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PROTON DISSOCIATION-INDUCED TAUTOMERIZATION OF 4-SUBSTITUTED 7-HYDROXYCOUMARIN AND ITS BRIDGED DIMER IN THE GROUND STATE

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Abstract – An investigation was undertaken to elucidate solvent effects on the intramolecular interaction between the 7-hydroxycoumarin chromophores in the title bridged dimer in the presence of tertiary amine. Analysis of equilibrium constants for the proton dissociation and proton dissociation-induced tautomerization of the title coumarin derivatives confirmed that both the hydroxycoumarin anion and the tautomer anion derived from the bridged dimer in methanol and acetonitrile are stabilized through the intramolecular hydrogen bonding interaction while dimethyl sulfoxide enables these anions to behave independently by its strong solvation effect.

Active research has been directed toward establishing the structure of tautomers generated by the prototropic isomerizations of various naturally-occuring amino- or hydroxy-substituted heterocyclic compounds in the ground and excited singlet states, owing to the fact that these pharmaceutically useful compounds frequently exhibit unexpected reactivities and properties in solution.[1] For example, the complicated pH-dependent fluorescence behavior of 7-hydroxycoumarin (7HC) and its derivatives has attracted considerable attention from spectroscopic and practical points of view, and many attempts have been made to unravel the structure of excited-state species that are responsible for the multiple fluorescence of hydroxy-substituted coumarins.[2] The recent finding that the 7HC-derived hydrogen-bonded complex, anion, and tautomer anion are produced in the ground state depending on both the amine basicity and the solvent property paved the way for characterizing the ground-state tautomer anion incorporated into the β-cyclodextrin cavity or the cationic micellar surface.[3–5] In addition, more basic tertiary amine and more polar aprotic and protic solvents were also found to prefer the formation of the tautomer anion that exists in the form of a proton-transferred ion pair.[3] Thus, if we take into account the fact that the ion pair is stable in the ground state and then exhibits intense absorption and fluorescence in the visible region, it is possible to find a new application of the hydroxycoumarin-derived tautomer ion pair through its further characterization in the ground state.[6] To this end we designed and synthesized *N*,*N*'-bis(7-hydroxycoumarin-4-ylmethylcarbonyl)-1,2-phenylenediamine (**1a**,

7HC-bridged dimer) and *N*-phenyl-2-(7-hydroxycoumarin-4-yl)acetamide (**1b**, reference monomer for **1a**)[5] and investigated solvent and tertiary amine effects on the proton dissociation equilibrium of **1**, hoping to elucidate the mode of intramolecular interaction between the two hydroxycoumarin chromophores in the 7HC-bridged dimer **1a** in the presence of triethylamine (TEA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Chart 1).[7]

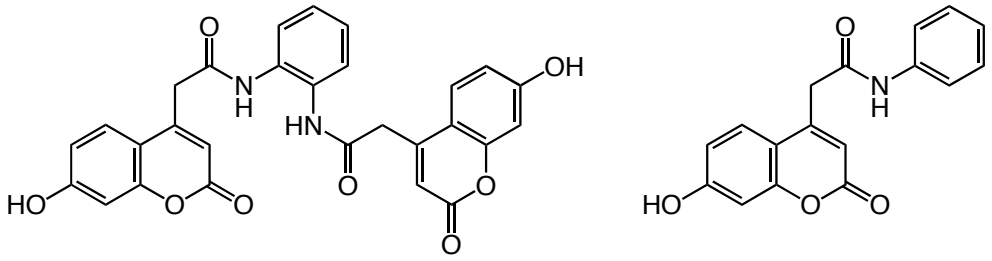

Chart 1

We demonstrated in a previous study that in methanol (MeOH) containing TEA there appears exclusively the hydroxycoumarin tautomer anion while TEA and DBU lead preferentially to the hydroxycoumarin anion and tautomer anion in acetonitrile (MeCN) and dimethyl sulfoxide (DMSO), respectively.[3] A simple and reliable method for discriminating between these two anion structures is to measure chemical shifts (δ) for the carbon signal of a given hydroxycoumarin derivative at the 7-position as a function of the amine concentration because the formation of the latter anion induces a much larger downfield shift of this carbon signal than that of the former. For this distinction the dependence of the δ value for the 7-C signal of **1b** on the amine concentaration was measured as typically shown in Figure 1 and the magnitude of $\Delta\delta$ was estimated using the δ values at [amine]= 0, 0.70 (TEA), and 0.10 (DBU) mol dm^{-3} ($\Delta\delta$= 11.00 and 6.60 ppm in MeOH-d_4-TEA and DMSO-d_6-DBU, respectively). Additionally, the relation between the δ value and the TEA concentration in MeCN-d_3 and DMSO-d_6, measured under the same conditions, gave the values of $\Delta\delta$= 0.30 ppm in the former solvent and 0.04 ppm in the latter solvent (data not shown). A comparison of these $\Delta\delta$ values confirms that proton transfer reactions with TEA in aprotic (MeCN and DMSO) and protic (MeOH) polar solvents preferentially afford the hydroxycoumarin anion **IB** and the hydroxycoumarin tautomer anion **IIB**, respectively, while the latter anion is exclusively formed in the aprotic polar solvent containing more basic DBU (Chart 2). These observations are consistent with our previous findings and, thus, led us to propose that the replacement of hydrogen at the 4-position of 7HC by the anilinocarbonylmethyl group exerts no effect on the proton dissociation pathway of the parent hydroxycoumarin, though it greatly decreases the $\Delta\delta$ value in the aprotic polar solvents.[3] Accordingly, a combination of the polar solvent and the tertiary amine base enables us to analyze the hydrogen bonding interaction of the **1a**-derived anion **IA** or tautomer anion **IIA** with the other hydroxycoumarin chromophore in **1a** as well as with protic solvent and protonated amine molecules.

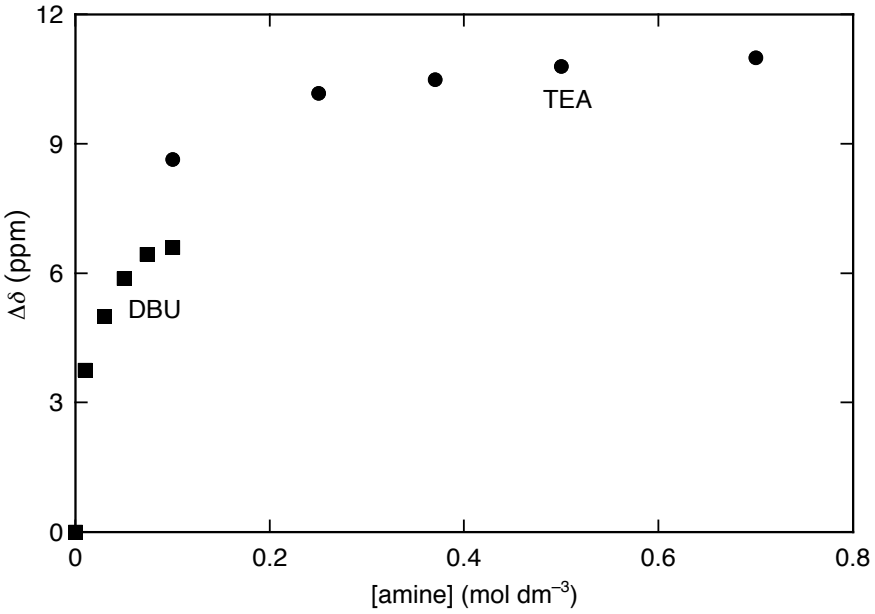

Figure 1. Difference in chemical shift ($\Delta\delta$) for the 7-C signal of **1b** (1.0×10^{-2} mol dm^{-3}) as a function of the amine concentration in MeOH-d_4 (●) and DMSO-d_6 (■) at room temperature. The $\Delta\delta$ is defined as $\Delta\delta = \delta_1 - \delta_2$ where δ_1 and δ_2 refer to the chemical shifts in the presence (δ_1) and absence (δ_2) of the amine.

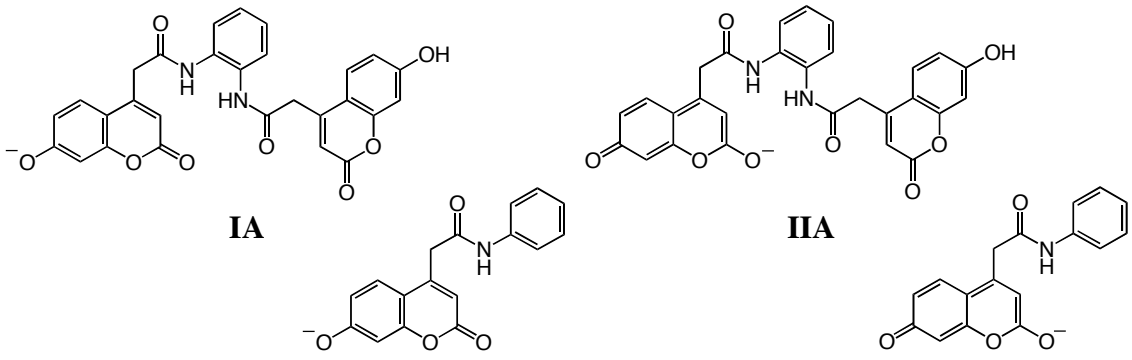

Chart 2

On the assumption that the hydrogen bonding interaction described above should be reflected in equilibrium constants for the two-step proton dissociation reactions of the bridged dimer **1a**, attempt was made to determine these equilibrium constants and to compare with those of the reference monomer **1b** in MeOH, MeCN, and DMSO at room temperature. As typically depicted in Figure 2, the presence of TEA in MeOH induced UV absorption spectral changes of **1a** with an isosbestic point at 341 nm. The changes in absorbance at 372 nm (ΔA) as a functrion of the TEA concentration ($[TEA]_0 >> [\mathbf{1a}]_0$, where the subscript 0 refers to the initial concentration) can be related to the equilibrium constant (K_a) for this proton dissociation reaction according to the following equation: $[\mathbf{1a}]_0/\Delta A = (\Delta\varepsilon K_a)^{-1}[TEA]_0^{-1} + (\Delta\varepsilon)^{-1}$. This equation is frequently utilized as the Benesi-Hildebrand

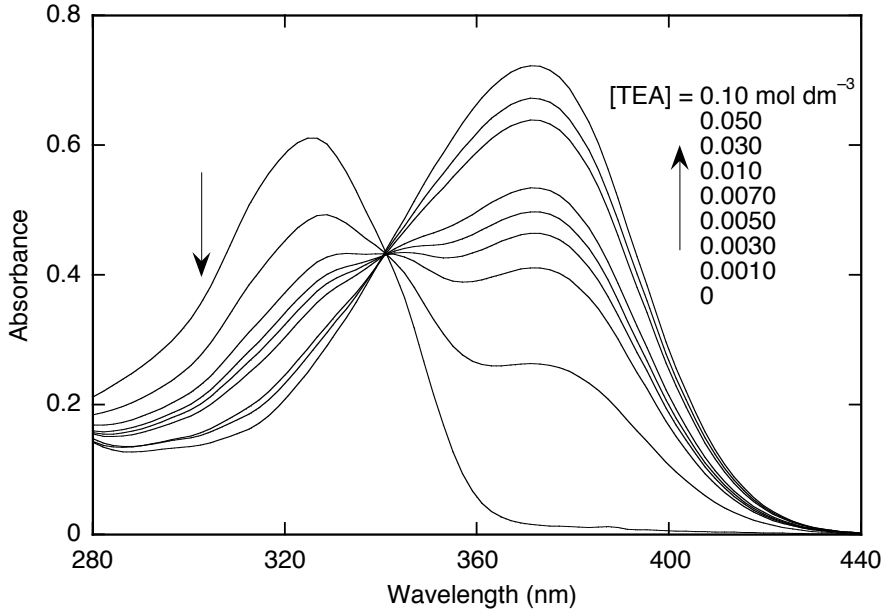

Figure 2. UV absorption spectral changes caused by the proton dissociation reaction of **1a** (2.5×10^{-5} mol dm^{-3}) in MeOH-TEA at room temperature.

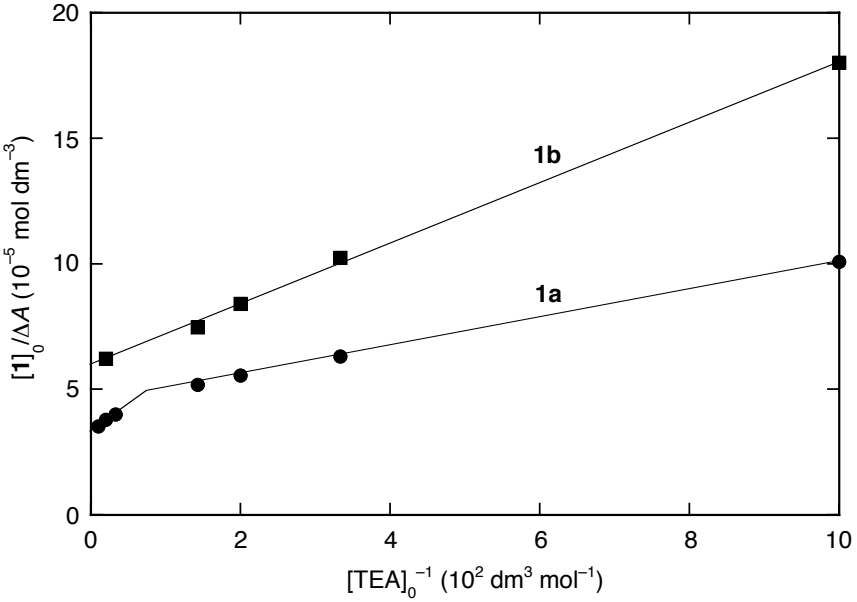

Figure 3. Benesi-Hildebrand plots for the proton dissociation reactions of **1a** and **1b** (2.5×10^{-5} mol dm^{-3}) in MeOH-TEA at room temperature.

expression, where $\Delta\varepsilon$ is the difference in molar absorption coefficient between the hydroxycoumarin anion or tautomer anion and **1a** at a given wavelength.[8] Interestingly, the plot of $[\mathbf{1}]_0/\Delta A$ versus $[\mathrm{TEA}]_0^{-1}$ was made up of two linear portions in the proton dissociation reaction of **1a**, whereas the reaction of **1b** gave the good linear plot (Figure 3). The former observation establishes that the proton dissociation of the bridged dimer **1a** proceeds in a stepwise manner and then each step has an equilibrium constant different from one another. The same two-step proton dissociation was found

to take place also in the reaction with TEA in MeCN. Because the ratio of intercept to slope of the linear plots or the linear portions for nonlinear plots enabled the estimation of the K_a values for given processes, these values were summarized in Table 1.

Table 1. Equilibrium constants (K_a) for the proton dissociation reactions of **1a** and **1b** (2.5×10^{-5} mol dm^{-3}) with tertiary amine in MeOH, MeCN, and DMSO at room temperature

Compound	Solvent	Amine	K_a (dm^3 mol^{-1})
1a	MeOH	TEA	980 (K_1)[a], 140 (K_2)[b]
1a	MeCN	TEA	370 (K_1)[a], 110 (K_2)[b]
1a	DMSO	TEA	40
1a	DMSO	DBU	1.7×10^4
1b	MeOH	TEA	490
1b	MeCN	TEA	50
1b	DMSO	TEA	30
1b	DMSO	DBU	1.5×10^4

[a] Equilibrium constant for the first-step proton dissociation reaction.
[b] Equilibrium constant for the second-step proton dissociation reaction.

Analysis of solvent effects on the extent of the proton dissociation confirms that there is a pronounced interaction between the two hydroxycoumarin chromophores in MeOH and MeCN irrespective of the structure of anions formed whereas DMSO prevents this interaction almost completely to afford the equilibrium constant of the same magnitude in any proton dissociation steps. The 7HC tautomer anion was previously demonstrated to be greatly stabilized not only through hydrogen bonding solvation by protic solvent molecules but also through hydrogen bonding interaction with protonated tertiary amines.[3] Thus, the finding that (on bridging the two 7-hydroxycoumarin chromophores) the K_a value for the first step of the tautomerization in MeOH is increased by a factor of 2 and that for the second step is lowered several times can be accounted for by hydrogen bonding solvation of the intramolecularly hydrogen bonded hydroxycoumarin tautomer anion **IIA**, as depicted in Figure 4(a). Both the intramolecular hydrogen bonding interaction and hydrogen bonding solvation of this anion assists the first-step proton transfer to TEA, whereas they suppresses the second-step proton dissociation to a measurable extent. The former hydrogen bonding interaction also provides a good explanation for an increase in the K_a value for formation of the **1a**-derived hydroxycoumarin anion **IA** in MeCN-TEA [Figure 4(b)]. Because no hydrogen bonding solvation occurs in this aprotic polar solvent, it is likely that the protonated TEA activates the second-step proton dissociation (through a hydrogen bond to the ester carbonyl oxygen) to some extent. As already described, both the bridged dimer **1a** and the reference monomer **1b** dissociate their hydroxyl protons in DMSO-TEA and DMSO-DBU to form the

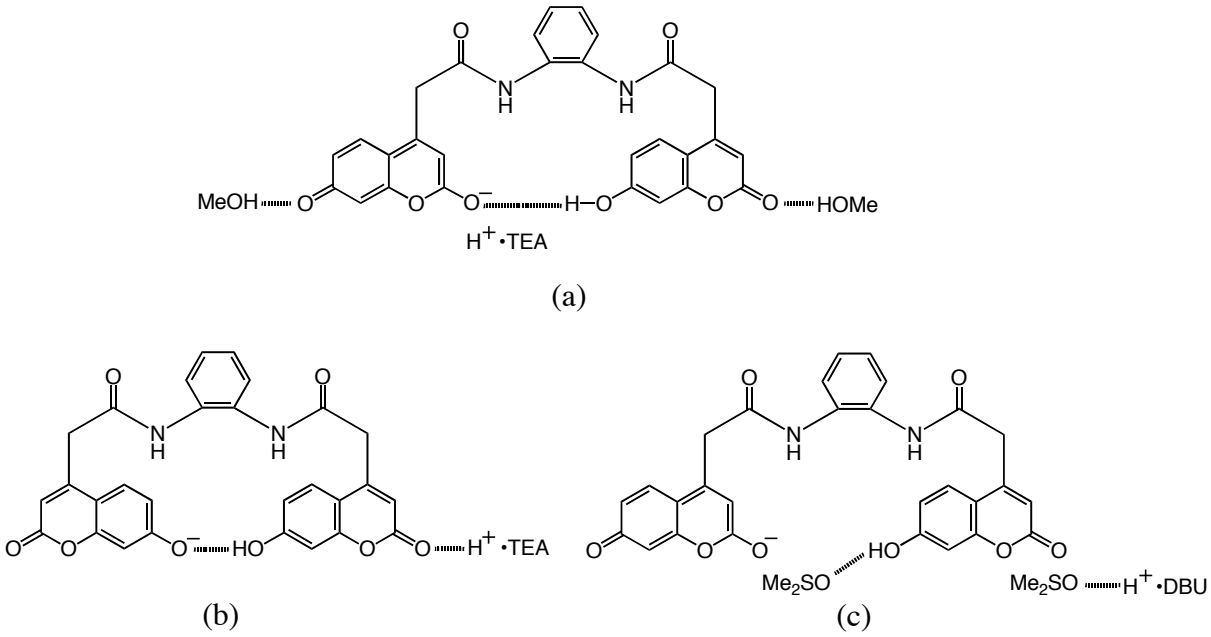

Figure 4. Schematic illustration for intramolecular hydrogen bonding interactions of the **1a**-derived hydroxycoumarin anion and tautomer anion and their interactions with solvent molecules.

anions **I** and **II**, respectively, and the K_a values for generation of these anions are of nearly the same magnitude between **1a** and **1b**. The latter finding substantiates the participation of strong hydrogen bonding solvation of the undissociated hydroxycoumarin chromophore in **1a** by DMSO, which enables the two chromophores in this 7HC-bridged dimer to behave independently as observed [Figure 4(c)].

As demonstrated in a previous paper, the 7HC-derived tautomer ion pair structure undergoes much more pronounced stabilization in the singlet excited state than in the ground state under basic conditions, owing to a substantial increase in the acidity of the hydroxy group.[3] The 7HC anion was also shown to serve as a precursor of the tautomer anion. In order to obtain additional evidence in support of the intramolecular hydrogen bonding interaction proposed in the preceding section, we chose the proton dissociation reactions of **1a** in MeOH-TEA and DMSO-DBU (where the tautomer anion is exclusively produced in the ground state and, hence, complicated proton dissociation behavior in the excited state may be avoided) and measured fluorescence decay curves for these solvent-amine systems.[9] In any systems the fluorescence decay curves were monoexponential functions with lifetimes of 1.6 ns in MeOH-TEA ([**1a**]= 2.5×10^{-5} mol dm^{-3}, [TEA]= 0.10 mol dm^{-3}, excitation wavelength= 341 nm) and 5.2 ns in DMSO-DBU ([**1a**]= 2.5×10^{-5} mol dm^{-3}, [DBU]= 1.0×10^{-2} mol dm^{-3}, excitation wavelength= 356 nm). In addition, the fluorescence lifetimes of **1b** in MeOH-TEA and DMSO-DBU were determined to be 4.5 ns and 4.9 ns under the same analytical conditions, respectively. If we consider that intramolecular interaction between the **1a**-derived two tautomer anions in the ground state should be strongly reflected in the fluorescence lifetime, a comparison of this lifetime between **1a** and **1b** reveals that the intramolecular interaction is negligible between the two tautomer anions formed in DMSO while these tautomer anions may interact with each other in MeOH (probably, intramolecular self-quenching) to result in a lowering of the emission lifetime. The fluorescence lifetime analysis described above,

therefore, renders intramolecular interaction and solvation models given in Figure 4 adequately valid. The findings obtained in this study may provide valuable information on designing the 7-hydroxycoumarin-derived tautomer ion pair as a novel coumarin dye for dye-sensitized solar cells.

ACKNOWLEDGMENTS

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7. Selected data for **1a**: mp 266.5–267.0 °C (EtOAc-hexane); IR (KBr) ν/cm^{-1}= 3214, 3140, 1701, 1605; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 3.85 (4H, s), 6.27 (2H, s), 6.74 (2H, s), 6.79 (2H, d, J= 8.0 Hz), 7.18 (2H, dd, J= 7.9, 7.9 Hz), 7.46 (2H, d, J= 7.9 Hz), 7.66 (2H, d, J= 8.0 Hz), 9.63 (2H, s), 10.57 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ= 39.6 (2C), 102.3 (2C), 111.5 (2C), 112.1 (2C), 113.0 (2C), 125.3 (2C), 125.5 (2C), 126.8 (2C), 131.9 (2C), 150.6 (2C), 155.0 (2C), 160.2 (2C), 161.2 (2C), 167.0 (2C). Anal. Calcd for $C_{28}H_{20}N_2O_8$: C, 65.62; H, 3.93; N, 5.47. Found: C, 65.66; H, 3.84; N, 5.77. TOF-MS: m/z calcd for $C_{28}H_{20}N_2O_8$ $[M + K]^+$ 551.57, found 551.68.
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9. Fluorescence lifetimes were measured with a time-correlated single-photon counting apparatus (Horiba NAES–700), which was equipped with a flash lamp filled with hydrogen. Analysis of the fluorescence decay curves was accomplished according to the previously described procedure.[10] Typically, 1×10^4 counts were sampled in the peak channel. Isosbestic points observed in UV absorption spectral changes were selected for excitation, and emission light was passed through an appropriate cutoff filter.
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