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Solvent effects on the absorption and fluorescence spectra of Zaleplon: Determination of ground and excited state dipole moments

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ABSTRACT

Solvent effects on the absorption and fluorescence spectra of Zaleplon, a nonbenzodiazepine sedative/hypnotic drug that is mainly used for the short term treatment of insomnia, were investigated in 18 different solvents with diverse polarities. Dipole moments of the ground and excited state (μ_g and μ_e) were determined by Lippert–Mataga, Bakhshiev, Reichardt, McRae and Suppan solvatochromic methods. The dipole moment of Zaleplon ground state in the gas phase has been calculated as $\mu_g = 10.95$ D (TD-DFT) with B3LYP/cc-pVTZ functional. There is a good agreement of theoretical data with Reichardt, McRae, and Suppan correlations, while some dissidence with Lippert–Mataga and Bakhshiev equations is suggesting the occurrence of specific solute–solvent interactions. Additionally, multiple linear regression analysis with Kamlet–Taft and Catalan solvatochromic models was applied to solute–solvent interactions. Dominant property of the solvent that affects the absorption band and Stokes shifts of Zaleplon is polarity of the solvent while the emission band is influenced mainly by solvent basicity.

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1. Introduction

Zaleplon (Fig. 1) is a nonbenzodiazepine sedative/hypnotic drug of the pyrazolopyrimidine class, which is mainly used for the short term (2 to 4 weeks) treatment of insomnia [1]. Zaleplon selectively binds to the benzodiazepine site (ω_1) on the α_1 -containing GABA_A receptors [2]. In addition, it exhibits strong anticonvulsant activity against pentylenetetrazole- and electroshock-induced convulsions [3]. Despite its great utility, poor water solubility leads to very low oral bioavailability of about 30% and various techniques have been used to enhance its solubility [4–10].

It is well known that the activity of the compound is mainly determined by its molecular structure. Likewise, spectral behavior of an organic molecule is strongly related to its structure in both ground and excited states. Therefore, a systematic analysis of the solvent effect can be very informative of physico-chemical processes in bulk solution. The solvent–solute interactions are commonly described in terms of van der Waals (non-specific) interactions, and in terms of specific interactions like hydrogen bonding. All these interactions have an electrostatic nature. The study of solvent effects on the structure and spectroscopic behavior of a solute are essential for the development of solution chemistry. The specific and non-specific interactions between the solvent and the solute molecules

are responsible for the change in molecular geometry, electronic structure and dipole moment of the solute. Upon electronic excitation, molecules may adopt geometries that are very different from those in their ground states, due to the different distribution of electrons in the molecule. This can result in an increased or decreased dipole moment of the excited state relative to the ground state. The determination of singlet excited-state dipole moment is based on the spectral shift caused either externally by electrochromism or internally by solvatochromism. Solvatochromic methods are widely used due to experimental simplicity [11,12,13], although more precise determination of dipole moments can be obtained by electrooptical methods [14]. The solvatochromic method is based on a linear correlation between the shift of absorbance and fluorescence maxima and solvent polarity functions. The most used solvent polarity functions are those obtained by Lippert–Mataga [15], Bakhshiev [16], Bilot–Kawski [17,18,19] and Chamma–Viallet [20] models. By using single- and multi-parameter analyses, the solvatochromic data can be used for quantitative estimation of the contribution of different interactions to the total effect of polarity on spectroscopic characteristics [21]. However, the multi-parameter analyses such as Kamlet–Taft or Catalan models provide better quantitative description of the solvatochromic shifts as they take into account both specific and non-specific solute–solvent interactions [22]. An advantage of Catalan's concept over the Kamlet–Taft solvatochromic model is the separation of non-specific solvent effects into two terms: polarity and polarizability.

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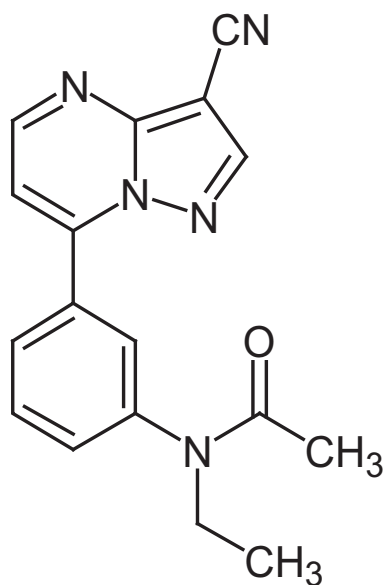


Fig. 1. Structure of Zaleplon.

The solvent-solute interaction can stabilize or destabilize the electronic excited states relative to the ground state of the chromophore, depending on the nature of the chromophore, solvent and electronic transition in solute molecule. The shift of the absorption maximum can be described as hypsochromic (blue) or bathochromic (red), depending on whether the λ_{max} occurs at a shorter or longer wavelength, respectively.

In this research paper, we have determined the difference ($\Delta\mu$) of ground and excited state dipole moments of Zaleplon (μ_g and μ_e , respectively) by using Lippert–Mataga, Bakhshiev, Reichardt, McRea and Suppan methods. The ground and excited state dipole moments have been theoretically calculated as well. The influence of solvents on absorption and fluorescence spectra along with solvatochromic behavior has been investigated using multiple linear regression analyses, with two sets of solvent parameters: (a) Kamlet–Taft and (b) Catalan solvent parameters.

Although the physical characteristics of Zaleplon (solubility, partition coefficient, etc.) are known [23], to the best of our knowledge, this is the first determination of ground and excited state dipole moments of Zaleplon as one of critical quantities describing the extent of molecular interaction. Understanding the influence of microenvironment on the spectroscopic properties of drugs could be very important for a better understanding the drug-solvent interactions in true biological systems [24]. Specifically, chemical species in their excited states may possess different reactivity that may lead to an unexpected pharmacokinetic pathway, which in turn may cause adverse effects [25]. This seems particularly important due to the known occurrence of the dose-sensitive photosensitivity reactions as adverse events in long-term clinical trials [26].

2. Experimental

Zaleplon (99.7% purity) was kindly donated by Belupo d. d. (Croatia) and used without further purification. The solvents used for the measurement of absorption and fluorescence spectra were: water, DMSO, acetonitrile, methanol, ethanol, acetone, 2-propanol, 1-butanol, dichloromethane, THF, ethylacetate, chloroform, diethylether, 1,4-dioxane, tetrachloromethane, cyclohexane, hexane and pentane. All of the solvents were of either HPLC or spectroscopic grade and used without further purification. The water used was deionized and then double distilled in an all-glass apparatus, first from an alkaline solution of KMnO_4 . All solvents were checked for

fluorescence impurities in a steady-state fluorescence apparatus in the wavelength ranges of interest. All measurements were carried out at room temperature keeping the drug concentration very low at 10 μM . Zaleplon stock solution (0.1 mM) was prepared by dissolving an appropriate amount of drug in each solvent. Due to the poor solubility of Zaleplon in water, cyclohexane, hexane, pentane, tetrachloromethane and diethylether, a small amount of either methanol (for water solution) or dichloromethane (for cyclohexane, hexane, pentane, tetrachloromethane and diethylether solutions) was used. The final concentration of the auxiliary solvent was 0.1% v/v of the final solution.

The absorption spectra were recorded on the Varian Cary 50 spectrophotometer. Fluorescence was measured on the OLIS RSM 1000F spectrofluorometer (Bogart, Georgia, USA). Each emission spectrum represents an average of 10,000 fluorescence spectra measured in 10 s. The multiple regression analyses of the absorption and emission maxima were carried out with Microsoft Excel software.

DFT and TD-DFT calculations were carried out using Gaussian 09 program package [27]. Initial optimization and frequency calculations were performed using B3LYP functional with standard split valence and polarized 6-31G(d) basis set for conformational space search [28,29]. From the theoretical benchmark for calculated ground-state dipole moment [30], a higher-level B3LYP/cc-pVTZ method, having the least mean absolute error compared to experimental values was chosen. Same method was used for TD-DFT calculations [31], and was used to investigate the change in dipole moment of the excited state. Solvent effects, through implicit solvation, were assessed by SMD model on the same level of theory [32].

3. Results and Discussion

3.1. Solvent Effects on the Absorption and Fluorescence Spectra of Zaleplon

Since the interaction of solute with the solvent modifies position, intensity and shape of absorption bands, they can be used to monitor the structural changes of a molecule during a physico-chemical process. Absorption and fluorescence spectra were investigated in non-polar, polar aprotic and polar protic solvents with diverse polarities. Zaleplon shows three absorption maxima (λ_{max}) at approximately 230, 290 and 340 nm. Due to spectral limitations i.e. cutoff wavelengths [33] of the used solvents, the most appropriate band for solvatochromic measurements was at 340 nm. Selected absorption and emission spectra of Zaleplon in different solvents are presented in Fig. 2. The values of the absorption spectral maxima are listed in Table 1.

From the absorption spectra shown in Fig. 2, it can be noticed that the absorption maxima shift to shorter wavelengths with the increase of solvent polarity (blue or hypsochromic shift), which implies the involvement of the $n \rightarrow \pi^*$ transition. This can be explained by the fact that n orbitals are more stabilized by hydrogen bonding or polar solvents than π^* orbitals [34].

Fluorescence spectral studies of Zaleplon were carried out at excitation wavelength of $\lambda_{\text{ex}} \approx 340$ nm in the same set of solvents. In contrast to absorption, the fluorescence spectra of Zaleplon display bathochromic shift with an increase of solvent polarity, which indicates a $\pi \rightarrow \pi^*$ transition. Bathochromic shift also indicates that the excited state is more polar than the ground state and thus stabilized in polar solvents. The Stokes shifts for all used solvents are presented in Table 1, where larger Stokes shifts indicate larger charge transfer transition.

3.2. Solvent Polarity Functions and Estimation of Ground State and Excited State Dipole Moments

The influence of solvent polarity or polar interactions on the fluorophore in the solute-solvent system can be estimated by

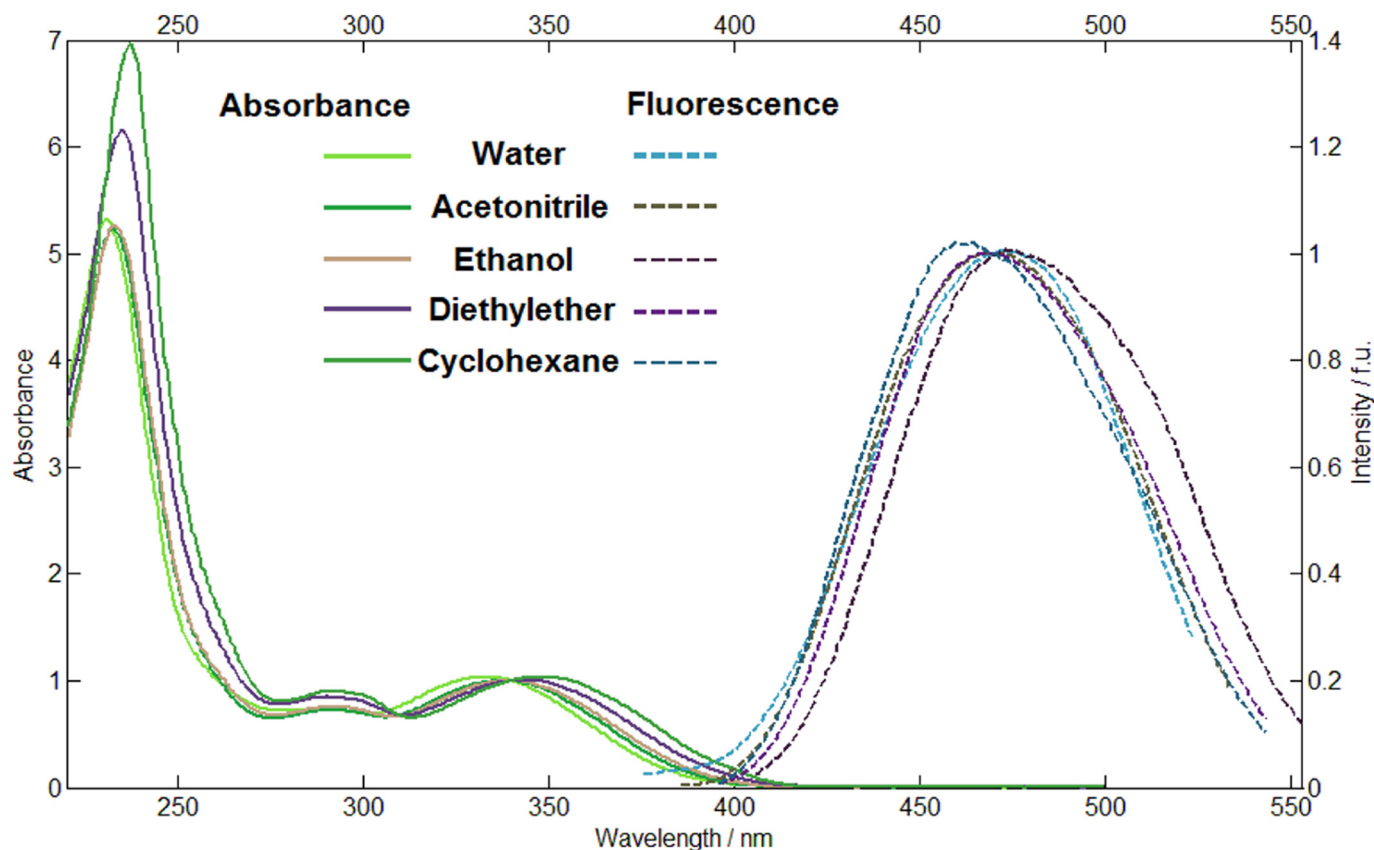


Fig. 2. Normalized absorption and emission spectra of Zaleplon ($c = 10 \mu\text{M}$) in selected solvents at 25°C . Limited number of spectra are shown for clarity. Spectra have been normalized at 340 nm (absorbance) and 470 nm (fluorescence). Spectra for all solvents are given in the Supplemental information (Figs. S4–S21) [35].

solvatochromic plots, such as Lippert–Mataga, Bakhshiev and others. By these methods, absorption and fluorescence shifts are followed using the solvent polarity function, described by dielectric constant (ϵ) and refractive index (n). These theories are

based on the Onsager's reaction field theory which describes non-specific electrostatic interactions in solvent-solute system. In the absence of intermolecular hydrogen bonds, and with an assumption that the Onsager's radius has a spherical shape, the solvent

Table 1
Absorption (λ_{abs}) and emission (λ_{em}) spectral characteristics, Stokes shifts ($\Delta\nu$), solvent parameters (n , ϵ), microscopic solvent polarity (E_{S}^{N}) and solvent polarity functions ($f1$, $f2$, $f3$, $f4$). Solvents are listed in the order of decreasing dielectric constants.

Solvent	$\lambda_{\text{abs}}/\text{nm}$	$\lambda_{\text{em}}/\text{nm}$	$\Delta\nu/\text{cm}^{-1}$	ϵ	$n(20^\circ\text{C})$	E_{S}^{N}	$f1(n,\epsilon)$	$f2(n,\epsilon)$	$f3(\epsilon)$	$f4(\epsilon)$
Water	333.5	472.4	8816.5	80.1	1.333	1	0.3201	0.9136	1.9269	0.9753
DMSO	339.5	482	8708.2	46.7	1.4793	0.4444	0.2631	0.8404	1.8768	0.9581
Acetonitrile	336.5	471.2	8495.3	37.5	1.3441	0.4599	0.3054	0.8631	1.8481	0.9481
Methanol	338.6	479.7	8687.0	32.7	1.3284	0.7623	0.3086	0.8547	1.8271	0.9407
Ethanol	338.9	476.3	8512.1	24.5	1.3614	0.6543	0.2887	0.8127	1.7736	0.9216
Acetone	340	471.5	8202.9	20.7	1.3588	0.3549	0.2843	0.7903	1.7357	0.9078
2-Propanol	341	475.7	8303.9	17.9	1.3776	0.5463	0.2720	0.7615	1.6985	0.8942
1-Butanol	342	479.6	8389.1	17.8	1.3993	0.5864	0.2641	0.7532	1.6970	0.8936
Dichloromethane	342.5	463.7	7631.4	8.93	1.4244	0.3086	0.2170	0.5902	1.4511	0.7986
THF	342	474.5	8165.0	7.58	1.4072	0.2068	0.2096	0.5491	1.3737	0.7669
Ethylacetate	342.5	473	8055.4	6.02	1.3724	0.2284	0.1996	0.4891	1.2519	0.7151
Chloroform	343.5	466.3	7666.7	4.81	1.4459	0.2593	0.1483	0.3709	1.1189	0.6558
Diethylether	342	465.5	7757.5	4.33	1.353	0.1173	0.1665	0.3763	1.0521	0.6248
1,4-Dioxane	344	474.8	8008.3	2.25	1.4224	0.1636	0.0245	0.0499	0.5882	0.3846
Tetrachloromethane	347.5	462.6	7160.0	2.24	1.4607	0.0525	0.0111	0.0232	0.5849	0.3827
Cyclohexane	349	463.8	7092.3	2.02	1.4262	0.0062	-0.0016	-0.0033	0.5075	0.3377
Hexane	346.5	461	7168.1	1.89	1.375	0.0093	-0.0001	-0.0002	0.4576	0.3080
Pentane	345.6	462.2	7299.5	1.84	1.358	0.0093	-0.0006	-0.0010	0.4375	0.2958

Values of the refractive index (n) and dielectric constant (ϵ) were obtained from the literature [36].

Values of the microscopic solvent polarity (E_{S}^{N}) were obtained from the literature [37].

$f1$ is the Lippert–Mataga solvent polarity function (Eq. (6)).

$f2$ is the Bakhshiev solvent polarity function (Eq. (7)).

$f3$ is the McRae polarity function (Eq. (9)).

$f4$ is the Suppan polarity function (Eq. (10)).

shifts are well interpreted by the solvent polarity functions. Related equations and solvent polarity functions are given below:

$$\bar{\nu}_a - \bar{\nu}_f = m_1 F_{\text{Lippert-Mataga}}(\epsilon, n) + \text{constant } m_1 = \frac{2(\mu_e - \mu_g)^2}{hca^3} \quad (1)$$

$$\bar{\nu}_a - \bar{\nu}_f = m_2 F_{\text{Bakhshiev}}(\epsilon, n) + \text{constant } m_2 = \frac{2(\mu_e - \mu_g)^2}{hca^3} \quad (2)$$

$$\frac{\bar{\nu}_a - \bar{\nu}_f}{2} = -m_3 F_{\text{Kawski-Chamma-Viallet}}(\epsilon, n) + \text{constant } m_3 = \frac{2(\mu_e - \mu_g)^2}{hca^3} \quad (3)$$

$$\bar{\nu}_a = -m_4 F_{\text{McRae}}(\epsilon) + \text{constant } m_4 = \frac{\mu_g(\mu_e - \mu_g)}{hca^3} \quad (4)$$

$$\bar{\nu}_a = -m_5 F_{\text{Suppan}}(\epsilon) + \text{constant } m_5 = \frac{\mu_g(\mu_e - \mu_g)}{hca^3} [5].$$

$$F_{\text{Lippert-Mataga}}(\epsilon, n) = \frac{\epsilon - 1}{2\epsilon + 1} - \frac{n^2 - 1}{2n^2 + 1} \quad (6)$$

$$F_{\text{Bakhshiev}}(\epsilon, n) = \frac{2n^2 + 1}{n^2 + 2} \left(\frac{\epsilon - 1}{\epsilon + 2} - \frac{n^2 - 1}{n^2 + 2} \right) \quad (7)$$

$$F_{\text{Kawski-Chamma-Viallet}}(\epsilon, n) = \frac{2n^2 + 1}{2(n^2 + 2)} \left(\frac{\epsilon - 1}{\epsilon + 2} - \frac{n^2 - 1}{n^2 + 2} \right) + \frac{3(n^4 - 1)}{2(n^2 + 2)^2} \quad (8)$$

$$F_{\text{McRae}}(\epsilon) = \frac{2(\epsilon - 1)}{\epsilon + 2} \quad (9)$$

$$F_{\text{Suppan}}(\epsilon) = \frac{2(\epsilon - 1)}{2\epsilon + 2} \quad (10)$$

$$a = \sqrt[3]{\frac{3V}{4\pi}} \quad (11)$$

The values ν_a and ν_f are the wave numbers (in cm^{-1}) of the absorption and emission maxima, respectively, $h = 6.6256 \cdot 10^{-34}$ J s is Planck constant, $c = 2.9979 \cdot 10^{10}$ cm s^{-1} is the speed of light, a is the Onsager radius, and $\Delta\mu = \mu_e - \mu_g$ is the dipole moment difference between the ground and excited states. Values m_1 , m_2 , m_3 , m_4 and m_5 represent the slopes of corresponding plots. The Onsager cavity radius $a = 4.23$ Å was estimated from Eq. (11), where $V = 316.5$ Å³ is the volume of the Zaleplon molecules calculated by Gaussian 09.

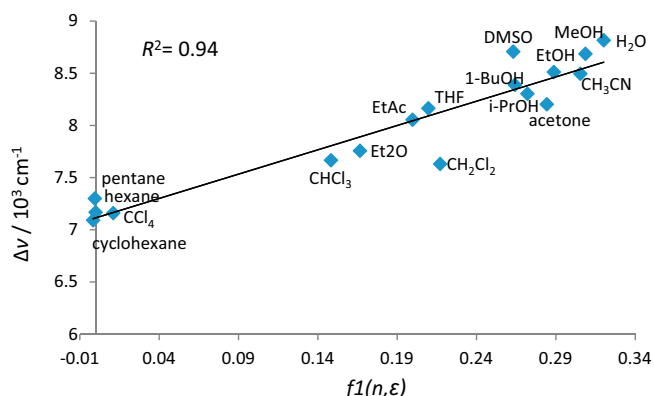


Fig. 3. Lippert-Mataga plot for Zaleplon in different solvents.

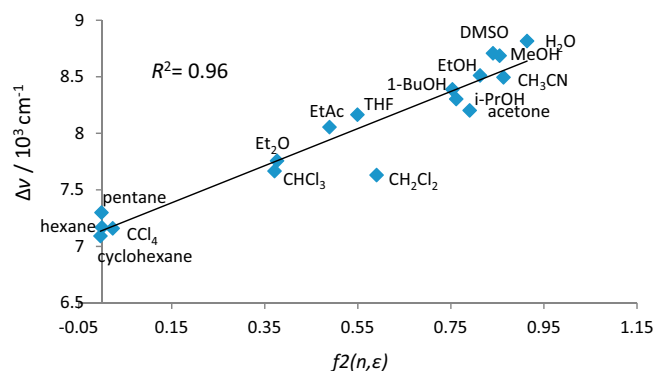


Fig. 4. Bakhshiev plot for Zaleplon in different solvents.

While Lippert-Mataga and Bakhshiev solvatochromic method both use absorption and emission spectral data, McRae and Suppan equations are based solely on absorption spectra. Figs. 3, 4, S1 and S2 (Supplementary information) show referred solvent polarity function plots for Zaleplon in different solvents, where the corresponding correlation factors (R^2) are denoted on the plots. The values of the obtained slopes, the calculated dipole moments and the corresponding changes of the dipole moments are given in Table 2. In Lippert-Mataga and Bakhshiev relations, data for 1,4-dioxane were offset so they were omitted from calculation. The linear dependence of Stokes shifts to these polarity functions indicates the existence of a general type of solute-solvent interaction. Solvatochromic shifts of Zaleplon cannot be explained with the Kawski-Chamma-Viallet polarity function (Eqs. (3) and (8)) due to the relatively poor correlation of data (not shown), suggesting the occurrence of specific solute-solvent interactions.

Another method based on the empirical polarity scale proposed by Reichardt and developed by Ravi [38] is given in Eq. (12):

$$\bar{\nu}_a - \bar{\nu}_f = m_6 E_T^N + \text{constant } m_6 = 11307.6 \left[\left(\frac{\delta\mu}{\delta\mu_B} \right)^2 \left(\frac{a_B}{a} \right)^3 \right] \quad (12)$$

where $\Delta\mu_B = 9$ D and $a_B = 6.2$ Å are the dipole moment change upon excitation and the Onsager radius for betaine dye used as a standard, respectively. This method considers the hydrogen bond donating/accepting characteristics of the solvent and often results in much better correlation of solvatochromic shifts with the microscopic solvent polarity parameter (E_T^N), rather than traditionally used polarity functions involving the dielectric constant and refractive index. Furthermore, this method minimizes error estimation of Onsager's cavity radius a . In Figs. 5 and S3 (Supplementary information), the linear dependence of the emission maximum (ν_f) and Stokes shifts ($\Delta\nu$) on the parameter E_T^N are shown, respectively. In both relations the data for water were excluded.

Table 2

Obtained values for the change of dipole moment ($\Delta\mu$), ground state (μ_g) and excited state (μ_e) dipole moments from solvatochromic and computational methods.^a

Used method	Slope/ cm^{-1}	$\Delta\mu/\text{D}$	μ_g/D	μ_e/D
Lippert-Mataga	4659	5.61		16.56 ^b
Bakhshiev	1640	3.33		14.27 ^b
Reichardt	2004	2.13		13.07 ^b
McRae	526	0.74		11.69 ^c
Suppan	1134	1.60		12.55 ^c
TD-DFT values		1.56	10.95	12.51

^a 1 Debye = 3.33564×10^{-30} Cm = 10^{-18} esu cm.

^b Excited-state dipole moment calculated from $\Delta\mu$ using theoretical value $\mu_g = 10.95$.

^c Theoretical μ_g value is used.

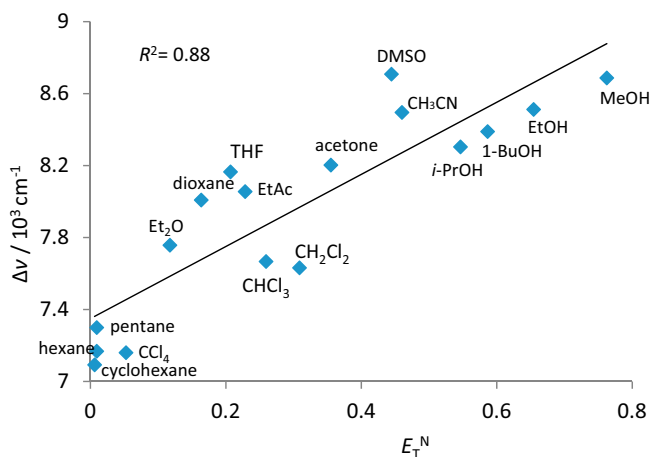


Fig. 5. Reichardt correlation of the Stokes shifts ($\Delta\nu$) for Zaleplon in different solvents.

The somewhat lower value for the Reichardt correlation ($R^2 = 0.88$ in Fig. 5) suggests that the contribution of hydrogen bonding to the solvation of Zaleplon is less important in comparison to the betaine dye used to construct the E_T^N scale. The calculated values for solvent polarity functions $f1(n,\epsilon)$, $f2(n,\epsilon)$, $f3(\epsilon)$ and $f4(\epsilon)$, as well as the E_T^N parameter, are summarized in Table 1.

Solvent-dependent spectral shifts interpreted in terms of the Lippert–Mataga and Bakhshiev equations describe the solvatochromic Stokes shift as a function of the change of the solute dipole moment upon excitation, $\Delta\mu = \mu_e - \mu_g$. Therefore, by calculating the slopes (m_1, m_2) from the corresponding equations (Eqs. (1) and (2)), $\Delta\mu$ can be calculated. Also, Reichardt's method, based on the empirical polarity scale E_T^N , can be used for the calculation of $\Delta\mu$ from solvatochromic shift, according to Eq. (13):

$$\Delta\mu = \mu_e - \mu_g = \sqrt{\frac{m_6 \times 81}{(6.2/a)^3 \times 11307.6}} \quad (13)$$

where m_6 is the slope of the linear plot of E_T^N vs. Stokes shift. The estimated values of $\Delta\mu$ (in Debyes), along with the corresponding slopes are shown in Table 2. All experimental excited state dipole moment values μ_e were calculated from the obtained values of $\Delta\mu$ using the theoretical value $\mu_g = 10.95$ (vide infra).

3.3. Quantum Chemical Calculations – Ground State Dipole Moment, μ_g

The excitation energies for six lowest excited states of Zaleplon were calculated by time-dependent functional theory (TD-DFT) with B3LYP functional, while environmental effects were modeled with a continuum solvation model. Conformational freedom was represented by using four different conformers in our analysis, spanning <6 kJ mol⁻¹ in the gas phase. Lowest energy transition in the gas phase, $\lambda = 354.9$ nm, corresponds to excitation from highest occupied molecular orbital (HOMO), to the lowest unoccupied molecular orbital (LUMO in Fig. 6). It is interesting to note that conformational freedom accounts for only $\Delta\lambda = 6$ nm. As implicit solvation was not included in this study, interaction of Zaleplon with individual solvent molecules may change and broaden individual bands of absorption, and so the error of TD-DFT transition energies is typically in the range of $\Delta\lambda = 30$ nm [39]. By using Boltzmann averaging, the dipole moment of Zaleplon in the ground state in gas phase is $\mu_g = 10.95$ D, while in the excited state a higher dipole moment is observed ($\mu_e = 12.51$ D). Similar has been observed for a range of molecules [40–42].

3.4. Multiple Linear Regression Analysis - Linear Solvation Energy Relationships

One of the most successful interpretations of solvent-induced spectral shifts is by linear solvation energy relationships (LSER). They are used to describe different interactions which contribute to the total effect of solvent polarity on spectroscopic characteristics of the solute. In comparison to single-parameter relationships discussed so far, the more advanced Kamlet-Taft (Eq. (14)) and Catalan (Eq. (15)) scales are multiple linear regressions of different solvent parameters:

$$y = y_o + \alpha\alpha + b\beta + c\pi^* \quad (14)$$

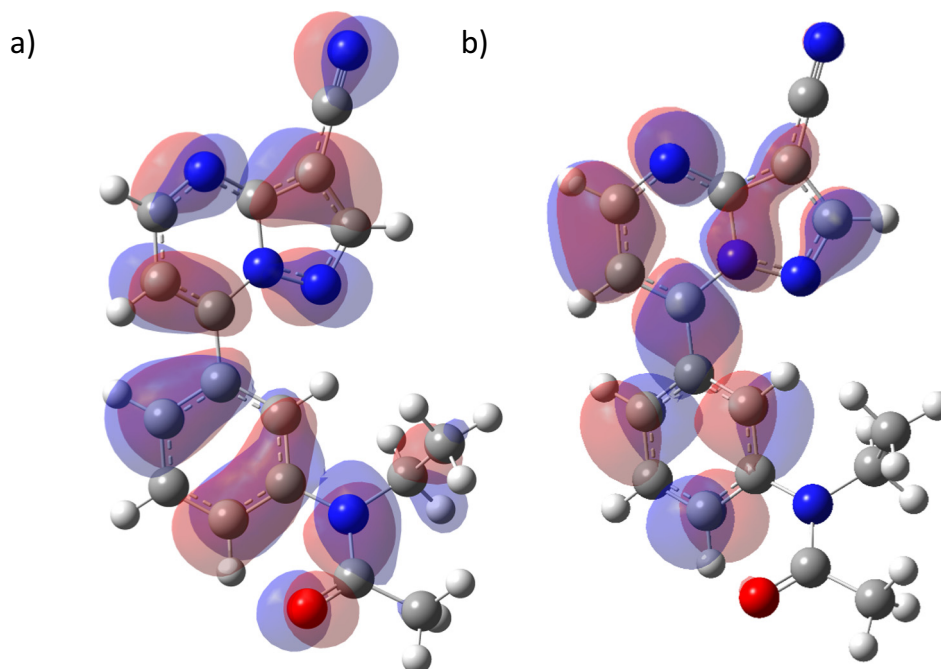


Fig. 6. a) HOMO and b) LUMO orbitals of Zaleplon, calculated at B3LYP/cc-pVTZ level of theory.

$$y = y_0 + aSA + bSB + cSP + dSdP \quad (15)$$

In both equations, y can be any of the spectral properties (eg. ν_a , ν_f , or $\Delta\nu$), and y_0 is the spectral property in the gas phase with no solvent effects, i.e. when all solvent parameters are equal to zero. In Eq. (14), α is a measure of the solvent hydrogen-bond donor (HBD) capacity, β is a measure of the solvent hydrogen-bond acceptor (HBA) capacity and π^* is the solvent polarity/polarizability that describes the ability of solvent to stabilize the charge or dipole of a molecule, depending the solvent dielectric constant. In Eq. (15), the parameters SA , SB , SP and SdP characterize solvent acidity, basicity, polarizability and polarity of a solvent, respectively. Values a–d are the regression coefficients describing sensitivity of the given property to the different types of solvent–solute interactions. The Kamlet–Taft and Catalan solvent parameters π^* , α , β , and SA , SB , SP , SdP , refractive index (n) and dielectric constant (ϵ), are obtained from the literature and listed in Table S1 (Supplementary information) [43–45].

Multiple linear regression analyses (MLR) according to Eqs. (14) and (15) were applied to the values of ν_a , ν_f and $\Delta\nu$. For initial calculations, all parameters from the corresponding equations were used. Any parameter with a corresponding value of $p > 0.05$ was considered insignificant. The insignificant parameter was then omitted from the equation and a new calculation with remaining parameters was performed until only significant parameters remained ($p \leq 0.05$). Resulting values of regression coefficients and correlation coefficients obtained from data for all 18 solvents are given in Table 3.

4. Conclusions

Based on the results in Table 3, according to the Kamlet–Taft model, the dominant property of the solvent that affects the absorption band, ν_a , of Zaleplon is the solvent polarity/polarizability (π , 70% contribution) and much less the solvent HBD (α , 30% contribution). However, the emission band, ν_f , is influenced mainly by the solvent basicity (β , 67.5% contribution) and less by the solvent polarity/polarizability (π , 32.5% contribution). The overall Stokes shifts, $\Delta\nu$, of Zaleplon are determined mostly by the polarity (π , 54.9% contribution) and less by the basicity of the solvent (β , 45.1% contribution). Positive correlation coefficients indicate the stabilization of the excited state. In the Catalan model, where non-specific solvent effects polarity and polarizability are separated, the solvent polarity (SdP) emerges as the dominant parameter influencing the Stokes shifts. The influences of solvent parameters on the absorption and emission bands in the Catalan model are similar to the Kamlet–Taft model, with SdP (63.6% contribution) being the dominant influence on the absorption band, and SB (58.4% contribution) being the dominant influence on the emission band. Therefore, we can

Table 3

Values of regression coefficients (a–d) according to Eqs. (14) and (15), with the corresponding correlation coefficients (R^2) obtained from MLR analysis.

	Spectral property	y_0/cm^{-1}	a (α or SA)	b (β or SB)	c (π or SP)	d (SdP)	R^2
Kamlet–Taft	ν_a	28,817	289.7	/	674.7	/	0.75
	%		30.0		70.0		
	ν_f	21,670	/	–687.6	–330.8	/	0.86
	%			67.5	32.5		
Catalan	$\Delta\nu$	7121	/	888.83	1080.94	/	0.86
	%			45.1	54.9		
	ν_a	28,809	377.3	/	/	657.8	0.88
	%		36.4			63.6	
Catalan	ν_f	21,725	/	–593.488	/	–422.178	0.75
	%			58.4		41.6	
	$\Delta\nu$	7110	587.1	539.3	/	1014.8	0.91
	%		27.4	25.2		47.4	

Values / denote unavailable or insignificant ($p > 0.05$) parameters.

Values % denote percentage contribution to the overall correlation.

conclude that the polarity of the environment surrounding the chromophore is the main factor that determines the solvent effect on the Stokes shifts of Zaleplon. Even though Zaleplon has four possible H-acceptor sites, the contribution of solvent's hydrogen bonding capability is minor, based on low values of coefficients that describe solvent acidity/HBD (α or SA) or basicity/HBA (β or SB). These results are in agreement with previously suggested by the plots of $\Delta\nu$ and ν_f vs. E_T^N (Figs. 5 and S3).

The excited state dipole moment was found to be higher in all methods when compared to the theoretically calculated ground state dipole moment, indicating larger polarity of Zaleplon and therefore increased sensitivity to solvent effects in the excited state. The increased polarity of the excited state also accounts for the observed bathochromic shift of the fluorescence spectra. Since Lippert–Mataga and Bakhshiev equations do not consider polarity of the solute, higher values of μ_e are obtained with these methods (Table 2).

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.saa.2019.01.023>.

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