

# CAFFEINE-SOLVENT INTERACTION STUDIED BY UV SPECTROMETRY AND MOLECULAR MODELING

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*Abstract.* Caffeine is known as an important substance in human life with both alimentation and medical issues. Biophysical approach of caffeine molecule was carried out in this study by applying quantum chemical methods and spectral recording. The focus of the present investigation was the evidencing of the solvent action on the electronic absorption transition of caffeine in the near ultraviolet range – for practical applications in extractive industry and chromatographic analysis of the product. The nature of solvent solute interactions was revealed by means of mathematical modeling. Linear correlation coefficient of 0.99 was found to the application of solvatochromic model of Lippert-Mataga that allowed the estimation of dipole moment in the excited state (9.2130 D) – based also on the dipole moment in the ground state (3.906 D) estimated by quantum chemical method. The application of Bakhshiev's solvatochromic model with linear correlation coefficient over 0.93 led to the evidence of universal solute-solvent interactions like induction forces and dispersive ones.

*Key words:* caffeine, quantum-chemical approach, solvatochromic effect.

## INTRODUCTION

Caffeine is one of the most spread stimulants of the central nervous system used by people almost everywhere. It is found mostly in coffee beans, tealeaves, cocoa beans and kola nuts. In humans, acting as an antagonist of adenosine receptors, caffeine can increase attention and reduce fatigue [16]. Its importance in cancer preventing and also in alternative cancer therapy as support drug was recognized as well as its action against Parkinson disease [3].

Caffeine is soluble in many solvents either in polar or in nonpolar ones. The most used solvents in caffeine extraction are water, chloroform and methylene chloride, but the last two of these solvents when used to separate caffeine from other compounds in aqueous solutions could be carcinogenic. A new technique that avoids these solvents uses carbon dioxide under high pressure.

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In this research we studied the behavior of caffeine in various polar and nonpolar solutions. The spectral behavior of caffeine molecules in solutions was analyzed both experimentally, with focus on the main solute-solvent interactions, and computationally, to find out the electro-optical and energetic parameters of caffeine molecule optimized configuration. The intermolecular interactions between caffeine and different polarity solvents were studied based on the electronic absorption spectra of such diluted solutions.

The electronic absorption spectra (EAS) of various organic compounds have been studied, in their turn, from theoretical point of view, aiming to find the correlation between the molecular structure and the electronic spectra [10–12] as well as to identify the main type of solute-solvent interactions from the solvent effect on the electronic transition energy [1, 4, 7, 13].

## MATERIALS AND METHODS

Caffeine molecule structural and energetic parameters were estimated by the quantum mechanics method –PM3 (semi-empirical calculation) implemented in the molecular modeling program–HyperChem-8.0.10 [9]. Polak-Ribiere optimization algorithm was applied as well as Restricted Hartree-Fock wavefunction with the convergence limit of 0.0001 and criterion of RMS gradient of 0.0001 kcal/(Å mol).

The parameters  $\epsilon$  and  $n$  for the used solvents are given in Table 1.

Table 1

Solvent electro-optical parameters

No.	Solvent	$\epsilon$	$n$	No.	Solvent	$\epsilon$	$n$
1	n-Hexane	1.88	1.3749	6	Isobutyl alcohol	17.93	1.3959
2	Carbon tetrachloride	2.24	1.4602	7	Isopropyl alcohol	18.92	1.3772
3	Chloroform	4.89	1.4459	8	Ethanol	24.55	1.3614
4	Acetic acid	6.20	1.3719	9	Methanol	32.66	1.3284
5	Butanol	17.51	1.3993	10	Water	78.36	1.3330

Electronic absorption spectra of pure crystallized caffeine in various solvents (all reagents from SIGMA) were recorded with UV 1700 Shimadzu spectrophotometer, in 1 cm quartz cells.

Solvent electro-optical macroscopic parameters are given in Table 1.

## RESULTS AND DISCUSSION

The structure of caffeine –  $C_8H_{10}N_4O_2$  (Fig. 1 b) was modeled by means of Hyper Chem software and it is shown in Fig. 1 a with 2-D electric charge density distribution. Caffeine dipole moment (Table 2) with a rather significant value of

3.906 D (compared to water dipole moment of 1.9 D and according to [8]) is lying mostly in the main molecular skeleton plane. From the charge density map distribution (Fig. 1) one can observe that the negative electric charge density on the oxygen atoms is about three time larger than that on the unsaturated nitrogen atom ( $-0.379$  and respectively  $-0.376$  in comparison to  $-0.133$ ). This could indicate the possibility of hydrogen bond formation with some solvent molecules. In Table 2 the molecular descriptors, structural and energetic parameters provided by quantum-chemical approach of caffeine structure are presented.

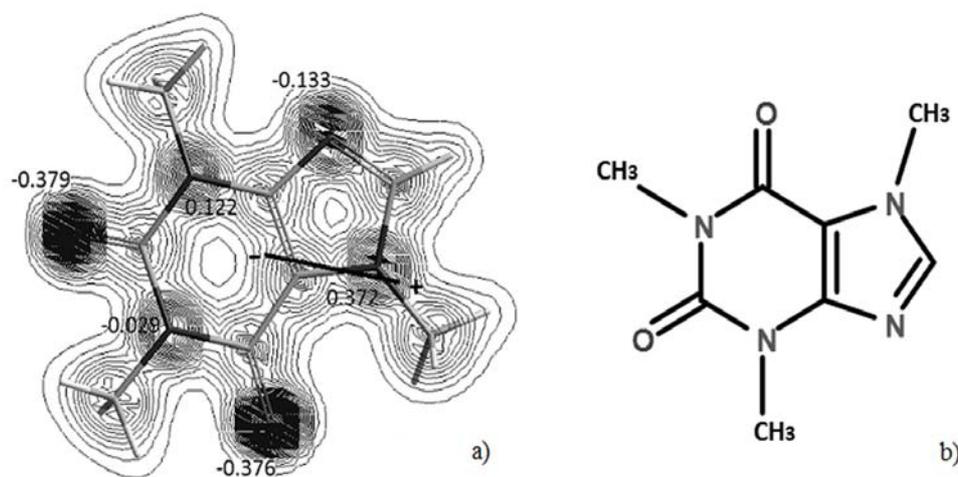


Fig.1. a. Caffeine optimized structure with isosurface (electric charge density 2-D map) and dipole moment, generated through quantum-chemical simulation; b. caffeine chemical structure.

Table 2

Numerical results of caffeine quantum-chemical approach

Energetic parameters		Molecular descriptors	
Total energy (kcal/mol)	-53928.04	Surface area ( $\text{\AA}^2$ )	366.25
Binding energy (kcal/mol)	-2508.70	Volume ( $\text{\AA}^3$ )	573.22
Heat of formation (kcal/mol)	-49.44	Polarizability ( $\text{\AA}^3$ )	18.87
$E_{\text{HOMO}}$ (eV)	-9.0017	Mass (Da)	194.19
$E_{\text{LUMO}}$ (eV)	-0.5384	Partition coefficient Log P	-1.06
$\Delta E$ (eV)	-8.4633	Dipole moment (D)	3.906

The frontier molecular orbitals (HOMO –highest occupied molecular orbital and LUMO – lowest unoccupied molecular orbital) are very popular quantum chemical parameters (Fig. 2). The energies of HOMO and LUMO orbitals, useful for estimating molecular reactivity and the ability to absorb light, are negative which indicates a stable structure [13].

From the viewpoint of charge transfer the relatively large value of  $E_{\text{HOMO}}$  ( $-9.0017$  eV) means that the ionization from this molecular state is more difficult, i.e. the molecule will hardly lose an electron. The HOMO–LUMO energy gap,  $\Delta E$ , of about  $-8.4633$  eV is also an important stability index reflecting the chemical stability of the caffeine molecule. From Fig. 2 one can easily observe the main change in electron density upon the two atomic rings of caffeine when passing from the ground state (HOMO level) to the excited one (LUMO level). The electron charge density switches, when the transition determined by light absorption occurs; two apparent orbital breaking down processes could be assumed based on the changes in charge density within the molecular skeleton regions marked in Fig. 2 with square and round contours.

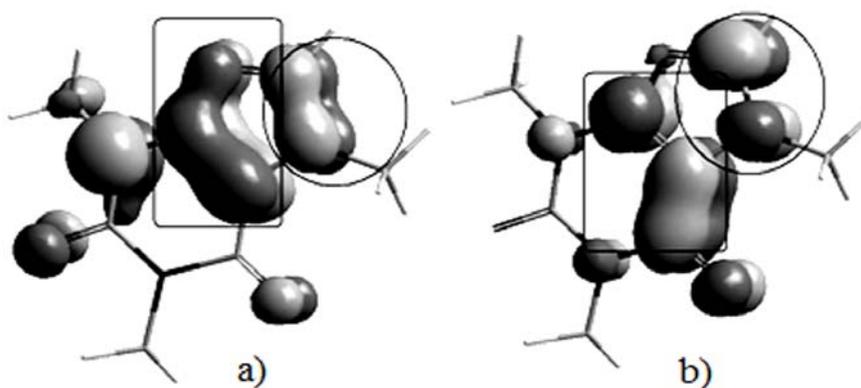


Fig. 2. Molecular simulated orbitals: a. HOMO; b. LUMO.

According to HyperChem simulation the caffeine EAS present maximal absorption bands in the UV range (Fig. 3 a). The spectrum recorded for caffeine ( $10^{-4}$  M) in water diluted solution as well as in water protonated solution (with 98% sulfuric acid of concentration) in Fig. 3 b is presented.

There is an evident similarity between the theoretical spectrum (Fig. 3 a) of isolated molecule and the spectrum recorded in aqueous diluted solution (Fig. 3 b), with the same group of bands and the same relative intensities but shifted positions in the wavenumber scale because of: (i) solvent presence; (ii) limited performances of modeling software. Following proton delivery from sulfuric acid dissociation in caffeine aqueous solution (estimated pH = 1.5), no measurable change in the caffeine band energy or intensity could be noticed (Fig. 3 b) – so that the bands could be assessed to  $\pi$ - $\pi^*$  transitions considering also their high energy (in UV range) and their hypsochromic shift to the solvent polarity increasing (Fig. 4) [14]. The experimentally recorded spectra of caffeine are presented in Fig. 4.

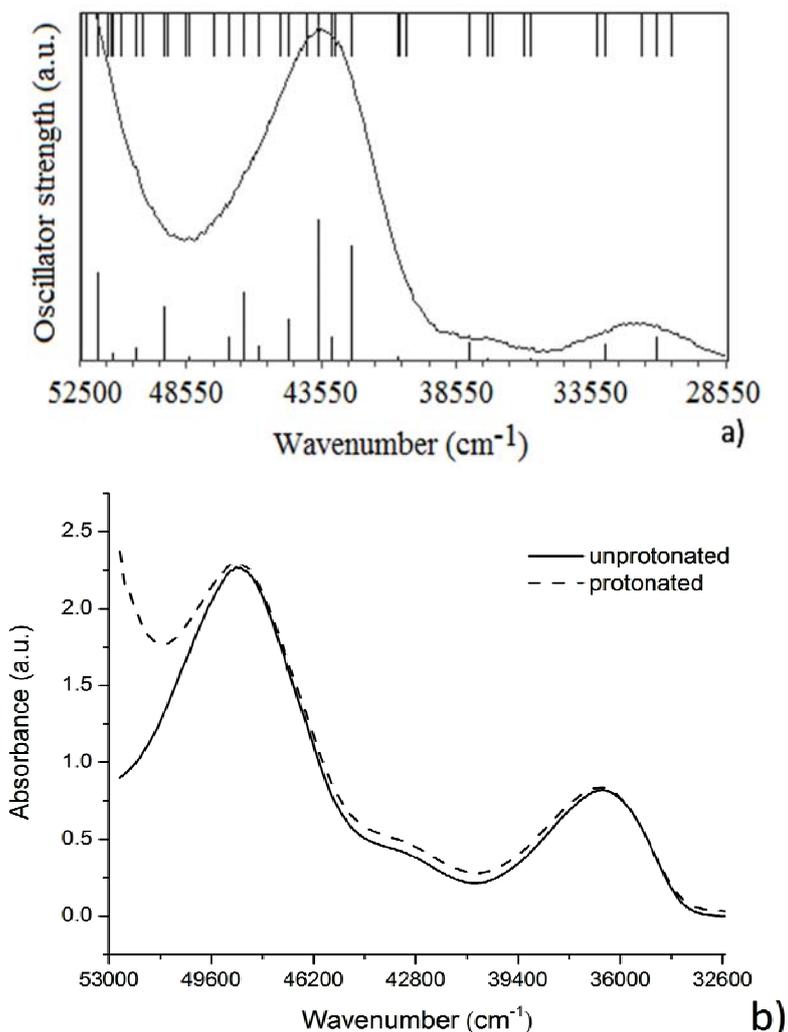


Fig. 3. a. Caffeine simulated EAS; b. caffeine recorded EAS – aqueous solutions.

The band from near UV range was chosen for solvatochromic effect study due to relatively larger number of solvents with transparency in this range. Solvent effect on the EAS transitions was analyzed based on solvatochromic theories like that of Lippert-Mataga [5] and Bakhshiev's [2]. In both theories the solute solvent interactions are supposed to have universal character being developed all over the solution volume, for highly diluted solutions, i.e.  $10^{-4} - 10^{-5}$  M; in contrast with these interactions also specific forces could appear like hydrogen bonds and other local interactions specific to certain solvent structure. According to Lippert-Mataga [5]

$$\Delta\bar{\nu} = \bar{\nu}_s - \bar{\nu}_0, \quad (1)$$

where  $\bar{\nu}_s$  is the wavenumber of studied molecule in solution and  $\bar{\nu}_0$  of the isolated molecule (in vapor state).

$$\Delta\bar{\nu} = \frac{2(f_L(\varepsilon) - f_L(n))}{4\pi\varepsilon_0 hca^3} (\mu_g - \mu_e)^2 + \text{const.} \quad (2)$$

where  $\mu_g$  and  $\mu_e$  are the dipole moments in the ground and excited state;  $h$  is Planck's constant,  $c$  is light velocity in the free space,  $a$  is the molecule radius,  $f_L(\varepsilon) = (\varepsilon - 1)/(2\varepsilon + 1)$ ,  $f_L(n) = (n^2 - 1)/(2n^2 + 1)$ . The  $\bar{\nu}_0$  was estimated as the limit of wavenumber for  $f_L(\varepsilon) - f_L(n) = 0$  [6, 15].

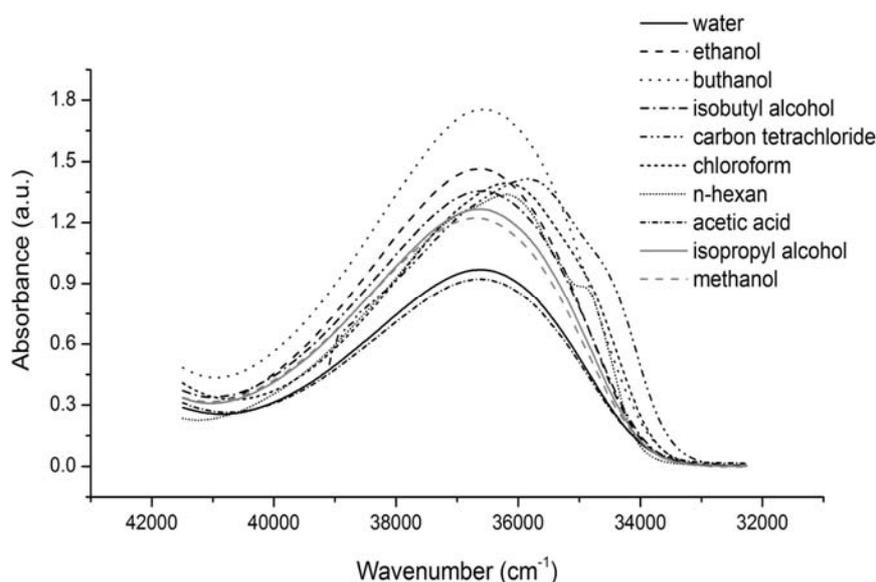


Fig. 4. The recorded spectra of caffeine in diluted solution with various solvents.

In Fig. 5 the relative good linear correlation between the two terms of formula (2) can be seen with several significant displacements for non-protic solvents (carbon tetrachloride, chloroform, acetic acid, n-hexane); the protic solvents being mainly the alcohols and water.

Better linearization was obtained removing two non-protic solvents, acetic acid and n-hexane; thus the new correlation coefficient became 0.99 (Fig. 6) empowering us to take the slope for dipole moment calculation in the excited state, according to [15].

For the two solvents peculiar intermolecular interactions are supposed to occur against the general solvent forces resulting in their lateral positions relatively

to the main theoretic line. From the regression line slope, (Fig. 6 and eq. (2)), the change in the caffeine dipole moment following the electronic transition could be estimated using molecular radius  $a$  determined from quantum chemical approach, as  $3 \cdot V/S = 4.70 \text{ \AA}$  (Table 2). Having the dipole moment in the ground state  $\mu_g$  from quantum chemical modeling (3.09 D – Table 2) the  $\mu_e$  value results as equal to 9.2130 D.

To get a deeper insight in the nature of solute-solvent interactions the Bakhshiev's theory was also applied further [2]. In the formula proposed by Bakhshiev for solvent effect shift the induction forces (due to induced dipole moments) between solvent molecules and solute ones are given by equation (3):

$$hc\Delta\bar{\nu}_{\text{ind}} = hc(\bar{\nu}_{\text{ind}} - \bar{\nu}_0) = -\frac{2n^2 + 1}{n^2 + 2} \left\{ \frac{2\mu_g(\mu_g - \mu_e \cos\varphi)}{a^3} \left[ \frac{\varepsilon - 1}{\varepsilon + 2} - \frac{n^2 - 1}{n^2 + 2} \right] + \frac{(\mu_g - \mu_e)^2}{a^3} \frac{n^2 - 1}{n^2 + 2} \right\} \quad (3)$$

where  $n$  and  $\varepsilon$  are solvent refractive index and, respectively, its dielectric constant,  $a$  is the molecule radius,  $\mu_g$  and  $\mu_e$  are the dipole moments in the ground and excited state while  $\varphi$  is the angle between the two electric vectors. For orientation (dipole-dipole) interactions:

$$hc\Delta\bar{\nu}_{\text{or}} = hc(\bar{\nu}_{\text{or}} - \bar{\nu}_0) = -\frac{hc^2 f}{8\pi m v_0 a^3} \frac{n^2 - 1}{n^2 + 2} \quad (4)$$

while dispersion forces (due to small temporary dipole moments caused by collisional deformation of electronic clouds) are given by:

$$hc\Delta\bar{\nu}_{\text{disp}} = hc(\bar{\nu}_{\text{disp}} - \bar{\nu}_0) = (\alpha_g - \alpha_e) \frac{3}{2a^3} \frac{I I'}{I + I'} \frac{n^2 - 1}{n^2 + 2} \quad (5)$$

where  $\alpha_g$  and  $\alpha_e$  are caffeine polarizabilities in the ground and excited state while  $I$  and  $I'$  are the ionizing potentials in the two electronic states. Searching for the dominant types of solvent influence forces the solvent parameter functions have been compared; so the function  $(n^2 - 1)/(n^2 + 2)$  has values between 0.20 and 0.26 as well as the function  $[(n^2 - 1)/(n^2 + 2)] \cdot [(2n^2 + 1)/(n^2 + 2)]$  that belongs to 0.24 – 0.34 range in contrast to  $[(2n^2 + 1)/(n^2 + 2)] \cdot [(\varepsilon - 1)/(\varepsilon + 2)]$  that is always  $> 1.00$ . Consequently, the orientation induction force contribution to the wavenumber solvent shift could be estimated as given by the term containing the function on the solvent dielectric constant,  $\varepsilon$ , which increases with solvent polarity; dispersive interactions could be considered as additive contribution, depending mainly on the solvent refractive index,  $n$ . Accordingly, we have constructed first the graph from Fig. 7, where  $f_{\text{IB}}(n) = (2n^2 + 1)/(n^2 + 2)$  and  $f(\varepsilon) = (\varepsilon - 1)/(\varepsilon + 2)$ .

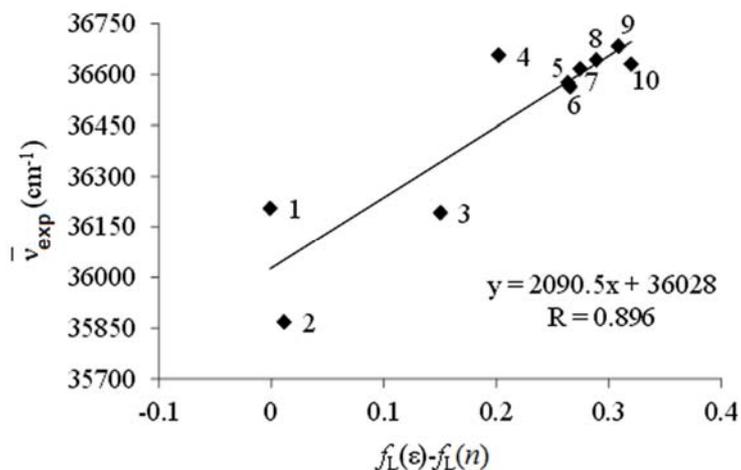


Fig. 5. Analysis of solvent shift effect on caffeine band according to Lippert-Mataga theory [5].

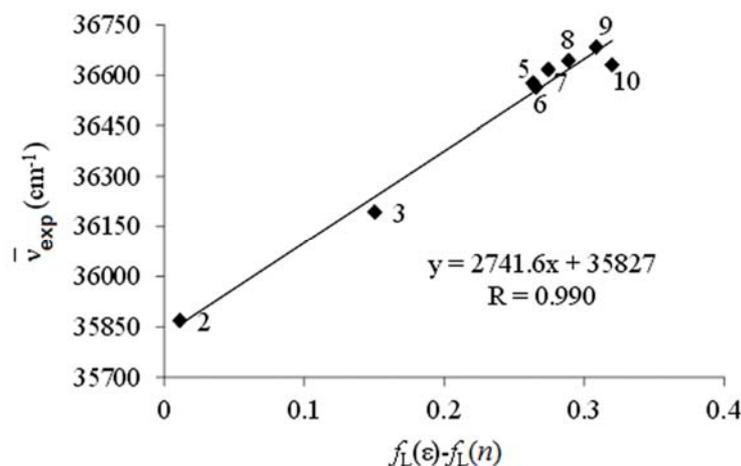


Fig. 6. Optimization of regression line approaching solvent shift effect according to Lippert-Mataga [5].

Next, two non-protic solvents – with the highest displacements (namely acetic acid and n-hexane) were taken off – since the correlation coefficient was under 0.90 – and the theoretic regression line was optimized as shown in Fig. 8. According to this theory the non-protic solvents could interact mainly by dispersion forces with the solute. The other two non-protic solvents containing chloride atoms were let further together with protic solvents based on the supposition that other intermolecular forces – except for dispersive ones – could be present in their case, namely specific interactions – that could bring them on the

protic solvent line defined for universal interactions. The very good correlation coefficient (Fig. 9) confirmed the pertinence of associating protic solvents with non-protic ones containing chloride atoms – when analyzing orientation-induction interactions, even if specific interactions like those developed by chloride are not considered in the solvatochromic theories. Practically the protic solvent capacity to develop orientation induction forces with caffeine was replaced in the case of carbon tetrachloride and chloroform by specific interactions of the same order of magnitude.

The displacement of the four non-protic solvent points (Fig. 9) raised the question about other interactions overlapped onto the orientation-induction ones. Thus the differences between the values calculated with the linear regression function  $\bar{\nu}_{\text{calc}} = 1064.3 \cdot f_{1B}(n) \cdot f_B(\epsilon) + 35462$  (Fig. 8) and the experimental values  $\bar{\nu}_{\text{exp}}$  were taken and represented *versus*  $f_{2B}(n) = (n^2 - 1)/(n^2 + 2)$  – resulting in Fig. 10 plot.

The new regression linear equation  $y = -9602.7 \cdot x + 2590.9$  allows the estimation of dispersion interaction contributions – that are dominant universal solute solvent interactions in the case of caffeine solutions in the four non-protic solvents.

To take into account caffeine orientation-induction forces together with dispersive ones for all solvents used in this study, the final calculated solvent shift was accomplished with the additive formula:

$$y = 1064.3 f_{1B}(n) f_B(\epsilon) + 35472 - 9602.7 f_{2B}(n) + 2590.9 \quad (6)$$

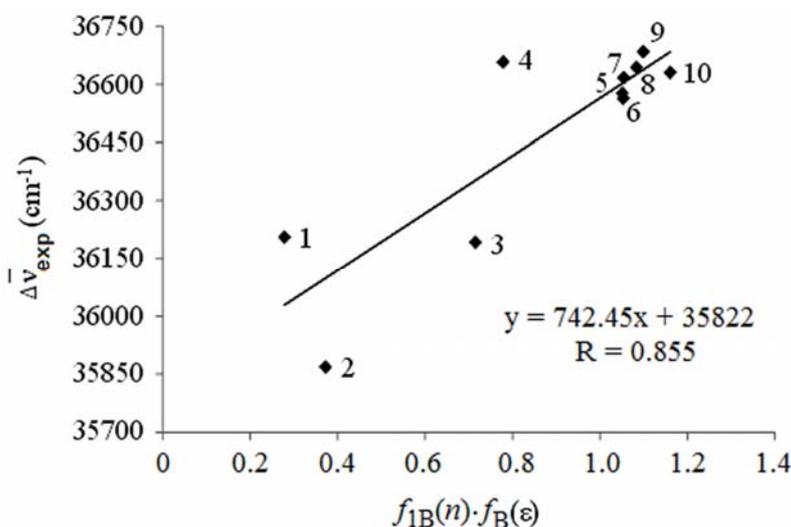


Fig. 7. Linear correlation between solvent shift of the wavenumber and Bakhshiev's function corresponding to orientation induction forces [2].

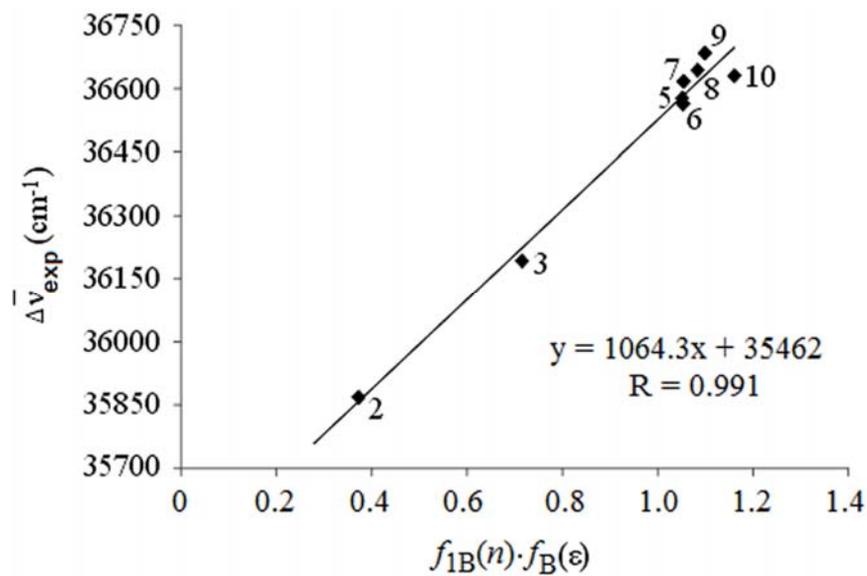


Fig. 8. Optimization of the regression approaching solvent shift effect according to Bakhshiev [2].

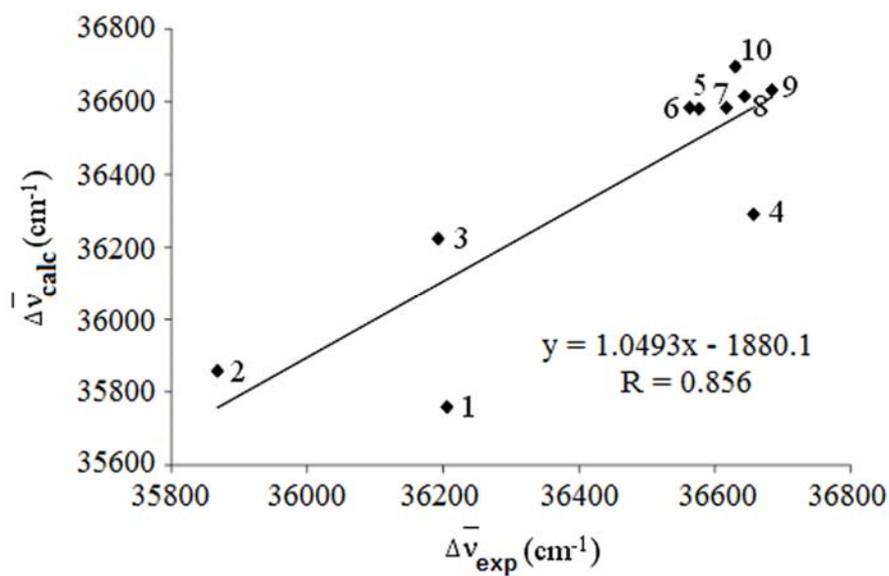


Fig. 9. Comparison of experimental solvent shift and that calculated on the basis of the supposition of orientation-induction interactions (according to the regression line from Fig. 7).

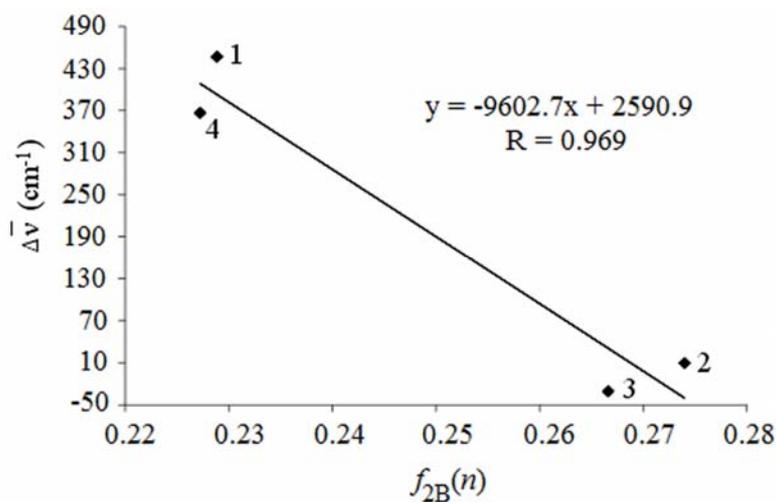


Fig. 10. Non-protic solvent investigation for dispersion interaction evidencing;  $\Delta \bar{\nu}$  is the difference between the values calculated with the linear regression function  $y = 1064.3 \cdot x + 35462$  and those experimentally acquired while  $f_{2B}(n)$  is solute-solvent dispersive interaction term in Bakhshiev's theory.

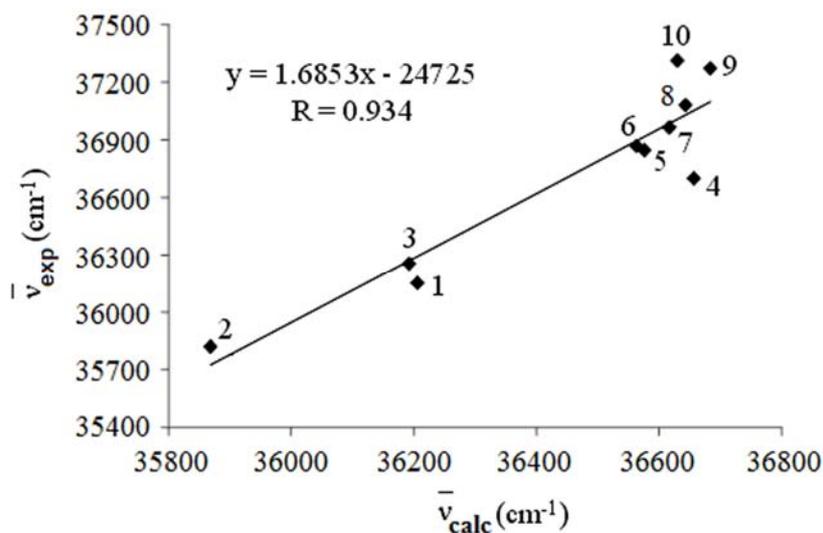


Fig. 11. Comparison of theoretical solvent shift for the caffeine band from near UV and the experimentally recorded band maximum.

In Fig. 11 the total solvent shift of the near UV band was represented *versus* experimentally recorded wavenumber in the band maximum. The non-protic solvent grouping around the regression line is accompanied by protic solvent partial displacement – and this one could be explained through the hydrogen bond

interaction with caffeine molecule – according to the data presented in Fig. 1 a (negative electric charge concentrated around oxygen and nitrogen atoms).

Now the correlation between experimental and calculated wavenumbers is reliable –  $R > 0.9$ . No correction could be proposed for the hydrogen bond interactions, specific for the protic solvent – mainly alcohols and water, containing OH groups.

## CONCLUSION

UV transparent solvents were used to record caffeine EAS and analyze solvent - solute interaction nature. This spectral analysis revealed the existence of both universal interactions (orientation, induction, dispersion) and specific, local ones like hydrogen bonds in the case of protic solvents and those specific to chloride solvents. Dipole-dipole universal intermolecular forces were found to dominate in the case of protic solvents. Caffeine dipole moment in the ground state was determined by quantum chemical modeling while in the excited state the dipole moment was estimated from solvatochromic theory. The study could be of interest for caffeine selective extraction from natural sources with solvents like those analyzed in this paper – quantitative estimation of caffeine concentration being possible with EAS recording and calibration curve. Also for analytical purposes chromatographic investigation data are needed about UV spectral behavior of caffeine solutions. Further study is planned to reveal caffeine spectral behavior in solvent mixtures.

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