Keto-Enol Equilibrium from Combining UV/vis Absorption Spectroscopy with Quantum Chemical Calculations

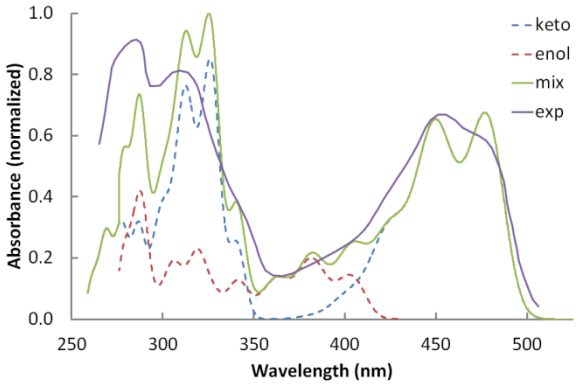
Freddy ZUTTERMAN,[a] Orian LOUANT,[a] Gabriel MERCIER,[b] Tom LEYSSENS,[b] and Benoît CHAMPAGNE[a]

[a.] *Laboratoire de Chimie Théorique, Unité de Chimie-Physique Théorique et Structurale, Namur Institute of Structured Matter, Université de Namur, rue de Bruxelles, 61, B-5000 Namur (BELGIUM).*

[b] *Institute of Condensed Matter and Nanosciences, Université Catholique de Louvain, 1 Place Louis Pasteur, B-1348 Louvain-La-Neuve (BELGIUM)*

benoit.champagne@unamur.be

TOC GRAPHICS



ABSTRACT

Salicylideneanilines are characterized by a tautomer equilibrium, between an enol and a keto form of different colors, at the origin of their remarkable thermochromic, solvatochromic, and photochromic properties. The enol form is usually the most stable but appropriate choice of substituents and conditions (solvent, crystal, host compound) can displace the equilibrium towards the keto form so that there is a need for fast prediction of the keto:enol abundance ratio. Here we demonstrate the reliability of a combined theoretical-experimental method, based on comparing simulated and measured UV/visible absorption spectra. The calculations of the excitation energies, oscillator strengths, and vibronic structures of both enol and keto forms are performed at the time-dependent density functional theory level of calculations by accounting for solvent effects using the polarizable continuum model. This approach is illustrated for two salicylideneaniline derivatives, which are present, in solution, under the form of keto-enol mixtures. The results are compared to those of chemometric analysis as well as *ab initio* predictions of the reaction free enthalpies.

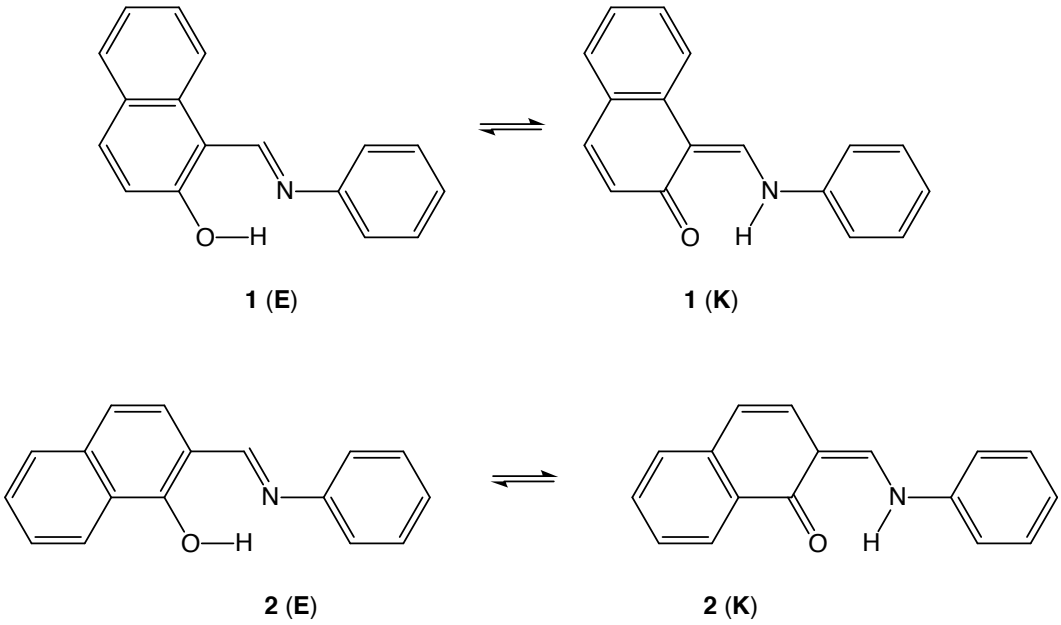
KEYWORDS: salicylideneaniline, UV/vis absorption, keto-enol tautomerism, computational spectroscopy, *ab initio* calculations

Salicylideneanilines (SA's) are dynamical systems, usually referred to as molecular switches,[1] that exhibit thermochromism,[2,3,4,5,6] photochromism,[3,4,7,8,9,10] solvatochromism,[4,11,12] and nonlinear optical (NLO) switching properties[12,13,14,15] both in solution and in the solid state. SA's can undergo keto-enol tautomerism when triggered by light or temperature changes.[16-17] This occurs for their *cis* isomer, which is characterized by an intramolecular H-bond. The *trans* isomers also exist but their energies are usually higher, owing to the breaking of this H-bond, and they cannot switch between an enol and keto form. It is crucial to know under which form SA's occur and to know how to control the majority form because it dictates the electronic and optical properties and the potential for applications in sensing and storage devices.

The relative amounts of *cis*-enol (*c*-enol) and *cis*-keto (*c*-keto) forms are governed by their difference of free enthalpy, ΔG^0_{KE} = G^0(*c*-keto) – G^0(*c*-enol). Experimentally, there are two main techniques to determine this ΔG^0, UV/vis absorption and NMR spectroscopies. For the latter, owing to the fast enol-keto interconversion with respect to the NMR timescale, peaks with chemical shifts in-between those of the pure *c*-enol and pure *c*-keto forms are observed if both forms are present. This technique, which requires the knowledge of the pure form chemical shifts has been shown to be moderately accurate. For instance, Nedeltcheva *et al.*[18] found, for SA **1** (Scheme 1), a rather large range of ΔG^0_{KE} values [-0.36; 1.31 kcal mol^{-1}], corresponding to K_T = [K]/[E] ranging from 1.83 to 0.11, as a function of the probed nucleus. Moreover, several NMR investigations led to the conclusion that the *c*-keto form is present in non-negligible amounts whereas the *c*-keto signature is absent from the UV/vis absorption spectrum.[19]

On the other hand, the UV/vis absorption technique can unambiguously detect the absence of one of the two forms within the limits of detection. Then, to determine ΔG^0_{KE}, it requires the presence of detectable amounts of the minority form and the use of chemometrics for data analysis. Assuming that the detection is possible if there is at least 5% of the minority form, the absence of absorption band typical of that species indicates that its free enthalpy is at least 1.75 kcal mol^{-1} higher than that of the majority form. However, this technique depends on the correct assignment of the observed absorption

bands, which is not necessarily straightforward since both forms can present several UV/vis absorption bands, overlapping to some extent. This assignment can be performed by varying the keto/enol ratios using solvents of different polarity but the formation of aggregates can cause errors by adding absorption and scattering contributions to the spectra. As an alternative to absorption spectra, excitation fluorescence spectra may provide similar information.[20]



Scheme 1. Enol-keto equilibrium of SA's **1** and **2**.

Interestingly, quantum chemical calculations can provide, in combination with the UV/visible experimental spectra, an alternative approach to chemometrics, under the same condition that both forms are present in solution. This approach consists in i) simulating the absorption spectra of the individual forms, accounting for their vibronic structure and then ii) in mixing both spectra in different proportions until a good match with the experimental spectrum is obtained. In this case, the accuracy of the method depends on the reliability of the quantum chemical calculations of the relative properties of the two forms, *i.e.* their electronic excitation energies, oscillator strengths, and vibronic structures. To the best of our knowledge, this approach, which accounts for the position, intensity, and shape of the absorption spectra as resulting from several electronic excited

states, has not been published so far and it constitutes the purpose of this Letter. To do that, SA's **1** and **2** (Scheme 1) were selected because they are among the few anils that are present in both enol and keto forms in common solvents at room temperature. In addition, both **1**[18,21,22,23,24,25,] and **2**[24,26,27] have already been extensively studied in the literature, which allows for comparison with our results.

TDDFT(time-dependent density functional theory)/B3LYP-35/6-311+G(d,p) calculations of the vertical excitation energies of **1** and **2** (Table S1), with solvent effects described using the Integral Equation Formalism (IEF) of the Polarizable Continuum Model (PCM), demonstrate that i) the enol and keto forms of **1** and **2** present several intense transitions ($0.06 < f < 0.60$) in the 240 nm - 420 nm window, ii) the lowest-energy transition is generally the most intense and dominantly of HOMO-LUMO character whereas the next one presents a strong HOMO-1-LUMO contribution (Figure S1), iii) the first absorption band of the keto form is systematically red-shifted by 40-50 nm with respect to its analog for the enol form, and iv) these calculations overestimate the maximum absorption energy by 0.25-0.40 eV. As discussed in previous investigations,[28,29] part of this difference originates from the physical difference between absorption maxima and vertical transition energies, in particular from the vibronic structure of the absorption band which does not attribute necessarily the largest intensity to the 0-0 band. In addition, in some cases (typically, the enol form of **2**), the comparison between the maximum absorption wavelength and the wavelength of the vertical transition is not straightforward because several enol and keto bands overlap. These optical properties were calculated for the *cis* conformer of both forms, which is by far the dominant species. Indeed, using geometries fully optimized at the MP2/6-311+G(d,p)/IEF-PCM level of approximation, the *cis* forms are more stable than their *trans* analogs, with $\Delta G^0_{tc} = G^0(trans) - G^0(cis) = 8.0 \pm 0.2$ kcal/mol for the enol forms and 6.1 ± 0.1 kcal/mol for the keto forms.

The UV/visible absorption spectra of all individual species were simulated at the TDDFT/6-311+G(d,p) level using the method described in the Supporting Information

(Figures 1 and 2). The reliability of this method that was recently shown in the case of quinacridone and fluorescent protein chromophores, was further substantiated in the case of two other SA derivatives (**3** and **4**), which, however, adopt only the enol form at room temperature (Figures S2 and S3, Supporting Information). **4** is one of the very few SA's of which the absorption spectrum of the enol form presents a (somewhat) resolved vibronic structure. For SA **3**, at short wavelength, the relative intensity with respect to the maximum absorption band is underestimated, which has been attributed to the B3LYP-35 XC functional from comparisons with CC2 calculations.[30] For compound **4**, the calculations appear to slightly blue-shift the transition around 300 nm with respect to the dominant transition. These highlight remaining challenges in predicting the full UV/visible absorption spectra of chromophores having several electronic excitations in that domain, whereas for the dominant lowest energy transition, the recent literature provides the necessary tools for predicting the excitation energies,[31] oscillator strengths,[32,33] and vibronic structures.[34,35,36]

In the case of compounds **1** and **2**, although at small excitation energies, the absorption profile is determined by a single excitation, one to four excitations dominate the spectrum at higher energy (in the 275 nm – 375 nm wavelength range). For each SA, the enol and keto forms spectra were then mixed in different ratios until best reproducing the experimental spectra (Figures 1 and 2). For SA **1**, a keto:enol ratio of 35:65 is found to match best. Thus, the equilibrium favors the enol form and ΔG^0_{KE} = 0.37 kcal mol^{-1}. This value is close to the 0.34 kcal mol^{-1} obtained by Antonov *et al.*[23] from chemometric analysis of UV/vis absorption spectra (Table 1). On the other hand, for **2**, the keto form is dominant, the ratio amounts to 70:30 and ΔG^0_{KE} = - 0.50 kcal mol^{-1}. A value of -0.13 kcal mol^{-1} has been reported by Fabian *et al.*,[27] also in favor of a majority of keto form. Like for compound **3**, it is noticeable that the simulated spectra underestimate the intensities of the peaks at higher energy (mostly for **1**) with respect to the lowest energy band. For SA **1**, an additional spectrum (Figure S4) was then simulated where a CC2-corrected oscillator strength was used for the second excited state of the enol form. It allows improving the agreement with the experimental spectrum, though this does not change the estimate of the keto:enol ratio.

The UV/visible-based ΔG^0_{KE} values obtained in this work and from chemometric analysis do not compare as well with those calculated directly at DFT and correlated wavefunction levels (Table 1). B3LYP-35 and M06 results, obtained after full geometry optimization at the same level of theory with the 6-311+G(d,p) basis set and the IEF-PCM method to account for solvent effects (acetonitrile for **1** and ethanol for **2**) systematically overstabilize the keto form by about 2 kcal mol^{-1}. MP2 results present the opposite behavior, with overestimation of ΔG^0_{KE} by ~3 kcal mol^{-1}. Following Ref. 37 the spin component-scaled MP2 (SCS-MP2) method was also employed to calculate the electronic energy. The overestimation was reduced by ~0.8 kcal mol^{-1}. Additional single-point CCSD(T) calculations on SA analogs of **1** and **2** also gave corrections smaller than 1 kcal mol^{-1} with respect to the MP2 results. So, neither SCS-MP2 nor CCSD(T) methods are sufficient to explain that the enol-keto equilibrium is slightly displaced towards the enol form in **1** but towards the keto form for **2**. These discrepancies with respect to experiment and the combined UV/vis absorption experiment/simulation approach led us to conclude that the IEF-PCM method without explicit solvent molecules is probably responsible for the remaining 2 kcal mol^{-1} difference.

Table 1. ΔG^0_{KE} (kcal mol^{-1}) as determined with different techniques.

	UV/vis absorption		**Direct calculation of ΔG^0_{KE}**			
	Chemometrics	**This work**	**B3LYP-35**	**M06**	**MP2**	**SCS-MP2[c]**
1	0.34[a]	0.37	-1.31	-1.32	3.53	2.76
2	-0.13[b]	-0.50	-2.82	-2.43	3.08	2.29

[a] Ref. 23; [b] Ref. 27. [c] based on geometry optimized at the MP2 level.

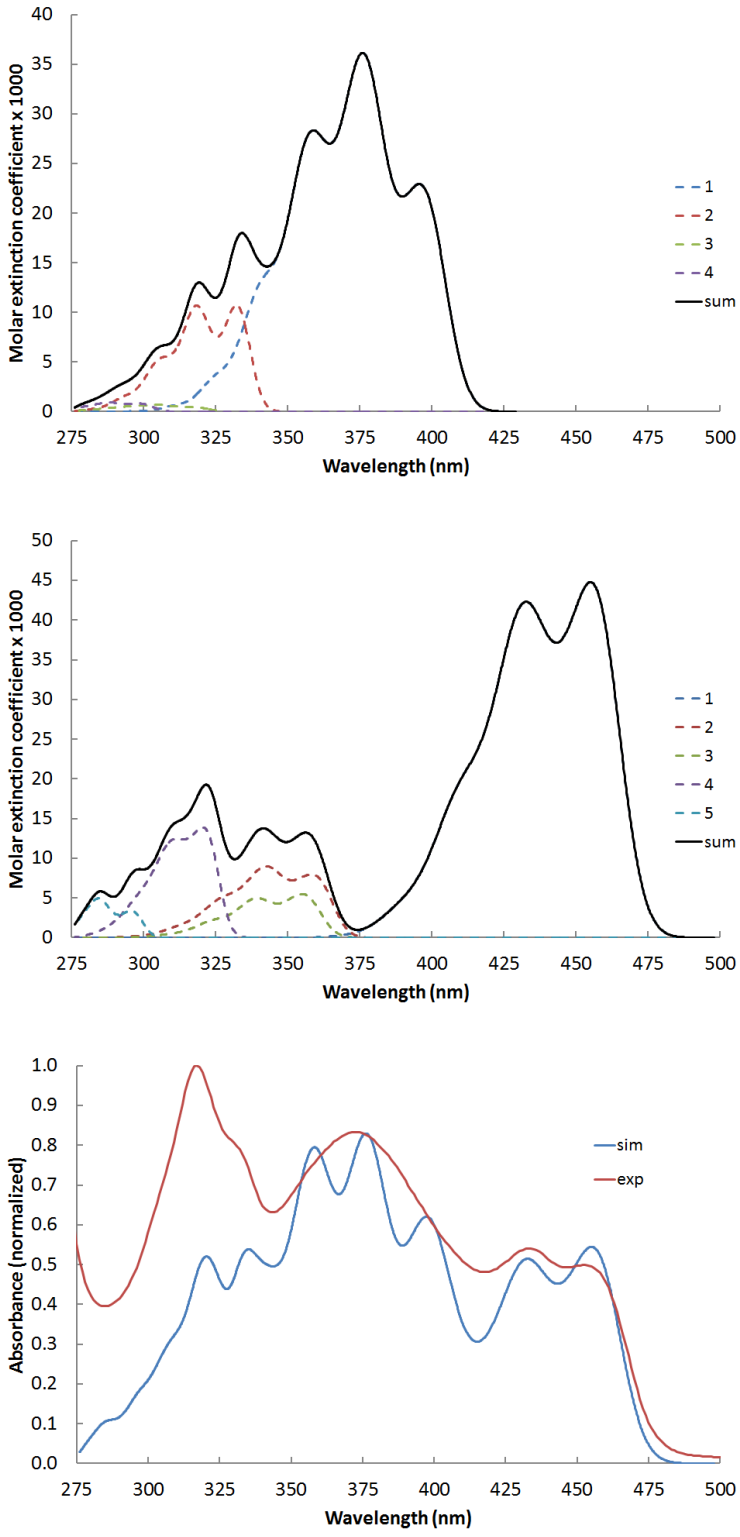


Figure 1: Simulated [TDDFT/B3LYP-35/6-311+G(d,p)/IEF-PCM(acetonitrile)] and experimental UV/visible absorption spectra of **1**. Top) simulated spectrum of the enol form and decomposition into its lowest-energy excited states contributions; Middle) simulated spectrum of the keto form and decomposition into its lowest-energy excited states contributions; and Bottom) Simulated spectrum for a 35:65 keto:enol mixture in comparison with experiment.

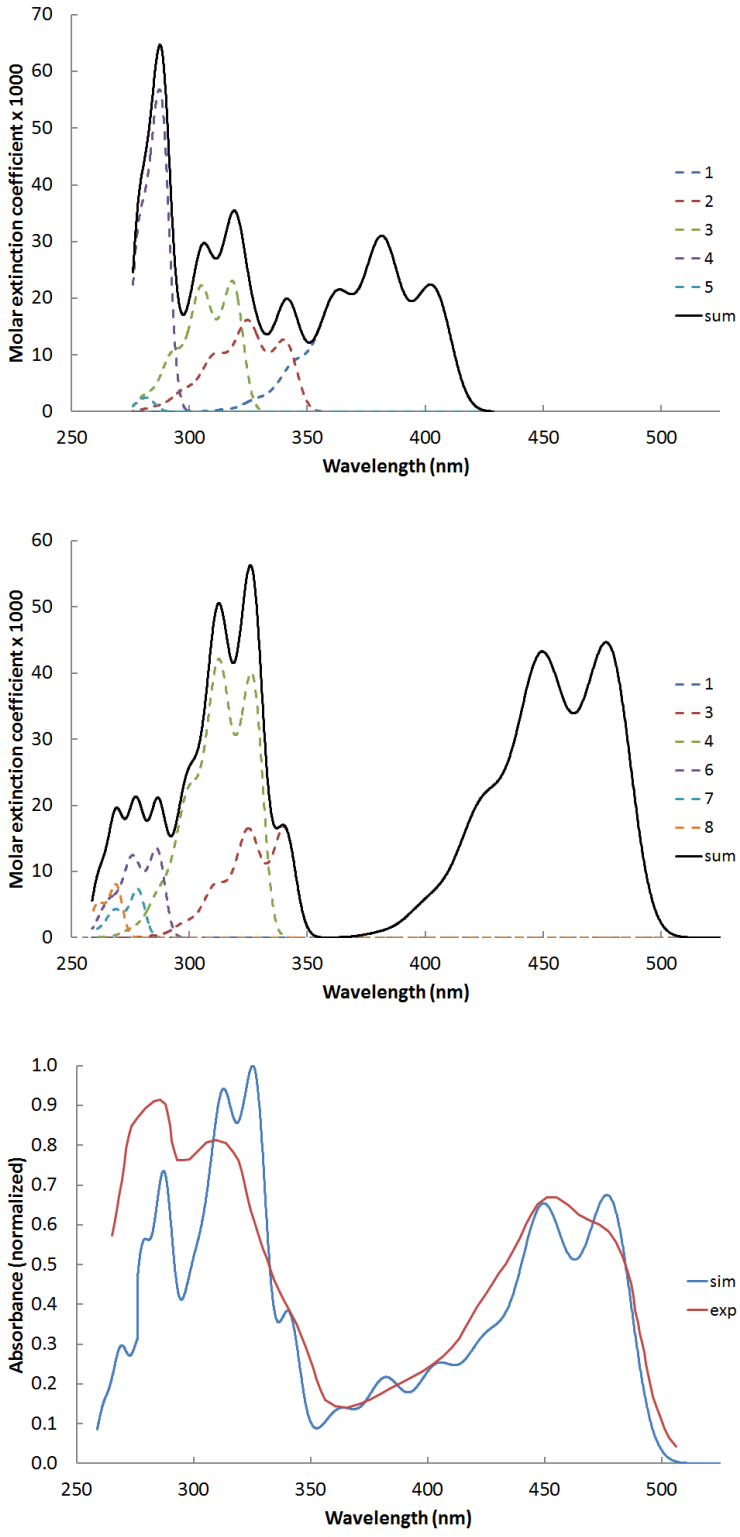


Figure 2: Simulated [TDDFT/B3LYP-35/6-311+G(d,p)/IEF-PCM(acetonitrile)] and experimental UV/visible absorption spectra of **2**. Top) simulated spectrum of the enol form and decomposition into its lowest-energy excited states contributions; Middle) simulated spectrum of the keto form and decomposition into its lowest-energy excited states contributions; and Bottom) Simulated spectrum for a 70:30 keto:enol mixture in comparison with experiment of Ref. 27.

ASSOCIATED CONTENT

Supporting Information: details on the theoretical and computational methods;

AUTHOR INFORMATION

Corresponding Author

B.C.: E-mail: benoit.champagne@unamur.be

F.Z.: E-mail: freddy.zutterman@unamur.be

ORCID

Benoît CHAMPAGNE: 0000-0003-3678-8875

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Notes

The authors declare no competing financial interest.

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