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Macrocyclic Transmembrane Anion Transporters via a One-Pot Condensation Reaction

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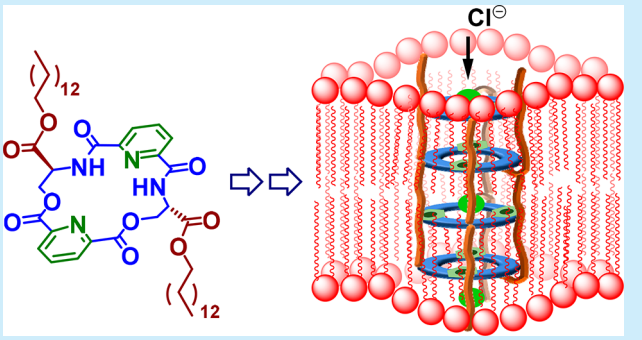
ABSTRACT: Synthetic chloride transporters are potential therapeutic agents for cystic fibrosis and cancer. Reported herein are macrocyclic transmembrane chloride transporters prepared by a one-pot condensation reaction. The most efficient macrocycle possesses a fine balance of hydrophobicity for membrane permeation and hydrophilicity for ion recognition. The macrocycle transports chloride ions by forming channels in the membrane. Hydrogen bonds and anion−π interactions assist chloride transport.



Natural ion channels carefully maintain the cellular concentrations of anions. Chloride ions play an important role in biological systems.[1] Faulty chloride channels are linked to diseases such as cystic fibrosis,[2−4] epilepsy,[5,6] and Bartter syndrome.[1,7−9] It is challenging to reconstitute natural chloride channels outside the cellular environment. Therefore, synthetic chloride transporters can be potential therapeutics or model systems to understand ion transport mechanisms.[10−15] Specifically, chloride channels have shown promise for treatment of cystic fibrosis and inducing apoptosis in cancer cells.[16−23]

Compounds with an affinity for anions via hydrogen bonding, anion−π interactions, or halogen bonding are attractive scaffolds for anion transport.[13,24−30] Cyclic scaffolds such as calixarenes,[31,32] calixpyrroles,[14,33,34] and peptides[35,36] are particularly interesting, as they possess a well-defined cavity for ion recognition. We have previously developed a C_3-symmetric triamide macrocycle appended with cholesterol units for chloride transport.[37] The one-pot synthetic route afforded macrocycles with identical R groups attached. Herein we report a C_2-symmetric chiral macrocycle scaffold that was readily synthesized by a one-pot condensation reaction between serine and pyridine derivatives. The macrocycle has an interesting cavity containing hydrogen-bond-donating NH groups and electron-deficient aromatic units for anion binding. The synthetic design enables the incorporation of two distinct R groups on the macrocycle periphery. The methodology was used to synthesize macrocycles **1**−**3** (Figure 1) with increasing numbers of long alkyl chains. The length of the alkyl chains was chosen such that they would span half of the lipid bilayer in their extended conformation. The hydrophobicity of the macrocycles increased in the order of **1**−**3**, with calculated log

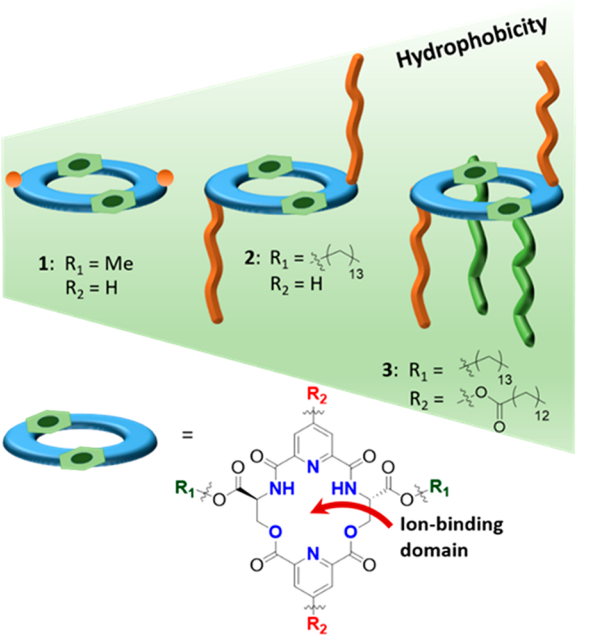


Figure 1. Macrocycles with varying hydrophobicity. The length of the alkyl chains is same for macrocycles **2** and **3**. R_1 and R_2 are depicted in different colors to differentiate their modes of attachment to the macrocycle.

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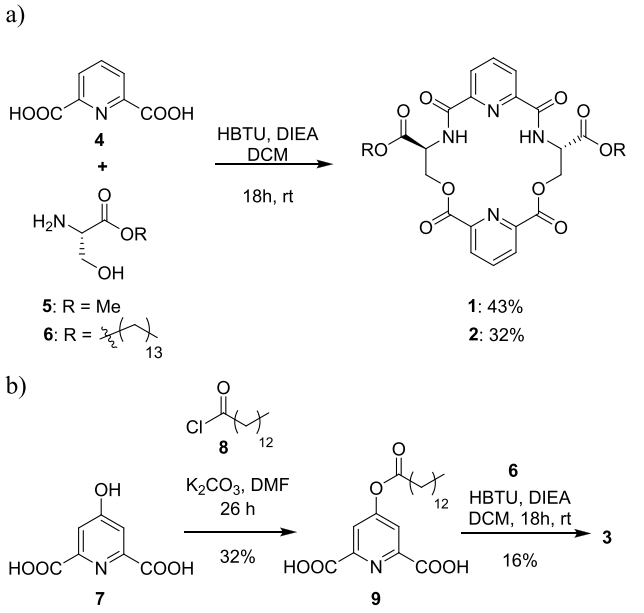
P values of 0.1, 11.7, and 22.1, respectively.[38] Macrocycle **2** with an optimal balance of hydrophobicity for membrane insertion and hydrophilicity for ion transport was the most efficient. The macrocycle was anion-selective because of the participation of amide NH groups in hydrogen bonding and the aromatic units in anion−π interactions. The macrocycle showed a preference for chloride ions.

Macrocycles **1**−**3** were synthesized by a one-pot condensation reaction between appropriately functionalized serine esters and dipicolinic acid derivatives (Scheme 1). Macrocycle

Scheme 1. Synthesis of Macrocycles



1 was synthesized in 43% yield by coupling of commercially available dipicolinic acid (**4**) and protected serine ester **5** in the presence of (2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*,*N*-diisopropylethylamine (DIEA) (Scheme 1a). In view of the higher nucleophilicity of the amine, the mechanism potentially involves the formation of the amide linkage to the pyridine unit followed by the ester linkage. In order to validate the structure of macrocycle **1**, it was also synthesized in a stepwise fashion (Scheme S1). Pyridyl dicarbonyl dichloride was coupled with 2 equiv of TBS-protected serine methyl ester. The adduct was deprotected and coupled with pyridyl dicarbonyl dichloride to give macrocycle **1**. Macrocycle **2** was synthesized in 32% yield by coupling of diacid **4** with functionalized serine ester **6**.[39] Macrocycle **3** was synthesized in 16% yield by coupling of ester **6** with diacid **9**, which was obtained by the reaction of acyl chloride **8** with 4-hydroxydipicolinic acid (**7**) (Scheme 1b).[39]

Vesicles made from egg yolk phosphatidyl choline (EYPC) and cholesterol (9:1) containing the pH-sensitive dye 8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt (HPTS) were used to study ion transport through macrocycles **1**−**3** (Figure 2a).[40,41] The macrocycles were allowed to equilibrate with the vesicles at pH 7.2, and NaOH was subsequently added to increase the external pH by 0.6 units. No significant increase in the concentration of deprotonated $HPTS^-$ was observed for any of the macrocycles, ruling out pathways that lead to an increase in the concentration of $HPTS^-$ (Figure 2a).

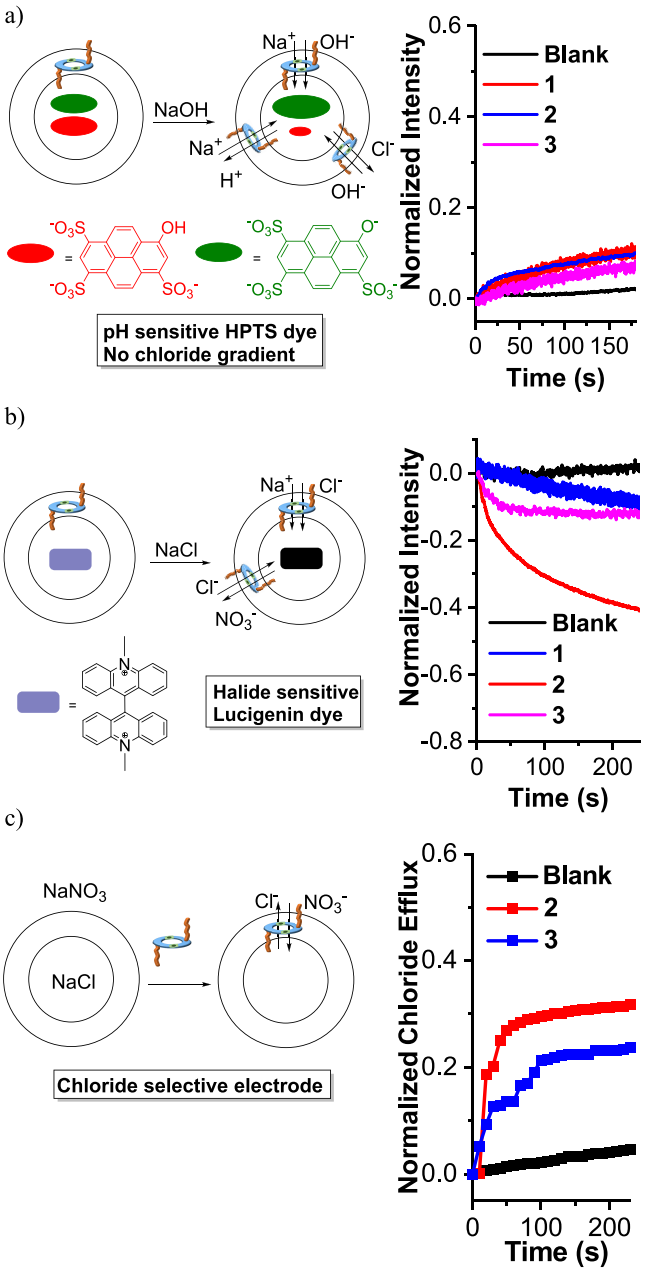


Figure 2. Studies to illustrate ion selectivity and compare the ion transport activities of macrocycles. (a) HPTS assay to assess ion transport activity. (b) Lucigenin assay for halide transport. (c) Chloride-selective electrode to assess chloride transport. The macrocycle concentration was 54.1 μM.

Varying the countercation of the base MOH (M = K^+, Li^+) did not lead to any increase in the ion transport activity (Figure S1). The studies indicated that the macrocycles did not transport cations. UV−vis spectroscopy in the presence of M^{2+}-sensitive arsenazo dye (M^{2+} = Ca^{2+}, Zn^{2+}, Cu^{2+}) also ruled out transport of divalent cations by the macrocycles (Figures S3 and S4).[42−44] Assays carried out using the halide-sensitive dye lucigenin showed that macrocycles **2** and **3** were chloride transporters (Figure 2b).[45] Macrocycle **1** without long alkyl chains did not show ion transport activity. The dialkylated macrocycle **2** was a better chloride transporter than tetraalkylated macrocycle **3**. This observation was corroborated using a chloride-selective electrode as the probe (Figure 2c).

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The ion transport mechanism was determined using the most efficient macrocycle, **2**. It was intriguing that although the macrocycle transported chloride ions, no internal pH increase was observed in the HPTS assay (Figure 2a). In contrast to the other assays in Figure 2, the HPTS assay did not have a chloride gradient. Hence, HPTS assays with varying internal and external buffer solutions were carried out to understand the role of anions in the transport process (Figures 3a and S5).

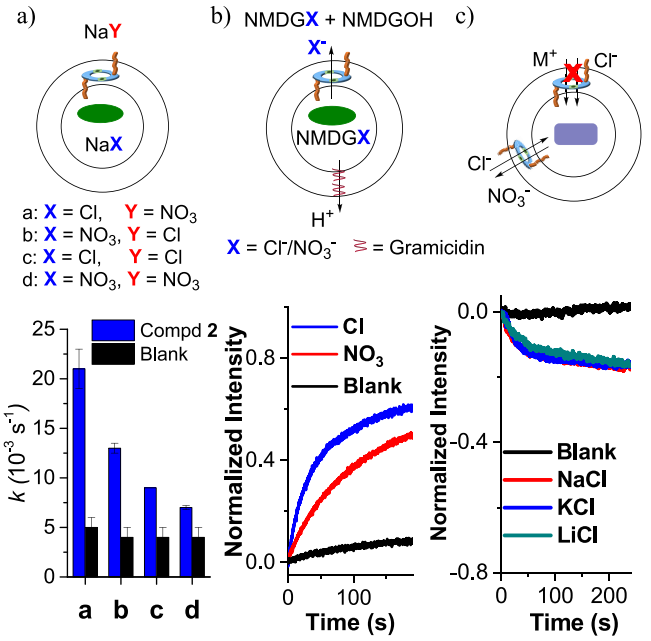


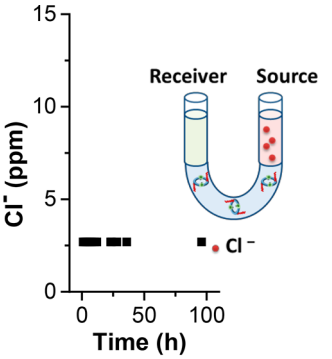
Figure 3. Assays to determine the mechanism of chloride transport (symport/antiport). (a) HPTS assays carried out with variation of the internal and external buffers to compare rates of Cl^- transport (54.1 μM macrocycle **2**). (b) Comparison of chloride and nitrate transport using the NMDG assay (54.1 μM macrocycle **2**). (c) Lucigenin assay to compare the effects of cations on chloride transport (21.64 μM macrocycle **2**).

The rate constants for ion transport were obtained by fitting the curves to a first-order exponential decay equation (eq S1). The maximum k values were observed when vesicles contained Cl^- inside and NO_3^- outside (a in Figure 3a). This suggests that chloride efflux is the driving force for influx of hydroxide ions, which increases the internal pH. The transport rate was lower when chloride was outside the vesicles and nitrate was inside (b in Figure 3a), suggesting that the macrocycle preferred to transport chloride over nitrate ions. The rates of ion transport were lowest in the HPTS assays without an anion gradient, (c and d in Figure 3a). To compare the rates of Cl^- and NO_3^- transport, the HPTS assay was carried out using a buffer containing *N*-methyl-D-glucamine (NMDG) chloride or nitrate (Figure 3b).[46] The pH gradient was introduced in the system by the addition of NMDGOH. The only cations present in the medium were the large membrane-impermeable NMDG ions and protons. Gramicidin A was introduced into the system to carry out H^+ efflux. In such a scenario, the macrocycle behaves as a uniporter carrying out Cl^- or NO_3^- transport exclusively. The rate of Cl^- transport was found to be higher than that of NO_3^- transport. This observation is also in line with rate constants observed for the HPTS assay (Figure 3a). To rule out the possibility of metal–halide cotransport, the lucigenin assay was carried out by varying the metal counterion. (Figure 3c). The ion transport rates were unaffected by the nature of the cation, further substantiating the fact that cations were not involved in the transport process.

Dose–response studies were carried out using the HPTS assay with a chloride gradient (Figure S6).[37] The plots were fitted to the Hill equation (eq S2) to obtain the EC_{50} value, i.e., the concentration of macrocycle required for half the maximum activity (Figure 4a). The EC_{50} value for macrocycle

a)

Macrocycle	EC_{50} (μM)	n
2	29.2	1.6
3	69.4	1.4



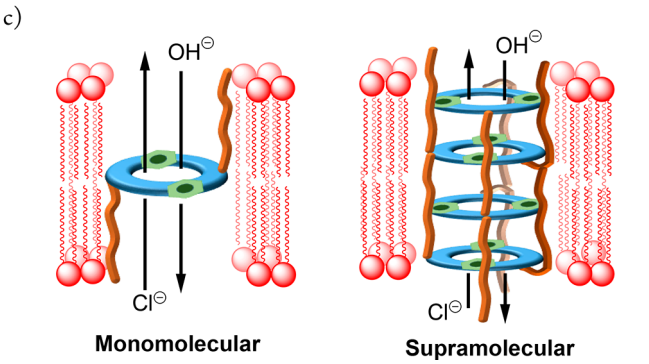


Figure 4. Mode of macrocycle–lipid interaction. (a) Hill analyses of macrocycles. (b) U-tube experiment to distinguish between carrier and channel mechanisms (1 mM macrocycle in the organic phase). (c) Possible modes of pore formation by macrocycle **2**.

2 (29.2 μM) was found to be 2.3 times lower than that for macrocycle **3** (69.4 μM). The Hill coefficient of 1.6 indicated that on an average a single ion was associated with one macrocycle. The macrocycle could function as a carrier, form a monomolecular pore or a stacked pore to accomplish this. The classical U-tube experiment was used to determine whether the macrocycle behaved as an ion carrier in the membrane (Figure 4b). The U-tube contained two aqueous layers separated by an organic phase. The donating aqueous arm of the U-tube contained NaCl, and the receiving arm contained water. Macrocycle **2** was dissolved in the organic phase. The concentration of chloride ions in the receiving arm did not increase with time, suggesting that macrocycle **2** did not function as an ion carrier and presumably formed a pore in the membrane. The computed electrostatic potential surface of macrocycle **1** (Figure S7) shows that the aromatic units being electron-deficient substituents can participate in anion–π interactions. The structures of macrocycles **1** and **2** bound with chloride ions (Figure S8) show that the amide NH bonds in the macrocycle can selectively bind with chloride ions via hydrogen bonding, similar to 2,6-diamidopyridyl-derived anion receptors.[47−50] The chloride selectivity can also be explained by the trend of $Cl^- > Br^- > I^-$ seen for anion–π interactions.[51]

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Two types of pores are proposed on the basis of the Hill coefficient (Figure 4c). A single macrocycle with alkyl chains on opposite sides could form the pore. This model is suggested because the length of macrocycle **2** with the alkyl chains stretched out on opposite sides is ca. 40 Å, which is the size of the lipid bilayer (Figure S8b). The flexible alkyl chains can also be on the same side of the macrocycle, which allows them to stack. The mode of stacking in Figure 4c is proposed on the basis of computational studies with the macrocycle dimer (Figure S9). Four macrocycles could stack to form the pore on the basis of the length of the dimer (ca. 24 Å). The ion can hop from one macrocycle to the other across the lipid bilayer. This model explains the lower activity of macrocycle **3**, where the larger number of alkyl chains could hamper macrocycle stacking.

Three macrocyclic systems with varying hydrophobicity have been synthesized in one pot. The smallest and most hydrophilic macrocycle, **1**, was not a good ion transporter. The most hydrophobic macrocycle, tetraalkylated macrocycle **3**, transported anions at a moderate rate (EC_{50} = 69.4 μM). Macrocycle **2** with two long alkyl chains was the best system (EC_{50} = 29.2 μM), with a correct balance of hydrophobicity for membrane insertion and hydrophilicity for anion transport. The macrocycle formed channels in the membrane and transported ions via a chloride-driven antiport mechanism. The mode of interaction between the macrocycle and the anions is a combination of hydrogen bonding and anion−π interactions. Such readily accessible chiral macrocycles decorated with different R groups are attractive scaffolds for developing gated or stimuli-responsive channels.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01699.

Synthetic procedures and characterization, assay details, and computational data (PDF)

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Notes

The authors declare no competing financial interest.

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