Chemical control over hemi-indigo photoswitches

Duindam, N.

Summary and Perspectives

Current applications of molecular photoswitches typically utilize changes in the isomeric ratio to alter chemical properties, whereas the continuous photoconversion that takes place at photoequilibrium is seldom used. In this thesis, chemical gating of photochemistry was explored as a strategy to extract progressive work from such dynamic interconversion. It has become increasingly clear that photoswitches are highly sensitive to external chemical stimuli, yet these effects remain underexplored and poorly understood. I proposed that chemically gated photoswitch properties provide a new approach to move beyond simple bistable switching and to ultimately enable molecular pumping. In this thesis, I systematically investigated the sensitivity of hemi-indigo dyes to hydrogen-bonding interactions and demonstrated how reversible control over such interactions enables quantitative gating of photochemistry.

In **Chapter 2**, a series of *N*-heterocyclic hemi-indigos was prepared and the influence of the protonation state on the thermal and photochemical isomerization properties was studied. Disruption and (re)formation of the intramolecular hydrogen bond resulted in reversible pH-activated double-bond isomerization. Strikingly, the protonation state also fully dictated the photochemical properties. Using a single wavelength of light, *Z*-to-*E* photoisomerization was unlocked only after protonation, while the reverse *E*-to-*Z* photoreaction occurred exclusively in the neutral state. This effectively transformed an otherwise bistable system into a monodirectional four-state photocycle. I proposed that under continuous irradiation, this simple photoswitch pumps protons directionally across the photoswitch scaffold.

Profound effects of non-covalent interactions on photochemistry are often explained by dissecting ground-state interactions. However, these effects can only be fully explained by studying the excited-state surface. In **Chapter 3**, the protonation-gated photochemistry of *N*-heterocyclic hemi-indigos was studied in more detail. To unravel the underlying mechanism, it was demonstrated that ESIPT (excited state proton transfer) in the excited states of the hydrogen-bonded species provides a de-excitation channel that outcompetes photoisomerization. By combining transient spectroscopy and state-of-the-art calculations, multiple decay channels and key trends in the excited-state lifetimes were identified, establishing the mechanistic basis for the protonation-gated photochemistry observed in **Chapter 2**.

In the preceding chapters, the quantitative *Z*-to-*E* photochemical conversion could be reverted by disrupting the intramolecular hydrogen bond by deprotonation. In **Chapter 4**, I

explored how alternative chemical stimuli can be used to trigger the reverse *E*-to-*Z* isomerization. Specifically, I examined how selective stabilization of the *Z*-isomer through chloride binding in pyrrole-derived hemi-indigo switches can drive thermal *E*-to-*Z* isomerization. Hemi-indigo based anion receptors equipped with one or two pyrrole rings were synthesized. It was observed that the *Z*-isomers bound chloride anions with up to three orders of magnitude higher affinity constants than the respective *E*-isomers. This selective chloride binding inverted the thermodynamic preference in favor of the *Z*-isomer and induced thermal *E*-to-*Z* isomerization. Consequently, photochemical *Z*-to-*E* photoisomerization could thus be complemented with quantitative chloride-driven *E*-to-*Z* isomerization to enable reversible switching.

In **Chapter 5,** I addressed key challenges in the field of photoswitchable transmembrane ion transporters by exploiting the unique photochemistry of hydrogen-bonded hemi-indigo switches. Often, photoswitchable receptors in the field of ion transport undergo incomplete photoisomerization to the inactive state, resulting in only partial deactivation of the transporter. A hemi-indigo receptor decorated with a dipyrrin moiety was synthesized as a photoswitchable structural mimic of the natural product prodigiosin, a highly active HCl-transporter. The protonated *Z*-isomer strongly bound chloride and facilitated strictly electroneutral HCl symport across POPC membranes. In addition, the activity profile was pH-dependent, with the highest activity observed at low pH. Irradiation with visible light resulted in high conversion to the inactive *E*-isomer and a concomitant drop in transport activity, representing a rare example of near-quantitative photodeactivation using visible light.

The monodirectional photocycle described in **Chapter 2** provided a conceptual strategy towards molecular pumping. However, to translate single-molecule directionality into the generation of macroscopic gradients, directional immobilization is required. In **Chapter 6** a membrane-spanning oligo-(*p*-phenylene)-polyol with a central hemi-indigo moiety was synthesized, and its immobilization across lipid bilayers was studied as a first step towards light-driven transmembrane proton pumping. Key future steps necessary to achieve light-driven proton pumping are also discussed.

The work described in this thesis outlines a conceptually new approach to achieving molecular pumping of substrates using chemically gated photochemistry. That is, if the binding/release of a substrate selectively inhibits one photoisomerization direction, this can be applied as a strategy toward the directional transport of that substrate. Different directional immobilization strategies of the small-molecule hemi-indigo proton pump are currently being explored, in order to generate sustained macroscopic gradients. The hemi-indigo

system is hampered by relatively low photochemical quantum yields, and research efforts are directed towards improving this while retaining the gated photochemistry. More broadly, I believe that systematic studies into the chemical gating of different photoswitchable receptors will uncover new means to uncouple forward and backward photoisomerization pathways, thereby paving the way toward extracting complex work from simple photoswitches.