Research Journal of Chemical Sciences ISSN 2231-606X
Vol. **8(9),** 7-11, September **(2018)** *Res. J. Chem. Sci.*

In silico DFT and ADME studies of Dehydrostenine A

Axel LONTSI TIWA[1,2*], Emmanuel NNANGA NGA[1,3,4], Alembert TIABOU TCHINDA[1]
[1]Institute of Medical Research and Medicinal Plants Studies (IMPM), P.O. Box 6163, Yaoundé, Cameroon
[2]Department of Organic Chemistry, University of Yaoundé I, P.O Box 812, Yaoundé, Cameroon
[3]Dept. of Pharmacy Galenic and Legislation, Faculty of Medicine and Biomedical Science, University of Yaoundé I, P.O Box 812 Cameroon
[4]Department of Pharmacy, Faculty of Medicine and Pharmaceutical Sciences, University of Douala, P.O Box 812, Douala, Cameroon
adonmage@gmail.com

Available online at: www.isca.in, www.isca.me
Received 27th June 2018, revised 14th August 2018, accepted 7th September 2018

Abstract

Alkaloids are secondary metabolites with more or less complex structures. It's interest in computerized chemistry is little noticed unlike phytochemistry. This work consists in calculating vibrational frequencies and physico-chemical properties of a firstly optimized dehydrostenine A (DsA), a true alkaloid isolated from Stemona sessilifolia. The structural analysis was carried out using aRMSD, which allowed to visualize the differences with the crystalline structure and calculate the deviations. The chemical properties were obtained with Qikprop and revealed a very good absorbability for human oral distribution.

Keywords: Dehydrostenine A, DFT, HOMO, LUMO, ADME.

Introduction

Alkaloids are natural substances most often derived from the plant world, the complexity of which has given them a particular interest in the chemistry of natural substances[1]. Defined as being nitrogenous substances, basic, of natural origin and of restricted distribution, their very varied chemical structure imposed a classification in true alkaloids, proto-alkaloids and pseudo-alkaloids[2]. Already widely used in traditional medicine, the isolation of certain alkaloids like reserpine and the success of the latter in pharmacy has insisted a thorough research on this class of metabolite[3]. Despite the toxicity and excellent pharmacological properties of alkaloids (stimulants, depressants, antifibrillants, analgesics, antiparasitic agents, etc.), their physicochemical studies by theoretical chemistry seems not very attractive[4,5]. In this work, we carry out a theoretical study of dehydrostenin A (DsA) which structure is shown in Figure-1, a true alkaloid isolated by Dong et al. from *Stemona sessilifolia* belonging to the family Stemonaceae, commonly used in Chinese medicine as antitussive and which analogs, stenine and stenine B, have shown strong anti-acetylcholinesterase[6,7]. In addition, we evaluate the precision of the theoretical structures and calculate the chemical properties (absorption distribution, metabolism, excretion, solubility, acidity coefficient) used in drug research, properties often difficult to obtain in reality| which experimental data can be dear and hard to obtain[8].

Methodology

In order to obtain the spatial structure of DSA in the gas phase, the different conformations were first soughted out using the OPLS_2005 force field algorithm available in Macromodel[9]. The lowest potential energy structure was therefore subjected to quantum computation in order to obtain vibratory frequency data, orbital boundaries and electrostatic electron distribution. For that we used the approximations B3LYP / 6-311G* thanks to Jaguar, a specialized software in DFT calculations and much used in quantum chemistry and material science[10-12]. Then, aRMDS was used to evaluate the quality of the theoretical structure[13]. Finally, we use LigPrep and Qikprop softwares (Schrodinger Inc, USA) to obtain the physicochemical properties, and check its "drug-likeness"[14,15]. The illustrations were made with the Maestro 2016-1 graphical user interface.

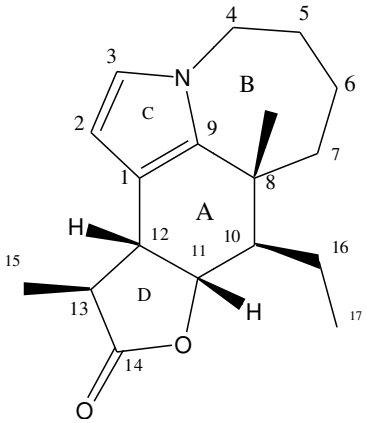

Figure-1: Chemical structure of dehydrostenin A.

Results and discussion

Geometry optimization: The optimized structure of DsA in gas phase is shown in Figure-2. Crystalline structure was obtained from the CCDC database, then subjected to a comparison the computed one using the Kabsh algorithm contained in the

aRMSD software[16]. This algorithm offers accelerated calculations as well as a visualization made possible thanks to VTK[17]. The illustration in Figure-3 clearly shows the main points of divergence between the optimized structure (red) and the crystalline one (green). The alkyl moieties and the dihydrofuran-2-one ring are the points of highest divergence which results from the fact that our reference structure is crystalline with lower liberty degree. The remain parts of the cyclic fragments in DsA display strong similarities, thus revealing the high accuracy of the DFT calculations. Since these visualizations cannot provide numerical data on angular and binding differences, Figure-4 completes the visualization better than traditional tables by illustrating discrepancies between moieties using red balls for high divergence and green balls for high convergence in 3D rendering[17]. Coefficient of determination calculations for distances and angles give values of 0.989 and 0.888 respectively confirming the high quality of theoretical calculations, for dihedrals values calculations are 0.914 for an average of 18.524 angular and dihedral errors, which is consistent with the data in Figure-5.

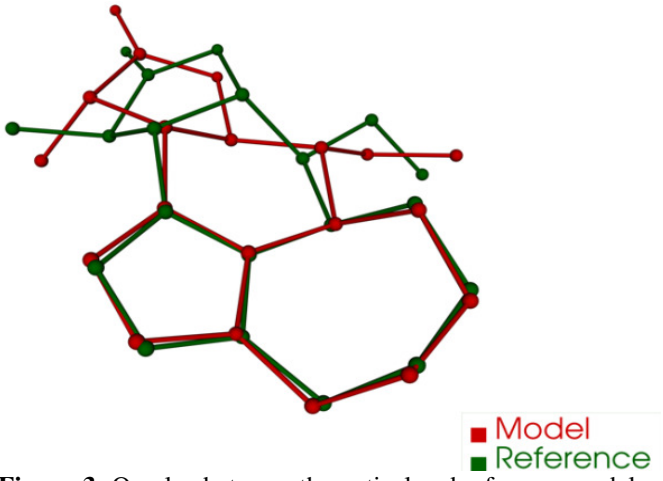

Figure-3: Overlay between theoretical and reference models.

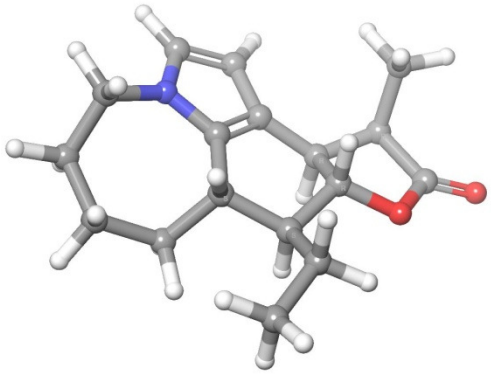

Figure-2: optimized structure of DsA.

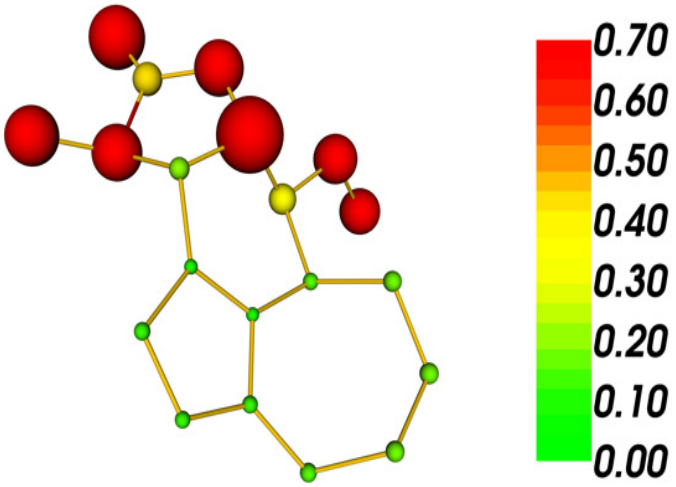

Figure-4: Visualization of discrepancies with VTK.

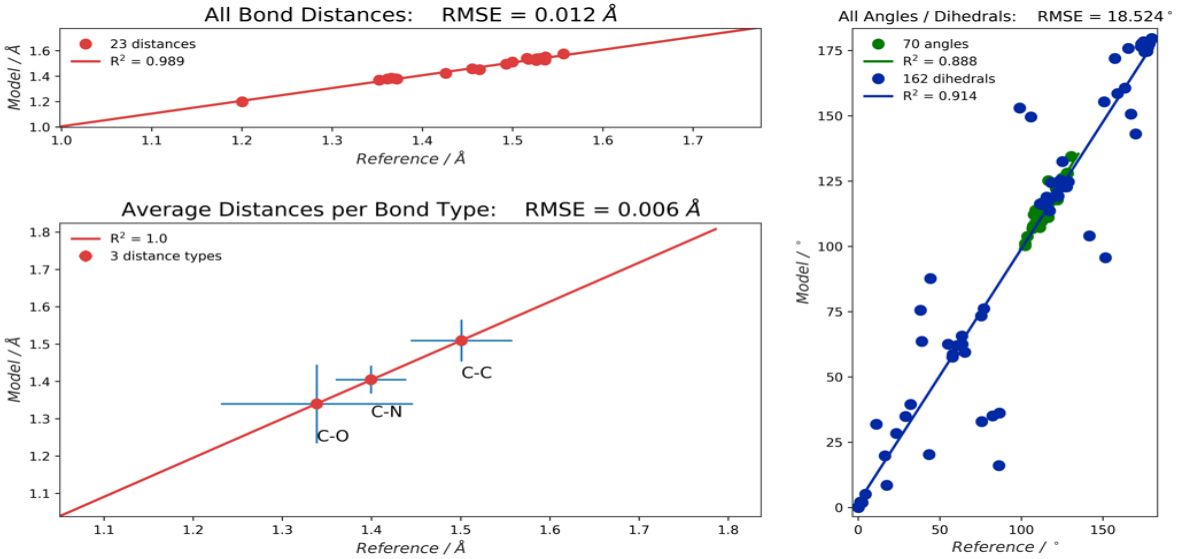

Figure-5: Statistical data between of chemical bonds and angles.

Molecular electrostatic potential: Among tools used in medicinal chemistry, electrostatic potential mapping is also widely used to detect holes in the target proteins and thus facilitate lead optimizations[18]. In organic chemistry, MEP (Molecular Electrostatic potential) is effective to visualize fragments capable of undergoing nucleophilic and electrophilic attacks in order to predict reactions[19]. Visualization is usually done with rainbow colorsfrom which the red areas represent the most electrophilic sites and the violet areas the most nucleophilic sites. Figure-6, resulting from DsA electrostatic potential computations, shows an electronic mapping on the title compound. We see that oxygen atoms can be prone to proton attacks and the two hydrogens that are adjacent to the nitrogen (H_3 and H_4) may participate in intermolecular hydrogen bonds, while the green zone over nitrogen heterocyclic fragment represents the aromatic ring systems at zero potential.

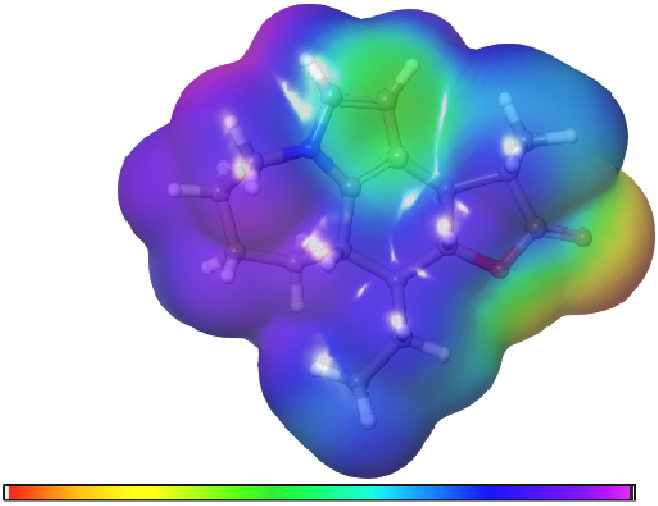

Figure-6: electrostatic potential on DsA.

Frontier orbitals: Molecular orbitals computations in quantum chemistry are a common activity because it is often needs to define degree of reactivity of a compound in different solvents[20]. The most used orbital boundaries are HOMO (Highest Occupied Molecular Orbitals) and LUMO (Lowest Unoccupied Molecular Orbitals), which difference in energy allows us to have a theoretical idea of a molecule reactivity. Here, DFT was used to perform simulations[21]. Figures-7 and 8 show HOMO and LUMO illustrations respectively. Their respective energies -0.21244eV and -.00917eV and the gap E = 0.20327eV suggest a high reactivity despite the calculations in gas phase[22].

ADME: The prediction of ADME (Absorption, Distribution, Metabolism, Excretion) is used in quantitative structure-activity relationship (QSAR) to compare obtained values with those already known and derived from experimental studies[23]. Moreover, it is often very difficult and expensive to obtain these values in laboratory, giving an important place to predictions by simulation in drug research[24]. Ligprep was used to prepare the title molecule to respect the conditions of neutral pH and obtain the different tautomers under these conditions and Qikprop was used to predict their physicochemical values[24]. Table-1 shows main descriptors data. We see that DsA has a rotable bond (ethyl moiety) whose mobility creates deviations from the crystalline structure (Figure-3). Molecular weight is low (273.374 Mw< 500 Da) and Table-2 indicates that DsA does not have hydrogen donors but instead has 3 sites capable of accepting hydrogen. The ionization and electron affinity potentials are in accordance with the values of the orbital energies. Total solvent accessible surface area (SASA) and associated data (FASA, FOSA, LPSA) indicate the absence of polar compounds (O, S, P, etc.) and a strong presence of hydrophobic compounds (saturated carbons and bound hydrogens). Polarizability and solubility (QPlogP) confirmed that DsA did not violate any Lipinski's "rule of Five" (Ro5 = 0), allowing it to be considered "drug-like"[25]. QPPMDCK Predicted apparent MDCK cell permeability in nm/sec and predicts good cell permeability (MDCK> 500). At the same time QPlogS values, Pcaco, and human oral absorption predictions have confirmed that DsA does not violate any of Jorgensen's rules (Ro3 = 0), making it a lead compound for oral administration drug development[26]. However, the biological activities on DsA did not give any satisfactory result even though his counterpart stenine A is very active[6,7]. This could lead to more investigation on pharmacophores impact. The possibilities of metabolism are: α, β-dehydrogenation on the carbonyl, the hydroxylation of the bonded to unsaturated rings, and a possible hydrogenation on the ester moiety, the latter being in accordance with data from Figure-6.

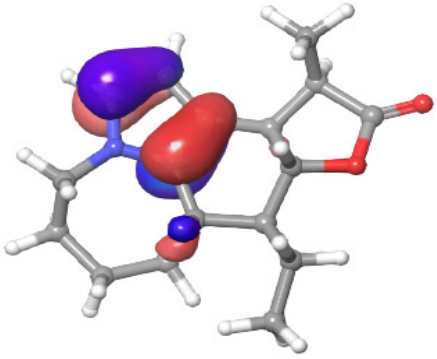

Figure-7: HOMO orbitals of DsA.

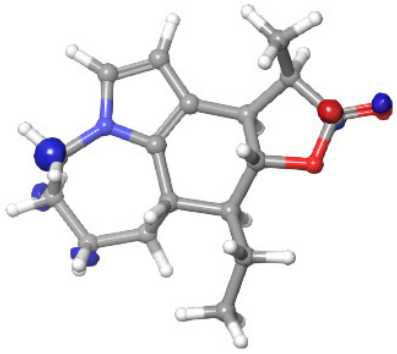

Figure-8: LUMO orbitals of DsA.

Table-1: Principal descriptors of DsA.

Principal descriptors	Rotor	mol_ MW	dipole	SASA	FOSA	FISA	PISA	WPSA	volume	Donor HB	Accpt HB	IP (eV)	EA (eV)	PSA	glob
Values	1	273.374	7.953	516.529	382.974	60.640	72.916	0	917.390	0	3	8.953	-0.826	41.140	0.883

Table-2(a): Chemical properties predictions of DsA.

Predictions for properties	QPlogPo/w	QPlogS	CIQPlogS	QPlogHERG	QPlogPw	QPlogPC16	QPPCaco (nm/sec)	QPlogPoct
Values	3.485	-4.272	-3.623	-3.757	4.605	7.796	2635.416	12.072

Table-2(b): Chemical properties predictions of DsA.

Predictions for Properties	QPlogBB	QPPMDCK (nm/sec)	QPlogKp	QPlog Khsa	Human Oral Absorption	Percent Human Oral Absorption	Rule of Five	Rule of Three	QPpolrz	Jm ($\mu g\ cm^{-2}\ hr^{-1}$)
Values	-0.014	1410.062	-2.284	0.436	3	100	0	0	30.614	0.076

Conclusion

The optimized structure of the DsA was determined in gas phase by the DFT method. This structure has been successfully compared to the crystalline structure using aRMSD, which has revealed some discrepancies at dihydrofurane and alkyl moieties. Reactivity was simulated by mapping the electrostatic density and atomic orbitals and these computations show that H_3 and H_4 atoms are the most nucleophilic sites and oxygen atoms are stand for the most electrophilic sites. Qikprop was used in this case to perform calculations that reveal the title compound "drug-likeness" and presented a conformance to both Lipinski's and Jorgensen's rules. We believe that these data may be useful during data collection in cheminformatics.

Acknowledgement

The authors are grateful of the Cameroonian Ministry of Research and Innovation for support.

References

1. Facchini P.J. (2001). Alkaloid biosynthesis in plants: biochemistry, cell biology, molecular regulation, and metabolic engineering applications. *Annual review of plant biology*, 52(1), 29-66.

2. Pilli R.A., Rosso G.B. and de Oliveira M.D.C.F. (2010). The chemistry of Stemona alkaloids: An update. *Natural product reports*, 27(12), 1908-1937.

3. Carlsson A., Lindqvist M. and Magnusson T.O.R. (1957). 3, 4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature*, 180(4596), 1200.

4. Gorrod J.W. and Wahren J. (1993). Nicotine and Related Alkaloids. London, England: Chapman and Hall, page xv. ISBN: 978-94-011-2110-1.

5. Turabekova M.A., Rasulev B.F., Dzhakhangirov F.N. and Salikhov S.I. (2008). Aconitum and Delphinium alkaloids: "Drug-likeness" descriptors related to toxic mode of action. *Environmental toxicology and pharmacology*, 25(3), 310-320.

6. Dong J.L., Yang Z.D., Zhou S.Y., Yu H.T., Yao X.J., Xue H.Y. and Shu Z.M. (2017). Two Stemona alkaloids from Stemona sessilifolia (Miq.) Miq. *Phytochemistry Letters*, 19, 259-262.

7. Lai D.H., Yang Z.D., Xue W.W., Sheng J., Shi Y. and Yao X.J. (2013). Isolation, characterization and acetylcholinesterase inhibitory activity of alkaloids from roots of Stemona sessilifolia. *Fitoterapia*, 89, 257-264.

8. Cronin M.T. (2003). Computer-aided prediction of drug toxicity and metabolism. In *Modern Methods of Drug Discovery,* Birkhäuser, Basel, 259-278.

9. Mohamadi F., Richards N.G., Guida W.C., Liskamp R., Lipton M., Caufield C. and Still W.C. (1990). Macro Model—an integrated software system for modeling organic and bioorganic molecules using molecular mechanics. *Journal of Computational Chemistry*, 11(4), 440-467.

10. Bochevarov A.D., Harder E., Hughes T.F., Greenwood J. R., Braden D.A., Philipp D.M., Rinaldo D., Halls M.D., Zhang J. and Friesner R.A. (2013). Jaguar: A High-Performance Quantum Chemistry Software Program with Strengths in Life and Materials Sciences. *Int. J. Quantum Chem*., 113(18), 2110-2142.

11. Becke A.D. (1993). Density-functional thermochemistry. III. The role of exact exchange. *The Journal of chemical physics*, 98(7), 5648-5652.

12. Lee C., Yang W. and Parr R.G. (1988). Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Physical review B*, 37(2), 785-789.

13. Wagner A. and Himmel H.J. (2017). aRMSD: A Comprehensive Tool for Structural Analysis. *Journal of chemical information and modeling*, 57(3), 428-438.

14. Release S. (2016). 3: LigPrep. *Schrödinger, LLC, New York, NY*.

15. Release Q.S. (2017). 1: Qik Prop. *Schrödinger, LLC, New York, NY*.

16. Kabsch W. (1976). A solution for the best rotation to relate two sets of vectors. *Acta Crystallographica Section A: Crystal Physics, Diffraction, Theoretical and General Crystallography*, 32(5), 922-923.

17. Schroeder W.J., Lorensen B. and Martin K. (2004). The visualization toolkit: an object-oriented approach to 3D graphics. Kitware.

18. Politzer P. and Murray J.S. (1991). Molecular electrostatic potentials and chemical reactivity. *Reviews Computational Chemistry*, 2, 273-312.

19. Politzer P. and Murray J.S. (2002). The fundamental nature and role of the electrostatic potential in atoms and molecules. *Theoretical Chemistry Accounts*: Theory, Computation, and Modeling (Theoretica Chimica Acta), 108(3), 134-142.

20. Gunasekaran S., Kumaresan S., Balaji R.A., Anand G. and Seshadri S. (2008). Vibrational spectra and normal coordinate analysis on structure of chlorambucil and thioguanine. *Pramana: Journal of Physics*, 71(6), 1291-1300.

21. Sajan D., Lakshmi K.U., Erdogdu Y. and Joe I.H. (2011). Molecular structure and vibrational spectra of 2, 6-bis (benzylidene) cyclohexanone: a density functional theoretical study. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 78(1), 113-121.

22. Sinha L., Prasad O., Narayan V. and Shukla S.R. (2011). Raman, FT -IR spectroscopic analysis and first-order hyperpolarisability of 3-benzoyl-5-chlorouracil by first principles. *Molecular Simulation*, 37(2), 153-163.

23. DiMasi J.A., Hansen R.W. and Grabowski H.G. (2003). The price of innovation: new estimates of drug development costs. *Journal of health economics*, 22(2), 151-185.

24. Hodgson J. (2001). ADMET-turning chemicals into drugs. *Nature Biotechnology*, 19(8), 722-726.

25. Lipinski C.A. (2004). Lead-and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today: Technologies*, 1(4), 337-341.

26. Jorgensen W.L. and Duffy E.M. (2000). Prediction of drug solubility from Monte Carlo simulations. *Bioorganic and medicinal chemistry letters*, 10(11), 1155-1158.