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ARTICLE

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Light-Modulated Self-Blockage of a Urea Binding Site in a Stiff-Stilbene Based Anion Receptor

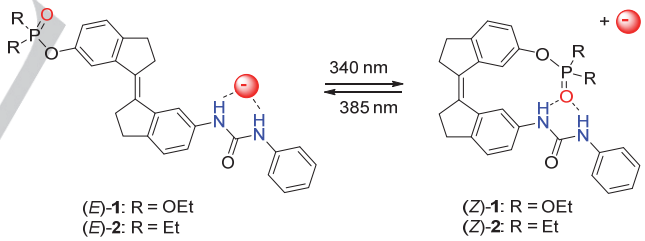
Jorn de Jong,[a] Ben L. Feringa,[a] and Sander J. Wezenberg*[a,b]

Abstract: Anion binding to a receptor based on stiff-stilbene, which is equipped with a urea hydrogen bond donating group and a phosphate or phosphinate hydrogen bond accepting group, can be controlled by light. In one photoaddressable state (*E* isomer) the urea binding site is available for binding, while in the other (*Z* isomer) it is blocked because of an intramolecular interaction with its hydrogen bond accepting motif. This intramolecular interaction is supported by DFT calculations and ^{1}H NMR titrations reveal a significantly lower anion binding strength for the state in which anion binding is blocked. Furthermore, the molecular switching process has been studied in detail by UV/Vis and NMR spectroscopy. The presented approach opens up new opportunities toward the development of photoresponsive anion receptors.

Introduction

Anion binding and transport play an important role in many biological processes, such as signal transduction, metabolism, osmosis, and pH-regulation.[1] Malfunction of the proteins that are involved in anion transport can lead to severe illnesses, among which are Dent disease, Bartter's syndrome, and cystic fibrosis.[2] Interestingly, a number of synthetic anion receptors were found to be capable of acting as membrane transporters and, because of their potential to replace faulty natural transporters as well as their ability to dissipate pH gradients (leading to apoptosis), they are considered as therapeutic agents.[3] Although a variety of synthetic anion receptors has been developed,[4] stimulus control of binding affinity and transport activity, as is often observed in proteins, is still a fundamental challenge in synthetic systems.

One of the most widely investigated methods to gain control over substrate binding makes use of photoswitchable scaffolds.[5,6] Our group recently developed molecular motor[7] and stiff-stilbene[8] derived bis-urea receptors. These responsive systems could be switched between (*E*)- and (*Z*)-isomers of which the latter had the highest anion binding affinity, in particular towards phosphate and acetate. The difference in binding affinity between the isomers was due to the possibility of forming four hydrogen bonding interactions between both urea groups and the anion in the (*Z*)-form, while in the (*E*)-form an anion could be bound only via two hydrogen bonds involving one urea unit because of steric constraints. Despite a large difference in binding affinity between the photoaddressable states, the (*E*)-isomer was, however, still capable of anion binding. Hence, we envisioned a new design for a photoresponsive receptor, containing an integrated host and guest functionality, in which the binding site is blocked in one state through intramolecular hydrogen bonding, while it is liberated and capable of anion binding in the other state (Scheme 1). Such an approach was first explored by the group of Shinkai for the "on" and "off" switching of metal complexation using an azobenzene backbone that was functionalized with a crown ether and an ammonium tail.[9] A similar concept has been applied to control the activity of an organocatalyst by means of switching the orientation of a hydrogen bond accepting moiety able to form an intramolecular hydrogen bond with thiourea and squaramide groups.[10] To the best of our knowledge, control of anion binding has not yet been demonstrated using this approach.



Scheme 1. Photocontrolled anion binding and release by blockage of the urea binding site through intramolecular hydrogen bonding.

Here we report photocontrol of anion binding affinity in stiff-stilbene based anion receptors **1** and **2** (see Scheme 1) containing a urea host functionality and a diethylphosphate or diethyl-phosphinate guest functionality. These receptors, which can be successfully isomerized using 340/385 nm light, show the typical anion binding behavior for mono-urea receptors in their (*E*)-configuration, whereas the binding strength is reduced in the (*Z*)-configuration. It is expected that this approach to control binding affinity externally with light will play an important role in the future development of anion receptors and transporters with regulatory affinity and transport activity.

Results and Discussion

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Receptor design and modeling

Urea is widely known as an excellent hydrogen bond donor and has frequently been incorporated into anion receptors.[4] For that reason, urea was chosen as the host functionality in our receptors. As it was previously encountered that strong intramolecular host-guest interaction can block photochemical isomerization in overcrowded alkene,[11] neutral hydrogen bond accepting moieties, instead of stronger accepting anionic ones, were selected as the complementary acceptor. Phosphorus-oxygen bonds are highly polarized and have been shown to be capable of participating in hydrogen bonding. Hence, a diethylphosphate group was initially chosen as the substituent that would be able to form an intramolecular hydrogen bond with the urea motif. Although this diethylphosphate group is a good hydrogen bond acceptor, it is known that when the ethoxy substituents at phosphorus are replaced by ethyl substituents, the hydrogen bond acceptor strength is increased.[12] Therefore, a second receptor containing a diethylphosphinate group was also considered.

To assess the viability of our designs, the geometries of the (*Z*)-isomers of these receptors were optimized by DFT on the B3LYP/6-31G++(d,p) level of theory (Figure 1). This level of theory was earlier found to be reliable for calculating anion hydrogen bonded complexes of bis-urea receptors.[7,8] For compound (*Z*)-**1**, the $N_1\cdots O$ and $N_2\cdots O$ bond distances obtained from the DFT calculations were 2.96 Å and 3.34 Å, respectively. Furthermore, the dihedral angle was found to be 6.6°, which is significantly smaller than what was calculated previously for stiff-stilbene based bis-urea phosphate and acetate complexes (11.0°).[8] The N···O distances calculated for (*Z*)-**2** were nearly identical (2.94 Å and 3.24 Å) while the dihedral angle is somewhat smaller (6.1°). A smaller dihedral angle may well originate from a stronger attractive interaction between both halves of the molecule which is expected in this case since diethylphosphinate is a stronger hydrogen bond acceptor than diethylphosphate. Overall, these calculations illustrate that intramolecular hydrogen bonding is feasible in these designs.

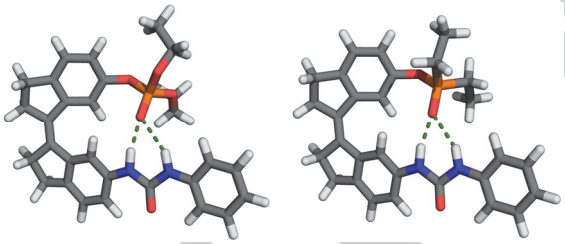


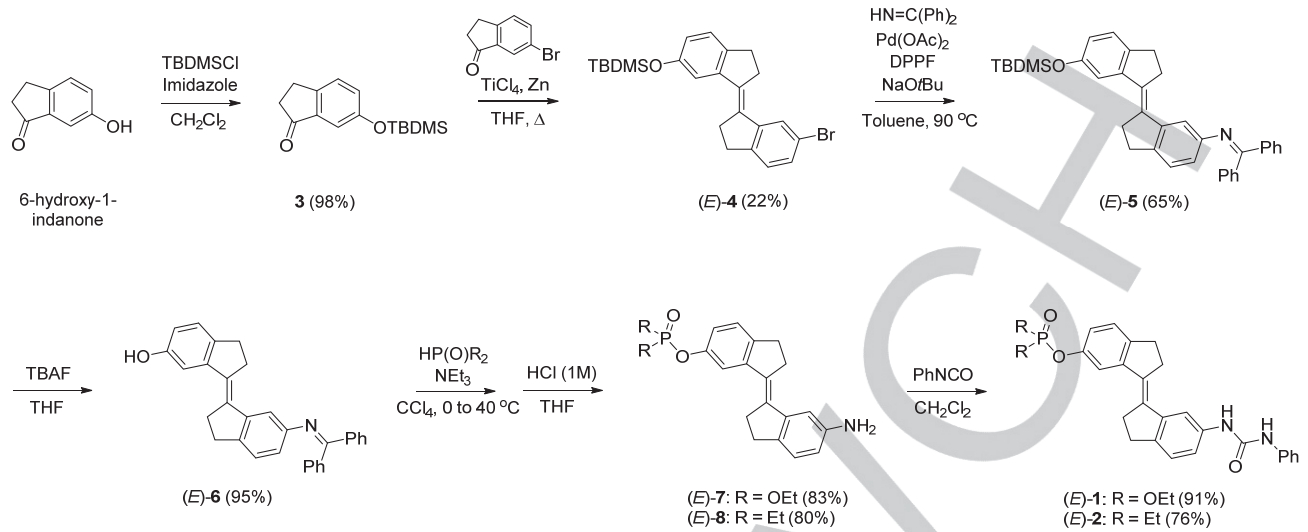
Figure 1. DFT optimized structures [B3LYP/6-31G++(d,p)] of (*Z*)-**1** (left) and (*Z*)-**2** (right).

Synthesis of desymmetrized receptors

The synthesis of receptors **1** and **2** is outlined in Scheme 2. Whereas the synthesis of symmetric stiff-stilbene switches through McMurry homocoupling of indanones is well described in the literature,[13] the preparation of desymmetrized stiff-stilbenes is challenging. Of the few known examples the majority is based on intramolecular McMurry coupling of bis-indanones affording only the (*Z*)-isomer due to steric constraints.[6f,14] We considered heterocoupling of differently substituted indanones to be more versatile as well as more suitable for further functionalization. Although cross McMurry reactions have been investigated for other substrates,[15] the only example found for indanones is the coupling of 5-dimethylamino-1-indanone with 5-bromo-indanone[16] and with 1-indanone,[17] however, synthetic details have not been reported. Toward the synthesis of receptors **1** and **2** a cross McMurry approach was taken. First, 6-hydroxyindanone was TBS protected using *tert*-butyldimethylsilyl chloride and imidazole as the base. Subsequently, the protected indanone **3** was coupled to 6-bromo-1-indanone, using a cross McMurry reaction, which successfully afforded the desired desymmetrized stiff-stilbene **4**.

When this cross McMurry reaction was carried out with **3** and 6-bromo-1-indanone in a 1:1 ratio, homocoupled product of **3**, homocoupled 6-bromo-1-indanone, and the desired heterocoupled product **4** were obtained in a 10:34:27 ratio. Apparently, the electron rich nature of indanone **3** renders it more activated to take part in the McMurry coupling than 6-bromo-1-indanone and hence, the formation of homocoupled **3** is favored. The addition of a slight excess of 6-bromo-1-indanone (1.25 equiv.) led to an increase in the amount of **4**, however, at the same time more of the 6-bromo-1-indanone homocoupled product was formed, which proved to be difficult to separate from the heterocoupled product by column chromatography. The crude product contained a 3:1 mixture of (*E*)-**4** and (*Z*)-**4** as was determined by ^{1}H NMR analysis. The homocoupled side-products could only be removed partially by column chromatography, but after a recrystallization step, the pure (*E*)-**4**-isomer was isolated in 22% yield. Its structure was unequivocally assigned based on a NOESY experiment showing a through space interaction between the stiff-stilbene CH_2-protons and the aromatic proton (Figure S4 in the Supporting Information). Since the (*Z*)-isomer could not be separated from the (*E*)-isomer, which remained present in the mother liquor after the recrystallization step, only the latter was used in the subsequent reaction steps.

The reaction of (*E*)-**4** with benzophenone imine following a palladium-catalyzed Buchwald-Hartwig amination procedure afforded (*E*)-**5**. The *tert*-butyldimethylsilyl protecting group was then removed by treatment with tetrabutylammonium fluoride. Compound (*E*)-**7** was obtained by phosphorylation of (*E*)-**6** via an Atherton-Todd reaction in which diethyl phosphite was converted into the more reactive diethyl chlorophosphate in the presence of triethylamine and carbon tetrachloride. The crude product was hydrolyzed directly by treatment with hydrochloric acid and was then reacted with phenyl isocyanate to give the desired receptor (*E*)-**1**. For the synthesis of (*E*)-**2**, first diethyl phosphine oxide was prepared by treatment of diethyl phosphite with ethylmagnesium bromide, using a modified literature procedure.[18] Then, (*E*)-**6** was again allowed to react under Atherton-Todd reaction conditions, followed by treatment of the crude product with hydrochloric acid and reaction with phenyl isocyanate to give (*E*)-**2**. Both receptors were fully characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and HRMS (Figure S1-S22 in the Supporting Information).



Scheme 2. Synthesis of receptors (*E*)-**1** and (*E*)-**2**.

Photoisomerization behavior

The photoisomerization behavior of receptors **1** and **2** was studied with UV/Vis and ^{1}H NMR spectroscopy. When solutions of (*E*)-**1** and (*E*)-**2** in degassed DMSO were irradiated with 340 nm light at room temperature, for both compounds, the intensity of the absorption maxima at λ = 344 and 360 nm decreased and simultaneously, a new absorption band appeared at longer wavelength (Figure 2). These spectral changes are indicative for the formation of the (*Z*)-isomer.[13] Irradiation was halted when no further changes were noted, *i.e.*, the photostationary state (PSS) was reached. Thereafter, the same samples were irradiated with 385 nm light to promote the reverse photochemical isomerization, which caused the absorption to increase. During 340 nm and 385 nm irradiation, a clear isosbestic point was observed at λ = 367 nm illustrating unimolecular conversion (Figure S25-S28 in the Supporting Information). Photoisomerization was repeated multiple times to test the fatigue resistance. Whereas for receptor **1** no significant signs of fatigue were noted upon multiple switching cycles, the observed decay in absorption for receptor **2** revealed that some degradation occurred (Figure 2, insets).

Next, photoisomerization was monitored by ^{1}H NMR spectroscopy in DMSO-d_6 (Figure 3). The urea protons of (*E*)-**1** appeared as two singlets at δ = 8.71 and 8.63 ppm. Upon irradiation of the NMR samples with 340 nm light a new single signal appeared at δ = 8.58 ppm, which is ascribed to formation of (*Z*)-**1**. Also two aromatic singlet signals for (*Z*)-**1** showed up at δ = 7.85 and 8.16 ppm, which is significantly shifted downfield compared to (*E*)-**1** (δ = 7.40 and 7.91 ppm). For compound **2**, the shift in urea signals upon 340 nm irradiation was found to be larger. Where the NH-signals of (*E*)-**2** are located at δ = 8.62 and 8.69 ppm, those of (*Z*)-**2** are shifted to δ = 8.34 and 8.87 ppm. These shifts are much larger than the ones observed for receptor **1** which may tentatively be ascribed to a stronger intramolecular interaction in the (*Z*)-configuration as was

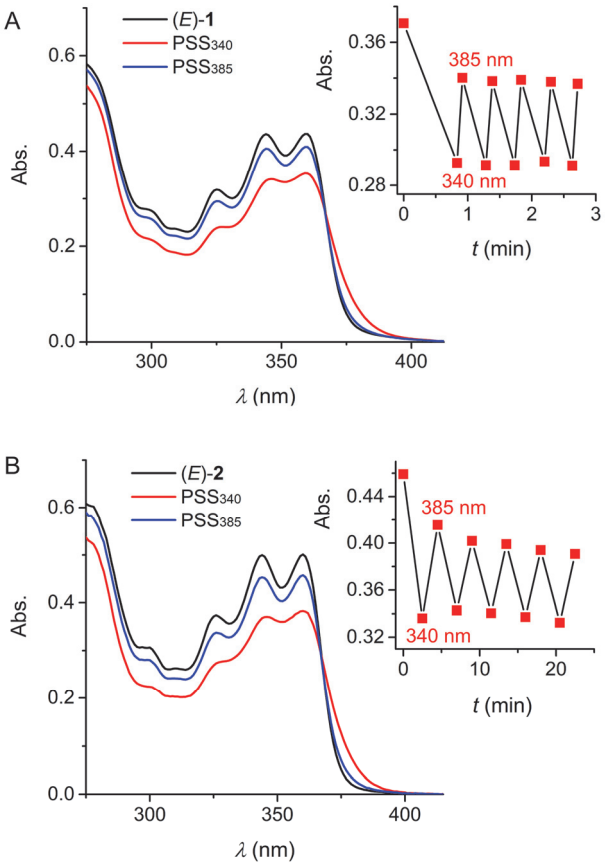


Figure 2. UV/Vis spectral changes starting from (*E*)-**1** (A) and (*E*)-**2** (B) upon 340 nm irradiation followed by 385 nm irradiation (c = 2 × 10^{-5} M in degassed DMSO). The insets show 340/385 nm irradiation cycles.

expected for the phosphinate as compared to the phosphate group (*vide supra*).

The PSS ratios were calculated by integration of the singlet signals belonging to the urea and aromatic protons, in addition to the diethyl phosphate and phosphinate CH_2-signals. The PSS_{340} ratios (*E*/*Z*) were found to be 47:53 and 42:58 for receptor **1** and **2**, respectively. The PSS_{385} ratios were determined to be 94:6 for **1** and 93:7 for **2**. These values are comparable to those reported for other stiff-stilbene switches.[13]

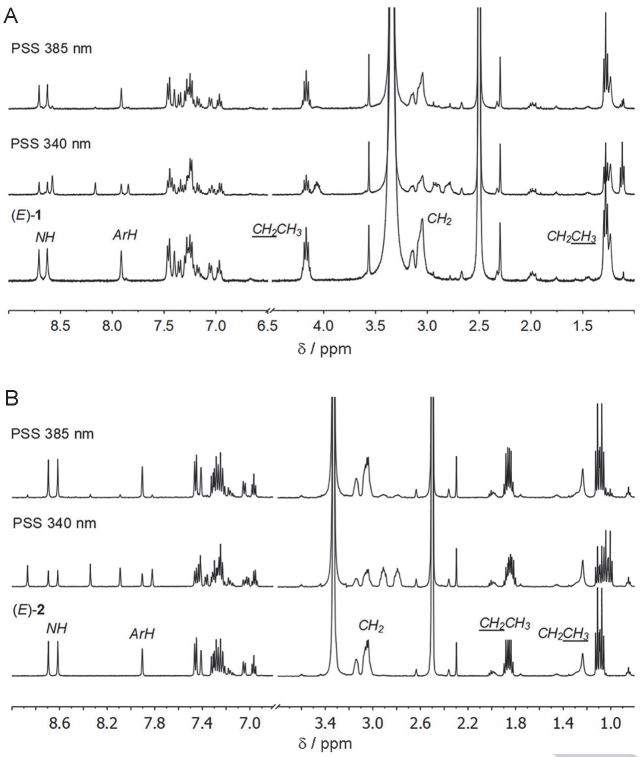


Figure 3. NMR spectral changes upon consecutive irradiation of solutions of (*E*)-**1** (A) and (*E*)-**2** (B) in degassed DMSO-d_6 with 340 nm and 385 nm light.

Anion binding strength

Showing that photoisomerization was found to be feasible, the anion binding affinities to the (*E*)- and (*Z*)-isomers of receptors **1** and **2** were determined using ^{1}H NMR titrations. Tetrabutylammonium salts of acetate ($CH_3CO_2^-$), dihydrogen phosphate ($H_2PO_4^-$) and chloride (Cl^-) were used and a mixture of DMSO/0.5%H_2O was chosen as the solvent. Stepwise addition of anions to (*E*)-**1** and (*E*)-**2** led to the typical downfield shifts of urea and aromatic singlet signals (Figures S31-S33 and S37-S39 in the Supporting Information). For $CH_3CO_2^-$ and $H_2PO_4^-$, the expected 1:1 binding stoichiometries could be confirmed by the construction of a modified Job plot (Figures S43, S44, S49, S50 in the Supporting Information). All the titration data were fitted to a 1:1 binding model with HypNMR[19] using the shifts in NMR signals belonging to the urea NH and the most downfield aromatic CH protons. The association constants found for both (*E*)-**1** and (*E*)-**2** (Table 1 and Figures S43-S54 in the Supporting Information) follow the order of anion basicity, i.e. the strongest binding for $CH_3CO_2^-$, slightly weaker binding for $H_2PO_4^-$, and the weakest binding for Cl^-. Overall, the calculated constants compare well with the values reported for other mono-urea receptors.[20,21]

Table 1. Anion binding constants in in DMSO-d_6/0.5%H_2O.[a]

Receptor	$CH_3CO_2^-$	$H_2PO_4^-$	Cl^-
(*E*)-**1**	1.5×10^3	6.2×10^2	32
(*Z*)-**1**[b]	1.2×10^3	3.1×10^2	22
(*E*)-**2**	1.4×10^3	7.2×10^2	30
(*Z*)-**2**[b]	8.4×10^2	2.9×10^2	18

[a] Anions were added as tetrabutylammonium salt. [b] Determined by competitive titration to PSS_{340} E/Z mixtures.

Because the synthetic pathways towards these receptors afforded only the (*E*)-isomers, the binding affinity of the corresponding (*Z*)-isomers was investigated by competitive titrations to PSS_{340} mixtures (see Figures S34-S36 and S40-S42 in the Supporting Information for details). Hence, first a solution of the respective (*E*)-isomer was irradiated to (partially) generate the (*Z*)-isomer, after which either $CH_3CO_2^-$, $H_2PO_4^-$, or Cl^- was added stepwise. The association constants of the (*Z*)-isomers (Table 1) were then obtained by fitting the data to 1:1 binding models, considering binding to both the (*E*)-isomer and (*Z*)-isomer happening at the same time, where the predetermined binding constants for the (*E*)-isomers were fixed.[22] As anticipated, the binding affinities obtained for the (*Z*)-isomers are all lower than those for the (*E*)-isomers. Furthermore, the diethylphosphinate group was found to possess the largest differences in binding strength between (*E*)- and (*Z*)-isomers, as was expected beforehand based on the stronger hydrogen bond accepting ability (*vide supra*). Nevertheless, the differences are not so pronounced as with our previously reported bis-urea receptors.[7,8] Although here the binding affinity can be successfully controlled by light-induced isomerization, it seems that intramolecular hydrogen bonding in the (*Z*)-configuration is not sufficiently strong to fully block urea-anion binding.[23]

Conclusions

In conclusion, we have developed two photoswitchable anion receptors based on a desymmetrized stiff-stilbene backbone which contain complementary host and guest functionalities. In the (*E*)-configuration, the urea binding site is exposed and available for anion binding, while in the (*Z*)-isomer the binding site is partially blocked as a result of intramolecular hydrogen bonding with a phosphate or phosphinate group. The

desymmetrized receptors were synthesized using a cross McMurry reaction and both receptors showed binding towards $CH_3CO_2^-$, $H_2PO_4^-$ and Cl^-, the strength of which could be modulated by photoisomerization with 340 and 385 nm light. Although the differences in binding affinity between the isomers are moderate, our results demonstrate that modification of stiff-stilbene with host and guest functionalities to control binding affinity is viable. Further fine-tuning and modification of the functional groups, for example by using stronger hydrogen bond donors or suitable macrocycles, will lead to receptors with larger differences in binding affinity between the photoaddressable states in the future. Such receptors may be used, among others, to control transmembrane transport by light.

Acknowledgements

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Keywords: molecular switches • photochromism • molecular recognition • anion binding • stiff-stilbene

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[23] The diethylphosphate group in compound **1** was derivatized to the phosphate anion (compound **S1**, Scheme **S1** in the Supporting Information) but, unfortunately, 385 nm induced *Z*-to-*E* photoisomerization was inhibited and eventually the compound degraded (Figures S29-S30 in the Supporting Information).

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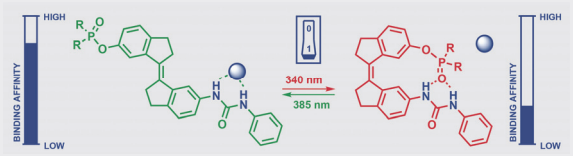

Anion binding to a urea receptor is blocked upon photoisomerization as a result of intramolecular hydrogen bond formation as is demonstrated by ^{1}H NMR titrations. The intramolecular interaction is supported by DFT calculations and the molecular switching process is studied in detail by UV/Vis and ^{1}H NMR spectroscopy.

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