DOI: 10.1002/ejoc.200901066

Enhancing the Reactivity of an Electrophilic Barbiturate Dye by Cooperative Hydrogen Bonding

Mirko Bauer[a] and Stefan Spange*[a]

Keywords: Donor-acceptor systems / Supramolecular chemistry / Hydrogen bonds / Lewis acids / Acidity / Electrophilicity

The supramolecular complex formation by cooperative hydrogen bonding of a highly dipolar barbiturate dye and 2,6-diacetamidopyridine is shown to have a marked effect on the reactivity of the barbiturate. The increase of both Lewis acidity and electrophilicity by hydrogen bonding is demonstrated by thermodynamic and kinetic studies using the electrophile–nucleophile recombination reaction with cyanide.

Introduction

For polar reactions the reactivity of a substrate can be described using thermodynamic and kinetic values such as equilibrium or rate constants. This reactivity depends on various chemical parameters in a complex way. For instance, solvent effects play a crucial role regarding the nucleophilicity of anions.[1a] The electron-donating ability of a substituent has a great impact on the electrophilicity of carbenium ions and related compounds.[1b,1c] Now the question arises whether a substituent containing a hydrogen bonding motif suitable for supramolecular recognition can be externally modified by complex formation so that an effect on the chemical reactivity of the substrate results.

Indeed, the alteration of a substrate's reactivity by supramolecular interactions, especially hydrogen bonding, is a common principle in nature, for instance in enzyme catalysis. Numerous model systems have been developed for mimicking this behaviour, yet most of them use hydrogen bonds for preorganising template effects only.[2,3] On the other hand, the impact on the reactivity by the direct modification of the electronic structure of a molecule by hydrogen bonds has been studied less intensely and is mainly restricted to solvation effects of protic solvents.[4,5] The few examples comprising definite hydrogen bonded complex formation include the increase of the acidity of 1,3-β-dicarbonyl compounds by one pK_a unit by addition of complementary receptors.[6] Also, the redox properties of flavine model compounds are changed upon hydrogen bond formation as could be shown by Rotello[7] and Goldenberg.[8] The displacement of a tautomeric or configurational equilibrium towards a single preferred isomer by adding a suitable receptor has recently been described by our group[9] and others.[10] These findings strongly suggest an impact of hydrogen bonding onto a molecule's electron distribution. But is cooperative hydrogen bonding based on the model of DNA base pairing also capable of changing the reactivity of an electronically coupled electrophile? To answer this question, a simple electrophile–nucleophile recombination may serve as a suitable model reaction. Such recombinations are generally well-defined second-order reactions whose kinetics have already been studied in detail.[1] In this work we will demonstrate for the first time that it actually is possible to influence the reactivity of a neutral electrophile by using an external complementary hydrogen bonding receptor.

A suitable system for our studies has been found in the barbituric acid-containing merocyanine dyes **BA1** and **BA2** (Figure 1). The zwitterionic resonance structure illustrates

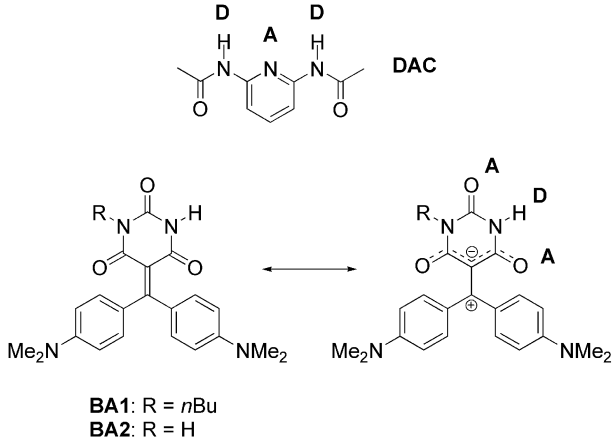


Figure 1. Electrophilic barbiturate dyes used in this study and the complementary receptor **DAC** (A = hydrogen-bond acceptor, D = hydrogen-bond donor).

[a] Department of Polymer Chemistry, Chemnitz University of Technology,
Strasse der Nationen 62, 09111 Chemnitz, Germany
Fax: +49-371-531-21239
E-mail: stefan.spange@chemie.tu-chemnitz.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901066.

that the barbiturate moiety serves as an electron-withdrawing substituent. Thus, the β-C-atom at the polarised double bond may act as a Lewis acid and electrophile as is already known from similar benzylidene barbiturates.[1c,2,11] As a complementary hydrogen bonding receptor the well established 2,6-diacetamidopyridine (**DAC**) was used.[7–9,12]

When **BA1** or **BA2** are treated with **DAC** and a nucleophile at the same time, multiple equilibria and their mutual influence have to be considered. In general, the involved equilibrium and rate constants can be depicted in a thermodynamic circle as is exemplified in Figure 2.

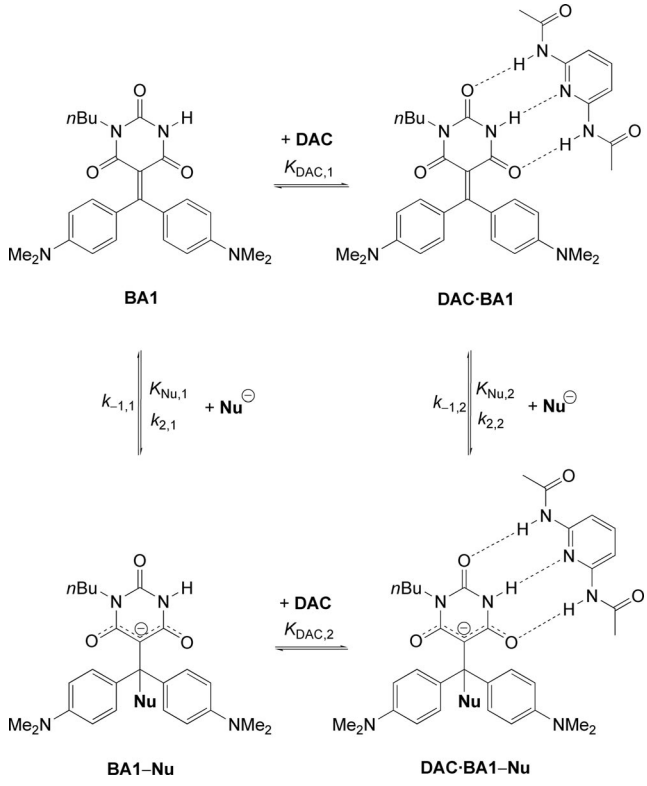


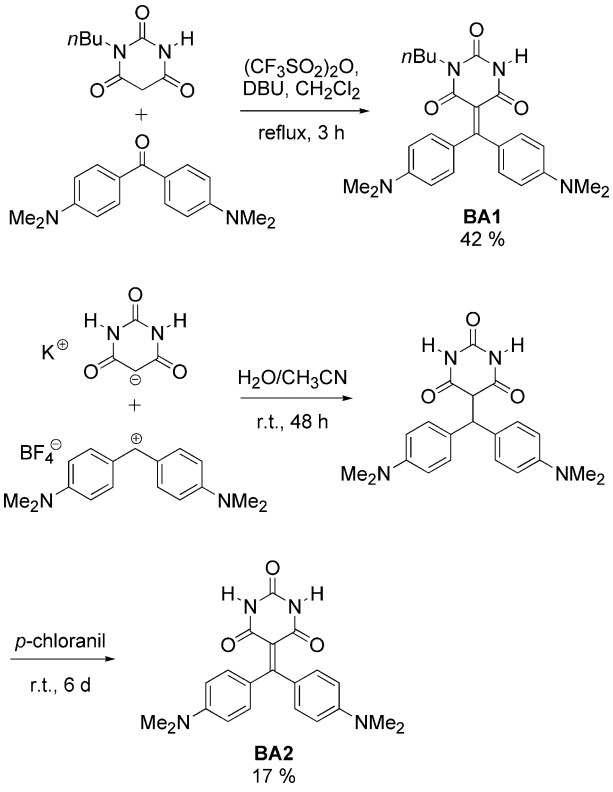
Figure 2. Thermodynamic circle comprising the equilibrium and rate constants of a mixture of **BA1**, **DAC** and a nucleophile **Nu**.

Results and Discussion

General Considerations

The barbiturate **BA1** was obtained by a simple one-step synthesis starting from triflic anhydride activated Michler's ketone (Scheme 1) which provides an easier access to this type of compounds compared to the previously published two-step procedure for the synthesis of **BA2**.[13]

A first impression of the interactions of these dyes with their surrounding can be derived from solvatochromic studies whereby specific and nonspecific interactions can be separated.[13,14] Hereto, the UV/Vis absorption maxima of **BA1** and **BA2** were measured in a set of 22–24 solvents and evaluated by multiple regression analysis using the solvent parameter set of Catalán[15] (see Supporting Information).



Scheme 1. Synthesis of compounds **BA1** and **BA2**.

For both dyes the UV/Vis absorption maximum is shifted towards lower energy with increasing dipolarity and polarizability of the solvent. This is a typical finding for dyes with a charge-transfer transition where the ground state is less polar than the excited state which proves that in the ground state the neutral resonance form of **BA1** and **BA2** (Figure 1, left) outweighs the zwitterionic one (Figure 1, right). Furthermore, a bathochromic shift of the UV/Vis absorption maxima with an increasing hydrogen bond donating (HBD) ability of the solvent is observed. These HBD solvents interact with the barbiturate's carbonyl moieties by which its electron density is reduced and the push-pull system is enhanced. In contrast, the solvent's hydrogen bond accepting capacity, which has the opposite effect and leads to a hypsochromic shift, is of minor importance. Thus, upon complexation of **BA1** or **BA2** with a complementary hydrogen bond receptor a net decrease of electron density and therefore an increase of reactivity can be expected.

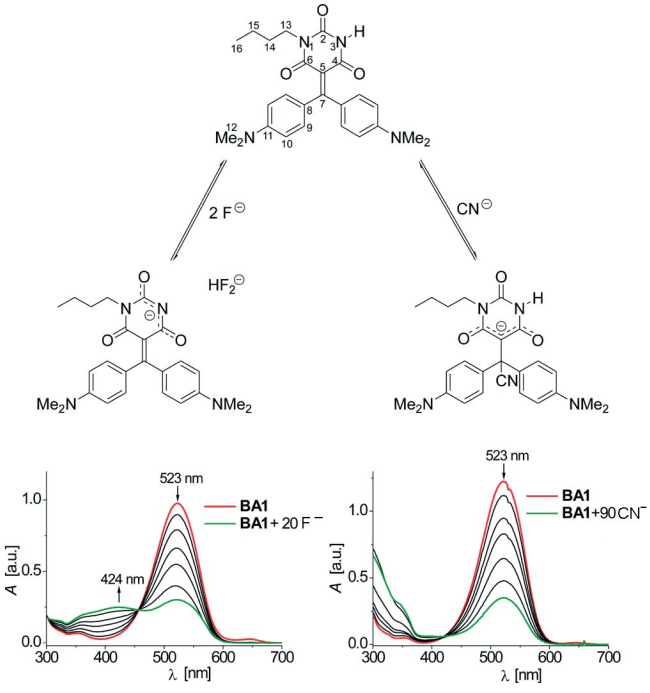
Binding Studies

The addition of the hydrogen bond donating receptor **DAC** to **BA1** or **BA2** indeed results in a bathochromic shift of the UV/Vis absorption band which is in line with the results of solvatochromic studies. By UV/Vis titration in dichloromethane the binding constants $K_{DAC,1}$ were found to be 1778 M^{-1} (**DAC·BA1**) and 1093 M^{-1} (**DAC·BA2**), respectively. These values indicate moderately strong hydrogen bonds and are comparable to other threefold hydrogen bonded complexes.[16] In the more polar solvent acetonitrile

this binding constant drops dramatically to 57 M^{-1} for **DAC·BA1** due to competitive hydrogen bonding to solvent molecules. As in less polar solvents like toluene the solubility is too low, dichloromethane was used for all other investigations.

To determine the reactivity of **BA1** and **BA2**, they were treated with a variety of potential nucleophiles, such as aliphatic or aromatic amines, halide and pseudohalide ions, tetramethylthiourea or mercaptoacetic acid. With added amines a characteristic UV/Vis shift is observed which can be attributed to general solvent effects. Among the other nucleophiles only fluoride and cyanide produced a significant, but distinct, change in the UV/Vis absorption.

With fluoride a hypso- and hypochromic effect is observed which is completely reversed in the presence of traces of water. Identical spectra are also obtained when hydroxide is added. This indicates an increase of electron density at the barbiturate moiety and a weaker push-pull system. The probable explanation of this effect is a deprotonation of the NH group (Scheme 2) which is also described for urea derivatives.[17] This assumption is further supported by an ^{1}H NMR titration where the disappearance of the NH signal and an upfield shift of all other signals is observed. It should be mentioned that the effects in the UV/Vis and NMR spectra are less pronounced for **BA1** than for **BA2** as the latter compound may be attacked at two NH groups.



Scheme 2. Reaction of **BA1** with tetra-*n*-butylammonium fluoride or cyanide and the respective UV/Vis spectra series.

On the other hand, when cyanide is added the UV/Vis absorption band decreases within several hours without development of a new band in the visible range. In a ^{1}H NMR experiment a second set of signals (including the NH signal) appears upfield-shifted which slowly gains intensity while the original signals diminish. In the ^{13}C NMR spectra (see SI) it is conspicuous that the signal of C-7 is shifted from δ = 178 ppm (**BA1**) to δ = 50 ppm (**BA1**–**CN**) indicating a change from sp^2 to sp^3 hybridization for C-7. The signal of C-5 shows an upfield shift of $\Delta\delta$ = 19 ppm to δ = 86 ppm for **BA1**–**CN** which is a typical value for barbiturate anions. At δ = 126 ppm a signal for covalently bound cyanide is observed. From these results it can be concluded that the expected nucleophilic attack actually takes place according to Scheme 2 whereby the chromophoric system is interrupted. A quantitative evaluation of the UV/Vis experiments according to a 1:1 stoichiometry yields the equilibrium constants $K_{Nu,1}$ and second-order rate constants $k_{2,1}$ given in Table 1. From Equation (1) the monomolecular dissociation rate constant $k_{-1,1}$ is accessible, too. While k_{-1} is hardly affected, K_{Nu} and k_2 are lower for **BA1** which can be readily explained with the electron-releasing effect of its *N*-(*n*-butyl) group.

$$K = k_2/k_{-1} \quad (1)$$

Table 1. Equilibrium and rate constants of the reaction of **BA1** and **BA2** with cyanide in dichloromethane.

	BA1	**BA2**
$K_{Nu,1}$ [M^{-1}]	319	1654
$k_{2,1}$ [M^{-1} s^{-1}]	3.1×10^{-2}	10.5×10^{-2}
$k_{-1,1}$ [s^{-1}]	9.7×10^{-5}	6.4×10^{-5}

In the presence of both, **DAC** and cyanide, a similar evaluation is only possible for **BA1**. For **BA2** an appropriate fitting of the binding isotherm could not be performed, so for the anionic **BA2-CN** the formation of complexes with a higher stoichiometry cannot be excluded. Yet, the recombination of **BA1** with cyanide proved to be a suitable model reaction for studying thermodynamic and kinetic effects of hydrogen bonding.

Hydrogen Bonding and Reactivity

While $K_{DAC,1}$ and $K_{Nu,1}$ might be determined directly (see above), this is not possible for the remaining $K_{DAC,2}$ and $K_{Nu,2}$. However, when solutions of **BA1** containing increasing amounts of **DAC** are titrated with cyanide the normalised binding isotherms get steeper and the observed values of $K_{Nu,obs}$ are rising (Figure 3). As the equilibration of **BA1** with **DAC** is much faster than with cyanide, these observed values can be interpreted as a weighed average of $K_{Nu,1}$ and $K_{Nu,2}$ [Equation (2)]. Notably, the ratio of the absorbance at different wavelengths remains almost constant throughout any titration. Hence the concentration effect of a higher $K_{DAC,2}$ is negligible and the mol fraction x of **DAC** complexed **BA1** is assumed to be constant.

$$K_{Nu,obs} = (1 - x)\, K_{Nu,1} + x\, K_{Nu,2} \text{ with } x = c_{DAC\cdot BA1}/c_{BA1,0} \quad (2)$$

Accordingly, a plot of $K_{Nu,obs}$ against x shows a linear relationship as can be seen in Figure 4. Extrapolation to x = 0 and x = 1 then yields the values for **BA1** ($K_{Nu,1}$ =

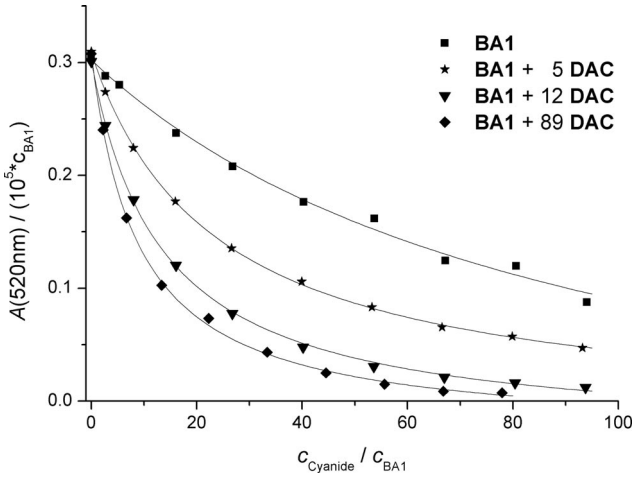


Figure 3. Normalised binding isothermes of the reaction of **BA1** with cyanide in the presence of increasing amounts of **DAC**.

381 M^{-1}) and **DAC·BA1** ($K_{Nu,2}$ = 3436 M^{-1}), respectively. A likewise treatment is also possible for the kinetic data (see Figure 5) whereby values of $k_{2,1} = 3.0 \times 10^{-2}$ $M^{-1} s^{-1}$ and $k_{2,2} = 5.2 \times 10^{-2}$ $M^{-1} s^{-1}$ are obtained. These results show that indeed the moderately strong hydrogen bonding between **BA1** and **DAC** is capable of reducing the electron density at the distant β-C-atom of **BA1** and of increasing measurably its electrophilicity as well as its Lewis acidity.

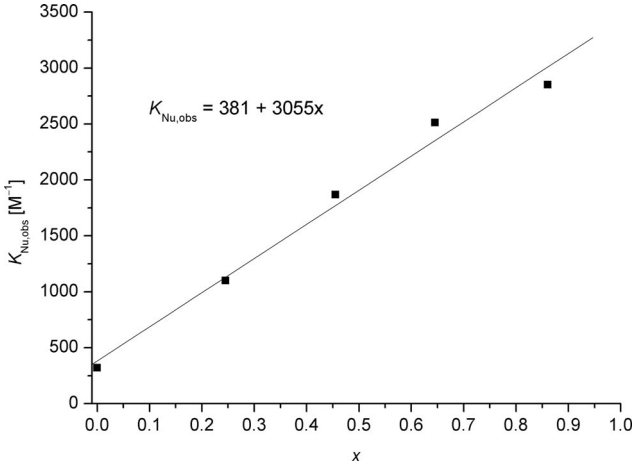


Figure 4. Plot of the observed binding constant $K_{Nu,obs}$ against the mol fraction x of **DAC·BA1**.

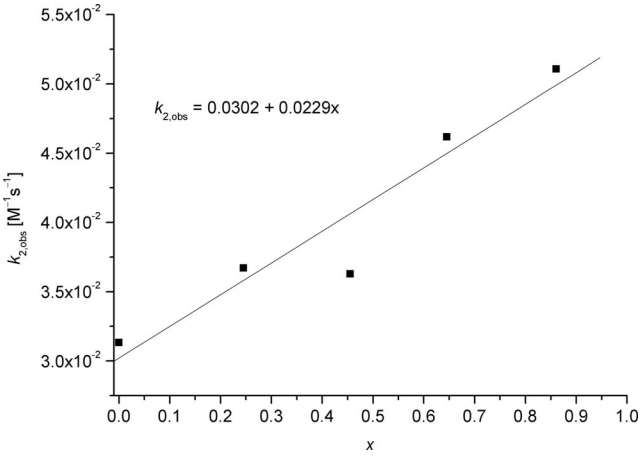


Figure 5. Plot of the observed second-order rate constant $k_{2,obs}$ against the mol fraction x of **DAC·BA1**.

Finally, the remaining binding constant can be derived from the thermodynamic circle, $K_{DAC,2}$ = 16035 M^{-1} (see Supporting Information). This increase is expected due to the anionic nature of **BA1–CN** which is known to enhance the strength of hydrogen bonds.[7,18] Using this binding constant the mol fraction of **DAC** complexed **BA1–CN** ($x_{BA1–CN}$) of the above data points can be calculated. A plot of the monomolecular electrophile-nucleophile dissociation rate constant $k_{-1,obs}$ against $x_{BA1–CN}$ then yields again a fairly linear correlation from which $k_{-1,1} = 9.7 \times 10^{-5}$ s^{-1} and $k_{-1,2} = 1.3 \times 10^{-5}$ s^{-1} is obtained (Figure 6).

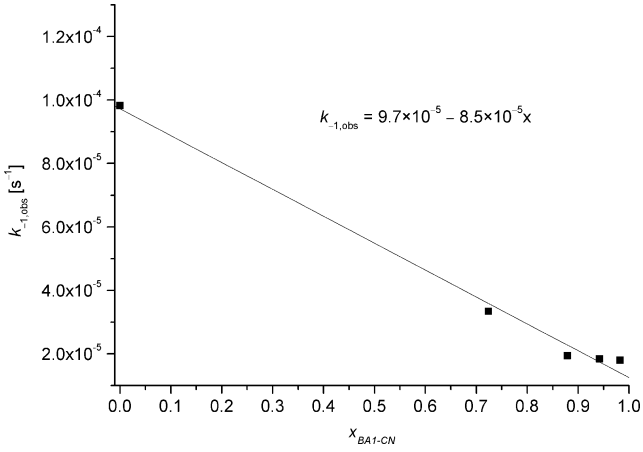


Figure 6. Plot of the observed first-order dissociation rate constant $k_{-1,obs}$ against the mol fraction $x_{BA1–CN}$ of **DAC·BA1–CN**.

In Figure 7 the aforementioned results are summarised. It can be seen that the hydrogen bond formation of **BA1** with **DAC** influences the dissociation rate constant of **BA1–CN** (k_{-1}) more than the recombination rate constant (k_2). This can be attributed to the formation of stronger hydrogen bonds of the anionic **BA1–CN** which results in a larger decrease in electron density at the electrophilic centre compared to the neutral **BA1**. The equilibrium constant K_{Nu} experiences the largest influence by hydrogen bonding as it comprises the opposing effects of both k_2 and k_{-1}.

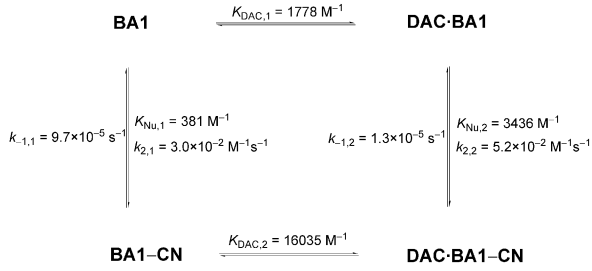


Figure 7. Compilation of the determined equilibrium and rate constants within the mixture of **BA1**, **DAC** and cyanide.

When comparing the effects of hydrogen bond complex formation (**BA1** vs. **DAC·BA1**, Figure 7) and *N*-alkyl substitution (**BA1** vs. **BA2**, Table 1) substantial differences can be recognised. As stated above, hydrogen bond formation has a greater impact on k_{-1} than on k_2 because hydrogen bonds in the anionic product are much stronger than in the neutral substrate. On the other hand, the *N*-(*n*-butyl) group in **BA1** affects mainly the recombination rate constant k_2 while k_{-1} remains almost constant compared to **BA2**. This is due to the weak electron-releasing effect of the alkyl group which is effective in the unreacted substrate but is almost cancelled by the negative charge in the cyanide adduct. As a result, the increase in K_{Nu} by hydrogen bonding complex formation exceeds the decrease by *N*-alkyl substitution which is remarkable regarding the noncovalent nature of hydrogen bonds.

Conclusions

The recombination reaction of the electrophilic barbiturate **BA1** with cyanide was studied in the presence of different amounts of the complementary hydrogen bond receptor **DAC**. Our investigations revealed that the hydrogen bonding leads to a decrease of the electron density in **BA1** which is not limited to the hydrogen bonding site but is also transmitted to a distant electrophilic centre via a conjugated π-system. Photometric measurements showed that both the rate constant and the equilibrium constant of this electrophile-nucleophile recombination increase upon hydrogen bond formation and allowed the calculation of those values for pure **BA1** and the complex **DAC·BA1**.

Experimental Section

General: Dichloromethane was freshly distilled from calcium hydride. Michler's ketone was crystallised several times from ethanol. Tetra-*n*-butylammonium cyanide was dried in vacuo at 50 °C. Tetra-*n*-butylammonium fluoride (1 M solution in THF) and tetra-*n*-butylammonium hydroxide (40% w/w solution in methanol) were used as received. The syntheses of **BA2**[13] and **DAC**[19] were published previously.

Details of the evaluation of the UV/Vis experiments are given in the Supporting Information.

Synthesis of 1-(*n*-Butyl)-5-{bis[4-(dimethylamino)phenyl]methylene}-barbituric Acid (BA1): A solution of Michler's ketone (794 mg, 2.96 mmol) in dichloromethane (10 mL) was treated with triflic anhydride (0.50 mL, 2.96 mmol) and stirred for 10 min. After addition of 1-*n*-butylbarbituric acid (818 mg, 4.41 mmol) stirring continued for 1 h. Afterwards 1,8-diazabicyclo[5.4.0]undec-7-ene (1.00 mL, 6.71 mmol) was added slowly, whereby a highly exothermic reaction occurred, and the mixture was refluxed for 3 h. The solution was washed 10 times with water and the solvent evaporated. The residue was subjected to column chromatography (silica gel, eluent: dichloromethane). The obtained solid was further purified by washing with toluene and dissolving in dichloromethane followed by extraction with water. Greenish shiny crystals (544 mg, 42%); m.p. 228–231 °C. ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 0.92 (t, J = 7.3 Hz, 3 H, 16-H), 1.33 (m, 2 H, 15-H), 1.57 (m, 2 H, 14-H), 3.12 (s, 12 H, 12-H), 3.78 (m, 2 H, 13-H), 6.66 (d, J = 8.9 Hz, 4 H, 10-H), 7.22 (d, J = 8.9 Hz, 4 H, 9-H), 7.86 (s, 1 H, 3-H) ppm. ^{13}C NMR (63 MHz, CD_2Cl_2): δ = 13.7 (C-16), 20.3 (C-15), 30.4 (C-14), 40.0 (C-12), 40.5 (C-13), 105.0 (C-5), 110.5 (C-10), 128.9 (C-8), 136.8 (C-9), 151.2 (C-2), 154.4 (C-11), 162.4 (C-6), 163.5 (C-4), 178.3 (C-7) ppm. $C_{25}H_{30}N_4O_3$ (434.54): calcd. C 69.10, H 6.96, N 12.89; found C 68.70, H 7.10, N 12.45.

NMR Investigation of BA1–CN: A solution of **BA1** in CD_2Cl_2 (0.04 mol L^{-1}) was treated with 1.9 equiv. of tetra-*n*-butylammonium cyanide. After 6 h the solution was only slightly colored and the ^{1}H NMR spectrum showed only signals of the product **BA1–CN**. ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 0.9–1.1 (m, 25.5 H, alkyl), 1.3–1.7 (m, 34 H, alkyl), 2.91 (s, 12 H, 12-H), 3.13 (m, 15 H, alkyl), 3.69 (m, 2 H, 13-H), 6.61 (d, J = 9.0 Hz, 4 H, 10-H), 6.86 (s, 1 H, 3-H), 7.18 (d, J = 9.0 Hz, 4 H, 9-H) ppm. ^{13}C NMR (63 MHz, CD_2Cl_2): δ = 13.9, 14.4, 19.7, 20.5, 30.9, 39.4 (alkyl), 40.6 (C-12), 50.3 (C-7), 58.8 (alkyl), 86.2 (C-5), 111.8 (C-10), 125.6 (cyano), 128.7 (C-8), 132.2 (C-9), 149.2 (C-11), 152.4 (C-2), 161.2 (C-6), 162.9 (C-4) ppm.

Supporting Information (see also the footnote on the first page of this article): Solvatochromic studies of **BA1** and **BA2**, ^{13}C NMR spectra of **BA1** and **BA1–CN**, and detailed evaluation of the UV/Vis experiments.

Acknowledgments

Financial support by the Deutsche Forschungsgemeinschaft (DFG) is gratefully acknowledged.

[1] a) S. Minegishi, R. Loos, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2005**, *127*, 2641–2649; b) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Y. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512; c) F. Seeliger, S. T. A. Berger, G. Y. Remennikov, K. Polborn, H. Mayr, *J. Org. Chem.* **2007**, *72*, 9170–9180.

[2] a) R. Ahuja, P.-L. Caruso, D. Möbius, W. Paulus, H. Ringsdorf, G. Wildburg, *Angew. Chem.* **1993**, *105*, 1082–1085; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1033–1036; b) T. M. Bohanon, P.-L. Caruso, S. Denzinger, R. Fink, D. Möbius, W. Paulus, J. A. Preece, H. Ringsdorf, D. Schollmeyer, *Langmuir* **1999**, *15*, 174–184.

[3] For a recent review see: L. J. Prins, P. Scrimin, *Angew. Chem.* **2009**, *121*, 2324–2343; *Angew. Chem. Int. Ed.* **2009**, *48*, 2288–2306.

[4] N. J. Pienta, R. J. Kessler, *J. Am. Chem. Soc.* **1993**, *115*, 8330–8339.

[5] X. Chen, J. I. Brauman, *J. Am. Chem. Soc.* **2008**, *130*, 15038.

[6] A. M. Kelly-Rowley, V. M. Lynch, E. V. Anslyn, *J. Am. Chem. Soc.* **1995**, *117*, 3438–3447.

[7] a) E. Breinlinger, E. Niemz, V. M. Rotello, *J. Am. Chem. Soc.* **1995**, *117*, 5379–5380; b) M. Gray, A. O. Cuello, G. Cooke, V. M. Rotello, *J. Am. Chem. Soc.* **2003**, *125*, 7882–7888.

[8] L. M. Goldenberg, O. Neilands, *J. Electroanal. Chem.* **1999**, *463*, 212.

[9] I. Bolz, S. Spange, *Chem. Eur. J.* **2008**, *14*, 9338–9346.

[10] V. Berl, I. Huc, J.-M. Lehn, A. DeCian, J. Fischer, *Eur. J. Org. Chem.* **1999**, 3089–3094.

[11] R. Bednar, O. E. Polansky, P. Wolschann, *Z. Naturforsch., Teil B* **1975**, *30*, 582–586.

[12] L. Yu, H.-J. Schneider, *Eur. J. Org. Chem.* **1999**, 1619–1625.

[13] M. Bauer, A. Rollberg, A. Barth, S. Spange, *Eur. J. Org. Chem.* **2008**, 4475–4481.

[14] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH, Weinheim, **2003**.
[15] J. Catalán, *J. Phys. Chem. B* **2009**, *113*, 5951–5960.
[16] J. R. Quinn, S. C. Zimmerman, J. E. Del Bene, I. Shavitt, *J. Am. Chem. Soc.* **2007**, *129*, 934–941.
[17] D. Esteban-Gómez, L. Fabrizzi, M. Licchelli, *J. Org. Chem.* **2005**, *70*, 5717–5720.
[18] T. Chin, Z. Gao, I. Lelouche, Y. K. Shin, A. Purandare, S. Knapp, S. S. Isied, *J. Am. Chem. Soc.* **1997**, *119*, 12849–12858.
[19] K. Kurita, R. L. Williams, *J. Heterocycl. Chem.* **1975**, *12*, 789–791.

Received: September 18, 2009
Published Online: December 3, 2009

