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Study of novel fluorescent coumarin-3,4-dihydropyrimidin-2(1H)-ones dyads. Estimation of ground- and excited-state dipole moments from a solvatochromic shift

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ABSTRACT

The photophysical properties like ground- and excited-state dipole moments, change in the dipole moment and fluorescence quantum yield of three coumarin-3,4-dihydropyrimidin-2(1H)-ones dyads **4a**–**c** are characterized. The study is carried out in various solvents at room temperature using absorption and steady-state fluorescence technique. The emission wavelengths of the 4a–c are quite sensitive to the polarity of solvents. Increasing solvent polarity red or bathochromic shifts of about 10 nm have been observed. The excited- and ground-state dipole moments are estimated using solvatochromic shift method. It was observed that dipole moments of the excited state were higher than those of the ground state, indicating a substantial redistribution of the π-electron densities in a more polar excited state for **4a**–**c**. The changes in dipole moment (Δμ) are calculated both from solvatochromic shift method and microscopic solvent polarity parameter. The bathochromic shift of the emission spectra and the increase in the excited-state dipole moment indicates $\pi \rightarrow \pi^*$ transitions as well as the possibility of intramolecular charge transfer (ICT) character in the emitting singlet state of **4a**–**c**. The relative quantum yields (Φ) are calculated using single point method. It is found that the quantum yields of the molecules vary (9 to 22%) with the change in the solvent polarity indicating the dependency of fluorescence nature on the solvent environment.

1. Introduction

Coumarins (2H-1-benzopyran-2-ones) are lactones of *o*-hydroxycinnamic acid widely distributed in plants, but also found in fungi and bacteria [1–3]. This numerous class of compounds (around 1.300 derivatives) occurs as single nucleus or as dyads combined with sugars or acids and presents many pharmacological properties, such as anti-inflammatory [4], anti-microbial [5], antioxidant [6] and anti-tumor activities [7–9]. The intrinsic photophysical features of coumarins enable their use as biological and chemical probes [10], which have been explored in the detection of proteins [11], metals [12], DNA/RNA [13], tumour cells [14], besides being useful as pH indicators [15].

In the last years, combination chemotherapy has been a common clinical strategy adopted to treat cancer and/or to overcome drug resistance. The development of more potent anti-breast cancer agents combining tissue selective effects with novel structures or new mechanism of action are still needed and very challenging, since molecules used to treat either primary or metastatic breast cancers are limited [8].

In the design of new drug prototypes, the concept of molecular hybridization is a useful tool and is based on the combination of pharmacophore moieties of different bioactive substances to produce a new dyad compound with improved affinity and efficacy [16]. This strategy has resulted in compounds with modified selectivity profile, different and/or dual mode of action and reduced undesired side effects. Musa et al. have reviewed the application of coumarins in the pharmacotherapy of breast cancer using this concept [17]. Recently, Sashidhara et al. [18] have disclosed a coumarin–monastrol dyad as potential anti-breast tumour-specific agent.

Cytogenetic analysis of tumour material has been greatly enhanced over the past 30 years by the application of a range of techniques based around fluorescence [19]. Optical techniques provide an accurate and rapid means to detect regions of cancer. In order to obtain optimal results from the flow cytometry analysis, especially when performing multidimensional analysis, it is vital that the appropriate combination of fluorochromes is used. To choose fluorochromes there are a number

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of different parameters to take into account. Each fluorochrome has distinct properties and is characterized by specific excitation and emission wavelengths. First, the fluorochrome must be excited by lasers available on the instrument. Second, the emission wave lengths are read by different detectors or photomultiplier tubes and the range of detection is limited by optical filters. This work represents a continuation of our systematic studies of highly fluorescent laser dyes [20,21]. The dipole moment of an excited state of a molecule provides information on their electronic and geometrical structure in the short lived state. Accordingly, the objective of this work is to study the spectroscopic properties and to estimate the ground- and excited-state dipole moments and also the change in the dipole moments of three coumarin-3,4-dihydropyrimidin-2(1H)-ones **4a**–**c** recently synthesized [22] (Fig. 1).

We anticipated that the presence of the 3,4-dihydropyrimidin-2(1H)-one ring as well as the substituents of the coumarin core could lead to interesting photophysical properties and those compounds could subsequently be used as cation extraction agents or signalling agents for cation recognition, as pH indicators and fluorescent probes.

2. Experimental methods

2.1. Apparatus

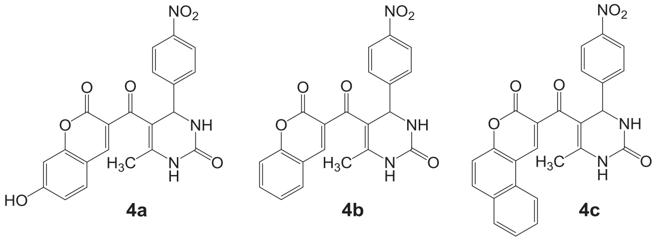
All spectrophotometric measurements were conducted at ambient temperature. UV/vis absorption spectra were recorded on a JENWAY spectrophotometer. The estimated experimental error was 2 nm on the band maximum and 5% on the molar extinction coefficient. Fluorescence work was performed on a JASCO-FP 8200 spectrofluorometer and data were analysed by appropriate software. Linear fit was done by using Origin 8.0 software. Density of the probe molecule was extracted from ACD/Chem Sketch software. The excitation source was a long life Xenon flash lamp. The fluorescence quantum yields were determined using fluorescein disodium salt ($\Phi = 0.9$) as standard and were determined using the classical formula:

$$\Phi_X = (\Phi_S A_S F_X {n_X}^2)/(A_X F_S {n_S}^2)$$

Where "A" is absorbance at the excitation wavelength, "F" the area under the fluorescence curve and "n" is the refractive index of the solvents used. Subscripts "s" and "x" refer to the standard and to the sample of unknown quantum yield, respectively. The excitation source was a long life Xenon flash lamp.

2.2. Materials

Coumarin-3,4-dihydropyrimidin-2(1H)-one derivatives **4a**–**c** were synthesized as reported in the literature [22]. Their molecular structure and purity was confirmed by NMR spectroscopy and mass spectrometry. The solvents used in the present study, namely dimethylsulfoxide (DMSO), acetonitrile (ACN), dimethylformamide (DMF), acetone, ethyl acetate, THF, dichloromethane and chloroform were of HPLC and spectroscopic grade (purchased from Fluka and Labosi). The required solutions were prepared at a fixed solute concentration (4×10^{-5} mol·dm^{-3}).



4a **4b** **4c**

Fig. 1. Structures of the compounds studied.

2.3. Estimation of the dipole moments

The dipole moment of a molecule in the excited state is determined by the effect of electric field (internal or external) on its spectral band position. The solvent dependence of the absorption and fluorescence band maxima is used to estimate the excitation-state dipole moments of different molecules. Two methods depending on the internal electric field effect (solvatochromism) have been employed in the present investigation.

2.3.1. Method I

Solvent dependence of absorption and fluorescence band maxima is used to estimate the excited-state dipole moments of different molecules. Eqs. (1) and (2) that afford the best results in the change of dipole moments of an excited molecule were suggested by A. Kawski and P. Bojarski [23–25]:

The difference $\overline{\nu}_a - \overline{\nu}_f$:

$$\overline{\nu}_a - \overline{\nu}_f = S_1 f(\varepsilon, n) + const \tag{1}$$

and the sum $\overline{\nu}_a + \overline{\nu}_f$:

$$\overline{\nu}_a + \overline{\nu}_f = -S_2 \Phi(\varepsilon, n) + const \tag{2}$$

where.

$$\Phi(\varepsilon, n) = f(\varepsilon, n) + 2g(n) \tag{3}$$

and

$$g(n) = \frac{3}{2} \frac{n^4 - 1}{(n^2 + 2)^2}. \tag*{(.(4))}$$

In these equations $\overline{V}_a$ and $\overline{V}_f$ are the absorption and fluorescence maxima (cm^{-1}), respectively, n and ε are the refractive index and the dielectric constant of solvents, respectively.

The expressions for the solvent parameters $f(\varepsilon,n)$ and $\Phi(\varepsilon,n)$ are given by A. Kawski and colleagues [23–25]:

$$f(\varepsilon, n) = \frac{2n^2 + 1}{n^2 + 2} \left[\frac{\varepsilon - 1}{\varepsilon + 2} - \frac{n^2 - 1}{n^2 + 2} \right] \tag{5}$$

$$\Phi(\varepsilon, n) = \left(\frac{2n^2 + 1}{(n^2 + 2)} \left(\frac{\varepsilon - 1}{\varepsilon + 2} - \frac{n^2 - 1}{n^2 + 2} \right) + \frac{3(n^4 - 1)}{(n^2 + 2)^2} \right). \tag{6}$$

The calculated values of solvent polarity parameters $f(\varepsilon,n)$ and $\Phi(\varepsilon,n)$ are given in Table 1.

Table 1
Summary of solvent properties and calculated values of solvent polarity parameters $f(\varepsilon,n)$ and $\Phi(\varepsilon,n)$.

Solvents	μ	ε	n	$f(\varepsilon,n)$	$\Phi(\varepsilon,n)$	E_T^N
$CHCl_3$	1.04	4.81	1.446	0.372	0.97	0.259
CH_2Cl_2	1.60	8.90	1.424	0.590	1.17	0.309
THF	1.75	7.58	1.407	0.549	0.55	0.207
Ethyl acetate	1.88	6.02	1.372	0.489	1.00	0.228
Acetone	2.88	20.70	1.359	0.790	1.28	0.355
ACN	3.92	37.50	1.344	0.863	1.33	0.460
DMF	3.82	38.00	1.430	0.839	1.42	0.386
DMSO	3.96	46.70	1.479	0.841	1.49	0.444