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An experimental and theoretical study of dipole moments of N-[4-(9-acridinylamino)-3-methoxyphenyl]methanesulfonamide

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Abstract

The excited state (S_1) dipole moment of m-AMSA (**1**), an acridine derivative with antitumor activity, was determined from solvatochromic shifts of the lowest energy absorption band in several organic solvents. The effect of the solute shape and the values of polarizability on the determined change of dipole moment between ground and excited state was discussed. The dipole moments in S_0 and S_1 state were calculated in gas phase with semiempirical quantum-chemical and DFT and CIS methods and in solvents with SM5.4A solvation model and compared with values obtained experimentally. All the results show that the dipole moment of compound **1** in the excited state is higher than that in the ground state. These methods quite well predict the values of $\Delta\mu$ between two states of an investigated compound.
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1. Introduction

Dipole moments are an important property of a molecule delivering information about its electronic and geometrical structure. The knowledge of a dipole moment of an excited molecule (μ_e) is very useful in explaining the nature of excited states and in describing the course of its photochemical transformations. While a dipole moment of chemical systems in the ground state (μ_g) can be measured, there are no unfailing techniques which permit determination of a dipole moment of low-living forms such as molecules in excited states. From among methods that determine the change of dipole moments concurrent to the electron excitation of molecules, the most often applied techniques are based on a linear relation between the wavenumbers of absorption or/and the fluorescence maxima and polarity function of a solvent, which usually takes into account both the relative permittivity (ε) and refractive index (n) of environment [1]. To determine the dipole moment in excited state with the solvatochromic method, several approaches were used including these developed by Lippert [2,3], Bakhshiev [4], Ravi et al. [5], Kawski–Chamma–Viallet [6,7] and Suppan [8,9].

Essential information on the dipole moments of molecules both in ground and excited state is delivered by quantum-chemical calculations which enable determination of absolute values μ_g and μ_e of molecules in the gas phase and in solution and additionally direction of their vectors.

N-[4-(9-Acridinylamino)-3-methoxyphenyl]methanesulfonamide [m-amsacrine or m-AMSA] (**1**) (Fig. 1) is an acridine derivative with antitumor activity [10]. There has been no work referring to compound **1** dipole moments so necessity of such studies seems to be evident. Recently, the dipole moments of acridine derivatives have been investigated both experimentally and theoretically [11,12]. Aaron and Maafi [11] examined the dipole moments of acridine and some of its derivatives: 9-aminoacridine, acridine yellow and proflavine. The ground state dipole moment of acridine derivatives measured in dioxane at 293 K is 2.99, 3.96, 5.23 and 6.33 D for acridine, proflavine, 9-aminoacridine and acridine yellow, respectively [11]. Those authors estimated the excited dipole moment from shifts of electron absorption and fluorescence spectra in solvents with different polarity and ability to form hydrogen bonds using Bakhshiev [4] and Kawski–Chamma–Viallet [6,7] approaches. They reported that the dipole moment of acridine derivatives was higher in the first excited state than in the ground state and differences ranged from 2.7 to 6.6 D. Sharma et al. [12] studying dipole moments of acriflavine and acridine orange

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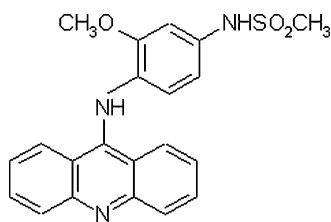*E-mail address:* kanowak@p.lodz.pl (K. Nowak).

Fig. 1. The structure of *N*-[4-(9-acridinylamino)-3-methoxyphenyl]methane-sulfonamide.

applied the theory proposed by Ravi et al. [5] and reported that $\mu_e - \mu_g$ were 1.83 and 2.27 D for acriflavine and acridine orange, respectively.

The dipole moment of molecules in the ground state is calculated by relative permittivity measurement of solutions which are prepared in nonpolar solvents. Experimental determination of μ_g of the investigated compound was not possible owing to very low solubility of highly dipolar molecule of **1** in nonpolar solvents. So, we calculated this value theoretically using the quantum-chemical methods. We reported earlier that these methods quite well predicted geometrical and electronic structures of an isolated molecule of a studied compound [13].

The goal of the present paper is to determine a dipole moment of antitumor drug *m*-AMSA (**1**) in excited state from shifts of electronic absorption band in different solvents. Next, we compared results of our experiments with theoretical results calculated both for isolated molecules with semiempirical methods and in solvents obtained with AM1 method and SM5.4A solvation model.

2. Methods

2.1. Absorption spectra

N-[4-(9-Acridinylamino)-3-methoxyphenyl]methanesulfo-namide hydrochloride (**1**) was purchased from Sigma (USA) and its purity was >98%. Solvents (acetone, nitrobenzene, nitroethane, acetonitrile, *N,N*-dimethylformamide, dimethylsulfoxide) were spectroscopic grade and were used as received.

The wavenumber of absorption maxima of **1** was determined from experimental UV–Vis absorption spectra of its diluted solutions in different solvents. Measurements were performed in a cuvette with 5 cm path length and spectra recorded at the temperature 25 °C with a Nicolet Evolution 300 spectrophotometer (Thermo Electron Corporation) with Vision PC program.

2.2. Theoretical calculations

Calculations with AM1 (Austin Model 1) [14,15], PM3 (Parameterized Model) [16] and MNDO [17,18] semiempirical method were carried out to provide a dipole moment in the ground and excited state of an isolated dye molecule. All semiempirical calculations were performed by means of HyperChem 5.1 package program [19]. Also density functional theory (DFT) using the hybrid Becke3–Lee–Yang–Parr functional (B3LYP) method [20] with the 6–31G(d) basic set was

applied to provide a dipole moment in the ground state and CIS method [21] with the same basic set to obtain a dipole moment in the excited state of an isolated molecule. In the DFT calculations, the Gaussian98 program [22] was used and in the CIS method the Gaussian03 program [23] was applied. Solvent effects were treated with the use of the SM5.4A solvation model [24] implemented in Amsol (6.5.1) program [25].

3. Results and discussion

3.1. Determination of a change in the dipole moment of compound **1** with the solvatochromic method

The solvatochromic method for determination of a dipole moment in excited S_1 state is based on a change of the position of maximum absorption induced by the reaction field. Taking into consideration the model of reaction field, Onsager equation of a shift in the maximum of absorption in a solvent with reference to an isolated molecule (in gas phase) is obtained [26]:

$$\bar{\nu}_A = -m_A(1 - \alpha f')^{-1}[f(1 - \alpha f)^{-1} - f'(1 - \alpha f')^{-1}]$$
$$-\frac{\mu_e^2 - \mu_g^2}{2hc}(2 - \alpha f')f'(1 - \alpha f')^{-2} \quad (1)$$

where

$$m_A = \frac{\vec{\mu}_g(\vec{\mu}_e - \vec{\mu}_g)}{hc} \quad (2)$$

where μ_g and μ_e are the dipole moments in the ground and excited state, respectively, α the mean polarizability of a molecule of dissolved substance, f and f' are the factors of the reaction field dependent on the shape and radius of cavity in the solvent, respectively, h the Planck constant and c is the speed of light. The reaction field depends on the shape of cavity which is occupied by a molecule in the solvent. The cavity is described as an ellipsoid with the principal axes $2a$, $2b$ and $2c$:

$$f = \frac{2}{abc}\frac{\varepsilon - 1}{2\varepsilon + 1}F(\varepsilon, A) \quad (3)$$

$$f' = \frac{2}{abc}\frac{n^2 - 1}{2n^2 + 1}F(n^2, A) \quad (4)$$

where

$$F(\varepsilon, A) = \frac{3A(1 - A)(2\varepsilon + 1)}{2[\varepsilon - (\varepsilon - 1)A]} \quad (5)$$

$$F(n^2, A) = \frac{3A(1 - A)(2n^2 + 1)}{2[n^2 - (n^2 - 1)A]} \quad (6)$$

where ε is the dielectric constant and n is the refractive index of the solvent. Constant A is defined as

$$A = \frac{abc}{2}\int_0^\infty \frac{ds}{(s + a^2)^{3/2} + (s + b^2)^{1/2} + (s + c^2)^{1/2}}, \quad (7)$$

where s is the parameter of integration. The value of A is 0.174, 1/3 and 0.583 in the case when it is assumed that cavity is ellipsoid of revolution ($b = c = a/p$, $p = 2$), sphere ($b = c = a/p$, $p = 1.0$) and flattened ellipsoid ($b = c = a/p$, $p = 0.4$), respectively [26].