Published in "RSC Advances 3(47): 25410–25416, 2013"
which should be cited to refer to this work.

Controlled tautomerism – switching caused by an "underground" anionic effect†

Liudmil Antonov,*[a] Vera Deneva,[a] Vanya Kurteva,[a] Daniela Nedeltcheva,[a] Aurelien Crochet[b] and Katharina M. Fromm[b]

In a previous communication, we demonstrated a conceptual idea for a tautomeric switching system based on implementation of a flexible piperidine unit in 4-(phenyldiazenyl)naphthalen-1-ol (**1**). The results showed that a directed shift in the position of the tautomeric equilibrium can be achieved through protonation/deprotonation in a number of solvents. However, the effect of the counter ion in the process of protonation was never considered. The crystallographic analysis of protonated cyano and nitro derivatives of 4-(phenyldiazenyl)-2-(piperidin-1-ylmethyl)naphthalen-1-ol have shown an interesting and unexpected feature: the counter ion is captured in the process of protonation and the shift in the position of the tautomeric equilibrium is achieved through a bridged complex formation. To the best of our knowledge this is a rare example when controlled shift in the position of tautomeric equilibrium is achieved through anion complexation. The results from the solid state analyses are confirmed by NMR spectroscopy in solution and by quantum-chemical calculations.

Introduction

The development of molecular devices is an exciting and promising idea,[2] which might establish the necessary ground for a technological jump in the future. The concept is based on the use of single molecules as building "hardware" elements (wires, switches, rectifiers, *etc.*) and their further suitable assembly into working devices by using chemical bonding or by intra-/intermolecular forces.[3] The quest for finding such molecular level "hardware" has increased dramatically over the last decade[4] and the main emphasis is given to organic and hybrid systems, because the wide range of molecular propensities can be combined with the versatility of synthetic chemistry to alter and optimize molecular structure in the direction of desired properties.

Virtually, every single molecule changes its behavior when acted upon by external stimuli, but its use as a molecular switch is possible only if these changes are reproducible, reversible and can be explicitly controlled and monitored.[5] There are many types of molecular switches known nowadays like photochromic systems, which are able to switch between electronic configurations when irradiated by light at a specific wavelength, host-guest molecular switches in which the compound is able to take up cations after a photochemical trigger and the most advanced ones – mechanically interlocked molecular switches, where the bistable states differ in the position of the macrocycle.[6]

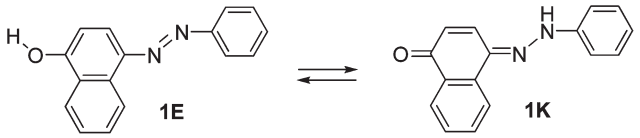
The main requirement in the design of new molecular switches is to provide fast and clean interconversion between structurally different molecular (on- and off-) states. On one side, taking into account this requirement, the tautomerism could be a possible elemental process, because the change in the tautomeric state is accomplished by a fast proton transfer reaction between two or more structures, each of them with clear and different properties. On the other side, the real tautomerism, by itself, means practically uncontrollable shift in the equilibrium under changing local environment. It is impossible, in general, to achieve full shift from one to another individual tautomer in a controlled manner.[7] Consequently, the main problem in developing tautomeric switching system is to provide conditions for a controlled shift of the tautomeric equilibrium in a way that the on- and off-states correspond to the individual tautomers. First really working example of such molecular switch was proposed in IBM Research-Zurich,[8] where the switching is mediated by a tautomerization reaction of metal-free naphthalocyanine. Using a low-temperature scanning tunneling microscope, a voltage pulse at the STM tip can induce a change in the orientation of the hydrogen atom-pair at the center of naphthalocyanine, leading to tautomeric switching between low and high conductance.

Another type of tautomeric switching systems, based on azodyes, have been reported to work in solution using number

[a]*Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev str., bl.9, BG-1113 Sofia, Bulgaria. E-mail: lantonov@orgchm.bas.bg*

[b]*Chemistry Department, University of Fribourg, Chemin du Muse, CH-1700 Fribourg, Switzerland*

† Electronic supplementary information (ESI) available: Additional figures from single crystal diffraction. CCDC 928932–928938. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra45326j



Scheme 1 Tautomeric equilibrium in **1**.

of stimuli.[1,9] One of these systems, based on the reversible change in the position of the tautomeric equilibrium of structurally modified 4-(phenyldiazenyl)naphthalen-1-ol (**1**, Scheme 1) upon protonation or complexation, was reported by us in solution.[1,10] The initial aim of the current communication was to report the possibilities to trigger switching properties by additional structural changes that affect the tautomerism in **1**. Unexpectedly, the obtained results shed surprising light on the actual switching mechanism upon addition of acid, which fells in contradiction with common expectations for stabilization of the individual tautomers through intramolecular hydrogen bonding. A combined interpretation of the obtained crystal structures, NMR solution data and DFT quantum-chemical calculations revealed that the process of switching is based not on a simple protonation process, but on complex formation driven by the counter ion of the added acid. To our best knowledge, this is one of the rare cases for such anion controlled[11] tautomeric conversion.

Results and discussion

General concept

Compound **1**, existing always as a mixture between enol (**E**) and keto (**K**) form, is one of first tautomeric systems, described almost 140 years ago.[7] The tautomeric equilibrium is extremely sensitive to changes in the environment (temperature, solvent, irradiation), providing easy shift in one or another direction, but never to the pure, individual, tautomers, a fact that makes this system unsuitable for switching purposes. Recently, we developed, a conceptual idea, shown in Fig. 1, where a controlled shift in this particular tautomeric equilibrium can be achieved by using adaptable nitrogen containing antenna.[1]

On one side, the enol stabilization in the off-state is achieved by engagement of the tautomeric proton in an intramolecular hydrogen bonding with the antenna, a sidearm connected to the tautomeric unit by a spacer in order to avoid conjugation with the tautomeric chromophore. On the other side, the engagement of this antenna by external stimuli (like the addition of an acid[1] or a metal ions[10]) switches to the keto tautomer as on-state. When the action of the stimuli is terminated, the tautomeric equilibrium returns back to the off-state. From the optical spectroscopy viewpoint, the protonation/complexation does not affect directly the tautomeric chromophore and the measured UV-Vis spectrum of the on-state corresponds to the optical response of the keto tautomer.

Developing structure **2**, where fully controlled shift in the tautomeric state was achieved by changing the acidity (Scheme 2), we have proven by using UV-Vis spectroscopy that this concept works.[1] The system was further developed by replacing

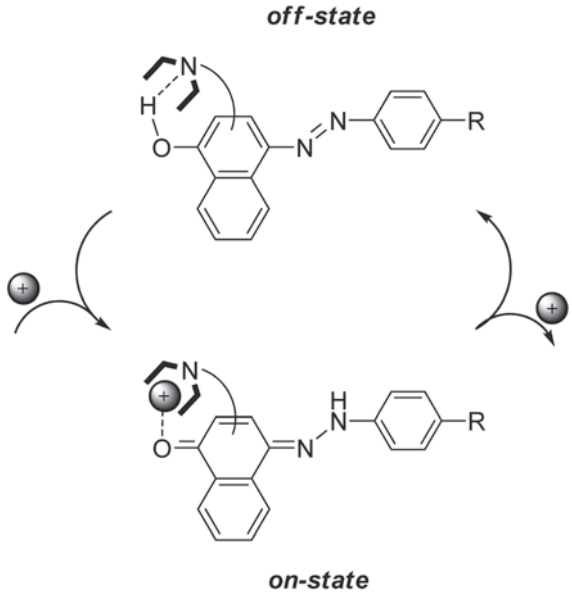
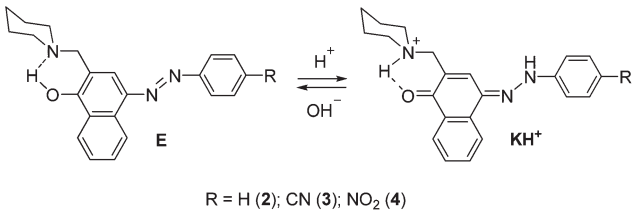


Fig. 1 Conceptual idea of molecular switch, based on controlled tautomeric transition.

the piperidine antenna by aza-15-crown-5 ether, which has shown remarkable complexation ability towards alkali and alkaline earth metal ions.[10] The accumulated knowledge showed that the switching action depends crucially on the relative stability of the tautomers used as tautomeric building block – the use of naphthol based azodyes and Schiff bases leads to switching, while the idea shown in Fig. 1 does not work in the case of phenols or anthranols due to the large difference in the stability of individual tautomers. However, even in the case of **2**, the relative stability of the tautomers can be modelled by the effect of the substituents in the phenyl ring: it is well known that the electron donors stabilize better the enol tautomeric form, while acceptors lead to increased stability of the keto tautomer in the backbone tautomeric block **1**.[12] Inclusion of electron acceptor substituents (compounds **3** and **4**) is especially suitable for studying the triggering ability of the antenna, because in these systems there is an interplay between two opposite trends – stabilization of the enol form by hydrogen bonding with the antenna nitrogen atom as it was shown already in **2** and stabilization of the keto tautomer by the substituents like NO_2 and CN in the phenyl ring as proven in solution for the substituted backbone tautomer **1**.[12,13]



Scheme 2 Switching of the tautomeric equilibrium in **2–4** under protonation/deprotonation – expected hydrogen bonding stabilization.

Returning back to Fig. 1 and Scheme 2, there is another question which has never been discussed. While in the off-state the stabilization of the enol form has been proven by single crystal structures in several cases with different antennas,[14] the suggested on-state stabilization is only experimentally supported using aza-15-crown-5 antenna in the case of metal ion addition.[10] To summarize, up to this moment, we did not have evidences that **KH**$^+$ structure, suggested on the base of expected hydrogen bonding stabilization, as written in Scheme 2, really exists.

Single crystal structures

Compounds **3** and **4** were isolated as pure enol forms in the solid state as seen, for example from the single crystal X-ray structure of the neutral **4**, shown on Fig. 2a. This clearly shows that the effect of the sidearm is strong enough to override the opposite action of the electron acceptor nitro group. However, the most interesting and unexpected results were obtained from the grown crystals of the protonated dyes.

This clearly shows that the effect of the sidearm is strong enough to override the opposite action of the electron acceptor nitro group. However, the most interesting and unexpected results were obtained from the grown crystals of the protonated dyes. As seen from Fig. 2b, when perchloric acid is used to protonate **4**, the tautomeric equilibrium is obviously shifted towards the keto structure, but not because of formation of a hydrogen bonding between protonated sidearm and keto form carbonyl group as expected according to Scheme 2.

Quite surprisingly, in this case the counter ion plays the role of a bridge connecting the NH group of the keto form and the protonated nitrogen of the piperidine unit. The same result is obtained when sulphuric acid is added (Fig. 2c). It is worth to note that the second acidic proton does not take part in the protonation process. As seen from Fig. 3 the acid forms chain through these free protons forming capturing dye molecules. At a first glimpse, the anionic stabilization of the keto tautomer can be attributed to the specific structure of both counter ions (ClO_4^- and HSO_4^-), which facilitates hydrogen bonding formation through oxygen atoms, but, as seen from Fig. 2d the same result is obtained even when **4** is protonated by HCl. In this case the intramolecular bridge is formed with participation of water molecules (Fig. 4). Evidently, in all these cases the counter ion stabilizes the keto structure and the actual switching is a consequence of the anion capturing (Scheme 3).

NMR analyses in solution

It is interesting to know whether the switching of the tautomeric equilibrium by anion capturing, as proven in solid state, proceeds in solution. Unfortunately the UV-Vis spectroscopy, as seen from Fig. 5, can only detect the shift of the equilibrium from the neutral enol, absorbing at ~440 nm, to the protonated **K**-form at 500 nm, without distinguishing between simply protonated dyes (**3KH**$^+$, **4KH**$^+$) or the anion bridged complex (**3KH**$^+$**X**$^-$, **4KH**$^+$**X**$^-$).

The observed spectral changes are identical and the position of the newly appeared band, belonging to the protonated specie,

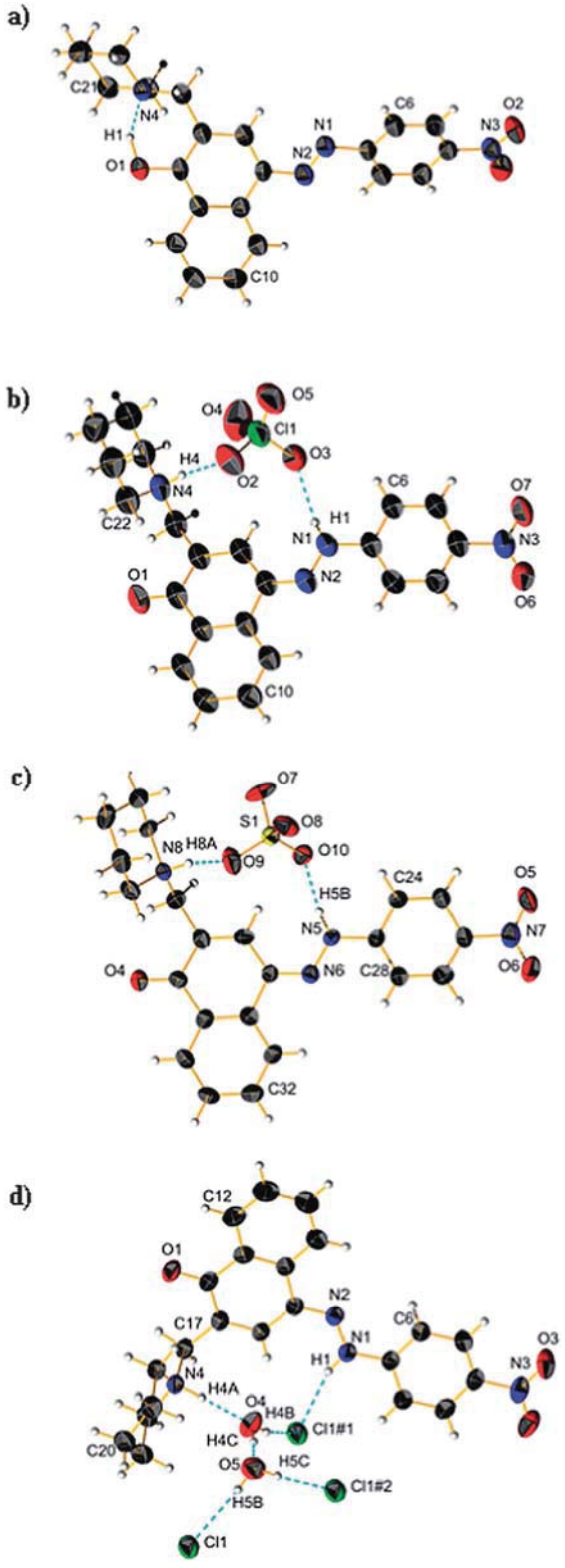


Fig. 2 View of the molecular structures of compound **4**: (a) the neutral enol form and the protonated keto forms (b) with $HClO_4$; (c) with H_2SO_4; (d) with HCl. Ellipsoids are drown with 50% probability. N atoms are given in blue, O in red, C in black, Cl in green, S in yellow and H in white.

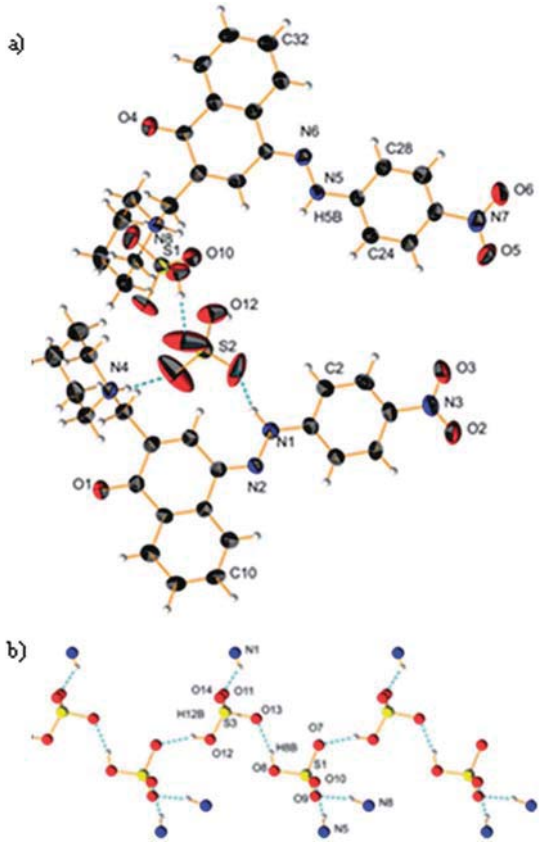


Fig. 3 View of the molecular structure of compound **4**: (a) the protonated keto form dimer with H_2SO_4 and (b) the counter anion chain in the packing of the keto form. Ellipsoids are drown with 50% probability. N atoms are given in blue, O in red, C in black, S in yellow and H in white.

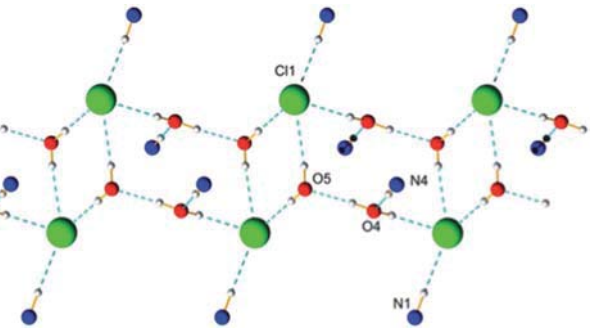
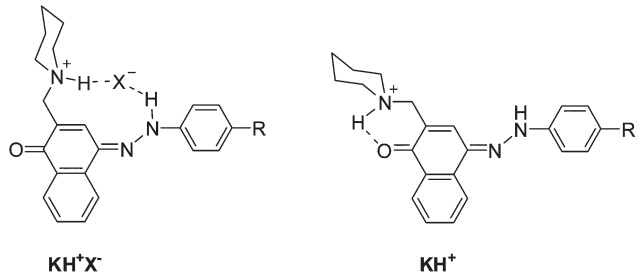


Fig. 4 View of the counter anion chain in the packing of the keto form of compound **4** with hydrochloric acid. Ellipsoids are drawn with 50% probability. N atoms are given in blue, O in red, Cl in green and H in white.

does not depend on the kind of the acid, which is added, namely H_2SO_4, $HClO_4$, HCl, CH_3COOH or HOOC–COOH.

The steric preferences of the ligand **3** (more soluble than **4**) and its 1 : 1 salt with oxalic acid were additionally studied by NMR spectroscopy. The spectra of the free ligand in deuterochloroform at room temperature show sharp and well defined signals characteristic for the single enol-tautomer. In contrast, a part of the signals in the spectra of the salt are broadened due to a slow exchange between two sites. These signals belong to CH-6



Scheme 3 Possible structures of the keto form under switching.

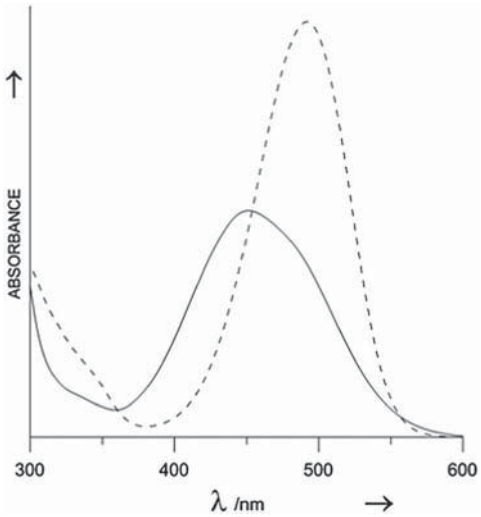


Fig. 5 Absorption spectra of **3** in $CHCl_3$ with addition of oxalic acid.

and protons of the 4-CNPh fragment close to the azogroup (2′and 6′), which is an indication that rotations around both C_q–N bonds are partially restricted. The latter can be due to interaction of the nitrogen atom with the acid resulting in a relatively fixed conformation. Unfortunately, the explicit ^{13}C data cannot be obtained in a reasonable time-scale. The most informative for the position of the tautomeric equilibrium signal, quaternary C-1, does not appear clearly in several solvent and solvent systems; the signal was always commensurable with the noise.

From the other side, the interactions of the singlet for CH-3 in the NOESY experiments serve additional information about the preferred conformation in solution. As illustrated in Fig. 6, clean interactions between CH-3 and spacer CH_2 and the two CH_2–N groups of piperidine (2″ and 6″) are registered in the spectrum of the free ligand, where the side chain is flexible, while none of them exist in the spectrum of the salt. The latter is an indication for space remoteness of these protons in the preferred conformation of the salt in chloroform, which is in full agreement with the crystallographic data.

Theoretical calculations in gas phase

Taking into account that the anion capturing complexes are neutral, it is not surprising that we were not able to

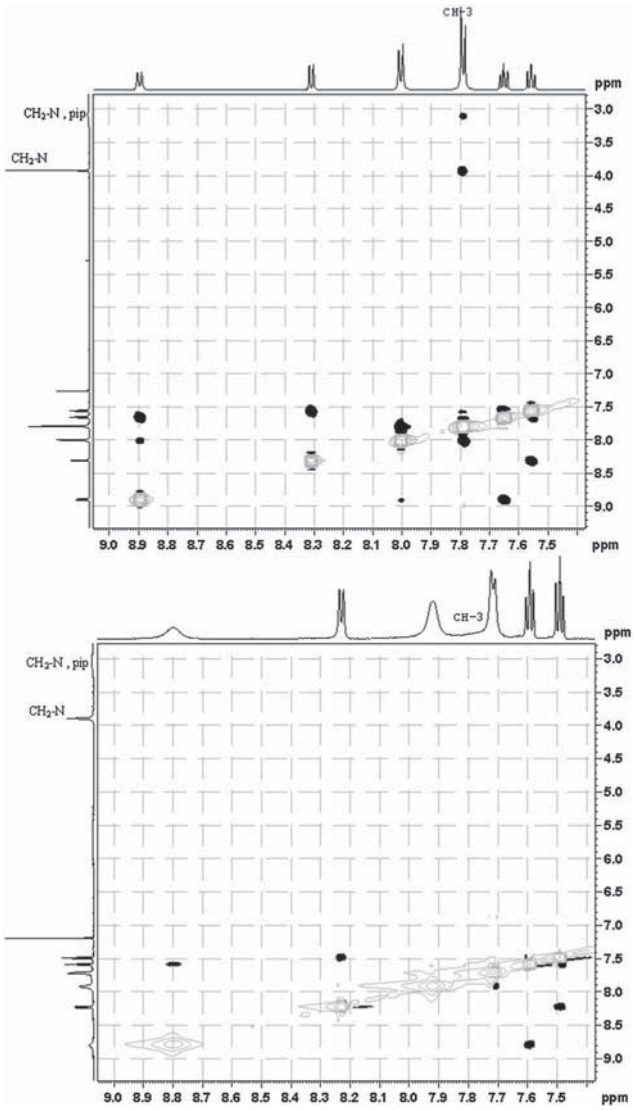


Fig. 6 NOESY spectra of the ligand (up) and its 1 : 1 salt with $(COOH)_2$ (down) in $CDCl_3$.

prove them by mass spectrometry neither in positive nor in negative mode. In this case only the quantum-chemical calculations can conform or reject the hypothesis for anion capturing.

The results for the relative stabilities of the tautomers in **4** and **3**, performed at M06-2X/def2TZVP level of theory[15] are summarized on Fig. 7 and S26.†

The small energy barrier, positive by using M06-2X and negative in the case of HF, in the parent compound without piperidine ring (Fig. 7a), accounts for the existence of both forms in the gas phase and in nonpolar solvents[15] with a slight domination of the more polar **K**-form in solution, which follows from the influence of the electron withdrawing nitro group. The addition of the piperidine ring widens the energy gap between the tautomers, stabilizing the enol form, as illustrated in Fig. 7b. As initially suggested, the protonation of the piperidine nitrogen atom is a suitable tool to shift the equilibrium from the enol to the keto form, stabilizing the latter by ~17 kJ mol^{-1}, through formation of intramolecular hydrogen bonding (Fig. 7c). The second stable protonated keto form – with the piperidine ring pointed towards the azodye backbone, is less stable compared to the enol tautomer by ~16 kJ mol^{-1}. The situation sharply reverses in the case of the bridged complex with the inorganic anion (Fig. 7d). Now the less stable keto form from Fig. 7c becomes more stable (by ~35 kJ mol^{-1} comparing to the complex of the enol form and by ~26 kJ mol^{-1} comparing to the other keto complex) due to the fact that perchlorate anion connects the NH group of the keto form and the protonated nitrogen from the piperidine unit like a bridge. In such a way the quantum chemical calculations confirm nicely the crystallographic and NMR results.

Conclusions

As seen, the presented results try to shed some light on the role of the anion in the process of tautomeric switching of azonaphthols under protonation. In the previous results we demonstrated the possibility to use tautomeric systems for optical switching giving a logical, common sense, explanation for the stabilization of keto tautomer by intramolecular hydrogen bonding between protonated antenna and the tautomeric carbonyl group. The results presented in the current communication clearly show that in solid state and in solution, the counter ion is actually responsible for the switching, which is a very interesting and unexpected phenomenon.

Experimental

The title compounds **3** and **4** were obtained by a previously described procedure.[1]

Orange crystals of the enol forms suitable for X-ray diffraction analysis were grown by slow evaporation method from acetone (**3**) or acetonitrile/chloroform solution (**4**). Keto forms crystallized in the same manner, but with addition of small drops of the corresponding acid. All geometric and intensity data were taken from the respective crystals, using Cu-K_α radiation ($\lambda = 1.54186$ Å), performed at 200 K on a STOE IPDS-IIT diffractometer equipped with an Oxford Cryosystem open flow cryostat.[17] Absorption correction was partially integrated in the data reduction procedure.[18] The structure was solved by SIR 2004 and refined using full-matrix least-squares on F^2 with the SHELX-97 package.†[19]

The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (Rheinstetten, Germany) at 25 °C as 2×10^{-3} M solutions in deuterochloroform in order to avoid trans-molecular interactions in NOESY experiments. The chemical shifts were quoted in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz.

Quantum-chemical calculations were performed by using the Gaussian 09 program suite.[20] The tautomeric forms of **3** and **4** along with their protonated and bridged complexes were optimized without restrictions and then

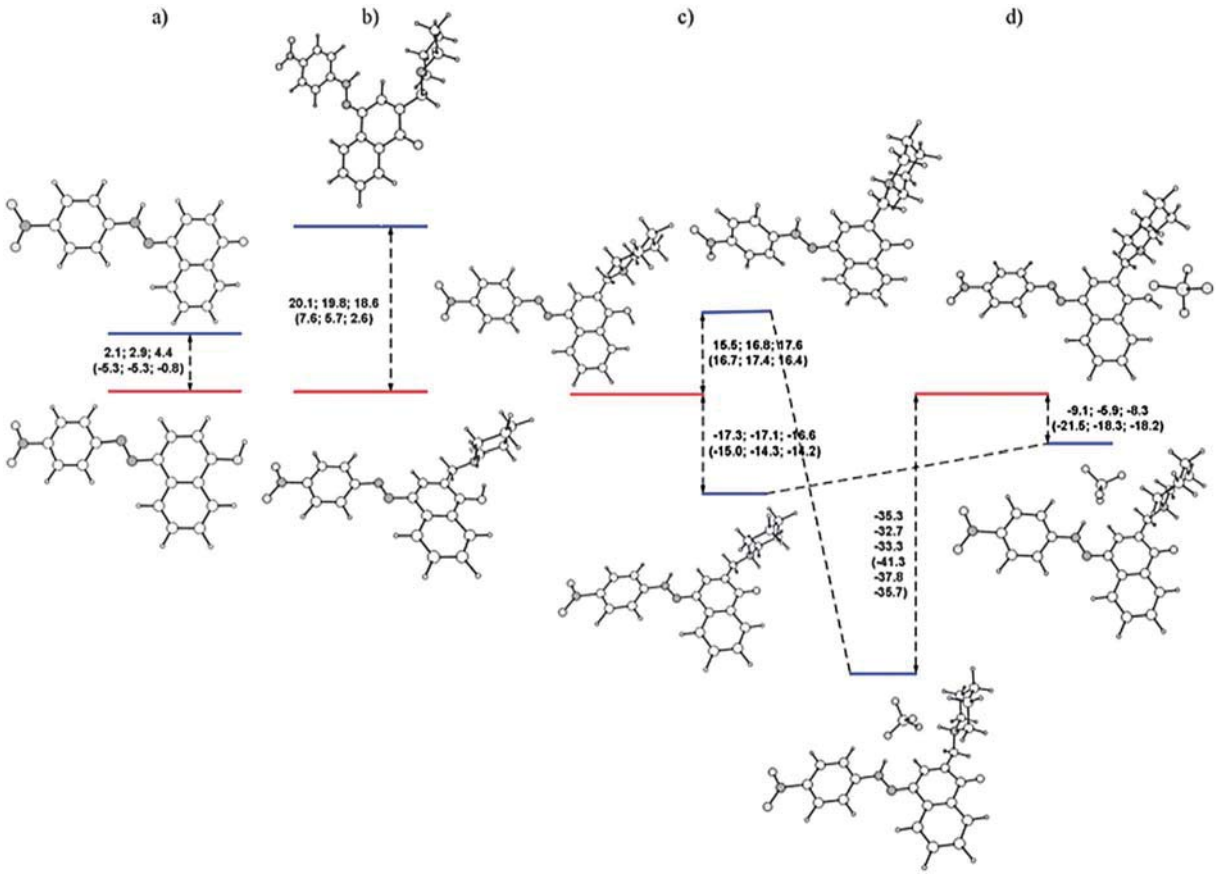


Fig. 7 Change of the relative energy (M06-2X/def2TZVP) of the tautomers of the parent compound **1** (a), **4** (b), $\mathbf{4H^+}$ (c) and $\mathbf{4H^+ClO_4^-}$ (d). The values of ΔE, ΔE + ZPE and $\Delta\Delta G$ are given in kJ mol^{-1} units.[16] The values in brackets are obtained by using HF/def2TZVP method.

were characterized as true minima by vibrational frequency calculations.

Acknowledgements

The work was supported by The Swiss National Science Foundation (SCOPES Program), The Bulgarian Science Found (projects TK-X-1716, RNF01/0110, UNA-17/2005 and DRNF-02-13/2009), Alexander von Humboldt Foundation and The Swiss Confederation Grant. The help of Prof. Dr Christoph Schalley (Free University of Berlin) in the investigations in gas phase by mass spectrometry is gratefully acknowledged.

Notes and references

1 L. Antonov, V. Deneva, S. Simeonov, V. Kurteva, D. Nedeltcheva and J. Wirz, *Angew. Chem., Int. Ed.*, 2009, **48**, 7875.

2 V. Balzani, A. Credi and M. Venturi, *Molecular Devices and Machines – Concepts and Perspectives for the Nanoworld*, WILEY-VCH, Weinheim, 2008.

3 (*a*) J. Steed and J. Atwood, *Supramolecular Chemistry*, WILEY-VCH, Weinheim, Chichester, 2009; (*b*) J. Atwood and J. Steed, *Encyclopedia of Supramolecular Chemistry*, CRC Press, Boca Raton, 2004.

4 P. Franzon, D. Nackashi, C. Amsinck, N. Di Spigna and S. Sonkusale, *IFIP International Federation for Information Processing*, 2007, **240**, 1.

5 *Molecular Switches*, ed. B. Feringa, WILEY-VCH, Weinheim, 2011, 2nd edn.

6 (*a*) M. Natali and S. Giordani, *Chem. Soc. Rev.*, 2012, **41**, 4010; (*b*) S. J. van der Molen and P. Liljeroth, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 2010, **22**, 133001; (*c*) F. M. Raymo, *Adv. Mater.*, 2002, **14**, 401; (*d*) B. Feringa, R. van Delden, N. Koumura and E. Geertsema, *Chem. Rev.*, 2000, **100**, 1789; (*e*) J.-P. Desvergne and H. Bouas-Laurent, *Chem. Commun.*, 1978, 403; (*f*) D. Leigh, J. Wong, F. Dehez and F. Zerbetto, *Nature*, 2003, **424**, 174; (*g*) V. Blanco, A. Carlone, K. D. Hänni, D. A. Leigh and B. Lewandowski, *Angew. Chem., Int. Ed.*, 2012, **51**, 5166.

7 P. J. Taylor, G. van der Zwan and L. Antonov, Tautomerism: Introduction, History and Recent Developments of Experimental and Theoretical Methods, in *Tautomerism: Methods and Theories*, ed. L. Antonov, Wiley-VCH, Weinheim, 2013.

8 (*a*) P. Liljeroth, J. Repp and G. Meyer, *Science*, 2007, **317**, 1203; (*b*) F. Mohn, L. Gross, N. Moll and G. Meyer, *Nat. Nanotechnol.*, 2012, **7**, 227.

9 (*a*) H. Y. Lee, X. Song, H. Park, M.-H. Baik and D. Lee, *J. Am. Chem. Soc.*, 2010, **132**, 12133; (*b*) A. Farrera, I. Canal,

P. Hidalgo-Fernández, L. Pérez-García, O. Huertas and F. J. Luque, *Chem.–Eur. J.*, 2008, **14**, 2277; (*c*) A. R. Todorov, M. Nieger and J. Helaja, *Chem.–Eur. J.*, 2012, **18**, 7269.
10 L. Antonov, V. Kurteva, S. Simeonov, V. Deneva, A. Crochet and K. M. Fromm, *Tetrahedron*, 2010, **66**, 4292.
11 P. A. Gale, J. R. Hiscock, N. Lalaloui, M. E. Light, N. J. Wells and M. Wenzel, *Org. Biomol. Chem.*, 2012, **10**, 5909–5915.
12 (*a*) J. Schreiber, J. Socha and K. Rothschein, *Collect. Czech. Chem. Commun.*, 1970, **35**, 857; (*b*) S. Kishimoto, S. Kitahara, O. Manabe and H. Hiyama, *J. Org. Chem.*, 1978, **43**, 3882; (*c*) S. Stoyanov, L. Antonov, B. Soloveytchik and V. Petrova, *Dyes Pigm.*, 1994, **26**, 149.
13 D. Nedeltcheva, L. Antonov, A. Lycka, B. Damyanova and S. Popov, *Curr. Org. Chem.*, 2009, **13**, 217.
14 L. Antonov, V. Kurteva, A. Crochet, L. Mirolo, K. Fromm and S. Angelova, *Dyes Pigm.*, 2012, **92**, 714.
15 M06-2X/def2TZVP level of theory was proven to provide best results in predicting tautomerism of azo-naphthols: S. Kawauchi and L. Antonov, *J. Phys. Org. Chem.*, 2013, **26**, 643.
16 The relative energies in gas phase are defined as follows: $\Delta E = E_{\mathbf{K}} - E_{\mathbf{E}}$, $\Delta\Delta G = \Delta G_{\boldsymbol{K}} - \Delta G_{\boldsymbol{E}}$. The negative values correspond to more stable **K** form and vice versa. ZPE is the abbreviation of zero-point energy correction.
17 J. Cosier and A. M. Glazer, *J. Appl. Crystallogr.*, 1986, **19**, 105.
18 E. Blanc, D. Schwarzenbach and H. D. Flack, *J. Appl. Crystallogr.*, 1991, **24**, 1035.
19 (*a*) M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano and D. Caro, *J. Appl. Crystallogr.*, 2005, **38**, 381; (*b*) G. M. Sheldrick, *SHELX-97: program for crystal structure refinement*, University of Göttingen, 1997.
20 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision A.02*, Gaussian Inc., Wallingford CT, 2009.