Molecular Recognition

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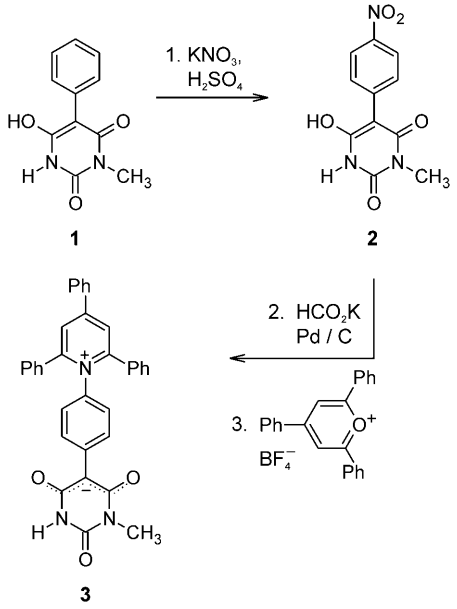
A Pyridinium–Barbiturate–Betaine Dye with Pronounced Negative Solvatochromism: A New Approach for Molecular Recognition**

*Ina Bolz, Dieter Schaarschmidt, Tobias Rüffer, Heinrich Lang, and Stefan Spange**

Dedicated to Professor Christian Reichardt

The perfection of the complementary hydrogen-bonding sequence of DNA base pairs fascinates many chemists and inspires them to use similar coupling motifs for the construction of supramolecular structures.[1] Often low-molecular-weight model systems are used, because the complexity of the tautomeric equilibria makes the simultaneous detection of structurally different bases difficult at the molecular level.[2,4] The adaptation of each tautomer of a DNA base to its complementary partner, however, does not appear to be an intrinsic property of the base, but rather is evidently also determined by the molecular environment of the molecule.[5] By using chromophoric probe molecules capable of adaptation, different hydrogen-bonding sequences can be distinguished. The capacity of adaptation is related to the controlled formation of defined tautomers, which are stabilized only upon complex formation.[6] Our underlying idea is that the electronic structure of the chromophore can be effectively modified by the formation of a supramolecular complex and can thus result in a change in its optical properties. On route to this challenging target, we have developed a new class of pyridinium–barbiturate–betaine dyes with exceptional solvatochromic properties and adaptable hydrogen-bonding sequences, which we are reporting here for the first time.

The pyridinium–barbiturate–betaine dye **3** was obtained from 1-methyl-5-phenylbarbituric acid (**1**) via **2** (Scheme 1). X-ray structure analysis shows that **3** is present in the crystal as a centrosymmetric dimer, which is held together by two moderately strong intermolecular hydrogen bonds between the partially negatively charged O1 atom and the N2 atom on the barbituric acid ring (Figure 1, Table 1).[7,8] Because of packing effects, there are two additional weak hydrogen bonds across O2···H–C28 and O1···H–C26.[9] As a result of this, a favorable conjugation between the electron-donating barbiturate unit and the electron-accepting pyridinium substituent is achieved.



Scheme 1. Synthesis of chromophore **3**.

A further indication of the presence of a pronounced push–pull system is given by the remarkably high negative solvatochromism, which leads to absorptions extending over practically the whole visible region from $\lambda = 380$ nm (in 2,2,2-trifluoroethanol) to $\lambda = 639$ nm (in 1,4-dioxane) (Figure 2). Since the absorption maxima cover an energy range of $\Delta\tilde{\nu} = -10683\ \mathrm{cm}^{-1}$, barbiturate **3** setsa new record for negative solvatochromic compounds. Because of this, barbiturate **3** exhibits a greater sensitivity towards changes in the solvent polarity than other known, structurally similar, betaine dyes (see the Supporting Information).[10,11]

The individual interactions of chromophore **3** with the solvent environment were investigated by means of linear solvation energy (LSE) relationships, using the empirical solvent parameters according to Kamlet and Taft[12] and Catalán.[13] The solvatochromism of **3** is thus determined principally by the hydrogen-bond-donor capacity and the dipolarity of the solvent, which bring about a hypsochromic shift of $\tilde{\nu}_{max}$. In addition, the high electron density of the enolate substituent enhances the basic character of the barbiturate acid unit, and consequently **3** is sensitive to acids and hydrogen-bonding donor sequences.

[*] I. Bolz, Prof. Dr. S. Spange
Institut für Chemie, Professur Polymerchemie
Technische Universität Chemnitz
Strasse der Nationen 62, 09107 Chemnitz (Germany)
Fax: (+49) 371-531-21239
E-mail: stefan.spange@chemie.tu-chemnitz.de
D. Schaarschmidt,[+] Dr. T. Rüffer,[+] Prof. Dr. H. Lang[+]
Institut für Chemie, Professur Anorganische Chemie
Technische Universität Chemnitz (Germany)

[+] Single-crystal X-ray structure analysis

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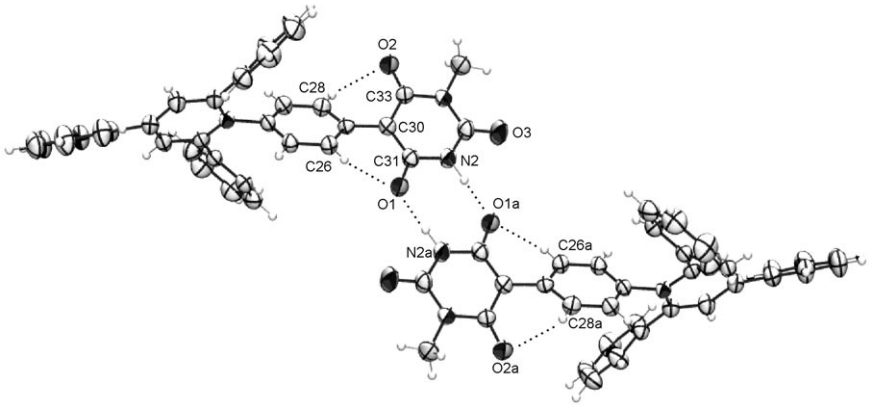


Figure 1. ORTEP drawing of the molecular structure of the centrosymmetric dimer of **3**. Complete numbering of the atoms can be found in the Supporting Information.

Table 1: Bond lengths d and bond angles θ of the hydrogen bonds in dimeric **3** (D = donor, A = acceptor).

Hydrogen bond		d [Å]			θ [°]
	D–H···A	D–H	H···A	D–H···A	D–H···A
intra	C26–H···O1	0.93	2.24	2.819(4)	120
intra	C28–H···O2	0.93	2.31	2.833(4)	115
inter	N2–H···O1	0.97(5)	1.83(5)	2.796(4)	173(4)

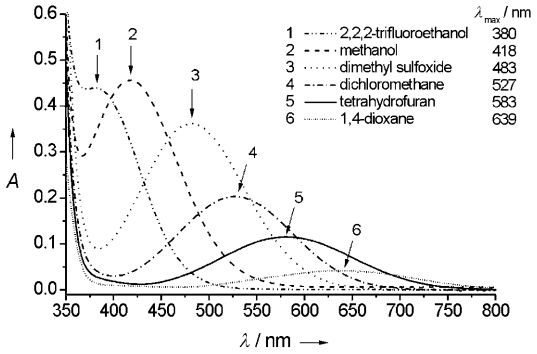
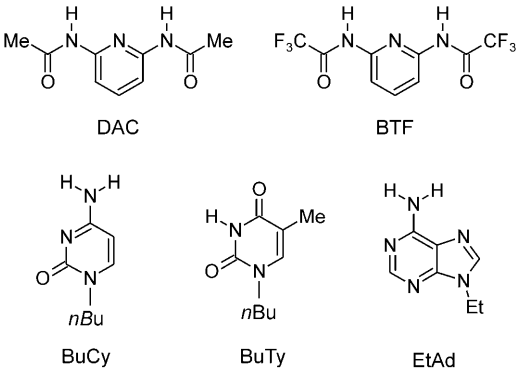


Figure 2. UV/Vis absorption spectra of **3** in six selected solvents of varying polarity. In the region shown, λ_{max} is independent of the dye concentration.

The influence of the chromophoric system of the betaine dye **3** through supramolecular binding is demonstrated by means of complexation experiments with five artificial receptors.[14] Because of their different amide substituents, the pyridine derivatives 2,6-diacetamidopyridine (DAC) and 2,6-bis(trifluoroacetamido)pyridine (BTF) are suitable for a systematic investigation of acid–base and noncovalent interactions. The nucleic acid bases 9-ethyladenine (EtAd), 1-*n*-butylcytosine (BuCy), and 1-*n*-butylthymine (BuTy) can mimic the base pairing found in nature (Scheme 2).

The formation of supramolecular complexes of betaine dye **3** with these five receptors can be followed by UV/Vis spectroscopy (Figure 3). Almost no change is observed on addition of BuTy or BuCy, as these compounds have only a donor–acceptor recognition system complementary to **3**. Besides, complex formation with BuCy is electronically limited, as **3** and BuCy mainly act as hydrogen-bond acceptors. The very weak complex formation expected therefore leads to no measurable shift in the UV/Vis absorption band.

Complete protonation of **3** is achieved by the addition of trifluoroacetic acid (TFA, $pK_A = 0.23$ in H_2O). This lowers the charge density in the barbiturate and a downfield shift of the ^{1}H NMR signal (Figure 4). In contrast, the signals of the H atoms on C26 and C28 show a marked upfield shift (black arrows, $\Delta\delta = 0.76$ ppm). This is



Scheme 2. The synthetic receptors employed.

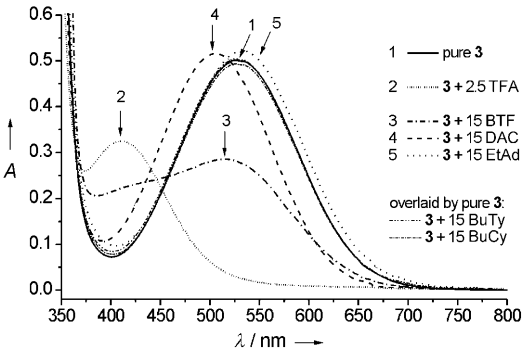


Figure 3. Shift of the UV/Vis absorption maximum of **3** (0.098 mmol L^{-1}, $\lambda_{max} = 533$ nm) in dichloromethane by acid–base interactions with TFA and by the formation of supramolecular complexes with the receptors BTF, DAC, and EtAd.

explained by the cleavage of both of the intramolecular nonclassical hydrogen bonds O···H–C. The repulsive interactions between the enol hydrogen atom and the H atoms on C26 and C28 cause a twist between the barbiturate unit and the phenylene ring, which makes the charge transfer more difficult. For the protonated chromophore **3**-H$^+$, a hypsochromic shift to $\lambda_{max} = 409$ nm is observed (Figure 3). An excess of TFA leads to multiple protonation of the barbiturate, which is detected both by a further hypsochromic shift of

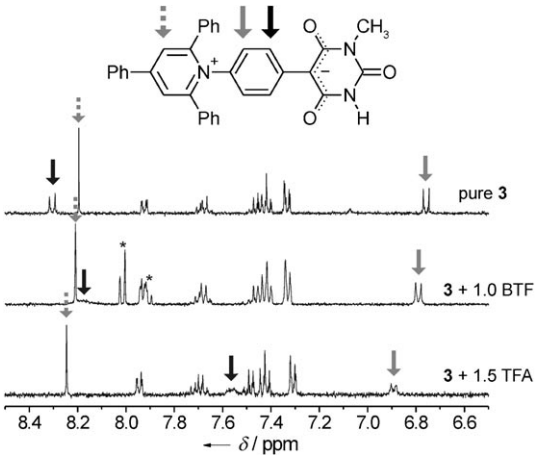


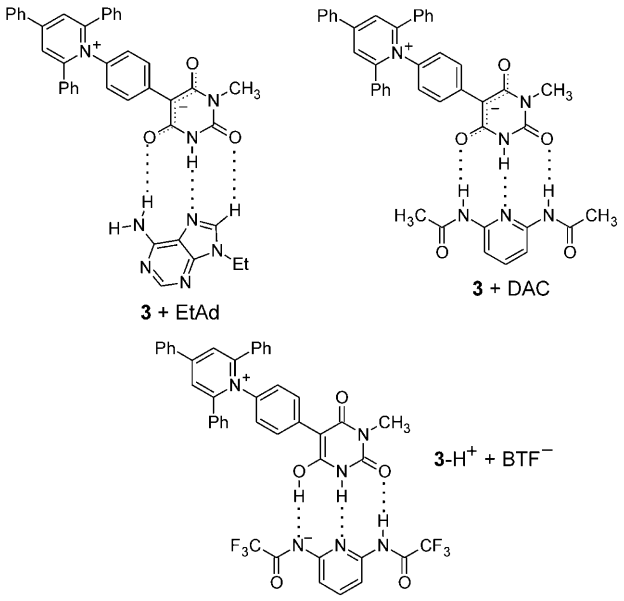
Figure 4. Sections of the ^{1}H NMR (400 MHz) spectra from the titrations of **3** (0.372 mmol L^{-1}) with TFA and the receptor BTF in CD_2Cl_2 (signals of the receptors are marked with asterisks).

λ_{max} with signal hypochromism, and by a broadening of the ^{1}H NMR signal with increasing TFA concentration.

The receptor BTF is acidic because of the two highly electron-withdrawing trifluoroacetyl substituents, and as a result consecutive association via acid–base and noncovalent interactions is observed with **3**. Here also protonation of the barbiturate unit hinders the charge transfer in **3**-H$^+$, which is evident in the UV/Vis experiment by a hypsochromic shift of $\Delta\lambda = 121$ nm to $\lambda_{max} = 412$ nm. The conjugated acid–base pair **3**-H$^+$/BTF$^-$ (Scheme 3) forms a very stable threefold hydrogen-bonded complex as a result of its favorable electrostatic interactions and its complementary AAD–DDA recognition sequences.[15]

As the receptor DAC is less acidic than BTF and has a complementary DAD recognition sequence, upon titration of **3** with DAC formation of a supramolecular complex through three hydrogen bonds is observed. ^{1}H NMR titration in CD_2Cl_2 was used to determine the association constant K_A from the downfield shift of the barbiturate NH hydrogen signal as a function of the receptor concentration ($K_A = (2718 \pm 38)\,M^{-1}$). Furthermore, the UV/Vis absorption maximum of **3** in dichloromethane undergoes a hyperchromic and a hypsochromic shift on addition of DAC ($\Delta\lambda = 21$ nm, $K_A = (2479 \pm 448)\,M^{-1}$). Both values for K_A are on the same order of magnitude and are typical for threefold hydrogen-bonding ADA–DAD systems.[15]

Formation of a supramolecular complex between **3** and EtAd in dichloromethane causes a small hyperchromic and a bathochromic shift of the UV/vis absorption maximum of **3** ($\Delta\lambda = 3$ nm, Table 2, Figure 3). In spite of this minimal change, the association constant of the **3** + EtAd complex can be determined as $K_A = (1309 \pm 179)\,M^{-1}$. On the basis of the work of Quinn et al.[16] a threefold hydrogen-bonded complex with Hoogsteen geometry is assumed for **3** + EtAd (Scheme 3). In this structure EtAd shows a complementary DAD recognition sequence and thus acts as an H-bond donor.



Scheme 3. Formation of supramolecular complexes of the pyridinium–barbiturate–betaine dye **3** with artificial receptors.

Table 2: Complexation properties of the pyridinium–barbiturate–betaine **3** in dichloromethane.

Receptor	Type of H bonds formed by **3**[a]		Number of H bonds	K_A [M^{-1}]	λ_{max} [nm][b]
DAC	DAD	enolate	3	2718 ± 38[c]	512
BTF	DDA	enol	3	[d]	412[e]
BuTy	AD	enolate	2	[f]	[f]
EtAd[g]	DAD	enolate	3	1309 ± 179 [h]	536
BuCy	AD	enolate	2	[f]	[f]

[a] D: H-bond donor, A: H-bond acceptor. [b] Complexed enolate form. [c] Determined by ^{1}H NMR titration. [d] Not measurable. [e] Complexed enol form. [f] No interaction. [g] Hoogsteen geometry. [h] Obtained by UV/Vis titration.

The new pyridinium–barbiturate–betaine dye **3** presented here permits the simultaneous spectroscopic monitoring of polarity changes, acid–base reactions, and the formation of supramolecular complexes with complementary H-bonding sequences, on the basis of its pronounced negative solvatochromism. It should be emphasized that each interaction between the chemical sensor **3** and the hydrogen-bond-donating receptors leads to a specific UV/Vis signal, which can be followed with the naked eye. We expect that this new class of UV/Vis probe molecules should find new applications.

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[1] a) J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, Wiley, Chichester, **2000**; b) H.-J. Schneider, A. Yatsimirsky, *Principles and Methods in Supramolecular Chemistry*, Wiley, Chichester, **2000**.

[2] a) J.-M. Lehn, *Science* **2002**, *295*, 2400 – 2403; b) *Highlights in Bioorganic Chemistry: Methods and Applications* (Eds.: C. Schmuck, H. Wennemers), Wiley-VCH, Weinheim, **2004**; c) *Functional Synthetic Receptors* (Eds.: T. Schrader, A. D. Hamilton), Wiley-VCH, Weinheim, **2005**.

[3] a) H. Ma, L. Nie, S. Xiong, *Supramol. Chem.* **2004**, *16*, 311 – 317; b) J. R. Quinn, S. C. Zimmerman, *J. Org. Chem.* **2005**, *70*, 7459 – 7467; c) G. K. Mittapalli, Y. M. Osornio, M. A. Guerrero, K. R. Reddy, R. Krishnamurthy, A. Eschenmoser, *Angew. Chem.* **2007**, *119*, 2530 – 2536; *Angew. Chem. Int. Ed.* **2007**, *46*, 2478 – 2484.

[4] a) R. W. Sinkeldam, Y. Tor, *Org. Biomol. Chem.* **2007**, *5*, 2523 – 2528; b) L. Zendlová, P. Hobza, M. Kabeláč, *J. Phys. Chem. B* **2007**, *111*, 2591 – 2609; c) X. Hu, H. Li, L. Zhang, S. Han, *J. Phys. Chem. B* **2007**, *111*, 9347 – 9354.

[5] C. M. Marian, *J. Phys. Chem. A* **2007**, *111*, 1545 – 1553.

[6] a) I. Bolz, C. May, S. Spange, *Arkivoc* **2007**, *iii*, 60 – 67; b) I. Bolz, C. May, S. Spange, *New J. Chem.* **2007**, *31*, 1568 – 1571; c) I. Bolz, C. Moon, V. Enkelmann, G. Brunklaus, S. Spange, *J. Org. Chem.* **2008**, *73*, 4783 – 4793; d) I. Bolz, S. Spange, *Chem. Eur. J.* **2008**, *14*, 9338 – 9346; e) I. Bolz, M. Bauer, A. Rollberg, S. Spange, *Macromol. Symp.* **2009**, in press.

[7] CCDC 732859 (**3**) and 732860 (BTF) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[8] According to the classification by Jeffrey, hydrogen bonds are classifield as "strong" (2.2–2.5 Å, 170–180°), "moderately strong" (2.5–3.2 Å, $>130°$, $<170°$), and "weak" (>3.2 Å, $>90°$, $<130°$): a) G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, Oxford, **1997**; b) T. Steiner, *Angew. Chem.* **2002**, *114*, 50 – 80; *Angew. Chem. Int. Ed.* **2002**, *41*, 48 – 76.

[9] Intra- and intermolecular π–π interactions apparently make only a secondary contribution to the overall stability. In any case, the almost planar arrangement between the barbiturate ring and the neighboring phenylene ring leads to the formation of two intramolecular, nonclassical O···C–H bonds (interplanar angle between the calculated mean planes: 28.7°) (T. Steiner, *Cryst. Res. Technol. Cryst. Rev.* **1996**, *6*, 1 – 57).

[10] a) C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH, Weinheim, **2003**; b) C. Reichardt, *Pure Appl. Chem.* **2008**, *80*, 1415 – 1432.

[11] Thiobetaine: C. Reichardt, M. Eschner, *Liebigs Ann. Chem.* **1991**, 1003 – 1012; Indane–betaine dye: P. Milart, *J. Chem. Res.* **2008**, 340 – 343.

[12] a) M. J. Kamlet, J.-L. M. Abboud, M. H. Abraham, R. W. Taft, *J. Org. Chem.* **1983**, *48*, 2877 – 2887; b) Y. Marcus, *Chem. Soc. Rev.* **1993**, *22*, 409 – 416.

[13] J. Catalán, *J. Phys. Chem. B* **2009**, *113*, 5951 – 5960. The correlation analyses can be found in the Supporting Information.

[14] Complex formation was verified by ^{1}H NMR and UV/Vis titration and is described in the Supporting Information.

[15] The determination of K_A for the formation of the complex **3**-$H^+ + TFA^-$ is not possible because of an overlap with the proton-transfer reaction (see Ref. [6d] and the Supporting Information).

[16] J. R. Quinn, S. C. Zimmerman, J. E. DelBene, I. Shavitt, *J. Am. Chem. Soc.* **2007**, *129*, 934 – 941.

