



Alkali Metal Chelation by 3-Hydroxy-4-Pyridinone

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ABSTRACT

Chelations of neutral and one-electron positive ionic alkali metals including Lithium (Li/Li⁺), Sodium (Na/Na⁺) and Potassium (K/K⁺) by 3-Hydroxy-4-Pyridinone (HPO) have been investigated by the *in silico* density functional theory (DFT) approach. The investigated single HPO and corresponding complex systems have been first optimized and their properties have been then evaluated for the minimized energy structures. Moreover, the atomic scale quadrupole coupling constant (QCC) properties have been evaluated for further investigations of the optimized complex systems. The results indicated that the neutral/ionic states of alkali metals are important for determining the complex systems in addition to their element types. Moreover, the effects of chelations on molecular orbitals could propose complex systems for different diagnostics activities. The atomic scale properties also indicated that all atoms of complex systems are important for chelation processes. And finally, the HPO structure could be proposed for alkali metal chelation with differential diagnostic activities.

Keywords: Pyridinone · Alkali metal · Chelation · DFT

Introduction

Alkali metal elements play important roles in biological systems, in which their balances in human cells are always important for health and well-being of body [1]. These elements, which are in positive ion forms, be recognized in blood by pathological tests to examine the health level of person [2]. Diagnoses of such elements are not actually easy and developing diagnostic kits are always necessary for the purpose [3]. Ion selective electrodes (ISE) are those devices for diagnosing

the elements; therefore, they need chelators to absorb the desired ionic elements [4]. To this aim, those compounds with carbonyl or hydroxyl groups could be proposed to absorb the ionic elements [5]. Among which, 3-Hydroxy-4-Pyridinone (HPO) (Fig. 1) is one of the good candidates for the purpose [6]. Lithium, Sodium and Potassium (Li, Na and K) are those alkali metals of this work to be chelated by HPO based on quantum computational methodologies (Fig. 2). One importance of Li is for psychotherapies, in

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which its amount in the body could maintain the personal mood and behavior and its discrepancies could yield mood disorders [7]. Both of Na and K are very much important for balancing the fluids in and around the cells, maintaining blood pressure, managing the muscle functions and operating the nerve systems [8–10]. In one hand; the diagnoses of these elements are important for body health examinations and on the hand; supplying body with these element resources are sometimes dominant for health maintenance [11].

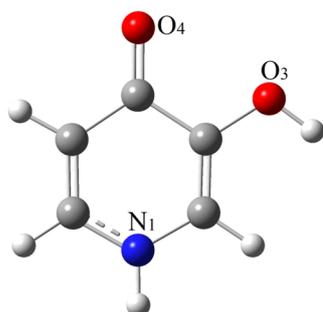


Fig. 1. 2D view of single HPO (3–Hydroxy–4–Pyridinone).

Within this work, individual chelations of neutral and ionic forms of Li, Na and P by HPO have been investigated employing the quantum computational methodologies (Tables 1 and 2, Figs. 1 and 2). One keto and one enol functional groups of HPO are the basic atomic sites for metal chelations, in which the possibility of such complex formation has been carefully examined here. Earlier works have introduced the HPO compounds are proper chelators for almost heavy elements for both of industrial and biological applications [12]. For example, iron chelation is one of the activities of HPO compounds, which are important for treatments of some special diseases such as Malaria [13]. Knowing details of interacting complex systems of HPO–metal are crucial to develop new functions for the HPO compounds, in which the obtained outputs by *in silico* computations could help to achieve the purpose [14–20]. It is worth to note that *in silico* computations are also so much useful for

interpreting the complicated biological systems, especially for the ligand–receptor interactions [21–23].

Materials and Methods

The B3LYP/3–21G* density functional theory (DFT) calculations have been performed to optimize the single HPO and each of interacting HPO–metal complex systems employing the Gaussian program [24] (Figs. 1 and 2). The original HPO (C₅H₅NO) has been obtained from the ChemSpider structure bank [25] with the ID of 94812 and then the HPO–metal complexes have been redesigned in this work. To ensure reaching to the global minimum structures, all optimizations have been examined by frequency calculations to avoid the imaginary frequencies. Moreover, the basis set super position error (BSSE) has been examined for all of interacting complex systems [26]. It is important to note that the metals have been considered in both of neutral and one–electron positive forms (metal/metal⁺) to consider all chelation possibilities. Based on the optimization processes, the values of total energy (TE), the highest occupied and the lowest unoccupied molecular orbitals (HE and LE), and dipole moment (DM) have been directly evaluated from the calculation outputs. Moreover, eqs. (1) and (2) have been used to evaluate the values of binding energy (BE) and energy gap (EG) for the optimized structures. All the obtained optimized properties are summarized in Table 1.

$$BE = E_{\text{Complex}} - E_{\text{HPO}} - E_{\text{Metal}} \quad (1)$$

$$EG = LE - HE \quad (2)$$

To further investigate the properties of the interacting HPO–metal/metal⁺ complex systems, the atomic scale quadrupole coupling constants (QCC) have been evaluated by the electric field gradient (EFG) tensor calculations at the same level of theory of optimization processes (Table 2). Nuclear quadrupole resonance (NQR) spectroscopy is a versatile technique for materials

characterizations at the atomic scales in both of experimental and computational aspects [27–32]. Herein, the values of QCC have been evaluated to emphasize on the characteristic interacting sites of

HPO–metal/metal⁺ complexes. The details of QCC evaluations have been very well described in an earlier work, if the reader is interested for calculation methodology [33].

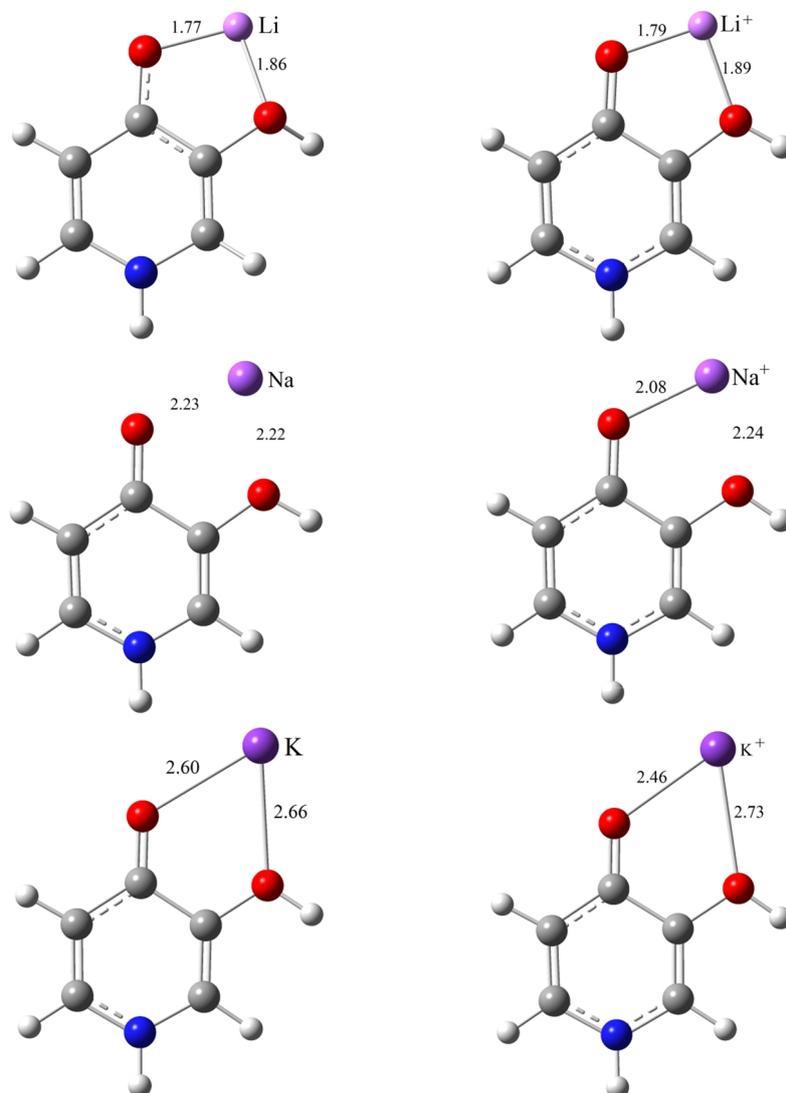


Fig. 2. 2D views of HPO complexes; atomic distances are written in Angstrom.

Results and Discussion

Within this work the possibility of neutral and ionic Li, Na and K alkali metal chelations by HPO have been examined based on the *in silico* DFT calculations (Tables 1 and 2, Figs. 1 and 2). The optimized properties have been obtained for the globally minimized energy structures in addition to the atomic-scale QCC properties to carefully examine the characteristics of single HPO and the interacting HPO–metal/metal⁺ complexes.

The panels of Fig. 2 exhibit the globally minimized complex systems of this work, in which the structural differences could be found by a quick look at them. In more details, the atomic positions of alkali metals between the 3–hydroxyl and 4–keto functional groups of HPO are changed based on two factors: first; the types of neutral and ionic metal atom could determine the position, second; the types of alkali metal elements could lead to a different position. The O–metal atomic distances

of HPO–metal/metal⁺ complexes could show the significant effects of mentioned two factors on the complex formations. All O–metal distances in the HPO–metal⁺ complexes are increased versus the

neutral–metal complexes whereas that of HPO–Li⁺ has been increased in comparison with HPO–Li complex. It is noted that the values have been obtained by the optimization processes.

Table 1: Optimized properties for single HPO and complexes*

Properties	Single	Complexes		
	HPO	HPO–Li/Li ⁺	HPO–Na/Na ⁺	HPO–K/K ⁺
TE eV	–10790	–10995/–10991	–15180/–15176	–27034/–27031
BSSE eV	—	0.77/0.73	0.86/0.90	0.78/0.79
BE eV	—	–2.32/–4.48	–1.61/–3.62	–1.41/–2.75
HE eV	–5.35	–2.05/–10.56	–1.95/–10.05	–1.89/–9.53
LE eV	–0.18	–0.79/–5.16	–1.38/–4.70	–1.15/–4.24
EG eV	5.17	1.26/5.40	0.57/5.35	0.74/5.29
DM Debye	7.48	4.80/5.09	11.50/4.99	10.51/5.10

*See Figs. 1 and 2 for graphical representations.

The results of Table 1 indicate that the HPO–Li/Li⁺ complexes are the strongest complexes based on the values of obtained BE. Moreover, the ionic metals are better candidates for complex formations than the neutral metals, in which their normal states are indeed one–electron positive ionic form. The values of BSSE show that the errors of energy calculations are almost negligible and the obtained values could be expected reliable enough for considerations. The obtained energy values of molecular orbitals (HE, LE and EG) indicate that the complexation itself and the type

of metal/metal⁺ complexation could have significant effects on characteristic properties of the single HPO and the corresponding complexes, in which the metal⁺ complexes have more significant effects than the neutral ones. The values of DM also show the effects for both of neutral and ionic metal complexations. As a concluding remark of optimizations process, it could be mentioned that the types of alkali elements and the neutral/ionic forms are very much important factors to have the desired HPO–metal/metal⁺ complex systems.

Table 2: Quadrupole coupling constants (Qcc kHz) for single HPO and complexes*

Atoms	Single	Complexes		
	HPO	HPO–Li/Li ⁺	HPO–Na/Na ⁺	HPO–K/K ⁺
N1	3740	4173/2851	3296/2960	3435/3064
O3	10317	10093/10309	9816/10340	9853/10338
O4	10440	8055/8533	9431/6965	9274/9501
Li/Li ⁺	—	280/230	—	—
Na/Na ⁺	—	—	1456/1394	—
K/K ⁺	—	—	—	1751/1284

*See Figs. 1 and 2 for graphical representations.

The values of QCC (Table 2) for nitrogen (N₁) and oxygen (O₃ and O₄) atoms of HPO and the

interacting alkali metal (Li/Li⁺) exhibit the effects of complexation on the atomic scale properties. It

is interesting that the N_1 is located far from the interaction region but the metal chelation has still significant effects on its properties. Careful examinations of oxygen properties could show that the most significant effects are seen for the HPO–Li/Li⁺ complexes, in which the BE of these complexes have been already reported as the best ones among the complex systems. Herein, the significant atomic effects are in agreement with the obtained values of BE for the investigated complex systems. Moreover, the values of QCC for interacting metal/metal⁺ counterparts could yield the importance of alkali atomic state for participating in interaction with HPO, in which such parallel results have been already seen for the alkali atomic position in the optimized complexes. As a concluding remark of this part, the atomic scale QCC properties could very well recognize the effects of chelation on the atoms of complex structures.

Conclusion

Within this work, Li/Li⁺, Na/Na⁺ and K/K⁺ alkali metal chelations by HPO were recognized based

References

1. A. Sigel, H. Sigel, R.K. Sigel; *The alkali metal ions: their role for life*. Cham, Switzerland: Springer, 2016.
2. J. Guon; *Method and composition for testing for the presence of an alkali metal*. United States Patent, USA, 1981.
3. Y. Li, Y. Lu, P. Adelhelm, M.M. Titirici, Y.S. Hu; Intercalation chemistry of graphite: alkali metal ions and beyond. *Chem. Soc. Rev.* 48 (2019) 4655–4687.
4. S. Komaba, T. Akatsuka, K. Ohura, C. Suzuki, N. Yabuuchi, S. Kanazawa, K. Tsuchiya, T. Hasegawa; All–solid–state ion–selective electrodes with redox–active lithium, sodium, and potassium insertion materials as the inner solid–contact layer. *Analyst* 142 (2017) 3857–3866.
5. M. Raban, R.A. Keintz, E.A. Noe; Alkali metal chelation by diacetamide. *Tetrahedron Lett.* 20 (1979) 1633–1636.
6. V.M. Nurchi, R. Cappai, K. Chand, S. Chaves, L. Gano, G. Crisponi, M. Peana, M.A. Zoroddu, M.A. Santos; New strong extrafunctionalizable tris (3, 4–HP) and bis (3, 4–HP) metal sequestering agents: synthesis, solution and in vivo metal chelation. *Dalton Transact.* 48 (2019) 16167–16183.
7. J. Undurraga, K. Sim, L. Tondo, A. Gorodischer, E. Azua, K.H. Tay, D. Tan, R.J. Baldessarini; Lithium treatment for unipolar major depressive disorder: Systematic review. *J. Psychopharmacol.* 33 (2019) 167–176.
8. T. Elfassy, Y. Mossavar-Rahmani, L. Van Horn, M. Gellman, D. Sotres-Alvarez, N.

on the in silico DFT approaches. Some trends could be included by the obtained results of single HPO and its corresponding complex systems. First, the type of neutral/ionic form and the element type of alkali metal are important for HPO–metal/metal⁺ complex formations. Second, binding strength of complexes are different based on the alkali metal states and types. Third, the Li/Li⁺ complexes are the most favorable ones among other complexes, especially the formation of HPO–Li⁺ is the most favorable one. Fourth, the molecular orbital properties are significantly changed during the complexations, in which the results complexes could be expected to show different behaviors. Fifth, the atomic scale QCC properties indicated the effects of complexation for all of the atoms of complex systems. Finally, the HPO structure could chelate alkali metals based on their states and types with a meaningful differential diagnostic activity.

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- Schneiderman, M. Daviglius, J.M. Beasley, M.M. Llabre, P.A. Shaw, G. Prado; Associations of sodium and potassium with obesity measures among diverse US Hispanic/Latino adults. *Obesity* 26 (2018) 442–450.
9. S.L. Jackson, M.E. Cogswell, L. Zhao, A.L. Terry, C.Y. Wang, J. Wright, S.M. Coleman King, B. Bowman, T.C. Chen, R. Merritt, C.M. Loria; Association between urinary sodium and potassium excretion and blood pressure among adults in the United States. *Circulat.* 137 (2018) 237–246.
10. T. Iwahori, H. Ueshima, N. Ohgami, H. Yamashita, N. Miyagawa, K. Kondo, S. Torii, K. Yoshita, T. Shiga, T. Ohkubo, H. Arima; Effectiveness of a self-monitoring device for urinary sodium-to-potassium ratio on dietary improvement in free-living adults: a randomized controlled trial. *J. Epidemiol.* 28 (2018) 41–47.
11. U.K. Udensi, P.B. Tchounwou; Potassium homeostasis, oxidative stress, and human disease. *Int. J. Clin. Experiment. Physiol.* 4 (2017) 111–122.
12. A. Cilibrizzi, V. Abbate, Y.L. Chen, Y. Ma, T. Zhou, R.C. Hider; Hydroxypyridinone journey into metal chelation. *Chem. Rev.* 118 (2018) 7657–7701.
13. P. Thipubon, W. Tipsuwan, C. Uthaipibull, S. Santitharakul, S. Srichairatanakool; Anti-malarial effect of 1-(N-acetyl-6-aminohexyl)-3-hydroxy-2-methylpyridin-4-one and green tea extract on erythrocyte-stage *Plasmodium berghei* in mice. *Asian Pacific J. Tropical Biomed.* 5 (2015) 932–936.
14. K. Harismah, M. Mirzaei, R. Moradi; DFT studies of single lithium adsorption on coronene. *Z. Naturforsch. A* 73 (2018) 685–691.
15. T. Partovi, M. Mirzaei, N.L. Hadipour; The C–H...O hydrogen bonding effects on the 170 electric field gradient and chemical shielding tensors in crystalline 1-methyluracil: A DFT study. *Z. Naturforsch. A* 61 (2006) 383–388.
16. M. Mirzaei, M. Meskinfam; Computational NMR studies of silicon nanotubes. *Comput. Theor. Chem.* 978 (2011) 123–125.
17. M. Mirzaei; Uracil-functionalized ultra-small (n, 0) boron nitride nanotubes (n= 3–6): Computational studies. *Superlat. Microstruct.* 57 (2013) 44–50.
18. M. Mirzaei; Effects of carbon nanotubes on properties of the fluorouracil anticancer drug: DFT studies of a CNT-fluorouracil compound. *Int. J. Nano Dimens.* 3 (2013) 175–179.
19. M. Mirzaei, R.S. Ahangari; Formations of CNT modified 5-(halogen) uracil hybrids: DFT studies. *Superlat. Microstruct.* 65 (2014) 375–379
20. E. Naderi, M. Mirzaei, L. Saghaie, G. Khodarahmi, O. Gulseren; Relaxations of methylpyridinone tautomers at the C60 surfaces: DFT studies. *Int. J. Nano Dimens.* 8 (2017) 124–131.
21. H. Nazemi, M. Mirzaei, E. Jafari; Antidepressant activity of curcumin by monoamine oxidase-A inhibition. *Adv. J. Chem. B* 1 (2019) 3–9.
22. Z.S. Alidoosti, M. Mirzaei; Comparative examination of moclobemide, tranlycypromine, phenelzine and isocarboxazid for monoamine oxidase-A inhibition. *Adv. J. Chem. B* 1 (2019) 23–28.
23. A.N. Esfahani, M. Mirzaei; Flavonoid derivatives for monoamine oxidase-A inhibition. *Adv. J. Chem. B* 1 (2019) 17–22.
24. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, et al.; Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford CT, 2016.
25. H.E. Pence, A. Williams; ChemSpider: an online chemical information resource, 2010.
26. S.F. Boys, F. Bernardi; Calculation of small molecular interactions by differences of

- separate total energies – some procedures with reduced errors. *Mol. Phys.* 19 (1970) 553–566.
27. H. Behzadi, N.L. Hadipour, M. Mirzaei; A density functional study of 17O, 14N and 2H electric field gradient tensors in the real crystalline structure of alpha-glycine. *Biophys. Chem.* 125 (2007) 179–183.
28. M. Mirzaei, N.L. Hadipour, M.R. Abolhassani; Influence of C-doping on the B-11 and N-14 quadrupole coupling constants in boron-nitride nanotubes: a DFT study. *Z. Naturforsch. A* 62 (2007) 56–60.
29. M. Mirzaei, N.L. Hadipour, A. Seif, M. Giah; Density functional study of zigzag BN nanotubes with equivalent ends. *Physica E* 40 (2008) 3060–3063.
30. M. Mirzaei, M. Yousefi; Computational studies of the purine-functionalized graphene sheets. *Superlat. Microstruct.* 52 (2012) 612–617.
31. A. Yaraghi, O.M. Ozkendir, M. Mirzaei; DFT studies of 5-fluorouracil tautomers on a silicon graphene nanosheet. *Superlat. Microstruct.* 85 (2015) 784–788.
32. Z. Samadi, M. Mirzaei, N.L. Hadipour, S.A. Khorami; Density functional calculations of oxygen, nitrogen and hydrogen electric field gradient and chemical shielding tensors to study hydrogen bonding properties of peptide group (OC-NH) in crystalline acetamide. *J. Mol. Graph. Model.* 26 (2008) 977–981.
33. M. Mirzaei, N.L. Hadipour; A computational NQR study on the hydrogen-bonded lattice of cytosine-5-acetic acid. *J. Comput. Chem.* 29 (2008) 832–838.

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