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СИНТЕЗ И СТРОЕНИЕ 4-(9-ГИДРОКСИ-1,4,7-ТРИОКСИНОНИЛ)ФТАЛОНИТРИЛА

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Взаимодействием 4-нитрофталонитрила с триэтиленгликолем в среде осушенного диметилсульфоксида в присутствии прокаленного карбоната калия в течение 12 ч при 60 °С получен 4-(9-гидрокси-1,4,7-триоксинонил)фталонитрил. Выделение целевого продукта осуществляли выливанием реакционной массы в холодную дистиллированную воду с последующей экстракцией дихлорметаном. После отгонки растворителя при пониженном давлении, заключительную очистку проводили методом колоночной хроматографии используя элюирующую смесь состава: этилацетат : гексан (1:3). После удаления растворителей при пониженном давлении продукт сушили в вакууме в течение 4 ч при 80 °С. Структура полученного соединения установлена на основании данных элементного анализа, ИК и ^{1}Н ЯМР спектроскопии, масс-спектрометрии и рентгеноструктурного анализа. В масс-спектре соединения обнаружены два сигнала, соответствующие комплексам с щелочными металлами: 299 $[M+Na]^+$ и 315 $[M+K]^+$ Da. Методом испарения растворителя из раствора 4-(9-гидрокси-1,4,7-триоксинонил)фталонитрила в этилацетате при пониженной температуре были получены монокристаллы, пригодные для рентгеноструктурного анализа. По данным кристаллографического исследования 4-(9-гидрокси-1,4,7-триоксинонил)фталонитрил в кристаллическом состоянии представляет собой моногидрат, в котором молекула воды координирована триэтиленгликольным фрагментом. Элементарная ячейка содержит четыре молекулы кристаллогидрата, связанных межмолекулярными водородными связями. Таким образом, триэтиленгликольный фрагмент образует хелатную полость, которая способна координировать молекулу воды или катионы щелочных металлов, таких как Na^+ и K^+. Геометрические характеристики, полученные оптимизацией моногидрата триэтиленгликользамещенного фталонитрила в газовой фазе методом DFT/B3LYP/6-31G(d,p), согласуются с данными рентгеноструктурного анализа.

Ключевые слова: 4-нитрофталонитрил, триэтиленгликоль, рентгеноструктурный анализ, теория функционала плотности

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SYNTHESIS AND STRUCTURE OF 4-(9-HYDROXY-1,4,7-TRIOXYNONYL)PHTHALONITRILE

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4-(9-Hydroxy-1,4,7-trioxynonyl)phthalonitrile was prepared by reaction of 4-nitrophthalonitrile with triethylene glycol in dry DMSO in the presence of fresh-calcined fine milled K_2CO_3 at 60 °C for 12 hours. The reaction mixture was poured into cold distilled water and extracted by CH_2Cl_2. Then the crude product obtained after solvent evaporation was purified by column chromatography on silica gel using elution mixture of ethyl acetate : hexane (1:3) and after that end product was dried at reduced pressure at 80 °C for 4 h. The product was characterized by IR and ^1H NMR spectroscopies, mass-spectrometry, elemental analysis and X-ray diffraction data. In MALDI-TOF spectrum, two signals located at 299 $[M+Na]^+$ and 315 $[M+K]^+$ Da were detected. Conformity between the calculated isotopic distributions and those derived from experimental data proves these assignments. A colorless monocrystal suitable for X-Ray measurements was grown up by low temperature solvent evaporation from a solution of 4-(9-hydroxy-1,4,7-trioxynonyl)phthalonitrile in ethyl acetate. X-ray studying showed that this compound is a monohydrate of 4-(9-hydroxy-1,4,7-trioxynonil)phthalonitrile with a water molecule located in lateral chain. Four molecules of 4-(9-hydroxy-1,4,7-trioxynonil)phthalonitrile and four water molecules were founded to be located in one unit cell with formatting eight intermolecular hydrogen bonds. Hence triethylene glycol fragment forms a chelate-like cavity which is able to hold a water molecule or a cation of alkali metal. It was found that its structure is very similar to that optimized at DFT/B3LYP/6-31G(d,p) level. The some bond lengths of theoretical calculations are found to be greater than experiment data because of close intermolecular interactions in solid state.

Key words: 4-nitrophthalonitrile, triethylene glycol, X-ray diffraction, DFT method

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INTRODUCTION

The substituted phthalonitriles are widely used as starting materials in the synthesis of phthalocyanines (Pcs) and macroheterocyclic compounds (Mcs) [1-6]. Nature, number and positions of substituents give a strong influence on the reactivity of phthalonitriles and properties of Pcs and Mcs derived from them. Selection of substituted phthalonitriles and diamines in the case of Mcs allows fine turning their properties and leads to new functional materials with desirable properties. For instance, introduction of bulky substituents on periphery of macrocycles like as long alkyl chains [7] and bulky *tert*-butyl groups [8] allows to obtain the products soluble in organic solvents what makes easier their purifications and opens the large opportunities to studying their structures and properties by the methods where solubility is important. The oligooxyethylene glycol substituted phthalonitriles with various functional groups at the terminal oxygens [9-12] were used as precursors in synthesis of Pcs and Mcs [13, 14]. Thus, Pcs bearing hydrophilic polyethylene glycol monomethyl ether groups have been studied as agents for photodynamic therapy [15, 16].

To the best of our knowledge the phthalonitrile bearing triethylene glycol substituent wasn't obtained for the moment. Although using of the phthalonitrile with functional OH group can lead to macrocycles which are of interest to polymers modification. Therefore the aim of this work is synthesis and structure studying of 4-(9-hydroxy-1,4,7-trioxynonyl)phthalonitrile.

EXPERIMENTAL

4-Nitrophthalonitrile has been prepared following the method described in the literature [17]. Reaction solvents were thoroughly dried before use according to standard procedures [18]. Column chromatography was conducted on silica gel Merck-60. TLC was performed on aluminum sheets precoated with silica gel 60 F_{254} (Merck). MALDI-TOF spectra were obtained with a Shimadzu Biotech Axima Confidence in positive ions field using 2,5-dihydroxy *benzoic acid (DHB)* as matrix. ^{1}H NMR spectra were recorded with an Avance-300 instruments in DMSO-D_6 with tetramethylsilane as inner standard. Chemical shifts are expressed in parts per million (ppm), and coupling constants (J) in Hertz (Hz). IR spectra were recorded on Avatar 360 FT-IR. Detection of carbon, hydrogen, nitrogen and oxygen was carried out with a FlashEA 1112 CHNS–O Analyzer. A monocrystal suitable for X-ray investigation was grown by low temperature solvent evaporation from a solution of 4-(9-hydroxy-1,4,7-trioxynonyl)phthalonitrile in ethyl acetate. The molecular structure of $C_{14}H_{16}N_2O_4{\cdot}H_2O$ in the crystalline state was determined using an Xcalibur R diffraction instrument with monochromatic MoK_α-radiation by ω-scanning method with CrysAlisPro software package [19]. Crystal is triclinic: a 7.4812(19), b 8.490(2), c 13.0208(19) Å, α 97.418(16), β 95.726(16), γ 112.50(2)°, V 747.5(3) Å^3, M 294.30, d_{calc} 1.308 g/cm^3, μ 0.100 mm^{-1}, Z 2, space group P–1, reflections collected: 6104; reflections unique = 3494, 2382 with $I > 2\sigma(I)$. The absorptions were corrected by SCALE3 ABSPACK multi-scan method. All non-H atoms were refined anisotropically by full-matrix least-squares method. All calculation were performed by using the SHELXL [20] and OLEX2 [21] software packages. The final refinement parameters: R_1 0.0502, wR_2 0.1247 [$I > 2\sigma(I)$], R_1 0.0761, wR_2 0.1502 (for all), S 1.040.

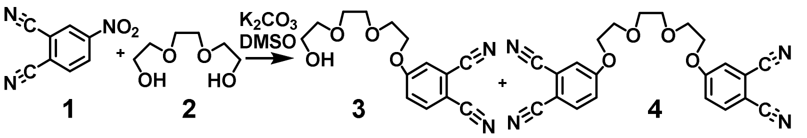
Quantum-chemical calculations were carried out with full geometry optimization at DFT/B3LYP/6-31G(d,p) level using Firefly software package [22]. Starting geometry for the calculation was derived from X-ray data. The optimized configuration was found to be in compliance with critical conditions [23]. Processing and presentation of the results were performed using Chemcraft software package [24].

SYNTHESIS

A mixture consisting of 1.49 g (8.0 mmol) 4-nitrophthalonitrile, 2.3 ml (16 mmol) triethylene glycol and 20 ml dry dimethyl sulfoxide was heated up to 50 ºC under argon. Then 3.2 g (23 mmol) fresh-calcined fine milled K_2CO_3 was added stepwise by a portion of about 0.5 g within 30 min intervals. The reaction mixture was heated up to 60 ºC and was stirred at this temperature for 12 h. After cooling to r.t., K_2CO_3 was filtered off and filtrate was concentrated up to 5 ml volume at reduced pressure and then was poured into 55 ml cold distilled water. This mixture was extracted with 3×40 ml portions of CH_2Cl_2, the combined extract was washed by 50 ml distilled water, and the organic layer was dried over Na_2SO_4. After that the extract was concentrated at reduce pressure and the product was purified by column chromatography on silica gel using elution mixture: ethyl acetate:hexane (1:3). Finally solvents were rotaevaporated and white powder was dried at reduced pressure at 80 °C for 4 h. Yield: 0.99 g (46 %). t_m = 141-142 ºC. R_f = 0.39 (Silica gel 60 F_{254}, CH_2Cl_2:CH_3OH:C_6H_{14} 10:1:3). IR (KBr) ν, cm^{-1}: 526; 725; 838; 893; 970; 997; 1044; 1097; 1127; 1255; 1321; 1422; 1488; 1560; 1598; 1716; 2228; 2853; 2919; 3090; 3427. ^{1}H-NMR (DMSO-d_6) δ, м.д.: 8.05 (m, 1H, H_{ar}), 7.78 (dd, J = 11.8, 2.6 Hz, 1H, H_{ar}), 7.46 (m, 1H, H_{ar}), 4.28 (s, 2H, CH_2), 3.77 (s, 2H, CH_2), 3.56 (m, 11H, CH_2, OH), 3.41 (d, J = 5.3 Hz, 2H, CH_2). Anal. calc. for $C_{14}H_{16}N_2O_4$, %: C 60.68; N 10.14; H 5.84. Found, %: C 62.68; N 10.61; H 5.76. MALDI-TOF m/z, Da: found: 299, 315, calculate: EM = 299 $[M + Na]^+$, $C_{14}H_{16}N_2O_4Na^+$; EM = 315 $[M + K]^+$, $C_{14}H_{16}N_2O_4K^+$.

RESULTS AND DISCUSSION

4-(9-Hydroxy-1,4,7-trioxynonyl)phthalonitrile was obtained by interaction of 4-nitrophtalonitrile **1** with triethylene glycol **2** in dimethyl sulfoxide (DMSO) in the presence of fresh-calcined fine milled K_2CO_3 following the procedure described in literature for olygooxyethylene phthalonitrile [25]. Since triethylene glycol has two terminal OH-groups, formation of **3** runs with participation of the first of them and that no gives much influence on reactivity of the second OH-group. Therefore a formation of bisphthalonitrile **4** as a side product takes place (Scheme).



Scheme
Схема

Variation of relationships between **1** and **2** at the range 1:2, 1:1 and 2:1 shown that the best yield of **3** is achieved while an excess of triethylene glycol was used. Separation of the products **3** and **4** has been done by column chromatography on silica gel using ethyl acetate:hexane (1:3) mixture.

The product **3** was characterized by mass-spectrometry, IR and ^{1}H NMR spectroscopies, elemental analysis and X-ray diffraction method data.

It worthy to note that no signal of molecular ion was detected in MALDI-TOF spectrum of **3**. But there are two signals located at 299 и 315 Da which correspond to [M+Na]$^+$ and [M+K]$^+$ ions. Conformity between the calculated isotopic distributions and those derived from experimental data proves this assignment. So electron density rich oxygens of triethylene glycol fragment of **3** are able to coordinate cations of alkali metal as it takes place in the case of crown ethers [13, 26, 27].

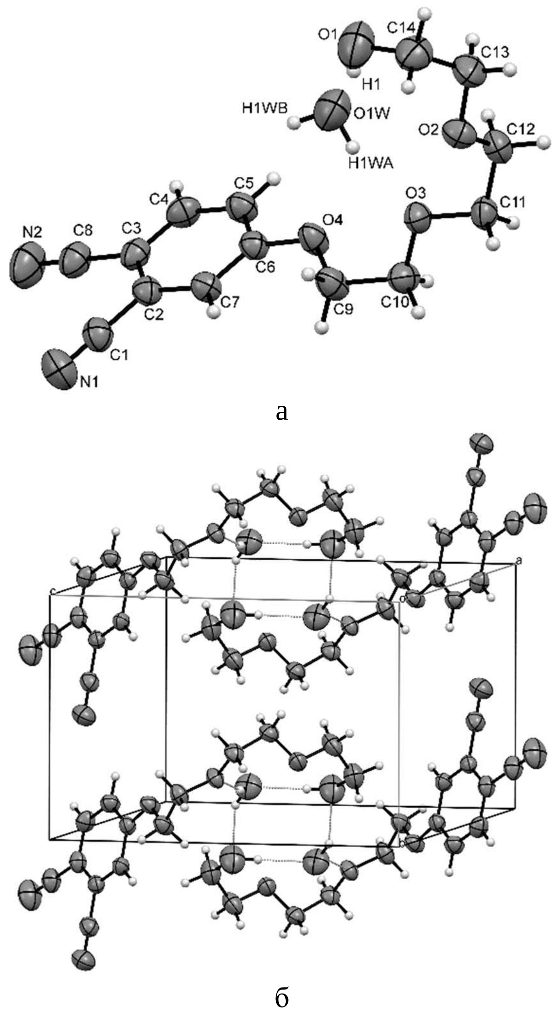
The dominant bands in the IR spectra of **3** are induced by vibrations of oxyethylene –C–O–C– (1127, 1096 *cm*$^{-1}$) and –CH$_2$– (2853, 2923 *cm*$^{-1}$) groups. Intense absorption bands observed at 2230 *cm*$^{-1}$ can be identified as stretching vibrations ν(C≡N).

^{1}H NMR data were found to be in agreement to literature data [14,28]. Signal at δ = 7.45-8.05 *ppm* corresponds to the resonance of benzene protons. The –O–CH$_2$–CH$_2$– units of triethylene glycol fragment were determined at δ = 4.28-3.41 *ppm*.

A colorless monocrystal suitable for X-Ray measurements was grown up by low temperature solvent evaporation from a solution of 4-(9-hydroxy-1,4,7-trioxynonyl)phthalonitrile in ethyl acetate. Crystal structure (a) and packing (b) of **3·H$_2$O** are shown in Figure.

It was established that compound **3** in crystalline state (triclinic crystal, *P*–1 space group) is a monohydrate. Four molecules of 4-(9-hydroxy-1,4,7-trioxynonil)phthalonitrile and four water molecules were founded to be located in one unit cell (Fig. b). Two intermolecular hydrogen bonds between hydrogen H1 of hydroxy group and oxygen O1W of water (1.963 Å) and between oxygen O3 of triethylene glycol fragment and hydrogen H1WA of water (1.981 Å) form crystalline structure of **3·H$_2$O** (Fig. b). The hydrogen H1WB of water is connected with another molecule **3** in the crystal pack (H1WB – O1). Hence, triethylene glycol fragment forms a chelate-like cavity which is able to hold a water molecule or a cation of alkali metal.

Quantum-chemical calculations at the DFT/B3LYP/6-31G(d,p) level were carried out with the aim to compare geometric characteristics of molecules in a solid and an isolated states. It was found that the calculated geometric parameters of monohydrate (**3·H$_2$O**) are similar to those derived from X-ray data (table). The trend of quantum-chemical calculations yielding heteroatom-hydrogen distances larger than experimental values is similar to that obtained previously [29, 30].

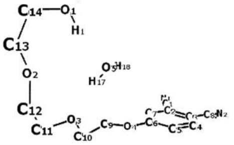
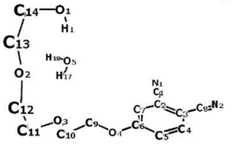


а

б

Fig. Crystal structure (a) and packing (b) of **3·H$_2$O** by X-ray analysis
Рис. Структура молекулы (а) и (b) упаковка кристалла молекулы **3·H$_2$O** методом РСА

Table
Selected experimental and calculated bond lengths (Å) and valence angles (˚) of 3·H₂O molecule
Таблица. **Экспериментальные и расчетные длины связей (Å) и валентные углы (˚) в молекуле 3·H₂O**

	X-ray diffraction	DFT B3LYP/6,31 G(d,p)
		
Bond lengh, Å		
r(O_1-H_1)	0.864	0.977
r(O_1-C_{14})	1.395	1.407
r(O_2-C_{12})	1.415	1.414
r(O_2-C_{13})	1.422	1.428
r(O_3-C_{10})	1.420	1.417
r(O_3-C_{11})	1.424	1.421
r(O_4-C_6)	1.347	1.352
r(O_4-C_9)	1.435	1.432
r(C_9-C_{10})	1.488	1.515
r(C_{11}-C_{12})	1.491	1.516
r(C_{13}-C_{14})	1.480	1.524
r(H_1-O_5)	1.963	1.891
Angle, °		
α(H_1-O_1-C_{14})	112.0	108.6
α(O_1-H_1-O_5)	163.7	171.0
α(O_1-C_{14}-C_{13})	111.8	113.6
α(C_{12}-O_2-C_{13})	113.4	113.9
α(O_2-C_{12}-C_{11})	110.1	108.1
α(O_2-C_{13}-C_{14})	109.5	109.1
α(C_{10}-O_3-C_{11})	112.1	114.1
α(O_3-C_{10}-C_9)	110.0	108.8
α(O_3-C_{11}-C_{12})	109.3	107.8
α(C_6-O_4-C_9)	118.2	119.1
α(O_4-C_9-C_{10})	108.7	107.8
α(H_{17}-O_5-H_{18})	99.8	103.7
α(H_{17}-O_5-H_1)	102.0	92.3
α(H_{18}-O_5-H_1)	122.3	99.6

The difference in position of water molecules in **3·H₂O** which is detected on going from theoretical model to X-ray data can be explained by participation of the water in intermolecular interactions with the second molecule of nitrile. So, the distance between O2 and O5 is equal to 2.975 Å for the theoretical data and to 3.147 Å for monocrystal. The maximal deviation (near 22.7˚) was observed for angles (H_{18}-O_5-H_1) between hydrogen of hydroxyl group of triethylene glycol fragment and oxygen of molecule of water. Rotational motions and flexibility of triethylene glycol fragment of **3** contribute to non rigidity of its structure.

CONCLUSION

4-(9-Hydroxy-1,4,7-trioxynonyl)phthalonitrile bearing triethylene glycol moiety was prepared by nucleophilic substitution of nitro group in 4-nitrophthalonitrile with triethylene glycol in the presence of K_2CO_3. The product was characterized by mass-spectrometry, IR and ^{1}H NMR spectroscopies, elemental analysis and X-ray diffraction data. It was established that phthalonitrile **3** in crystalline state is a monohydrate. The geometric parameters of **3** derived from X-ray analysis were found to be in agreement with those carried out by theoretical calculations at DFT/B3LYP/6-31G(d,p) level.

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