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Research paper

Structure and stability of complexes of agmatine with some functional receptor residues of proteins

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ABSTRACT

The paper reports the results of a theoretical study of the conformational behavior and basicity of biogenic amine agmatine. The complexes modelling of agmatine – protein interaction are also under scrutiny of our investigation using the Becke3LYP and B97D levels of the density functional theory. The relative stabilities (Gibbs energies) of individual complexes are by both DFT methods described equally. Hydration has a dramatic effect on the hydrogen bonded complexes studied. The pairing acidic carboxylate group with different agmatine species resulted in charged hydrogen bond complexes containing negatively charged acetate species acting as proton acceptors.

1. Introduction

Agmatine 1-(4-aminobutyl guanidine) is one of the precursors of arginine containing a guanidine residue and serving as cell-signaling molecule. Agmatine is produced by the enzyme arginine decarboxylase localized in mitochondrial fraction of most mammalian cells and identified in brain, liver, adrenal gland, kidney, small intestine and macrophages [1]. Agmatine was initially investigated as an endogenous ligand at α2-adrenoceptors and imidazoline receptors [2]. However, current knowledge of agmantine pharmacological and physiological functions indicates much greater therapeutic potential of the compound [1–3]. It was shown that agmatine may play important roles in diseases such as diabetes, Alzheimer's disease, anxiety disorder, depression, drug addiction, and cancer [3]. Agmatine itself is a highly hydrophilic compound with ClogP equal to −1.8 [4] and guanidine functionality representing the strongest basicity among the amine derivatives [5]. Toninello et al. examined the structural preference of agmatine species computationally using B3LYP/6–31G** density functional theory (DFT) [6]. The proteins and enzymes commonly use the guanidine group of the guanyl species to recognize and bind anionic sites through ionic and hydrogen bonding interactions [7,8]. The experimental structural data indicate that the agmatine in the active site of biopolymers exists in its diprotonated form [9,10]. Systematic analyses of available structural crystallographic data of the agmatine with proteins have shown that Gly and Asp residues of proteins are in the position to have ionic or hydrogen bond interaction with the positively charged guanidine moiety. The positively charged amino group of agmatine interacts with complementary sites of Glu and Ser. The "spacer" —C_4H_8— forms hydrophobic bonds with Tyr or Val [9,11]. The bulk of these hydrogen bonds are ionic-type interactions. However, despite of their great pharmacological importance, the detailed nature of these interactions still remains one of the structurally and energetically less well characterized.

The present paper reports in detail the structural data for agmatine, its mono- and di-cations and their interaction with amino acid residues typical for binding sites of biopolymers. They are selected to model the typical interaction of agmatine with the hydrogen bonding interaction sites of biopolymers. Model chemistry at the DFT level was applied for this study. The molecular structure of various species of agmatine and overall shape its complexes with selected amino acid residues are examined in this work. Of particular interest is the molecular structure of agmatine and how this structure is changed upon protonation, molecular complexation and/or solvation. The typical receptor fragments are not confined as in real receptor sites, therefore the obtained geometries and thermodynamic quantities cannot be directly applied to interactions in the receptor sites, in which the fragments will embedded in protein structures and have limited mobility and possibly also conformational flexibility and/or bonding ability. Nevertheless,

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the study provides useful information about speciation and typical geometries of individual bonds, which will be helpful in further studies.

2. Computational details

The geometry of agmatine species and their molecular complexes (Fig. 1) have been completely optimized with the Gaussian 09 program [12] at the Becke3LYP level of DFT [13–16] and B97D Grimme's functional including dispersion [17] using the polarized triple-ζ 6–311++G(d,p) basis set [18]. Effect of water hydration on the species investigated was computed by means of the conductor-like polarizable continuum model (CPCM) [19,20]. The structures of all gas-phase and condensed-phase (CPCM) species were fully optimized without any geometrical constraint. The gas-phase proton affinity and basicity of agmatine was computed the same way as in our previous publications [21,22].

The macroscopic pK_a values were computed using program SPARC [23–26]. The interaction energy, ΔE, for the interaction of polar groups of agmatine (Agm) with complementary sites of amino acids (AA) in relevant biopolymers is given by the following equation

$$\Delta E = E[\mathrm{Agm}\cdots\mathrm{AA}] - \{E[\mathrm{Agm}] + E[\mathrm{AA}]\} \quad (1)$$

where E[Agm] and E[AA] are the energies of the agmatine species and Lewis acid molecules, respectively, and E[Agm AA] is the energy of the complex.

3. Results and discussion

3.1. Molecular structure of the agmatine species

In an organism agmatine is formed by enzymatic decarboxylation of L-arginine. The basicity of agmatine is derived from the presence of guanidine and amine moieties at both termini of molecule. The high basicity of the guanidine moiety is derived from the guanidine conjugation system that is formed after protonation. Agmatine contains five rotatable bonds and can be present in different conformations in different structural environments. Neutral species agmatine can be present in three conformational forms (amino tautomers I and II and imino tautomer III). The relative stability of these tautomeric forms is presented in Table 1. Based on the relative Gibbs energies the amino tautomer II is the most stable species (Fig. 1) in both gas-phase and aqueous environment. As regards of imino tautomers two conformers (cyclic structure IIIa and "extended" form IIIb, Fig. 1S of Supplementary information) were considered. The high and negative relative entropy change

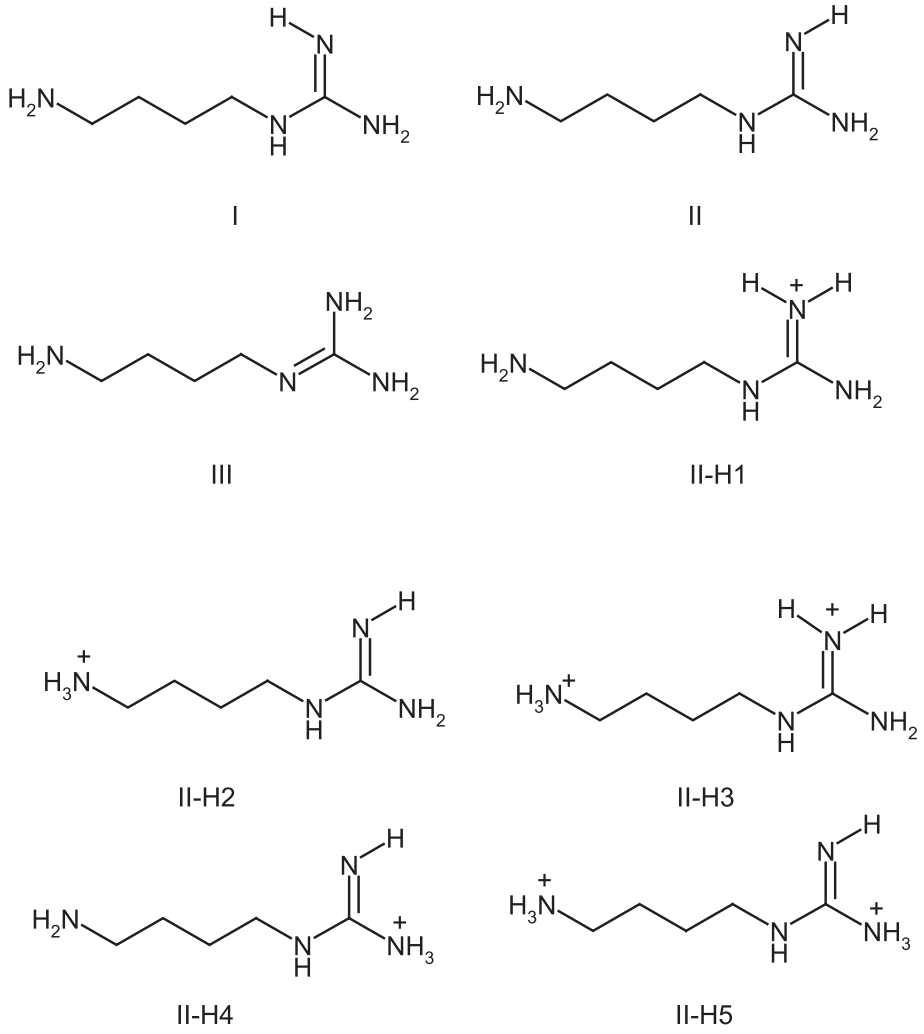

Fig. 1. Structure of the agmatine species studied.