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Molecular ion fishers as highly active and exceptionally selective K^+ transporters

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ABSTRACT: We report here a unique ion-fishing mechanism as an alternative to conventional carrier or channel mechanisms for mediating highly efficient and exceptionally selective transmembrane K^+ flux. The molecular framework, underlying the fishing mechanism and comprising a fishing rod, a fishing line and a fishing bait/hook, is simple yet modularly modifiable. This feature enables rapid construction of a series of molecular ion fishers with distinctively different ion transport patterns. While more efficient ion transports are generally achieved by using 18-crown-6 as the fishing bait/hook, ion transport selectivity (K^+/Na^+) critically depends on the length of the fishing line, with the most selective **MF6-C14** exhibiting exceptionally high selectivity ($K^+/Na^+ = 18$) and high activity ($EC_{50} = 1.1$ mol% relative to lipid).

Artificial molecular machine is a rapidly developing science that often takes a cue from macroscopic objects.¹⁻¹¹ Recent years have seen a range of fascinating molecular machineries, performing macroscopic functions at the molecular level. Notable examples include molecular muscle,¹ shuttle,² switch,³ rotor,^{3,4} propeller,⁵ pump,⁶ walker,⁷ mover,⁸ nanocar,⁹ synthesizer^{10,11} and balance.¹² Awarding of the 2016 Nobel Prize in Chemistry to Jean-Pierre Sauvage,¹ Sir J. Fraser Stoddart² and Bernard L. Feringa³ undoubtedly will catalyze the field to a new height in both fundamental and practical settings.

Although these recent burgeoning scientific advances in molecular machines have greatly increased our ability to precisely manipulate requisite molecular motions and macroscopic functions at the molecular level, researching novel membrane-active molecular machines has lagged far behind. Recently, Zhu and his colleagues reported an interesting example of a rotaxane-derived molecular ion shuttle, non-selectively transporting K^+ ions via a shuttling mechanism with moderate activity ($EC_{50} = 3$ mol% relative to lipid).¹³ We also elaborated a molecular swing mechanism for swinging ions across membrane in a highly efficient but weakly K^+ -selective manner.¹⁴ Differing from commonly seen carrier¹⁵⁻¹⁹ and channel²⁰⁻³¹ mechanisms, these alternative ion-shuttling and -swinging mechanisms^{13,14} suggest that unconventional ion transport mechanisms could also work properly in membrane environment.

Herein, we disclose another unconventional ion-fishing mechanism for delivering highly active and exceptionally selective transport of K^+ ions. Despite their simple structure and ease synthesis, a number of these ion fishers are highly K^+ -

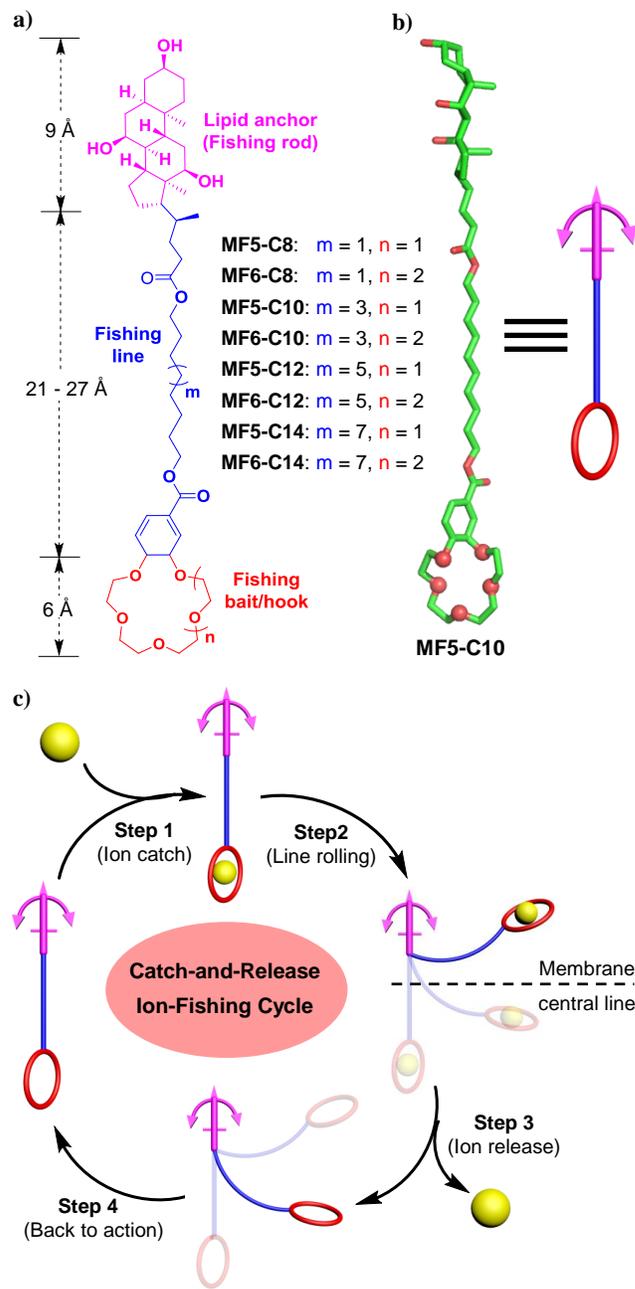


Figure 1. a) Molecular design of ion fishers MF5s and MF6s. b) Computationally optimized structure of MF5-C10 at the B3LYP/6-31G* level. c) Proposed catch-and-release ion-fishing mechanism for fishing ions across membrane.

selective, with the most selective **MF6-C14** transporting K^+ ions three times as fast as the complex and non-selective rotaxane-based ion shuttle,¹³ and with an exceptional K^+/Na^+ selectivity of 18 seven times that of the molecular swing ($K^+/Na^+ = 2.4$).¹⁴ These ion fishers therefore are among the most selective K^+ transporters.³²⁻³⁶ In fact, the highest unambiguously determined K^+/Na^+ selectivity of 9.8 was achieved only in 2017 through a combinatorial screening.³⁷

We have a long interest in developing novel membrane-active transporters.^{14,37-40} Inspired by the popular angling fishing method where recreational fishers use a combination of fishing tackles to catch fish, we designed a series of molecular ion fishers (**MFs**), performing a catch-and-release ion-fishing function within the context of lipid membrane. Structurewise, we covalently integrate three essential and modularly tunable types of fishing tackles (e.g., fishing rod, fishing line and fishing bait/hook) with appropriate dimensions into nanometer-sized **MFs**. The combined hydrophobic length (30 - 36 Å, Figure 1a) matches a typical hydrophobic membrane thickness (34 Å). Serving as the lipid anchor to firmly anchor the **MFs** into one side of the membrane region, the hydroxyl-rich cholesterol group with a rigid and linear backbone also functions as a rigid fishing rod to orient both the flexible alkyl chain-based fishing ropes of 21 - 27 Å and a crown ether-based fishing bait/hook mostly in parallel with the hydrophobic lipid tails. Energetically, the computationally optimized linear conformation is at its thermodynamically most stable state (see **MF5-C10**, Figure 1b).

Apparently, the catch-and-release fishing activity should take place in four sequential steps (Figure 1c). First, the **MF** in a fully extended state catches an ion through its fishing bait/hook from one side of the membrane. Driven by an ion concentration gradient, it curls up to allow the ion to cross the central line of the hydrophobic membrane region in step 2. After some further upward movement toward the membrane-water interface, it releases the ion to the other side of the membrane in step 3, and returns to its most stable extended state in step 4 to start another ion-fishing cycle. Since the ion experiences the most pronounced energetic penalty in the center of the hydrophobic membrane region, the ability of **MFs** to overcome such resistance and bring the ion to cross the membrane central line determines whether the proposed fishing mechanism could work in lipid membrane or not and the ion-fishing efficiency.

To examine the applicability and efficacy of the hypothetical ion-fishing mechanism, we designed two sets of **MFs**, containing 15-crown-5 (**MF5**) or 18-crown-6 (**MF6**) units as the fishing bait/hook, respectively, with the fishing line tuned from C_8H_{16} to $C_{14}H_{28}$. Using the pH-sensitive HPTS assay (Figure 2a), K^+ ions are found to transport faster than Na^+ ions by most **MFs**, with **MF6-C8** displaying the highest transport activity (Figure 2b). While **MF6-C8** at 2.5 μM and **MF6-C14** at 10 μM achieve R_K^+ values of > 93%, the R_K^+ values of < 6% for all control compounds (**FR-C8**, **FR-C10**, **C5** and **C6**, Figure S1c) at 10 μM are comparable to the background signal (3.4%).

The Hill analyses were conducted to determine EC_{50} values for Na^+ and K^+ ions (Figures S2-S5 and Table 1). Six out of eight **MFs** are found to be K^+ -selective. **MF5-C10**, **MF6-C8**, **MF6-C12** and **MF6-C14** exhibit both high activity ($EC_{50} = 0.81 - 2.7 \mu M = 0.37 - 1.2 \text{ mol\%}$ relative to lipid) and high selectivity ($K^+/Na^+ > 7$), and **MF5-C12** and **MF5-C14** are weakly active but Na^+ -selective.

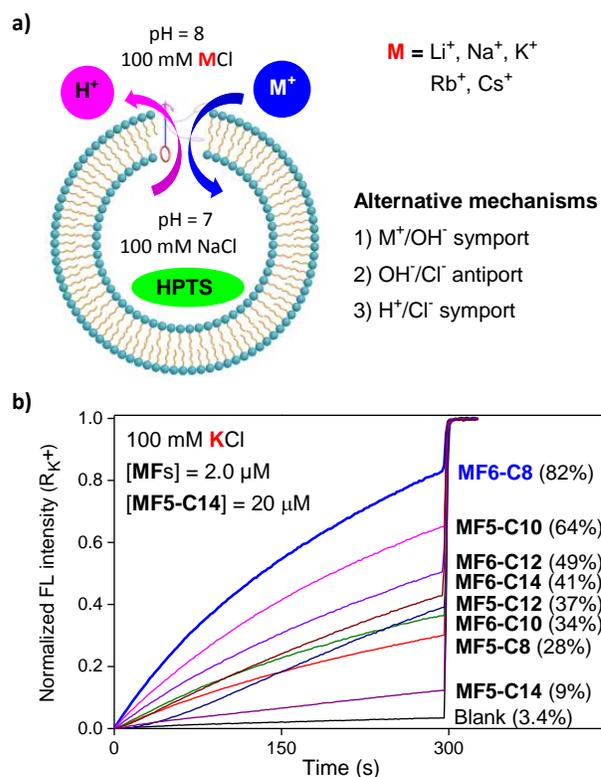


Figure 2. a) pH-sensitive HPTS assay for ion transport study. b) K^+ transport curves for various **MFs**. $R_K^+ = (I_{K^+} - I_0)/(I_{Triton} - I_0)$

Although ratio of EC_{50} values is a widely used parameter for comparing ion transport selectivity, they might not be sufficiently accurate when transporters (1) have a poor solubility, (2) experience self-aggregation or unfavorable interactions with lipids or (3) form a multi-molecular channel whose active components do not increase proportionally with the increased concentrations. For instance, **MF6-C12**, requiring an un-obstructed large space for proper function via an ion-fishing mechanism, may find surrounding environment over-crowded at high concentrations. That is, are these two ion fishers, having high K^+/Na^+ selectivity of > 28 estimated from the EC_{50} values, truly so K^+ -selective?

To alleviate these possible issues, we previously used highly K^+ -selective **5F8** (Figure S6) as the reference channel and proposed the use of ratio of R_K^+/R_{Na^+} as a complementary and reliable index for selectivity assessment.³⁷ In our previous work, **5F8** was unambiguously determined to have K^+/Na^+ selectivity of 9.8 using single-channel current measurements, with ratios of 4.5 and 14.7 for $EC_{50}(Na^+)/EC_{50}(K^+)$ and R_K^+/R_{Na^+} , respectively.

In this work, we found that membrane dialysis method, rather than flash column chromatography, to separate the excessive un-encapsulated HPTS from LUVs consistently produces LUVs that exhibit low background signals of 3 - 8% (Figure S7). Using these tight LUVs, the $EC_{50}(K^+)$ of **5F8** was re-determined to be 5.2 μM (Figure S6), which is similar to previously determined 5.5 μM .³⁷ Importantly, at $[5F8] = 11 \mu M$ where **5F8** elicits a R_K^+ value of 92.3%, R_K^+/R_{Na^+} was determined to be 9.6 (Figure S8), which is nearly identical to the absolute K^+/Na^+ selectivity of 9.8. This suggests ratios of R_K^+/R_{Na^+} determined using LUVs with low background signals allows ion selectivity to be gauged reliably even though it still may differ from the true ion selectivity.

To obtain meaningful R_M^+ values (R_K^+ , R_{Na^+} , etc) and ratio **R**

Table 1. Determined values for EC_{50} (μM), $EC_{50}(\text{Na}^+)/EC_{50}(\text{K}^+)$ and $R_{\text{K}^+}/R_{\text{Na}^+}$.

	MF5-C8	MF5-C10	MF5-C12	MF5-C14	MF6-C8	MF6-C10	MF6-C12	MF6-C14
$EC_{50}(\text{Na}^+)^a$	5.1 ± 0.2	10.1 ± 0.2	30.9 ± 2.9	55.9 ± 1.7	10.1 ± 0.8	4.6 ± 0.2	49.2 ± 3.4	$>> 70$
$EC_{50}(\text{K}^+)^a$	4.6 ± 0.3	1.4 ± 0.1	$>> 30$	$>> 70$	0.81 ± 0.1	2.7 ± 0.1	1.7 ± 0.1	2.5 ± 0.1
$\frac{EC_{50}(\text{Na}^+)}{EC_{50}(\text{K}^+)}$	1.1	7.2	< 1	< 1	12.5	1.7	28.9	> 28
$R_{\text{K}^+}/R_{\text{Na}^+}^{+b}$	1.1	5.2	1.8	0.3	7.1	1.4	7.8	18.0

^a [Total lipid] = 219 μM . ^b See Figure S9 for more detail.

(e.g., $R_{\text{K}^+}/R_{\text{Na}^+}$) for a reliable comparison of ion selectivity, it is imperative to determine R_{M^+} at the concentration where the channel's transport activity has been maximized to $> 90\%$ or reached saturation over 300 s for the most active ion (Figures 3a and S9). Following this criterion, we have obtained all R_{M^+} values ($\text{M} = \text{Li}^+, \text{Na}^+, \text{K}^+, \text{Rb}^+$ and Cs^+) for all eight MFs (Figure S9), with ratios of $R_{\text{K}^+}/R_{\text{Na}^+}$ presented in Table 1.

As evidenced from R_{M^+} and ratio R values, seven out of eight MFs are K^+ -selective, including MF5-C12 otherwise shown to be Na^+ -selective using EC_{50} values. The most K^+ -selective MF6-C14 displays exceptional K^+/Na^+ selectivity of 18 (Figure 3a), yet with high activity ($EC_{50} = 2.5 \mu\text{M}$ or 1.1 mol% relative to lipid). MF6-C8 ($EC_{50} = 0.81 \mu\text{M}$) and MF6-C12 ($EC_{50} = 1.7 \mu\text{M}$) also display high K^+/Na^+ selectivities of 7.1 and 7.8, respectively.

Interestingly, although MF5-C14 is weakly active, it displays good Na^+/K^+ selectivity of 3.6 and high selectivity against Rb^+ ($\text{Na}^+/\text{Rb}^+ = 21$) and Cs^+ ($\text{Na}^+/\text{Cs}^+ = 65$). More interestingly, all eight MFs do not transport Li^+ ions (Figure S9). This consistent observation is in sharp contrast to our best knowledge that all crown ether-based ion channels with ion transport activities tested against Li^+ ions all transport Li^+ ions. This may imply that the large dehydration energy of Li^+ ions can't be compensated for by the crown ether unit that functions through a fishing mechanism, but likely can be sufficiently compensated for by a channel mechanism.

The M^+ ions as the main transport species were established by the chloride-sensitive SPQ assay (Figure 3b). Compared to anion channel L8³⁹ that causes 65% fluorescence quenching of SPQ dye at 3 μM , that no significant fluorescence quenching by both MF6-C8 and MF6-C14 was observed signifies the inability of MFs to transport anions.

The transport rates between K^+ and H^+ were compared using a proton carrier FCCP (Figure 3c). With respect to no change in fluorescence intensity between FCCP alone and the background signal, a net increase of 44% between transport activities mediated by MF6-C14 in the absence (55%) and presence (99%) of FCCP suggests K^+ to be transported much faster than H^+ . Similar conclusion can be drawn for MF6-C8 (Figure S10).

The carboxyfluorescein-leakage assay ($\lambda_{\text{ex}} = 492 \text{ nm}$, $\lambda_{\text{em}} = 517 \text{ nm}$, Figure S11) shows that melittin, which forms a pore of $> 1 \text{ nm}$ or efficiently lyses the membrane at low concentrations, results in large increases in fluorescence by 54% and 86% at 100 nM and 200 nM, respectively. In contrast, both MF6-C8 and MF6-C14 produce changes of $< 2\%$ at 5 μM . These results support well-maintained membrane integrity in the presence of MFs, ruling out the membrane-lysing activity of MFs.

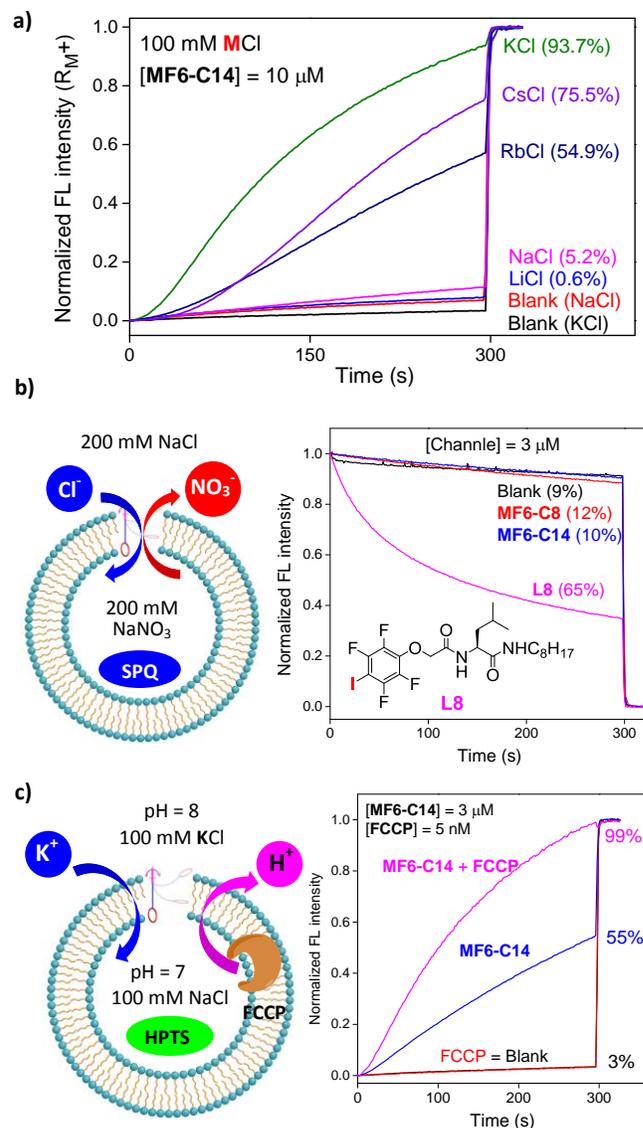


Figure 3. a) Ion transport percentages (R_{M^+}) for MF6-C14 at 10 μM . b) SPQ assay to confirm the inability of MFs to transport anions. c) FCCP-based HPTS assay to confirm that MF6-C14 transports K^+ ions faster than H^+ ions.

Additional structure-activity-relationship studies on shorter MF6-C2, MF6-C4 and MF6-C6 (Figures 4 and S12-S14) reveal that the K^+ transport activity peaks at MF6-C8 ($EC_{50} = 0.81 \mu\text{M}$), with the highest K^+/Na^+ selectivity achieved by MF6-C14.

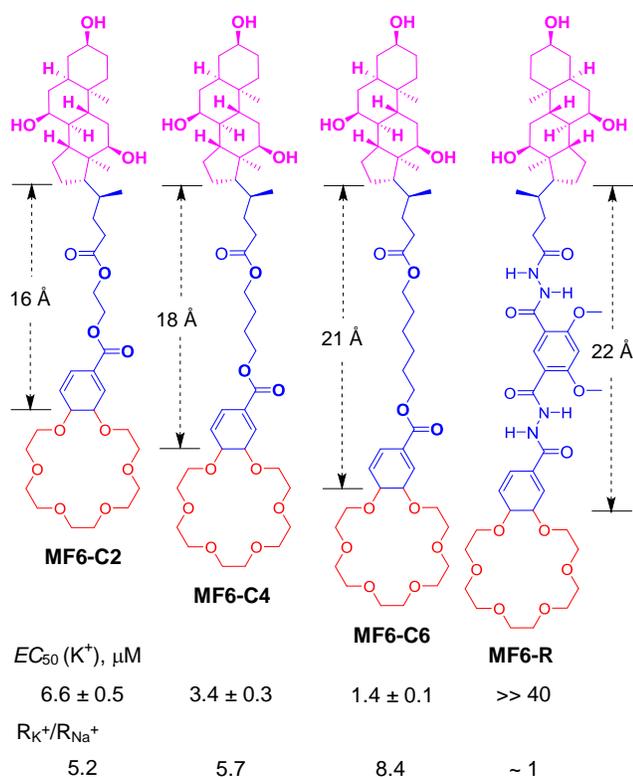


Figure 4. Structures and ion transport properties of the shorter (MF6-C2, MF6-C4 and MF6-C6) and more rigid (MF6-R) MFs.

Further, from the stepwise analyses of catch-and-release ion-fishing cycle (Figure 1c), this ion-fishing mechanism shares some similarity with but also differs from carrier and channel mechanisms. Like carriers, MFs are not simultaneously open to both the intra- and extra-cellular environments. Like channels, they do follow a defined pathway with one end fixed in the lipid membrane through the cholesterol unit to facilitate ion transport via a fishing mechanism. To examine to which of the two mechanisms the ion-fishing mechanism is closer, we conducted single-channel current measurements on MF6-C14. The fact that our extensive efforts failed to record single-channel current traces suggests these ion fishers likely operate in a carrier-like mechanism.

Lastly, unlike the conventional ion carriers that can move freely and randomly in both vertical and lateral directions, the MFs can only move the same way laterally. More specifically, the rigid cholesterol backbone, which acts as the lipid anchor, can't move vertically, with the remaining flexible part freely curling up or down in a manner akin to a fishing process. Consequently, one expects to see greatly diminished ion-fishing activity upon replacing the flexible fishing rope with a rigid one that can't bend. We therefore prepared MF6-R rigidified by intramolecular H-bonds (Figure 4). Consistent with the proposed ion-fishing mechanism, MF6-R indeed exhibits extremely weak activities ($EC_{50} \gg 40 \mu M$) for both K^+ and Na^+ ions (Figure S13b).

In summary, we have established here a novel “catch-and-release ion-fishing” strategy for achieving highly efficient and remarkably selective transport of K^+ ions across membrane. It is also of exceptional interest to note that all eight ion fishers studied herein do not transport Li^+ ions, a feature that is

unprecedented among ion channels derived from crown ethers. Further, it is believed that this class of ion fishers does not have a single ion permeation pathway to follow. Rather, while operating in a more carrier-like mechanism, they fish ions through numerous pathways that are more defined than carriers but less defined than channels. Given their highly modular nature and ease of synthesis, a broad range of molecular ion fishers can be readily envisioned, possibly exhibiting outstanding membrane transport properties for promising medical applications.

ASSOCIATED CONTENT

Supporting Information. Synthetic procedures and a full set of characterization data including 1H NMR, ^{13}C NMR and MS as well as a complete set of ion transport study. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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Graphic for the Table of Contents