

# Molecular Dynamics simulation of Pyrazole aqueous solution at 298.15, 303.15 and 308.15 K

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## Abstract

M D simulation of Pyrazole aqueous solution at 298.15, 303.15 and 308.15 K was carried out by using OPLS force field from this simulation we calculate RDF of N-H... OH<sub>2</sub> and N...HOH type of interactions the results show that the hydration shell around N-H site at 5Å<sup>0</sup> is decade with increasing temperature and reformed at 10Å<sup>0</sup>, so N site has two conserved hydration shells at approximate 4 and 6Å<sup>0</sup> respectively these are stable in this temperature range but the order and number of water molecules are varying with temperature specially the hydration shell at 4Å<sup>0</sup>.

Keywords: Pyrazole, Molecular dynamics, interaction simulation

## Introduction

Pyrazole considered one of the raising interesting species as a molecule or moiety as well it has draw a remarkable attention for long time in bio-chemistry by being as a part of many drugs such as [1, 5], food dyes [6, 7], Pesticide and Herbicide agents [8, 10] or cellular fission agent [11]. In modern Pyrazole has great importance in designing molecular relays, switches [12] and hybrid nano-device [13] systems these applications are based on proton transfer behavior of Pyrazole molecule with itself and other molecules [14]. In the present theoretical methods become very important tool by which we can get a useful information of Pyrazole system including Ab-initio[15], DFT[16, 17], semi-empirical [18-19] Molecular Dynamic (MD) simulations considered a powerful tool to elucidate the molecular behavior at microscopic level and means used to connect it with macroscopic description [20] and now these methods were connected with practical data by many search groups[21-24] So the aim of this study is to get a picture on the molecular interaction that exist between solvated Pyrazole molecules with its environment of solvent water molecules and prepare a basis by which we can connect with practical experimental data.

## Method and calculations

The semi-empirical geometry optimization calculations and MM MD (classical molecular mechanics molecular dynamics) simulations were carried

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out using programs included in Hyperchem 8.0.8 package, the simulation calculations were accomplished in Excel (2007) program that satisfied through dynamic data exchange protocol between Hyperchem and Office programs. All calculations were done with personal lap top LG with processor intel® Core™2 Duo CPU. The geometry of Pyrazole molecule was optimized using PM3 (parameterized model number 3) semi-empirical method using Polak-Rebeire algorithm, the structural data including bond lengths, bond angles, charge distribution and atom numbering are given in table (1) and figure(1A,1B). The values of independent internal coordinates that displayed in the above figures and table are (9) bond lengths and (7) bond angles the remaining (5) coordinates (according to the low 3N-6) are the dihedral angles which take the (0) value for this planer molecule at its ground state. In addition the charge distribution upon the molecule is shown in figure (2). Pyrazole molecule and 212 water molecules with periodic boundary conditions represented by cubic box with length of 18.7A<sup>0</sup>, dielectric of the media was kept constant and inner and outer radius cutoff was 5.35 and 9.35 A<sup>0</sup> respectively, we use standard OPLS (optimized potentials for liquid simulations) force field method for simulation three temperatures were taken (298.15, 303.15 and 308.15 K). The TIP3P model (transferable intermolecular potentials 3 point charge water model) was adopted for water–water interactions. This is a three-site water model which has been widely used for pure water as well as for aqueous ionic and non-ionic solutions. To carry out the simulations, we employed a time step of 0.0001 ps and a thermal bath coupling parameter of 1ps. An auxiliary simulation of pure water under identical conditions was also carried out. In this case, the simulation length was 5 ps.

### **Results and discussion**

At it must pay the attention to the simulation in this study is carried out under classical conditions where we ignored a quantum effects such as ionization, bond breaking or formation as initial approximation. To connect between the macroscopic isothermal and its equivalence on the microscopic level, the microscopic temperature that calculated from equation [25]:

$$T(t) = \frac{1}{(3N - n)K_B} \sum_{i=1}^N \frac{|P_i(t)|^2}{m_i} \dots\dots\dots(1)$$

Where T: temperature (K)

t: time in Pico second (ps)

N: number of atoms

n: number of constrained degrees of freedom

p: linear momentum (g.A<sup>0</sup>.ps<sup>-1</sup>)

q: generalized coordinate in Angstrom (A<sup>0</sup>)

m: atom mass (g) (gram)

This relates to average kinetic energy of the system that settled after each time step from previous time trajectory by the equation

$$q(t+\Delta t) = q(t) + \frac{P(t)}{m} \Delta t \dots\dots\dots(2)$$

$$P(t+\Delta t) = P(t) + m a(t) \Delta t \dots\dots\dots(3)$$

(a) Linear acceleration in  $\text{Å}^0.\text{ps}^{-2}$  the temperature histogram over the simulation period time shows that the system has reached equilibrium at the simulation temperatures as shown in figures (3, 4 and 5). Also the average of temperature was reported in table (2). The difference between the values of simulation temperatures and their average is due to dynamic nature of the kinetic energy transfer during random motion of the molecules, this deviation will be remarkable at the microscopic level.

**Analysis of solution structure**

The radial distribution function measures how atoms and molecules organize around each other, it provides structural properties such as details on the local structure, the following expressions is used to calculate RDF between to selected atoms A and B [26]

$$g_{AB}(r) = \frac{\rho_{AB}(r)}{\rho_{Bulk}} \dots\dots\dots(4)$$

Where  $g_{AB}$ : radial distribution function of B type atoms around A type atom  
 $\rho_{AB}(r)$ : number density of B type atoms that have a distance r from A type atom ( $\text{Å}^0^{-3}$ )

The local density  $\rho_{AB}(r)$  is given by [26]:

$$\rho_{AB}(r) = \frac{\langle N_B(r, \Delta r) \rangle}{V(r, \Delta r)} \dots\dots\dots(5)$$

$\langle N_B(r, \Delta r) \rangle$ : Average number of B type atoms that have a distance between r and  $\Delta r$  from A type atom

$V(r, \Delta r)$ : Volume of spherical shell between r and  $\Delta r$  ( $\text{Å}^0^3$ )

The value of spherical thickness  $\Delta r$  which is chosen small enough to provide important features of RDF but large enough to assure good statistics, finally the  $g_{AB}$  was normalized according to the equation [25]

$$\frac{1}{V} \int g_{AB}(r) dr = 1 \dots\dots\dots(6)$$

V: volume of the simulation solution ( $\text{Å}^0^3$ )

RDF was displayed in figures (6, 7, 8, 9, 10 and 11). RDF for all figures indicate few numbers of water molecules at a distance smaller than  $3.9\text{Å}^0$  because the steric effect of residual sides of Pyrazole that prevent water from being closer to the specific interaction sites of Pyrazole, the interaction N-H...OH<sub>2</sub> at 298.15K Figure (6) indicate high order of water molecules around

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acidic proton of Pyrazole specially at a distance approximate to  $5\text{A}^0$  which we can consider it as a main hydration shell at this temperature (include about 45 water molecules) the sharpness of the peaks that exist in this figure is similar to that of solid state materials[27] make we propose the water molecules in these hydration shells is (bulk water) or they have semi regular lattice[28] , this behavior is described as a structure making property in practical volumetric and viscometric studies[29,30], the second highest peak near  $7.3\text{A}^0$  belong to the second hydration shell which contains 15 water molecules, the distance between first and second hydration shells is  $2.3\text{A}^0$  correspond to the diameter of water molecule, in the site N...HOH at the same temperature as indicated in figure (7) the regulation of water molecules around  $5\text{A}^0$  is less than that of the previous site where there are a remarkable amount of non-ordered dense water molecules contribute with ordered water molecules in this hydration shell in addition there is a second hydration shell around this site contains ordered water molecules at about  $6.4\text{A}^0$ . At 303.15K figure (8) indicate decrease of the order of water molecules around N-H site also there is a strong hydrogen bonding with one water molecule has a distance  $2.9\text{A}^0$  that contribute with increasing thermal energy by disorder raising of water molecules around N-H site, in other hand the regulation around N site [figure(9)] at about  $3.9\text{A}^0$  is increased which seems as water molecules have transferred their ordered structures around this site and lifting the N-H site this perhaps due to the increasing vibrational motion of N-H bond and the water molecule that attached with it by hydrogen bonding this motion act to destroy ordered structures around this site and act to push these structures away to other site N.

Figure (10) indicate returning the order of water molecules around N-H site at 308.15K but the maximum intensity is shifted near  $10\text{A}^0$  away from raising vibrated species and the sequence of intensities is reversed from that of figure (6) at 298.15K indicating the decrease of stability of bulk water as it become close to N-H site while figure (11) indicate the site N has approximately similar structure of hydration shells in 298.15K and 308.15K, it can be estimate that in spite of ignoring the effect of ionization and association in this work and left them as a subject of other works we can conclude that increasing the value of limited apparent molal volume with increasing temperature agrees with shifting of hydration shell at N-H from  $5\text{A}^0$  to  $10\text{A}^0$  also the effect of Pyrazole molecule as a structure-breaking material agrees with decay of hydration shell in N-H site at 303.15K and this decay behavior is the major in observation in the practical study.

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**References**

- 1- Jones M. (1953), "Betazole as gastro-secretion stimulant", *J. Amer. Chem. Soc.*, **75**, 4048.
- 2- Uda Y. (1970), "biological assay of Difenamizole", *Takeda Kenkyusho*, **29**, 42.
- 3- Likforman J., (1987), "Fomepizole properties as Ethylene Glycole antidote", *J. Toxicole. Clin. Exp.*, **7**, 373.
- 4- Mizoule J. (1979), "Anti-inflammatory drugs", *Arch. Int. Pharmacodyn.*, **238**, 305.
- 5- Sydel K. (1964), "new anti bacterial compounds containing Pyrazole ring", *Arzine mittel-Forsch*, **14**, 1294.
- 6- Freeman X. (1950), "Tetrazole use as a food dyes", *J. Assoc. Offic. Agr. Chem.*, **33**, 937.
- 7- Stange X. (1978), "Orange B pigment", *Fed. Reg.*, **43**, 45611.
- 8- Shirakura S. (1995), "Azimsulfuron herbicide", *Weed Res. Japan*, **40**, 299.
- 9- Cole L. (1993), "Fpronil pesticide properties", *Pest. Biochem. Physiol.*, **46**, 47.
- 10- Yamamoto S. (1992), "using of Halosulfuron-methyl as herbicide", *ACS Symposium Series*, **504**, 34.
- 11- Krystof V., Cankar P., Frysova I., Slouka J., Kontopidis G., Dzubak P., Hajduch M., Srovnal J., de Azevedo J., Orsag M., Paprskarova M., Rolcik J., Latr A., Peter M. And Strnad M (2006), "4-Arylazo-3, 5-diamino-1H-pyrazole CDK Inhibitors: SAR Study, Crystal Structure in Complex with CDK2, Selectivity, and Cellular Effects", *J. Med. Chem.*, **49**, 6500.
- 12- Sakai S. (1995), "Theoretical study on molecular electronic devices Assessment of switching by hydrogen transfer for pyrazole model", *Nanotechnology*, **6**, 75-80.
- 13- Cardini G. and Muniz-Miranda M. (2002) "Density Functional Study on the Adsorption of Pyrazole onto Silver Colloidal Particles", *J. Phys. Chem. B*, **106**, 6875.
- 14- Alkorta I., Elguero J., Foces-Foces C., and Infantes L., (2006) "Classification of hydrogen-bond motives in crystals of NH-pyrazoles a mixed empirical and theoretical approach", [www.arkat-usa.org](http://www.arkat-usa.org).
- 15- Hargittai I., Brunvoll J., Foces-Foces C., Lamas-Saiz A. and Elguero J. (1993), "A comparison of the structures of pyrazole, 3, 5-dimethylpyrazole and 3,5-bis(trifluoromethyl)pyrazole: theoretical calculations (STO-3G), microwave, electron diffraction and crystallography", *J. Mol. Str.*, **291(2-3)**, 211.
- 16- De Paz J., Elguero J., Foces-Foces C., Lamas-Saiz A., Aguilar-Parrilla F., Klein O. and Limbach H., (1997), "Theoretical study of the structure and tautomerism of N1-unsubstituted pyrazoles in the solid state", *J. Chem. Soc., Perkin Trans.*, **2**, 101.
- 17- Li X. and Liao S. (2009), "Theoretical study of proton transfer in triflic acid/water, imidazole and pyrazole clusters", *J. Mol. Str. THEOCHEM*, **897**, 66.
- 18- Jorge D., Leonardo M. and Gustavo E. (1993), "Theoretical study of pyrazole elimination of N-alkyl pyrazoles", *J. Phys. Org. Chem.*, **2(3)**, 225.
- 19- Liu X., Guo J., An D., Wang D., Ren A. and Feng J. (2011), "Theoretical Study on the Two-Photon Absorption Properties of Pyrazole Aluminum Compounds", *Acta Phys. Chim. Sin.*, **27(10)**, 2303.

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- 20- Sethna, J., (2008), "Entropy Order Parameters and Complexity", second edition, Oxford University Press, India.
- 21- Yildirim I. and Kandemirli F. (2011), "synthesis and theoretical calculations of 1H-Pyrazole 3-carboxamide and 3- carboxylate derivatives", *Heterocyclic Communications*, **11(3-4)**, 223.
- 22- Ramondo F., Tanzi L., Campetella M., Gontrani L., Mancini G., Pieretti A. and Sadun C. (2009), "Hydration of diazoles in water solution: pyrazole. A theoretical and X-ray diffraction study", *Phys. Chem. Chem. Phys*, **11**, 9431.
- 23- Matos I., Perez-Mayoral E. , Soriano E., Zukal A., Martin-Aranda R., Lopez-Peinado A., Fonseca I. and Cejka J. (2010), "Experimental and theoretical study of pyrazole N-alkylation catalyzed by basic modified molecular sieves", *Chemical Engineering Journal*, **161(3)**, 377.
- 24- Yu X., Liu R., Peng H., Huang H., Li X., Zheng B., Yi P., and Chen Z. (2010), "NMR and Theoretical Study on Interactions between Diperoxovanadate Complex and Pyrazole-like Ligands", *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **75(3)**, 1095.
- 25- Cramer, C. (2004), "Essentials of computational chemistry", second edition, John Wiley & Sons Ltd, Minnesota USA.
- 26- Marquez, A. and Balbuena, P. (2001), "Molecular dynamics study of Graphite/Electrolyte interfaces", *J. Electro. Chem. Soc.*, **148(6)**, A624.
- 27- Chandler, D. (1987), "Introduction to statistical mechanics", first edition, Oxford university press, New York.
- 28- Kanno, H., Yonehama, K., Somraj, A. and Yoshimura, Y. (2006), " Structure-making ions become structure breakers in glassy aqueous electrolyte solutions", *Chemical Physics Letters*, **427(1-3)**, 82.
- 29- Parmer, M., Sharma, P. and Guleria, M. (2009), "A comparative study of partial molar volumes of some hydrated and unhydrated salts of transition metal sulphates and magnesium sulphate in water at different temperatures", *Indian Journal of Chemistry*, **48A**, 57.
- 30- Klofutar, C., Horvat, J., Bester-Rogac, M. and Rudan-Tasic, D. (2009), "Viscosity of Aqueous Solutions of Tetramethyl-, Tetraethyl-, Tetra-n-propyl-, Tetra-n-butyl and Tetra-n-pentylammonium Cyclohexylsulfamates from 293.15 K to 323.15 K", *Acta Chim. Slov*, **56**, 188.

**Table (1) independent bond angle values**

Angle	Value (degree.)
2-3-5	107.313
3-5-4	108.71
5-4-1	109.098
4-1-2	108.012
7-2-1	126.566
6-1-4	125.994
8-4-5	125.451

Table (2) the value of temperature average of simulation

T (simulation)/k	T(average)/k
298.15	299.25
303.15	302.15
308.15	308.56

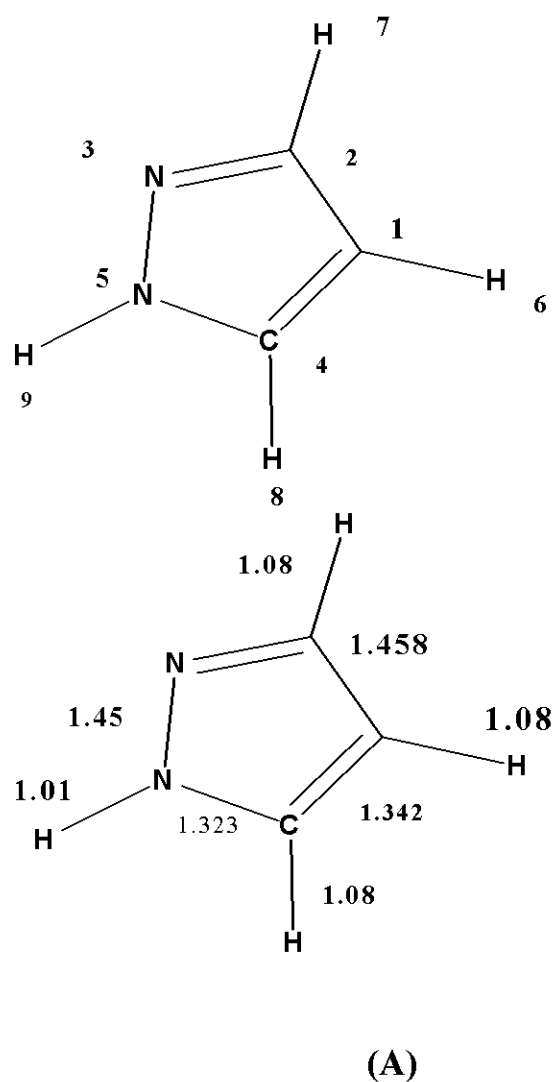


Figure (1) (A) the number labeling of the molecule (B) the values of bond lengths of Pyrazole A<sup>0</sup>

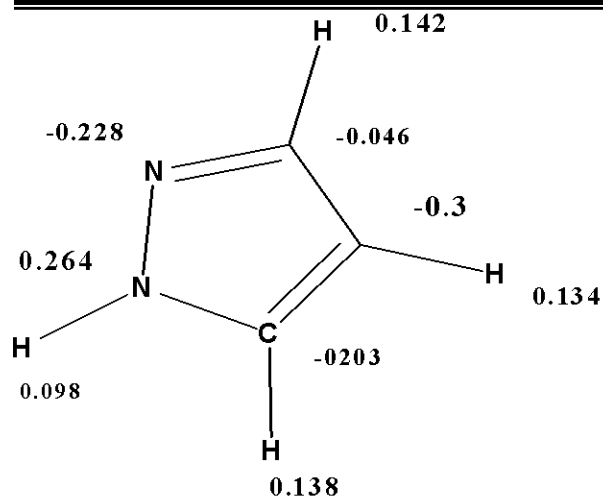


Figure (2) charge distribution on Pyrazole atoms

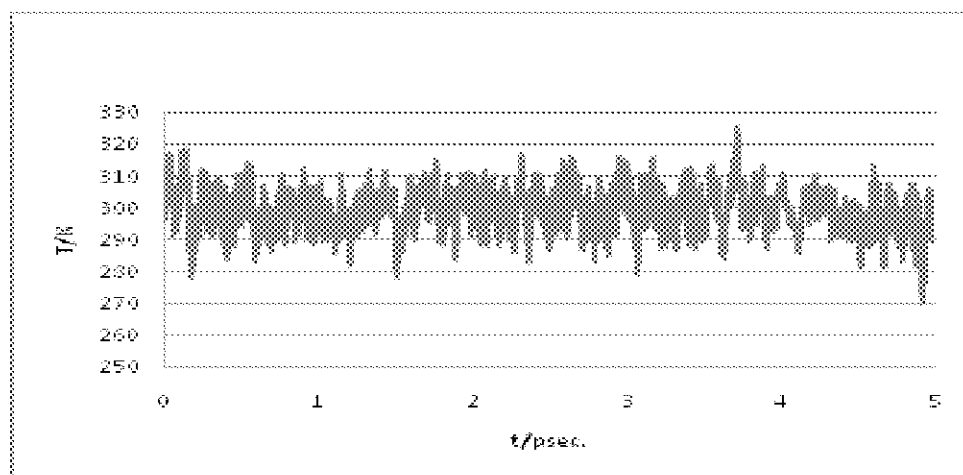


Figure (3) temperature simulation histogram at 298.15k

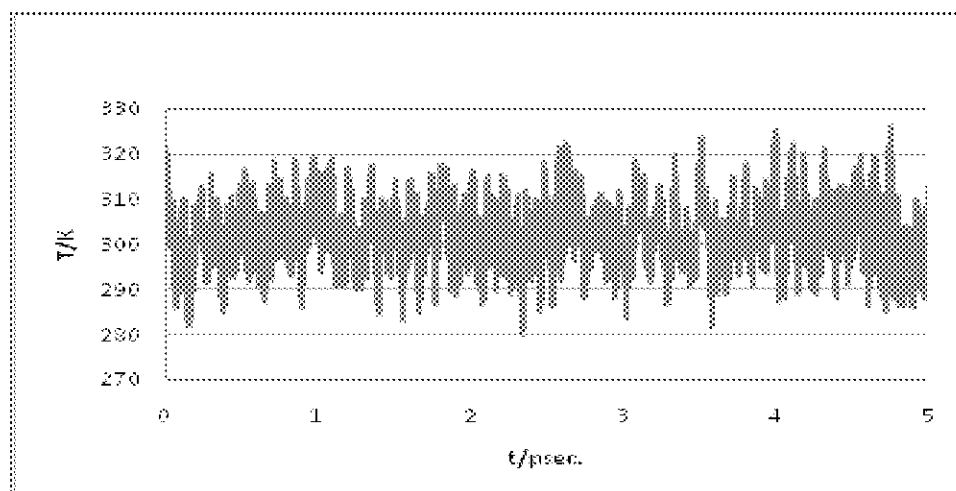


Figure (4) temperature simulation histogram at 303.15k



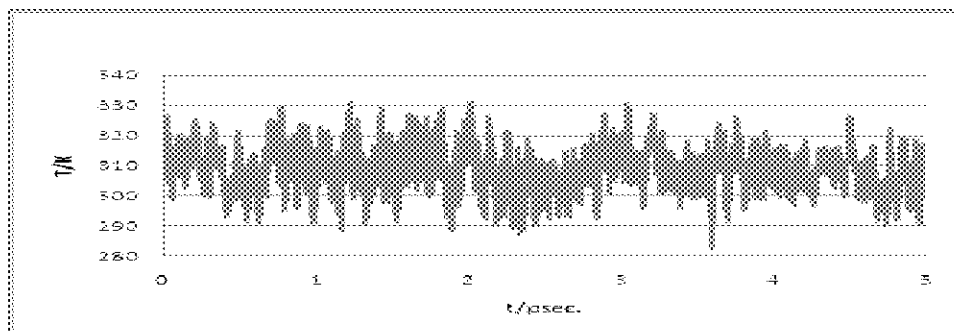


Figure (5) temperature simulation histogram at 308.15k

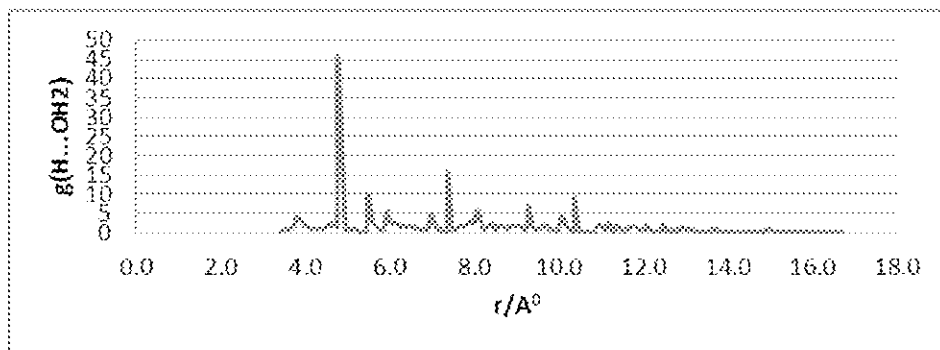


Figure (6) RDF of N-H.....OH<sub>2</sub> interaction at 298.15k

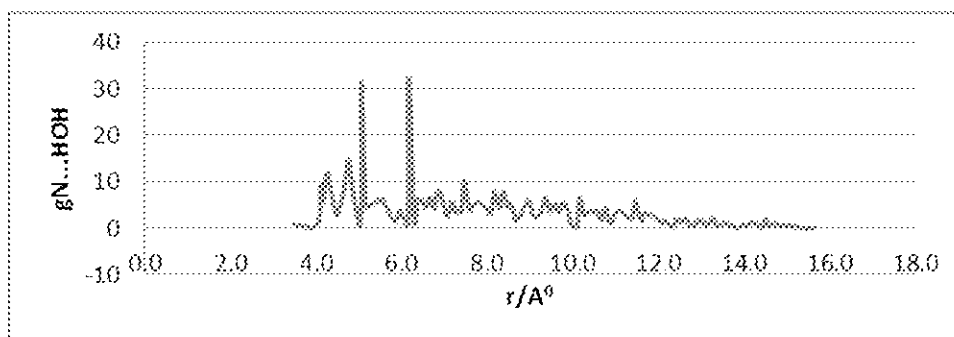


Figure (7) RDF of N.....HOH interaction at 298.15k

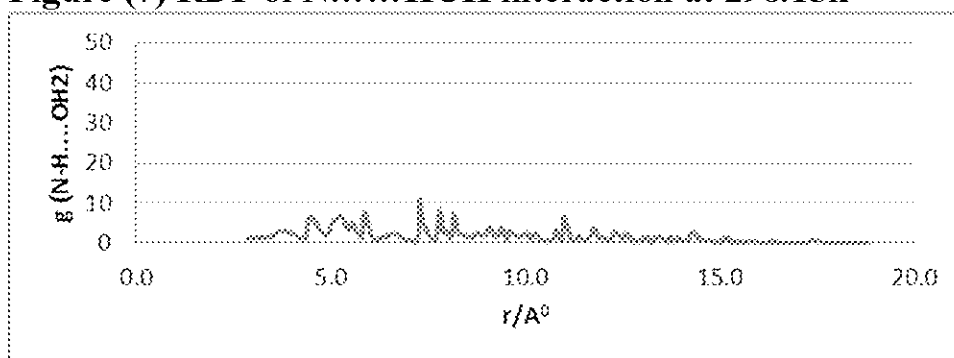


Figure (8) RDF of N-H.....OH<sub>2</sub> interaction at 303.15k

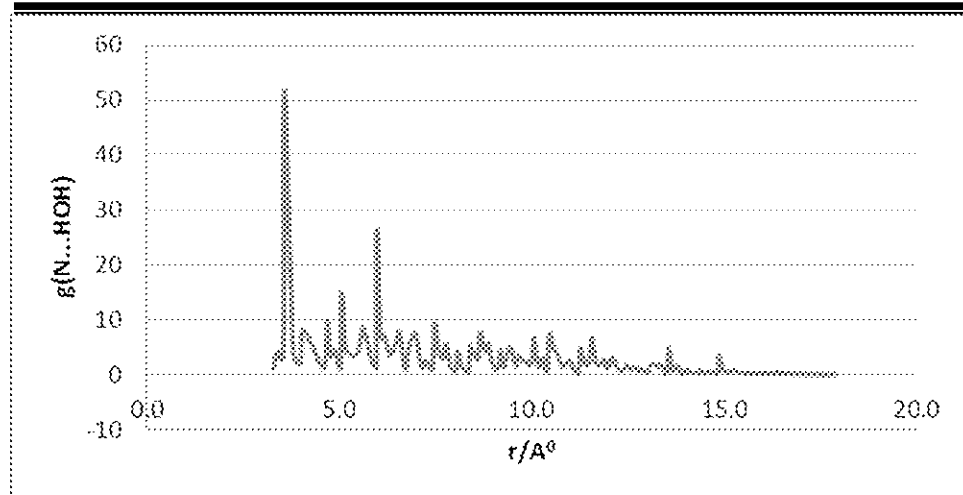


Figure (9) RDF of N.....HOH interaction at 303.15k

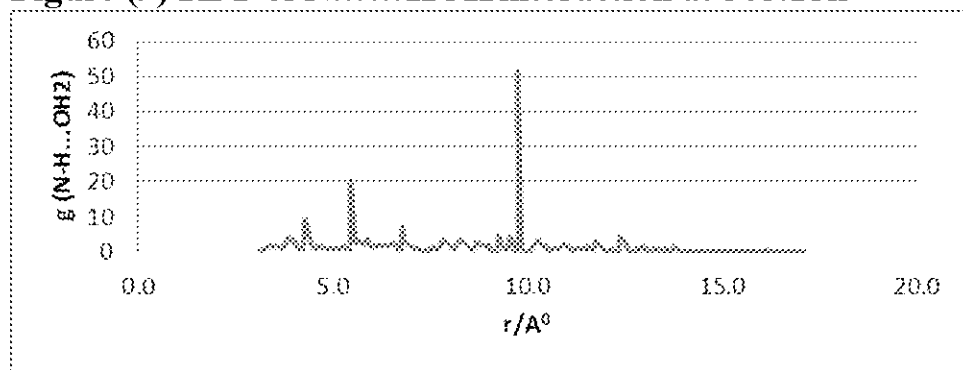


Figure (10) RDF of N-H.....OH<sub>2</sub> interaction at 308.15k

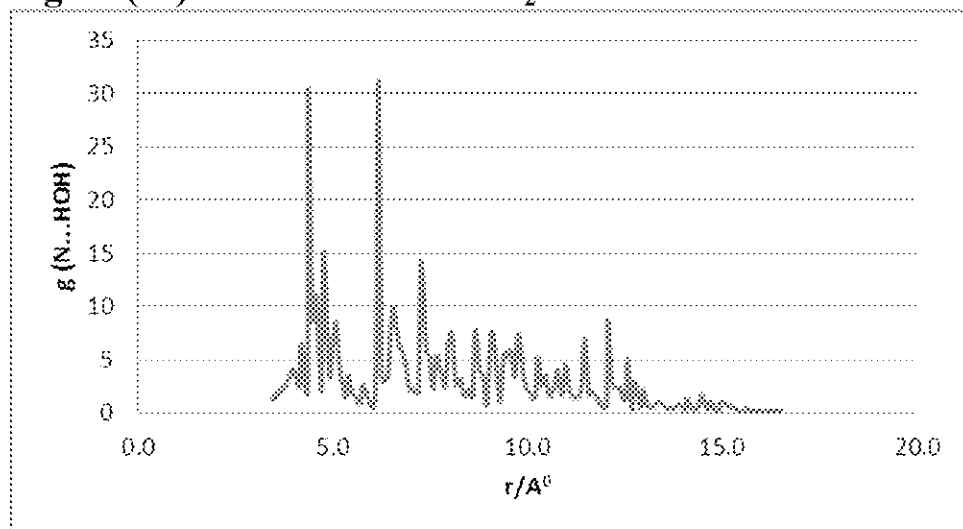


Figure (11) RDF of N.....HOH interaction at 308.15k

## محاكاة الديناميك الجزيئي للمحلول المائي للبايرازول في درجات حرارة (298.15, 303.15 و 308.15 مطلقاً)

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### الخلاصة

تم اجراء محاكاة الديناميك الجزيئي للمحلول المائي للبايرازول في درجات حرارة ( 303.15, 298.15 و 308.15 درجة مطلقاً باستخدام مجال قوة OPLS. من هذه المحاكاة تم حساب دالة التوزيع القطري للتداخل الجزيئي  $N-H...OH_2$  و كذلك  $N...HOH$  وقد بينت النتائج بان طبقة التميؤ الرئيسية حول الموقع N-H تقع على بعد  $5A^0$  حيث تضمحل هذه الطبقة بزيادة درجة الحرارة لتشكل طبقة تميؤ جديدة عند  $10A^0$ . كذلك فان موقع التداخل N يمتلك طبقتي تميؤ مستقرتين عند  $4A^0$  و  $6A^0$  في هذا المدى الحراري ولكن انتظام وعدد جزيئات الماء يكون متغير بتغير درجة الحرارة وخاصة للطبقة  $4A^0$ .

الكلمات المفتاحية: بايرازول، ديناميك جزيئي، محاكاة التداخل