Tautomeric Switches

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Exploiting Tautomerism for Switching and Signaling**

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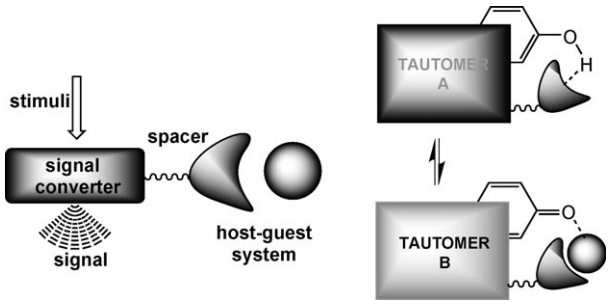
Herein, we demonstrate a conceptual idea for a tautomeric switch based on implementation of a flexible piperidine unit in 4-(phenyldiazenyl)naphthalen-1-ol. The results show that a directed shift in the position of the tautomeric equilibrium can be achieved through protonation/deprotonation in a number of solvents. The developed molecular switch, in spite of the simple host–guest system, has shown acceptable complexation ability towards small alkali- and alkaline-earth-metal ions and can be a promising basis for further development of effective molecular sensors through implementation of azacrown ethers.

Organic molecular materials are increasingly recognized as suitable molecular-level elements (such as switching, signaling, and memory elements[1]) for molecular devices, because the wide range of molecular characteristics can be combined with the versatility of synthetic chemistry to alter and optimize molecular structure in the direction of desired properties. Virtually every molecule changes its behavior when acted upon by external fields or other stimuli. True molecular switches undergo reversible structural changes, caused by a number of influences, which give a variety of possibilities for control. Several classes of photoresponsive molecular switches are already known; these operate through processes such as bond formation and bond breaking, *cis–trans* isomerization, and photoinduced electron transfer upon complexation.[2] A conceptual scheme of a molecular switch based on molecular recognition is shown in Scheme 1. The host–guest system represents, for instance, a crown ether that can bind ions or a cyclodextrin that can bind other small molecules. It is bound to a signal converter. The complexation behavior is monitored by the state of the signal converter, and in turn its optical or electronic properties are determined by the complexation state of the host–guest system.



Scheme 1. Molecular switch based on molecular recognition (left) and conceptual idea for a tautomerism-based molecular switch (right).

The main requirement in the design of new molecular switches is to provide fast and clean interconversion between structurally different molecular states (on and off). Tautomerism could be a possibility, because change in the tautomeric state can be accomplished by a fast proton transfer reaction between two or more structures, each of them with clear and different molecular properties.[3] Therefore, our aim herein is to show how tautomerism can be exploited for signal conversion. The conceptual idea of such a device is presented in Scheme 1. In this structure, a change in tautomeric state, labeled A and B, is linked to changes in the complexation abilities of the host–guest system by modulating the propensity of the system to hydrogen bond to the antenna. At the same time, engagement of this antenna causes a change in the tautomeric state. The sensitivity of the electronic ground and excited states of the tautomeric forms to environment stimuli (light, pH value, temperature, solvent) and to the presence of a variety of substituents or to hydrogen bonding can be exploited in the design of flexible tools for control.

Obviously, such a device should be based on a tautomeric structure with easy proton exchange between the tautomers, which means that they must coexist in solution. At the same time, a main feature of systems of tautomers coexisting in solution is that the overall optical response is a mixture of the optical responses of the individual tautomers. Consequently, in the design of tautomeric switches, conditions for obtaining pure end tautomer in the corresponding off and on states must be provided.

Herein we report the properties of two tautomeric switches, namely **3** and **4** (Scheme 2), based on 4-(phenyldiazenyl)phenol (**1**) and 4-(phenyldiazenyl)naphthalen-1-ol (**2**).

The parent compound **2** is the first dye that was shown to tautomerize by Zincke and Bindewald in 1884.[4] It has been the object of many spectral and theoretical studies[5] because its tautomeric forms coexist in solution and the equilibrium

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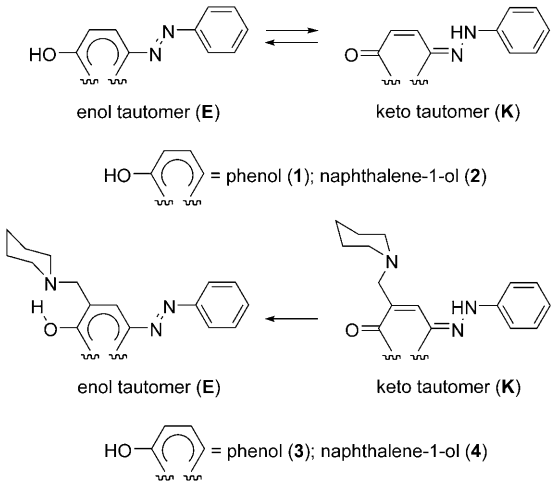


Scheme 2. Tautomeric equilibria in compounds **1**–**4**.

can be markedly shifted by changing the solvent environment. However, the pure individual tautomers have never been observed at room temperature.

For the phenol analogue **1**, the relatively unstable keto form cannot be detected.[6] Relative stabilities[7] of the **K** and **E** tautomers in **1**–**4** were calculated at the HF/6-31G** level of theory, which was found to give acceptable results for this class of compounds.[5] The energy difference between the tautomeric forms in **1** is large, accounting for the absence of the keto tautomer **K** in appreciable concentration (Figure S1 in the Supporting Information). In the case of **2**, the moderate energy gap allows both tautomeric forms to be observed (Figure 1).[5] The piperidine moiety in compounds **3** and **4** stabilizes the enol forms **E** relative to the keto forms **K**.

The absorption spectra of **1**–**4** shown in Figure 2 and the estimated tautomeric constants for **2** and **4** collected in Table 1 fully support the theoretical expectations. In both **1** and **3** only the absorption maximum of the enol form around 350 nm is observed, irrespective of the solvent. The tautomeric equilibrium in **2** is strongly solvent-dependent. Polar solvents favor the **K** tautomer, but specific solute–solvent interactions can have the opposite effect.[8] For instance, chloroform stabilizes the more polar **K** tautomer through hydrogen bonding with the carbonyl oxygen atom, while the more polar acetone shifts the equilibrium towards the less polar enol form. However, the individual, pure tautomers cannot be obtained under any conditions.

The addition of the piperidine fragment in **4** changes the situation dramatically. Hydrogen bonding between the piperidine nitrogen atom and the enol OH group shifts the equilibrium fully (within the detection limits, see Figure S2 in the Supporting Information) to the enol form in most solvents. The data given in Table 1 show that in acetone, chloroform, and acetonitrile (ACN), where a substantial amount of the keto form of **2** is available**, 4K** is not presented. In solvents with both proton donor and acceptor properties (alcohols

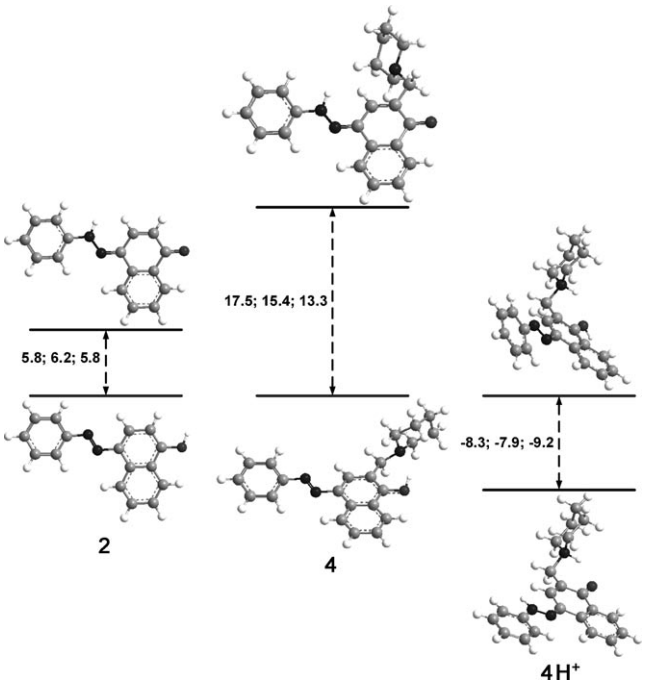


Figure 1. Change of the relative energy (HF/6-31G**) of the tautomers of **2**, **4**, and **4**H^+. The values of ΔE, $\Delta E + ZPE$, and $\Delta\Delta G$ are given in kJ mol^{-1}.

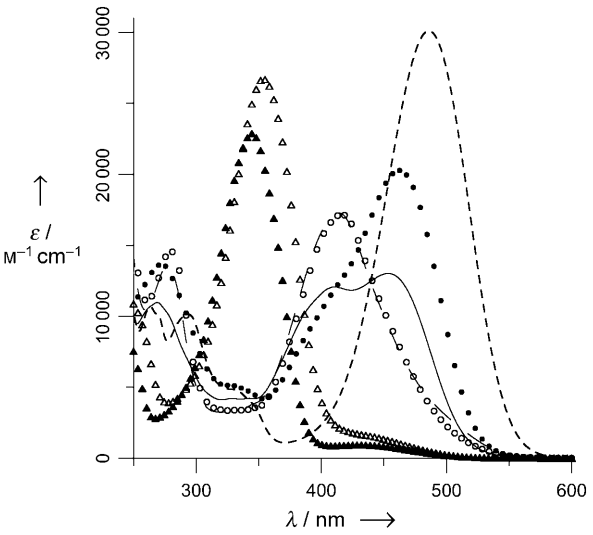


Figure 2. Absorption spectra of **1**–**4** in various solvents: **1** (▲) and **3** (△) in acetonitrile, **2** in acetonitrile (——) and chloroform (●), **4** in acetonitrile (– – –) and chloroform (○), **4**H^+ in acetonitrile (-----).

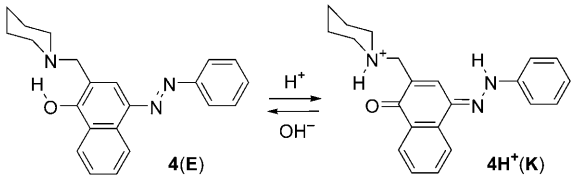
Table 1: Tautomeric constants ($K_T = [\mathbf{K}]/[\mathbf{E}]$)[a] of **2** and **4** in selected solvents at room temperature.

	I[b]	II	III	IV	V	VI
2	0.09 (5.94)[c]	1.34 (−0.71)	0.37 (2.42)	0.20 (3.97)	0.49 (1.75)	0.57 (1.38)
4	< 0.005 (> 13)	0.08 (6.23)	0.04 (7.95)	0.17 (4.35)	0.43 (2.09)	0.08 (6.23)

[a] See Ref. [10]. [b] Solvents (dielectric constants): I cyclohexane (2.02), II $CHCl_3$ (4.90), III acetone (20.7), IV absolute ethanol (24.5), V methanol (32.6), VI acetonitrile (36.6). [c] Calculated ΔG values (kJ mol^{-1}) are given in parentheses.

and water), the keto form is present in detectable amounts, approximately the same as in **2**. Moreover, the mass spectrum of **4** shows fragmentation that is typical for the enol form (see Supporting Information).[9]

As suggested from Figure 1, the protonation of the piperidine nitrogen atom is a suitable tool to switch the equilibrium from pure enol to pure keto form. The calculated relative energies of **K** and **E** in compound **4** change from 17.5 to $-8.3\ \mathrm{kJ\,mol^{-1}}$ upon protonation of the piperidine nitrogen atom ($pK_a = 6.5$ in ACN). The keto form is stabilized through hydrogen bonding with the carbonyl oxygen atom (Scheme 3). Indeed, the equilibrium switches from enol to ketone, as is apparent from the spectra of **4** and $\mathbf{4}H^+$ in



Scheme 3. Protonation of **4**.

acetonitrile (Figure 2). The conjugate acid $\mathbf{4}H^+$ exhibits a new absorption band at 480 nm with twice the molar absorptivity of the most intense band of **4**. Further addition of acid (pH < 3) leads to protonation of the tautomeric fragment, resulting in the appearance of a new band at approximately 540 nm (Figure S3 in the Supporting Information). The same band is observed in acidic solutions of **2** (Figure S4 in the Supporting Information).

Because the piperidine fragment is attached to the azonaphthol moiety through a saturated spacer, the absorption spectra of **4** and $\mathbf{4}H^+$ in acetonitrile are nearly identical to those of the pure **E** and **K** tautomeric forms of **2**, respectively, which have been determined by an advance curve-fitting procedure in ethanol.[11] This chemometric procedure estimates the positions of **2E** and **2K** as 407 ($\varepsilon = 15\,500\ \mathrm{M^{-1}\,cm^{-1}}$) and 480 nm ($\varepsilon = 34\,400\ \mathrm{M^{-1}\,cm^{-1}}$), in close agreement with the spectral maxima of **4** ($\lambda_{max} = 413$ nm, $\varepsilon = 15\,600\ \mathrm{M^{-1}\,cm^{-1}}$) and $\mathbf{4}H^+$ (λ_{max} 486 nm, $\varepsilon = 31\,400\ \mathrm{M^{-1}\,cm^{-1}}$) in acetonitrile. Thus, **4** is a tautomeric device, in which the tautomeric equilibrium can be switched by the addition of acid or base. Hence, the concept for a tautomerism-based molecular switch, described in Scheme 1, works.

The complexation of **4** with alkali- and alkaline-earth-metal perchlorates was investigated spectrophotometrically (see Figure 3 as a typical representation of the process), and the corresponding stability constants of the complexes are listed in Table 2. As expected, the complexation ability decreases sharply with increasing ion radius. From a spectral point of view (Figure 3), complex formation is accompanied by the appearance of a band at 486 nm, exactly where $\mathbf{4}H^+$ absorbs, and by the disappearance of the enol band at 413 nm. Owing to the very limited solubility of $BeSO_4$ in dry ACN it was not possible to measure the stability constant in ACN, but we have detected complex formation in acetonitrile/water 1:1, thus indicating a potentially large stability constant in ACN. No complex was detected in the same solvent mixture with $Mg(ClO_4)_2$ up to a pM value of 1.5.

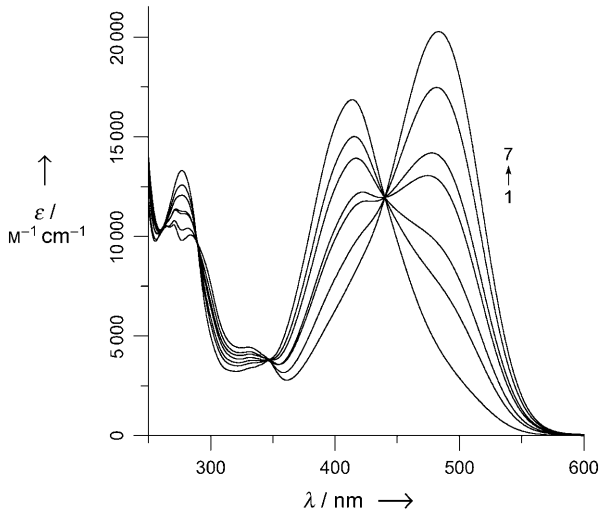


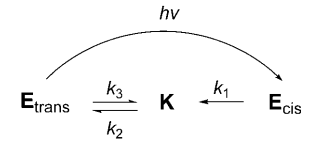
Figure 3. Spectrophotometric titration of **4** with $Mg(ClO_4)_2$ in dry acetonitrile. Concentration of the salt: 0, 6.63×10^{-6}, 6.63×10^{-5}, 1.32×10^{-4}, 3.31×10^{-4}, 3.98×10^{-4}, $5.30\times10^{-4}\ \mathrm{mol\,L^{-1}}$.

Table 2: Stability constants ($\log\beta$) of the complexes of **4** with alkali- and alkaline-earth-metal ions (as perchlorate salts) in dry ACN.[a]

	Li^+	Na^+	K^+	Be^{2+}[b]	Mg^{2+}	Ca^{2+}
4	0.63 ± 0.08	ca. -0.5	–	2.30 ± 0.03	3.43 ± 0.13[c]	ca. 1.0

[a] Estimated using the spectra of **4** and $\mathbf{4}H^+$ as references. [b] As sulfate in ACN/H_2O 1:1. [c] No complex detected in ACN/H_2O 1:1.

How does the addition of the piperidine fragment influence the proton exchange rate? In previous flash photolysis studies,[12] it has been found that the **E** form undergoes light-induced *trans–cis* isomerization (Scheme 4), whereas the keto tautomer does not show any detectable transient signal. The *cis* enol tautomer does not undergo direct *cis–trans* relaxation. Rather, it proceeds by tautomerization to the **K** form to restore the thermal-equilibrium tautomeric ratio. The process of relaxation of $\mathbf{E}_{cis}$ to **K** is thus governed by the rate constant k_1 for the reaction $\mathbf{E}_{cis}\rightarrow\mathbf{K}$, and the restoration of the tautomeric equilibrium is defined by $k_{II} = k_2 + k_3$.



Scheme 4. Kinetic scheme of the relaxation of excess $\mathbf{E}_{cis}$ generated by flash photolysis.

A typical kinetic curve obtained with **4** in methanol is shown in Figure 4. A fast process of accumulation of the keto tautomer is followed by a slower process of returning to the equilibrium state. The corresponding rate constants for **1**–**4** are collected in Table 3. Solutions of $\mathbf{4}H^+$ do not show any transients, a behavior that is typical for the keto tautomer.[12]

As seen, the implementation of the flexible piperidine unit assists proton transfer, increasing the k_{II} values substan-

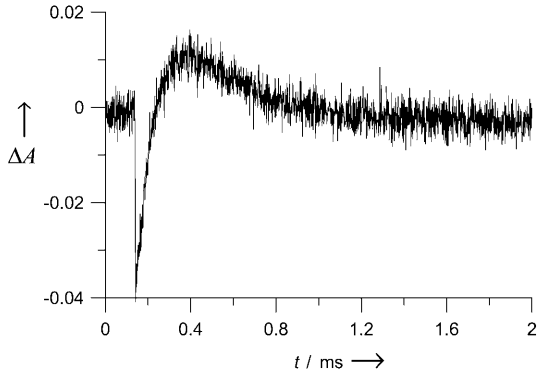


Figure 4. Time dependence of the transient absorption of the solution of **4** in methanol at 500 nm.

Table 3: Rate constants of **1**–**4** in methanol.

Compound	k_I [s^{-1}]	k_{II} [s^{-1}]	λ_{obs} [nm]
1	–[a]	$2.40 \pm 0.02 \times 10^{0}$	425
2	$2.78 \pm 0.04 \times 10^{2}$	$2.00 \pm 0.07 \times 10^{2}$	500
3	–[a]	$3.62 \pm 0.05 \times 10^{2}$	425
4	$1.12 \pm 0.04 \times 10^{4}$	$3.21 \pm 0.15 \times 10^{3}$	500

[a] Too fast to be measured with the available setup.

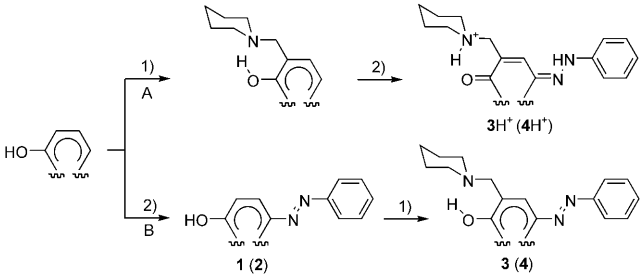
tially. Probably, the piperidine nitrogen atom acts as a proton crane, as has been described for 7-hydroxy-8-(*N*-morpholinomethyl)quinoline.[13] The fact that proton exchange is facilitated could be supported by the change in the position in the tautomeric equilibrium in **3** with addition of water (Figure S5 in the Supporting Information), which cannot be achieved in the parent compound **1**.

By the attachment of a flexible piperidine fragment to **2**, we were able to demonstrate the concept of a tautomeric switch, in which a directed shift in the position of the tautomeric equilibrium is achieved either by protonation or by complexation with small alkali- or alkaline-earth-metal ions in a number of solvents. The system holds promise for the development of effective molecular sensors through the implementation of suitable host–guest systems.

Experimental Section

The title compounds **3** and **4** were obtained by two independent pathways (Mannich reaction then diazo coupling or the reverse sequence) by the protocols summarized in Scheme 5. The position of the absorption band in the spectra of the products showed that the protonated forms were isolated from diazo coupling of intermediates (pathway A), while Mannich reaction of **1** or **2** (pathway B) led directly to the desired deprotonated products. To our knowledge, there is no record of the synthesis of **3**, while only one paper reports on the preparation of **4** by pathway A,[14] where $\mathbf{4}H^+$ was isolated, as indicated by the surprising shift of the long-wavelength absorption band. The deprotonation of $\mathbf{3}H^+$ and $\mathbf{4}H^+$ was achieved by treatment of acetonitrile solutions with aqueous ammonia and subsequent selective extraction with cyclohexane.

Experimental procedures, characterization data, and NMR spectra for all compounds are provided in the Supporting Information along with the details for the spectral measurements and data fitting as well as for the quantum chemical calculations.



Scheme 5. Synthesis of azo compounds $\mathbf{3}H^+$($\mathbf{4}H^+$) and **3**(**4**). 1) HCHO, piperidine, *p*-toluenesulfonic acid, benzene; 2) $PhNH_2$, conc. HCl, $NaNO_2$, H_2O, acetone.

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[1] *Electron Transfer in Chemistry*, *Vol. 1* (Eds.: V. Balzani, P. Piotrowiak, M. A. J. Rodgers, J. Mattay, D. Astruc, H. B. Gray, J. Winkler, S. Fukuzumi, T. E. Mallouk, Y. Hass, A. P. de Silva, I. Gould), Wiley-VCH, Weinheim, **2001**; *Molecular Switches*, *Vol. 1* (Ed. B. L. Feringa), Wiley-VCH, Weinheim, **2001**.
[2] J. Andreasson, S. D. Straight, T. A. Moore, A. L. Moore, D. Gust, *J. Am. Chem. Soc.* **2008**, *130*, 11122–11128.
[3] *Hydrogen-Transfer Reactions*, *Vol. 1* (Eds.: J. T. Hynes, J. P. Klinman, H. H. Limbach, R. L. Schowen), Wiley-VCH, Weinheim, **2007**.
[4] T. Zincke, H. Bindewald, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 3026–3033.
[5] D. Nedeltcheva, L. Antonov, A. Lycka, B. Damyanova, S. Popov, *Curr. Org. Chem.* **2009**, *13*, 217–240; I. Sheikhshoaie, W. M. F. Fabian, *Curr. Org. Chem.* **2009**, *13*, 147–171.
[6] J. N. Ospenson, *Acta Chem. Scand.* **1951**, *5*, 491–509.
[7] The relative energies in the gas phase are defined as follows: $\Delta E = E_{\mathbf{K}} - E_{\mathbf{E}}$, $\Delta\Delta G = \Delta G_{\mathbf{K}} - \Delta G_{\mathbf{E}}$. Negative values correspond to a more stable **K** form. ZPE is the abbreviation of zero-point energy correction. See the Supporting Information for computational details.
[8] W. M. F. Fabian, L. Antonov, D. Nedeltcheva, F. S. Kamounah, P. J. Taylor, *J. Phys. Chem.* **2004**, *37A*, 7603–7612.
[9] D. Nedeltcheva, V. Kurteva, B. Damyanova, S. Popov, *Rapid Commun. Mass Spectrom.* **2009**, *23*, 1727–1734.
[10] The tautomeric constants for **2** and **4** have been estimated according to the chemometric procedure described in reference [11]. In the case of **4**, the tautomeric ratio has been estimated additionally using the spectra of **4** and $\mathbf{4}H^+$ in ACN as spectra of the enol and keto tautomers, respectively.
[11] S. Stoyanov, L. Antonov, B. Soloveytchik, V. Petrova, *Dyes Pigm.* **1994**, *26*, 149–158; L. Antonov, D. Nedeltcheva, *Chem. Soc. Rev.* **2000**, *29*, 217–227; L. Antonov, S. Stoyanov, *Anal. Chim. Acta* **1995**, *314*, 225–232.
[12] P. Jacques, *Dyes Pigm.* **1988**, *9*, 129–135, and references therein.
[13] C. J. Jalink, A. H. Huizer, C. A. G. O. Varma, *J. Chem. Soc. Faraday Trans.* **1992**, *88*, 1643–1651; E. J. A. de Bekker, A. Pugzlys, C. A. G. O. Varma, *J. Phys. Chem. A* **2001**, *105*, 399–409.
[14] W. E. Hahn, J. Weglewski, *Acta Chim.* **1966**, *11*, 67–74.

