



Quantum chemical study on phenethylamines reveals new cation structures



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ABSTRACT

Phenethylamines are compounds known by their psychoactive and stimulant effects. Their physiological activity is strongly conformer dependent. In this work, the quantum chemical investigation of neutral and cationic phenylethylamine, amphetamine and methamphetamine was performed in order to determine the most stable physiologically relevant conformers. Calculations were performed employing density functional theory and ω B97XD functional. A previously unknown double-ring cation structure formed by cyclization of aliphatic tail was found for all three molecular species. Calculations performed on several levels of theory reveal significant stability of these double-ring cations relative to other conformers. The transition state structures and energies for the cyclization reactions have been determined. Their stability and structural properties are discussed, as well as the possibility for their experimental observation. The significance of dispersion and $\text{NH} \cdots \pi$ interactions between side chain and phenyl ring on stability of phenethylamines and their charged forms were pointed out.

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1. Introduction

Phenethylamines are a broad class of chemical compounds derived from phenylethylamine (2-phenylethylamine), best known by their various influences on the central nervous system (CNS). Phenethylamine (PEA) is naturally present in humans, animals, plants and some sorts of food [1]. Alongside with its mood elevating and euphoriant effect, it is found that PEA behaves as a neuromodulator and neurotransmitter in the CNS [2]. Moreover, it is clinically proved that its concentration rises in a human body during physical activity [3]. If phenethylamines are present in plants, they can act as insect deterrents or increase the resistance to fungus [4]. Substituted PEA compounds, such as amphetamine (1-phenylpropan-2-amine, AA) and methamphetamine (*N*-methyl-1-phenylpropan-2-amine, MA), have similar chemical structure and biological properties as PEA. Their chemical structures are given in Fig. 1. Since AA possesses one chiral carbon atom, it exists in two enantiomer forms. The dextrorotatory enantiomer, with (*S*) absolute configuration, exhibits stronger biological activity. Methamphetamine also exists in two enantiomeric forms. Both are neurotoxic because they damage dopamine and serotonin neurons in the CNS and cause strong addiction [5]. As in the case of AA, the dextrorotatory enantiomer of MA with (*S*) absolute configuration is a much stronger CNS

stimulant [6]. It is illegally used as a drug for mood elevation and increasing concentration [7], but also for some medical treatments such as narcolepsy [8]. The levorotatory enantiomer has a much weaker influence on the CNS and it is used in some countries as a nasal decongestant.

The presence of methyl and amino groups within the flexible side chain of phenethylamines enables existence of several conformers for each species. Specific conformation of these molecules is a key for activating targets in CNS, because their activation is based strongly upon molecular complementarity. The conformations of phenethylamines are found to be governed by dispersive interactions and intramolecular $\text{NH} \cdots \pi$ interactions [9]. These interactions were analyzed in similar systems and it was shown that they play an important role in their stability [10].

Several experimental and theoretical studies examined conformational isomers of phenethylamines [9,11–17]. Sun et al. [11] have spectroscopically determined the existence of five PEA conformers. The authors proposed the most stable conformation. Weinkauff et al. [12] have studied geometries of PEA conformers, as well as their cations. Employing density functional theory, they demonstrated the existence of at least two cation conformers of PEA, which differ strongly in geometry from the neutral PEA conformers. They also recorded a high resolution multiphoton ionization photoelectron (MPI-PE) spectrum of PEA and concluded that a charge delocalization is equally shared between the benzene chromophore and amino group. This was not a surprising result since

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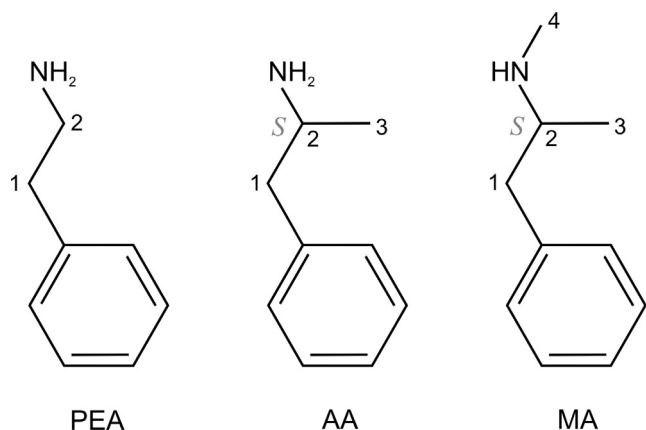


Fig. 1. Chemical structures of the phenethylamines examined in this work: phenethylamine (PEA), amphetamine (AA) and methamphetamine (MA). Numbers show numeration of carbon atoms in the side chain. Absolute configuration of the chiral C2 atom is indicated for AA and MA enantiomers studied in this work.

separate ionization energies of these groups are similar. Various conformations of AA and MA have also been reported in the literature [13–16]. These conformations are mainly influenced by dispersive interactions between side chains and the phenyl ring [17]. Energy differences between all these conformers are reported to be ≈ 1 kJ mol^{−1}.

In the present work, we perform geometry optimizations of several most stable neutral and cationic conformers of PEA, AA and MA molecules. We focus only on those enantiomers that exhibit the highest biological activity, namely (*S*)-AA and (*S*)-MA (cf. Fig. 1). We find a new cyclic cation structures which can be formed by cyclization of the aliphatic tail. These structures have not been reported previously in the literature. Preliminary examination of these cyclic cations reveals their high stability. The transition states for their formation are found and their validation by IRC calculation is conducted. Activation energies for cyclization reactions are reported. Finally, a brief review of their further chemical transformation toward neutral species will be disclosed.

2. Computational details

Calculations were performed with the GAUSSIAN program package [18]. Density functional theory (DFT) with the ω B97XD functional [19] was employed for electronic structure calculations. This functional is found to be particularly successful in describing non-bonded interactions due to the presence of dispersion terms [20,21]. All calculations were performed in the C1 point-group symmetry in vacuum with the 6-311++G(2df,2pd) basis set. The employed Pople basis set with diffuse and polarization functions enables proper description of non-covalent interactions (dispersion and NH $\cdots\pi$ interactions) present in studied systems. Besides, M06-2X [22] and B3LYP [23–26] functionals as well as the CC2 coupled cluster method [28] were employed in order to gain additional insight into stability of the conformers. The later method implemented in TURBOMOLE program package [29] was used with cc-pVTZ basis set. The geometry optimization of cations was performed employing unrestricted formalism, since the number of electrons is odd. For IRC calculations, maximum step size was set to 5 and HPC algorithm [27] was employed. Ionization energies are calculated as the differences between the sum of electronic and zero point energies of the corresponding neutral and cation species. The electron removed in the ionization process is assumed to have zero values of potential and kinetic energies.

3. Results and discussion

3.1. Phenylethylamine

We optimized the geometries of the three most stable conformers of PEA found in previous studies [11,12] at ω B97XD/6-311++G(2df,2pd) level. Their structures and energies relative to the most stable one are displayed in Fig. 2a. According to their order of stability, they are labelled PEA1, PEA2 and PEA3. PEA1 and PEA2, in which the NH₂ group is *gauche* to the phenyl ring, have energies that differ by only 0.026 kJ mol^{−1}. This small energy difference implies that both conformers are populated at room temperature. Stabilization of PEA1 and PEA2 conformers stems from the NH $\cdots\pi$ interaction, which lacks in PEA3 (with *anti* position between NH₂ and phenyl). Therefore, PEA3 is by 2.99 kJ mol^{−1} less stable than PEA1. The order of stability presented in the current study is the same as found in previous calculations of Weinkauff et al. [12] at B3LYP/6-31+G* level. The similar order of stability is obtained with other methods, as we shall discuss later. Selected geometry parameters of these conformers are collected in Table 1. Lengths of C_{Ph}-C1, C1-C2 and N-C2 bonds differ by 0.01 Å at most. Also, the C1-C2-N-H dihedral angle has a similar value for PEA2 and PEA3 but slightly larger for PEA1. The C_{Ph}-C1-C2-N dihedral angle amounts to 180 degrees in PEA3, whereas it is approximately 60 degrees in PEA1 and PEA2 conformers.

Optimized geometries of the cations and their relative energies to the most stable one are presented in Fig. 2b. Cations arising from specific PEA conformers are depicted on their right side in Fig. 2. The most stable cation was found to be PEA3⁺. We have found that the PEA2⁺ cation converges to PEA1⁺. A similar conclusion was obtained previously by Weinkauff et al. [12]. These authors proposed that charge-dipole interactions (present in *gauche* and *anti* conformers) and charge delocalization effects (in *anti* conformers) are the cause of significant geometry differences between neutral and cationic species. Selected bond lengths and dihedral angles of the optimized cations are presented in Table 1. The main structural differences occur in the amino group which becomes planar, similar to the case of ammonia ionization [30]. The formation of cations is further followed by shortening of the C_{Ph}-C1 and N-C2 bonds by ≈ 0.05 Å, and by elongation of the C1-C2 bond by ≈ 0.16 Å. Torsion angles τ_1 (C_{Ph}-C1-C2-N) and τ_2 (C1-C2-N-H) change upon ionization in the case of PEA1⁺ by 8 and −23 degrees, respectively. Smaller dihedral angle changes are found in the case of PEA3⁺.

By performing further analyses of the cation conformers, we found a new structure in which the flexible tail closes to form a ring. This structure is presented in Fig. 2c. A new chemical bond is formed between the nitrogen and a carbon atom from the phenyl group. The length of this bond amounts to 1.54 Å. The carbon atom bound to the nitrogen atom, exhibits weakening of the other bonds it forms with neighbouring C atoms. These bonds are found to be elongated from 1.40 to 1.48 Å, whereas the rest of the phenyl ring structure undergoes slight deformations. Formation of this structure is also followed by stretching of the N-C2 bond and significant changes in the torsion angles (cf. Table 1). The amino group is found to be nonplanar, contrary to the other cation conformers. We have marked this structure as PEA0⁺, because it is by far the most stable compared to other cations. Its ground state lies 29.37 kJ mol^{−1} below the PEA3⁺ ground state, and its structure differs significantly from the structure of other PEA neutrals and cations.

Since neutral PEA conformers differ slightly in energy, we calculated their energies with M06-2X [22] and B3LYP [23–26] functionals (with the 6-311++G(2df,2pd) basis), and also on CC2/cc-pVTZ level, in order to check confidence of present results. Calculations

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