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Influence of functional groups on the C_α–C_β chain of L-phenylalanine and its derivatives

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ABSTRACT

L-phenylalanine (L-phe) consists of three different functional groups, i.e., phenyl, carboxyl (–COOH) and amino ($–NH_2$), joining through the C_α–C_β bridge. Substitution of these groups produces 2-phenethylamine (PEA) and 3-phenylpropionic acid (PPA). Electronic structures of L-phe, PEA and PPA together with smaller "fragments" L-alanine and benzene were determined using density functional theory (DFT), from which core and valence shell ionization spectra were simulated. Comparison of the spectra reveals that core shell ionization energies clearly indicate that the carbon bridge is significantly affected by their functional group substitutions particularly at the C_α site. In the valence space, quite unexpectedly, the frontier orbitals are concentrated on the benzene group although some energy splitting is observed. The orbitals which significantly affect the C_α–C_β carbon backbone are from the inner valence shell in the ionization energy region of 20–26 eV of the molecules.

1. Introduction

Amino acids are the control units of proteins and play important roles in determining their structures and functions. Further, only 20 naturally existing amino acids form almost all proteins in the cellular processes. Gas phase electronic structural studies of amino acids are relevant to understand their intrinsic properties that in turn will provide insights into their interactions in polypeptides and the behaviour of larger molecules such as proteins [1–3].

L-alanine (L-ala) is the smallest chiral aliphatic amino acid, which comprises carboxyl, amino and a methyl groups attached to the alpha carbon, C_α. The essential aromatic amino acid L-phenylalanine (L-phe) is related to L-ala by replacement of a hydrogen atom on the methyl group of L-alanine by a phenyl ring. Recent data mining studies indicate that the amide–aromatic interactions of phenylalanine play a vital role in the stabilization of protein residues over large configurational spaces [4]. Thus, L-phe is one of the most significant amino acids [3,4–8]. Previous research findings suggest that intramolecular interactions of aromatic amino acids may involve different mechanisms from their aliphatic components [2,9]. Thus studies on the influence of the functional groups of L-phe through their substitution will help us gain insight with respect to the interactions among the function groups in the aromatic amino acids [2].

In L-phe, three different functional groups, that is, an amino group ($–NH_2$), a carboxyl group (–COOH) and an aromatic group ($C_6H_5CH_2–$), are connected at the chiral C_α carbon. In order to study the interactions and the role of a particular functional group in L-phe, it is logical to study L-phe derivatives formed by removal of a specific functional group, i.e., the substitution effects. For example, when the amino group of L-phe is removed, it forms 3-phenylpropionic acid (PPA) [10,11], a metabolite of the monoamine oxidase inhibitor antidepressant phenelzine [12]. Alternatively, if the carboxyl group is removed from L-phe, then it forms another important aromatic compound, 2-phenethylamine (PEA) [13–15]. Despite these changes the carbon bridge, C_α–C_β, remains in the model molecules. The objective of this study is to investigate the influence of the individual functional groups on the carbon bridge of L-phenylalanine.

2. Computational details

Computational details of this study are the same as in our previous work [2,16]. That is, density functional theory (DFT) models are employed. Specifically, vertical core shell ionization studies are carried out using the LB94/et-pVQZ//B3LYP/TZVP model [17,18], whereas valence shell ionization spectra are calculated using the SAOP/TZ2P//B3LYP/TZVP model [19,20]. Gaussian 03 computational chemistry program [21] is used for optimization whereas other calculations are performed using the Amsterdam Density Functional (ADF) chemistry package [22]. Note that the Gaussian basis set TZVP is from Godbout et al. [23], whereas TZ2P is a Slater type triple zeta plus double polarization basis set [24].

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3. Results and discussion

3.1. Core ionization and energy shift

The ground electronic state structures of the model molecules and their atom labelling scheme are shown in Fig. 1. Note that the structure of L-ala in this work is not the global minimum structure, but the second local minimum (structure 3 in Ref. [25]), as this structure best resembles the L-phe conformer in this work. All the structures are shown using the recently developed 3D-PDF technique [26], where the molecules can be observed in 3D space within the PDF file with a single mouse click (activable 3D pdf file is provided as supplementary material). The geometrical parameters of the model molecules and the vertical core ionization spectra were previously discussed [2].

The core shell energy shifts at the carbon sites of the model molecules are shown in Fig. 2, where ΔE_1 (left hand panel) reveals the interactions between phenyl and alaninyl in L-phe with respect to their free molecules, whereas ΔE_2 (middle panel) and ΔE_3 (right hand panel) reveal interactions of the amino group and the carboxyl group, respectively, with the remaining L-phe fragments. As shown by ΔE_1 all carbon ionization energies of L-phe increase with respect to the corresponding sites in alanine and benzene molecules, indicating that the interactions of the functional groups in L-phe are quite different from the cases in alanine and benzene, respectively. In particular, the ionization energy of the C_γ site on the phenyl ring increases as large as 0.51 eV. In L-phe, the D_{6h} high point group symmetry of benzene is broken so that charge distribution in L-phe is no longer the same on all carbon sites in the hexagon ring. The C_γ site directly connects the phenyl ring with the L-phe side chain and therefore, the energy changes apparently on the C_γ site. The trend in ΔE_2 reveals that removal of the amino group leads to a general decrease in ionization energy of the carbon bridge (C_α–C_β) but the C_1 site, which is contained in the carboxyl group, displays an opposite trend, increasing by 0.40 eV. Unsurprisingly, the largest effect is apparent for the C_α site, as the removed amino group is directly connected on this carbon atom.

The ionization energy changes are associated with the removal of the carboxyl group from L-phe, –COOH, forming PEA (ΔE_3) again show that the C_α site ionization energy drops most significantly with an energy of -1.21 eV and the energies of all carbon sites are lowered. From the energy shifts indicated in Fig. 2, it is observed that the interactions between –COOH and $-NH_2$ are stronger than the interactions between the alaninyl and phenyl fragments in L-phe. Both –COOH and $-NH_2$ groups are connected on the chiral carbon C_α and obviously, removal of either group will lead to the loss of chirality of the molecule and hereby alter the charge distribution of the derivatives. As a result, the core ionization energy must change.

3.2. Valence shell ionization spectra

Fig. 3 compares the resulting valence ionization spectra of the molecules. In the inner valence space, certain spectral similarities reveal a clear "fragments-in-molecule" picture in the spectra. For example, the spectra of the amino acids, L-phe and L-ala (last two spectra), show similarities in the inner valence shell in the region of IP > 20 eV; whereas the benzene and PEA pair which do not contain the –COOH group are not related to ionization processes in the region of 26 eV < IP < 35 eV. In the outer valence space, interactions and chemical bonding are so strong that it is very difficult to differentiate the fragmental contributions. The outer most frontier orbitals, however, indeed show certain fragment related features. In the case of the highest occupied molecular orbitals (HOMO) of the model molecules, the finger print of the four fold of six degenerate orbitals of benzene appears in the HOMOs of all the model molecules with a phenyl ring (except for alanine), although the break of high symmetry may split the six degenerate orbitals in other aromatic species. This observation supports our earlier finding that not all chemical reactions happen in frontier orbitals for biomolecules of more than one functional groups [9,26].

Fig. 3 also presents the valence ionization spectra of all derivatives of L-phe, including its "fragment" molecules, benzene and L-alanine. The similarities in the region between 26 and 35 eV between benzene and PEA, as well as between L-phe and L-ala, indicate that the amino group ($-NH_2$) does not contribute to this region, whereas the ionization happening in this region must be from the carboxyl group (at ca. 30 and 32 eV) and its interaction with the amino group (ca. 27 eV). The valence region of 20–26 eV

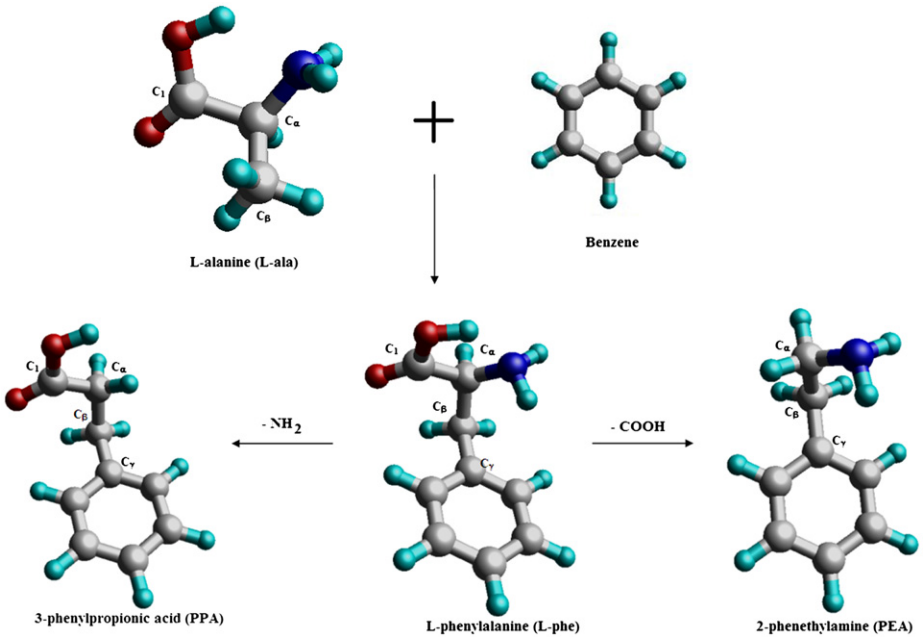

Fig. 1. Ground state electronic structures of the model molecules and their nomenclature. (Activable 3D structures provided as supplementary material).