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Engineering Light-Mediated Bistable Azobenzene Switches Bearing Urea D-Aminoglucose Units for Chiral Discrimination of Carboxylates

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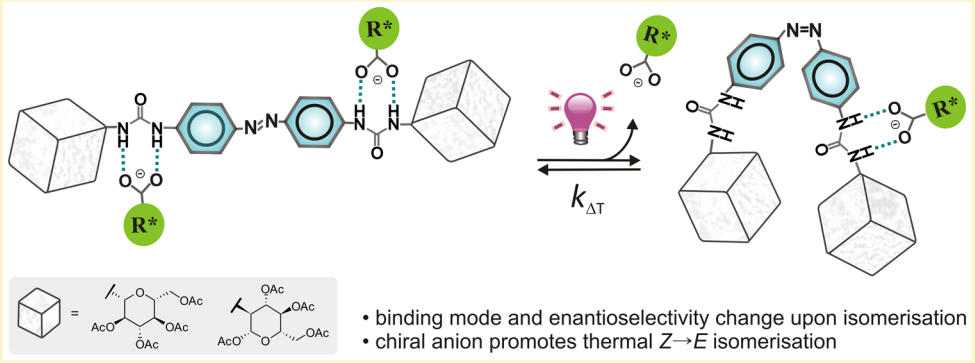
Supporting Information



ABSTRACT: The symmetrical molecular receptors **1a** and **1b** consisting of a photochemically addressable azobenzene tether functionalized with urea hydrogen-bonding groups and D-carbohydrates as chiral selectors were developed to achieve control over the chiral recognition of α-amino acid-derived carboxylates. The photo- and thermally interconvertible planar *E*-**1** and concaved *Z*-**1** were found to exhibit different affinities, selectivities, and binding modes toward these biologically important anions in a highly polar medium (DMSO + 0.5% H_2O). Binding affinity for the same enantiomerically pure guest was up to 3 times higher for *E*-**1** than for *Z*-**1** (cf. parameter β). In addition, the rate of thermal $Z \rightarrow E$ isomerization was found to depend on the chiral binding ability of *Z*-**1**, i.e., more strongly bound carboxylate enantiomer as well as higher enantiomer concentration caused faster relaxation to *E*-**1**.

INTRODUCTION

In natural systems, recognition and transport of chiral ions, ranging from simple amino acids to more complex peptides, is mainly realized by highly specialized receptors.[1] Frequently these bioreceptors act as switches, for which the corresponding conformational state may be selectively triggered by external stimuli, such as temperature, pH, ion gradient, and light.[2] Recognition of chiral molecules by artificial systems, however, still remains a great challenge, despite remarkable progress that has been made in supramolecular chemistry[3] during the past two decades, particularly in the field of ion recognition.[4] Indeed, a relatively small number of receptors exhibiting a high level of chiral recognition (expressed as $\alpha = K_R/K_S \geq 2$),[5] arise mainly from the fact that such synthetic molecular receptors have to distinguish between subtle structural differences in isoenergetic enantiomers, and this process is likely not purely static.[6] Lessons from Nature suggest that many weak, directional noncovalent interactions (i.e., H-bonds and London dispersion forces), originating from receptor constituents with a rational spatial arrangement, have to be taken into account to render such interactions strong and specific. The mutual interplay of these interactions, however, is difficult to predict in silico, in particular when solvent effects are also included. Nonetheless, to help in designing potential chiral anion receptors, one can take advantage of the three-point-attachment concept, which assumes that at least three interactions need to exist between the receptor and guest molecules.[7] This empirical rule of thumb is mostly implemented by installing chiral scaffolds in the proximity of an anion binding pocket previously proven to be effective for achiral anions, e.g., a urea group that is tailored for carboxylate binding.[8] A chiral barrier is usually introduced by installing carbohydrates[9] or amino acids,[10] and also binaphthyl derivatives.[11] Recently, we exploited the former approach in the construction of receptors able to efficiently differentiate chiral carboxylates (with α up to 4),[9a,c,d] and even to predict their configuration.[9b] Furthermore, although switching of a receptor's binding properties was already employed for the recognition of an achiral guest, both charged[12,13] and electrically neutral,[14] its utilization in chiral recognition is, to the best of our knowledge, limited only to neutral guests.[15] Of a number of stimuli which can potentially be used as triggers for such transformation,[16] the unique features of light, i.e., its unmatched spatial resolution and electrically neutral character, render it particularly useful.[16−18] Moreover, light-triggered transformation is generally reversible and can be easily fine-

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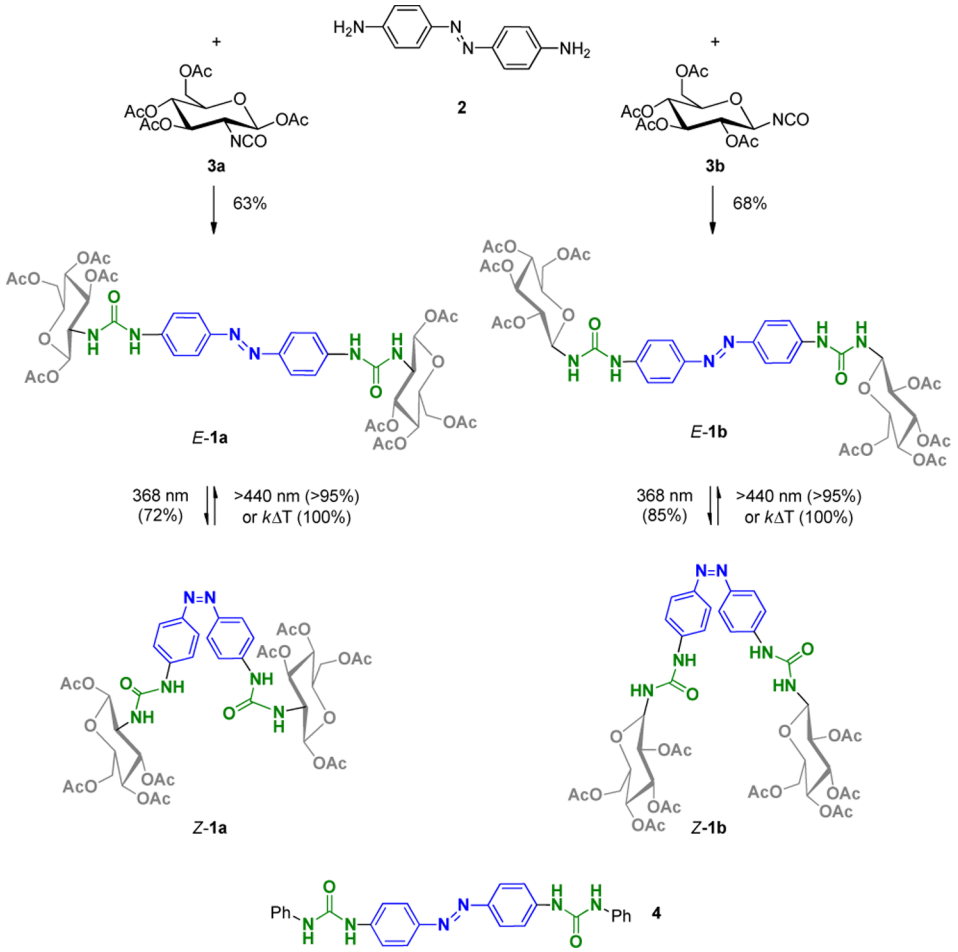
Scheme 1. Synthesis of Receptors *E*-1 and Their Isomerization to *Z*-1[a] and the Structure of Reference Achiral Receptor 4



[a]Switchable core shown in blue, anion binding sites in green, and chiral barrier in gray.

tuned to selectively affect only the chosen molecules. The photoactive moieties that are often applied in such transformations include diaryl- and dithienylethene, spiropyran, and azobenzene (AB) derivatives.[16,19,20] Among these, the latter appear to be the most useful, owing to their synthetic availability, robustness, and large-amplitude structural changes between extended (*E*) and folded (*Z*) isomers.[21] The latter feature has been utilized for the construction of photoresponsive supramolecular catalysts.[12c,14c,22] For example, an AB chromophore was employed for the photocontrol of basicity,[22a] nucleoside coupling,[14c] solvolysis,[12c,22b,c] Knoevenagel condensation,[22d] and Morita–Baylis–Hillman reaction.[22e] Very recently, we have shown that light can be used for control of the benzoate binding by the model phenylurea receptor **4** based on the robust azobenzene tether.[13d] Inspired by these results, we envisioned that exchanging the achiral phenyl group for a carbohydrate scaffold should enable light-mediated control over the receptor's chiral discrimination properties toward anionic species. Furthermore, because kinetic rate of thermal $Z \rightarrow E$ isomerization was found to strictly depend on the anion binding properties of the achiral **4**, we were interested in evaluating a possible influence of enantiomeric carboxylate on this process. In this study, we explored this concept of dynamic recognition by synthesizing and evaluating chiral anion binding properties of new hybrid receptors **1** (Scheme 1). The thermodynamically stable near planar receptors *E*-**1** were synthesized in good yields by reacting 4,4′-diaminoazobenzene **2** with known β-D-glucopyranose isocyanates **3a** or **3b**.

RESULTS AND DISCUSSION

The V-shaped *Z*-**1** receptors were then produced by $E \rightarrow Z$ isomerization driven by irradiation with UVA light (368 nm, 60 W). They spontaneously re-equilibrated with first-order kinetics at rates ($t_{1/2}$ = 65 and 144 min for *Z*-**1a** and *Z*-**1b**, respectively) similar to those previously reported for model achiral receptor **4** ($t_{1/2}$ = 108 min).[13d] The binding properties of receptors **1** were investigated in DMSO-d_6 + 0.5% H_2O by titration under ^{1}H NMR control or by isothermal $Z \rightarrow E$ isomerization titration under UV–vis control. The anion coordination mode changes from 1:1 + 1:2 to exclusively 1:1 (host–guest) when *E*-**1** interconverts to *Z*-**1**.[23] To clarify the comparison between association constants for *E*- and *Z*-**1**, the K_a mentioned in the main text for *E*-**1** refers to the first association constant ($K_{a,1}$). As model anions, we chose various carboxylates, given that amino acids as well as more complex peptides and proteins exist in such form under physiological conditions. Several reports indicate that binding affinities toward model chiral anions (e.g., mandelate) are almost 1 order of magnitude smaller than those for model achiral ones (e.g., benzoate),[5] which means that artificial chiral receptors need to be inherently potent in achiral anion recognition.[24] Therefore,

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we first determined binding properties of receptors **1a** and **1b** toward model achiral acetate and benzoate (Table 1). The

Table 1. Stability Constants K_a (M^{-1}) for Receptors 1 with Model Achiral Carboxylates[a]

entry	receptor	anion	$K_{a,E\text{-isomer}}$[b]	$K_{a,Z\text{-isomer}}$[c]
1	**1a**	$MeCO_2^-$	836	756[d]
2		$PhCO_2^-$	306	192
3	**1b**	$MeCO_2^-$	870	816[d]
4		$PhCO_2^-$	316	105
6	**4**[e]	$PhCO_2^-$	989	231

[a]Determined using ^{1}H titration in DMSO-d_6 + 0.5% H_2O at 298 K. Anions were added as tetrabutylammonium (TBA) salts. Estimated errors are ±10% (detailed error estimates are given in Table S2). [b]Titration carried out in the dark. [c]Titration conducted immediately after the UV irradiation. [d]Determined using isothermal $Z \rightarrow E$ isomerization titration under UV−vis control. [e]Data taken from ref 13d.

association constants (K_a's) for benzoate with receptors *Z*-**1** were virtually equal and, as in the case of achiral receptor **4**, considerably smaller than for *E*-**1**. The lower binding ability of receptors *Z*-**1** suggests that in this folded conformation two para-substituted urea-sugar groups are still far away from each other, thus preventing their potential cooperativity effect. This may suggest that binding of the carboxylate anion is occurring on the periphery of the chiral receptors *Z*-**1**. In addition, one can assume that acidity of the NH urea protons is reduced in the *Z*-conformation, which results from the weaker π-electron conjugation as compared with the planar *E*-isomer.[25]

Receptors *E*-**1** bound acetate more strongly than benzoate, in line with the basicity of these anions in DMSO (acetate is more basic than benzoate). These differences were, however, rather small (the K_a ratio for *E*-**1** with acetate vs benzoate is ∼2.7), which suggests $\pi-\pi$ interactions between rings of benzoate and β-D-glucopyranose; moreover, in another study we very recently found similar favorable interactions involving sugar moieties.[9a,b] Determination of K_a for receptors *Z*-**1** with acetate, on the other hand, proved impossible under ^{1}H NMR titration, owing to very rapid thermal re-equilibration to *E*-**1**, after the addition of 1 equiv of acetate (Figure S10). Such acceleration of thermal rate constants results from efficient anion-mediated electron density transfer to the N═N bond of *Z*-**1**.[13d] To determine these values, we have taken advantage of the $Z \rightarrow E$ isomerization titration procedure which allows accurate determination of both K_a and rate constant for the saturated complex of *Z*-receptor with an anion (k_{HG}) for processes with slow and fast kinetics.[13d] These values are comparable for both *Z*-**1a** and *Z*-**1b**, which indicates that, unlike for benzoate, the steric hindrance generated by bulky sugar moieties in both isomers of **1** is insufficient to prevent strong binding with small acetate, because the K_a values for *Z*-**1** are only slightly lower than for *E*-**1**. Nonetheless, sufficiently high affinities for the achiral carboxylates prompted us to carry out more comprehensive studies to elucidate the chiral properties of receptors **1**. As model chiral guests, we chose mandelate (Man) and *tert*-butyloxycarbonyl-NH-protected phenylalanine (Phe) and tryptophan (Trp) which are typically employed for the chiral recognition studies.[5c]

Initial titration experiments with mandelates revealed that receptors **1** bound them very weakly (K_a ∼ 20 M^{-1}) and without any selectivity toward a particular enantiomer. Similar anion binding behavior was observed for structurally related aromatic ureas having identical sugar moieties as in receptor **1b**.[9c] Presumably, the presence of decreased negative charge density on the carboxylate group, resulting from intramolecular hydrogen bonding with the hydroxyl group, is responsible for the weak interaction of Man with receptors **1**.[5a,b,10] Nevertheless, the values obtained for other carboxylates were high enough to be considered reliable and are presented in Table 2.

Table 2. Stability Constants K_a (M^{-1}) for Receptors 1 with Model Chiral Carboxylates[a]

				E-isomer		*Z*-isomer		
entry	receptor	anion	abs conf	K_a[b]	α[c]	K_a[d]	α[c]	β[e]
1	**1a**	Phe	D	55	1.61	30	1.00	0.45
2			L	89		30		0.66
3	**1b**	Phe	D	63	1.19	39	1.25	0.38
4			L	53		31		0.41
5	**1a**	Trp	D	143	1.12	68	1.48	0.52
6			L	127		46		0.64
7	**1b**	Trp	D	124	1.61	76	1.31	0.39
8			L	77		58		0.25

[a]Determined using ^{1}H titration in DMSO-d_6 + 0.5% H_2O at 298 K. Estimated errors are <15% for *E*-**1** and <20% for *Z*-**1** (detailed error estimates are given in Table S3). Anions were added as tetrabutylammonium (TBA) salts. Man, mandelate; Phe, phenylalanine; Trp, tryptophan. [b]Titration carried out in the dark. [c]$\alpha = K_D K_L^{-1}$. [d]Titration conducted immediately after the UV irradiation. [e]See main text for the definition.

Analysis of this data reveals some general trends. First, just as previously mentioned, receptors *E*-**1** bind anions 2−3 times more strongly than *Z*-**1**. Second, *E*- and *Z*-isomers of receptors **1** prefer carboxylates derived from D-amino acids (except *E*-**1a**, which binds L-Phe more strongly than D-Phe). Analysis of the shift changes of the sugar protons induced by the addition of the D-enantiomeric guests suggest additional interactions, e.g., titration of receptors **1a** with D-Trp causes moderate downfield shift of the anomeric proton whereas addition of L-Trp to **1a** has virtually no effect on this resonance. A similar trend was observed for the receptors bearing chiral substituents derived from D-glucose.[5b,9c,d] Third, both receptors **1a** and **1b** bind Trp stronger than Phe. Because the bulkiness and relative basicity of the carboxylate group are comparable for both Phe and Trp, the preference for Trp anion is likely attributed to a favorable intermolecular interaction between anion and receptor, in particular between indole NH proton and carbonyl group of the sugar moieties. This assumption is supported by the observation that indole NH proton shows a moderate downfield shift (up to 0.25 ppm) upon complexation with receptors **1**. Notably, larger chemical shift changes are observed for more stable complexes, e.g., for receptor *Z*-**1a**, the changes are $\Delta\delta$ = 0.20 ppm for D-Trp vs $\Delta\delta$ = 0.14 ppm for L-Trp, respectively. Furthermore, resonances of all sugar acetyl groups, which are excellent indicators of the chiral binding event,[9] shifted upfield during titration, indicating interaction with a negative charge of an anion as well as with a ring current of its aromatic ring. The highest enantioselectivity was observed for receptor **1a** (entries 1 and 2 for *E*-isomer and entries 5 and 6 for *Z*-isomer). On the contrary, receptor **1b** exhibits rather low enantioselectivity (except *E*-**1b** with Trp), despite the fact that the corresponding K_a within *E*- and *Z*-isomers changes substantially. In the case of receptor **1a**, this feature allows

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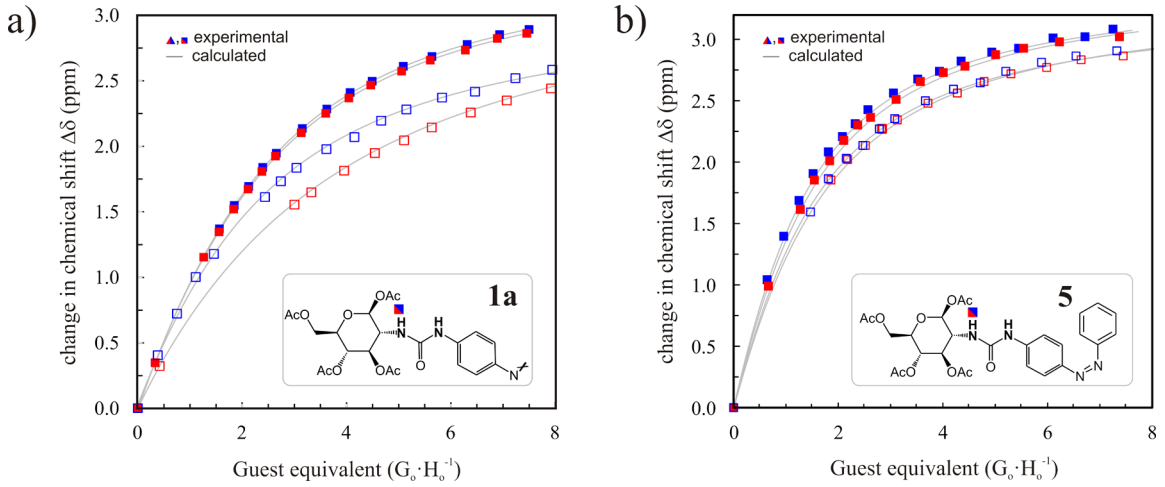

Figure 1. Patterns of chemical shift changes for aliphatic urea protons in receptor **1a** (a) and **5** (b) during ^{1}H NMR titration with D-Trp (blue points) and L-Trp (colored in red). *E*-Isomer (closed symbols), *Z*-isomer (open symbols); gray lines represent fitted binding isotherms; aromatic urea protons exhibit similar binding behavior (see Supporting Information (SI)).

for a temporal light-driven "turn-off" of the chiral discrimination of Phe, i.e., stable *E*-**1a** binds D-Phe stronger than L-Phe (α = 1.61), whereas no such preference is observed for transient *Z*-**1a** (α = 1.00). This moderate level of enantioselectivity of *Z*-**1a** is clearly visible in the different behavior of ^{1}H NMR signals of urea protons during titrations with Trp (Figure 1a).

One can see that the binding pattern for the urea protons demonstrate that *E*-**1a** binds Trp stronger than *Z*-**1a** (i.e., changes in the chemical shifts are higher in the former case) as well as that D-Trp is bound stronger than L-Trp. In addition, contrary to the *Z*-isomer, slight differences between urea protons for *E*-**1a** and D- vs L-Trp indicates weak chiral recognition properties. To determine if the second urea-sugar moiety is required to achieve enantioselective recognition, we decided to synthesize reference receptor **5** and evaluate its binding properties with Trp anions (Figure 1b). Furthermore, in contrast to receptors **1**, the lack of a second urea group will result in both the *E*- and *Z*-isomer of receptor **5** to only form 1:1 complexes with carboxylates. The ^{1}H NMR titrations reveal that compound **5**, similarly to receptor *E*-**1a** (Figure 1a), was not able to differentiate between enatiomeric Trp, with K_a values identical within experimental error (for D-Trp, the values are K_a = 109 M^{-1} vs K_a = 97 M^{-1}, and for L-Trp, K_a = 98 M^{-1} vs K_a = 105 M^{-1}, for *E*-**5** vs *Z*-**5**, respectively). This clearly indicates that the second urea-sugar moiety is crucial to achieve enantiodifferentiation between Trp for the *Z*-isomer of receptor **1a**. This is in line with our previous report on the chiral discrimination by static sugar receptors based on the diindolylmethane scaffold.[9d]

Although receptors **1** exhibit rather moderate chiral recognition, it should be emphasized that a high level of enantiodiscrimination is not very common in the supramolecular chemistry of carboxylates, even for static molecular receptors. On the other hand, from the point of view of modern chiral stationary phases in HPLC or GC, the selectivity at a level of 1.1 is not only sufficient but is even optimal.[5a,7] In view of these facts, chiral recognition properties of model dynamic receptors **1** are encouraging and further work is needed to fine-tune their selectivities for particular chiral carboxylates.

It should be highlighted that to date, to describe chiral recognition, parameter α (i.e., K_R/K_S or K_D/K_L), describing the discrimination ratio between enantiomers of the guest, has solely been employed. In Nature, however, the vast majority of so-called chiral natural products exist in enantiomerically pure form. Therefore, to compare synthetic receptors for the same enantiomerically pure guest, whose binding properties in principle depend on its state, as is the case here, we propose to use the normalized binding amplification parameter β (eq 1).

$$\beta = \frac{K_a^{max} - K_a^{state_x}}{K_a^{max}}$$

$$K_a^{max} = \max(\{K_a^{state_1}; K_a^{state_2}; ...; K_a^{state_n}\}) \quad (1)$$

where K_a^{max} is the highest association constant K_a from the set of possible states of the receptor and $K_a^{state_x}$ is the K_a in any other state. The value of parameter β is always located between 0 and 1, which easily allows for evaluation of the relative discrimination ability of the switchable receptor for both achiral and chiral guests. For example, the value of β close to 0 indicates no difference of K_a between states, whereas a value of β close to 1 indicates very strong preference for one of the receptor states toward the guest molecule. In this work, receptors **1** can exist only in two states (i.e., *E*- or Z-isomer), K_a^{max} is higher for *E*-isomer, and so $\beta = (K_{a,E} - K_{a,Z})/K_{a,E}$. The highest β parameter was observed for the binding of receptor **1a** with L-enantiomer of the guest, i.e., L-Phe and L-Trp were bound almost three times stronger by *E*-**1a** than by *Z*-**1a** (β = 0.66 for L-Phe and β = 0.64 for L-Trp, respectively). In contrast, parameter β for receptors **1b** does not exceed 0.4, which further confirms weaker chiral discrimination properties of the 1-aminoglucose pedant arm.

To evaluate a possible influence of enantiomeric carboxylate on the rate of $Z \rightarrow E$ thermal back-isomerization, we conducted additional experiments similar to those performed for achiral acetate, in which we studied how the rate constant of the $Z \rightarrow E$ isomerization depends on the amount of Trp added (Figure 2).

In addition, this procedure allows for direct comparison with values of K_a, and thus α, derived from ^{1}H NMR titrations. In supramolecular recognition of chiral species, the quality and reliability of α is a serious issue when the K_a for corresponding enantiomers cannot be accurately determined.[5a,26] Furthermore, some of the reported enantioselectivities which act as the

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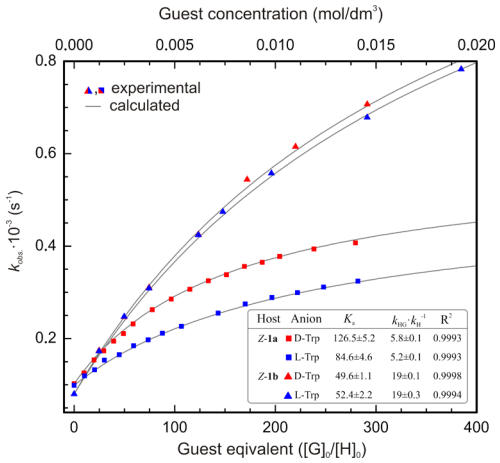


Figure 2. Changes in observed rate constant (k_{obsd}) of thermal $Z \rightarrow E$ isomerization of receptors *Z*-**1a** (squares) and *Z*-**1b** (triangles) upon addition of D-Trp (colored in blue) and L-Trp (colored in red) at 298 ± 0.1 K along with calculated values of $K_{a,Z}$, k_{enh} (k_{HG}/k_H), and R^2 (inset table); $c_{Z\text{-}1} = 5 \times 10^{-5}$ M; k_H, rate constant without anion added; k_{HG}, rate constant for saturated complex.

golden standard are actually consequences of experimental errors.[5a,26d] As can be seen from Figure 2, the excellent fit of the data points to the equation derived for a simple 1:1 binding mode (see Experimental Section and Figures S67 and S68 for the residual analysis) clearly confirms stochiometry of the complexes of receptors *Z*-**1** with enantiomeric carboxylates. The K_a value for *Z*-**1a** is slightly higher than that obtained from ^{1}H NMR titration experiments, e.g., for D-Trp, the values are K_a = 126 M^{-1} vs K_a = 68 M^{-1}, and for L-Trp, K_a = 85 M^{-1} vs K_a = 46 M^{-1}, for UV–vis vs ^{1}H NMR, respectively. However, for *Z*-**1b**, these differences are negligible. Overall, the enantiomeric discrimination α for receptors *Z*-**1a** is virtually equal to that obtained from ^{1}H NMR titrations (1.49 vs 1.48), whereas for *Z*-**1b**, it is slightly lower (1.06 vs 1.31, for UV–vis vs ^{1}H NMR, respectively). Given that the determined parameters are insensitive to the receptor concentration and considering the excellent calculated fit ($R^2 > 0.999$ and $\chi^2 \cong 10^{-12}$–10^{-11}), the results derived from UV–vis isothermal titration are likely to be more reliable. In addition, the thermal rate constant enhancement k_{enh} (i.e., k_{HG}/k_H) for *Z*-**1a** ranges from 5.2 for L-Trp to 5.8 for D-Trp, i.e., the D-enantiomer causes faster relaxation to *E*-**1a**, whereas nearly identical rates (k_{enh} = 19) for *Z*-**1b** independently prove that virtually no chiral differentiation is occurring in this case. Because the anion is not consumed during reaction, one can assume that the anion acts as a "catalyst" of this thermal back-isomerization process.

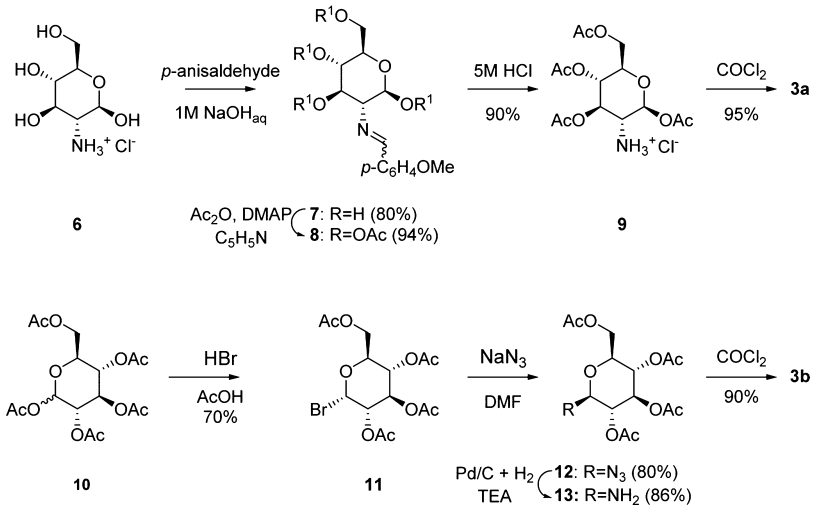
In conclusion, by combining together sugar scaffolds, urea groups, and the azobenzene moiety, we obtained two new chiral receptors able to selectively sense biologically important chiral carboxylates. Because the binding affinities toward chiral carboxylates differ between photoswitchable *E*- and *Z*-isomers, we have shown, for the first time, that light can be used for switching of the chiral recognition, allowing even for the complete "turn-off" of this phenomenon. Furthermore, because the stability of *Z*-isomers of **1** is anion- and temperature-dependent, one can consider chiral anion and temperature as factors allowing for predictable stepwise control of the chiral event, with the chiral properties of the receptor increasingly resembling those of the *E*-isomer as time passes.

EXPERIMENTAL SECTION

Materials and Methods. All the reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed avoiding moisture by standard procedures and under a nitrogen atmosphere. Flash column chromatography was performed on silica gel (230–400 mesh), and thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument at 400 and 100 MHz. NMR signals were assigned with the help of DEPT, COSY, HMBC, HMQC, and NOESY experiments. Proton and carbon chemical shifts are reported in ppm (δ) ($CDCl_3$, ^{1}H NMR δ = 7.26 and ^{13}C NMR δ = 77.26, or DMSO-d_6, ^{1}H NMR δ = 2.54 and ^{13}C NMR δ = 39.52). *J* coupling constants values are reported in hertz. Melting points are uncorrected. High resolution mass spectra (HRMS) were recorded using ESI-TOF. The UV–vis spectra were recorded at 298 K on a spectrophotometer equipped with a Peltier thermostated cell holder (temperature accuracy ±0.1 °C).

Compound **2** was prepared as previously described,[13d] and known sugar isocyanates **3a** and **3b** were prepared as described in Scheme 2. ***Caution!*** *All operations with phosgene should be carried in a well ventilated hood, and the rotary evaporator should be equipped with a water jet pump to adsorb the unreacted gaseous phosgene.*

Scheme 2. Synthesis of the Sugar Isocyanates 3a and 3b



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2-Deoxy-2-[[(4-methoxyphenyl)methylene]amino]-β-D-glucopyranose (7). The compound was synthesized according to the adapted procedure of Silva et al.[27] D-Glucosamine hydrochloride **6** (30.0 g, 139 mmol) was dissolved in 1 M $NaOH_{aq}$ (150 mL), and then freshly distilled *p*-anisaldehyde (17.0 mL, 139 mmol) was added. The mixture was stirred at rt for 1 h. The white precipitate was filtered off, washed with cold water (250 mL) and EtOH−Et_2O mixture (250 mL, 1:1, v/v), and dried under high-vacuum, yielding product **7** (33.1 g, 80%), mp 174 °C, $[\alpha_D]$ = +29° (*c* = 1.0 M, DMSO). ^{1}H NMR (400 MHz, DMSO): δ = 8.12 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 6.6 Hz, 1H), 4.92 (d, *J* = 5.3 Hz, 1H), 4.82 (d, *J* = 5.6 Hz, 1H), 4.70 (t, *J* = 7.1 Hz, 1H), 4.55 (t, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 3.76−3.70 (m, 1H), 3.56−3.39 (m, 2H), 3.28−3.20 (m, 1H), 3.19−3.10 (m, 1H), 2.80 (t, *J* = 8.9, 1H). ^{13}C NMR (100 MHz, DMSO): δ = 161.3, 161.1, 129.7, 129.1, 113.9, 95.7, 78.2, 76.9, 74.6, 70.4, 61.3, 55.3.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-[[(4-methoxyphenyl)-methylene]amino]-β-D-glucopyranose (8). The compound was synthesized according to the adapted procedure of Potter et al.[28] To a cold mixture of **7** (12.0 g, 41.0 mmol) in pyridine (65 mL) were added acetic anhydride (36.0 mL) and then DMAP (0.12 g, 1.00 mmol) at 0 °C. The reaction was stirred until it became a homogeneous solution and then overnight at rt. The solution was poured into ice-cold water (350 mL), and the white precipitate was filtered off, washed with cold water (2 × 50 mL) and Et_2O (2 × 50 mL), and recrystallized from EtOH, yielding white crystals of product **8** (17.9 g, 94%), mp 169 °C, $[\alpha_D]$ = +96° (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO): δ = 8.28 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.08 (d, *J* = 8.2 Hz, 1H), 5.45 (t, *J* = 9.7 Hz, 1H), 4.98 (t, *J* = 9.6 Hz, 1H), 4.30−4.18 (m, 2H), 4.05−3.97 (m, 1H), 3.79 (s, 3H), 3.45 (t, *J* = 9.6, 1H), 2.02 (s, 3H), 1.98 (s, 6H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ = 170.0, 169.4, 169.0, 168.6, 164.4, 161.8, 129.9, 128.3, 114.2, 92.5, 72.4, 72.3, 71.6, 67.8, 61.7, 55.4, 20.5, 20.4, 20.2.

1,3,4,6-Tetra-O-acetyl-2-amino-2-deoxy-β-D-glucopyranose (9). The compound was synthesized according to the adapted procedure of Potter et al.[28] To a solution of **8** (15.0 g, 32.3 mmol) in refluxing acetone (80 mL) was added 5 M aqueous solution of HCl (8 mL) dropwise. After ca. 5 min, a white precipitate started to form. After vigorous stirring for 30 min, the reaction was cooled to rt, and the precipitate was filtered off and washed successively with acetone (2 × 20 mL) and Et_2O (2 × 50 mL). The crude product was recrystallized from MeOH, yielding white crystals of product **9** (10.1 g, 90%), mp 230 °C, $[\alpha_D]$ = +33° (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO): δ = 8.91 (s, 3H), 5.93 (d, *J* = 8.6 Hz, 1H), 5.37 (t, *J* = 9.8 Hz, 1H), 4.92 (t, *J* = 9.5 Hz, 1H), 4.18 (dd, *J* = 12.2, 4.0 Hz, 1H), 4.06−3.95 (m, 2H), 3.54 (t, *J* = 9.5 Hz, 1H), 2.17 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ = 170.0, 169.8, 169.3, 168.7, 90.1, 71.6, 70.3, 67.8, 61.3, 52.2, 21.0, 20.9, 20.5, 20.4.

2,3,4,6-Tetra-O-acetyl-1-bromo-1-deoxy-α-D-glucopyranose (11). The compound was synthesized according to the adapted procedure of Potter et al.[28] To a vigorously stirred mixture of commercially available β-D-glucose pentaacetate **10** (27.2 g, 69.0 mmol) in glacial AcOH (115 mL) was carefully added 33% HBr in AcOH (100 mL) dropwise, and the resulting yellow solution was stirred at rt overnight. Then the reaction mixture was poured into cold water (1500 mL), and the initially formed precipitate was filtered off and dissolved in $CHCl_3$ (400 mL). The filtrate was extracted with $CHCl_3$ (2 × 100 mL), and the combined organic extracts were successively washed with saturated $NaHCO_3$ (2 × 250 mL), water (2 × 60 mL), and brine (2 × 120 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated off at ≤30 °C. The crude product was recrystallized from Et_2O/petroleum ether mixture, yielding a white solid of anomerically pure **11** (33.1 g, 70%), mp 86 °C, $[\alpha_D]$ = −195° (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (d, *J* = 4.0 Hz, 1H), 5.54 (t, *J* = 9.7 Hz, 1H), 5.15 (t, *J* = 9.5 Hz, 1H), 4.82 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.35−4.25 (m, 2H), 4.12 (d, *J* = 10.4 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.0, 169.9, 169.6, 86.7, 72.2, 70.7, 70.3, 67.3, 61.0, 20.79, 20.78, 20.75, 20.68.

2,3,4,6-Tetra-O-acetyl-1-azide-1-deoxy-β-D-glucopyranose (12). The compound was synthesized according to the adapted procedure of Takahashi et al.[29] NaN_3 (7.6 g, 117 mmol) and **11** (15.7 g, 38.0 mmol) were suspended in anhydrous DMF (150 mL), and the resulting suspension was stirred at 50 °C for 2 h. The solvent was evaporated off at ≤40 °C, and the residue was partitioned between $CHCl_3$ (200 mL) and water (100 mL). The aqueous phase was discarded, and organic phase was successively washed with water (2 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated off, and the crude yellow product was washed with cold Et_2O, yielding pure **12** (12.1 g, 80%) in the form of a white solid, mp 128 °C, $[\alpha_D]$ = +30° (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.21 (t, *J* = 9.5 Hz, 1H), 5.09 (t, *J* = 9.7 Hz, 1H), 4.94 (t, *J* = 9.2 Hz, 1H), 4.64 (d, *J* = 8.9 Hz, 1H), 4.26 (dd, *J* = 12.5, 4.8 Hz, 1H), 4.16 (dd, *J* = 12.5, 2.3 Hz, 1H), 3.79 (ddd, *J* = 10.0, 4.7, 2.3 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.2, 169.4, 169.3, 88.0, 74.1, 72.7, 70.7, 68.0, 61.8, 20.8, 20.7 (s, 2C).

2,3,4,6-Tetra-O-acetyl-1-amino-1-deoxy-β-D-glucopyranose (13). The compound was synthesized according to the adapted procedure of Ichikawa et al.[30] To a solution of **12** (6.7 g, 18.0 mmol) in EtOAc (200 mL) and Et_3N (3 mL)was carefully added a suspension of Pd/C (0.7 g, 5%$_{wt}$) in EtOAc (10 mL) . The mixture was then vigorously stirred under a H_2 atmosphere (1 atm) until TLC analysis showed complete consumption of the azide ($t \sim 12$ h). The solution was filtered over a pad of Celite and washed thoroughly with EtOAc (∼200 mL). The solvent was evaporated, and the crude product was recrystallized from a minimum amount of EtOAc at rt, yielding white crystals of **13** (5.7 g, 86%), mp 115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.22 (d, *J* = 9.6 Hz, 1H), 5.02 (t, *J* = 9.7 Hz, 1H), 4.81 (d, *J* = 9.6 Hz, 1H), 4.22 (d, *J* = 4.8 Hz, 1H), 4.18 (dd, *J* = 6.2, 2.8 Hz, 2H), 4.09 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.73−3.63 (m, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.3 (s, 2C), 169.7, 85.0, 73.2, 72.8, 72.1, 68.8, 62.4, 20.9, 20.9, 20.74, 20.73.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-isocyanato-β-D-glucopyranose (3a). The compound was synthesized according to the procedure of Ávalos et al.[31] To a solution of amine hydrochloride **9** (3.8 g, 10.0 mmol) in a heterogeneous mixture of CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ solution (80 mL) was added a 20% solution of $COCl_2$ in $PhCH_3$ (2.5 equiv, 25.0 mmol, 13.2 mL) at 0 °C. After 30 min of vigorous stirring, the phases were separated and the organic layer was washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated off at ≤30 °C, and the crude product was recrystallized from Et_2O/petroleum ether mixture, yielding white crystals of **3a** (3.50 g, 95%), mp 75 °C, $[\alpha_D]$ = +33° (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.59 (d, *J* = 8.6 Hz, 1H), 5.14 (t, *J* = 9.8 Hz, 1H), 5.00 (t, *J* = 9.7 Hz, 1H), 4.28 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.07 (dd, *J* = 12.5, 2.0 Hz, 1H), 3.88−3.81 (m, 1H), 3.80−3.73 (m, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 169.9, 169.7, 168.8, 126.8, 92.6, 73.4, 73.0, 67.6, 61.5, 57.0, 20.9, 20.8, 20.6 (s, 2C).

2,3,4,6-Tetra-O-acetyl-1-deoxy-1-isocyanato-β-D-glucopyranose (3b). The compound was synthesized according to the modified procedure of Ávalos et al.[31] To a solution of amine **13** (3.47 g, 10.0 mmol) in a heterogeneous mixture of CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ solution (80 mL) was added a 20% solution of $COCl_2$ in $PhCH_3$ (2.5 equiv, 25.0 mmol, 13.2 mL) at 0 °C. After 30 min of vigorous stirring, the phases were separated and the organic layer was washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated off at ≤30 °C, and the crude product was recrystallized from Et_2O/petroleum ether mixture, yielding white crystals of **3b** (3.40 g, 90%), mp 117 °C (lit. 117−119 °C).[28] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.18 (t, *J* = 9.6 Hz, 1H), 5.10 (t, *J* = 9.7 Hz, 1H), 4.99 (t, *J* = 9.1 Hz, 1H), 4.79 (d, *J* = 8.8 Hz, 1H), 4.23 (dd, *J* = 12.5, 4.8 Hz, 1H), 4.13 (dd, *J* = 12.5, 2.2 Hz, 1H), 3.75 (ddd, *J* = 9.9, 4.8, 2.3 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.71, 170.24, 169.38, 169.34, 127.16, 82.85, 74.15, 72.56, 67.90, 61.71, 20.83, 20.66 (s, 2C), 20.63.

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*Receptor E-**1a***. 4,4′-Aminoazobenzene **2** (0.423 g, 2.0 mmol) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isocyanato-β-D-glucopyranose **3a** (1.64 g, 4.4 mmol) were refluxed in MeCN (20 mL) for 12 h under argon atmosphere. The precipitate was filtered off, washed with hot MeCN (∼50 mL), suspended in Et_2O (20 mL), and vigorously stirred for 10 min. The orange solid was filtered off and dried at high vacuum to afford title compound *E*-**1a** (1.21 g, 63%), mp 245 °C, $[\alpha_D] = +24°$ (c = 1.0, DMSO). ^{1}H NMR (400 MHz, DMSO): δ = 9.09 (s, 2H), 7.76 (d, J = 8.9 Hz, 4H), 7.57 (d, J = 8.9 Hz, 4H), 6.32 (d, J = 9.4 Hz, 2H), 5.91 (d, J = 8.7 Hz, 2H), 5.38 (t, J = 9.9 Hz, 2H), 4.92 (t, J = 9.6 Hz, 2H), 4.20 (dd, J = 12.3, 4.4 Hz, 2H), 4.10−3.87 (m, 6H), 2.05 (s, 6H), 2.02 (s, 6H), 1.99 (s, 6H), 1.93 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ = 170.1, 169.8, 169.3, 169.0, 154.3, 146.6, 142.8, 123.4, 117.8, 92.1, 72.4, 71.3, 68.2, 61.6, 52.9, 20.6, 20.5, 20.4 (s, 2C). HRMS (ESI, MeOH): m/z $[M + Na]^+$ calcd for $C_{42}H_{50}N_6O_{20}Na$ 981.2972, found: 981.2953. Anal. Calcd for $C_{42}H_{50}N_6O_{20}$: C 52.61, H 5.26, N 8.76, found: C 50.99, H 5.36, N 8.39.

*Receptor E-**1b***. 4,4′-Aminoazobenzene **2** (0.43 g, 2.0 mmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isocyanate **3b** (1.64 g, 4.4 mmol) were refluxed in MeCN (20 mL) for 12 h under argon atmosphere. The precipitate was filtered off, washed with hot MeCN (∼50 mL), suspended in Et_2O (20 mL), and vigorously stirred for 10 min. The orange solid was filtered off and dried at high vacuum to afford title compound *E*-**1b** (1.30 g, 68%), mp 217 °C, $[\alpha_D] = -57°$ (c = 1.0, DMSO). ^{1}H NMR (400 MHz, DMSO): δ = 9.14 (s, 2H), 7.79 (d, J = 8.9 Hz, 4H), 7.59 (d, J = 9.0 Hz, 4H), 7.00 (d, J = 9.7 Hz, 2H), 5.39 (dt, J = 21.0, 9.5 Hz, 4H), 4.93 (dt, J = 14.0, 9.6 Hz, 4H), 4.22−4.07 (m, 4H), 3.99 (d, J = 10.4 Hz, 2H), 2.00 (s, 12H), 2.00 (s, 6H), 1.95 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ = 170.1, 169.6, 169.5, 169.4, 153.8, 146.9, 142.3, 123.5, 118.1, 78.2, 72.7, 71.8, 70.3, 68.1, 61.9, 20.6, 20.5, 20.4 (s, 2C). HRMS (ESI, MeOH): m/z $[M + Na]^+$ calcd for $C_{42}H_{50}N_6O_{20}Na$ 981.2978, found: 981.3012. Anal. Calcd for $C_{42}H_{50}N_6O_{20}$: C 52.61, H 5.26, N 8.76, found: C 50.94, H 5.37, N 8.66.

*Receptor E-**5***. 4-Aminoazobenzene (0.20 g, 1.01 mmol) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isocyanato-β-D-glucopyranose **3a** (0.42 g, 1.12 mmol) were refluxed in MeCN (10 mL) for 12 h under argon atmosphere. The solvent was evaporated, and the orange residue was suspended in Et_2O (∼20 mL) and vigorously stirred for 30 min. The orange solid was filtered off and recrystallized from aqueous MeOH to yield orange needle-like crystals of title compound *E*-**5** (0.44 g, 77%), mp 232−233 °C, $[\alpha_D] = +9.8°$ (c = 1.06, MeOH). ^{1}H NMR (400 MHz, DMSO): δ = 9.13 (s, 1H), 7.89−7.77 (m, 4H), 7.64−7.46 (m, 5H), 6.34 (d, J = 9.4 Hz, 1H), 5.92 (d, J = 8.7 Hz, 1H), 5.38 (dd, J = 10.3, 9.5 Hz, 1H), 4.93 (t, J = 9.6 Hz, 1H), 4.20 (dd, J = 12.3, 4.5 Hz, 1H), 4.11−4.05 (m, 1H), 4.03 (dd, J = 10.3, 8.0 Hz, 1H), 3.96 (dd, J = 20.0, 10.1 Hz, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ = 170.0, 169.7, 169.2, 169.0, 154.3, 152.1, 146.4, 143.5, 130.7, 129.3, 123.8, 122.2, 117.8, 92.1, 72.4, 71.3, 68.3, 61.6, 52.9, 20.6, 20.5, 20.4. HRMS (ESI, MeOH): m/z $[M + Na]^+$ calcd for $C_{27}H_{30}N_4O_{10}Na$ 593.1860, found: 593.1856. Anal. Calcd for $C_{27}H_{30}N_4O_{10}$: C 56.84, H 5.30, N 9.82, found: C 56.86, H 5.43, N 9.91.

Photoisomerization Studies. For photochemical production of samples enriched in *Z* isomer, we used a custom-made Rayonet type photoreactor, equipped with eight blacklight fluorescent lamps (nominal power = 9 W, λ_{max} = 368 nm) and with an effective air cooling system to maintain a fixed temperature (≤26 °C) inside the photoreactor chamber. To ensure homogeneous irradiation, the sample was spinned at 4 rpm. Blue light irradiation experiments were carried out with an SMD Power-LED bulb (3.3 W, λ_{max} = 410 nm). Photoisomerization of receptors **1** was carried out in quartz cuvette (V = 3.5 mL, l = 10 mm) or in a quartz NMR tube (ϕ = 5 mm, l = 7 in, limit 600 MHz). Time required to reach photostationary state (PSS) using UV or blue-light was found to be ca. 30 s for diluted receptor solution ($c \sim 10^{-5}$ M) and ∼30 min for the concentrated receptor solution ($c \sim 10^{-2}$ M). The rate of thermal $Z \rightarrow E$ isomerization of pure *Z*-**1** and their anion complexes were calculated by monitoring the absorption change of *Z* and *E* isomers in the dark at 298.0 ± 0.1 K. The observed first-order rate (k_{obsd}) is an average of the k_{obsd} determined by the Marquard nonlinear technique at four different wavelengths as implemented in Cary WinUV Software 5.0.0.999. Practically linear ($R^2 \geq 0.998$) Arrhenius and Eyring plots indicate that during thermal back-isomerization of pure *Z*-**1** only one mechanism occurs (Table S1).

Titration Experiments. Tetrabutylammonium (TBA) salts were used as a source of anions. $TBACH_3CO_2$ and $TBAC_6H_5CO_2$ were purchased from Sigma-Aldrich and chiral carboxylic acids (mandelic acid, *N*-Boc-protected $PheCO_2H$ and $TrpCO_2H$) from TCI Europe. TBA salts of chiral carboxylates were prepared by the addition of a standardized solution of TBAOH in methanol (∼1.0 M, 1.0 equiv, Sigma-Aldrich) to the corresponding solution of mandelic acid or *N*-Boc-protected $PheCO_2H$ and $TrpCO_2H$ in methanol. The resulting mixture was stirred for 1 h, and solvent was evaporated off to yield a crude salt which was further dried under high vacuum over solid P_4O_{10}. HPLC grade water was added to the commercially available DMSO-d_6 of 99.80% isotopic purity or nondeuterated DMSO (≥99.5%) to obtain 0.5% water concentration.

^{1}H NMR Titration Procedure. The DMSO solution of a receptor (ca. 10^{-2} M) was titrated in an NMR tube with the 0.1−0.2 M solution of a respective TBA salt. The solution of the salt contained a certain amount of the receptor to keep receptor concentration constant during the titration; 16 to 20 data points were recorded, depending on the shape of the titration curve. However, it was important to choose such volumes of aliquots so that most of the data points could occur in close proximity of the inflection point of the respective titration curve. Such a procedure allows for more precise calculation of the binding constants. Moreover, we took into account the shift changes of all protons present in the receptor and guest molecules. In all cases, DMSO-d_6 + 0.5% H_2O was used as a solvent mixture. Titration of pure *E*-**1** was conducted in an amber NMR tube, and titration of a mixture of *E*- and *Z*-**1** was conducted in a quartz NMR tube (ϕ = 5 mm, l = 7 in, limit 600 MHz). In the latter case, photoisomerization of *E*-**1** was carried out before anion was added. A nonlinear curve fitting for the 1:1 or 1:2 binding model was carried out with the HypNMR 2008 Software[32] and allows the determination of the global association constant. Determination of K_a's for *Z*-**1** was carried out using fully relaxed values of K_a's for *E*-**1** which were generally similar to those obtained during titration of pure *E*-**1** in the dark. However, when the fitting algorithm failed to converge, fixed values of K_a's for *E*-**1** were instead used to determine K_a for *Z*-**1**.

Isothermal $Z \rightarrow E$ Isomerization Titration Procedure. The DMSO solution of a receptor **1** enriched in *Z* isomer ($c_{total} = 5 \times 10^{-5}$ M) was titrated in an NMR tube with a 0.1−0.2 M solution of a respective TBA salt. The kinetics without and with anion added were recorded and analyzed to give k_{obsd} as described in Photoisomerization Studies. Time required for the total relaxation to *E*-**1** was ∼2−3 h. Usually no less than 15 kinetics were recorded, depending on the shape of the titration curve. The experimental data points, i.e., k_{obsd} determined for various amounts of guest added ($[G]_0$), were then fitted to the following equation:[13d]

$$\frac{k_H + k_{HG}K_{a,Z}[G]_0}{1 + K_{a,Z}[G]_0}$$

where k_H is k_{obsd} without anion added. A least-squares fitting procedure gave parameters of interest, i.e., $K_{a,Z}$ and k_{HG}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00200.

Copies of ^{1}H and ^{13}C NMR spectra, photochemical and binding properties of receptors **1**, and references (PDF)

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Notes

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■ REFERENCES

(1) Petsko, G. A.; Ringe, D. *Protein structure and function*; New Science Press: London, 2004.

(2) Ha, J.-H.; Loh, S. N. *Chem. - Eur. J.* **2012**, *18*, 7984−7999.

(3) Steed, J. W.; Atwood, J. L. *Supramolecular chemistry*; John Wiley & Sons: New York, 2013.

(4) Evans, N. H.; Beer, P. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11716−11754.

(5) Note that to describe enantiodiscrimination phenomena in the supramolecular systems, parameter α, i.e., ratio between association constants for *R* and *S* (or D and L) enantiomers, is commonly employed. For reviews concerning chiral ion recognition, see: (a) Ulatowski, F.; Jurczak, J. *Asian J. Org. Chem.* **2016**, DOI: 10.1002/ajoc.201600093. (b) Granda, J. M.; Jurczak, J. Sugar decorated receptors for chiral anions. In *Carbohydrate Chemistry*; The Royal Society of Chemistry: London, 2014; Vol. *40*, pp 445−460. (c) Leung, D.; Kang, S. O.; Anslyn, E. V. *Chem. Soc. Rev.* **2012**, *41*, 448−479. (d) Stibor, I.; Zlatušková, P., Chiral recognition of anions. In *Anion Sensing*; Springer: New York, 2005; pp 31−63;. (e) Pu, L. *Chem. Rev.* **2004**, *104*, 1687−1716. For selected examples demonstrating receptors with a high level of chiral discrimination, see refs 9a, c, d. (f) Fukuhara, G.; Inoue, Y. *Chem. - Eur. J.* **2010**, *16*, 7859−7864.

(6) Lingenfelder, M.; Tomba, G.; Costantini, G.; Colombi Ciacchi, L.; De Vita, A.; Kern, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4492−4495.

(7) (a) Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347−362. For a recent review concerning chiral recognition models, see: (b) Lämmerhofer, M. *J. Chromatogr. A* **2010**, *1217*, 814−856 and references cited therein..

(8) Blažek Bregović, V.; Basarić, N.; Mlinarić-Majerski, K. *Coord. Chem. Rev.* **2015**, *295*, 80−124.

(9) (a) Granda, J. M.; Jurczak, J. *Chem. - Eur. J.* **2015**, *21*, 16585−16592. (b) Granda, J. M.; Jurczak, J. *Chem. - Eur. J.* **2014**, *20*, 12368−12372. (c) Hamankiewicz, P.; Granda, J. M.; Jurczak, J. *Tetrahedron Lett.* **2013**, *54*, 5608−5611. (d) Granda, J. M.; Jurczak, J. *Org. Lett.* **2013**, *15*, 4730−4733.

(10) Ulatowski, F.; Jurczak, J. *Tetrahedron: Asymmetry* **2014**, *25*, 962−968.

(11) Pu, L. *Chem. Rev.* **2004**, *104*, 1687−1716.

(12) For photoresponsive cation receptors, see: (a) Ducrot, A.; Verwilst, P.; Scarpantonio, L.; Goudet, S.; Kauffmann, B.; Denisov, S.; Jonusauskas, G.; McClenaghan, N. D. *Supramol. Chem.* **2012**, *24*, 462−472. (b) Hunter, C. A.; Togrul, M.; Tomas, S. *Chem. Commun.* **2004**, 108−109. (c) Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *J. Am. Chem. Soc.* **2003**, *125*, 2224. (d) Shinkai, S.; Nakaji, T.; Nishida, Y.; Ogawa, T.; Manabe, O. *J. Am. Chem. Soc.* **1980**, *102*, 5860. For reviews, see: (e) Bianchi, A.; Delgado-Pinar, E.; García-España, E.; Giorgi, C.; Pina, F. *Coord. Chem. Rev.* **2014**, *260*, 156−215. (f) Desvergne, J.-P.; Bouas-Laurent, H.; Perez-Inestrosa, E.; Marsau, P.; Cotrait, M. *Coord. Chem. Rev.* **1999**, *185*, 357. (g) Shinkai, S.; Manabe, O. In *Host Guest Complex Chemistry III*; Springer: New York, 1984; p 67.

(13) For photoresponsive anion receptors, see: (a) Cafeo, G.; Kohnke, F. H.; Mezzatesta, G.; Profumo, A.; Rosano, C.; Villari, A.; White, A. J. P. *Chem. - Eur. J.* **2015**, *21*, 5323−5327. (b) Wezenberg, S. J.; Vlatković, M.; Kistemaker, J. C. M.; Feringa, B. L. *J. Am. Chem. Soc.* **2014**, *136*, 16784−16787. (c) Choi, Y. R.; Kim, G. C.; Jeon, H.-G.; Park, J.; Namkung, W.; Jeong, K.-S. *Chem. Commun.* **2014**, *50*, 15305−15308. (d) Dabrowa, K.; Niedbala, P.; Jurczak, J. *Chem. Commun.* **2014**, *50*, 15748−15751. (e) Hua, Y.; Flood, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 12838. (f) Wang, Y.; Bie, F.; Jiang, H. *Org. Lett.* **2010**, *12*, 3630. For a review, see: (g) Lee, S.; Flood, A. H. *J. Phys. Org. Chem.* **2013**, *26*, 79−86 and references cited therein..

(14) For photoresponsive receptors for neutral guests, see: (a) Berryman, O. B.; Sather, A. C.; Rebek, J., Jr *Chem. Commun.* **2011**, *47*, 656−658. (b) Yashima, E.; Noguchi, J.; Okamoto, Y. *Macromolecules* **1995**, *28*, 8368. (c) Wurthner, F.; Rebek, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1727. (d) Ueno, A.; Yoshimura, H.; Saka, R.; Osa, T. *J. Am. Chem. Soc.* **1979**, *101*, 2779−2780.

(15) For reviews concerning light-switchable catalysis, see: (a) Yashima, E.; Noguchi, J.; Okamoto, Y. *Macromolecules* **1995**, *28*, 8368−8374. (b) Ueno, A.; Saka, R.; Takahashi, K.; Osa, T. *Heterocycles* **1981**, *15*, 671 . Note that these receptors utilize azobenzene moiety for photo- and thermal conformational switching and sugar derivatives for chiral discrimination of the guests..

(16) Dürr, H.; Bouas-Laurent, H. *Photochromism: Molecules and Systems*; Elsevier Science: New York, 2003.

(17) Balzani, V.; Credi, A.; Venturi, M. *Chem. Soc. Rev.* **2009**, *38*, 1542−1550.

(18) Ballardini, R.; Balzani, V.; Credi, A.; Gandolfi, M. T.; Venturi, M. *Acc. Chem. Res.* **2001**, *34*, 445−455.

(19) Szymański, W.; Beierle, J. M.; Kistemaker, H. A. V.; Velema, W. A.; Feringa, B. L. *Chem. Rev.* **2013**, *113*, 6114−6178.

(20) Brieke, C.; Rohrbach, F.; Gottschalk, A.; Mayer, G.; Heckel, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8446−8476.

(21) (a) Bandara, H. M. D.; Burdette, S. C. *Chem. Soc. Rev.* **2012**, *41*, 1809−1825. (b) Beharry, A. A.; Woolley, G. A. *Chem. Soc. Rev.* **2011**, *40*, 4422−4437. (c) Merino, E. *Chem. Soc. Rev.* **2011**, *40*, 3835−3853.

(22) (a) Peters, M. V.; Stoll, R. S.; Kühn, A.; Hecht, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5968. (b) Samanta, M.; Krishna, V. S. R.; Bandyopadhyay, S. *Chem. Commun.* **2014**, *50*, 10577. (c) Lee, W.-S.; Ueno, A. *Macromol. Rapid Commun.* **2001**, *22*, 448. (d) Berryman, O. B.; Sather, A. C.; Lledó, A.; Rebek, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9400. (e) Imahori, T.; Yamaguchi, R.; Kurihara, S. *Chem. - Eur. J.* **2012**, *18*, 10802. For reviews concerning artificial photoswitchable catalysts, see: (f) Blanco, V.; Leigh, D. A.; Marcos, V. *Chem. Soc. Rev.* **2015**, *44*, 5341. (g) Imahori, T.; Kurihara, S. *Chem. Lett.* **2014**, *43*, 1524. (h) Neilson, B. M.; Bielawski, C. W. *ACS Catal.* **2013**, *3*, 1874. (i) Stoll, R. S.; Hecht, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5054.

(23) The relative distance between centroids of urea groups in *E*-**1** is estimated to be 14.0 Å, and thus it is likely that they cannot bind an anion cooperatively. This implies that the values of microscopic first binding constants (K_m) are half of the determined values of macroscopic ones (K_a); see ref 26c for more information. These K_H values match the K_a values obtained for *Z*-**1** with the same anion.

(24) For selected examples, see: Liu, S. Y.; Law, K. Y.; He, Y. B.; Chan, W. H. *Tetrahedron Lett.* **2006**, *47*, 7857−7860 and refs 9c, d, 10..

(25) The *E*-*p*-phenylazo fragment is known to act as a moderate electron-withdrawing group (EWG) with a value of the substituent constant (σ_p = +0.64) comparable with that for the CN group. In the *Z*-isomer, one can assume that the EWG effect is weaker. For discussion, see: (a) Kyziol, J.; Frej, H. *Chem. Pap.* **1988**, *42*, 781. (b) Harper, D. A. R.; Vaughan, J. *The Chemistry of the Hydrazo, Azo and Azoxy Groups, Part 1*; Patai, S., Ed.; John Wiley & Sons: New York, 1975; p 225.

(26) For reviews concerning accurate determination of association constants from titration experiments, see: (a) Ulatowski, F.; Dąbrowa, K.; Bałakier, T.; Jurczak, J. *J. Org. Chem.* **2016**, *81*, 1746−1756. (b) Thordarson, P. *Chem. Soc. Rev.* **2011**, *40*, 1305−1323. (c) Lowe, A. J.; Pfeffer, F. M.; Thordarson, P. *Supramol. Chem.* **2012**, *24*, 585−594. For a recent discussion concerning the reliability of parameter α in regard to chiral recognition of carboxylates, see: (d) Ulatowski, F.; Jurczak, J. *J. Org. Chem.* **2015**, *80*, 4235−4243. (e) As stated by one of the reviewers: "The conclusions from the so-called golden standard work are completely wrong as those authors used the outdated and inaccurate Benesi−Hildebrand method to obtain their enantioselectivities. Reanalysis of that data with nonlinear methods suggests an α of 1."

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(27) Silva, D. J.; Wang, H.; Allanson, N. M.; Jain, R. K.; Sofia, M. J. *J. Org. Chem.* **1999**, *64*, 5926−5929.
(28) Potter, A.; Sowden, J. C.; Hassid, W.; Doudoroff, M. *J. Am. Chem. Soc.* **1948**, *70*, 1751−1752.
(29) Takahashi, S.; Okada, A.; Nishiwaki, M.; Nakata, T. *Heterocycles* **2006**, *69*, 487−495.
(30) (a) Ichikawa, Y.; Matsukawa, Y.; Nishiyama, T.; Isobe, M. *Eur. J. Org. Chem.* **2004**, *2004*, 586−591. (b) Ichikawa, Y.; Nishiyama, T.; Isobe, M. *J. Org. Chem.* **2001**, *66*, 4200−4205.
(31) Ávalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C.; Pérez, E. M. S. *Eur. J. Org. Chem.* **2006**, *2006*, 657−671.
(32) Rodríguez-Barrientos, D.; Rojas-Hernández, A.; Gutiérrez, A.; Moya-Hernández, R.; Gómez-Balderas, R.; Ramírez-Silva, M. T. *Talanta* **2009**, *80*, 754−762.

DOI: 10.1021/acs.joc.6b00200
J. Org. Chem. 2016, 81, 3576−3584