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Dedicated to Professor Ion Grosu
on the occasion of his 65th anniversary

CLICK SYNTHESIS AND COMPLEXATION PROPERTIES OF A NEW UNSYMMETRICAL MACROCYCLE BEARING 1,4-DIOXABENZENE AND TRIAZOLE UNITS**

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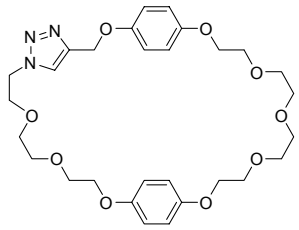
We report herein synthesis of a new triazole-based unsymmetrical macrocycle through Copper(I) catalyzed Alkyne - Azide Cycloadditon (CuAAC), using a copper(I)-*N*-heterocyclic carbene complex as catalyst. The obtained macrocycle was characterized by NMR spectroscopy and High Resolution Mass Spectrometry (HRMS). The complexation ability of the macrocycle towards various cations as well as its selectivity for a particular metal-ion was investigated by HRMS experiments.



INTRODUCTION

Macrocycles and their host-guest complexes hold a central place in supramolecular chemistry.[1] To date, there are several well established procedures that enable efficient preparation of macrocyclic compounds such as high dilution technique, use of ions or small molecules as templates and dynamic combinatorial chemistry as well as combination of these techniques.[1,2] One of the key requirements for the preparation of this type of compounds is use of a highly efficient reaction in the macrocyclization step.[3]

Copper(I) catalyzed alkyne - azide cycloadditon (CuAAC) is one of the most widely used *click* reaction that found applications in many fields ranging from supramolecular chemistry[4] to material sciences[5] and medicinal chemistry.[6] One of the most preeminent applications in supramolecular chemistry is the synthesis of mechanically interlocked structures such us rotaxanes[7] and catenanes[8] mainly due to the orthogonality of the reactive groups, mild reaction conditions (compatible with the noncovalent interactions required for building up these molecules) and its high yields.

This reaction has also been applied for synthesis of macrocycles with ion recognition properties.[9] Relevant examples include macrocyclic peptides,[10] sugar-containing macrocycles,[11] crown ether[12] and cyclophanes.[13] Despite the numerous macrocyclic structures obtained by

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CuAAC, its use in this field is somehow limited by the high dilution conditions imposed to favor macrocyclization over the oligomerization products which results in degradation of the catalyst before the reaction completion.[14] Thus, to circumvent these issues, several catalytic systems were reported over the years displaying a moderate efficiency such as the use of copper tube flow reactors,[15] immobilization of the catalyst on a solid support[16] or use of a variety of copper sources in presence of various heteroaryl ligands.[14]

In this context, we set to study the use of the copper(I)-*N*-heterocyclic carbene complex **I**[17] (Figure 1) as single catalyst for the efficient synthesis of an unsymmetrical macrocycle through CuAAC click reaction without addition of any supplementary co-ligand.

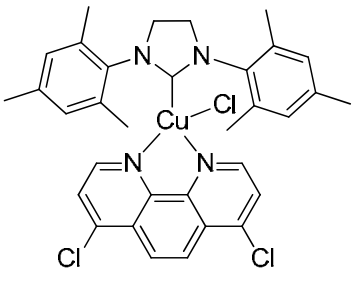

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Fig. 1 – Structure of the copper(I)–*N*-heterocyclic carbene complex **I** used as catalyst in CuAAC reaction.

RESULTS AND DISCUSSION

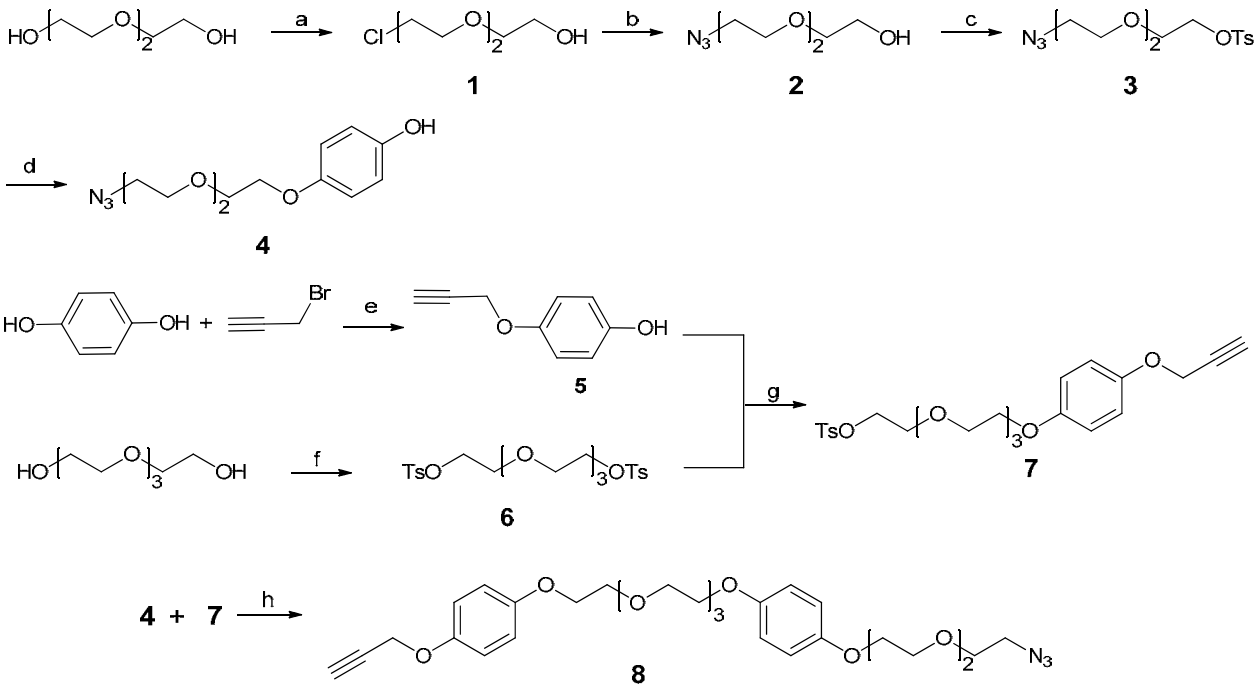
Synthesis of the macrocycle precursor

The macrocycle presented in this work was designed to be obtained by intramolecular CuAAC reaction. Therefore we needed to prepare first a precursor that contained azide and ethynyl reactive groups in the same molecule. To do so, we synthesized two key intermediates: compound **4** containing the azide reactive group and compound **7** bearing the ethynyl functionality (Scheme 1).

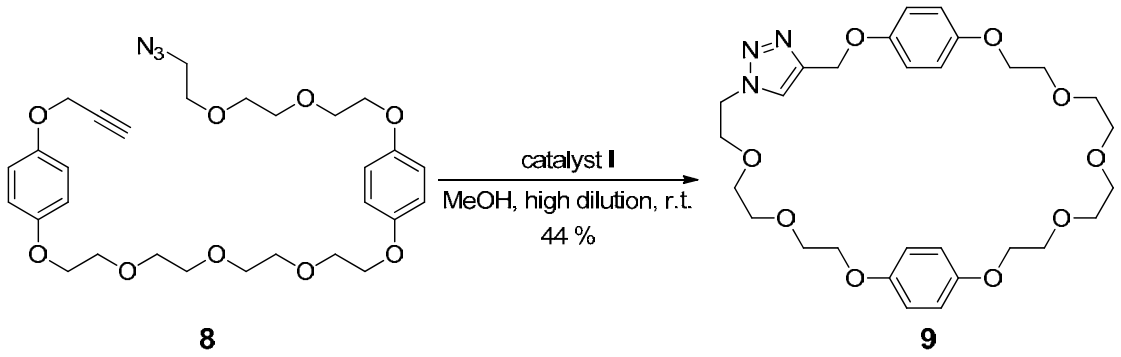
Compound **4** was obtained in four steps: first the triethylene glycol was unsymmetrically chlorinated and the chlorine atom in **1** was further substituted with azide group.[18] Activation of the hydroxyl group for the nucleophilic substitution by tosylation yielded compound **3** that was subsequently reacted with excess of hydroquinone to afford the target azido-decorated intermediate **4**.

In order to synthesize the ethynyl functionalized derivative **7**, the tetraethylene glycol was first ditosylated[19] and then reacted with a substoichiometric amount of monopropargyl hydroquinone **5** that was obtained by treatment of propargyl bromide with hydroquinone in large excess.

Next, the reaction between compounds **4** and **7** in presence of potassium carbonate yielded podand **8** in good yield (72%).



Scheme 1 – Synthesis of the macrocycle precursor 8. Reagents and conditions: (a) $SOCl_2$, Py, $CHCl_3$, reflux, 15%; (b) NaN_3, NH_4Cl, water, reflux, 92%, (c) tosyl chloride, KOH, DCM, 0°C, 85%; (d) hydroquinone, K_2CO_3, acetonitrile, 15%; (e) K_2CO_3, acetonitrile, reflux, 78%; (f) tosyl chloride, KOH, DCM, 0°C, 88%; (g) K_2CO_3, acetone, reflux, 52%; (h) K_2CO_3, acetonitrile, reflux, 72%.



Scheme 2 – High-dilution, CuAAC synthesis of macrocycle 9 using copper(I)-*N*-heterocyclic carbene complex I as catalyst.

Synthesis of the macrocycle 9

With the precursor **8** in our hands we moved to the macrocyclization reaction by CuAAC (Scheme 2). Use of copper(I)-*N*-heterocyclic carbene complex **I** as catalyst allowed the macrocyclization reaction to conveniently occur. Thus, the catalyst was dissolved in methanol and the high dilution required to favour the formation of the macrocycle over the oligomerization products was ensured by slow addition (8 hours) of the solution of **8** in DCM/ methanol (1/3 v/v). In addition, the catalyst was air-stable.[17] Macrocycle **9** was obtained in 44 % yield after purification by column chromatography.

Formation of macrocycle **9** was confirmed by NMR and HRMS spectra (see Supporting Information).

Complexation studies

The complexation ability of the macrocycle **9** towards alkali metal-ions was further investigated. Compound **9** was able to form complexes with all tested metal-ions as inferred from ESI(+)-HRMS experiments. The ESI(+)-HRMS spectra of the complexes obtained by treatment of macrocycle **9** 1.5 x 10^{-3} M in acetonitrile as solvent with 3 equivalents of $LiBF_4$, $NaBF_4$, KBF_4, $RbBF_4$ or CsF showed peaks corresponding to **9•M**$^+$ adducts at *m/z* =580.2886 [M+Li^+], 596.2623 [M+Na^+], 612.2365 [M+K^+], 658.1851, [M+Rb^+] and 706.1785 [M+Cs^+] respectively, as base peaks in all cases (see Supporting Informations Figure S18 to S22). Macrocycle **9** showed low affinity for ammonium ions. The ESI(+)-HRMS of the solution obtained by treatment of macrocycle **9** 1.5 x 10^{-3} M in acetonitrile with 3 equivalents of NH_4BF_4 displayed the protonated molecular ion of **9** at *m/z*= 574.2805 as base peak and the peak corresponding to **9•NH$_4^+$** adduct at *m/z*= 591.3066 [M+NH_4^+] in about 4 % intensity (see Supporting Information, Figure S23).

In order to investigate the selectivity of compound **9** for a particular metal-ion, competition complexation experiments were performed. Thus, **9** (1 equivalent) 1.5 x 10^{-3} M in acetonitrile was treated with a mixture containing equimolar amounts of $LiBF_4$, $NaBF_4$, KBF_4, $RbBF_4$ and CsF (1 equivalent each salt). The relative intensity of the peaks corresponding to [**9**·Li^+], [**9**·Na^+], [**9**·K^+], [**9**·Rb^+] and [**9**·Cs^+] adducts, determined from ESI(+)-HRMS spectrum (Figure 2) were 0%, 100%, 92%, 73% and 95% respectively. The results were in agreement with a non-selective recognition behaviour toward the complexation of alkaline metal ions.

EXPERIMENTAL

General experimental data. All commercially available reagents were used without further purification. Thin layer chromatography (TLC) was performed on silica gel 60 coated aluminium F_{254} plates and visualised by UV irradiation at 254 nm or by staining with potassium permanganate solution. Preparative column chromatography was carried out using silica gel 60 (0.040-0.063 mm) from Merck. The NMR spectra were recorded on a Bruker Avance 400 MHz or Bruker Avance 600 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) using residual solvent peak as internal reference. High resolution mass spectra were recorded on a Thermo Scientific (LTQ XL, Orbitrap) spectrometer, in positive ion mode, using Electrospray or APCI techniques.

***2-(2-(2-Chloroethoxy)ethoxy)ethanol* (1)**

To a solution of triethylene glycol (33.5 mL, 37.5g, 250 mmol, 1 eq.) in chloroform (50 mL), pyridine (20.2 mL, 19.75g, 250 mmol, 1 eq.) and $SOCl_2$ (18.2 mL, 29.75g, 250 mmol, 1 eq.) were added and the reaction mixture was stirred under reflux for 24h. After cooling at room temperature DCM (50 mL) was added and the reaction mixture was washed with water (40 mL). Next, the aqueous phase was extracted with DCM (2x25 mL). The combined organic phases were dried

over anhydrous $MgSO_4$ and the solvent was evaporated under *vacuum*. The crude of reaction contained compound **1** in a mixture with unreacted triethyleneglycol and the corresponding dichloro- derivative. Vacuum distillation (0.16-0.20 mbar) yielded three fractions, first fraction collected between 92–94˚C, the second fraction 99–106˚C and a third fraction at over 109˚C. Third fraction contained the highest amount of **1**. Further purification by column chromatography on silica gel, using a gradient of ethyl acetate : petroleum spirit, 40–60 °C 1:2 to 1:0 v/v (R_f: 0.34) as eluent resulted in pure 5.96 g of **1** (15 % yield) as colourless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H (ppm): 3.60–3.66 (overlapped peaks, 4H, CH_2), 3.69 (s, 4H, CH_2), 3.72–3.78 (overlapped peaks, 4H, CH_2). **^{13}C APT NMR** (100 MHz, $CDCl_3$), δ_C (ppm): 42.8, 61.9, 70.5, 70.8, 71.5, 72.6.

***2-(2-(2-Azidoethoxy)ethoxy)ethanol* (2)**

To a solution of **1** (3 g, 17.8 mmol, 1 eq.) in water (30 mL), NaN_3 (11.57 g, 178 mmol, 10 eq.) and NH_4Cl (11.2 g, 213.6 mmol, 12 eq.) were added. The resulted solution was stirred at 90 ˚C for 24 h. After cooling at room temperature and filtration of the precipitated inorganic salts, the aqueous phase was extracted with ethyl acetate (7x40mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. We obtained 2.86 g (92 % yield) as a yellow liquid that was used in the next step without further purification. TLC (silica gel, ethyl acetate/ petroleum spirit, 40–60 °C, 2:3 v/v, R_f=0.34). **^{1}H NMR** (600 MHz, $CDCl_3$), δ_H (ppm): 3.40 (t, ^3J = 5.0 Hz, 2H, CH_2), 3.62 (t, ^3J = 4.4 Hz, 2H, CH_2), 3.66–3.71 (overlapped peaks, 6H, CH_2), 3.75 (t, ^3J = 4.4 Hz, 2H, CH_2). **^{13}C APT NMR** (150 MHz, $CDCl_3$), δ_C (ppm): 50.8, 61.9, 70.2, 70.6, 70.8, 72.6.

***2-(2-(2-Azidoethoxy)ethoxy)ethyl 4-methylbenzenesulfonate* (3)**

Compound **2** (2.62 g, 14.95 mmol, 1 eq.) and tosyl chloride (2.85 g, 14.95 mmol, 1 eq.) were dissolved in DCM (20 mL). The solution was cooled on an ice bath and KOH (3.35 g, 59.8 mmol, 4 eq.) was added in small portions. The reaction mixture was stirred for 90 min at 0 ˚C and at room temperature for additional 20 h. Next, water (50 mL) and DCM (20 mL) were added and the organic and aqueous phases were separated. The aqueous phase was extracted with DCM (4x20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent 4.17 g compound **3** (yellow liquid, 85 % yield) were obtained. TLC ((silica gel, ethyl acetate : petroleum spirit, 40–60 °C, 1:1,v/v, R_f= 0.54). **^{1}H NMR** (600 MHz, $CDCl_3$), δ_H (ppm): 2.45 (s, 3H, CH_3), 3.37 (t, ^3J = 5.0 Hz, 2H, CH_2), 3.60 (s, 4H, CH_2), 3.64 (t, ^3J = 5.0 Hz, 2H, CH_2), 3.70 (t, ^3J = 4.8 Hz, 2H, CH_2), 4.16 (t, ^3J = 4.8 Hz, 2H, CH_2), 7.34 (d, ^3J = 8.2 Hz, 2H, CH_{Ar}), 7.80 (d, ^3J = 8.2 Hz, 2H, CH_{Ar}).**^{13}C APT NMR** (150 MHz, $CDCl_3$), δ_C (ppm): 50.8, 60.5, 69.0, 69.4, 70.2, 70.8, 71.0, 128.1, 130.0, 133.2, 145.0.

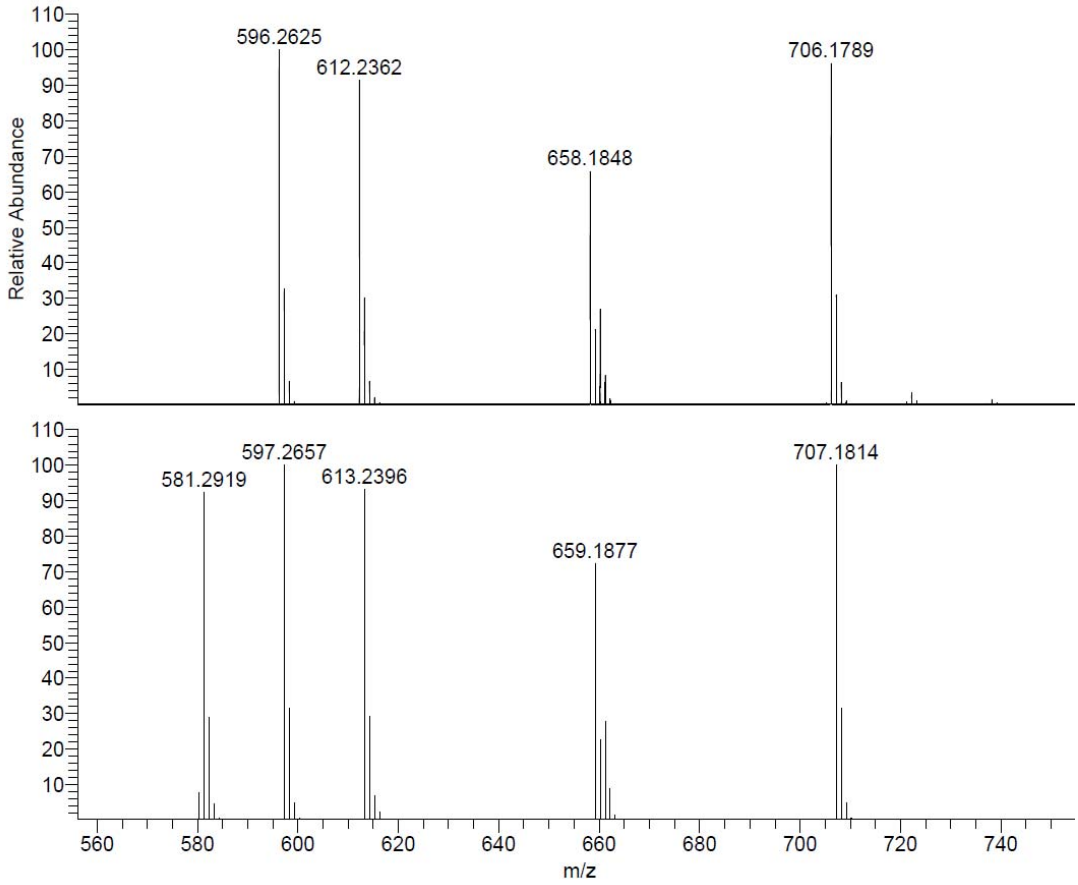


Fig. 2 – ESI(+)-HRMS spectra of **9** 1.5 mM in acetonitrile, in presence of equimolar amounts of $LiBF_4$, $NaBF_4$, KBF_4, $RbBF_4$ and CsF (top). Comparison of the experimental spectra (top) and simulated isotopic patterns of [**9**Li^+], [**9**·Na^+], [**9**·K^+], [**9**Rb^+] and [**9**·Cs^+] adducts (bottom).

***4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)phenol* (4)**

A solution of compound **3** (3.796 g, 11.54 mmol, 1 eq.) in acetonitrile (150 mL) was flushed with argon, then hydroquinone (6.347 g, 57.7 mmol, 5 eq.) and K_2CO_3 (15.92 g, 115.4 mmol) were added. The reaction mixture was stirred at reflux, under argon atmosphere, for 24 h. After evaporation of the solvent, water (150 mL) was added and the mixture was extracted with ethyl acetate (5 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous $MgSO_4$ and the solvent evaporated under vacuum. The crude of reaction was purified by column chromatography using silica gel as stationary phase and a gradient of ethyl acetate: petroleum spirit, 40–60 °C 2:3 to 1:1 v/v as eluent. Compound **4** 0.46 g (15 % yield) was obtained as a brown oil. **TLC** (silica gel, ethyl acetate : petroleum spirit, 40–60 °C 1:2, R_f=0.22).**^{1}H NMR** (600 MHz, $CDCl_3$), δ_H (ppm): 3.39 (t, ^3J = 5.0 Hz, 2H, CH_2), 3.66–3.71 (overlapped signals, 4H, CH_2), 3.72–3.75 (m, 2H, CH_2), 3.84 (t, ^3J = 4.8 Hz, 2H, CH_2), 4.07 (t, ^3J = 4.9 Hz, 2H, CH_2), 4.51 (br.s, 1H, OH), 6.75 (d, ^3J = 9.0 Hz, 2H, CH_{ar}), 6.80 (d, ^3J = 9.0 Hz, 2H, CH_{ar}.). **^{13}C APT NMR** (150 MHz, $CDCl_3$), δ_C (ppm): 50.9, 68.3, 70.1, 70.2, 70.9, 71.0, 116.0, 116.2, 149.8, 153.2. ESI(+)–HRMS (*m/z*): Calculated for $C_{12}H_{17}N_3O_4$: 290.1111, found 290.1134 [M+Na$^+$].

***4-(Prop-2-yn-1-yloxy)phenol* (5)**

In a 250 mL flask, propargyl bromide (1.75 g, 14.7 mmol 1 eq.), hydroquinone (8 g, 72.7 mmol, 5 eq.) and K_2CO_3 (40.57 g, 294 mmol, 20 eq) in acetonitrile (200 mL) were added. The reaction mixture was stirred under reflux for 24h. After completion of the reaction, the solid was removed by filtration and the solvent was evaporated in vacuum. The crude of reaction was purified by column chromatography using silica gel as stationary phase and a gradient of ethyl acetate petroleum spirit, 40–60 °C 1:4 to 1:2 as eluent. We obtained 1.69 g of **5** (78 % yield). **TLC** (silica gel, ethyl acetate : petroleum spirit, 40–60 °C 1:3, R_f=0.34). **^{1}H NMR** (600 MHz, CD_3OD), δ_H (ppm): 2.89 (t, ^4J = 2.3 Hz, 1H, CH), 4.61 (d, ^4J = 2.3 Hz, 2H, CH_2), 6.70 (d, ^3J = 8.9 Hz, 2H, CH_{Ar}), 6.82 (d, ^4J = 8.9 Hz, 2H, CH_{Ar}). **^{13}C APT NMR** (150 MHz, CD_3OD), δ_C (ppm): 56.8, 75.5, 79.0, 116.2, 116.5, 150.4, 151.9.

***((Oxy-bis(ethane-2,1-diyl))-bis(oxy))-bis(ethane-2,1-diyl)-bis(4-methylbenzenesulfonate)* (6)**

Tetraethylene glycol (29.13 g, 150 mmol, 1 eq.) in CH_2Cl_2 (150 mL) was treated with tosyl chloride (57.2 g, 300 mmol, 2 eq.). The mixture was cooled on an ice bath and KOH (67.2 g, 1.2 mol, 8 eq.) was added in small portions. The reaction mixture was stirred at 0 ˚C for 3 h and at room temperature for additional 20h. After this time, water (300 mL) and DCM (150 mL) were added and the organic phase was separated and washed with water (100 mL). The combined aqueous phases were extracted with DCM (1x150 mL and 1x100 mL). The combined organic phases were washed with water (100 mL), dried over $MgSO_4$ and the solvent was evaporated in vacuum. We obtained 66.18 g of **6** (88 % yield) as a colourless liquid. **TLC** (silica gel, ethyl acetate: petroleum spirit, 40–60 °C 1:1, R_f=0.26). **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H (ppm): 2.44 (s, 6H, CH_3), 3.53–3.59 (overlapped signals, 8H, CH_2), 3.68 (t, ^3J = 4.8 Hz, 4H, CH_2), 4.15 (t, ^3J = 4.8 Hz, 4H, CH_2), 7.34 (d, ^3J = 8.2 Hz, 4H, CH_{Ar}), 7.79 (d, ^3J = 8.2 Hz, 4H, CH_{Ar}). **^{13}C APT NMR** (150 MHz, $CDCl_3$), δ_C (ppm): 21.8, 68.8, 69.4, 70.7, 70.9, 128.1, 130.0, 133.2, 145.0.

***2-(2-(2-(2-(4-(Prop-2-yn-1-yloxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate* (7)** Compound **5** (0.8 g, 5.4 mmol, 1 eq.), compound **6** (10.84 g, 21.6 mmol, 4 eq.) and K_2CO_3 (7.45 g, 54 mmol, 10 eq.) were dissolved in acetone (125 mL). The reaction mixture was stirred under reflux for 48h. After filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel using a gradient of ethyl acetate: petroleum spirit, 40–60 °C 1:2 to 1:1 v/v) to give 1.35 mg compound **7** (52 % yield) as a colourless oil. **TLC** (silica gel, ethyl acetate : petroleum spirit, 40–60 °C 2:1, R_f=0.46). **^{1}H NMR** (600 MHz, $CDCl_3$), δ_H (ppm): 2.44 (s, 3H, CH_3), 2.50 (t, ^4J = 2.4 Hz, 1H, CH), 3.56–3.61 (overlapped signals, 4H, CH_2), 3.63–3.65 (m, 2H, CH_2), 3.67–3.73 (overlapped signals, 4H, CH_2), 3.81–3.84 (m, 2H, CH_2), 4.06–4.09 (m, 2H, CH_2), 4.13–4.16 (m, 2H, CH_2), 4.64 (d, ^4J = 2.3 Hz, 2H, CH_2), 6.85 (d, ^3J = 9.1 Hz, 2H, CH_{Ar}), 6.90 (d, ^3J = 9.1 Hz, 2H, CH_{Ar}), 7.33 (d, ^3J = 8.1 Hz, 2H, CH_{Ar}), 7.79 (d, ^3J = 8.3 Hz, 2H, CH_{Ar}). **^{13}C APT NMR** (150 MHz, $CDCl_3$), δ_C (ppm): 21.7, 56.6, 68.1, 68.7, 69.3, 69.9, 70.6, 70.7, 70.8 (2C), 75.4, 79.0, 115.6, 116.2, 128.0, 129.9, 133.1, 144.9, 151.9, 153.7. ESI(+)–HRMS (*m/z*): Calculated for $C_{24}H_{30}O_8S$: 501.1554, found 501.1590 [M+Na$^+$].

***1-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4-(2-(2-(2-(2-(4-(prop-2-yn-1-yloxy)phenoxy) ethoxy)ethoxy) ethoxy)ethoxy) benzene* (8)**

Compound **4** (151 mg, 0.565 mmol, 1.1 eq.) and compound **7** (247 mg, 0.514 mmol, 1 eq.) were dissolved in acetonitrile (15 mL) and Cs_2CO_3 (838 mg, 2.57 mmol, 5 eq.) was added. The mixture was flashed with argon and stirred for 24 h under reflux. After evaporation of the solvent, an aqueous solution of NaOH 10 % (20 mL) was added and the mixture was extracted with ethyl acetate (2x50 mL and 4 x 25 mL). The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the crude of reaction was purified by column chromatography on silica gel using a mixture of ethyl acetate: petroleum spirit, v/v 40–60 °C 2:1 v/v as eluent (R_f=0.55). We obtained 0.232 g of **8** (72 % yield) as a yellowish oil. **^{1}H NMR** (600 MHz, $CDCl_3$), δ_H (ppm): 2.50 (t, ^4J = 2.3 Hz, 1H, CH), 3.39 (t, ^3J = 5.0 Hz, 2H, CH_2), 3.66-3.70 (overlapped signals, 8H, CH_2), 3.70–3.75 (overlapped signals, 6H, CH_2), 3.81–3.85 (overlapped signals, 6H, CH_2), 4.04–4.09 (overlapped signals, 6H, CH_2), 4.63 (d, ^4J = 2.3 Hz, 2H, CH_2), 6.83 (s, 4H, CH_{ar}), 6.85 (d, ^3J = 9.1 Hz, 2H, CH_{Ar}), 6.90 (d, ^3J = 9.1 Hz ,2H, CH_{Ar}). **^{13}C APT NMR** (150 MHz, $CDCl_3$), δ_C (ppm): 50.9, 56.7, 68.2 (2C), 70.0 (2C), 70.1, 70.2, 70.8 (2C), 70.9, 71.0 (3C), 71.0, 75.4, 79.0, 115.7 (3C), 116.2, 152.0, 153.3 (2C), 153.9. ESI(+)–HRMS (*m/z*): Calculated for $C_{29}H_{39}N_3O_9$: 596.2579, found 596.2621 [M+Na$^+$].

***2,10,13,16,21,24,27,30,33-nonaoxa-5,6,7-triazatetracyclo [32.2.2.2^{17,20}.1^{4,7}]hentetraconta-1(36),4(41),5, 17,19,34,37,39-octaene* (9)**

In a two-neck flask, methanol (100 mL) was added and flushed with argon for 10 min. Then, copper(I)–*N*-heterocyclic carbene complex **I** (12 mg, 0.0183 mol, 7 mol %.) was added. A solution of **8** (152 mg, 0.265 mmol) dissolved in methanol/DCM (4 mL, 3/1 v/v) was added over 8 hours using a push-syringe and the reaction mixture was stirred at room temperature, under argon, for 3 days. After evaporation of the solvent, water (10 mL) was added and the mixture was extracted with ethyl acetate (1x20 mL and 3 x 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$

and evaporated. After purification by column chromatography on silica gel using a mixture of ethyl acetate and methanol 9:1 v/v as elution system (R_f=0.49) 67 mg of macrocycle **9** (44 % yield) were obtained as colourless oil . **^{1}H NMR** (600 MHz, $CDCl_3$), δ_H (ppm): 3.63–3.66 (m, 2H, CH_2), 3.66–3.77 (overlapped peaks, 12H, CH_2), 3.86 (overlapped peaks, 6H, CH_2), 3.93–3.99 (overlapped peaks, 4H, CH_2), 4.03 (*t*, ^3J=4.8 Hz, 2H, CH_2), 4.47 (t, ^3J=4.8 Hz, 2H, CH_2), 4.99 (s, 2H, CH_2), 6.67 (s, 4H, CH_{Ar}), 6.76 (d, ^3J = 9.3 Hz, 2H, CH_{Ar}), 6.78 (d, ^3J = 9.3 Hz, 2H, CH_{Ar}), δ 7.97 (s, 1H, $CH_{triazole}$). **^{13}C APT NMR** (150 MHz, $CDCl_3$), δ_C (ppm): 50.7, 62.4, 68.1, 68.3, 68.4, 69.3, 69.9, 70.0 (2C), 70.5, 70.7, 70.8, 70.9 (2C), 71.2, 115.5, 115.7, 115.8 (2C), 124.7, 143.9, 152.7, 153.0, 153.4, 153.6. **ESI(+)-HRMS (*m/z*)**: Calculated for $C_{29}H_{39}N_3O_9$: 574.2759, found 574.2789 [$M+H^+$].

CONCLUSIONS

In summary, we described synthesis and characterization of a new triazole-based unsymmetrical macrocycle, using a precusrsor that contained in the same molecule two reactive functional groups. The triazole ring was efficienly formed in the macrocyclization step by CuAAC reaction in presence of a copper(I)-*N*-heterocyclic carbene complex as catalyst. Complexation experiments showed that the synthesized macrocycle was able to recognize all the investigated alkali metal-ions, namely Li^+, Na^+, K^+, Rb^+ and Cs^+. However, the competition experiments were in agreement with a non-selective complexation behaviour. The high macrocyclisation yield and the ease of the procedure promts toward future design and synthesis of more selective and specific triazole-based macroxyclic receptors for metal ions.

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Supporting Information Available. Full spectroscopic data for all new compounds. HR-MS spectra of the alkali-metal ions complexes.

REFERENCES

1. (a) E. Weber, F. Vögtle and A. K. Burrell, "Macrocycles", Springer-Verlag, 1992; (b) J.-M. Lehn, "Supramolecular Chemistry. Concepts and Perspectives," Wiley-VCH Verlag GmbH, 1995.
2. M. Matache, E. Bogdan and N. D. Hădade, *Chem. Eur. J.,* **2014**, *20,* 2106–2131.
3. D. Pasini, "Synthesis of Macrocycles and Click Chemistry" in "Click Reactions in Organic Synthesis" Wiley VCH Verlag GmbH, 2016, p. 287–307.
4. L. Xu, Y. Li and Y. Li, *Asian J. Org. Chem*., **2014**, *3*, 582–602.
5. (a) P. L. Golas and K. Matyjaszewski, *Chem. Soc. Rev*., **2010**, *39*, 1338–1354; (b) K. Kacprzak, I. Skiera, M. Piasecka and Z. Paryzek, *Chem. Rev*., **2016**, *116*, 5689–5743; (c) L. Liang and D. Astruc, *Coord. Chem. Rev.,* **2011**, *255*, 2933–2945.
6. J. Hou, X. Liu, J. Shen, G. Zhao and P. G. Wang, *Expert Opin. Drug Discov.,* **2012**, *7*, 489–501.
7. B. E. Fletcher, M. J. G. Peach and N. H. Evans, *Org. Biomol. Chem.,* **2017**, *15*, 2797–2803.
8. K. D. Hänni and D. A. Leigh, *Chem. Soc. Rev.,* **2010**, *39*, 1240–1251.
9. (a) R. Peng, Y. Xu and Q. Cao, *Chinese Chem. Lett.,* **2018**, *29*, 1465–1474; (b) D. Pasini, *Molecules,* **2013**, *18*, 9512–9530.
10. J. M. Holub and K. Kirshenbaum, *Chem. Soc. Rev.,* **2010**, *39*, 1325–1337.
11. (a) A. Ajay, S. Sharma, M. P. Gupt, V. Bajpai, H. B. Kumar, M. P. Kaushik, R. Konwar, R. S. Ampapathi and R. P. Tripathi, *Org. Lett.,* **2012**, *14*, 4306–4309; (b) V. L. Campo, I. M. Ivanova, I. Carvalho, C. D. Lopes, Z. A. Carneiro, G. Saalbach, S. Schenkman, J. Santana da Silva, S. A. Nepogodiev and R. A. Field, *Tetrahedron,* **2015**, *71*, 7344–7353; (c) A. A. Salman, M. Tabandeh, T. Heidelberg and R. S. D. Hussen, *Carbohyd. Res.,* **2015**, *406*, 41–45.
12. (a) Y. S. L. Choo, P. G. Waddell and A. C. Benniston, *Eur. J. Org. Chem*., **2019**, 2560–2565; (b) J. Romański and P. Jaworski, *Phosphorus, Sulfur, Silicon Relat. Elem.,* **2017**, *192*, 231–234.
13. Y. Yu, Y. Li, S Chen, T. Liu, Z. Qin, H. Liu and Y. Li, *Org. Lett.,* **2016**, *18,* 3394–3397.
14. G. Chouhan and K. James, *Org. Lett.,* **2011**, *13*, 2754–2757.
15. A. R. Bogdan and K. James, *Chem. Eur. J.,* **2010**, *16*, 14506–14512.
16. V. Haridas, K. Lal, Y. K. Sharma and S. Upreti, *Org. Lett.,* **2008,** *10*, 1645–1647.
17. P. Bruyat, A. Gautier, L. Jean and P.-Y. Renard, *J. Org. Chem.,* **2018**, *83*, 13515–13522.
18. N. D. Bogdan, M. Matache, V. M. Meier, C. Dobrotă, I. Dumitru, G. D. Roiban and D. P. Funeriu, *Chem. Eur. J.,* **2010**, *16*, 2170–2180.
19. K. M. Bonger, R. J. B. H. N. Van den Berg, L. H. Heitman, A. P. IJzerman, J. Oosterom, C. M. Timmers, H. S. Overkleeft and G. A. van der Marel, *Bioorg. Med. Chem.,* **2007**, *15*, 4841–4856.