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Azobenzene-Based Macrocyclic Arenes: Synthesis, Crystal Structures and Light-Controlled Molecular Encapsulation and Release

Yuezhou Liu[+], Hongliang Wang[+], Peiren Liu, Huangtianzhi Zhu, Bingbing Shi,* Xin Hong* and Feihe Huang*

Abstract: Azobenzene (azo)-based macrocycles are highly fascinating in supramolecular chemistry because of their light-responsiveness. In this work, a series of azo-based macrocyclic arenes **1**, **2**, **3** and **4** distinguished by the substituted positions of azo groups are rationally designed and synthesized via a fragment cyclization method. From the crystal and computed structures of **1**, **2** and **3**, we observe that the cavity size of these azo-macrocycles decreases gradually upon *E*→*Z* photoisomerization. Moreover, light-controlled host–guest complexations between azo-macrocycle **1** and guest molecules (7,7,8,8-tetracyanoquinodimethane, terephthalonitrile) are successfully achieved. This work provides a simple and effective method to prepare azo-macrocycles, and the light-responsive molecular encapsulation systems in this work may further advance the design and applications of novel photo-responsive host–guest systems.

The arrival of any novel kind of macrocyclic hosts can significantly meet the research needs of host–guest chemistry and further enrich the field of supramolecular chemistry. During the past decades, a great deal of macrocyclic host molecules, such as crown ethers, cyclodextrins, calixarenes, cucurbiturils and pillararenes were designed and reported.[1-17] The manipulation of molecular encapsulation and release of the macrocyclic hosts by external stimuli showed excellent performance in biomedicine, catalysis, polymer materials, absorption and separation, and so on.[3-8] Among various external stimuli, light responsiveness is very fascinating due to its environmental-friendly, efficient and non-invasive characteristics.[18] Light-controlled molecular encapsulation and release were achieved in many instances.[19-23] Usually, by exploiting light-responsive guest molecules, light-controlled molecular encapsulation and release were realized. However, due to the lack of strategies in constructing photo-responsive hosts which have efficient light-controlled molecular shapes and cavity sizes and show sufficient binding affinity changes by photoisomerization, light-controlled molecular encapsulation and release systems relying on photo-responsive host molecules are still rare. Therefore, it is important to develop photo-responsive macrocycles for light-controlled molecular encapsulation and release systems. Azobenzene (Azo), owing a light-induced *E*↔*Z* isomerized feature, is an outstanding building block for light responsive structures and materials.[24-27] To date, just few examples of macrocycles containing azo units were reported.[28-31] However, these photo-responsive macrocycles usually need relatively complicated organic synthesis and purification, which greatly impeded the development of photo-responsive macrocycles. In addition, these azo-macrocycles were constructed by para-substituted azos, macrocycles fabricated by meta- and ortho-substituted azos have been rarely reported. Here, we designed and synthesized a series of photo-responsive azo-macrocycles distinguished by the substituted position of azos via a fragment cyclization method.

Our design of these azo-macrocycles **1**, **2** and **3** is shown in Scheme 1. Three fragments, **6**, **8**, and **10**, containing one azo unit and two 1,4-dimethoxybenzene units were firstly prepared. Then azo-macrocycles **1**, **2** and **3** were synthesized by a fragment cyclization method. Compounds **6** and **8** were prepared from a Friedel-Crafts alkylation reaction between bis(hydroxyethyl)-azobenzene and 1,4-dimethoxybenzene in the presence of trifluoromethanesulfonic acid as the catalyst in CH_3NO_2, and the reaction gave **6** and **8** in 45% and 17% yield, respectively. Because the structure of ortho-substituted azo **10** is more crowded than those of **6** and **8**, which hindered the reaction process, it is hard to get **10** in the same way. In order to get the fragment **10**, compound **9**, containing a nitrobenzene unit and a 1,4-dimethoxybenzene unit, was prepared. Then compound **10** was obtained by the reduction reaction of **9** (43% yield). With these three intermediates **6**, **8** and **10** in hand, three azo-macrocycles **1**, **2** and **3** were synthesized via fragment cyclization reactions by mixing the intermediate with paraformaldehyde in the presence of BF_3•(OEt_2) as the catalyst in $ClCH_2CH_2Cl$.[32] The reactions gave the targeted azo-macrocycles **1**, **2** and **3** in 62%, 54% and 26% yield, respectively. Interestingly, after the cyclization reaction of **10**, an ortho-position azo-macrocycle **4** was also obtained (7% yield). The structures of **1**, **2**, **3** and **4** were characterized by ^{1}H NMR, ^{13}C NMR, MALDI-TOF-MS and X-ray single crystal diffraction (Figure S1–S29).

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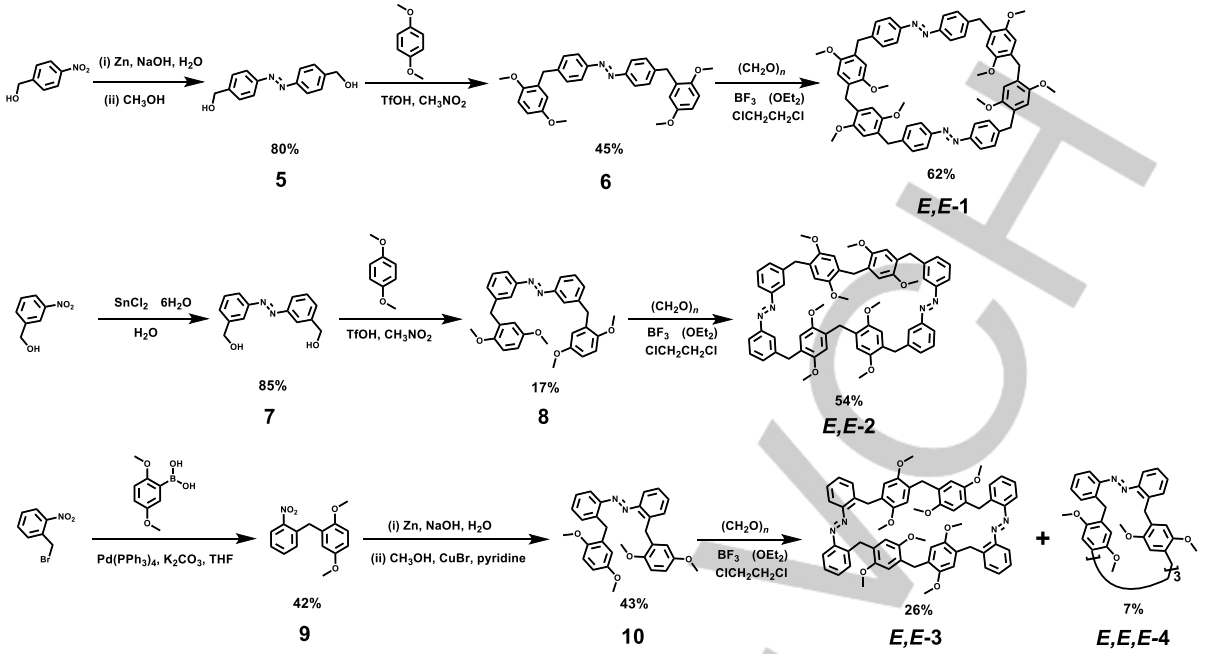

Scheme 1. Synthesis of azo-macrocycles **1**, **2**, **3** and **4**.

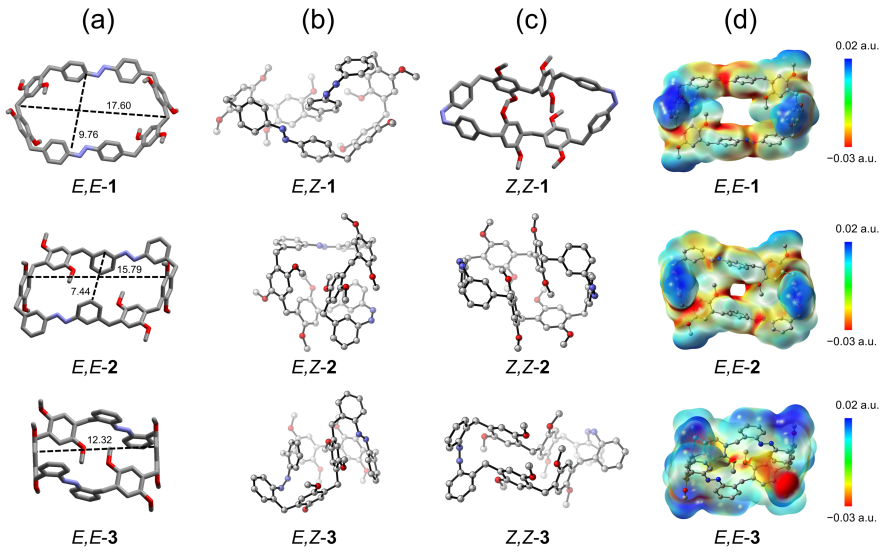

Figure 1. (a) Crystal structures of *E,E*-**1**, *E,E*-**2** and *E,E*-**3**; (b) Computed structures of *E,Z*-**1**, *E,Z*-**2** and *E,Z*-**3**; (c) Crystal structure of *Z,Z*-**1** and computed structures of *Z,Z*-**2** and *Z,Z*-**3**; (d) Electrostatic potential surfaces of *E,E*-**1**, *E,E*-**2** and *E,E*-**3**.

High-quality orange single crystals of *E,E*-**1**, *E,E*-**2** and *E,E*-**3** suitable for X-ray single crystal diffraction were obtained by slow evaporation in acetonitrile within 2 days. X-ray crystallographic analysis revealed that *E,E*-**1** is an oblate hexagonal macrocycle, and the length and width of *E,E*-**1** are 17.60 Å and 9.76 Å, respectively (Figure 1a and S20). Besides, C−H···O interactions with H···O distances of 2.68 and 2.66 Å, a C−H···N interaction with an H···N distance of 2.63 Å and a C–H···π interaction with an H···π-plane distance of 2.61 Å were observed. Moreover, a face-to-face π-stacking interaction is noticed in the crystal structure. The related centroid–centroid distance is 3.89 Å and the dihedral angle is 0.59°. We tried to grow crystals of **1** upon UV irradiation at 365 nm. Orange needle-like crystals were successfully obtained by slow evaporation of a chloroform solution of **1** within 2 days. X-ray crystallographic analysis revealed that the structure of *Z,Z*-**1** is twisted and the cavity becomes narrow compared with the cavity of *E,E*-**1** (Figure 1c and S22). Moreover, C−H···O interactions with H···O distances of 2.61 and 2.69 Å, a C−H···N interaction with an H···N distance of 2.74 Å and C–H···π interactions with H···π-plane distances of 2.32 and 2.56 Å are observed. Furthermore, single crystal structure analysis of *E,E*-**2** shows that the length and width of *E,E*-**2** are about 15.79 and 7.44 Å, respectively, and the crystal structure is stabilized by multiple C–H···π interactions with H···π-plane distances of 2.40, 2.76, 2.39, and 2.75 Å (Figure 1a and S24). X-ray crystallographic analysis reveals that the length of *E,E*-**3** is 12.32 Å, and the cavity size is much smaller than those of *E,E*-**1** and *E,E*-**2** (Figure 1a and S26). Moreover, a C−H···O interaction with an H···O distance of 2.50 Å and C–H···π interactions with H···π-plane distances of 2.71 and 2.78 Å are observed. We also got the crystals of *E,E,E*-**4** by slow evaporation in CH_2Cl_2 within 2 days. X-ray crystallographic analysis reveals that *E,E,E*-**4** has a clover-like cavity in the solid state, and the crystal structure is stabilized by a C−H···π interaction with an H···π-plane distance of 2.15 Å (Figure 2 and S28). The structures of *E,Z*-**1**, *E,Z*-**2**, *E,Z*-**3**, *Z,Z*-**2**, and *Z,Z*-**3** were optimized with density functional theory (DFT) calculations (Figure 1b and 1c). Based on these structural

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analysis, we inferred that the cavity size of these azo-macrocycles decreased gradually upon *E*⟶*Z* photoisomerization.

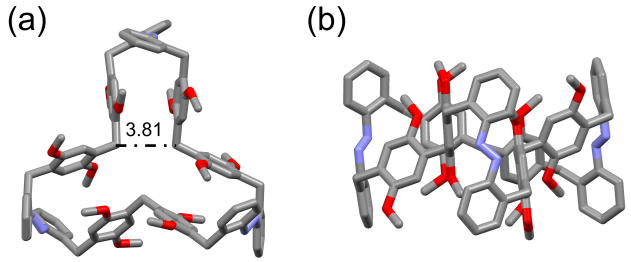

Figure 2. Crystal structure of *E,E,E*-**4**: (a) top view; (b) side view. Hydrogen atoms are omitted for clarity.

The photoisomerization behaviours of **1**, **2** and **3** were first investigated by UV-Vis spectroscopy (Figure S30). Fresh $CHCl_3$ solutions of **1**, **2** and **3** were prepared. Upon irradiation with UV light (365 nm), a decreasing peak around 334 nm corresponding to the π−π* transition and an intensive peak around 442 nm corresponding to the n−π* transition were observed, indicating the *E* → *Z* photoisomerization of these azo-macrocycles.[33,34] Moreover, reversible transformation was realized upon irradiation with visible light (420 nm). The *E*↔*Z* photoisomerization could be recycled for at least 5 times without obvious photo-fatigue. Furthermore, ^{1}H NMR experiments were carried out to study the photoisomerization behaviours of **1**, **2** and **3**. For **1**, the disappearance of the signals of protons ^{E,E}H and the generation of signals of protons ^{Z,Z}H indicated that *E,E*-**1** was almost completely converted into *Z,Z*-**1** after irradiation with UV light (365 nm) (Figure S31). Furthermore, after irradiation with visible light (420 nm), the light-induced *Z* → *E* isomerization renewedly generated 92% of *E,E*-**1**. The photoisomerization behaviours of **2** and **3** were analogous to those of **1**. Upon irradiation with UV light (365 nm), the conversion efficiencies of *E,E*-**2** and *E,E*-**3** were 70% and 56%, respectively, and the percent contents of *E,E*-**2** and *E,E*-**3** were 72% and 82%, respectively, after irradiation with visible light (420 nm) (Figure S32 and S33). These results indicated that the photoisomerization behaviour of macrocycle **1** was more reversible compared with that of macrocycle **2** or **3**.

DFT calculations were performed to study the thermodynamic stabilities of the isomers of **1**, **2** and **3**. Consistent trend of thermodynamic stabilities was identified for the azo-macrocycles **1**, **2** and **3** (Figure S52); the *E,E*-isomers are the most stable. The lowest energy conformation of *Z,Z*-**1** was 5.3 kcal/mol higher in free energy as compared to that of *E,Z*-**1**, and 17.6 kcal/mol higher in free energy than that of *E,E*-**1**. The *E,E*-**2** and *E,E*-**3** are also at least 5 kcal/mol more favorable than the corresponding *E,Z*- and *Z,Z*-isomers.

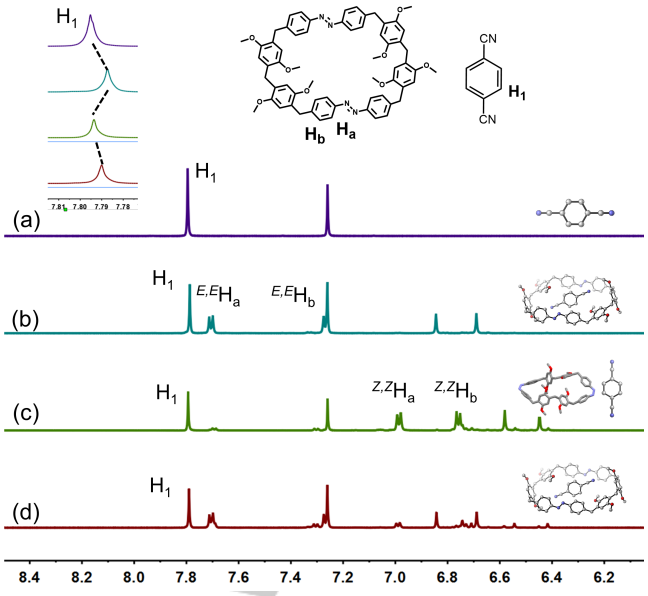

Figure 3. Partial ^{1}H NMR spectra (600 MHz, $CDCl_3$, 298 K): (a) terephthalonitrile (2.00 mM); (b) *E,E*-**1**⊃terephthalonitrile (2.00 mM); (c) after photoirradiation at 365 nm (30 minutes), (d) after further photoirradiation at 420 nm (30 minutes).

After the photo-responsiveness of **1**, **2** and **3** was demonstrated, light-controlled molecular encapsulation and release relying on **1**, **2** and **3** was investigated. Host–guest interactions are significantly influenced by the molecular electrostatic potential of host molecules.[35] Therefore, the electrostatic potential surfaces of *E,E*-**1**, *E,E*-**2** and *E,E*-**3** were computed (Figure 1d). The red region showed the area with negative charge while the blue region revealed the area with positive charge, and we could infer that these macrocycles might have host–guest interactions with electron-deficient guests. A typical electron-deficient molecule, 7,7,8,8-tetracyanoquinodimethane (TCNQ), was chosen as a model guest molecule. ^{1}H NMR experiments were carried out in $CDCl_3$ to study the host–guest complexation (Figure S34–S36). After mixing TCNQ with *E,E*-**1**, *E,E*-**2** or *E,E*-**3**, the signal of protons on TCNQ shifted upfield obviously, indicating the formation of the host–guest complex. Furthermore, ^{1}H NMR titrations were carried out to evaluate the stoichiometry and association constant K_a (Figure S44–S49). By a mole ratio plot, 1 : 1 stoichiometry was obtained for these complexations. The K_a values were estimated to be 487 ± 26 M^{-1}, 236 ± 9 M^{-1} and 46 ± 5 M^{-1} for *E,E*-**1**⊃TCNQ, *E,E*-**2**⊃TCNQ and *E,E*-**3**⊃TCNQ, respectively. The host–guest complex of *E,E*-**1**⊃TCNQ was also optimized by DFT calculations (Figure S56). Moreover, only *E,E*-**1** showed the ability to capture terephthalonitrile into the cavity. From the ^{1}H NMR results, after mixing terephthalonitrile with *E,E*-**2** or *E,E*-**3**, no obvious chemical shift change was observed (Figure S38 and S39), indicating that there was no or very weak complexation between them in $CDCl_3$. Contrastively, distinct chemical shift changes of protons on *E,E*-**1** and terephthalonitrile were observed after adding 1.00 equiv. of terephthalonitrile into a solution of *E,E*-**1** (Figure 3a, 3b and S37). The peaks related to $^{E,E}H_a$ on *E,E*-**1** and H_1 on terephthalonitrile shifted upfield. The K_a value was estimated to be 34.1 ± 4.4 M^{-1} for *E,E*-**1**⊃terephthalonitrile in a 1 : 1 complexation mode. As mentioned above, the photoisomerization behaviour of macrocycle **1** was

more reversible compared with that of macrocycle **2** or **3**. Therefore, the light-controlled encapsulation and release of guest molecules based on **1** was more effective. After photoirradiation (365 nm) of *E,E*-**1**⊃TCNQ or *E,E*-**1**⊃terephthalonitrile, a downfield chemical shift was observed for protons on guest molecules (Figure 3c, S40b, S43b), indicating the transformation of *E,E*-**1**→*Z,Z*-**1** led to the release of guest molecules from the cavity. Next, after exposing to visible light (420 nm), the peak of protons on guest molecules shifted upfield (Figure 3d, S40c, S43c), demonstrating that the guest molecules were renewedly encapsulated into the cavity of *E,E*-**1**. For *E,E*-**2**⊃TCNQ, after photoirradiation (365 nm), TCNQ was released from the cavity of macrocycle **2** (Figure S41b). However, after exposing to visible light (420 nm), TCNQ was difficult to be captured into the cavity within 30 minutes (Figure S41c). For *E,E*-**3**⊃TCNQ, the twisted structure and steric repulsion of macrocycle **3** play an important role in the light-controlled encapsulation and release of TCNQ, causing that TCNQ was difficult to be released from the cavity of macrocycle **3** after photoirradiation at 365 nm within 30 minutes (Figure S42).

In conclusion, photo-responsive azo-based macrocyclic arenes **1**, **2** and **3** distinguished by the substituted positions of azo groups were prepared via fragment cyclization reactions. Furthermore, an ortho-position azo-macrocycle **4** was also obtained. Excitingly, we not only got the crystal structures of *E,E*-**1**, *E,E*-**2**, *E,E*-**3** and *E,E,E*-**4**, but also obtained the crystal structure of *Z,Z*-**1** upon UV irradiation at 365 nm. In addition, azo-macrocycle *E,E*-**1** can form host–guest complexes with electron-deficient molecules, TCNQ and terephthalonitrile. The encapsulation and release of guest molecules can be controlled by photo irradiations. This work provided a novel, straightforward and high-efficiency approach to fabricate photo-responsive azo-macrocycles. Based on the innovative structures, host–guest complexation and light-responsiveness of these azo-macrocycles, we believe that they may be widely applied in crystal engineering, biomedicine and polymer materials and promote the development of supramolecular chemistry.

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Keywords: macrocycles • supramolecular chemistry • light-responsiveness • host–guest systems • photochemistry

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A series of azobenzene-based macrocyclic arenes **1**, **2** and **3** are synthesized, and light-controlled molecular encapsulation and release are realized based on macrocycle **1**.