



Double amino acid – A novel molecule enabling peptide interpenetrating structures



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ABSTRACT

Peptide chains might be linked with one another using various external bifunctional molecules. We postulate an existence of a novel molecule termed 'double amino acid' containing four functional groups connected to one C atom ((NH₂)₂C(COOH)₂). Using correlated ab initio approach (QCISD and MP2 methods) we provide its structure, simulated IR spectrum and verify its stability in gas and aqueous phases. The proposed double amino acid is predicted to enable the design of a novel family of interpenetrating peptides in which it is expected to serve as a built-in amino acid residue that might be shared by two independent peptide chains.

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1. Introduction

The importance of amino acids is undisputable. Assembled into various proteins, the amino acids (AA) comprise the second largest component of human cells and tissues. Their natural ability to group into chains (peptides) [1,2] and to form large and complicated structures (such as proteins) is constantly investigated, both experimentally and theoretically. The proteinogenic AAs attract obvious and understandable attention, however, the significance of natural but non-proteinogenic (i.e., not encoded in the genetic code) amino acids has also been confirmed [3]. Although various types of higher-order peptide and protein structures have already been investigated thoroughly, the possible existence of mutually interpenetrating peptides (formed by sharing amino acid residues) has not been considered thus far.

In this Letter, we postulate the possible existence of an amino acid that may serve as a peptide linkage of new type due to its tetrafunctional structure. In particular, the system we propose, when assembled into a peptide chain, should enable the formation of peptide interpenetrating structures (rather than crosslinked peptides obtained with commonly used bifunctional reactants). The predicted structures of two representative species of such interpenetrating peptides (composed of α -helix Ala chains) are demonstrated and discussed.

2. Methods

The preliminary search for various isomeric (NH₂)₂C(COOH)₂ (labeled DAA) structures was initially performed using the second-order Møller–Plesset perturbational method (MP2) and the aug-cc-pVDZ basis set [4] and then refined by employing the quadratic configuration interaction method including single and double substitutions (QCISD) [5–7] and the same aug-cc-pVDZ basis set (both in the gas phase and including solvent effects). The final equilibrium structures and harmonic vibrational frequencies were determined using the QCISD method with the aug-cc-pVDZ basis set. The reported Gibbs free energies (ΔG) for decarboxylation of both DAA (i.e., canonical DAA) and [−]DAA (i.e., half- and fully-zwitterionic DAA) were obtained at the QCISD/aug-cc-pVDZ level whereas those for the remaining larger systems (DAA(Ala)₄ in its canonical and zwitterionic forms) were calculated using the B3LYP method [8,9] and the 6 – 31 + G* basis set [10,11]. The equilibrium geometries of DAA(Ala)₄ in its canonical, half-zwitterionic, and fully-zwitterionic structures, as well as the structure of the DAA(Ala)₁₂ were determined at the B3LYP/6 – 31 + G* level. The effects of surrounding water molecules were approximated by employing the polarized continuum solvation model (PCM) [12–14] within a self-consistent reaction field treatment, as implemented in the GAUSSIAN09 program (the default options for PCM and the dielectric constant of 78.39 for water were used). All calculations were performed using the GAUSSIAN09 program package [15].

3. Results and discussion

The novel molecule we propose is described by the (NH₂)₂C(COOH)₂ formula and consists of two amino and two carboxyl

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groups connected to the same C atom. Formally, any organic compound with an amine and a carboxylic acid functional group is an amino acid. Albeit most proteinogenic α -amino acids possess hydrogen atom linked to the α -carbon, this is not always the case (known exceptions include amino isobutyric acid and dehydroalanine). Thus, the molecule whose possible existence and stability we postulate, given by the $(\text{NH}_2)_2\text{C}(\text{COOH})_2$ formula, might be termed an amino acid, despite the absence of hydrogen atom on the α -carbon. Moreover, we suggest to term it a 'double amino acid' (DAA) since the number of its functional groups is doubled with respect to a regular AA.

We found several isomers of DAA that are locally geometrically stable (in aqueous and gas phases). As expected, canonical structures $((\text{NH}_2)_2\text{C}(\text{COOH})_2)$ dominate in the gas phase, whereas half-zwitterionic $((\text{NH}_3^+(\text{NH}_2)\text{C}(\text{COOH})(\text{COO}^-))$, labeled $^+\text{DAA}^-$ and fully-zwitterionic $((\text{NH}_3^+)_2\text{C}(\text{COO}^-)_2)$, labeled $^{++}\text{DAA}^{--}$ forms are predicted to predominate in the presence of water solvent [16] (whose influence was approximated by employing the polarized continuum solvation model as implemented in GAUSSIAN09 package). The equilibrium structures of the most stable isomers in both gas and aqueous phases are presented in Figure 1 together with the corresponding simulated IR spectra (to enable their future experimental identification). The global minimum predicted for the gas phase corresponds to the canonical form of DAA (with two NH_2 and two COOH groups intact) whereas the half-zwitterionic form ($^+\text{DAA}^-$) was found to be the most stable in aqueous solution. The geometrical structures and harmonic vibrational frequencies characterizing these species (obtained using the QCISD method

with the aug-cc-pVDZ basis set) indicate that the hydrogen bonds formed between the amino and carboxyl groups are crucial for their stability. Albeit the presented structures represent the global minima, other low-energy isomers/conformers were also predicted (i.e., three and five isomeric structures in gas and aqueous phase, respectively) to be competitive as their relative energies do not exceed those of the most stable structures by more than 5 kcal/mol. Most of those low-energy isomers, however, are in fact conformers that differ from one another only by mutual functional group orientations and thus the resulting H-bond network.

Due to its rather untypical structure (two carboxyl groups bound to the same C atom), the stability of the DAA might be questioned. Since decarboxylation is the most intuitive and probable fragmentation process this system may be vulnerable to, we verified the stability of DAA with respect to CO_2 loss. As expected, we found canonical DAA to be susceptible to decarboxylation in the gas phase (the Gibbs free energy (ΔG) for this reaction is -16.4 kcal/mol) which is typical also for various common amino acids (ΔG values for the analogous reactions involving isolated glycine and alanine read -16.7 and -15.6 kcal/mol, respectively, as we determined at the same theory level). In the presence of polar solvent (water), however, typical amino acids exist as zwitterions and are stable with respect to decarboxylation. Indeed, the positive ΔG values of ca. 50–54 kcal/mol are predicted for zwitterionic glycine and alanine when the CO_2 loss is considered at such conditions. Analogous observations might also be made for simple peptides, e.g., we found the Ala-Ala-Ala tripeptide to be unstable in gas phase ($\Delta G = -8$ kcal/mol) but stable in water ($\Delta G = 62$ kcal/

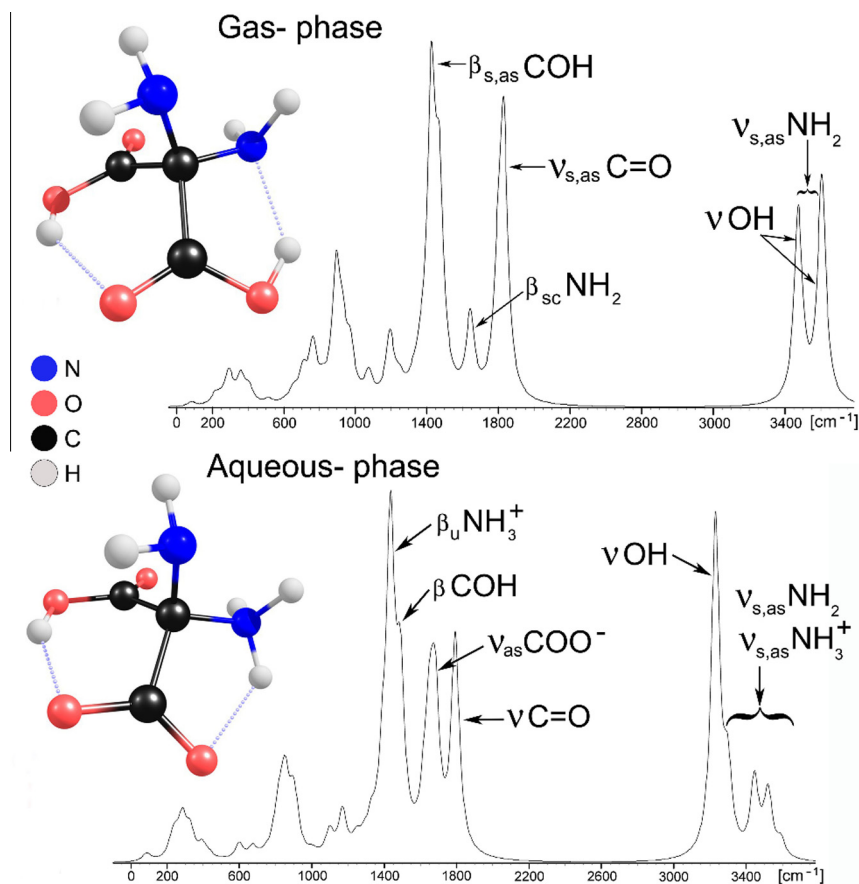


Figure 1. The equilibrium structures of the most stable isomers of DAA in gas (top) and aqueous (bottom) phase. The corresponding simulated IR spectra are based on the calculated harmonic vibrational frequencies (the lorentzian peaks with fwhm of 54 cm^{-1} were assumed). Selected vibrations are indicated with: β -bending, ν -stretching, s -symmetrical, as -asymmetrical, sc -scissoring, u -umbrella. The presented geometrical structures and vibrational frequencies were determined at the QCISD/aug-cc-pVDZ level.

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