Journal of Fundamental and Applied Sciences

ISSN 1112-9867

Available online at http://www.jfas.info

Research Article

INVESTIGATIONS OF THE BINDING PARAMETRES OF THE INTERACTION OF N'-FERROCENYLMETHYL-N'-PHENYLACETO- AND PROPIONOHYDRAZIDE WITH DNA

H. Mouada, T. Lanez*, E. Lanez

University of El Oued, VTRS Laboratory, B.P.789, 39000, El Oued, Algeria

Received: 08 February 2019 / Accepted: 20 April 2019 / Published online: 01 May 2019

Abstract

Herein we describe the determination of binding parameters of the interaction of N'-ferrocenylmethyl-N'-phenylacetohydrazide (FcA) and N'-ferrocenylmethyl-N'-phenyl-propionohydrazide (FcP) derivatives with chicken blood double-stranded DNA (cb-ds DNA) in phosphate buffer (PB) solution at physiological pH 7.2 by electronic spectroscopy and molecular docking calculations. The results indicated that both FcA and FcP bind DNA in groove binding mode, values of binding constants and binding free energy obtained from electronic spectroscopy measurements and molecular docking calculations were in good agreement.

Key words: DNA, interaction, electronic spectroscopy, molecular docking.

1. INTRODUCTION

The study of the interaction between organometallic compounds and DNA can be considered as a powerful means for the evaluation of pharmacological activity of these compounds [1-3]. The interaction is studied by different techniques such as cyclic voltammetry [4], electronic spectroscopy [5], infrared spectroscopy [6] and molecular docking [7].

Author Correspondence, e-mail: touhami-lanez@univ-eloued.dz

doi: http://dx.doi.org/10.4314/jfas.v11i2.21

Ferrocene derivatives bearing two nitrogen atoms in their molecular structures can be of great interest in the field of pharmacology. Starting from this fact, the interaction of two ferrocene derivatives: N'-ferrocenylmethyl-N'-phenylacetohydrazide (FcA) and N'-ferrocenylmethyl-N'-phenylpropionohydrazide (FcP) (figure 1) with chicken blood double-stranded DNA in phosphate buffer solution at physiological pH 7.2 was studied using electronic spectroscopy and molecular docking calculations.

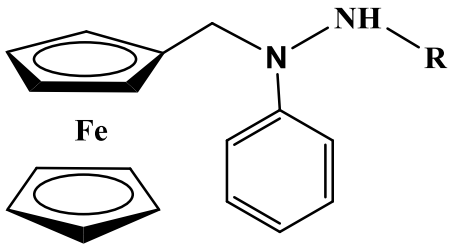

Fig.1. Structure of N'-ferrocenylmethyl-N'-phenylacetohydrazide (R = Me) and N'-ferrocenylmethyl-N'-phenylpropionohydrazide (R = Ph)

2. EXPERIMENTAL

2.1. Chemicals and Reagents

All the chemicals were of analytical grade and were used without any further purification.

2.2. Synthesis

N'-ferrocenylmethyl-N'-phenylacetohydrazide and N'-ferrocenylmethyl-N'-phenylpropiono-hydrazide were synthesized from the reaction of the well-known quaternary salt *N*,*N*,*N*-trimethylammoniomethylferrocene iodide [8] and phenylacetohydrazide and phenylpropionohydrazide respectively. The two obtained compounds gave spectroscopic data in accordance with reported methods [9].

2.3. DNA extraction

DNA was extracted from chicken blood by Falcon method [10]. The purity of DNA sample was determined using the ratio of the absorbance A_{260}/A_{280}. The obtained ratio was equal to 1.97, indicating the purity of DNA [11]. The concentration of the extracted DNA was measured by electronic spectroscopy at 260 nm using the molar extinction coefficient of 6600 $M^{-1}\cdot cm^{-1}$ [12].

2.4. Apparatus and Procedures

UV experiments were carried out on a UV-Vis spectrometer, (Shimadzu 1800, Japan). The spectroscopic response of 1mM of both studied compounds in 0.1M aqueous buffer phosphate solution (KH_2PO_4/K_2HPO_4) at pH 7.2 was first recorded without DNA and then in the presence of gradually increasing concentration of DNA solution, all experiments were conducted at 298 K.

3. RESULTS AND DISCUSSION

3.1. UV-Visible Spectroscopic Study

Measurement of the binding constants and binding free energies of FcA and FcP with DNA was achieved by recording the electronic specter of a solution of 1mM of FcA and FcP in 0.1 M aqueous buffer phosphate solution in the absence and presence of gradually increasing concentration of DNA solution at pH 7.2. The electronic specters are presented in the following figure 2 which illustrates that the absorbance of both FcA and FcP decreases with the gradual increase of DNA concentration.

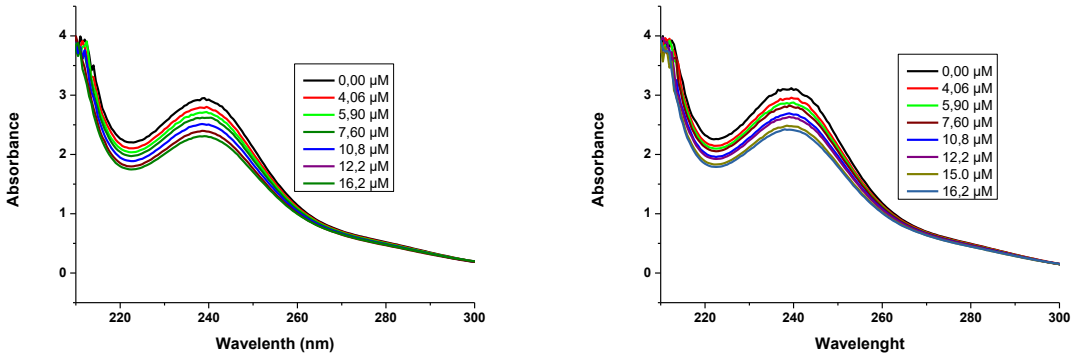

Fig.2. UV-Vis absorption spectra of 1 mM of FcA (a) and FcP (b) in the absence and presence of DNA

The binding constants were obtained from the variation in absorbance values by increasing DNA concentration using the following equation (1) [13].

$$\frac{A_0}{A-A_0} = \frac{\varepsilon_G}{\varepsilon_{H-G}-\varepsilon_G} + \frac{\varepsilon_G}{\varepsilon_{H-G}-\varepsilon_G}\frac{1}{K[DNA]} \qquad (1)$$

where [DNA] is the DNA concentration (µM), K is the binding constant (M^{-1}), A_0 and A are the absorbance of ligand in the absence and presence of DNA, respectively, and ε_G ($M^{-1}cm^{-1}$) and ε_{H-G} ($M^{-1}cm^{-1}$) are their respective extinction coefficients.

The binding constant values were obtained from the ratio of the slope to the intercept of the plots presented in figure 3 and are reported in Table 1.

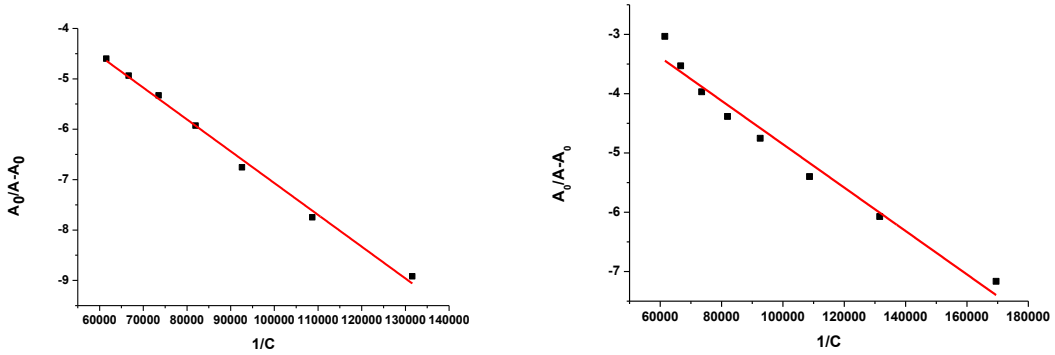

Fig.3. Plots of $A_0/(A-A_0)$ *vs.* $1/[DNA]$ used to calculate the binding constant of the adducts FcA-DNA and FcP-DNA

Table 1. Binding constants and binding free energies of FcA and FcP with DNA

Adduct	Equation	K(M^{-1})	-ΔG ($KJ.mol^{-1}$)
FcA-DNA	$y = -6\times10^{-5}x - 0,7585$	1.26×10^{4}	23.4
FcP-DNA	$y = -3.6\times10^{-5}x - 1,1896$	3.3×10^{4}	25.8

3.2. Molecular Docking Studies

Results obtained from electronic spectroscopy experiments were validated by molecular docking simulation. The simulation allow the exploration of additional information of the FcA and FcP conformation and their orientation in the active site of the DNA, the docking also allows visualizing the intercalation pattern of the ligands with DNA.

3.2.1. Structural optimization

The chemical structures of FcA and FcP were fully optimized using Gaussian 09 program package [14], and the B3LYP level of theory [15,16] with 6-311++G(d,p) basis set. Geometries of the complexes were fully optimized by employing the density functional theory, without imposing any symmetry constraints.

3.2.2. Docking simulations

The molecular docking studies of FcA and FcP into DNA were carried out using AutoDock 4.2 docking software [17]. The optimized structures of FcA, FcP and DNA were imported to the AutoDock molecular docking software. All docking studies were carried out on a Pentium 3.30 GHz and RAM 4.00 Go microcomputer MB memory with Windows 7 operating system.

The crystal structure of DNA (PDB ID: 1BNA) selected from protein data bank (http://www.rcsb.org./pdb) [18] was chosen as the receptor. All hydrogen atoms and gassier charges were added to the DNA and non-polar hydrogen atoms were merged. The best conformation was selected with the lower docking energy [19].

At the end of docking runs, diverse binding energies of the ligand were obtained with their respective conformations; the stable conformation, which corresponds to the lowest binding energy, was chosen as the best pose and was used in the docking analysis.

The binding energies of the docked structures with DNA are summarized in table 2. The binding constants were calculated using equation (2).

$$\Delta G = -RT \ln K \qquad (2)$$

where ΔG is the binding free energy in KJ.mol^{-1}, R is the gas constant, 8.32 J.mol^{-1}K^{-1} and T is the absolute temperature, 298K.

Table 2. Binding constant and binding free energy values obtained for FcA –DNA and FcP-DNA adduct by molecular docking simulation

	FcA	FcP
$-\Delta G$(kJ·mol^{-1})	21.7	21.0
K(M^{-1})	6.3×10^{3}	4.8×10^{3}

The results indicate that the ligand FcA interact with DNA by the nitrogen atom via a hydrogen bond to the hydrogen atom of DT20 :OP1, DT19 :O3, the length of the band is equal to 2.073 Å (Figure 4a). However, the ligand FcP is attached to DNA by two hydrogen band DA6 :H61 with the length 1.679 Å and DA6 :N6 with length equal to 2.163 Å. (Figure 4b).

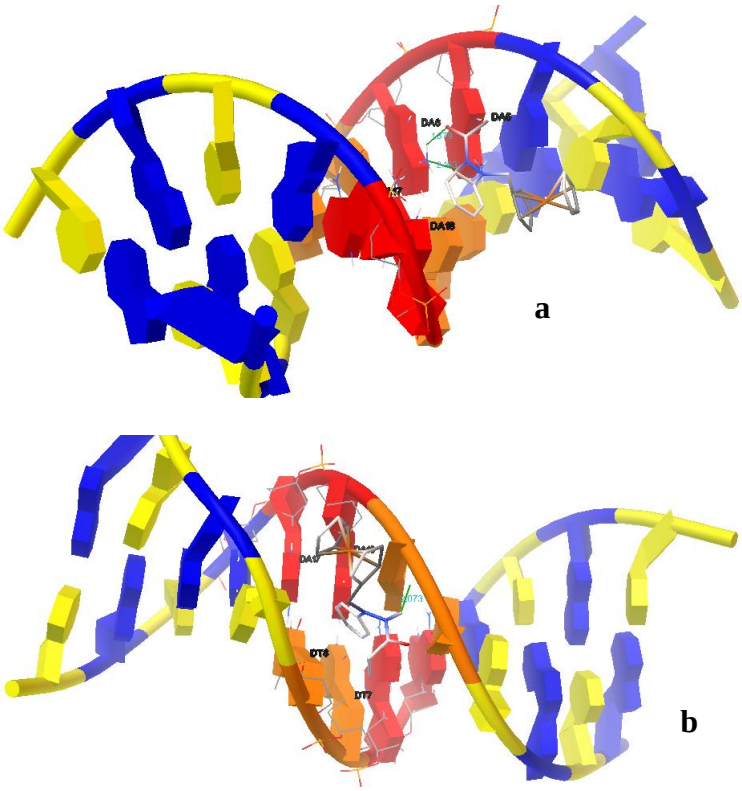

Fig.4. Docking poses of FcA (a), FcP (b) with DNA (PDB ID: 1BNA) illustrating the interactions between DNA and the examined ligands, color codes: DA: red, DC: yellow, DG: blue, DT: dark brown, and ligands: green color

4. CONCLUSION

Electronic spectroscopic assays accompanied by molecular docking calculations were used to study the interaction of N'-ferrocenylmethyl-N'-phenylacetohydrazide and N'-ferrocenylmethyl-N'-phenylpropionohydrazide with DNA. The electronic spectroscopic experimental results and molecular docking studies indicate that both ligands possess significant binding affinity towards DNA via electrostatic interactions as the dominant mode. Furthermore the order of magnitude of binding energies confirms the electrostatic interaction of both studied compounds with DNA. These results clearly indicate that both componds can cause conformational changes in the structure of DNA, which subsequently slowing down the cell replication process and eventually preventing the cell death.

5. ACKNOWLEDGEMENTS

The authors are grateful to the Algerian Ministry of Higher Education and Research for financial support (project code: B00L01UN390120150001). We would also like to thank Mr Ali Tliba (VTRS staff) for his help.

6. REFERENCES

[1] Lanez E, Bechki L, Lanez T. Computational molecular docking, voltammetric and spectroscopic DNA interaction studies of 9n-(ferrocenylmethyl)adenine Chem. Chem. Technol., 2019, 13(1), 11–17 . doi: https://doi.org/10.23939/chcht13.01.011

[2] Shafqat A, Ataf A A, Badshah A, Imtiaz U-D, Bhajan L, Saqib K, Shafiq U. DNA interaction, Antibacterial and Antifungal studies of 3-nitrophenylferrocene, J. Chem. Soc. Pak., Vol. 35, No.3, 2013, 922-928

[3] Ou ZB, Lu YH, Lu YM, Chen S, Hong Xiong Y, Zhou X H, Mao ZW, Le XY. A copper(II) complex with 2-(2'-pyridyl)benzimidazole and l-arginine: synthesis, structure, antibacterial activities, and DNA interaction. J. Coordinat. Chem. 2013, 66(12), 2152-2165, doi: 10.1080/00958972.2013.800195

[4] Radi A, Eissa A, Nassef HM. Voltammetric and spectroscopic studies on the binding of the antitumor drug dacarbazine with DNA. J. Electroanalytical Chem. 2014, 24(28),717–718: doi: 10.1016/j.jelechem.2014.01.007

[5] Shorkaei MR, Asadi Z, Asadi M. Synthesis, characterization, molecular docking and DNA binding studies of Al(III), Ga(III) and In(III) water-soluble complexes. J. Molecular Structure, 2016, 1109, 22e30. doi: 10.1016/j.molstruc.2015.12.070

[6] Bi S, Zhou H, Wu J, Wang Y. Interaction of dextromethorphan hydrobromide with DNA: multispectral, voltammetric, and molecular docking technology. J. Biomol. Struct. and Dynamics, 2018, 36(5), 1154-1160. doi: 10.1080/07391102.2017.1313781

[7] Lanez T, Lanez E. A Molecular Docking Study of N-Ferrocenylmethylnitroanilines as Potential Anticancer Drugs. International Journal of Pharmacology, Phytochemistry and Ethnomedicine, 2016, 2, 5-12. doi: 10.18052/www.scipress.com/IJPPE.2.5

[8] Osgerby J, Pauson P. J. Chem. Soc., 1958, 642, 656. doi: 10.1039/JR9580000656

[9] Terki B. PhD. Dissertation, Batna 2001.

[10] Sambrook J, Fritsch E, Maniatis T. Molecular Cloning: A Laboratory Manual, 2nd edn., Cold Spring Harbour Laboratory Press, New York 1989, 1626-1644.

[11] Glasel J. Biotechniques, 1995, 8, 62.

[12] Vijayalakshmi R, Kanthimathi M, Subramanian V. *et al*. Biochem. Biophys. Res. Commun., 2000, 271, 731. doi :10.1006/bbrc.2000.2707

[13] Brett C, Brett A. Electrochemistry: Principles, Methods and Applications, Oxford Science University Publications, Oxford 1993, 256-276.

[14] Frisch M, Trucks G, Schlegel H. *et al*. Gaussian 09. Gaussian Inc., Wallingford CT, 2009.

[15] Becke A. Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys., 1993, 98, 5648. doi : 10.1063/1.464913

[16] Miehlich B, Savin A, Stoll H. *et al*. Results obtained with the correlation energy density functionals of becke and Lee, Yang and Parr. Chem. Phys. Lett., 1989, 157, 200. doi: 10.1016/0009-2614(89)87234-3

[17] Morris G, Ruth H, Lindstrom W. *et al*. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J. Comput. Chem., 2009, 30, 2785. doi : 10.1002/jcc.21256

[18] Berman H, Westbrook J, Feng Z *et al*. The Protein Data Bank. Nucl. Acids Res., 2000, 28, 235.

[19] Lanez T, Benaicha H, Lanez E *et al*. Electrochemical, spectroscopic and molecular docking studies of 4-methyl-5-((phenylimino)methyl)-3H- and 5-(4-fluorophenyl)-3H-1,2-dithiole-3-thione interacting with DNAJ. Sulfur Chem., 2018, 39, 76. doi:10.1080/17415993.2017.1391811

How to cite this article:
Mouada H, Lanez T, Lanez E. Investigations of the binding parametres of the interaction of n'-ferrocenylmethyl-n'-phenylaceto- and propionohydrazide with DNA. J. Fundam. Appl. Sci., 2019, *11(2), 875-882*.