

Communication

Synthesis and Structural Analysis of a Nitrobenzofurazan Derivative of Dibenzo-18-Crown-6 Ether

Alexandru Bujor ¹, Victorita Tecuceanu ², Anamaria Hanganu ^{1,2}  and Petre Ionita ^{1,*} 

¹ Faculty of Chemistry, University of Bucharest, 90 Panduri, 050663 Bucharest, Romania

² 'C. D. Nenitzescu' Institute of Organic and Supramolecular Chemistry of the Romanian Academy, 202B Spl. Independentei, 060023 Bucharest, Romania

* Correspondence: petre.ionita@chimie.unibuc.ro

Abstract: Nitrobenzofurazan derivatives are well known for their fluorescence, whilst crown ethers are known for their complexing capacity toward cationic species. In this study, we present the synthesis and structural characterization of a new derivative containing both nitrobenzofurazan moieties and a crown ether core. The new compound was obtained from dibenzo-18-crown-6 ether, which was first nitrated, reduced to the corresponding amine, and subsequently derivatized with NBD. Structural analyses performed by IR, NMR, UV-Vis, and MS confirmed its structure and physico-chemical behavior toward the complexation of alkaline cations.

Keywords: crown ether; NBD; supramolecular



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1. Introduction

Crown ethers are a class of organic compounds that possess several extraordinary properties such as a strong cation complexation ability. In 1967, research regarding the synthesis and complexation behavior of many such compounds was published, including dibenzo-18-crown-6 ether [1], and in 1987, the Nobel Prize was awarded for the development of a new area, supramolecular chemistry [2]. Currently, crown ethers are found in applications such as supramolecular chemistry, catalysis, analytical chemistry, and the separation of metal ions or chiral compounds; many reviews are available in the literature [3,4].

Nitrobenzofurazan (nitro-1,2,3-benzoxadiazole) derivatives are used as chromophores or fluorophores. A facile method to label amines is the use of a 4-chloro-7-nitrobenzofuran reagent (4-chloro-7-nitro-1,2,3-benzoxadiazole), also known as NBD-chloride [5]. Molecules containing both an NBD moiety and a crown ether one are of high interest for the design of smart fluorescence and complexation systems [6,7].

In this study, we present the synthesis and characterization of a novel derivative that contained a crown ether core (DB18-C-6) functionalized with NBD moieties, as well as a few characteristics of the complexation processes with potassium and sodium cations.

2. Materials and Methods

All chemicals and solvents were purchased from Chimopar, Merck, or Sigma-Aldrich and were used as received. The UV-Vis measurements were obtained using a UVD-3500 double-beam spectrometer, and the IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. The NMR spectra were measured either in chloroform-*d*₁ or DMSO-*d*₆ using a Bruker Advance spectrometer operating at 500 MHz for ¹H and 125 MHz for ¹³C. The residual solvent peaks were used as an internal reference for the chemical shifts (δ , ppm). The MS spectra were recorded on a Varian 310 MS LC/MS/MS triple quadrupole mass spectrometer fitted with an electrospray ionization interface (ESI).

DN-DB18-C-6. A total of 5 g DB18-C-6 was suspended in 30 mL warm acetonitrile; (at about 50 °C) 10 mL nitric acid (65%) was then slowly added under stirring, and the reaction was kept for another 2 h for completion at room temperature. Ice was then added,

and the mixture was left until the ice was beginning to melt. This was followed by filtration. The filtrate was washed with cold water and left to dry in the open air. The yields were almost quantitative [8,9]. Alternatively, the same products could be obtained following the procedure using a mixture of acetic acid and chloroform as the solvents, and isomers can be isolated by crystallization [8].

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$, δ ppm, J Hz): 7.89 (dd, 2H, H_{Ar} , 2.6 Hz, 9.0 Hz), 7.72 (d, 2H, H_{Ar} , 2.6 Hz), 7.16 (d, 2H, H_{Ar} , 9.0 Hz), 4.23–4.20 (m, 8H, CH_2), 3.91–3.83 (m, 8H, CH_2) ppm. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ ppm, J Hz): 7.88 (dd, 2H, H_{Ar} , 2.5 Hz, 8.9 Hz), 7.71 (d, 2H, H_{Ar} , 2.5 Hz), 6.86 (d, 2H, H_{Ar} , 8.9 Hz), 4.25–4.22 (m, 8H, CH_2), 4.04–4.01 (m, 8H, CH_2) ppm. $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ ppm): 153.47, 147.74, 140.97, 117.37, 110.17, 106.82, 68.83, 68.79, 68.15, 68.02 ppm.

DA-DB18-C-6. A total of 2 g DN-DB18-C-6 was dissolved in 40 mL DMF at 100 °C; 2 g Raney Ni was then carefully added under stirring [9], followed by the dropwise addition of 3.5 mL hydrazine hydrate (at around 70 °C). After 30–60 min, the solution was filtered off, water was added, and the mixture was extracted several times with DCM. The organic layer was separated and dried over anhydrous sodium sulphate, and the solvent was removed. The yields were around 90%. Another possibility for the reduction of nitro groups is the use of Zn and acetic acid in methanol [10]; in this case, impure amino derivatives are obtained.

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$, δ ppm, J Hz): 6.62 (d, 2H, H_{Ar} , 8.5 Hz), 6.24–6.23 (m, 2H, H_{Ar}), 6.07–6.04 (m, 2H, H_{Ar}), 4.66 (s, 4H, NH_2), 3.97–3.90 (m, 8H, CH_2), 3.82–3.75 (m, 8H, CH_2) ppm. $^{13}\text{C-NMR}$ (125 MHz, $\text{DMSO-}d_6$, δ ppm): 149.24, 149.14, 143.47, 143.39, 139.20, 139.12, 115.82, 115.63, 105.40, 105.35, 100.84, 100.75, 69.40, 69.24, 69.22, 69.20, 69.13, 69.03, 67.74, 67.64 ppm.

Bis-NBD-DB18-C-6. Dark, red-brown solid $\text{C}_{32}\text{H}_{28}\text{N}_8\text{O}_{12}$ with a molecular weight of 716 and (-)ESI-MS of 715 was obtained. A total of 1 g DA-DB18-C-6 was added to 100 mL acetonitrile. This was stirred for approximately 5 min, followed by the addition of 1 g NBD-Cl and 5 g sodium hydrogen carbonate. The mixture was stirred at room temperature overnight; the next day, it was filtered off (the solid could be also washed with small portions of DCM), and the solvent was removed. The residue was chromatographed on a silica gel column using a mixture of DC and methanol (9/1 *v/v*) as an eluent.

Yields about 40%. Elemental analysis: calculated: C53.63%, H3.94%, N15.64%; found C53.84%, H4.02%, N15.55%. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$, δ ppm, J Hz): 10.99 (s, 2H, NH), 8.50 (dd, 2H, H_{Ar} , 1.8 Hz, 8.9 Hz), 7.09–7.06 (m, 4H, H_{Ar}), 6.99 (dd, 2H, H_{Ar} , 2.3 Hz, 8.5 Hz), 6.63 (dd, 2H, H_{Ar} , 1.9 Hz, 8.9 Hz), 4.17–4.07 (m, 8H, CH_2), 3.90–3.83 (m, 8H, CH_2) ppm. $^{13}\text{C-NMR}$ (125 MHz, $\text{DMSO-}d_6$, δ ppm): 148.82, 147.15, 145.31, 144.73, 143.57, 132.19, 129.13, 122.76, 116.89, 113.07, 109.57, 101.93, 69.27, 69.17, 68.35, 68.27 ppm. IR (cm^{-1}): 3629, 2922, 2852, 1726, 1569, 1508, 1447, 1237, 1124, 1045, 731, 582, 452.

3. Results

The starting material used in our work was commercially available crown ether DB18-C-6. This was first nitrated to obtain the dinitro derivative DN-DB18-C-6 (Figure 1), followed by a reduction to the corresponding diamine DA-DB18-C-6; finally, by coupling with NBD-chloride, the novel derivative *bis*-NBD-DB18-C-6 was obtained (Figure 1).

The nitration of DB18-C-6 yields two geometric isomers, commonly named as *cis* and *trans*, and their physical characteristics are quite similar; for example, the IR, UV-Vis, and NMR data are identical (however, the melting points are different) [8]. The nitration procedure can be performed either with a mixture of nitric acid in acetic acid [8] or with nitric acid in acetonitrile [9]. The separation of DN-DB18-C-6 *cis* and *trans* isomers can be achieved by recrystallization [8,9]. The reduction of nitro derivatives to amino derivatives can be performed with Zn and acetic acid [10] or by hydrazine and Raney Ni [9]. Both procedures occur with over 80% yields [11]. As DN-DB18-C-6 and DA-DB18-C-6 were obtained practically in our study by following the procedures in the literature, only the $^1\text{H-}$ and $^{13}\text{C-NMR}$ data were recorded to (re)confirm the structure of these compounds

(NMR data are shown in the Experimental part as δ ppm values and in the Supplementary Materials as Figures S1–S5).

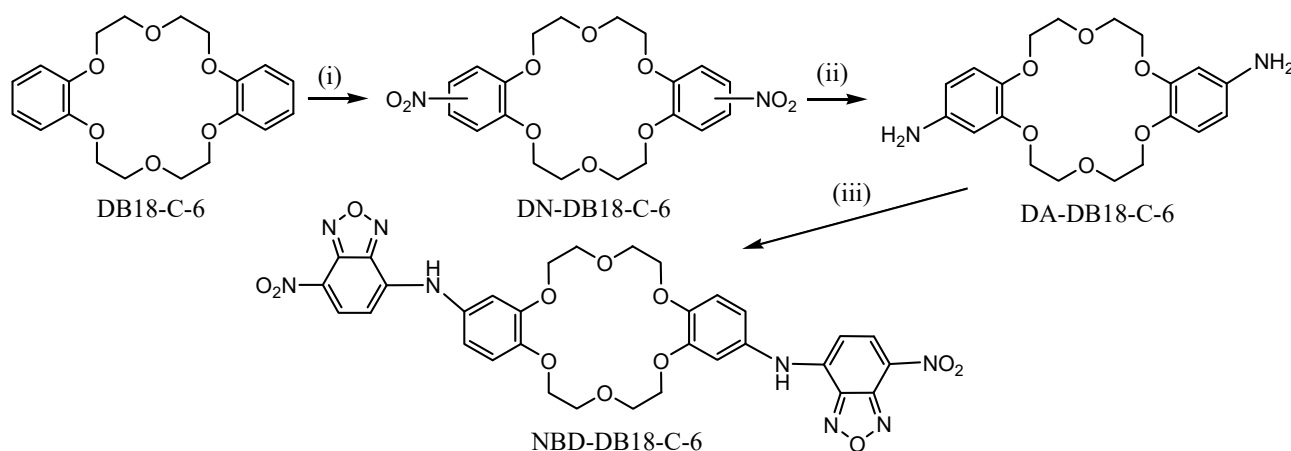


Figure 1. Synthesis of *bis*-NBD-DB18-C-6: (i) nitric acid in acetonitrile; (ii) hydrazine and Raney Ni in DMF; (iii) NBD-Cl and sodium hydrogen carbonate in acetonitrile.

The last step of the synthesis was the derivatization of the diamine with NBD-chloride (a specific reagent for amines), affording moderate–high yields of the novel compound, which was denoted as *bis*-NBD-DB18-C-6 (Figure 1). For this, a full physico-chemical characterization was performed. The ^1H -NMR spectrum (see also Figure S6 in the Supplementary Materials) showed the hydrogen nucleus from the amino groups at 10.99 ppm, and the two hydrogen nuclei from the NBD moiety appeared as doublets at 8.50 ppm and 6.63 ppm. Aromatic hydrogens from the benzene rings were present at 6.99–7.90 ppm and at 3.83–3.90 ppm and 4.07–4.17 ppm for the aliphatic $-\text{CH}_2-$ groups. The ^{13}C -NMR values (Figure S7 in the Supplementary Materials) were also consistent with the structure.

The IR spectrum of the novel compound *bis*-NBD-DB18-C-6 showed the expected bands, corresponding with the amino groups at 3629 cm^{-1} , the aromatic rings at 2922 cm^{-1} , the nitro groups at 1569 cm^{-1} , and the crown ether moiety at 1237 cm^{-1} (see Figure S8 in the Supplementary Materials). The UV–Vis spectrum was also consistent with the proposed structure; the preeminent band was recorded at 472 nm, corresponding with the NBD moieties (Figure S9 in the Supplementary Materials).

The ESI-MS spectrum of the *bis*-NBD-DB18-C-6 compound (Figure 2) recorded in a negative mode showed a value of $715\text{ } m/z$ as the molecular peak ($\text{M}-\text{H}^+$), which was also proof of the structure.

An important behavior of the novel compound *bis*-NBD-DB18-C-6 was noticed whilst recording the ESI-MS spectrum in a positive mode (see Figure S10 in the Supplementary Materials). Thus, the formation of supramolecular complexes of the *bis*-NBD-DB18-C-6 derivative with Na and K cations was easily noticed as peaks that appeared at $739\text{ } m/z$ ($\text{M} + \text{Na}^+$) and $755\text{ } m/z$ ($\text{M} + \text{K}^+$). Supplementary peaks of the corresponding complexes with ammonium, sodium, and potassium cations were recorded at values of 556, 561, and $577\text{ } m/z$. These were attributed to the $538\text{ } m/z$ residue that matched the mono-substituted amino-DB18-C-6 with the NBD moiety. Such evidence of the formation of supramolecular complexes highlighted the ability of the *bis*-NBD-DB18-C-6 compound to be easily involved in supramolecular interactions, constituting a facile method for chemosensor materials [12,13].

To investigate further the complexing ability of the *bis*-NBD-DB18-C-6 compound toward K^+ and Na^+ cations, several NMR experiments were performed. Thus, after dissolving the crown ether derivative *bis*-NBD-DB18-C-6 in $\text{DMSO}-d_6$, either potassium nitrate or sodium nitrate was added, and the spectra were recorded again to check if there were any changes that could be noticed in the corresponding ^1H -NMR spectra values. Table 1 shows the observed changes and Figure 3 shows the actual superposed spectra.

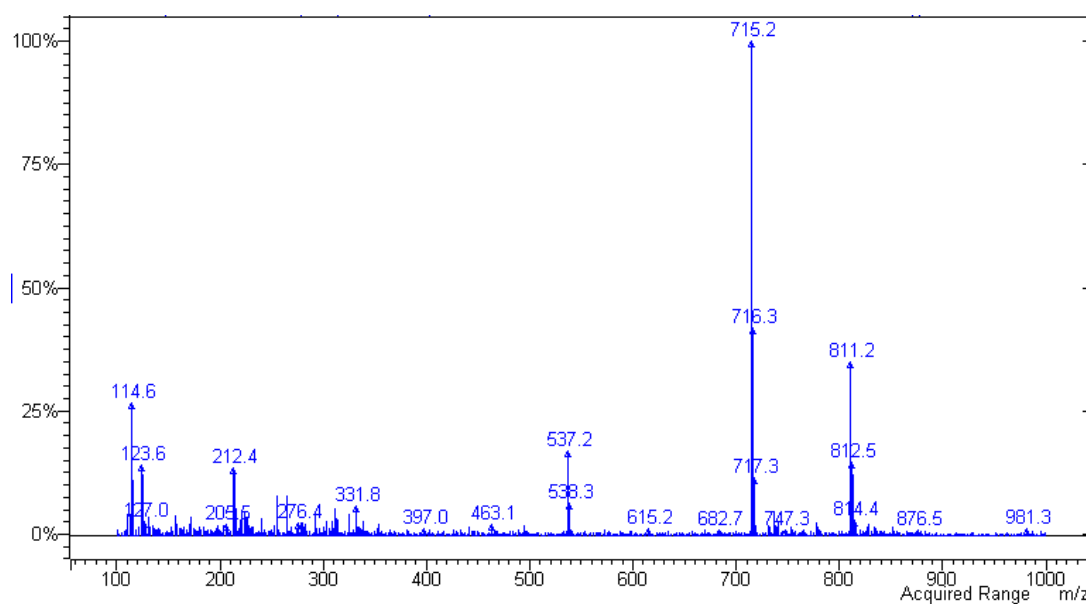


Figure 2. Full (-)ESI-MS spectrum of *bis*-NBD-DB18-C-6.

Table 1. Changes in chemical shifts upon complexation of *bis*-NBD-DB18-C-6 with K^+ and Na^+ cations.

Compound	Chemical Shifts (δ ppm)						
	H_{NH}	H_{Ar}	H_{Ar}	H_{Ar}	H_{Ar}	H_{ether}	H_{ether}
<i>bis</i> -NBD-DB18-C-6	11.00	8.50	7.08	6.99	6.62	4.17–4.07	3.88
<i>bis</i> -NBD-DB18-C-6 + K^+	11.03	8.53	7.15	7.06	6.64	4.29–4.11	3.95
<i>bis</i> -NBD-DB18-C-6 + Na^+	11.03	8.52	7.11	7.02	6.60	4.21–4.09	3.04

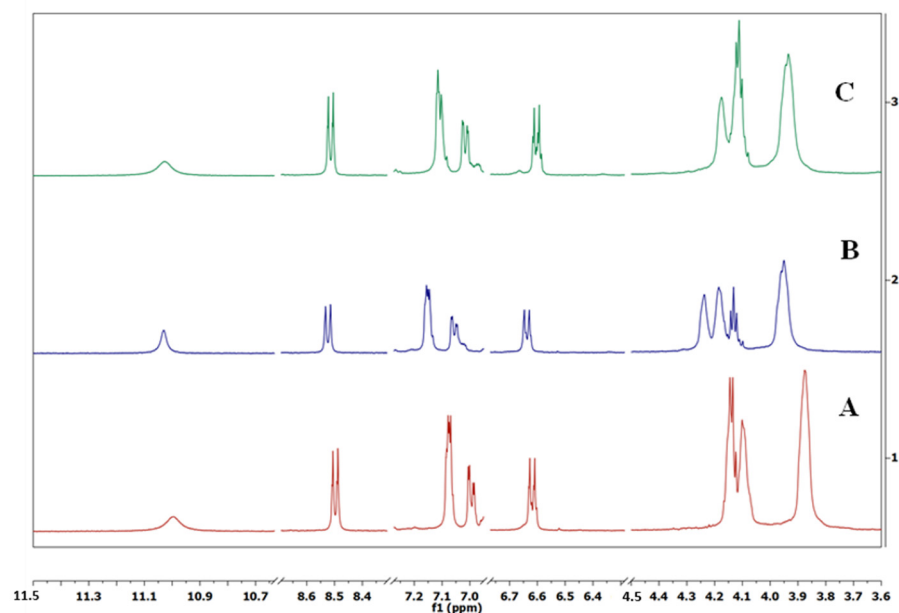


Figure 3. Superposed 1H -NMR spectra of (A) *bis*-NBD-DB18-C-6, (B) *bis*-NBD-DB18-C-6 + K^+ , and (C) *bis*-NBD-DB18-C-6 + Na^+ .

Thus, it was easily observed that both cations had an influence on the chemical shifts (measured as δ values); these shifts were higher in the case of the potassium cation compared with those recorded for the sodium one. This again emphasized the capacity

of the crown ether derivative to create complexes with alkaline cations; the complexation was stronger in the case of potassium, as this cation fits more effectively inside crown ether [14–16].

4. Conclusions

Starting from the well-known crown ether DB18-C-6, a new nitrobenzofurazan derivative was obtained and characterized by IR, UV-Vis, MS, and NMR. The synthesis involved three steps; all of them worked with good yields. The structural analysis confirmed the proposed chemical structure and highlighted the complexing capacity toward alkaline cations. Such compounds can easily find applications in materials chemistry as well as in the processes of sensing and detecting cations [17–20].

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/chemistry4040110/s1>, Figure S1: ^1H -NMR spectrum of DN-DB18-C-6 recorded in $\text{DMSO}-d_6$; Figure S2: ^1H -NMR spectrum of DN-DB18-C-6 recorded in chloroform- d ; Figure S3: ^{13}C -NMR spectrum of DN-DB18-C-6 recorded in chloroform- d ; Figure S4: ^1H -NMR spectrum of DA-DB18-C-6 recorded in $\text{DMSO}-d_6$; Figure S5: ^{13}C -NMR spectrum of DA-DB18-C-6 recorded in $\text{DMSO}-d_6$; Figure S6: ^1H -NMR spectrum of *bis*-NBD-DB18-C-6 recorded in $\text{DMSO}-d_6$; Figure S7: ^{13}C -NMR spectrum of *bis*-NBD-DB18-C-6 recorded in $\text{DMSO}-d_6$; Figure S8: IR spectrum of *bis*-NBD-DB18-C-6; Figure S9: UV-Vis spectrum of *bis*-NBD-DB18-C-6; Figure S10: Full (+)ESI-MS spectrum of *bis*-NBD-DB18-C-6, showing the formation of the supramolecular complexes.

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References

1. Pedersen, C.J. Cyclic polyethers and their complexes with metal salts. *J. Am. Chem. Soc.* **1967**, *89*, 2495–2496. [CrossRef]
2. Lehn, J.M. Supramolecular chemistry: Where from? Where to? *Chem. Soc. Rev.* **2017**, *46*, 2378–2379. [CrossRef] [PubMed]
3. Izatt, R.M.; Pawlak, K.; Bradshaw, J.S.; Bruening, R.L. Thermodynamic and kinetic data for macrocycle interaction with cations, anions, and neutral molecules. *Chem. Rev.* **1995**, *95*, 2529–2586. [CrossRef]
4. Li, J.; Yim, D.; Jang, W.D.; Yoon, J. Recent progress in the design and applications of fluorescence probes containing crown ethers. *Chem. Soc. Rev.* **2017**, *46*, 2437. [CrossRef] [PubMed]
5. Coman, A.G.; Stavarache, C.; Paun, A.; Popescu, C.C.; Hădăde, N.D.; Ionita, P.; Matache, M. A novel profluorescent paramagnetic diaza-crown ether: Synthesis, characterization and alkaline metal-ion complexation. *RSC Adv.* **2019**, *9*, 6078–6083. [CrossRef] [PubMed]
6. Móczár, I.; Huszthy, P. Optically active crown ether-based fluorescent sensor molecules: A mini-review. *Chirality* **2018**, *2*, 97–109. [CrossRef] [PubMed]
7. Minkin, V.I.; Dubonosov, A.D.; Bren, V.A.; Tsukanovb, A.V. Chemosensors with crown ether-based receptors. *Arkivoc* **2008**, *iv*, 90–102. [CrossRef]
8. Feigenbaum, W.M.; Michel, R.H.J. Novel polyamides from macrocyclic ethers. *Polym. Sci. Part A Polym. Chem.* **1971**, *9*, 817–820. [CrossRef]
9. Glushko, V.N.; Sadovskaya, N.Y.; Blokhina, L.I.; Zhila, M.Y.; Belus, S.K.; Vashchenkova, E.S.; Shmeleva, I.A. Synthesis of isomeric dinitro and diamino derivatives of polycyclic crown ethers: Dibenzo-18-crown-6 and dibenzo-24-crown-8. *Rus. J. Gen. Chem.* **2018**, *88*, 1595–1600. [CrossRef]
10. Bujor, A.; Matei, I.; Culita, D.C.; Hanganu, A.; Tecuceanu, V.; Ionita, P. Linear and cyclic ethylene-glycols labelled with nitrobenzofurazan motifs. *Rev. Roum. Chim.* **2022**; in press.

11. Dongyun, W.; Chunhai, Y.; Beibei, Z.; Bolun, Y. Synthesis and characterization of trans-di(nitrobenzo)- and di(aminobenzo)-18-crown-6 derivatives with high selectivity. *Synth. Comm.* **2018**, *48*, 329–335. [[CrossRef](#)]
12. Gutowska, N.; Seliger, P.; Romański, J.; Zięba, M.; Adamus, G.; Kowalczyk, M. Mass spectrometry reveals complexing properties of modified pnp-lariat ether containing benzyl derivative of (s)-prolinamine. *Molecules* **2020**, *25*, 136. [[CrossRef](#)] [[PubMed](#)]
13. Zaitsev, S.Y.; Solovieva, D.O.; Zaitsev, I.S. Membrane and films based on novel crown-containing dyes as promising chemosensing materials. *Materials* **2010**, *3*, 5293–5310. [[CrossRef](#)] [[PubMed](#)]
14. Rodrigue, A.; Bovenkamp, J.W.; Lacroix, B.V.; Bannard, R.A.B.; Buchanan, G.W. Complexes of 18-crown-6 macrocyclic ethers obtained from ethereal solvents. Complexes of potassium and sodium salts with host: Guest ratios of 1:2 and 1:3. *Can. J. Chem.* **1986**, *64*, 808–815. [[CrossRef](#)]
15. Lvova, L.; Acciari, E.; Mandoj, F.; Pomarico, G.; Natale, C.D.; Paolesse, R. Crown-porphyrin ligand for optical sensors development. *Proceedings* **2018**, *2*, 922. [[CrossRef](#)]
16. Valeur, B. Design principles of fluorescent molecular sensors for cation recognition. *Coord. Chem. Rev.* **2000**, *205*, 3–40. [[CrossRef](#)]
17. Zaleskaya-Hernik, M.; Dobrzycki, Ł.; Karbarz, M.; Romański, J. Fluorescence recognition of anions using a heteroditopic receptor: Homogenous and two-phase sensing. *Int. J. Mol. Sci.* **2021**, *22*, 13396. [[CrossRef](#)] [[PubMed](#)]
18. Iannazzo, D.; Espro, C.; Ferlazzo, A.; Celesti, C.; Branca, C.; Neri, G. Electrochemical and fluorescent properties of crown ether functionalized graphene quantum dots for potassium and sodium ions detection. *Nanomaterials* **2021**, *11*, 2897. [[CrossRef](#)] [[PubMed](#)]
19. Zheng, B.; Wang, F.; Dong, S.; Huang, F. Supramolecular polymers constructed by crown ether-based molecular recognition. *Chem. Soc. Rev.* **2012**, *41*, 1621–1636. [[CrossRef](#)] [[PubMed](#)]
20. Bem, M.; Badea, F.; Draghici, C.; Caproiu, M.T.; Vasilescu, M.; Voicescu, M.; Beteringhe, A.; Caragheorgheopol, A.; Maganu, M.; Constantinescu, T.; et al. Synthesis and fluorescent properties of new derivatives of 4-amino-7-nitrobenzofurazan. *Arkivoc* **2007**, *xiii*, 87–104. [[CrossRef](#)]