

Scientific research article

***In situ* tracking ion-exchange during Li⁺/Na⁺/K⁺ substitution: Bipolar disorder treatment through drug delivery system**

Fateme Mollaamin^{1,*} & Majid Monajjemi²

¹Department of Biomedical Engineering, Faculty of Engineering and Architecture, Kastamonu University, Kastamonu, Turkey

²Department of Biology, Faculty of Science, Kastamonu University, Kastamonu, Turkey

*E-mail: fmollaamin@kastamonu.edu.tr

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SUMMARY

Introduction: Bipolar disorder (BD) is considered one of the most dangerous diseases in developed countries. Despite scientific efforts, BD remains a significant concern due to its wide range of side effects. Various drugs based on lithium salts have been instrumental in treating patients with this disorder. However, the main issue with lithium salts is their known toxic effects, which can vary depending on the dose, route, and duration of administration. It is important to also consider the anionic component of lithium salts in any treatment plan. Research into novel algorithms for rare events has led to improvements in force-field parameters and an increase in the understanding of lipid membrane protein transmembrane. These advancements have allowed for the simulation of a comprehensive model of lithium-ion diffusion into channels. Additionally, Ge, Sn/Si-nanoparticles have been utilized as excipients in pharmaceutical nano biotechnology. More recently, silicon/germanium oxide has been developed for use in drug delivery systems. **Methodology:** A comprehensive investigation on Li⁺Na⁺(SiOGe), Li⁺K⁺(SiOGe), Li⁺Na⁺(SiOSn), and Li⁺K⁺(SiOSn) was accomplished by the "CAM-B3LYP-D3/6-311+G (d,p)" level of DFT theory. The hypothesis of the ions transporting was corroborated through density distributions of CDD, TDOS, and ESP for nanoclusters of Li⁺Na⁺(SiOGe), Li⁺K⁺(SiOGe), Li⁺Na⁺(SiOSn), and Li⁺K⁺(SiOSn). **Results:** This ion transport produces an electrochemical gradient that is crucial for several cellular activities, such as cell volume regulation, electrical excitability, and secondary active transport. Properties of GSK-3 as a specific function for BD drug design came out from data researches, which are important to several of central processes, such as glycogen synthesis and gene therapy. Through docking with 6tcu, the amounts of the Gemdock have sequenced as Li⁺K⁺(SiOGe) > Li⁺Na⁺(SiOGe) > Li⁺K⁺(SiOSn) > Li⁺Na⁺(SiOSn), indicates the instability of these complexes by GSK3b folded monomer. In other words, instability in cytoplasm solution means stability in complexes structures or due to the heteroclusters properties. These perfect and accurate structures from ion channels have largely modified for improving our understanding of the molecular details and ion selectivity and conduction. The current study aims to explore various aspects, including describing the atomic detail structure, molecular and functional properties, and consequently, its incomplete action due to structural alterations.

Keywords: Cell membrane; ion transport; Li⁺Na⁺ & Li⁺K⁺; Si-based nanostructure; DFT.

RESUMEN

Seguimiento *in situ* del intercambio iónico durante la sustitución de Li⁺/Na⁺/K⁺: Tratamiento del trastorno bipolar mediante un sistema de administración de fármacos

Introducción: El trastorno bipolar (TB) se considera una de las enfermedades más peligrosas en los países desarrollados. A pesar de los esfuerzos científicos, el TB sigue siendo una preocupación importante debido a su amplia gama de efectos secundarios. Diversos fármacos basados en sales de litio han sido fundamentales en el tratamiento de pacientes con este trastorno. Sin embargo, el principal problema con las sales de litio son sus conocidos efectos tóxicos, que pueden variar según la dosis, la vía de administración y la duración de la misma. Es importante considerar también el componente aniónico de las sales de litio en cualquier plan de tratamiento. La investigación de nuevos algoritmos para eventos raros ha permitido mejorar los parámetros del campo de fuerza y profundizar en la comprensión de la membrana transmembrana de las proteínas lipídicas. Estos avances han permitido la simulación de un modelo integral de la difusión de iones de litio en canales. Además, se han utilizado nanopartículas de Ge, Sn/Si como excipientes en nanobiotecnología farmacéutica. Más recientemente, se ha desarrollado óxido de silicio/germanio para su uso en sistemas de administración de fármacos. **Metodología:** Se realizó una investigación exhaustiva sobre Li⁺Na⁺(SiOGe), Li⁺K⁺(SiOGe), Li⁺Na⁺(SiOSn) y Li⁺K⁺(SiOSn) mediante el nivel "CAM-B3LYP-D3/6-311+G (d,p)" de la teoría DFT. La hipótesis del transporte de iones se corroboró mediante distribuciones de densidad de CDD, TDOS y ESP para nanoagrupaciones de Li⁺Na⁺(SiOGe), Li⁺K⁺(SiOGe), Li⁺Na⁺(SiOSn) y Li⁺K⁺(SiOSn). **Resultados:** Este transporte de iones produce un gradiente electroquímico crucial para diversas actividades celulares, como la regulación del volumen celular, la excitabilidad eléctrica y el transporte activo secundario. Las propiedades de GSK-3 como función específica para el diseño de fármacos para el trastorno bipolar surgieron de la investigación de datos, que son importantes para varios procesos centrales, como la síntesis de glucógeno y la terapia génica. Mediante el acoplamiento con 6tcu, las cantidades de Gemdock se secuenciaron como Li⁺K⁺(SiOGe) > Li⁺Na⁺(SiOGe) > Li⁺K⁺(SiOSn) > Li⁺Na⁺(SiOSn), lo que indica la inestabilidad de estos complejos por el monómero plegado de GSK3b. En otras palabras, la inestabilidad en la solución citoplasmática implica estabilidad en las estructuras de los complejos o se debe a las propiedades de los heterogrupos. Estas estructuras perfectas y precisas de los canales iónicos se han modificado en gran medida para mejorar nuestra comprensión de los detalles moleculares, la selectividad y la conducción iónica. El presente estudio pretende explorar diversos aspectos, incluyendo la descripción de la estructura atómica detallada, las propiedades moleculares y funcionales y, en consecuencia, su acción incompleta debido a alteraciones estructurales.

Palabras clave: Membrana celular; transporte iónico; Li⁺Na⁺ y Li⁺K⁺; nanoestructura basada en Si; DFT.

RESUMO

Rastreamento *in situ* da troca iônica durante a substituição de Li⁺/Na⁺/K⁺: Tratamento do transtorno bipolar por meio de sistemas de liberação de fármacos

Introdução: O transtorno bipolar (TB) é considerado uma das doenças mais perigosas em países desenvolvidos. Apesar dos esforços científicos, o TB continua sendo uma preocupação significativa devido à sua ampla gama de efeitos colaterais. Diversos fármacos à base de sais de lítio têm sido fundamentais no tratamento de pacientes com esse transtorno. No entanto, a principal questão com os sais de lítio são seus conhecidos efeitos tóxicos, que podem variar dependendo da dose, via de administração e duração do tratamento. É importante também considerar o componente aniônico dos sais de lítio em qualquer plano de tratamento. A pesquisa de novos algoritmos para eventos raros levou a melhorias nos parâmetros de campos de força e a um aumento na compreensão da transmembrana de proteínas de membrana lipídica. Esses avanços permitiram a simulação de um modelo abrangente de difusão de íons de lítio em canais. Além disso, nanopartículas de Ge, Sn/Si têm sido utilizadas como excipientes em nanobiotecnologia farmacéutica. Mais recentemente, o óxido de silício/germânio foi desenvolvido para uso em sistemas de liberação de fármacos. **Metodologia:** Uma investigação abrangente sobre Li⁺Na⁺(SiOGe), Li⁺K⁺(SiOGe), Li⁺Na⁺(SiOSn) e Li⁺K⁺(SiOSn) foi realizada utilizando o nível "CAM-B3LYP-D3/6-311+G (d,p)" da teoria DFT. A hipótese do transporte iônico foi corroborada pelas distribuições de densidade de CDD, TDOS e ESP para os nanocúmulos de Li⁺Na⁺(SiOGe), Li⁺K⁺(SiOGe), Li⁺Na⁺(SiOSn) e

$\text{Li}^+\text{K}^+(\text{SiOSn})$. **Resultados:** Esse transporte iônico produz um gradiente eletroquímico crucial para diversas atividades celulares, como a regulação do volume celular, a excitabilidade elétrica e o transporte ativo secundário. As propriedades da GSK-3, como função específica para o planejamento de fármacos para doenças bipolares, emergiram das pesquisas de dados, sendo importantes para diversos processos centrais, como a síntese de glicogênio e a terapia gênica. Através do acoplamento com 6tcu , as quantidades do Gemdock foram sequenciadas como $\text{Li}^+\text{K}^+(\text{SiOGe}) > \text{Li}^+\text{Na}^+(\text{SiOGe}) > \text{Li}^+\text{K}^+(\text{SiOSn}) > \text{Li}^+\text{Na}^+(\text{SiOSn})$, indicando a instabilidade desses complexos devido ao monômero dobrado da GSK3b. Em outras palavras, a instabilidade na solução citoplasmática significa estabilidade nas estruturas dos complexos ou devido às propriedades dos heterocúmulos. Essas estruturas perfeitas e precisas de canais iônicos foram amplamente modificadas para aprimorar nossa compreensão dos detalhes moleculares, da seletividade iônica e da condução. O presente estudo visa explorar vários aspectos, incluindo a descrição da estrutura em detalhes atômicos, propriedades moleculares e funcionais e, conseqüentemente, sua ação incompleta devido a alterações estruturais.

Palavras-chave: Membrana celular; transporte iônico; Li^+Na^+ e Li^+K^+ ; nanoestrutura à base de Si; DFT.

1. INTRODUCTION

Bipolar disorder (BD) is one of the most dangerous diseases in many countries around the world, particularly in developed communities and societies. Despite scientific attempts to combat it, BD remains a major health concern due to its wide range of side effects. Various drugs based on lithium salts have been instrumental in treating this condition. However, the main issue with lithium salts is their known toxic effects, which can vary depending on the dose, route, and duration of treatment. It is also important to consider the anionic component of lithium salts in any treatment plan. Therefore, selecting the appropriate anionic structures in lithium salts is crucial not only for reducing toxicity but also for effectively treating this dangerous disease. While lithium ions are abundant in nature, they are not essential co-factors in biological systems. Elements such as Na, K, Ca, and Mg play important roles as co-factors in biological processes. Transition metals like Fe, Zn, and Cu also have significant roles in various biological mechanisms. As a result, lithium ions have been largely excluded from these biological systems as they have become more complex over time [1–7]. Research into designing effective drugs to alleviate the bipolar effects of BD involves studying the effects of lithium salts with anionic segments that have antioxidant-DNA interactions to prevent damage to the structure of blood plasma. The use of lithium salts for bipolar patients has become increasingly popular over the decades. Most patients have shown positive responses to these salts in BD therapy [8–16]. The use of lithium salts instead of NaCl has advantages, and the successful use of lithium salts in bipolar treatments warrants further research into their impacts on other biochemical systems, particularly in biology and their functions as modulators or regulators of physiological tissues [17–22].

Many researchers have worked on the effects of lithium salts including several organic solvents structures such as lithium carbonate (Li-CAR), pyruvate (Li-PYR), succinate (Li-SUC), fumarate (Li-FUM) as well as ascorbate (Li-ASC) on the active sites of DNA-8-hydroxy-2'-deoxyguanosine (8-OH-dG) of blood samples from healthy human compared with bipolar patient. The last results indicated which in BD patients, Li-PYR considerably decreased amounts of plasma 8-OH-dG, while other materials did not have a considerable effect. In conclusion, it has been confirmed that Lithium pyruvate decreases DNA damage in BD patients. In other words, the potential of this structure has strong role not only as a mood stabilizer, but also as an anti-cancer compound. According to these results, we simulate our work to explore the

possibility of using SiOGe and SiOSn nanocages for ion transport of Li^+Na^+ and Li^+K^+ by employing quantum ab-initio calculations. We have analyzed the structural and electronic properties of $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, and $\text{Li}^+\text{K}^+(\text{SiOSn})$ nanoclusters using state-of-the-art computational techniques.

2. THEORITICAL BACKGROUND

2.1. Materials and Computation

The aim of this study is to transport alkali metal ions of Li^+ , Na^+ , K^+ by (SiOGe) and (SiOSn) nanocages towards formation of $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, and $\text{Li}^+\text{K}^+(\text{SiOSn})$ (Fig. 1) which can increase the ion transfer in human cells.

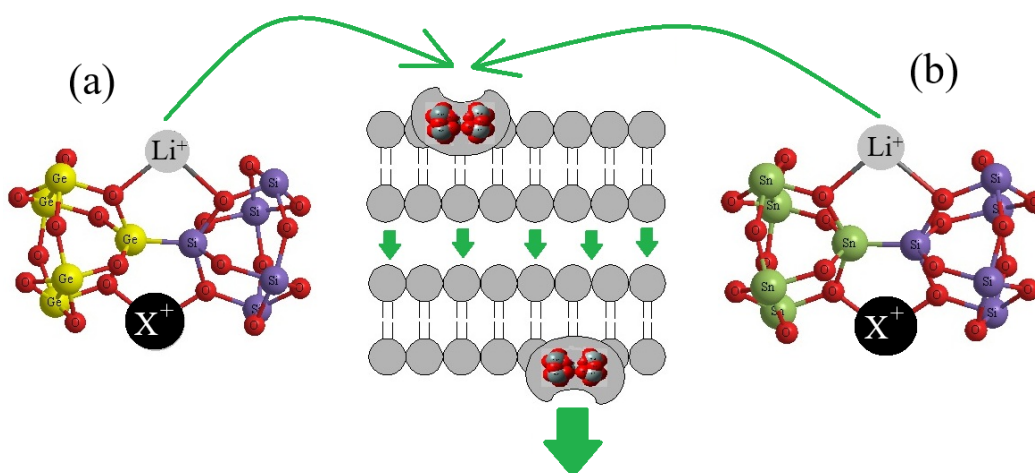


Figure 1. Ion Transport of Li^+ , Na^+ , K^+ across cell membrane by SiOGe or SiOSn (X) nanocage through formation of a) $\text{Li}^+\text{X}^+(\text{SiOGe})$ and b) $\text{Li}^+\text{X}^+(\text{SiOSn})$, nanoclusters. (X=Na or K).

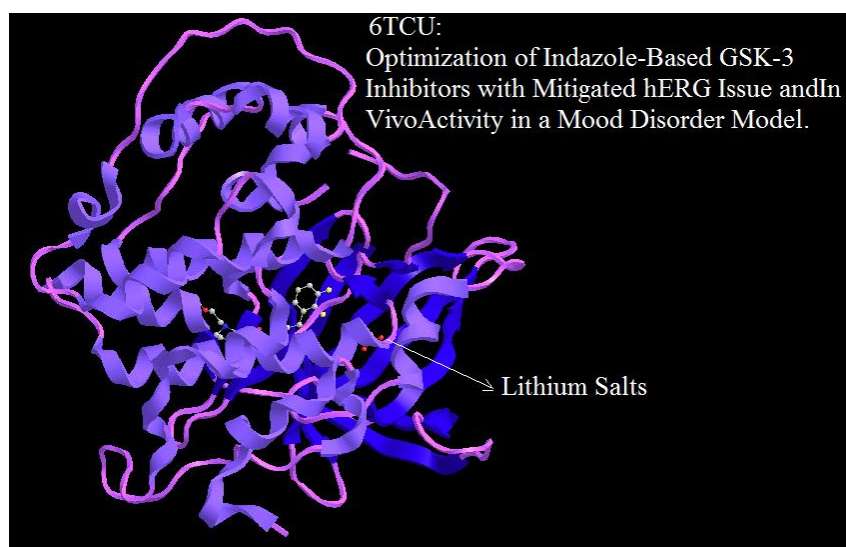
The Bader theorem [23] was explored during ion transporting through formation of $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, and $\text{Li}^+\text{K}^+(\text{SiOSn})$ nanoclusters (Fig. 1) [24–26] due to Gaussian16 [27] and GaussView 6.1 [28]. The coordination input for ion transporting by $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, and $\text{Li}^+\text{K}^+(\text{SiOSn})$ has been LANL2DZ and 6-311+G (d,p) basis sets.

2.2. Lithium's neurotrophic effects in BD

The most common occurrence in structural neuroimaging testing with lithium treatment is related to the gray matter volume in the brain, showing enhancement in amounts [29, 30]. An important study showed that individuals with BD who were not treated with lithium had significantly reduced volumes compared to normal individuals [31]. Additional MRI testing indicated that the gray and white matter volumes, as well as total gray matter volumes, were significantly increased in lithium-treated patients relative to untreated patients [32]. Another study showed that gray matter density was greater in individuals with BD compared to normal individuals [33]. An MRI study also found that the total hippocampal volume was significantly larger in lithium-treated individuals with BD compared to healthy un-medicated patients (by 14%) [34]. It is worth noting that MRS testing has analyzed the beneficial effects of lithium treatment on abnormal concentrations of markers of neuronal integrity, such as NAA and myoinositol, in individuals with BD [30, 31]. Additionally, decreased choline levels were also observed after chronic lithium treatment for BD [37].

2.3. Neuroprotection of Lithium salts

GSK-3 is a serine/threonine kinase that regulates diverse cellular metabolism and directly regulates cell replication. Properties of GSK-3 as a specific function for BD drug design came out from data researches, which are important to several of central processes, such as glycogen synthesis and gene therapy [38]. It is notable that all of these items are amazingly related to the pathophysiology of severe abnormal mood disorders. Recently, Benedetti and coworkers [39] exhibited, which a polymorphism in the GSK-3 gene can be associated with BD. GSK-3 β basically enable to inhibit cyclic AMP response element binding protein (CREB), β -catenin, and several transcription factors (Scheme 1).



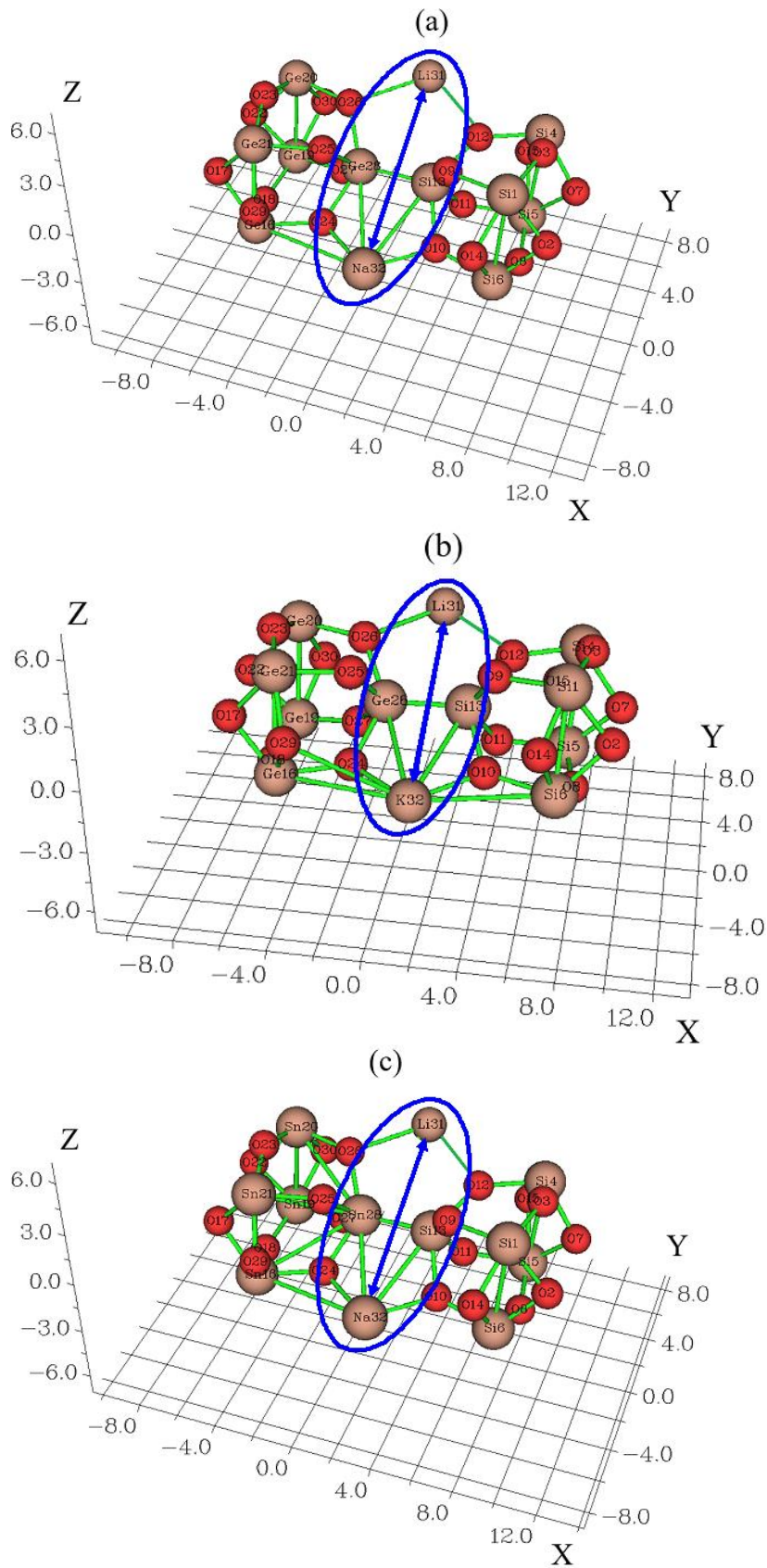
Scheme 1. Glycogen synthase kinase-3 beta (GSK3b) in complex with Lithium salts [39].

GSK-3 is also directly regulated by signals originating from Wnt pathway, the PI-3kinase (PI3K) pathway, protein kinase A (PKA), and protein kinase C (PKC). PKC also causes the phosphorylate and inactivate GSK-3 β in vitro [39, 40], as well as regulating of GSK-3 during signaling routs the activity of this critical enzyme.

3. RESULTS AND DISCUSSION

3.1. Charge density differences analysis

Charge densities differences (CDD) amounts can be estimated through considering isolated or no interacting atoms. This approximation can be used due to the superposition from the primary position of the self-consistency cycle in the code where accomplish the density functional theory (Fig. 2a, b, c, d) [41].



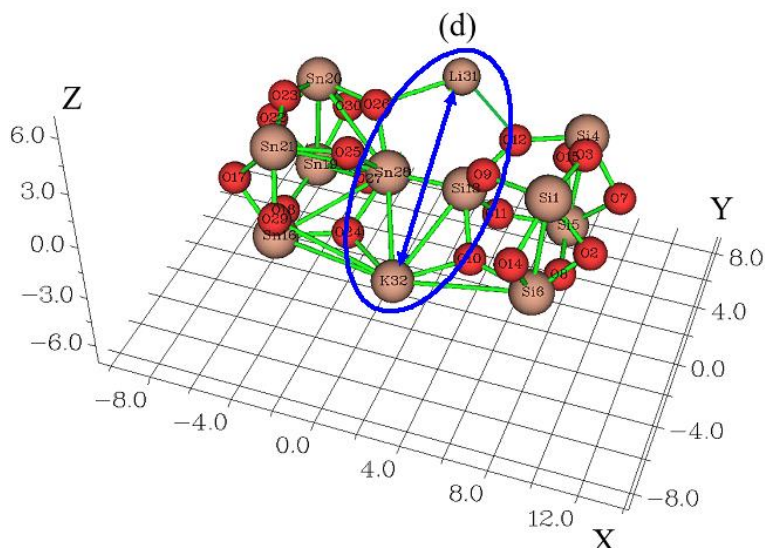


Figure 2. CDD graphs for a) $\text{Li}^+\text{Na}^+(\text{SiOGe})$, b) $\text{Li}^+\text{K}^+(\text{SiOGe})$, c) $\text{Li}^+\text{Na}^+(\text{SiOSn})$, d) $\text{Li}^+\text{K}^+(\text{SiOSn})$ nanoclusters on the X,Y and X axes (Bohr).

Atomic charge was discussed during ion transferring through formation of $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, and $\text{Li}^+\text{K}^+(\text{SiOSn})$ nanoclusters, respectively (Tables 1 and 2).

Table 1. Charge distribution (Q/coulomb) for heteroclusters of $\text{Li}^+\text{Na}^+(\text{SiOGe})$ and $\text{Li}^+\text{K}^+(\text{SiOGe})$.

$\text{Li}^+\text{Na}^+(\text{SiOGe})$		$\text{Li}^+\text{K}^+(\text{SiOGe})$	
Atom	Charge	Atom	Charge
Si(1)	1.47	Si(1)	1.46
O(2)	-0.66	O(2)	-0.69
O(3)	-0.84	O(3)	-0.83
Si(4)	1.43	Si(4)	1.43
Si(5)	1.45	Si(5)	1.46
Si(6)	1.46	Si(6)	1.45
O(7)	-0.68	O(7)	-0.65
O(8)	-0.84	O(8)	-0.83
O(9)	-0.79	O(9)	-0.79
O(10)	-1.00	O(10)	-1.06
O(11)	-0.80	O(11)	-0.80
O(12)	-0.95	O(12)	-0.94
Si(13)	1.64	Si(13)	1.60
O(14)	-0.73	O(14)	-0.71
O(15)	-0.72	O(15)	-0.76
Ge(16)	1.41	Ge(16)	1.39
O(17)	-0.65	O(17)	-0.67
O(18)	-0.78	O(18)	-0.78
Ge(19)	1.40	Ge(19)	1.38
Ge(20)	1.39	Ge(20)	1.39
Ge(21)	1.40	Ge(21)	1.39
O(22)	-0.67	O(22)	-0.62
O(23)	-0.78	O(23)	-0.78
O(24)	-0.96	O(24)	-1.00
O(25)	-0.78	O(25)	-0.79
O(26)	-0.91	O(26)	-0.92

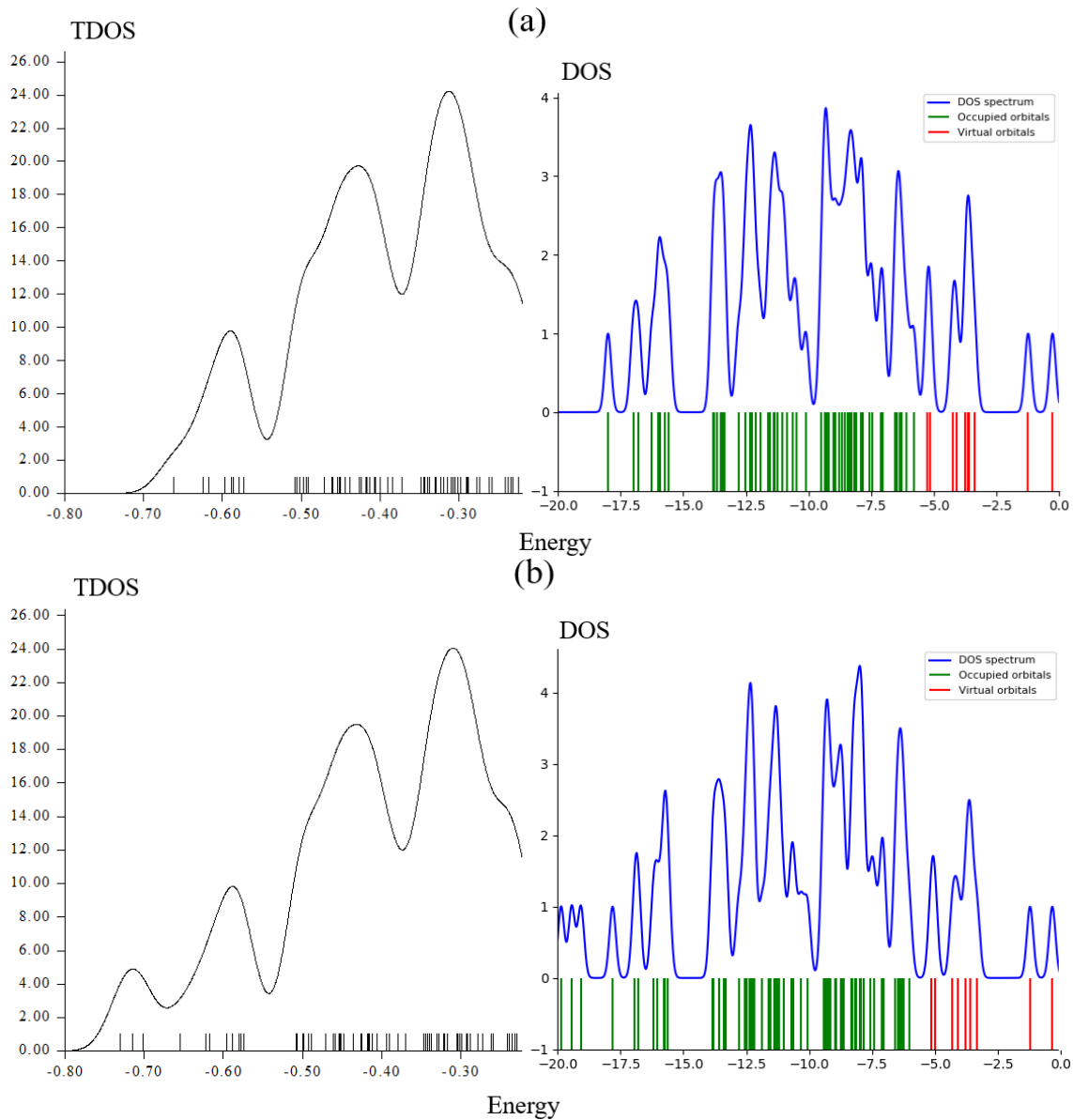
O(27)	-0.78	O(27)	-0.76
Ge(28)	1.30	Ge(28)	1.23
O(29)	-0.74	O(29)	-0.70
O(30)	-0.72	O(30)	-0.73
Li(31)	0.74	Li(31)	0.73
Na(32)	0.72	K(32)	0.92

Table 2. Charge distribution (Q/coulomb) for heteroclusters of Li⁺Na⁺(SiOSn) and Li⁺K⁺(SiOSn).

Li ⁺ Na ⁺ (SiOSn)		Li ⁺ K ⁺ (SiOSn)	
Atom	Charge	Atom	Charge
Si(1)	1.46	Si(1)	1.43
O(2)	-0.63	O(2)	-0.63
O(3)	-0.83	O(3)	-0.85
Si(4)	1.41	Si(4)	1.38
Si(5)	1.44	Si(5)	1.42
Si(6)	1.46	Si(6)	1.42
O(7)	-0.72	O(7)	-0.66
O(8)	-0.83	O(8)	-0.85
O(9)	-0.79	O(9)	-0.78
O(10)	-1.00	O(10)	-1.06
O(11)	-0.81	O(11)	-0.80
O(12)	-0.95	O(12)	-0.94
Si(13)	1.39	Si(13)	1.37
O(14)	-0.76	O(14)	-0.72
O(15)	-0.69	O(15)	-0.71
Sn(16)	1.69	Sn(16)	1.69
O(17)	-0.81	O(17)	-0.81
O(18)	-0.88	O(18)	-0.88
Sn(19)	1.69	Sn(19)	1.70
Sn(20)	1.67	Sn(20)	1.67
Sn(21)	1.69	Sn(21)	1.70
O(22)	-0.84	O(22)	-0.83
O(23)	-0.89	O(23)	-0.89
O(24)	-1.06	O(24)	-1.11
O(25)	-0.91	O(25)	-0.90
O(26)	-1.00	O(26)	-1.00
O(27)	-0.93	O(27)	-0.92
Sn(28)	1.83	Sn(28)	1.72
O(29)	-0.89	O(29)	-0.89
O(30)	-0.86	O(30)	-0.86
Li(31)	0.70	Li(31)	0.71
Na(32)	0.66	K(32)	0.89

3.2. TDOS analysis

Molecular orbital amounts have been calculated using according to Gaussian curves including unit altitude and entire width at "half maximum (FWHM)" of 0.3 eV by "GaussSum 3.0.2" [42] through total density of states (TDOS) diagrams. Regarding ion transport behavior through formation of $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, and $\text{Li}^+\text{K}^+(\text{SiOSn})$ nanoclusters, TDOS has been measured (Fig. 3a, b, c, d).



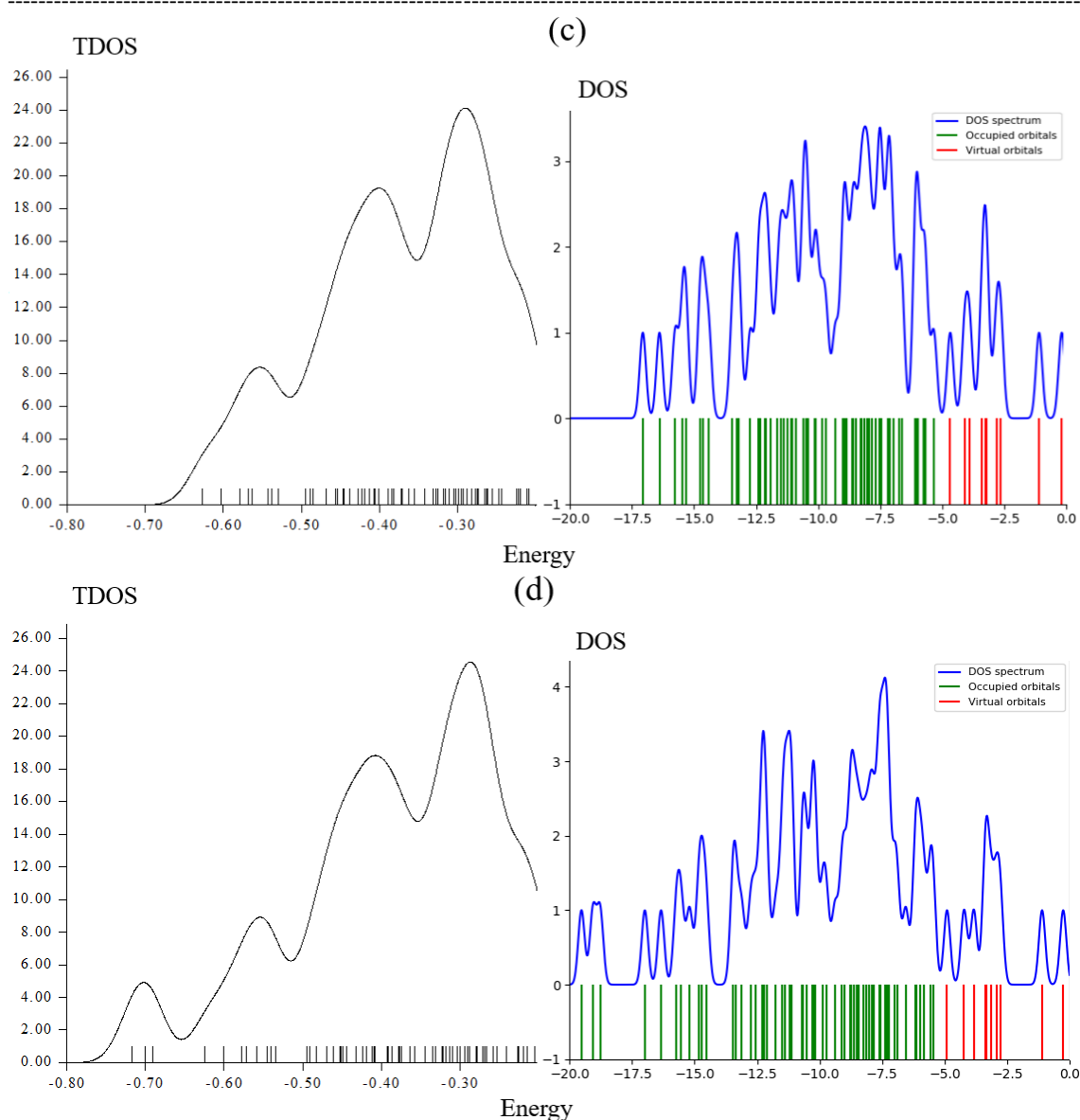


Figure 3. DOS/TDOS graphs versus Energy (a.u.) of a) $\text{Li}^+\text{Na}^+(\text{SiOGe})$, b) $\text{Li}^+\text{K}^+(\text{SiOGe})$, c) $\text{Li}^+\text{Na}^+(\text{SiOSn})$, d) $\text{Li}^+\text{K}^+(\text{SiOSn})$ nanoclusters.

3.3. ESP analysis

Molecular electrostatic potential (ESP) is calculated based on nuclear and electronic charge distributions, allowing identification of electrophilic and nucleophilic regions. Negative and positive amounts illustrate the situation of currents that are dominated by either charge density or electrostatic potential [43]. It is notable that measuring ESP takes much more time-consuming than calculating other functions. Moreover, the ESP estimation in Multiwfn [44, 45] can be estimated by nuclear attractive integrals rather than using approximate methods. Therefore, the output data can be derived from the generated data by Multiwfn from those outputs of the other quantum chemistry codes. For increasing the speed up of ESP estimation, Multiwfn delete unnecessary integrals which have little contributions (Fig. 4a,b,c,d).

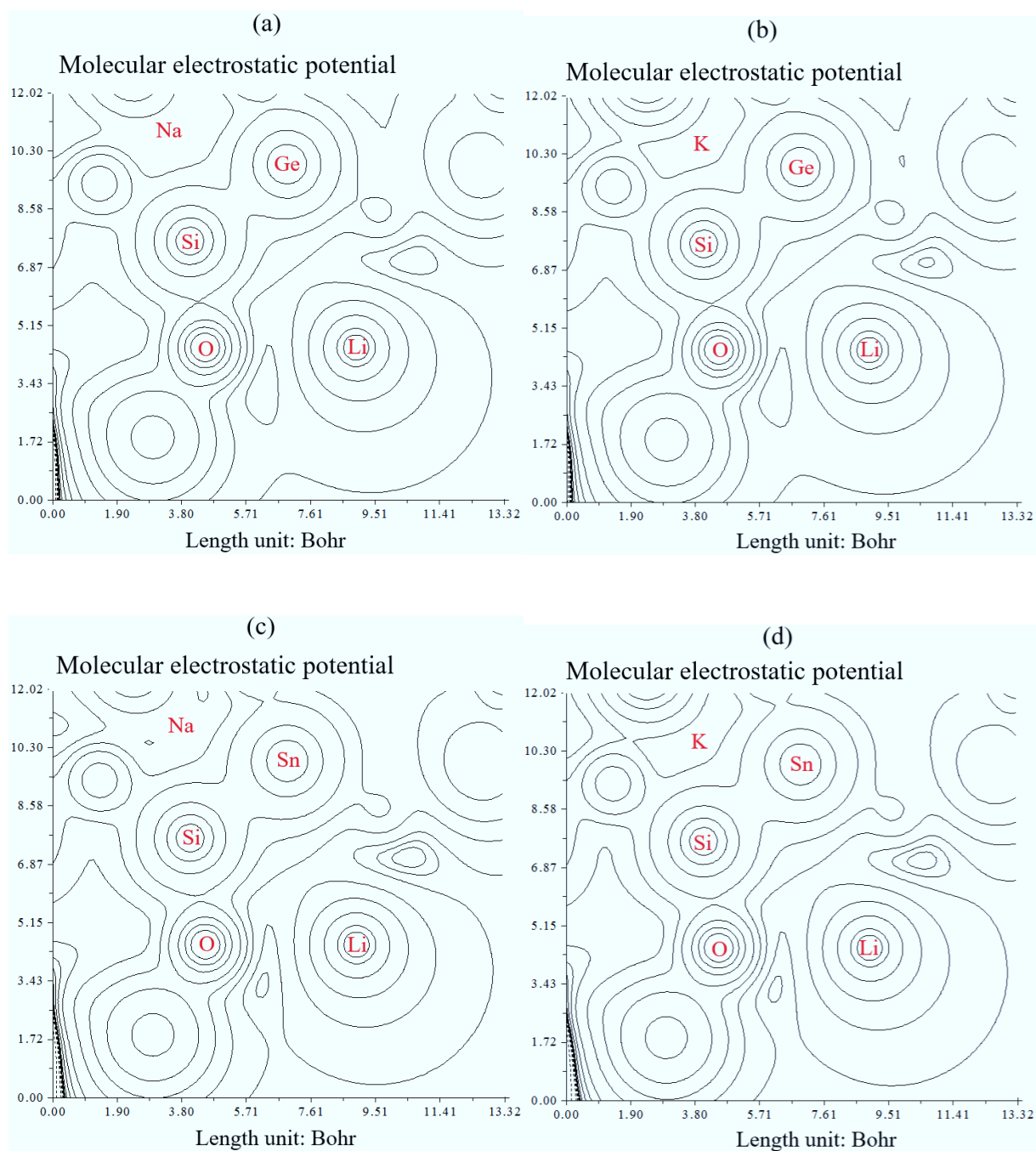


Figure 4. The counter map of ESP graphs for a) $\text{Li}^+\text{Na}^+(\text{SiOGe})$, b) $\text{Li}^+\text{K}^+(\text{SiOGe})$, c) $\text{Li}^+\text{Na}^+(\text{SiOSn})$, d) $\text{Li}^+\text{K}^+(\text{SiOSn})$ nanoclusters.

Moreover, stability energy and intermolecular orbital overlap integral are important in discussions HOMO-HOMO and LUMO-LUMO overlapping of hetero-clusters in $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, $\text{Li}^+\text{K}^+(\text{SiOSn})$. The applied wavefunction level is CAM-B3LYP-D3/6-311+G (d, p) that corresponds to HOMO and LUMO, respectively (Table3).

Table 3. Dipole moment (debye), LUMO, HOMO, and energy gap (ΔE) for Li⁺Na⁺(SiOGe), Li⁺K⁺(SiOGe), Li⁺Na⁺(SiOSn), and Li⁺K⁺(SiOSn) heteroclusters.

Heteroclusters	$E_s \times 10^{-3}$ (kcal/mol)	Dipole moment (debye)	E_{HOMO} (eV)	E_{LUMO} (eV)	$\Delta E = E_{LUMO} - E_{HOMO}$ (eV)
Li ⁺ Na ⁺ (SiOGe)	-972.0110	2.0853	-5.8010	-5.2579	0.5431
Li ⁺ K ⁺ (SiOGe)	-989.4186	1.5622	-6.0315	-5.1446	0.8869
Li ⁺ Na ⁺ (SiOSn)	-970.3922	5.0772	-5.3386	-4.6734	0.6651
Li ⁺ K ⁺ (SiOSn)	-987.7889	6.4714	-5.4629	-4.9025	0.5604

These perfect and accurate structures from ion channels have largely modified for improving our understanding of the molecular details and ion selectivity and conduction.

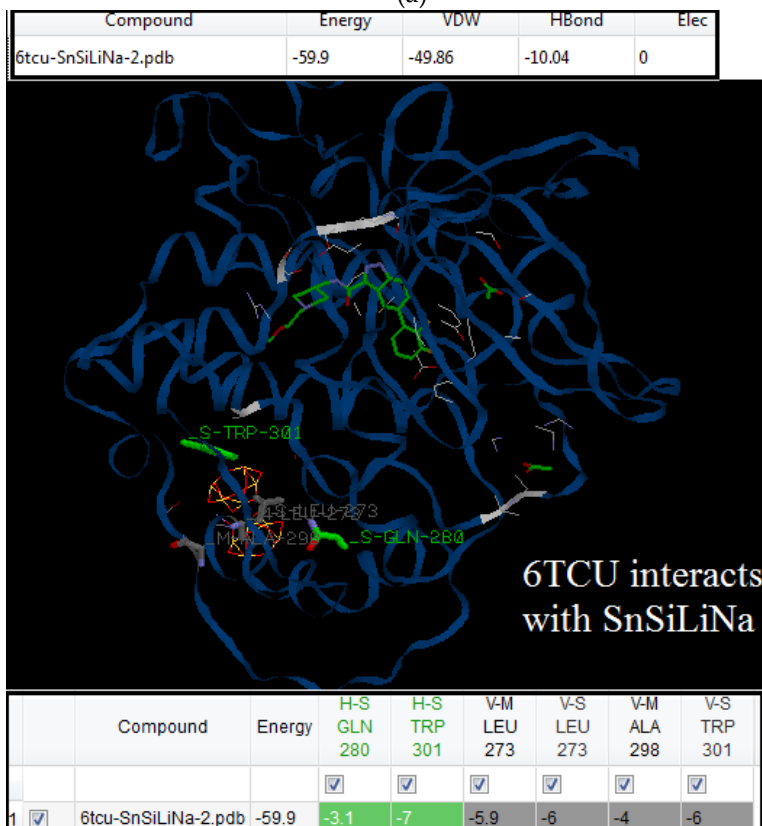
3.4. Docking interpretations of various structures

The structure of GSK3b folded monomer by high resolution: (6TCU) (Scheme 2), extracted by Prati *et al.* [46]. In addition, the geometry of the structure was carefully optimized, and the positions of the side chains were clearly depicted. The molecular docking of four ligands from Table 4 have been interacted with this structure of (6TCU) to evaluate much more considerable changes in interactions [47, 48]. The main contribution to the total energy in these complexes arises from van der Waals interactions, with values of -54.16, -49.86, -46.06, and -21.74 kcal/mol, respectively (Table 4). In addition, in all four complexes the G-scores are low and around 8 for all of them, which means the stability of these complexes in the complexes increase due to Li⁺ diffusion. As it can be seen from Table 4 for the docking with 6tcu, the amounts of the Gemdock have sequenced as follows Li⁺K⁺(SiOGe) > Li⁺Na⁺(SiOGe) > Li⁺K⁺(SiOSn) > Li⁺Na⁺(SiOSn), indicates the instability of these complexes by GSK3b folded monomer [49–54]. In other words, instability in cytoplasm solution means stability in complexes structures or due to the heteroclusters properties.

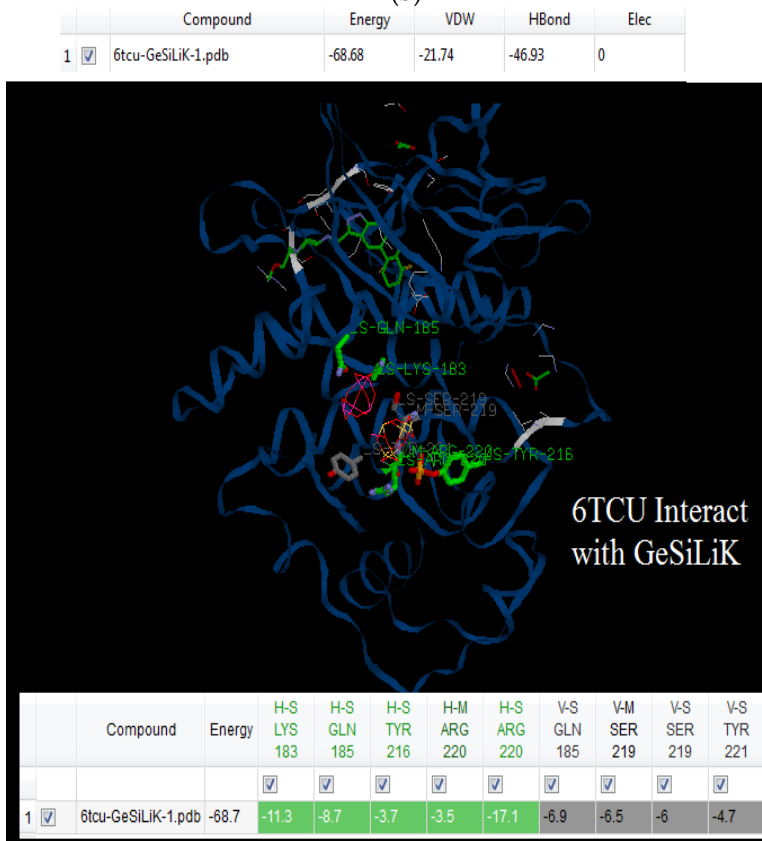
Table 4. Total Docked, Van der Waals, and H-bond, including Glide scores of the best four configurations of ligands- GSK3b within the active site of 6TCU

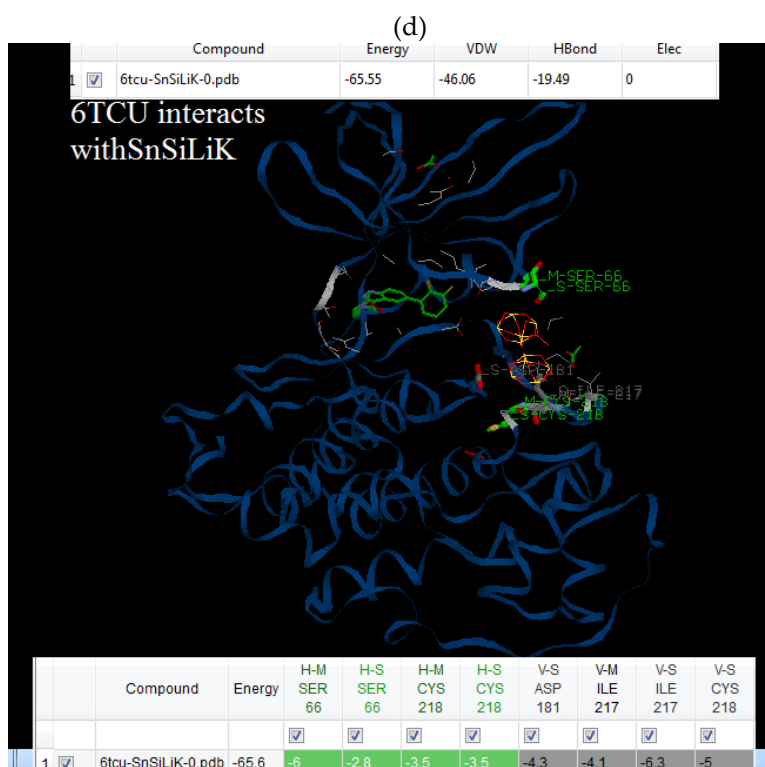
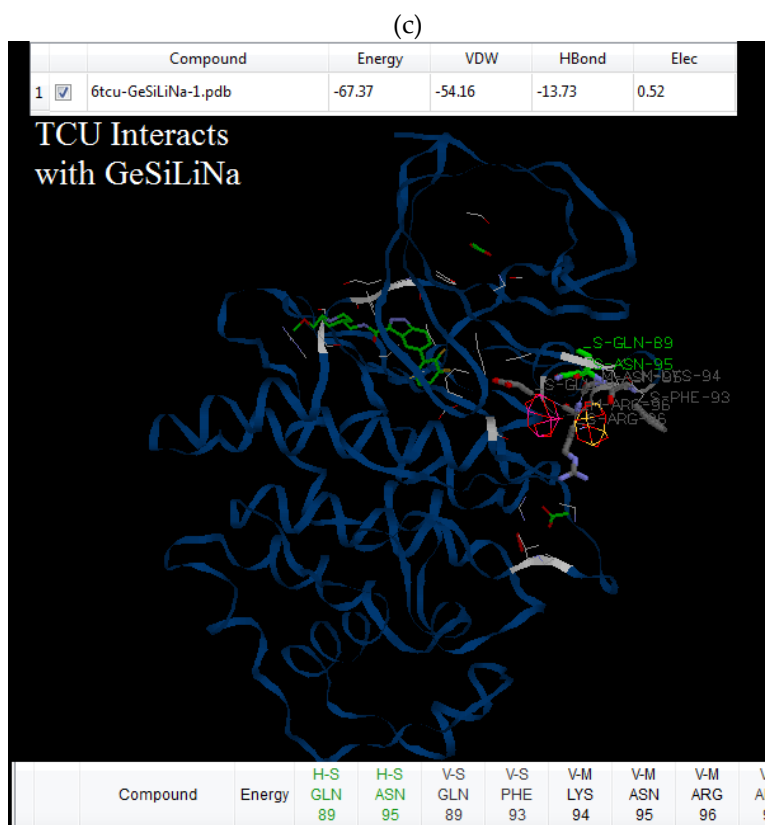
Heteroclusters- 5SYF	Gemdock	Vander Waals	H-Bond	Gscore	Best Amino acid interaction
Li ⁺ Na ⁺ (SiOGe)	-67.37	-54.16	-13.73	-8.12	H-S-ASN
Li ⁺ K ⁺ (SiOGe)	-68.68	-21.74	-46.93	-8.73	H-S-ARG
Li ⁺ Na ⁺ (SiOSn)	-59.9	-49.86	-10.04	-8.41	H-S-TRP
Li ⁺ K ⁺ (SiOSn)	-65.55	-46.06	-19.49	-8.55	V-S-ILE

(a)



(b)





Scheme 2. Interaction analysis of for Heteroclusters with 6TCU [46].

4. CONCLUSIONS

The present research article investigated the ion transporting of Li^+ , Na^+ , K^+ by (GeO–SiO) and (SnO–SiO) heteroclusters in the human cell through formation of $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, $\text{Li}^+\text{K}^+(\text{SiOSn})$ heteroclusters by quantum mechanics methods. The changes of charge distribution explained a notable charge transfer towards $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, $\text{Li}^+\text{K}^+(\text{SiOSn})$. Besides, thermodynamic parameters describing ion transporting through formation of alkali metals-based nanoclusters of $\text{Li}^+\text{Na}^+(\text{SiOGe})$, $\text{Li}^+\text{K}^+(\text{SiOGe})$, $\text{Li}^+\text{Na}^+(\text{SiOSn})$, $\text{Li}^+\text{K}^+(\text{SiOSn})$ have been investigated including internal process of the adsorbent–adsorbate system. Na^+ and K^+ channels share the same general architecture, with four protein subunits arranged around a central ion conducting pore. Regarding the docking with 6tcu, the amounts of Gemdock have been sequenced as: $\text{Li}^+\text{K}^+(\text{SiOGe}) > \text{Li}^+\text{Na}^+(\text{SiOGe}) > \text{Li}^+\text{K}^+(\text{SiOSn}) > \text{Li}^+\text{Na}^+(\text{SiOSn})$. This indicates the instability of these complexes by GSK3b folded monomer. In other words, instability in cytoplasmic solution may lead to stability in complex structures, possibly due to the properties of Heteroclusters.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS CONTRIBUTIONS

Fatemeh Mollaamin: Conceptualization and idea, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing-original draft preparation, Visualization, Supervision, Project administration. Majid Monajjemi: Methodology, Software, Formal analysis, Investigation, Data Curation, Writing-review and editing, Visualization, Resources.

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