A Simple Phenol-Indole Dye as a Chromogenic Probe for the Ratiometric Determination of Water Content in Organic Solvents

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A simple dye having phenol and indole moieties was synthesized and its chromogenic signaling behaviors for the determination of water content in organic solvents were investigated. The compound revealed a pronounced chromogenic behavior in response to the variation of water content in water miscible aprotic organic solvents of acetone, acetonitrile, THF, and dioxane. Significant red shifts and changes in absorption spectra allowed a ratiometric analysis of the signaling behavior. The chemosensing behaviors were particularly pronounced in water content in less than 10% that is suitable for the application of the compound as a probe for the determination of water content in binary aqueous organic solutions having lower water content.

Key Words: Chromogenic dye, Water content, Organic solvent, Solvatochromism, Ratiometry

Introduction

Determination of polarity of microenvironment or water content in chemical and biological systems is very important.[1,2] For this purpose, functional dyes are generally useful as signal transducers to convert a chemical interaction or recognition process into an optically detectable signal.[3] In particular, multi-information dyes were introduced to describe merocyanine type dyes, which feature pH sensitive absorption spectra and simultaneously exhibit wavelength shifts in absorption maximum with changing solvent polarity.[4] They have been applied as solvatochromic probes for the analysis of solvent mixtures and as colorimetric pH indicators.

Solvent polarity and the local environment have profound effects on the spectral properties of polar compounds.[5] One common use of the solvent effects on the probe molecules is to determine the polarity of the probe binding site on the biomacromolecules.[6] When it dissolved in environments of different polarity a dramatic change in absorption or emission characteristics was developed. Also important is the application as a probe for the determination of water content in organic solutions.[7,8] As a probe for the water content in organic solvents, many interesting sensing systems including merocyanine dyes,[9,10] fluoresceins,[11] flavone derivatives,[12] membrane[5] and optical-fiber sensor employing acridine dyes[13] have been reported, and well discussed in a recent report.[14] Also interesting in this purpose is the chromogenic behavior which can be easily detected and sometimes allowed naked-eye monitoring of the systems.[15]

Indole derivatives have been utilized as a chromophore or fluorophore for the construction of chromogenic or fluorogenic chemosensor.[16,17] They are based on the well known binding motif of calixarene, and function as an interesting signaling subunit. In this paper, we report the solvatochromic behavior of a simple dye having phenol and indole functions as a solvent polarity probe for aqueous solutions. The prepared dye exhibited a pronounced chromogenic behavior in response to the changes in water content of the binary aqueous solutions of common aprotic water miscible organic solvents.

Experimental Section

General. All solvents were purchased from Aldrich Chemical Co. as 'anhydrous' or 'spectroscopic grade'. Acetone was used after storing with molecular sieve 4A. Indole, 4-hydroxy-3,5-dimethylbenzaldehyde, 4-methoxybenzaldehyde, and 4-methylbenzaldehyde were purchased and used without further purification. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Varian Gemini-2000 spectrometer. Mass spectral data were obtained with a Micromass Autospec mass spectrometer. UV-vis spectra were recorded with a Jasco V-550 spectrophotometer.

Synthesis of 1-3.

Preparation of 1: To a solution of 4-hydroxy-3,5-dimethylbenzaldehyde (150 mg, 1 mmol) and indole (234 mg, 2 mmol) in methanol was added $KHSO_4$ (136 mg, 1 mmol) and the mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was partitioned between dichloromethane and water. The organic layer was separated and washed with water and evaporated. The crude product was purified by the column chromatography (hexane: ethyl acetate=3:1, v/v) to afford dark red colored **1**. Yield=65%. ^{1}H NMR δ7.85 (br s, 2H), 7.40 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.4 Hz, 2H), 7.15 (t, *J*=8.4 Hz, 2H), 7.00 (t, *J*=8.2 Hz, 2H), 6.94 (s, 2H), 6.61 (m, 2H), 5.74 (s, 1H), 2.15 (s, 6H). ^{13}C NMR δ150.7, 137.0, 135.9, 129.0, 127.4, 123.8, 122.8, 122.1, 120.4, 120.2, 119.4, 111.2, 39.5, 16.1; HRMS (EI) *m/z* calcd for $C_{25}H_{23}N_2O$ 366.1732, found 366.1707.

Preparation of 2 and 3: Compounds **2** and **3** were prepared similarly by using 4-methoxybenzaldehyde and 4-methylbenzaldehyde following the procedure for **1**.

2: The crude product was purified by column chromatography (hexane: ethyl acetate=5:1, v/v) to afford red colored **2.** Yield =84%. ^{1}H NMR δ7.91 (br s, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 7.17 (t, *J*=7.2 Hz, 2H), 7.00 (t, *J*=6.9 Hz, 2H), 6.82 (d, *J*=8.4 Hz, 2H), 6.67 (m, 2H), 5.84 (s, 1H), 3.78 (s, 3H). ^{13}C NMR δ158.2, 137.0, 136.5, 129.9, 127.3, 123.7, 122.1, 120.3, 120.2, 119.4, 113.8, 111.3, 55.3, 39.4. HRMS (EI) *m/z* calcd for $C_{24}H_{21}N_2O$ 352.1576,

found 352.1544.

3: The crude product was purified by column chromatography (hexane: ethyl acetate=7:1, v/v) to afford red colored **3.** Yield =62%. ^{1}H NMR δ7.90 (br s, 2H), 7.40 (d, *J*=7.5 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.23 (d, *J*=7.8 Hz, 2H), 7.16 (t, *J*=8.2 Hz, 2H), 7.08 (d, *J*=7.8 Hz, 2H), 7.00 (t, *J*=8.0 Hz, 2H), 6.67 (m, 2H), 5.85 (s, 1H), 2.32 (s, 3H). ^{13}C NMR δ141.3, 137.0, 135.8, 129.2, 128.8, 127.4, 123.8, 122.1, 120.2, 120.1, 119.4, 111.2, 39.9, 21.1. HRMS (*EI*) m/z calcd for $C_{24}H_{21}N_2$ 336.1626, found 336.1652.

Measurements of UV-vis Spectra. The UV-vis spectra were obtained at a constant concentration of **1** in solvent systems containing varying amount of water. Mixed aqueous solvent systems were obtained by mixing appropriate amount of stock solution of **1** (1.0×10^{-3} M in organic solvent) with water and finally diluted with the same organic solvent to make the solutions having desired water content and concentration of the compound **1**.

Results and Discussion

Phenol-indole dye **1** was prepared by the reaction of 4-hydroxy-3,5-dimethylbenzaldehyde with indole in the presence of $KHSO_4$ in moderate yield (65%).[16] Two other indole derivatives **2** and **3** having methoxy and methyl substituents on the phenyl ring were also prepared similarly as control compounds.[18] All the prepared compounds exhibited a characteristic singlet resonance in ^{1}H NMR spectra obtained in $CDCl_3$ for the bridging methine protons at δ5.74, 5.84, and 5.85 ppm for **1**, **2**, and **3**, respectively.

First, we measured the absorption spectra of **1** in a series of common organic solvents (Figure 1). Generally, compound **1** revealed a light yellow color in relatively nonpolar solvents and more intense pink color in polar solvents. For example, in toluene, compound **1** showed a strong absorption band at 447 nm and resulted in a faint yellow colored solution. However, in more polar solvent of methanol, a new strong absorption band at 524 nm appeared and the solution color turned into pink.

Based on these solvatochromic behaviors of **1**, we next carried out a preliminary survey to assess the ability of compound **1** in reporting the variation of solvent polarity or water content in common water miscible organic solvents. The UV-vis spectra of **1** in a series of pure and 30% aqueous solutions were measured. Significant changes in spectra as well as solution color were observed in common organic solvents of acetone, acetonitrile, dioxane, and THF except for methanol. Based on these, the effects of water content on the absorption spectra in these solvents were systematically investigated.

In dioxane, compound **1** showed a broad absorption band at 459 nm and the solution color is light yellow. As the content of water increased, the absorption band at 459 nm was progressively red shifted toward 530 nm with a significant hyperchromism (Figure 2). With increasing water contents, the solution color transformed gradually to orange and finally into a deep pink one. Because the changes in absorption maximum and absorbance of **1** were considerable, we tried to ratiometrically analyze the spectral responses of the system. The use of variation in the ratio of the two prominent absorptions at 459 nm (A_{459}) with respect to 525 nm (A_{525}) was successful: a plot of A_{459}/A_{525} as a function of water content resulted in a nice profile and signals well the changes in water content of the aqueous dioxane system (inset of Figure 2). The ratio A_{459}/A_{525} changed about 8-fold from 4 to 0.5. Noteworthy, the most dramatic changes were observed in the region from 0 to 5% water

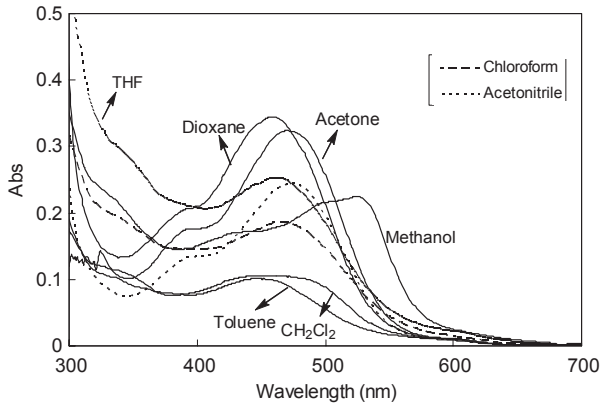


Figure 1. UV-vis spectra of **1** in common organic solvents. [**1**] = 5.0×10^{-5} M.

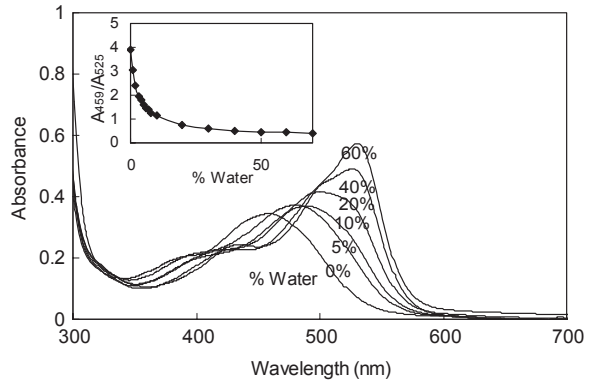
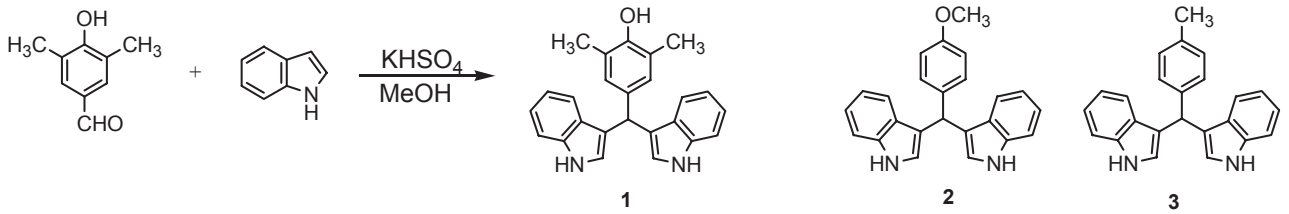


Figure 2. UV-vis absorption spectra of **1** in aqueous dioxane solution of varying water content. Inset shows the changes in A_{459}/A_{525} as a function of water content. [**1**] = 5.0 x 10^{-5} M.



Scheme 1. Synthesis of phenol-indole dye.

content, that spans over 70% of the total changes in the absorbance ratio. After that, the ratio progressively decreased up to 30% water and then remained relatively constant. Beyond 70% water content, compound **1** starts to precipitate and the relevant spectra were not measurable. This observation suggests that the dye **1** could be used as an efficient and naked-eye detectable molecular probe for the measurement of water content in aqueous dioxane, particularly in lower region of less than 10% water. From the ratiometric changes of A_{459}/A_{525} as a function of water content, detection limit for the water content in dioxane was calculated as 0.33%.[19]

The chromogenic behavior of **1** might be due to the enhanced intramolecular charge transfer (ICT) process upon interaction with strongly hydrogen bond forming water molecules. The strong hydrogen bondings between OH(phenol)···OH(water) and/or NH(indole)···OH(water) of phenol and indole group of **1** seem to cooperatively enhance the ICT process between phenol and indole moieties.[20] The OH group of phenol is known to be an active hydrogen bond former, forming an interaction with water of 6.2 or 4.0 kcal/mol, depending on whether phenol is the proton donor or acceptor, respectively. Similarly, the NH···OH-bond formed by indole amounts to some 5.5 kcal/mol, slightly weaker than the preceding OH···O phenol case.[20] The ICT process between phenol and indole moieties[21] was found to be facilitated by the presence of polar solvents.[22] The control compounds **2** and **3**, which devoid of phenolic hydroxyl group, does not exhibit any discernible changes in absorption spectra in response to the variations in water content. The insensitive response of **1** toward changes in water content in methanol solution is due to the strongly hydrogen bond forming properties of methanol. These observations indicated that the control of ICT between phenol and indole chromophore by hydrogen bonding with water is responsible for the prominent solvatochromism of **1**.

Compound **1** also exhibited a prominent solvatochromic behavior in aqueous acetonitrile. Phenol-indole **1** dissolved in acetonitrile exhibited an absorption maximum centered at 474 nm and revealed a yellow color. Addition of incremental amount of water into the solution resulted in a progressive red shift toward 526 nm and finally developed an intense pink color. The UV-vis spectra shown in Figure 3 clearly revealed changes in absorbance at 474 and 526 nm. The ratiometric analysis was also applicable and signals nicely the changes in water content. As can be seen in the inset of Figure 3, the changes in A_{474}/A_{526} was prominent up to 10% water content and beyond that the changes are somewhat leveled off. Furthermore, the color transition in higher water content region could be monitored with the naked eye. From the changes in A_{474}/A_{526} as a function of water content, detection limit for the water content in acetonitrile was determined as 0.31%.

In acetone, the solution color of **1** was a light yellow and transformed progressively to a deep pink one as the water content increased (Figure 4). The absorption band at 470 nm was progressively red shifted toward 529 nm with significant hyperchromism with increasing water content. The ratiometric plot of the ratio of A_{470}/A_{529} as a function of solvent composition again signals well the changes in water content of the solvent mixture (inset of Figure 4). In this case, too, the most dramatic changes were observed around up to 10% water content which spans over 60% of the total changes in the absorbance ratio. From the changes in A_{470}/A_{529} as a function of water content, detection limit for the water content in acetone was estimated as 0.52%.

In 100% THF solution, the absorption spectrum showed a maximum absorbance at 463 nm. With increasing water content, a progressive red shift of the 464 nm band to 530 nm was observed. The ratio A_{464}/A_{530} decreased steadily in response to

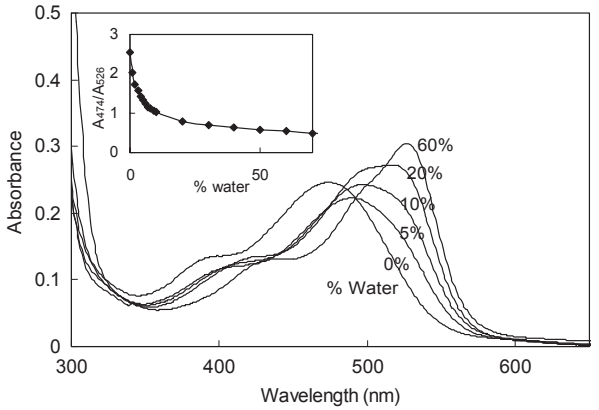


Figure 3. UV-vis absorption spectra of **1** in aqueous acetonitrile solution of varying water content. Inset shows the changes in A_{474}/A_{526} as a function of water content. [**1**] = 5.0×10^{-5} M.

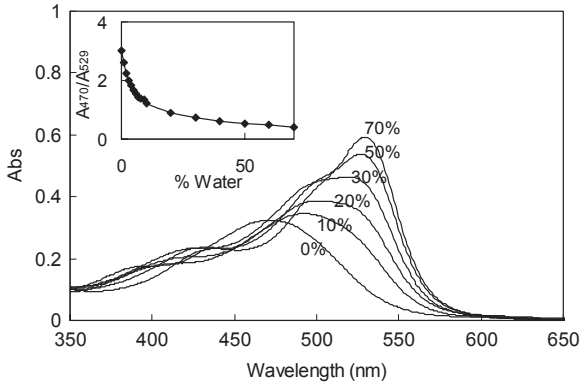


Figure 4. UV-vis absorption spectra of **1** in aqueous acetone solution of varying water content. Inset shows the changes in A_{470}/A_{529} as a function of water content. [**1**] = 5.0×10^{-5} M.

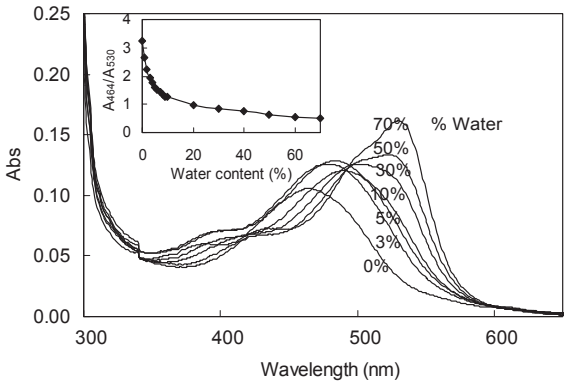


Figure 5. UV-vis absorption spectra of **1** in aqueous THF solution of varying water content. Inset shows the changes in A_{464}/A_{530} as a function of water content. [**1**] = 5.0×10^{-5} M.

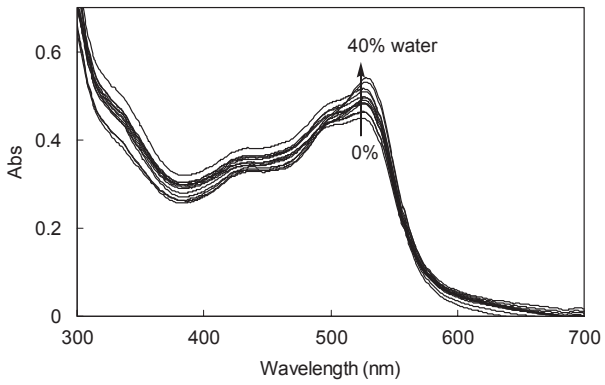


Figure 6. UV-vis absorption spectra of **1** in aqueous methanol solution of varying water content. [**1**] = 5.0×10^{-5} M.

the water content particularly significantly in less than 10% water content, that is a sufficient change for the sensing of water content in aqueous THF. The detection limit for the water content in THF was found to be 0.41%.

We finally tried to assess the possibility of the signaling of water content in methanol. In methanol, the changes in the UV-vis spectra of **1** was not so pronounced and the λ_{max} was slightly red shifted from 524 to 528 nm with increasing water content (Figure 6). Compound **1** dissolved in methanol which has a sufficiently polar nature as well as a strong hydrogen bonding capability, already interacts strongly with solvent molecules, and further increases in water content did not induce any appreciable changes in the absorption behavior of the compound.

Conclusion

We have prepared a series of simple compounds having indole and substituted phenyl moieties and investigated their chemosensing behaviors for the probing of water content in common organic solvents. The phenol-indole dye exhibited a pronounced spectral changes in response to the changes in water content in acetone, acetonitrile, dioxane, and THF. The spectral changes were analyzed by the ratiometric approach and resulted in a nice signaling of water content in surveyed organic solvents. The phenol-indole dye can be used as a probe for the determination of water content, particularly from 0.5% to 10% region, in common water miscible aprotic organic solvents.

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