Short Note

6-(2'-(4''-Oxabutyloxy)phenyl)-1,6,11-triaza-3,9,14,17,22,25-hexaoxa-2(1,2)(4-methylbenzena)-10(1,2)(5-methylbenzena)bicyclo(9.8.8)heptacosaphane Sodium Bromide Dichloromethane

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Abstract: Potassium ion sensors are important for the study of concentration profiles in tissues. The synthesis of a cryptand suited for potassium ions and the crystal structure of it with a chelated sodium ion are presented.

Keywords: potassium; sodium; cryptand; crystal structure

Citation: Jochem, M.; Schollmeyer, D.; Detert, H. 6-(2'-(4''-Oxabutyloxy)phenyl)-1,6,11-triaza-3,9,14,17,22,25-hexaoxa-2(1,2)(4-methylbenzena)-10(1,2)(5-methylbenzena)bicyclo(9.8.8)heptacosaphane Sodium Bromide Dichloromethane. *Molbank* **2022**, *2022*, M1348. <https://doi.org/10.3390/M1348>

Academic Editor: René T. Boéré

Received: 4 January 2022

Accepted: 22 February 2022

Published: 3 March 2022

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1. Introduction

Potassium is an essential macronutrient for plant growth and development. Potassium, the most abundant intracellular cation, is essential for the proper functioning of all cell types [1]. K^+ ions are of a critical role in organisms, e.g., for the cell potential, which is maintained by the Na^+/K^+ pump. The possibility of measuring potassium levels in living cells, especially in the presence of other alkali-cations, is therefore of high interest for medical purposes and physiological studies [2,3]. The sensing of potassium concentrations is also important for the study of stress factors such as heat and aridity, problems of climate change. Most potassium sensing systems are composed of a chelating unit connected to a dye or fluorophore. The chelating unit can be a crown ether [4–7], calixarene [8] or cryptand [9–11]. Chelation of the cationic potassium ions changes the electron distribution in a dye if it is conjugated to a nitrogen of the cryptand [12–14].

Potassium is the perfect ion to fill the cavity of 18-crown-6 and the related 2,2,2-cryptand, whereas 15-crown-5 prefers the smaller sodium ion [15]. On the other hand, sandwich complexes of crown ethers with cations too large for the cavity [16], as well as complexation of smaller ions with only a part of a larger crown, have been observed [17].

We hereby report an improved synthesis of a cryptand **1** suitable for attachment to a fluorescent dye. The first synthesis of this cryptand was reported by He et al. [5]. It consisted in a four-step process composed of amide formation/reduction cascade, a more recent route achieves the cryptand formation via a two-step alkylation sequence [14]. Changing the procedure to a double cyclization reaction in one pot provided higher yields than the known literature methods. Finally, the cryptand was isolated via column chromatography on silica gel, but instead of the pure ligand, its complex with sodium bromide was obtained.

Despite a high selectivity for potassium ions as shown elsewhere, the triazacryptand is shown to chelate sodium ions with only a part of the tricyclic system resembling a typical crown ether. Herein, we report an improved synthesis of a triazacryptand and the first crystal structure of a sodium complex of it, obtained from cocrystallization with sodium bromide.

2. Results

Two procedures for the synthesis of the cryptand **1** (Scheme 1) from diamine **3** have been reported in the literature. The dioxaoctane bridges are formed either via a twofold acylation/reduction sequence or in two separate alkylation steps. Changing the procedure to a one-pot double cyclization provided significantly higher yields (24% vs. 18%).

Scheme 1. Synthesis of the title compound **2**, the sodium bromide complex of cryptand **1**.

The double cyclization of diamine **3** with dibromodioxaoctane **4** was performed under pseudo high-dilution conditions with concentrations of the reactive agents below the millimolar range via slow addition of **3** and **4** into the reaction vessel. Chromatography of the product on silica with chloroform-ethanol was followed by toluene-ethanol mixtures.

Compound **1** was obtained via a cyclization reaction with two equivalents of compound **4** and compound **3** employing a low millimolar dilution and very slow addition of both compounds in the desired ratio. Aqueous work-up, drying and evaporation of the solvent dichloromethane followed by chromatography on silica yielded a highly viscous, brownish oil with few and far between crystals. The obtained single crystal contains one equivalent of sodium bromide.

3. Crystal Structure

The complex **2** of ligand **1**, shown in Figure 1, with sodium bromide crystallizes in the triclinic system with two molecules per unit cell, and each complex is accompanied by one dichloromethane solvent molecule [18]. Crystal data for $C_{40}H_{57}BrCl_2N_3NaO_8$ ($M = 881.86$ g/mol): triclinic, space group $P\bar{1}$, (no. 2), $a = 13.0218(6)$ Å, $b = 13.4232(6)$ Å, $c = 14.0528(7)$ Å, $\alpha = 74.897(4)^\circ$, $\beta = 74.232(4)^\circ$, $\gamma = 63.961(3)^\circ$, $V = 2095.43(19)$ Å³, $Z = 2$, $T = 120(2)$ K, $\mu(\text{CuK}\alpha) = 1.173$ mm⁻¹, $D_{\text{calc}} = 1.397$ g/cm³, 17,904 reflections measured ($2.10^\circ \leq 2\theta \leq 28.57^\circ$; 9891 unique ($R_{\text{int}} = 0.032$ $R\sigma = 0.0395$), which were used in all calculations. The final $R1$ was 0.0529 ($I > 2\sigma(I)$) and $wR2$ was 0.1193 (all data). The complexes are centrosymmetrically arranged and connected via Coulomb interactions with the bromide ions between them. A hydrogen bond from the aromatic methyl group and the oxygen of the methoxy group ($C32-H32B-O10 = 3.476$ Å, angle $C-H-O = 164.2^\circ$; $H32B-O10A = 2.533$ Å) connects the two molecules in the unit cell to a centrosymmetric dimer. The shape of the coordination sphere is that of a slightly distorted and elongated trigonal trapezohedron. Two nitrogens occupy the apical positions, and six oxygens are coordinated to the sodium, adopting median positions. The main axis $N33-Na-N34$ is bent (angle $N-Na-N = 169.63(9)^\circ$ and the $Na-N$ bonds are significantly longer ($2.648(3)$ Å, $2.669(3)$ Å) than all $Na-O$ bonds (mean length $2.509(61)$ Å). See Supplementary Materials for all coordinates, bonds and angles as obtained by x-ray diffraction.

Figure 1. Crystal structure of **2**, the title compound.

4. Discussion

Despite a high selectivity for potassium ions as shown elsewhere, the triazacryptand is shown to chelate sodium ions with only a part of the tricyclic system resembling a typical crown ether. Crown ether complexes of alkali ions have been widely studied [19]. Sodium ions display coordination numbers of eight, e.g., to six oxygen atoms in 18-crown-6 and two solvent molecules on the exposed north and south pole of the plane. For example, in the sodium complex with 18-crown-6 and THF, the distances of sodium ion and oxygens of the crown ether are in the range of 2.73–2.79 Å, whereas the THF oxygens are significantly closer (2.33 Å). Herein, we report an improved synthesis of cryptand **1** and a crystal structure of sodium bromide chelated by this triazacryptand. As in the Crown ether complex, sodium is coordinated by eight donor atoms, six oxygen atoms and the two bridgehead nitrogen atoms of the cryptand. The distances between the oxygens in **2** and the central cation adopt intermediate values (mean length: 2.51 Å). The nitrogen in the bridge belonging to the methoxyethoxy aniline subunit and this side chain are not involved in sodium complexation. Uniquely, the sodium complex was isolated after several washing steps with distilled water and chromatography on silica. This indicates a significant binding constant. Izatt et al. reported that a complex of potassium iodide with cryptand [3.3.3] could be chromatographed on alumina, but decomplexation occurred upon treatment with silica [20]. Complexation studies of this cryptand with larger alkali ions will be performed. This unit is planned to be the electronic link between a complexed potassium ion and a fluorophore.

5. Conclusions

Cryptand **1** offers eleven coordination sites, eight of them are employed in the complexation of sodium (shown by bonds in Figure 1). The mean distances between the central ion and the oxygens is significantly shorter than in related 18-crown-6 complexes and also shorter than the sodium-nitrogen distances. In accordance with previous reports on fluorescence-labeled cryptands [5,6,11,14] and their outstanding selectivity for potassium,

we can conclude that a competitive complexation of sodium does not affect the labeled part of the molecule and, therefore, does not result in false-positive signaling of potassium.

6. Materials and Methods

NMR spectra were prepared using an Avance II 400 with a 5 mm BBFO-head with z-Gradient and ATM. TLC plates used were ALUGRAM SIL G/UV₂₅₄ from Macherey-Nagel. Solvents used were dioxane from fisher scientific, distilled over potassium hydroxide, and dichloromethane from VWR. Sodium carbonate was EMSURE iso from Merck Millipore.

Synthesis of 6-(2'-(4''-Oxabutyloxy)phenyl)-1,6,11-triaza-3,9,14,17,22,25-hexaoxa-2(1,2)(4-methylbenzena)-10(1,2)(5-methylbenzena)bicyclo(9.8.8)heptacosaphane **1** and its sodium bromide complex **2** (Figure 2).

Figure 2. Triazacryptand as free ligand with numbering according to NMR assignments.

A three necked round-bottomed flask was equipped with a mechanical stirrer, a y-piece, a coil condenser and two fine-dosage funnels, then flushed with nitrogen for 30 min. The flask was charged with sodium carbonate (911 mg, 8.6 mmol, 2.0 eq), which was then suspended in dioxane (100 mL) and the mixture was heated to reflux. Funnel A was filled with a solution of compound **3** (2.00 g, 4.3 mmol, 1.0 eq) dissolved in dioxane (100 mL) and funnel B was filled with a solution of *bis*-2-(bromoethoxy)ethane (2.37 g, 8.6 mmol, 2.0 eq) in dioxane (100 mL). Both funnels were adjusted to guarantee a static stream of about 1 drop per 10 s for funnel 1 and 1 drop per 20 s from funnel 2. After about 24 h both solutions had been completely added, after which the reaction mixture was stirred under reflux for another 10 days until no change in composition of the mixture was found by TLC-MS.

The mixture was then concentrated under reduced pressure to remove most of the dioxane, after which a mixture of two immiscible oils (colorless and brown) remained. These were dissolved in dichloromethane (100 mL) and water (100 mL), the aqueous phase extracted two times with dichloromethane. The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure to give a brownish oil. The oil was purified by two consecutive column chromatographic steps, first on flash silica (4.0 × 35 cm, 1.4 bar) with chloroform/ethanol (0–2%) as eluent, then on silica (2.8 × 20 cm) with toluene/ethanol (0–10%) as eluent. The fractions containing the desired product after the second column were combined and concentrated under reduced pressure. The residue was taken up in water and dichloromethane (50 mL each) and stirred for 3 h. The organic phase was treated like this two additional times. Drying over magnesium sulfate and concentration under reduced pressure gave a light brownish tar. The thus obtained oil was dissolved in dichloromethane, and slow evaporation of the solvent led to a few single crystals of the title compound **2** (<1%), whereas most of the product was obtained as a brown sticky tar refraining from crystallization. Upon lyophilization, 716 mg of the free

ligand **1** could be obtained as an almost colorless foam in 24% yield. For NMR assignment information see Supplementary Materials.

HR-ESIMS (ACN): 347.7067, 347.2088 $[M+2H]^{2+}$ (calcd. for $C_{39}H_{56}N_3O_8^{2+}$ 347.7045, 347.2028), 694.4095 $[M+H]^+$ (calcd. for $C_{39}H_{55}N_3O_8^+$ 694.4067), 716.3876 $[M+Na]^+$ (calcd. for $C_{39}H_{54}N_3O_8Na^+$).

IR(**1**) ν_{max}/cm^{-1} : 3030, 2923, 2871, 1747, 1607, 1591, 1508, 1456, 1413, 1346, 1254, 1180, 1126, 1035, 913, 841, 816, 743.

1H -NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, $J = 7.8, 1.4$ Hz, 1H, H4'), 6.98–6.90 (m, 3H, H3', H5', H6'), 6.88 (d, $J = 7.8$ Hz, 2H, Ha5, Ha7), 6.65 (dd, $J = 7.9, 1.0$ Hz, 2H, Ha4, Ha8), 6.57 (d, $J = 1.5$ Hz, 2H, Ha2, Ha10), 4.20 (dd, $J = 5.5, 4.1$ Hz, 2H, H2''), 4.02 (t, $J = 5.8$ Hz, 4H, H4, H8), 3.94 (t, $J = 5.8$ Hz, 4H, H5, H7), 3.80 (dd, $J = 5.5, 4.1$ Hz, 2H, H3''), 3.73 (t, $J = 6.0$ Hz, 8H, H15, H16, H23, H24), 3.71–3.59 (m, 8H, 27, 32, 44, 49), 3.50–3.26 (m, 11H, H12, H19, H20, H27, H5''), 2.23 (s, 6H, Ha12, Ha11).

^{13}C -NMR (101 MHz, $CDCl_3$) δ 153.26 (C10, C a1), 152.28 (C2'), 138.37 (C1'), 138.12 (C2, C a6), 132.61 (C a3, Ca9), 122.55 (C3'), 121.73 (C4', C5'), 121.45 (C a5, C a7), 120.87 (C a4, C a8), 114.30 (C6'), 113.93 (C a2, C a10), 71.24 (C3''), 71.19 (C13, C18, C21, C26), 70.05 (C15, C16, C23, C24), 67.89 (C2''), 67.19 (C4, C8), 59.10 (C5''), 53.93 (C12, C19, C20, C27), 53.05 (C5, C7), 21.07 (C a11, C a12).

Supplementary Materials: The following supporting information can be downloaded at online, containing Synthetic details, crystallographic information, and NMR spectra of **1**. Reference [21] is cited in the supplementary materials.

Author Contributions: Conceptualization, M.J. and H.D.; methodology, M.J.; X-ray analysis D.S.; resources, H.D.; writing—original draft preparation, M.J. and H.D.; writing—review and editing, M.J. and H.D.; visualization, M.J.; supervision, H.D.; project administration, H.D.; funding acquisition, H.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: CCDC 2130482 (2) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif accessed on 1 January 2022.

Conflicts of Interest: The authors declare no conflict of interest.

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