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Comparative Computational Investigation of the Electronic Structure and Global Reactivity of Dopamine, Norepinephrine, and Epinephrine

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Abstract: ***Neurotransmitters play fundamental roles in regulating communication within the nervous system, with catecholamines such as dopamine, norepinephrine, and epinephrine exhibiting closely related molecular structures but distinct biological functions. In this study, a computational chemistry approach was used to investigate the electronic properties and global reactivity descriptors of these three catecholamines. Density functional theory calculations were used to obtain frontier molecular orbital energies, from which the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), HOMO-LUMO energy gap, ionization potential, electron affinity, chemical hardness, chemical softness, chemical potential, electronegativity, and electrophilicity index were determined. Among the investigated molecules, dopamine showed the smallest HOMO-LUMO gap (5.6061 eV) and the lowest chemical hardness (2.8030 eV), suggesting greater electronic softness and potential chemical reactivity. Epinephrine exhibited the largest HOMO-LUMO gap of 5.8434 eV and the highest chemical hardness of 2.9217 eV, indicating comparatively greater electronic resistance to perturbation. Norepinephrine showed intermediate values for several descriptors. The results show how small structural differences among biologically related catecholamines can lead to measurable differences in their calculated electronic properties. The study also demonstrates how computational chemistry and Python-based data analysis can extract and interpret molecular properties from quantum chemical calculations.***

Keywords: dopamine; norepinephrine; epinephrine; density functional theory; HOMO; LUMO; chemical hardness; electrophilicity; computational chemistry

1. Introduction

Neurotransmitters are biologically active molecules that transmit and regulate signals within the nervous system[1]. Their molecular structures determine how they interact with biological targets and influence their chemical and electronic behavior. Among the major classes of neurotransmitters, catecholamines are particularly important because they contain a characteristic catechol group together with an amine-containing side chain. Dopamine, norepinephrine, and epinephrine belong to this structurally related family and participate in different physiological processes.

Dopamine is an important neurotransmitter involved in several neurological processes, including movement, motivation, reward, and cognition[2]. Norepinephrine is involved in attention, arousal, and physiological stress responses. Epinephrine, also a hormone, is structurally related to norepinephrine and plays an important role in the physiological response to stress. Although these molecules share substantial structural similarity, small changes in their molecular structures can modify their electronic properties. For example, dopamine contains a primary amine, whereas norepinephrine contains an additional hydroxyl group on the side chain. Epinephrine contains a methyl-substituted secondary amine. Such structural changes may influence the distribution and accessibility of electrons within the molecules.

Computational chemistry provides a way to investigate these differences at the molecular level[3]. Quantum chemical calculations can provide molecular orbital energies and other electronic properties that are difficult to obtain directly through simple experimental measurements[4]. In particular, frontier molecular orbital theory focuses on the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). The energy difference between these orbitals, commonly referred to as the HOMO-LUMO gap, is often used as an indicator of a molecular system's electronic stability and potential reactivity. In addition to the HOMO-LUMO gap, frontier orbital energies can estimate global reactivity descriptors such as ionization potential, electron affinity, chemical hardness, chemical softness, chemical potential, electronegativity, and electrophilicity. Comparative analysis of these descriptors can therefore provide insight into how structural modifications influence the electronic characteristics of related molecules. This study computationally investigates and compares the electronic and global reactivity properties of dopamine, norepinephrine, and epinephrine. The study also demonstrates a computational workflow in which molecular properties obtained from quantum chemical calculations can be systematically extracted, organized, and analyzed using Python.

2. Materials and Methods

2.1 Molecular systems

Three structurally related catecholamines were selected for the computational investigation:

1) Dopamine
2) Norepinephrine
3) Epinephrine

These molecules provide a useful comparison because they share a common catecholamine framework while differing in the substitution pattern of the amine-containing side chain.

2.2 Quantum Chemical Calculations

The molecular structures were investigated using DFT[5]. We used Gaussian 09 for the quantum chemical calculations[6]. The Gaussian output files were generated during the calculations. The optimized molecular structures helped to obtain the corresponding molecular orbital energies. The HOMO and LUMO energies were extracted. The calculations were carried out with the B3LYP functional, 6-31G (d) basis set, 0 charge, and 1 multiplicity.

2.3 Frontier Molecular Orbital Analysis

The HOMO and LUMO energies were utilized to calculate the frontier orbital energy gap[7] . A larger HOMO-LUMO gap is generally associated with greater electronic stability, whereas a smaller gap is commonly interpreted as indicating greater ease of electronic excitation and comparatively greater chemical reactivity.

2.4 Global Reactivity Descriptors

The ionization potential (I) and electron affinity (A) were estimated from frontier orbital energies using Koopmans-type relationships[8] . These descriptors provide a comparative framework for evaluating the electronic characteristics of the three catecholamines.

2.5 Python-based data analysis

The Gaussian output files were analyzed using Python. The cclib library parsed Gaussian output files and extracted molecular orbital energies and other computational properties. Python-based calculations then derived the global reactivity descriptors. The extracted data were organized into structured datasets using the pandas library. This approach reduces manual extraction from lengthy Gaussian output files and provides a reproducible workflow for analyzing multiple molecular systems. The Python-based workflow enabled consistent extraction of the calculated molecular properties from the Gaussian output files. This facilitated direct comparison of the electronic and global reactivity descriptors obtained for dopamine, norepinephrine, and epinephrine.

1) HOMO and LUMO
   homo_index = data.homos[0]
   homo = data.moenergies[0][homo_index]
   lumo = data.moenergies[0][homo_index + 1]
2) HOMO-LUMO gap
   gap = lumo - homo
3) Ionization potential
   IP = -homo
4) Electron affinity
   EA = -lumo
5) Chemical hardness
   hardness = (IP - EA) / 2
6) Chemical softness
   softness = 1 / (2 * hardness)
7) Chemical potential
   chemical_potential = -(IP + EA) / 2
8) Electronegativity
   electronegativity = -chemical_potential
9) Electrophilicity
   electrophilicity = (chemical_potential ** 2) / (2 * hardness)
10) Print results

```
print("Molecular Properties")
print("----------------------------")
print("HOMO:", homo, "eV")
print("LUMO:", lumo, "eV")
print("HOMO-LUMO Gap:", gap, "eV")
print("Ionization Potential:", IP, "eV")
print("Electron Affinity:", EA, "eV")
print("Chemical Hardness:", hardness, "eV")
print("Chemical Softness:", softness, "eV^-1")
print("Chemical Potential:", chemical_potential, "eV")
print("Electronegativity:", electronegativity, "eV")
print("Electrophilicity:", electrophilicity, "eV")
```

3. Results and Discussion

3.1 Frontier molecular orbital properties

Table 1 presents the calculated frontier molecular orbital energies. The calculated HOMO-LUMO gaps reveal differences in the electronic structures of the three molecules despite their close structural relationship. Dopamine showed the smallest energy gap, approximately 5.6061 eV. Norepinephrine showed an intermediate gap of approximately 5.8096 eV, while epinephrine exhibited the largest gap at approximately 5.8434 eV. The relatively smaller HOMO-LUMO gap of dopamine suggests that its frontier electronic states are more closely spaced than those of norepinephrine and epinephrine. Within the framework of frontier molecular orbital theory, this can be associated with comparatively greater electronic responsiveness and chemical softness. Epinephrine showed the largest HOMO-LUMO gap among the three molecules. The larger gap suggests comparatively greater resistance to electronic perturbation. Norepinephrine occupied an intermediate position. These differences are particularly interesting because the three molecules possess closely related structures. The results therefore show that subtle structural modifications can influence the calculated frontier-orbital characteristics of biologically important molecules.

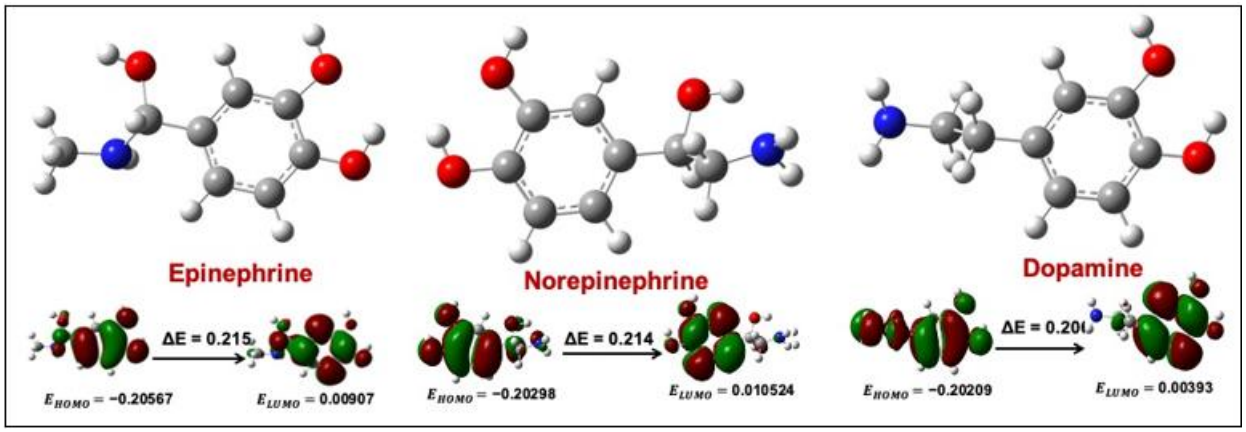

Figure 1: The optimized structures of Epinephrine, Norepinephrine, and Dopamine with their corresponding HOMO-LUMO values.

Table 1: HOMO, LUMO, and HOMO-LUMO energy gap of the investigated catecholamines

Molecule	HOMO (eV)	LUMO (eV)	HOMO-LUMO Gap (eV)
Dopamine	−5.4991	0.1069	5.6061
Norepinephrine	−5.5234	0.2863	5.8096
Epinephrine	−5.5966	0.2468	5.8434

3.2 Ionization potential and electron affinity

Table 2: Frontier-orbital-derived ionization potential and electron affinity

Molecule	Ionization Potential, I (eV)	Electron Affinity, A (eV)
Dopamine	5.4991	−0.1069
Norepinephrine	5.5234	−0.2863
Epinephrine	5.5966	−0.2468

Table 2 presents the calculated ionization potential and electron affinity values. Epinephrine exhibited the highest estimated ionization potential at 5.5966 eV, followed by norepinephrine at 5.5234 eV and dopamine at 5.4991 eV. Within the Koopmans-type approximation used here, a higher ionization potential indicates that greater energy would be required to remove an electron from the corresponding frontier orbital. Dopamine displayed the lowest estimated ionization potential among the three molecules. This observation is consistent with its relatively high-lying HOMO compared with the other two compounds. The calculated electron affinities were negative for all three molecules. Dopamine showed an electron affinity of −0.1069 eV, whereas norepinephrine and epinephrine showed −0.2863 and −0.2468 eV, respectively. The negative values are estimates derived from orbital energies rather than directly calculated electron-attached states. They suggest that electron addition is not strongly favorable within the approximation employed.

3.3 Chemical hardness and softness

Table 3: Global chemical reactivity descriptors

Molecule	Hardness, η (eV)	Softness, S (eV^{-1})
Dopamine	2.8030	0.1784
Norepinephrine	2.9048	0.1721
Epinephrine	2.9217	0.1711

Table 3 shows the chemical hardness and softness values. Dopamine exhibited the lowest chemical hardness, 2.8030 eV, and the highest chemical softness, 0.1784 eV^{-1}, among the three molecules. Norepinephrine exhibited an intermediate hardness of 2.9048 eV, while epinephrine showed the highest hardness at 2.9217 eV. The corresponding softness values followed the opposite trend. This inverse relationship is expected because softness was calculated from chemical hardness. The results suggest that dopamine is softer and more electronically responsive, whereas epinephrine is harder and less susceptible to electronic perturbation. The observed trend broadly follows the HOMO-LUMO gap because chemical hardness is directly related to the separation between the frontier orbitals.

The trend can be summarized as:
Hardness: Dopamine < Norepinephrine < Epinephrine and Softness:
Dopamine > Norepinephrine > Epinephrine

3.4 Chemical potential and electronegativity

Table 4: Chemical potential and electronegativity

Molecule	Chemical Potential, μ (eV)	Electronegativity, χ (eV)
Dopamine	−2.6961	2.6961
Norepinephrine	−2.6186	2.6186
Epinephrine	−2.6749	2.6749

Table 4 presents the calculated chemical potential and electronegativity values. Dopamine exhibited the most negative chemical potential, with a value of −2.6961 eV, while norepinephrine showed the least negative value of −2.6186 eV. The calculated electronegativity follows the relationship $\chi = -\mu$, so dopamine has the highest calculated electronegativity, followed by epinephrine and norepinephrine. These descriptors provide additional information about the molecules' tendency to attract electronic density. However, because they are derived from frontier orbital energies, interpret the values primarily in a comparative rather than absolute sense.

3.5 Electrophilicity index

Table 5: Electrophilicity Index

Molecule	Electrophilicity Index, ω (eV)
Dopamine	1.2966
Epinephrine	1.2245
Norepinephrine	1.1802

Dopamine exhibited the highest calculated electrophilicity index, 1.2966 eV, followed by epinephrine (1.2245 eV) and norepinephrine (1.1802 eV). The electrophilicity index combines information from the chemical potential and chemical hardness and provides a descriptor for comparing the tendency of molecular systems to accept electron density. The higher value calculated for dopamine therefore indicates a comparatively greater electrophilic character within the descriptor framework used in this study. However, electrophilicity should not be interpreted as a direct prediction of biological activity or neurotransmitter function. Rather, it provides information about the intrinsic electronic characteristics of the isolated molecular systems under the computational conditions employed.

4. Comparative Electronic Behavior

Property	Dopamine	Norepinephrine	Epinephrine
HOMO (eV)	−5.4991	−5.5234	−5.5966
LUMO (eV)	0.1069	0.2863	0.2468
HOMO-LUMO gap (eV)	5.6061	5.8096	5.8434
Ionization potential (eV)	5.4991	5.5234	5.5966
Electron affinity (eV)	−0.1069	−0.2863	−0.2468
Hardness (eV)	2.8030	2.9048	2.9217
Softness (eV^{-1})	0.1784	0.1721	0.1711
Chemical potential (eV)	−2.6961	−2.6186	−2.6749
Electronegativity (eV)	2.6961	2.6186	2.6749
Electrophilicity (eV)	1.2966	1.1802	1.2245

Overall, dopamine displayed the smallest HOMO-LUMO gap, lowest chemical hardness, highest softness, and highest electrophilicity index. Epinephrine exhibited the largest HOMO-LUMO gap and highest chemical hardness, together with the lowest softness. Norepinephrine generally occupied an intermediate position, although its chemical potential and electrophilicity did not strictly follow the ordering observed for the HOMO-LUMO gap. The results suggest that the electronic properties of these structurally related catecholamines are sensitive to changes in their side-chain substitution. In particular, the progression from dopamine to norepinephrine and epinephrine produces measurable differences in frontier orbital energies and derived global descriptors.

Another objective of this work was to demonstrate a reproducible approach to extracting molecular properties from quantum chemical output files. Gaussian output files contain a large amount of information, much of which is difficult to analyze manually when investigating multiple molecules. Python provides a convenient solution. In this study, the cclib library was used to read Gaussian output files and retrieve molecular orbital energies. These values were processed in Python to calculate the desired descriptors. The same workflow can be extended to larger molecular datasets. For example, Gaussian output files for additional neurotransmitters can be processed automatically, and the resulting molecular properties stored in a structured-pandas DataFrame. This would allow systematic investigation of relationships between molecular structure and electronic descriptors. Visualization using matplotlib could further allow comparisons of HOMO-LUMO gaps, hardness, softness, and electrophilicity among different neurotransmitters. Thus, the computational workflow developed in this study provides not only information about the selected catecholamines but also demonstrates how scientific programming can improve computational chemistry data analysis.

Several limitations should be considered when interpreting the results. First, the ionization potential and electron affinity values reported in this study were derived from frontier molecular orbital energies using Koopmans-type relationships. Therefore, these values should not be interpreted as equivalent to experimentally measured ionization potentials or rigorously calculated electron affinities. Second, the calculated descriptors describe the molecular systems under the specific computational conditions used in the Gaussian calculations. Molecular properties can change with computational method, basis set, molecular conformation, protonation state, and solvent environment. This consideration is particularly important for neurotransmitters because they can exist in different protonation states under physiological conditions. Consequently, future work should investigate the relevant protonated, deprotonated, or zwitterionic forms and evaluate the influence of an appropriate solvent model. Finally, electronic descriptors alone cannot establish biological activity. The biological functions of dopamine, norepinephrine, and epinephrine depend on their interactions with receptors, transporters, enzymes, and other biological components. Therefore, interpret the present calculations as a study of intrinsic molecular electronic properties rather than a direct model of neurotransmitter function.

5. Conclusions

A comparative computational investigation of dopamine, norepinephrine, and epinephrine was performed using frontier molecular orbital energies and global chemical reactivity descriptors. The three catecholamines exhibited distinct electronic characteristics despite their close structural relationship. Dopamine showed the smallest HOMO-LUMO gap (5.6061 eV), lowest chemical hardness (2.8030 eV), highest softness (0.1784 eV^{-1}), and highest electrophilicity index (1.2966 eV) among the three molecules. Epinephrine exhibited the largest HOMO-LUMO gap (5.8434 eV) and highest chemical hardness (2.9217 eV), indicating comparatively greater electronic stability within the framework of the descriptors used. Norepinephrine generally displayed intermediate frontier-orbital characteristics. The study demonstrates that small structural differences between closely related neurotransmitters can lead to measurable differences in their calculated electronic properties. It also demonstrates the usefulness of Python and cclib for automating the extraction and analysis of molecular properties from Gaussian output files. Further investigation involving molecular electrostatic potential maps, atomic charges, dipole moments, vibrational properties, protonation states, solvent effects, and additional neurotransmitters would provide a more comprehensive understanding of the relationship between molecular structure and electronic behavior.

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