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A light-regulated synthetic ion channel constructed by an azobenzene modified hydraphile

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ABSTRACT

Biological ion channels are key molecules for cellular regulation and communication. To mimic the structure and functions of nature ion channels, a new class of light-regulated transmembrane ion channels was reported based on tri(macrocycle) hydraphile and azobenzene photoswitch (hydraphile **1**). The liposome-based proton transport assays showed that hydraphile **1** exhibited excellent transmembrane activity (Y), and Y_{max} arrived 0.7 at 40 μmol/L. The successful isomerization of azobenzene moiety was confirmed and qualified by UV and NMR spectra. Upon alternative irradiation of 365 nm UV light and 450 nm visible light, the transmembrane activity of hydraphile **1** was regulated between 0.35 and 0.5, reversibly. All the obtained results have demonstrated the promise of developing excellent synthetic ion channels with ion gating properties based on simple molecular design.

1. Introduction

Amongst various forms of input stimuli, light stands out as one of the most promising stimulation modalities for use in life science research because it offers nonphysical contact, controllable intensity, and high temporal and spatial precision. Recently, the use of light has been greatly improved in bioimaging, photoregulation of gene expression, photo-release of drug, and light-gated ion channel transport [1,2]. Although light-sensitive ion translocation (rhodopsin [3]) is limited in natural occurring organisms, light-gated ion channels can enable the direct manipulation of cellular excitability in genetically modified cells because cell activation can be directly linked to the diffusion of ions across the cell membrane [4].

Over the last few decades, many light-regulated artificial ion channels have been reported [5–9]. There are now two principal strategies for constructing light-responsive ion channels. The first strategy uses "optochemical genetics" [5,6], where the channel protein is genetically encoded with a photoreceptor that undergoes a photochemical reaction, moving in or out of the ion channel (ON or OFF) to gate ion flow by way of major conformation or polarity changes. However, this approach requires complex fabrication steps, involves design difficulties, and is sometimes unpredictable. Thus, it can be used on only a few well-characterized protein channels. The alternative approach uses synthetic light-responsive ion channels by attaching a photoswitch to the channel molecules, which then regulates ion translocation by reversibly changing the channel structures or ion dipole interactions [7–9]. Azobenzene is one of the most commonly used photoswitches due to a large change in azobenzene length and geometry upon photoisomerization from a linear and mostly planar *trans* form to a kinked 3D *cis* form, in addition to its short response time [10]. Several successful light-regulated ion channels were constructed due to the reversible photoregulation of azobenzene [7a,11].

"Hydraphiles", so called because they are amphiphiles and they are two-headed and reminiscent of the mythical hydra serpent, represent one kind of typical single-molecular channel models devoted by Gokel et al. [12]. The hydraphiles have three diaza-18-crown-6 residues linked and terminated by alkyl chains, in which the inner macroring embeds in the membrane and the two terminal rings are near the bilayer surface by supramolecular interactions between lipid and hydraphile. Research shows that the terminal substitution and the spacer length have great effect on the transport activity [12e,f], and the closer of the spacer lengths are to the thick of bilayer lipid membrane, the more efficient of the transport activity of the hydraphiles. Meanwhile, several of the

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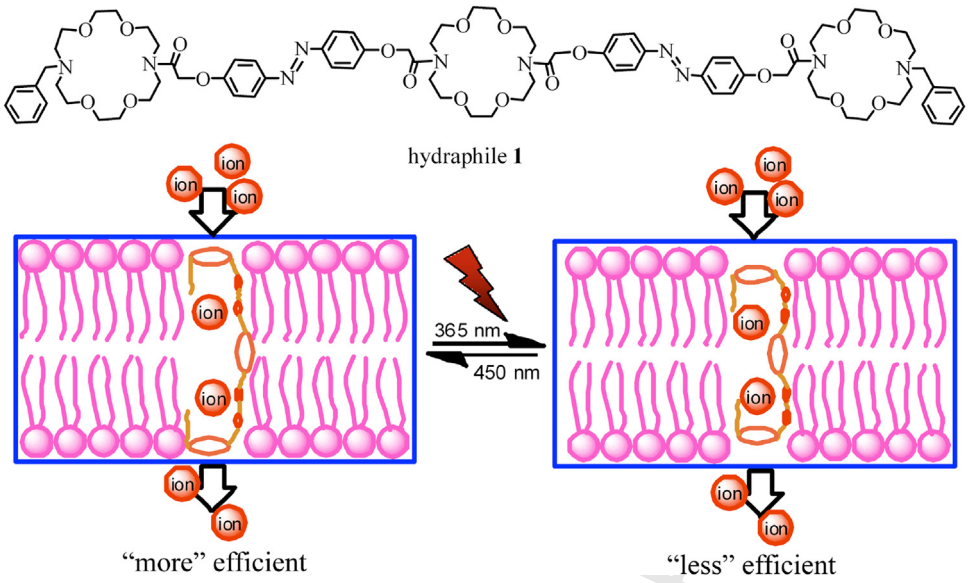

Scheme 1. The schematic presentation of the structures and transmembrane ion transport of hydraphile **1**.

hydraphile channels are biologically active and show antibacterial [12g], and anticancer toxic behavior [12a,h]. Taking inspiration from the work of Gokel et al., we used the classic backbone of the "hydraphiles" as the transmembrane channel and introduced azobenzene as the photoswitch to construct light-regulated ion channel (hydraphile **1**). As shown in Scheme 1, the photoisomerization of azobenzene induced the change of the transmembrane length of the channel, thus regulated the ion transport reversibly.

2. Experimental

2.1. Materials

All starting materials were obtained from commercial suppliers and were used without further purification unless otherwise stated. All air- or moisture-sensitive reactions were performed using oven-dried or flame-dried glassware under an inert atmosphere of dry argon. Egg yolk phosphatidylcholine (EYPC) was obtained from Avanti Polar lipids as a solution in chloroform (25 mg/mL).

2.2. Characterizations

Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded on a Bruker Avance 500 (400 MHz) spectrometer. Mass spectra were recorded on a Micromass GCTTM and a Micromass LCTTM. Fluorescence measurements were performed on a Varian Cary Eclipses fluorescence spectrometer equipped with a stirrer and a temperature controller (kept at 25 °C unless otherwise noted). Absorption spectra were recorded on a Shimadzu UV-2550 UV-vis spectrometer. A Mini-Extruder used for the preparation of large unilamellar vesicles (LUVs) was purchased from Avanti Polar lipids. The size of EYPC vesicles was determined using a Delsa^{TM} Nano Submicron Particle Size and Zeta Potential Particle Analyzer (Beckman Coulter Inc., USA). A 365 nm LED lamp (30 mW/cm^2) was used for photolysis of compounds and photocontrolled experiments.

2.3. HPTS assay

Preparation of large unilamellar vesicles (LUVs) and determination the transport activity of the compounds with the HPTS assay were as same as the description in our previous report [11a,b]. Here, the mixture of EYPC and cholesterol (10:1, w:w) was used for the membrane of LUVs, and 8-hydroxy-1,3,6-pyrenetrisulfonate (HPTS) was used as the pH-sensitive fluorescent probe, the final concentration of the lipids in the experiments was 33 μmol/L (assuming 100% of lipids were incorporated into liposomes), and the size of the vesicles was around 150 nm. In the time-dependent change in fluorescence intensity, 30 μL, 0.5 mol/L KOH was added at t = 50 s, 30 μL transporter in DMSO with different concentrations was added at t = 100 s, and 60 μL of 5% Triton X-100 aqueous solution was added at t = 350 s for final completed balance. Time courses of fluorescence intensities I_t were obtained by first, ratiometric analysis ($R = I_{t,450}/I_{t,405}$) and second, normalization according to Eq. (1),

$$I_t = \frac{(R - R100)}{(R\infty - R100)} \quad (1)$$

where $R_{100} = R$ before addition of transporter and $R_\infty = R$ after addition of Triton X-100. I_t at 350 s just before addition of Triton X-100 was defined as transmembrane activity Y.

2.4. Synthesis of hydraphile **1**

Compound **8**: Under Ar gas protection, compound **9** (0.2 g, 0.76 mmol) was dissolved in 10 mL dry CH_2Cl_2. Sodium hydride (73 mg, 3.05 mmol) was added slowly and stirred for 15 min at room temperature, then bromoacetyl bromide (0.17 mL in 7 mL dry CH_2Cl_2) was added dropwise to the flask and stirred for another 6 h at room temperature (Scheme 2). The reaction solution was concentrated in vacuum and chromatographed on a column of silica (silica gel, 20% methanol/CH_2Cl_2) to obtain 0.28 g (73%) compound **8** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (d, 4H, J = 3.1 Hz), 3.75 (d, 4H, J = 5.3 Hz), 3.71–3.56 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.44, 168.71, 70.95, 70.81, 70.70, 70.45, 69.82, 69.54, 69.17, 69.10, 50.53, 50.50, 48.54. MS (EI): m/z Calcd. for $C_{16}H_{28}Br_2N_2O_6$ $[M]^+$: 504.2. Found: 504.2.

Compounds **7** and **5** were synthesized as the reported references [11c,a]. Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 5H), 3.91 (s, 4H), 3.63 (d, 6H, J = 14.4 Hz), 3.52 (d, 8H, J = 14.4 Hz), 3.14 (s, 4H), 2.73 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.47, 128.98, 128.32, 127.04, 70.09, 69.91, 68.36, 66.69, 57.04, 56.00, 48.82. MS (EI): m/z Calcd. For $C_{19}H_{32}N_2O_4$ $[M]^+$:

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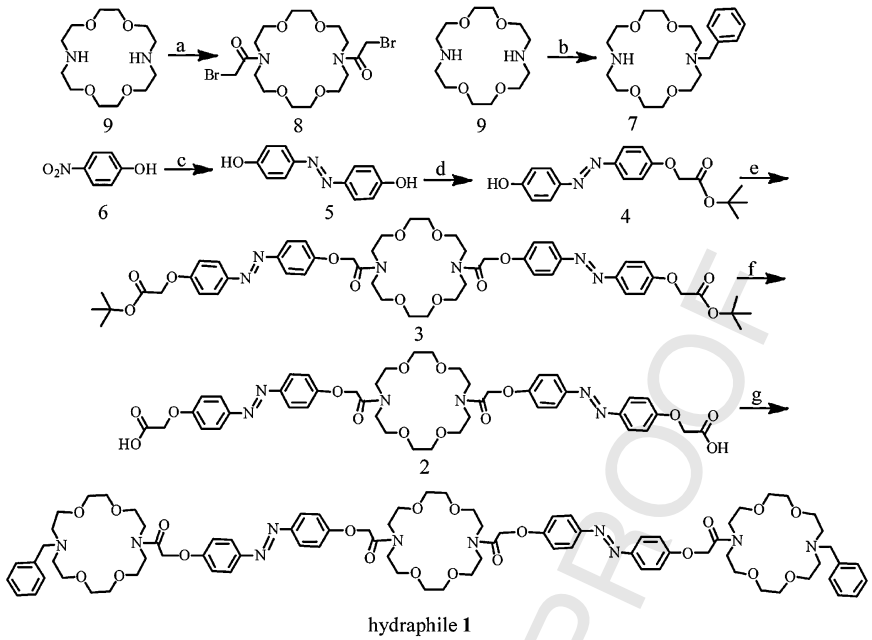

Scheme 2. Synthesis of hydraphile **1**. Reagents and conditions: (a) bromoacetyl bromide/NaH, CH_2Cl_2, 73% yield; (b) benezyl bromide, K_2CO_3, 46% yield; (c) H_2O/KOH, 64% yield; (d) *tert*-butyl bromoacetate, K_2CO_3, acetonitrile, 56% yield; (e) **8**, K_2CO_3/TBAB, acetonitrile, 93% yield; (f) TFA/CH_2Cl_2, 96% yield; (g) 1-chloro-*N*,*N*,2-trimethylpropenylamine, CH_2Cl_2; **7**, TEA/CH_2Cl_2, 68% yield.

352.2. Found: 352.2. Compound **5**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 2H), 7.87–7.57 (m, 4H), 6.95–6.87 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.22, 150.49, 129.40, 121.02. MS (EI): *m/z* Calcd. for $C_{12}H_{10}N_2O_2$ $[M]^+$: 214.0742. Found: 214.0741.

Compound **4**: Compound **5** (1 g, 4.67 mmol) and potassium carbonate (1.9 g, 14 mmol) were dissolved in dry acetonitrile. A solution of *tert*-butyl bromoacetate (0.69 g, 4.67 mmol) in 10 mL dry acetonitrile was added dropwise to the reaction system. The reaction kept refluxing for 10 h. After cooling to room temperature, and then filtered. After evaporation solvent, the product was chromatographed on a column of silica (silica gel, 0.5% methanol/CH_2Cl_2) to obtain 0.85 g (56%) compound **4** as an orange powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dt, 4H, J = 13.1, 5.9 Hz), 7.04–6.89 (m, 4H), 4.60 (s, 2H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.99, 159.65, 158.21, 147.51, 146.98, 124.65, 124.32, 115.78, 114.80, 82.93, 65.74, 28.06. MS (EI): *m/z* Calcd. for $C_{18}H_{20}N_2O_4$ $[M]^+$: 328.1423. Found: 328.1420.

Compound **3**: Under anhydrous condition, compound **8** (0.3 g, 0.59 mmol), compound **4** (0.58 g, 1.78 mmol), potassium carbonate (0.325 g, 2.36 mmol) and a trace of tetrabutylammonium bromide were dissolved in dry acetonitrile. The reaction was refluxed overnight. After cooling to room temperature, and then filtered. After evaporation solvent, the product was chromatographed on a column of silica (silica gel, 0.5% methanol/CH_2Cl_2) to obtain 0.55 g (93%) compound 10 as an orange powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (dd, 8H, J = 8.2, 3.7 Hz), 7.02 (dd, 8H, J = 26.3, 8.5 Hz), 4.85 (d, 4H, J = 6.1 Hz), 4.59 (s, 4H), 3.772–3.575 (m, 24H), 1.56 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.64, 159.83, 147.50, 124.43, 124.39, 114.94, 114.82, 82.69, 70.68, 69.06, 65.78, 59.17, 28.05, 24.26, 19.81, 13.75. MS (ESI): *m/z* Calcd. for $C_{52}H_{66}N_6O_{14}$ $[M+H]^+$: 999.4637. Found: 999.4714.

Compound **2**: Under Ar gas protection, compound **3** (0.2 g, 0.2 mmol) was dissolved in 8 mL dry CH_2Cl_2. Then 2 mL trifluoroacetic acid was added, and stirred for 3 h at room temperature. After evaporation solvent, the compound **2** (0.17 g) was obtained. Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 8H), 7.06 (d, 8H, J = 7.3 Hz), 4.99 (s, 4H), 4.75 (s, 4H), 3.69–3.55 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.92, 160.31, 145.54, 124.06, 114.90, 82.69, 70.21, 68.42, 64.73, 41.02. MS (ESI): *m/z* Calcd. for $C_{44}H_{50}N_6O_{14}$ $[M+H]^+$: 887.3385. Found: 887.3385.

Hydraphile **1**: Under Ar gas protection, compound **2** (0.2 g, 0.23 mmol) was dissolved in 10 mL dry CH_2Cl_2. Then 0.5 mL 1-chloro-*N*,*N*,2-trimethylpropenylamine was added, and stirred for 3 h at room temperature. After evaporation solvent, the intermediate product (0.17 g) was added to next step directly. Under Ar gas protection, intermediate product (0.2 g, 0.57 mmol) and triethylamine were dissolved in 8 mL dry CH_2Cl_2. Then a solution of compound **7** in 8 mL dry CH_2Cl_2 was added dropwise to this reaction system, and stirred for 8 h at room temperature. After removing solvent, the product was chromatographed on a column of silica (silica gel, 2% methanol/CH_2Cl_2) to obtain 0.24 g (68%) compound as an orange powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, 8H, J = 8.1 Hz), 7.31 (s, 10H), 7.04 (d, 8H, J = 8.1 Hz), 4.85 (s, 8H), 3.78–3.59 (m, 76H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.02, 165.23, 147.50, 124.43, 114.94, 70.69, 70.52, 79.52, 67.40, 48.64, 47.38, 45.81, 8.63. MS (ESI): *m/z* Calcd. for $C_{82}H_{110}N_{10}O_{20}$ $[M+H]^+$: 1555.7898. Found: 1555.7994.

3. Results and discussion

3.1. Synthesis of hydraphile *1*

Gokel and co-workers designed a series of tri(macrocyle) hydraphiles with different spacer lengths, in which the hydraphiles exhibited incompetent or poor ion transport when the covalent connectors was less than 8 carbon atoms or more than 16 carbon atoms in dioleoylphosphatidylcholine (DOPC) bilayer membranes [12h]. The optimal spacer length for hydraphiles in such membranes is 12–16 methylenes. Based on their research, we hoped that replacement of the methylene linker in the tri(macrocyle) hydraphile with an azobenzene motif would give a structurally-regulated photosensitive hydraphile channel. As shown in Scheme 1, a bromoacetic acid substituted dihydroxyazobenzene was selected as the connector due to its similar length to that of 14 carbon chain. It is expected that hydraphile **1** in its *trans* form would form efficient channel for ion transport, while

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the photoisomerization of the hydraphile (in its *cis* form) would decrease the transmembrane activity due to the reduced molecular length equal to that of 10–11 carbon chain. The reversible photoisomerization, therefore, induced light-regulated ion transport across lipid bilayers. Hydraphile **1** was synthesized in several simple procedures with high yields (as shown in Scheme 2). All the compounds were well characterized and confirmed by ^{1}H NMR, ^{13}C NMR and mass spectra.

3.2. Channel transport assay by HPTS vesicle analysis

A 8-hydroxy-1,3,6-pyrenetrisulfonate (HPTS) labeled LUV (150 nm diameter, 10% cholesterol in egg yolk phosphatidylcholine (EYPC)) fluorescence assay was carried out to explore the transport activity of hydraphile **1**. In this assay, the ion transport through the membranes was accessed by the change in ratio fluorescence intensity at 510 nm (I_{450}/I_{405}) of the pH-sensitive HPTS dye entrapped inside the vesicles. A pH gradient across the vesicle membrane was introduced by addition of base (potassium hydroxide). If the channel mediates ion transport, potassium ions should flow inside the vesicles, along with OH^- (symport) or H^+ (antiport) to maintain charge balance. The resultant increase in pH would cause a deprotonation of the HPTS dye in the vesicles. For each set of experiments, although the vesicle concentration is not known precisely, it is constant throughout the experiments. The concentration-dependent assays were not stopped until the value of transmembrane activity (*Y*, ratiometric fluorescence intensity of HPTS at 350 s) achieved the maximum. Firstly, the solvent effect on the transmembrane activity was detected, in which DMSO was used as the blank and showed ignorable activity (~0.07), suggesting the successful preparation of vesicles for further assay. As shown in Fig. 1, addition of hydraphile **1** caused a rapid increase and followed by a slow and almost linear increase in the normalized ratiometric fluorescence of HPTS, suggesting the successful transport of K^+ cations and the rapid partition of the channel in lipid bilayers [13]. A variation in the concentration of hydraphile **1** induced a corresponding change in the transmembrane activity, displaying efficient transmembrane activity with $Y_{max} \sim 0.7$ at 40 μmol/L of hydraphile **1** (final concentration). The addition with higher concentration failed to achieve higher transmembrane activity due to the precipitation from the solution. When the transmembrane activity observed at 350 s were plotted as function of concentration, it exhibited a linear relationship at initial and a flattened tendency for the higher concentrations, which was indicative of the single-molecular channel transport. All these suggested that hydraphile **1** formed efficient transmembrane channel in lipid bilayers and provided the possibility for the further regulation of ion transport upon light irradiation.

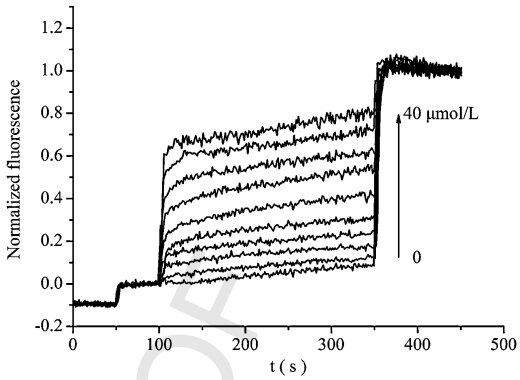

Fig. 1. HPTS assays of hydraphile **1** for K^+ transport with increasing final concentrations from 0 to 40 μmol/L, the presented curves were assigned to DMSO (blank), 0.037, 0.075, 0.15, 0.6, 2.5, 5.0, 10.0, 20.0, and 40.0 μmol/L, respectively.

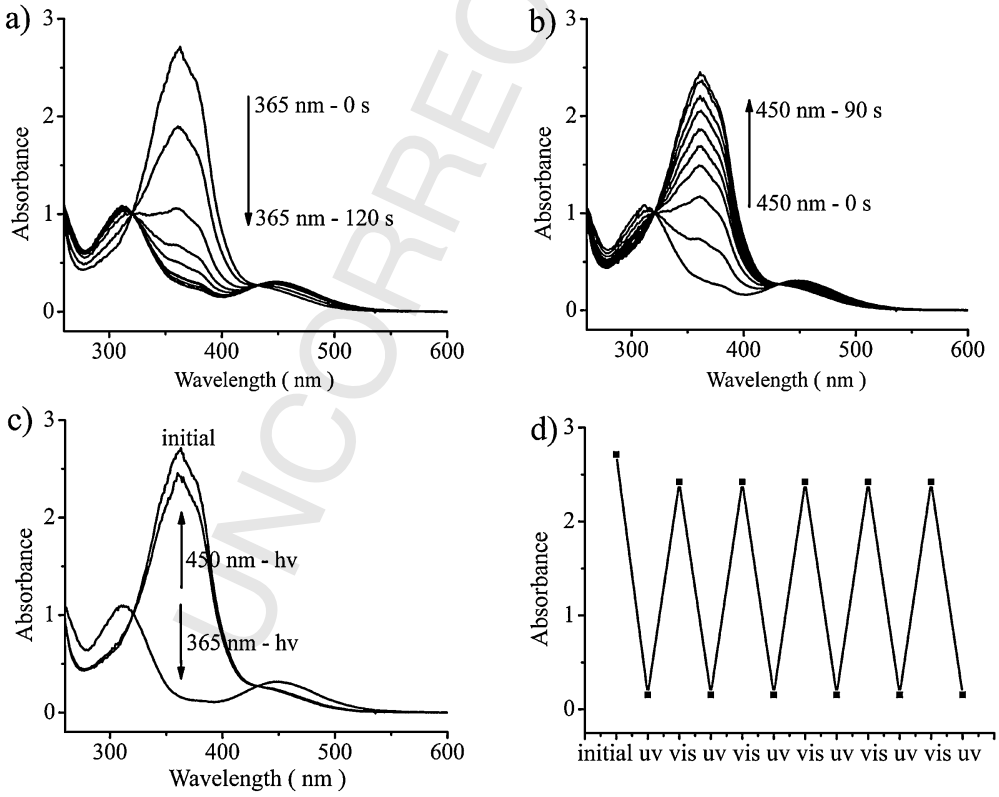

Fig. 2. Evolution of the UV-vis absorption spectra of hydraphile **1** solution (0.2 mmol/L in DMSO) as a function of irradiation time. (a) Upon the irradiation of 365 nm UV light (5 mW/cm^2), *t* (s) = 0, 5, 10, 15, 20, 25, 30, 35; (b) Upon the irradiation of 450 nm light (5 mW/cm^2), *t* (s) = 0, 3, 6, 9, 12, 18, 22, 30, 40, 60; (c) Switching cycles under alternating irradiation with 365 nm UV light and 450 nm visible light (2 min each). And (d) the absorbance at 360 nm from (c) procedure.

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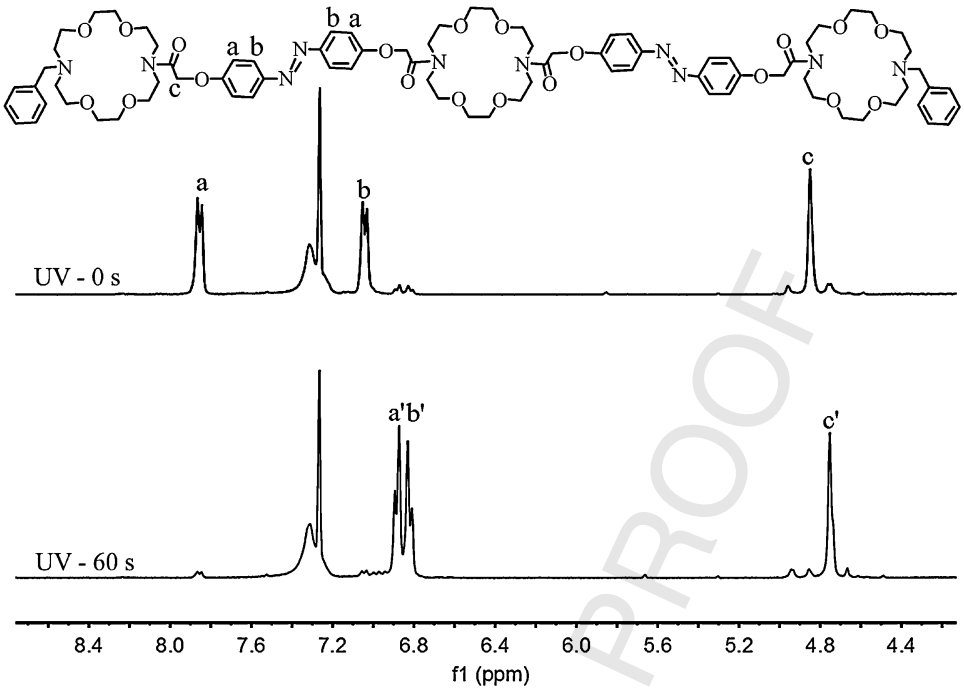

Fig. 3. The NMR spectra for hydraphile **1** solution (8 mmol/L in $CDCl_3$) before irradiation and after 60 s exposure to UV light (365 nm, 10 mW/cm^2).

3.3. Photo-regulated ion transport

Before investigating the light-regulated action for the ion transport by the isomerization of azobenzene group, the fact that *trans*-azobenzene was indeed reversibly isomerized to the *cis*-isomer was confirmed firstly by UV–vis spectroscopic studies in the solution state. As shown in Fig. 2a, upon 365 nm UV irradiation and with an increase in irradiation time, the absorption band at 360 nm decreased, which was accompanied by the appearance of a band at 450 nm, indicating the photo-isomerization of hydraphile **1** from its *trans* form to *cis* form. The generation of isosbestic points at 320 nm and 430 nm indicated the clean photoisomerization reaction for hydraphile **1** upon irradiation. Conversely, the irradiation with 450 nm visible light induced the recovery of the *trans*-isomer and the *trans–cis* cycle was reversible under alternating irradiation with 365 nm UV light and 450 nm visible light (as shown in Fig. 2b and d). The conversion ratio of *trans*- to *cis*-isomers could be determined by the corresponding proton NMR studies as illustrated in Fig. 3. Selective irradiation at 365 nm increased the amount of *cis*-isomer and a final ration of 10:90 (*trans*:*cis*) was observed by NMR. All these indicated the reversible photo-regulation on the molecular structure.

The photo-regulated ion transport of the molecules in BLMs was also investigated by HPTS assays. A 365 nm and a 450 nm LED lamps with an intensity of 30 mW/cm^2 were used to irradiate the DMSO stock solutions containing hydraphile **1**. In this experiment, to ensure the obtained ion transport was induced from *trans*- or *cis*-isomer, the DMSO solution of hydraphile **1** was irradiated with corresponding light for minutes prior to addition to the vesicle suspension in the assay. To optimize the photo-regulation of transmembrane activity, 5 μmol/L hydraphile **1** (final concentration) was applied. As illustrated in Fig. 4a, the transmembrane activity of hydraphile **1** was around 0.45 before any irradiation. It was noticed that 10% *cis*-isomer was already present in the fresh prepared compound, irradiation with 450 nm light was firstly performed in order to detect the transmembrane activity of *trans*-isomer. As expected, the transmembrane activity was increased to 0.5 after 10 min pre-irradiation with 450 nm light. Then the DMSO stock solution was irradiated with 365 nm light for 10 min, and the transmembrane activity decreased to 0.35. It indicated that

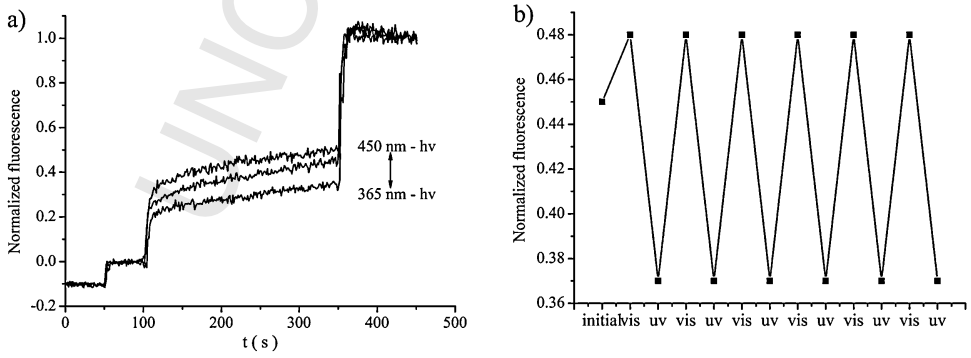

Fig. 4. (a) Observed change in transmembrane activity of HPTS assay of hydraphile **1** (5.0 μmol/L, final concentration) upon the irradiation of light-365 nm UV light or 450 nm visible light, the middle one is the original activity without any irradiations; (b) cycles of transmembrane activity under alternating irradiation with 365 nm UV light and 450 nm visible light (5 min each). Irradiation condition: 365 nm UV light and 450 nm visible light, intensity: 10 mW/cm^2.

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trans-isomer of hydraphile **1** provided higher transmembrane activity than that of *cis*-isomer. Meanwhile, the transmembrane activity showed reversible regulation upon alternative irradiation of 365 nm UV light and 450 nm visible light (as shown in Fig. 4b). All these verified the intention for the initial design of light-regulated ion channel by reversible regulation of the transmembrane length of molecule. Although the obtained regulation between *trans* and *cis*-isomers was relative small (transmembrane activity decreased 0.15 from *trans* to *cis*), it was assured that excellent light-regulated ion channel could be constructed by further molecular optimization in future.

4. Conclusion

In summary, we have demonstrated a new type of light-regulated synthetic ion channel based on azobenzene substituted tri (macrocycle) hydraphile **1**. HPTS vesicle assay confirmed the efficient transport of hydraphile **1** for ion across the lipid bilayers. Photoisomerization of the azobenzene using 365 nm UV light and 450 nm visible light resulted in the attenuation of channel transmembrane activity. Work is ongoing to create and development of these robust synthetic gated ion channels, which would exhibit great potential in various nanotechnology and biomechanical applications.

Acknowledgments

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References

[1] (a) C. Brieke, F. Rohrbach, A. Gottschalk, G. Mayer, A. Heckel, Light-controlled tools, Angew. Chem. Int. Ed. 51 (2012) 8446–8476;
(b) A.A. Beharry, G.A. Woolley, Azobenzene photoswitches for biomolecules, Chem. Soc. Rev. 40 (2011) 4422–4437;
(c) D. Habault, H. Zhang, Y. Zhao, Light-triggered self-healing and shape-memory polymers, Chem. Soc. Rev. 42 (2013) 7244–7256.
[2] (a) W. Szymański, J.M. Beierle, H.A.V. Kistemaker, W.A. Velema, B.L. Feringa, Reversible photocontrol of biological systems by the incorporation of molecular photoswitches, Chem. Rev. 113 (2013) 6114–6178;
(b) R. Givens, M.B. Kotala, J.I. Lee, Dynamic Studies in Biology, Wiley-VCH Verlag GmbH & Co. KGaA, 2005, pp. 95–129;
(c) P. Gorostiza, E. Isacoff, Optical switches and triggers for the manipulation of ion channels and pores, Mol. BioSyst. 3 (2007) 686–704.
[3] G. Nagel, D. Ollig, M. Fuhrmann, et al., Conversion of channelrhodopsin into a light-gated chloride channel, Science 296 (2002) 2395–2398.
[4] (a) R.J. Thompson, M.F. Jackson, M.E. Olah, et al., Activation of pannexin-1 hemichannels augments aberrant bursting in the hippocampus, Science 322 (2008) 1555–1559;
(b) S. Sundelacruz, M. Levin, D.L. Kaplan, Role of membrane potential in the regulation of cell proliferation and differentiation, Stem Cell Rev. Rep. 5 (2009) 231–246.
[5] (a) M.R. Banghart, M. Volgraf, D. Trauner, Engineering light-gated ion channels, Biochemistry 45 (2006) 15129–15141;
(b) T. Fehrentz, M. Schönberger, D. Trauner, Optochemische genetik, Angew. Chem. Int. Ed. 50 (2011) 12156–12182;
(c) M.R. Banghart, A. Mourot, D.L. Fortin, et al., Photochromic blockers of voltage-gated potassium channels, Angew. Chem. Int. Ed. 48 (2009) 9097–9101;
(d) M. Volgraf, P. Gorostiza, R. Numano, et al., Allosteric control of an ionotropic glutamate receptor with an optical switch, Nat. Chem. Biol. 2 (2006) 47–52.
[6] (a) A. Koçer, M. Walko, W. Meijberg, B.L. Feringa, A light-actuated nanovalve derived from a channel protein, Science 309 (2005) 755–758;
(b) W. SzymaŃski, D. Yilmaz, A. Koçer, B.L. Feringa, Bright ion channels and lipid bilayers, Acc. Chem. Res. 46 (2013) 2910–2923;
(c) C. Bao, H. Jia, T. Liu, Y. Wang, W. Peng, L. Zhu, Synthesis of artificial ion channels in bilayer membrane, Prog. Chem. 24 (2012) 1337–1345.
[7] (a) P.V. Jog, M.S. Gin, A light-gated synthetic ion channel, Org. Lett. 10 (2008) 3693–3696;
(b) P. Osman, S. Martin, D. Milojevic, C. Tansey, F. Separovic, Optical modulation of the insertion of gramicidin into bilayer lipid membranes, Langmuir 14 (1998) 4238–4242.
[8] (a) V. Borisenko, D.C. Burns, Z. Zhang, G.A. Woolley, Optical switching of ion-dipole interactions in a gramicidin channel analogue, J. Am. Chem. Soc. 122 (2000) 6364–6370;
(b) L. Lien, D.C.J. Jaikaran, Z. Zhang, G.A. Woolley, Photomodulated blocking of gramicidin ion channels, J. Am. Chem. Soc. 118 (1996) 12222–12223.
[9] L. Husaru, R. Schulze, G. Steiner, et al., Potential analytical applications of gated artificial ion channels, Anal. Bioanal. Chem. 382 (2005) 1882–1888.
[10] (a) A.A. Beharry, G.A. Wolley, Azobenzene photoswitches for biomolecules, Chem. Soc. Rev. 40 (2011) 4422–4437;
(b) D.G. Flint, J.R. Kumita, O.S. Smart, G.A. Woolley, Using an azobenzene cross-linker to either increase or decrease peptide helix content upon trans-to-cis photoisomerization, Chem. Biol. 9 (2002) 391–397;
(c) M.L. Rahman, G. Hegde, S.M. Sarkar, M.M. Yusoff, Synthesis and photoswitching properties of azobenzene liquid crystals with a pentafluorobenzene terminal, Chin. Chem. Lett. 25 (2014) 1611–1614.
[11] (a) T. Liu, C. Bao, H. Wang, et al., Light-controlled ion channels formed by amphiphilic small molecules regulate ion conduction via cis–trans photoisomerization, Chem. Commun. 49 (2013) 10311–10313;
(b) T. Liu, C. Bao, H. Wang, et al., Self-assembly of crown ether-based amphiphiles for constructing synthetic ion channels: the relationship between structure and transport activity, New J. Chem. 38 (2014) 3507–3513;
(c) C.L. Murray, G.W. Gokel, Spacer chain length dependence in hydraphile channels: implications for channel position within phospholipid bilayers, J. Supramol. Chem. 1 (2001) 23–30.
[12] (a) G.W. Gokel, S. Negin, Synthetic ion channels: from pores to biological applications, Acc. Chem. Res. 46 (2013) 2824–2833;
(b) A. Nakano, Q. Xie, J.V. Mallen, L. Echegoyen, G.W. Gokel, Synthesis of a membrane-insertable, sodium cation conducting channel: kinetic analysis by dynamic 23Na NMR, J. Am. Chem. Soc. 112 (1990) 1287–1289;
(c) G.W. Gokel, Hydraphiles: design, synthesis and analysis of a family of synthetic, cation-conducting channels, Chem. Commun. 1 (2000) 1–9;
(d) C.L. Murray, H. Shabany, G.W. Gokel, The central 'relay' unit in hydraphile channels as a model for the water- and-ion 'capsule' of channel proteins, Chem. Commun. 23 (2000) 2371–2372;
(e) M.E. Weber, P.H. Schlesinger, G.W. Gokel, Dynamic assessment of bilayer thickness by varying phospholipid and hydraphile synthetic channel chain lengths, J. Am. Chem. Soc. 127 (2005) 636–642;
(f) O. Murillo, I. Suzuki, E. Abel, et al., Synthetic transmembrane channels: functional characterization using solubility calculations, transport studies, and substituent effects, J. Am. Chem. Soc. 119 (1997) 5540–5549;
(g) W.M. Leevy, G.M. Donato, R. Ferdani, et al., Synthetic hydraphile channels of appropriate length kill *Escherichia coli*, J. Am. Chem. Soc. 124 (2002) 9022–9023;
(h) B.A. Smith, M.M. Daschbach, S.T. Gammon, et al., In vivo cell death mediated by synthetic ion channels, Chem. Commun. 47 (2011) 7977–7979.
[13] C.P. Wilson, C. Boglio, L. Ma, S.L. Cockroft, S.J. Webb, Palladium(II)-mediated assembly of biotinylated ion channels, Chem. Eur. J. 17 (2011) 3465–3473.

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