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Unexpected formation of dinaphthoaza-17-crown-5 ether containing γ-aminopiperidine subunit

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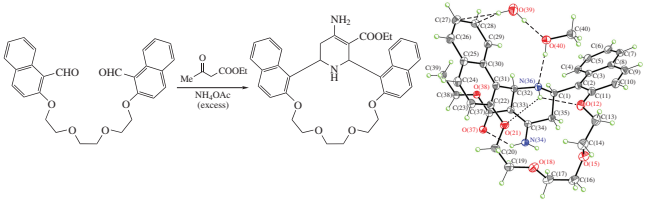
New dinaphthoaza-17-crown-5 derivative containing γ-aminopiperidine subunit was synthesized by the one-pot Petrenko–Kritschenko multicomponent condensation based on 2,2′-[3,6-dioxaoctane-1,8-diylbis(oxy)]di(1-naphthaldehyde) as the podand. The crystal structure of the new azacrown compound was elucidated by X-ray diffraction.



In our previous studies, the successful use of podand in domino synthesis of azacrown compounds containing nitrogen heterocycle has been reported.[1,2] For further preparation of new azacrown derivatives with biophore groups, modification of multicomponent condensation reactions based on the Petrenko–Kritschenko reaction and Soldatenkov's studies[3–6] was employed in this research.

First, podand **1** containing a polyether chain with four oxygen atoms reacted with ethyl acetoacetate; second, a large amount of ammonium acetate (20 moles per one mole of the aldehyde) was used; third, the presence of glacial acetic acid was crucial to catalyze this reaction. After 24 h of processing (TLC controlled), enamino compound **3**† was formed instead of expected keto one **2** (Scheme 1).

Under modified conditions of the Petrenko–Kritschenko reaction, the carbonyl group of expected compound **2** was transformed into the enamino one due to large excess of ammonium acetate, high temperature and long reaction time. Structural features of product **3** have been established in detail by single crystal X-ray diffraction study (Figure 1 and Online Supplementary Materials).‡

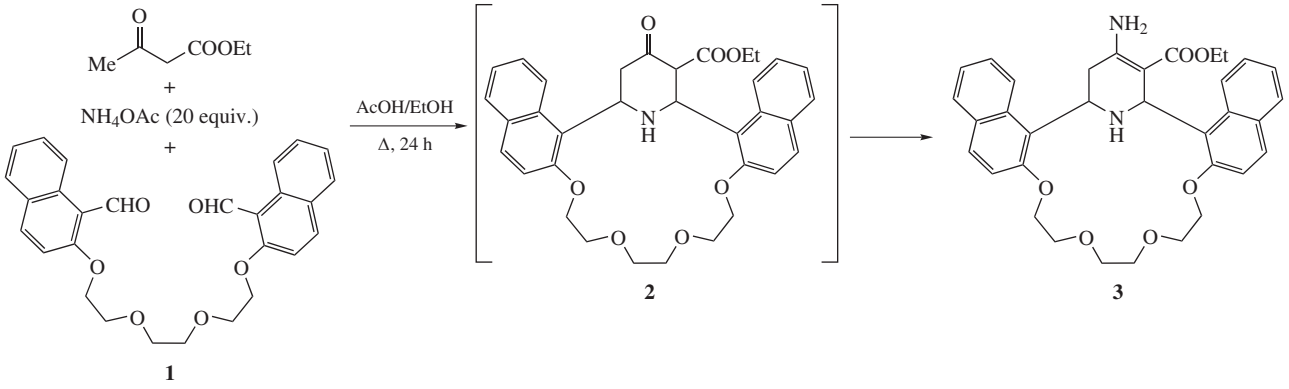
The aza-17-crown-5-ether ring in compound **3** adopts a bowl conformation, which is stabilized by the three intramolecular N–H···O and one intermolecular O–H···N hydrogen bonds (Table S1, see Online Supplementary Materials) as well as the intermolecular O(39)–H(39)E···πC(27)–C(28) hydrogen bonding interaction [O(39)···C(27) 3.4665(17) Å, O(39)···C(28) 3.2885(16) Å,

† *2⁴-Amino-2³-ethoxycarbonyl-2¹,2²,2⁵,2⁶-tetrahydro-4,7,10,13-tetraoxa-2(2,6)-pyridina-1(2,1),3(1,2)-dinaphthalenacyclotridecaphane* **3**. A mixture of podand **1** (200 mg, 0.44 mmol, 1 equiv.), ethyl acetoacetate (63 mg, 1.1 equiv.), ammonium acetate (672 mg, 20 equiv.) and glacial acetic acid (13 mg, 0.5 equiv.) was refluxed in dry ethanol (6 ml) for 1 day. After the reaction was complete (TLC control), the mixture was cooled to room temperature, extracted with ethyl acetate (3×10 ml), the extracts were washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave a residue which was subjected to column chromatography with a gradient elution of ethyl acetate–hexane (2 : 1) and then recrystallized from methanol and dichloromethane to obtain the pure white product **3** (150 mg, 60%), mp 186–188 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 0.80 (t, 3H, Me, ^3J 7.0 Hz), 2.32 (dd, 1H, 35-CH_{eq}, ^2J 15 Hz, ^3J 3 Hz), 2.76 (dd, 1H, 35-CH_{ax}, ^2J 14 Hz, ^3J 3 Hz), 3.70–3.74 (m, 4H, 16,17-CH_2), 3.78–3.81 (m, 4H, 14,19-CH_2), 3.88–3.91 (m, 4H, 13,20-CH_2), 4.37–4.40 (m, 2H, CH_2Me), 5.10 (d, 1H, 32-CH, ^3J 11 Hz), 5.19 (t, 1H, 1-CH, ^3J 11 Hz), 5.42 (t, 1H, NH, ^3J 11 Hz), 7.17 (d, 2H, H-10,23, ^3J 9 Hz), 7.30–7.34 (m, 4H, H-5,28, NH_2), 7.39–7.43 (2H, H-6,27), 7.52–7.54 (m, 2H, H-7,26), 8.19 (d, 2H, H-9,24, ^3J 9 Hz), 8.34 (d, 2H, H-4,29, ^3J 8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.66 (CH_2*Me*), 47.14 (C^{35}), 56.72 (OCH_2Me), 58.01 (C^1), 60.64 (C^{32}), 62.49, 66.85, 67.09, 69.57, 69.76, 70.04 (6×OCH_2), 109.85 (C^{33}), 112.61, 112.92, 119.52, 120.91, 122.09, 123.28, 123.40, 123.50, 126.87, 127.48, 128.38, 128.60, 129.31, 129.33, 129.90, 130.60, 131.95, 132.62, 154.82, 154.89 (20×$C_{naphtho}$), 155.18 (C^{34}), 169.14 (C=O). HRMS, *m/z*: 569.2662 $[M+H]^+$ (calc. for $C_{34}H_{37}N_2O_6^+$, *m/z*: 569.2652). Atom numeration in the NMR spectra corresponds to that given in Figure 1.

‡ Single-crystal X-ray diffraction data for compound **3** were collected on the 'Belok' beamline of the National Research Center 'Kurchatov Institute' (Moscow, Russian Federation) using a Rayonix SX165 CCD detector at λ = 0.78790 Å. A total of 720 images for two orientations of the crystal was collected using an oscillation range of 1.0° and φ scan mode. The data were indexed and integrated using the utility iMOSFLM from the CCP4 program suite,[8] and then scaled and corrected for absorption using the Scala program.[9] All calculations were carried out using the SHELXTL program suite.[10]

Crystal data for **3**·*MeOH*·H_2O. $C_{35}H_{42}N_2O_8$ (M = 618.71), monoclinic, space group $P2_1/n$, at T = 100 K: a = 12.490(3), b = 20.595(4) and c = = 13.061(3) Å, β = 109.90(3)°, V = 3159.1(14) Å^3, Z = 4, d_{calc} = 1.301 g cm^{-3}, $F(000)$ = 1320, μ = 0.115 mm^{-1}. 27774 reflections (7317 independent reflections, R_{int} = 0.028) were measured and used in the refinement. The refinement converged to R_1 = 0.037 for 6533 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.099 for all independent reflections, S = 1.051. The hydrogen atoms of the NH groups as well as the OH groups of the solvate molecules were objectively localized in the difference-Fourier map and refined isotropically with fixed displacement parameters [U_{iso}(H) = 1.2 U_{eq}(N) and 1.5 U_{eq}(O)]. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.5 U_{eq}(C) for the methyl groups and 1.2 U_{eq}(C) for the other groups].

CCDC 1900622 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



Scheme 1

H(39)E···C(27) 2.57(2) Å, H(39)E···C(28) 2.47(2) Å, ∠O(39)–H(39)E···C(27) 174.8(17)°, ∠O(39)–H(39)E···C(28) 152.3(17)°] (see Figure 1). The conformation of the C(11)–O(12)–C(13)–C(14)–O(15)–C(16)–C(17)–O(18)–C(19)–C(20)–O(21)–C(22) polyether chain is g^+-g^+-*t*-g^+-g^--*t*-g^+-g^+-g^- (*t* is *trans*, 180°; *g* is *gauche*, ±60°). The central 1,2,5,6-tetrahydropyridine ring has a slightly distorted unsymmetrical chair conformation. The naphthalene substituent at the C(32) carbon atom occupies the sterically more favorable equatorial position.

In the crystal, the molecules of **3** form H-bonded wave-like chains along the crystallographic *b* axis by the intermolecular N–H···O hydrogen bonds through the solvate water molecules (Figure S2 and Table S1, see Online Supplementary Materials).

In summary, modification of the Petrenko–Kritschenko reaction towards podand **1** by application of a large excess of ammonium acetate and prolongation of the reaction time afforded unexpected azacrown compound containing γ-aminopiperidine fragment. This novel macroheterocycle with two different amine functionalities can be a useful building block for further synthetic manipulations and drug development. According to the PASS (Prediction of Activity Spectra for Substances) program, compound **3** has the potential to exhibit membrane permeability inhibitor (66%), septic shock treatment (64%) and antiprotozoal activity (60%).[7]

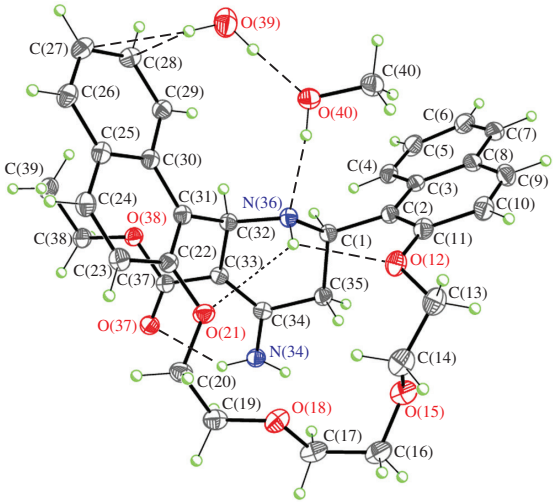


Figure 1 Molecular structure of **3**·MeOH·H_2O. Dotted and dashed lines indicate the intramolecular N–H···O and intermolecular O–H···N and O–H···O hydrogen bonds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.033.

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