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Controlling Binding Affinities for Anions by a Photoswitchable Foldamer

Ying Wang,[†,‡] Fusheng Bie,[†,‡] and Hua Jiang*[,†]

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Photochemistry, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, China, and Graduate University of Chinese Academy of Sciences, Beijing, China

hjiang@iccas.ac.cn

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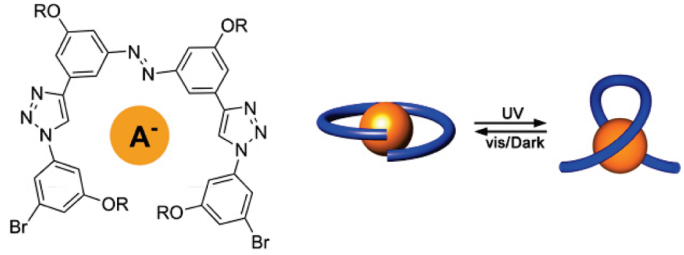
ABSTRACT



A photoswitchable foldamer containing an azobenzene and phenyl-1,2,3-triazole motif was found to show photochemical/dark isomerization in a controllable and reversible manner in both the absence and presence of anions. The transformation in conformation of the foldamer leads to changes in binding affinities for anions to a certain extent that depends on the size and the geometrical shape of the anions.

Light-controlled molecular recognition, well-known to manipulate the conformation of receptors by light to control its binding affinity for guest molecules, has found many applications in material sciences and biology.[1] In the past decades, several photoswitchable receptors such as aza-crowns[2] and aza-calixcrowns[3] were developed to binding cations in a controllable manner. Among them, light-induced changes in molecular geometry were realized through the photoswitch of azobenzenes,[4] which display an extended and planar conformation in the steady *trans* form but a compact and twisted geometry in the *cis* form during irradiation with UV light. However, to date, there are few systems that display a light-controllable binding affinity for anions.[5]

Previous studies show that the aryl-triazole group can serve as an effective hydrogen bond donor for anion binding.[6] These aryl-triazole-based receptors including macrocycles[7] and foldamers[7b,8] have been proven to have high affinity and selectiveness for anions, especially for halide ions. A recent report demonstrates that the conformational preorganization of aryl-triazole pentads was also found to have a decisive effect on the binding affinity for halide ions.[9] Taking

[†] Chinese Academy of Sciences.
[‡] Graduate University of Chinese Academy of Sciences.

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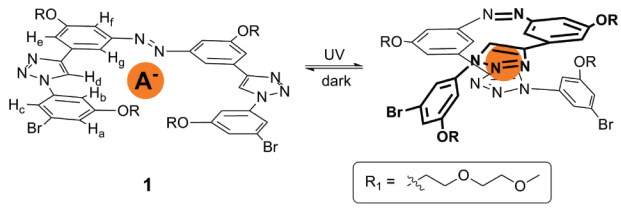
advantage of the strong C−H···anion interaction between the triazole and the anions and the photoisomerization of azobenzen, we thus envisioned that plugging the photoresponsive azobenzene into the phenyl-triazole oligomers could provide a photoswitchable foldamer with controllable changes in binding affinity for anions due to the light-controlled transition in conformation. We propose (Scheme 1) that while

Scheme 1. Photoswitch **1** Studied Herein and Proposed Different Binding Model for Its Two Photoisomers to Anions



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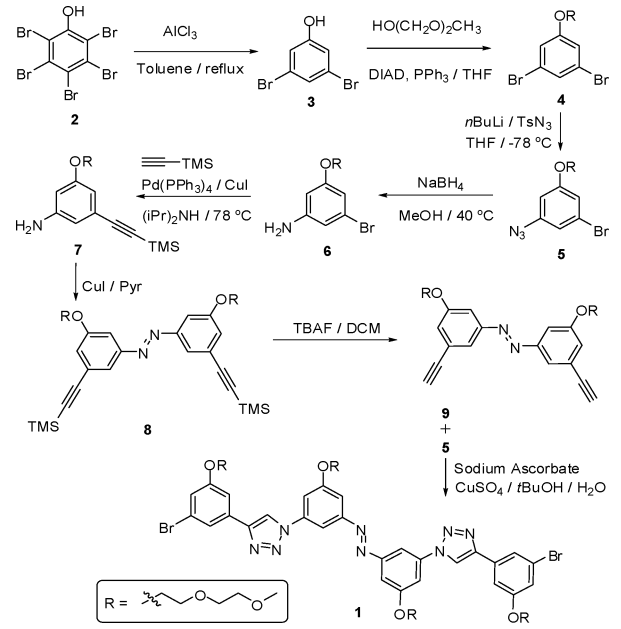
1 adopts the *trans* conformation (**1**$_{trans}$), its binding affinities for anions would be weak as a result of the extended conformation of the azobenzene core; however, while **1** adopts the *cis* form (**1**$_{cis}$) upon irradiation with UV light, its binding to the anions would be strengthened as a result of the spatial preference between the anions and the receptor. The controllable affinities for anions could thus be achieved through reversible photoisomerization.

To evaluate this hypothesis, photoswitch **1** (Scheme 1) was designed to possess two phenyl-1,2,3-triazole units with an azobenzene moiety at the core. The chain length of **1** was deliberately chosen to allow folding of the entire chain but avoid π-stacking within intramolecular strand in the *trans* form.[10] A water-soluble 2-(2-methoxyethoxy)-ethoxy side chain was introduced to each phenyl group because it was proven be conducive to the folding in polar solvents such as acetone via solvophobic interaction.[11]

The synthesis of compound **1** is outlined in Scheme 2. The starting material pentabromophenol **2** was reduced to give **3**. Via a Mitsunobu reaction,[12] a water-soluble side chain was attached to provide **4**, one bromo of which was converted to azide followed by reduction to give **6**. Compound **6** was ethynylated to generate **7** by the Sonogashira reaction with excess (trimethylsilyl)-acetylene.[13] Then, coupling **7** itself in the presence of CuI afforded azobenzene **8**, followed by removal of the TMS group under a basic conditions to yield **9**. Finally, compound **1** was obtained by coupling **8** with **5** through "click chemistry".[14]

Scheme 2. Synthesis of Photoswitch **1**



The photoresponsive properties of **1** were first investigated by UV−vis spectroscopy in acetone (Figure S1 in Supporting Information). Upon UV light irradiation, the intensity of the $\pi-\pi^*$ transition band at 339 nm shows a sharp descent by 80%, and the intensity of the n−π^* transition band at 440 nm slightly increased, indicative of the photoisomerization of **1** from the *trans* to the *cis* state.[15] After irradiation of the above solution with the visible light, 77% intensity of the absorption at 339 nm was recovered, suggesting that the *cis* reversibly switched to the *trans*. NMR measurements provided additional information about the photoisomerization of **1**. At a normal state, **1** prefers to exist in the *trans* form, and the folding of **1**$_{trans}$ was strongly suggested by the correlations (strong H_d-H_g rather than H_d-H_e) in 2D NOESY spectrum (Figure S2 in Supporting Information), in which the signals were assigned on the basis of 2D NMR experiments (Figures S3−S6 in Supporting Information). **1**$_{trans}$ photoisomerized to **1**$_{cis}$ rapidly upon irradiation at 365 nm light, and the ratio of **1**$_{trans}$/**1**$_{cis}$ was determined to be 18:82 while a photostationary state was achieved. Isomerization caused a typical change in the ^{1}H NMR spectra of **1** (Figure 1):[16] the protons H_e, H_g and especially H_f shift dramatically to the high field ($\Delta\delta = -0.99$ ppm for H_e, -1.03 ppm for H_f, and -0.34 ppm for H_g), and the triazole was also considerably shifted to the upfield ($\Delta\delta = -0.23$ ppm). In the NOE spectrum of **1**$_{cis}$ (Figure S7 in Supporting Information), H_d simultaneously has strong correlations with H_c, H_b, H_e and H_g. Because of the properties of azobenzene and the symmetric structure of **1**, it is reasonable to speculate that **1**$_{cis}$ adopted a scissor-like conformation in solution

(10) Intramolecular π-stacking would help to stabilize the conformation of the helix but hinders the isomerization upon irradiation with UV light.

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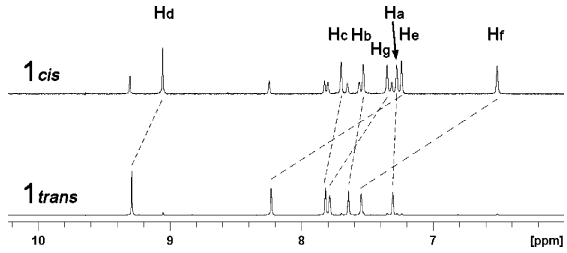

Figure 1. Partial ^{1}H NMR spectra (400 MHz, d_6-acetone, 25 °C) of $\mathbf{1}_{trans}$ and $\mathbf{1}_{cis}$. [**1**] = 2 mM.

(Scheme 1). An overall *trans* conformation was reproduced when $\mathbf{1}_{cis}$ was kept in the dark for over 10 days at ambient temperature, indicating a reversible transformation between $\mathbf{1}_{trans}$ and $\mathbf{1}_{cis}$ (Figure S12 in Supporting Information).

Both of the UV−vis spectra of $\mathbf{1}_{trans}$ and $\mathbf{1}_{cis}$ showed little change upon addition of nBu$_4$N$^+$Cl$^-$ up to 40 equiv (Figures S13 and S14 in Supporting Information), and therefore the binding properties of $\mathbf{1}_{trans}$ and $\mathbf{1}_{cis}$ were investigated by ^{1}H NMR spectroscopy. Titration of nBu$_4$N$^+$Cl$^-$ to $\mathbf{1}_{trans}$ produced a considerable shift in signals of H$_c$, H$_d$ and H$_g$ (Figure 2 and Figure S15 in Supporting Information), indicative that

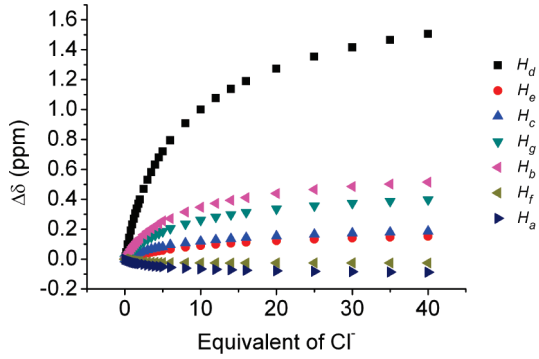

Figure 2. Changes in ^{1}H chemical shift for several protons of $\mathbf{1}_{trans}$ (d_6-acetone, 2 mM, 25 °C) upon addition of chloride ions.

these protons, which were supposed to be located at the inner cavity of the foldamer, participate in hydrogen bonding to the chloride ion.[17] When 40 equiv of chloride was added, the triazole proton H$_d$ signal dramatically downshifted from 9.28 to 10.79 ppm and signals for H$_b$ and H$_g$ also downshifted up to $\Delta\delta$ = 0.51 and 0.40 ppm, respectively. The titration curve was fitted well to a 1:1 binding model by using the EQNMR program[18] to generate the binding constant to be 70 M^{-1} (Figure S16 in Supporting Information), which is much smaller than that of the oligo(phenyl-1,2,3-triazole) foldamers[8a] as a result of the structural disturbance caused by the introduction of azobenzene into the strand. The 1:1 stoichiometry was also confirmed by a Job's plot (Figure S17 in Supporting Information).

The titrations of other anionic guests with different size or shape gave shifting patterns similar to those observed in the case of chloride, and the fitting analyses show a 1:1 binding stoichiometry for $\mathbf{1}_{trans}$ with all of these studied anions (Figures S18−S29 in Supporting Information). The binding constants were determined to be 22 M^{-1} for bromide, 38 M^{-1} for hydrogen sulfate, 11 M^{-1} for iodide and 10 M^{-1} for nitrate ions (Table 1), providing a preference for $\mathbf{1}_{trans}$ to

Table 1. Association Constants (M^{-1}) of $\mathbf{1}_{trans}$ and $\mathbf{1}_{cis}$ with Various Anions at Ambient Temperature and Calculated Changes in ^{1}H Chemical Shift ($\Delta\delta$) of 1,2,3-Triazole Proton H$_d$ upon Addition of 40 equiv of Anions[a]

	K_a (M^{-1})		$\Delta\delta$ (ppm)		
anions (A$^-$)	$\mathbf{1}_{trans}$	$\mathbf{1}_{cis}$	$\mathbf{1}_{trans}$	$\mathbf{1}_{cis}$	$K_{a,\,trans}/K_{a,\,cis}$
Cl$^-$	70	290	1.50	1.75	4.1
Br$^-$	22	87	1.11	1.27	3.9
I$^-$	11	31	0.51	0.63	2.8
NO_3^-	10	21	0.33	0.42	2.1
HSO_4^-	38	66	0.27	0.39	1.7

[a] The association constants were calculated by WinEQNMR.[18] The relative errors for the values are less than 10%.

bind the anions in the order of Cl$^-$ > HSO_4^- > Br$^-$ > I$^-$ ≈ NO_3^- as a result of the electrostatic nature of the hydrogen-bonding interaction.[19]

We next explored the binding properties of $\mathbf{1}_{cis}$ to all of the anions mentioned above. The ^{1}H NMR spectra of $\mathbf{1}_{cis}$ show a change totally different from that of $\mathbf{1}_{trans}$ upon the titrations of nBu$_4$N$^+$Cl$^-$ (Figure 3 and Figure S30 in

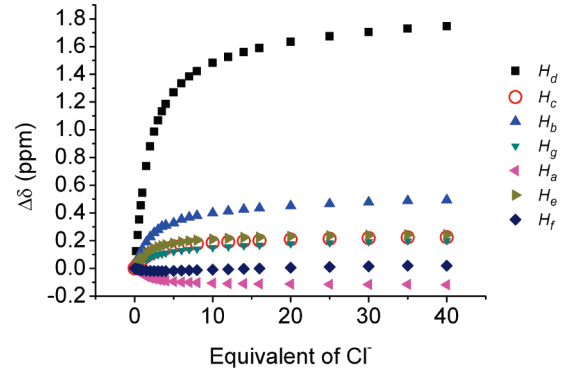

Figure 3. Changes in ^{1}H chemical shift for several protons of $\mathbf{1}_{cis}$ (d_6-acetone, 2 mM, 25 °C) upon addition of chloride ions.

Supporting Information). After 40 equiv of chloride was added, an obvious downshift of the signals of H$_b$, H$_e$ and H$_g$ (with $\Delta\delta$ = 0.49, 0.24, and 0.20 ppm, respectively) can be

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observed, indicating a strong interaction between all of these protons and the chloride ion. Besides, the triazole showed a more significant downfield shift ($\Delta\delta = 1.75$ ppm) than that in the case of $\mathbf{1}_{trans}$. A Job's plot confirmed a 1:1 binding stoichiometry for the complexation (Figure S32 in Supporting Information). These result may suggest that, in the complex, the two crossed branches of $\mathbf{1}_{cis}$ clamp the chloride in their interspace. A fit to the chemical shift titration data gave a binding constant K_a of 290 M^{-1}, which is 4.1-fold greater than that in the case of $\mathbf{1}_{trans}$. The enhancement of the binding affinity may suggest an improvement in spatial complementarity among the host−guest system.[20,21]

Titration of the other anions produced similar changes in ^{1}H NMR spectra of $\mathbf{1}_{cis}$ (Figures S33−S44 in Supporting Information), showing that $\mathbf{1}_{cis}$ binds these anions in the same manner as to the chloride. The binding constants of $\mathbf{1}_{cis}$ to these anions were calculated to be 87 M^{-1} for bromide, 66 M^{-1} for hydrogen sulfate, 31 M^{-1} for iodide and 21 M^{-1} for nitrate (Table 1), indicative of an overall enhancement in the binding affinity for all of these anions while the conformation of **1** transformed from the *trans* to the *cis*. It is evident that the enhancement is more sensitive to anions with small size. For example, while chloride has 4.1-fold enhancement, bromide and iodide have 3.9- and 2.8-fold, respectively. This is because the inner cavity of $\mathbf{1}_{cis}$ is inevitably smaller than that of $\mathbf{1}_{trans}$. Also, the enhancement is highly dependent on the geometric shape of the anions.[22] Photoisomerization of $\mathbf{1}_{trans}$ produced the largest changes in binding affinity for the spherical halides, a moderate change for the trigonal planar nitrate, but the smallest change for the tetrahedral anions, hydrogen sulfate. Because complementarity between the receptor and anion is crucial in selectivity, we speculated that, in the presence of anions, $\mathbf{1}_{cis}$ preferred to form a spherical cavity to hold the anions (Scheme 1). This may be evidenced by the comparatively large downshift of H_b in anion titration experiments.

Irradiation of $\mathbf{1}_{trans}$ in the presence of 4 equiv of chloride for 5 min gave a sharp descent on the intensity of band at 339 nm, but 81% of the intensity was recovered after the solution was further irradiated with the visible light for 8 min (Figure 4). After several cycles of alternate irradiation with UV and visible lights, **1** still showed very good recoverability (Figure 4, insert). When the content of chloride was further increased to 40 equiv, **1** showed properties identical to those in the case of 4 equiv of chloride (Figure S45 in Supporting Information). ^{1}H NMR investigation also confirmed the reversible isomerization of **1** in the presence of anions. In the presence of 4 equiv of chloride, exposure of $\mathbf{1}_{trans}$ to 365 nm light gives 85% of $\mathbf{1}_{trans}$ converted to $\mathbf{1}_{cis}$ in the photostationary state. However, $\mathbf{1}_{trans}$ was reobtained when the mixture was further stored in the dark at ambient temperature for over 14 days (Figure S46 in Supporting Information). These data hint that the photoswitch still shows reversible isomerization in the presence of anions.

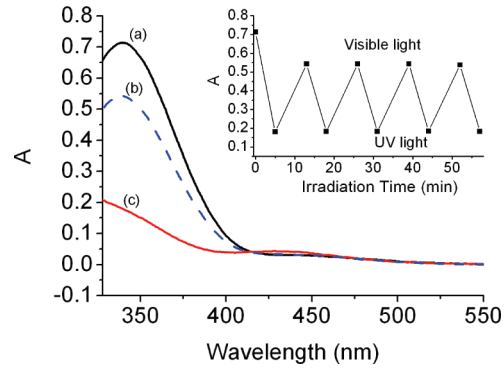

Figure 4. UV−vis spectra of (a) $\mathbf{1}_{trans}$ (30 μM, acetone) in the presence of 4 equiv of chloride ions. (b) Irradiation with 365 nm light for 5 min, then (c) irradiation with visible light for 8 min. The insert figure reflects the changes of the absorbance at 339 nm upon alternate irradiation with UV and visible light.

To summarize, the azobenzene-triazole based photoswitchable foldamer presents a controllable change in binding affinity for anions, which is highly dependent on the size and shape of the anions. Although the changes in the anion binding affinity of the present system is not so significant, this research still provides a useful method to obtain anion receptors that can totally change their binding behavior to anions by using light as a trigger, thus providing a potential application in light-controlled anion transport and separation.[23]

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Supporting Information Available: Synthesis of **1**. Titration experiments, 2D NMR spectra, and the Job's plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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