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Hydrogen-bonding donor-acceptor Stenhouse adducts

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Abstract: The binding of donor-acceptor Stenhouse adducts (DASAs) bearing hydrogen-bond recognition groups by Hamilton-type receptors significantly influenced their photoswitching properties by altering thermal barriers to isomerization. The thermal barrier between the most stable linear isomer and the photo-generated isomer is lowered on binding to a receptor, and this barrier is crucial for switching properties. The thermal isomerization was shown to proceed via a stepwise linear-enol-keto mechanism in DMSO where the barrier to tautomerisation is within $2 \text{ kJ}\cdot\text{mol}^{-1}$ of that of the rate-determining step, which may be important for analyzing switching properties.

Introduction:

Photochromic molecules[1] can be isomerized with light to give different optical absorption properties. Examples that respond to visible light[2] have significant advantages as they allow the highly selective and non-destructive addressing of the photochromic molecule, while leaving other colorless components of the mixture untouched. These tools[3] allow light to be used to precisely control energy transfer,[4] self-assembly,[5] or modify material properties[6] amongst other applications. While organic molecules such as dithienylethene,[7] spiropyran,[5, 8] oxazine[9] and azobenzene[6c, 10] have been known for decades to display photochromic properties, more recently hemithioindigo,[11] indigos,[12] heterodiazocines,[13] arylhydrazones,[14] azo-BF₂ derivatives,[15] imidazolyl-based radicals[16] and coumarin-dienes[17] have all demonstrated excellent visible-light switching properties. Reverse photochromic molecules[18] are those where the thermally stable form is colored, and irradiation results in the formation of a transient colorless form. Donor-acceptor Stenhouse Adducts (DASAs, Figure 1a)[19] are a class of reverse photochromic molecules overlooked[20] until 2014.[21] Since these initial reports[21] a range of applications have already been demonstrated,[22] including as sensors[23] and for drug release,[24] and compatibility with orthogonal switches[22d, 25] and second-order nonlinear optical properties[26] have been investigated. These DASAs can be synthesized in two very simple steps which can be conducted by undergraduate students. The mechanism of switching has been proposed,[27] probed computationally[28] and experimentally,[29] and the role of the hydroxyl group[30] and solvent has been investigated.[28c] The introduction of aniline donors[31] reduces the energy difference between the two isomers, and allows favorable switching in a wide range of solvents, in part by improving the solubility of the cyclic form.

New acceptor groups offer potential for tuning the dark equilibria as well as far-red absorption capabilities.[32] We recently reported[33] on the structure-function relationship of a

series of DASAs, identifying that small changes in the substituents on the amine donor have dramatic influences on the thermodynamic stabilities of the linear and cyclic forms, as well as controlling their thermal switching steps. That work established that while optical properties of DASAs can remain relatively constant, their switching properties vary significantly between very similar molecules. Concentration effects have been explored,[33-34] and high concentrations were shown to stabilize the enol tautomer of the cyclic structure (b, Figure 1). Intramolecular interactions with a pendant aromatic unit significantly influence switching rates,[33] and the first examples of encapsulation have been recently reported,[35] offering potential for DASAs to have their properties tuned by their local environments. Recognizing that barbituric acid groups are excellent hydrogen bonding partners for the Hamilton-type receptors[36] (for examples, see ref [37]), herein we compare DASA 1[33] with DASAs **2** and **3** that are capable of hydrogen bonding interactions to influence their switching properties (see Figure 1 for structural formulae).

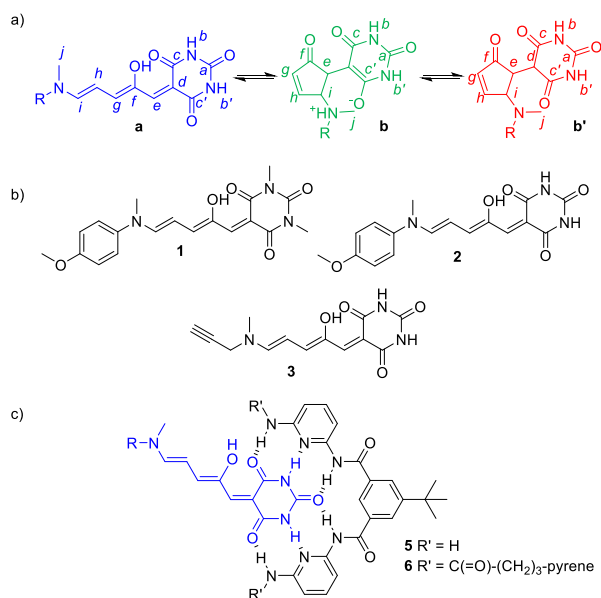


Figure 1. a) Common isomers of donor-acceptor Stenhouse adducts (DASAs) and the atom labelling scheme adopted. b) DASAs studied in this work. c) Host-guest interactions between DASAs and Hamilton-type receptors.

Results and Discussion:

Synthesis and thermal isomerization:

We prepared DASAs with free amido units on the barbituric acid acceptor group that could act as hydrogen bond donors;[38] experimental details and characterization is given in SI-3 to SI-6. As is often the case for DASAs, compounds **1** and **2** were each isolated as the essentially pure colored isomers. Upon dissolving in DMSO-*d*₆ each was observed by ¹H NMR spectroscopy to form an equilibrium mixture of colored (linear) and colorless (cyclic) isomers (Figure 2). For DASA **1** this process can be monitored as a smooth transition between the linear (**1a**) and the cyclic keto isomer (**1b'**), with no observable intermediates (Figure 2a). From the rate of this thermal isomerization at 298 K, we find the thermal barrier to ring closing to be 92 kJ·mol⁻¹,[39] close to the value found in CDCl₃ (90 kJ·mol⁻¹),[33] with an overall difference in energy between the linear and cyclic isomers of <1 kJ·mol⁻¹ at room temperature. For DASA **2** the ¹H NMR signals corresponding to the linear isomer are broadened as result of the slow rotation around the C₁-N bond (see Figure 1 for atom labelling), as previously described.[31b, 33] Two additional sets of signals arise from cyclic isomers (Figure 2b) and the major cyclic isomer can be unambiguously assigned to the keto tautomer.[40] When DASA **2** is dissolved in DMSO-*d*₆, a thermal equilibrium is slowly established,[41] and the relative abundances of the three isomers are shown in Figure 3.[42]

The equilibration data for DASAs **1**, **2** and **3** indicate that the mechanism of thermal isomerization is to initially form the enol isomer, in agreement with computational studies.[29c, 30, 33] In line with our previous study,[33] we also find the relative stabilities of the linear, keto and enol forms are within 2 kJ·mol⁻¹ in DMSO-d₆.

The enol-keto tautomerization is slow, with an energy barrier very similar to that of the ring closing reaction (enol-keto: 88 kJ·mol⁻¹; ring-closing: 91 kJ·mol⁻¹ at 298 K respectively, see SI-7.5).[2] This is an important discovery as it indicates that this final tautomerization step should not be ignored when considering DASA switching properties.

The linear and cyclic forms of DASAs are known to have different stabilities in polar protic solvents,[21] and proton transfer is suggested to occur at key points during the reaction mechanism.[29c, 30, 33] We considered whether water content plays an important role in the rate of thermal isomerization,[28c][44] and in particular to lower the barrier(s) to isomerization. To test this, we compared the thermal barriers of linear → enol → keto transformations for compounds **1** and **2**, which differ only by the methylation of the barbituric acid amines.

The barrier to ring closing for DASA **2** in DMSO-d₆ (91 kJ·mol⁻¹) was almost identical to that found for DASA **1** (92 kJ·mol⁻¹), indicating replacing the N-methyl groups with protons had a minimal impact on this process. On increasing the water content to 10% the ring-closing barrier for DASA **2** was slightly lowered (90 kJ·mol⁻¹), and the use of 10% D₂O slightly increased the barrier (92 kJ·mol⁻¹).[45] This data highlights that although water may be involved in the crucial steps of DASA isomerization,[30][46] it appears to have a relatively modest influence on overall switching rates in DMSO.

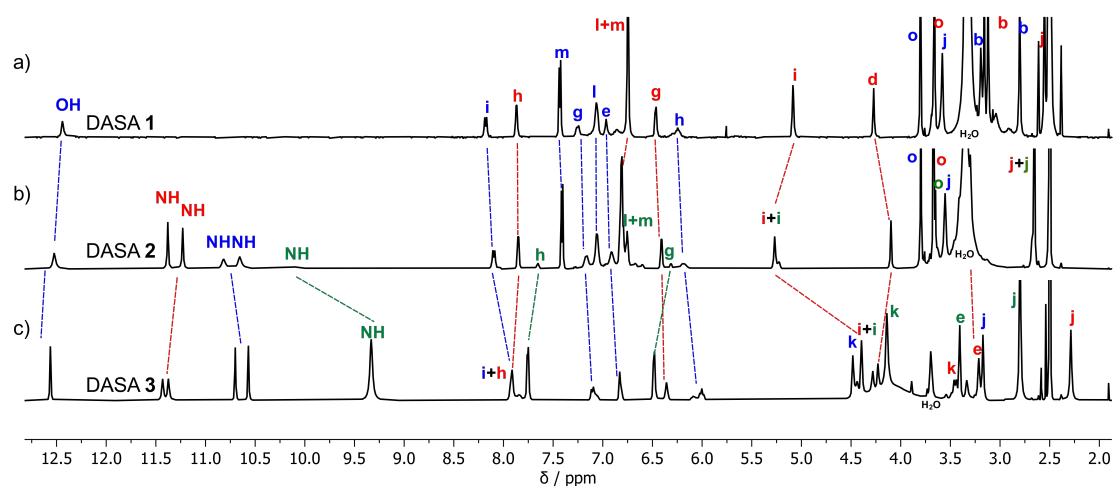


Figure 2. ¹H NMR spectra (600 MHz, DMSO-d₆, 298 K) of samples of a) **1**, b) **2** and c) **3**. The signals at 11.5–9 ppm are characteristic for the barbituric acid NH protons. Blue corresponds to the linear isomer, green to the enol and red to the keto.

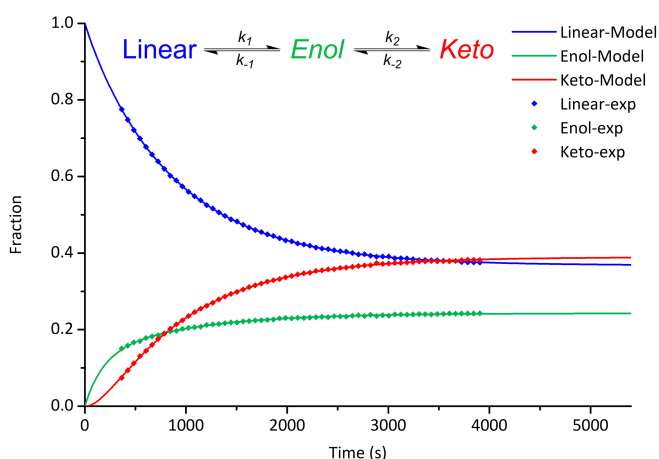


Figure 3. a) Relative abundances of isomers of DASA **2** after dissolving in DMSO- d_6 , measured from ^1H NMR peak integrals and fitted to a linear-enol-keto kinetic model. See SI-7 for spectra. Calculated rate constants and barriers are given in SI-7.5.

Table 1. Barriers to isomerization for DASA **2** with receptors **5** or **6** in 2-MeTHF.^[a]

	$t_{1/2}$ /min ^[b] (Apparent 2b → 2a barrier / kJ·mol ⁻¹)	τ / ms ^[c]	% cyclic formed from intermediate ^[d]
1	26 (92)	— ^[e]	— ^[e]
2	55 (94)	210	90
2+5	2.9 (87)	11	6
2+6	3.7 (87)	0.47	~0

[a] Measured by electronic absorption spectroscopy. [b] Apparent thermal half-life of the cyclic isomer, measured by UV-visible absorption with long (20 s) irradiation experiments at 298 K, see SI-11. $t_{1/2}$ is approximately determined the rate of ring-opening, as shown by previous work.[33] [c] Time constant for decay of the intermediate, as measured by transient absorption at 640 nm following a 5 ns pulse, at 293 K, see SI-12. [d] Difference between the absorption recovered after excitation with 5 ns laser pulse, assumed to the formation of the cyclic isomer. [e] not measured.

Photoswitching:

A representative absorption spectrum of **2** in 2- methyltetrahydrofuran (2-MeTHF) is shown in Figure 4. The visible absorption band of compound **2** is blue shifted relative to DASA **1** ($\Delta\lambda_{\text{max}} \sim 5$ nm),[47] and photoswitching properties are in line with previous studies. Solutions of DASAs **1** and **2** were subjected to a series of irradiation-dark switching cycles (SI-11). The apparent thermal half-life of the free amine derivative **2** (55 min) is significantly longer than the N-methylated derivative **1** (26 min[33]) measured under identical conditions.[48]

Host-guest chemistry:

We investigated reported Hamilton-type receptors **5** and **6**[37a, 37b, 37f] (see Figure 1) for their ability to bind DASA **2** in 2 MeTHF solutions, with DASA **1** acting as a control compound incapable of engaging in recognition interactions with the receptors. These receptors were selected to improve solubility in organic solvents, with receptor **6** also have the potential for fluorescence read-out. The addition of an excess of receptor **5** to a solution of DASA **2** results in an increase in absorption as the linear isomer is stabilized by hydrogen bonding, which is observed by a sequential increase in absorption upon a series of additions of aliquots of the receptor (Figure 5).[48]

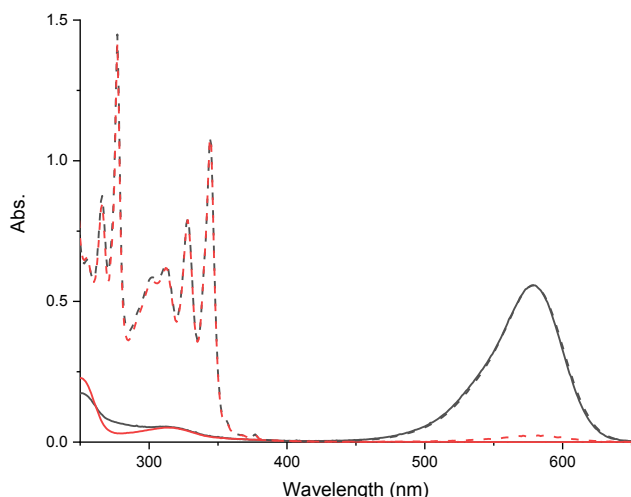


Figure 4. UV-visible absorption spectrum of DASA **2** in 2-MeTHF in the dark (solid black) and under constant 567 nm irradiation (solid red). Identical sample with 1 equiv. of receptor **6** equilibrated in the dark (dashed black) and under constant 567 nm irradiation (dashed red).

The absorption maximum was not found to significantly change upon addition of excess receptor (Figure S45), but the photoswitching properties are significantly altered. Approximately the same bleaching is observed upon irradiation as in the absence of the receptor (>97%), but the thermal half-life decreases from 55 min to just 3 min. While this macroscopic difference appears large, it corresponds to a change in energy barrier of ~ 7 $\text{kJ}\cdot\text{mol}^{-1}$ at room temperature. The addition of excess pyrene-functionalized receptor **6** to a solution of DASA **2** in 2-MeTHF results in a similar increase in absorption, and a small (~ 3 nm) red shift in absorption (Figure S48). As well as the thermal half-life time being shorter (4 min), the system resists photoisomerisation with only 20% decrease in absorption upon irradiation compared to >99% in the absence of the receptor (Figure S48). This indicates the linear form of DASA **2** is stabilized relative to the cyclic form upon binding to the receptors **5** or **6**, and that the thermal barrier to ring opening is significantly lowered upon binding the receptor.

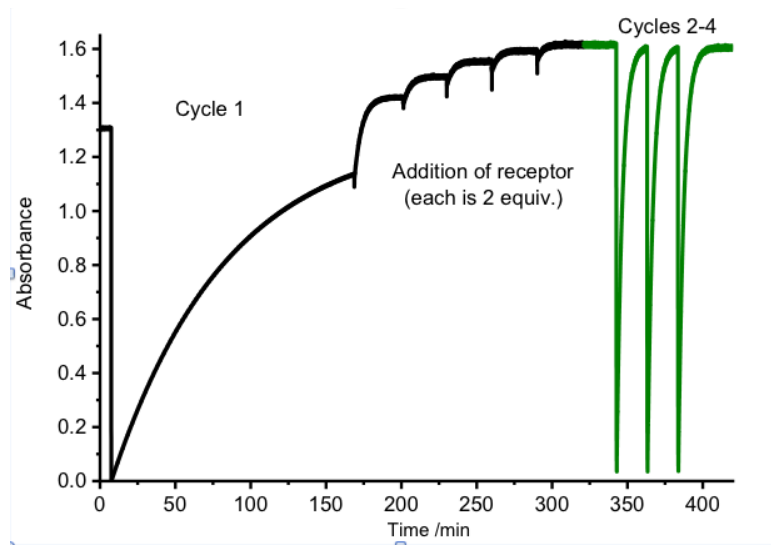


Figure 5. The absorbance at 580 nm of sample of DASA **2** in 2-MeTHF before (black) and after (green) the addition of 10 equivalents of receptor **5**, subjected to switching cycles of 20 s 567 nm LED, 167 min dark (cycle 1) and 20 s irradiation, 20 min dark (cycles 2-4).

Transient absorption spectroscopy.

Transient absorption spectroscopy was used to investigate the origin of the observed change in behavior following excitation with a 5 ns pulse (key data in Figure 6, Table 1, SI-12). In the visible spectral region, the spectra are dominated by two main spectral features, namely a negative band which corresponds to ground state bleaching/depopulation of the initial form(s) and a positive signal which corresponds to the absorption of a transient (Figure S53).

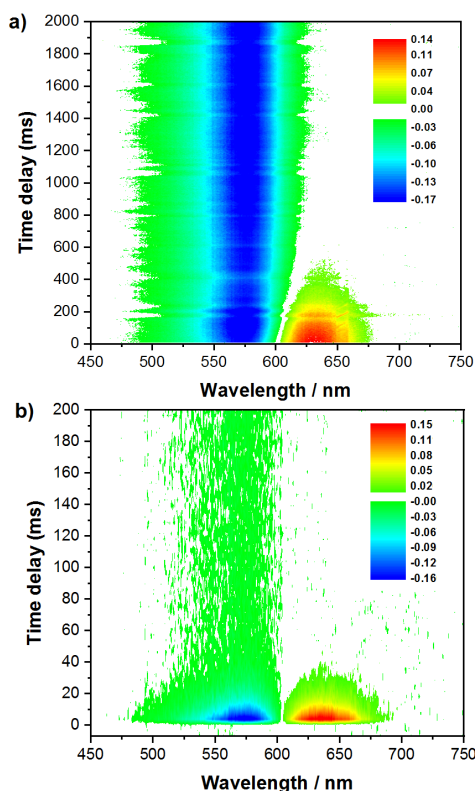


Figure 6. Transient absorption map of a) **2** and b) **2+5** following 5 ns pulse at wavelength of maximum absorption.

Several observations were made for the switching of DASA **2**, DASA **2** with excess receptor **5** (**2+5**) and DASA **2** with excess receptor **5** (**2+6**) on exciting with a single 5 ns width laser pulse:

i) The bleaching of the main absorption band (efficiency of excitation) in the visible wavelength range (560–580 nm) was 40–60%. In contrast to the 20–40 s LED excitation discussed previously, a 5 ns laser excitation pulse is too short to allow a thermal generation of a population of the most favorable isomer(s) for cyclization in the ground state and to re-excite these with the remainder of the excitation pulse.

ii) The last state observable by visible absorption before cyclization has an absorption band at 640 nm, red-shifted with respect to the absorption band of the linear isomer **2a**. This state is located on the potential surface of the ground state. The lifetime of this state is not affected by either the presence of molecular oxygen or by the concentration of the compound. According to the model proposed by Feringa et al. for related DASAs,[28c, 29a, 29d, 30] this state would correspond to the **2a'** (EEE) isomer (**2a'**, Figure 9).

iii) The lifetime of this transient state is related to the amount of cyclic isomer that is formed (following the ns excitation during which time no significant accumulation of cyclic isomer is observed in most cases). For **2** in 2-MeTHF the lifetime of the intermediate is 210 ms, which leads to the formation of 90% of the cyclic isomer. For **2+5** the lifetime of 11 ms produces 8% of the cyclic isomer, and for **2+6** the lifetime of the intermediate is just 0.47 ms results in no formation of the cyclic isomer all (within the detection limit of the experiment). This observation is consistent with the binding by the receptor lowering the barrier between the intermediate required for cyclisation and the most stable linear isomer, resulting in the back reaction being fast compared with the forward ring-closing reaction.

iv) The overall accumulation of the cyclic isomer is then related to: the lifetime of the transient state with absorption at 640 nm; the efficiency to form the cyclic isomer from this transient state; the rate of the ring opening of the cyclic isomer (i.e. the reverse reaction, approximated as $t_{1/2}$); and the photon flux of the excitation beam.

Therefore, for **2+5** or **2+6** where longer 20–40 s irradiation is used (i.e. using LEDs) the photon flux is insufficient to overcome the low efficiency of formation of the cyclic isomer and the increased rate of ring opening, resulting in no significant accumulation of cyclic isomer.

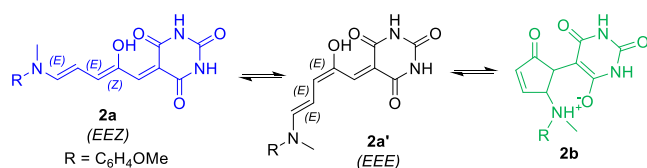


Figure 7. The mechanism of DASA **2** isomerization upon irradiation with visible light. Following a 5 ns irradiation pulse **2a** is isomerized to intermediate **2a'** in 40–60% yield. This thermally unstable isomer (lifetime in 2-MeTHF = 210 ms) can proceed to ring closure to generate cyclic isomer **2b**, or relax back to **2a**, depending on the relative energy barriers. On binding receptor **5** or **6** the thermal barrier between **2a'** and **2a** is sufficiently low that a rapid isomerization back to **2a** preferentially occurs. Receptor binding also lowers the barrier to ring opening (between **2b** and **2a'**), and stabilizes the linear **2a** relative to cyclic **2b**. E and Z labels refer to the stereochemistry of the C-C bonds, noting that each has considerable double bond character.[31b, 33]

Conclusions

DASAs featuring barbituric acid groups available for hydrogen bonding allow their switching properties to be controlled by host-guest interactions. The mechanism of thermal isomerization of DASAs **1–3** in DMSO was shown to proceed via a stepwise linear-enol-keto mechanism with similar energy barriers between the ring closing and tautomerization reactions for DASAs **2** and **3**, with water concentration found to have a minimal effect on these rates. Transient absorption spectroscopy identified that the lifetime of the colored transient state (proposed to be **2a'**) is related to the proportion of cyclic isomer formed. This indicates that a sufficiently high thermal barrier between the intermediate (**2a'**) and the most stable linear isomer (**2a**) is crucial for allowing the cyclic isomer to be formed, and may be the most important barrier for determining effective switching properties, in line with recent reports.[29d] The binding of DASA **2** by receptors **5** or **6** stabilizes the linear isomer (**2a**) relative to the cyclic isomer (**2b**), and the barrier between the intermediate (**2a'**) and the linear isomer (**2a**) is lowered by more than the barrier between the intermediate (**2a'**) and cyclic forms (**2b**). Care should be taken when comparing photoswitching of DASAs using short cf. long pulses/prolonged irradiation as it is likely that irradiation of the long-lived intermediate (~200 ms) could be important for the observed isomerization of DASAs.

Experimental Section

Experimental details and spectra can be found in the Supporting Information.

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Keywords: photochromic • photoswitch • host-guest • hydrogen-bonding • kinetics

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- [38] Initial attempts using activated furfuraldehyde 4 and diethylamine resulted in the formation of a salt, with diethylamine deprotonating the barbituric acid group. This is in agreement with expectations based on the reported pKa values of diethylbarbituric acid [see, a) K. Kunitatsu, R. Parsons, *J. Electroanal. Chem. Interfacial Electrochem.* 1979, 100, 335-363.] and protonated diethylamine [see, b) H. K. Hall, *J. Am. Chem. Soc.* 1957, 79, 5441-5444.]. p-Methoxy-N-methylaniline and N-methylpropargylaminium are more amenable donor groups for forming DASAs as the pKa values of their protonated forms [see, c) W. R. Abrams, R. G. Kallen, *J. Am. Chem. Soc.* 1976, 98, 7777-7789] indicate they will not deprotonate the barbituric acid group.
- [39] With conservative uncertainties of 25 % placed on the rate constant data, the uncertainties in these energies are (also conservatively) placed at 1 kJ·mol⁻¹.
- [40] About 24 % of the sample is present as an additional minor cyclic isomer at equilibrium, and most of the associated ¹H NMR signals are obscured by the signals corresponding to the linear isomer and cyclic keto tautomer. As a result no ¹H-¹H COSY interactions in the aliphatic region were observed. The upfield shifts of the ¹H and ¹³C NMR signals corresponding to H_h and C_h, assigned by ¹H-¹³C HSQC NMR spectroscopy, suggest this minor cyclic isomer is the enol tautomer as observed for aliphatic amines, see Ref 21b.
- [41] Although some of the signals are overlapping (e.g. the signals at 6.25 ppm), each of the three isomers has at least three non-overlapping signals which could be used to determine an average relative abundance.
- [42] In DMSO-d₆ solution DASA 3 exists as two linear conformers as well as two cyclic isomers that are distinguishable by ¹H NMR spectroscopy, with the enol tautomer as the most stable cyclic isomer. The two cyclic isomers are distinguished by the ¹H NMR

- chemical shift of the barbituric acid NH protons. The N-methyl (H_j) ¹H NMR signal of the keto tautomer is shifted upfield by 0.5 ppm compared to the analogous signal of the enol tautomer, allowing reliable assignment of these tautomers.
- [43] As result of the solvent used in the synthesis, alkyne derivative 3 was isolated almost exclusively in the cyclic form. The stacked ¹H NMR spectra of this experiment are shown in SI-7.4. The thermal equilibration of DASA 3 in DMSO-d₆ was studied similarly to DASA 2, and the isomerization was consistent with the same mechanism. For DASA 3 we find that although the enol form is slightly more stable than the keto, the barriers (enol-keto: 90 kJ·mol⁻¹; ring closing: 92 kJ·mol⁻¹, both at 298 K) remain similar to that for DASA 2.
- [44] The influence of water content DASA isomerization in DMSO-d₆ has been previously studied, see ref 28c.
- [45] The barrier to the enol-keto tauomerization was also lowered by (~3-4 kJ·mol⁻¹) when 10% water or D₂O was included. These barriers are based on the observed changes in equilibration kinetics measured by ¹H NMR, see SI-8.
- [46] The role of water molecules in mediating the ring-closing reaction has been proposed, see reference 30.
- [47] In DMSO some switching is observed, but switching (both with light and thermally) is slow and fatigue resistance is poor. Photoswitching is possible in chloroform and 2-MeTHF, although low solubility of the free DASAs prevented NMR experiments so the following discussion is limited to UV-visible absorption experiments (see SI-9 for NMR spectra of DASA 2 in CDCl₃). The apparent thermal half-life values of DASAs are generally longer in 2-MeTHF than chloroform (ref [33]) allowing easier analysis. Addition of excess receptor 5 to DASA 2 in chloroform results in a 3 nm redshift and 15% increase in absorption, and the thermal half-life time is shorter. For a discussion of the data in chloroform, see SI-10.1.
- [48] The addition of receptor 6 did not change the switching properties of DASA 1 (Figure S43).