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Membrane Transport

Rigid Oligoperylenediimide Rods: Anion–π Slides with Photosynthetic Activity[**]

Alejandro Perez-Velasco, Virginie Gorteau, and Stefan Matile[*]

To combine ion-channel[1] and photosynthetic activity[2–4] productively is one of the great challenges of synthetic multifunctional nanoarchitecture. One expectation is the ability to compensate the transmembrane electronic imbalance caused by photoinduced active electron transport with passive anion transport in the other direction. Such electroneutral electron–anion antiport should prevent saturation of the system by membrane polarization.[2] The problem is the high, but so far elusive, anion selectivity required to avoid collapse of the entire multifunctional system.[4]

The recent introduction of rigid-rod oligo(*p*-phenylene)-*N*,*N*-naphthalenediimide (O-NDI) anion–π slides has provided a new approach to transmembrane anion transport that focuses on anion–π interactions[5] for selectivity and multi-ion hopping.[6] Photosynthetic activity remains, however, inaccessible with O-NDI anion–π slides for synthetic reasons.[4,6] Herein, we introduce the differently colored oligo(*p*-phenylene)-*N*,*N*-perylenediimide (O-PDI) rods **1** and **2** as anion–π slides with photosynthetic activity (Figure 1).

PDIs are π-acidic n-semiconductors.[7,8] These properties are compatible with electron transport in one direction and anion transport by anion–π interactions in the other. The ideal topology of the PDI chromophore to align with the lipid tails in one leaflet of a bilayer membrane has been noted recently.[4] In rigid O-PDI rod **1** (Figure 1), two PDIs are unbendably placed in line to reach the matching length to span a lipid bilayer membrane. Anionic triglutamate tails were added at one end to obtain the water solubility needed to assure delivery to membrane vesicles, intervesicular transfer, oriented partitioning, and parallel self-assembly. Pyrrolidinyl substituents were added to the PDI core because the 1,7-bis(pyrrolidin-1-yl)-3,4:9,10-perylene-bis(dicarboximide) chromophore was shown by Wasielewski and co-workers to have optoelectrical characteristics similar to those of chlorophyll, the green pigment of plants (Figure 1).[7] For instance, face-to-face dimers of these green PDIs were found to undergo symmetry-breaking, relatively long-lived photoinduced charge separation (lifetime $\tau \approx 4$ ns, depending on solvent; photoinduced charge separation in linear dimers was less favorable).[7a]

Rigid O-PDI rod **1** was synthesized in 12 steps from commercially available starting materials, such as perylene dianhydride and glutamate (Scheme S1 and Figures S1–S3, Supporting Information). Synthetic procedures and analytical and spectroscopic data for all new compounds can be found in the Supporting Information.[9]

Egg yolk phosphatidylcholine large unilamellar vesicles (EYPC LUVs) loaded with the pH-sensitive fluorescent probe 8-hydroxy-1,3,6-pyrenetrisulfonate (HPTS) were used to evaluate the activity of rigid O-PDI rod **1** as an anion–π slide.[6,9,10] Vesicles with internal NaBr were diluted with isoosmolar buffer containing different salts MX, and rod **1** was added (Figure 2). This version of the HPTS assay[6,9] fails to detect the ability of rod **1** to dissipate the applied transmembrane NaX and MBr gradients by transmembrane

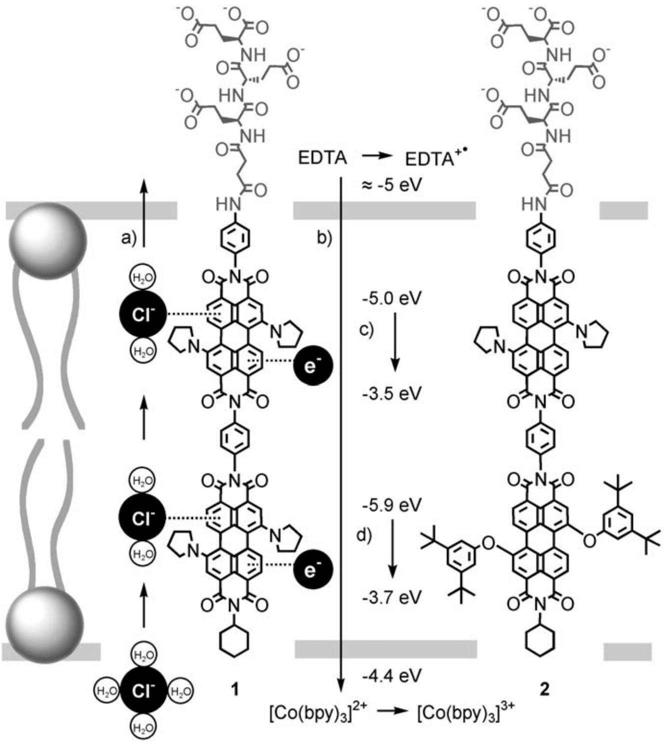

Figure 1. Rigid O-PDI rods **1** and **2** with anion transport and photosynthetic activity. a) Passive anion efflux is thought to occur by anion–π interactions on the π-acidic PDI surfaces. b) Active, photoinduced electron influx with frontier orbital energy levels of external ethylenediaminetetraacetic acid (EDTA) donors, internal [Co(bpy)$_3$]$^{3+}$ (bpy = 2,2′-bipyridine) acceptors, and PDIs with c) two pyrrolidinyl and d) two phenoxy core substituents (from refs. [3] and [7]).

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[*] Dr. A. Perez-Velasco, V. Gorteau, Prof. S. Matile
Department of Organic Chemistry, University of Geneva
1211 Geneva (Switzerland)
Fax: (+41) 22-379-3215
E-mail: stefan.matile@chiorg.unige.ch
Homepage: http://www.unige.ch/sciences/chiorg/Matile/Group/

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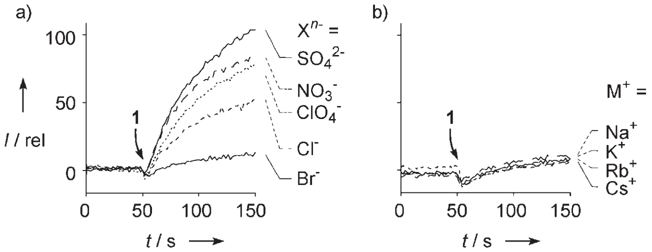

Figure 2. Anion transport activity of O-PDI **1**. Change in HPTS emission *I* during addition of **1** (1.5 µM) to EYPC LUVs⊃HPTS in MX (100 mM); a) M = Na, X varied (50 mM for Na_2SO_4), b) X = Br, M varied, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, 10 mM), pH 7.0.

cation (M = Na) or anion (X = Br) exchange (antiport), because both processes do not cause a change in intravesicular pH. However, the assay becomes exceptionally informative as soon as rod **1** can transport intravesicular Na^+ or Br^- but fails to transport extravesicular M^+ or X^- in the other direction. The applied NaX and MBr gradients can in this case be partially relieved only by either H^+/Na^+ or OH^-/Br^- antiport. The resulting formal H^+ or OH^- pumping into vesicles is then detectable by HPTS as an intravesicular decrease or increase in pH. This pumping assay is attractive because it works only in intact vesicles and with highly selective ionophores.

According to this assay, the response to the addition of O-PDI **1** to EYPC LUVs exposed to opposing Br^-/NO_3^- gradients was indeed a strong increase of intravesicular pH (Figure 2a). Similar increases of intravesicular pH were found with external SO_4^{2-}, ClO_4^-, and even Cl^- instead of NO_3^- (Figure 2a), and with internal Cl^- instead of Br^- (Figure S7, Supporting Information). The application of cation gradients did not cause similar changes in intervesicular pH (Figure 2b). These findings revealed that rod **1** transports anions rather than cations, with a preference for OH^- over SO_4^{2-}, NO_3^-, ClO_4^-, and Cl^-. They further demonstrated that rod **1** transports anions across intact vesicle membranes and firmly excluded the occurrence of less specific transport mechanisms as well as lysis.

The creation of anionic transporters in neutral bilayer membranes that attract anions rather than cations has rarely been achieved before. The anion selectivity of **1** excluded participation from the anionic peptide tail to mediate transport, and thus supported the potential of anion–π interactions along the π-acidic O-PDI and O-NDI[6] rods as a promising strategy to transport anions across bilayer membranes. Indeed, the apparent preference for Cl^- ($\Delta G_{\mathrm{hydr}} \approx 370\ \mathrm{kJ\,mol^{-1}}$) over ClO_4^- ($\Delta G_{\mathrm{hydr}} \approx 230\ \mathrm{kJ\,mol^{-1}}$) demonstrated that the dehydration penalty alone is insufficient to account for the observed anion selectivity sequence, and thus confirmed the occurrence of compensatory contributions from anion binding to the π slide, possibly together with relatively weak size-exclusion phenomena.[6,10] The results on ion selectivity in HPTS assays in the presence of an additional pH gradient, including poor halide discrimination except for the disfavored F^-, were in agreement with these interpretations and differed clearly from the results with the more π-acidic O-NDIs (Figures S8–S10, Supporting Information).[9]

The photosynthetic activity of the anionic O-PDI π slide **1** in the neutral EYPC LUVs was determined with the "Hurst assay".[3] In this assay, intravesicular photoreduction of $[Co(bpy)_3]^{3+}$ is detected as a change in absorption around 320 nm (Figure 3a); EDTA is used as an external hole acceptor (Figure 1). The dark reduction of $[Co(bpy)_3]^{3+}$ with EDTA is unfavorable. Successful photoreduction thus converts photonic energy into chemical energy.

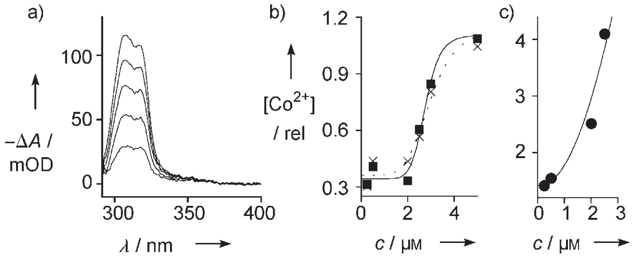

Figure 3. Photosynthetic activity of a,b) O-PDI **1** and c) **2**. a) Differential absorption spectra of EYPC LUVs⊃$[Co(bpy)_3]^{3+}$ with externally added EDTA and **1**, which show increasing change at 320 nm after 10, 20, 30, 40, and 50 min of irradiation (Xe lamp, cutoff at 580 (**1**) or 480 nm (**2**)). b) Photoreduction of $[Co(bpy)_3]^{3+}$ after 15 min of irradiation as a function of concentration of **1** in the absence (■) and presence (×) of carbonylcyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP; 5 µM), detected as change in absorption at 320 nm as illustrated in (a). c) The same for **2**, but without FCCP.

According to the Hurst assay, O-PDI rod **1** exhibited significant photosynthetic activity (Figure 3a and b). The Hill plot revealed a Hill coefficient $n = 8.7 \pm 2.6$, which indicates unusually high cooperativity. This finding demonstrated that self-assembly is essential for photosynthetic activity, that is, the existence of a supramolecular function.[10,11] It further revealed that the self-assembly of the active structure is endergonic. As with all $n > 1$ systems, all nonspecific structural and photophysical studies will thus fail to report on the active structure.[10–13]

The Hill plots for the photosynthetic activity of O-PDI rod **1** measured in the presence and absence of FCCP were nearly superimposable (Figure 3b). This insensitivity toward the proton carrier FCCP demonstrated that photosynthesis by O-PDI rod **1** is electroneutral.[2,3,10] This finding supported the constructive combination of active electron influx with passive anion efflux, that is, the constructive combination of ion transport and photosynthetic activity by the electron–anion antiport.

Advanced O-PDI rod **2** was synthesized next in 15 steps (Figure 1; Scheme S2 and Figures S4–S6, Supporting Information). Compared to O-PDI rod **1**, the green 1,7-bis(pyrrolidin-1-yl)-3,4:9,10-perylene-bis(dicarboximide) chromophore in the inner leaflet of the bilayer membrane is replaced by a red 1,7-bis(3,5-di-*tert*-butylphenoxy)-3,4:9,10-perylenebis(dicarboximide) chromophore with two phenoxy rather than two pyrrolidinyl substituents in the core. The activity and selectivity of O-PDI rod **2** to transport anions across vesicle membranes was similar to that of O-PDI rod **1** (Figures S7–S10, Supporting Information). The apparent photosynthetic activity of O-PDI rod **2**, detectable at concentrations as low as 500 nM, was clearly higher than that of O-PDI rod **1** (Figure 3c). The Hill coefficient, however, decreased to $n = 2.4 \pm 0.5$.[13] Competing precipitation at high concentrations (above 5 μM) prevented completion of the Hill plot with the determination of maximal activity.

Photophysical insights from closely related PDI dyads[7] implied that several possibilities exist to explain the increased photosynthetic activity of O-PDI **2**, which include absorption at a broader range of visible light, energy transfer, electron transfer, and prolonged, directional photoinduced charge separation (Figure 1). However, with structural and photophysical studies being meaningless for $n > 1$ systems (Figure 3b and c), and other parameters, such as partitioning and intervesicular transfer, likely to contribute, we concluded that the origins of the meaningful apparent difference in activity of rods **1** and **2** cannot be determined at this stage. With the unknown effective concentrations of $n > 1$ systems, the unknown rate-limiting steps recorded in the Hurst assay, and the lack of comparable positive controls, it is not meaningful to comment on the absolute photoactivity of rods **1** and **2**.

In summary, we have introduced O-PDIs as a new class of membrane-active rigid-rod molecules.[14] Their ability to mediate the passive transport of ions and the active transport of electrons with light across intact vesicle membranes was demonstrated unambiguously. Constructive combination of the two functions in passive/active anion–electron antiport is indicated with the electroneutrality of photosynthetic activity. High cooperativity in Hill plots for photosynthetic activity revealed the occurrence of endergonic self-assembly into supramolecular active structures. The ability of anionic rods to selectively attract anions (rather than cations) is considered as strong evidence for the potential of anion–π interactions to transport anions across bilayer membranes. The introduced system produces stimulating questions for experts in the respective domains and offers an ideal starting point for the development of refined functional systems.

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[12] The Hill plot for ion-transport activity exhibited pseudo-linear behavior at low, nanomolar concentrations (Figure S11, Supporting Information). This less informative behavior suggested that ion transport is mediated by either 1) monomeric rod **1** or, more likely,[6] 2) an exergonic self-assembly, which would then further undergo endergonic self-assembly into the unstable higher-order quaternary structure that is needed for photosynthesis. In any case, different Hill plots confirmed that the suprastructural requirements for ion transport and photosynthesis are different, with the latter being more demanding.[13]

[13] The experimentally confirmed[7a] stabilization of photoinduced charge separation in face-to-face π-stacked PDIs could be considered as one possible explanation for the need of supramolecular active structures for photosynthetic activity of **1** and **2**.

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