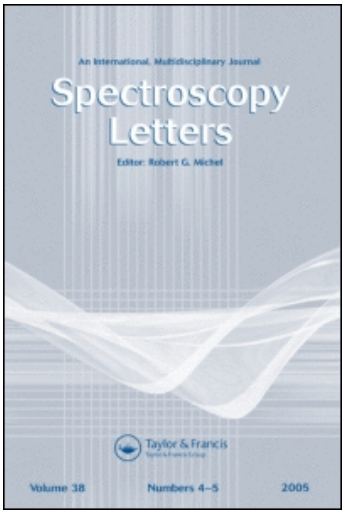

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A. El assyry[a]; B. Benali[a]; A. Boucetta[a]; Z. Lazar[a]; B. Lakhrissi[b]; M. Massoui[b]; D. Mondieig[c]
[a] Laboratoire d'Opto-électronique et de Physico-Chimie des Matériaux, Département de Physique, Faculté des Sciences, Kénitra, Morocco [b] Laboratoire de Chimie des Agroressources, Département de Chimie, Faculté des Sciences, Kénitra, Morocco [c] CPMOH, Université Bordeaux1, Talence, France

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Solvent Effect on the Electronic States Properties of Benzodiazepine-2,4-dione Using the Dielectric Continuum Model

A. El assyry[1], B. Benali[1], A. Boucetta[1], Z. Lazar[1], B. Lakhrissi[2], M. Massoui[2], and D. Mondieig[3]

[1]Laboratoire d'Opto-électronique et de Physico-Chimie des Matériaux, Département de Physique, Faculté des Sciences, Kénitra, Morocco
[2]Laboratoire de Chimie des Agroressources, Département de Chimie, Faculté des Sciences, Kénitra, Morocco
[3]CPMOH, Université Bordeaux1, Talence, France

ABSTRACT The molecular properties of benzodiazepine-2,4-dione that depend on the nature of the solvent have been investigated using the dielectric continuum model and the Dimroth polarity parameter $E_T(30)$. The difference of dipole moments between the ground and excited states has been evaluated. The results indicate that the stabilization of the first excited state S_1 is less marked than the destabilization of the ground state, and the solute–solvent interactions are more important in the ground state than in the excited state.

KEYWORDS benzodiazipine-2,4-dione, dielectric continuum model, dimroth polarity parameter $E_T(30)$, dipole moment, solvatochromism, stokes shift

INTRODUCTION

Benzodiazepine-2,4-dione is not a planar molecule, composed of a six-membered phenyl ring condensed with a seven-membered heterocyclec (Fig. 1). We were interested in the molecular properties of the molecule because several publications recently indicated that some benzodiazepine derivatives have been studied because of their biological activity as carcinostatic compounds [1–4] and were highly effective for the relief of anxiety.[5,6] They have a lower potential for addiction than do many other drugs that were used earlier and are less likely to cause death or serious, lasting harm when taken in overdoses. There are now several dozen benzodiazepine drugs in clinical use worldwide, although use has become less popular because of side effects, including dependence. The various compounds appear to differ primarily in their pharmacokinetics, that is, the speed with which they are taken up and eliminated by the body, rather than in differences in their clinical effects.[7] This pharmacological interest has motivated the search for methods of synthesis of substituted benzodiazepines.[8,9]

Because of this pharmacological interest, and in absence of fundamental spectroscopic data in the literature on these compounds, we considered it useful in this work to discuss some of their molecular properties using a continuum model. Last, this could explore advantage of the reactivity and

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Address correspondence to B. Benali, Laboratoire d'Opto-électronique et de Physico-Chimie des Matériaux, Département de Physique, Faculté des Sciences, Kenitra, Morocco.
E-mail: benali_bouziane@yahoo.fr

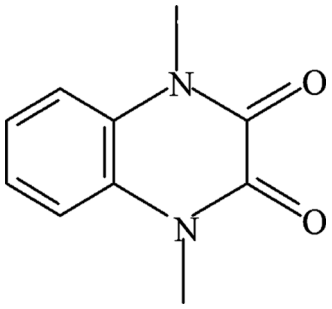

FIGURE 1 Chemical diagram of benzodiazepine-2,4-dione.

the mechanisms implying the role of benzodiazepine in biological systems like those mentioned above.

MATERIALS AND METHODS

Benzodiazepine-2,4-dione was synthesized in the laboratory of one of the authors, and the synthesis and purification methods have been described elsewhere.[10] The structure of this molecule is displayed in Fig.1. All the solvents used are commercial and of spectroscopy grade. Fluorescence and absorption spectra were observed with a spectrofluorometer (Fluoromax-3, Jobin-Yvon) and a spectrophotometer (Cary 5G, UV-Visible-NIR), respectively. The emission was monitored with a system consisting of a spectrograph and a Hamamatsu C4880 Streakscope, capable of simultaneous spectral and time-resolved data acquisition with nanosecond or picosecond resolution. All the experiments were carried out at room temperature. Experimental technique and apparatus used for experiments are described elsewhere.[11]

RESULTS AND DISCUSSION

The absorption spectra of benzodiazepine-2,4-dione in various solvents at room temperature are displayed in Fig. 2a,b. The spectral behavior of the molecule in aprotic solvents (Fig. 2a) and in butanol or dipropylether (Fig. 2b) are different. In *n*-hexane, *n*-butylchloride, and acetone, the intense π–π^* absorption band is localized around 283 nm and has a shoulder around 306 nm. The low intensity shoulder is attributed to the singlet n–π^* transition band absorption. Elsewhere, Fig. 3 shows the fluorescence spectra of the molecule in polar and nonpolar solvents at room temperature. In *n*-hexane, the spectrum presents a wide band located between 290 nm and 450 nm having a maximum at 313 nm. These characteristics vary with the solvent polarity.

Table 1 collects the maximum absorption and fluorescence emission bands of benzodiazepine-2,4-dione for each solvent used and the corresponding Dimroth polarity parameter $E_T(30)$.[12] The applied Onsager function $[f(D) - f(n^2)]$ according to the dielectric continuum model [13–17] is given by the relation (1):

$$f(D) - f(n^2) = \left[\frac{2(D-1)}{(2D+1)}\right] - \left[\frac{2(n^2-1)}{(2n^2+1)}\right] \qquad (1)$$

where n and D represent respectively the refraction index and the permittivity of the medium.

A first analysis of Table 1 shows that Stokes shift increases with the solvent polarity, thus translating a dipole moment in the singlet state S_1 different to that in the ground state. One can note, as the solvent is able to form a hydrogen bond, the Stokes shift becomes more important. This phenomenon is due to the formation of a hydrogen bond complex between the benzodiazepine-2,4-dione and the solvent molecules in the ground state and excited state. This result indicates that the shift due to the hydrogen bond is more pronounced in ethanol and butanol. This can be explained by the fact that OH radical of ethanol can be associated either with the NH benzodiazepine-2,4-dione molecule to form $NH\cdots O$ type of complex or with its aromatic ring to form $(OH\cdots\pi)$ type of complex in the ground and excited states. We initially try to describe the solvatochromism shift of the first singlet state of this molecule using the dielectric continuum model. To this end, the variations of $\Delta\nu_{st}$ according to $[f(D)–f(n^2)]$ are represented in Fig. 4, so that only the contributions of the dipole–dipole type are taken into account. Figure 4, shows that the dielectric continuum model does not make it possible to describe the solvent effect on the benzodiazepine-2,4-dione. Alcohols and dipropylether in particular induce an additional deviation compared with what the only dipole–dipole interactions provide. Indeed, if one compares two solvents of close permitivity (like acetonitrile and methanol), one notes an additional displacement of approximately 130 cm^{-1} in methanol.

This additional displacement is consecutive with the formation of a hydrogen bond between benzodiazepine-2,4-dione and solvent. By consequence,

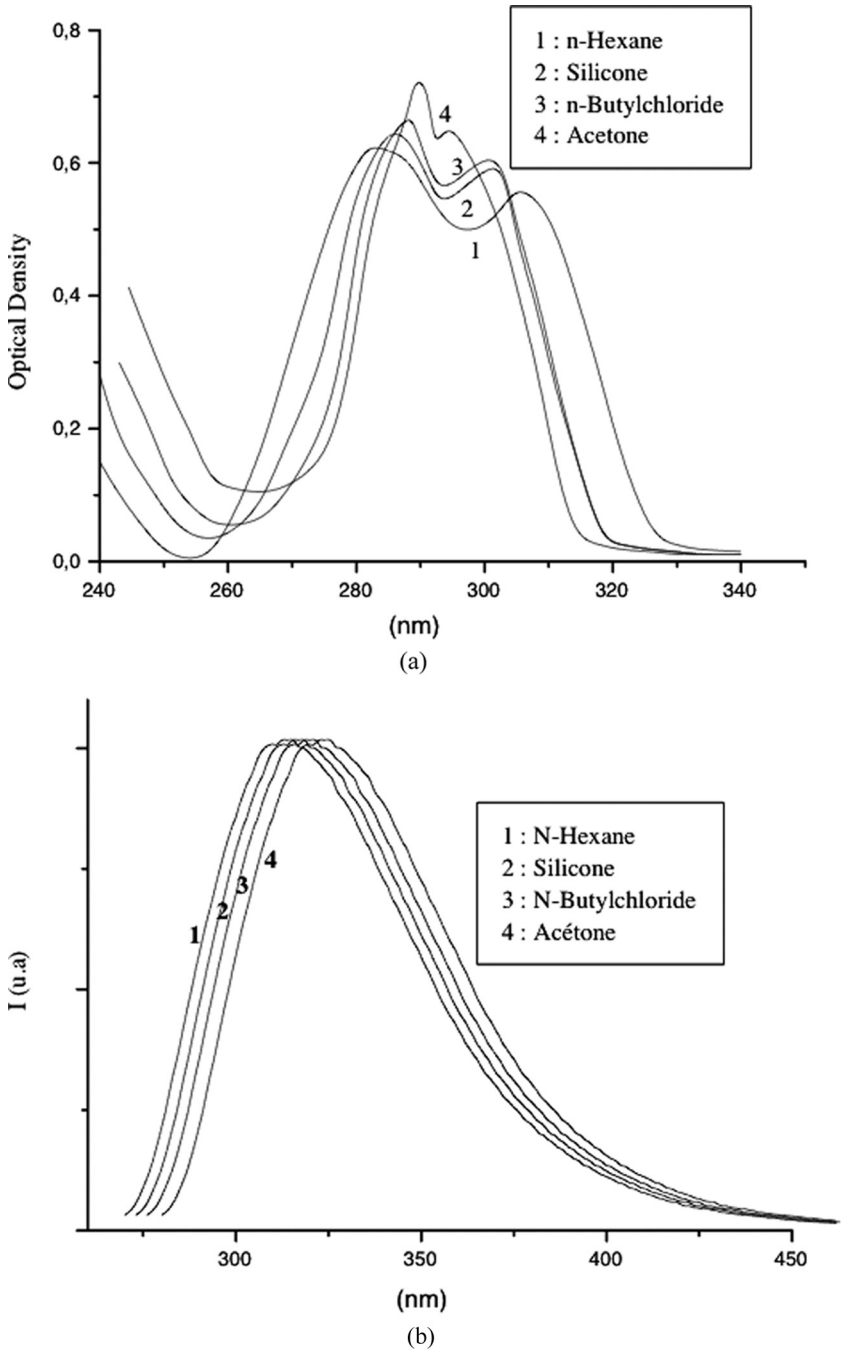

FIGURE 2 **Absorption spectra of the benzodiazepine-2,4-dione at room temperature in various solvents; C = 10^{-4} M. (a) Solvent polarity effect; (b) hydrogen bond effect.**

it was necessary to call upon the empirical parameters of solvent polarity. One of the most used scales utilizes the Dimroth polarity parameter $E_T(30)$.[12,18–20] Figure 5 represents the evolution of Stokes displacement of the molecule according to this parameter.

As noted, we obtain a rather linear relation between $\Delta\nu_{st}$ and $E_T(30)$. This empirical parameter thus makes it possible to account for the benzodiazepine-2,4-dione solvatochromic shift for all studied solvents, including alcohols. The linear regression calculation for Stokes shift gives:

$$\Delta\nu_{st} = 2090 + 77\ E_T(30) \qquad (2)$$

As the Dimroth parameter is known to hold account of the specific interactions of hydrogen bond type, it appears here clearly that the formation of hydrogen bond plays a part in the solvatochromy of the

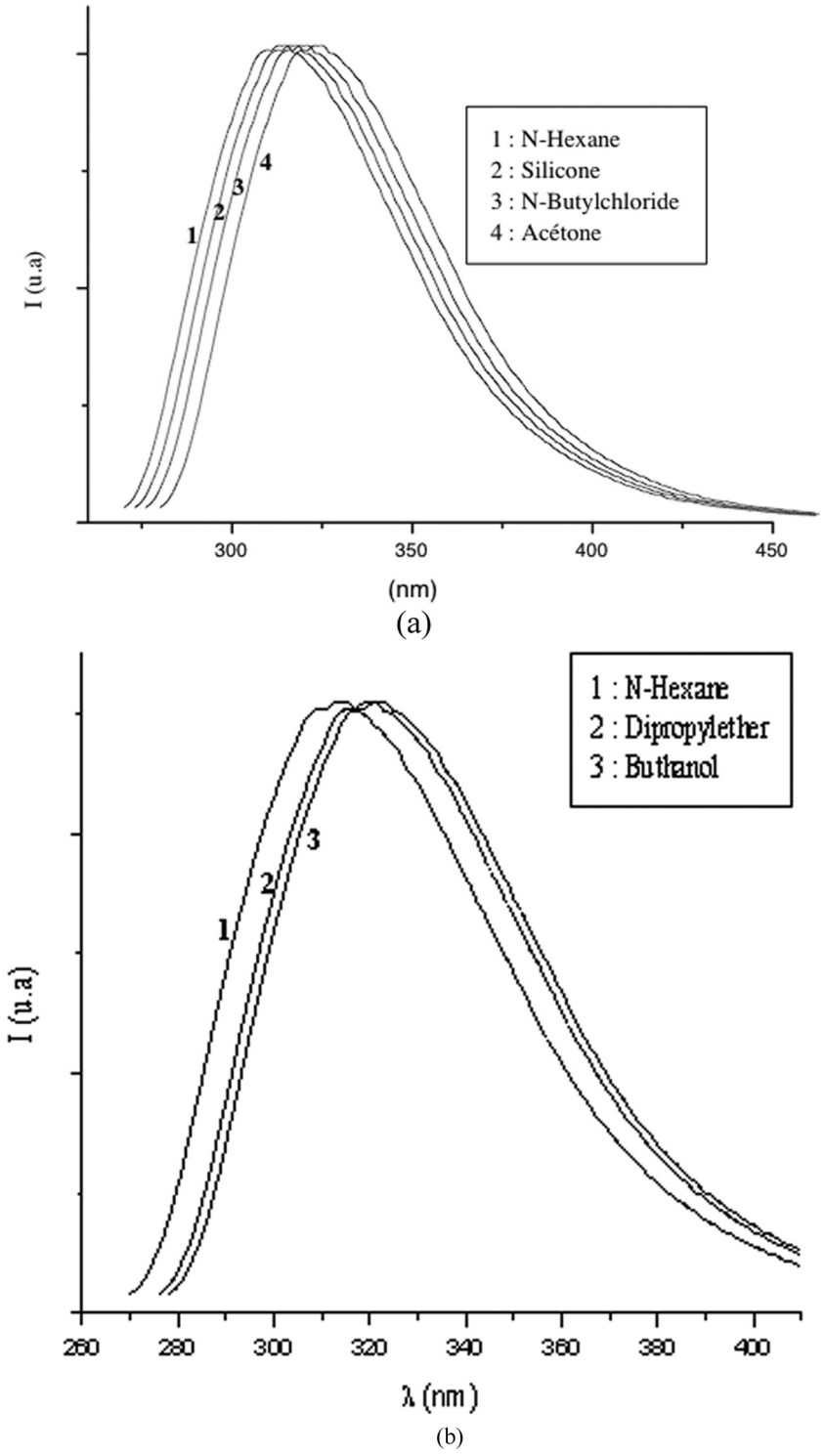

FIGURE 3 **Normalized fluorescence spectra of the benzodiazepine-2,4-dione at room temperature, C = 10^{-4} M, λ_{exc} = 286 nm. (a) Solvent polarity effect; (b) hydrogen bond effect.**

electronic states of the molecule, which enables us to confirm the conclusions that were obtained with the model of the dielectric continuum.

For more precision, Fig. 6 gathers the variations of maximum absorption and fluorescence bands according to the Dimroth parameter. These maxima evolve differently when $E_T(30)$ increases. The linear regression calculation for the maximum absorption bonds parameter (ν_a) gives the following equation (3) with a resolution of 58%:

TABLE 1 Physicochemical Parameters of Solvents: $E_T(30)$ and Maximum Absorption and Fluorescence Emission Bands of Benzodiazepine-2,4-Dione for Each Solvent Used

Solvents	μ (Debye)	E_T (30) (kcal/mol)	D	n	$f(D,n)$	$f(D) - f(n^2)$	ν_a (cm^{-1})	ν_f (cm^{-1})	ν_a–ν_f (cm^{-1})
n-Hexane	0.00	31.0	1.91	1.3878	0.00	0.00	33200	31948	1252
Silicone	1.17	—	2.46	1.3775	0.063	0.12	33222	31645	1577
Dipropylether	1.30	34,5	4.34	1.3526	0.152	0.33	34500	31250	3250
n-butylchloride	1.90	—	7.35	1.4000	0.209	0.41	33445	31347	2098
THF	1.63	37,4	7.58	1.4050	0.210	0.42	34602	31446	3156
Acetone	2.70	42,2	20.49	1.3500	0.246	0.57	33784	30959	2825
Acetonitrile	3.44	45,6	37.50	1.3440	0.306	0.61	34129	30581	3548
Propanol	1.70	49,2	20.52	1.3800	0.262	0.55	34782	31104	3678
Butanol	1.66	50,2	15.94	1.3900	0.276	0.53	34843	30959	3884
Ethanol	1.66	51,9	24.30	1.3590	0.289	0.58	34843	31152	3691
Methanol	1.70	55,4	32.61	1.3200	0.311	0.62	34782	31104	3678

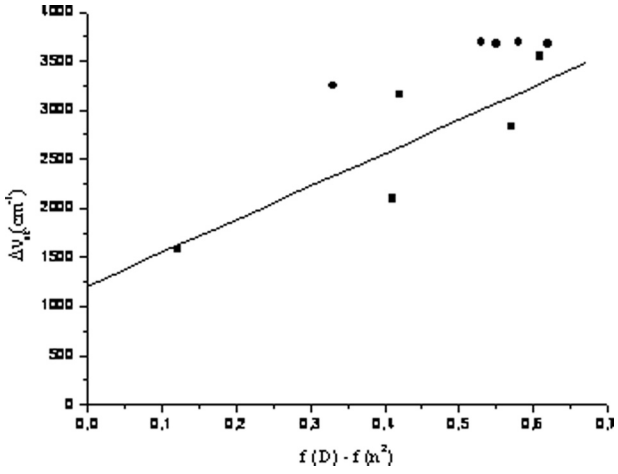

FIGURE 4 Evolution of $\Delta\nu_{st}$ according to $[f(D) - f(n^2)]$ of benzodiazepine-2,4-dione. The hydroxylic solvents and the DPE are represented by the full disks and the other solvents by the rectangles.

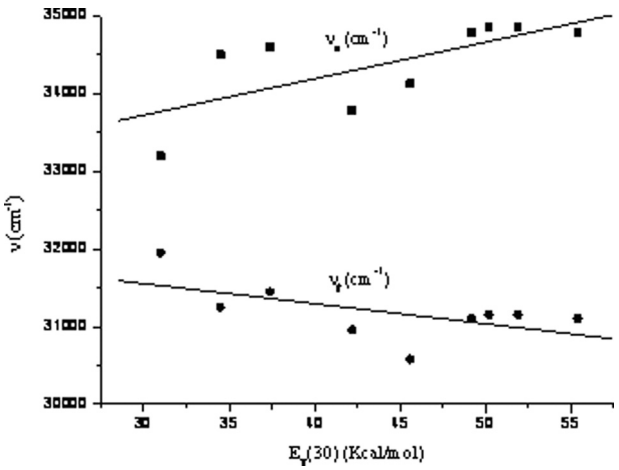

FIGURE 6 Evolution of benzodiazepine-2,4-dione's maximum bands of absorption (ν_a) and defluorescence (ν_f) according to the Dimroth parameter $E_T(30)$.

$$\nu_a = 32,310 + 47\ E_T(30) \qquad (3)$$

The linear regression calculation for the maximum fluorescence bands parameter (ν_f) gives the following equation (4) with a resolution of 60%:

$$\nu_f = 32,329 - 26\ E_T(30) \qquad (4)$$

It appears that the stabilization of the first excited state S_1 (slope of -26) is less marked than that of the ground state (slope of 47). Consequently, the solute–solvent interactions are more important in the ground state ($\mu = 3.91$ D calculated from the RHF/STO-3G) than in the excited state

Figure 7 shows the evolution of $\Delta\nu_{st}$ according to $f(D, n)$. The linear regression calculation for these parameters gives the following equation (5) with a resolution of 85%:

$$[\Delta\nu_{st} = 1282 + 7891\, f(D, n)] \qquad (5)$$

If we take into account only hydrogen bond solvents, it becomes possible to estimate the difference of the dipole moment between the ground and the excited state. According to equation (6) of the Lippert–Mataga method,[21] this difference is given by

$$\Delta\nu_{st} = \nu_a - \nu_f = \frac{2(\mu_e - \mu_f)^2}{hca^3} f(D, n) + Cte \qquad (6)$$

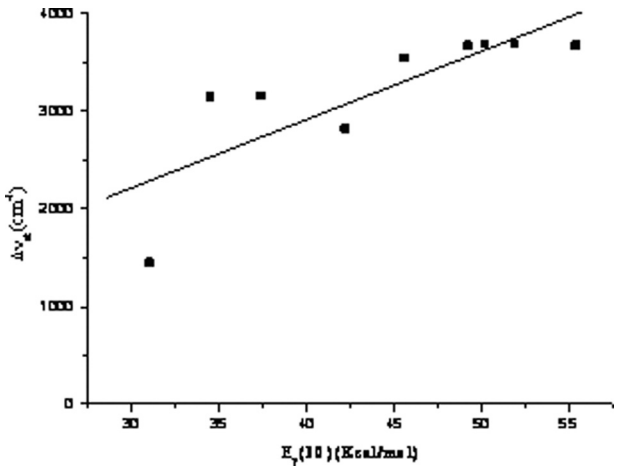

FIGURE 5 Evolution of $\Delta\nu_{st}$ according to $E_T(30)$ of benzodiazepine-2,4-dione.

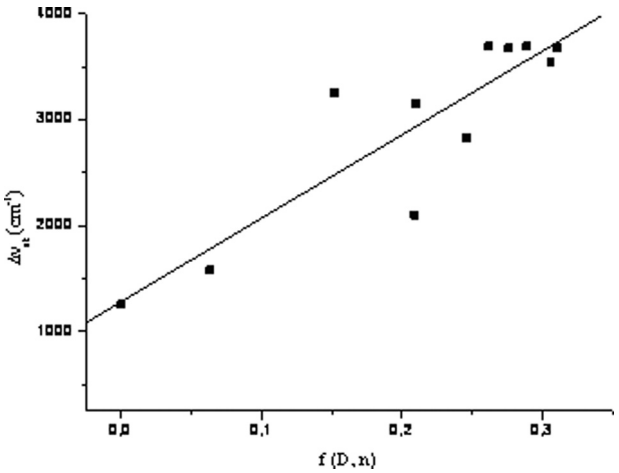

FIGURE 7 Stokes shift according to $f(D, n)$.

where h is Planck's constant, c is the speed of light, a is Onsager's sphere radius determined by crystallographic data,[22] ($a^3 = 35.937$ Å^3), and μ_f and μ_e are respectively the dipole moment of the molecule in the ground and excited states. By applying this formula and a plot of Fig. 7, the difference of the dipole moment is estimated at 5.47 Debye. The result indicates a considerable dielectric effect on the orientation vector of the benzodiazepine-2,4-dione molecule in the ground and excited sates. Also, with this value, the difference of the dipole moment appears to be in agreement with the values found for similar molecules such as coumarins.[23,24]

CONCLUSIONS

The properties of the electronic states of benzodiazepine-2,4-dione have been investigated in solvents using the dielectric continuum model and the Dimroth polarity parameters of solvents $E_T(30)$. The linear regression calculation for the maxima absorption bonds parameter (ν_a) and the maxima fluorescence bands parameter (ν_f) show that the solute–solvent interactions are more important in the ground state than in the excited state. This model is adequate for nonhydroxylic solvents. In protic solvents, where association by hydrogen bonding may exist, the dielectric continuum is not perfect. Elsewhere, the obtained difference value of the dipole moment indicates a considerable dielectric effect on the orientation vector of the benzodiazepine-2,4-dione molecule in the ground and excited states.

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