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Anion–π Slides for Transmembrane Transport

Jiri Mareda and Stefan Matile*[a]

Abstract: The recognition and transport of anions is usually accomplished by hydrogen bonding, ion pairing, metal coordination, and anion–dipole interactions. Here, we elaborate on the concept to use anion–π interactions for this purpose. Different to the popular cation–π interactions, applications of the complementary π-acidic surfaces do not exist. This is understandable because the inversion of the aromatic quadrupole moment to produce π-acidity is a rare phenomenon. Here, we suggest that π-acidic aromatics can be linked together to produce an unbendable scaffold with multiple binding sites for anions to move along across a lipid bilayer membrane. The alignment of multiple anion–π sites is needed to introduce a cooperative multi-ion hopping mechanism. Experimental support for the validity of the concept comes from preliminary results with oligonaphthalenediimide (O-NDI) rods. Predicted by strongly positive facial quadrupole moments, the cooperativity and chloride selectivity found for anion transport by O-NDI rods were consistent with the existence of anion–π slides. The proposed mechanism for anion transport is supported by DFT results for model systems, as well as MD simulations of rigid O-NDI rods. Applicability of anion–π slides to achieve electroneutral photosynthesis is elaborated with the readily colorizable oligoperylenediimide (O-PDI) rods. To clarify validity, scope and limitations of these concepts, a collaborative research effort will be needed to address by computer modeling and experimental observations the basic questions in simple model systems and to design advanced multifunctional anion–π architectures.

Keywords: anion–pi interactions • cooperative phenomena • ion channels • ion selectivity • ion transport • quadrupole moments

Introduction

In this concept article, we focus on the possible use of anion–π interactions for selective and efficient anion transport across lipid bilayer membranes. In biology, the selectivity of ion transport is of vital importance. In natural cation channels, selectivity often originates from the ion coordination to preorganized arrays of oxygen lone pairs,[1] whereas cation–π interactions are much less important than expected.[2] In biological anion channels, hydrogen bonding, ion pairing, and anion–dipole interactions contribute to selectivity.[3] So far, anion–π interactions[4–11] are not known in biological anion channels. Actually, the evidence for the existence of anion–π interactions beyond the virtual world is scarce.[4–11] The question if anion–π interactions could be used to create significant function such as transmembrane transport is therefore timely, attractive, and very demanding. To achieve this function, anion recognition by anion–π interactions has to be combined with anion translocation. This combination is not an easy one, because tight binding of ions tends to decelerate rather than accelerate translocation. In biological anion and cation channels, the alignment of several ion binding sites one after another is employed to bypass this dilemma and combine selectivity with speed.[1,3] The cooperative transport of ions along such strings of partially occupied ion binding sites is referred to as multi-ion hopping (vide infra).[12,13] To achieve significant transmembrane transport with anion–π interactions, it is therefore essential to align multiple π-acidic aromatic binding sites in series. Anions could then move fast and selectively along these anion–π "slides."

A complementary approach has been explored almost a decade ago to achieve transmembrane potassium transport with cation–π interactions. In that case, π-basic, rigid-rod *p*-oligophenyls (POPs) were expected to act as transmembrane cation–π slides (Figure 1 A). More recently, π-acidic, rigid-rod oligonaphthalenediimides (O-NDIs) have been introduced to tackle the much more challenging anion–π slides (Figure 1 B).[15–17] With the colorizable oligoperylenediimides (O-PDIs), finally, the usefulness of anion–π slides to create electroneutral photosystems have been explored (Figure 1 C).[18] In the following, we briefly summarize these breakthroughs and outline the emerging concept of anion–π slides. Along the way, we will also address the issue of how to detect and describe anion selectivity sequences and cooperative multi-ion hopping mechanisms. We will also elaborate on perspectives such as the challenge of how to produce superslides possessing π-moieties (or chromophores) with quadrupole moments up to +55 B (Buckinghams); that is, far exceeding those of hexafluorobenzene (+9.5 B) or trinitrobenzene (+20 B).[4]

Discussion

Anion–π Interactions: Anion–π interactions are defined as nonbonding, favorable interactions between an electron-deficient or π-acidic aromatic system and an anion.[4–11] Anion–π interactions are clearly less widespread than the complementary cation–π interactions. This is reasonable because most aromatic π-systems are electron-rich or π-basic, and many excellent examples from chemistry and biology serve as constant reminders of the crucial importance of cation–π interactions.[2] The complementary π-acidic aromatics are

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[a] Dr. J. Mareda, Prof. S. Matile
Department of Organic Chemistry
University of Geneva, Geneva (Switzerland)
Fax: (+41) 22-379-3215
E-mail: stefan.matile@unige.ch

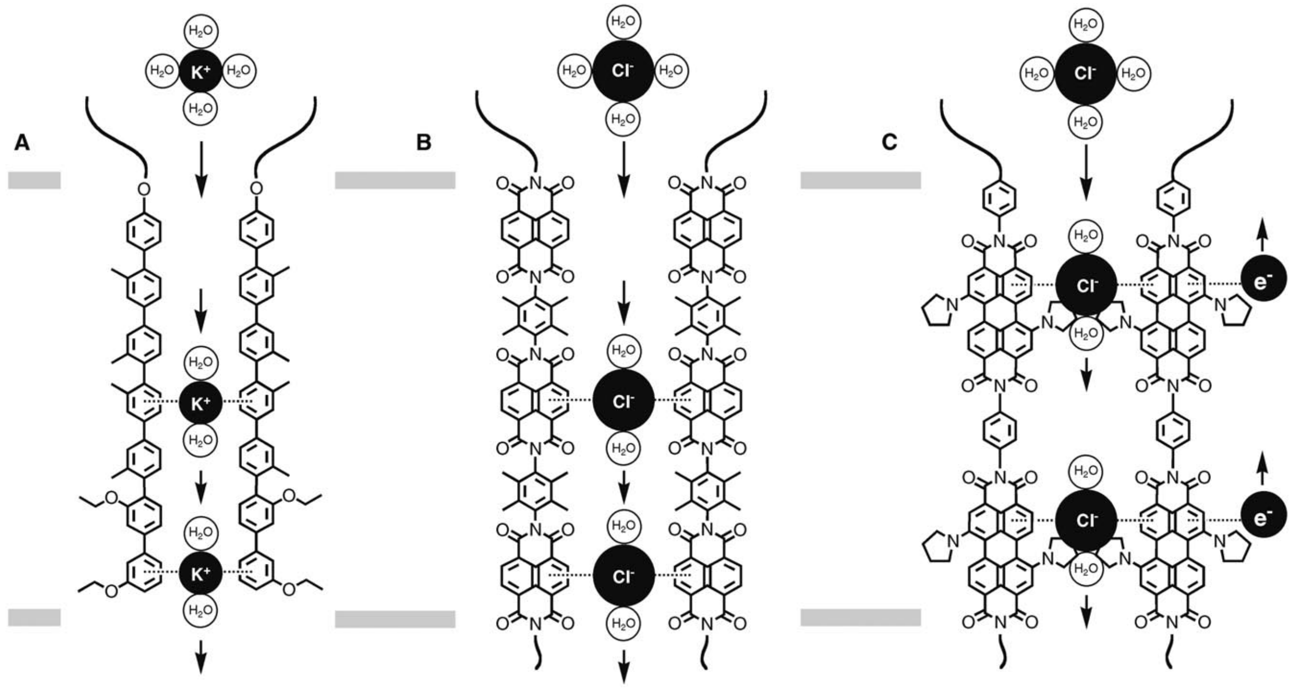

Figure 1. General structure of cation–π and anion–π slides. A) Rigid *p*-oligophenyl (POP) rods for selective potassium transport across bilayer membranes, B) oligonaphthalenedimide (O-NDI) rods for selective chloride transport, and C) oligoperylenedimide (O-PDI) rods for active, electroneutral electron/anion antiport with light.

relatively rare in chemistry and biology. The interactions of anions with π-acidic aromatics are governed by electrostatic and ion-induced polarization forces. The polarizability of the aromatic system determines the significance of anion-induced polarization to anion–π interactions. The importance of electrostatic contributions is also revealed by the permanent quadrupole moment Q_{zz} (Figure 2). The parameter Q_{zz} describes the vertical charge distribution on both sides of the central plane of the aromatic system. The common π-basic aromatics have negative Q_{zz}. Examples include benzene with $Q_{zz}=-8.5$ B[4] or pyrene (**1**) with $Q_{zz}=-13.8$ B (Figure 3).[15] For anion–π interactions, π-acidic aromatics with positive permanent quadrupole moments Q_{zz} are required. The classical hexafluorobenzene has $Q_{zz}=+9.5$ B, cyanuric acid a bit less ($Q_{zz}=+7.0$ B), trinitrobenzene much more ($Q_{zz}=+20$ B).[4] Charge-transfer interactions can have an important stabilizing influence in aromatic–anion interactions, particularly with easily oxidizable anions such as iodide. With weakly basic anions, such as fluoride, the formation of covalent bonds is conceivable (e.g., with electrophilic centers in heterocyclic aromatics such as the carbonyl carbons of pyridinediones, vide infra).

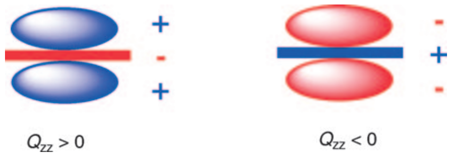

Figure 2. Schematic side view of π-acidic (left) and π-basic (right) aromatic rings (solid lines) between their electron-poor (blue) and electron-rich (red) π-clouds, with indication of the negative and positive axial quadrupole moments Q_{ZZ} that are used to quantify π-basicity and π-acidity, respectively.

Until recently, anion–π interactions have been a topic of interest in computational chemistry with limited experimental support to examples from selected crystal structures.[6–8] However, increasing experimental evidence is emerging in support of the occurrence of anion–π interactions in solution.[9–11,15–17] These developments have been reviewed recently in pioneering milestone reviews of this emerging area.[4,5]

For the creation of anion–π slides, we selected naphthalenediimides (NDIs)[19] as π-acidic[15,16] modules. Their ability to interact with anions is unexplored. However, the formation of aromatic electron donor–acceptor interactions is known from charge-transfer complexes with π-basic aromatics.[19–27] Moreover, NDIs are excellent electron acceptors ($E_{HOMO}=-7.07$ eV),[28] and their face-to-face π-stacks rank among the best organic n-semiconductors.[29,30] Considering these outstanding characteristics, we were not surprised to compute a $Q_{zz}=+14.7$ B for N-unsubstituted NDIs (MP2/6-311G**//PBE1PBE/6-311++G** methods).[16]

The *N*-tetramethylphenyl (TMP) substituent in NDI **2** (Figure 3) caused an additional increase and gave $Q_{zz}=+18.6$ B, which is one of the largest global quadrupole moments known today.[4,16] This increase occurred because the perpendicular orientation of the NDI and the phenyl planes

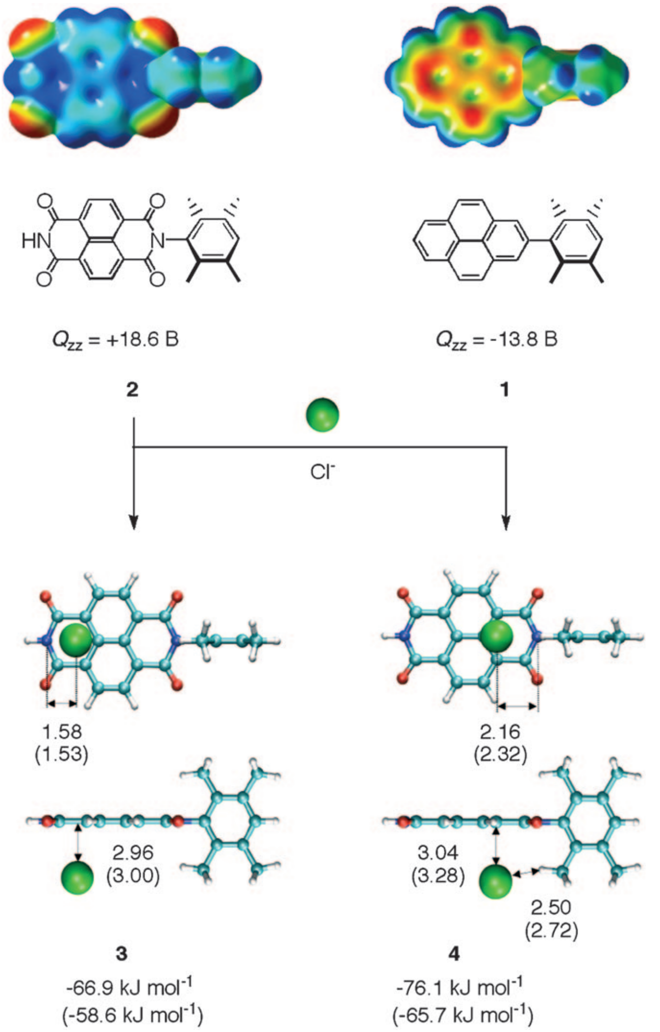

Figure 3. Electrostatic potential surfaces and Q_{ZZ} of pyrene **1** and N-substituted NDI **2** (blue positive, red negative, ±120.0 kJ mol^{-1}, MP2/6-311G**) and ball-and-stick DFT optimized (PBE1PBE/6-311++G**) structures of chloride-NDI complexes without (**3**) and with (**4**) interference from TMP viewed from the top (top) and the side (bottom, atom color coding, anions green). Indicated are pertinent distances (in Å), interaction energies (MP2/6-311G** method, in kJ mol^{-1}); values for bromide complexes are in parentheses (adapted from ref. [16]).

removed contributions from the negative phenyl quadrupole moment that accounts for the strongly π-basic surfaces and added the perpendicular local quadrupole moment oriented along the phenyl plane that accounts for the weakly π-acidic periphery. The electrostatic potential surfaces of NDI **2** nicely illustrates how the perpendicular orientation of NDI and phenyl planes produce a π-acidic face, in which the positive NDI surface extends in a continuous way to the equatorial region of the phenyl (Figure 3). Preservation of this facial π-acidity in rigid O-NDI rods suggests that the attractive interactions of anions with anion–π slides could be quite powerful (see below).

The computed electrostatic potential surfaces of NDI **2** confirmed the pyridinedione heterocycle as one of the most electron-deficient subunits. Chloride binding on a pyridinedione without an adjacent TMP substituent produced complex **3** with the anion centered 2.96 Å from the aromatic plane and shifted by 1.58 Å along the *N,N*-axis to arrive nearly in the middle of the heterocycle. In the gas phase and neglecting dehydration penalty, the anion–π interaction energy was computed to a quite significant interaction energy $E_{\text{int}} = -66.9$ kJ mol^{-1}.

In the alternative complex **4** with the chloride near the other pyridinedione, steric interference from the adjacent TMP substituent pushes the chloride by 0.58 Å toward naphthalene core (compare the lateral anion displacements of 1.58 Å for **3** vs. 2.16 Å for **4**, Figure 3). The coinciding increase in distance from the aromatic plane by 0.08 Å confirmed that TMP interference weakens anion–π interactions. However, the total change in interaction energy caused by the TMP substituent was computed to increase to $E_{\text{int}} = -76.1$ kJ mol^{-1}. This increasing rather than decreasing anion affinity was supported by the short H−Cl contact of 2.50 Å in **4**, implying that the loss in anion–π interaction caused by the TMP substituent is overcompensated by a quasi-linear $C{-}H\cdots Cl^-$ hydrogen bond[31,32] to the same substituent.[16]

Comparison of the optimized geometries for chloride complexes **3** and **4** with the corresponding bromide complexes revealed that the TMP substituent pushes the bromide by 0.21 Å farther off the optimal binding site on the pyridinedione acceptor (compare the lateral anion displacements in Figure 3). The coinciding 0.19 Å increase of vertical displacement suggested that the weakening of anion–π interactions by TMP interference should be more pronounced for the larger bromide compared to the smaller chloride. The overall weakened binding energies found for bromide compared to chloride suggested that O-NDI π-slides could transport anions with chloride selectivity. Efforts to compare these computational data with experimental data from anion binding studies in the gas phase by mass spectrometry are ongoing; preliminary results are very encouraging.

Cation–π slides: The availability of cation–π slide **5** was essential to support approaches toward their much more challenging π-acidic counterparts (Figures 1 A and 4).[14] When we made cation–π slide **5** about a decade ago, cation–π interactions were still thought to account for the selectivity of biological potassium channels.[1,2] Importantly, computational studies indicated that arene arrays with arene–arene distances fixed to bind potassium best, fail to reproduce the full selectivity sequence of biological channels, in part because rubidium and cesium are rejected for simple steric reasons.[2] This prediction was supported by amphiphilic resorcin[4]arenes as synthetic potassium channels with fixed arene-arene distances ($K^+ > Na^+ \gg Rb^+$ selectivity).[33] However, arene arrays with flexible arene–arene distances to accommodate every cation as best as possible were computed to roughly reproduce the biologically relevant Eisenman IV selectivity sequence ($K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$).[2,34] Potassium and larger cations are preferred by dynamic arene arrays, because they do not require full dehydration. Among these larger cations, the smallest is best because binding to the arene array is naturally strongest.

We thought that bundles of *p*-septiphenyl **6** could produce the string of dynamic, noncovalent arene arrays required for cooperative potassium transport with Eisenman IV.[14] However, the cation selectivity found for **6** followed an Eisenman III series ($Rb^+ > K^+ > Cs^+ > Na^+ \approx Li^+$) and was rather weak. According to Eisenman theory, ion selectivity originates from the extent of compensation of the dehydration penalty by binding to the channel, with the extremes reaching from negligible binding in Eisenman I ($Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$) to exceptional binding in Eisenman XI ($Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$).[34] From this point of view, the poor selectivity suggested that cation binding by cation–π slides **6** is too weak (Figure 4, wavy arrow). One possibility to improve cation–π interactions was to increase the proximity between monomeric or only loosely bundled POPs **6**. The iminodiacetate (IDA) ligand at one end of the *p*-septiphenyl rods was introduced for this purpose. Coordination of one multivalent polyhistidine ligand to the several Cu-IDA termini caused the assembly of transmembrane POP rods. The obtained cation–π slide bundles **5** showed clearly improved cation selectivity and the biologically relevant Eisenman IV. Ligand-gated assembly of POP bundles **5** was supported by CD spectroscopy, their transmembrane orientation by fluorescence depth quenching. Several structural modifications, including rod elongation or shortening, and an increase or decrease in rod asymmetry strongly reduced transport activity.[35]

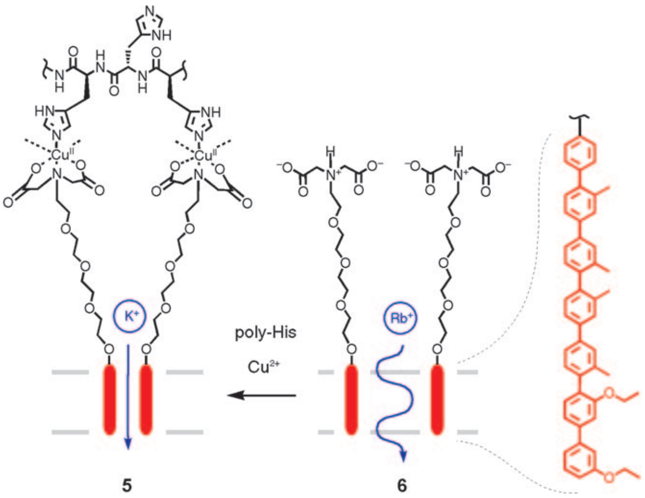

Figure 4. POP rods as cation-π slides. Programmed assembly with Cu^{2+} and poly-His changes the weak Eisenman III selectivity of the poorly assembled (or monomeric) cation–π slides **6** to the more pronounced Eisenman IV selectivity of the more tightly assembled cation–π slide bundle **5**.

Although always difficult to say conclusively with complex systems, these results with cation–π slides **5** and **6** were overall compatible with cation–π interactions along the π-basic phenyl rings of the POP scaffold as origin of transport activity and selectivity. These meaningful results with cation–π slides encouraged us to tackle the much more demanding anion–π slides.

The concept of anion–π slides: O-NDI rod **7** was considered as representative anion–π slide for the modeling at PBE1PBE/6-311++G** level (Figure 5).[16] The length of the rigid-rod scaffold of **7** (32.5 Å, N1–N6 distance) roughly matches the thickness of standard lipid bilayer membranes. This hydrophobic matching is crucial to assure transmembrane rod orientation.[35,36] In transmembrane orientation, O-NDI **7** offers six NDI binding sites S1–S6, with two identical minima per NDI that are separated by a small but computable barrier ($\Delta E_{Cl} \approx 16\,kJ\,mol^{-1}$, precise transition-state energy unknown). The terminal S1 and S6 sites are slightly higher in energy ($\Delta E_{Cl} = 9.2\,kJ\,mol^{-1}$), an effect that could influence both entry into and release from the slide. Between the NDI binding sites, the π-acidic edge of the TMP spacers produce the maxima anions have to overcome to move on along the slide (transition-state energy unknown).

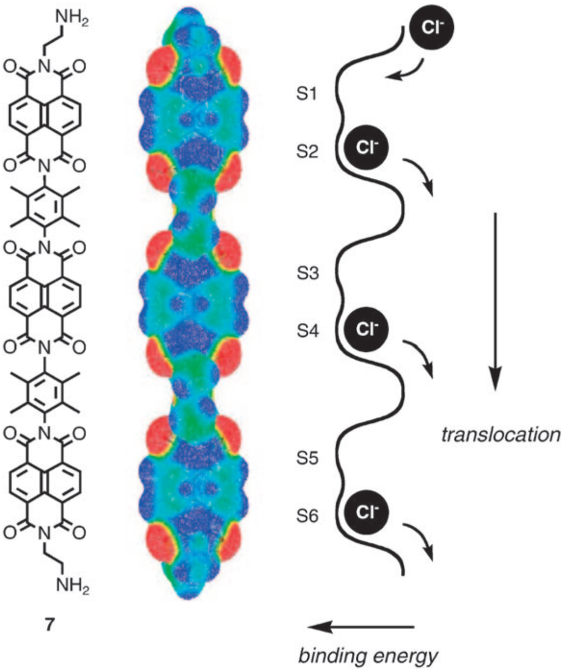

Figure 5. The concept of anion–π slides. The "blue face" of the electrostatic potential surface of O-NDI rod **7** (adapted from ref. [15]) supports the possibility of multi-ion hopping along the anion–π sites S1–S6 as indicated in the qualitative energy diagram.

From the six binding sites in the qualitative energy profile of O-NDI slide **7**, presumably no more than three will be occupied in the resting state. Charge repulsion between bound anions will hinder the binding of more than one anion per NDI. These selectively bound anions in, for example, binding sites S2, S4, and S6 will hinder the binding of less recognized anions and thus induce selectivity. However, would this tight binding of the three recognized anions also slow down their translocation along the slide and across the membrane? The mechanism envisioned to combine selectivity and speed in anion–π slides is similar to the multi-ion hopping present in many biological ion channels.[1,3,12,13] In multi-ion hopping, the thermodynamic stability needed for selectivity is coupled with kinetic lability and cooperativity. Consider a recognized anion approaching, driven by a transmembrane gradient, O-NDI **7** in the resting state with the same preferred anions in positions S2, S4, and S6 (Figure 5). Binding to position S1 will repel the anion in position S2. Its translocation to position S3 will repel the anion in position S4 to position S5 and cause the release of the anion in position S6. To liberate position S1 for the transport of the next anion, the three anions newly in positions S1, S3, and S5 will then have to collectively diffuse to positions S2, S4, and S6.

Overall, multi-ion hopping along anion–π slides is expected to enable instantaneous release of strongly bound anions on one side of the membrane in response to anion binding on the other side. In this process, the anion entering the membrane on one side is not the same exiting on the other. Structural insights from biological potassium[1] and chloride channels[3] essentially confirm the validity of this mechanistic picture on the highest level of sophistication of supramolecular architecture.

In this context, the term "slide," implying facilitated, passive movement along a robust scaffold, is probably inappropriate to describe cooperative multi-ion hopping along "bumpy slides." Newton's balls have been suggested[37] to better illustrate at least aspects of the multi-ion hopping mechanism envisioned with anion–π slides (Figure 6).

These mechanistic considerations imply that the determination of anion selectivity sequences[38,39] would not suffice to demonstrate the existence of anion–π slides. Experimental support for the occurrence of multi-ion hopping would be required as well. The traditional proof of cooperative transport is an anomalous mole fraction effect (AMFE).[12,13,39] To determine an AMFE, the dependence of the transport activity on the mole fraction of mixtures of preferred ("fast") and disfavored ("slow") anions is measured (Figure 6). Linear dependence indicates the absence and nonlinear dependence the presence of cooperative transport of the fast anions. In the presence of an AMFE, the activity found with mixtures is lower than expected from that of the pure anions. This underadditivity shows that the persistent binding of just one of the fast anions is insufficient to accelerate transport. Binding of a single fast anion may even hinder the transport of the slow anion and reduce the observed global activity. The rapidly increasing activity with an increasing excess of the fast anion then confirms that the binding of more than one of the fast anions is needed to really move fast. This indication of cooperative anion transport implies the occurrence of multi-ion hopping and thus the successful creation of an anion–π slide.

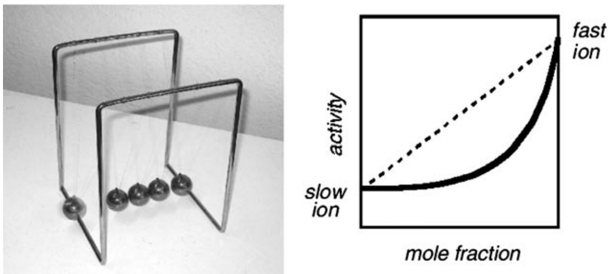

Figure 6. Newton's balls to illustrate (left), and the AMFE required to support multi-ion hopping (right). An anomalous mole fraction effect refers to a non-linear (solid line) rather than a linear (dotted line) dependence of transporter activity on the mole fraction of mixtures of preferred (fast) and disfavored (slow) ions.

The relation between AMFE and multi-ion hopping has been studied extensively for biological ion channels.[12,13,39] Considering the complexity of the involved processes, it is not surprising to learn that this relation is not always straightforward. All interpretations should thus be formulated and appreciated with appropriate caution.

O-NDI rods as anion-π slides: To explore the concept of anion–π slides experimentally, O-NDI rods **8**–**11** were synthesized in several steps from commercially available starting materials (Figure 7).[15–17] O-NDI rod **8** is uncharged and symmetric, with Boc-protected glycines at both ends. According to an assay based on pH-sensitive fluorescent probes, O-NDI rod **8** did indeed prefer to transport anions rather than cations across neutral lipid bilayers. The halide selectivity sequence VI ($Cl^- \sim F^- > Br^- > I^-$)[38] found experimentally showed that any eventual cost of at most partial anion dehydration (Figure 1, vide infra) is fully compensated by strong binding to O-NDI rod **8**.[15] The found selectivity sequence supported the existence of strong operational anion–π interactions and was in agreement with selectivity sequences computed for anion–NDI complexes. O-NDI rod **8** exhibited a clear AMFE for Cl^- as a fast anion and I^- as a slow anion. As elaborated in the preceding section, this observation is very important, because it provides experimental support of a cooperative multi-ion hopping mechanism and thus the existence of anion–π slides. This is presumably the first time that AMFE has been observed for synthetic transporters in fluorogenic vesicles.[37,40–46]

Interface engineering[47] was important to better understand the nature of anion–π slides.[15–17] The introduction of charges at both ends of O-NDI rods deactivated the anion–π slides. Considering the difficulty of charged termini to translocate across a bilayer membrane,[48] this finding could be interpreted as support of the importance of transmembrane rod orientation for activity. The introduction of charges only at one end in O-NDI rod **9** slightly increased activity and strongly reduced selectivity to a very weak halide V ($Cl^- \geq Br^- \geq I^- \sim F^-$). These trends could suggest that charge repulsion reduces the proximity of O-NDI rods in transmembrane O-NDI bundles to facilitate anion translocation, but also reduces anion recognition (Figure 7, wavy arrow). This interpretation was supported by the reduced activity but increased selectivity obtained with O-NDI hairpin **10**. This suggested that covalent capture in **10** could in-

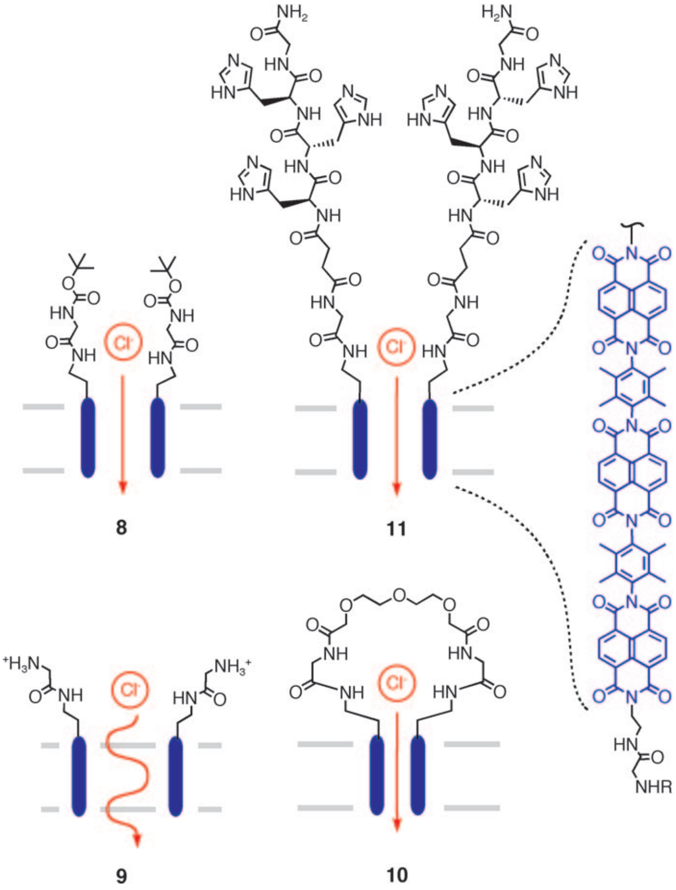

Figure 7. O-NDI rods as anion–π slides. Compared to neutral O-NDI bundles **8**, charge repulsion in cationic O-NDI bundles **9** weakly increases activity but strongly decreases selectivity, covalent capture in O-NDI bundles **10** decreases activity and increases selectivity, and hydrophilic anchoring in O-NDI bundles **11** strongly increases activity and weakly decreases selectivity (R = Boc or Fmoc).

crease the proximity of O-NDI rods in transmembrane O-NDI bundles to maximize anion recognition at the cost of hindered anion translocation. A much more dramatic increase in activity without significant losses in anion selectivity was obtained with the attachment of terminal histidine (His) tags. This effect was attributed to "hydrophilic anchoring"[47,18] of O-NDI rod **11**, a highly effective strategy not only to prevent reorientation of the rods in the membrane, but also to improve their delivery to the membrane and facilitate their reversible transfer between vesicles.[17]

O-PDI rods as anion-π slides with photosynthetic activity: The creation of electroneutral artificial photosystems was envisioned as an attractive application of anion–π slides.[18] The combination of ion transport with photosynthetic activity is of interest to avoid the membrane polarization that causes rapid saturation with unidirectional electron transport.[49,50] For electroneutral photosynthesis, compensation of active electron transport in one direction by passive anion transport in the other direction would be ideal. This active/passive electron/anion antiport requires synthetic access to multifunctional photosystems that can not only capture and convert light into transmembrane electron flow, but also transport anions with very high selectivity. With O-NDI anion–π slides, this appears possible. However, the synthesis of NDI chromophores remains very difficult,[19,27,28] not to mention about fully colorized O-NDI rods. In clear contrast, the synthesis of PDIs of various colors is unproblematic.[51–53] Like NDIs, PDIs are π-acidic n-semiconductors that can be variably colorized, reduced, and oxidized. PDIs with two pyrrolidinyl core substituents are capable of symmetry-breaking photoinduced charge separation similar to chlorophyll, the green pigment of plants (Figure 8).[52] Moreover, PDIs seem to align favorably in one leaflet of a lipid bilayer.[27] Rigid O-PDI rod **12** with two green PDI chlorophyll mimics in line appeared perfect to span a lipid bilayer membrane and act as both photosystem and anion–π slide.[18] Anionic triglutamate tails were added to reproduce the benefits from hydrophilic anchoring[47] observed with O-NDI π-slides[17] and assure oriented membrane binding of asymmetric systems such as **13**.

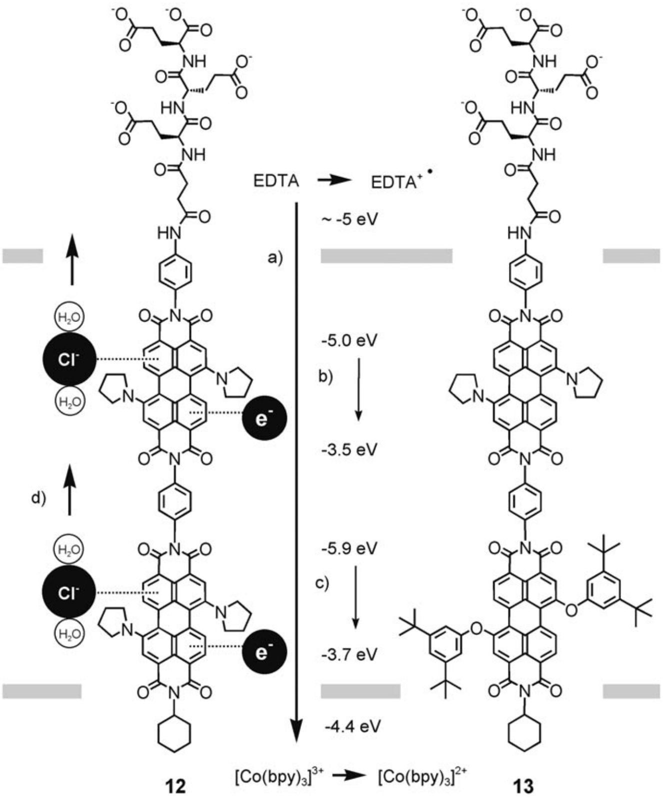

Figure 8. O-PDI rods as anion–π slides with photosynthetic activity. The active, photoinduced transport of electrons from external EDTA donors to internal $[Co(bpy)_3]^{3+}$ acceptors by O-PDI photosystems **12** and **13** (a–c) is thought to be compensated by passive anion antiport along the same multifunctional anion–π slides **12** and **13** (d). Frontier energy orbital levels in eV (electron volts, against vacuum) refer to HOMO (EDTA), LUMO $[Co(bpy)_3]^{3+}$, or both (PDIs).

O-PDI rod **12** was found to transport anions across bilayer membranes about as selectively as O-NDI rods. Anion selectivity with an anionic peptide anchor was particularly convincing and in support of anion–π interactions as the origin of anion selectivity. Photosynthetic activity of O-PDI rod **12** was characterized in vesicles with EDTA (EDTA = ethylene diamine tetraacetic acid) as an external electron donor and $[Co(bpy)_3]^{3+}$ (bpy = bipyridine) as an internal electron acceptor.[50] Their frontier energy orbital levels reveal that reduction of $[Co(bpy)_3]^{3+}$ by EDTA in the dark is thermodynamically unfavorable. Occurrence of the same process with light thus converts photonic into chemical energy. This system is convenient, because photosynthesis is reported as changes in cobalt absorption during photoreduction. Under these conditions, electroneutral photosynthetic activity was found to require the endergonic[54] self-assembly of O-PDI rod **12** into at least nonameric bundles.

In O-PDI dyad **13**, one of the two green PDIs in O-PDI rod **12** is replaced by a red PDI with two phenoxy substituents in the core.[51–53] The external triglutamate assures that the red PDI acceptor ends up in the inner leaflet of the lipid bilayer membrane. In this arrangement, the red PDI may contribute to photosynthesis by, on the one hand, absorbing and transferring photonic energy to the green PDI and, on the other hand, accepting electrons on the way from the green PDI to the final cobalt acceptor. In agreement with these expectations, the photosynthetic activity of the O-PDI dyad **13** was higher than that of the unicolor O-PDI **12**.

Perspectives

The concept of anion–π slides proposes that anions can be moved selectively and fast along a molecular rod that contains several π-acidic aromatics along the scaffold. In this concept, the proposed use of anion–π interactions to selectively transport anions across lipid bilayer membranes is new. The concept of anion–π slides further proposes a linear arrangement of a series of anion–π sites to combine selectivity with speed. Although the envisioned cooperative multi-ion hopping mechanism is the general answer of biological ion channels to the challenge how to be both fast and selective, it has not received much explicit attention in synthetic ion channels and pores.

A substantial and consistent collection of computational and experimental evidence in support of anion–π slides is available.[15–18] The quadrupole moments computed for NDIs are among the strongest known in the literature. Steric and electronic substituent effects are identified as rational tools to modulate magnitude and selectivity of anion–π interactions. O-NDI and O-PDI rods with distinct facial π-acidity consistently prefer to transport anions rather than cations, independent of substantial structural variations of the rod termini. Among anions, O-NDI and O-PDI rods prefer those that are difficult to dehydrate, a preference that indicates strong anion binding to the anion–π slide. The existence of a multi-ion hopping mechanism is supported by an AMFE, and applicability of anion–π slides is exemplified with electroneutral photosynthesis.

This encouraging evidence in support of the concept of anion–π slides should not distract the readers from the current situation in the field. Substantial computational but very little experimental evidence in support of anion–π interactions in solution is available today.[4–11] Moreover, it is important to mention the difficulty in predicting the structure of aromatic–anion complexes and the difficulty in evaluating the importance of anion–π interactions in mediating host–guest interactions, since other interactions like C–H···π can be stronger (Figure 3).[55] Eventual contributions from covalent capture with weakly basic anions and charge-transfer interactions with oxidizable anions remain to be identified and quantified. Very preliminary results suggest that the former is more likely than the latter (i.e., rapid H/D-exchange with fluoride, no color change with iodide). Moreover, the complex question concerning the extent of dehydration required for anion–π interactions awaits clarification. It is clear that with diameters larger than that of water, complete dehydration is not necessary and is thus very unlikely to occur (Figure 1).[2] One referee correctly pointed out that evidence for favorable interactions of lone pairs on oxygen atoms with electron-poor aromatic systems[5,56] implies that anions could retain their complete solvation shell and still have favorable interactions with anion–π slides. Considering these fundamental questions, anion–π slides are enormously complex and ambitious systems, and all results obtained and interpretations made must be appreciated with appropriate caution. Simple anion binding, phase transfer and U-tube studies in bulk membranes[57] with anion–π model systems (e.g., NDI cyclophanes[58]) appear unavoidable to carry out future developments on solid grounds. Preliminary results in this direction are very encouraging.

Two general approaches to refine anion–π interactions on π-acidic NDI surfaces are easily identifiable. Most importantly, the introduction of π-accepting groups as core substituents is expected to produce exceptionally powerful anion–π interactions.[19,27,28,30] Preliminary computational studies revealed absolutely spectacular quadrupole moments of up to $Q_{zz} = +55.5$ B for 2,6-dicyano-NDI **14** and the so far inexistent (and possibly explosive) 2,3,6,7-tetracyano-NDI **15** (Figure 9). Computational anion binding studies on these superb anion–π acceptors are ongoing in parallel to synthetic studies toward sticky models[30] and slides with maximized facial π-acidity. The alternative introduction of π-donors as NDI core substituents is very attractive to modulate color and redox properties without global structural changes in higher order architectures.[27,28] For anion–π slides, these approaches are more problematic because color comes at the cost of reduced anion–π interactions and the synthesis of multicolor O-NDI rods remains very difficult.

The second important aspect with anion–π interactions on π-acidic NDI surfaces concerns contributions from the imide substituents. Computational studies suggest that the current TMP group contributes significantly to anion selectivity and anion translocation. Extensive TMP replacement,

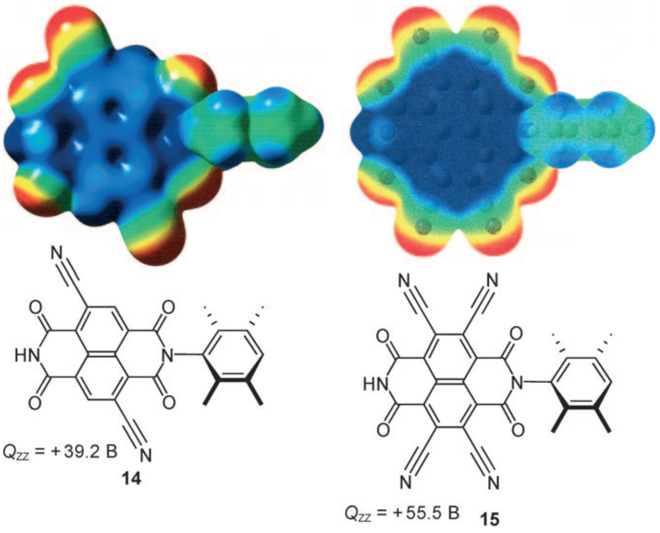

Figure 9. Electrostatic potential surfaces and Q_{ZZ} (MP2/6-311G**) of NDIs **14** and **15** (±120.0 kJ mol^{-1}; blue positive, red negative).

from simple phenyls to higher aromatics with functionalized side chains, looks unproblematic and very attractive to build refined anion–π sites and anion–π slides.

The current concept of anion–π slides totally ignores supramolecular chemistry. This is regrettable, because all experimental evidence points toward transmembrane bundles as active suprastructures. The perspective to include supramolecular considerations into the design of anion–π slides is most attractive. Moreover, design strategies for intermolecular multi-ion hopping between staggered π-acceptors of neighboring rods may be developed to ultimately lead to refined architectures with increased affinity, perfect selectivity, and broad applicability.

The concept of anion–π slides combines a basic research topic with the creation of supramolecular multifunctional architectures. Evidently this is not yet the time to predict specific potential practical applications. However, the general importance of selective anion recognition and translocation in many areas, reaching from drug discovery (e.g., replacement therapies for anion channelopathies such as cystic fibrosis)[40] to diagnostics, sensing, and optoelectronic materials, implies that the development of fundamental concepts such as anion–π slides is highly relevant also from a practical point of view. Overall, this is an adventurous concept that builds on scarce and mostly indirect experimental evidence. Future developments will reveal eventual significance with regard to both basics and applications. They are awaited with curiosity and impatience.

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