}H_{44}Cl_2O_{10}N_2$: C, 54.24; H, 6.63; Cl, 10.68; N, 4.22; Found: C, 54.54; H, 6.60; Cl, 10.68; N, 4.02.

Conclusions

1,4,10,13-Tetraoxa-7,16-diazoniumcyclo-octadecane bis (4-chloro-2-methyl-phenoxyacetate) **1** has been synthesized by the reaction of 1,10-diaza-18-crown-6 ether with 4-chloro-2-methyl-phenoxyacetic acid in a ratio of

Table 3 Hydrogen bond geometry (Å, °)

D-H...A	D-H	H...A	D...A	D-H...A
N1-H1...O2[ii]	0.89(2)	1.83(2)	2.698(2)	165(2)
N1-H2...O3	0.93(2)	1.81(2)	2.708(2)	161(2)

Symmetry code: [ii]2-x, 1-y, 2-z

1:2 (yield 98%). The structure of **1** has been proved by the data of elemental analysis, IR spectroscopy, NMR (^{1}H, ^{13}C) technique and X-ray diffraction analysis. X-ray diffraction analysis has shown that the crown ether cation is centrosymmetric. The packing is characterized by a ribbon-like structure stabilized by hydrogen bonds. The title compound is a representative of a novel class of physiologically active compounds possessing immunodepressant properties. The investigation of physiological activity of **1** will be conducted in a new future.

Additional material

Additional file 1: Crystallographic information. Contains all relevant CIF information.

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Authors' contributions
SNA carried out the synthetic experiments and drafted the manuscript. ANM has formulated the research idea and prepared the manuscript draft version. RGM prepared the manuscript for submission and coordinated final formulation. US collected the X-ray data and performed the structure solution. Authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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