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Self-Assembled Columnar Triazole-Quartets - an example of synergetic H-bonding / Anion- π Channels

Shao-Ping Zheng,^[a,b] Yu-Hao Li,^[a] Ji-Jun Jiang,^[a] Arie van der Lee,^[b] Dan Dumitrescu^[c] and Mihail Barboiu*^[a,b]

Dedicated to Jean-Marie Lehn for his 80th birthday

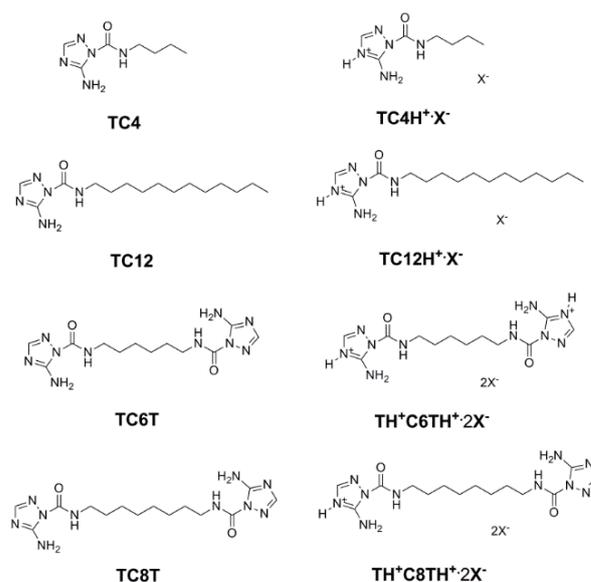
Abstract: The self-assembly of triazole-amphiphiles has been examined in homogenous solution, in the solid state and in the bilayer membranes. Single-crystal X-ray diffraction structures show that stacked protonated Triazole-quartets- T_4 quartets are mutually stabilized by strong recognition with two inner anions. Anion H-bonding/ion-pairing are combined with anion- π recognition to produce columnar architectures, resulted through anion- π interactions between anions and triazole moieties of vicinal T_4 quartets. In bilayer membranes, low transport activity is observed when the T_4 channels are operated as H^+/X^- translocators, but higher transport activity is observed when X^- translocation was performed in the presence of K^+ -carrier valinomycin. The anions channel results are interpreted as arising from discrete stacks of T_4 -quartets where transport would occur through the stacked T_4 macrocycles. These self-assembled channels presenting amazing structural behaviours, directionality, strong anion encapsulation via H-bonding supported with vicinal anion- π interactions are proposed as artificial supramolecular channels that transport anions across lipid bilayer membranes.

Ion transmembrane translocation through protein channels is of great significance for regulating the cellular signalling pathways.^[1,2] A number of important diseases, arising from dysregulation of biological channels, known as “channelopathies” are related to defects observed in the protein structures.^[3,4] Synthetic ion-channels can replace them as a novel medical therapy, having great potential in anticancer treatment. The expectations are related to compensate the transmembrane charge imbalance caused by cation/proton transport which creates a positive potential outside the cell membrane with anion symport, which is electrochemically transported out of the cell.^[4-6] Several H^+/Cl^- symporters such as red pigment prodigiosin,^[7] bis(melamine)-bispidine,^[3] calix[4]arene-amide,^[8] tren-amide,^[9] tris-ureas or tris-thioureas,^[10] perenosin,^[11] imidazole-linked pyrrole amide^[12] are all used as potent anticancer agents. K^+/Cl^- symporters such as crown-ethers,^[13] calix[4]pyrrole^[14] or oxacalix

[2]arene[2]triazine^[15] performing synergetic co-transport are also essential for the apoptotic cell death of cancer cells.^[16]

To achieve further significant transmembrane transport, it is essential to construct novel channel-type architectures aligning multiple binding sites, as mostly demonstrated within cation-channels.^[17a-19] In protein channels, the alignment of binding sites pointing toward a central pore is used to combine selectivity *via* precise bonding in the selectivity filters with high speed multi-ion hopping translocation along pore-aligned recognition sites.^[20] Within this context the selective anion recognition observed with synthetic carriers has to be combined with fast anion translocation along multi-ion hopping directional pathways in anion channels as observed for anion- π slides.^[21-25] So far, the combination of selective anion recognition *via* hydrogen bonding, ion-pairing and anion-dipole interaction^[4-11] with high rate anion- π oriented translocation^[21-25] is not known among artificial anion channels. The possibility to create synergetic selectivity/translocation functions with anion channels is therefore attractive and interesting. Importantly, the anion- π interactions, not known in biological channels, has been extensively used for anion encapsulation and recognition.^[26-32]

Within this context, we discovered that protonated amino-triazole (TH^+) amphiphiles form self-assembled anion channels of stacked Triazole-quartets- T_4 stabilized by inner H-bonded anions (Scheme 1).



Scheme 1. Molecular structures of amino-Triazole (T) amphiphiles **TC4**, **TC12**, **TC6T**, **TC8T** and their protonated (TH^+) **TH⁺C4**, **TH⁺C12**, **TH⁺C6TH⁺**, **TH⁺C8TH⁺** counterparts.

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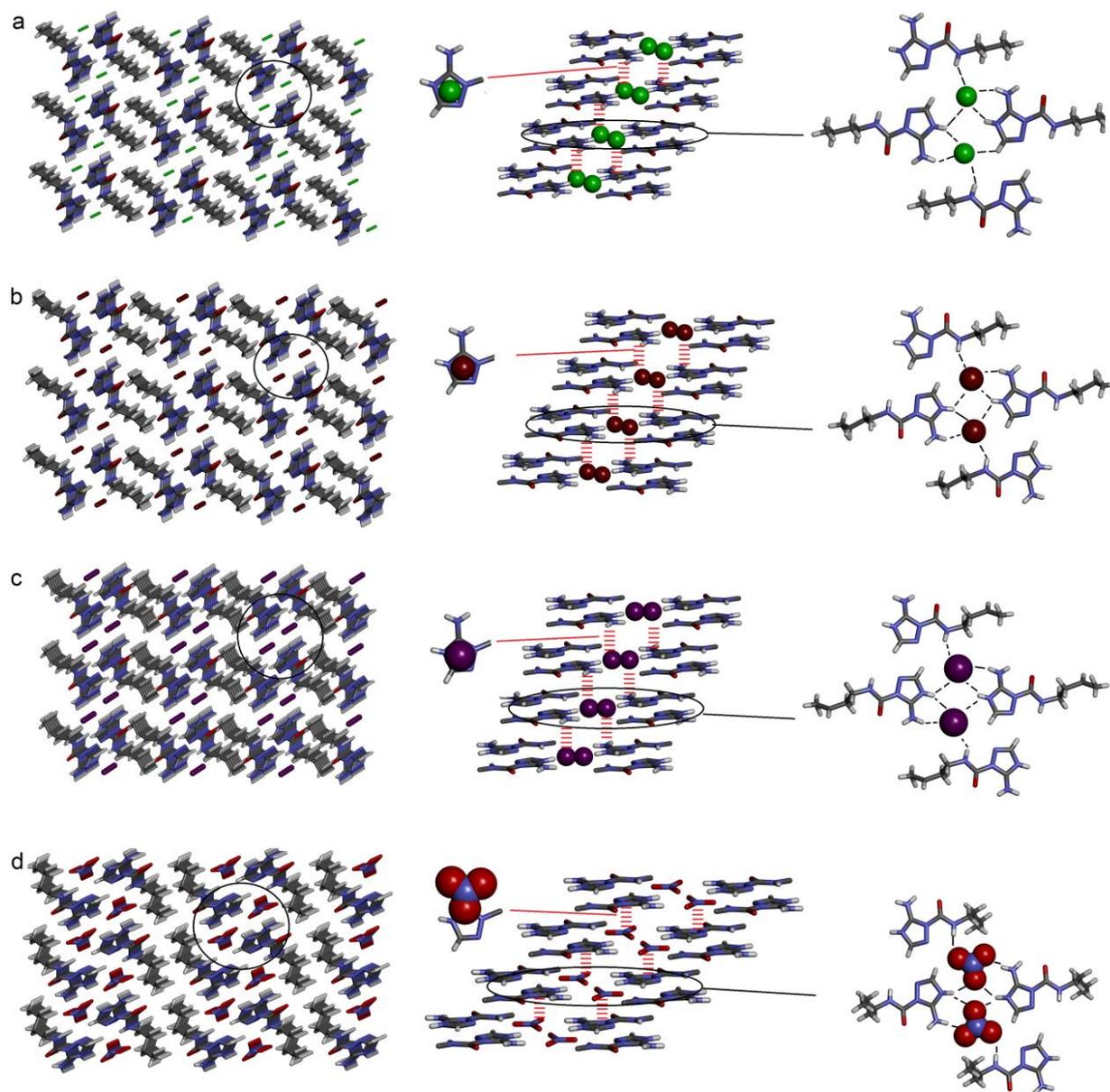


Figure 1. X-ray crystal structures of $\text{TH}^+\text{C}_4\text{-X}^-$; $\text{X}^- =$ a) Cl^- , b) Br^- , c) I^- and d) NO_3^- . (left) crystal packing revealing the formation of the anion-channels; (center) side view in stick of layered-type stacks of T quartets generating channels of anions, inset represents top-view of anion- π interactions (red lines within the channels); (right) top view in stick of planar T quartets recognizing two anions *via* synergistic H-bonding. Anions are presented in ball representation.

The templating H-bonded anions are strongly interacting *via* anion- π interactions with triazoles of vicinal quartets that could self-direct their translocation along anion-selective T_4 pores. These columnar aggregates provide excellent reasons to be considered as functional anion channels in bilayer membranes.

Single-crystals of $\text{TH}^+\text{C}_4\text{-X}^-$, $\text{TH}^+\text{C}_{12}\text{-X}^-$, $[\text{TH}^+\text{C}_6\text{TH}^+]\text{-2X}^-$ and $[\text{TH}^+\text{C}_8\text{TH}^+]\text{-2X}^-$ with different anions ($\text{X}^- = \text{Cl}^-$, Br^- , I^- , NO_3^-) were obtained through slow evaporation from water/methanol solutions at room temperature. Analysis of X-ray single-crystal structures of protonated triazole amphiphiles $\text{TH}^+\text{C}_4\text{-X}^-$ (Figure 1), $\text{TH}^+\text{C}_{12}\text{-X}^-$ and $[\text{TH}^+\text{C}_6\text{TH}^+]\text{-2X}^-$ (Figure 2) and $[\text{TH}^+\text{C}_8\text{TH}^+]\text{-2X}^-$ (Figure S31, S32) ($\text{X}^- = \text{Cl}^-$, Br^- , I^- , NO_3^-), reveals the H-bonding of

2 anions by a planar triazole-quartet T_4 . Two anions are synergistically H-bonded *via* N-H and - NH_2 groups of two triazoles and *via* external amide -CO-NH bonds of two other vicinal triazoles (Figure 1-3). Interestingly, one apical position site of the anion ($\text{TH}^+\text{C}_4\text{-X}^-$; $\text{X}^- = \text{Cl}^-$, Br^- , I^- , NO_3^- ; Figure 1) or two apical position sites of a sandwiched anion ($\text{TH}^+\text{C}_{12}\text{-X}^-$, $[\text{TH}^+\text{C}_6\text{TH}^+]\text{-2X}^-$; Figure 2, $\text{X}^- = \text{Cl}^-$, Br^- , NO_3^-) are occupied by the triazole rings from vicinal T_4 quartets. The halogens ($\text{X}^- = \text{Cl}^-$, Br^- , I^-) are centred to the triazole ring, while the interaction between the triazole-ring and the bound NO_3^- induces a lateral contact with the amino group of the triazole (Figure 2).

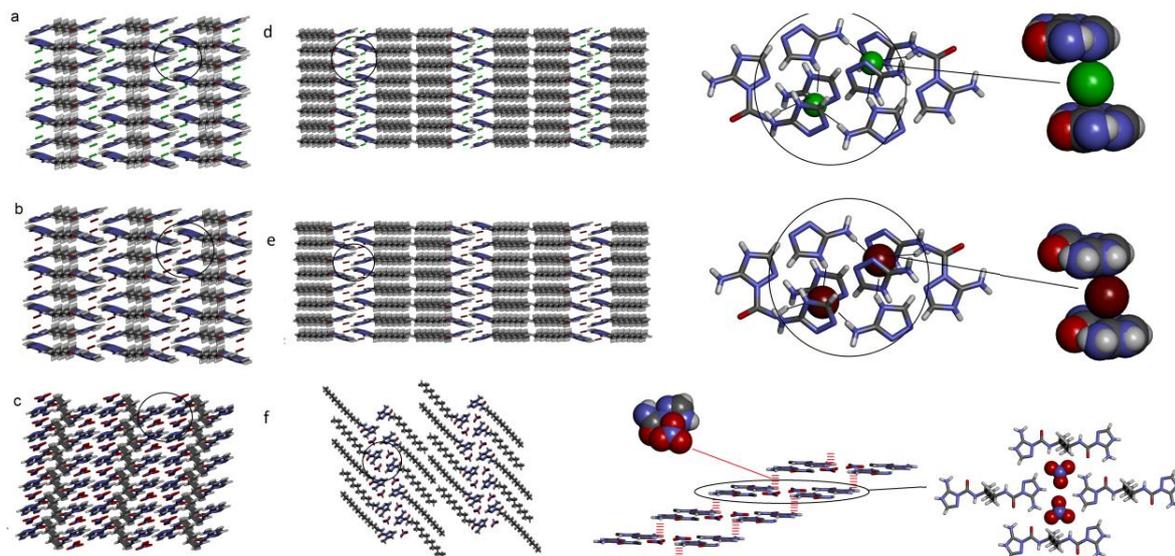


Figure 2. X-ray crystal structures of **TH*C6TH*·2X⁻**, X⁻ = a) Cl⁻, b) Br⁻ and c) NO₃⁻ and **TH*C12·X⁻**, X⁻ = d) Cl⁻, e) Br⁻ and f) NO₃⁻ (left) crystal packing revealing the formation of the anion-channels; (right) top view in stick of planar T quartets recognizing two anions *via* synergistic H-bonding and anion- π interactions (black lines within the channels); last example shows the layered-type stacks of T quartets generating channels of NO₃⁻ anions, inset represents the view of anion- π interactions. Anions are presented in ball representation.

The distance between all kinds of anions X⁻ and triazole centroid is 3.2-3.7 Å, indicating rather strong anion- π contacts. The presence of the anions is essential for channel generation, while only highly compact structures are generated in solid state of the unprotonated **TC4**, **TC6T** and **TC8T**, resulting in the formation of complex H-bonding networks (see Supporting information Figures S33).

This amazing combination of classical H-bonding / ion pairing with non-classical anion- π interactions generates channels with interior free void pore openings for anion binding averaging 3 to 4 Å wide and 9-10 Å length. The robustness of the pores is strengthened with synergistic hydrophobic interactions between the lateral CH₃-(CH₂)_{3,11}- and central -(CH₂)_{6,8}- chains, alternatively connecting with each other in between each quartet level and forming an environmentally hydrophobic and protective shell for the channels. From X-ray single-crystal data of the T-quartet channels reported here, it can be concluded that: (i) two anions can be recognized by individual T-quartets *via* synergistic H-bonding/ion pairing; (ii) Complementary anion- π stacking between triazole rings and anions from two different successive T-quartets, enables a columnar T-quartet organization, achieving a anion- π slide channel-shaped pathway for anions translocation; (iii) the T-quartet for anion channels are reminiscent with the previously reported imidazole I-quartet for water channels^[33-35] or Guanosine G-quartet for K⁺ channels.^[36-38]

The ¹H-NMR (Figures S1-S22) and MS spectra (see Supporting Information) of all synthesized compounds are in agreement with the proposed formulas. The ¹H-NMR spectra of protonated **TH*C4·X⁻** (Figure 3a), **TH*C12·X⁻** (Figure S1) and **[TH*C8TH*]·2X⁻** (Figure S2) X⁻ = Cl⁻, Br⁻, I⁻ and NO₃⁻ indicated a stable downfield shift of ~ 0.75 ppm of the H1 in the triazole ring after protonation, which is indicative of strong H-bonding with the X⁻ anion and is reminiscent with the presence of the dissociated salt in aqueous solution for all the studied anions. In the case of **[TH*C6TH*]·2X⁻** (Figure 3b) we observed a maximum downfield

shift of $\Delta\delta \sim 0.75$ ppm for the NO₃⁻, while upfield shifted ($\Delta\delta = -0.05$ to -0.3 ppm) peaks relative to the NO₃⁻ are observed for the other anions Cl⁻, Br⁻, I⁻, suggesting their close proximity with the triazole moiety.

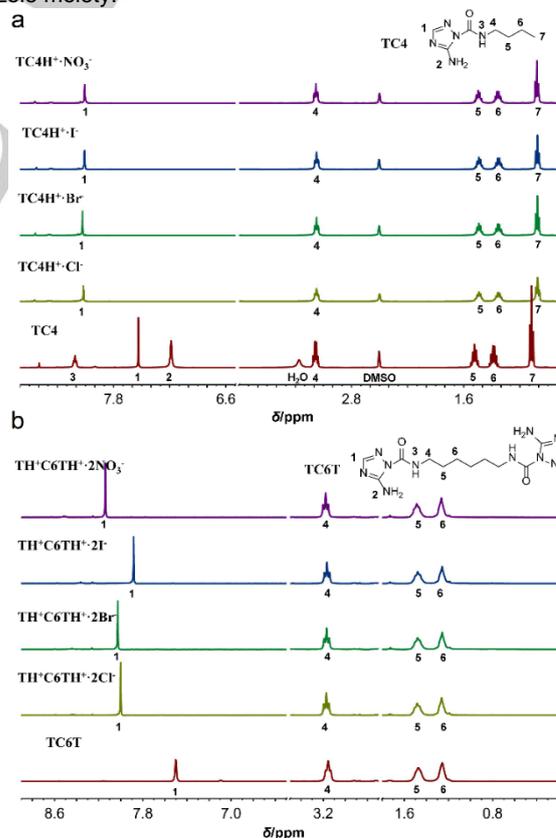


Figure 3. ¹H-NMR spectra (298K, D₂O and *d*₆-DMSO) of (a) **TC4** and protonated **TH*C4·X⁻**, X⁻=Cl⁻, Br⁻, I⁻ and NO₃⁻ and (b) **TC6T** and protonated **[TH*C6TH*]·2X⁻** with NO₃⁻, I⁻, Br⁻, Cl⁻, respectively.

COMMUNICATION

The ion-transport activities were evaluated by HPTS assay.^[39,40] EYPC liposomes (Large Unilamellar Vesicles-LUV, 100 nm) were filled with a pH-sensitive dye, 8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt (HPTS) and 100 mM NaCl in a phosphate buffer (10 mM, pH 6.4). The liposomes were then suspended in an external phosphate buffer (10 mM, pH 6.4) containing 100 mM of MCl, $M^+ = Li^+, Na^+, K^+, Rb^+, Cs^+$ or 100 mM of KX, $X^- = Cl^-, Br^-, I^-, NO_3^-$. Then, after addition of $TH^*C4\text{-}Cl^-$, $TH^*C12\text{-}Cl^-$, $[TH^*C6TH^*]_2Cl^-$, $[TH^*C8TH^*]_2Cl^-$ into LUVs solution from DMSO solutions, an external pH gradient was created by addition of NaOH. The internal pH change inside the liposome was monitored by the change in the fluorescence of HPTS. A series of activity tests of protonated $TH^*C4\text{-}Cl^-$, $TH^*C12\text{-}Cl^-$, $[TH^*C6TH^*]_2Cl^-$, $[TH^*C8TH^*]_2Cl^-$ were performed by using in the extravesicular solution of NaCl and KCl in the absence or presence of H^+ selective carrier, Carbonyl cyanide-p-trifluoromethoxyphenylhydrazone (FCCP) or K^+ selective carrier, valinomycin, respectively (Figure 4). Since varying different MCl salts, $M^+ = Li^+, Na^+, K^+, Rb^+, Cs^+$ in the extravesicular solution caused insignificant differences in the transport activity, confirming that **TC4** and **TC6T** compounds are not cation-selective (Figure S23). We directly aimed our focus toward the transport of different anions, especially Cl^- , Br^- , I^- , NO_3^- . As a result, $TH^*C4\text{-}Cl^-$, $TH^*C12\text{-}Cl^-$, $[TH^*C6TH^*]_2Cl^-$ and $[TH^*C8TH^*]_2Cl^-$ all showed similarly very low transport activity without FCCP on the channel-mediated anion efflux, which is practically not stimulated by the addition of FCCP as proton carrier as well, confirming that the proton transport is not a rate-limiting barrier responsible for the slow anion translocation through the channels. Then, the introduction of K^+ selective carrier valinomycin determining a K^+ influx from extravesicular solution results in the observation of a better enhancement of the fluorescence intensity than addition of FCCP, with a special emphasis for $TH^*C12\text{-}Cl^-$ channel (Figure 4). K^+ influx creates a positive potential inside the vesicle membrane; for which the extravesicular X^- anions would be dragged into the inner side of vesicles according to its electrochemical gradient. This may disclose the main rate-determining step during the cotransport of H^+/Cl^- , which originates from weak Cl^- flow stuck along the channel, thus weakly compensating H^+ efflux by FCCP or accompanying OH^-/K^+ in the presence of valinomycin. Based on these findings, a possible transport mechanism was proposed here in the presence of FCCP (Figure 4a) and valinomycin (Figure 4b). Further evidence of anion selectivity for $TH^*C4\text{-}Cl^-$, $TH^*C12\text{-}Cl^-$, $[TH^*C6TH^*]_2Cl^-$ and $[TH^*C8TH^*]_2Cl^-$ in the order of $Cl^- \approx Br^- > I^- > NO_3^-$ was then demonstrated when X^- translocation was performed in the presence of K^+ carrier valinomycin (Figure S27). The anion selectivity was unaffected by the presence of various anion channels. However, the rate of the translocation is strongly affected in the case of $TH^*C12\text{-}Cl^-$ with valinomycin, which can replace the rate-limiting anion transport with faster K^+ transport as the counterion pathway.

We further performed planar lipid bilayer experiments to give more details on the channel formation behaviours of $TH^*C12\text{-}Cl^-$ (Figures S28-S30). The transport activity is rather slow to initiate, and increasing amounts of $TH^*C12\text{-}Cl^-$ are not generating stronger activity, both in terms of length of opening periods and intensity of conductance. The observed intermediary states between erratic and multi-level conductances are reminiscent with the formation of large pores, but of the conductance of a

single channel opening is hazardous in the present case, the cation translocation is related to the dynamics of the T-quartet aggregates within bilayers.^[17b] Thus, this conducting behavior is related to a kind of 'supramolecular polymorphism' in the bilayer membrane.^[17c]

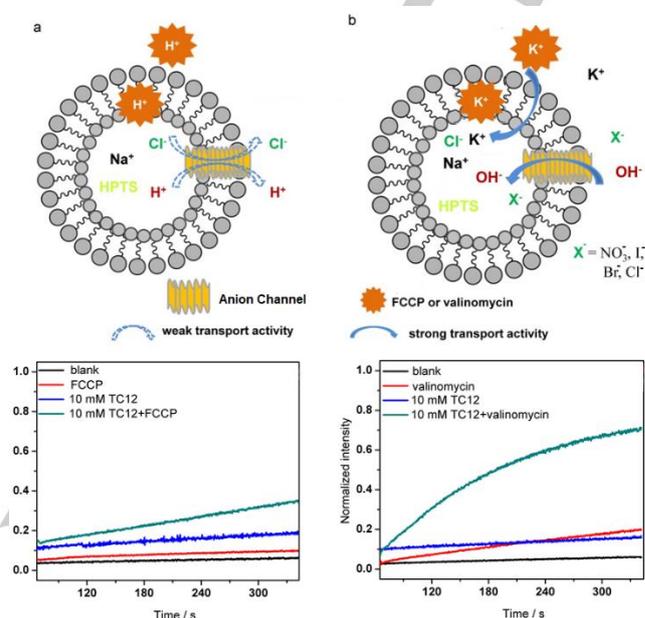


Figure 4. Proposed transport mechanism and the comparison of the transport activity of $TH^*C12\text{-}Cl^-$ a) in the absence and the presence of $50\ \mu M$ FCCP as H^+ carrier or b) in the absence and the presence of $50\ \mu M$ valinomycin as K^+ carrier. External composition of LUV is 100 mM NaCl or KCl in 10 mM phosphate buffer at pH 6.4.

Hill analysis^[40,41] revealed 4 times better activity in the presence of valinomycin, confirming the above proposed mechanism (Table 1, Figure S27). Compound $TH^*C12\text{-}Cl^-$ is one order of magnitude more active than $[TH^*C6TH^*]_2Cl^-$ in the presence of valinomycin, as it has the lower EC_{50} for all anions, following the transport activity sequence of $Br^- > Cl^- > I^- > NO_3^-$ (Table 1, Figures S25-S27). The Hill coefficients are representative channels belonging to the type II class channels, $n < 1$, and their formation is exergonic.^[41]

Table 1. Hill analysis results of compounds $TH^*C12\text{-}Cl^-$ and $[TH^*C6TH^*]_2Cl^-$ with or without Val, EC_{50} values expressed as mol% (% molar of the compound / lipid needed to obtain 50% ion transport activity) and n is Hill coefficient.

Compound	n	EC_{50} /mol%
$TH^*C12\text{-}Cl^-$, KCl	0.54	38.38
$TH^*C12\text{-}Cl^-$, KCl+Val	0.58	9.14
$TH^*C12\text{-}Cl^-$, KBr+Val	0.77	4.47
$TH^*C12\text{-}Cl^-$, KI+Val	0.66	17.85
$TH^*C12\text{-}Cl^-$, KNO_3 +Val	0.80	19.23
$[TH^*C6TH^*]_2Cl^-$, KCl+Val	0.50	50.88
$[TH^*C6TH^*]_2Cl^-$, KBr+Val	0.60	121.41
$[TH^*C6TH^*]_2Cl^-$, KI+Val	0.89	28.53
$[TH^*C6TH^*]_2Cl^-$, KNO_3 +Val	0.63	101.33

In conclusion, self-assembled Tetrazole T-quartet T_4 Channels display channel-like anion binding behaviors combining classical hydrogen bonding/ion pairing recognition with proximal anion- π interactions. The anion multivalent recognition by the triazole quartets completely replacing the water molecules around the hydrated anion, like in natural channels, is appropriate to generate the formation of channel-type superstructures, since a pair of encapsulated anions interact with more than one T_4 entity stacked within the channel.^[42] The anion translocation mediated by T_4 presented would then be interpreted as multiple copies of the $T_4 \cdot X_2^-$ quartets self-assembling in oligomeric channels $(T_4 \cdot X_2^-)_n$. The Triazole-quartet channels described here, are very intriguing electrogenic anion channels, presenting a remarkable combination of functions, anion/cation or anion/proton selectivities. Specifically, we have demonstrated that simple structural variation from short to long alkyl chains would strongly influence the transport activities of anions. This is a significant step forward toward the development of electrogenic anion channels with high selectivity.

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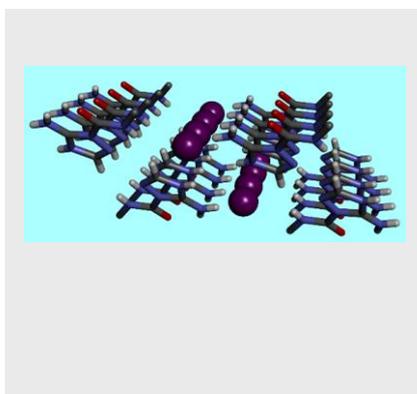
Keywords: anion channel • self-assembly • X-ray structure • hydrogen-bonding • Triazole 5

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COMMUNICATION

The presented work shows an impressive activation of the electrogenic anion transport achievable using simple artificial Triazole Quartet anion channels and valinomycin K⁺ carrier.



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Self-Assembled Columnar Triazole-Quartets - an example of synergetic H-bonding / Anion- π Channels

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