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Z/E (C=C)-isomerization and fluorescence modulation of imines of 7-*N,N*-dialkylamino-4-hydroxy-3-formylcoumarins in organic solvents

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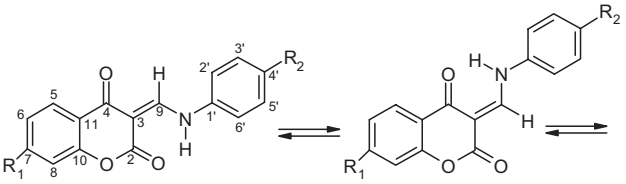
Abstract

Imines of 7-dialkylamino-3-formyl-4-hydroxycoumarins have been found to exist in *Z*-ketoenamine form in crystal state and undergo *Z/E*-isomerization around C=C bond in organic solvents at room temperature. Activation energies of isomerization have been measured experimentally and calculated by the DFT B3LYP method. Transition of ketoenamine form of *p*-nitrophenylimines into (hydroxy)imine form at low concentration (10^{-5} M) in polar solvents is accompanied by strong increase in fluorescence.

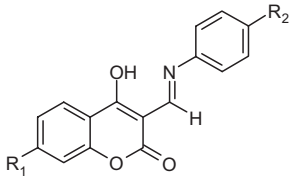
Keywords: coumarin; fluorescence; imines; isomerization; solvents.

Introduction

Noncovalent interactions play an important role in organic chemistry, in formation and function of supramolecular structures and biochemical substrates (Williams et al., 1993; Uekama et al., 1998; Patony et al., 2004). Moreover, solvatochromic compounds sensitive to the noncovalent interactions are of substantial interest for creation of novel sensor systems (Rudzinski and Nocera, 2001; Yarmoluk et al., 2002). Heteroaromatic imines are well known for their ability to undergo solvent driven isomerizations (Herkstroeter, 1976; Garnovskii et al., 2002). Previously we have found that some imines of formyl(hydroxy)coumarins can undergo *E/Z*-isomerization around both C=N- and C=C-bonds (Traven et al., 2007, 2009). Solvatochromic behavior of coumarin derivatives are of special interest owing to their prominent fluorescence potential (Haugland, 1996). In this paper, we studied *Z/E*-isomerization and transformations of imines **1–3** of 7-dialkylamino-3-formyl-4-hydroxycoumarins in organic solvents followed by strong increase of fluorescence.



where R_1=NEt_2, R_2=H (**1**); R_1=NEt_2, R_2=NO_2 (**2**);



R_1=NMe_2, R_2=NO_2 (**3**)

where R_1=NEt_2, R_2=H (**1**); R_1=NEt_2, R_2=NO_2 (**2**); R_1=NMe_2, R_2=NO_2 (**3**).

Results and discussion

We found that both N-H and H_9 signals in ^{1}H NMR spectra appear as pairs of doublets at 11–14 ppm and 8.7–8.9 ppm, respectively (Table 1). Splitting of these signals is due to scalar interaction between NH and H_9 protons. This indicates the presence of imines **1–3** in solution in the *E*- and *Z*-ketoenamine forms. Coupling constants in both isomers are approximately 13–15 Hz, which corresponds to the *trans*-orientation of C_9-H and NH bonds. As one can see from the structures of two ketoenamine isomers, this orientation of C_9-H and NH bonds is stabilized by intramolecular H-bonds formed between NH proton and carbonyl oxygen either in position 4 (in *E*-isomer) or in position 2 (in *Z*-isomer).

^{13}C NMR spectra of compounds **1–3** also confirm their existence as *E*- and *Z*-ketoenamine isomers. For example, signal of atom C_4 of the predominant isomer at δ 180.1 of imine **1** is shifted to lower field compared to that of the minor

Table 1 Chemical shifts of *E*- and *Z*-isomers in ^{1}H NMR spectra of **1–3** ($CDCl_3$).

Compound number	N-H		H_9		H_5	
	E-	*Z*-	*E*-	*Z*-	*E*-	*Z*-
1	13.62	11.71	8.74	8.92	7.87	7.94
2	13.70	11.64	8.71	8.89	8.30	8.21
3	13.82	11.79	8.83	8.98	8.35	8.35

isomer (at δ 176.8), whereas the signal of atom C_2 has opposite shielding effect. Signal of atom C_2 of the predominant isomer at δ 163.8 is shifted to higher field compared to that of the minor isomer (at δ 165.3). This can easily be explained by the existence of two hydrogen bonds -C_4=O…H-N and C_2=O…H-N in *E*- and *Z*-(keto)enamines correspondingly. The C_2 signals appear as doublets owing to spin-spin interaction of atom C_2 with proton H_9. Heteroconstant of the minor isomer is definitely larger ($J_{C2,H9}$ is equal to 9.94 Hz) than that of the major isomer ($J_{C2,H9}$ is equal to 3.07 Hz). The noted values of $J_{C2,H9}$ suggest that the minor isomer is *Z*-ketoenamine, because this isomer possesses transoid orientation of C_2C_3 and C_9H bonds. As a result, the major isomer should be considered as *E*-isomer.

The assignment of signals of *E*- and *Z*-isomers has been supported by quantum mechanical calculations [B3LYP DFT GIAO/6-31++G(2d,p)] (Table 2).

Compound **1** reaches equilibrium state immediately after dissolution both in polar and in nonpolar solvents. Compounds **2** and **3** do that only in polar solvents (DMSO). When dissolved in nonpolar $CDCl_3$, they isomerize slowly from *Z*- to *E*-ketoenamine form (Figure 1).

Several compounds with enamine structure have been reported to undergo *Z/E*-isomerization around C=C bond, induced by solvents (Hamdi et al., 1993; Hobley et al., 2000; Traven et al., 2005; Berthet et al., 2006; Manaev et al., 2006). By monitoring the intensities of the signals of *E*- and *Z*-isomers of compound **2** with time at several temperatures between 30°C and 50°C, we calculated rate constants and activation energy of the *Z/E*-isomerization. Activation energy of the reaction is 132.6±6.2 kJ/mol, which is 50 kJ/mol more than that of ketoenamines unsubstituted at the position 7 (approximately 84 kJ/mol) (Traven et al., 2009).

The value of activation energy of the C_3-C_9 bond rotation in compound **2** was also estimated using the quantum mechanical calculations by the Hartree-Fock method in 6-31++G(d,p) basis set. The theoretical value of 158.5 kJ/mol is notably larger than the 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 corresponds to the solution.

Table 2 Calculated chemical shifts in ^{1}H and ^{13}C NMR spectra (ppm) of *E*- and *Z*-isomers of **1** (experimental values are given in parentheses).

Atom	*E*-Isomer	*Z*-Isomer
NH	12.93 (13.62)	12.26 (11.71)
H_9	9.29 (8.74)	9.52 (8.92)
C_2	163.14 (163.80)	168.14 (165.30)
C_4	186.87 (180.05)	180.51 (176.80)

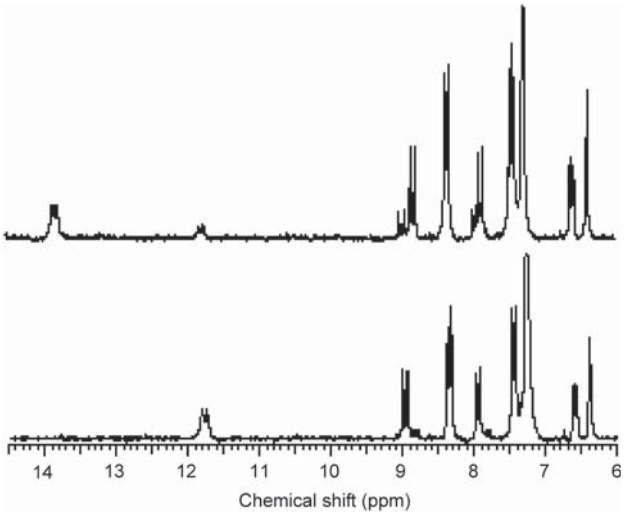


Figure 1 ^{1}H NMR spectra of **2** ($CDCl_3$) after dissolution (down) and after 50 h (up).

Other transformations of compounds **2** and **3** can be seen upon dilution of their solutions in polar organic solvents (DMSO, DMF and ethanol) and recording of electron absorption and emission spectra (Figure 2).

Absorption maxima of different isomeric forms of **2** have been calculated by using the B3LYP TD DFT method in the 6-31++G(2d,p) basis set (Table 3) (Fabian et al., 2002; Dreuw and Head-Gordon, 2005; Jacquemin et al., 2005).

According to the quantum chemical calculations, we conclude that the (hydroxy)imine form predominates in diluted solutions (concentration near to 10^{-5} M). This form turns out to be responsible for more than 100-fold increase in fluorescence.

X-Ray studies confirm the ability of imines **1–3** to exist in the (keto)enamine form. The double bond C_3=C_9 in crystals of compound **2** (Figure 3) is much shorter (1374 Å) than that of unsubstituted imines (1410 Å). This result is also supported by [B3LYP/6-31G(d,p)]-calculations. The shortening of the C_3=C_9-bond seems to be the reason of the mentioned increase in the activation energy of *E/Z*-isomerization of **2**.

Conclusion

Imines of 7-dialkylamino-3-formyl-4-hydroxycoumarins seem to exist in crystal state as pure *Z*-ketoenamines and undergo *E*-isomerization when dissolved in organic solvents. Polar solvents weaken strong intramolecular H-bonds in nitroketoenamines **2** and **3**, so that their isomerization into (hydroxy)imine tautomer becomes possible with a strong increase in fluorescence.

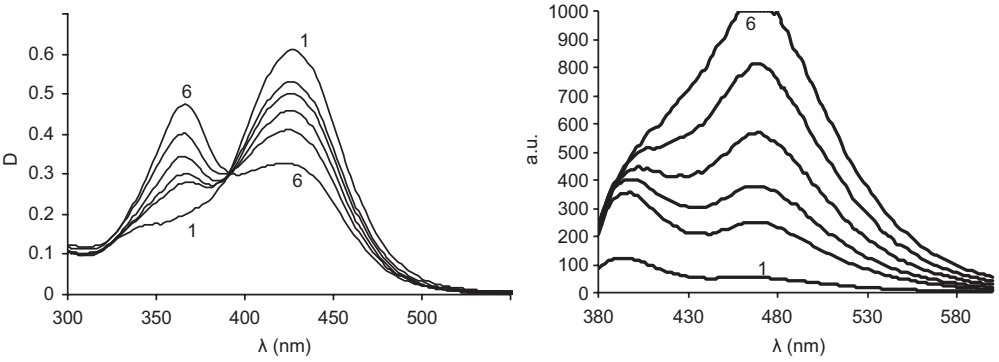


Figure 2 Electron absorption (left) and fluorescence spectra (right) of **2** in DMF immediately after dissolution (1) and in 12, 30, 90, 132 and 240 min (2–6) at room temperature.

Table 3 The longest wavelength bands in EAS of isomeric forms of compound **2**, calculated with the B3LYP TD DFT method in 6-31++G(2d,p) basis set and experimental data.

Isomer	λ_{max} (calculated), nm	λ_{max} (measured), nm
2, *Z*-(keto)enamine	431	434
2, *E*-(keto)enamine	429	434
2, (hydroxy)imine	400	362

Experimental section

^{1}H and ^{13}C NMR spectra were acquired on a Bruker WP 200 MHz spectrometer in CD_3OD, $CDCl_3$ and DMSO-d_6 and on Unity Plus 400 MHz (Varian) spectrometer in DMSO-d_6. Chemical shifts are relative to TMS as an internal standard. Mass spectra were recorded on a Finigan mass spectrometer at an energy of ionizing electrons of 70 eV and a temperature of the source of 150°C. Concentration of compound **2** in ^{1}H NMR kinetic studies was 1–3 mM. Signals of *E*- and *Z*-ketoenamine forms have been registered in the intervals of 6–70 min. First spectrum was recorded 5–6 min after the preparation of solution. Relative concentrations of *E*- and *Z*-isomers were calculated using integral intensities of the related signals. Rate constants *k* have been calculated by the first-order kinetic equation $\ln(c)=k\cdot t$. All quantum mechanical calculations were carried out with GAUSSIAN 98 suite of programs (Frisch et al., 1998). Geometry optimization was carried out with density functional theory (DFT) (Parr and Yang, 1989) using the Becke's hybrid exchange functional and non-local, correlation functional of Lee, Yang and Parr (B3LYP) (Lee et al., 1988) and 6-31++G(d,p) basis set. The ^{1}H and ^{13}C chemical shieldings were calculated using the GIAO method with 6-31++G(2d,p) basis set (Wolinski et al., 1990). To calculate absolute values of chemical shifts, isotropic shieldings were calculated for TMS using the same basis set. Calculations of the energy profile for the rotation of C_3-C_9 bond was carried out using the Hartree-Fock method and 6-31++G(d,p) basis set. Full geometry optimization was carried out for all the intermediate structures of scanned torsion angle C_3-C_9 with stepwise changes of 5 or 30° (this torsion angle was kept fixed for each structure during the optimization). X-Ray diffraction study of **2** was carried out with a Bruker SMART APEX2 CCD diffractometer using Mo-Kα radiation at room temperature. Crystal structure was solved by direct methods followed with Fourier synthesis using SHELXS-97 (Sheldrick, 1997). All non-hydrogen atoms were refined using anisotropic full-matrix approximation using SHELXL-97 (Sheldrick, 1997). Coordinates of hydrogen atoms were calculated. Atom coordinates, bond lengths, and angle values were deposited to Cambridge Crystallographic Data Centre (CCDC). These data are available via www.ccdc.cam.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336-033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 700853.

Synthesis of compounds 1–3

Solution of 7-*NN*-diethylamino-4-hydroxycoumarin (0.5 mg, 2.1 mmol) and amine (2.1 mmol) in DMF (3.5 ml) was heated at 120°C for 10 min. The crystals that formed after cooling were filtered off, washed with water, and dried in air.

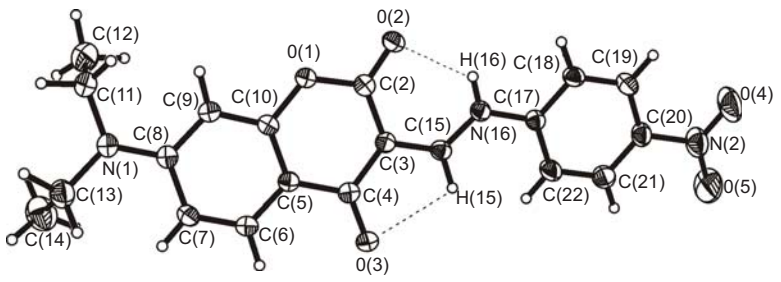


Figure 3 Crystal structure of compound **2**.

7-NN-Diethylamino-3-(phenylamino)methylen-2H-chromen-2,4(3H)-dione (1) Yellow crystals, m.p. 149–150°C (Lit. 153°C) (Ollinger et al., 1975), ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 13.66 (d, 0.8 H, NH, $J_{NH,9}$=13.3); 11.69 (d, 0.2 H, NH, $J_{NH,9}$=14.4); 8.98 [d, 0.2 H, H(9), $J_{NH,9}$=14.4]; 8.82 [d, 0.8 H, H(9), $J_{NH,9}$=13.3]; 7.95 [d, 0.2 H, H(5), $J_{5,6}$=9.2]; 7.86 [d, 0.8 H, H(5), *J*=9.2], 7.38–7.52 [m, 2 H, H(6), H(8)], 7.21–7.38 [m, 3H, H(1′), H(2′), H(4′), 6.58] [dd, 1 H, H(6), $J_{5,6}$=9.2, $J_{5,7}$=2.6]; 6.38 [d, 1 H, H(6), $J_{5,6}$=2.6], 3.45 (q, 4H, CH_2, *J*=6.7), 1.24 (t, 6H, CH_3).

7-NN-Diethylamino-3-[(4-nitrophenyl)amino]methylen-2H-chromen-2,4(3H)-dione (2) Yellow crystals, m.p. 281–282°C, ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 13.68 (d, 0,7 H, NH, $J_{NH,9}$=13.4), 11.72 (d, 0.3 H, NH, $J_{NH,9}$=14.4), 8.87 [d, 0.3 H, H(9), $J_{NH,9}$=14.4], 8.69 [d, 0.7 H, H(9), $J_{NH,9}$=13.4], 8.12–8.40 [m, 2 H, H(3′), H(5′)], 7.60–8.90 [m, 1 H, H(5)], 7.2–7.50 [m, 2 H, H(2′), H(6′)], 6.47 [dd, 1 H, H(6), $J_{5,6}$=9.2, $J_{5,7}$=2.6], 6.23 [d, 1 H, H(6), $J_{5,6}$=2.6], 3.35 (q, 4 H, CH_2, *J*=6.7), 1.12 (t, 6 H, CH_3). MS (70 eV), *m/z* 382 $[M]^+$. Analysis: calculated for $C_{17}H_{13}NO_3$: C, 62.99; H, 5.02; N, 11.02. Found: C, 62.91; H, 5.20; N, 11.06.

7-NN-Dimethylamino-3-[(4-nitrophenyl)amino]methylen-2H-chromen-2,4(3H)-dione (3) Yellow crystals, m.p. 319–320°C (Lit. 320°C) (Wolfbeis, 1977), ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 13.84 (d, 0.9 H, NH, $J_{NH,9}$=13.4), 11.4 (d, 0.1 H, NH, $J_{NH,9}$=14.4), 8.9 [d, 0.1 H, H(9), $J_{NH,9}$=14.4], 8.83 [d, 0.9 H, H(9), $J_{NH,9}$=13.4], 8.36 [d, 2H, H(3′), H(5′), *J*=9.23], 7.98 [d, 0.1 H, H(5), $J_{5,6}$=9.2]; 7.89 [d, 0.9 H, H(5), *J*=9.2], 7.42 [d, 2H, H(2′), H(6′), *J*=9.23], 6.63 [dd, 1 H, H(6), $J_{5,6}$=9.2, $J_{5,7}$=2.6], 6.49 [d, 1H, H(6), $J_{5,6}$=2.6], 3.12 [s, 4H $N(CH_3)_2$].

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