J Fluoresc (2011) 21:1061–1067
DOI 10.1007/s10895-010-0778-y

ORIGINAL PAPER

Solvatochromic and Fluorescence Behavior of Sulfisoxazole

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Received: 22 August 2010 / Accepted: 23 November 2010 / Published online: 24 December 2010

Abstract The Fluorescence spectroscopic and solvatochromic behavior of Sulfisoxazole, a sulfa drug with antimicrobial activities, in various pure solvents of different polarity and hydrogen bonding capability is reported. The fluorescence emission spectrum of sulfisoxazole was found to be solvent polarity dependent, where a notable red shift in emission maximum was observed with increasing solvent polarity as well as hydrogen bonding capability. The effects of the latter two solvent parameters were quantitatively investigated using the methods of Lippert–Mataga and solvatochromic comparison method (SCM) that is based on the Kamlet-Taft equation. Particularly, the Lippert–Mataga method was applied to estimate the dipole moment of the excited state (μ_e) upon plotting Stokes shift versus solvent polarizability (Δf), where a value of 11.54 Debye was obtained. On the other hand, applying the multiple regression analysis to the SCM method revealed that solvent polarizability (π^*) and hydrogen-bond donor capability (α) approximately equally stabilize sulfisoxazole in the excited state with minor destabilization contribution by the hydrogen-bond acceptor capability (β). These findings revealed that the excited state of sulfisoxazole is stabilized by polar solvents, indicating that this drug molecules exhibit larger dipole moment in the excited state than in the ground state, which in turn implies that a potential intramolecular charge transfer (ICT) occurs after excitation.

Keywords Fluorescence spectroscopy · Solvatochromism · Lippert-Mataga method · Solvatochromic comparison method (SCM) · Hydrogen bonding · Charge transfer · Pharmaceutical drug · Photophysical properties

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Introduction

The interests in photochemical and photophysical properties of drug molecules have been related to various health problems induced by their high potential photoreactivity. Broad spectrum of chemical species, including drug molecules, behave differently in their excited state in comparison to their ground states. This phenomenon can be attributed to the fact that several atomic centers may possess different electronic distributions at the excited state that significantly differ from those at the ground state [1–3]. Hence, when chemical species in their excited states have relatively higher dipole moment than those of the ground states, they may possess different reactivity at their excited states. Such variation in chemical species' behaviors, drug molecules in particular, at the excited state may lead to unexpected pharmacokinetic pathway, which in turn may cause undesired consequences [4]. Great attention has recently been directed toward the fact that various photomutagenic and photoallergic symptoms are induced in patients who have been exposed to various radiations including sunlight, while being treated with photosensitive drugs [5–10]. Hence, establishing understandable and comprehensible protocols for photosensitive drug molecules is of particular interest and importance in the landscapes of chemical and biomedical sciences. In particular, the photosensitization phenomenon with its undesirable and desirable consequences is considered as one of the most biological concerns of interaction with electromagnetic radiation. For example, photosensitization

with desirable consequences was employed in various applications including photodynamic therapy such as cancer treatment, and inactivation of viruses [11–14]. However, such interaction could be undesirable in many occasions, where unexpected consequences may occur; this includes the side effects of many photosensitive drugs. Furthermore, it is noteworthy mentioning that the basic requirement for the photosensitization to occur is to have the photosensitizer in biological medium, where changes of different kinds in the biological medium can be observed. On the other hand, the side effects of photosensitization can be minor such as cutaneous reactions or sever including genetic mutation that may consequently initiate developing mutagenic diseases.

Importantly, in order to understand and efficiently predict the behavior of potential photosensitizing drug, a variety of photophysical and photochemical studies need to be conducted; this includes examining the influence of various medium properties on the photophysical and photochemical behavior of the photosensitizer, such as pH, ionic strength, and chemical contents of the medium, solvatochromic effects in particular. Solution composition and other physical properties have a notable influence on the photophysical and photochemical properties of the photosensitive molecules. Interestingly, fluorescence spectroscopy is a universal technique that can be used for examining any change in local microenvironment of broad range of molecules, including pharmaceutical drugs. In principle, upon excitation of the molecules, the molecules possess higher polarity, and hence the solvent environment in this case plays an important role in stabilizing or destabilizing the excited state, which may lead to red-shift or blue-shift in the fluorescence emission spectrum of the molecules, respectively [1, 15]. The Solvatochromic investigation provides important details about the behavior of drug molecules in various environments of different polarities that resemble the natural cellular environments, which in turn offers gaining valuable insights regarding understanding their mechanisms of action at the molecular level. Several previous reports have appeared in the literature concerning the effect of solvents of different polarities on the spectra of a photosensitive species, emission spectra in particular [16–23].

Sulfisoxazole (4-amino-N-(3,4-dimethyl-1,2-oxazol-5-yl) benzenesulfonamide) is a sulfonamide drug belongs to the family of sulfa drug, which are widely used as antimicrobial agents [24–26]. These sulfonamide drugs share a basic chemical structure comprising a sulfanilamide group and five- or six-member heterocyclic ring. Sulfisoxazole is an antibacterial agent mainly used to prevent or treat various kinds of bacterial infections in humans and animals. Importantly, sulfisoxazole, and other sulfa drugs, possess high potential of photosensitizing [4], which in turn could initiate unexpected pharmacokinetic pathway after administration upon being exposed to various kinds of irradiation [27, 28]. Thus, such potential photosensitizing of sulfisoxazole necessitates investigating and characterizing the photophysical properties of this drug. The goal of the present study is to investigate the influence of solvent's polarity on the photophysical properties of the antimicrobial drug sulfisoxazole (see structures in Fig. 1) utilizing fluorescence spectroscopy. In particular, the steady state fluorescence spectra of sulfisoxazole were collected in different solvents with the purpose of correlating these fluorescence data with solvents' physical properties; including dielectric constant, orientation polarizability (Δf), and polarity index (E_T (30)). Furthermore, the value for dipole moment of sulfisoxazole at the ground and excited states were estimated based upon using combination of experimental results and theoretical calculation.

Experimental

Sulfisoxazole and quinine sulfate were purchased from Sigma-Aldrich and used as received. Sulfuric acid and all solvents (spectroscopic grade) were obtained from different commercial resources. Stock solution of sulfisoxazole with concentration of 1×10^{-3} M was prepared in methanol. Equal concentrations sulfisoxazole (1×10^{-5} M) were prepared in different solvents by withdrawing an appropriate volume of sulfisoxazole stock solution, then evaporating the methanol under relatively low pressure using a fume-hood followed by re-dissolving the drug residues in appropriate volume of the solvents. Aqueous solutions of sulfisoxazole and quinine sulfate were prepared in Milli-Q ultrapure water (Millipore). The steady state fluorescence spectra of sulfisoxazole in different solvents were collected

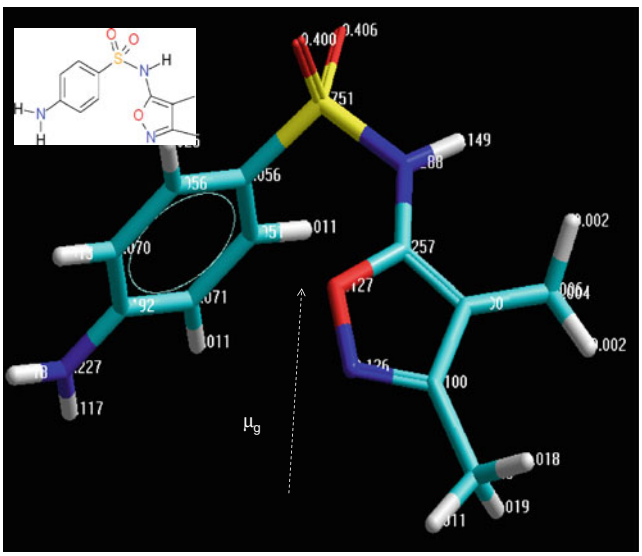


Fig. 1 Optimized 3-D geometry of SXZ in the ground state; inset: chemical structure

using RF-5301PC spectrofluorimeter (Shimadzu, Japan) equipped with a 150 W xenon lamp. Fluorescence measurements were performed using 1.0 cm quartz cuvette with both excitation and emission bandwidths set on 5 nm and an excitation wavelength of 275 nm. Temperature was controlled using constant-temperature cell holder connected with water circulator (Shimadzu, Japan), where all measurements were performed at 25 °C. Fluorescence quantum yield (Φ_f) calculation was conducted using quinine sulfate (in 0.05 mol.L^{-1} sulfuric acid) as a reference (Φ_f=0.52, λ_{ex}= 360 nm) [1]. Absorption spectra were recorded using Jasco UV–Vis spectrophotometer (USA). 3-D structure optimization of sulfisoxazole and quantum mechanics calculation were performed based on combination of semiemperical and molecular mechanics (MM+) calculations using HyperChem 8.0 software package (HyperCube Inc., Gainesville, FL, USA).

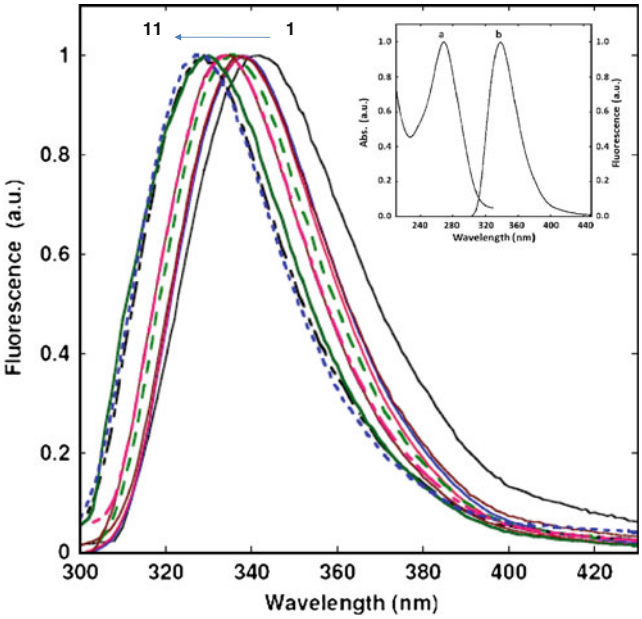


Fig. 2 Normalized fluorescence emission spectra (λ_{ex}=275 nm) of SXZ (1×10^{-5} M) in different solvents (1) water, (2) methanol, (3) ethanol, (4) isopropanol, (5) DMSO, (6) acetonitrile, (7) dichloromethane, (8) ethyl acetate, (9) 1,4-dioxane, (10) diethyl ether, (11) chloroform. Inset: normalized absorption and fluorescence emission spectra in methanol

Results and Discussion

Solvent Effects on the Fluorescence Spectrum of Sulfisoxazole

The fluorescence emission spectra of sulfisoxazole were obtained in solvents of different polarities and hydrogen bonding abilities; namely, polar protic, polar aprotic and nonpolar solvents. The normalized fluorescence emission spectra of sulfisoxazole in the solvents under investigation are shown in Fig. 2. The inset shows the absorption and fluorescence emission spectra of sulfisoxazole in methanol, from which it can be noticed that both spectra exhibit a single band at 275 and 338 nm that correspond to the absorption and fluorescence emission maxima, respectively. Similar single-band absorption and fluorescence emission spectra were observed in all solvents. It is noteworthy mentioning that no correction was performed to the steady state fluorescence emission spectra against the inner filter effect, where shift observed in spectra is independent of this effect, whereas negligible effect was observed upon calculating the fluorescence quantum yield. Photophysical properties of sulfisoxazole along with physical properties of solvents under investigation are summarized in Table 1. As can be noticed in Fig. 2, a notable blue shift in fluorescence emission spectra of sulfisoxazole can be observed with decreasing solvent polarity, whereas no significant shift is observed in absorption spectra with varying the solvent polarity (data not shown), and hence a related increase in the Stokes shift. Interestingly, this result indicates that sulfisoxazole in its excited state is more stabilized in polar solvents than in nonpolar ones. Generally, fluorophores exhibit larger dipole moment (μ_e) in their excited state in comparison to the dipole moment in the ground state (μ_g). Hence, the solvent dipoles reorient themselves accordingly around the fluorophore upon being excited, which in turn results in decreasing the energy of the excited state in polar solvents [1]. Furthermore, It is anticipated that the increase in Stokes shift with increasing solvent polarity can be attributed to various factors, including the presence of the donating group, namely the amino group, at the para position of the phenyl ring relative to the accepting group, namely the sulfonyl group (see inset in Fig. 1). Hence, this kind of arrangement of donating-accepting groups can induce intramolecular charge transfer that is more stabilized by polar solvents, and hence greater Stokes shift is observed. Proposed model for the expected ICT is presented in Scheme 1. Thus, an attempt has been made to construct a correlation between the fluorescence emission maxima of sulfisoxazole and the dielectric constant of the solvent as illustrated in Fig. 3. As can be observed from Fig. 3, the position of the fluorescence emission maxima of sulfisoxazole increased gradually with increasing the dielectric constant of the solvent, which indicates that it is not only the potential intramolecular charge transfer that contributes to the variation in Stokes shift, but also there are other factors affecting such variation upon using various solvents ranging from nonpolar to polar.

Accordingly, we need to quantitatively verify the effect of solvent polarity on the steady-state fluorescence emission spectra of sulfisoxazole, where the solvent refractive

Table 1 Photophysical properties of sulfisoxazole in different solvents along with their physical parameters

Solvent	Δf	$E_T(30)$, Kcal.mol^{-1}	ε (1)	Viscosity, cP	π^*	β	α	$\Delta\nu_{ss}(\nu_{em}-\nu_{ex})$, cm^{-1}	ϕ_f
Polar protic									
Water	0.320	63.1	80.1	0.890	1.09	0.18	1.17	8928	0.002
Methanol	0.310	55.4	33.0	0.544	0.6	0.62	0.93	7658	0.001
Ethanol	0.289	51.9	25.3	1.074	0.54	0.77	0.83	7383	0.007
Isopropanol	0.276	48.4	20.2	2.038	0.48	0.95	0.76	7295	0.009
Polar aprotic									
DMSO	0.264	44.8	47.2	1.987	1.00	0.76	0	6998	0.019
Ethyl acetate	0.200	38.1	6.1	0.423	0.55	0.45	0	7373	0.024
Acetonitrile	0.305	45.6	36.6	0.369	0.75	0.31	0.19	7324	0.005
Dichloromethane	0.218	40.7	8.9	0.413	0.82	0	0.3	7058	0.003
Nonpolar									
Chloroform	0.153	39.1	4.8	0.537	0.58	0	0.44	6965	0.002
1,4-Dioxane	0.022	36.0	2.2	1.177	0.55	0.37	0	7123	0.036
Diethyl ether	0.167	34.5	4.3	0.224	0.27	0.47	0	6941	0.021

Abbreviations

Δf orientation polarizability, $E_T(30)$ surface polarity, π^* dielectric effect of solvent, β hydrogen-bond acceptor ability, α hydrogen-bond donor ability, ν wavenumber, $\Delta\nu_{ss}$ Stokes shift, ϕ_f fluorescence quantum yield

(1) CRC Handbook of Chemistry and Physics, 90th Ed. (2010)

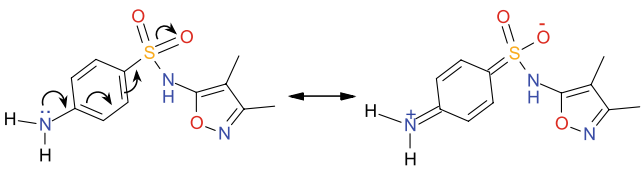
index has to be considered in addition to the solvent dielectric constant. A combination of these two factors defines the solvent polarity, namely the orientation polarizability (Δf) according to the equation [1]:

$$\Delta f = \frac{\varepsilon - 1}{2\varepsilon + 1} - \frac{n^2 - 1}{2n^2 + 1} \quad (1)$$

where, ε and n are the solvent dielectric constant and refractive index, respectively. Hence, the Δf relationship takes into account the effect of solvents dipoles reorientation and solvent electrons redistribution on the total polarity of the solvent; where, the first term $\left(\frac{\varepsilon-1}{2\varepsilon+1}\right)$ and second term $\left(\frac{n^2-1}{2n^2+1}\right)$ represent the contribution of a combination of solvents dipoles reorientation and solvent electrons redistribution, and the effect of only electrons redistribution, respectively. Commonly, the effect of solvent polarity on emission spectral properties of a fluorophore is investigated according to changes observed in Stokes shift (ν_{ex}–ν_{em}) and Φ_F in various solvents. The effect of solvent polarity on Stokes shift of a fluorophore is presented according to the Lippert–Mataga relationship, where this equation correlates the energy difference (cm^{-1}) between absorption and emission maxima to the orientation polarizability [1]:

$$Stokes\ Shift = \frac{2\left(\mu_g - \mu_e\right)^2}{hca^3}\Delta f + const. \quad (2)$$

where, *Stokes Shift* is the difference between the excitation (ν_{ex}) and emission (ν_{em}) maxima in terms of wavenumber (cm^{-1}); μ_g and μ_e are the dipole moments of the molecule in its ground and excited states, respectively; α is the cavity



Scheme 1 Proposed ICT for Sulfisoxazole

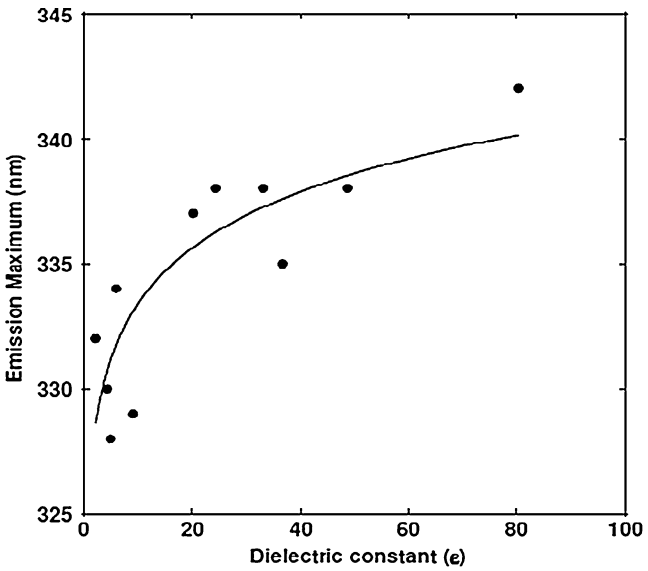


Fig. 3 Plot of variation of emission fluorescence maximum of SXZ (1×10^{-5} M) vs. dielectric constant of different solvents (λ_{exc}=275 nm)

radius in which the fluorophore resides, h is Planck's constant, c is speed of light. A plot of Stokes shift versus Δf of sulfisoxazole is illustrated in Fig. 4. As can be noticed from Fig. 4, significant change in Stokes shift was observed with increasing solvent polarity. However, It is noteworthy mentioning that Lippert–Mataga does not consider other solvent parameters; particularly, the solvent capability of hydrogen bonding. Thus, the data presented in Fig. 4 were subdivided into two groups, namely capable and incapable of hydrogen bonding, where linear fitting was applied to each group separately. However, the insignificant increase in Stokes shift of sulfisoxazole observed in nonpolar and polar aprotic solvents compared to the significant increase in polar protic solvents indicates that hydrogen bonding contributes effectively in stabilizing the sulfisoxazole in its excited state. In addition, sulfisoxazole exhibited relatively higher Stokes shift in protic solvents, alcohols in particular, with decreasing molecular size, which can be attributed to the fact that smaller alcoholic molecular size can form stronger hydrogen bonding. Hence, based on these findings, the μ_e can be estimated from the slope of the linear relationship between Stokes shift and Δf. A slope of 491 was obtained, which corresponds to the value of $\left(\frac{2(\mu_g-\mu_e)^2}{hca^3}\right)$. The μ_e and cavity radius were estimated based on molecular mechanics (MM+) calculation, and found to be equal to 5.8 A and 7.18 Debye, respectively. Figure 1 shows the 3-D optimized structure of sulfisoxazole, where as can be noticed the phenyl ring in a geometry that is approximately parallel to that of the imidazoline ring, which accounts for the optimized cavity radius obtain for sulfisoxazole. Based on these values of μ_e and α, the value of μ_e was calculated and found to be equal to 11.54 Debye. This value of μ_e is an indication of the high polarity of sulfisoxazole in the excited state compared to the ground state, which in turn is stabilized by polar solvent and consequently a larger Stokes shift is observed. For that reason, it is proposed that intramolecular charge transfer occurs across the sulfisoxazole molecules after excitation.

In Addition, the solvent effect on the spectral properties of sulfisoxazole has been further investigated using the Reichardt–Dimroth method [29], which is based upon correlating the Stokes shift of the fluorophore to $E_T(30)$ of the solvent, where $E_T(30)$ is the solvent polarity parameter introduced by C. Reichardt [29]. Hence, The significant difference between this method and Lippert–Mataga method is incorporating the capability of hydrogen bonding, in addition to the solvent polarity, into the solvent parameter. Figure 5 shows the plot of Stokes shift of sulfisoxazole as a function of E_T (30). As can be noticed from Fig. 5, analogous trend to the plot of Stokes shift versus Δf was observed, where gradual increase in Stokes shift was observed with increasing $E_T(30)$ of the solvent. Similarly, subdividing the solvents into protic and aprotic solvents was also performed. However, similar poor regression coefficient was observed for the aprotic solvents in both plots.

In view of this situation, neglecting the capability of hydrogen bonding of both the solvent and fluorophore during investigating solvent polarity effect on spectral properties of the fluorophore is considered as a shortcoming of the Lippert–Mataga method, whereas combining the polarity and capability of hydrogen bonding of the solvent could cause huge deviation from linearity. Interestingly, a

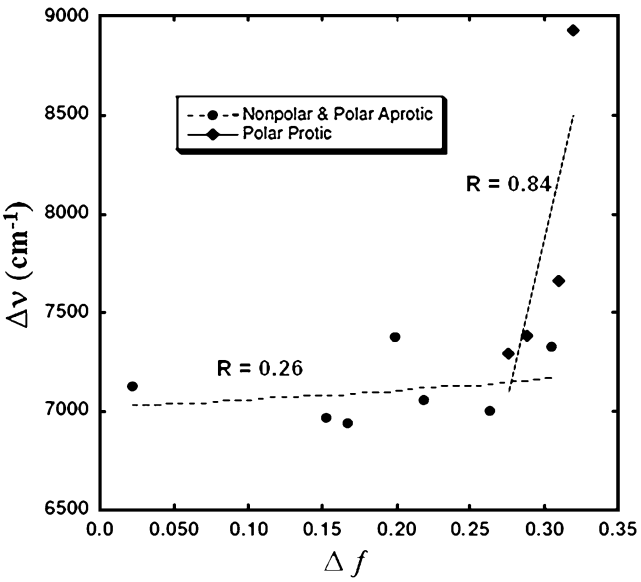


Fig. 4 Plot of Stokes shift (Δν) of SXZ (1×10^{-5} M) vs. Δf of different solvents (λ_{ex}=275 nm)

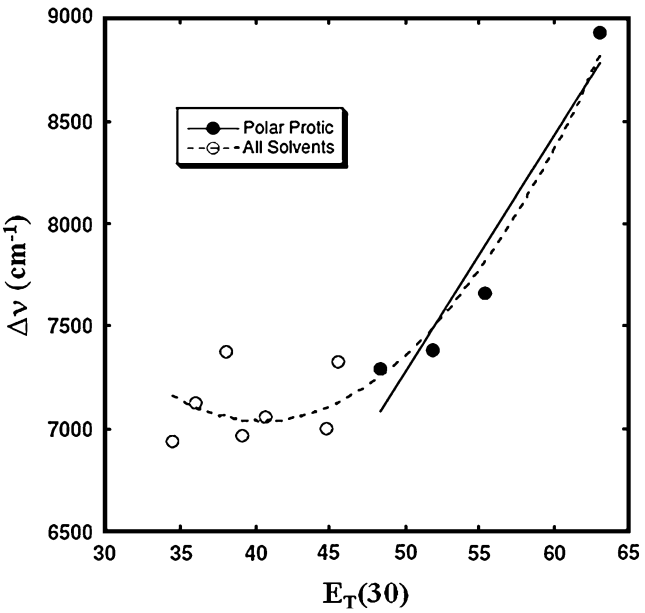


Fig. 5 Plot of Stokes shift (Δν) of SXZ (1×10^{-5} M) vs. $E_T(30)$ of different solvents (λ_{ex}=275 nm)

new method of solvatochromic analysis was proposed by Kamlet et al. [30], which takes into consideration the effect of individual solvent's parameter on the spectral properties of the fluorophore. This approach is known as solvatochromic comparison method (SCM), which is presented via the linear solvation energy relationship or Kamlet-Taft expression:

$$\Delta v = \Delta v_0 + c\pi^* + b\beta + a\alpha \quad (3)$$

where, $\Delta\nu$ is the Stokes shift (cm^{-1})observed in the solvent; $\Delta\nu_0$ is the Stokes shift independent of solvent effects; π^* is the dielectric effects of solvents (polarizability); β is the hydrogen-bond acceptor capability; α is the hydrogen-bond donor capability; c, b, and a are the coefficients that indicate the contribution of each parameter. The Stokes shift data of sulfisoxazole was analyzed using the Kamlet-Taft relationship and fitted with multiple regression analysis using parameters in Table 1. Hence, the following equation was obtained:

$$\Delta v = 6542(\pm 450) + 821(\pm 557)\pi^* - 155(\pm 413)\beta + 846(\pm 217)\alpha;$$

$$R = 0.82$$

As can be noticed from the previous equation, coefficient c and a are approximately the same, which indicates that solvent polarizability and hydrogen donation capability of the solvent influence equally the Stokes Shift of sulfisoxazole, where the positive sign implies stabilization. On the other hand, the low value obtained for b indicates that hydrogen acceptor capability has a minor effect on the Stokes shift of sulfisoxazole, where the negative sign implies destabilization. These findings can be attributed to the fact that although the lone pair of the nitrogen of amino group is not available for hydrogen bonding because of its involvement in the ICT, other nitrogen atoms, namely the nitrogen of sulfonyl and imidazoline ring, are still available for hydrogen bonding, and hence equal stabilization effect on the excited state of sulfisoxazole was observed for both solvent parameters.

Furthermore, one of the central parameters that are also influenced by the solvent effect is the quantum yield. The fluorescence quantum yield is estimated for sulfisoxazole in different solvents using the equation [1]:

$$\Phi_F(s) = \left(\frac{A_r}{A_s}\right) \cdot \left(\frac{F_s}{F_r}\right) \cdot \left(\frac{n_s^2}{n_r^2}\right) \cdot \Phi_F(r) \quad (4)$$

where, r and s refer to reference and sample, respectively; A is the absorbance at the excitation wavelength; F is the fluorescence intensity; n is the refractive index of the medium. The variation in the fluorescence quantum yield is plotted against the solvent orientation polarizability and displayed in Fig. 6. As can be noticed from Fig. 6, the Φ_F decreases as Δf increases. It was anticipated that the plot of Φ_F vs. Δf could exhibit two correlations, one for solvents of high polarity and the other is for those of lower polarity, which implies the formation of ICT that is stabilized by polar solvents and emitting local excited state (LE) in non- or low polar solvents. However, it is noteworthy mentioning viscosity is another factor that could significantly contribute to the Φ_F. For instance, as shown in Table 1, although DMSO and isopropanol possess approximately similar Δf, Φ_F in DMSO is about two times higher than Φ_F in isopropanol. Hence, this can be attributed to the larger energy barrier of rotation observed in solvents of higher viscosity. Interestingly, the highest Φ_F was observed in 1,4-dioxane, where this solvent possess the lowest Δf and relatively higher viscosity in comparison to other nonpolar solvents, and hence these two combined factors account for this observation.

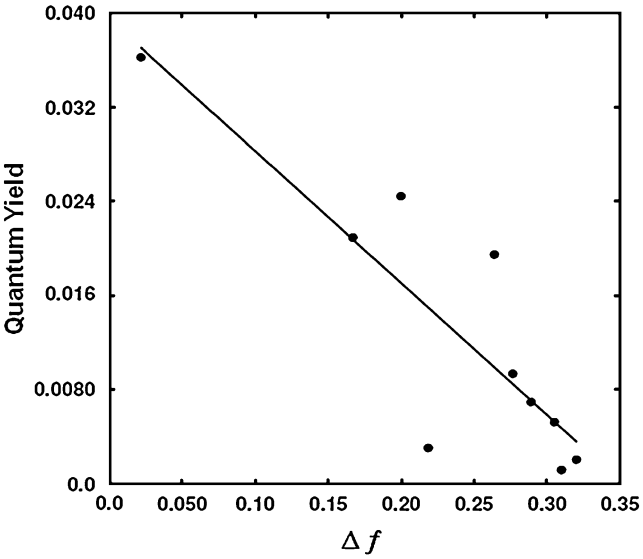


Fig. 6 Plot of quantum yield of SXZ (1×10^{-5} M) vs. Δf of different solvents (λ_{ex}=275 nm)

Conclusion

We have demonstrated that photophysical properties of sulfisoxazole, steady state fluorescence emission in particular, are solvent dependent. Analysis of the fluorescence data using the Lippert–Mataga technique and solvatochromic comparison method (SCM) revealed that The observed solvatochromism of sulfisoxazole is notably influenced by various solvent parameters. In particular,, the solvent parameters, namely polarizability (π^*) hydrogen bond donor (α), and hydrogen bond acceptor (β) contribute majorly in stabilizing and negligibly destabilizing sulfisoxazole in the excited state, respectively. These results indicate that stability

of sulfisoxazole in the excited state increases with increasing solvent polarity and capability of hydrogen bonding, which in turn implies that the prospectivity of intramolecular charge transfer (ICT) to occur increases with increasing the solvent polarity and capability of hydrogen bonding. The findings reported herein could be used to gain conclusive knowledge concerning the pharmacokinetics of this drug, and other structurally related drugs, under various biological circumstances that resemble experimental conditions investigated in this report.

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