Electrophilicity

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Adjustable Electrophilicity by Cooperative Hydrogen Bonds**

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The alteration of a substrate's reactivity by supramolecular interactions, especially the formation of hydrogen bonds, is a common principle in nature: numerous reactions are efficiently catalyzed by enzymes. To understand and use this principle, a number of model systems has been developed which, however, mainly focus on the preorganizing template effects of hydrogen bonds.[1] Their impact on the reactivity of a substrate by influencing its electronic structure has been studied less intensely.[2,3] These few known systems have in common that hydrogen bonding occurs directly at the reactive center so that charges can be well stabilized. Beyond that we were interested in the question whether electronic effects arising from formation of defined hydrogen bonds can be transmitted to a distant, yet electronically coupled, reactive center? For this purpose, a simple electrophile–nucleophile combination provides a suitable model reaction as it often follows well-defined second-order kinetics and is very sensitive to electronic effects. The general principle underlying this question is depicted in Figure 1.

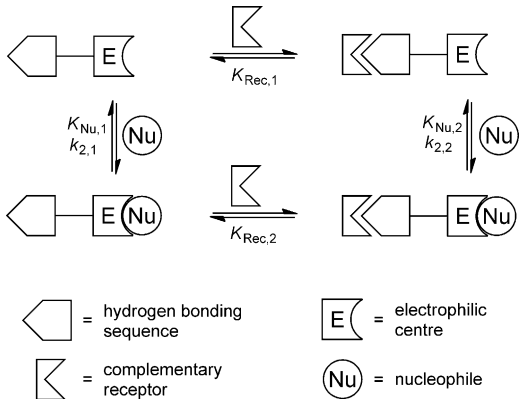
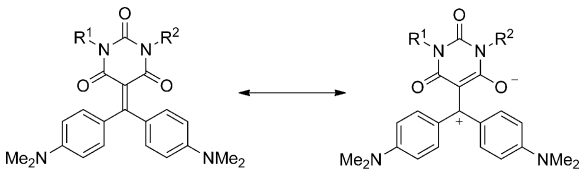


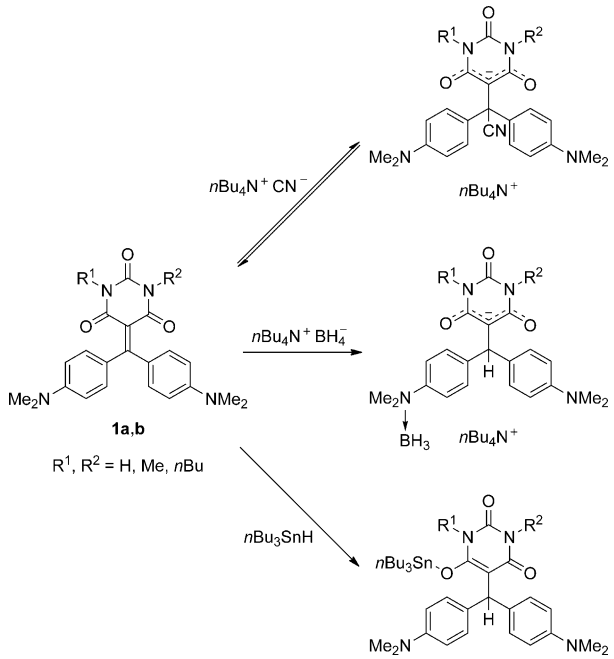
Figure 1. Combination of an electrophilic center with a hydrogen-bonding motif and their mutual influence.

As model electrophiles we used the barbiturate merocyanines **1a**[4] and **1b**[5] shown in Scheme 1. These may also be described by zwitterionic resonance structures which explains the strong polarization of the central C–C double bond. The associated electron deficiency at the β carbon atom is reflected in the characterization of such compounds as Lewis acids[6] and electrophiles.[7] These intensely colored barbiturates react with different nucleophiles (tetra-*n*-butylammonium boranate (TBABH), tetra-*n*-butylammonium cyanide (TBACN) and tri-*n*-butyltin hydride (TBTH)) in dichloromethane (DCM) to form colorless products (Scheme 2).[8] Therefore, the progress of the reaction can easily be monitored using UV/Vis spectroscopy. At the same time, the acceptor–donor–acceptor (ADA) hydrogen-bonding sequence of the mono-N-alkylated derivative **1a** allows for the complexation of several complementary receptors which differ in their electronic properties as well as their



1a: R^1 = *n*Bu, R^2 = H
1b: R^1 = R^2 = Me

Scheme 1. Molecular structure of the electrophilic merocyanines **1a**,**b** employed in this study.



Scheme 2. Reaction of **1a**,**b** with different nucleophiles in CH_2Cl_2.

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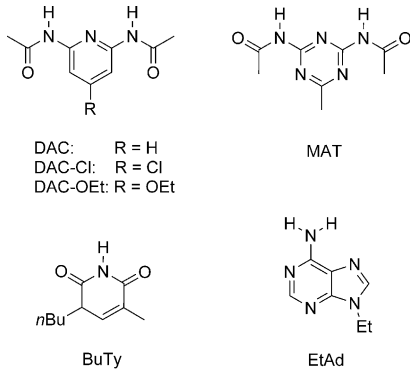
number of hydrogen-bonding sites (Scheme 3). The association constants of this complex formation were determined by UV/Vis and NMR titration experiments (Table 1).



Scheme 3. Molecular structure of the receptors employed in this study.

Table 1: Association constants and free complexation enthalpies of several **1a**–receptor complexes in CH_2Cl_2.

Receptor	K_A [M^{-1}]	$\Delta G°_{Rec}$ [kJ mol^{-1}]
DAC-Cl	2362[a]	−18.9
DAC	1778[a]	−18.2
DAC-OEt	1644[a]	−18.0
MAT	156[a]	−12.3
EtAd	43[b]	−9.2
BuTy	15[b]	−6.6

[a] determined by UV/Vis titration. [b] Determined by NMR titration

The triple hydrogen-bonded 2,6-diacetamidopyridine (DAC) derivatives have rather high association constants of about $2\times10^3\,M^{-1}$, which can be explained with the partial negative charge at the barbiturate carbonyl groups. With the increasing electron demand of the receptor substituent the acidity of its NH moieties and therefore the complex stability increases in the order DAC-OEt < DAC < DAC-Cl. Owing to the preference of the *s-cis* conformation of the amide groups in MAT[9] and the resulting destabilizing secondary interactions this receptor binds to **1a** to a much lesser extent. The stability of the complex with the nucleic acid derivatives EtAd and BuTy is even lower as they can only form two hydrogen bonds.

The attack of cyanide upon **1a** is an equilibrium reaction which has been studied in detail.[4] The other two nucleophiles react quantitatively, so that solely the rate constant $k_{2,1}$ is accessible (see Table 2). The determined values for $k_{2,1}$ do not correlate with the nucleophilicity parameters N of Mayr et al.[11] which can partly be attributed to the different reference solvents. However, the stannane TBTH reacts several orders of magnitude faster than expected. This may be due to a preorganizing coordination of the metal center by the barbiturate carbonyl groups.[10] The influence of such a coordination is exemplified by comparison with the reactivity of the borane triethylamine complex $H_3B{\cdot}NEt_3$ ($N=8.9$[11a]): it is nearly as reactive as TBTH ($N=10.0$) but has no free coordination site and therefore does not react even after several days.

Table 2: Nucleophilicity parameters of the nucleophiles employed,[11] rate constants of their reaction with **1a** ($k_{2,1}$) and DAC·**1a** ($k_{2,2}$), and difference of the free activation enthalpies in CH_2Cl_2.

Nucleophile	N (s)	$k_{2,1}$ [$M^{-1}s^{-1}$]	$k_{2,2}$ [$M^{-1}s^{-1}$]	$\Delta\Delta G^{+}_{Nu}$ [kJ mol^{-1}]
TBACN	16.3 (0.70)[a]	0.014	0.049	−3.1
TBTH	10.0 (0.55)[b]	0.040	0.107	−2.4
TBABH	14.9 (0.79)[c]	0.048	0.186	−3.4

[a] In acetonitrile. [b] In CH_2Cl_2. [c] In DMSO

When these electrophile–nucleophile combinations are carried out in the presence of the receptor DAC an acceleration of the reaction is observed in all cases. As the equilibration of hydrogen-bonded complexes occurs much faster than the nucleophilic attack, the observed rate constant $k_{2,obs}$ can be treated as the weighted average of free and complexed **1a** and thus be described by Equation (1). Accordingly, a plot of $k_{2,obs}$ against the molar fraction of DAC-complexed **1a**, x, shows a linear relationship (Figure 2). The rate constants of the reaction of free **1a** ($k_{2,1}$) and DAC·**1a** ($k_{2,2}$) are then calculated by extrapolation to $x=0$ and $x=1$, respectively (see Table 2).

$$k_{2,obs} = (1-x)\,k_{2,1} + x\,k_{2,2} \quad (1)$$

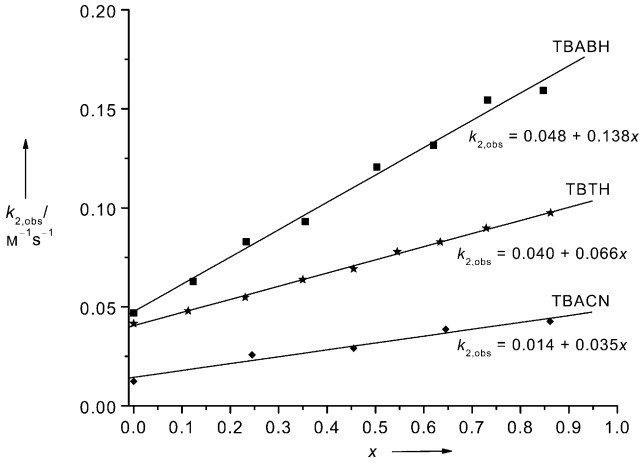


Figure 2. Rate constants $k_{2,obs}$ of the reaction of **1a** with different nucleophiles in the presence of the receptor DAC as a function of the molar fraction x of DAC-complexed **1a**.

Upon complexation of the electrophile with DAC, the free activation enthalpy for all three nucleophiles is lowered by about 3 kJ mol^{-1} corresponding to a decrease of the reaction time to one third of its original value. This effect is not dependent on the structure of the products. Thus, it can be concluded that it is not only due to the stabilization of the **1a**–nucleophile adduct by complexation with DAC. Instead, the redistribution of electron density in the transition state by hydrogen bonding has significant impact on the reaction rate.

In principle, interfering effects may arise from interactions between the nucleophile and the receptor. These can be assessed using the N,N′-dialkylated electrophile **1b** which cannot form a receptor complex. Within the error limit, the rate of the nucleophilic attack upon **1b** and a mixture of **1b** and a receptor is equal. Hence, interactions of this kind are presumed to be not relevant. The same result is obtained from NMR spectra where no signals are shifted when adding TBACN or TBABH to DAC.

As TBABH evokes the strongest effect, this nucleophile was chosen for further investigations to evaluate the influence of the number and strength of the formed hydrogen bonds. Again, when using other receptors with a DAD hydrogen-bonding motif, a linear dependence of $k_{2,obs}$ on x is observed (Figure 3). The slope, and therefore the electrophilicity of the

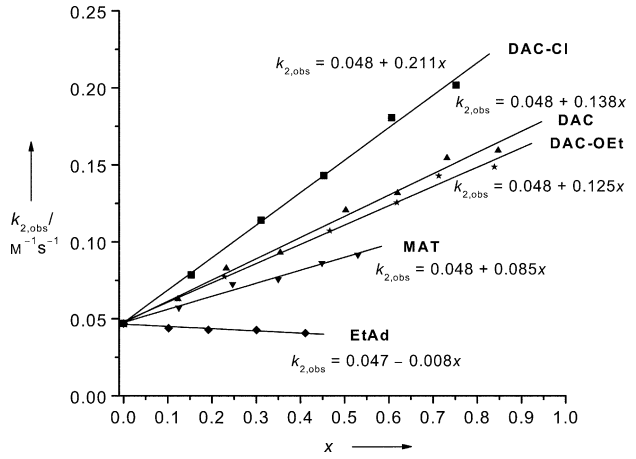


Figure 3. Rate constants $k_{2,obs}$ of the reaction of **1a** with TBABH in the presence of various receptors as a function of the molar fraction x of receptor-complexed **1a**.

1a–receptor complexes, increases with increasing complex stability (see Table 3). So the strength of the hydrogen bonds, which correlates with the association constant, has a significant impact on the electron density of the substrate and thus on its reactivity. Even the rather weak complex MAT·**1a** shows a considerable increase in reactivity. As displayed in Figure 4 there is a nearly linear relationship between the free enthalpy of the complex formation and the free activation enthalpy of the nucleophile addition.

Studies by Rotello et al. indicate that of the different energetic components of a hydrogen bond, the polarization term is mainly responsible for changes of the electronic structure of a hydrogen-bonded substrate.[3b,12] Within the substrate it induces a shift of electron density towards the

Table 3: Comparison of the rate constants and free activation enthalpies of the reaction of various **1a**–receptor complexes with TBABH.

Receptor	$k_{2,2}$ [$M^{-1}s^{-1}$]	$\Delta\Delta G^{\neq}_{Nu}$ [kJ mol^{-1}]
DAC-Cl	0.258	−4.1
DAC	0.186	−3.4
DAC-OEt	0.174	−3.2
MAT	0.132	−2.5
EtAd	0.039	+0.5

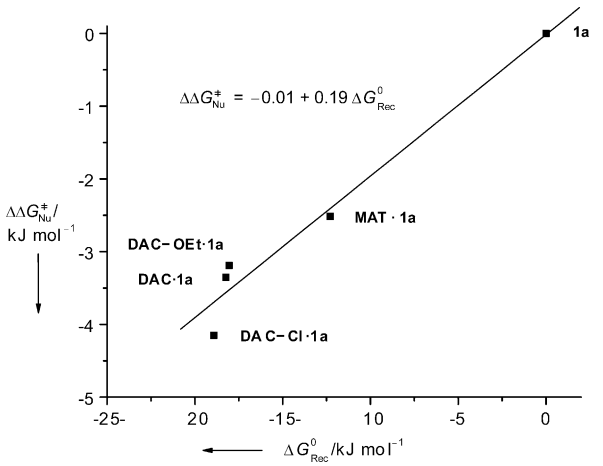


Figure 4. Difference of the free activation enthalpies of the nucleophilic attack at **1a**–receptor complexes as a function of the free complex-formation enthalpies of these complexes.

acceptor group enhancing the polarization of the molecule and thus enlarging the electron deficiency at the electrophilic center. This effect gets stronger with increasing electron deficiency of the hydrogen-bond donor, which results in a higher binding energy of the hydrogen bond. Thus, both complex stability and electrophilicity increase in the order DAC-OEt < DAC < DAC-Cl. The receptor MAT is not fully comparable to the DAC derivatives owing to its different secondary interactions. Yet, its results fit well into the correlation of Figure 4.

A special situation occurs with the nucleic acid derivatives because they provide no DAD sequence, only a donor–acceptor (DA) motif. While the receptor BuTy has no measurable effect on the rate constant, EtAd shows an unexpected behavior: a decrease of the electrophilicity of **1a**. A probable explanation is provided by the occurrence of several isomeric complexes. In the Watson–Crick and Hoogsteen complex a similar accelerating effect as found for the DAD complexes should occur. However, in both reverse geometries no hydrogen bond is formed to the carbonyl group at C4 which neighbors the C–C double bond. Then, the formation of a hydrogen bond at the barbiturate NH group leads to an increase in electron density which in turn results in the observed deceleration of the recombination reaction. With regard to the higher stability of the Hoogsteen pair,[13] in our system the reverse-Hoogsteen complex is assumed to be the dominant species (see Supporting Information for further information).

In ternary systems consisting of an electrophile with a molecular recognition site, a complementary receptor, and a nucleophile, we could show for the first time that electronic changes induced by the formation of defined hydrogen-bonded complexes can be transmitted to a distant reactive center. Thus, an alteration of the substrate's electrophilicity is achieved whose direction (accelerating or decelerating) can be determined by a variation of the hydrogen-bonding sequence of the receptor. Furthermore, electronic effects within the receptor influence the strength of the hydrogen bonds which also has a marked impact on the electrophilic

center. In principle, this enables an infinitely variable adjustment of the reactivity of a substrate which may open up new perspectives in organocatalysis and contribute to our understanding of enzymatic activity.

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