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Spectral-luminescent and solvatochromic properties of anticancer drug camptothecin

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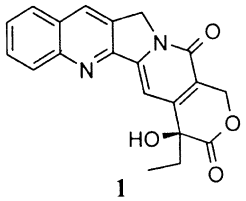
Abstract

The spectral characteristics of camptothecin have been investigated in solvents of various polarity and proton donating ability. The effect of the solvent on the spectral characteristics and the dipole moment in the excited state have been estimated. Different theoretical approaches have been compared in order to estimate the excited-state dipole moment. It has been shown that camptothecin's emission is very sensitive to quenching with Co^{2+} ions.

Keywords: Camptothecin; Solvatochromism; Dipolar moments; Fluorescence quenching

1. Introduction

(+)-Camptothecin (CPT, **1**) is a pentacyclic alkaloid isolated and characterized by Wall et al. [1,2] and Wall and Wani [3] in 1966 from *Camptotheca acuminata* and shown to exhibit potent cytotoxic activity against a range of tumor cell lines. Therefore, camptothecin has been the subject of extensive research especially for the design of water soluble derivatives [4–11], and more recently, stable lactone analogues [12–16]. At physiological pH, the lactone is easily hydrolysed to the biologically inactive carboxylate, which binds to human serum albumin, lowering the effective concentration of CPT [17–20]. This facile hydrolysis of the lactone represents a challenging problem and its labile nature has been attributed to the α-hydroxy group which is believed to accelerate the hydrolysis through intramolecular hydrogen bonding [14,21]. Although numerous analogues of CPT containing modifications in the lactone ring have been prepared, none have proven to be as active as CPT itself.



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Another way to solve the problem of lactone ring moiety instabilitity was proposed by Birke at al. [18]. They proposed to use liposomal stabilisation of camptothecin lactone ring. In the work [18], it was demonstrated that liposome-bound camptothecin is stable, so suggesting that liposomes may serve as useful drug delivery systems for solubilizing camptothecin and conserving both its lactone ring and antitumor activity.

The fact that liposome-associated camptothecin is stable suggests that the drug's lactone ring penetrates into the bilayer. Two types of spectroscopic data could be used to support this notion. This first type of evidence could come from shifting of drug's emission spectrum observed upon association with membrane. Such a spectral shift is indicative of a change in the dielectric constant of the medium surrounding the fluorophore, as when a compound leaves an aqueous environment and intercalates in between the lipid acyl chains.

Additional evidence that camptothecin's fluorochrome penetrates into the lipid bilayer could come from quenching data. Fluorescence quenching by iodide was studied by Burke et al. [18] and Burke and Tritton [21]. Camptothecin, free in solution, was quenched readily by iodide, when the drug was bounded to DMPC membranes the quenching was decreased. Membrane-bound drug was much less accessible to quenching by iodide, presumably because the fluorochrome locates deep with the bilayer.

In order to give an interpretation to these spectroscopic data, a detailed steady-state photophysical study of camptothecin appears to be necessary.

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The aim of the present paper is to follow the influence of polarity and proton-donating ability of the solvents on the characteristics of camptothecin electronic spectra and to study the quenching data of camptothecin with electron acceptor Co^{2+} ions. Dipole moment determination and quantum-chemical calculations are carried out to estimate the changes in the π-electron distribution in ground and in fluorescence excited state.

2. Experimental details

2.1. Materials

The separation, identification and purification of camptothecin were described earlier [22]. The organic solvents used were all of spectrophotometric grade and were used as supplied from Fluka. The cobalt salt ($CoCl_2 \cdot 6H_2O$) used in quenching experiments was purchased from Merck. Quinine sulfate used as fluorescence standard for quantum yield determination was purchased from Fluka.

2.2. Spectroscopic measurements

The electronic absorption spectra were measured using Jasco V-530 UV-Vis spectrophotometer. Fluorescence emission spectra were recorded on PTI-QM1 fluorescence spectrophotometer. Fluorescence quantum yields were with reference to the absorption and fluorescence spectra of quinine sulfate in 0.5 M H_2SO_4 solution ($\varphi_f = 0.546$) [23,24]. The calculated relative fluorescence quantum yields were the values corrected for refraction index differences between the measured and standard solutions [25]. The equation, used in calculations of fluorescence quantum yields is:

$$\varphi_{fU} = \varphi_{fR} \frac{S_U}{S_R} \frac{(1 - 10^{-D_R})}{(1 - 10^{-D_U})} \frac{n_U^2}{n_R^2} \quad (1)$$

where φ_f is the quantum yield, D the absorbance on the excitation wavelength, S the integrated emission band area, n the solvent refractive index, U and R refer to the unknown and reference (standard), respectively. All fluorescence measurements were conducted for dilute solutions in absorbance range of 0.1–0.15 at the excitation wavelength (concentrations, 10^{-5} to 10^{-6} mol dm^{-3}).

The fluorescence quenching measurements were monitored using PTI-QM1 spectrometer.

2.3. Fluorescence quenching measurements

The quenching constants k_q were calculated by means of Stern–Volmer relation [26,27]:

$$\frac{I}{I_0} = 1 + k_q \tau_f [Q] \quad (2)$$

where I_0 and I represent the fluorescence intensity of the fluorophore in the absence and presence of quencher molecules of concentration $[Q]$, τ_f is the radiative lifetime in the absence of the quencher. Fluorescence lifetime τ_f of camptothecin without quenchers in water solution was reported by Burke et al. [18] to be 4.2 ns.

Quenching of camptothecin fluorescence emission with Co^{2+} ions in water solution was studied at increasing concentration of cobalt ions ($CoCl_2$). Co^{2+} concentration range was (0–1.2) × 10^{-2} M.

2.4. Theoretical calculations

Semiempirical calculations were performed using the original parameters of the program AM1 [28] based on the restricted Hartree–Fock (RMF). This method is included in MOPAC version 6.0 [29] and is commonly accepted to allow a better description of the lone-pair–lone-pair repulsion in several compounds [30].

Geometries for ground and excited states were optimized in internal coordinates. The calculations were carried out with full geometry optimization without any assumption of symmetry.

Mulliken population analyses [31] charges used to discuss the electron distributions and dipolar moments.

2.5. Dipole moments determinations

In order to determine the excited-state dipole moments by the solvatochromic method a few approaches were used:

(a) Lippert–Mataga equation [32]:

$$\upsilon_A - \upsilon_F = \frac{2(\mu_e - \mu_g)^2}{hca_0^3} \left[\frac{\varepsilon - 1}{2\varepsilon + 1} - \frac{n^2 - 1}{2n^2 + 1} \right] \quad (3)$$

(b) Bakhshiev's formula [33]:

$$\upsilon_A - \upsilon_F = \frac{2(\mu_e - \mu_g)^2}{hca_0^3} \left[\frac{\varepsilon - 1}{\varepsilon + 2} - \frac{n^2 - 1}{n^2 + 2} \right] \frac{2n^2 + 1}{n^2 + 2} \quad (4)$$

(c) Suppan approach [34]:

$$\frac{\mu_e}{\mu_g} = \frac{(\upsilon_f)_1 - (\upsilon_f)_2}{(\upsilon_a)_1 - (\upsilon_a)_2} \quad (5)$$

where $(\upsilon_f)_1 - (\upsilon_f)_2$ and $(\upsilon_a)_1 - (\upsilon_a)_2$ the differences in emission and absorption maximum in wavenumbers between two solvents.

(d) Bakhshiev's modification of the method of spectral shifts [35–37]:

$$\upsilon_s = C_2 \left(\frac{2n^2 + 1}{n^2 + 2} \frac{\varepsilon - 1}{\varepsilon + 2} + p_s \frac{n^2 - 1}{n^2 + 2} \right) + \upsilon_s^0 \quad (6)$$

$$\Delta\upsilon_{af} = \Delta C_{af} \left(\frac{2n^2 + 1}{n^2 + 2} \left[\frac{\varepsilon - 1}{\varepsilon + 2} - \frac{n^2 - 1}{n^2 + 2} \right] + p_{af} \frac{n^2 - 1}{n^2 + 2} \right) + \Delta\upsilon_{af}^0 \quad (7)$$

$$\mu_E = \sqrt{\mu_G^2 - C_2 hca^3} \quad (8)$$

$$\Delta\mu = \sqrt{0.5\Delta C_{af} hca^3} \quad (9)$$

$$\cos\theta = \frac{1}{2\mu_G\mu_E}\left[(\mu_G^2 + \mu_E^2) - \frac{\Delta C_{af}}{2C_2}(\mu_G^2 - \mu_E^2)\right] \quad (10)$$

where ν_A and ν_F are the wavenumbers (cm^{-1}) of the absorption and emission maxima, respectively; μ_g and μ_e the permanent dipole moments in the ground and first excited states, respectively; a_0 is the Onsager cavity radius; ε the dielectric constant; n the solvent refractive index; h the Plank's constant and c the speed of light; ν_s half sum of the emission and absorption maxima: $\nu_s = (\nu_F + \nu_A)/2$; $\Delta\nu_{af}$ the difference between absorption and emission maxima in wavenumbers (i.e. Stokes shift); C and p with corresponded indices depending on deformational solute polarizability; ν_0 (with corresponded indices) are the constants'-values, attiributed to the spectral parameters in gas-phase; $\Delta\mu$ the vector difference between μ_e and μ_g; θ the angle between the ground- and excited-state dipole moment vectors.

3. Results and discussions

3.1. Absorption and emission properties

3.1.1. Absorption

In Table 1, the absorption wavelengths are presented. Fig. 1 shows the absorption spectra of camptothecin in various solvents with different polarity and photon donating-ability.

Absorption spectra in the region 200–420 nm consist of four bands of π–π* nature. As in the case of quinoline [38], the n–π* absorption band of camptothecin is hidden by the intense long-wavelength π–π* band. By the growth of solvent polarity, short-wavelength shifts in the absorption maxima are observed (up to 11 nm, Fig. 2). This fact points out that dipole moment of camptothecin at excited state is lower than the corresponding dipole moment in ground state: increasing solvent polarity stabilizes the ground state to a greater degree than the electronically excited state and, the absorption spectrum tends to shift to shorter wavelength with the increasing solvent polarity [39]. The largest blue (short-wavelength) shifts of long-wavelength absorption maxima are observed in proton-donating solvents, such as *iso*-propanol, methanol, water (see Table 1 and Fig. 1). Taking into account that, according to quantum chemical calculations (see Fig. 3), electronic density redistributes from carbonyl group to quinoline moiety on excitation, one could explain the additional blue shifts of long-wavelength absorption maxima of camptothecin in proton donating solvents by interaction of hydrogen-bond donor solvents with unshared valence electron pairs of carbonyl group. The latter is charge donor in the excited state. This interaction prevents the charge transfer from the carbonyl group to quinoline moiety in an excited state and, consequently destabilizes the charge-transfer excited state relative to the ground state, so that the absorption spectra tend to shift to higher energies with increasing hydrogen-bond donor capacity of the solvent [39].

3.1.2. Fluorescence

Fluorescence of camptothecin is associated with the extended conjugation of the quinoline ring system (Fig. 1). The fluorescence emission spectra of camptothecin consist of only one wide fluorescent band in all the solvents used (see Table 2 and Fig. 4) and are the mirror image of corresponding absorption spectra. The fluorescence spectra are independent of the excitation wavelength and have a clear vibronic structure in non-polar solvents (Fig. 4).

In contrast to the absorption spectra, the wavelengths of fluorescence bands are not much affected by change in the solvent polarity and/or the hydrogen-bonding ability (Table 2 and Fig. 4). This could be explained by the fact that despite the qualitative similarity of solvent polarity

Table 1
UV-Vis spectroscopic data[a] of camptothecin in solvents with different polarities and hydrogen-bonding abilities

Solvent	ε	λ^1_{abs} (shoulder)	λ^2_{abs}	λ^3_{abs} (shoulder)	λ^4_{abs}	λ^5_{abs}	λ^6_{abs}
Tetrachloromethane	2.2	388	370	335	290	–	–
Benzene	2.3	387	369	336	–	–	–
Toluene	2.4	387	369	336	–	–	–
Dichloromethane	3.9	381	364	335	287	254	230
Chloroform	4.7	380	363	336	289	256	244
Ethyl acetate	6.0	380	363	336	289	254	–
Tetrahydrofuran	7.6	380	365	335	290	254	247
iso-Propanol	18.3	373	358	335	288	253	218
Acetone	20.7	379	364	333	–	–	–
Methanol	32.6	370	358	333	288	253	220
Benzonitrile	25.2	379	364	–	–	–	–
Acetonitrile	36.2	377	362	333	287	253	223
Dimethylformamide	36.7	377	362	334	–	–	–
Water (PBS-buffer)	78.3	369	354	336	287	253	218

[a] Here, ε is dielectric permeability of the solvent; and λ^{1-6}_{abs} are the positions of the maxima in the absorption spectra (nm).

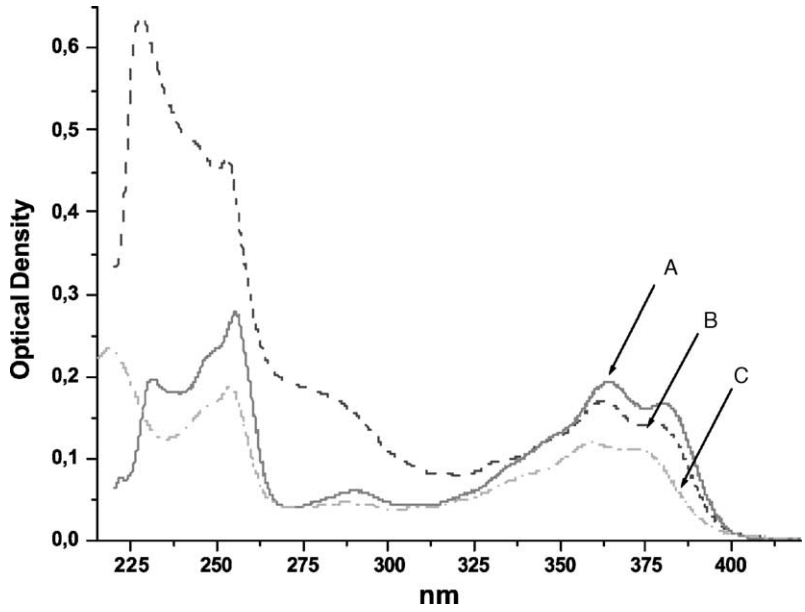

Fig. 1. Absorption spectra of camptothecin in: (A) dichloromethane, (B) acetonitrile, and (C) *iso*-propanol.

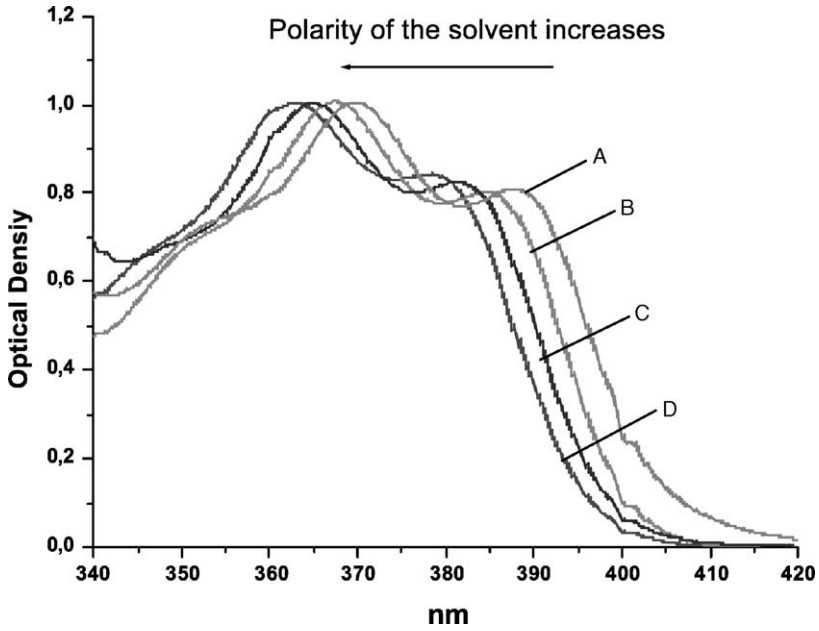

Fig. 2. Solvatochromic shift of camptothecin absorption spectra with grows of solvent polarity: (A) toluene, (B) tetrahydrofuran, (C) acetone, and (D) acetonitrile.

and hydrogen-bonding electrostatic influence upon fluorescence and absorption spectra, the relaxation processes occurring subsequent to the absorption and fluorescence, tend to shift fluorescence to longer wavelength with an increase in solvent polarity and hydrogen-bonding capacity [39]. As a result, the emission bands of camptothecin was practically not shifted with the increase in solvent polarity or proticity, while the absorption bands clearly shifted to shorter wavelength by the same solvent effects.

As it can be seen from the data cited in Table 2 that camptothecin has relatively high (in comparison with quinoline [38]) fluorescence quantum yields, $\varphi_f = 0.34$–0.76, which increase with solvent polarity. This fact indicates the absence of any serious deactivating influence of the n–π^* states of quinoline ring and the n–π^* states of the carbonyl group on the spectral-luminescence characteristics of camptothecin.

Evidently, the triplet levels of n–π^*, localized on the carbonyl group lie at considerably greater energy than the

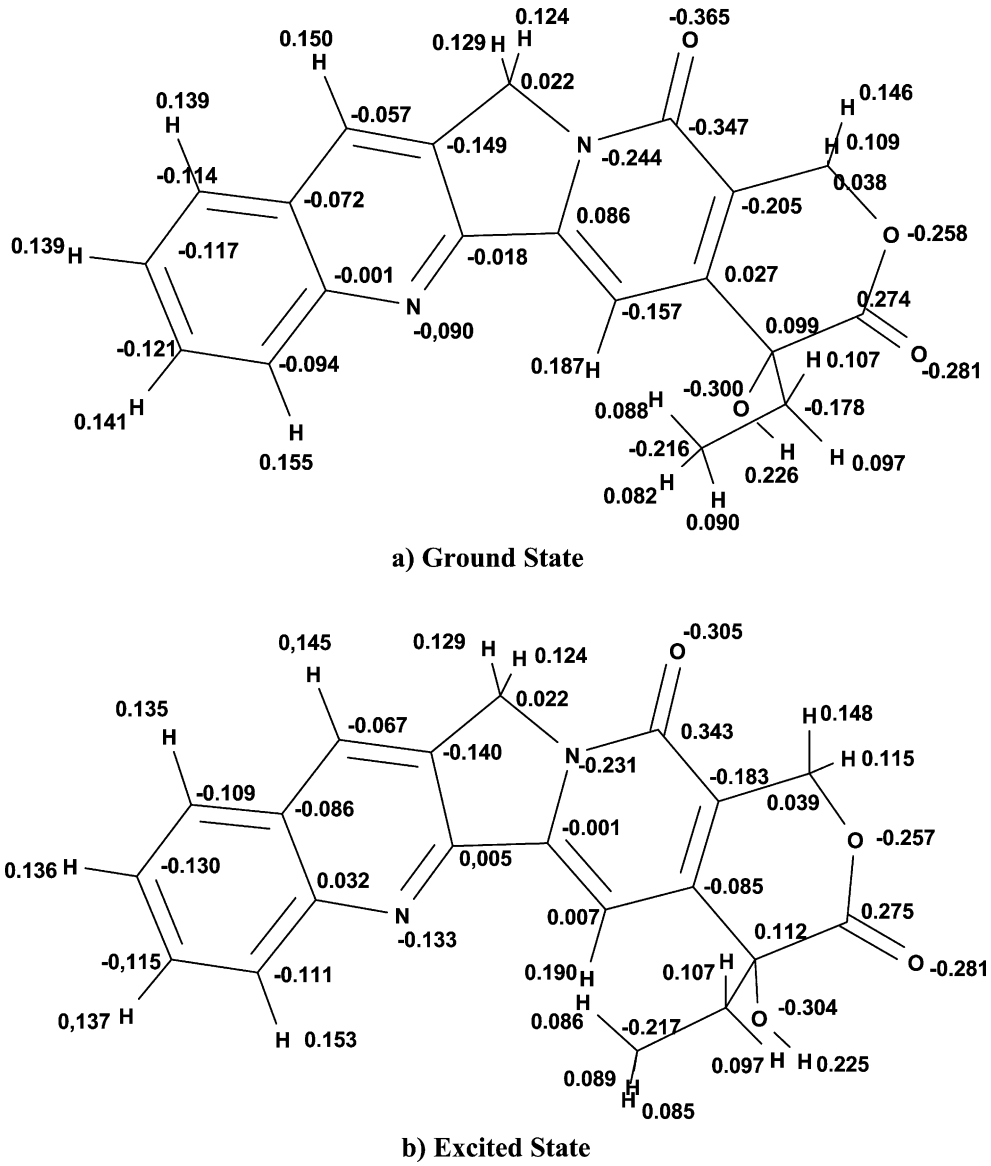

Fig. 3. Calculated charge distribution in: (a) S_0 and (b) S_1 electronic state of camptothecin.

lower singlet state of camptothecin and intersystem conversion may not occur concurrently with fluorescence at room temperature. It is possible, that the efficiency of intersystem conversion in conditions of thermal activation would be increased, leading to decrease of quantum yield, however, a detailed study of this fact is outside the realms of current work.

Another factor may influence the observed high fluorescence intensity of camptothecin, is the existence of a strained five-membered ring. The fluorescence intensities of quinolines with condensed alicyclic groups, are found to be depending on the number of methylene groups in the neighboring ring [40]. The more strained five-membered rings hinder the n–π* transition of quinoline, whereby the energy of the latter increases and the fluorescence become more intense in comparison with the quinoline or six-membered ring condensed structure [40].

As shown in the experiments with quinoline, *iso*-quinoline, phenantridine, and 5,6-benzoquinoline, the solvent may not only change the arrangement of the singlet n–π* and π–π* levels, but also promotes the vibrational spin–orbital interaction between the lowest $S_{\pi-\pi^*}$ and the higher $S_{n-\pi^*}$ level with subsequent transition to the triplet level. This vibrational interaction is more probable in hydrocarbon solvents. In protic solvents, such interaction is insignificant, and as a result the fluorescence intensity is higher [41]. This fact may be the cause of increase in the fluorescence quantum yield of camptothecin with increase of solvent polarity and/or proton donating ability (see Table 2).

Table 2
Spectral-luminescent characteristics[a] of camptothecin in solvents of varying solvent polarities and hydrogen-bonding abilities

Solvent	ε	n	λ_f	$\Delta\lambda_{ST}$	φ_f
Tetrachloromethane	2.24	1.4574	424	37	0.34
Benzene	2.28	1.5011	424	37	0.56
Toluene	2.38	1.4961	424	43	0.57
Dichloromethane	3.90	1.4242	420	40	0.57
Chloroform	4.70	1.4459	420	40	0.61
Ethyl acetate	6.02	1.3723	422	42	0.59
Tetrahydrofuran	7.6	1.4076	422	42	0.62
Iso-propanol	18.3	1.3747	420	47	0.62
Acetone	20.74	1.3588	423	44	0.63
Methanol	32.63	1.3286	421	51	0.62
Benzonitrile	25.2	1.5289	422	43	0.64
Acetonitrile	36.2	1.3441	420	43	0.69
Dimethylformamide	36.7	1.4303	420	43	0.72
Water (PBS-buffer)	78.3	1.3333	420	51	0.76

[a] Here ε and n are the dielectric permeability and refractive index of the solvent; λ_f and $\Delta\lambda_{ST}$ the positions of the maxima in the fluorescence spectra (nm) and the Stokes shift of the fluorescence (nm), respectively; and φ_f is the quantum yield of fluorescence.

3.1.3. Fluorescence quenching

We examined the behavior of camptothecin molecule towards the Co^{2+} ions, for monitoring the camptothecin in biologically-oriented energy and charge transfer studies.

The Stern–Volmer plot for camptothecin quenching by Co^{2+} ions (see Fig. 5) yielded a quenching rate of $1.53 \times 10^{10}\,(M\,s)^{-1}$.

The calculated quenching rates for camtothecine–Co^{2+} pair is of diffusion limit ($\sim 10^{10}\,(M\,s)^{-1}$) and comparable to the quenching rate $k_q \sim 1.05 \times 10^{10}\,(M\,s)^{-1}$, found for the quenching of camptothecin by iodide ions in PBS buffer [21].

Table 3
Dipole moments, calculated by different approaches

Approach (formula)	a_0	μ_g	$\Delta\mu = \mu_g - \mu_e$	μ_e	θ
AM1 calculations	6.14[a]	6.945[a]	2.067	4.878	9
Lippert–Mataga (formula (3))	6.14[a]	6.945[a]	6.296	0.649	–
Bakhshiev (formula (4))	6.14[a]	6.945[a]	3.691	3.253	–
Suppon (formula (5))	–	6.945[a]	4.752	2.193	–
Bakhshiev modification (formulas (6)–(10))	6.14[a]	6.945[a]	3.767	5.051	32

Here, values of ground-state (μ_g) and excited-state (μ_e) dipole moments are in Debye; value of Onsager radius a_0 is in Å; θ the angle between ground- and excited-state dipole moment vectors is in degrees.
[a] Calculated by AM1 method.

3.2. Excited-state dipole moment

A few approaches were used to estimate excited-state dipole moment of camptothecin (see Table 3). Three of them, (formula of Lippert–Mataga (formula (3); see Fig. 6a), Bakshiev's solvatochromic method (formula (4); see Fig. 6b), and Suppon method (formula (5)), where an assumption have been made that the vector of ground-state dipole moment co-linear to the vector of excited-state dipole moment. By contrast, Baksihiev's modification of the method of spectral shifts (formulas (6)–(10)) takes into account the angle between the ground- and excited-states dipole moment vectors.

The molecular parameters required to estimate excited-state dipole moment (radius of Onsager cavity (~6.14 Å) and the ground-state dipole moment μ_g (~6.9 D)) were determined in the AM1 approximation (see Fig. 7) [28].

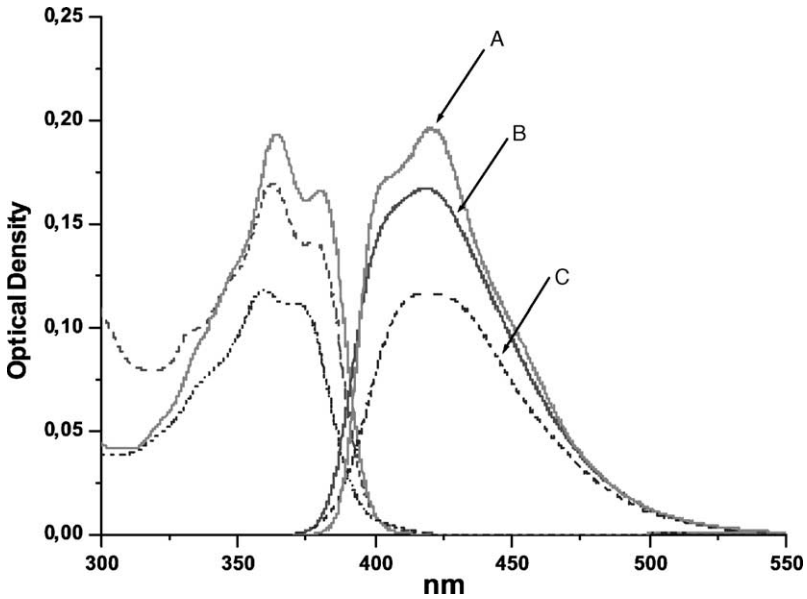

Fig. 4. Absorption and fluorescence spectra of camptothecin in: (A) dichloromethane, (B) acetonitrile, and (C) *iso*-propanol.

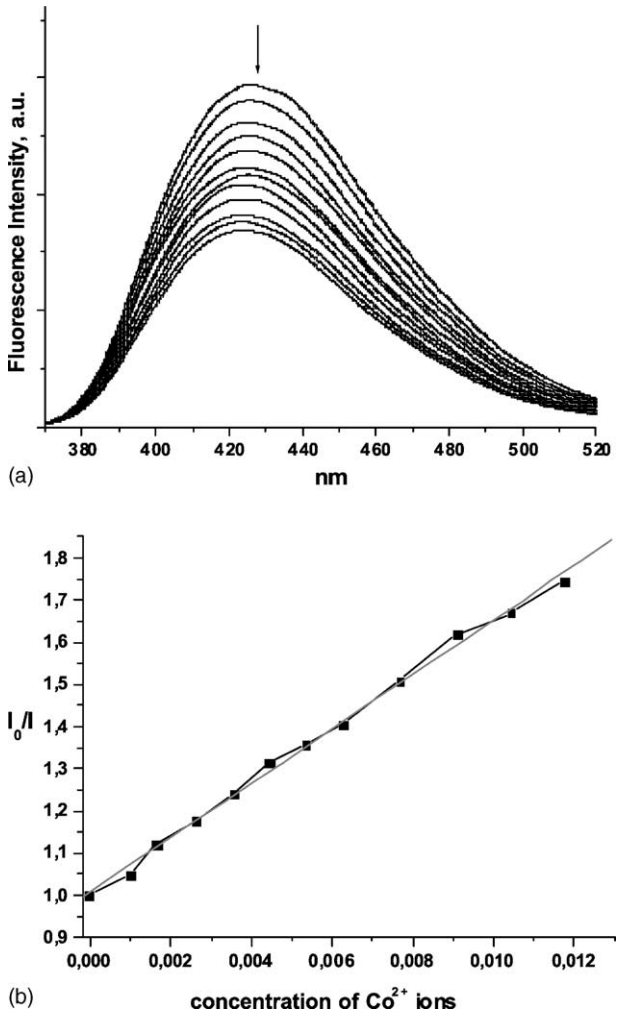

Fig. 5. Fluorescence emission quenching of camptothecin in: (a) the water solution with increasing Co^{2+} concentration and (b) corresponding Stern–Volmer plot.

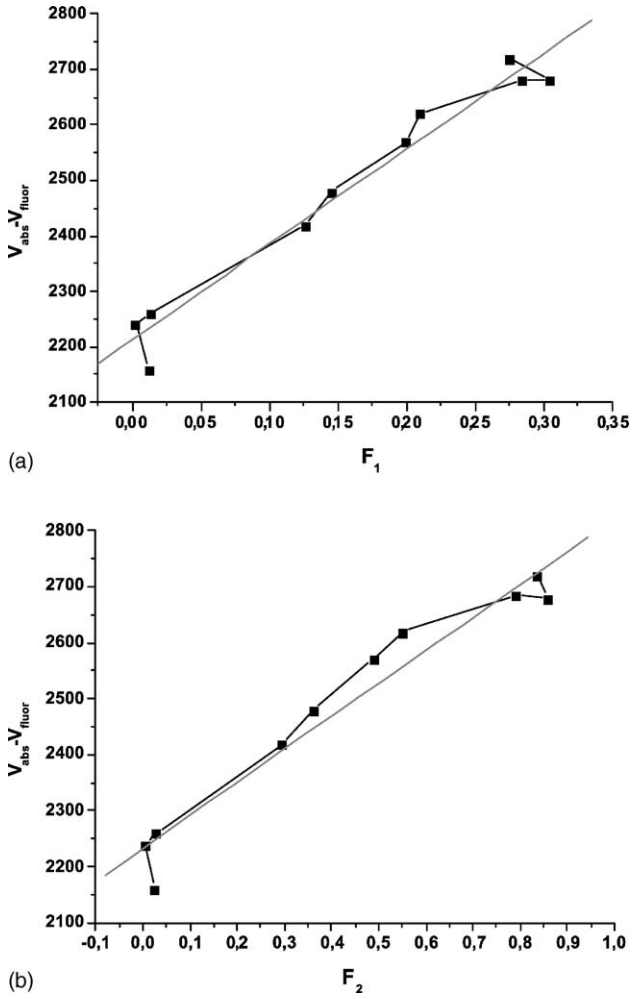

Fig. 6. (a) Mataga–Nishimoto's and (b) Bakhshiev's correlation for camptothecin.

The Onsager cavity radius a_0 which appears in formulas [3,4,6–10] approximates the dipole moment of a molecule by a point dipole in the center of a spherical cavity with radius a. For non-spherical molecules such as camtothecine, Lippert [32] suggested to take a_0 as 40% of long axis of an ellipsoid enclosing the molecule. In this work we used this suggestion.

Formula (5) enables one to avoid the error caused by uncertainty in Onsager radius determination, though the possibility of error in excited-state dipole moment estimation still exists because of the assumption that ground- and excited-state dipole moments are co-linear. In some cases the above assumption is not valid [35–37].

As could be seen from Table 3, the best coincidence with the calculated by AM1 method μ_e (∼4.9 D) has the excited-state dipole moment, evaluated by formulas [6–10], $\mu_e \sim 5.0$ D. In general, the decrease of the dipole moment value of camptothecin with excitation could not be mentioned as considerable.

4. Conclusion

It has been shown that despite the change of dipole moment on excitation, no significant fluorescence shift has been observed for camptothecin at increasing solvent polarities. This fact means the impossibility to monitor the change in dielectric constant of the medium surrounding the camptothecin molecule by fluorescence spectroscopy, for instance, when the compound leaves an aqueous environment and intercalates in between the lipid acyl chains.

Fluorescence quenching of camptothecin fluorescence emission with Co^{2+} ions has yielded a high quenching rate at diffusion rate limit $\sim 10^{10}$ $(M\,s)^{-1}$.

Taking into account that camptothecin fluorescence is very sensitive to quenching, and provided that the membrane-bound camptothecin [18] is much less accessible to quenchers, one could make a suggestion that the quenching experiments may be used for evidence that camptothecin's fluorochrome penetrates into the lipid bilayer.

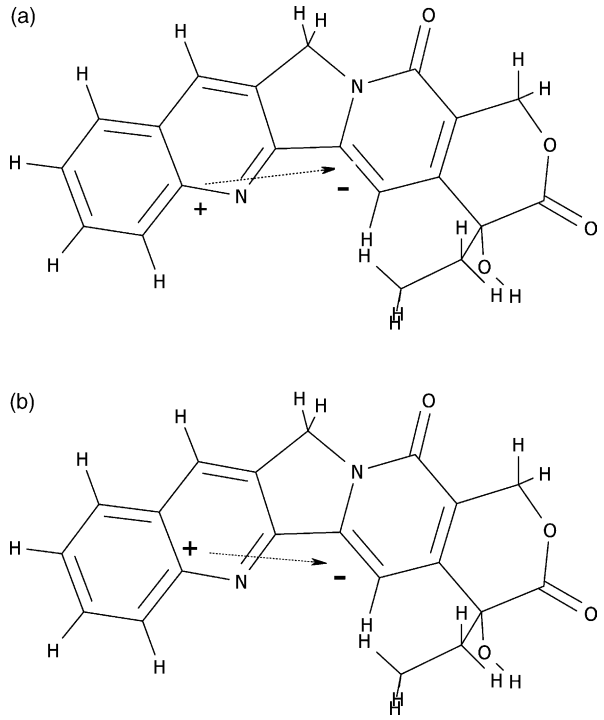

Fig. 7. Calculated dipole moment direction in: (a) S_0 and (b) S_1 electronic state of camptothecin.

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