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Synthesis, solvatochromic properties, and dipole moments of Fmoc-L-alaninol

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ABSTRACT

An efficient protocol for the activation of *N*-(9-Fluorenylmethoxycarbonyl)-L-alanine [Fmoc-Ala-OH] employing 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholinomethylene)] methanaminium hexa-fluorophosphate [COMU] and its reduction into (9*H*-fluoren-9-yl)methyl 1-hydroxypropan-2-ylcarbamate [Fmoc-L-alaninol] using sodium borohydride has been described. The method is trouble-free, quick and free from racemization. Fmoc-L-alaninol was characterized by ^{1}H and ^{13}C NMR, and mass spectral studies. The electronic absorption and fluorescence emission spectra of Fmoc-L-alaninol have been studied in solvents of different polarities, and the data were used to study the solvatochromic properties. The spectral variations were analyzed by the linear solvation energy relationship concept to visualize the nature and extent of solvent–solute interactions. Experimental values of ground-(μ_g) and excited-state (μ_e) dipole moments of Fmoc-L-alaninol were calculated by the solvatochromic shift method, and theoretical μ_g values were evaluated by quantum chemical calculations using Gaussian 03 and Chem3D Ultra 8.0. The higher value of excited-state dipole moment than the ground-state value indicates a substantial redistribution of π–electron densities in a more polar excited-state. Also, fluorescence emission peak undergoes a hypsochromic shift with increase in the polarity of the solvent, confirming $n \rightarrow \pi^*$ transition.

1. Introduction

Terminal protected amino alcohols are the main intermediates in the synthesis of peptide bond surrogates and also amino aldehydes [1–3] which in turn are used as inhibitors of α-chymotrypsin [4], *m*-calpain [5] and HIV protease [6,7]. They are also used in the asymmetric synthesis [8,9] and in the synthesis of some insecticidal compounds [10]. Their major role as important intermediates for the synthesis of vicinal diamines [11,12] has been successfully proved. Apart from these, β-amino alcohols are also used as precursors for N^{α}-protected *p*-nitrophenyl carbonate [13] union which in turn are used as the elementary units for the aggregation of oligopeptidyl carbamates [14]. Fmoc-L-alaninol is one of the β-amino alcohols.

It is highly desirable to have a high yield methodology for the synthesis of β-amino alcohols since they are extensively used as mentioned earlier. The reduction of carboxylic acid into β-alcohols was achieved using AlH_3, $LiAlH_4$, DIBAL, BH_3·THF, diisobutyl aluminium hydride [15], $NaBH_4$-I_2 [16] etc. N^{α}-protected amino alcohols are also synthesized by the reduction of alkyl esters of amino acids [17,18] and active esters of amino acids [19] with $NaBH_4$ at 0 °C. Synthesis of di- and tri-peptide alcohols by the reaction of *N*-protected (α-aminoacyl)benzotriazoles and *N*-protected (α-dipeptidoyl) benzotriazoles was reported by Katritzky et al. [20]. Several reagents like cyanuric chloride [21], acid fluorides [22], HBTU [23], HATU, Boc_2, T3P [24] were used for the activation of carboxyl group followed by a subsequent reduction using sodium borohydride to synthesize β-amino alcohols.

Recognizing the importance of peptidomimetics and the significant use of amino alcohols, the conversion of Fmoc-Ala-OH into Fmoc-L-alaninol using 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholinomethylene)] methanaminium hexa-fluorophosphate [COMU] coupling agent has been reported in the present paper. The efficiency of conversion is high, and the yield obtained is more than that obtained from the earlier reported protocols. It is free from the use of toxic substances. The side chain reactions are minimized to a greater extent due the use of the COMU as an activating reagent. Therefore, the protocol reported herein is advantageous over the other protocols, proposed earlier.

Dipole moment gives a direct measure of the electron distribution in a molecule. Photon causes excitation of electron in a molecule resulting in the redistribution of charges leading to conformational changes in the excited-state. This leads to an increase or decrease of the dipole moment of an excited-state (μ_e) as compared to the ground-state (μ_g). The

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excited-state dipole moment of a molecule is highly useful in providing valuable information on the electronic and geometrical structures of the molecule in the short-lived excited-state. The knowledge of dipole moments of the first electronically excited-singlet state (S_1) of the molecules reflects the charge distribution in the molecule and facilitates to predict the site of attack by electrophilic and nucleophilic reagents in some photochemical reactions. Detailed information on the theory of dipole moments is available in the literature [25–30].

All the experimental methods available so far for the determination of singlet excited-state dipole moments are based on the spectral shift caused either externally by electrochromism or internally by solvatochromism. The electro-optic methods (electrochromism) such as electric-dichroism [30], electronic polarization of fluorescence [31], microwave conductivity [32] and Stark splitting [33] are considered to be very accurate. As they are considered as equipment sensitive, their use is limited and the studies have been restricted to relatively very simple molecules. As the solvatochromic method does not use any external field [34,35], it is experimentally much simpler and widely accepted. It is based on a linear correlation between the wavenumbers of the absorption and emission maxima and solvent polarity function which involves relative permittivity, ε_r, and refractive index, n, of the medium [36–40]. The solvatochromic method yields fairly satisfactory results, under suitable conditions [40]. There is another method called, the thermochromic method [41–46], which gives the accurate values of dipole moments. This method makes use of the same expressions as in the solvatochromic method, but instead of many solvents, only the absorption and fluorescence shifts are measured using one selected solvent of moderate polarity as a function of temperature. An interesting paper on thermochromism describing the dipole moments and specific interactions in Coumarin 153 has been also published recently [47]. Experimental and theoretical studies on ground- and excited-state dipole moments of variety of fluorescent molecules using the solvatochromic method have been reported in the recent past [41–52].

To the best of our knowledge, there are no reports on the synthesis of Fmoc-L-alaninol using COMU, and also there is a lack of information on both experimental and theoretical data on its dipole moments. The solute–solvent interaction of Fmoc-L-alaninol has not been studied yet. Moreover, electrostatic forces play a crucial role in defining the structures and properties of biomolecules such as amino acids and peptides. An important contribution to electrostatic forces is from permanent electric dipole moments. The dipole moment of amino acids afford the evidence for whether they exist in the form of zwitterions or not. This prompted us to carry out the present investigation. The objectives of the present work are: (i) To synthesize Fmoc-L-alaninol (Fig. 1) employing COMU from protected alcohol using a facile and high yield protocol and (ii) to study the influence of various solvents of different polarities on the electronic excited states, and hence on the absorption and the fluorescence spectra of Fmoc-L-alaninol for the determination of the dipole moments in the ground- and excited-states by solvatochromic shift methods.

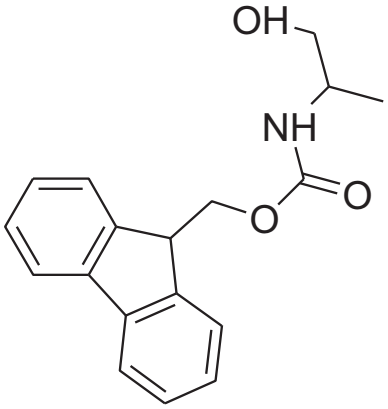

Fig. 1. Molecular structure of Fmoc-L-alaninol.

2. Calculation of dipole moments

2.1. Theoretical ground-state dipole moment and computational details

The ground-state dipole moment (μ_g) of Fmoc-L-alaninol was determined theoretically by quantum chemical calculations using Gaussian 03 program [53]. In the first step of density functional theory (DFT) calculation, the geometry taken from the starting structure was optimized and the calculations were performed with B3LYP functional and 6-31G+* basis set with appropriate scale factors. Theoretical μ_g value was also calculated using the AM1 method by means of the MOPAC program using Chem3D Ultra 8.0 software. All these computations were carried out with a Core i5 PC on Windows 7 operating system.

2.2. Experimental ground- and excited-state dipole moments

Experimental ground-state and excited-state dipole moments were determined by the solvatochromic method using the equations proposed by Bakhshiev [36], Bilot–Kawski [37–39], and Reichardt [35,54]. Literature survey shows that the Bakhshiev and Bilot–Kawski equations give the best results [48–52], while the use of the Reichardt equation minimizes the error in estimation of Onsager radius (a), since it involves the ratio of two Onsager radii (a_B/a) [35,48]. Hence, these equations are used for determining dipole moments.

Bakhshiev equation [36]:

$$\overline{\nu}_a - \overline{\nu}_f = m_1 F_1 + \text{constant}. \tag{1}$$

Bilot–Kawski equation [37–39]:

$$\frac{\overline{\nu}_a + \overline{\nu}_f}{2} = -m_2 F_2 + \text{constant} \tag{2}$$

where $\overline{\nu}_a$ and $\overline{\nu}_f$ are the wavenumbers corresponding to absorption and fluorescence maxima in cm^{-1}, and m_1 and m_2 are the slopes of linear graphs corresponding to Eqs. (1) and (2). F_1 and F_2 are Bakhshiev and Bilot–Kawski polarity functions respectively and are given by,

$$F_1 = \frac{2n^2+1}{n^2+2}\left(\frac{\varepsilon_r - 1}{\varepsilon_r + 2} - \frac{n^2-1}{n^2+2}\right) \tag{3}$$

$$F_2 = \frac{2n^2+1}{2(n^2+2)}\left(\frac{\varepsilon_r - 1}{\varepsilon_r + 2} - \frac{n^2-1}{n^2+2}\right) + \frac{3\left(n^4-1\right)}{2(n^2+2)^2} \tag{4}$$

where ε_r and n are the relative permittivity and the refractive index of the solvent respectively.

$$m_1 = \frac{2\left(\mu_e - \mu_g\right)^2}{hca^3} \tag{5}$$

$$m_2 = \frac{2\left(\mu_e^2 - \mu_g^2\right)}{hca^3} \tag{6}$$

where μ_e and μ_g are the excited- and ground-state dipole moments of the solute molecule, respectively. The symbols h and c are Planck's constant and velocity of light in vacuum, respectively. 'a' is the Onsager cavity radius of the solute molecule and its value can be evaluated by the atomic increment method [55]. Assuming that the symmetry of the investigated solute molecule remains unchanged upon electronic transition, and that the ground- and excited-state dipole moments are