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Structural Elucidation of Drug Aspirin by Using Various Software Tools Like HyperChem, Argus Lab, ChemSketch, Avogrado and Chemeo Database

Laxmi K*

Department of Chemistry, Chaitanya Bharathi Institute of Technology (CBIT), Gandipet, Hyderabad, India

Abstract

Aspirin (Acetyl Salicyclic Acid) is known for its use as antipyretic, analgesic and anti-inflammatory drug, in this paper, a computational study of Aspirin is carried out using various software tools like, Hyperchem, Argus lab, Chemsketch, Avagrado and Chemeo database. QSAR Properties and Molecular properties of Aspirin obtained by using Hyperchem 7.5 software. The electronic properties and Electrostatic Potential (ESP) of the compound Aspirin were obtained by using Argus lab software. Molecular Properties and 3D optimized forms of Aspirin were obtained by using Chemsketch software. Avogadro version 1.1 is used to interpret theoretically the structural properties of Aspirin in detail and using this software the molecule properties and standard representations of Aspirin were obtained. By, using Chemeo database the Chemical and Physical Properties of Aspirin were determined.

Keywords: Aspirin; Hyperchem; Argus lab; Chemsketch and Avogadro; Standard molecular structure representations; QSAR studies; Chemeo database

Introduction

Many scientists analysed willow extract in early 1800s to obtain the active compound and as a result Salicin (the Latin name for willow) in purified state is obtained. Heyden Chemical Company, in Germany manufactured the modified form of salicin which is used for medical applications. But this form was found to cause stomach irritation and it was further modified [1,2]. The modified product, Acetyl Salicyclic Acid with the trade name Aspirin was identified and registered by the Bayer Company in 1899. Since 1915 Aspirin is used all over the world for the purpose of effective and safe pain relief and is available to the public without specific prescription. The beneficial effects of willow bark were explained by Reverend Stone in the 18th century and this led to the modern era of Aspirin. A Scottish physician Thomas MacLagan in 1876 reported the successful use of salicin (willow powder extract) in the treatment of fever and rheumatism [1].

In view of the medicinal importance of the drug Aspirin, this compound is studied computationally by using various software tools like Hyperchem, Argus Lab, Chemsketch and Avogrado.

Materials and Methods

Hypothetical study of aspirin by HyperChem 7.5 software

Quantum mechanical calculations were done by using the HyperChem 7.5 software [3] to obtain the spectral data. The molecule is built with the help of HyperChem tools and by applying Ab Initio optimized semi empirical single point AM1 method, the molecule is geometrically optimized (Figures 1 and 2).

QSAR studies (Quantitative structure activity relationship studies): Calculation and estimation of a variety of molecular descriptors commonly used in QSAR studies can be done by obtaining the QSAR Properties. By this analysis the relationship between the structure of the compound with its physicochemical properties and biological activities can be studied. with the help of QSAR method the properties of new chemical compounds can be obtained, and this method enables the collection of data, selection of molecular descriptors and evaluates the model.

Single point AM1 method is used to obtain the QSAR properties of Aspirin. These properties include surface area, volume, hydration energy, log P, refractivity, polarizability, mass, total energy as given in Table 1. Molecular properties like total energy, binding energy, enthalpy (heat of formation), electronic energy, nuclear energy and dipole moment of Aspirin obtained by using single point AM1 method were given in Table 2.

Quantum chemical parameters like the energy of the highest occupied molecular orbital (EHOMO), energy of the lowest unoccupied molecular orbital (ELUMO), the energy gap (ELUMO-HOMO) of Aspirin were given in Figures 3 and 4. These Quantum chemical calculations enables to interpret the reaction mechanisms. The values of EHOMO, ELUMO and ELUMO-HOMO of Aspirin are 9.905104 eV, -0.762959 eV and 9.142145 eV respectively (Figures 3 and 4). EHOMO and ELUMO indicating the frontier molecular orbital

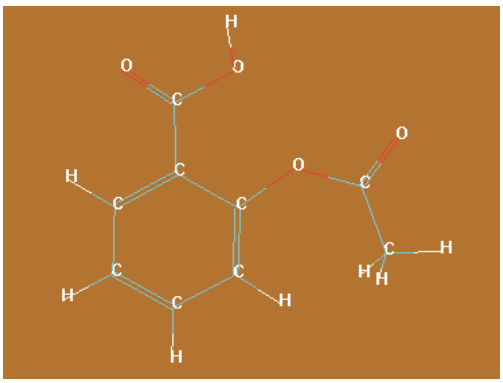

Figure 1: Structure aspirin obtained by using HyperChem 7.5 software.

***Corresponding author:** Laxmi K, Department of Chemistry, Chaitanya Bharathi Institute of Technology (CBIT), Gandipet, Hyderabad- 500 075, India, Tel: 98495 98234; E-mail: katangurulaxmi@gmail.com

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energies [4-6] are significant parameters used to predict the reactivity of a chemical species. Electron donating ability of a molecule is indicated by EHOMO. For Aspirin the higher value of EHOMO indicates that the tendency of Aspirin to donate the electrons to the suitable acceptor molecule having low energy possessing empty molecular orbital. For Aspirin the highest occupied molecular orbitals are confined to the carbon atoms having double bond and on the central part of the molecule.

The complete surface of Aspirin with electrostatic potential, total charge density and 3D mapped iso surface are given in Figure 5. The underlying molecular structure of Aspirin is shown in the figure that uses a clipping plane as a cutaway of the surface.

Hypothetical study of aspirin by Argus lab software

An electronic structure program Argus Lab based on the quantum mechanics gives the potential energies and determines the molecular structures. Argus Lab also performs the geometry optimization of structure and gives vibration frequencies of coordinates of atoms, bond length, bond angle and pathway of reactions [7]. Structure Aspirin built by using Argus Lab software is given in Figure 6

Electronic properties: Theoretically by using PM3 method the Highest Occupied Molecular Orbital (HOMO) and the Lowest unoccupied Molecular Orbital of Aspirin were determined as given in Figures 7a and 7b respectively.

It is important to examine the E HOMO and E LUMO to explain the electronic properties of the compound. This was done theoretically using PM3. The blue region representing the positive phase of the orbital indicates the increase in electron density and the red region which stands for the negative phase of the orbital denotes the decrease in electron density [8-10].

Electrostatic Potential (ESP) of aspirin: The complete surface of Aspirin with the color map is shown in Figure 8. In this figure a clipping plane is used as a cutaway of the same surface and from this the underlying molecular structure [8-10] is understood. The various colors in the color map represents the ESP energy (in hartrees). The magnitude and polarity of the electrostatic potential is indicated by the surface color. For a positive test charge the regions of highest stability are shown by the red end of the spectrum and the regions of least stability are indicated by the magenta/blue end of the spectrum.

Net charge	0.00 e
Surface area (approx)	302.5°A^2
Surface area (Grid)	342.55°A^2
Volume	531.06°A^3
Hydration energy	-4.71 kcal/mol
Log P	-0.26
Refractivity	48.00°A^3
Polarizability	17.39°A^3
Mass	180.16 amu

Table 1: QSAR properties of aspirin obtained by using HyperChem 7.5 software.

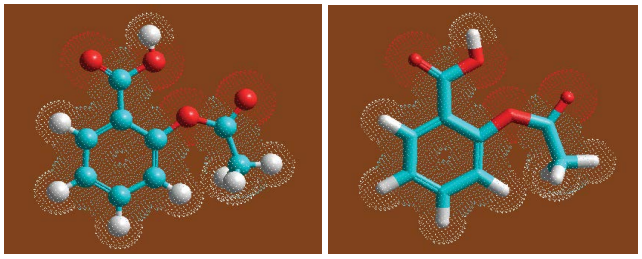
Total energy	-58660.7578 kcal/mol
Binding energy	-2324.7648 kcal/mol
Heat of formation	-131.7028 kcal/mol
Electronic energy	-284743.187 kcal/mol
Nuclear energy	226082.437 kcal/mol
Dipole moment	5.577 D
Dipole X	4.8589 D
Dipole Y	-2.7372 D
Dipole Z	0.00471 D
RMS gradient	0.00748 kcal/°A mol
Gradient X	0.00150 kcal/°A mol
Gradient Y	0.00496 kcal/°A mol
Gradient Z	0.00539 kcal/°A mol

Table 2: Molecular properties of aspirin obtained by using HyperChem 7.5 software.

Hypothetical study of aspirin by Chemsketch

The systematic names of Aspirin in accordance to both IUPAC and CAS Index nomenclature rules were obtained by applying the ACD/ Name features of chemsketch. The chemical structures from these names were also determined by making use of the above features. Aspirin is found to have the Molecular Formula of $C_9H_8O_4$ and its formula weight is 180.15742 as determined by chemsketch. Name of structure is 2-(acetyloxy)benzoic acid.

InChI name of aspirin: In Chemsketch the exact configuration of a molecule is indicated by the IUPAC [11] International Chemical Identifier, InChI which was developed as an accurate code.



(a) Ball and cylinders (b) Tubes model

Figure 2: Various forms of aspirin obtained by using HyperChem 7.5 software.

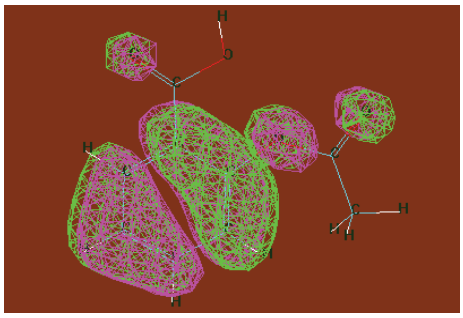


Figure 3: HOMO of aspirin (3D iso surface). Energy=-9.76198 eV.

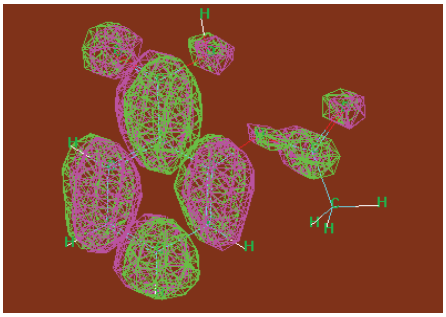
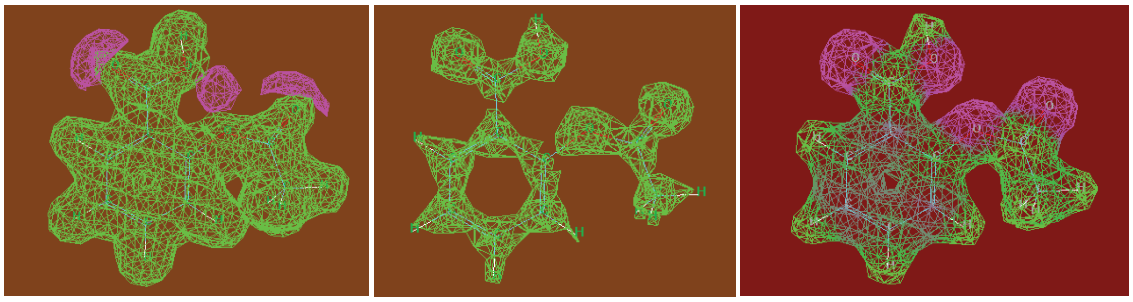


Figure 4: LUMO of aspirin (3D iso surface). Energy=-0.666362 eV.



(a) Electrostatic potential (b) Total charge density (c) 3D mapped iso surface

Figure 5: The complete surface of aspirin with electrostatic potential, total charge density and 3D mapped iso surface obtained by using HyperChem 7.5 software.

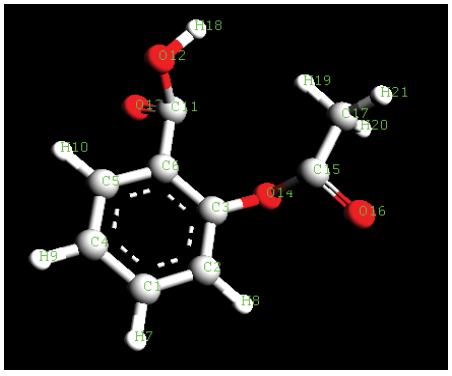
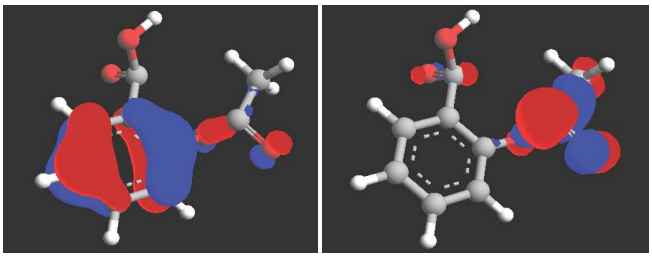


Figure 6: Structure aspirin built by using Argus Lab software.



(a) (b)

Figure 7: HOMO and LUMO of aspirin obtained by using Argus Lab software.

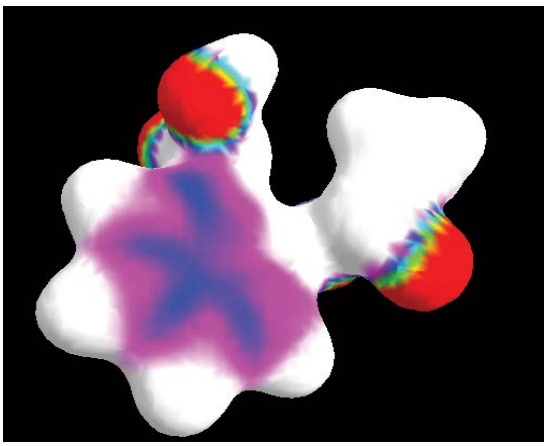


Figure 8: ESP mapped density of aspirin as obtained by using Argus Lab software.

InChI=InChI=1S/$C_9H_8O_4$/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h2-5H,1H3, (H,11,12).

SMILES [12,13] Notation O=C(C)Oc1ccccc1C(=O)O.

'Auxiliary Information' (AuxInfo) of aspirin: With the help of AuxInfo [14] it is possible to redraw the structure as it gives knowledge of atom non-stereo equivalence, mapping input atom positions to output positions, and 'reversibility' data.

AuxInfo=AuxInfo=1/1/N:12,6,4,5,2,11,3,1,7,13,8,9,10/E:(11,12)/rA:13CCCCCCCOOOCCO/rB:s1;d1;d2;s3;s4d5;s3;s7;d7;s1;s10;s11;d11;/rC:400,-346,0;400,-115,0;200,-462,0;200,0,0;0,-346,0;0,-115,0;200,-693,0;400,-808,0;0,-808,0;600,-462,0;800,-346,0;1000,-462,0;800,-115,0.

Calculated log P =1.19 ± 0.23

Algorithms for calculating properties: The properties like Basic Macroscopic Properties (Molar Volume (MV), Molar Refractivity (MR), and Parachor (Pr)), Derived Macroscopic Properties (Density (d), Refractive Index (n), and Surface Tension (γ)), The Dielectric Constant ε, Polarizability, Monoisotopic Nominal and Average Mass of Aspirin were determined with the help of ACD/ChemSketch (Table 3). These properties can be evaluated by considering the additive atomic or group increments [15,16].

3D representations of Aspirin obtained by using ChemSketch software: 3D Optimised Forms of Aspirin were obtained by using ACD/3D Viewer which is a rapid precise 3D modeling and visualization program [17-20]. ACD/3D Viewer is incorporated fully with ACD/ChemSketch and there by permits to produce 2D structures and rapidly acquires their 3D representations in a conspicuous 16 color display (Figure 9).

Hypothetical Study of Aspirin by Avogadro Software Tool

A chemical builder Avogadro is a balanced sustainable software tool which is helpful in featuring the vision and analytical studies. This project of Avogadro has good administration in fields of bioinformatics, computational chemistry, materials science and other areas like architecture. Avogadro version 1.1 is a new version with special properties and this can be used even in crystallography. On the theoretical basis the structural aspects of Aspirin were analysed in detail with the help of Avogadro version 1.1.

The structure of Aspirin [17-20] (Figure 10) is constructed by applying Avogadro software and once the structure is built the molecule is geometrically optimized and the following properties of Aspirin were determined.

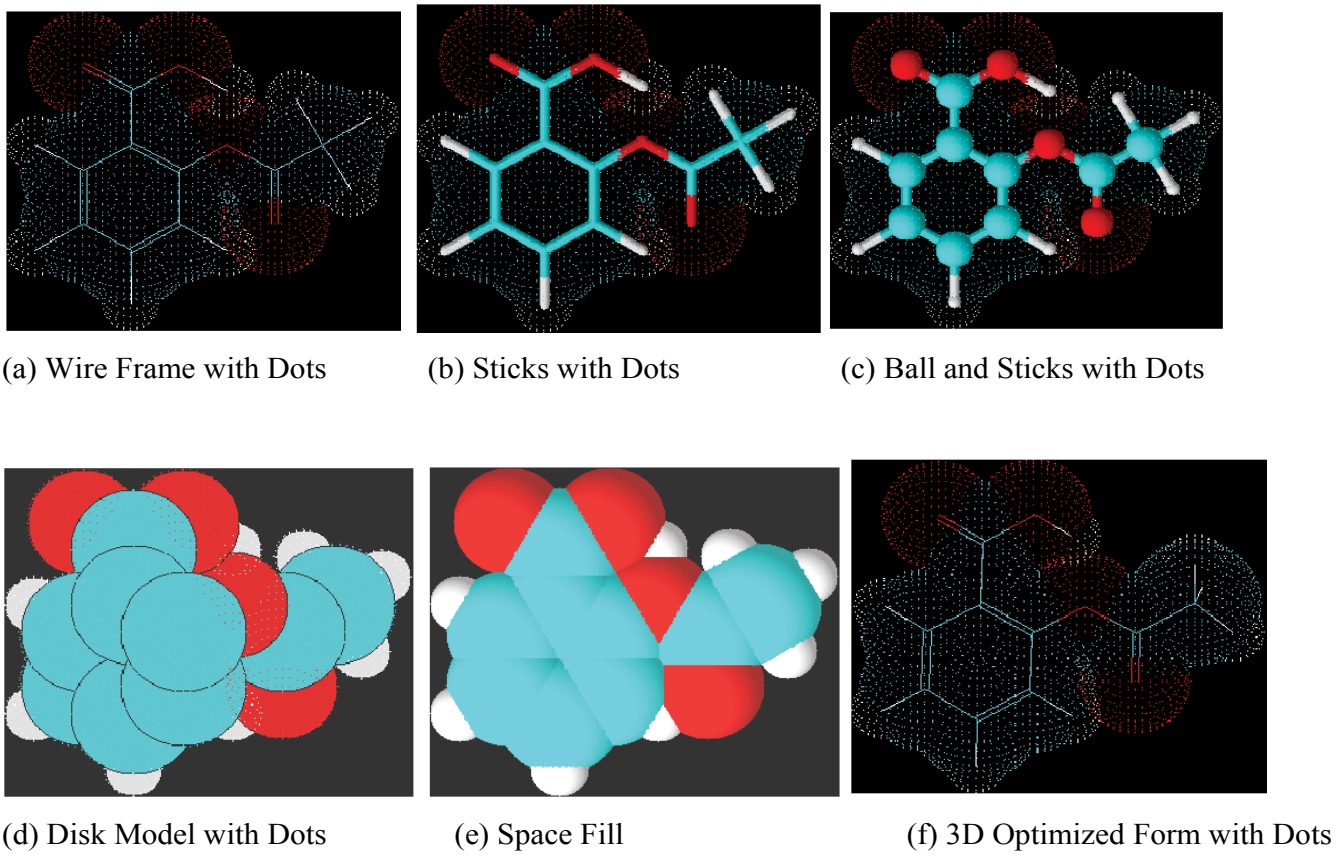


Figure 9: Various forms of 3D representations of aspirin obtained by using ChemSketch software.

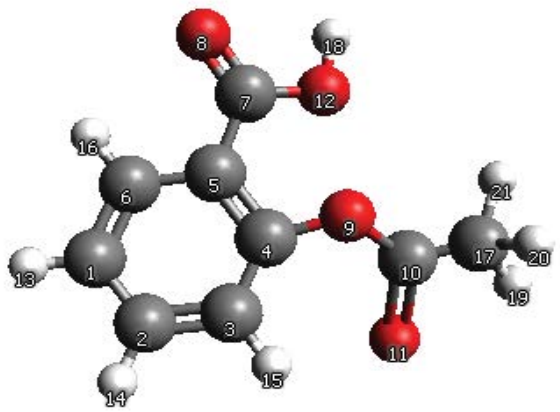
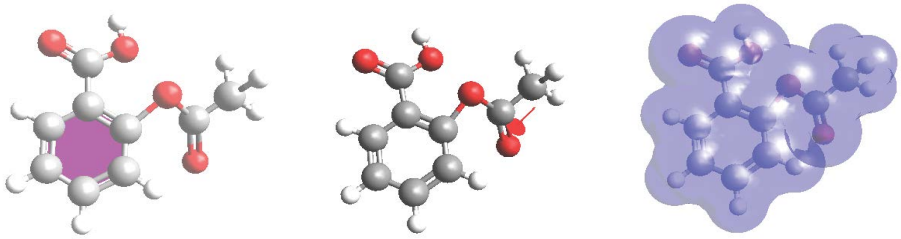


Figure 10: Structure aspirin built by using Avogadro Lab software.

Molecular Properties by using ChemSketch	
Molecular formula	$C_9H_8O_4$
Formula weight	180.15742
Composition	C(60.00%) H(4.48%) O(35.52%)
Molar refractivity	44.52 ± 0.3 cm^3
Molar volume	139.5 ± 3.0 cm^3
Parachor	370.9 ± 4 cm^3
Refractive index	1.550 ± 0.02
Surface tension	49.8 ± 3 dyne/cm
Density	1.290 ± 0.06 g/cm^3
Polarizability	17.65 ± 0.5 $10^{-24}cm^3$
RDBE	6
Monoisotopic mass	180.042259 Da
Nominal mass	180 Da
Average mass	180.1574 Da
M+	180.04171 Da
M-	180.042807 Da
$[M+H]^+$	181.049535 Da
[M+H]-	181.050632 Da
$[M-H]^+$	179.033885 Da
[M-H]-	179.034982 Da

Table 3: Molecular properties of aspirin obtained by using ChemSketch.

Characteristics like molecule, atom, bond, angle, torsion, and conformer properties were obtained by the "Properties" selection and with these settings the compositions of the molecule and atoms present can be determined. Energy of Aspirin is found to be 90.4508 KJ/mol. Conformer search by systematic rotor search indicate that Number of atoms are 21 and Number of rotatable bonds are 3 in Aspirin. For example, clicking on "Molecule Properties" will provide the molecular characteristics like molecular weight, energy KJ/mole, chemical formulae, estimated dipole moment etc., Table 4 gives the molecular information of Aspirin obtained by using Avogadro Lab software.



(a) Aspirin—Ring Form (b) Aspirin—Dipole (c) Aspirin—Vanderwaals Surfaces

Figure 11: Standard representations of aspirin obtained by using Avogadro Lab software.

Molecular Properties by using Avogadro Lab Software	
Molecular weight	180.157 g/mol
Chemical formula	$C_9H_8O_4$
Estimated dipole moment	2.358/1.761
Number of atoms	21
Number of bonds	21

Table 4: Molecular properties of aspirin obtained by using Avogadro Lab software.

Property	Value	Unit	Source
Δ_fG° Standard Gibbs free energy of formation	-371.98	kJ/mol	Joback Method
Δ_fH°gas Enthalpy of formation at standard conditions	-513.64	kJ/mol	Joback Method
Δ_{fus}H° Enthalpy of fusion at standard conditions	21.19	kJ/mol	Joback Method
ΔvapH° Enthalpy of vaporization at standard conditions	71.15	kJ/mol	Joback Method
log_Poct/wat Octanol/Water partition coefficient	1.31	--	Crippen Method
Pc Critical Pressure	4082.92	kPa	Joback Method
Tboil Normal Boiling Point Temperature	659.32	K	Joback Method
Tc Critical Temperature	868.49	K	Joback Method
log_{10}WS Log 10 of water solubility	-2.18	mol/l	Chemeo
Vc Critical Volume	0.48	m^3/kg-mol	Joback
McVol McGowan's characteristic volume	111.59	ml/mol	McGowan

Table 5: Physical properties of aspirin obtained by using Chemeo Database.

Property	Value	Unit	Temperature (K)	Source
Cp, gas Ideal gas heat capacity	313.39	J/mol × K	659.32	Joback Method
(η)Dynamic viscosity	0.0000687	Pa × s	659.32	Joback Method
ΔfusH Heat of fusion	29.17	kJ/mol	409.2	NIST Webbook
ΔfusH Enthalpy of fusion at a given temperature	31.01	kJ/mol	412.7	NIST Webbook
ΔfusH Enthalpy of fusion at a given temperature	29.8	kJ/mol	414	NIST Webbook

Table 6: Temperature dependent properties of aspirin obtained by using Chemeo Database.

The different standard representations like ring form, dipole form and Vanderwaals surfaces of aspirin as obtained by using Avogadro Lab software are given in Figure 11.

Results and Discussion

Chemical and physical properties of aspirin by Chemeo database

A research project of Ceondo Ltd, Chemeo was started in 2009 and its objective is to facilitate as a best basis of obtaining the chemical and physical data which is useful in various pharmaceutical, chemical, oil and gas industries (Tables 5 and 6).

Chemeo [21] is the biggest free database used deriving the data related to chemical and physical properties and is very much helpful for the process industry. Using Chemeo the biggest database the properties of Aspirin were determined, and the data obtained is as follows

InChI: InChI=1S/$C_9H_8O_4$/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h2-5H,1H3, (H,11,12).

InChI Key: BSYNRYMUTXBXSQ-UHFFFAOYSA-N.

Formula: C9H8O4.

SMILES: CC(=O)Oc1ccccc1C(=O)O.

Molecular Weight: 180.16.

CAS: 50-78-2.

Comparative study of aspirin using Hyperchem and Argus lab software tools

The tendency of Aspirin to donate the electrons to the suitable acceptor molecule is indicated by the higher value of EHOMO as obtained by the Hyperchem studies. The highest occupied molecular orbitals (HOMO) for Aspirin are on the central part of the molecule localized to the carbon atoms having double bond.

The electronic properties of the Aspirin were indicated by the E HOMO and E LUMO as obtained by the Argus lab software. The central part of the aspirin which is indicated with the red region stands for the negative part of the orbital corresponds to HOMO as shown by the Argus lab. This result agrees with the hyperchem study data.

Comparative study of aspirin using ChemSketch, Avogadro and Chemeo database software tools

All the three techniques of ChemSketch software, Avogadro software and Chemeo database indicated that the molecular formula of Aspirin is same being $C_9H_8O_4$. Molecular weight of Aspirin as indicated by all the techniques is same being 180.16 amu.

International Chemical Identifier, InChI of Aspirin as obtained by both the techniques of ChemSketch software and Chemeo database are in good agreement. SMILES Notation of Aspirin as obtained by ChemSketch software and Chemeo database were found to be the same.

Conclusion

From the above computational studies, it is clearly inferred that Aspirin is a chemically reactive compound. Physicochemical aspects of Aspirin were clearly interpreted by the Hyperchem study. The presence

of potential donor atoms in Aspirin were confirmed by the calculation of HOMO and LUMO frontier orbital energies for the optimized form of Aspirin.

The persistent favorable conformation of Aspirin is obtained by applying the Argus Lab software and this is also in agreement with results obtained by using Avogrado software tool and chemeo database.

Aspirin therapy is considered as an effective agent for the cardiovascular disease prevention and this indicates its socioeconomic prospective. In conclusion, these studies do not only present us the opportunity to take a critical look at this novel compound but has also given us the opportunity to compile fundamental result on properties that cannot be calculated in the laboratory.

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