

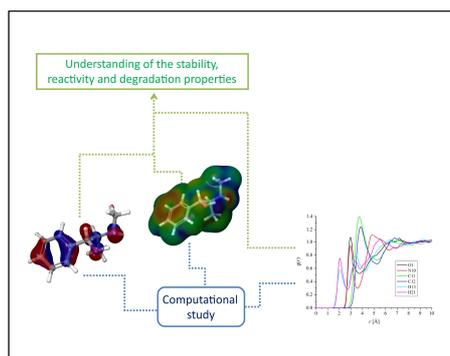


# Computational Studies of Stability, Reactivity and Degradation Properties of Ephedrine; a Stimulant and Precursor of Illicit Drugs

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## Keywords:

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Molecular dynamics;  
Intramolecular noncovalent interactions;  
Bond dissociation energy.

## ABSTRACT

Some of the most important properties of ephedrine (EPH) molecule, related to its stability, reactivity and degradation have been computationally addressed in this work. The study has been performed based on the combination of classical and quantum-mechanical calculations to yield the lowest energy conformer. Furthermore, the most important intramolecular noncovalent interactions have been identified and their influence on the structural features have been analyzed. Energy and distribution of the frontier molecular orbitals have been analyzed in order to address the stability and charge transfer properties. The average local ionization energy descriptor has been used in order to identify the molecular sites that are sensitive towards the electrophilic attacks. Bond dissociation energies for hydrogen abstraction have been calculated in order to identify the sites of EPH sensitive towards the autoxidation mechanism. Interactions of EPH have been also investigated using the molecular dynamics simulations and calculations of radial distribution functions.

## Introduction

Ephedrine, with the chemical name of ((1R,2S)-2-(methylamino)-1-phenylpropan-1-ol; EPH) is an active component of the Ephedra plant and is a well-known medication, stimulant and precursor for the synthesis of illicit drugs. These facts mark it as one of the most important compounds in the market. From a medical standpoint, it increases the blood pressure, in which it has been applied as

bronchodilator [1]. It is also used to treat influenza and hypotension [2]. EPH belongs to sympathomimetic amines and substituted amphetamines, which are known for their stimulant effects [3]. Regarding its stimulant effects, some athletes have abused EPH, so the World Anti-doping Agency (WADA) has limited its presence in the urine of athletes to 10 µg/ml [4]. From the aspect of structure, EPH is very similar to

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the methamphetamine. Therefore, it is not strange that EPH is used as a substitute for recreational drugs, or as a precursor for the synthesis of recreational drugs [5, 6]. Because of this, its production in pure form is closely monitored. However, it is easily available, since it is a frequent component of dozens “over-the-counter” medications [7]. Once introduced into the organism, many pharmaceuticals are excreted in the unchanged form, in the form of urine or metabolites, which eventually end up in water resources. Pharmaceuticals were detected in environmental waters throughout the world and their increasing pollution is one of the global problems of community [8, 9]. They have been detected in concentrations of several  $\text{ng}/\text{cm}^3$ . EPH is yet another pharmaceutical molecule detected in the tap water [2, 9, 10]. The ecological toxicity of EPH to aquatic organisms has been confirmed [9, 11], which necessitates the exploration of new efficient methods to remove it from water [12]. EPH is gaining in popularity regarding its overuse; therefore, the increased interest of the scientific community over the last few years in properties of EPH is not strange at all [13-17]. In the same time, computational analyses of the pharmaceuticals have become an indispensable tool for the investigation of various molecular properties, which could be important during the synthesis of new pharmaceutical derivatives [16]. Modern computational methods could indicate potential degradation intermediates, which are often even more toxic than their parent compounds [18]. Hereby, the aim of this work has been set to improve understanding the stability, reactivity and degradation properties of EPH. In this study, we have investigated fundamental reactive properties of EPH, using both density functional theory (DFT) calculations and molecular dynamics (MD) simulations. DFT calculations have given us an insight into structural, global, and local reactivity properties of matters [19-21]. Bond dissociation energies for hydrogen abstraction (H-BDE)

provided valuable information on molecular sites prone to autoxidation mechanism. On the other side, understanding interaction of EPH with water is of importance for the understanding of its fate in environmental waters, which have been addressed in this work by MD simulations.

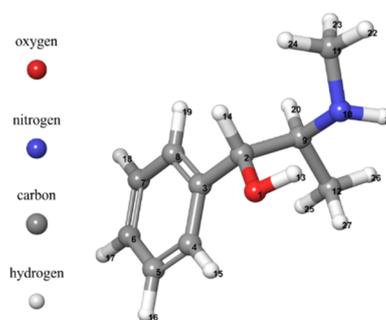


Fig. 1. Geometrically optimized structure of EPH.

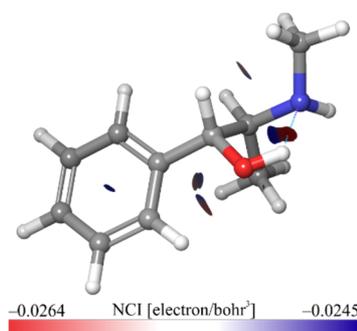


Fig. 2. Intramolecular noncovalent interaction and RDG surface of EPH.

## Materials and Methods

Schrödinger Materials Science Suite 2020-1 was applied in this work, in order to study the properties of EPH molecule based on computations. MacroModel [22], Jaguar [5], Desmond [8] and Maestro [18] programs for generation of conformers, DFT calculations, MD simulations, and preparation and visualization of results have been used, respectively. DFT calculations have been obtained employing the B3LYP functional [29], with 6-31G(d,p) basis set. MD simulations were obtained by the OPLS3 force field [26, 30-32] by placing one EPH molecule into the cubic simulation box filled with approximately 2000 water molecules. The most important parameters of MD simulation were as following: simulation time was set to 10 ns, temperature to

300 K, pressure to 1.0325 bar and cut-off radius to 10 Å, while the MD system was considered as isothermal-isobaric (NPT) ensemble. Water was modeled using the simple point charge model [33].

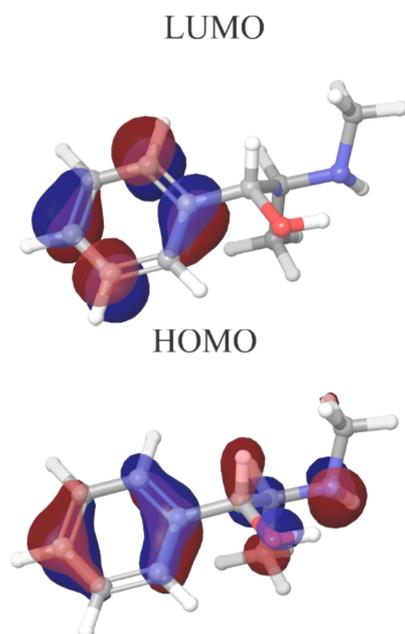


Fig. 3. Frontier molecular orbitals of EPH.

## Results and Discussion

### Structure and Intramolecular Noncovalent Interactions of EPH

The lowest energy conformation of EPH was used for all further calculations related to stability, reactivity and degradation properties. The lowest energy conformation was obtained after the geometric optimizations at the B3LYP/6-31G(d,p) level of theory on all possible conformations of EPH, which has been previously generated by MacroModel program on the basis of OPLS3e force field. Optimized geometry of the lowest energy conformer is presented in Fig. 1. In order to understand the structure of EPH, we were interested in finding if there exist significant intramolecular noncovalent interactions that would influence the structure of the considered lowest energy conformation of EPH or not. The search and analysis of intramolecular noncovalent interactions was performed on the basis of procedures developed by Johnson et al [34, 35], which are implemented in Jaguar program. The

identified intramolecular noncovalent interaction, together with the corresponding reduced density gradient (RDG) surface is presented in Fig. 2. Within the structure of the lowest energy conformer of EPH, only one, but rather strong/significant noncovalent interaction has been identified. Its strength, expressed in terms of electron density, has been calculated to be  $-0.0264$ . This noncovalent interaction is formed between the hydrogen atom belonging to the OH group and the nitrogen atom, and its bond critical path is indicated by the blue dotted line in Fig. 2. Also, the bond critical point is clearly enclosed by the red-colored RDG surface, confirming the presence of the hydrogen bond. It is also observable that this noncovalent interaction significantly affects the structure of EPH, since the OH group orients towards this interaction.

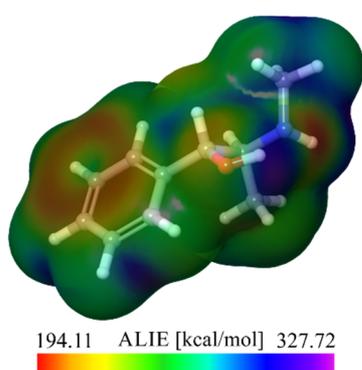
### Frontier Molecular Orbitals and ALIE Surface

Frontier molecular orbitals belong to a group of the most important global stability and reactivity parameters. Usually, the topology and energy values of the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO, respectively) are visualized and reported. These orbitals indicate two very important aspects of a molecule. First, the energy difference between the HOMO and LUMO, known as the HOMO-LUMO gap, indicates the overall stability of a molecule. The higher this value is, the more stable molecule is. Second, the distribution of these orbitals, showed in Fig. 3, indicates the charge transfer that occurs within the molecule, which helps in identification of the possible reactive sites.

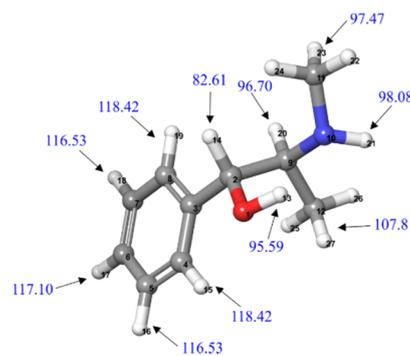
As expected, the HOMO-LUMO gap of the EPH molecule is taking a relatively high value equal to 6.30 eV, showing that the molecule exhibits a considerable stability. Although this parameter cannot be considered as an absolute stability indicator, its high values show that this molecule is highly stable and that its degradation under natural conditions is not probable. On the other

side, the distribution of HOMO and LUMO orbitals clearly indicates the direction of charge transfer. Namely, according to the Fig. 2, HOMO is delocalized over the whole molecule, while the LUMO is localized within the benzene ring. Such distribution indicates that the charge transfer occurs from aliphatic to aromatic part of the molecule. In terms of reactivity, it is also useful to identify the molecular sites that are sensitive towards the various types of attacks. In these regards, the quantum molecular descriptor called average local ionization energy (ALIE) [36, 37] have proven to be particularly useful for the identification of the molecular sites prone to electrophilic attacks. This quantity is usually presented in the form of density surface to which the values of ALIE have been mapped [37-45]. The corresponding ALIE surface of EPH is presented in Fig. 4.

The presented ALIE indicates that, in terms of sensitivity towards the electrophilic attacks, there are two specific sites within EPH molecule. Namely, the lowest values of ALIE indicate where the electrons are the least tightly bonded to the molecule, i.e. where it is necessary to invest the lowest amount of energy in order to remove an electron. Such sites are the most sensitive towards the electrophilic attacks and it can be seen in Fig. 4 that such sites within EPH are around the benzene ring and in the near vicinity of nitrogen atom. These sites are characterized by the lowest ALIE values of around 194 kcal/mol.



**Fig. 4.** ALIE surface of EPH.

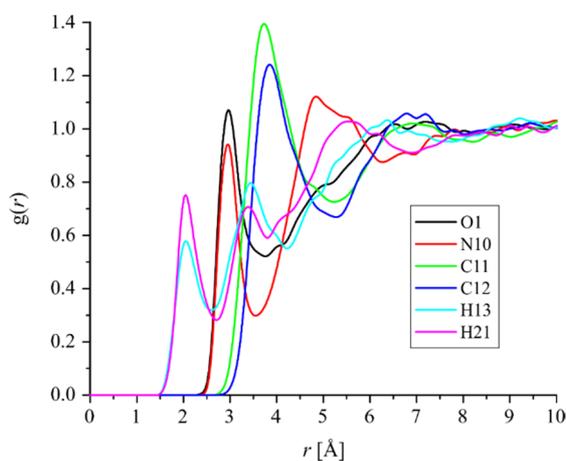


**Fig. 5.** H-BDE values of EPH molecule.

### *Bond Dissociation Energies for Hydrogen Abstraction*

It has been demonstrated that the bond dissociation energies for hydrogen abstraction (H-BDE) have an important role in medicinal chemistry because it can be used in order to predict the molecular sites where carbon-hydrogen bonds are broken for hydroxylation (46). Additionally, from the aspect of pharmaceutical sciences, it is also important to mention that H-BDE are important computational approach for the assessment of sensitivity of molecule's degradation by autoxidation [47, 48]. It has been established that the critical values of H-BDE indicating sensitivity towards the autoxidation are located in the interval between 70 kcal/mol to 85 kcal/mol, while the range between 85 and 90 kcal/mol can also be considered as important [47-49]. The H-BDE values of EPH molecule are summarized in Fig. 5. H-BDE results as presented in Fig. 5 show interesting property of EPH molecule. Namely, the H-BDE for the hydrogen atom H14 is significantly low (82 kcal/mol) to indicate that EPH molecule could be sensitive towards the autoxidation mechanism at precisely this molecular site. This also means that one of the initial degradation steps could be via the detachment of H14. This result is completely in accordance with the experimental observation reported in the recent reference by Chen co-workers [12]. In the mentioned study, the authors have performed the photocatalytic degradation of EPH in the presence of several newly synthesized

photo-catalysts. Namely, the degradation intermediate, which is practically the dehydrated EPH molecule with  $m/z$  148, was experimentally identified in the mentioned study as one of the initial degradation intermediates.



**Fig. 6.** Selected RDFs for EPH in water.

### *Influence of Water*

The influence of water on the atomic features of EPH molecule was investigated via MD simulation. Namely, the interactions between water molecules and corresponding atoms of molecule can be investigated by using the radial distribution functions (RDF). This quantity provides information about the probability of finding a particle at certain position in space, with respect to the distance between particles. In this work, the RDFs were calculated with respect to the corresponding atom of EPH and the oxygen atom of water molecules. The obtained curves indicate at which distances from certain atom, the probability of finding a water molecule is the highest. Sharper and higher  $g(r)$  curve at certain distance, indicates the higher probability of finding a water molecule. The most important RDFs in case of the EPH molecule in water are presented in Fig. 6. The obtained results regarding RDFs are also quite interesting. Not only that hydrogen molecules belonging to O and N atoms have their maximal  $g(r)$  values located at very low distance of just 2.0 Å, but two and three distinct solvation spheres also characterize their RDFs,

respectively. When compared, it appears that the hydrogen atom H21 is having stronger interactions with water molecules than hydrogen atom H13, due to the significantly higher  $g(r)$  values and the higher number of solvation spheres. Oxygen and nitrogen atoms are also having significant interactions with water molecules, as evidenced by the sharp  $g(r)$  curves whose maximal values are located at distances of around 2.7 Å. While  $g(r)$  curve is higher in case of the oxygen atom, the  $g(r)$  curve in case of the nitrogen is slightly sharper. RDFs of carbon atoms belonging to methyl groups should be also mentioned, thanks to their high and sharp  $g(r)$  curves located at rather high distances of around 4 Å. Therefore, it can be stated that the EPH molecule is having relatively significant interactions with water molecules, mainly due to the OH and NH groups.

### **Conclusion**

Analyses Details of obtained information from computational study via DFT calculations and MD simulations revealed the most important properties of EPH molecule related to stability, reactive and degradation properties. The analysis of electron density identified one very strong intramolecular noncovalent interaction that involves the hydrogen atom of OH group and the nitrogen atom. The bond critical point of this noncovalent interaction is also enclosed by the reduced density gradient surface, indicating strong hydrogen bond. This noncovalent interaction also significantly influences the geometry of EPH structure, as it orients the OH group towards the nitrogen atom. Energies of frontier molecular orbitals indicate high stability of this molecule, while their distribution indicates that the charge transfer occurs from aliphatic to aromatic part of the molecule. The most sensitive molecular site of the EPH towards the electrophilic attacks is certainly the nitrogen atom, according to the ALIE values mapped to the electron density surface. In terms of autoxidation mechanism, the

calculations of H-BDE indicated that the most sensitive site could be the site of hydrogen atom H14. Namely, the lowest H-BDE value was calculated precisely for this atom and the importance of this molecular site has been also confirmed by the experimental study of Chen and co-workers [12], where the degradation intermediate corresponding to EPH molecule without the H14 atom has been identified. According to the MD simulation, EPH has relatively significant interactions with water molecules,

mainly due to the contributions of OH and NH groups. The two corresponding hydrogen atoms, H13 and H21, are having sharp  $g(r)$  curves located at low distances of 2 Å, which indicates strong interactions with water molecules.

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