Solvatochromic properties of Schiff bases derived from 5-aminobarbituric acid: chromophores with hydrogen bonding patterns as components for coupled structures†

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A switchable and chromophoric Schiff base, containing an enolizable barbiturtic acid moiety as a novel UV/vis probe, is presented that can synergistically measure both polarity effects and hydrogen bonding patterns.

The detection of acid–base and dipolar sites on amino acid crystals, synthetic poly(amino acids), sugars and polysaccharides using solvatochromic dyes has been reported.[1–4] However, the use of common solvatochromic probes, which are not suitable for recognizing specific hydrogen bonds, only allow the determination of an average acidity or basicity for the surface sites measured.[3,4] For applications in biologically- or medicinally-relevant analytes, UV/vis probes are demanded whose UV/vis absorption changes significantly upon complex formation as a function of the supramolecular interaction.

According to their definition, supramolecular structures are built up as a result of non-covalent interactions between individual building blocks.[4–6] The principle of reversibility guarantees that the individual building blocks are assembled according to a thermodynamic equilibrium constant, and can be separated again, as with Lego building blocks.[5–9] Recently, we reported boronic acid-tetherable chiral 1,2-diol-functionalized nitroaniline derivatives for this purpose.[10]

In order to construct bi- and multifunctional probes, we searched for compounds with two different non-covalent binding points where both the principle of reversibility and a solvatochromic π-electron system is available. For this, it is necessary for the molecules on the periphery to be functionalized in such a way that they can be chemically bonded-to and separated again from other functional molecules.

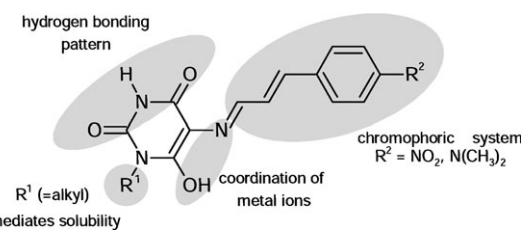
In this Letter we report on the solvatochromic properties of Schiff bases derived from 5-aminobarbituric acid derivatives and *para*-substituted cinnamaldehydes (Scheme 1), and their potential for supramolecular complex formation.

Recently, it has been shown that related Merocyanine dyes create new self-assembled structures,[11] or are effective sensitizers with interesting photophysical properties.[12] More importantly, such dyes exhibit hydrogen bonding patterns with an ADA sequence (A = hydrogen bond acceptor site, D = hydrogen bond donor site), which allows selective binding to bases offering a complementary DAD pattern. These dyes contain the barbituric acid moiety as an electron withdrawing group, which complicates the recognition of bases.

We chose solvatochromic and enolizable organic chromophores with hydrogen bonding functions because of their potential to bind reversibly to metal ions and/or complementary bases such as 2,6-diaminopyridine derivatives or others.[13–16] Furthermore, the 5-aminobarbituric acid unit can be substituted at one of the ring nitrogen atoms, which is suitable for adjusting the solubility of the compound while retaining the ADA sequence. In a previous study, we reported on the synthesis and solid state structure of Schiff bases derived from 5-aminobarbituric acid derivatives and *para*-substituted cinnamaldehydes (Scheme 2).[17] The enol form appears to be more stable than the keto form, which is confirmed by solid state ^{13}C NMR and FTIR spectroscopy.

It should be emphasized that the enolizable barbituric acid moiety serves as a (+M)-substituent, in contrast to the established Merocyanine dyes, where the barbituric acid is a (−M)-substituent. This feature is of importance for the construction of chromophoric probes relating to this type of compound, which are still not established for probing molecular recognition.

We now want to show if and how the free ADA function (**1b**, **2b**) and those capped by the use of *N*,*N*-disubstituted barbituric acid (**1a**, **2a**) affect the chromophoric π-electron system as a result of interactions with the surroundings of the molecules, and what proportion of these are dipole–dipole and/or hydrogen bond or acid–base interactions. Also, the influence of *para*-substituents, such as nitro or *N*,*N*-dimethylamino, on the solvatochromic behavior of the Schiff bases was investigated. To separate the individual solvation effects, we



Scheme 1 Chemical structure and possible functionalities of the target Schiff bases.

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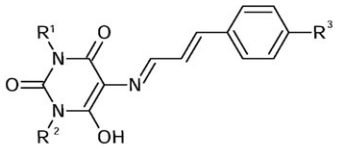
† Electronic supplementary information (ESI) available: Detailed experimental section, determination of K_A, all results of the multiple correlation analyses, push–push character of **2a** and **2b**, UV/vis studies of **1a** and **1b** in the presence of DAP or DAC, ^1H NMR and IR spectra of **1b** + DAC, and DSC traces. See DOI: 10.1039/b702483e



	$R^3 = NO_2$	$R^3 = N(CH_3)_2$
$R^1 = R^2 = CH_3$	**1a**	**2a**
$R^1 = H$, $R^2 = n\text{-}C_4H_9$	**1b**	**2b**

Scheme 2 Novel solvatochromic compounds.

used the simplified Kamlet–Taft equation (eqn. (1)), from which the coefficients of the individual interaction contributions can be determined using multiple correlation analysis.[2,18–21]

$$\tilde{\nu}_{max} = \tilde{\nu}_{max,0} + a\alpha + b\beta + s\pi^* \quad (1)$$

$\tilde{\nu}_{max}$ is the longest wavelength UV/vis absorption maximum of the compound measured in a particular solvent, $\tilde{\nu}_{max,0}$ is that of a non-polar reference solvent, α is the hydrogen bonding acidity, β describes the hydrogen bonding basicity and π^* is the dipolarity/polarizability of the solvent. *a*, *b* and *s* are the solvent-independent correlation coefficients, which allow the effects of a particular parameter on the solvatochromic properties of the compounds to be determined. The quality of the regression analyses is defined by number of solvent used (*n*), correlation coefficient (*r*), standard deviation (SD), and significance (*F*) for the solvatochromism.

Furthermore, UV/vis titration experiments were used to obtain information on the binding of the Schiff bases to 2,6-diaminopyridine derivatives.[17,22–24] Fluorescence probes, such as amino-substituted acridizinium derivatives or ribonucleosides of 5-fluorophore-linked unnatural bases, whose emission intensity increases upon complex formation with biologically or medicinally relevant analytes, are well known in the literature.[25] Moreover, complex formation of different barbituric acid derivatives is reported by optical spectroscopy, where the fluorescence or absorption intensity increases upon addition of host molecules.[26]

Table 1 UV/vis absorption maxima ($\tilde{\nu}_{max}$) of **1a**, **1b**, **2a** and **2b** in selected solvents, the empirical Kamlet–Taft parameters[18–21] α, β, π^* and the extent of the solvatochromic absorption shift

				$\tilde{\nu}_{max}/10^{-3}$ cm^{-1}			
Solvent	α	β	π^*	**1a**	**1b**	**2a**	**2b**
Tetrahydrofuran	0.00	0.55	0.58	20.4[a]	20.3	20.5[c]	20.5[c]
Dichloromethane	0.13	0.10	0.82	20.5[a]	20.6[a]	19.9	19.9
DMF[d]	0.00	0.69	0.88	20.1[a]	20.0[b]	20.4	20.4
Dimethyl sulfoxide	0.00	0.76	1.00	20.6[b]	20.3	20.3	20.4
Methanol	0.98	0.66	0.60	22.5	22.6	20.5[c]	20.4
TFE[e]	1.49	0.00	0.73	22.6	22.7	20.1	20.1
HFP[f]	1.96	0.00	0.65	22.8[c]	22.9[c]	19.8[b]	19.8[b]
$\Delta\lambda$/nm				46	64	18	18
$\Delta\tilde{\nu}$/cm^{-1}				2160	2923	732	732

[a] Excluded from correlation. [b] Highest bathochromic shift. [c] Highest hypsochromic shift. [d] *N*,*N*-Dimethylformamide. [e] 2,2,2-Trifluoroethanol. [f] 1,1,1,3,3,3-Hexafluoro-2-propanol.

The solvatochromism of compounds **1a** and **1b** has been investigated in a set of 25 solvents. **2a** and **2b** are only tested in ifferent solvents with characteristic polarity. The $\tilde{\nu}_{max}$ data and the Kamlet–Taft parameters used for the multiple correlation analyses in selected solvents are summarized in Table 1.

It is remarkable that the *para*-substituted *N*,*N*-dimethylamino compounds **2a** and **2b** do not show a pronounced solvatochromism, because the enol form of the barbituric acid moiety dominates. Furthermore, this is clear confirmation that a push–push π-electron system is present. Thus, these types of compound seem unsuitable for observing supramolecular hydrogen bonding using UV/vis spectroscopy. In contrast, the *para*-nitro-substituted compounds **1a** and **1b** show evident solvatochromism as a function of solvent polarity. Characteristic UV/vis spectra of compound **1b** measured in various solvents are shown in Fig. 1.

Multiple correlation analyses of the $\tilde{\nu}_{max}$ data with the Kamlet–Taft parameters for compounds **1a** and **1b** gave eqn. (2) and eqn. (3), which are obtained from the best fit by considering the significance of the respective solvent parameter that contributes to the shift of $\tilde{\nu}_{max}$.

$$\tilde{\nu}_{max} \times 10^{-3} \times [\mathbf{1a}] = 21.56 + 0.89\alpha - 0.68\pi^*$$
$$n = 18;\ r = 0.907;\ SD = 0.2615;\ F < 0.0001 \quad (2)$$

$$\tilde{\nu}_{max} \times 10^{-3} \times [\mathbf{1b}] = 21.26 + 1.02\alpha - 0.84\beta$$
$$n = 18;\ r = 0.899;\ SD = 0.327;\ F < 0.0001 \quad (3)$$

With increasing the hydrogen bond acceptor (HBA) strength of the solvent, a bathochromic shift of compound **1b** is measured, which is readily explained by the acidity of the enol or NH hydrogen atom. They can interact with a HBA solvent as hydrogen bond donor (HBD) groups. Thus, a base attack upon the barbituric acid moiety enhances the push character of this group, which is reflected by the bathochromic shift of the UV/vis band. In contrast, the HBD property of the solvent (α term) has an opposite effect on $\tilde{\nu}_{max}$, which indicates a disturbing of the conjugation. A specific attack, most likely upon the azomethine nitrogen atom or enol oxygen atom,

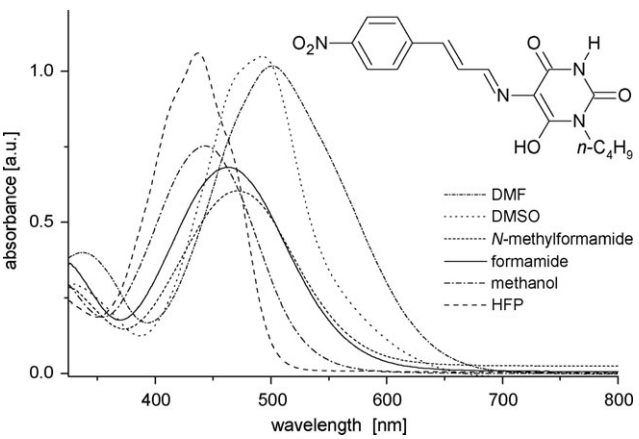


Fig. 1 UV/vis spectra of **1b** dissolved in six solvents of different polarity, *i.e.* HFP, methanol, formamide, *N*-methylformamide, dimethyl sulfoxide (DMSO) and DMF. The position of λ_{max} is independent of the chromophore concentration.

takes place. Both options are possible and have a similar effect on the shift of $\tilde{\nu}_{max}$. However, the π^* term of the solvent, the dipolarity/polarizablity, has a negligible effect on $\tilde{\nu}_{max}$ for compound **1b**, which supports the interpretation of the UV/vis spectroscopic results that contributions of the hydrogen bonds dominate. In contrast to compound **1b**, the 1,3-dimethyl-substituted derivative **1a** shows no significant influence of the β term on $\tilde{\nu}_{max}$, whereas the influence of the α term is related to that of **1b**. This comparison shows that the NH moiety of **1b** is of importance for interaction with bases. The formation of various specific hydrogen bonds between the solvent and the solvatochromic probe may possibly explain the UV/vis shifts. The contribution of each of the specific interactions (solvent/enol oxygen atom, solvent/azomethine nitrogen atom and solvent/enol hydrogen atom) can have a different effect by changing the nature and geometry of the solvent. This behaviour explains the mediocre correlation coefficients of the multiple square analyses, because each solvent most likely interacts in another way with the probe (NH or enol). Another support for this interpretation is the unsymmetric band form observed in the UV/vis spectra, which indicates that various electronic transitions or a variety of differently-solvated aggregates contribute.

The potential of compounds **1a** and **1b** for supramolecular complex formation with the adenine-mimetic bases 2,6-diaminopyridine (DAP) and 2,6-diacetamidopyridine (DAC) has been investigated by UV/vis titration.

Decomposition of the Schiff base **1b** was observed in the presence of DAP, which is a stronger Lewis base.[27] The nature of the solvent has a strong effect on this reaction. Protic solvents like methanol expedite the decomposition of the Schiff base.

In the UV/vis study in dichloromethane (DCM) using dye **1a** and DAC, a negligible influence with increasing DAC concentration on the intensity of the UV/vis band of **1a** was observed. **1a** bears an acid enol moiety in the same way as **1b**. Obviously, an interaction of weak base DAC with the enol site has no effect on the UV/vis spectrum.

In contrast, the UV/vis absorption intensity of **1b** is enhanced in the presence of an excess amount of DAC (Fig. 2). It is supported that in DCM, a rapid equilibration between both the keto and enol forms of **1b** occurs. The switching between them is associated with dramatic changes in the extent of π-conjugation. The position of this equilibrium is displaced due to complexation with DAC. The formation of the solvatochromic enol form of **1b** is indicated by the increase of its UV/vis absorption band.

The enol tautomer of **1b** and DAC can form an unnatural base pair system (Scheme 3). The formation of the 1 : 1 complex **1b** + DAC is assumed to be due to the mono-*N*-butyl substitution of **1b**, which has only one ADA binding site.

From eqn. (6) (see ESI), the association constant, K_A, of **1b** + DAC in DCM has been determined to be 51 M^{-1} (see Fig. 2).[22–24] The order of magnitude of K_A fits in with the expected order for DAD–ADA pair formation ($K_A \sim 10^2$–10^3 M^{-1}).[14]

Due to the position of the UV/vis band of **1b** not being influenced by DAC, a classical acid–base equilibrium with DAC can be excluded. Therefore, the enol site is likely not to be involved in complex formation. The slight hypsochromic shift ($\Delta\lambda$ = 3 nm) is assigned to other interactions. Thus, a higher concentration of DAC is not meaningful.

^{1}H NMR spectroscopy is not applicable because of the low solubility of the Schiff bases in weaker polarity solvents than DMSO. Moreover, complex formation between **1b** and DAC is observed by concentration-dependent ^{1}H NMR experiments in d_6-DMSO due to a weak downfield shift of the NH proton of the Schiff base **1b** in the presence of DAC.

The DSC thermogram of the solid 1 : 1 complex **1b** + DAC shows an endothermic transition at 196 °C. For comparison, **1b** and DAC melt at 247 and 206 °C, respectively. Therefore, this transition can be attributed to the melting of the complex affected by a small amount of unbound DAC at approximately 211 °C. Similar results have been reported for the interaction of an alkylated barbituric acid with an adenine or thymine derivative.[28]

In this communication, we have introduced a novel dye of a Schiff base of type **1b**, containing the barbituric acid entity in its enol form, that is suitable as a UV/vis probe. The electron donating strength of the barbituric acid moiety is significantly enhanced by interaction with hydrogen bond accepting solvents or the complementary base DAC, as shown by UV/vis spectroscopy. Furthermore, complex formation was found in the latter in the solid state. The low chemical persistence of the

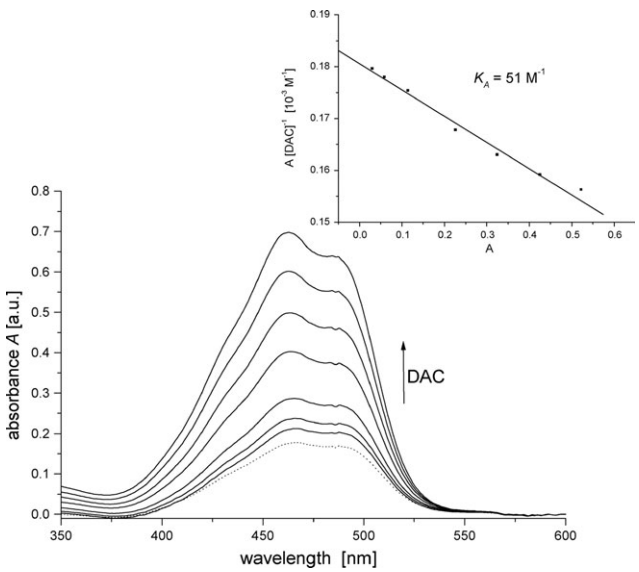
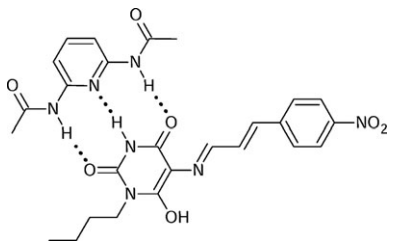


Fig. 2 UV/vis spectra of the Schiff base **1b** (0.03 mmol l^{-1}, dotted line) with increasing amount of added DAC (0.17, 0.33, 0.67, 1.34, 2.01, 2.67 and 3.34 mmol l^{-1}) in DCM. Inset: The Scatchard plot at 463 nm for determining the K_A of DAC with **1b**.



Scheme 3 Assumed complex formation between the Schiff base **1b** and DAC in DCM.

Schiff Bases can be circumvented by another synthetic strategy, which will be reported at a later time. Nevertheless, these novel types of enolizable barbituric acid derivatives are promising candidates for measuring the effects of complementary hydrogen-bonded complexes, as well as the polarity of the environment.

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Experimental

General

Unless otherwise noted, all materials were used as received from commercial suppliers without further purification. All reaction solvents were re-distilled over appropriate drying agents prior to use. The Schiff bases **1a**, **1b**, **2a** and **2b**, and the model base DAC, were prepared as previously described.[17,29] Synthesis and characterization of the complex **1b** + DAC is described in the ESI.†

Instrumentation

The UV/vis absorption spectra of freshly prepared solutions were obtained by means of an MCS 400 diode-array spectrometer (Carl Zeiss Jena). Multiple regression analysis and linear curve-fitting were performed with the Origin 5.0 statistical program.

Binding studies

The binding between the model bases DAP or DAC and the hosts **1a** or **1b** were investigated by UV/vis spectroscopy. All UV/vis titrations were performed using DCM (freshly distilled from CaH_2). The decomposition of **1b** in the presence of DAP was additionally performed in methanol (freshly distilled from Na). A typical binding experiment involved the titration of **1b** (1.0 ml, 0.03 mmol l^{-1}), where 0.01–1.00 ml aliquots of the guest stock solution (16.72 mmol l^{-1}) were added. The solutions were then made up to 5.0 ml. The increase in absorption intensity at 463 nm was monitored as a function of guest concentration. The quantitative determination of the association constant K_A was based on the absorbance variation of the host (H) in the presence of the guest (G) at a particular concentration. A detailed explanation is given in the ESI.†

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