

Exploring Tautomerism in Organic Compounds: Spectral Properties, Structural Dynamics, and Potential Applications

Habilitation reference about scientific contributions
of assist. prof. Vera Deneva, PhD

Institute of Organic Chemistry with Centre of Phytochemistry Bulgarian
Academy of Sciences, for application in the procedure for associate professor in
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Introduction

This habilitation reference is based on twenty (16) original scientific articles ten (6) from the list of publications "V" and ten (10) from the list of publications "G". My scientific contributions are in the field of tautomeric systems - tautomeric behavior of organic compounds, including azo dyes, Schiff bases and related compounds; understanding of the factors that influence tautomeric equilibria; spectroscopic studies - UV-Vis absorption and fluorescence.

This reference summarizes the most significant scientific contributions reported in the period 2017-2023 in the following scientific areas:

1. Tautomerism in azo dyes;
2. Tautomerism in Schiff bases;
3. Other tautomeric systems;
4. Other topics.

1. Tautomerism in azo dyes [1–6].

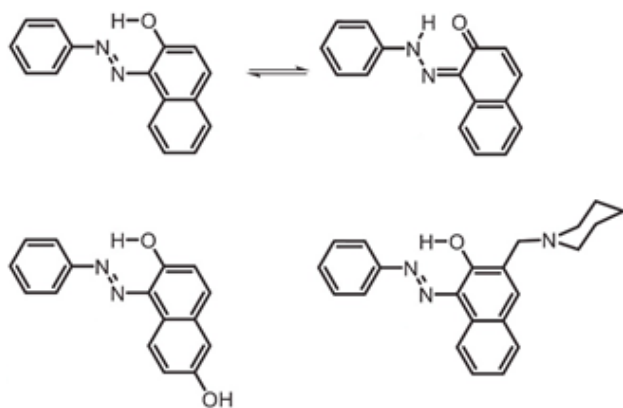
Aromatic azo derivatives, such as azo dyes, have long been recognized as a significant class of colorants with extensive practical applications in various industries, including textiles, food, paper printing, and liquid crystalline displays. The unique electronic and optical properties of azo compounds make them highly desirable for use in nonlinear optical (NLO) devices and other advanced technologies. One intriguing aspect of azo dyes is their ability to exist in different tautomeric forms, which can significantly influence their chemical and physical properties.

Tautomerism refers to the reversible isomerization between constitutional isomers, known as tautomers, that differ in the position of a proton. This phenomenon plays a crucial role in the reactivity and behavior of many organic compounds. In the case of azo dyes, tautomerism can affect their color, stability, and photochemical properties.

One common approach on understanding the factors that influence tautomeric equilibria in azo compounds and developing strategies to control and manipulate their tautomeric states, involves the introduction of specific functional groups or substituents that can act as proton donors or acceptors, thereby influencing the position of the tautomeric equilibrium.

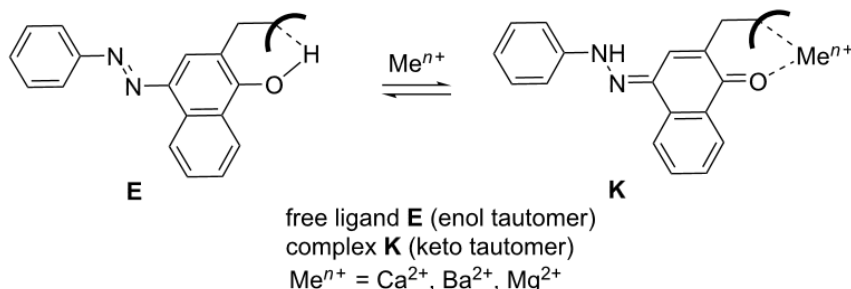
1.1 Tautomerism in azonaphthol dyes [1–3].

The tautomeric behavior of aryl azo derivatives of naphthols, focusing on structural modifications to control proton transfer are explored in publication 1 (Scheme 1). Sudan I, a widely used azo dye, serves as a reference point for tautomeric equilibrium in different solvents. By introducing additional functional groups and sidearms to the azo derivatives, we investigated the competition for the tautomeric proton. Experimental methods used include UV-Vis and NMR spectroscopy, quantum-chemical calculations, and crystallographic analysis. The obtained spectroscopic and computational results revealed that structural modifications influence tautomerism. Also, the formation of complexes with alkaline earth metal ions results in significant spectral shifts, aiding in the detection of specific cations.



Scheme 1: Tautomeric equilibrium and structures of the investigated compounds in publication 1.

Publication 2, explores the use of tautomerism as a primary signaling mechanism in metal sensing, focusing on a ligand with 4-(phenyldiazenyl) naphthalene-1-ol as a tautomeric block and an amide group as a metal capturing antenna (Scheme 2). The study investigates the tautomeric equilibrium between enol and keto forms, with the potential for intramolecular hydrogen bonding to stabilize the enol form. Strong bathochromic and hyperchromic effects are observed in the visible spectra upon complex formation with alkaline earth metal ions. The research aimed to develop a system, where metal ion complexation shifts the tautomeric equilibrium towards the keto tautomer for enhanced stability.



Scheme 2: Conceptual idea for tautomeric metal sensing described in publication 2.

Publication 3, discusses the theoretical design of tautomeric optical sensors based on 4-(phenyldiazenyl) naphthalene-1-ol ligands for metal ion detection (Figure 1). The organic molecules utilize a side ionophore group connected to the tautomeric backbone to stabilize the enol form in the absence of metal ions and shift towards the keto form upon metal ion complexation. The study explores the effect of symmetric tweezer-like ionophores on the tautomeric state and complexation ability of the ligands. Theoretical calculations suggest that the designed sensors could be suitable for detecting alkali earth metal ions by shifting the tautomeric equilibrium.

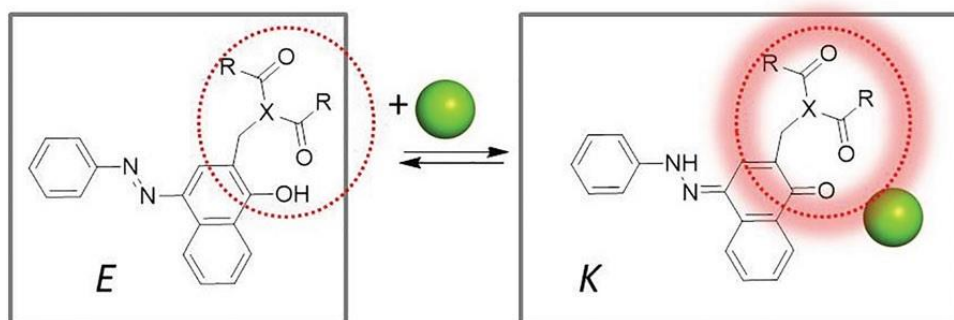
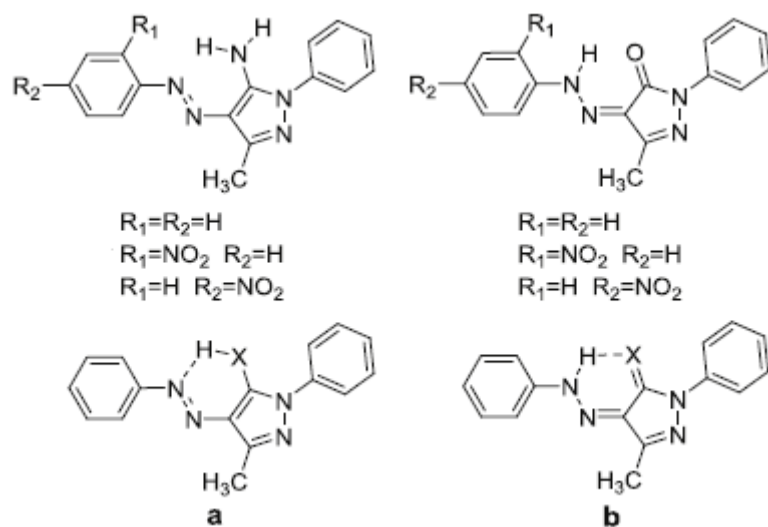


Figure 2. Graphical abstract of publication 3.

1.2 Border cases of azo and hydrazo tautomers [4].

Publication 4 investigates the tautomeric state of two series of azo dyes using molecular spectroscopy (UV-Vis and NMR) and quantum-chemical calculations (Scheme 3). The results show that one series exists in the azo tautomeric form, while the other series exists in the hydrazone tautomeric form. The presence of a nitro group does not significantly affect the tautomeric state. The compounds studied can be used as model tautomers in NMR evaluations of tautomeric azo dyes. The conclusions about tautomerism in solution are valid in the solid state as well.



Scheme 3. Investigated compounds and sketch of their tautomeric forms (bottom, azo, enol-like **a** and hydrazo, keto-like **b**, X = O or NH).

1.3 The switching mechanism in ethyl-2-(2-(quinolin-8-yl)hydrazono)-2-(pyridin-2-yl)acetate [5].

Publication 5 investigates the switching mechanism of a rotary switch compound, ethyl-2-(2-(quinolin-8-yl) hydrazono)-2-(pyridin-2-yl) acetate, through a combination of experimental and theoretical methods (Figure 3). NMR, UV-Vis, and ultrafast spectroscopy techniques were used to study the isomerization process. Theoretical calculations were performed to explore different mechanisms, including out-of-plane rotation, in-plane inversion, and proton transfer. The results suggest that the proton transfer mechanism, involving the transfer of a proton from one form to another through a chain of reactions, is the most likely

mechanism for the switching process. The study provides new insights into the mechanism of isomerization in rotary switches and hydrazone tautomerism.

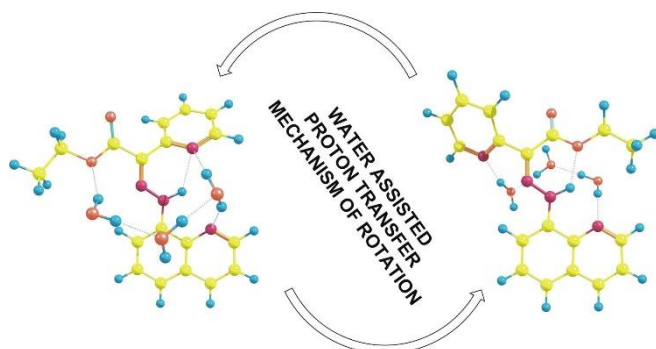


Figure 3. Graphical abstract of publication 5.

1.4 Tautomeric state in 4-OH coumarin based rotary switch [6].

Two new 4-OH coumarin based rotary switches, containing fixed carbonyl groups in the rotor, have been synthesized and their properties have been studied by combined use of DFT calculations and molecular spectroscopy (UV–Vis absorbance and emission, NMR) (publication 6, Figure 4). It was found that the structure of the stator (naphthyl or quinolyl moiety) and solvents polarity do not influence their azo-hydrazone tautomerism. Both compounds exist as keto (hydrazone) tautomers. The NMR data indicate a mixture of *E* (major) and *Z* (minor) keto form isomers in solution. The results are in very good agreement with ground state DFT calculations. The keto tautomers exhibit different emission behavior depending on the structure of the stators. According to the spectral data and the TDDFT analysis, the observed emission originates from the excitation of the keto tautomers and does not include excited state proton transfer. It was shown that the protonation is a suitable stimulus for *E/Z* switching, where a possible mechanism is sketched. The addition of acid leads to the protonation of the quinolyl nitrogen atom, which slightly affects the *E/Z* isomerization ratio.

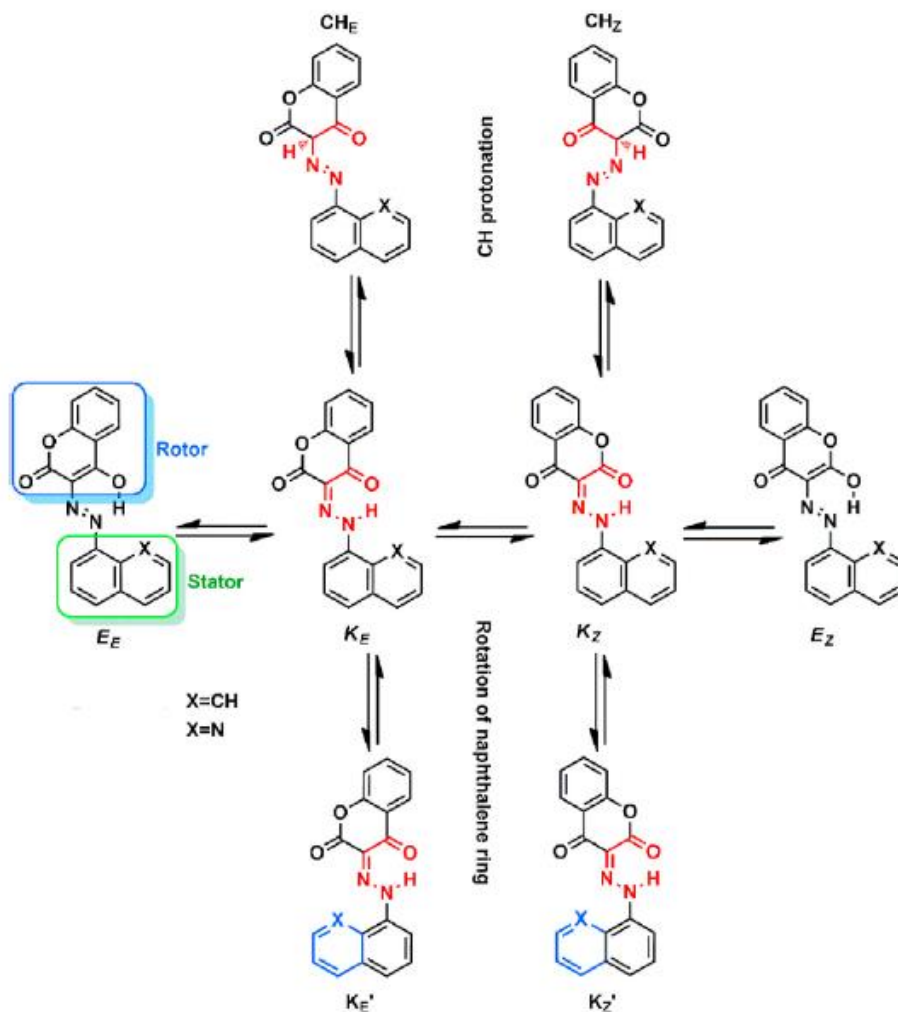


Figure 4. Graphical abstract of publication 6.

2. Tautomerism in Schiff bases [7–9].

Tautomerism in Schiff bases involves the reversible migration of a proton between different positions within the molecule, leading to the existence of two or more isomeric forms. This dynamic equilibrium plays a crucial role in the reactivity, stability, and properties of Schiff bases, impacting their applications in areas such as coordination chemistry, catalysis, and biological processes. Understanding and controlling tautomerism in Schiff bases is essential for harnessing their full potential in various fields.

2.1 Tautomerism in 4-substituted phthalimide 2-hydroxy-Schiff bases [7].

Publication 7 discusses the synthesis and characterization of two 4-substituted phthalimide 2-hydroxy-Schiff bases with different 2-hydroxyaryl moieties (Figure 5). Compound with the naphthyl moiety shows a solvent-dependent tautomeric equilibrium, while no tautomerism is observed in compound with the phenyl moiety. Both compounds exhibit excited state intramolecular proton transfer (ESIPT) with high rates of photoconversion to keto tautomers and ketoemissions with large Stokes shifts in various solvents. The study combines experimental UV-Vis spectroscopy, crystallography, and fluorescence spectroscopy with

theoretical DFT calculations to investigate the tautomeric behavior and ESIPT mechanism in these compounds.

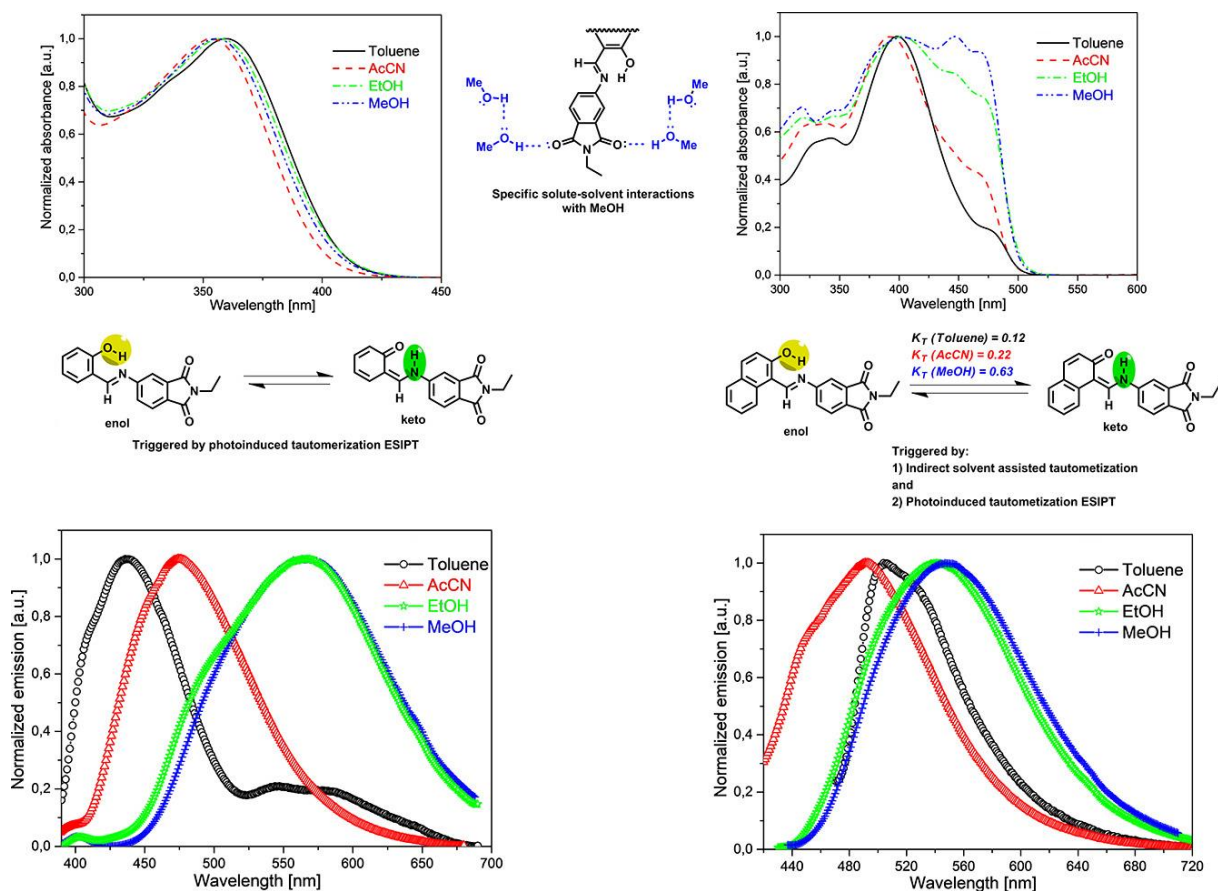


Figure 5. Graphical abstract of publication 7.

2.2 Tautomerism in 7-OH quinoline Schiff bases [8].

Publication 8 describes two novel Schiff bases derived from 7-hydroxyquinoline were synthesized and studied for their tautomeric behavior as potential bistable switches (Figure 6). The compounds exhibited a mixture of enol and keto tautomers in solution, with one compound existing solely in the enol form. Upon irradiation, both compounds demonstrated rotation around a specific bond through excited state intramolecular proton transfer, indicating their suitability as bistable switches. Complex formation with acidic counter ions prevented intramolecular rotation upon protonation, suggesting potential applications in molecular machine design.

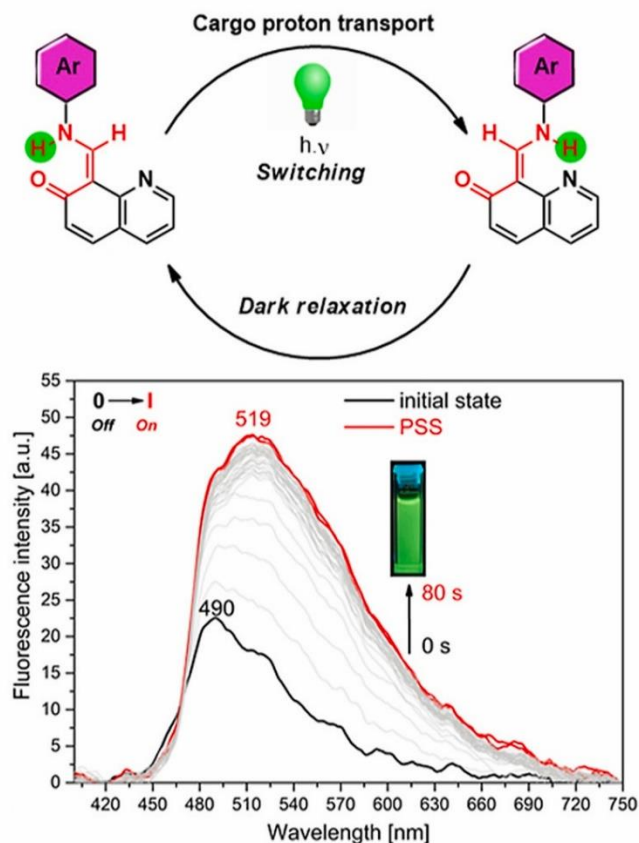


Figure 6. Graphical abstract of publication 8.

2.3 Tautomerism in benzothiazol picolin/isonicotinamides Schiff bases [9].

Publication 9 explores the ground state tautomerism and excited state proton transfer in two new molecular switches, N-(benzo[d]thiazol-2-yl) picolinamide and N-(benzo[d]thiazol-2-yl) isonicotinamide, using spectroscopy and DFT calculations. While theoretical calculations suggest two potential switching pathways for N-(benzo[d]thiazol-2-yl)picolinamide (Figure 7), experimental results show a preference for excited state proton transfer from the amide NH to the benzothiazole nitrogen in both compounds. This indicates a common photodynamic behavior in the studied molecules. The study sheds light on the photophysics and proton transfer dynamics of these molecular switches, contributing to the understanding of their potential applications in optoelectronic devices.

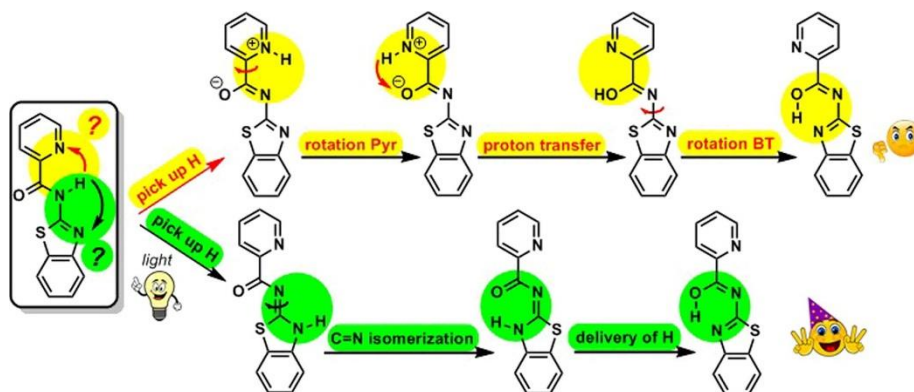
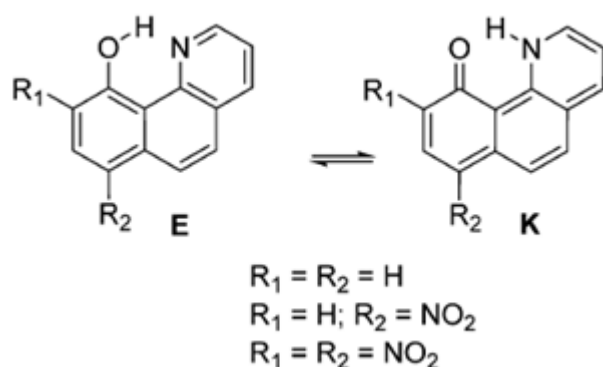


Figure 7. Graphical abstract of publication 9.

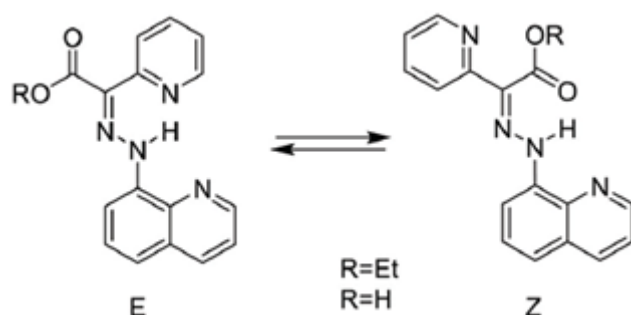
3. Other tautomeric systems [10–14].

Publication 10 investigates the proton transfer in 10-hydroxybenzo[h]quinoline (HBQ) and its structurally modified compounds through experimental and theoretical methods (Scheme 4). The incorporation of electron acceptor substituents on position 7 of the HBQ backbone led to the appearance of a keto tautomer in the ground state and changes in the excited state potential energy surface. The obtained results revealed a transition from a single- to a double-well proton transfer mechanism, influenced by solvent environments. The absorption spectra of the compounds show a red-shifted band indicating ground state tautomerism. Fluorescence arises from the keto form even when the enol form is excited, suggesting excited state intramolecular proton transfer.



Scheme 4. HBQ and nitro substituted compounds.

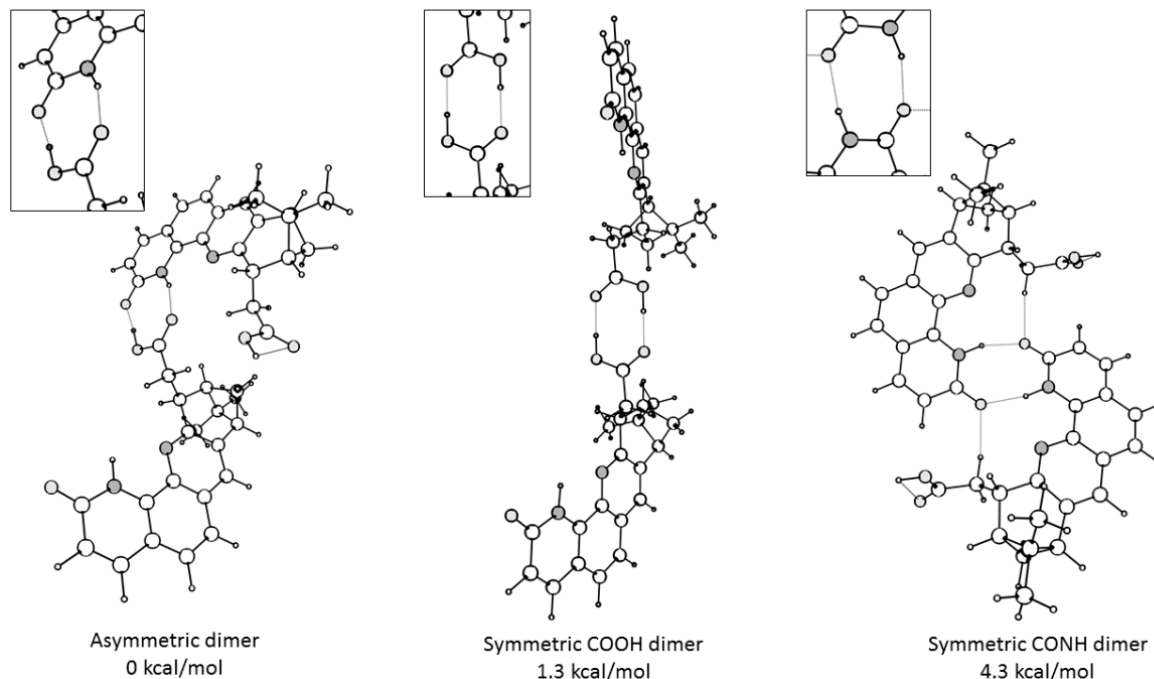
A new rotary switch compound (publication 11, Scheme 5), designed with a pyridyl ring and a COOH group as sub-rotors, demonstrates anti-Kasha behavior in its excited state intramolecular proton transfer (ESIPT). It exhibits a single isomer in the ground state due to the engagement of the pyridyl nitrogen atom. The presence of acidic functionality in the rotor allows for ESIPT, leading to anti-Kasha behavior, a rare phenomenon in ESIPT reactions. Experimental and theoretical methods were combined to study the spectral and switching properties of the compound.



Scheme 5. Rotary switches discussed in publication 11.

The tautomeric behavior and self-association in both solution and solid state of two pinene-type ligands is explored in publication 12. The first synthesized ligand is an acetylated derivative of 5,6-pinene-bipyridine which shows keto-enol tautomerism. This equilibrium was studied using NMR and UV-Vis spectroscopy in different solvents, with results supported by DFT calculations. The second ligand, derived from an oxidized pinene-phenanthroline unit, exists as a single tautomer in solution and is capable of forming dimers (Scheme 6) through

hydrogen bonding, as evidenced by X-ray structure determination and also confirmed by DFT studies. This work provides insight into new chiral ligands and contributes to the understanding of tautomerism in pinene-derived compounds.



Scheme 6. Dimers of the investigated compounds in publication 12.

The tautomeric behavior of favipiravir in solution using molecular spectroscopy and quantum-chemical calculations (publication 13, Figure 8), involves a dynamic equilibrium between different structural forms of a compound, which can influence a drug's biological activity and effectiveness. The study found that in most organic solvents, the enol tautomer of favipiravir is more stable, whereas in the presence of water, the keto form is favored. This is due to specific solute-solvent interactions. The addition of alkaline-earth-metal ions results in deprotonation and complexation, leading to the formation of 2:1 (ligand:metal) complexes. The theoretical predictions showed that the metal ion would be captured between the carbonyl groups due to a size-fit effect. This is the first detailed experimental investigation into the tautomeric properties of favipiravir in solution.

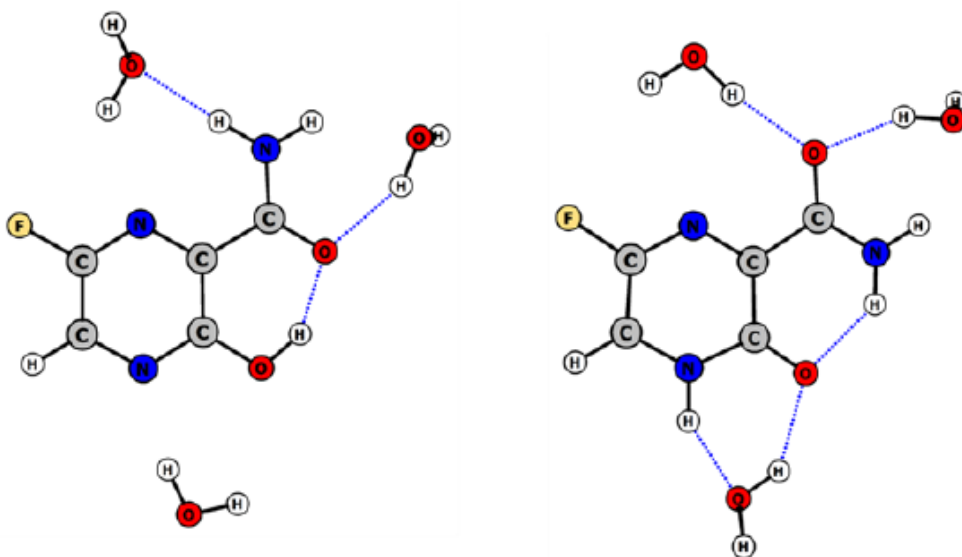


Figure 8. The optimized geometry (M06-2X/def2-TZVPPD) of water–favipiravir clusters with three water molecules.

The tautomeric behavior of a series of compounds based on a 1,3,5-triazine core linked to various aromatic arms through an amino group was examined in publication 14, Figure 9. The obtained results conclude that there is no evident proton transfer occurring either in the ground or excited state based on absorption and emission spectra. The potential for compounds with hydroxyl groups is noted, as they may stabilize the compounds' structures, affect their properties, and encourage proton transfer. The approach used in the design of new OLEDs includes machine learning-based methods and computer-aided simulations to predict the properties of potential organic diodes before synthesis, underscoring the relevance of this research in advancing OLED materials.

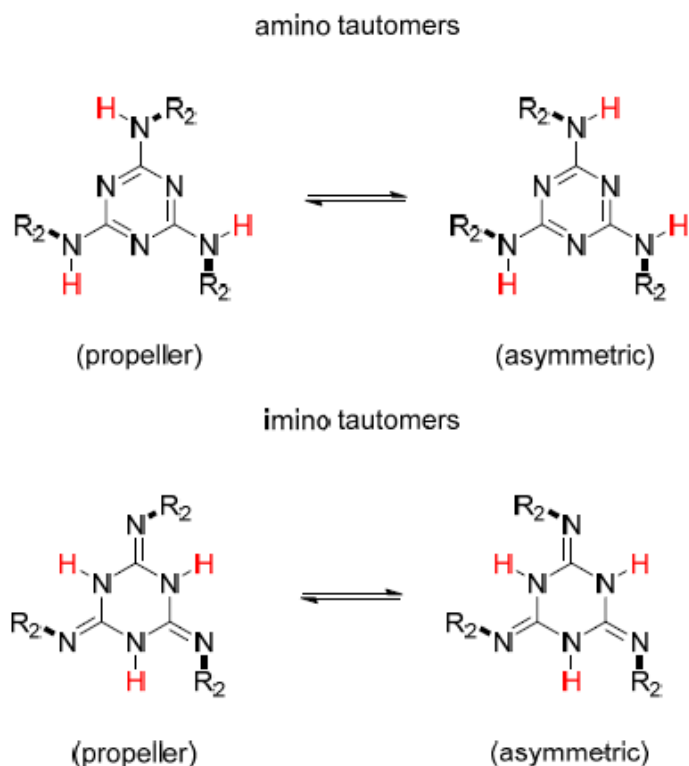


Figure 9. Possible tautomers and corresponding isomers described in publication 18.

4. Other topics [15,16].

Publication 15 explores the use of near-infrared spectroscopy for rapidly quantifying the active components in *Arnicae flos*, a substance derived from the *Arnica montana L.* and *Arnica chamissonis Less.* plants. They are used in herbal medicine, particularly for their anti-inflammatory properties. The study aims to provide a non-destructive and quick method to analyze the pharmacologically relevant components of *Arnicae flos* (phenolic acids, flavonoids, and sesquiterpene lactones). A calibration model using NIR spectra was developed to quantify the content of these active components in *Arnicae flos* samples, with high performance liquid chromatography used as a reference technique. Our attention was focused on thirteen active components and compared different methods of spectral preprocessing. We found out that a step-by-step filter provided better signal-to-noise ratio and calibration for seven of these components (including protocatechuic acid, chlorogenic acid, caffeic acid) compared to direct raw spectra processing and the conventional Golay-Savitzky procedure (Figure 10). The paper discusses the importance of *Arnicae flos* in the pharmaceutical market and indicates a demand for reliable analytical techniques to ensure its quality and safety. The findings suggest that NIR

spectroscopy, with the step-by-step filter, could be a promising method for analyzing this raw material efficiently.

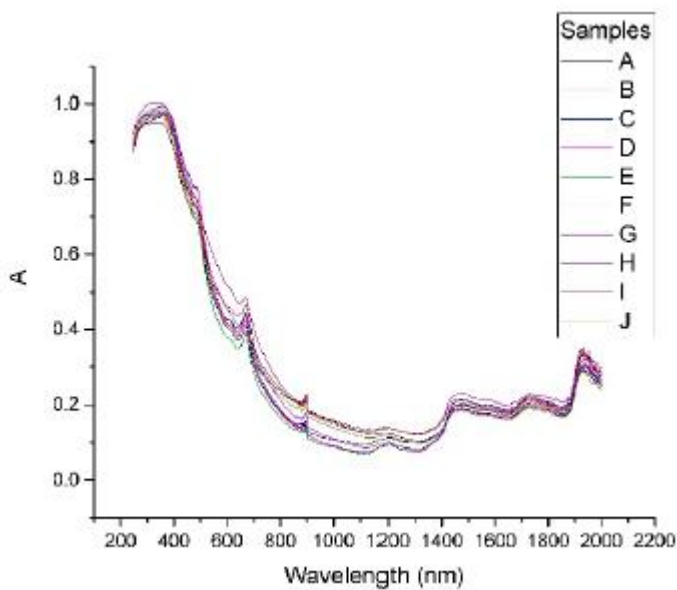


Figure 10. Raw diffuse-reflectance spectra in the 250–2000nm range, obtained from dried *Arnicae flos*.

Publication 16, explores the use of Raman spectroscopy as a rapid, non-destructive analytical technique to classify Bulgarian wines and assess their chemical composition (Figure 11). The study specifically aims to classify wines based on variety and geographic origin, and to develop calibration models for measuring phenolic compounds in wine using Raman spectroscopy. It highlights the potential of Raman spectroscopy for measuring phenolic compounds in both red and white wines, and discusses the benefits of vibrational techniques for food and beverage authenticity control. Raman spectroscopy is contrasted with infrared spectroscopy, noting its advantage for analyzing water-rich samples like wine due to the weak water signals in its vibrational fingerprint range.

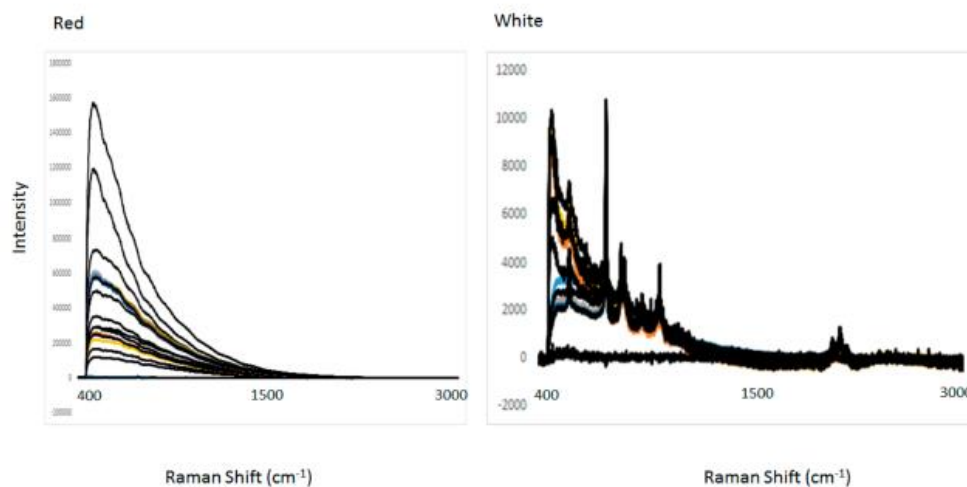


Figure 11. Typical spectra of red and white wine samples sourced from different varieties and regions and analyzed using Raman spectroscopy.

The synthesis, crystallographic, chromatographic, femtosecond and NMR studies mentioned in the presented literature review were carried out in the framework of a collaborative research activity by colleagues at the Institute of Organic Chemistry with the Centre for Phytochemistry (IOCCP), Institute of Electronics, Institute of Mineralogy and Crystallography at the Bulgarian Academy of Sciences (BAS), University of Chemical Technology and Metallurgy, Sofia, Faculty of Chemistry - University of Copenhagen, Denmark, Faculty of Chemistry - University of Fribourg, Switzerland and University of Roskilde, Faculty of Science and Environment, Denmark.

Conclusions

Currently, my research interests are mainly focused on the study of light-powered molecular machines, their tautomeric states, complexation abilities, and potential applications in areas such as molecular switches and smart receptors. My future research will continue in the following research areas:

1. Exploration of tautomeric states and complexation abilities of various organic compounds, shedding light on their structural properties and behaviors.
2. Combination of theoretical modeling, experimental techniques, and spectroscopic analyses to understand the properties of the newly designed organic compounds.
3. Development of materials with potential applications in nanotechnology, drug delivery, and molecular computing.

The above research will be developed through active cooperation within the IOCCP-BAS and the Bulgarian scientific community, as well as through international collaborations with colleagues from other research institutes - Department of Chemistry, University of Copenhagen, Denmark, Department of Chemistry, University of Fribourg, Switzerland and Roskilde University, Department of Science and Environment, Denmark.

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