QUANTUM-MECHANICAL CHARACTERIZATION AND SPECTRAL STUDY OF CURCUMIN

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Curcumin is a natural substance with anti-inflammatory, antioxidant, antiviral, anti-cancer and cholesterol reduction effects. A quantum-mechanical characterization for Curcumin tautomers was performed by using Density Function Theory (DFT) method from Spartan'14 program. The contribution of different types of interactions to spectral shifts in solutions of the studied molecule was established by solvatochromic study. The excited state dipole moments of the curcumin tautomers are estimated.

Keywords: Curcumin, quantum-mechanical characterization, solvatochromic study, excited state dipole moment.

1. Introduction

Curcumin is the active ingredient in turmeric (made from beets of Curcuma longa), a member of the ginger family (Zingiberaceae). Chemically, curcumin is a diaryl-heptanoid, belonging to the group of curcuminoids, which are natural phenols responsible for yellow color. Turmeric has been used of traditional Indian folk medicine, for the treatment of many diseases such as diabetes, liver disease, rheumatoid arthritis, atherosclerosis, infectious diseases and cancers [1].

Curcumin is the most powerful natural anti-inflammatory, antioxidant with antiviral effects, anti-cancer and cholesterol reduction substance [2]. Curcumin has been reported that reduce amyloid pathology in Alzheimer transgenic mice [3], and also that it alters the cytokine profiles [4]. Recent clinical studies reported that curcumin could be orally administered up to 12 g/day without any toxic effect in humans [5].

It is sold as an herbal supplement, cosmetics ingredient, food flavoring and food coloring or a food additive. Scientific research over more than four decades has confirmed the diverse pharmacological effects of curcumin and established its

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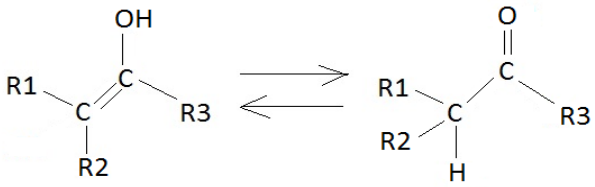
ability to act as a chemopreventive agent, as well as a potential therapeutic agent against several chronic diseases [6 - 8].

It is known that curcumin shows prototropic (keto-enol) tautomerism [9-12]. It is a tautomeric compound existing in enolic form in organic solvents and as a keto form in water. Interest about curcumin's form in solution has appeared because there is a strong relationship between the tautomeric structures and the effects on biological systems [1, 13].

There is a substantial number of theoretical studies and experimental data [14-19], showing the strong predominance of the enol–keto form in solution. In organic chemistry, keto–enol tautomerism refers to a chemical equilibrium between a keto form (a ketone or an aldehyde) and an enol (an alcohol).

In Scheme 1 are given the enol-keto tautomerism (enol form left and keto form right).



Scheme 1. Enol–keto tautomerism (enol form left; keto form right)

The aims of this study are to show some electro-optical properties of curcumin using molecular modeling; to establish the contribution of each type of interactions to the total spectral shift and to estimate the excited state's parameters from solvatochromic study.

2. Experimental details

Curcumin was purchased from Sigma–Aldrich Chemical Company and was used without further purification. The spectrally grade solvents were purchased from Merck and Sigma–Aldrich Chemical Company.

Electronic absorption spectra of curcumin were recorded in 17 solvents at room temperature with QE65000 UV-Vis Ocean-Optics Spectrometer. The statistical analysis of the solvatochromic data was performed using Origin Pro8 program.

Some theoretical properties were calculated using the Density Functional Theory [20] with basis function B3LYP/6-31G* [21] by means of the molecular modeling program, Spartan'14 [22]. The QSAR and electro-optical parameters of the studied compound obtained by this method are correlated with those obtained from the solvatochromic analysis.

The structures of curcumin tautomers optimized by Spartan'14 program are illustrated in Figs. 1a and 1b.

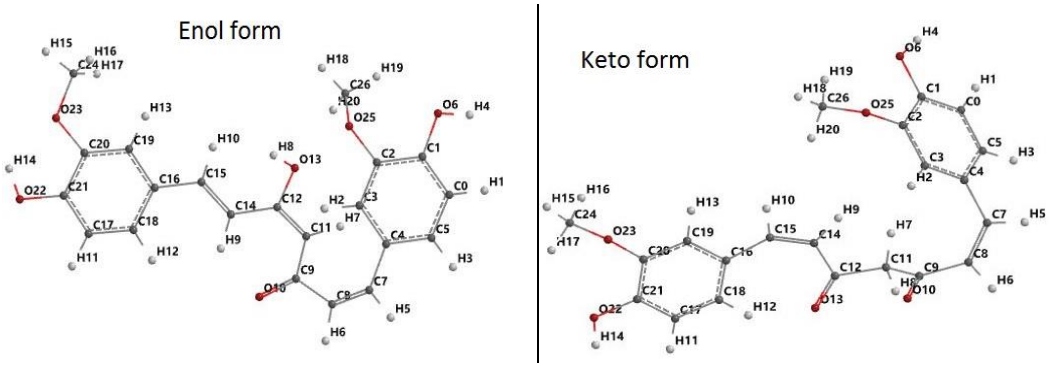


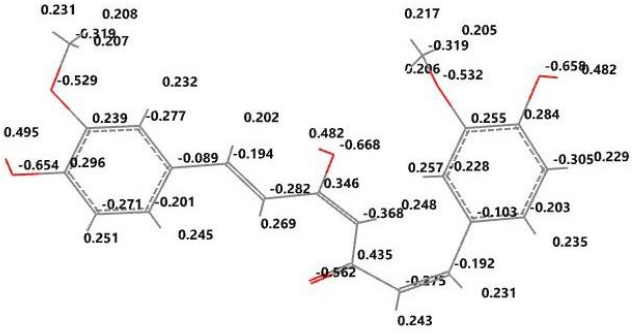
Fig. 1. Optimized structures of curcumin tautomers

The optimized structures of curcumin tautomers belong to the CS class symmetry: the molecule of this group have only one element of symmetry: the identity (E).

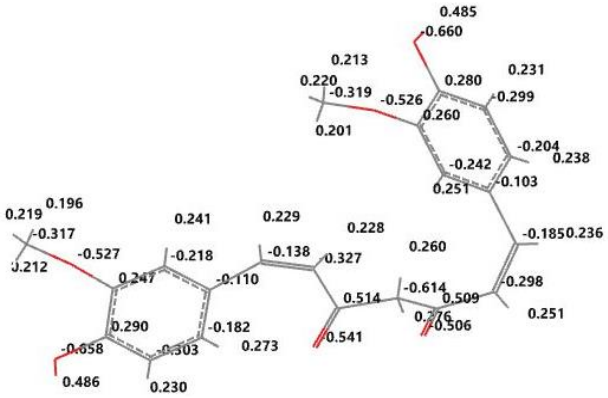
3. Results and discussions

The B3LYP basis function (Becke's three- parameter functional using the Lee-Yang-Parr correlation functional) [23] in combination with the 6-31G* basis set is used to obtain optimized structures of curcumin (Fig. 1).

The atomic charges of curcumin derivatives, computed by Spartan'14 in percents of electron elemental charge ($e = 1.6021662 \times 10^{-19}$ C) are listed in Fig. 2a for the enol form and Fig. 2b for the keto form.



a) Enol form



b) Keto form

Fig. 2. Atomic charges for curcumin tautomers

The greater negative values of atomic charges are located near O atoms.

Some properties and QSAR parameters [24] of tautomeric Curcumin was calculated by Spartan'14 program (Table 1).

Table 1.

Computed properties of Curcumin by Spartan'14

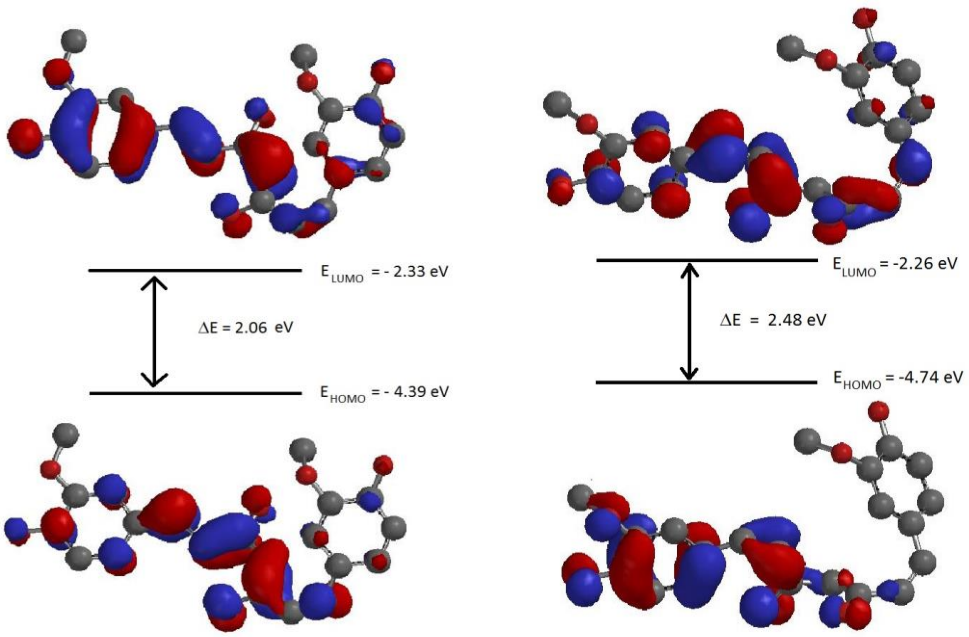
No.	Properties	Values of enol form	Values of keto form
1	Dipole moment (D)	6.35	6.19
2	Total energy (a.u)	-1263.10	-1263.10
3	Solvation Energy (kJ/mol)	-79.74	-84.77
4	E_{HOMO} (eV)	-4.39	-4.74
5	E_{LUMO} (eV)	-2.33	-2.26
6	Weight (a.m.u)	368.39	368.39
7	Area (Å^2)	403.31	403.22
8	Volume (Å^3)	379.40	380.40
9	Polar surface area (Å^2)	83.30	78.98
10	Log P	3.43	4.23
11	Polarizability	71.67	71.65
12	Enthalpy $H°$ (a.u)	-1262.71	-1262.71
13	Constant volume heat capacity C_v (J/mol)	304.41	302.74
14	Entropy $S°$ (J/mol)	623.32	622.51
15	Free energy Gibbs $G°$ (a.u)	-1262.78	-1262.78
16	$\Delta E = \lvert E_{HOMO} - E_{LUMO} \rvert$ (eV)	2.06	2.48

Positive value of log P (partition coefficient octanol / water) indicates that the compounds are lipophilic, they do not dissolve in water and the bioavailability is low. Polar surface area is defined as a sum of surfaces of polar atoms in a molecule, the values of this (less than 90 Å^2) demonstrating that the molecules penetrate the blood-brain barrier. The energy of solvation is the amount of energy

necessary for dissolving a solute in a solvent, the negative values of this showing that the dissolving process is exothermic.

The Frontier Molecular Orbitals determine the molecular chemical stability, chemical reactivity and chemical hardness–softness of a molecule, playing an important role in the optical and electric properties [25]. It is also used to determine the interaction of the molecule with the other species.

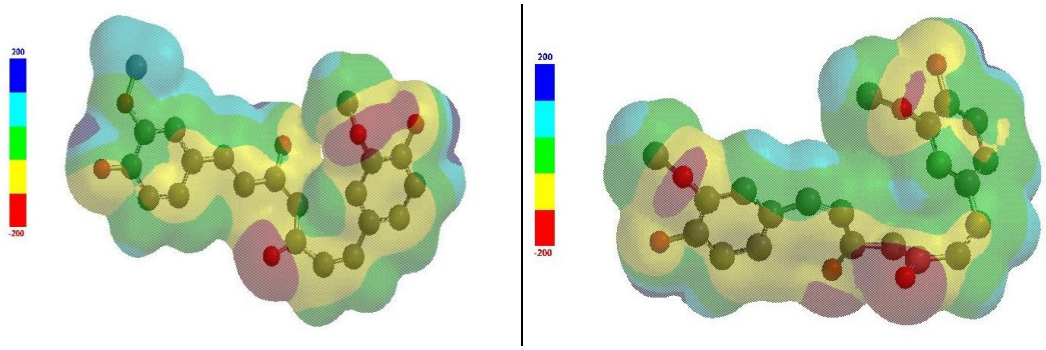
The Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) for this two tautomeric structures of Curcumin are illustrated in Figs. 3a (enol form) and 3b (keto form).



a) FMO's of enol form b) FMO's of keto form

Fig. 3. Frontier Molecular Orbitals of curcumin by Spartan'14

In Fig. 4, the surface distribution of molecular electrostatic potential is shown in order to emphasize the specific reactive regions of the molecule.



a) Enol form b) Keto form

Fig. 4. 3D-geometry of the distribution electrostatic potential of Curcumin tautomers

The 3D-dimensional geometry of molecular electrostatic potential distribution highlights the existence of four regions with increased electronegativity in which oxygen atoms are involved and that play a role in their coupling to different structures in which ions are positively charged.

A multilinear dependence of the type (1) was used in order to decide which interaction has a larger contribution on the spectral shifts of Curcumin measured in the solvents:

$$\upsilon_{calc.} = \upsilon_0 + C_1 f(n) + C_2 f(\varepsilon) + C_3\alpha + C_4\beta \quad (1)$$

The Kamlet and Taft solvent parameters used in LSER [26, 27], the wavenumbers of electronic absorption spectra, the polarizability function and the polarity function are given in Table 2. The hydrogen bond donor acidity of the solvent is given by the parameter α, β being the hydrogen bond acceptor basicity of the solvent, while the polarizability function $f(n) = \frac{n^2-1}{n^2+2}$ and the solvent polarity function $f(\varepsilon) = \frac{\varepsilon-1}{\varepsilon+2}$ are described by the refractive index n and the electric permittivity ε.

Table 2.

Kamlet and Taft solvent parameters used in LSER, the wavenumbers of electronic absorption spectra, the polarizability function and the polarity function

No.	Solvent	ν (cm^{-1})	*f(n)*	*f(ε)*	*α*	*β*
1	1-Butanol	23384.15	0.237	0.833	0.84	0.84
2	1-Hexanol	23384.15	0.252	0.839	0.8	0.84
3	1-Pentanol	23426.34	0.248	0.825	0.8	0.84
4	1-Propanol	23554.35	0.234	0.866	0.84	0.9
5	2-Butanol	23426.34	0.24	0.852	0.69	0.8
6	2-Propanol	23554.35	0.23	0.849	0.76	0.84
7	Acetonitrile	24080.72	0.212	0.924	0.19	0.4
8	Water	23300.25	0.206	0.964	1.17	0.47

9	Benzyl alcohol	23133.69	0.313	0.804	0.6	0.52
10	1,4-Dioxane	23946.93	0.255	0.289	0	0.37
11	DMF	23342.13	0.258	0.925	0	0.69
12	DMSO	23216.4	0.283	0.939	0	0.76
13	Ethanol	23640.66	0.221	0.895	0.86	0.75
14	Ethyl acetate	24125.45	0.227	0.628	0	0.45
15	Ethylene glycol	23257.98	0.259	0.93	0.9	0.52
16	Formamide	23426.34	0.271	0.973	0.71	0.48
17	Methanol	23858.38	0.203	0.909	0.98	0.66

The characteristics of the multiple linear regressions (1), for the absorption and the fluorescence spectra are listed in Table 3.

Table 3.

Regression coefficients v_0, C_1, C_2, C_3, C_4 and their standard error, correlation coefficient R, standard deviation SD, number of validated points N

Multiple linear regression characteristics of Curcumin solutions							
$v_0 \pm \Delta v_0$	$C_1 \pm \Delta C_1$	$C_2 \pm \Delta C_2$	$C_3 \pm \Delta C_3$	$C_4 \pm \Delta C_4$	R	SD	N
26808.27± 305.46	-9542.15± 1048.70	-610.36± 199.32	-329.41± 87.52	-382.68± 169.30	0.88	113.15	17

A good correlation between the parameters from Eq. 10 is observed (correlation coefficient $R > 0.88$). Spectral shifts toward to red by passing the studied molecule from gas phase to liquid phase in the solvents from Table 2 were recorded (see the negative values of the coefficients C_1, C_2 and C_3 from Table 3).

There is a good linear correlation between the calculated and experimental values of the wavenumbers in the maximum of the visible band of curcumin Fig. 5 (R=0.91, SD = 96.65 with intercept = 2067.68 and slope = 0.91).

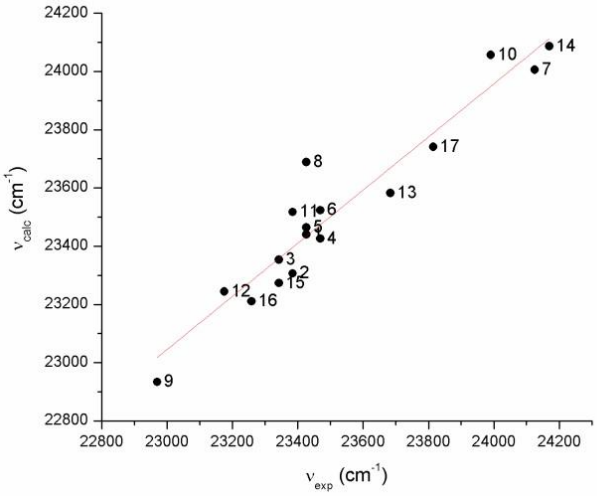


Fig. 5. $\bar{\upsilon}_{calc}$ (cm^{-1}) vs. $\bar{\upsilon}_{exp}$ (cm^{-1}); the numbers reffer to the positions of the solvents

The contribution of different types of interactions to spectral shifts in solutions of the studied molecule was established by solvatochromic study. The contribution of each type of interaction to the total spectral shift (in percentage %) is provided in Table 4.

Table 4.

The contribution of each type of interaction to the total spectral shift (in %)

	Solvent	C_1 $f(n)$ (%)	C_2 $f(\varepsilon)$ (%)	C_3 α (%)	C_4 β (%)
1	1-Butanol	67.14	15.10	8.22	9.54
2	1-Hexanol	68.67	14.62	7.53	9.18
3	1-Pentanol	68.49	14.57	7.63	9.30
4	1-Propanol	66.01	15.63	8.18	10.18
5	2-Butanol	68.49	15.55	6.80	9.16
6	2-Propanol	66.82	15.78	7.62	9.79
7	Acetonitrile	72.18	20.12	2.23	5.46
8	Water	63.02	18.86	12.36	5.77
9	Benzyl alcohol	77.09	12.67	5.10	5.14
10	1,4-Dioxane	88.44	6.41	0	5.15
11	DMF	74.82	17.16	0	8.02
12	DMSO	75.76	16.08	0	8.16
13	Ethanol	65.38	16.94	8.78	8.90
14	Ethyl acetate	79.59	14.08	0	6.33
15	Ethylene glycol	69.92	16.06	8.39	5.63
16	Formamide	71.88	16.51	6.50	5.11
17	Methanol	63.15	18.09	10.52	8.23

The spectral shifts are due to the universal interactions (polarization, dispersion, orientation-induction interactions) in absorption as one can see in Table 4.

The regression coefficients C_1 and C_2 from Eq. (1) depend on the microscopic parameters of the solute molecule [28] as it follows:

$$C_1 = \frac{2\mu_g(\mu_g - \mu_e\cos\varphi)}{hca^3} + 3kT\frac{\alpha_g - \alpha_e}{a^3} \tag{2}$$

$$C_2 = \frac{\mu_g^2 - \mu_e^2}{hca^3} - \frac{2\mu_g(\mu_g - \mu_e\cos\varphi)}{hca^3} - 3kT\frac{\alpha_g - \alpha_e}{a^3} + \frac{3}{2}\frac{\alpha_g - \alpha_e}{a^3}\frac{I_u I_v}{I_u + I_v} \tag{3}$$

Equations (2) and (3) allow estimating the dipole moment and the polarizability of the spectrally active molecule in its excited states.

By summing (2) and (3), it results Eq. (4):

$$C_1 + C_2 = \frac{\mu_g^2 - \mu_e^2}{hca^3} + \frac{2}{3}\frac{\alpha_g - \alpha_e}{a^3}\frac{I_u I_v}{I_u + I_v} \tag{4}$$

The molecular radius a can be computed by using the values of volume and surface area in ground state of the respective molecule (for two tautomers).

The following notations were made in Eqs. (2) – (4): μ_g and μ_e are the dipole moments of the molecule in the ground and excited states, respectively, φ is the angle between them, α_g and α_e are the polarizabilities of the molecule in its ground and excited states, respectively, a is the radius of the molecule, h is the Planck's constant, k is the Boltzmann's constant, T is the absolute temperature, I_u is the solute molecule's ionization potential and I_v is the solvent's ionization potential.

The polarizability in the excited state of spectrally active molecule can be expressed by Eqs. (5), as it results from (4). The data from Table 4 (for *C1* and *C2*) and Table 2 (for α_g and I_g of the solute) were used in order to estimate the excited state polarizability.

$$\left.\begin{aligned} \alpha_e &= 83.39305 - 0.13698\,\mu_e^2 \quad \text{enol} \\ \alpha_e &= 82.57466 - 0.12999\,\mu_e^2 \quad \text{keto} \end{aligned}\right\} \qquad \begin{matrix} (5a) \\ (5b) \end{matrix}$$

By substituting Eqs. (5) in equation (2) one obtains:

$$\left.\begin{aligned} 0.000739\,\mu_e^{\,2} - 0.56511\,\mu_e \cos\varphi + 5.42036 &= 0 \quad \text{enol} \\ 0.000695\,\mu_e^{\,2} - 0.54622\,\mu_e \cos\varphi + 5.21813 &= 0 \quad \text{keto} \end{aligned}\right\} \qquad \begin{matrix} (6a) \\ (6b) \end{matrix}$$

In order to obtain real solutions of equation (6), its discriminant must be positive.

$$\left.\begin{aligned} \Delta_{enol} &= (0.56511 \cdot \cos\varphi)^2 - 4 \times 0.000739 \times 5.42036 \geq 0 \\ \Delta_{keto} &= (0.54622 \cdot \cos\varphi)^2 - 4 \times 0.000695 \times 5.21813 \geq 0 \end{aligned}\right\} \qquad \begin{matrix} (7a) \\ (7b) \end{matrix}$$

It results that the angle φ must satisfy the inequality: $\varphi < 77.05°$ for enol form and
$\varphi < 77.83°$ for keto form.

The angle is $\varphi \leq 75°$ and the acceptable values of the dipole moment in the excited state are: $9 \leq \mu_e \leq 49$ D, when the angle φ varies between $0 \leq \varphi \leq 75$ degrees.

4. Conclusions

The quantum-mechanical study of Curcumin tautomers demonstrates that: the molecule is lipophilic compound, the values of polar surface aria show that the molecule can penetrate the cell membranes and the blood-brain barrier, the dissolving process is exothermic. The universal interactions of the dispersive type $C_1\ f(n)$ are prevalent in Curcumin solutions. The bathochromic shift of the electronic absorption band of Curcumin proves the increase in the molecular dipole moment by excitation.

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