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Multi-State Regulation of the Dihydrogen Phosphate Binding Affinity to a Light- and Heat-Responsive Bis-Urea Receptor

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Supporting Information

ABSTRACT: A responsive bis-urea receptor can be switched between three isomers using light and heat as evidenced by ^{1}H NMR and UV−vis spectroscopy. Anion binding experiments (^{1}H NMR titrations, ESI-MS) reveal a high selectivity for dihydrogen phosphate. Importantly, a large difference in binding affinity to the interchangeable isomers is observed, which is further rationalized by DFT calculations. As a consequence, the amount of bound substrate can be controlled via photo- and thermal isomerization in a three-step process.

In biological systems, receptor proteins facilitate the transport of anions across membranes, which is crucial for various physiological functions such as osmosis, cell signaling, and metabolism.[1] Cellular uptake of anions can be regulated by low-affinity and high-affinity transport systems, typically involving different receptors. It is fascinating that certain proteins are able to switch between two distinct affinity modes via a phosphorylation mechanism and, in that way, control the rate of anion transport.[2]

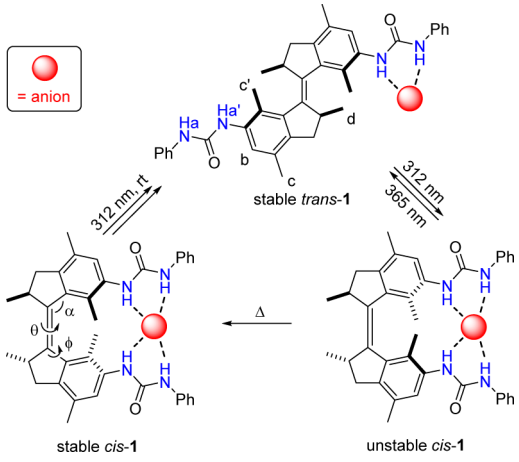
Due to the principal role of anions in biological processes, chemists endeavor to develop artificial receptors that imitate natural protein carrier molecules.[3] Toward this goal, impressive progress has been made in anion receptor chemistry over the past decade.[4] Among the most widely employed organic receptors are those that contain hydrogen-bond-donating urea groups. The groups of Umezawa,[5] Reinhoudt[6] and Gale,[7] for example, have developed phenyl spaced bis-ureas that show excellent selectivity for oxo-anions [especially dihydrogen phosphate ($H_2PO_4^-$) and acetate ($CH_3CO_2^-$)]. Phosphates are particularly interesting targets because of their vital role in many biological processes such as energy storage and signal transduction.[8] However, where numerous systems for the selective complexation of anions have been developed and optimized, very few efforts have been devoted to affinity switching.[9]

The use of light as external trigger has proven to be highly promising for the control of substrate binding. Pioneering work in this field was conducted by Shinkai et al., who reported on a bis-crown ether modified azobenzene switch that displays photocontrollable affinity for cations.[10] This work has stimulated further developments in the photogated binding and transport of cationic and neutral guests.[11] However, the effective switching of anion binding affinity has, to the best of our knowledge, only been demonstrated for halide ions.[9c−e,h] Furthermore, all photoresponsive receptors reported in the literature up to now incorporate two-state molecular switches (i.e., azobenzene, dithienylethene, and stilbene).

Unidirectional molecular rotary motors are unique multistage light- and heat-responsive switches.[12,13] We have recently shown that the switching between three stages in the rotary cycle of a first-generation molecular motor, equipped with an organocatalyst, can be used to control the conversion and stereoselectivity in a chemical reaction.[14]

Herein, we report the design and functioning of the molecular motor derived bis-urea receptor **1** (Scheme 1) of which three isomers are easily interconverted by applying light and heat. This compound shows an excellent binding affinity and selectivity for $H_2PO_4^-$ in the highly polar DMSO/0.5% H_2O solvent mixture. Moreover, the switchable isomers possess different anion complexation properties. Hence, the fraction of bound substrate can be regulated in a three-state switching process in a defined order of events.[15] This opens up new prospects toward the development of artificial oxo-anion carriers with regulatory affinity and transport properties.

Scheme 1. Isomerization Behavior and Possible Anion Coordination Modes of Bis-Urea Receptor 1



The stable *cis*- and *trans*-isomers of bis-urea receptor **1** were identically prepared by reaction of the corresponding diamine precursor with phenyl isocyanate in CH_2Cl_2 [see the Supporting Information (SI) for details on synthesis and

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characterization]. The desired products were isolated in excellent yield (~80%) and used as racemates. Bis-urea compounds are able to self-associate in solution,[16] but the formation of dimers or higher-order aggregates was excluded by ^{1}H NMR dilution studies in DMSO-d_6 ($c \leq 0.01$ M, see Figures S5–6, SI).

The photochemical and thermal isomerization behavior of **1** was examined using ^{1}H NMR and UV–vis spectroscopy. Irradiation of a solution of stable *trans*-**1** with 312 nm light at 20 °C led to ^{1}H NMR spectral changes that are characteristic for transition to the unstable *cis*-isomer (Figure 1).[17,18] Upfield

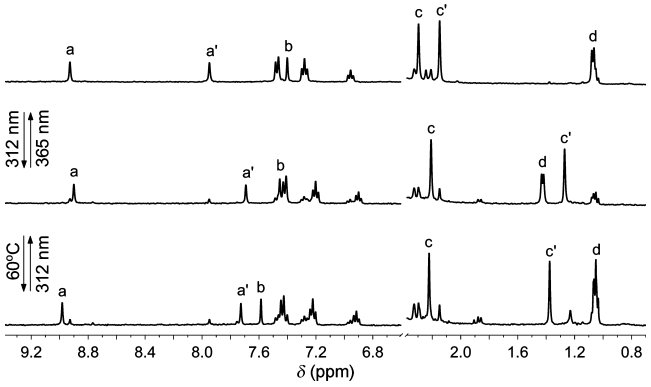

Figure 1. Aromatic and aliphatic region in the ^{1}H NMR spectrum of stable *trans*-**1** (top) at 1 mM in DMSO-d_6/0.5%H_2O). Spectral changes after irradiation with 312 nm light at 20 °C for 2 h (mid) followed by heating at 60 °C for 24 h (bottom). For the proton assignment, see Scheme 1.

shifted signals of the urea (H_a) and aromatic methyl (H_c) protons are an effect of the increased shielding in the *cis*-configuration, whereas deshielding of the methyl groups (H_b, H_d) is observed. Furthermore, the photostationary state (PSS) for this isomerization step was found to have a *cis:trans* ratio of 80:20 (Figures S7–8, SI). Subsequent heating of the irradiated sample resulted in equilibration from the unstable to stable *cis*-isomer. Alternatively, upon irradiation with 365 nm light the initial spectrum of stable *trans*-**1** was regenerated.[19]

Likewise, exposure of the stable *cis*-isomer to 312 nm light at 20 °C gave direct access to the PSS mixture of stable *trans*-**1**/unstable *cis*-**1**).[20] Again, the latter isomer could be smoothly converted into either stable *trans*-**1** or *cis*-**1** upon applying light (365 nm) or heat, respectively (see Figure S9, SI).

In the UV–vis spectrum, irradiation of stable *trans*-**1** with 312 nm light caused a bathochromic shift of the absorption maximum (λ_{max} = 324 nm → λ_{max} = 332, 355 nm, Figure S10, SI). After the PSS was reached, heating of the sample resulted in a hypsochromic shift to 330 nm. Comparable with the ^{1}H NMR studies, these spectral changes illustrate the formation of the higher energy, unstable *cis*-isomer, which is followed by thermal isomerization to give stable *cis*-**1**.

The rate constants of the thermal isomerization step were determined at five different temperatures by following the decrease in absorption at 365 nm (Figure S11, SI). Using the Eyring equation, the Gibbs free energy of activation ($\Delta^{\ddagger}G°$) was calculated as 105 kJ/mol corresponding to a half-life ($t_{1/2}$) of around 147 h at 20 °C. This is comparable to the values reported previously for molecular motors with a similar core structure as **1**.[14,17]

Anion complexation was predicted to be the strongest in the *cis*-configuration due to the possibility of forming four hydrogen bonds (see Scheme 1). Therefore, initial binding studies were performed with stable *cis*-**1** using ^{1}H NMR titrations in DMSO-d_6/0.5%H_2O. Among a range of anions (added as tetrabutyl ammonium salts, see Table 1), the stepwise addition of $CH_3CO_2^-$ and $H_2PO_4^-$ provoked the biggest downfield shifts for the urea ^{1}H NMR signals, indicative of anion binding (Figures S12–16, SI).

Table 1. Anion Binding Constants of Bis-Urea 1 (M^{-1})[a]

anion	stable cis-**1**[b]	stable trans-**1**[c]
Cl	26	
Br	<10	
NO_3	–	
CH_3CO_2	1.3×10^3	71
H_2PO_4	7.5×10^3	1.3×10^2
HSO_4	–	

[a]Anions were added as tetrabutyl ammonium salt (c = 5 mM in DMSO-d_6/0.5%H_2O). [b]Nitrate and sulfate did not induce significant ^{1}H NMR spectral changes. [c]Not determined for other anions than $CH_3CO_2^-$ and $H_2PO_4^-$.

The shape of the titration curves and Job plot analyses (Figures S21–22, SI) point to the expected 1:1 binding stoichiometry.[21] This was further supported by mass spectrometric analysis (ESI-MS) of anion/stable *cis*-**1** mixtures, displaying the peaks belonging to the species $[\mathbf{1}\supset CH_3CO_2]^-$ and $[\mathbf{1}\supset H_2PO_4]^-$ (Figure 2). Hence, the titration data were

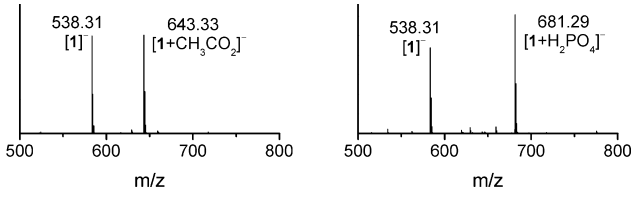

Figure 2. ESI mass spectra (negative mode) of (left) CH_3CO_2/ and (right) H_2PO4/stable *cis*-**1** complexes prepared in MeCN.

fitted to a 1:1 binding model using HypNMR software,[22] and the calculated stability constants (K_a) are given in Table 1. It can be seen that stable *cis*-**1** strongly and preferentially binds $H_2PO_4^-$ and that $CH_3CO_2^-$ binding is also substantial. These K_a values are in similar range as those previously reported for other successful bis-urea receptors.[5−7]

The titration of $[Bu_4N]^+[CH_3CO_2]^-$ and $[Bu_4N]^+[H_2PO_4]^-$ to stable *trans*-**1** led to similar ^{1}H NMR spectral changes. However, in this case Job plot analysis clearly indicated the presence of 2:1 anion/receptor complexes (Figure S21, SI). Since in the *trans*-configuration the relative distance between the two urea substituents is too large to bind an anion cooperatively, each of them will bind an anion distinctively via only two hydrogen bonds (see Scheme 1). These titration data were therefore analyzed considering the formation of both 1:1 and 2:1 complexes assuming that binding of the first anion does not influence that of the second (for further details see Scheme S3 and Figure S23, SI). The difference in anion coordination mode of *trans*-**1** as compared to *cis*-**1** is reflected in much lower stability constants (see Table 1).[23]

As the difference in K_a between *cis*- and *trans*-isomers is the largest with $H_2PO_4^-$, this anion was selected for *in situ* affinity

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switching studies (*vide infra*). First, we additionally determined its stability constant for binding to unstable *cis*-**1**. This was done by competitive titration to an equimolar *cis*/*trans* mixture, obtained after irradiation of stable *trans*-**1**. The data were evaluated in terms of three anion complexes (i.e., *trans* 1:1, 2:1 and *cis* 1:1) and by using the known stability constant of anion binding to the *trans*-isomer (for details see Figure S24, SI). The calculated constant ($K_a = 2.3 \times 10^3\ M^{-1}$) revealed a remarkable difference in anion complexation properties of the stable and unstable *cis*-isomers.

To gain more insight in the binding mode, geometry optimizations of the stable and unstable *cis*-**1**$\supset H_2PO_4^-$ complexes were performed on the B3LYP/6-31G++(d,p) level of theory using an IEFPCM, DMSO solvation model (see SI for details). Two of the previously proposed coordination motifs were considered.[5] The first one shares three oxygen atoms in urea hydrogen bonding, while the second has two oxygen atoms bound separately to each urea group. The latter possible structure was found to have the lowest energy minimum (see Figure 3 and the SI).

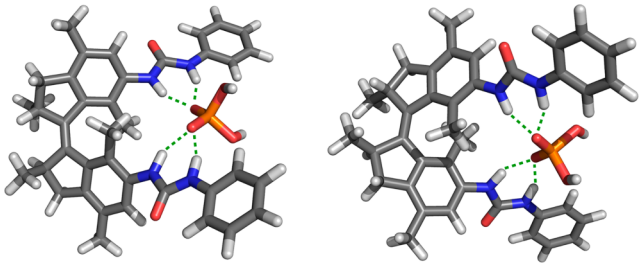

Figure 3. Energy minimized structures [B3LYP/6-31G++(d,p)] of (left) stable and (right) unstable *cis*-**1**$\supset H_2PO_4^-$.

The main differences between the minimized structures of the stable and unstable isomers are the torsional angles (θ, ϕ) at and neighboring the central double bond (see Table 2).[24]

Table 2. Selected Dihedral and Bond Angles (deg)[a]

complex	θ	ϕ	α
stable *cis*-**1**$\supset H_2PO_4^-$	3.3	36.6	132.1
unstable *cis*-**1**$\supset H_2PO_4^-$	−25.0	−26.4	129.3

[a]See Scheme 1 for the angle designation.

Apparently, the binding site of the unstable form is somewhat more opened resulting in a lower $H_2PO_4^-$ affinity. The hydrogen-bond distances are all in the same range (N···O = 2.89−2.91 Å), which is in line with the distances observed in the solid-state structure of an earlier described bis-urea benzoate complex.[7]

The difference in binding affinity to each isomer allows for unique multistage control of bound and unbound phosphate levels. To demonstrate this, ^{31}P NMR spectra were recorded of a 1:1 mixture of **1** and $[Bu_4N]^+[H_2PO_4]^-$ (1 mM in DMSO-d_6)[25] that was sequentially irradiated and heated (Figure 4). Starting from stable *trans*-**1**, photoisomerization (312 nm) to unstable *cis*-**1** is accompanied by an upfield shift in ^{31}P signal, which is further shifted upfield after thermal isomerization (60 °C) to stable *cis*-**1**. Subsequent photoisomerization (312, 365 nm) regenerates stable *trans*-**1** after which the same cycle can be repeated. According to the known stability constants and PSS ratio, the fraction of bound $H_2PO_4^-$ at the used

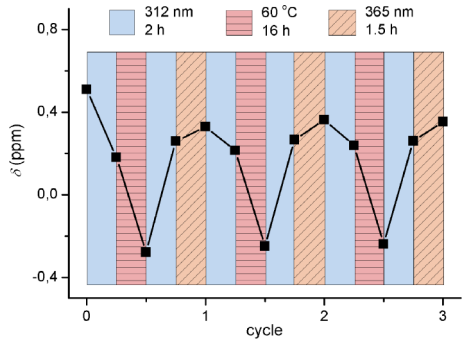

Figure 4. Reversible light/heat controlled uptake and release of $H_2PO_4^-$ monitored by the ^{31}P NMR chemical shift.

concentration varies between 20%, 48%, and 61% in the three addressable and distinct states.[26]

In summary, we have presented a bis-urea receptor that is derived from a first generation molecular motor. This receptor, which is highly selective for $H_2PO_4^-$ binding, can be switched photochemically and thermally between three isomers with distinct anion binding affinities. This offers an unprecedented three-stage control of the bound substrate level. In addition, this represents to our knowledge the most effective photoswitchable receptor for oxo-anions. New opportunities will therefore arise for future development of photoswitchable oxo-anion transporters. These may find application in, for example, photocontrolled drug delivery and the regulation of anion transport across the cell membrane. Current efforts in our lab are directed toward these goals.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization of new compounds, ^1H NMR dilution and isomerization studies, ^1H NMR titration curves and data analysis, Job plot and Eyring plot analysis, theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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