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A Voltage-Responsive Synthetic Cl⁻-Channel Regulated by pH

Shao-Ping Zheng, Ji-Jun Jiang, Arie van der Lee, and Mihail Barboiu*

Abstract: Transmembrane protein channels are an important inspiration for the design of artificial ion channels. Their dipolar structure helps overcome the high energy barrier to selectively translocate water and ions sharing one pathway, across the cell membrane. Herein, we report that the amino-imidazole (Imu) amphiphiles self-assemble via multiple H-bonding to form stable artificial Cl⁻-channels within lipid bilayers. The alignment of water/Cl⁻ wires influences the conduction of ions, envisioned to diffuse along the hydrophilic pathways; at acidic pH, Cl⁻/H⁺ symport conducts along a partly protonated channel, while at basic pH, higher Cl⁻/OH⁻ antiport translocate through a neutral channel configuration, which can be greatly activated by applying strong electric field. This voltage/pH regulated channel system represents an unexplored alternative for ion-pumping along artificial ion-channels, parallel to that of biology. ■■ Abstract was shortened to fit within allotted space. ■■

Transmembrane protein channels^[1–4] and carriers^[5] facilitate the ion transport across the cell membrane maintaining most of the vital functions.^[6–10] Any defects of these systems would cause specific diseases related to disorders of ion flux, clinically called *channelopathies*.^[11–15] For instance, cystic fibrosis (CF) is associated with defective Cl⁻ conductance along CFTR channel due to unexpected mutations.^[16,17] Synthetic ion transporters have greatly emerged in recent decades, as novel treatment approaches to replace the deficient proteins with structurally simpler compounds to effectively restore the transport biofunction.^[18–21] Inspired by prodigiosin, a natural H⁺/Cl⁻ carrier with potent anticancer activity,^[22–25] studies toward active synthetic transporters open up new avenues for the development of antitumor agents.^[26–29] Compared with extensively documented Cl⁻-carriers/ionophores that translocate themselves across membrane,^[29–34] examples of synthetic Cl⁻-channels^[35–40] providing hydrophilic interiors for successive ion hopping along selective conducting pathway, remain rare.

Natural channels present frequent open-closed transitions,^[41] usually relying on external triggers such as voltage,^[42–44] light,^[45,46] temperature,^[47,48] redox^[49] or molecular^[50]

agents, to generate action potential as signal transduction. CLIC (Intracellular Chloride Channel) protein family found in human nuclear membranes is a class of voltage-sensitive Cl⁻-channel which widely performs in transepithelial ion absorption and secretion in the kidney.^[51] Among this family, CLIC1 exists in two forms into lipid bilayers, either as soluble monomers,^[52] or as an active Cl⁻ channel, built through a pH-dependent state transition from soluble CLIC1.^[53] Determination of CLIC1 structure in the membrane^[54,55] confirms a concentration-dependent oligomerization event, resulting in the formation of a voltage-responsive Cl⁻ channel. However, few examples of voltage-responsive synthetic channels are reported in the literature.^[56–58]

Herein, we report a series of amino-imidazole (Imu) amphiphiles that form self-assembled Cl⁻/water channels in the lipid bilayers. Similar to natural protein CLIC1's,^[51–55] two different pH-dependent self-assembled channel configurations are found. Moreover, at high basic pH, Cl⁻ channel can be greatly activated, simultaneously resulting in a voltage-responsive channel. The formation of ion channels was evidenced by X-ray crystal structures of **Imu-2** and **Imu3-HCl**, as well as planar lipid bilayer assays showing step-like conductance profile. These columnar aggregates different from other stimulus-activated channels^[59–66] provide excellent reasons to be considered as dually pH/voltage-triggered biomimetic Cl⁻ channel with high performance in bilayer membranes. Interestingly, the channels show pH and voltage-dual responsive properties, with ion transport activated under low and high pH (with no activity at intermediate) and the application of a high membrane potential. The dual-responsiveness is an important merit of the work, which remains as a previously unreported behavior and would surely inspire future research in this area.

The reaction between substituted amino-imidazoles and corresponding alkyl-isocyanates readily afforded compounds **Imu1–3** (Figure 1). It's noted that electrophilic isocyanate group selectively reacted with N2-imidazole ring, which is more nucleophilic than -NH₂ group. The 4-substitution of imidazole with different electron-withdrawing side groups results in the formation of more acidic C1-H groups (imidazole ring) as potential anion binding sites.

Single-crystals of **Imu2** and **Imu3H⁺·Cl⁻** were obtained by slow evaporation of water/methanol or ethanol solution at room temperature.^[67] As shown in Figure 1, the single-crystal packings reveal that neutral **Imu2** and protonated **Imu3H⁺·Cl⁻** undergo self-assembly via extended H-bonding networks and form pores with water/anion wires arrays found inside.

Analysis of **Imu2** crystal packing shows heteromeric H-bonding associations of interdigitated amino-imidazole terminal heads, interacting on one side with their neighbors via four -CO⋯H₂N- (*d*_{N-H} = 3.00 Å) H-bonds between **Imu2** head units, which presents an unusual tetrahedral geometry (Fig-

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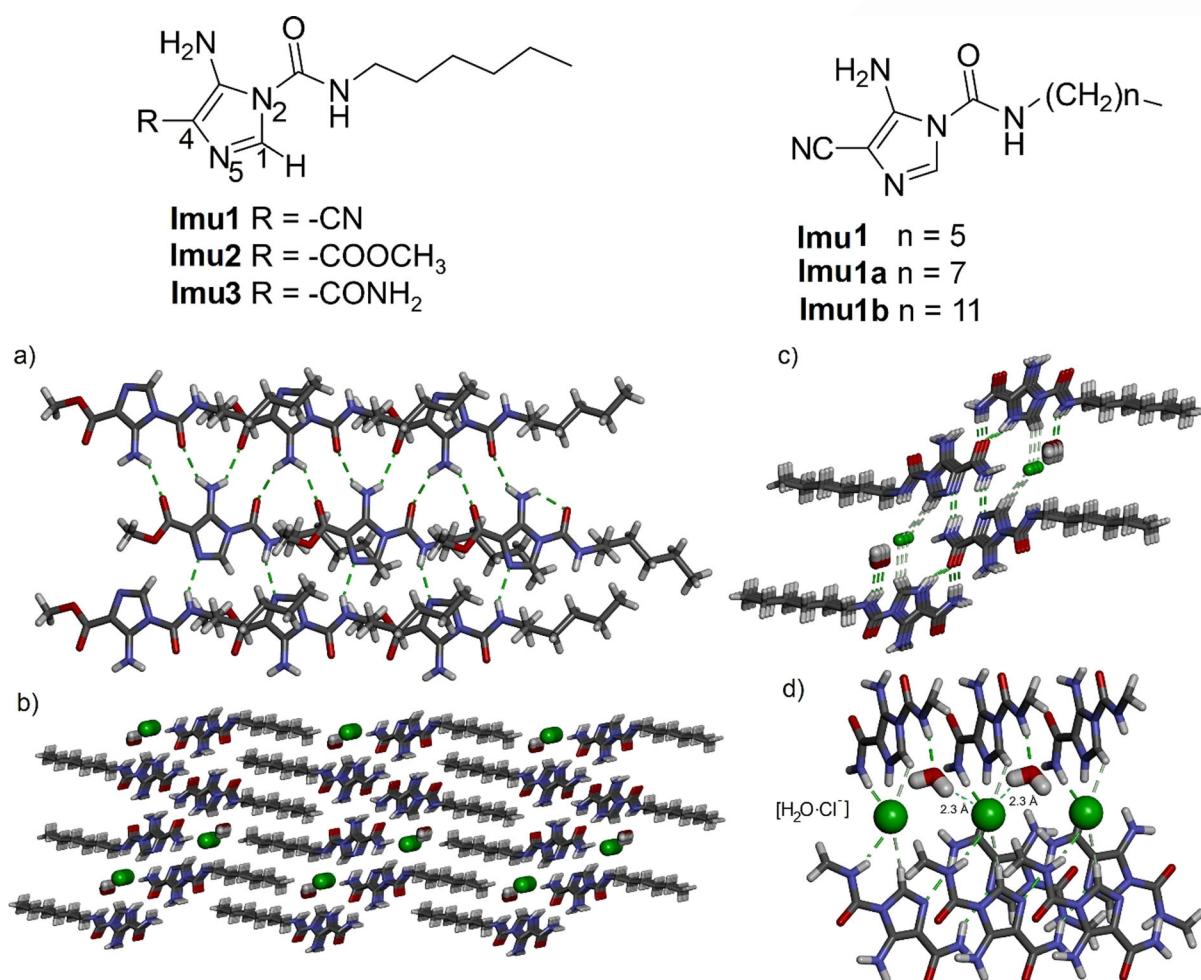


Figure 1. Chemical structures of **Imu1–3**; a) X-ray single-crystal packing in stick representation of **Imu2**; b) X-ray single-crystal packing in stick representation of **Imu3H⁺·Cl⁻**; c) top view and d) lateral view of the channels revealing the formation of the anion–water wires via synergetic N–H and C–H hydrogen bonding. Anions are presented in ball model.

ure 1 a). In the crystal, zipper-like layers are formed, further interconnected via double $-\text{N}_{\text{im}} \cdots \text{NHCO}-$ H-bonds ($d_{\text{N-H}} = 3.00 \text{ \AA}$) on the other side of **Imu2** heads. The successive H-bonding sequences strongly enforce the channel-type winding of **Imu2** strands allowing considerable overlap between the hydrophobic alkyl chains of the monomers. Therefore, the intermolecular hydrogen bonding affords a preorganized channel-like structure with two unique lumens in turn aligned. The robustness of the continuous alignment of **Imu2** results from the compatibility and the simultaneous effect of H-bonding and hydrophobic interaction, which may be associated with the stable oligomers observed in membranes.

The single-crystal packing of protonated **Imu3H⁺·Cl⁻**, reveals that one third of the molecules are protonated. They tend to assemble in a “head-to-head” conformation via $-\text{CO} \cdots \text{H}_2\text{N}$ and $-\text{CO} \cdots \text{N}_{\text{im}}$ H-bonds ($d_{\text{N-H}} = 3.00 \text{ \AA}$) between the **Imu3** head units on one side, while double H-bonds via $-\text{N}_{\text{im}} \cdots \text{NHCO}-$ motifs ($d_{\text{N-H}} = 3.00 \text{ \AA}$) are formed on the other side. Alternative H-bonding dimers form successive layers in tight contact with the neighboring ones. This assembled pattern encapsulates water/chloride-wires filling the interior void of about 5 \AA in diameter (Figure 1 b–d). The inner pore

superstructure is asymmetrically surrounding the Cl^- anions via multiple hydrogen bonding interactions: $\text{C-H} \cdots \text{Cl}^-$ ($d_{\text{C-H-Cl}} = 2.6 \text{ \AA}$), $-\text{CONH} \cdots \text{Cl}^-$ ($d_{\text{C-H-Cl}} = 2.6 \text{ \AA}$) and $-\text{CO-NH}_2 \cdots \text{Cl}^-$ ($d_{\text{C-H-Cl}} = 2.8 \text{ \AA}$), while the remaining space is closed by vicinal alkyl chains. Moreover, bridging water molecules are present in this pocket as a result of strong anion-dipole interaction from $\text{O}_2\text{H}-\text{Cl}$ ($\approx 2.3 \text{ \AA}$).

The alignment of water molecule-anion within single wire through channel may act as driving force for ion permeation.^[40a, 58b] The water-anion wires within channels anticipate, to some extent, the Cl^- transport activity responsive to outer pH change in the following transport experiments. There are probably two different water/anion binding configurations corresponding to acidic $[\text{H}_2\text{O} \cdots \text{Cl}^-]$ and basic $[\text{OH}^- \cdots \text{H}_2\text{O} \cdots \text{Cl}^-]$ pH conditions. Our findings may be related to imagination that complex protein anion-channels can be bio-mimicked using simpler compounds displaying constitutional functions like the natural ones.

The ion transport activities of **Imu1–3** were fully investigated across EYPC-LUVs (egg yolk phosphatidylcholine large unilamellar vesicles)^[68] loaded with a pH-sensitive dye HPTS (8-hydroxypyrene-1,3,6-trisulfonate) and NaCl

(100 mM) and suspended in buffers (100 mM, MCl, $M^+ = Li^+$, Na^+ , K^+ , Rb^+ , Cs^+). While varying cation in the extravesicular buffer or introducing FCCP (carbonyl cyanide-4-(trifluoromethoxy)-phenylhydrazone) as H^+ carrier didn't make any differences (Figure S6)

A series of assays: HPTS (10 μ M)/NaCl (100 mM, pH 6.4) containing LUVs were suspended in the extravesicular buffer solution (100 mM NaCl) with different pH values: 7.4, 8.4, 9.4, 10.4, 11.4), showed that the fluorescence ratio intensity gradually improved, especially with a significant increase from pH 8.4 to pH 11.4 implying a new translocation mechanism through assembled channels **Imu1**, **Imu1a** and **Imu2**, respectively (Figure 2c,d, Figure 2a,b, S8). **Imu3** hardly showed transport activity irrespective of pH values (Figure S8e), and control experiments of LUVs loaded with Na_2SO_4 (50 mM) instead of NaCl provided low transport activities of **Imu** channels (Figure S7). Interestingly, the Cl^- transport activities-related fluorescence ratio changes of **Imu1** (Figure S10b), **Imu1a** (Figure S8c) and **Imu2** (Figure S8d), dropped out when outer pH was changed from 7.4 to 8.4, then increased back to the maximum at pH 11.4. Accordingly, the Cl^- transport is highly dependent on pH: a) at lower pH values, **Imu** compounds are protonated under weakly acidic condition, which then induces a Cl^-/H^+ symport along the assembled channel, and the proton transport is

activated via inner water wires [$H_2O \cdot Cl^-$]; b) increasing pH to 8.4 gradually neutralizes the protonated **Imu** channels and consequently weakens transport activity; c) at higher pH 8.4–11.4, the increased OH^- concentration introduces another new Cl^-/OH^- antiport mechanism favored by translocation of OH^- -anions [$OH \cdot H_2O \cdot Cl^-$] within channels, greatly improving Cl^- transport efficiency.

Pseudo-first-order initial transport rate constants are strongly dependent on Δ pH (pH difference between intra- and extravesicular media) giving a transport rate sequence **Imu3** \ll **Imu1** $<$ **Imu1a** $<$ **Imu2** with maximum transport rate values at Δ pH = 5 or 6, quite in accordance with their fluorescence ratio change at the same Δ pH (Figures S8, S10 and Table S1). Meanwhile, Cl^- flow speed in **Imu2**-based channel was shown much better than that in **Imu1a**-based channel with pH increase, though **Imu1a** has higher transport activity (EC_{50}), also suggesting the cooperative translocation of water wires within **Imu2**-assembled channel is evenly distributed along the whole hopping path, rendering a manner of transport rate whose steady increase only depends on OH^- concentration.

The conductances of **Imu1a** or **Imu2** channels were assessed by the bilayer clamp technique in 1 M KCl solution as electrolyte with different pH values (4, 7, 8, 11). Thereby after addition of compound solution, distinct channel opening and closing states confirmed the formation of **Imu1a**- or **Imu2**-based channel (Figure 3a–h). **Imu2**'s multi-conductance channel is also reminiscent of the same channel characteristic of CLIC1 channel.^[69]

Varied conductance level, higher channel opening probability, longer retention time and better channel shape were more recorded at high pH 8 and 11 (Figure 3c,d,g,h), while at pH 4 and 7 (Figure 3a,b,e,f) the lower level dominated at the expense of the closed baseline state. I - V plots at different pH values (Figure 3i,j) more obviously demonstrated a significant increase of transmembrane ionic current by changing pH from 4 to 11. The magnitude of the smallest openings observed at lower pH for protonated channel configuration is inferior to the regular activities of electroneutral channel configuration at basic pH. For both compounds, I - V plots showed a linear variation (i.e., ohmic behavior) at low potential, while at higher potential they became asymmetric and seemed greatly responsive toward either negative or positive voltage applied, especially at basic pH, leading us to speculate **Imu1a**- and **Imu2**-built channels are simultaneously triggered by high voltage. This hypothesis is confirmed by the perfect fitting of current versus voltage curves with 2-parameter exponential function (Figure S13, S14) which represents a kind of sharp current increase with changing voltage behavior. Usually ion transport property of a nano-channel relies on channel shape, channel surface charge distribution, and the wettability of the channel.^[70] Multiple conducting species illustrate "supramolecular polymorphism" commonly observed with synthetic channel-forming compounds.^[71] We therefore equate the lower Cl^-/H^+ symport conducting state with a fully assembled channel behaving strong electrostatic interaction and the higher Cl^-/OH^- antiport state with the same channel but in a form of single hydrated anion species. Their orderly flow toward one

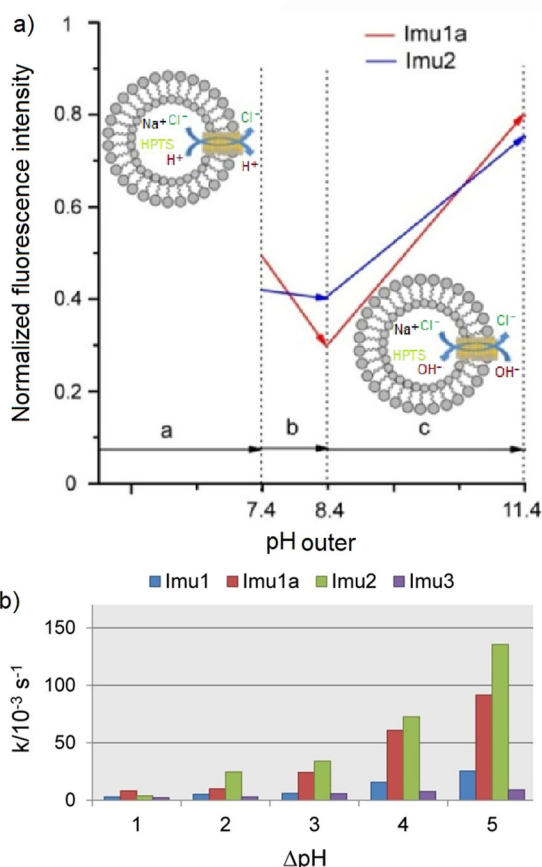


Figure 2. a) Normalized fluorescence intensity versus outer pH for **Imu1a** and **Imu2**, (insets) proposed transport mechanisms; b) pseudo-first-order initial transport rate constants for **Imu1–3** versus Δ pH between intra- and extravesicular media.

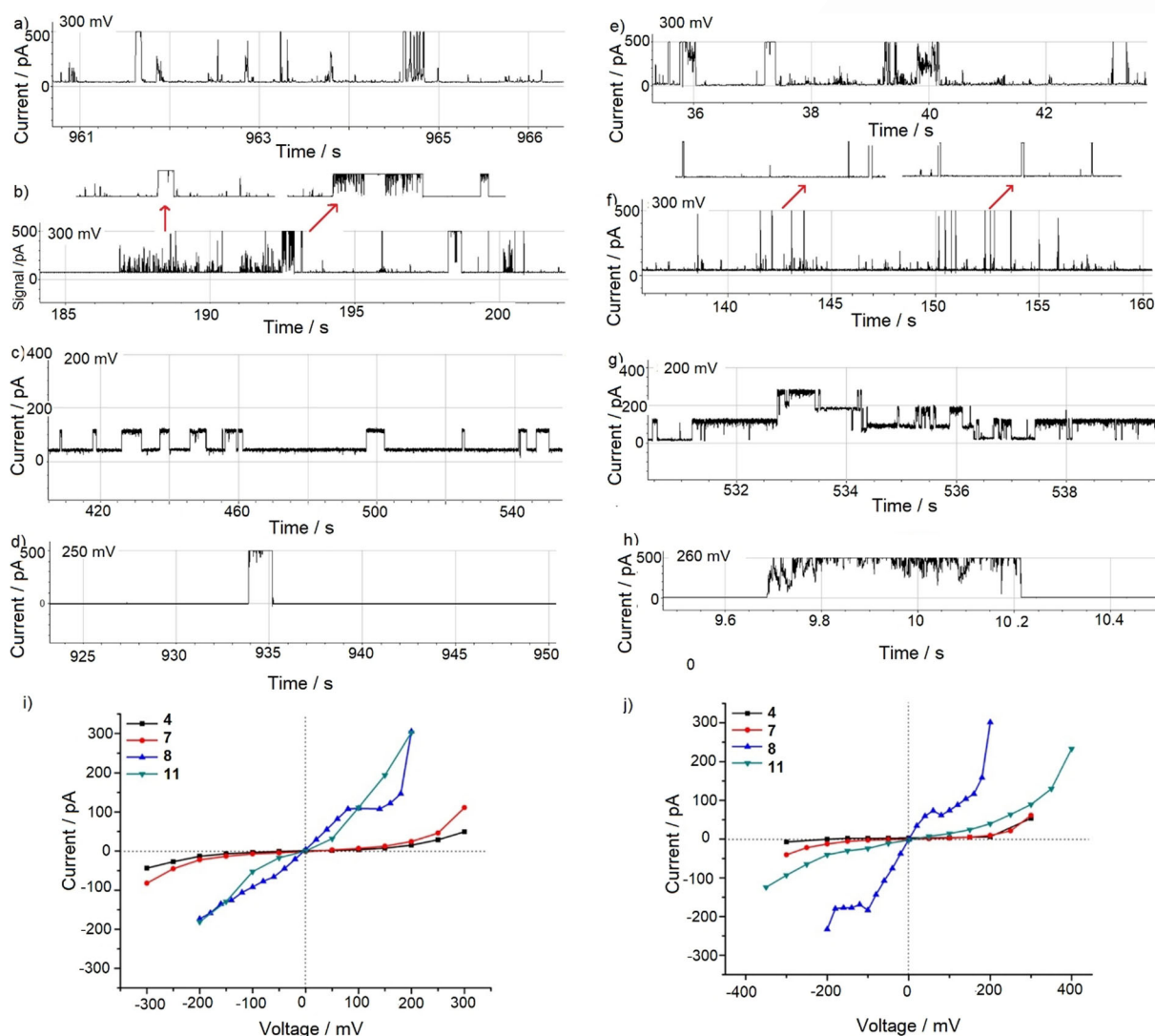


Figure 3. Channel conductance of **Imu1a**-based channel at pH a) 4, b) 7, c) 8, d) 11 and of **Imu2**-based channel at pH e) 4, f) 7, g) 8, h) 11; *I*-*V* plots for i) **Imu1a** and j) **Imu2** recorded in KCl solution at pH 4, 7, 8 and 11, respectively.

direction creates a dynamic charge distribution along the channel, which can certainly be stimulated if a strong electric field is applied.

In summary, we've designed an original class of synthetic self-assembled chloride channels **Imu1–3** providing remarkable combination of functions very close to natural ones (i.e. CLIC1): synergetic pH regulation and voltage sensitivity. Their signal sensitivity is related to the alignment of chloride-water single file along channel acting as driving force for permeating H₂O-mediated Cl⁻ transport and responding to pH change. At acidic pH, Cl⁻/H⁺ symport conducts along a partly protonated channel mainly driven by hydrogen bonding interactions. When switched to basic pH, higher Cl⁻/OH⁻ antiport hydrated anions are transported through a neutral channel configuration, which can be greatly activated by applying strong electric field. Conversely, the molecular-scale hydrodynamics of water and anions within channels, could also provide inspirations for the systematic

rationalization of active stimuli responsive channels. Work is in progress to pursue such studies.

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Conflict of interest

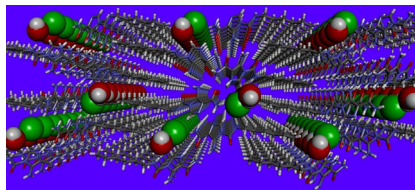
The authors declare no conflict of interest.

Keywords: biomimetics · H-bonding · ion channels · self-assembly · water/Cl⁻ wires

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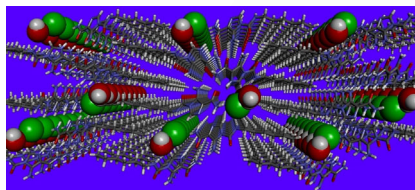
Communications

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