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Flipping the Switch on Chloride Concentrations with a Light-Active Foldamer

Yuran Hua and Amar H. Flood*

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405

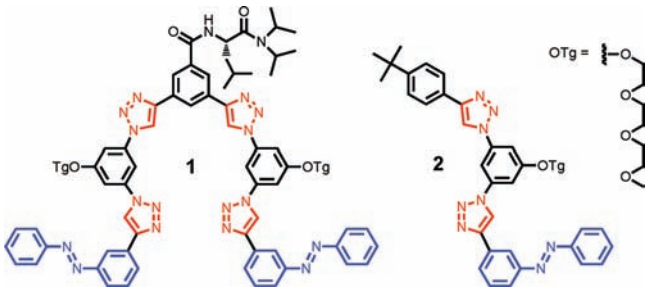
Received June 30, 2010; E-mail: aflood@indiana.edu

Abstract: Here we demonstrate a bioinspired system where light stimulus is used to trigger the wavelength-dependent release and then reuptake of chloride ions in nonaqueous solutions. A chiral aryl-triazole foldamer with two azobenzene end groups has been synthesized to define a folded binding pocket for chloride ions that unfolds with UV light to liberate the chloride. The *trans*-dominated helical foldamer becomes less stable upon photoisomerization to the *cis* forms. Simultaneously, the observed binding affinity shows an ~10-fold reduction from $K = 3000\ M^{-1}$ (MeCN, 298 K). Control of chloride levels using light is demonstrated by switching the conductivity of an electrolyte solution up and down.

Regulating the availability of bioactive compounds is a fundamental feature of biology that is being studied[1] and emulated[2] with the aid of designer molecules. Pioneering work[3] on photocaged Ca^{2+}, which involves the photolysis of a covalent bond as a means to release the cation into solution, has led to a plethora of caged compounds[1] for studying biochemical pathways. In the hopes of achieving true biological emulation, supramolecular systems are being investigated as candidates for the reversible and stimuli-responsive control over local chemical concentrations. An early example is the photogated binding[4] and transport[5] of alkali metal cations using an azobenzene-modified bis-crown ether. These concepts, while honed in the manipulation of cations (including transition metals),[6] have yet to be fully realized with anions where understanding and controlling their concentrations is important for investigating diseases like cystic fibrosis[7] and for affecting environmental remediation.[8] At present, there are only a few isolated examples of photocontrolled binding[9,10] using anion receptors for which the mechanisms of action are not always obvious.[10] In order to address the fundamental ideas and explore novel designs for the photocontrol of anions, we report on a switchable foldamer-based receptor (**1**, Scheme 1) that can reversibly and predictably modulate (Figure 1) the concentration of chloride in nonaqueous solvents.

Receptor **1** employs the *cis*/*trans* photoisomerization of azobenzene[11] and the ability of aryl-triazole foldamers[12,13] to bind anions using CH hydrogen bonds.[14] The light-switchable receptor takes advantage of the known chain-length dependence in the helical stability of solvophobic foldamers.[15] Azobenzene has been used previously to change the stability of foldamers;[16] however, those designs place the azobenzene in the center of the oligomer, which can prevent the isomerization from occurring.[16a,b]

Scheme 1. Receptor **1** and Model Compound **2**



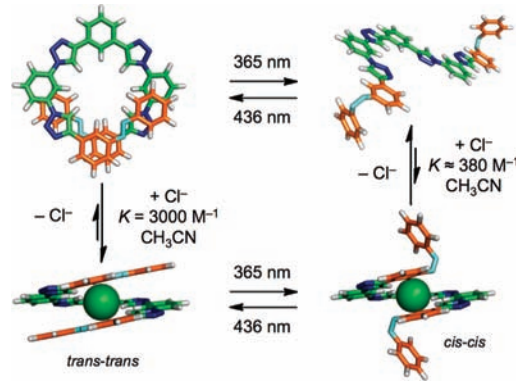


Figure 1. Proposed cycle of photodriven binding and release of chloride (structures from modeling;[17] see text for binding constant determination).

Here we propose a new mechanism for controlling the helical-to-random coil equilibrium: The thermodynamically favored *trans* form of azobenzene is coplanar with the aryl-triazole backbone,[17] while the *cis* form breaks coplanarity. This modulation alters the number of $\pi-\pi$ contacts (Figures 1 and 2a) involved in stabilizing the helical form of the foldameric receptor. Thus, there can exist three isomers: $\mathbf{1}_{trans\text{-}trans}$, $\mathbf{1}_{cis\text{-}trans}$, and $\mathbf{1}_{cis\text{-}cis}$. Each isomer is expected to have different helical stabilities arising from three, two and one $\pi-\pi$ overlapping residues, respectively. Consistently, molecular modeling shows[17] isomer $\mathbf{1}_{trans-trans}$ prefers the helical form and is more organized than $\mathbf{1}_{cis-cis}$, which is dominated by random coil conformations. By accessing the *cis* and *trans* forms of azobenzene with 365-nm (UV) and 436-nm (visible) light, it should be possible to destabilize and stabilize the helix, correspondingly. Therefore, when the helix-to-random coil equilibrium and subsequently the preorganization of the receptor are affected,[18] the concentrations of bound and free chloride can be controlled using different colors of light.

Given the new mode of action, the photocontrolled stability of both the helical foldamer and the chloride−receptor complex have to be independently verified. We do this here by taking advantage of spectroscopic signatures of the *cis* and *trans* forms of azobenzene,[11] the circular dichroism (CD) response provided by the amino acid derived side chain on **1**, and the known chloride binding behaviors of aryl-triazole receptors.[12,14,18] CH_3CN is used as a "poor" solvent to help stabilize the folded state[15] while retaining compound solubility. Lastly, we use the conductivity of a salt solution to verify the photoregulation of chloride concentrations.

Receptor **1** and control compound **2** (Scheme 1) were prepared[17] from alkynyl and azide building blocks by taking advantage of the

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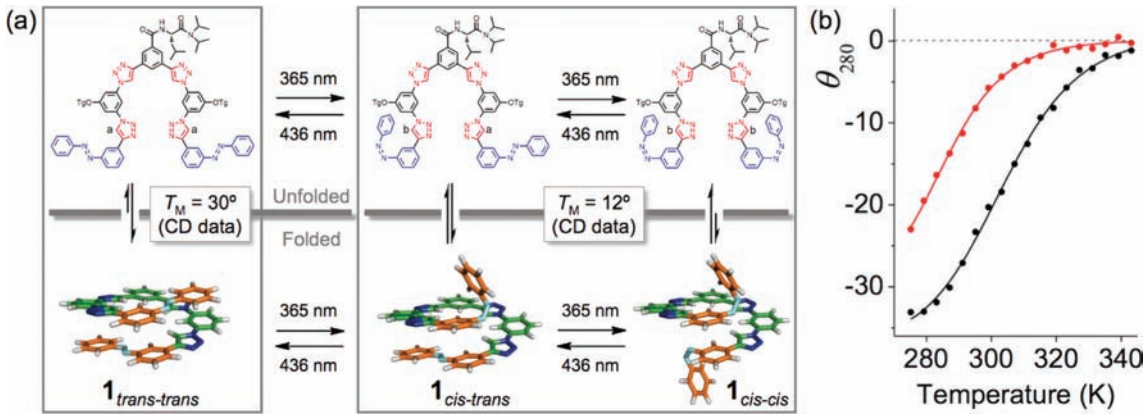

Figure 2. (a) Representations of the helical-to-random coil equilibria for $\mathbf{1}_{trans-trans}$ and the UV-driven PSS (66% $\mathbf{1}_{cis-trans}$ + 33% $\mathbf{1}_{cis-cis}$). (b) Variable-temperature CD spectra of $\mathbf{1}_{trans-trans}$ (black line) and the UV-PSS exposure (red line) (200 μM, CH_3CN).

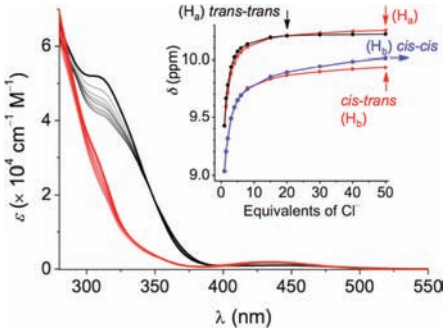

Figure 3. Absorption spectra of $\mathbf{1}_{trans-trans}$ (thick black trace, 100 μM, MeCN, 298 K) upon addition of TBACl up to 20 equiv. The same data are shown for the UV-based PSS (thick red trace) upon addition of 200 equiv. Inset: NMR titration[17] (10 mM, CD_2Cl_2, 298 K) with arrows showing saturation of the triazoles' peak shifts (protons labeled in Figure 2a).

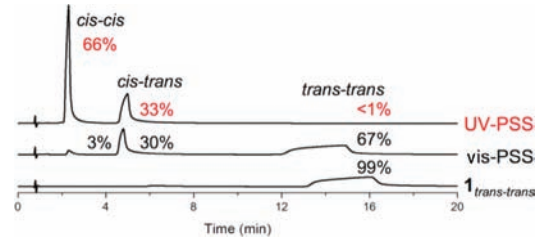

Figure 4. RP-HPLC traces for the PSSs obtained after exposure to UV (top) and visible (middle) light. Each peak had the same ESI-MS response for $(M + HCOO^-) = 1467.7$ *m/z*. Bottom: $\mathbf{1}_{trans-trans}$ (C_{18} support, 95% CH_3CN:5% H_2O:0.1% HCOOH).

modularity of click chemistry.[19] Compound identity was confirmed by electrospray ionization mass spectrometry (ESI-MS) and NMR spectroscopy.[17] *Trans*- and *cis*-**2** provided NMR signatures evident in spectra of **1**. Broad NMR spectra of **1**[17] (CD_3CN) were sharpened when using CD_2Cl_2 and upon addition of tetrabutylammonium chloride (TBACl). **1** was prepared directly as a mixture of the three isomers. Isomer $\mathbf{1}_{trans-trans}$ can then be separated from the other isomers utilizing flash column chromatography with C_{18}-functionalized silica gel.

The photoisomerization of receptor **1** can be unambiguously identified from both electronic absorption and NMR spectroscopies (298 K) and using reversed-phase high-performance liquid chromatography (RP-HPLC). Upon exposure of the receptor solution to UV light (~5 min), the spectrum with a band at 310 nm (Figure 3, thick black trace) transformed into the spectrum with a new band at 430 nm (Figure 3, thick red trace). Visible light (~5 min) largely restores the initial spectrum,[17] fully consistent with the photochemical behavior of azobenzenes.[11] The photochemistry of model compound **2** was investigated using NMR spectroscopy[17] to establish the *cis*:*trans* ratios of its photostationary states (PSSs). In both CD_3CN and CD_2Cl_2, UV irradiation yielded a 20:80 (*trans*:*cis*) ratio, while visible light was able to reverse the composition to 80:20. It can be inferred, therefore, that the PSSs of receptor **1** will be a linear combination of these. To quantify these PSSs, RP-HPLC was used to measure (Figure 4) the ratios of isomers on account of the long half-life of the *cis*-azobenzene in this molecular scaffold ($t_{1/2} \gg 96$ h).[17] By using the 99% $\mathbf{1}_{trans-trans}$ sample as a time calibrant for the RP-HPLC, the PSSs for UV and visible light are 0:33:66% and 67:30:3%, respectively.

On the basis of the proposed mechanism (Figure 1), the stability of the helical foldamer is expected to decrease (Figure 2a) upon UV irradiation to the *cis*-dominated PSS according to the chain-length dependence of solvophobic foldamers.[15] This hypothesis was verified using variable temperature (VT) CD spectroscopy (Figure 2b). The melting temperature, T_M, defined as the temperature when half of the molecules unfold, was found to be 30 °C. Thus, $\mathbf{1}_{trans-trans}$ displays good folding in CH_3CN, and at 25 °C, 66% of the molecules are folded. For the solution dominated by the $\mathbf{1}_{cis-cis}$ isomer (PSS-UV), the melting temperature decreased to 12 °C such that ~75% of the receptors are unfolded into random coils. VT-NMR spectra are consistent with the T_M values.[17] The helical form of receptor **1** is more preorganized[18] for anion binding with all the CH groups directed into the cavity's center. Consequently, the *trans* forms are expected to have stronger chloride binding than the *cis* isomers.

The chloride affinity of pure isomer $\mathbf{1}_{trans-trans}$ was examined by a titration (100 μM, CH_3CN, 298 K) with TBACl in the dark. Equilibrium restricted factor analysis[20] of the changes in the electronic absorption spectra (Figure 3, black traces) gave an association energy of $\Delta G(\mathbf{1}_{trans-trans}) = -20$ kJ mol^{-1} ($K_a = 3000$ M^{-1}). When the same titration was conducted after exposing the receptor solution to UV light (Figure 3a, red traces), the apparent chloride affinity was reduced to $\Delta G(\mathbf{1}_{PSS\text{-}UV}) = -15$ kJ mol^{-1} ($K_a = 380$ M^{-1}). Exposure to 436-nm light restored the dominance of the *trans*−*trans* isomer in solution and the stronger chloride affinity: $\Delta G(\mathbf{1}_{PSS\text{-}vis}) = -20$ kJ mol^{-1} ($K_a = 3000$ M^{-1}).[17]

At the visible PSS, isomer $\mathbf{1}_{cis-trans}$ is present at 30% and it is expected to have an intermediate binding strength to the other isomers. To test this idea, a competitive titration was conducted by NMR spectroscopy (298 K).[17] CD_2Cl_2 was used to obtain sharp peaks facilitating interpretation. Fortuitously, equal concentrations of the three isomers (10 mM total concentration) can be obtained

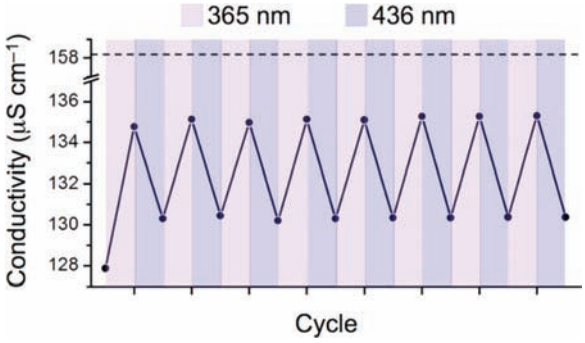

Figure 5. Light-driven cycles of the solution conductivity obtained upon exposure to UV (purple) and visible (blue) light. The electrolyte solution contains equimolar concentrations of TBACl and receptor **1** (1 mM, CH_3CN, 298 K). The first point is the addition of $\mathbf{1}_{trans-trans}$, and the dashed line corresponds to the conductivity in the absence of receptor.

by mixing the PSS-UV and PSS-vis solutions. The signals for the triazole protons, two each for $\mathbf{1}_{trans-trans}$ and $\mathbf{1}_{cis-cis}$ and four for $\mathbf{1}_{cis-trans}$, all shift the greatest degree compared to the other protons. These large ~1 ppm shifts are consistent with all the triazole CH protons forming hydrogen bonds[12,14,18] with the chloride inside folded conformations of the three isomers. Based on the point at which chloride−receptor saturation occurs (Figure 3, inset) and from the approximate binding constants in CD_2Cl_2,[17] the relative order in the chloride affinities is as predicted: $\mathbf{1}_{trans-trans} > \mathbf{1}_{cis-trans} > \mathbf{1}_{cis-cis}$.

The association constants for the two PSSs indicate that the chloride levels can be regulated with light. To test this idea, a conductivity experiment[21] was performed (Figure 5) with equimolar concentrations of **1** and TBACl (1 mM, CH_3CN, 298 K). Based on the binding constants, the concentration of free chloride will be 0.23 mM for the visible PSS and this will increase to 0.56 mM upon exposure to UV light. These differences are sufficient for a proof of principle demonstration.

According to eq 1,[22] the solution phase electrical conductivity (κ) is directly related to the concentration (C) and diffusion coefficient (D) of all the charged species in solution; all other symbols have their usual meaning.

$$\kappa = (Fe/k_BT) \cdot \sum |z_i|^2 D_j C_j \qquad (1)$$

In solution, three species are responsible for the conductivity: TBA^+, chloride, and the complex **1**•Cl^-. While the concentration of TBA^+ remains unchanged, altering the binding strength of the receptor changes the relative fraction of the free and bound chloride. Formation of the **1**•Cl^- complex results in a larger charge carrier with a smaller diffusion coefficient.

In the absence of the receptor, the conductivity of the salt solution is 158 μS cm^{-1}. Upon addition of $\mathbf{1}_{trans-trans}$, the conductivity decreases, as expected, to 128 μS cm^{-1}. Irradiating the sample with UV light caused an increased conductivity (135 μS cm^{-1}), which is attributed to an increase in the chloride concentration. Irradiation with visible light lowered the conductivity (130 μS cm^{-1}) on account of the recapture of the chloride by the *trans*-dominated receptors. This cycle can be repeated over eight times (Figure 5). Using eq 1 and estimates for the diffusion coefficients[17] of **1**•Cl^-, TBA^+, and chloride, the relative change in conductivity is dominated by the calculated change in free chloride levels.[17]

In conclusion, we present the first demonstration of regulating chloride concentrations by photoisomerization of a receptor. Isomerization alters the effective chain length, and thus the helical stability of the aryl-triazole foldamer. The *trans*-dominated isomers are more preorganized for chloride binding, and an ~10-fold reduction in binding affinity was induced by the *trans*-to-*cis* isomerization in CH_3CN. A robust chloride binding and release cycle can be achieved by alternately irradiating the sample with UV and visible light.

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Supporting Information Available: General methods, compound syntheses, molecular modeling, NMR data, UV−vis spectra of photoisomerizations and TBACl titrations, NMR titrations, CD spectra, diffusion NMR, and conductivity analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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