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Review

Recent advances in click-derived macrocycles for ions recognition

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ABSTRACT

The Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) reaction, popularly known as the "click reaction", have been widely used in chemosensor field. This reaction gives a mild and efficient coupling reaction between the binding site and the reporter. In addition, the formation 1,4-disubstituted 1,2,3-triazole linker shows a high binding affinity toward both anions and metal ions. Recently researches revealed this reaction is also an efficient tool to form rigid or shape-persistent, preorganized macrocyclic species. This review summarized the recent advances in click derived macrocyclic receptors for recognition of anion, metal ion and ions pair.

1. Introduction

Macrocyclic receptors bearing preorganized cavities and multivalent binding sites are the major hot topic in supramolecular chemistry [1–6]. Functionalized macrocycles are not only used in molecular recognition and sensing, but also found applications in molecular machines and devices, supramolecular polymers, stimuli-responsive materials and drug-delivery systems. However, the design and synthesis of novel macrocyclic hosts with good host-guest properties still remains a challenge.

The Cu(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction, also known as "click reaction", has had an enormous impact on the field of organic chemistry due to its high efficiency, mild reaction conditions, and technical simplicity [7–10]. Recently, this reaction has also been widely used in chemosensor filed for it's effectively coupling method, and can be acted as a linker between the binding site and the reporter [11–13]. Importantly, the formation 1,4-disubstituted 1,2,3-triazole is a good donor for both anion and canion *via* different binding mechanisms (Fig. 1). The heterocycle ring can coordinate with cation *via* the N2 or N3 atom of the triazole, while the acidic C5-H proton can bind with anion *via* the C5-H . . . anions hydrogen bonding interaction, which can be further enhanced by converting the 1,2,3-triazole unit into a 1,2,3-triazolium cation. The latter is expected to be an even-more-efficient anion captor using anion-π interaction as an alternative binding mechanism. In addition, when the C5-H proton of triazole/triazolium was displaced by a halogen atom like iodine or bromine, a halogen bond interaction mechanism will be applied in selective anion detection.

Due to its mild reaction conditions and technical simplicity, click reaction is viewed as an efficient and flexible strategy for preparing macrocycles with different purposes. There are two main strategies for the synthesis of cyclic triazole receptors (Fig. 2). The first involves the macrocyclization of a bifunctional acyclic monomer containing a free acetylene and a free azide termini (method A), while the second strategy is achieved by cyclization between a diazole and a dialkyne monomers (method B). To avoid the linear oligomers byproducts, the macrocyclization is usually conducted under high dilution conditions. The reported yield of the macrocyclization is about 40%–50%. Better product yields could be realized when the acetylene and azide groups inside the monomers are preorganized to reduce the entropy loss [14–16], or the macrocycle product shows low solubility in the reaction solution [17], which crash it out of the reaction mixture.

In this review, we would like to focus our attention on macrocyclic receptors with using the click reaction as the macrocyclization method, in which the triazole ring is used as both anion and cation binding site for ions recognition. The alkylation triazolium macrocycles also belong to this catalog. Macrocycles like cyclam, calixarenes, cyclodextrins bearing pendant triazole ligands for recognition are excluded from the present review. The review is structured in several sections according to the recognition guests (anions, metal ions and ions pair), the sensing mechanism and the structural characteristics of host.

2. Recognition of anions

Anions have a major role in industry, the environment, and biology. The research of anion recognition has attracted more and more attention over the last few decades [18–22]. Despite numerous

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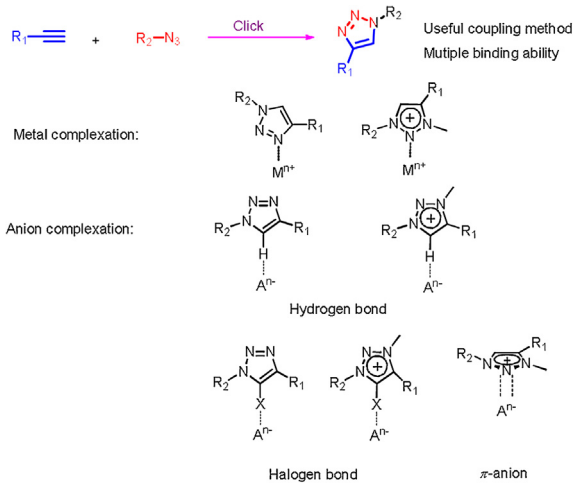

Fig. 1. The click-derived click ring as multiple binding donor for metal ions and anions.

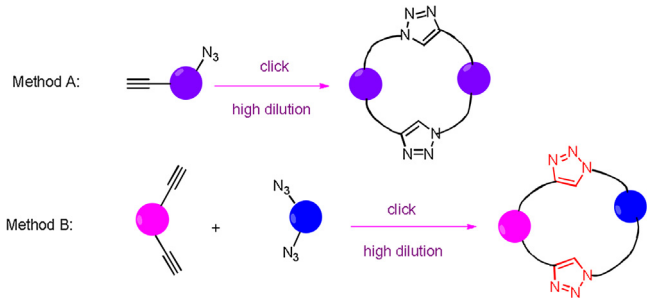

Fig. 2. Formation of cyclic triazoles higher oligomers *via* different methods.

anion receptors have been developed in this field, it continues to be a real challenge for selective anion recognition, especially in water and biological media [23,24]. To gain the desired selectivity, many research groups have developed different approaches. Effective anion receptors are often constructed from a combination of strong hydrogen-bond donors, positively charged moieties, and Lewis acid metal ions. Recently, the 1,2,3-triazole moiety has been shown to play an important role as an anion binding motif through multiple weak C—H hydrogen bonds to stabilize anions.

2.1. Recognition of halides

In 2008, the pioneering work by Flood and co-workers reported a rigid and preorganization [3_4]triazolophane **1** (Fig. 3) [25]. This macrocycle has a diameter of about 3.8 Å, and the four triazoles and four phenylene CH groups direct into the cavity. Triazolophane **1** displays a high affinity toward Cl^- *via* multiple triazole C–H···anion and phenyl C–H···anion hydrogen bonding interaction as shown in Fig. 3, followed by Br^- >> F^- >> I^-. In CH_2Cl_2 solution, the association constant of **1**-Cl^- was calculated to be K_a = (130,000 ± 30,000) L/mol; ΔG = −7.0 kcal/mol (CH_2Cl_2, 298 K), which approaches the traditional NH donors from pyrrole.

Continue this work, more [3_4]triazolophanes **(2a–c)** (Fig. 3) with different substituents on the phenylene linkers were designed and prepared [26]. The halide anions binding affinity of **2a–c** were determined by UV–vis and ^{1}H NMR titrations. All these triazolophanes show a high selectivity toward size comparable Cl^- and Br^- anions (Cl^- > Br^-), which is about 1.5 and 3 orders of magnitude larger than the smaller F^- and larger I^- anions, respectively. Compared with **1**, the anions binding affinity of **2a–c** reduced for replacing the *t*-butyl groups with strong electron donation OTg

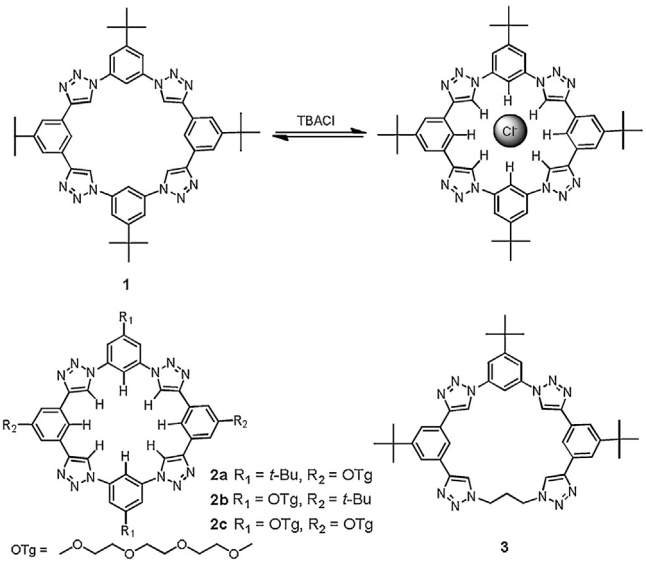

Fig. 3. Representative [3_4]triazolophanes **1**–**3** reported by Flood *et al.*

groups. It also can be envisioned that the triazolophane **3** [27], in which one phenyl linker is replaced by a methylene-based (CH_2) one, will show a weaker halide anions binding affinity for the flexible cavity and the weak CH hydrogen bond of propylene.

The triazolium cation is known to be more strong anion affinity than the neutral triazole donor. Thus, a bis-triazolium bile acid-based macrocycle **4** (Fig. 4) was designed by Pandey *et al.* using click reaction [28]. The ^{1}H NMR titration results reveal that this receptor exhibits selectivity for binding of chloride ion, followed by

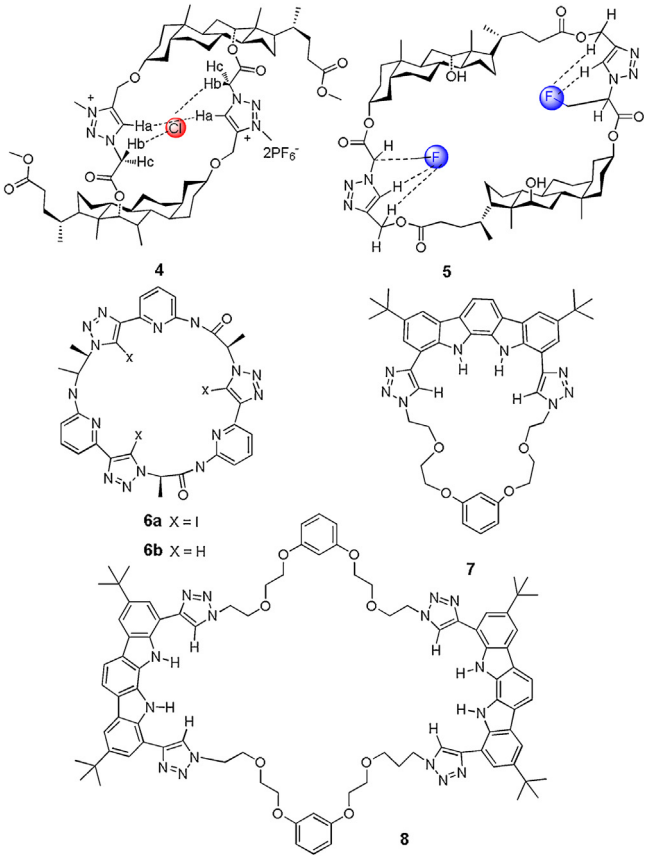

Fig. 4. Chemical structures of macrocycles **4**–**8**.

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