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Z/*E*(C=C)-isomerization of coumarin enamines induced by organic solvents

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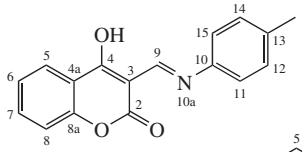
Imines of 3-formyl-4-hydroxycoumarin have been found to exist in *E*- and *Z*-ketoenamine forms in a crystal state and undergo *Z*/*E*-isomerization around the C=C bond in organic solvents (*e.g.*, $CHCl_3$).

Noncovalent interactions play an important role in organic chemistry, in the formation and function of supramolecular structures and various biological substrates.[1–3] Moreover, solvatochromic compounds sensitive to the noncovalent interactions are of interest for the creation of novel sensor and signaling systems.[4,5] Heteroaromatic imines are well known for their ability to undergo solvent driven isomerizations.[6–9] The solvatochromic behaviour of coumarin derivatives is of special interest due to their prominent fluorescence potential.[10] Earlier, we have found some imines of 8-formyl-7-hydroxycoumarin to undergo *E*/*Z*-isomerization around the C=N bond followed by fluorescence modulation.[11]

Here, we report the *Z*/*E*-isomerization of imines **1** and **2** of 3-formyl-4-hydroxycoumarin induced by organic solvents. Spectral grade $CDCl_3$ and [$^2H_6$]DMSO have been used. The structure of imine **1** has been studied by Wolfbeis *et al.*,[12] however, its *E*/*Z*-isomerization has not been reported.



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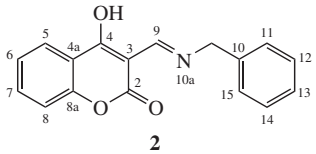

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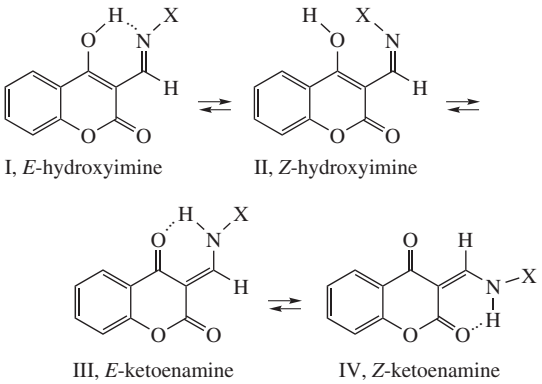
Due to a solvent impact on the hydrogen bonding in compounds **1** and **2**, one can expect solvent driven tautomeric transformations and *E*/*Z*-isomerizations, including rotation around both C=N and C=C bonds (Scheme 1).

Imines **1** and **2** have been synthesized by straightforward procedure from 3-formyl-4-hydroxycoumarin and related amines – *p*-toluidine and benzylamine, respectively. Their structures have been confirmed by ^{1}H and ^{13}C NMR spectroscopy and comparison of their melting points with published data.[12,13,†]

The most characteristic signals of imines **1** and **2** in ^{1}H NMR spectra (both in $CDCl_3$ and in [$^2H_6$]DMSO) belong to protons 9-H located at 8.5–9.5 ppm and to the exchangeable (OH or NH) protons, which form intramolecular hydrogen bonds and can be seen in the region of 12–14 ppm for all four isomers. We have found both exchangeable and 9-H signals to appear in ^{1}H NMR spectra as pairs of doublets (see Online Supplementary Materials). Splitting of these signals is due to scalar interaction between NH and 9-H protons. This indicates on the existence of imines **1** and **2** in solution in the *E*- and *Z*-ketoenamine forms. The ratio of signal intensities is equal for both NH and 9-H doublets and corresponds to the relative contents of *E*- and *Z*-isomers in solution. Coupling constants in both (*E*- and *Z*-) isomers are about 13–15 Hz, which correspond



I, *E*-hydroxyimine II, *Z*-hydroxyimine

III, *E*-ketoenamine IV, *Z*-ketoenamine

Scheme 1 Tautomeric forms of 3-formyl-4-hydroxycoumarin imines.

† *3-(*p*-Tolylaminomethylene)chroman-2,4-dione* **1**. Yellow needle-like crystals (from ethanol), mp 192–194 °C (lit.,[12] mp 191 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 13.60 (d, 0.66H, NH, $J_{10,9}$ 13.7 Hz), 11.91 (d, 0.34H, NH, $J_{10,9}$ 14.5 Hz), 9.98 (d, 0.34H, 9-H, $J_{9,10}$ 14.5 Hz), 9.87 (d, 0.66H, 9-H, $J_{9,10}$ 13.7 Hz), 8.04 (dd, 1H, 5-H, $J_{5,6}$ 7.7 Hz, $J_{5,7}$ 1.7 Hz), 7.66–7.70 (m, 1H, 7-H), 7.53–7.58 (m, 2H, 6-H, 8-H), 7.20–7.40 (m, 4H, 1′-H, 2′-H, 4′-H, 5′-H), 2.39 (s, 3H, Me).

3-(Benzylaminomethylene)chroman-2,4-dione **2**. Yellow crystals (from toluene), mp 165–167 °C (lit.,[13] 167–168 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 12.30 (m, 0.7H, NH), 10.50 (m, 0.3H, NH), 8.66 (d, 0.3H, 9-H, $J_{9,10}$ 14.9 Hz), 8.49 (d, 0.7H, 9-H, $J_{9,10}$ 13.8 Hz), 8.07 (dd, 0.3H, 5-H, $J_{5,6}$ 7.7 Hz, $J_{5,7}$ 1.07 Hz), 8.08 (dd, 0.9H, 5-H, $J_{5,6}$ 7.7 Hz, $J_{5,7}$ 1.5 Hz), 7.55–7.66 (m, 1H, 7-H), 7.42–7.53 (m, 2H, 6-H, 8-H), 7.20–7.40 (m, 5H, 1′-H, 2′-H, 3′-H, 4′-H, 5′-H).

Table 1 Results of GIAO chemical shift calculations for representative nuclei in *E*- and *Z*-ketoenamine forms of **1**. Shown are isotropic values calculated using TMS as standard. Experimentally measured values are shown in parentheses.

Hydrogen and carbon nuclei	Isotropic chemical shift/ppm	
	E-isomer	*Z*-isomer
NH	12.60 (13.60)	11.40 (12.00)
9-H	9.07 (8.90)	9.46 (9.00)
C(2)	167.80 (163.60)	169.30 (165.20)
C(3)	105.10 (98.37)	107.10 (98.39)
C(4)	188.30 (181.60)	184.30 (178.50)
C(9)	161.62 (154.60)	160.67 (153.20)
C(10)	124.32 (137.62)	124.24 (134.48)

to the *trans*-orientation of C(9)–H and N–H bonds. As one can see from the structures of two ketoenamine isomers, this orientation of C(9)–H and N–H bonds is stabilized by intramolecular H-bonds formed between NH proton and carbonyl oxygen in either the 4-position (in *E*-isomer) or the 2-position (in *Z*-isomer).

The ^{13}C NMR spectra of both imines confirm their existence as two *E*- and *Z*-ketoenamine isomers. Signals of atom C(4) of predominant isomers (at 181.6 and 181.2 ppm, respectively, for imines **1** and **2**) are shifted to lower field comparing to that of the minor isomers (at 178.5 and 178.4 ppm, respectively), whereas the signal of atom C(2) has opposite shielding effect. This can easily be explained by existence of two hydrogen bonds, C(4)=O···H–N and C(2)=O···H–N in *E*- and *Z*-ketoenamines, respectively. Signals of atom C(2) of predominant isomers (at 163.6 and 163.7 ppm, respectively) are shifted to higher field comparing to that of the minor isomers (at 165.2 and 164.9 ppm, respectively). Both C(2) signals appear as doublets due to the spin–spin interaction of atom C(2) with proton 9-H. Heteroconstants of minor isomers turned to be definitely larger ($J_{C(2),9\text{-H}}$ 9.94 and 10.9 Hz, respectively, for imines **1** and **2**) than that of major isomers ($J_{C(2),9\text{-H}}$ 3.07 Hz for both imines). The above values of $J_{C(2),9\text{-H}}$ show the minor isomers to be *Z*-ketoenamines, since these isomers possess transoid orientation of C(2)–C(3) and C(9)–H bonds. As a result major isomers should be considered as *E*-isomers.

There are no signals of *E*- and *Z*-hydroxyimine tautomers both in the ^{1}H NMR and in the ^{13}C NMR spectra. These data agree with results of AM1 calculations: energies of formation of *E*- and *Z*-hydroxyimine tautomers are 6–6.5 kcal mol^{-1} higher than those of *E*- and *Z*-ketoenamines.

The energies of formation of *E*- and *Z*-ketoenamines, III and IV, charge distribution and lengths of intramolecular hydrogen bonds in both isomers have been calculated using the B3LYP DFT method implied in Gaussian 98 and basis set 6-311++G(d,p).[14–17] Results of the calculations show that *E*-ketoenamine has lower energy of formation than Z-isomer and, therefore, is more stable (ΔE = 0.65 kcal mol^{-1}). Such an energy difference corresponds to the thermodynamic equilibrium between two states with populations of ~75 and ~25%, respectively, which are close to the experimentally measured values (~70 and 30%). B3LYP DFT calculations with gauge-including atomic orbitals (GIAO) method have been used to estimate isotropic chemical shifts of hydrogen and carbon nuclei in both isomers of **1**. Calculated values show good qualitative agreement with the experimental values (Table 1). Results of GIAO calculations also helped to confirm assignments of signals 9-H in *E*- and *Z*-isomers: 9-H in *E*-ketoenamine has higher field shift (8.9 ppm) comparing to *Z*-isomer (9.00 ppm).

X-ray studies confirm the ability of 3-formyl-4-hydroxycoumarin imines to exist in two ketoenamine forms. We have found the crystal packing of **2** to be formed by two isomer molecules (**A** and **B**), located in the same position of crystallographic cell. Individual structures of these molecules are shown in Figure 1.‡ One can see that molecules **A** and **B** are *E*- and *Z*-ketoenamine isomers respectively. Selected bond distances and angles of imine **2** are given in Online Supplementary Materials.

As one could expect, ^{1}H NMR spectra of the imines are sensitive to the solvent and also change with time upon the dissolution of the substances. Thus, in spectrum recorded for freshly prepared solution in $CDCl_3$ intensity of lower field doublet of 9-H proton (9.00 ppm, $J_{9,10a}$ 14.4 Hz: *Z*-isomer) of imine **1** is much higher than analogous higher field signal (8.90 ppm, $J_{9,10a}$ 13.9 Hz: *E*-isomer). Measurement of the spectrum of the same solution after 25 h at room temperature shows a decrease of intensity of the signal at 9.00 ppm from 90 to 30% and corresponding increase of the intensity of the doublet at 8.90 ppm from 10 to 70%. Predominance of the *Z*-isomer in freshly prepared solution seems to be explained by its preference in the crystal state.

The equilibrium also depends on temperature. Thus, at 40 °C equilibrated content of *E*-isomer decreases to 65% and amount of *Z*-isomer proportionally increases to 35%. Cooling of this solution to room temperature during several hours restores the previous *E*/*Z* ratio (70 and 30%). Monitoring of the intensities of the signals of *E*- and *Z*-isomers of imine **1** with time at several temperatures between 30 and 50 °C allows us to calculate *E*/*Z* isomerisation rate constants at these temperature points. Decay of the signals of *Z*-isomer and growth of the signals of *E*-isomer on the initial stage of the reaction (~10% of turnover) turned to be well described by the first-order kinetics. Using this assumption, activation energy of 84±6 kJ mol^{-1} for isomerization of imine **1** *Z*-ketoenamine form to correspondent *E*-isomer was calculated from the linear fitting of the ln k to the values of 1/T (Figure 2, inset).

The activation energy of the C(3)–C(9) bond rotation in compound **1** was also estimated using the quantum mechanical calculations by the Hartree–Fock method in 6-31++G(d,p) basis set. Theoretical value of 130 kJ mol^{-1} is notably larger than experimentally measured one. The most probable explanation could be related to the solvent effects. Indeed, calculations were carried out *in vacuo*, whereas experimentally measured value

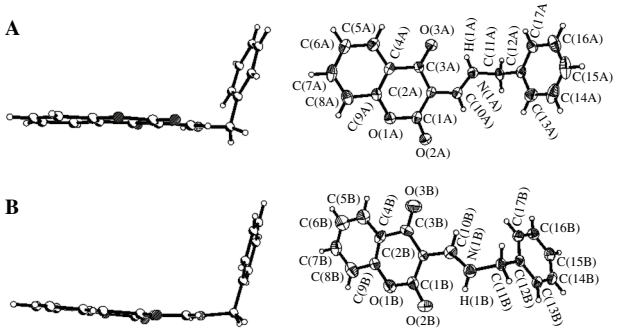


Figure 1 The molecular structure of *E*- and *Z*-ketoenamine isomers of imine **2**.

‡ *X-Ray diffraction data.* At 25 °C crystals of **2** ($C_{17}H_{13}NO_3$, M = 279.28) are triclinic, space group $P\bar{1}$, a = 10.669(2), b = 11.983(2) and c = = 12.169(2) Å, α = 62.38(3)°, β = 89.29(3)°, γ = 81.67(3)°, V = 1361.3(5) Å^3, Z = 4, d_{calc} = 1.36 g cm^{-3}, μ = 0.094 mm^{-1}, reflections observed/independent 9513/5301, 379 parameters refined, R = 0.075 for 2608 reflections with $F_0 > 4\sigma(F_0)$. Reflections were collected on a Bruker SMART APEX2 CCD diffractometer using MoKα radiation. Crystal structure was solved by direct methods followed with Fourier synthesis using SHELXS-97. All non-hydrogen atoms were refined using anisotropic full-matrix approximation using SHELXL-97. Coordinates of hydrogen atoms were calculated.

CCDC 700853 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

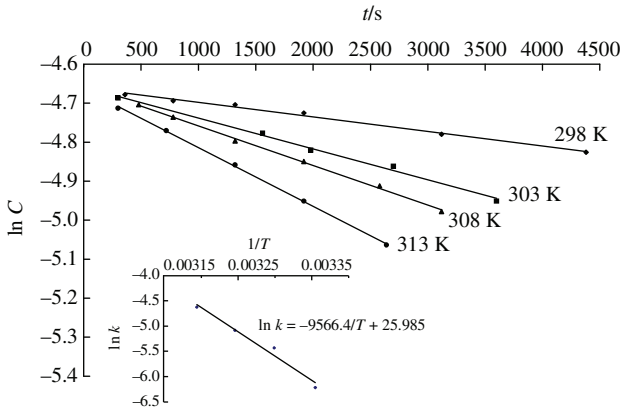


Figure 2 Monitoring of the intensities of the signal of imine **1** *Z*-isomer with time at different temperatures.

corresponds to the chloroform solution. Difference between calculated and experimental values (46 kJ mol^{-1}) is in fact close to the difference between activation energy calculated both *in vacuo* and in CH_2Cl_2 solution (55 kJ mol^{-1}) for *E*/*Z*-isomerization of spiropyran merocyanine carried out using similar DFT approach.[18]

We have found that the solvent effect on *Z*/*E*-isomerization becomes greater when a more polar solvent is used. Thus, the ^{1}H NMR spectrum of imine **1** reflects evidences of its much faster isomerization in [$^2H_6$]DMSO solution. Signal of 9-H at 8.70 ppm is a broad singlet immediately after dissolution of imine **1** in [$^2H_6$]DMSO. This broad signal disintegrates into two doublets at 8.66 ppm (*E*-isomer, $J_{9,10a}$ 13.5 Hz, 73%,) and at 8.72 ppm (*Z*-isomer, $J_{9,10a}$ 14.8 Hz, 27%) after 4 h. One can observe similar changes with doublet in lower field (11–14 ppm) arisen from resonance of NH protons. Two broad NH signals at 13.4 ppm and at 11.7 ppm are seen in ^{1}H NMR spectrum immediately after the dissolving of imine **1** in [$^2H_6$]DMSO. The intensities of signals at 13.5 ppm (*E*-isomer) and 11.8 ppm (*Z*-isomer) have the same ratio as two signals of 9-H proton seen in the spectrum after 4 h. No additional changes in ^{1}H NMR spectra of imine **1** can be detected after that period of time.

Thermodynamic equilibrium between two isomers of imine **1** is reached even faster in CD_3OD comparing with that in $CDCl_3$ and [$^2H_6$]DMSO. Two broad 9-H singlets of different intensities can be seen in ^{1}H NMR spectrum immediately after the dissolving of imine **1**. The signal at 8.94 ppm with higher intensity corresponds to *E*-isomer, whereas lower intensity signal at 9.06 ppm belongs to *Z*-isomer. Ratio of intensities of these signals does not change in time. Absence of splitting of these two signals is very likely to be due to fast H/D exchange of NH proton in ketoenamine forms in CD_3OD.

The behaviour of imine **2** in organic solvents is somewhat different from that of imine **1**. Two 9-H proton doublets appear in ^{1}H NMR spectra of **2** recorded both in $CDCl_3$ and in [$^2H_6$]DMSO immediately after preparation of the solution. Intensity of high-field signal at 8.5 ppm (*E*-isomer) is higher than low-field signal at 8.68 ppm (*Z*-isomer). Ratio of intensities changes slightly in different solvents and is near to 65:35. The NH signal of *E*-isomer is observed at 12.2 ppm, whereas analogous signal of *Z*-isomer is seen at 10.5 ppm. Ratio of the signals that belong to *E*- and *Z*-isomers remains unchanged with time. Two broad signals are exhibited in ^{1}H NMR spectrum of imine **2** solution in CD_3OD. Ratio of their intensities is also remained unchanged after preparation of the solution.

A few examples of *E*/*Z*-isomerization around the C=C bond induced by solvents have been reported. All deal with enamine structures.[19–21] Earlier, we found that indoline merocyanines derived from 3-formyl-4-hydroxycoumarins exist as mixtures of *E*- and *Z*-isomers.[19] Berthet and coworkers have reported coexistence of spirooxazine and its four transoid photomerocyanines.[20] The *trans-trans-cis*/*trans-trans-trans* isomerization of photochromic spiropyran merocyanines has been also studied both experimentally[19] and using DFT calculations[14] to explain the solvatochromic effects and sensing properties of organic substrates.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.07.014.

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