

In-Depth Investigation of Solvatochromism, Excited State Dipole Moments and Preferential Solvation of Antibiotic Agents

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Abstract:

The solvatochromism, excited state dipole moment and preferential solvation studies of antibiotic agents namely sulfamethoxazole (SMX) and Trimethoprim (TMP) have been carried out using UV-visible absorption and fluorescence techniques. The absorption and fluorescence spectra of these molecules reveal the notable spectral shifts corresponding to changes in solvent polarity. Further, a profound understanding of the solvatochromic behavior of antibiotic agents has been comprehended based on Lippert-Mataga, Reichardt's, Kamlet-Traft and Catalan's linear regression methods. The excited state dipole moment is estimated based on solvatochromism in pure solvents by different models. The probable cause for the increase in dipole moment in the excited state is discussed and expanded the contribution of intramolecular charge transfer (ICT) utilizing the resonance structure of these molecules. Furthermore, the dependability of excited state dipole moment and change in dipole moment on solute polarizability is discussed. The preferential solvation study of antibiotic agents in the THF-Water mixture is carried out.

Key Word: Antibiotic agents, dipole moment, preferential solvation, Solvatochromism,

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I. Introduction

Sulfamethoxazole (SMX) and Trimethoprim (TMP) drug molecules act as antimicrobial agents used in the treatment of infections caused by bacteria. SMX and TMP are collectively called co-trimoxazole and it is abbreviated as TMP-SMX [1-2]. SMX and TMP drugs are cost-effective and used for the treatment of many types of illnesses. SMX belongs to the class of sulfonamides, among the sulfonamides, SMX is considered as an effective antibacterial agent. SMX contains the -SO₂ functional group which might be responsible for the antimicrobial activity. SMX is used to cure several infections namely, prostatitis, bronchitis, and urinary tract infections [3]. SMX also exhibits important photophysical and physicochemical properties such as absorption, fluorescence, fluorescence quenching [4], polymorphism [5] and the capability to form metallic complexes of pharmaceutical interest [6]. TMP belongs to the class of diaminopyrimidines. It is chosen as a bacterial dihydrofolate reductase inhibitor for veterinary and clinical use [7]. TMP in combination with other drugs is used to treat many types of pneumonia and combination with certain sulfonamides results in the synergistic antibacterial activity by blocking the folic acid metabolism [8].

Fluorescence spectroscopy is an admirable research tool in the field of pharmacy and medicine [9-11]. It is used as an excellent diagnostic tool with high specificity and sensitivity used in medical microbial field for numerous purpose [12]. Also, this technique used in forensic science [9], food analysis [13] and medical science [14]. Since the decades, the study of the photophysical characteristics of numerous fluorophores has been the subject of several investigations [15-29]. The various theories based on solvatochromic shift that are used to calculate the excited state dipole moments namely Lippert-Mataga (L-M) [30], Bakhshiev's (B) [31], Kawski-Chamma-Viallet (K-C-V) [32], Bilot-Kawski (B-K) [33] and Reichardt's microscopic solvent polarity parameter (E_N^T) [34].

The preferential solvation is a subject of present interest. The behavior of drugs in both pure and mixture of solvents is commonly estimated for pre-formulation and designing the purification methods of liquid medicine [35]. Also, solvent mixture influences the optical response namely absorption, emission and Stoke's shift and physicochemical features namely solubility, solute-solvent interaction processes based on the different

binary compositions. Recently, we have reported the computational studies on SMX and TMP drug molecules [37]. In continuation of our previous work, herein we report the solvatochromism, ground/excited state dipole moments and preferential solvation. To the best of our information, this is the first report on the detailed investigation of solvatochromism ground/excited state dipole moments and preferential solvation of SMX and TMP using various solvatochromic approaches in pure solvents. The experimental outcomes are analyzed using the Lippert-Mataga bulk solvent polarity parameter, Kamlet-Traft and Catalan polarity parameter [29], Reichardt's microscopic solvent polarity parameter (E_N^T) [30]. The computational method was used to calculate the ground and excited state dipole moment of SMX and TMP molecules. The experimental excited state dipole moment of SMX and TMP has been estimated using various theories based on solvatochromic data namely, Bakshiev's, Bilot-Kawski, Kawski-Chamma-Viallet and Reichardt's microscopic solvent polarity parameter (E_N^T).

II. Material and Methods

Materials

The titled molecules SMX and TMP were purchased from Sigma Aldrich, India with a definite purity of 99% and were used further as received. The spectroscopic grade solvents are used and were purchased from S.D Fine Chemicals Ltd., India. The double distilled water was used for the entire study. The molecular structure of SMX and TMP is given in Figure 1. The refractive index (n), dielectric (ϵ) and solvent polarity parameter (E_N^T) are taken from the literature [39][40].

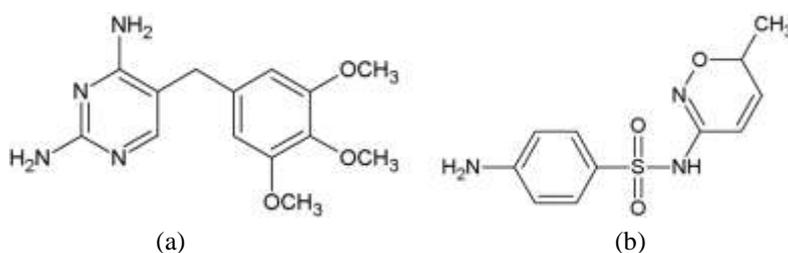


Figure 1: The molecular structure of (a) SMX and (b) TMP molecules.

Computational methods

The quantum chemical calculations were carried out using Gaussian 09 software [41] at CAM-B3LYP level of theory with 6-311++G (d, p) level of basis set. The DFT and TD-DFT calculations were carried out with IEEPCM model in vacuum. The results were examined using Gauss View 6.0 visualization program [42].

Spectroscopic methods

The UV-absorption spectra of SMX and TMP were recorded using Spectrofluorometer (LABINDIA, Model: UV-3092) in the range of 200-400 nm. The fluorescence spectra were recorded using a spectrofluorometer (Agilent, U.S.A, Model: Cary Eclipse-3000) in the range of 250-500 nm range. The concentration of SMX and TMP was kept low at 5×10^{-5} M to diminish the self-absorption/ formation of aggregation. The refractive index (n), dielectric constant (ϵ) and polarity parameter (E_N^T) values of solvent are taken from the literature[38][34].

III. THEORY

Solvatochromism in neat solvents

examine solvatochromism in the titled molecules the spectral parameters (wavenumber maxima of absorption, fluorescence and Stoke's shift) are correlated with $\Delta F_{L-M}(\epsilon, n)$ according to Eqn.1

$$\Delta F_{L-M}(\epsilon, n) = \frac{(\epsilon-1)}{(2\epsilon+1)} - \frac{n^2-1}{2n^2+1} \quad (1)$$

The spectral properties are also examined using multiple linear regression methods (MLR) suggested by Kamlet (Eqn.2) and Catalan (Eqn.3).

$$y = y_0 + a\alpha + b\beta + c\pi^* \quad (2)$$

$$y = y_0 + aSA + bSB + cSP + dSdP \quad (3)$$

where, y is the spectroscopic property under observation, y_0 is the spectroscopic property in the gas phase, α characterizes the hydrogen bond donor (HBD) strength, β characterizes the hydrogen bond acceptor (HBA) strength, π^* characterizes the non-specific dielectric interactions. SP, SdP, SA and SB are describing the solvent polarizability, solvent dipolarity, solvent acidity and solvent basicity respectively. a , b , c , and d are measures of contribution of solvents HBD/acidity, HBA/basicity, non-specific dielectric interaction/polarity and dipolarity respectively. The value of α , β and π^* and SA, SB, SP and SdP are taken from literature [29].

Estimation of ground state dipole moment

The ground state dipole moment of titled molecules is obtained by quantum chemical calculations. The computations were carried out by using the Gaussian09 software at the CAM-B3LYP level of theory and 6-311++G (d, p) basis set.

Estimation of excited state dipole moment

The excited state dipole moment of investigated molecules is computed using quantum chemical calculations. These calculations were carried out at CAM-B3LYP level of theory and 6-311++G (d, p) basis set using TD-DFT.

The excited state dipole moment (μ_e) of investigated molecules were calculated based on the experimental solvatochromism data using various models proposed by Lippert- Mataga, Bakhshiev and Kawski–Chamma–Viallet for a spherical molecule with isotropic polarizability. These methods are described in the Eqs. (4), (5) and (6) respectively.

$$(\bar{\nu}_a - \bar{\nu}_f) = m_{L-M} F_{L-M}(\epsilon, n) + \text{Constant} \quad (4)$$

$$(\bar{\nu}_a - \bar{\nu}_f) = m_B F_B(\epsilon, n) + \text{Constant} \quad (5)$$

$$\frac{(\bar{\nu}_a + \bar{\nu}_f)}{2} = -m_{K-C-V} F_{K-C-V}(\epsilon, n) + \text{Constant} \quad (6)$$

Whereas, $\bar{\nu}_a$ is the absorption wavenumber maxima and $\bar{\nu}_f$ is the fluorescence wavenumber maxima, $F_{L-M}(\epsilon, n)$, $F_B(\epsilon, n)$ and $F_{K-C-V}(\epsilon, n)$ are Lippert-Mataga, Bakhshiev’s and Kawski–Chamma–Viallet polarity function parameters respectively which depend on dielectric constant and refractive index of solvents. m_{L-M} , m_B and m_{K-C-V} are slopes of Lippert-Mataga, Bakhshiev’s and Kawski–Chamma–Viallet equations respectively and are given by Eqs. (7), (8) and (9)

$$m_{L-M} = \frac{2(\mu_e - \mu_g)^2}{hc a^3} \quad (7)$$

$$m_B = \frac{2(\mu_e - \mu_g)^2}{hc a^3} \quad (8)$$

$$m_{K-C-V} = \frac{2(\mu_e^2 - \mu_g^2)}{hc a^3} \quad (9)$$

Where c is the velocity of light, h is Planck’s constant and ‘ a ’ is Onsager cavity radius of the molecule and μ_g is the ground state dipole moment and μ_e is the excited state dipole moments of the molecule. The μ_e can be calculated using Eqs.13-15 by knowing slope and other terms.

The μ_e can also be calculated by the method based on empirical solvent polarity parameter (E_N^T) using the Eqs. (10) and (11)

$$\bar{\nu}_a - \bar{\nu}_f = m_{E_N^T} E_N^T + \text{Constant} \quad (10)$$

$$\text{Where slope } m_{E_N^T} = 11307.6 \left[\left(\frac{\Delta\mu}{\Delta\mu_B} \right)^2 \left(\frac{a_B}{a} \right)^3 \right] \quad (11)$$

Here, $\Delta\mu_B = 9D$ and $a_B = 6.2 \text{ \AA}$ are the change in dipole moment and Onsager radius of the Betaine dye respectively and $\Delta\mu$ and a are the corresponding measures of the molecule of interest.

Effect of polarizability on excited state dipole moment and change in dipole moment

The effect of solute polarizability on the excited state dipole moment and change in dipole moment can be accomplished by using the Bilot-Kawski model. The Stoke’s shift ($\bar{\nu}_a - \bar{\nu}_f$) values can be calculated using Bilot-Kawski model as given as

$$(\bar{\nu}_a - \bar{\nu}_f) = m_{B-K} F_{B-K}(\epsilon, n) + \text{Constant} \quad (12)$$

Where, m_{B-K} is the slope of the plot ($\bar{\nu}_a - \bar{\nu}_f$) versus $F_{B-K}(\epsilon, n)$ and is given by

$$m_{B-K} = \frac{2(\mu_e - \mu_g)^2}{hc a^3} \quad (13)$$

$F_{B-K}(\epsilon, n)$ is the Bilot-Kawski polarity function and is $F_{B-K}(\epsilon, n)$ is given by Eqn (14)

$$F_{B-K}(\epsilon, n) = \frac{\frac{\epsilon-1}{2\epsilon+1} \frac{n^2-1}{2n^2+1}}{\left(1 - \frac{2\alpha}{a^3} \frac{\epsilon-1}{2\epsilon+1}\right) \left(1 - \frac{2\alpha}{a^3} \frac{n^2-1}{2n^2+1}\right)^2} \quad (14)$$

where, $2\alpha/a^3$ is the polarizability factor, α is the solute polarizability, a is the Onsager cavity radius of molecule and other terms have their usual meaning. The excited state dipole moment can be calculated for different values of $2\alpha/a^3$ using the values of m_{B-K} obtained by plotting the linear correlation of ($\bar{\nu}_a - \bar{\nu}_f$) versus $F_{B-K}(\epsilon, n)$.

Preferential solvation study

The maximum wavenumber ($\bar{\nu}_{12}$) in an ideal case of the spectroscopic parameter in a binary mixture is given by Eqn.15.

$$\bar{\nu}_{12} = \bar{\nu}_1 X_1 + \bar{\nu}_2 X_2 \quad (15)$$

Where X_2 is the bulk mole fraction of solvent 2 and X_1 is the bulk mole fraction of solvent 1, $\bar{\nu}_1$ is the absorption/fluorescence maximum wavenumber of sulfa drugs in solvent 1, $\bar{\nu}_2$ is the absorption/fluorescence maximum wavenumber of titled molecules in solvent 2.

The $\bar{\nu}_{12}$ in non-ideal case can be expressed as in Eqn.16

$$\bar{\nu}_{12} = \bar{\nu}_1 X_1^L + \bar{\nu}_2 X_2^L \quad (16)$$

where X_2^L is the local mole fraction of solvent 2 and X_1^L is the local mole fraction of solvent 1 in the cybotactic area of a molecule. The other terms have their usual meanings.

IV. RESULTS AND DISCUSSION

Solvatochromism in pure solvents

Steady-state absorption and emission spectra of SMX and TMP were recorded in various solvents with different polarities and are given in Figure 2 and Figure 3. The spectral parameter namely, the maxima of absorption ($\bar{\nu}_a$ in cm^{-1}) and maxima of emission ($\bar{\nu}_f$ in cm^{-1}) and Stoke's shift ($\Delta\bar{\nu}$ in cm^{-1}) values are given in Table 1. In SMX, it is observed that the absorption spectra show blue-shift (hypsochromic shift) of nearly 16 nm when solvent is changed from non-polar toluene to polar-aprotic Chloroform. When solvent is changed from non-polar toluene to polar-protic solvent water, the absorption spectra show again blue shift of nearly 18 nm. The blue shift in absorption wavelength causes the more stabilization of ground state compared to the excited state. This increasing in the energy difference between ground and excited state characteristics the $n \rightarrow \pi^*$ transition. The $n \rightarrow \pi^*$ transition in SMX is due to the presence of -N in the sulfonamide group. The emission spectrum shows red-shift (bathochromic shift) of nearly 27 nm when the solvent is changed from non-polar toluene to polar-aprotic Chloroform. But, when the solvent is changed from non-polar toluene to polar-protic solvent water, the emission spectrum shows red shift of nearly 37nm. The red-shift with increasing solvent polarity implies $\pi \rightarrow \pi^*$ transition. The $\pi \rightarrow \pi^*$ transition occurs because of hydrogen bond formation between the solute and polar protic solvents at the sulfonyl oxygen.

In TMP, when the solvent is changed from non-polar toluene to polar-aprotic DMF and polar protic water, there is no significant shift in the absorption spectra. This indicates that the energy distribution in ground state is not affected by hydrogen bonding and change in polarity of solvents. The emission spectra show red-shift of nearly 45nm when solvent is changed from non-polar toluene to polar-aprotic DMF, also when solvent changed from non-polar toluene to polar-protic water again emission maxima show the red shift of nearly 44nm. In both the titled molecules, the maxima of absorption show a moderate shift in spectra band than the maxima of fluorescence, this suggests that solvation is larger in the excited than the ground state. The mechanisms of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ are given in Figure 4 and Figure 5 respectively. For both molecules exhibits a significant spectral shift with increasing polarity of solvents implies that the possible use of these molecules in polarity sensing probe.



Figure 2: Absorption spectra of (a) SMX and (b) TMP molecule in neat solvents. **Figure 3:** Fluorescence spectra of (a) SMX and (b) TMP molecule in neat solvents.

Table 1: Spectral Parameters of SMX and TMP molecules in neat solvents of different polarity.

Solvents	SMX			TMP		
	λ_a (nm)	λ_f (nm)	$\Delta\bar{\nu}$ (cm^{-1})	λ_a (nm)	λ_f (nm)	$\Delta\bar{\nu}$ (cm^{-1})
Hexane	280	300	2380	287	301	2491
Toluene	283	309	2973	289	333	4572
Benzene	277	327	5520	286	330	4662
1,4 Dioxane	-	-	-	292	339	4748
THF	271	334	5552	289	336	4840
Ethyl Acetate	-	-	-	288	338	5136
Chloroform	267	327	6872	-	-	-
DCM	266	326	6919	286	336	5203
DCE	267	328	6965	287	338	5257
DMF	-	-	-	291	346	5462
DMSO	274	342	7256			
1-deconol	271	338	7314	-	-	-
Octanol	-	-	-	274	345	7510
Hexanol	-	-	-	291	344	5294
Iso-propanol	271	339	7401	-	-	-

Butanol	270	338	7451	290	345	5497
Propanol	269	339	7676	290	346	5581
Methanol	268	340	7901	288	345	5736
Water	265	342	8666	283	346	6433

THF-Tetrahydrofuran, DCM-Dichloromethane, DCE-Dichloroethane, DMF-Dimethylformamide, DMSO-Dimethyl Sulfoxide.

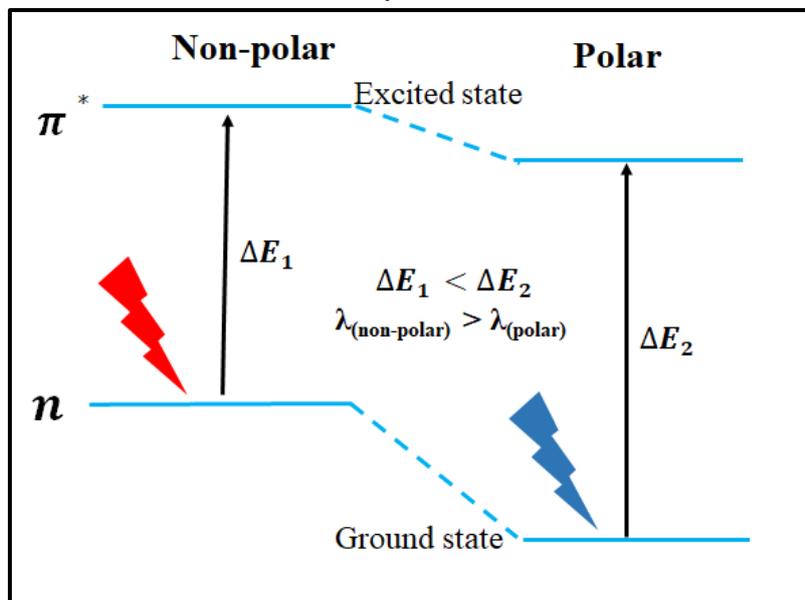


Figure 4: The $n \rightarrow \pi^*$ transition in sulfa drug molecules in non-polar (Toluene) and polar (Water) solvents.

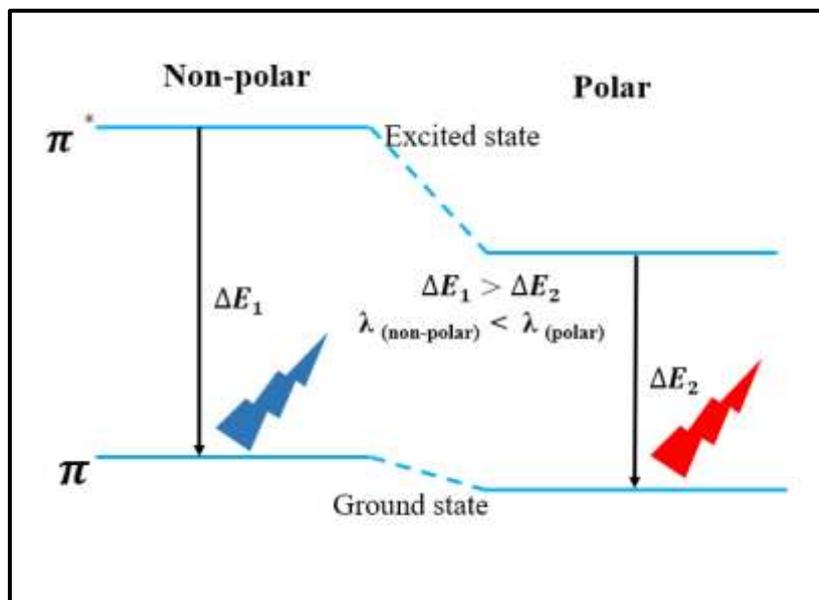


Figure 5: The $\pi \rightarrow \pi^*$ transition in sulfa drug molecule in non-polar (Toluene) and polar (Water) solvents.

To get the further visualization of the solvatochromic behavior of titled molecules, spectroscopic parameters are correlated with different solvent polarity functions. The absorption ($\bar{\nu}_a$), emission ($\bar{\nu}_f$) and Stoke's shift ($\Delta\bar{\nu}$) are correlated with bulk solvent polarity parameters ΔF_{L-M} and E_N^T . For SMX, the correlation coefficient for ΔF_{L-M} corresponding to absorption are $r = 0.79$, for fluorescence $r = 0.83$ and for Stoke's shift $r = 0.84$. This implies that absorption wavenumber, emission wavenumber and Stoke's shift gives moderate correlations. The moderate correlation of ΔF_{L-M} suggests that this is not a suitable polarity scale to explain the solvent effects. This could be due to the reason that the ΔF_{L-M} polarity scale does not consider specific solute-solvent interactions such as hydrogen bonding effect, complex formation and charge transfer. Therefore, an effort has been made to correlate spectroscopic parameters of investigated molecules with E_N^T . The correlation

coefficients for E_N^T corresponding to absorption are $r = 0.65$, for emission $r = 0.83$ and for Stoke's shift $r = 0.84$. In this case also the correlations are almost moderate. This motivated us to correlate the spectroscopic parameters with E_N^T distinctly for alcohols and non-alcohols as shown in Figure 6 for SMX. It has been found that the correlation plots have shown good correlation for non-alcohols and alcohols separately for emission and Stoke's shift. The noticeable good double linear correlation obtained in emission and Stoke's shift specifies that solvent stabilization of excited states is due to a variety of solute-solvent interactions such as dipole-dipole interactions and hydrogen bonding. In protic solvents, the enrichment of polarity results in the stabilization of the molecule via hydrogen bonding. In aprotic solvents, dipole-induced dipole and dipole-dipole forces are assumed to be the major interaction taking place between SMX and solvent environment [18].

In TMP, further investigation into the influence of absorption on various polarity scales was not carried out further because of the reason mentioned earlier. In case of fluorescence and Stoke's shift the least square correlations are moderate (for emission $r = 0.68$ and for Stoke's shift $r = 0.78$). The poor/moderate correlation indicates the presence of specific solvent effects in addition to general solvent effect. Hence, the ΔF_{L-M} suggests that this is not a suitable polarity scale to explain the solvent effects in the titled molecules. Further, the spectroscopic parameters are correlates with E_N^T , in case of fluorescence and Stoke's shift the correlations are moderate (for fluorescence $r = 0.69$ and for Stoke's shift $r = 0.81$). This motivated us to correlate the spectroscopic parameters with E_N^T distinctly for alcohols and non-alcohols as shown in Figure 7 for TMP. It has been found that the correlation coefficients are appreciably good for plots of E_N^T versus emission and Stoke's shift in non-alcohols and alcohols separately. Even though, the correlations have enhanced in few cases with E_N^T separately for alcohols and non-alcohols, it is hard to draw conclusion about the possible reasons of solvatochromism. However, these correlations indicate the possible role of both general solvent effects and specific solvent effects.

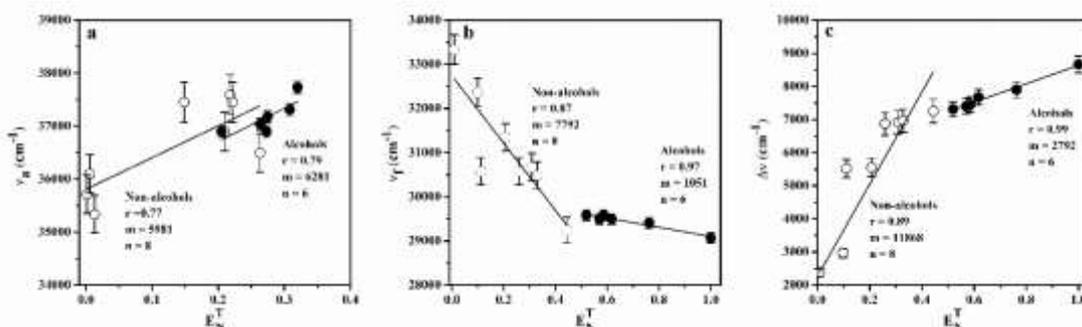


Figure 6: The plot of (a) $\bar{\nu}_a$ vs E_N^T , (b) $\bar{\nu}_f$ vs E_N^T and (c) $\Delta\bar{\nu}$ vs E_N^T for SMX molecule.

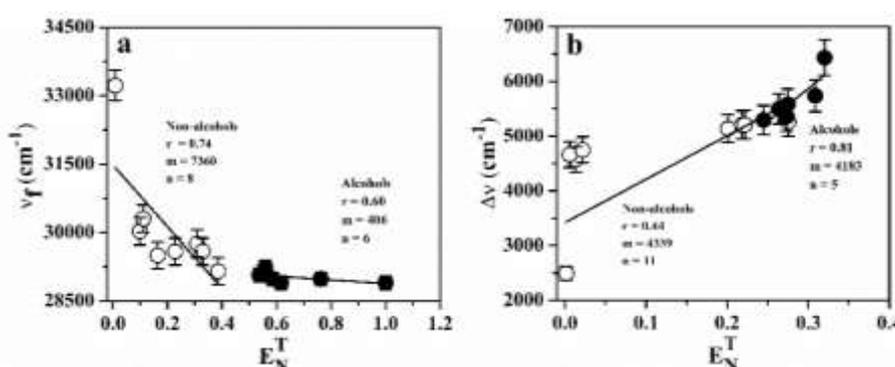


Figure 7: The plot of (a) $\bar{\nu}_f$ vs E_N^T and (b) $\Delta\bar{\nu}$ vs E_N^T for TMP molecule.

The correlations based on the ΔF_{L-M} and E_N^T gives solute-solvent interactions mechanisms which are collective of general and specific solute-solvent interaction mechanisms. But these methods are incapable to categorize the individual contribution from either general or specific solute-solvent interaction mechanisms. Due to this factor, to identify the specific contribution from hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) and non-specific dielectric interactions, the absorption wavenumber, emission wavenumber and Stoke's shift are correlated with solvent polarity parameter proposed by Kamlet and coworkers based on linear regression. The Kamlet parameter contains hydrogen bond donor ability of a solvent (α), hydrogen bond

acceptor ability of a solvent (β) and non-specific dielectric interaction (π^*). The multiple linear regression is carried out and correlation data is presented in Eqs. (21) and (22).

SMX

$$\begin{aligned} \bar{\nu}_a(\text{cm}^{-1}) &= 35827 + 840 \alpha - 159 \beta + 1274 \pi^* & r &= 0.73 \\ \bar{\nu}_f(\text{cm}^{-1}) &= 33050 - 1017\alpha - 1529 \beta - 2691\pi^* & r &= 0.93 \\ \Delta\bar{\nu}(\text{cm}^{-1}) &= 2776 + 1851\alpha + 1369 \beta + 3966 \pi^* & r &= 0.90 \end{aligned} \quad (21)$$

TMP

$$\begin{aligned} \bar{\nu}_f(\text{cm}^{-1}) &= 32188 - 307\alpha - 1604 \beta - 2868 \pi^* & r &= 0.89 \\ \Delta\bar{\nu}(\text{cm}^{-1}) &= 3021 + 659\alpha + 799\beta + 2462 \pi^* & r &= 0.97 \end{aligned} \quad (22)$$

From above equations, it is endorsing that non-specific dielectric interaction (π^*) of solvents has a major influence on the SMX and TMP molecules. Though, the contributions from HBD and HBA cannot be ignored. From MLR data HBA influence is more than HBD in all investigated molecules.

From Kamlet's analysis, it is tough to identify the individual contributions due to the solvents dipolarity and polarizability. Therefore, to overcome these difficulties, the spectral parameters are correlated with solvent polarity parameter scale proposed by Catalan and co-workers based on linear regression. The Catalan solvent polarity scale includes solvent acidity (SA), solvent basicity (SB), solvent polarity (SP) and solvent dipolarity (SdP). The SB is equivalent to HBA and SA is equivalent to HBD on Kamlet's scale. The multiple regression is carried out based on the Catalan scale and correlation data is presented in Eqs. (23), (24).

SMX

$$\begin{aligned} \bar{\nu}_a(\text{cm}^{-1}) &= 36894 + 72 \text{SA} - 315 \text{SB} - 1508 \text{SP} - 1836 \text{SdP} & r &= 0.76 \\ \bar{\nu}_f(\text{cm}^{-1}) &= 37252 - 2257\text{SA} - 1825 \text{SB} + 6479 \text{SP} - 1573 \text{SdP} & r &= 0.93 \\ \Delta\bar{\nu}(\text{cm}^{-1}) &= 358 + 2329 \text{SA} - 1509\text{SB} - 4971 \text{SP} + 3411 \text{SdP} & r &= 0.90 \end{aligned} \quad (23)$$

TMP

$$\begin{aligned} \bar{\nu}_f(\text{cm}^{-1}) &= 39625 - 1924 \text{SA} - 2054 \text{SB} - 11166 \text{SP} - 1261 \text{SdP} & r &= 0.91 \\ \Delta\bar{\nu}(\text{cm}^{-1}) &= 1785 + 1729 \text{SA} - 1005 \text{SB} - 7387 \text{SP} + 1350 \text{SdP} & r &= 0.96 \end{aligned} \quad (24)$$

The above results suggest that, the correlation is comparatively good compared to Kamlet's regression. The correlation data based on emission and Stoke's shift indicates that the solvent polarizability influence is more compared to solvent dipolarity, solvent acidity and solvent basicity. The solvent basicity influences more than the solvent acidity. The results obtained by Kamlet's and Catalan are in good agreement with each other.

Estimation of Ground and Excited state dipole moment based on solvatochromism in pure solvents.

The ground state (GS) and excited state (ES) dipole moment of investigated molecules in the gaseous phase were computed by quantum, chemical calculations using Gaussian09 software at CAM-B3LYP level theory and 6-311++G(d,p) basis set. These values are tabulated in Table 2. The SMX molecule have large ground state dipole moment (5.02) than TMP. The large dipole moment is due the polar nature and asymmetric geometry of SMX molecule. The computational calculations indicate that the excited state dipole moment of investigated molecules is greater than the ground state. The magnitude and directions of dipole moment vector in ground state and excited state for the investigated molecules are given in Figure 8.

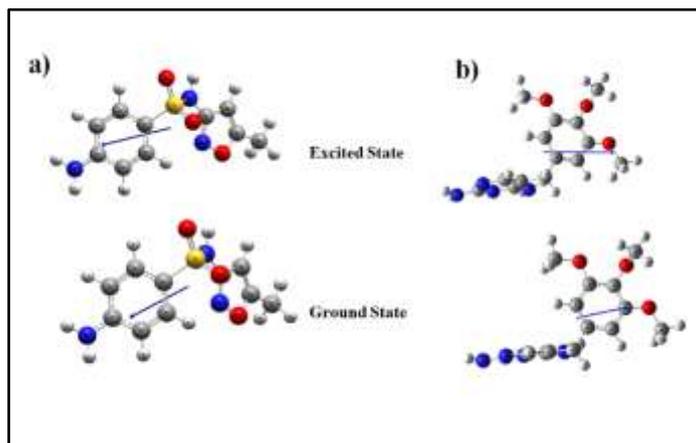


Figure 8: The magnitude and directions of dipole moment vector for (a) SMX and (b) TMP molecule in ground and excited states.

Table 2: The theoretically calculated ground state dipole moments (μ_g) (D), Onsager radius values(a) (Å), excited state dipole moment (μ_e) (D) and change in dipole moment ($\Delta\mu$) (D) obtained using various models for SMX and TMP.

Methods		SMX		TMP	
		$\mu_g = 5.02$	$a = 4.06$	$\mu_g = 1.02$	$a = 4.45$
		μ_e	$\Delta\mu$	μ_e	$\Delta\mu$
Computational method		6.44	1.42	1.72	0.70
Lippert-Mataga		11.93	6.91	5.86	4.84
Bakhshiev		9.12	4.10	4.09	3.07
Kawski-Chamma-Viallet's		6.45	1.43	3.93	2.91
E_N^T	Non-alcohols	10.49	5.47	3.49	2.47
	Alcohols	7.56	2.54	3.39	2.37

The solvatochromic information obtained in solvents of different polarities for investigated molecules given in Table 1 has been used in this section. The ES dipole moment of SMX and TMP molecules was calculated by Lippert-Mataga, Bakhshiev's Kawski-Chamma-Viallet and Reichardt's models using Eqns. (7), (8), (9) and (11) and respective linear correlation plots for SMX and TMP are given in Figure 9 and Figure 10. The better correlations coefficients ranging from 0.92 to 0.99 are attained for all these plots. The excited state dipole moments are calculated by using the slope obtained from respective plots and ground state dipole moment are calculated by computationally. The ES dipole moment is calculated from slope obtained by respective plots and GS dipole moment are calculated computationally. These values are also tabulated in Table 2, As from Table 2, The ES dipole is greater than the GS for SMX and TMP molecules. This is well aligned with computational one. The raise in dipole moment in the ES could be due to intramolecular bonding between solute-solvent, redistribution of charge density takes place between the electronic states, Intramolecular charge transfer (ICT) and the geometrical variations in the electronic states. The ICT in the titled molecules leads to the resonance structure as shows in Figure 11 and Figure 12.

The ES calculated from Lippert-Mataga correlations model are higher than other models. This is due to the fact that the polarizability of the molecules is neglected in this method. As from Table 2, the μ_e calculated from K-C-V method are smaller than other model and are nearly equal to the value obtained from computational method. This differences in ES dipole moment value obtained from different models could be due to different assumptions made in different models. The change in dipole moment values obtained from various models are also tabulated in Table 2. The noticeable was observed in the $\Delta\mu$ value obtained from various models. These noticeable difference in $\Delta\mu$ values understandable in terms of effect of solute polarizability. As mentioned earlier, in Lippert-Mataga, the term polarizability was neglected, however in the Bakhshiev's model assumed the solute polarizability factor $2\alpha/a^3 = 1$. Therefore, the significant difference in $\Delta\mu$ values calculated using different models are clearly indicate that the polarizability of solute affects the $\Delta\mu$ of the investigated molecules upon excitation [39].

To understand the effect of solute polarizability on the ES and change in dipole moments, the Bilot-Kawski model was used according to Eqn (13). The polarizability dependent polarity function $F_{B-K}(\epsilon, n)$ for different values of $2\alpha/a^3 (0 \leq 2\alpha/a^3 \leq 1)$ is calculated from Eqn (14) and is given in Table 3. The excited state dipole moments and change in dipole moments calculated for different values of $2\alpha/a^3 (0 \leq 2\alpha/a^3 \leq 1)$ are also given in Table 3. As observed from Table 4, with increase in $2\alpha/a^3$ the excited state dipole moment and change in dipole moment values decreases continuously. The change in dipole moment values calculated for two values of $2\alpha/a^3 = 0$ and $2\alpha/a^3 = 1$ differ by 25% for all the titled molecules, confirming that the excited state dipole moment and change in dipole moment was affected by polarizability of solute molecule. These results indicate the importance of consideration of polarizability of solute molecule in estimating its excited state dipole moment.

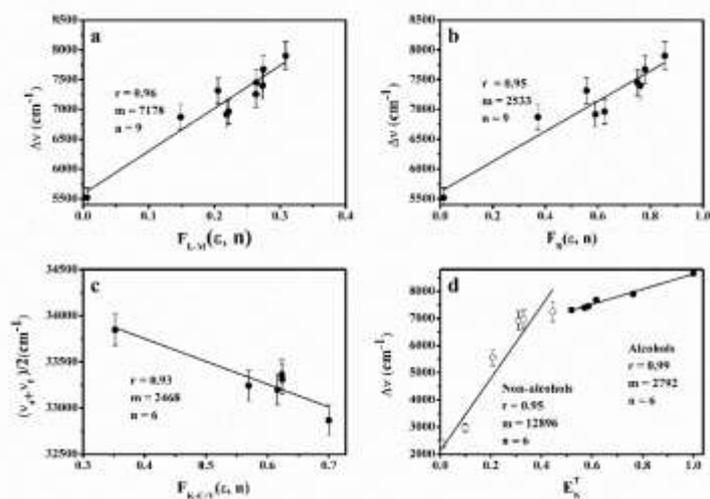


Figure 9: Solvatochromic linear correlation of (a) Lippert-Mataga, (b) Bakshiev's, (c) Kawski-Chamma-Viallet and (d) Reichardt's method for SMX molecule.

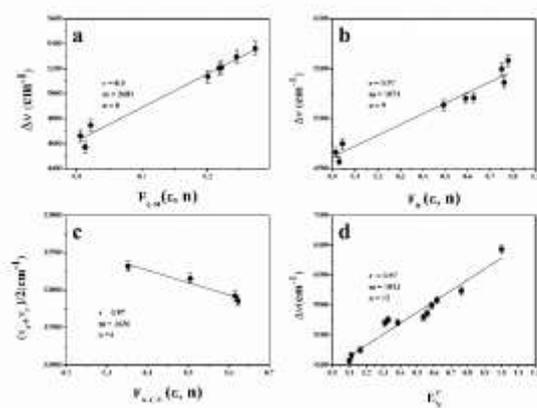


Figure 10: Solvatochromic linear correlation of (a) Lippert-Mataga, (b) Bakshiev's, (c) Kawski-Chamma-Viallet and (d) Reichardt's method for TMP molecule.

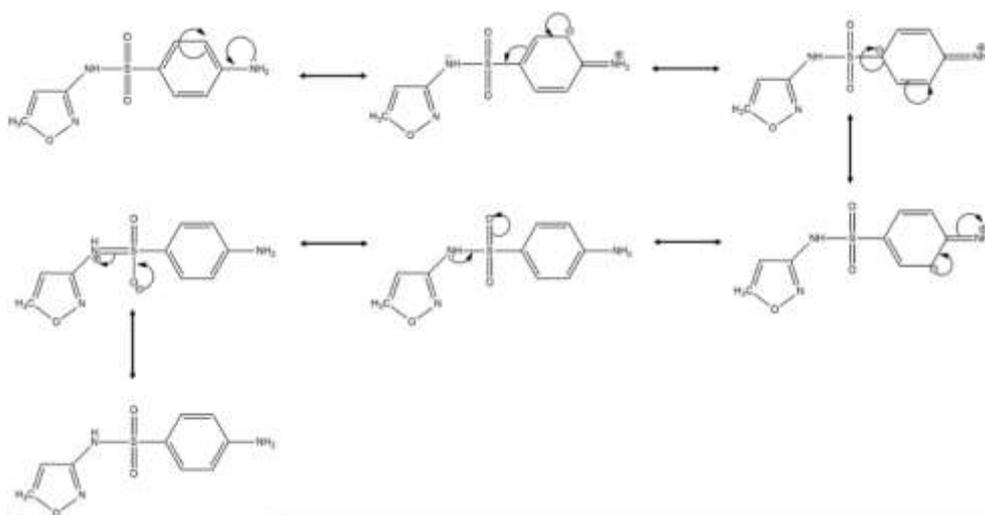


Figure 11: Resonance structures of SMX molecule.

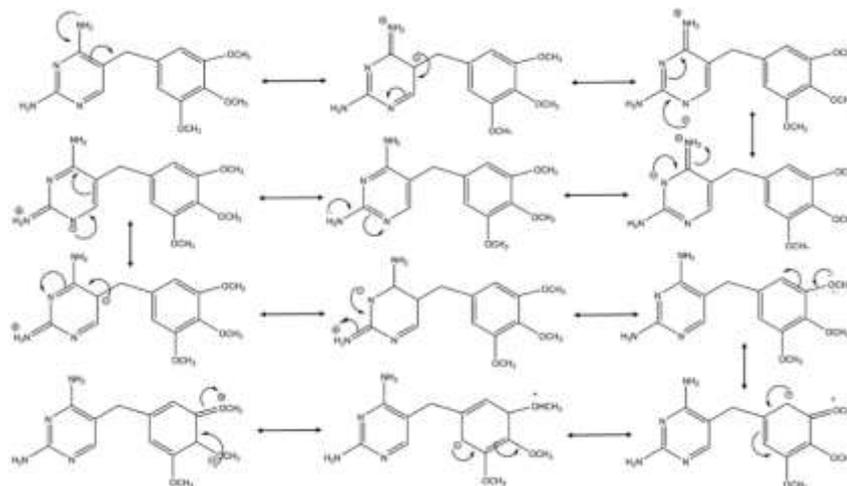


Figure 12: Resonance structures of TMP molecule.

Table 3: Polarizability dependent polarity function of $F_{B-K}(\epsilon, n)$ ($0 \leq 2\alpha/a^3 \leq 1$) values, $\mu_{e(B-K)}(D)$ and $\Delta\mu_{(B-K)}(D)$ for SMX and TMP as a function of $2\alpha/a^3$ parameter

Solvents	$F_{B-K}(\epsilon, n)$ ($0 \leq 2\alpha/a^3 \leq 1$)										
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Hexane	0.00075	0.00079	0.00084	0.00089	0.00094	0.0010	0.00107	0.00114	0.00121	0.0013	0.00139
Toluene	0.01321	0.01416	0.01522	0.01638	0.01766	0.01908	0.02065	0.02240	0.02436	0.02655	0.02902
Benzene	0.00594	0.00636	0.00683	0.00734	0.00790	0.00852	0.00920	0.00997	0.01081	0.01176	0.01283
1,4 Dioxane	0.02164	0.02306	0.02461	0.0263	0.02815	0.03018	0.03240	0.03485	0.03756	0.04055	0.04387
THF	0.20964	0.22744	0.24739	0.26985	0.29524	0.32409	0.35703	0.39486	0.43859	0.48947	0.54916
Ethyle acetate	0.20083	0.21685	0.23469	0.25464	0.27702	0.30224	0.33079	0.36327	0.40041	0.44316	0.49267
DCM	0.26358	0.23725	0.25872	0.28297	0.31051	0.34192	0.37792	0.41959	0.46797	0.52465	0.59161
Chloroform	0.14855	0.16077	0.17439	0.18963	0.20675	0.22604	0.24789	0.27272	0.30111	0.33371	0.37139
DCE	0.22161	0.30910	0.26432	0.29002	0.31933	0.35293	0.39168	0.43668	0.48931	0.55138	0.62529
DMF	0.27455	0.30060	0.33025	0.36419	0.40327	0.44857	0.50148	0.56380	0.63793	0.72709	0.83572
DMSO	0.26319	0.26319	0.31896	0.35317	0.39273	0.43883	0.49295	0.55706	0.63377	0.72662	0.84052
1-Decanol	0.20585	0.22388	0.24416	0.26707	0.29307	0.32275	0.35670	0.39589	0.44139	0.49461	0.55737
1-Octanol	0.10273	0.11047	0.11903	0.12849	0.13901	0.15072	0.16380	0.17847	0.19497	0.21361	0.23476
Hexanol	0.24437	0.26638	0.29126	0.31951	0.35174	0.38874	0.43149	0.48122	0.53953	0.60853	0.69100
Iso propanol	0.27275	0.27275	0.32420	0.35518	0.39054	0.43114	0.47808	0.53274	0.59696	0.67313	0.76450
Butanol	0.26358	0.28733	0.31418	0.34471	0.37960	0.41972	0.46616	0.52031	0.58402	0.65967	0.75053
Propanol	0.27449	0.29908	0.32688	0.35848	0.39461	0.43615	0.48425	0.54039	0.60648	0.68506	0.77958
Methanol	0.30835	0.33505	0.36518	0.39938	0.43843	0.48329	0.53521	0.59579	0.66715	0.75212	0.85456
Water	0.31991	0.34819	0.38021	0.41667	0.45844	0.50661	0.56262	0.62830	0.70612	0.79941	0.91280
Molecule $\mu_{e(B-K)}(D)$ as a function of $2\alpha/a^3$											
SMX	9.85	9.42	9.00	8.59	8.18	7.77	7.37	6.96	6.56	5.75	5.75
TMP	5.38	5.16	4.93	4.71	4.49	4.27	4.05	3.84	3.63	3.41	3.20
Molecule $\Delta\mu_{(B-K)}(D)$ as a function of $2\alpha/a^3$											
SMX	4.83	4.40	3.98	3.57	3.16	2.75	2.35	1.94	1.54	0.73	0.73
TMP	4.36	4.14	3.91	2.55	3.47	3.25	3.03	2.82	2.61	2.39	2.18

Preferential solvation study

Preferential solvation study of SMX

The optical absorption (ground state) and emission (excited state) spectra of SMX in THF-Water binary system are illustrated in Figure 13. The absorption and emission spectra of investigated molecules have not shown any systematic variation on increasing the concentration of water. In all the binary composition, non-linear relationship of spectral property ($\bar{\nu}_{12}$) with increase in mole fraction of water ($X_2 = 0.28$ to $X_2 = 0.97$) has been observed. This signifies that non-ideal solvation response of solute as shown in Figure 14.

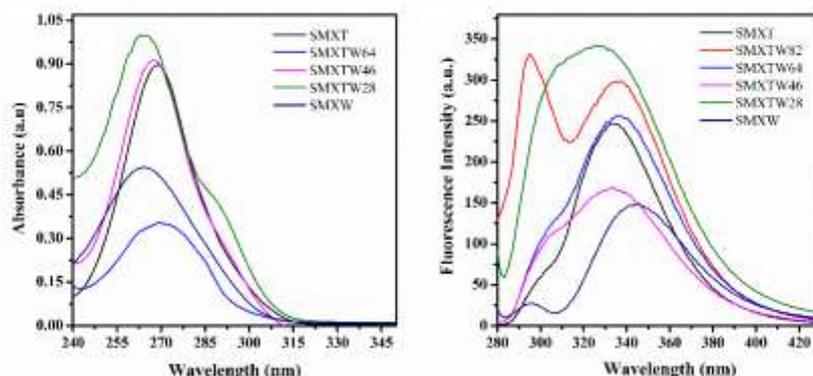


Figure 13: The optical absorption and emission spectra of SMX in THF-H₂O binary system

In the ground state, the variation of $\bar{\nu}_{12}$ with increase in water mole fraction in THF and water mixture is given in the Figure 13. From the Figure, the non-linear variation of $\bar{\nu}_{12}$ with increase in the mole fraction of water indicates that SMX is preferentially solvated by one of the solvents. In going from $X_2 = 0$ to $X_2 = 1$, the $\bar{\nu}_{12}$ values are undergoing minimum ($X_2 = 0.28$) followed by maximum ($X_2 = 0.50$) and minimum ($X_2 = 0.63$ and 0.72) and then maximum ($X_2 = 0.80$) and minimum ($X_2 = 0.85$ and 0.90) and again maximum ($X_2 > 0.90$). From this random trend in the variation, the minimum values of $\bar{\nu}_{12}$ indicates SMX is solvated by THF and the maximum $\bar{\nu}_{12}$ values indicate SMX is solvated by water. This is evidenced by the positive and negative values of δ_{12} at respective mole fractions from the Table 4. Negative δ_{12} values indicate that SMX is solvated by THF and positive δ_{12} values indicate that SMX is solvated by water. The preferential solvation of SMX based on the random variation of $\bar{\nu}_{12}$ with different mole fraction of the mixture approximates the existence of solute-solvent and solvent-solvent interactions.

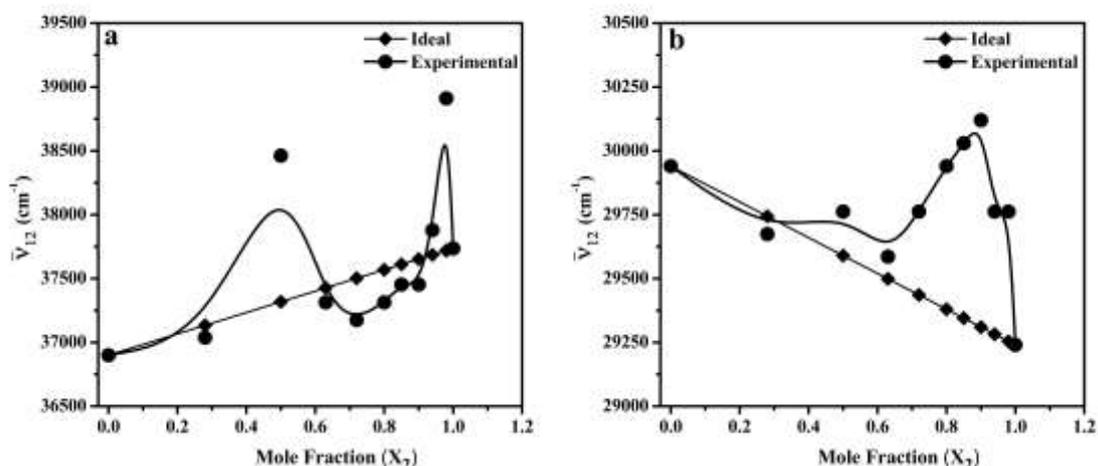


Figure 14: The plot of $\bar{\nu}_{12}$ versus mole fraction of Water for (a) Absorption and (b) Emission of SMX in THF-Water mixture.

The values of $\bar{\nu}_{12}$ in all the mole fractions is greater than that in the pure THF. This indicates the hydrogen bond formation between THF and water [14]. Since at low water concentration there is a monomer water molecules availability. Also, at high concentration of water there are monomer THF molecules

availability. This approximates the possibility of hydrogen bond formation between THF and water. This occurs due to more hydrogen bond accepting capacity of THF ($\beta = 0.55$) and more hydrogen donating capacity of water ($\alpha = 1.17$). In this regard, THF and water mutually prefers one another rather than the SMX molecules. Further, increase in water proportion leads to the decrease and increase in the $\bar{\nu}_{12}$ values. The decrease in the $\bar{\nu}_{12}$ values indicate free availability of water molecules for H-bonding with $-C=O$ elements of SMX. In water rich region the increase in $\bar{\nu}_{12}$ values are evidence for water self-association complex. Also, SMX is solvated by THF through H-bonding between pair of electrons present in THF and $-NH_2$ element of SMX. This gives the clear proof for the competition between the solute-solvent and solvent-solvent interactions.

In the excited state, the variation of $\bar{\nu}_{12}$ with increase in water mole fraction in THF and water mixture is given in the Figure 13. From the Figure, the non-linear variation of $\bar{\nu}_{12}$ with increase in the mole fraction of water indicates that SMX is preferentially solvated by one of the solvents. The non-linear response indicates that, in water rich region SMX is solvated by THF and in THF rich region SMX is solvated by water. This is confirmed by negative values of δ_{12} for mole fractions $X_2 > 0.28$ which indicates that SMX is solvated by THF in water rich region. It happens due to, in water rich region water being hydroxylic solvent create a net of hydrogen bonded self-association complex. This leads to SMX is solvated by THF due to enough availability of THF molecules in this region. This happens through the formation of hydrogen bond between $-NH_2$ component of SMX and pair of electrons present in THF. The increase in THF proportion ruptures the water self-association complex through the solvent-solvent interaction due to its high hydrogen accepting capacity ($\beta = 0.55$). Then the water with high hydrogen donating capacity ($\alpha = 1.17$) donates hydrogen bond to $-S=O$ component of SMX leads to SMX solvated by water in THF rich region. In solution with higher water proportion the strong net of hydrogen bonded self-association complex of water molecules pushes the SMX molecules towards THF due to hydrophobic repulsion. This indicates that the SMX prefers the THF for solvation. This provides an indication for the competition between solute-solvent and solvent-solvent interactions. In the present study the SMX-water interaction dominates at low water proportion and water-water interaction dominate at high water proportion.

Preferential solvation study of TMP

The optical absorption (ground state) and emission (excited state) spectra of TMP in THF-Water binary system are illustrated in Figure 15. The absorption and emission spectra of investigated molecules have not shown any systematic variation of in the respective wavelength maxima on increasing the concentration of water. In all the binary composition, non-linear relationship of spectral property ($\bar{\nu}_{12}$) with increase in mole fraction of water has been observed. This signifies that, non-ideal solvation response of solute as shown in Figure 16.

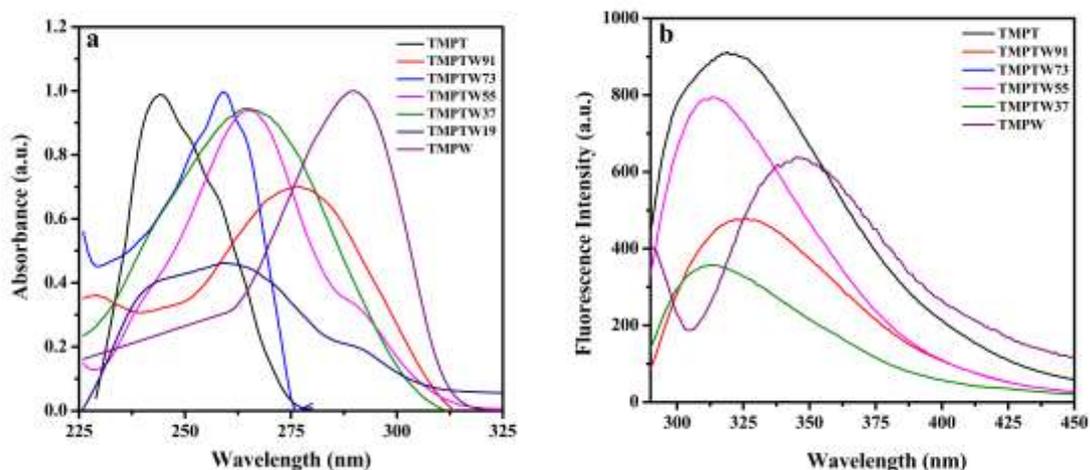


Figure 15: The optical absorption and emission spectra of TMP in THF-H₂O binary system

In ground state, the $\bar{\nu}_{12}$ values are higher for all the mole fractions $X_2 > 0.28$ compared to the $\bar{\nu}_{12}$ values measured in pure components ($\bar{\nu}_1$ and $\bar{\nu}_2$). In excited state, the $\bar{\nu}_{12}$ values are higher from $X_2 > 0.28$ to $X_2 = 0.90$ than the $\bar{\nu}_{12}$ values measured in pure components ($\bar{\nu}_1$ and $\bar{\nu}_2$). But beyond $X_2 = 0.90$ mole fraction the $\bar{\nu}_{12}$ is decreases abruptly. This behavior confirms the presence of synergistic effect [40]. This is also confirmed by the shift in spectral maxima of TMP which are laid beyond the either side for both the solvents in solvent mixture. The synergistic effect is frequently occurred in a binary mixture, where one solvent act as a hydrogen bond

donor and another one acts as a hydrogen bond acceptor. In THF-Water binary mixture, water acts as a hydrogen bond donor (from Kamlet and Taft: $\alpha = 1.17$, $\beta = 0.18$) and THF acts as a hydrogen bond acceptor (from Kamlet and Taft: $\alpha = 0.00$, $\beta = 0.55$). The synergistic nature observed here may result in forming the association complex of water and THF. This occurs through a hydrogen bond interaction between pair of electrons in THF and water molecules.

Otherwise, both interactions (solvent-solvent or solute-solvent) play a major role in determining the preferential solvation nature of the TMP. When the small quantity of water is added to a solution of TMP and THF, $\bar{\nu}_{12}$ values is increased. This implies that, preferentially protic solvent replaces the aprotic solvent molecules in the solvation shell of TMP. In this situation, local excess model could not be applied to undertake the preferential solvation parameter due to the presence of synergistic effect. This suggests this molecule for the moisture and water detection in the organic solvents [21].

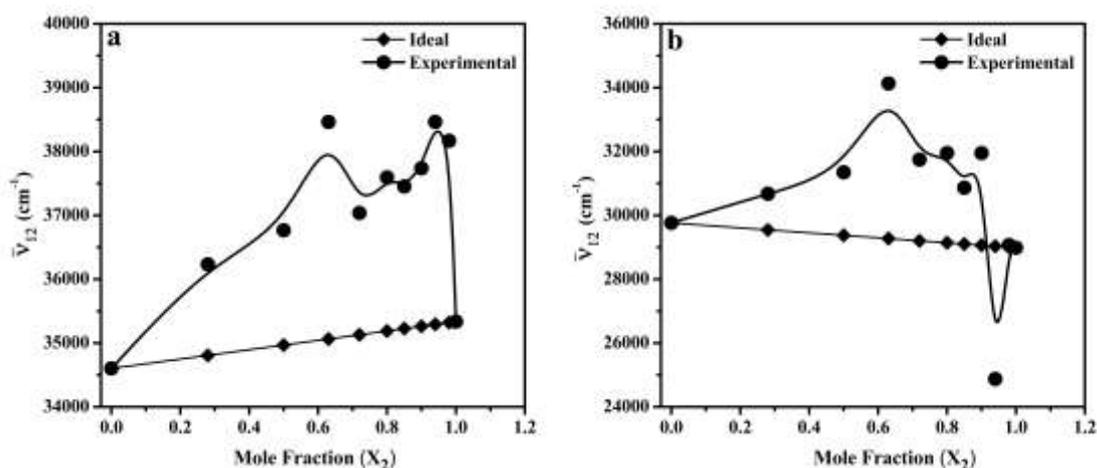


Figure 16: The plot of $\bar{\nu}_{12}$ versus mole fraction of Water for (a) Absorption and (b) Emission of TMP in THF-Water mixture.

V. CONCLUSION

The investigation of solvatochromism in antibiotic agents reveals that, in SMX, there is an hypsochromic shift in absorption and bathochromic shift in fluorescence spectra. This indicates the involvement of $n \rightarrow \pi^*$ transition in ground state and $\pi \rightarrow \pi^*$ transition in excited state. In TMP, no shift in absorption spectra is observed and the bathochromic shift is observed in fluorescence spectra suggesting the presence of $\pi \rightarrow \pi^*$ transition in excited state. The sensitivity of the titled molecules to spectral shifts with increasing solvent polarity suggests their possible use in polarity sensing. Kamlet-Taft and Catalan's linear regression methods confirms the dominance of non-specific solute-solvent interactions. The calculated excited state dipole moment for the titled molecules is larger than that of the ground state. The relationship between the excited state dipole moment, change in dipole moment and polarizability spotlight the importance of considering solute polarizability in solvatochromic models. The non-linear correlation between wavenumber and the mole fraction of water for SMX suggests a competition between solute-solvent and solvent-solvent interactions. The synergistic effect observed in the case of TMP suggests the possible use of this molecule in moisture and water detection in organic solvents. This study reports the comprehensive investigation into solvatochromism, excited state dipole moments and solvation in antibiotic agents. The promising outcomes suggest the possible applications of SMX and TMP molecules in the areas such as polarity sensing and moisture detection, in addition to their established biomedical and pharmaceutical applications.

References

- [1] Thiebault, Thomas. "Sulfamethoxazole/Trimethoprim Ratio As A New Marker In Raw Wastewaters: A Critical Review." *Science Of The Total Environment* 715 (2020): 136916, Doi: 10.1016/J.Scitotenv.2020.136916.
- [2] Sivagourounadin, Kiruthika. "Hypnotics And Sedatives." *Introduction To Basics Of Pharmacology And Toxicology: Volume 2: Essentials Of Systemic Pharmacology: From Principles To Practice* (2021): 97-129, Doi: 10.1007/978-981-33-6009-9_6.
- [3] Smego, Raymond A., Mark B. Moeller, And Harry A. Gallis. "Trimethoprim-Sulfamethoxazole Therapy For Nocardia Infections." *Archives Of Internal Medicine* 143.4 (1983): 711-718, Doi: 10.1001/Archinte.1983.00350040101013.
- [4] Zhang, Xue- Hong, Et Al. "Synthesis And Interaction Of Bovine Serum Albumin With P- Hydroxybenzoic Acid Derivatives." *Luminescence* 28.3 (2013): 419-426, Doi: 10.1002/Bio.2402.
- [5] Lu, Jie, And Sohrab Rohani. "Polymorphism And Crystallization Of Active Pharmaceutical Ingredients (Apis)." *Current Medicinal Chemistry* 16.7 (2009): 884-905, Doi: 10.2174/092986709787549299.

- [6] Iqbal, M. S., Et Al. "Pharmacokinetic Study Of A New Derivative Of Sulfamethoxazole." *Arzneimittelforschung* 62.10 (2012): 487-489, Doi: 10.1055/S-0032-1321853.
- [7] Wróbel, Agnieszka, Et Al. "Trimethoprim And Other Nonclassical Antifolates An Excellent Template For Searching Modifications Of Dihydrofolate Reductase Enzyme Inhibitors." *The Journal Of Antibiotics* 73.1 (2020): 5-27, Doi: 10.1038/S41429-019-0240-6.
- [8] M. G. Papich, "Trimethoprim And Sulfamethoxazole," *Papich Handb. Vet. Drugs*, (2021): 945–947, Doi: 10.1016/B978-0-323-70957-6.00556-2.
- [9] Naresh, Kommu. "Applications Of Fluorescence Spectroscopy." *J. Chem. Pharm. Sci* 974 (2014): 2115.
- [10] A. Bose, I. Thomas, And E. Abraham, "International Journal Of Advances In Pharmaceutical Analysis Fluorescence Spectroscopy And Its Applications: A Review Qr Code *Correspondence Info," *Int. J. Adv. Pharm. Anal.*, 08.01, (2018): 1–8.
- [11] Shahzad, Aamir, Et Al. "Emerging Applications Of Fluorescence Spectroscopy In Medical Microbiology Field." *Journal Of Translational Medicine* 7 (2009): 1-6, Doi: 10.1186/1479-5876-7-99.
- [12] Chakraborty, Jaya, And Surajit Das. "Application Of Spectroscopic Techniques For Monitoring Microbial Diversity And Bioremediation." *Applied Spectroscopy Reviews* 52.1 (2017): 1-38, Doi: 10.1080/05704928.2016.1199028.
- [13] Kharbach, Mourad, Et Al. "Current Application Of Advancing Spectroscopy Techniques In Food Analysis: Data Handling With Chemometric Approaches." *Foods* 12.14 (2023): 2753.
- [14] Sahu, Ranjit K., And Shaul Mordechai. "Spectroscopic Techniques In Medicine: The Future Of Diagnostics." *Applied Spectroscopy Reviews* 51.6 (2016): 484-499, Doi: 10.1080/05704928.2016.1157809.
- [15] Sidir, Yadigar Gülseven. "The Solvatochromism, Electronic Structure, Electric Dipole Moments And Dft Calculations Of Benzoic Acid Liquid Crystals." *Liquid Crystals* 47.10 (2020): 1435-1451, Doi: 10.1080/02678292.2020.1733685.
- [16] Chandrasekhar, S., Et Al. "Quantum Chemical And Solvatochromic Studies Of Biological Active 1, 3, 4-Thiadiazol Coumarin Derivatives." *Chemical Data Collections* 29 (2020): 100516, Doi: 10.1016/J.Cdc.2020.100516.
- [17] Kumar, N. Sunil, Et Al. "Theoretical And Experimental Studies On Electronic Structure And Photophysical Properties Of Biological Active Substituted Hydroxyquinolin-2 (1h)-One Fluorophore." *Chemical Physics Impact* 6 (2023): 100136, Doi: 10.1016/J.Chphi.2022.100136.
- [18] Raghavendra, U. P., Et Al. "Solvatochromic Studies Of Biologically Active Iodinated 4-Aryloxymethyl Coumarins And Estimation Of Dipole Moments." *Journal Of Molecular Liquids* 202 (2015): 9-16, Doi: 10.1016/J.Molliq.2014.12.003.
- [19] Melavanki, Raveendra, Et Al. "Quantum Chemical Computations, Fluorescence Spectral Features And Molecular Docking Of Two Biologically Active Heterocyclic Class Of Compounds." *Journal Of Photochemistry And Photobiology A: Chemistry* 404 (2021): 112956, Doi: 10.1016/J.Jphotochem.2020.112956.
- [20] Lokshin, Vladimir, Et Al. "Dipole Moments Of Conjugated Donor–Acceptor Substituted Systems: Calculations Vs. Experiments." *Rsc Advances* 11.2 (2021): 934-945, Doi: 10.1039/D0ra10182f.
- [21] Husain, Shahid, Et Al. "Spectral Characteristics Of 3, 5-Diaminobenzoic Acid In Pure And Mixed Solvents: Experimental And Theoretical Study." *Journal Of Molecular Liquids* 368 (2022): 120783, Doi: 10.1016/J.Molliq.2022.120783.
- [22] Shkooor, Mohanad, Et Al. "Experimental And Dft/Td-Dft Computational Investigations Of The Solvent Effect On The Spectral Properties Of Nitro Substituted Pyridino [3, 4-C] Coumarins." *Journal Of Molecular Liquids* 313 (2020): 113509, Doi: 10.1016/J.Molliq.2020.113509.
- [23] Matiadis, Dimitris, Et Al. "Synthesis And (Fluoro) Solvatochromism Of Two 3-Styryl-2-Pyrazoline Derivatives Bearing Benzoic Acid Moiety: A Spectral, Crystallographic And Computational Study." *Journal Of Molecular Liquids* 331 (2021): 115737, Doi: 10.1016/J.Molliq.2021.115737.
- [24] Deepa, H. R., Et Al. "Solvatochromic Shift Studies In Ld-425 And Ld-423: Estimation Of Ground And Excited State Dipole Moments." *Journal Of Molecular Liquids* 181 (2013): 82-88, Doi: 10.1016/J.Molliq.2013.02.016.
- [25] Almandoz, M. C., Et Al. "Uv–Vis Spectroscopic Study And Dft Calculation On The Solvent Effect Of Trimethoprim In Neat Solvents And Aqueous Mixtures." *Spectrochimica Acta Part A: Molecular And Biomolecular Spectroscopy* 129 (2014): 52-60, Doi: 10.1016/J.Saa.2014.02.191.
- [26] Almandoz, M. C., M. I. Sancho, And S. E. Blanco. "Spectroscopic And Dft Study Of Solvent Effects On The Electronic Absorption Spectra Of Sulfamethoxazole In Neat And Binary Solvent Mixtures." *Spectrochimica Acta Part A: Molecular And Biomolecular Spectroscopy* 118 (2014): 112-119, Doi: 10.1016/J.Saa.2013.08.060.
- [27] Mohan, Makesh, Et Al. "Photophysical And Electrochemical Properties Of Organic Molecules: Solvatochromic Effect And Dft Studies." *Optical Materials* 77 (2018): 211-220, Doi: 10.1016/J.Opmat.2018.01.031.
- [28] Kisiel, Zbigniew, And Krzysztof Habdas. "Electric Dipole Moments From Stark Effect In Supersonic Expansion: N-Propanol, N-Butanol, And N-Butyl Cyanide." *Molecules* 28.4 (2023): 1692, Doi: 10.3390/Molecules28041692.
- [29] Hassell, W. F., Et Al. "New Microwave Procedure For Determining Dipole Moments And Relaxation Times." *Tetrahedron* 20.9 (1964): 2137-2155, Doi: 10.1016/S0040-4020(01)98487-X.
- [30] Mataga, Noboru, Yozo Kaifu, And Masao Koizumi. "Solvent Effects Upon Fluorescence Spectra And The Dipolemoments Of Excited Molecules." *Bulletin Of The Chemical Society Of Japan* 29.4 (1956): 465-470.
- [31] Abbaz, Tahar, Amel Bendjeddou, And Didier Villemain. "Density Functional Theory Studies On Molecular Structure And Electronic Properties Of Sulfanilamide, Sulfathiazole, E7070 And Furosemide Molecules." *J. Appl. Chem* 12.1 (2019): 60-69.
- [32] Kawski, A. "On The Estimation Of Excited-State Dipole Moments From Solvatochromic Shifts Of Absorption And Fluorescence Spectra." *Zeitschrift Für Naturforschung A* 57.5, (2002): 255-262.
- [33] Bilot, L., And Alfons Kawski. "Der Einfluß Des Lösungsmittels Auf Die Elektronenspektren Lumineszierender Moleküle." *Zeitschrift Für Naturforschung A* 18.1 (1963): 10-15, Doi: 10.1515/Zna-1963-0103.
- [34] Reichardt, Christian. "Solvatochromic Dyes As Solvent Polarity Indicators." *Chemical Reviews* 94.8 (1994): 2319-2358, Doi: 10.1021/Cr00032a005.
- [35] Yazdanshenas, Rahil, And Farrokh Gharib. "Spectrophotometric Determination Of Preferential Solvation And Solvation Shell Composition Of Morin Hydrate In Some Water-Aliphatic Alcohol Mixed Solvents." *Journal Of Molecular Liquids* 243 (2017): 414-419, Doi: 10.1016/J.Molliq.2017.08.064.
- [36] Castro, Gabriela Tatiana, Et Al. "Solubility And Preferential Solvation Of Piroxicam In Neat Solvents And Binary Systems." *Zeitschrift Für Physikalische Chemie* 232.2 (2018): 257-280.
- [37] Annoji Reddy R, Et Al. "Theoretical And Experimental Investigations Of Antibiotic Agents Sulfamethoxazole (Smx) And Trimethoprim (Tmp) By Density Functional Theory." *Mapana Journal Of Sciences* 22.1 (2023), Doi:10.12723/Mjs.64.10
- [38] Kamlet, Mortimer J., Et Al. "Linear Solvation Energy Relationships. 23. A Comprehensive Collection Of The Solvatochromic Parameters, ρ^* , α , β , And π^* , And Some Methods For Simplifying The Generalized Solvatochromic Equation." *The Journal Of Organic Chemistry* 48.17 (1983): 2877-2887.
- [39] Miotke-Wasilczyk, Marta, Et Al. "The Role Of Hydrogen Bonding In Paracetamol–Solvent And Paracetamol–Hydrogel Matrix

