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Solvatochromism and linear solvation energy relationship of the kinase inhibitor SKF86002

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ABSTRACT

We studied the spectroscopic characteristics of SKF86002, an anti-inflammatory and tyrosine kinase inhibitor drug candidate. Two conformers SKF86002A and SKF86002B are separated by energy barriers of 19.68 kJ·mol^{-1} and 6.65 kJ·mol^{-1} due to H-bonds, and produce the three major UV–Vis absorption bands at 325 nm, 260 nm and 210 nm in cyclohexane solutions. This environment-sensitive fluorophore exhibited emission in the 400–500 nm range with a marked response to changes in environment polarity. By using twenty-two solvents for the solvatochromism study, it was noticed that solvent polarity, represented by dielectric constant, was well correlated with the emission wavelength maxima of SKF86002. Thus, the SKF86002 fluorescence peak red shifted in aprotic solvents from 397.5 nm in cyclohexane to 436 nm in DMSO. While the emission maximum in hydrogen donating solvents ranged from 420 nm in *t*-butanol to 446 nm in *N*-methylformamide. Employing Lippert-Mataga, Bakhshiev and Kawski models, we found that one linear correlation provided a satisfactory description of polarity effect of 18 solvents on the spectral changes of SKF86002 with R^2 values 0.78, 0.80 and 0.80, respectively. Additionally, the multicomponent linear regression analysis of Kamlet-Taft ($R^2 = 0.94$) revealed that solvent acidity, basicity and polarity accounted for 31%, 24% and 45% of solvent effects on SKF86002 emission, respectively. While Catalán correlation ($R^2 = 0.92$) revealed that solvatochromic change of SKF86002 emission was attributed to changes in solvent dipolarity (71%), solvent polarity (12%), solvent acidity (11%) and solvent basicity (6%). Plot of Reichardt transition energies and emission energies of SKF86002 in 18 solvents showed also a linear correlation with $R^2 = 0.90$. The dipole moment difference between excited and ground state was calculated to be 3.4–3.5 debye.

1. Introduction

SKF86002, given a IUPAC name 6-(4-fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)-imidazo[2,1-*b*]thiazole, is a low molecular weight heterocycle. It was first synthesized by Bender et al., and was tested for its anti-inflammatory activity [1,2]. Later, it was identified as p38α inhibitor [3]. Pargellis et al., demonstrated that SKF86002 can act as a fluorescent marker upon binding to the ATP active pocket of p38α [4]. It was revealed that not only is SKF86022 able to bind to the mitogen-activated protein kinase (p38α), but also to other kinases viz. Pim1, ASK1, HCK and AMPH [5]. Hence, SKF86002 is a small kinase inhibitor, able to act as a self-fluorescent reporter and/or probe for candidate ATP-competitive inhibitors [5].

Photophysical studies have recently received much attention, since the spectral parameters are very sensitive to the change in microenvironment [6]. Therefore, different models have been progressively developed for analyzing the photophysical properties of fluorescent compounds. Lippert-Mataga (L-M) [7,8], Bakhshiev [9], and Bilot-Kawski [10,11] (often called Kawski-Chamma-Viallet) [12,13] models are commonly applied to investigate solvent effects on the spectral characteristics of dye molecule and to estimate the change in dipole moment between the ground and excited state [14]. They are easily employed, however cannot account for stabilization of dyes based on hydrogen bonding [15,16]. However, it was later discovered that if aprotic and protic solvents were plotted separately using Kawski model, then dipole moment differences for H-bond and non-H-bond environments could be evaluated [17,18] This has opened the door for studying compounds capable of strong H-bond formation [19].

Models which can separately evaluate different modes of solute-solvent interactions have also been developed. By using Kamlet-Taft and Catalán models, one can qualitatively and quantitatively investigate the specific (H-bond) and non-specific (due to change in dipolarity and polarizability) interactions [20]. Since SKF86002 is an ATP competitive inhibitor, investigating the mechanism of its binding to target protein relies on understanding of its physicochemical characteristics. This

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would be beneficial for optimizing the drug efficacy and minimizing side effects for newly developed drugs.

To the best of our knowledge, there are no detailed UV–Vis spectroscopic studies on SKF86002 (Fig. 1). The reported studies showed that SKF86002 exhibits fluorescence which was greatly enhanced upon binding to the target protein [21]. Therefore, we present an intensive spectral study on SKF86002 in solvents with varying polarity and hydrogen bond strength.

2. Experimental and computational

2.1. Materials

All solvents were of spectroscopic or HPLC grade. They were selected to cover a broad range of solvent polarity and hydrogen bond strength. Cyclohexane (CH), dichloromethane (DCM), ethanol (EtOH), 2-propanol (iPrOH), and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich Pty Ltd. Methanol (MeOH), *t*-butanol (*t*-But), ethylene glycol (EG), allyl alcohol (allyl), *N*-methylformamide (NMF), toluene (Tol), xylene (Xyl), pyridine (Pyd), acetonitrile (ACN), *N*,*N*-dimethylformamide (DMF), 1,4-dioxane (Diox), tetrahydrofuran (THF), ethylacetate (EtAc), 1,2-dichloroethane (DCE), acetone (Act), and chloroform ($CHCl_3$) were obtained from Thermo Fisher Scientific Inc. Water used was double-distilled deionized water. SKF86002 was purchased from Sapphire Bioscience Pty Ltd. Quartz cuvettes with a path length of 1 cm were purchased from Starna Pty Ltd.

2.2. Methods

All solutions of SKF86002 were prepared and left overnight for equilibration. A matched pair of quartz cuvette was loaded with a 3 μM of SKF86002 for absorbance measurement. For excitation and emission measurements, 0.3 μM solutions of SKF86002 were used. The absorption measurements were conducted at room temperature using a Perkin-Elmer LAMBDA 1050 UV/Vis/NIR spectrophotometer. While the excitation and emission experiments were done on a Perkin Elmer LS55 Fluorescence Spectrometer at room temperature as well. Blank samples devoid of SKF86002 were used for background absorbance, scatter and fluorescence corrections.

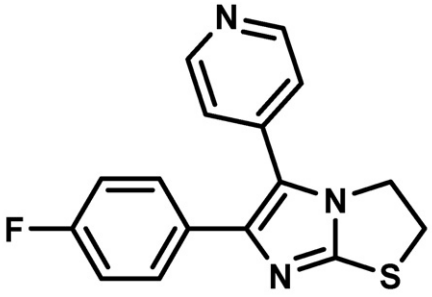
2.3. Computational details

Density functional theory (DFT) based Becke three-parameters Lee-Yang-Parr hybrid functional (B3LYP) [25] in combination with B3LYP/6-31 + G(d) basis set was employed in the calculations. The geometry of SKF86002 was originally optimized using B3LYP/6-31G(d) model and reoptimized using the B3LYP/6-31 + G(d) model (B3LYP/6-31G(d)// B3LYP/6-31 + G(d)). The UV–Vis spectrum in cyclohexane solution was calculated using time dependent density functional theory (TD-DFT) and conductor-like polarizable continuum model (CPCM) [26]. Absorption UV–Vis spectrum in methanol were calculated for the lowest 30 excited states of singlet–singlet transitions. All calculations performed using Gaussian 09 computational chemistry package [27] on Swinburne University Supercomputing Facility.

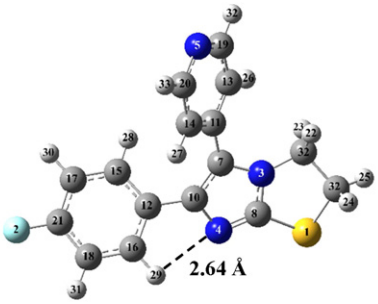
3. Results and discussion

3.1. The UV–Vis absorption spectrum in cyclohexane solution and the role of hydrogen bond

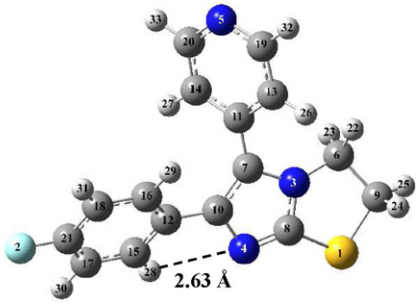
The measured absorption spectrum of SKF86002 is composed of three absorption bands. The wavelengths of absorption maxima are listed in Table 1. Using a 3 μM solution of SKF86002 in cyclohexane, we could reveal only two absorption peaks at 253.5 nm and 216.5 nm, as shown in Fig. 2 (solid black spectrum). These two maxima have a high optical density in all studied solvents ranging from 0.5 to 3.2, however we observed a small band around 320 nm (OD < 0.1). Therefore, we used a higher concentration of SKF86002 which helped to resolve it into a distinct absorption peak, refer to the inset of Fig. 2. Generally, SKF86002 absorption maxima in different solvents can be shown, with an order of increasing optical density, at approximately $\lambda_1 = 325$ nm, $\lambda_2 = 260$ nm and $\lambda_3 = 210$ nm.



Two-dimensional (2D) chemical Structure



Optimized 3D structure of SKF86002 isomer A.



Optimized 3D structure of SKF86002 isomer B.

Fig. 1. Chemical structure of SKF86002 (2D) and quantum mechanically optimized isoenergy isomers (A) and (B) of SKF86002 in three-dimensional (3D) space in cyclohexane solution (pale blue shows the positions of the possible H-bond).