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Self-assembly of Crown Ether-based Amphiphiles for Constructing Synthetic Ion Channels: The Relationship between Structure and Transport Activity

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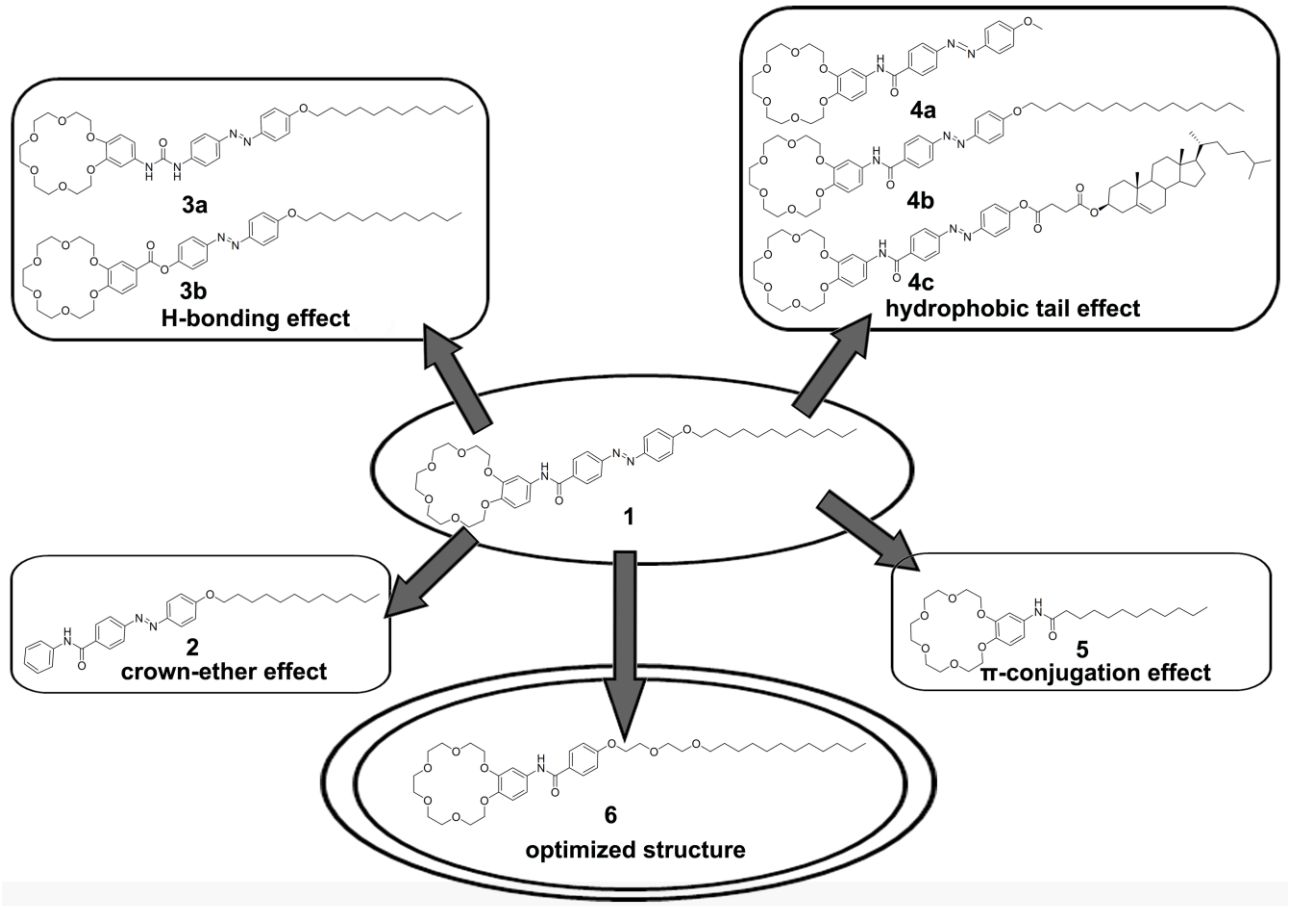
Synthetic ion channels arise great interest due to their ability to mimic the biological functions of nature ion channels. Although a number of synthetic ion channels have been reported and displayed the biomedical applications, the design criteria for efficient synthetic ion channels remain essentially obscure. According to the structure framework of our previously prepared synthetic ion channel (compound **1**), in this study, a series of amphiphilic small molecules (compounds **2, 3a-3b, 4a-4c and 5**) with structural simplicity were designed to explore the relationship between the molecular structure and the transport activity in this system. By adjusting the substituted functional moieties in the four building blocks, it concluded that appropriate supramolecular interactions and reasonable water solubility favored improving the transport activitiy of the channels. Finally, compound **6** with optimized structure was prepared using favorable crown ether, amide, diethylene glycol-substituted benzene, and dodecyl hydrophobic moieties as building blocks. It exhibited efficient channel transport with significantly improved transport activity, in which the value of EC_{50} decreased 3 times than that of compound **1**. These results provide some useful experience for developing excellent synthetic ion channels based on artful regulation on the structures of facially synthetic small molecules.

Introduction

Biological ion channel is a kind of protein micropore in the cell membrane, it plays an important role to communicate chemically and electrically with the extracellular environment.[1-2] The ability to simulate the ionic transport process of ion channels would enhance better understanding of how ion channels work and provide tools for many applications in life science and materials science.[3-6] So far, numerous artificial ion channels have been constructed on the basis of the modification of natural occurring motifs from protein[7-11] and peptides.[12-14]

Recently, scientists were focusing on the development of totally synthetic molecules to construct ion channels,[15-19] the diverse structures allowed exploring the mechanism of complex channel proteins and furnish lipid and cellular membranes with artificial functions. The structures of synthetic channels can be classified into two types, namely, unimolecular and self-assembled channels. Among them, most were constructed on the supramolecular architectures, where controlled assembly of such preorganized molecules induced the formation of synthetic ion channels.[20-24] Comparing with those constructed by a unimolecular macromolecule,[25-28] the utilization of supramolecular self-assembly offers simple synthesis, easy functionalization, and structural tunability to guide the formation of ion channel. Important achievements have been obtained on the derivatives of urea/amide macrocyles,[29-31] oligophenyl barrel-stave structures,[32-33] and oligoester bola-amphiphiles,[34-35] as well as others.

Although structurally diverse molecules have been reported to construct synthetic ion channels by supramolecular self-assembly, the knowledge of the elusive active structures is still inexperienced. Matile *et al* have concluded some design rule of the self-assembled ion channels,[36-37] which is quite different from those routine supramolecular self-assembled systems. They are mainly classified into two types, including Class I with an endergonic process from unstable supramolecules and Class II with an exergonic process from stable supramolecules. And the unstable ion channels are often preferable over stable ones to avoid precipitation of the hydrophobic prechannels from the media. Up to now, several groups have studied the structure-activity relationships in their unique channel systems including the effect of molecular length, polar, cyclic diameter, and so on.[12, 26, 32] All these suggested the important role of molecular structure on channel activity and provided some significant guidance for the design of efficient ion channels, although general rules are still hard to be drawn.



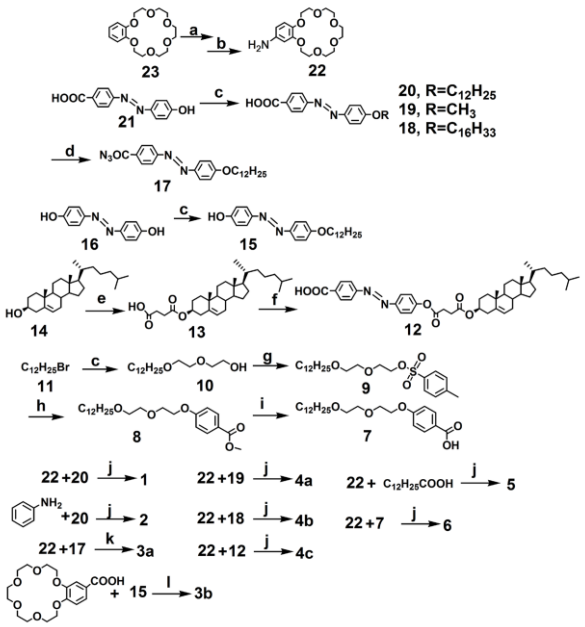
Scheme 1. Structures of amphiphilic small molecules **1-6** for self-assembled synthetic ion channels.

Recently, we have reported an self-assembled synthetic ion channel based on the structurally simple amphiphilic small molecule **1** (as shown in Scheme 1),[38] in which the self-assembled crown ether channel induced successful K^+ ion transport across the BLMs. It showed relative poor transport activity (Class II channel) without UV light irradiation, however, the photoisomerization of azobenzene (Class I channel) significantly improved its transport activity. The improvement on transport activity by molecular isomerization indicated the key role of molecular structures, which inspired us to create efficient synthetic ion channels by molecular optimization rather other constructing new system with unknown challenge. Therefore, based on the simple molecular framework of compound **1**, a series of modular modifications (Scheme 1, compounds **2-5**) was carried out to explore the relationship between the molecular structure and ion transport activity in this self-assembled ion channel system, and finally to guide the optimization of molecular structure (Scheme 1, compound **6**) for efficient channel ion transport.

Results

Molecular design and synthesis

In compound **1**, the molecular framework concludes four functional building blocks: a benzocrown ether macrocycle, an amide group, a conjugated azobenzene aromatic group, and an alkyl chain for hydrophobic tail. These building blocks are commonly used and classic functional groups for designing amphiphilic supramolecular systems,[24, 38-40] where the crown ether macrocycle and alkyl chain moieties endowed amphiphilic character, the amide group provided complemented H-bonding interaction, and the azobenzene moiety could offer suitable π-interaction in *trans*-state as well as its light-regulation between *trans*- and *cis*-isomers. The light-regulation of azobenzene on transport activity had been studied in our previous paper,[38] therefore, we contemplated the π-conjugation control of azobenzene in this paper. After self-assembly, the up-down stacked crown ether groups formed channel for ion transmembrane transport since crown ethers are typical functional group for cation transport ether by carrier or channel mechanism.[24, 26, 41-44] To explore the structure effect on transport activity, modification works were carried out according to the four functional building blocks of compound **1**, respectively. For example, compound **2**, with benzene insteading of 18-benzocrown-6 functional moiety, was designed to explore the contribution of crown ether on transmembrane transport; compounds **3a**-**3b**, with urea or ester



Scheme 2. Synthesis procedure for amphiphilic compounds **1-6**. Reagents and conditions: (a) 70% HNO_3, HOAC/$CHCl_3$, rt, 24h. (b) 80% $N_2H_4{\cdot}H_2O$, 10% Pd/C, 1, 4-dioxane, reflux, 3h. (c) $BrC_{12}H_{25}$, $BrC_{16}H_{33}$, or $CH_3I/K_2CO_3/KI/DMF$, reflux, 48 h. (d) $SOCl_2$ reflux, then TEA/CH_2Cl_2, NaN_3, 0-5°C for 0.5 h and rt overnight. (e) succinic anhydride, n-heptane, reflux, 21h. (f) 1-Chloro-N,N,2-trimethylpropenylamine, CH_2Cl_2, 4h, rt: then 21, TEA/CH_2Cl_2, 0-5°C for 0.5 h and rt overnight. (g) 4-Methylbenzenesulfonic acid, CH_2Cl_2, 0-5°C for 0.5 h and rt, 8h. (h) Methyl 4-hydroxybenzoate, Cesium carbonate, DMF, 110°C, 12h. (i) methanol/THF (1/1), NaOH, 50°C, 5h. (j) 1-chloro-N,N, 2-trimethylpropenylamine, rt, 3h, then DIEA/CH_2Cl_2, 0-5 °C for 0.5 h and rt overnight. (k) toluene, reflux, 5h. (l)DMAP, EDC, CH_2Cl_2, rt, 2h.

moieties insteading of amide functional moiety, were selected to study and compare the H-bonding effect on the channel activity; compounds **4a-c** with methyl (**4a**), hexadecyl (**4b**) and cholesterol (**4c**) substitutions were respectively programmed to inspect the effect of hydrophobic tails; and compound **5** without azobenzene was synthesized to discuss the action of π-conjugation interaction. After exploring the relationship between the molecular structure and channel activity among these molecules, an optimized molecule (compound **6**) was finally deduced to realize the efficient ion transport.

All the compounds were obtained in several steps with high yields from commercial starting materials following typical and general reactions, including nitration, nitro reduction, diazotization, etherification, amidation, esterification reactions, and so on (as shown in Scheme 2). The ^1H, ^{13}C NMR, and MS spectra were in agreement with the proposed formula.

Ion channel transport

Two main methods were carried out to characterize the ion transport of the synthetic ion channels,[36, 37] consisting of the conductance experiments in planar membrane by a patch-clamp technique and the fluorescence assay on a labeled large unilamellar vesicles (LUV). The patch-clamp experiments reveal the electrophysiological signals and provide the diagnostic information for ion channel transport of compounds. As shown in Figure 1A, it exhibited single-channel current

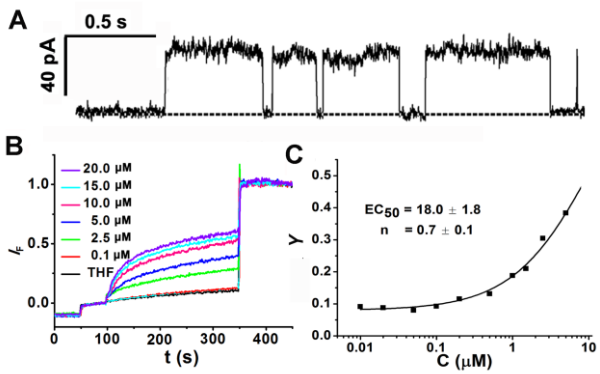


Figure 1. (A) Planar bilayer voltage clamp experiment: the ion current traces of compound **1** with concentration of 0.8 μM at the applied voltage of 50 mV. (B) Changes in ratiometric fluorescence intensity I_F of HPTS assay during addition of compound **1** (final concentration, 0-20 μM) for K^+ transporting using 10 mM HEPES, 100 mM KCl, pH=7.0 as external buffer. (C) The representative Hill plot of transmembrane activity after THF backgroup correction.

openings with a relatively long duration when the concentration of compound **1** lowered to 0.8 μM, and the signals scaled linearly in current-voltage relationships (Figure S1). Single-channel conductance experiments revealed the channel-transport mechanism in partial planar lipid membranes. However, it couldn't provide more information such as supra-structures and transport activity of channels. Especially, the later one is the key characteristic for ion transports in relevant applications because the total amount of ion transported is relative to the multichannels on the whole cell membrane rather than a single channel. Thus, a 8-hydroxy-1,3,6-pyrenetrisulfonate (HPTS) labelled LUV fluorescence assay was carried out to explore the transport activity of the channels. The concentration-dependent assays were not stopped until the value of transmembrane activity (Y, ratiometric fluorescence intensity of HPTS) achieved the maximum. Here the value of Y only represents the transport ability at a certain concentration, and itself couldn't be used for comparison of transport activity. If the obtained Y_{max} is bigger than 50%, EC_{50} (the concentration of transport required to achieve 50% activity) and Hill coefficient n value fitting from the dose response curves are further used to quantify the transport activity under the same manipulation condition. Generally, n > 1 indicated the unstable Class I channel, and n < 1 indicated the stable Class II channel.[36] As shown in Figure 1B, addition of compound **1** caused a faster increase in the normalized ratiometric fluorescence of HPTS, suggesting the successful transport of K^+ cations. Figure 1C showed the Hill plot of the transmembrane activity of compound **1**, which quantified the transport activity of EC_{50} at 18.0 ± 1.8 μM and Hill coefficient n at 0.7 ± 0.1. Based on the value of Y_{max} (Y_{max} ≈ 0.5 at 20 μM after THF backgroup correction) and n (n < 1), it indicated the class II channel of compound **1** that exhibited poor transport activity.

Structure effect on transport activity.

To improve the transmembrane activity of these amphiphilic small molecules, the structure effect on transport activity was

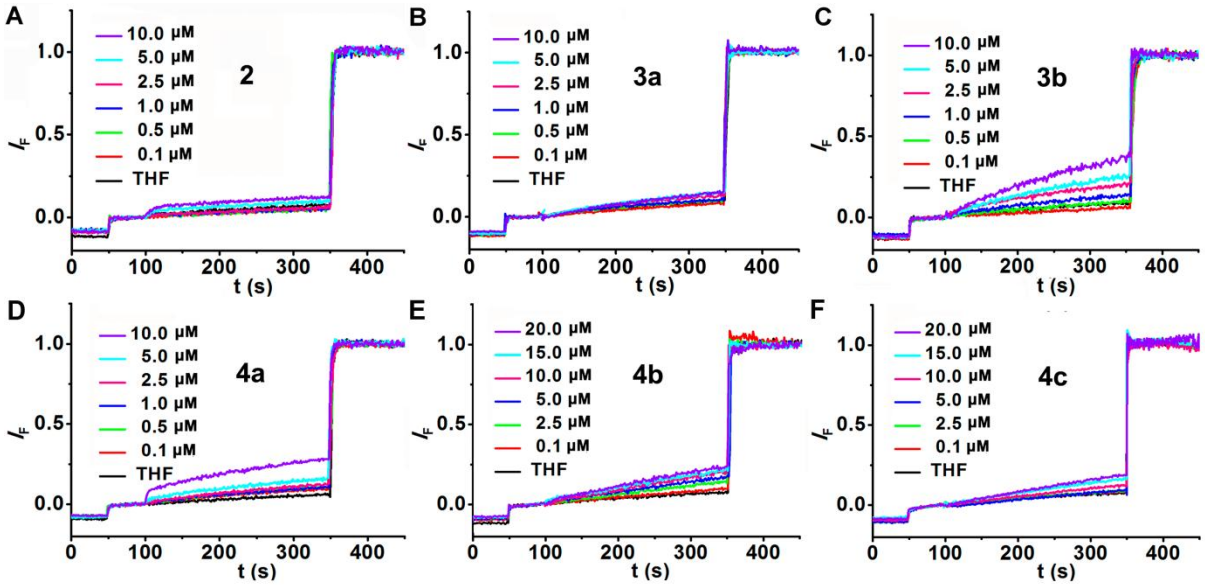


Figure 2. Changes in ratiometric fluorescence intensity I_F of HPTS assay during addition of (A) compound **2**, (B) **3a**, (C) **3b**, (D) **4a**, (E) **4b** and (F) **4c** for K^+ transporting under same condition as that for compound **1**.

explored, in which compounds **2-5** with changed building blocks were analyzed by HPTS LUV fluorescence assay. Firstly, the role of crown ether moiety on the transport activity was explored. As shown in Figure 2A, no obvious enhancement of transmembrane activity for compound **2** as increasing concentrations suggested that the moiety of benzocrown ether provided the transport-structure fraction as expected. Figure 2B and 2C exhibited the changes of HPTS fluorescence during addition of compounds **3a** and **3b**, and unexpectedly, both of them presented poor transmembrane activity. Compared with compound **1**, the introduction of urea moiety of compound **3a** decreased its transmembrane activity significantly, and the transmembrane activity achieved maximum at 10 μM with Y_{max} < 0.1. Meanwhile, the absent of H-bonding interaction in compound **3b** also induced poorer transport activity with $Y_{max} \approx$ 0.3 at 10 μM. It suggested that suitable H-bonding interaction in the structure framework was favorable for improving the transport activity.

Then, the transport activity of compounds **4a-c** with different hydrophobic tails were observed. As shown in Figure 2D-F, both of the short methyl tail (**4a**) and long hexadecyl tail (**4b**) displayed poorer transmembrane activity than compound **1** with Y_{max} < 0.25 at 10 μM and 20 μM, respectively, and the addition with higher concentration failed to achieve higher transmembrane activity due to the precipitation from the solution. It suggested that the length of hydrophobic alkyl chain played important role on the transport activity, and suitable length of alkyl chain (like dodecyl chain) are favorable for ion transport. As for compound **4c**, a cholesterol moiety was introduced to replace the alkyl chain as the hydrophobic tail as well as provide strong Van der waals interaction for the molecular self-assembly. Comparing with compound **1**, the introduction of cholesterol moiety induced an even poorer transmembrane activity (Y_{max} < 0.2 at 20 μM Figure 2F). All these suggested that selection of hydrophobic tails had great effect on the transport activity.

Finally, the π-conjugation effect was explored by comparing transport activity between compound **5** and compound **1**. During the process, compound **5** was found having good solubility in both buffer solution and water, and no precipitation was appeared even the concentration was up to 80 μM. As illustrated in Figure 3A, the Y_{max} could achieve 1.0 when the concentration of compound **5** increased to 30 μM. The fitted Hill coefficient n was bigger than 1 (n = 2.7 ± 0.4, Figure 3B), suggesting the efficient Class I channel transport although the overall transport activity was just improved a little with decreased EC_{50} value from 18.0 μM of compound **1** to 14.6 μM of compound **5**. These indicated that the π-conjugation interaction was unnecessary, instead, the absent of azobenzene moiety somewhat improved the transport activity due to the enhanced solubility of molecules.

Discussion

All above indicated that molecular structure had great effect on the transport activity of channels in these amphiphilic small

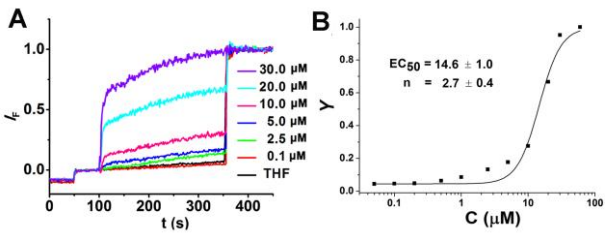
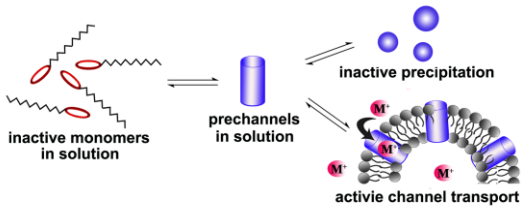


Figure 3. (A) Changes in ratiometric fluorescence intensity I_F of HPTS assay during addition of compound **5**. (B) The representative Hill plot of transmembrane activity after THF backgroup correction.



Scheme 3. The schematic presentation of the dynamic balance relationship of compounds in solution and membrane.

molecules, and the further study on the relationship between the molecular structure and transport activity could guide the design of excellent ion channels with efficient transmembrane activity. As illustrated in Scheme 3, it is a dynamic balance for the distribution of the compounds in solid, solution and membrane phase, where the inactive monomers would self-assembled into active aggregates as prechannels, and the formed prechannels would further participate the ion transport on the membrane or further aggregate to form precipitate from media.[36, 37] Therefore, how to increase the participation in membrane is the key role to improve transport activities.

For compound **1**, the poor transport activity should be attributed to the compete precipitation from media since the concentration higher than 20 μM would induce visible precipitate in buffer. It was also the main reason for compounds **3b**, **4a**, **4b** and **4c** that showed similar but reduced transport activity as that of compound **1**. It indicated that the solubility in media, namely, hydrophilicity played a key role on the transport activity. And the differential on transport activity meant the noticeable role for the self-assembled interactions. Especially for compound **4c**, the introduction of cholesterol greatly decreased its transport activity. This obvious decrease should be resulted from its strong self-assembled property. As listed in Table 1，comparing with compound **1**, compound **4c** could form stable gel in a series of polar or apolar organic solvents, and form fibrous aggregates in ethanol and micelle or rod-like aggregates in buffer (Figure 4). Thus, the strong self-assembled ability of compound **4c** induced "premature saturation" for increasing fibrilogenesis, thereby reducing the effective prechannel concentration in the membrane.[45]

Compound **3a** exhibited different reason for its poor transport activity due to the presence of urea moiety in the molecule. During the HPTS fluorescence assay, it was noticeable that compound **3a** showed good solubility in buffer

Table 1. The gelation ability test for compounds **1** and **4c.**

Solvents/ compounds	$CHCl_3$ hexane	CH_2Cl_2 EtOAC	toluene THF	benzene DMF	xylene acetone	MeOH dioxane	EtOH
1	S	S	S	S	S	S-P	S-P
	I	S-p	S	S	S-P	S	
4c	S	S	CG (4)	S	CG (3)	CG (1)	CG (1)
	I	OG (4)	S	S	OG (3)	S	

S: Solution P: precipitate I: insoluble CG: clear gel OG: opaque gel. The number in the parentheses is the critical gel concentration (mg/mL).

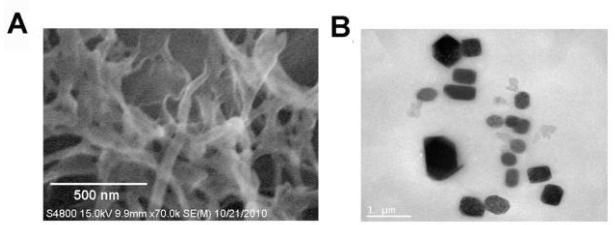


Figure 4. Direct micromorphology observation of the self-assembled compound **4c**: (A) SEM image of xerogel from ethanol; (B) TEM image from 10 mM HEPES buffer (pH=7.0, 100 mM KCl).

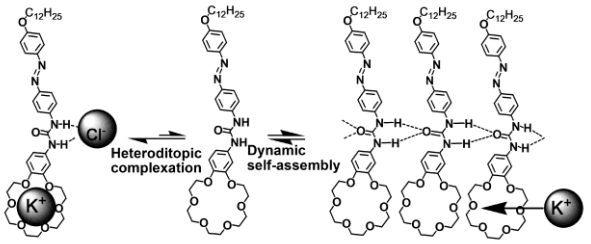


Figure 5. The dynamic equibalance of heteroditopic receptor **3a** in buffer solution and solid state.[24]

solution, and there was no any precipitation appeared even the concentration was up to 80 μM, which was contrary to the poor solubility in pure water. Considering urea moiety is a good anion receptor, the good solubility should be attributed to the formation of heteroditopic complexation between compound **3a** and salts. Then, the dynamic self-assembly of compound **3a** in solution and solid state could be illustrated as Figure 5,[24] it was also a competition relationship among the heteroditopic complexation, monomer and channel-like self-assembly. Although compound **3a** bypasseed the solubility problem in media, the preferable formation of the complexation determined its poor even negligible transport activity.

The improved transport activity of compound **5** further confirmed the important role of molecular hydrophilicity, in which the absent of azobenzene π-conjugation moiety in compound **5** greatly improved its hydrophilicity. However, as illustrated in Scheme 3, too good water solubility would improve the amount of inactive monomers which was also unfavourable for the formation of active channel, thereby limited the much improvement of transport activity of compound **5**. All these suggested that suitable hydrophilicity and supramolecular self-assembly interactions was the principal issue to improve the ion transport efficiently in these amphiphiles-based ion channels.

Based on relationship between molecular structure and transport activity, compound **6** with optimized structure was designed and synthesized (Scheme 1) in which the favorable crown ether, amide, and dodecyl hydrophobic moieties were kept for the self-assembled interactions and the azobenzene moiety was replaced by a diethylene glycol-substituted benzene to moderately adjust the hydrophilicity content. Figure 6A-B illustrated the HPTS assay of compound **6**, which showed the

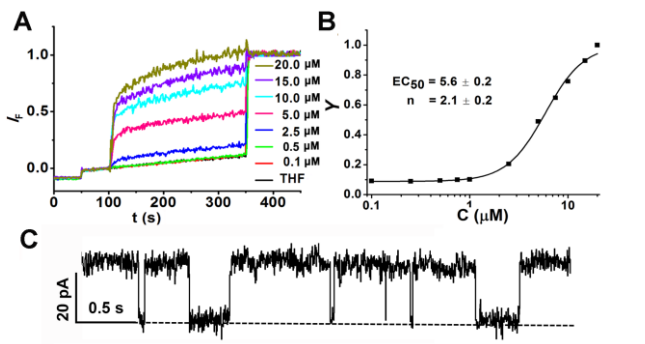


Figure 6. (A) Changes in ratiometric fluorescence intensity I_F of HPTS assay during addition of compound **6** (0-20 μM, final concentrations). (B) The representative Hill plot of transmembrane activity after THF backgroup correction. (C) The ion current traces of compound **6** at 2.5 μM at applied voltage of 50 mV.

activity with Y_{max} arrived 1.0 at 20 μM and EC_{50} at 5.6 ± 0.2 μM with Hill coefficient n > 1 (~2.1, Class I channel). The optimized compound **6** showed significantly improved transport activity as expected in which the value of EC_{50} decreased over 3 times than that of compound **1**. Moreover, the presence of signal channel current in patch-clamp experiments in Figure 6C (Figure S2) confirmed the channel transport. It exhibited the successful optimization for efficient synthetic ion channel by simple structure adjustment from poor Class II channel to preferable Class I channel.

Conclusions

In conclusion, this report synthesized a series of benzocrown ether based amphiphilic molecules (compounds **1**-**6**) to achieve efficient synthetic self-assembled ion channels by simply regulating the molecular structures. The ability of these compounds to transport cations was assessed in both liposome membrane and planar bilayers membrane. The comparison of transport activity between compounds **1**-**5** with alternate building blocks indicated the relationship between the molecular structure and transport activity in this amphiphiles system, in which the molecule requires to meet the following prerequisites: 1) it possesses a transport-structure fraction; 2) suitable supramolecular interactions to support the channel-like self-assembly; 3) reasonable hydrophilicity to inhibit the competed precipitation from media. Inspiring from above criteria, compound **6** with optimized structure was prepared and displayed significantly improved transport activities. The system we described here is believed to provide some guidance for constructing efficient ion channel based on the self-assembly of crown ether-based amphiphilic small molecules.

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Notes and references

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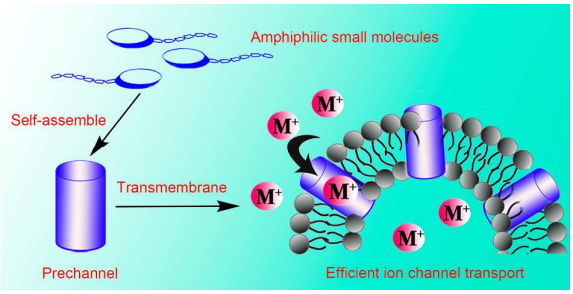
Table of contents:



Efficient ion transport was achieved from crown ether amphiphiles-based ion channel by simply regulating the molecular structures.