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A Sandwich Azobenzene-diamide Dimer for Photoregulated Chloride Transport

Manzoor Ahmed,[a] Surajit Metya,[a] Aloke Das,[a] and Pinaki Talukdar*[a]

Abstract: There has been a tremendous evolution for artificial ion transport systems, especially gated synthetic systems, which closely mimic their natural congeners. Herein, we demonstrate a *trans*-azobenzene based photo-regulatory anionophoric system that transports chloride by forming a sandwich dimeric complex. Further studies confirmed a carrier-mediated chloride-anion antiport mechanism, and the supramolecular interactions involved in chloride recognition within the sandwich complex were revealed from theoretical studies. Reversible *trans-cis* photoisomerization of the azobenzene was achieved without any significant contribution from the thermal *cis* → *trans* isomerization. Photoregulatory transport activity across the lipid bilayer membrane inferred an outstanding off-on response of the azobenzene photo-switch.

Gating, 'the timely opening and closing of ion channels', is one of the most crucial features associated with natural ion transport systems[1] for controlling vital functions of osmotic regulation, nerve transmission, muscle excitation, ionic homeostasis, growth, and development.[2] Stimuli like membrane potential, pH change, chemical messengers and light are responsible for this regulatory behavior inside the physiological systems.[3] However, any misregulation proves detrimental for human health causing numerous diseases, collectively called "channelopathies".[4] Although significant efforts have already been made to mimic the behavior of natural ion transport systems, athwart both ion channels and ion carriers,[5] still the regulatory transport systems which promise practical applications in curing "channelopathies" are rare. Synthetic gated systems usually involve the use of light, pH, ligand, voltage, etc.[6] Among these all, light regulatory systems are of particular interest because of their intensity tunability, non-physical contact, and high spatiotemporal precision.[7] 'Optochemical genetics' is one of the ways to incorporate a photoreceptor to the natural channel protein to attain the photo-regulatory ion transport behavior, however, it involves a complex design strategy, complex fabrication and is often unpredictable.[8] The alternative approach involves the incorporation of a photoswitch to a simple yet all functional synthetic ion transporter.[9] Azobenzene is one of the most commonly used photo-switches because of its substantial change in length, conformation and dipole moments upon *trans*-*cis* photoisomerization, in addition to its short response-time.[10] The *trans* → *cis* isomerization occurs upon exposure to UV light (~ 365 nm), while the *cis* → *trans* isomerization takes place by visible light (~ 450 nm). Moreover, the *cis* → *trans* isomerization also occurs thermally owing to the thermodynamic stability of the *trans* isomer resulting in spontaneous *cis* → *trans* even in dark.

Due to planar and extended conformation, the *trans* conformation of azobenzene was incorporated for achieving the active state of bioengineered protein[11] and self-assembled synthetic channels.[12] On the other hand, the design of synthetic anion carriers utilized the *cis* conformation of azobenzene because the twisted conformation of the photoswitch assures the optimum proximity of ion recognizing groups ensuring efficient ion binding.[13] However, the thermal stability of the *cis*-form was not investigated. We envisaged that an adequately designed *trans*-azobenzene can provide an anion binding cavity involving its aryl C–H that is *ortho* to the azo group. Herein, we report an intramolecular-hydrogen bonded *trans*-azobenzene-diamide system that forms an efficient photoswitchable chloride carrier and also offers a thermally stable inactive state in the *cis*-conformation.

The structure of the *trans*-azobenzene-diamide based anion receptor system is illustrated in Figure 1A. In the receptor, the amide $N–H_1$, $C_{Ar}–H_2$ create the anion binding site. In this site, the presumed repulsion between the anion and the nearest azo nitrogen is masked by the intramolecular six-membered $N_{azo}\cdots H_3–N$ hydrogen bond using a second amide moiety. Interestingly, that the $N–H_3$ moiety would also provide an additional hydrogen bond for anion recognition. The possibility of a further anion recognition through $C_{Alk}–H_4\cdots$anion hydrogen bond was also envisaged. In the lipid bilayer membrane, the receptor would facilitate the transport of anions. The *trans* to *cis* photoisomerization of the receptor at 365 nm would lead to a drastic change in the planarity and proximity of the anion recognizing groups leading to poor anion binding and transport.[14] We envisaged that in the *cis*-conformation, the $N–H_3$ group would be involved in an intramolecular five-membered $N_{azo}\cdots H_3–N$ hydrogen bond providing significant thermal stability to the *cis* isomer.[15] Therefore, the *cis* to *trans* isomerization can be achieved entirely by light at 450 nm to regain the active state back and hence a photoregulated artificial ion transport system will be generated out. Structural modification in terms of lipophilicity, as per Lipinski rule[16] was expected to influence the permeability as well as the transport affinity of these anionophores.[17] The logP and pK_a values of these compounds were calculated using the Marvin Sketch program (Figure 1B).[18]

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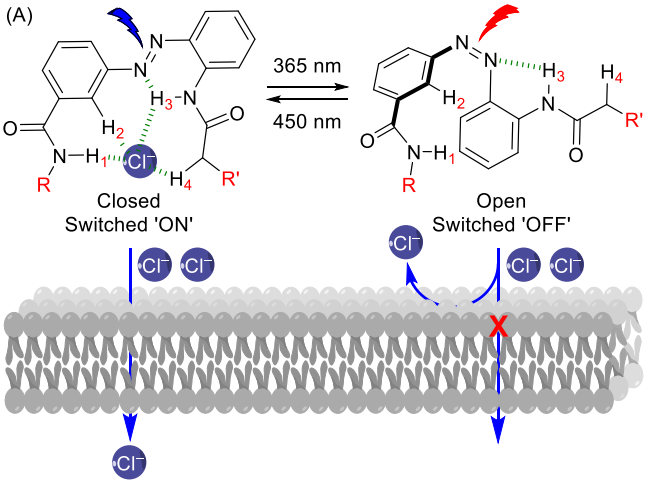

(B)

Compound	R	R'	pK_a(H_1)	pK_a(H_2)	logP
1a	4-CF_3-Ph	Me	11.44	12.24	6.29
1b	4-^{t}Bu-Ph	Me	11.76	12.38	6.95
1c	4-*Br*-Ph	Me	11.48	12.25	6.18
2a	4-CF_3-Ph	CN	11.30	11.92	5.54
2b	4-^{t}Bu-Ph	CN	12.17	11.52	6.20
2c	n-Hexyl	CN	14.29	11.69	4.85

Figure 1. Design and working principle of light regulatory synthetic ion transporter (A). Chemical structures, pK_a values of N-H_1 and N-H_2 protons, logP values of compounds **1a-1c** and **2a-2c** (B).

The synthesis of the desired anionophores **1a-1c** was achieved through four step synthetic strategy starting from *N*-(2-nitrophenyl)propionamide **3** (Scheme S1), and cyano based compounds **2a-2c** were synthesized through a different five step synthetic strategy starting from mono Boc-protected *o*-phenylenediamine **7** (Scheme S2).

At first, the Cl^- binding studies of **1b** was investigated through ^{1}H NMR titration by titrating TBACl into a solution of host **1b** in CD_3CN at 298 K. Upon the gradual addition of TBACl, the downfield shift of protons H_1, H_2, H_3, H_4, and H_5 were observed, indicating the involvement of N–H_1···Cl^-, C_{Ar}–H_2···Cl^-, N–H_3···Cl^-, C_{Alk}–H_4···Cl^- and C_{Ar}–H_5···Cl^- hydrogen bond interactions in the recognition of the anion (Figure S30). Further analysis of the data by Bindfit program[19] gave a 1:1 (Host:Guest) binding stoichiometry with Cl^-binding constant ($K_{a(1:1)}$ = 110 ± 3.3 M^{-1}). The ^{1}H NMR titration of **2b** with TBACl showed a similar binding interaction mode with a higher Cl^- binding constant ($K_{a(1:1)}$ value of 515 ± 12.7 M^{-1} (Figure S31). The stronger binding of **2b** with the anion was rationalized based on the stronger hydrogen bonding interaction between its H_4 proton and the Cl^- ion than that between the H_4 proton of **1b** and the anion. The larger downfield shift for H_4 proton of **2b** than that of **1b** is a consequence of the stronger hydrogen bonding. Binding studies of the *cis* form for **1b** furnished Cl^- binding constant $K_{a(1:1)}$ = 88 ± 0.4 M^{-1} (Figure S32), which is lower as compared to the *trans* form of **1b**. The direct evidence of chloride binding of **1b** with 1:1 receptor:Cl^- binding stoichiometry was obtained from the electrospray ionization mass spectrometric (ESI-MS) study. The mass spectrometric data provided peaks at *m/z* = 463.1960 and 465.1944, which correspond to the [**1b**+Cl^-] complex in the solution state (Figures S13). Moreover, the presence of a [(**1b**)$_2$+Cl^-] complex at *m/z* = 891.4943 and 893.5034 was also evident.

Next, the ion transport activities of compounds **1a-1c** and **2a-2c** were examined across large unilamellar vesicles (LUVs), prepared from egg-yolk phosphatidylcholine (EYPC) lipid entrapped with 8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt (HPTS, 1 mM) containing 10 mM of HEPES buffer and 100 mM of NaCl (see the supporting information).[20] During the fluorescent studies, a pH gradient of 0.8 (pH_{in} = 7 and pH_{out} = 7.8) was created with NaOH and the collapse of pH gradient was monitored by fluorescence at λ_{em} = 510 nm (λ_{ex} = 450 nm) after addition of each compound. All the anionophores exhibited efficient transport activity with the activity sequence of **1a** > **2a** > **1c** > **1b** > **2b** > **2c** (Figure 2A). From dose-responsive plots, using Hill analysis, the half-maximal effective concentration (EC_{50}) values comes out to be **1a** = 0.198 ± 0.002 μM, **2a** = 0.277 ± 0.032 μM, **1c** = 0.419 ± 0.050 μM, **1b** = 0.912 ± 0.113 μM, **2b** = 1.5 ± 0.056 μM and **2c** = 1.554 ± 0.102 μM (Figures S35–S40). The Hill coefficient values of *n* ~ 2 for all compounds indicate the involvement of two molecules in catalyzing the ion transport process. The aforedescribed ESI-MS data having the signals of [(**1b**)$_2$+Cl^-] complex provided the direct evidence of the 2:1 receptor-Cl^- stoichiometry. Moreover, Compound **1b**, possessing lower binding affinity showed better transport activity as compared to the cyano bearing compound **2b**, most probably because of poor lipid bilayer permeation of hydrophilic cyano group. Similarly, **1a** showed better transport as compared to **2a**. Compound **2c** containing an aliphatic side chain connected to amide N-H_1 showed the least activity plausibly due to the absence of (C_{Ar}–H_5···anion) interactions.

Subsequently, the Cl^- leakage for compounds **1a-1c** and **2a** was monitored across EYPC-LUVs⊃lucigenin at λ_{em} = 535 nm (λ_{ex} = 455 nm) by creating a Cl^-/NO_3^- gradient across the lipid membrane. All of them showed a significant Cl^- transport across the lipid membrane.[21] Dose-responsive Cl^- leakage for compound **1a** is shown in Figure 3A. Hill analysis for the compounds **1a**, **1b**, **1c**, and **2a** furnish the EC_{50} of 1.26 ± 0.092 μM, 4.76 ± 0.136 μM, 2.83 ± 0.207 μM and 2.53 ± 0.114 μM

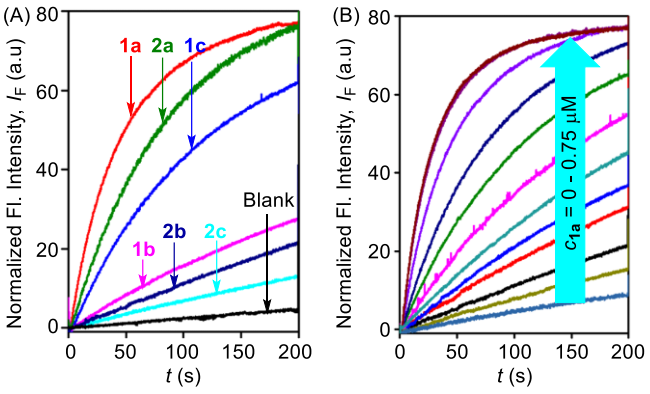

Figure 2. Activity comparison of **1a-1c** and **2a-2c** (0.3 μM each) across EYPC-LUVs⊃HPTS (A). Concentration-dependent activity of compound **1a** (B).

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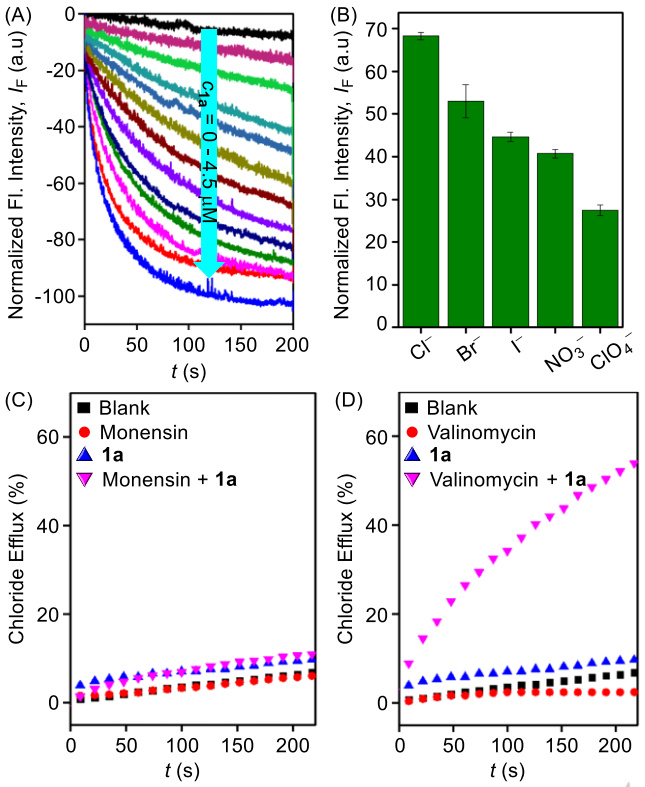

Figure 3. Concentration-dependent activity of compound **1a** across EYPC-LUVs⊃Lucigenin (A). Anion selectivity of **1a** (0.3 μM) by varying external as well as internal anions across EYPC-LUVs⊃HPTS, each bar graph represents mean ion transport activity, calculated from three independent experiments (B). Normalized chloride efflux of **1a** in the presence and absence of Monensin (C), and in the presence and absence of Valinomycin (D).

(Figure S42–S45) and Hill coefficient *n* = 2 confirming the involvement of two molecules in the anion transport process. Compounds **2b** and **2c** could not be evaluated due to precipitation in the buffer at higher concentrations. Further, variation in the extravesicular MCl (M^+ = Li^+, Na^+, K^+, Rb^+, and Cs^+) salt solutions does not make any significant change in the transport activity of **1a** (*c* = 3 μM), which rules out any involvement of cations in an overall ion transport process (Figure S47).

Anion selectivity was investigated using EYPC-LUVs⊃HPTS (see the supporting information). Variation of extravesicular as well as intravesicular anions using different NaX salt solutions (X^- = Cl^-, Br^-, I^-, NO_3^-, and ClO_4^-) makes a significant change in the transport rate, confirming the involvement of anions in the transport process,[22] with an activity sequence of $Cl^- > Br^- > I^- > NO_3^- > ClO_4^-$ (Figure 3B). The better transport rate of Cl^- upon others is rationalized to the perfect fit of the anion in the binding pocket of the active ion transport system.

The operative mechanism was further analysed through modified lucigenin essay. LUV's were entrapped with NaCl (200 mM) and 1 mM of lucigenin dye. The transport activity of **1a** was monitored in the presence of isoosmolar Na_2SO_4 and $NaNO_3$ in the external buffer. NO_3^- transport occurred with the concomitant efflux of Cl^- ions, and on the other hand, SO_4^{2-} being more hydrophilic is not transported easily, suggesting the operation of antiport mechanism (Figure S48).[22] The antiport process was further confirmed through ISE studies. EYPC-LUVs entrapped with KCl (300 mM) were prepared and suspended in an external potassium gluconate solution. Cl^- efflux using Cl^- sensitive electrode was monitored in the presence and absence of monensin (a H^+/K^+ antiporter) and valinomycin (a highly selective K^+ transporter). No considerable change in Cl^- efflux was observed in presence of monensin (Figure 4A), and On the other hand, a significant increase in Cl^- efflux in presence of valinomycin was observed (Figure 4B), hence validating the antiport mechanism for the ion transport process.[23] Additionally, the proposed carrier mechanism was confirmed by U-tube experiment (Figure S50).

Based on the experimentally determined Hill coefficient value of *n* ~ 2 and chloride-anion antiport mechanism, the geometry-optimized structure of the [(**1a**)$_2$+Cl^-] complex was obtained first by generating the most probable sandwich conformation by using CONFLEX 8 program (Figure S68), [24] and subsequently optimizing the generated conformation by Gaussian 09 program[25] using B3LYP functional and 6-311G(d,p) basis set.[26] The geometry optimized structure of [(**1a**)$_2$+Cl^-] complex indicated that two receptor molecules are oriented in an anti-parallel fashion to form a sandwich structure around the central Cl^- ion (Figure 4). The structure confirmed that each receptor participates in the anion recognition through N−H_1···Cl^- (H_1···Cl^- = 2.42 Å), C_{Ar}−H_2···Cl^- (H_2···Cl^- = 2.80 Å), N−H_3···Cl^- (H_3···Cl^- = 2.86 Å), C_{Alk}−H_4···Cl^- (H_4···Cl^- = 2.79 Å), and C_{Ar}−H_5···Cl^- (H_5···Cl^- = 2.70 Å) hydrogen bonding interactions.

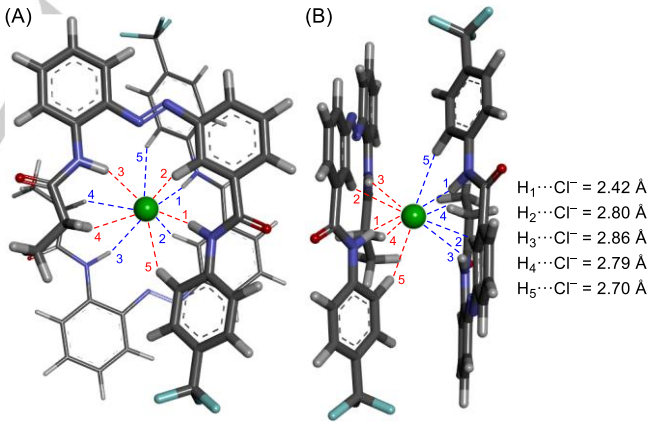

Figure 4. Top (A) and side (B) views of the geometry-optimized structure of [(**1a**)$_2$+Cl^-] complex.

The existence, as well as strength of various hydrogen-bonding interactions between the Cl^- and N-H/C-H groups of each of the two receptor molecules in the [(**1a**)$_2$+Cl^-] complex, was further confirmed through natural bond orbital (NBO) analysis. The NBO calculations, which determine the second-order perturbation energy ($E^{(2)}_{n\rightarrow\sigma^*}$) between the filled lone pair orbitals (n) of the anion and the vacant σ^* orbitals of the N−H/C−H groups, are performed at the B3LYP/6-311G(d,p)

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level of theory using NBO 6.0 software.[27] The NBO overlap between the lone pair and σ* orbitals for all the five hydrogen-bond interactions are shown in Figure S70 and different components of the total NBO interaction value of a specific interaction are listed in Table S4. It has been found that the $N-H_1\cdots Cl^-$ hydrogen bonding interaction is much stronger than the other four hydrogen bonding interactions present there.

The photoisomerization studies of the compounds **1a**, **1c**, **2a,** and **2c** were carried through UV-Vis and ^{1}H NMR spectroscopy. Fresh solutions of these compounds in acetonitrile showed an intense absorption peak at 380 nm (corresponding to π-π* transition) and a relatively weak absorption peak at 450 nm (corresponding to *n*-π* transition). The UV irradiation of these compounds at 365 nm led to a substantial decrease in the π-π* absorption band, and on the other hand, the intensity of the *n*-π* transition band increases slightly (Figures S55–S58). These changes were consistent with *trans* → *cis* photoisomerization of an azobenzene subunit.[28] Meanwhile, the reverse photoisomerization, *cis* → *trans* was achieved by irradiating the samples at 450 nm and can also occur thermally. Thermal back-isomerisation from *cis* → *trans* follows a first order rate law with the half-life of 32 ± 1 h. Photoregulation, through the process of alternating photoirradiation at two different wavelengths of 365 nm and 450 nm was carried out for several repeating cycles without the loss of efficiency. Photoisomerization behavior of these compounds was also studied through ^{1}H NMR spectroscopy. The photoirradiation of these samples in DMSO-d_6 at 365 nm makes a significant change in the proton signals indicative of *trans* → *cis* photoisomerization (Figures S51-S54). compound **1a** showed good thermal stability (half-life of 32 ± 1 h) in the photoisomerized *cis* form likely due to intramolecular hydrogen bonding of amide $N-H_3$ with one of the azo nitrogen (Figure S59).[15] The similar behavior was reflected in the lucigenin activity of **1a** in its *cis* form. No significant increment in the transport activity was observed while keeping the sample in dark and monitored for 5 h of time (Figure 5a, Figure S63).

After analyzing the photoisomerization behavior of these anionophores, photoswitchable ion transport of **1a**, **1c,** and **2a** were investigated using lucigenin essay. The ion transport

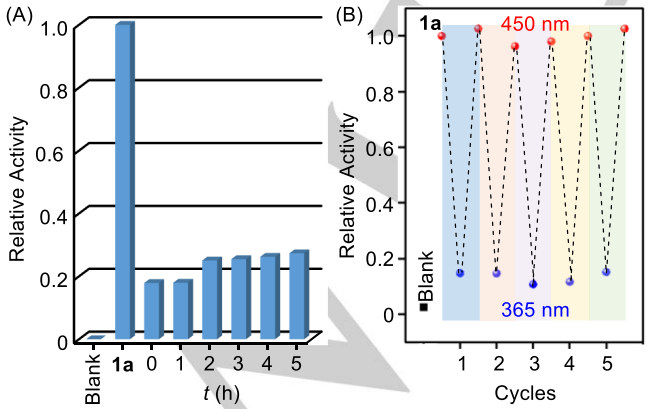

Figure 5. Transport activity of **1a** (3.5 μM) in *trans* and *cis* form across EYPC-LUVs⊃Lucigenin (A). Photo regulated transport activity of **1a** (3 μM) taken at *t* = 280 s under alternating photo irradiation at two different wavelengths of 365 nm and 450 nm across EYPC-LUVs⊃Lucigenin (B).

activity of anionophores **1a**, **1c** and **2a** (*c* = 3.0 μM, ACN:MeOH (4:1)), was drastically reduced upon photoirradiation of the samples at 365 nm, due to *trans* to *cis* photoisomerization, which was efficiently regained back upon 450 nm irradiation. The reason for less activity of *cis* form can be due to the because of less binding affinity as compared to the *trans* form, however, the change in the conformation and planarity can effect the formation of active receptor-anion complex for the necessary ion transport process. Also, the effect due to the change in the lipid permeation and mobility of the *cis* form cannot be ruled out as the reason for less activity of the *cis* form. Photoregulatory behavior in the transport activity was efficiently carried out for several repeating cycles (see Figures 5B, S560, S61, and S62). The ratio of the transport rates for the anionophores in the corresponding active *trans* form to that of inactive *cis* form comes out to be 100:18 for **1a**, 100:6 for **1c**, 100:31 for **2a**. Photo regulatory transport activity was also achieved *in situ* in the presence of EYPC-LUVs⊃HPTS.[5m] The transport activity of **1a** got decreased by photoirradiation at 365 nm for 2 min, which on the other hand was regained back through photo irradiation at 450 nm for 5 min (Figure S64).

In summary, we have developed a *trans*-azobenzene-diamide-based synthetic photoswitchable anionophoric system that forms a sandwich complex with a chloride ion for its transport across the lipid membrane. The most active transporter **1a**, decorated with a 4-(trifluoromethyl)phenyl aminoformyl and a propionamide groups, provided EC_{50} = 0.199 μM and Hill coefficient of *n* ~ 2 when measured across EYPC-LUVs⊃HPTS. Detailed mechanistic studies confirmed that **1a** functions as an anion carrier with Cl^-/anion antiport as the main operative process. Photoirradiation of the *trans*-isomer at 365 nm resulted in the very fast conversion to its *cis*-isomer, which was thermally stable at ambient temperature and amenable to very rapid back conversion exclusively by photoirradiation at 450 nm. Such *cis-trans* reversible photoisomerization behavior of the anionophore was utilized to achieve very efficient light-gated off-on Cl^- transport over several cycles. Beyond this photoswitchable transport activity, the very slow *cis* → *trans* thermal isomerization and short response-time of *cis-trans* photoisomerization, the present system can also be incorporated into several supramolecular artifacts with potential applications, which include soft materials,[29] stimuli-responsive systems[30] and in possible biological applications.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: gating • azobenzene • anionophore •antiport • photoregulation

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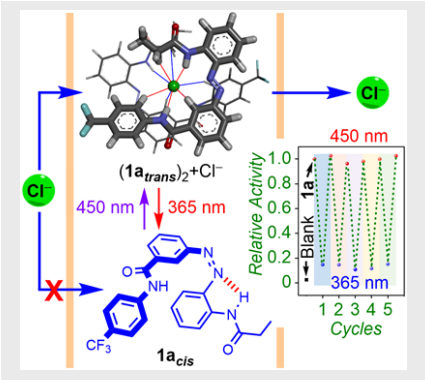

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A Sandwich Azobenzene-diamide Dimer for Photoregulated Chloride Transport

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