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Single amino acid mutation in alpha-helical peptide affect second harmonic generation hyperpolarizability

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ABSTRACT

We investigate the effect of side chain on the first-order hyperpolarizability in α-helical polyalanine peptide with the 10th alanine mutation (Acetyl(ala)$_9$X(ala)$_7$NH$_2$). Structures of various substituted peptides are optimized by ONIOM (DFT: AM1) scheme, and then linear and nonlinear optical properties are calculated by SOS//CIS/6-31G* method. The polarizability and first-order hyperpolarizability increase obviously only when 'X' represents phenylalanine, tyrosine and tryptophan. We also discuss the origin of nonlinear optical response and determine what caused the increase of first-order hyperpolarizability. Our results strongly suggest that side chains containing benzene, phenol and indole have important contributions to first-order hyperpolarizability.

1. Introduction

Second harmonic generation (SHG), a well known nonlinear optical phenomenon, was first demonstrated in crystalline quartz in 1961 [1]. Shortly thereafter, SHG was also recognized in biological tissue by Derr et al. and Zaret in 1965 [2,3] which was the pioneering study of biological SHG phenomenon. Myosin, microtubule and collagen [4–6] polymeric proteins have previously been detected with strong intrinsic SHG signals in living tissues. At the same time, SHG phenomenon has been widely exploited for biological imaging technique with many unique advantages including intrinsic optical sectioning, non-invasive observation, deep tissue penetration, and endogenous contrast specificity [7]. More recently, it has been used to probe local structure and detect diseases early [8].

Since many studies performing on biological proteins are based on the second harmonic generation technique, there are growing interest and significance among experimental and theoretical scientists in detailed characterization of SHG intensity and its origin. For theoretical studies, the precise quantum chemical calculations of the second harmonic generation hyperpolarizability in biological systems are still difficult and out of today's computer power because of the large number of atoms in biological protein. A lot of effort has been done in the past few years in order to identify SHG signs of biological structures. Some scientists suggest that the SHG hyperpolarizability can be interpreted as the summation of the building blocks containing peptide bond [9–17], which is the fundamental structural unit in protein. The additive model therefore is widely used for predicting the first-order hyperpolarizability of macromolecule by elementary building blocks (e.g. *N*-methylacetamide). The first study of first-order hyperpolarizability for α-helical peptide using additive model was reported by Mitchell et al. [9,10]. Recently, Simpson and co-workers implemented a data analysis and visualization program to calculate the nonlinear optical properties of proteins based on the additive model (NLOPredict) [11]. In the additive model, the final first-order hyperpolarizability is influenced by the choice of original building blocks but the effects of variable side chains in peptides are not considered.

As we known, the side chains are important in distinguishing amino acids, unfortunately, they are neglected in these predictions by the additive model. In order to provide more information on the effect of side chain, we investigate in the present Letter the first-order hyperpolarizability of substituted peptides in the isolated system of gas phase. Helices are ubiquitous in protein, especially in some strong SHG response proteins (such as myosin and collagen), which is characterized by i, $i+4$ CO–HN hydrogen bonds with typical Ramachandran dihedral angle φ approximately $-60°$ and ψ approximately $-45°$. Consequently the α-helical structure is used as the peptide backbone for illustrating the side chains effect on the first-order hyperpolarizability. We choose 17 alanines to form the α-helical peptide, for that is sufficiently stable in α-helical structure (Acetyl(ala)$_{17}$NH$_2$) [18–20]. And the 10th alanine is substituted by other common amino acids (Acetyl(ala)$_9$X(ala)$_7$NH$_2$) in order to get rid of the effect of structural change in both ends. Base on these substituted α-helical peptides, we discuss how single amino acid mutation affect the first-order hyperpolarizability. What's more, we also pay much

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attention to the origin of nonlinear optical response for interpreting the variation of first-order hyperpolarizability in different amino acids substituted peptides.

2. Computation methods and processes

All calculations are performed using the GAUSSIAN 03 programs [21]. The ONIOM (Our own N-layer Integrated molecular Orbital molecular Mechanics) scheme [22,23], which has been implemented in the Gaussian suite of programs, is used to optimize the ground-state structures. It is an efficient geometry optimization scheme to determine calculation results with less expenditure of computational effort. And this procedure has previously been widely used in other studies of helical peptides [24–27]. The ONIOM method is a versatile and popular hybrid computational method that divides the system into several onion-like layers, treating the center as high layer with expensive method, while outer layers can be treated with less expensive methods. In this Letter, the two-layered ONIOM (high and low) method is used for quantum calculations. We divide α-helical peptide into two layers, treating the peptide backbone (equivalent to a corresponding peptide containing only glycines) as the high layer with the Becke3–Lee–Yang–Parr functional [28–30] at D95 (d,p) basis set [B3LYP/D95 (d,p)], and all side chains as the low layer with AM1 [30,31] semiempirical molecular orbital method. The initial structure of α-helical polyalanine peptide is obtained from literature [25], and the optimized structure of polyalanine and Cartesian coordinates are giving in Figure 1. All geometries are then fully optimized in all internal degrees of freedom.

For this Letter, we focus on the systematic comparison among the polarizability and first-order hyperpolarizability of the α-helical peptides with single amino acid mutation in the 10th alanine. The configuration interaction among singly excited configurations (CIS) [32,33] method, which is widely used for the calculation of first-order hyperpolarizability, combined with the sum-over-states (SOS) [34,35] is employed to calculate the linear and nonlinear optical properties for substituted α-helical peptides. We have also calculated the static first-order hyperpolarizabilities of amino acids (tryptophan and tyrosine) at 6-31G*, 6-31 + G* and 6-31++G* basis sets to check the effect of diffuse functions. The values of tryptophan are 1.79×10^{-30}, 1.53×10^{-30} and 1.45×10^{-30} cm^5/esu for 6-31G*, 6-31 + G* and 6-31++G*, respectively. And the values of tyrosine are 1.03×10^{-30}, 0.85×10^{-30} and 0.87×10^{-30} cm^5/esu, respectively. These results show that the first-order hyperpolarizabilities obtained with different basis sets are similar in our studied systems. And the value of tryptophan also presents larger first-order hyperpolarizability as compared to tyrosine. This trend is similar to the experiment findings [36]. The variation trends of first-order hyperpolarizability in all substituted α-helical peptides remain unaltered by considering the diffuse functions of basis sets in the calculations. Accordingly, all discussions and studies in the text are basic on the 6-31G* basis set in order to save costs. So the SOS//CIS/6-31G* method is considered to be reasonable for systematic comparisons in the studied systems.

The compact expression of the tensor component of polarizability and the frequency-dependent first-order hyperpolarizability, which can be obtained from transition moment, dipole moment and transition energy, $\alpha_{ij}(-\omega_p;\omega)$ and $\beta_{ijk}(-\omega_p;\omega_1,\omega_2)$ can be written as follows:

$$\alpha_{ij}(-\omega_p;\omega) = (2\pi/h)\sum_p \sum_m{}' \frac{\langle g|r_i|m\rangle\langle m|r_j|g\rangle}{(\omega_{mg}-\omega_p)} \tag{1}$$

$$\beta_{ijk}(-\omega_p;\omega_1,\omega_2) = (2\pi/h)^2 \sum_p \left\{ \sum_{mn(m\neq n)}{}' \frac{\langle g|r_i|n\rangle\langle n|\Delta r_j|m\rangle\langle m|r_k|g\rangle}{(\omega_{ng}-\omega_p)(\omega_{mg}-\omega_2)} + \sum_m{}' \frac{\langle g|r_i|m\rangle\langle m|\Delta r_j|m\rangle\langle m|r_k|g\rangle}{(\omega_{mg}-\omega_p)(\omega_{mg}-\omega_2)} \right\} \tag{2}$$

For the linear response, the average polarizability is defined as:

$$\langle\alpha\rangle = \frac{1}{3}(\alpha_{xx}+\alpha_{yy}+\alpha_{zz}) \tag{3}$$

For the first-order nonlinear response, we are interested in the vector component along the ground state dipole moment direction (β_{vec}) and the total hyperpolarizability (β_{tot}), which are defined as:

$$\beta_{vec} = (\mu_x\beta_x + \mu_y\beta_y + \mu_z\beta_z)/|\mu| \tag{4}$$

$$\beta_{tot} = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2} \tag{5}$$

And

$$\beta_i = \frac{1}{3}\sum_j(\beta_{ijj}+\beta_{jij}+\beta_{jji}) \ (i,j=x,y,z) \tag{6}$$

Before attempting to compute the first-order hyperpolarizability with truncated sum-over-states (SOS) method, it is necessary to investigate the behavior of the convergence in the summation of the excited states, in order to obtain reliable results. Figure 2 shows plots of the calculated first-order hyperpolarizability varied with the number of excited states (alanine, phenylalanine, tyrosine and tryptophan substituted peptides are shown in the left figure, and the other amino acids substituted peptides are shown in the right figure). It demonstrates that all substituted α-helical peptides have very similar convergence behaviors and show some excited states which make significant contributions to the first-order hyperpolarizability. There are no obvious increases when the summations of excited states are more than 25. The convergence reaches after summation over 50 excited states, and it indicates that a reasonable approximation can be obtained by truncating the 50 excited states in our calculations. Accordingly, all discussions and studies in the following are based on the truncated SOS method with 50 excited states.

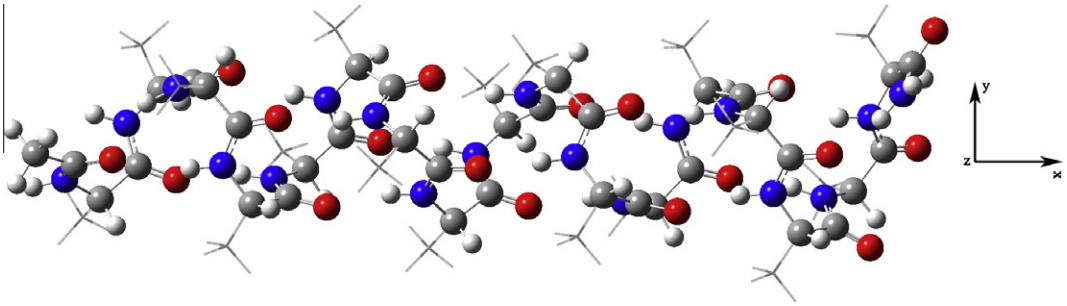

Figure 1. The optimized geometry of alpha-helical peptide and Cartesian coordinates.