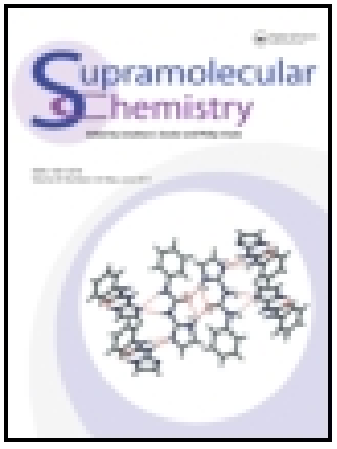

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Transmembrane anion transport mediated by adamantyl-functionalised imidazolium salts

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Transmembrane anion transport mediated by adamantyl-functionalised imidazolium salts

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We present the design, synthesis and transmembrane anion transport properties of a new class of mobile organic transporters, possessing a central imidazolium cation and two external adamantyl units. We demonstrate herein that the imidazolium cation can be incorporated in the structure of active mobile anion transporters. Depending on the nature of the counter-anion of the salt, as well as the extravesicular anions, different anion selectivities were obtained. We show the importance of the H2 proton of the imidazolium cation in order to obtain a higher binding constant of the chloride anion. Furthermore, we demonstrate the importance of the flexibility of the spacers between the adamantyl groups and the imidazolium cation in the transport process.

Keywords: anion transmembrane transport; mobile transporter; imidazolium salts

1. Introduction

Anion transport across cell membrane is an important biological process which is regulated by transmembrane ion channels (*1*). The malfunction of chloride channels generally results in a multitude of diseases, such as osteoporosis or formation of kidney stones (*2*). Cystic fibrosis represents the most common disease involving anion transport in the human body (*3*). This disease is the result of an altered chloride ion diffusion caused by a mutation of the cystic fibrosis transmembrane regulator (CFTR) protein (*2*, *3*).

Interest regarding the design and development of artificial anion transporters as possible solutions to cure such malfunctions has increased significantly over the past decades (*4*). Therefore, supramolecular chemists focused their attention on the use of small molecules which possess the capacity to act as anion transporters, both to regulate these ion gradient disorders and to better understand the importance of such processes in biological systems. In terms of mechanisms, synthetic transporters can operate via two distinct mechanisms. The first one involves the formation of a transmembrane channel, which can be formed by a single molecule, or by a supramolecular assembly of several molecules, depending on the size of the monomer. On the other hand, the second mechanism of anion transport involves small molecules acting as mobile carriers. They can cross the cell membrane as an anion–transporter complex, allowing ionic exchange between the extra- and intravesicular media (*5*). The activity of ion transporters is generally based on the exploitation of weak interactions between ions and the transporter, such as hydrogen bonds (*6*), anion–π (*7*) or cation–π (*8*). Our group recently reported the preparation of imidazolium, benzimidazole and benzimidazolium-based anion transporters that can self-assemble into ion channels via π-stacking intermolecular interactions to allow anion diffusion (*9–13*). Mechanistic studies revealed that the transport of chloride across the membrane was possible through anion–π interactions with the aromatic units of the transporter (*9*). In order to get a better understanding of the role of the imidazolium cation in the transport process, as well as the influence of the structure of the transporter in terms of self-aggregation capacity in the bilayer, we designed a new family of imidazolium salts bearing adamantyl moieties (Figure 1).

We first hypothesised that the presence of adamantyl groups on the imidazolium central cation still confers the transporter the required lipophilicity to penetrate and diffuse through a phospholipid membrane (*14*), but the presence of the two adamantyl groups avoids their self-aggregation and formation of transmembrane channels. Herein, we present the transmembrane transport properties of adamantyl-functionalised imidazolium carriers, demonstrating the importance of the nature of their counter-anion and its impact on the anion transport process. Finally, kinetic studies allow us to demonstrate the mobile anion transport mechanism.

2. Results and discussion

2.1 Synthesis

Synthesis of imidazolium salt **1a** was adapted from an existing procedure (*15*, *16*). The symmetric imidazolium

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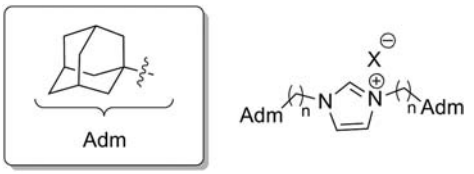

Figure 1. Adamantyl-imidazolium salts ($n = 0–2$).

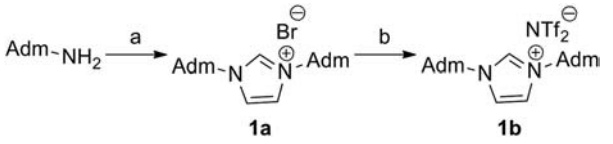

Figure 2. Synthesis of imidazolium salts **1a** and **1b**. Reagents and conditions: (a) formaldehyde, glyoxal, HBr, MeOH; (b) $LiNTf_2$, MeOH.

salt was obtained through the condensation of formaldehyde, adamantylamine and glyoxal, in the presence of HBr (Figure 2).

All other imidazolium bromide salts were prepared following a general procedure. First, the corresponding adamantane alcohol was brominated (*17*, *18*). Then, two successive nucleophilic substitutions were performed using the corresponding imidazole in order to generate the bromide salts **8a**, **9a**, **10a** and **11a** (Figure 3). Finally, the anion metathesis yielded compounds **1b**, **8b**, **9b–9d**, **10b** and **11b** as air-stable salts (Figures 2, 4 and 5).

2.2 *Transmembrane anion transport activity and mechanism*

We first studied the influence of the nature of the cationic unit regarding the chloride transport properties. Our assays were conducted using standard Egg Yolk Phosphatidyl Choline (EYPC) liposomes containing a 100 mM NaCl and 2 mM lucigenin solution. Lucigenin is a fluorescent

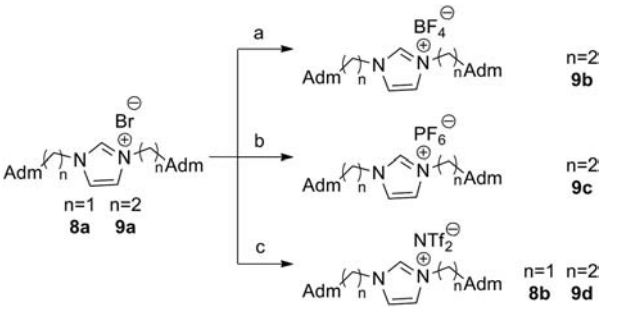

Figure 4. Synthesis of imidazolium salts **8b**, **9b**, **9c** and **9d**. Reagents and conditions: (a) $NaBF_4$, MeOH; (b) KPF_6, MeOH; (c) $LiNTf_2$, MeOH.

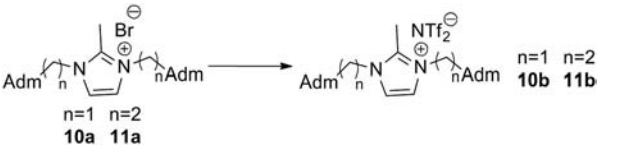

Figure 5. Synthesis of imidazolium salts **10b** and **11b**. Reagents and conditions: $LiNTf_2$, MeOH.

probe that possesses the particularity to have its fluorescence quenched in the presence of chloride anions. Thus, a raise in fluorescence while the transporter is injected indicates a transport of Cl^- outside of the liposomes (*19*). At the end of each fluorescence experiments, Triton-X was added in order to lyse the liposomes and observe full lucigenin fluorescence.

As shown in Figure 6, bringing more flexibility between the adamantyl groups and the imidazolium cation tends to raise the transport efficiency, the most efficient transporter being **9a**. In addition, transporter **11a** was designed to investigate the contribution of the most acidic proton of the imidazolium ring H2. This proton is known to be involved in hydrogen-bond formation with anions (*20*). Replacing this H2 proton by a methyl group prevents the

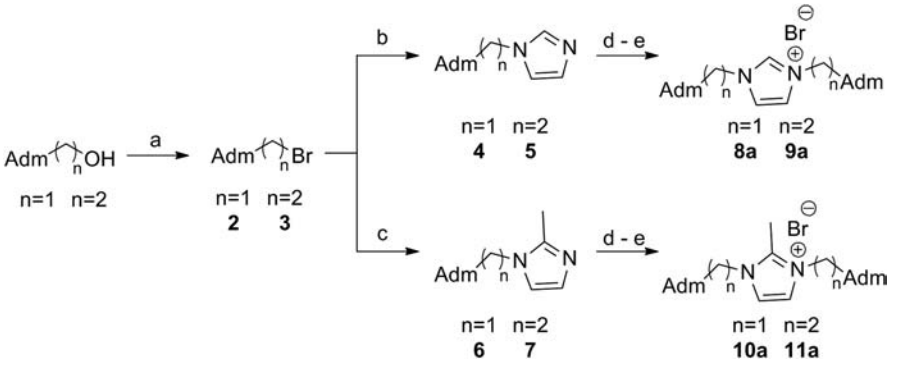

Figure 3. Synthesis of imidazolium salts **8a**, **9a**, **10a** and **11a**. Reagents and conditions: (a) HBr; (b) imidazole, NaH, DMF; (c) 2-methylimidazole, NaH, DMF; (d) ($n = 1$), **2**, DMF, microwave; (e) ($n = 2$), **3**, DMF.

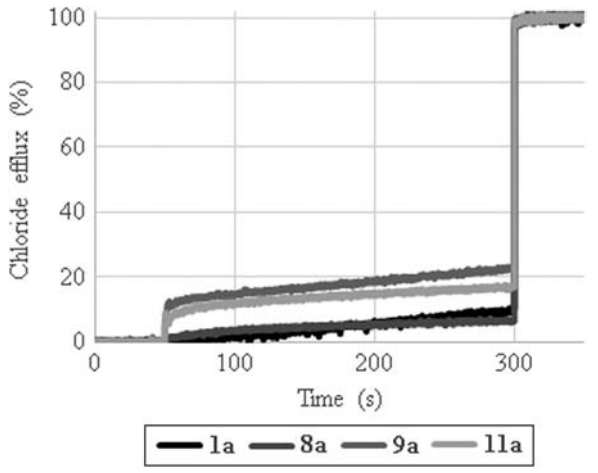

Figure 6. Relative chloride transport activity of different bromide imidazolium salts at 15 mol% relative to EYPC. Intravesicular: 2 mM lucigenin, 100 mM NaCl, 10 mM phosphate buffer (pH = 6.2). Extravesicular: 100 mM $NaNO_3$, 10 mM phosphate buffer (pH = 6.2).

hydrogen-bond formation, resulting in a less efficient transporter. One main advantage of using imidazolium salts as synthetic anion transporters is that it is easily possible to replace their counter-anion. As compound **9** showed the best transport efficiency, we decided to use it as scaffold and study the influence of the nature of different counter-anions with compounds **9a–9d** (Figure 7).

The transport assays were performed with transporters possessing the same cation, but different counter-anions and showed that the most efficient transporter bears the more lipophilic anion (Figure 7). The chloride transport

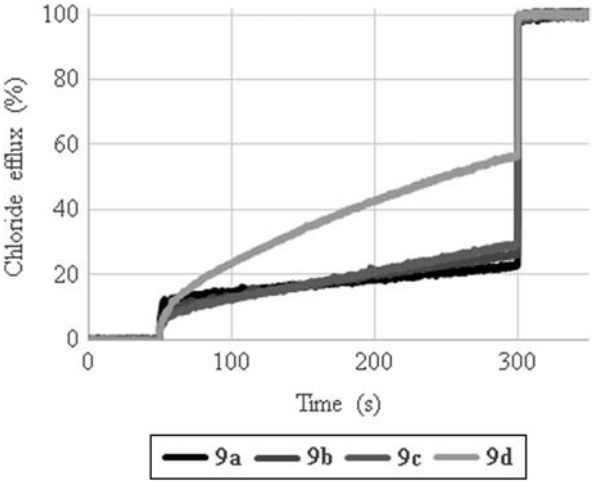

Figure 7. Relative chloride transport activity of imidazolium salt **9** bearing different counter-anion (**9a–9d**) at 15 mol% relative to EYPC. Intravesicular: 2 mM lucigenin, 100 mM NaCl, 10 mM phosphate buffer (pH = 6.2). Extravesicular: 100 mM $NaNO_3$, 10 mM phosphate buffer (pH = 6.2).

activity of these salts follows the Hofmeister sequence, as we previously reported (*9*), following the order: $Br^- < BF_4^- < PF_6^- < NTf_2^-$. This result is directly correlated to the capacity of these molecules to partition and insert into the phospholipid bilayer.

In order to confirm our initial hypothesis on the capacity of these molecules to act as mobile ionic transporters, we performed chloride transport studies in hybrid EYPC: cholesterol liposomes (7:3) (Figure 8). Cholesterol has the property to rigidify the liposomes membrane by increasing the energy barrier of normal phospholipids movements inside the membrane (phospholipids rotations, lateral diffusion or phospholipid flip–flop) (*21*). In the case of a transmembrane ion channel, the chloride transport is independent on the nature of the phospholipid used, but the transport rate in the case of mobile carriers is slowed down by a lower diffusion in a rigidified membrane, which is translated by a large difference between the normal and the rigidified liposomes.

As shown in Figure 8, the chloride efflux is slower in cholesterol-doped EYPC liposomes, which is a characteristic for a mobile ion carrier. Similar results were obtained for transporters **9a** and **11b** (Figures S1 and S2 in the ESI).

Kinetic parameters of the transport process were determined by varying the concentrations of the carrier in both types of liposomes (Figure 9).

For each transport experiment, an initial rate (V_o) was measured after the injection of the transporter at less than 10% of the maximum transport process and the results were transposed on a graph for a Hill analysis (Figure 10).

Figures 9 and 10 clearly show that transporter **9d** becomes slower and less efficient in rigidified liposomes, at high concentrations. Table 1 shows that Hill coefficients and EC_{50} values are different depending on the composition of the liposomes. Originally, the Hill coefficient described the number of monomers needed to aggregate into an active assembly in the chloride transport process. However, obtaining Hill coefficient values superior to 1 is quite characteristic for synthetic transporters forming unstable supramolecular structures (*22*). The trend observed in these experiments is that the Hill coefficient is higher in a more rigidified membrane. Our hypothesis is that there is an equilibrium between the complexed monomer with a chloride and the free monomer inside the bilayer, and the transport process occurs via a cooperative interaction between the monomers, but not by a channel-forming mechanism. In the case of the rigidified liposomes, where the diffusion of the transporter inside the membrane is decreased, the transport essentially requires a larger number of mobile monomers in order to perform the transport. The property of these adamantyl-functionalised salts to act as mobile transporters is also supported by the transport assays performed in dipalmitoylphosphatidylcholine (DPPC) liposomes (Figure S3 in the ESI). Because the transport

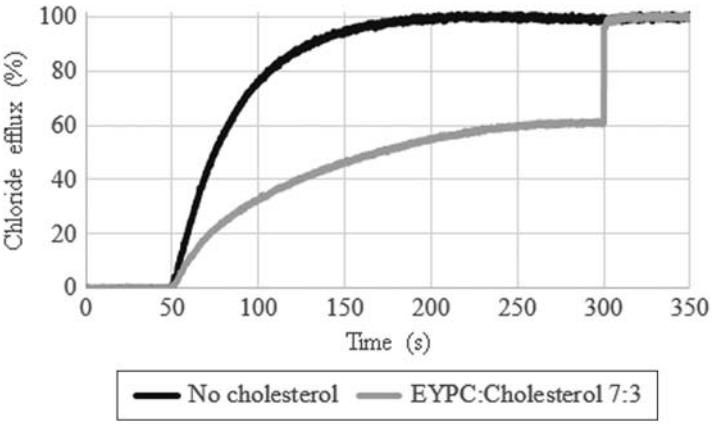

Figure 8. Relative chloride transport activity of imidazolium salt **9d** at 20 mol% relative to EYPC or EYPC:cholesterol (7:3). Intravesicular: 2 mM lucigenin, 100 mM NaCl, 10 mM phosphate buffer (pH = 6.2). Extravesicular: 100 mM $NaNO_3$, 10 mM phosphate buffer (pH = 6.2).

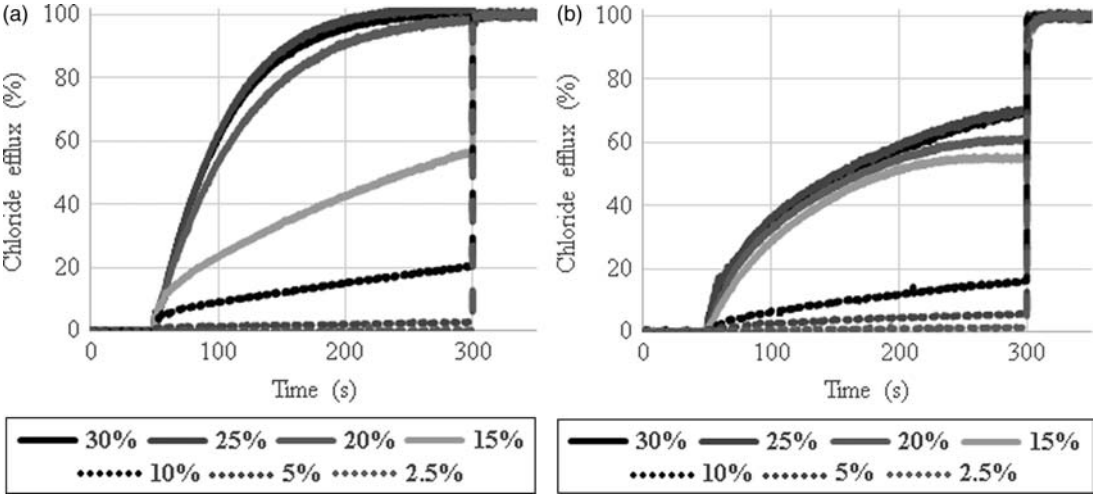

Figure 9. Relative chloride transport activity of transporter **9d** at different concentrations in (A) EYPC liposomes and (B) EYPC: cholesterol 7:3 liposomes. Intravesicular: 2 mM lucigenin, 100 mM NaCl, 10 mM phosphate buffer (pH = 6.2). Extravesicular: 100 mM $NaNO_3$, 10 mM phosphate buffer (pH = 6.2).

in rigidified membrane may be influenced by a different partition of the transporter (*6*), classical U-tube experiments were performed with compound **9d** and confirmed the proposed carrier mechanism (Figure S18 in the ESI).

For a mobile ion carrier, the binding efficiency of the chloride anion is crucial for the transport process. This mechanism implies that the carrier binds the anion in the intravesicular solution, penetrates and diffuses through the phospholipid bilayer as a complex and releases it in the extravesicular solution. We determined the chloride-binding association constant of different transporters, possessing different cationic structures (Table 2) (*23*).

The results shown in Table 2 suggest that the H2 proton on the imidazolium cation is very important for the binding of the chloride. As previously shown, a better chloride association increases the transport efficiency, but this is not the only parameter that governs the transport process. Indeed, the flexibility of the cation also plays an important role in the transport process. Even though molecule **9a** seems to strongly bind chloride anions, data could not be fitted into a 1:1 model and its association constant could not be calculated (Figure S12 in the ESI). However, as we previously showed, transporter **9a** bearing a bromide counterion is less efficient than its analogue **9d** bearing an NTf_2 counterion.

As the difference in their transport activity cannot be explained by the binding of the chloride during the transport process, we decided to perform an anion selectivity assay. The principle is the same as in the

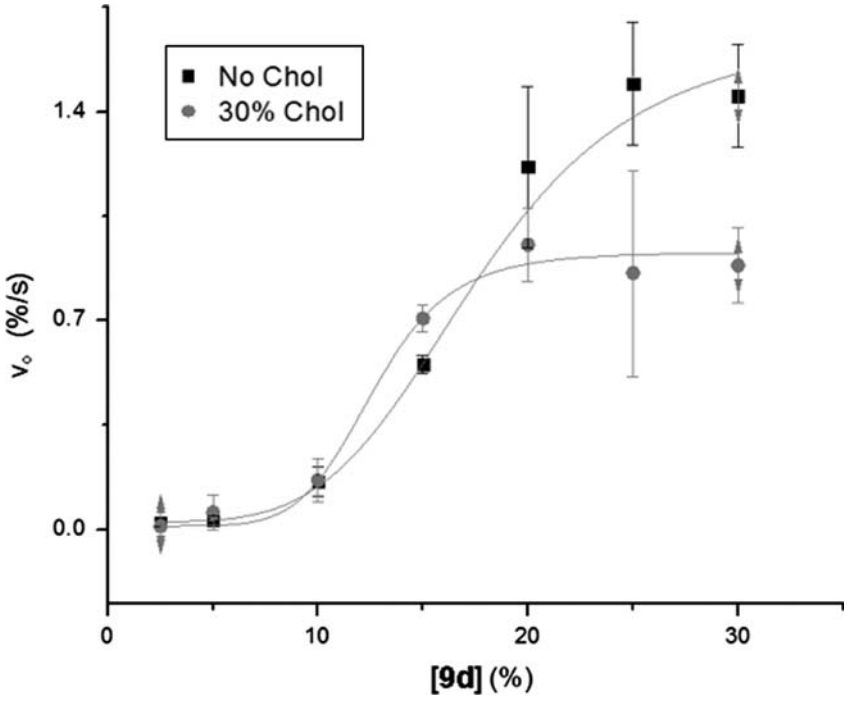

Figure 10. Hill plot analysis obtained from data shown in Figure 9 in EYPC liposomes (squares) and EYPC:cholesterol 7:3 liposomes (circles). The concentration of the transporter is reported relative to the lipid concentration.

Table 1. Kinetic parameters of molecule **9d**.

Liposome composition	Hill coefficient	EC_{50} (%)[a]
EYPC	4.5 ± 0.6	17.7 ± 0.9
EYPC:cholesterol 7:3	7 ± 1	12.5 ± 0.5

[a] Relative to the lipid concentration.

Table 2. Binding constants of chloride[a] with transporters **1b**, **8b**, **9a**, **9d**, **10b** and **11b** in chloroform.

Compound	K_a (M^{-1})
1b	1224
8b	1578
9a	–[b]
9d	1356
10b	172
11b	191

[a] Added as TBAC salt, fitting a 1:1 model.
[b] Data could not be fitted into a 1:1 model (ESI).

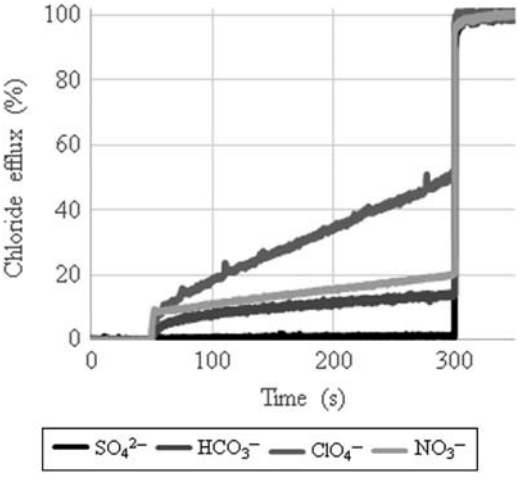

Figure 11. Relative chloride transport activity of imidazolium salt **9a** at 15 mol% relative to EYPC. Intravesicular: 2 mM lucigenin, 100 mM NaCl, 10 mM phosphate buffer (pH = 6.2). Extravesicular: 100 mM Na**X** or Na_2**X**, 10 mM phosphate buffer (pH = 6.2 or 7.4 for $NaHCO_3$).

lucigenin-based fluorescence assays, but the extravesicular free anions are varied (Figures 11 and 12).

The results shown in Figures 11 and 12 demonstrate completely different behaviours of transporters **9a** and **9d** in the presence of different extravesicular anions. Transporter **9a** shows an anion selectivity following the order of the hydration energy of each extravesicular free anion: SO_4^{2-} (–1080 kJ/mol) < HCO_3^- (–360 kJ/mol) < NO_3^- (–320 kJ/mol) < ClO_4^- (–260 kJ/mol) (Figure 11) (*24*). The anion selectivity in these experiments still follows the Hofmeister sequence. Bromide being more labile than the NTf_2^-, a quick anion exchange can take place with the excess of anions of the extravesicular solution, before undergoing the anion transport process. In other words, these results suggest that the actual salt involved in the chloride transport is the one bearing the

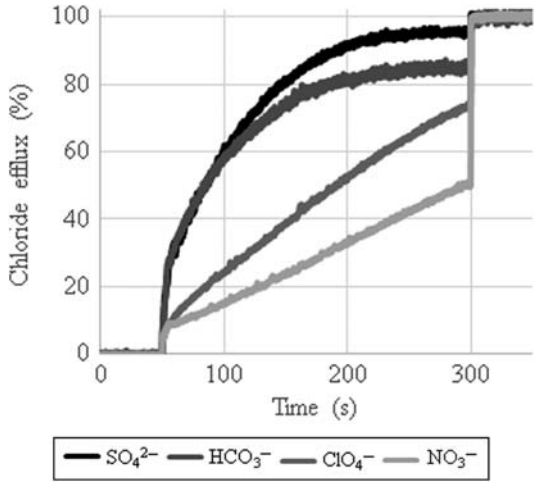

Figure 12. Relative chloride transport activity of imidazolium salt **9d** at 15 mol% relative to EYPC. Intravesicular: 2 mM lucigenin, 100 mM NaCl, 10 mM phosphate buffer (pH = 6.2). Extravesicular: 100 mM Na**X** or Na_2**X**, 10 mM phosphate buffer (pH = 6.2 or 7.4 for $NaHCO_3$).

extravesicular anion (Figure 13). In the case of the sulfate anion, the most hydrated anion, the newly formed sulfate salt is completely solvated and cannot penetrate into the bilayer anymore, explaining the lack of chloride transport.

Transporter **9d** (Figure 12) shows a completely different anion selectivity: $NO_3^- < ClO_4^- < HCO_3^- < SO_4^{2-}$, where sulfates as extravesicular anions increase the chloride transport efficiency. This result not only confirms the anion transport selectivity of transporter **9d**, but also shows an odd anion selectivity, not related to the hydration energy of extravesicular anions. In order to get a better understanding of the selectivity observed for transporter **9d**, transport studies using the 8-hydroxy-1,3,6-pyrenetrisulfonate (HPTS) were performed (Figure 14). HPTS is a pH-sensitive probe that possesses a protonated and a deprotonated ($pK_a \approx 7.4$) (*25*) form with different excitation wavelengths, respectively, 403 and 460 nm, and the same emission wavelength at 510 nm. The ratio of emission between the protonated (I_0) and the deprotonated (I_1) form is directly related to the pH of the solution containing the probe, hence to the transport of protons across the phospholipid bilayer (*26*).

The anion selectivity observed in the HPTS assays follows almost the same order as the one observed in the lucigenin-based transport assays (Figure 14), although in this case a greater alkalinisation of the liposomes for the bicarbonate anion ($pK_a = 6.4$) (*27*) can be observed. This is probably simply due to the bicarbonate, acting as a base, and alkanisation is not only indicative of proton efflux, but also related to an acid–base reaction between the bicarbonate anion and the intravesicular solution, i.e. the bicarbonate influx. In the case of the sulfate ($pK_a = 1.9$) (*27*), nitrate ($pK_a = -1.64$) (*28*) and perchlorate ($pK_a \approx -8$) (*28*) anions, they follow exactly the same order as in the lucigenin-based transport assays (Figure 12). The pK_a of their acid–base couples are too low to deprotonate the HPTS probe. In these experiments, the pH changes can only be related to OH^- or H^+ flux. After addition of the transporter **9d** to the external solution containing the sulfate anions, an alkalinisation of the liposomes occurs. The sulfate is poorly membrane permeable, hence the alkalinisation process is likely caused by H^+ diffusion (*26*). This means that the SO_4^{2-}/Cl^- antiport and Cl^-/H^+ symport processes are greatly favoured, compared with the other anions used. In the case of the perchlorate anion, the pH variation is not the same, only a light acidification of the interior of the liposomes being observed. This result is

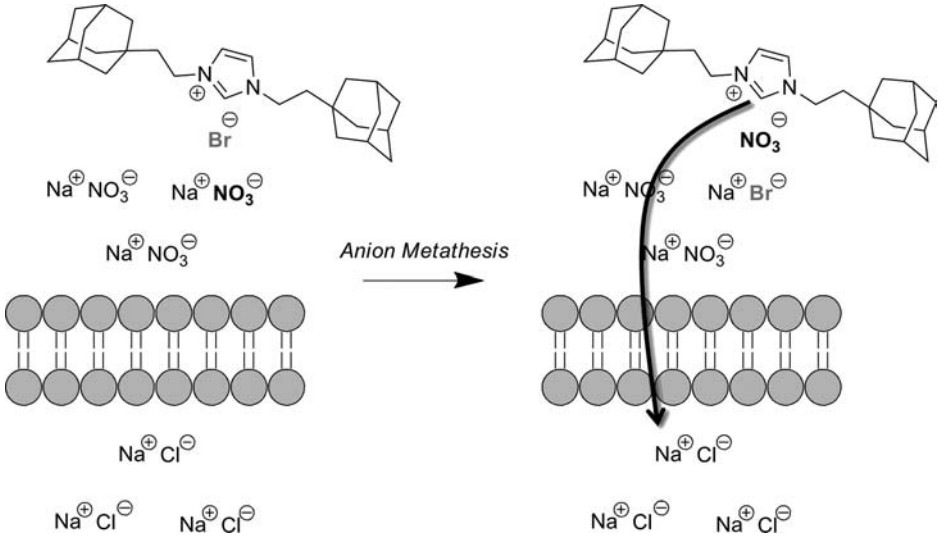

Figure 13. Anion metathesis between transporter molecule **9a** and extravesicular anion before undergoing chloride transport process.

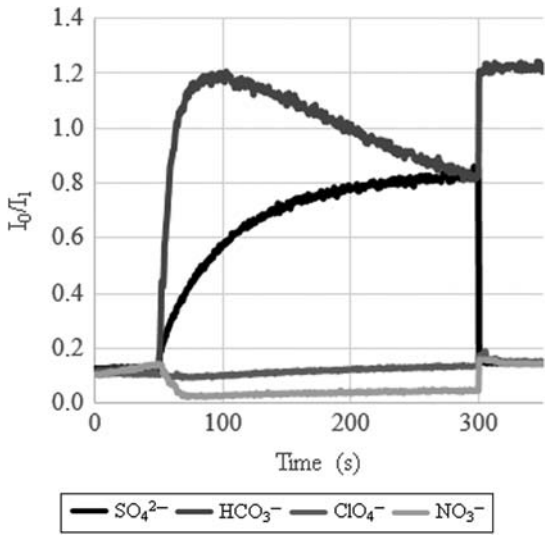

Figure 14. HPTS-based transport assay of imidazolium salt **9d** at 15 mol% relative to EYPC. Intravesicular: 0.1 mM HPTS, 100 mM NaCl, 10 mM phosphate buffer (pH = 6.2). Extravesicular: 100 mM Na**X** or Na_2**X**, 10 mM phosphate buffer (pH = 6.2 or pH = 7.4 for $NaHCO_3$).

more consistent with a Cl^-/ClO_4^- antiport process. Finally, in the case of the nitrate anion, a faster NO_3^-/H^+ symport process than the Cl^-/NO_3^- antiport process can be observed.

The correlation of these results with those obtained from the lucigenin-based transport assays (Figure 12) shows that it is possible to tune the chloride transport process of molecule **9d** by favouring its Cl^-/H^+ symport and X^-/Cl^- antiport process while preventing the X^-/H^+ symport. This hypothesis is also supported by the results obtained when perchlorate was used as an internal anion (Figure S16 in the ESI).

3. Conclusion

In conclusion, we successfully designed a new class of mobile anion transporters, possessing a central imidazolium cation and two external adamantyl units. These salts possess the capacity to transport chloride outside liposomes, acting as mobile transmembrane carriers. We demonstrated herein that the imidazolium cation can also be incorporated in the structure of mobile transporters. Depending on the nature of the counter-anion of the salt, as well as the extravesicular anions, different anion selectivities were obtained. We confirmed the importance of the H2 proton of the imidazolium cation in order to obtain a higher binding constant between the chloride anion and the imidazolium salt. We also demonstrated the importance of the flexibility of the spacers between the adamantyl groups and the imidazolium cation in the transport process. This is not surprising as the transport process is a complex one, where multiple equilibria are involved and where media with different polarities have to be crossed from one side of the membrane to the other one. The mobile transporter needs a good complexation of the anion during the transport process, but has to be able to release it on the other side of the membrane. A greater flexibility in the transporter's structure may benefit to a conformational change depending on the polarity of the media, resulting in different binding affinities to the transported anion.

4. Supporting Information

Procedures for the syntheses of the imidazolium salts, their characterisation, liposomes preparation, fluorescence assays, NMR titrations and U-tube experiments can be found here: http://dx.doi.org/10.1080/10610278.2014.969265

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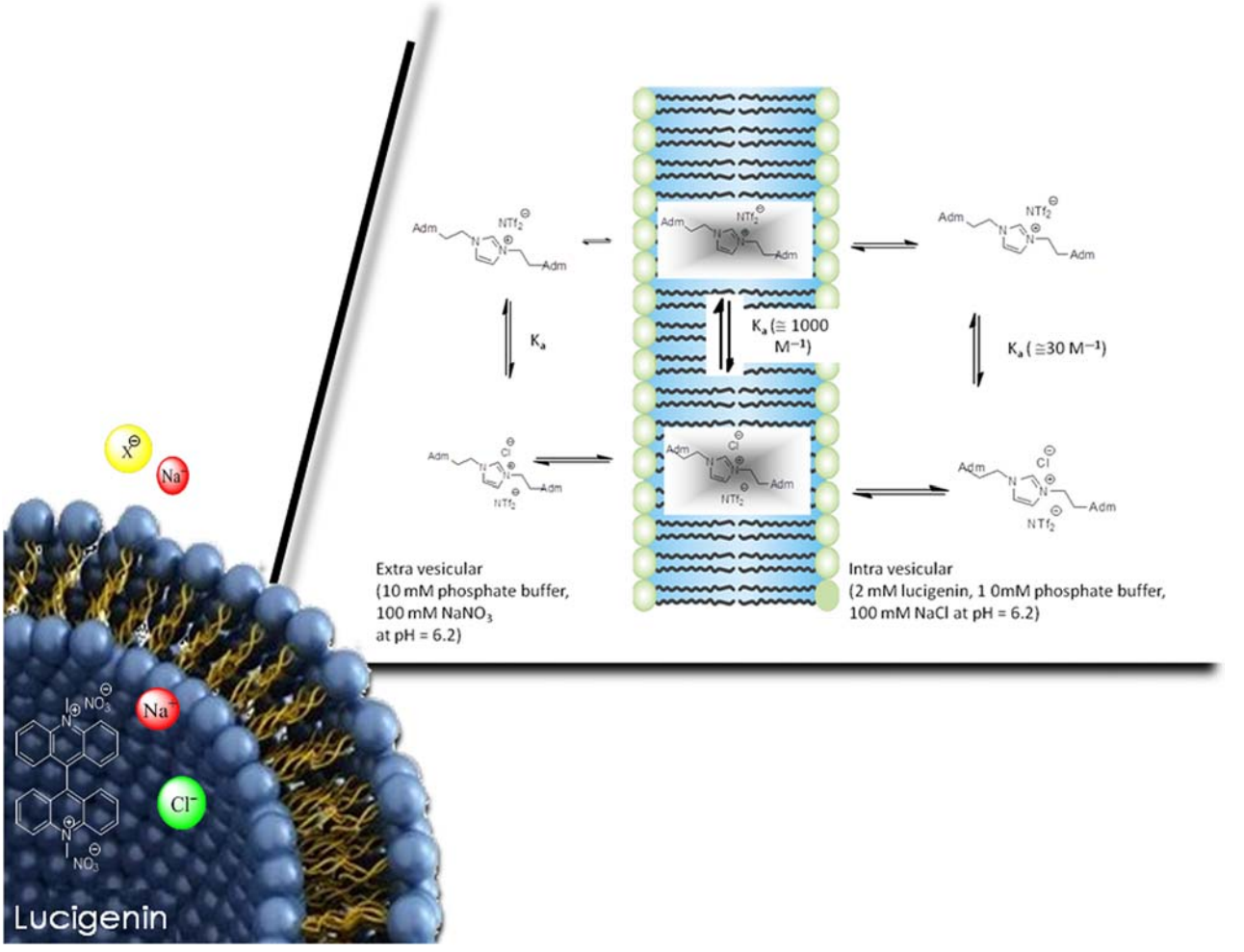

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Transmembrane anion transport mediated by adamantyl-functionalised imidazolium salts

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