Macrocycles

DOI: 10.1002/anie.200903156

A Modular Approach to Functionalized and Expanded Crown Ether Based Macrocycles Using Click Chemistry**

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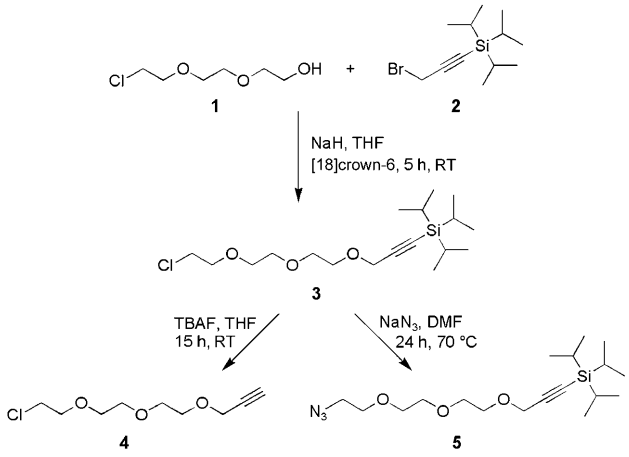
The synthesis and properties of macrocyclic structures is a topic that has stimulated the interest of chemists for many years. Indeed, macrocycles can be obtained from a variety of reactions and find applications in a wide range of fields, such as catalysis, metal extraction, and molecular recognition.[1] A continual synthetic challenge in macrocyclic chemistry is the effectiveness of the strategies employed in their preparation. Recently, the pioneering studies from Sharpless et al. and Meldal et al. on copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) have paved the way for the development of novel robust, efficient, and orthogonal synthetic approaches.[2] This reaction, often assimilated to the click chemistry philosophy, has been widely applied to the versatile and efficient synthesis or functionalization of a broad range of molecules, surfaces, and macromolecular architectures.[3]

The supported synthesis of macrocycles by CuAAC intramolecular cyclization of azide–alkyne difunctional amino acids was first reported by Meldal et al.[4] Since then, the CuAAC synthesis of macrocycles has been primarily applied to peptidic and carbohydrate structures, with monocycle yields ranging from 20 to 95% depending on the length, conformation, and sequence of the linear precursors, and on the experimental conditions.[5] High-dilution conditions (ca. 1–2 mM) are usually necessary to decrease the occurrence of step-growth polymerization in favor of the formation of macrocyclic monoadducts,[6] whilst for select systems, the formation of macrocyclic dimers by head-to-tail cyclodimerization predominates.[7] More recently, CuAAC intramolecular cyclizations have also been performed on tailor-made α-azide-ω-alkyne linear macromolecular precursors under pseudo-high-dilution conditions using a continuous addition system, leading to a range of novel macrocyclic polymers.[8]

This increased efficiency in macrocyclization afforded by CuAAC chemistry, and especially for ultralarge rings, therefore opens up significant opportunities to prepare a range of novel macrocycles based on well-studied systems, such as crown ethers. Similarly, several strategies have been used for the step-wise construction of monodisperse oligomers, dendritic macromolecules, and linear or cyclic polymer chains.[9]

Uniting these two concepts, we present herein an efficient strategy for the synthesis and characterization of a series of molecularly defined ethylene glycol based oligomers and their associated macrocycles that significantly enhances structural diversity for these materials. By combining protection–deprotection and CuAAC exponential chain-growth strategies, α-azide-ω-alkyne-functionalized oligo(ethylene glycol) derivatives were prepared (degree of polymerization $DP = 2^n$, with $n = 0$–3) and CuAAC intramolecular cyclization utilized to give a series of novel, molecularly defined macrocycles with 1–8 triazole units in the cyclic backbone.

For a successful exponential growth strategy, the selection of highly efficient coupling and protection–deprotection reactions is crucial. Accordingly, the CuAAC process is an ideal coupling reaction as it is quantitative, tolerant to a wide range of reaction conditions; the azide and alkyne groups are facile to introduce and to protect, respectively. Commercially available 2-[2-(2-chloroethoxy)ethoxy]ethanol **1** was chosen as an elementary tri(ethylene glycol) building block, as its halogen and alcohol chain ends are readily converted into the required azide and triisopropylsilyl-protected alkyne functionalities by straightforward azidation and alkylation procedures, respectively (Scheme 1). The diprotected unimer **3** was synthesized by nucleophilic substitution of triisopropylsilyl (TIPS) propargyl bromide **2** with the sodium salt of **1**.[10] Quantitative TIPS deprotection and azidation of **3** were achieved using 5 equiv of tetrabutylammonium fluoride



Scheme 1. Synthesis of α,ω-diprotected unimer **3**, monoprotected ω-alkyne unimer **4** and α-azide unimer **5**.

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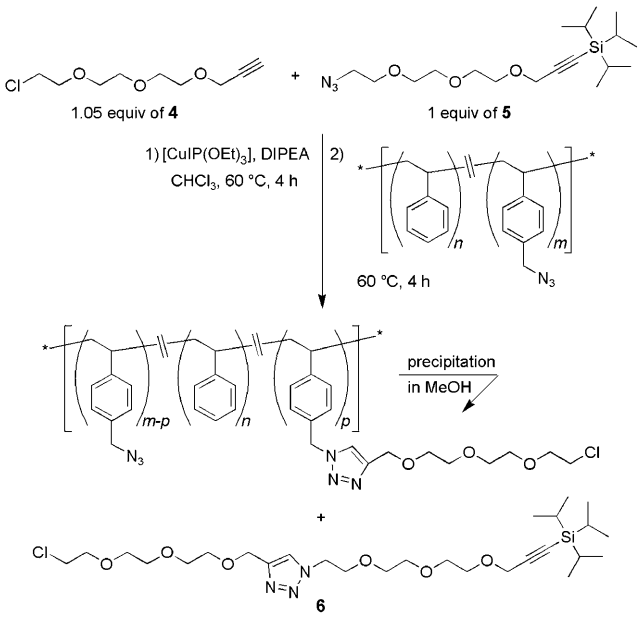
[**] The authors are grateful to Dr. E. Jeanneau from the Centre de Diffractométrie Henri Longchambon, Université Claude Bernard Lyon 1, for the single X-ray data collection, structure solutions, and refinements.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903156.

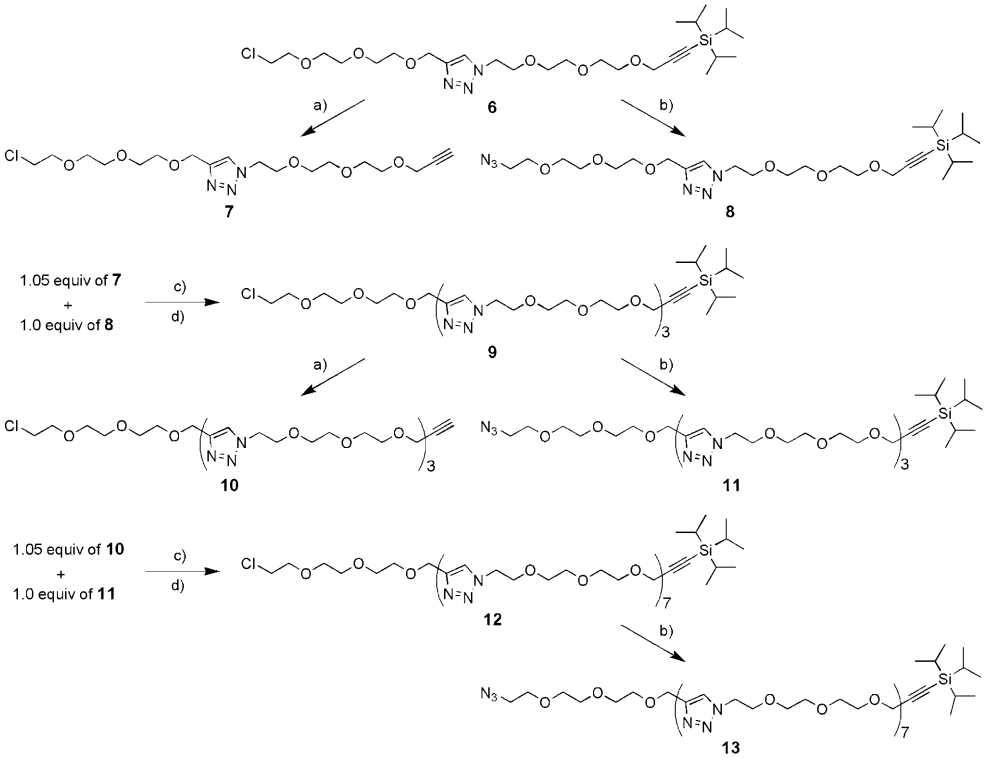
(TBAF) to give **4**, or 3 equiv of sodium azide in DMF to give **5**. As previously mentioned,[11] triisopropylsilyl (TIPS) was preferred to trimethylsilyl (TMS), as partial removal of the TMS group was observed during reaction with sodium azide.

CuAAC coupling of **4** and **5** in chloroform at 60 °C using [CuIP(OEt)$_3$] and diisopropylethylamine (DIPEA) as the catalytic system yielded the desired α-chloro-ω-TIPS-diprotected dimer **6** in almost quantitative yields (Scheme 2). To ensure the absence of contamination from lower oligomer starting materials in the final product, a slight excess (1.05 equiv) of alkyne **4** was employed in the coupling reaction, and this excess was removed using a novel polymer-based scavenging technique based on the method of Monteiro et al. for the purification of alkyne- or azide-functionalized polymers using resins bearing the corresponding azide or alkyne groups.[12] In the previous work, the separation of dendritic polymers from functionalized linear precursors of the same chemical nature requires the use of crosslinked resins. For the separation of α,ω-diprotected dimer **6** from the excess alkyne unimer **4**, a non-crosslinked polymer substrate bearing azide groups could be used, and the soluble nature of the scavenger increases the efficiency of the process. Therefore, poly(styrene-*co*-4-azidomethyl styrene) ($M_n \approx 150$ kDa, 10 mol% of azidomethyl units, 2 equiv of azides according to the excess of alkyne groups) was added to the reaction media and stirred for four additional hours to promote the CuAAC grafting of the excess of alkyne derivative **4** to the random copolymer backbone.[13] After the scavenging reaction, pure α-chloro-ω-TIPS-diprotected dimer **6** could be easily recovered by precipitation of the grafted random copolymer in methanol. The efficiency of this purification procedure was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy, high-resolution mass spectrometry (HRMS), size-exclusion chromatography (SEC), and FTIR spectroscopy, with all methods confirming the high purity of **6** and the absence of unreacted starting materials.



Scheme 2. Synthesis by CuAAC coupling of α-ω-protected dimer **6**, and purification of excess ω-alkyne unimer **4** using a poly(styrene-*co*(4-azidomethyl styrene)) soluble scavenger. DIPEA = diisopropylethylamine.

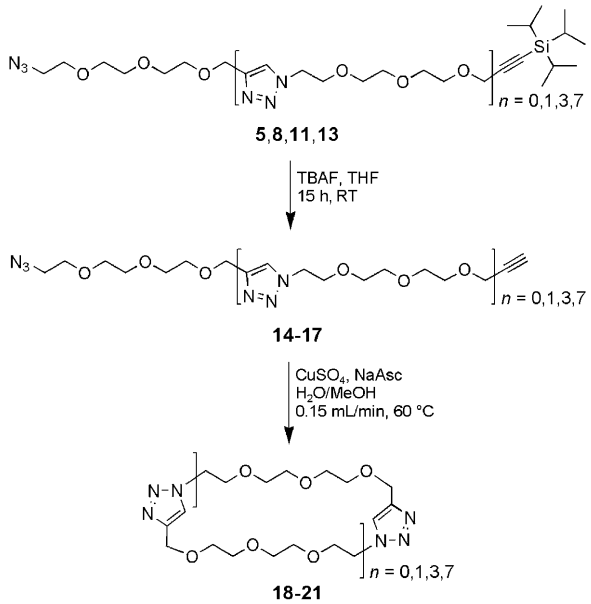
This high level of synthetic ease and efficiency allows the exponential chain-growth strategy to be a facile process yielding higher-generation functionalized oligomers up to the octamer (Scheme 3); that is, α-chloro-ω-alkyne (**7** and **10**), α-azide-ω-TIPS (**8**, **11**, and **13**), and α-chloro-ω-TIPS (**9** and **12**). Although limited in this case to tri(ethylene glycol) building blocks and a DP of 8, the power of this strategy can be appreciated by facile extension to higher-generation hetero-



Scheme 3. Iterative strategy for the synthesis of molecularly defined mono- and di-protected tri(ethylene glycol)-based oligomers ($n = 2$, 4, and 8): a) TBAF, THF, 15 h, RT; b) NaN_3, DMF, 24 h, 70 °C; c) [CuIP(OEt)$_3$], DIPEA, $CHCl_3$, 4 h, 60 °C; d) Addition of poly(styrene-*co*-(4-azidomethyl styrene)), further reaction for 4 h at 60 °C and purification by precipitation in MeOH.

functionalized oligomers eventually prepared from a wide variety of other building blocks.

The last step before cyclization was TBAF deprotection of α-azide-ω-TIPS derivatives **5**, **8**, **11**, and **13** to give α-azide-ω-alkyne reactive oligomers **14–17** with DP = 2^n and n = 0–3 (Scheme 4). This pathway was preferred to the azidation of



Scheme 4. Synthesis of molecularly defined α-azide-ω-alkyne reactive oligomers **14–17** and corresponding macrocycles **18–21**. NaAsc = sodium ascorbate.

α-chloro-ω-TIPS derivatives to avoid any thermal CuAAC step-growth polymerization prior to the cyclization step. The resulting α-azide-ω-alkyne oligomers **14–17** were stored at −20 °C, and were found to be stable for several months at this temperature. The efficiency and the orthogonal character of each step of this iterative step growth strategy was verified using ^{1}H and ^{13}C NMR spectroscopy by monitoring the chemical shifts of the groups adjacent to the chain ends and triazole groups. Furthermore, SEC and HRMS characterization of each intermediate confirmed the absence of lower and higher generation byproducts and showed single molecular ions corresponding to the desired functionalized oligomers.

The fundamental synthetic challenge, that is, the optimization of macrocyclic formation from the molecularly defined α-azide-ω-alkyne oligomers **14–17**, was then examined using a pseudo-high-dilution strategy. Previous studies regarding the effect of monomer dilution during the CuAAC step-growth polymerization of α-azide-ω-alkyne monomers have shown that yields of monocyclization as high as 60% could be attained using monomer concentrations of about 1 mM.[14] To improve the yield and efficiency of macrocycle formation, cyclization experiments were performed using a peristaltic pump for the controlled addition of monomer solutions to a solution of the catalytic system maintained at 60 °C. In this way, the reaction mixture contains a relatively dilute solution of the monomer at all times, and the monomer is exposed to a much higher concentration of catalyst to ensure a fast CuAAC intramolecular reaction.

Initially, a solution of α-azide-ω-alkyne unimer **14** in H_2O was added dropwise (0.15 mL min^{-1}) to a solution of $CuSO_4$·5 H_2O and sodium ascorbate in water maintained at 60 °C, and after complete addition macrocycle **18** was purified by recrystallisation from diethyl ether. ^{1}H and ^{13}C NMR of the resulting macrocycle revealed the appearance of a new triazole proton signal at δ = 7.98 ppm and an associated shift of the signals corresponding to the methylene groups adjacent to the triazole ring at δ = 4.69 and 4.47 ppm. The disappearance of the signals corresponding to the CH_2N_3 and $CH_2C{\equiv}CH$ chain ends further confirmed the quantitative intramolecular cyclization reaction. Furthermore, the complex splitting patterns for the resonances corresponding to the $-OCH_2CH_2O-$ moieties compared to the signals for the corresponding linear derivative was diagnostic for a more constrained, cyclic system. Finally, the lack of discernable differences between the linear and cyclic species in the HRMS spectra verifies the absence of coupled, higher-molecular-weight derivatives.

The CuAAC cyclization reaction was found to be a facile process for all α-azide-ω-alkyne oligomers **14–17** that were studied, with yields of 85–90% in each case at concentrations significantly greater than for traditional click-based approaches. SEC, HRMS, and ^{1}H and ^{13}C NMR spectroscopy confirmed the formation of the targeted macrocycles **18–21** with ring sizes ranging from 14 to 56 atoms and the number of triazole units contained within the macrocycle ranging from 1 to 8. Therefore, this strategy allows the efficient synthesis of novel crown-ether based macrocycles containing aromatic, electron-rich triazole rings that are capable of supramolecular interactions.

The efficiency of this strategy can be seen in Figure 1: the SEC traces are narrow and monomodal in all cases. Moreover, these results highlight the dramatic effect that macrocyclization has on molecular size, showing a decrease in hydrodynamic volume after cyclization that is fully consistent with the formation of cyclic species. Mass spectrometry analyses of α-azide-ω-alkyne precursors and the corresponding macrocycles matched the anticipated molecular formulas very well (Table 1). The physical properties of the macrocycles were also significantly different compared to their corresponding noncrystalline linear analogues; for example, the macrocycles **18** and **19** are highly crystalline (Table 1). Comparison of the melting temperatures obtained from DSC with those for the well-known crown ethers, such as [12]crown-4 and [18]crown-6 (T_m = 16 °C and 40 °C, respectively), also showed a significant enhancement, presumably owing to the contribution of the highly polar and hydrogen bonding triazole unit(s).

Table 1: Molar mass and thermal properties of macrocycles **18–21**.

No.	Theor. M_w (g mol^{-1})	m/z [g mol^{-1}]	T_m [°C]	ΔH_m [J g^{-1}]
18	213.2	214.0 [M+H$^+$]	90	52
19	426.5	449.2 [M+Na$^+$]	118	59
20	852.9	875.3 [M+Na$^+$]	–	–
21	1705.8	1727.4 [M+Na$^+$]	–	–

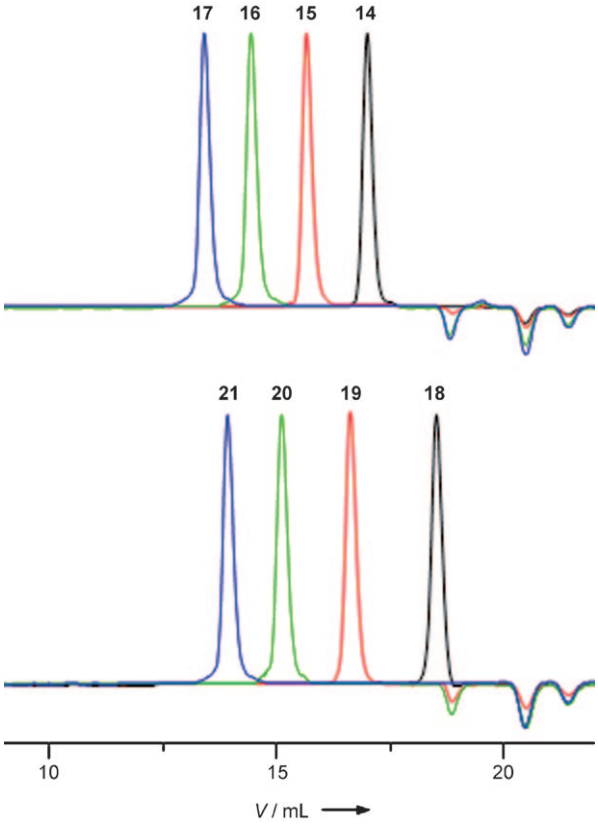


Figure 1. Size-exclusion chromatography traces of molecularly-defined α-azide-ω-alkyne oligomers **14**–**17** and corresponding macrocycles **18**–**21**.

Examination of single crystals of the macrocycles **18** and **19** by X-ray diffraction experiments (Figure 2) confirmed their rigid and strained cyclic conformation. In comparison

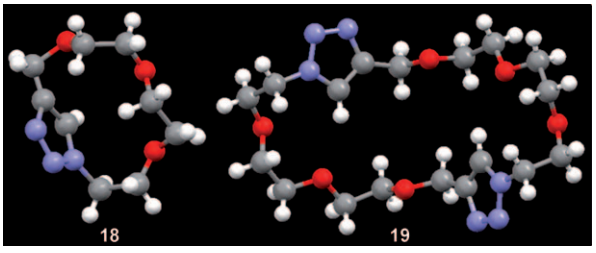


Figure 2. X-ray structures of macrocyclic unimer **18** and dimer **19**. C gray, O red, N blue, H white.

with the circular structure of well-known crown ethers, macrocycles **18** and **19** adopt an ellipsoidal conformation resulting from the rigid and planar triazole linkage(s). Significantly, this shape distortion may allow tuning of the cavity size and the number of triazole units can also be varied to provide further control over binding properties.

In conclusion, the construction of molecularly defined α-azide-ω-alkyne oligomers, from the unimer to the octamer, was performed using an iterative synthetic method based on CuAAC couplings, azidation, and TIPS-deprotection modification of the chain ends. Subsequent CuAAC intramolecular cyclization, performed under pseudo-high-dilution conditions, was shown to be a facile, high-yielding process, giving a series of novel macrocycles in which the ring size and number of electron-rich triazole units in the macrocycle can be accurately controlled. The correlation between ring size, number of triazole units, and binding properties toward organic or metallic cations is currently under investigation.

Experimental Section

Characterization and methods for all compounds can be found in the Supporting Information. CCDC 735276 and CCDC 735277 contain 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/data_request/cif.

Single-crystal X-ray diffraction data for **18**: $C_9H_{15}N_3O_3$, $M_r = 213.24$, $0.49 \times 0.15 \times 0.1$ mm^3, monoclinic ($P2_1/c$), $a = 9.5901(7)$, $b = 13.4823(7)$, $c = 9.3915(8)$ Å, $\beta = 118.249(11)°$, $V = 1069.67(17)$ Å^3, $Z = 4$, $\mu = 0.10$ mm^{-1}, $T = 293$ K, 2665 measured reflections, 1559 independent (R(int) = 0.046), R ($F^2 > 2\sigma(F^2)$) = 0.059, $wR(F^2) = 0.052$, $\Delta\rho$ (min,max) = −0.17, 0.15 e Å^3. **19**: $C_{18}H_{30}N_6O_6$, $M_r = 426.47$, $0.12 \times 0.06 \times 0.05$ mm^3, monoclinic ($C2/c$), $a = 25.507(10)$, $b = 4.4464(11)$, $c = 18.584(4)$ Å, $\beta = 101.60(3)°$, $V = 2064.6(10)$ Å^3, $Z = 4$, $\mu = 0.87$ mm^{-1}, $T = 150$ K, 8821 measured reflections, 2588 independent (R(int) = 0.046), R ($F^2 > 2\sigma(F^2)$) = 0.091, $wR(F^2) = 0.250$, $\Delta\rho$ (min,max) = −0.65, 0.57 e Å^3.

Received: June 11, 2009
Published online: August 4, 2009

Keywords: click chemistry · copper · cyclization · iterative strategies · macrocycles

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