Computational Study of Physicochemical Properties of (Ortho-Meta-, and Para-) Hydroxyacetanilide Isomers Using HyperChem

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Abstract:
This study analyzes the use of quantum mechanical computational methods, specifically AM1 and PM3, applied in HyperChem 8.0, to calculate the optimized molecular geometry. The study deals with Hydroxyacetanilide and its positional isomers (para-, meta-, and ortho-). different physicochemical properties were computed at the equilibrium state, such as Total energy, Electronic energy, Dipole moment, HOMO and LUMO energies, Energy gap, and Infrared (IR) spectra.The theoretical results showed that the meta- isomer displayed the lowest total energy and dipole moment values, indicating greater stability and a more uniform charge distribution. Conversely, the ortho- isomer showed higher dipole moment values as a result of steric effects and increased electron repulsion between adjacent functional groups, giving rise to lower stability. The para- isomer (Paracetamol) demonstrated intermediate behavior.Additionally, a strong agreement between the AM1 and PM3 methods was observed, supporting the accuracy of the computational approach. These results underline the significant role of positional isomerism in influencing the physicochemical properties of molecules and may contribute to a improved understanding of their behavior in pharmaceutical applications.

Keywords: Paracetamol, Hydroxyacetanilide , HyperChem, AM1 and PM3.
Note: Not applicable.

Introduction

Paracetamol (acetaminophen) is one of the most widely used analgesic and antipyretic agents worldwide. It is commonly prescribed for the management of mild to moderate pain and fever owing to its effectiveness and relatively low risk of side effects relative to other non-steroidal anti-inflammatory drugs (NSAIDs) (Brunton et al.-2018). Unlike traditional NSAIDs, paracetamol shows limited anti-inflammatory activity and is regarded as safer for gastrointestinal use (Sweetman-2017).

Chemically, paracetamol is referred to as p-hydroxyacetanilide and is composed of a benzene ring bonded with hydroxyl (–OH) and acetamide ($–NHCOCH_3$) groups in the para position (NCBI-2024).

In addition to the para isomer, the hydroxyl and acetamide groups can adopt ortho and meta positions on the benzene ring, producing structural isomers with different physicochemical properties .

These functional groups strongly affect its chemical and physical properties, structural stability, and chemical reactivity (Clayden et al.-2012). The analysis of physicochemical properties of paracetamol and its deriva tives is important for understanding their molecular properties and potential biological activity (Leach-2001).

Theoretical chemistry methods, particularly semi-empirical approaches, provide an efficient and low- cost method way to calculate molecular parameters such as total energy frontier molecular orbitals (HOMO and LUMO), and dipole moment (Jensen-2017).

In this study, HyperChem is used to carry out geometry optimization and analyze the physicochemical properties of paracetamol and its derivatives. The calculated results may give useful information into structure–activity relationships, which are important in drug.

Experimental

The computational study was performed using HyperChem software, an advanced and widely utilized molecular modeling tool for constructing and analyzing organic compounds(Hypercube lnc.-2010).

This program enables the development of molecular structures and the evaluation of various physicochemical properties, such as bond angles,

bond lengths, and heat of formation. It also allows the estimation of molecular stability and potential energy surfaces, which are useful in determining the most stable molecular configuration (Leach-2001).

Computational Methods: Semi-empirical computational approaches were employed in this study. These methods are derived from empirical data and are based on approximations of quantum mechanical theories, such as the Hartree–Fock method.

Compared to ab initio methods, semi-empirical techniques are faster and more suitable for large organic molecules while still providing reliable and accurate results (Cramer-2013).

Semi-empirical Methods Used:

1. AM1 Method

The Austin Model 1 (AM1) method is considered one of the most reliable semi-empirical approaches for calculating molecular properties. It is used to estimate heat of formation dipole moment, electronic energy, and other structural parameters such as bond lengths and bond angles (Dewar-1985).

2. PM3 Method

The Parametric Method 3 (PM3) is an improved and modified version of AM1, developed to overcome some of its limitations. It is based on the Neglect of Diatomic Differential Overlap (NDDO) approximation and is widely used for studying organic molecules and predicting their properties with reasonable accuracy (Stewart-1989).

Types of Calculations:

1. Single Point Calculation

Single-point energy calculations were performed to determine the molecular energy at a fixed geometry.

2. Geometry Optimization

Geometry optimization was carried out to obtain the most stable molecular structure corresponding to the minimum energy configuration.

3. Vibrational Frequency

Vibrational frequency analysis was used to examine molecular vibrations and confirm the stability of the optimized structures.

4. Transition State
Transition state calculations were applied to investigate possible reaction pathways and intermediate structures.
5. Frontier Molecular Orbitals.
HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) analyses were performed to evaluate molecular reactivity and electronic properties.
6. Dipole moment.

Previous Studies

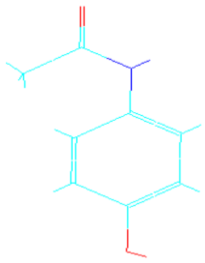
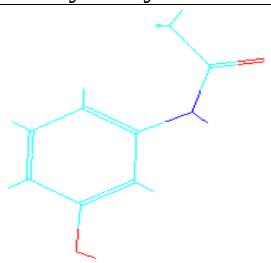
Many studies have explored the physicochemical and theoretical properties of Paracetamol and similar compounds using various computational methods(Prescott-2000, Jensen-2017).
examined the pharmacological and physicochemical properties of paracetamol, indicating its stability and safety profile relative to other medication. Their work stressed the importance of molecular structure in influencing drug activity (Prescott-2000).
(Dewar-1985) introduced the AM1 semi-empirical method, which has been commonly used for calculating molecular properties such as heat of formation, dipole moment, and electronic energy. This method has been applied extensively in the study of organic compounds .
(Stewart-1989) introduced the PM3 method as an advanced version of AM1 to improve the accuracy of semi-empirical calculations. PM3 has been effectively used to investigate molecular structures and predict physicochemical properties of various organic molecules.
(Leach-2001) showed the application of HyperChem in computational chemistry, showing its ability to develop molecular models and assess their properties efficiently.
In addition, (Jensen-2017) explained the significance of computational chemistry methods in estimating molecular behavior and understanding structure–activity relationships, especially in drug discovery and development.(Mahdi-2025) investigated Diclofenac derivatives using quantum mechanical and artificial intelligence methods. The study showed that electronic properties, such as total energy, molecular orbitals, and

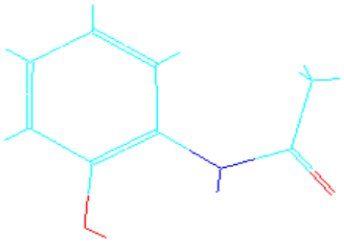
charge distribution, play an important role in determining structural stability and chemical reactivity, which are important for predicting drug behavior and enhancing drug design.

These studies confirm that semi-empirical methods combined with molecular modeling software provide an effective approach for studying the physicochemical properties of drug molecules such as Hydroxyacetanilide isomers.

Results and Discussion

Theoretical study of Hydroxyacetanilide isomers:


Para- Hydroxyacetanilide ($C_8H_9NO_2$)

Meta- Hydroxyacetanilide ($C_8H_9NO_2$)



Ortho- Hydroxyacetanilide ($C_8H_9NO_2$)

Fig. (1) Molecular structures of Hydroxyacetanilide isomers

1. Calculation of the equilibrium geometry:

carried out to obtain the lowest energy structures.

A set of thermodynamic and electronic properties was calculated, including total energy, binding energy, electronic energy, and nuclear energy, using semi-empirical methods (AM1 and PM3).

The results indicate that the ortho- isomer of Hydroxyacetanilide shows the greatest dipole moment level, suggesting higher molecular polarity due to the close closeness of the substituents within the molecule. This proximity results in to an asymmetry in charge arrangement and increased electronic repulsion, thereby decreasing the relative molecular stability .

On the other hand , the meta- isomer of Hydroxyacetanilide shows the smallest dipole moment value using both AM1 and PM3 methods, indicating a more uniform charge distribution and reduced molecular polarity. This can be due to the relative spacing between the functional groups, which decreases electronic repulsion and increases molecular stability.

Furthermore, the results reveal a clear similarity in the total energy values of the Hydroxyacetanilide isomers using both AM1 and PM3 methods, indicating good conformity between the two computational approaches in evaluating the physicochemical properties of the studied molecules. However, the meta isomer is regarded the highly stable due to its lower total

energy and dipole moment values compared to the other isomers.

Table (1) shows some physical properties of Hydroxyacetanilide isomers at the equilibrium geometry using AM1 and PM3 methods.

		Total Energy (kcal/mol)		Binding Energy (kcal/mol)		Electronic Energy (kcal/mol)		Nuclear Energy (kcal/mol)		Dipole moment (deybes)	
		AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
1	p- Hydroxyacetanilide	-46026.53	-42346.42	-2125.12	-2132.72	-211954.19	-207007.36	165927.83	164660.98	2.486	2.516
2	M- Hydroxyacetanilide	-46027.25	-42347.18	-2126.00	-2133.53	-212573.14	-207475.61	166545.91	165128.42	1.697	1.695
3	O- Hydroxyacetanilide	-46022.62	-42343.31	-2121.33	-2129.62	-215504.19	-210501.60	169481.63	168158.56	2.739	2.604

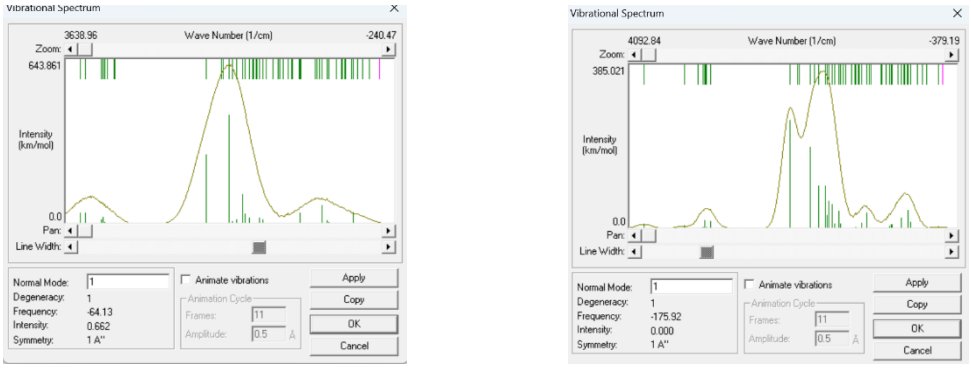
2. Infrared (IR) Spectra Computation:

empirical methods (AM1 and PM3).

The principal molecular vibrations of these isomers, which include multiple functional groups, were detected and are shown in Figures (2, 3 and 4), indicating the vibrational motions related to the calculated frequencies (cm^{-1}). The results indicated strong agreement between both computational methods.

Table (2) shows a comparison between the measured and predicted vibrational frequencies of the selected para- isomer of Hydroxyacetanilide at the optimized geometry using AM1 and PM3 methods.

	Experimental [13]	AM1	PM3
C-C	1300-1100	1256.33	1228.23
C=C	1600-1475	1465.97	1598.27
C-O	1163-1258	1185.45	1132.42
C=O	1775-1660	1667.87	1698.71
C-H	3023	3065.12	3029.74
O-H	3100-2800	3134.48	3232.43
N-H	3400-3180	3256.80	3214.73



AM1 PM3

Figure (2) The calculated vibrational spectra of para- isomer of Hydroxyacetanilide using the AM1 and PM3 methods.

Table (3) shows a comparison between the measured and predicted vibrational frequencies of the selected Meta- isomer of Hydroxyacetanilide at the optimized geometry using AM1 and PM3 methods.

	Experimental [13]	AM1	PM3
C-C	1300-1100	1263.62	1246.12
C=C	1600-1475	1473.82	1479.18
C-O	1163-1258	1137.28	1134.29
C=O	1775-1660	1654.64	1653.26
C-H	3023	3053.75	3027.23
O-H	3100-2800	3721.65	3232.19
N-H	3400-3180	3432.12	3126.64

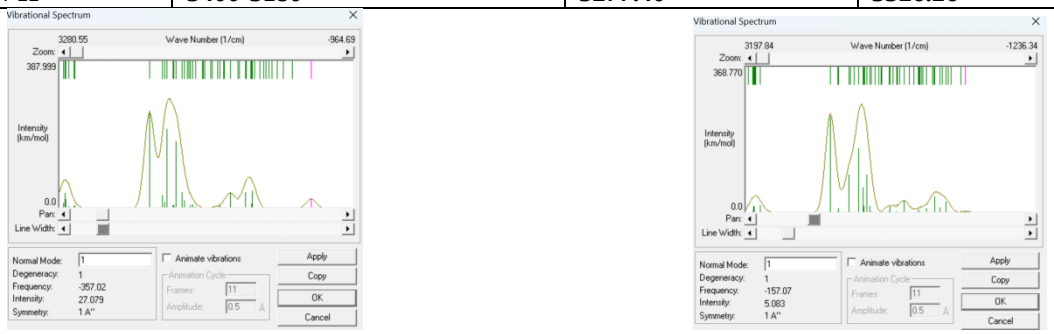


AM1 PM3

Figure (3) The calculated vibrational spectra of Meta- isomer of Hydroxyacetanilide using the AM1 and PM3 methods.

Table (4) presents a comparison between the experimental and theoretical vibrational frequencies of the studied Ortho- isomer of Hydroxyacetanilide at the geometry using AM1 and PM3 methods.

	Experimental [13]	AM1	PM3
C-C	1300-1100	1265.16	1234.29
C=C	1600-1475	1443.62	1438.38
C-O	1163-1258	1132.27	1147.69
C=O	1775-1660	1617.58	1633.22
C-H	3023	3026.15	3026.28
O-H	3100-2800	3621.33	3150.67
N-H	3400-3180	3277.40	3326.26



AM1 **PM3**

Figure (4) The calculated vibrational spectra of Ortho- isomer of Hydroxyacetanilide using the AM1 and PM3 methods.

3. Theoretical Atomic Charge Calculation:

The computed dipole moment values of the investigated drugs showed that Ortho- isomer Hydroxyacetanilide has the highest dipole moment (2.739, 2.604) Deybes, while Meta- isomer Hydroxyacetanilide has the lowest dipole moment (1.697, 1.695) Deybes among the investigated compounds. The detected differences in the physical and chemical properties of (ortho-, meta-, and para-) Hydroxyacetanilide isomers result from variations in the positional arrangement of the functional groups on the aromatic ring.

In the ortho-isomer, the close arrangement of the hydroxyl and amide groups enhances internal hydrogen bonding, causing increased charge polarization and a higher dipole moment. This structural arrangement also increases electronic coupling between adjacent functional groups.

However, the meta-isomer presents reduced electronic coupling between functional groups due to their relative positions, resulting in a more uniform charge distribution and consequently a lower dipole moment.

The para-isomer (Paracetamol), with functional groups located opposite one another, allows for a more uniform distribution of electron density across the molecule. This configuration results in to moderate dipole moment values and increased structural stability.

Therefore, the positional isomerism strongly affects the electron structure, charge distribution, and binding potential of Hydroxyacetanilide isomers, which may ultimately determine their binding strength and biological effect.

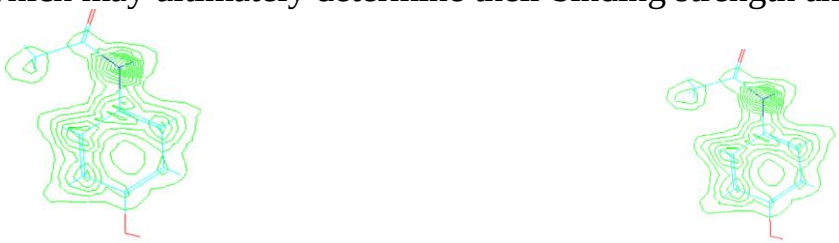


Figure (5) displays the electron distribution of isomer p- Hydroxyacetanilide by using the AM1 and PM3 methods.



Figure (6) displays the electron distribution of isomer M- Hydroxyacetanilide by using the AM1 and PM3 methods.



Figure (7) displays the electron distribution of isomer O- Hydroxyacetanilide by using the AM1 and PM3 methods.

4. Potential Molecular Electrostatic

In the study, the energies of filled and vacant molecular orbitals were

computed using the Hyper Chem. software using semi-empirical methods AM1 and PM3.

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were calculated. The HOMO represents the highest occupied energy level filled with electrons, while the LUMO indicates the lowest unoccupied energy level.

These values are essential for understanding the structural stability and chemical reactivity . Low energy difference between HOMO and LUMO reveals that the molecule is highly active, while a high energy difference reflects higher stability.

Was calculated using the following equation:

$$\Delta E = E\{LUMO\} - E\{HOMO\}$$

methods.

Table (5): presents a comparison between the measured and calculated HOMO and LUMO energies and the energy gap (ELUMO-EHOMO) for the (para-, meta-, ortho-) Hydroxyacetanilide Isomers, at optimized geometry using semi-empirical methods (AM1 and PM3).

		E HOMO (ev)		E LUMO (ev)		ELUMO - E HOMO	
		AM1	PM3	AM1	PM3	AM1	PM3
1	p- Hydroxyacetanilide	10.199-	-9.891	0.1012	0.3708	10.3002	10.2618
2	m- Hydroxyacetanilide	-9.669	-9.638	0.2283	0.1488	9.8973	9.7868
3	o- Hydroxyacetanilide	-9.6929	-9.7008	0.2156	0.1285	9.9085	9.8293

Conclusion

This study reports a theoretical investigation using quantum mechanical calculation methods through the HyperChem 8.0 program. The semi-empirical methods AM1 and PM3 were employed to analyze the molecular properties.

The research focuses on Hydroxyacetanilide and its positional isomers (ortho-, meta-,para-). The optimized geometrical structures and several physicochemical properties were calculated at the equilibrium state.

A comparison between the AM1 and PM3 methods was performed to evaluate the reliability of the computational results.

The results showed that the position of functional groups strongly influences the electronic behavior and molecular stability. The meta- isomer showed the greatest stability, as indicated by its iower total energy and dipole moment values. Conversely, the ortho- isomer exhibited lower stability due to steric effects and internal interactions, while the para- isomer (Paracetamol) demonstrated intermediate behavior. Additionally, the LUMO–HOMO energy gap analysis showed that molecules with smaller energy gaps tend to be more chemically reactive, whereas those with larger gaps are more structurally stable.

Overall, the results indicate that molecular structure plays an important role in controlling the reactivity and stability of Hydroxyacetanilide isomers, which may influence their biological effect.

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دراسة حاسوبية للخصائص الفيزيائية والكيميائية للهيدروكسي أسيتانيليد وايزومراته (أورثو، ميتا، بارا) باستخدام برنامج HyperChem

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مستخلص البحث:
تقوم هذه الدراسة بتحليل استخدام الطرق الحسابية الميكانيكية الكمية، وبالتحديد AM1 وPM3 المطبقة في برنامج HyperChem 8.0، لحساب الهندسة الجزيئية المثلى. تتناول الدراسة الهيدروكسي أسيتانيليد وايزومراته الموضعية (بارا، ميتا، وأورثو). وقد تم حساب الخصائص الفيزيائية والكيميائية المختلفة عند حالة الاتزان مثل الطاقة الكلية، والطاقة الإلكترونية، وعزم ثنائي القطب، وطاقات HOMO وLUMO، وفجوة الطاقة، وأطياف الأشعة تحت الحمراء (IR).أظهرت النتائج النظرية أن الايزومر الميتا أظهر أقل قيم للطاقة الكلية وعزم ثنائي القطب، مما يدل على استقرارية أكبر وتوزيع أكثر تجانسًا للشحنة. وعلى العكس، أظهر الايزومر الأورثو قيمًا أعلى لعزم ثنائي القطب نتيجة للتأثيرات الفراغية وزيادة التنافر الإلكتروني بين المجاميع الوظيفية المتجاورة، مما أدى إلى انخفاض الاستقرارية. أما الايزومر البارا (الباراسيتامول) فقد أظهر سلوكًا متوسطًا.بالإضافة إلى ذلك، لوحظ توافق قوي بين طريقتي AM1 وPM3، مما يدعم دقة المنهج الحسابي. وتؤكد هذه النتائج الدور المهم للايزومرات الموضعية في التأثير على الخصائص الفيزيائية والكيميائية للجزيئات، وقد تسهم في تحسين فهم سلوكها في التطبيقات الصيدلانية.

الكلمات المفتاحية :الباراسيتامول ، الهيدروكسي أسيتانيليد ، HyperChem. ، AM1 , PM3
ملاحظة : هل البحث مستل من رسالة ماجستير او اطروحة دكتوراه ؟ نعم : كلا : √