Functional Supramolecular Systems

DOI: 10.1002/ange.201003722

A Chiral and Colorful Redox Switch: Enhanced π Acidity in Action**

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Herein, we introduce simple sulfur redox chemistry[1,2] to generate enhanced π acidity,[3–5] demonstrate the functional relevance of the investigated system through anion transport experiments,[2,4–7] and create the switchable chiral π-acidic surfaces that are needed for future applications toward asymmetric anion–π catalysis. Efforts to expand the number of noncovalent interactions available to construct new supramolecular systems with significant functions such as sensors, optoelectronic devices, and catalysts or drugs are of paramount importance.[4] To contribute to this adventure, we have explored the use of potential-macrodipole,[2,7] anion-macrodipole,[7] aromatic electron donor-acceptor[7] as well as anion–π interactions[4,5] to build stimuli-responsive transport systems[4–7] in lipid bilayer membranes. Core-substituted naphthalenediimides (cNDIs)[8] are ideal to explore the usefulness of anion–π interactions to create functional systems because the quadrupole moment of the parent NDI **1** is already $Q_{ZZ} = +19$ B (Figure 1a and b).[3–5] This intrinsic π acidity is very high, as high as that of the explosive trinitrotoluene (TNT).[3–5] The introduction of two cyano π acceptors in the cNDI core doubles the quadrupole moment to $Q_{ZZ} = +39$ B, which is the highest value known to date.[4] This increase in π acidity is reflected in decreased LUMO energy levels from −4.31 eV to −4.62 eV, and increased anion binding affinity, charge mobility and anion transport activity.[4,8,9] Synthetic efforts to further lower LUMO energies and generate enhanced π acidity by adding more cyano π acceptors into the cNDI core failed so far despite much interest in academia and industry.[4,8,9]

In the search for synthetic routes to "super-π-acidity", we considered that oxidation of sulfide donors[10] in the core of cNDIs could reversibly yield chiral sulfoxides and powerful sulfone acceptors (Figure 1). Aromatic sulfur compounds, particularly thiophenes, are ubiquitous in materials sciences because of the high conductivity of their π stacks.[1] Their reversible oxidation has been much less explored to generate functional systems, although elegant examples exist for fluorescent sensors, p- to n-charge mobility inversion (oligothiophene oxidation), switchable secondary peptide structures, amyloid disease prevention, and voltage-gated synthetic ion channels.[1,2] In the following, we present synthesis, optoelectronic properties, anion transport activity and computational studies of the cNDIs **2**–**9** (Figure 1). Tetrasulfone **9** emerges as the most π-acidic cNDI known today, and the resulting anion transport activity is naturally outstanding.

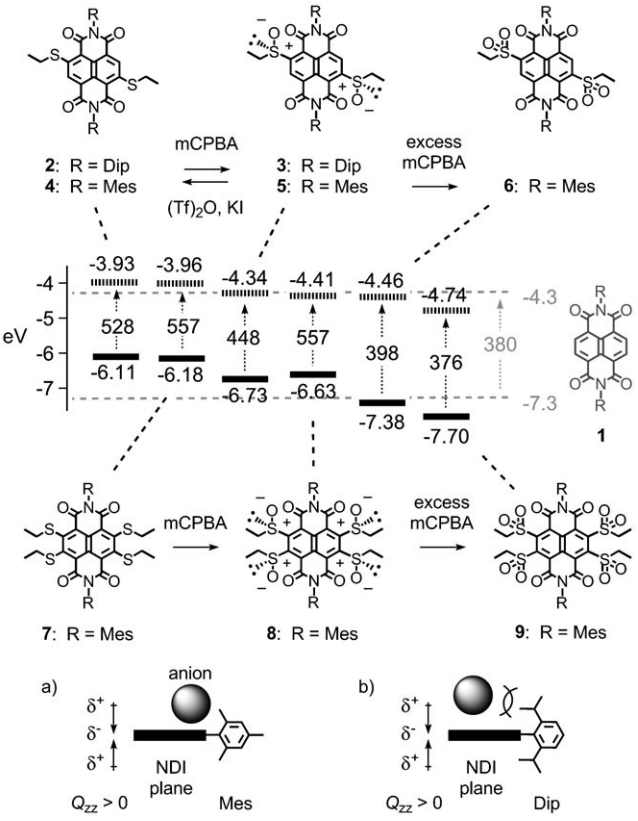

Figure 1. Structures, frontier orbital energies, absorption maxima and a) favorable and b) unfavorable anion complexes of anion–π redox switches. HOMO (bold) and LUMO (dashed) energies are in eV against vacuum compared to native NDI **1** (gray), and absorption maxima in nm (dashed arrows).

The cNDI **2** with two sulfide donors in the core and two diisopropylphenyl (Dip) substituents in the periphery was prepared as described in the literature (Supporting Information, Figure S1).[10,11] To enable anion–π interactions on the most electron-deficient pyridinedione heterocycles, the obstructing Dip substituents (Figure 1b) were replaced by

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[**] We thank D.-H. Tran for contributions to synthesis, D. Jeannerat, A. Pinto, and S. Grass for NMR measurements, the Sciences Mass Spectrometry (SMS) platform at the Faculty of Sciences, the University of Geneva for mass spectrometry services, the Swiss National Supercomputing Center (CSCS) in Manno for CPU time, and the University of Geneva and the Swiss NSF for financial support. J.M. is a fellow of the Roche Research Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201003722.

mesityl (Mes) substituents which allow for a practical compromise between acceptable anion–π interactions and reasonable solubility (Figure 1a).[4] Reactivity and optoelectronic properties of the Mes- and Dip-cNDIs were roughly the same. Namely, conversion of the π-donating sulfides **4** into π-accepting sulfoxides **5** with stoichiometric and sulfones **6** with an excess of *m*-chloroperoxybenzoic acid (*m*CPBA) resulted in the downfield shift of the signals corresponding to the protons in positions 3 and 7 of the naphthyl core ($\delta =$ 8.81 ppm to 9.66 ppm in the ^{1}H NMR spectra; Figure 2l–n). The absorption maxima suffered a hypsoschromic shift from a strong, broad charge-transfer (CT) band at 528 nm for sulfide cNDIs to weakened CT at 448 nm for sulfoxide cNDIs and complete CT-silencing for sulfone cNDIs (Figure 2e–g; Supporting Information, Table S1). The π,π* transition responded to sulfur oxidation with a weak bathochromic shift from 382 nm for sulfide cNDIs to 398 nm for sulfone cNDIs. None of the sulfur containing cNDIs was fluorescent.

Cyclic voltammetry (CV) revealed a significant increase in π acidity in response to the oxidation of the sulfur substituents in the core (Figure 2a–c). LUMO energies relative to the vacuum were obtained by subtraction of −5.1 eV for Fc/Fc$^+$ from the first redox potential at −1.17 V for sulfide cNDIs, −0.76 V for sulfoxide cNDIs, and −0.64 V for sulfone cNDIs (Figure 1; Supporting Information, Table S1). HOMO–LUMO gaps were calculated from the onset of the lowest energy absorptions to approximate the HOMO energies (Figure 1).

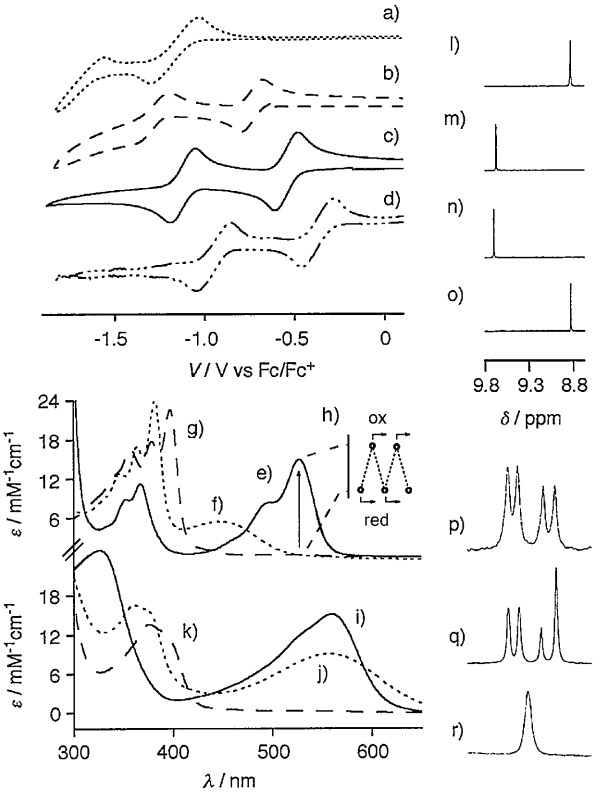

Figure 2. Cyclic voltammograms (a–d), absorption spectra (e–k), and ^{1}H NMR spectra (l–r) of cNDIs **4**–**9**. This covers sulfide **4** (a, e, h, l, o), sulfoxide **5** (b, f, h, m), and sulfone **6** (c, g, n) compared to tetrasulfide **7** (i), tetrasulfoxide **8** (j), and tetrasulfone **9** (d, k), colorimetric redox switching with **4** and **5** (h), **4** as product of the reduction of **5** (o), and racemic **5** (p), enantioenriched **5** (q) and achiral **4** (r) in the presence of the shift reagent (−)-(*R*)-TFAE (250 equiv, $CDCl_3$, 50 °C; Supporting Information, Figure S5). Fc/Fc$^+$ = ferrocene/ferrocenium.

The reversibility of sulfide oxidation was confirmed by reduction of **5** with triflic anhydride $(Tf)_2O$ and KI (Figure 2o vs 2l). Colorimetric redox switching was readily demonstrated for repeated reduction and oxidation cycles for **4** and **5** (Figure 2h; Supporting Information, S4). In the presence of the chiral shift reagent (−)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol (TFAE, or Pirkle's alcohol),[12] the NMR signals for the protons in positions 3 and 7 of the naphthyl core in chiral sulfoxide **5** (but not achiral sulfide **4**) splitted into four equal resonances (Figure 2p vs. 2r). Asymmetric oxidation of **4** with *tert*-butylhydroperoxide (TBHP) catalyzed by (*R*)-(+)-1,1′-bi(2-naphthol) (*R*-binol, 20%) and Ti(O*i*Pr)$_4$ (10%) changed the magnitude of the split signals of **5** (Figure 2q).[11,13] The upfield signals for the pair of enantiomers integrated for an enantiomeric excess of 40% *ee*. Their 1:1 ratio compared to the *meso* diastereomer suggested that the second sulfide oxidation occurs without stereoselectivity (Supporting Information, Figure S5). The circular dichroism (CD) spectrum of enantioenriched **5** showed a weakly negative Cotton effect (CE) for the CT band at 449 nm and a stronger positive CE at 303 nm (Supporting Information, Figure S6).

Today, the use of standard intermolecular interactions to build functional systems that can transport ions across lipid bilayers is almost routine.[5–8] In a recent inversion of paradigm, activity to transport anions was considered as a tool to identify more exotic interactions and to assess their functional relevance for translocation and catalysis, where much weaker interactions are of interest than for simple binding.[4,14] For this purpose, the ability of cNDIs **2**–**6** to use anion–π interactions to transport anions across lipid bilayer membranes was evaluated with the 8-hydroxy-1,3,6-pyrenetrisulfonate (HPTS) assay. In this assay, EYPC-LUVs⊃HPTS are exposed to a transmembrane pH gradient. These are large unilamellar vesicles composed of egg yolk phosphatidylcholine and loaded with the pH-sensitive fluorophore HPTS. The internal pH probes report the ability of externally added cNDIs to mediate the dissipation of transmembrane pH gradients (Supporting Information, Figure S8). Dose–response curves obtained for cNDIs **2**–**6** were then subjected to Hill analysis to give the effective monomer concentrations (EC_{50}) needed to reach 50% activity. For sulfide **4**, an EC_{50} value of (13.9 ± 1.2) μM was found (Figure 3a, □; Supporting Information, Table S2). This value improved with sulfide oxidation to $EC_{50} = (2.1 \pm 0.2)$ μM for sulfoxide **5** and $EC_{50} = (1.8 \pm 0.4)$ μM for sulfone **6** (Figure 3a, △ and ○). Increasing activity with increasing π acidity was in support of operational anion–π interactions in the Mes-cNDI series. In the Dip-cNDI series, activity decreased with π acidity from $EC_{50} = (0.9 \pm 0.1)$ μM for **2** to $EC_{50} = (3.5 \pm 0.4)$ μM for **3**, probably owing to the decreasing partitioning of more hydrophilic transporters (Supporting Information, Table S2). This dichotomic behavior with obstructed anion–π interactions in the Dip series was essential to corroborate the functional relevance of the operational anion–π interactions in the Mes-cNDI series **4**–**6**.[7c]

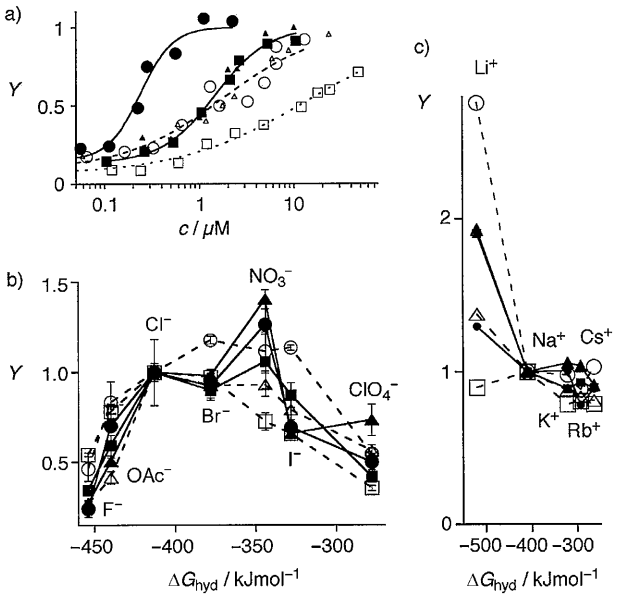

Figure 3. a) Transport activity and b and c) selectivity of **4** (□), **5** (△), **6** (○), **7** (■), **8** (▲) and **9** (●). a) Dependence of the fractional activity *Y* on cNDI concentration with Hill analysis. b, c) Dependence of *Y* on the dehydration energy of external anions (b; 100 mM NaX, inside 100 mM NaCl) and cations (c; 100 mM XCl, inside 100 mM NaCl), normalized for $Y=1$ for Na^+ and Cl^-.[11]

The ion selectivity of cNDIs **2**–**6** was determined by external ion exchange. The high sensitivity to external anion exchange and the negligible sensitivity to external cation exchange (except for Li^+) implied selectivity for anions (Figure 3b, c). The global anti-Hofmeister behavior in the halide series, preference for oxyanions, occasional nitrate recognition, and fluoride/acetate rejection with increasing π acidity were roughly as those described for dicyano cNDIs and can be interpreted as support for strong, π–π enhanced anion–π interactions at work (Supporting Information, Table S2).[4] Anion selectivity sequences were partially obscured by a lithium anomaly that gained in importance with increasing sulfide oxidation (Figure 3b,c). This effect was attributed to the binding of lithium to the pocket formed by sulfone and diimide oxygens and considered as an attractive approach to Lewis-acid enhanced π acidity.

Quantum chemical computations suggested that the π acidity of cNDIs with two sulfones in the core is comparable to that of previously investigated dicyano cNDIs.[5a,11] Comparison of the electrostatic surface potentials (ESP) of disulfone **6** and dicyano cNDIs revealed only slightly less electron-deficient surfaces for the former (Supporting Information, Figure S21).[11] This suggested that oxidation of the four sulfides in the core of cNDI **7** should provide access to the enhanced π acidity that could not be reached with tetracyano cNDIs (Figure 1).[4] Tetrasulfide **7** was readily prepared by adapting procedures reported previously in the literature;[10b] oxidation to tetrasulfoxide **8** with stoichiometric and tetrasulfone **9** with an excess of mCPBA was unproblematic.[11] Solutions of the super-π-acid **9** in MeOH or dimethylsulfoxide (DMSO) turned black within hours, as did the spots on the thin layer chromatograms.

The transport activity of tetrasulfone **9** was outstanding: $EC_{50}=(239\pm24)$ nM is the best value for anion–π transporters known so far (Figure 3a, ●).[4] The Hill coefficient $n=2.5\pm0.7$ confirmed that the active structure is an unstable supramolecule composed of at least three monomers. The anti-Hofmeister selectivity topology with AcO^-/F^- exclusion and significantly enhanced nitrate recognition found for **8** and **9** supported strong anion recognition (Figure 3b, ●, ▲). Compared to disubstituted cNDIs (Figure 2e–g), the absorption spectra of tetrasubstitued cNDIs were broadened and showed a stronger, more bathochromic CT band for tetrasulfoxide **8** and a stronger hypsochromic effect for the π,π* bands (Figure 2i–k). The origin of these differences is unknown, but chromophore twisting resulting from topological crowding with four substituents in the core is likely to contribute (Figure 4). The cyclic voltammograms of di- and tetrasubstituted cNDIs were identical in appearance (Figure 2a–d; Supporting Information, Figure S7). From the first redox potential at −0.36 V, a LUMO energy of −4.74 eV was obtained for **9** (Figure 1). This finding demonstrated that with tetrasulfone cNDI **9**, the so far elusive "super-π-acidity" has finally been realized.

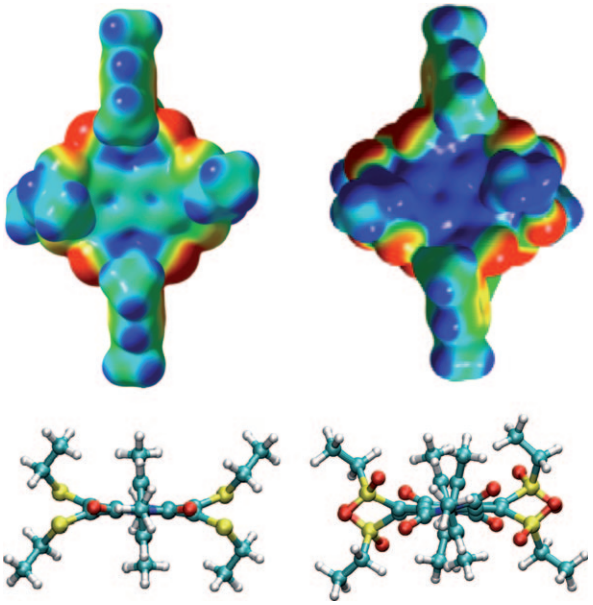

Figure 4. Electrostatic surface potentials computed for optimized structures viewed from the top (blue +1.24, green 0, red −1.24 eV, PBE1PBE/6-311G**) and side views of ball and stick representations along the *N*,*N*′ axes (atom color coding) of tetrasulfide cNDI **7** (left) and tetrasulfone cNDI **9** (right).

Molecular models confirmed the validity of this interpretation. The exceptional ESP of super-π-acid **9** with a deeply blue aromatic surface contrasted well with the greenish surfaces of the less π-acidic tetrasulfide **7** (Figure 4, top). Increasing peripheral crowding with increasing sulfur oxidation slightly twisted the pyridinedione heterocycles in tetrasulfone **9** out of the naphthyl plane. This unprecedented NDI deplanarization is presumably subject to extensive atropisomerism of the ethylsulfonyl side chains (Figure 4, bottom).

In summary, we have presented a facile access to aromatic surfaces that unify "super-π-acidity", operational anion–π interactions, chirality, and red coloration in a switchable manner. π-Acidic cNDIs with sulfur substituents in their core are of fundamental interest in materials science (for example, air-stable *n*-semiconductors with high charge mobility)[1,9] and organocatalysis. In view of the stabilization of cationic transition states by cation–π interactions as classical motif in catalysis, and particularly carbocation chemistry,[14] anion–π interactions have the potential to stabilize the complementary anionic reactive intermediates such as enolates.

Received: June 18, 2010
Published online: September 13, 2010

Keywords: anion–π interactions · chirality · ion transport · molecular switches · π acidity

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