Structural and Energetic study of Lithium ions with fatty acid methyl ester [FAME (9Z-18:1) + Li+] using quantum chemical method (PM3)

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Abstract

Lithium (Li) ions are being used in a variety of fields ranging from energy storage to the treatment of mental illnesses including bipolar disorder and schizophrenia. Lithium caton (Li^+) is able to form cationic adducts with various compounds and they can stabilize the biomacromolecules that interact with. Here, the interaction of lithium ions with fatty acid methyl ester [FAME (9Z-18:1)] has been theoretically investigated to gain insight into the structure and energetics of [FAME (9Z-18:1) + Li^+]. All theoretical calculations were performed using Gaussian09 software via a graphic user interface. Geometry optimisations with harmonic vibrational analysis of conformations for chelated and extended forms of [FAME (9Z-18:1) + Li^+] were carried out using semi-empirical method PM3. To obtain accurate energetic, zero-point energy (ZPE) corrections were included in all optimized energies and relative energies between conformers. The calculations indicated that the chelated form is relatively more stable than extended forms by 25 and 118 $kJmol^{-1}$ when lithium is bound to the carbonyl oxygen (O-Li^+) or olefin (C=C-Li^+), respectively. The comparison between the relative stabilization energies of extended (O-Li^+) versus extended (C=C-Li^+) reveals that the lithium cation energetically prefers to bind to with carbonyl oxygen over the carbon-carbon double bond.
Keywords: lithium ions, geometry optimization, sim-empirical method, Gaussian 09.

الدراسة التركيبية والطاقية لأيونات الليثيوم مع الأحماض الدهنية ميثيل استر [+Li + (9Z–18:1) FAME] باستخدام الطريقة الكيميائية الكمومية (PM3)

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الملخص

تُستخدم أيونات الليثيوم (Li) في العديد من المجالات ابتداءً من تخزين الطاقة إلى علاج الأمراض العقلية بما في ذلك اضطراب ثنائي القطب وانفصام الشخصية. أيون الليثيوم الموجب (+Li) قادر على تكوين مقاربات كاتيونية بمركبات مختلفة ويمكنه تثبيت الجزيئات الحيوية التي تتفاعل معها. هنا، تم التحقيق نظريًا في تفاعل أيونات الليثيوم مع استر ميثيل الأحماض الدهنية [(9Z–18: 1) FAME] وذلك لإكتساب المعرفة حول بنية وطاقة [+ Li + (9Z–18: 1) FAME]. تم إجراء جميع الحسابات النظرية باستخدام برنامج Gaussian09 عبر واجهة المستخدم الرسومية. كما تم إجراء تحسينات هندسية مع تحليل اهتزازي توافقي للأشكال المخلبية و الممتدة لـ [+ Li + (9Z–18: 1) FAME] باستخدام الطريقة شبه التجريبيةPM3 . وللحصول على الطاقة الصحيحة، تم تضمين تصحيحات طاقة نقطة الصفر (ZPE) في جميع الطاقات المحسّنة والطاقات النسبية بين المطابقين. أشارت الحسابات إلى أن الشكل المخلبي أكثر استقرارًا نسبيًا من الأشكال الممتدة بمقدار kJmol⁻ 25 1و118 kJmol⁻¹ وذلك عندما يرتبط الليثيوم بأكسجين الكربونيل (O–Li +) أو الأوليفين (C = C–Li +) على التوالي. ومن المقارنة بين طاقة الاستقرار النسبية لشكل الممتد (O–Li+) ضد الشكل الممتد (+C=C–Li) تبين إن أيون الليثيوم يفضل من حيث الطاقة الارتباط بأكسجين الكربونيل أكثر من كربون= كربون الرابطة الثنائية.

الكلمات المفتاحية: أيون الليثيوم، التصحيح الهندسي، الطريقة شبه التجريبية، برنامج Gaussian09.

Introduction:

Lithium is a naturally occurring element in the Earth's crust and is also found in trace amounts inside the human body [1]. Lithium (Li) ions are being used in a variety of fields ranging from energy storage to the treatment of mental illnesses including bipolar disorder and schizophrenia [1, 2]. Lithium ions (Li^+) are able to form cationic adducts with various compounds [3-5] and they can stabilize the biomacromolecules that interact with. To enhance the sensitivity and selectivity of quantitation of 3-OH steroids, Wang et al (2020) developed a method for the quantitation of 3-OH steroids by LC-MS/MS coupled with post-column addition of lithium (Li) ions to the mobile phase [6]. The sensitivity and selectivity were significantly enhanced by 1.53–188 times for 13 different types of 3-OH steroids [4]. In addition, lithium ions are used to improve the fragmentation of lipids and to determine the position of double bond [7, 8].

Fatty acids are the major components of lipids [9]. The major structural components of fatty acid are double bond geometry, double bond position and methyl branching [10]. The biological functions of fatty acid and lipids are determined by their double position and geometry, chain length, presence of methyl branches and other structural motifs [10]. The most analysis method for fatty acid is by gas chromatography/mass spectrometry (GC/MS) analysis of fatty acid methyl esters (FAMEs)derived by derivatization of any lipid [11]. Tans et al (2021) reported a robust and rapid detections of lipids using lithium adducts and atmospheric pressure (AP) matrix - assisted laser desorption/ionization (MALDI). The matrix combination of lipids and lithium resulting in reduced spectral complexity and enhanced lipid detection [12, 13]. Nevertheless, the routes by which Li ions can interact with lipids have not been adequately defined.

In the absence of robust experimental methods, gaining insights into the three dimensional (3D) structure and energetics of ions in gas phase passes a significant challenge. Modern computational chemistry provides a range of robust tools to probe ion chemistry. It is a good tool for understanding and exploring experimental results

and can provide insights where experimental measurements are not possible.

In computational chemistry, Parametric Method 3 (PM3) is a semiempirical method for the quantum calculation of molecular electronic structure. Semiempirical computational methods (e.g. PM3) involve set of approximations that include parameters derived from experimental data in order to simplify the approximation to the Schrodinger equation [14] and are parameterized to reproduce chemical properties [15].In the PM3 method, these parameters have been generated for the majority of the main group elements including parameters for lithium [16-19]. The accuracy of PM3 and other semi-empirical methods in modelling molecular structures and energy have been extensively evaluated by comparing with standard validation sets such as G2 set and the density functional theory (DFT) and comparison to experimental and the computational geometries [18-20]. The comparison suggests that PM3 provides relatively good geometries, which can provide a starting structure for a subsequent higher-level calculation such as DFT [16]. PM3 can provide useful indications of the magnitude of energy differences (relative energy). Compared with ab initio [21] or DFT methods, semiempirical methods (PM3) are substantially faster [8]. Thus, they are appropriate for very large molecular systems (e.g., biological systems) [22]. This study aims to computationally study the structure and energy of lithium ionized fatty acid methyl ester [FAME (9Z-18:1) + Li^+] by means of quantum chemical methods.

2. Methods:
2.1. PM3 calculation

PM3 method was chosen as a better method because it is computationally less expensive than **ab** initio functional or density functional theory (DFT) but also it has model results that are more representative to physicochemical aspects. PM3 method has a higher calculation speed compared to the **ab** initio method [23].

The computational calculation has been done through the following steps, that is: (1) drawing a 3D structure, (2) choosing the PM3 semi-empirical method, (3) optimizing the geometry structure. (4)

Vibrational frequencies calculations. (5) visualizing the molecular structure that produced.

The computationally-optimized geometries are generated by energy minimization. All theoretical calculations were performed using Gaussian09 software [24] via a graphic user interface (Webmo). Firstly, geometry optimizations with harmonic vibrational analysis of conformations for chelated and extended forms of double bond positional of [FAME (9Z-18:1) +Li$^+$] were carried out using semi-empirical method PM3 [22-24] based on starting geometries from molecular calculations which taken from CHARM [25]. Frequencies were also calculated using analytical gradient procedures and based on these the located stationary points were identified as minima. To obtain accurate energetic, zero-point energy (ZPE) corrections were included in all optimized energies and relative energies between conformers.

2.2. Lipid nomenclature

The recommended nomenclature of the position and stereochemistry of double bonds within a lipid [10, 26, 27] was adopted. In FAME (9Z-18:1), for example, the 9 number indicates the number of carbon-carbon bonds from the carboxylate moiety and Z indicates the stereochemistry where Z refers to the cis configuration of the double bond within the acyl chain. However, the traditional nomenclature "*n*-x" has been widely used [26]. In this nomenclature, "*n*" refers to the number of carbon atoms in the acyl chain while "x" indicates the position of the double bond with respect to the terminal methyl group. However, this nomenclature does not indicate the stereochemistry of the double bonds.

For instance, the traditional nomenclature of the (11Z- 18:1) is 18:1 (*n*-7) as it is shown in figure 1.
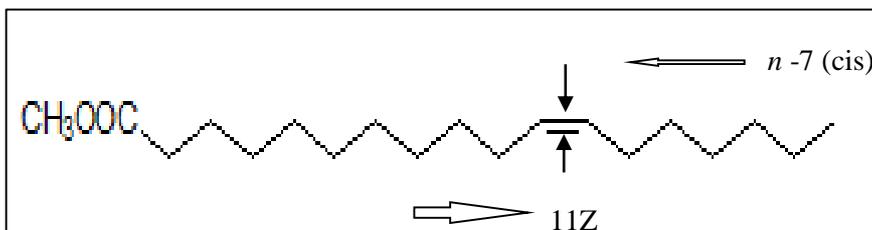
Figure 1. The difference between the recommended and traditional nomenclature of (18:1) fatty acid methyl ester.

3. Results and discussions

Firstly, to provide a rapid structure and energetic estimation, geometry optimization of fifteen representative conformations of [FAME (9Z-18:1) + Li$^+$] where Li$^+$ is associated with both carbonyl oxygen (C=O...Li$^+$) and carbon-carbon double bond (C=C...Li$^+$) (the so-called "chelated" forms) were carried out at semi-empirical method PM3 with harmonic vibrational analysis. All input geometries optimized to unique local minima on the potential energy surface (PES). The results calculated PM3 energies (E^*), corrected energies (including ZPE) (E), and relative stabilities (ΔE_{rel}) which are given as difference in corrected (including ZPE) energies between the lowest energy conformer and the other less preferable conformers, of [FAME (9Z-18:1) + Li$^+$] are given in Table 1, with structures of optimized PM3 shown in Figure 2. From Table 1, the optimized minimum energy conformer of the lowest energy derived from PM3 is geometry **5**, which suggests that, this conformer represents the global minimum on the potential energy surface for [FAME (9Z-18:1) +Li$^+$]. The relative stabilities between lowest energy form (geometry **5**) and other chelated forms range from 0-20 kJ mol^{-1} (Table 1). According to that, geometry **5** is energetically preferable. In addition, two conformations of isomer complexes with Li$^+$, where Li$^+$ is associated with either carbonyl oxygen (C=O...Li$^+$) or with carbon-carbon double bond (C=C...Li$^+$) in their extended forms were optimized at PM3 level of theory (figure3).

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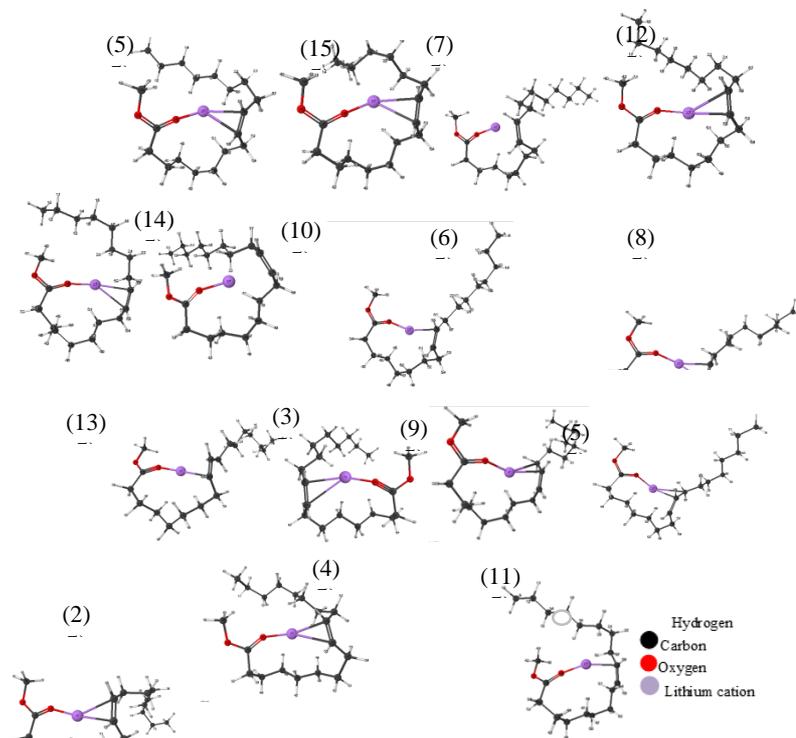
Figure 2: PM3 optimised chelated structures of fatty acid methyl ester [9Z-18:1] complexed with Li (I), are ordered from the lowest to the highest energy
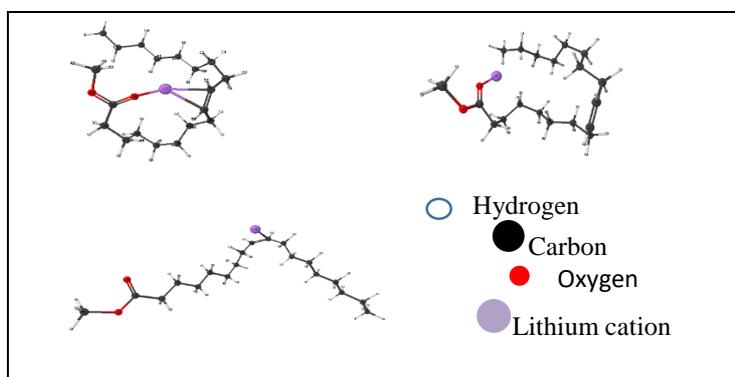
Figure 3. Computed PM3 representative structures of [FAME (9Z-18:1) + Li$^+$] isomer in its chelated and extended forms

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The PM3 relative energies of these extended forms are listed in table 1 where: E* is PM3 optimized energies, E corrected energies including ZPE, ΔE*and ΔE are relative energies. All energies are given in kJmol-1., while their PM3 optimized structures are provided in Figure 3. From Table 1, it can be seen that the lowest energy chelated form (geometry 5) is relatively more stable than the extended forms by 25 and 118 kJmol-1 when lithium is bound to the carbonyl oxygen (O-Li+) or olefin (C=C-Li+), respectively. In addition, all chelated forms are more stable than the extended forms.

Table 1: Calculated energies of [FAME (9Z-18:1) + Li$^+$] conformations.

Geometry	E^*	ΔE^*	ZPE	E	ΔE_{rel}
5	-658	0	1347	688	0
15	-653	5	1347	694	6
7	-651	7	1345	694	6
12	-651	7	1346	695	7
14	-649	9	1346	696	8
10	-650	8	1346	696	8
6	-645	13	1345	700	12
8	-643	15	1345	702	14
13	-643	15	1345	702	14
3	-643	15	1345	703	15
9	-642	16	1346	704	16
1	-640	18	1346	706	18
2	-639	19	1346	707	19
4	-637	21	1346	707	19
11	-639	19	1346	708	20
Extended O-Li$^+$	-633	25†	1350	717	29†
Extended C$_2$-Li$^+$	-540	118†	1343	803	115†

†The relative energies of extended forms relative to the lowest energy chelated conformer (geometry 5). The geometries order from the lowest energy conformer to the highest energy conformer with respect to the corrected energies.

When it comes to the comparison between the relative stabilization energies of extended (O-Li+) versus extended (C=C-Li+), the lithium cation energetically prefers to bind to with carbonyl oxygen over the carbon-carbon double bond. This is owing to that Li ions had a higher affinity for carbonyl groups. Thus the extended O-Li+ conformer is relatively more stable and energetically more preferable by 86 kJmol-1 than the extended C=C-Li+ conformer.

Conclusion:

In conclusion, the PM3 computations indicate the chelated form (geometry **5**), in which the lithium cation interacts with both carbonyl oxygen and carbon-carbon double bond is energetically favorable and more stable over the other chelated forms and the two extended forms, in which the lithium cation interacts either with the carbonyl oxygen or with the carbon- carbon double bond.

References

[1] Besekar. A, and R. Immanuel. (2023) Detection of Lithium Carbonate: A Deadly Medicines and Its Effects in Human Body. International Journal of Novel Research and Development. 8(8)

[2] Torri, R,. Luis, P,. Philip, G,. Bruce, R,.andHoria, P., (2012). Interactions of lithium ions with lipid membranes. Biophysical journal. 102. 96a. 10.1016

[3] Kamal Z, Dutta S, Rahman S, et al., (2022). Therapeutic Application of Lithium in Bipolar Disorders: A Brief Review. Cureus 14(9): e29332. DOI 10.7759/cureus.29332

[4] Bayer, E., Gfrörer, P., and Rentel, C., (1999), Coordination-ionspray-MS (CIS-MS), a universdetection and characterization method for direct coupling with separation techniques. Angew. *Chem. Int. Ed. Engl.*38: 992–995

[5] Kostiainen, R., and Kauppila, T,J. (2009). Effect of eluent on the ionization process in liquid chromatography-mass spectrometry. *J. Chromatogr*. A. 1216: 685–699.

[6] Wang, Q,. Shimizu, K ,. Meahata, K., Pan, Y, Sakurai, K,. Hikida, T,. Fukada, Y,.and Takao, T. (2020). Lithium ion adduction enables UPLC-MS/MS-based analysis of multi-class

3-hydroxyl group-containing keto-steroids. *Journal of Lipid research, 61(4), 570-579.*

[7] Adams, J., and M. L. Gross. (1986). Energy requirement for remote charge site ion decompositions and structural information from collisional activation of alkali metal cationized fatty alcohols. J. Am. Chem. Soc. 108: 6915-6921

[8] Adams, J., and M. L. Gross. (1987). Tandem mass spectrometry for collisional activation of alkali metal-cationized fatty acids: a method for determining double bond location. Anal. Chem. 59: 1576-1582

[9] J. T. Brenna, M. Plourde, K. D. Stark, P. J. Jones and Y. H. Lin, (2018) Best practices for the design, laboratory analysis, and reporting of trials involving fatty acids, Am. J. Clin. Nutr., 108(2), 211–227

[10] Zhen Wang, a,bTingxiangYang,a J. Thomas Brenna *c,d and Dong Hao Wang (2024) Fatty acid isomerism: analysis and selected biological functions, Food Funct., 15, 1071

[11] J. T. Brenna, (2013) Fatty acid analysis by high resolution gas chromatography and mass spectrometry for clinical and experimental applications, Curr. Opin. Clin. Nutr. Metab. Care, 16(5), 548–554

[12] Tran A; Wan L; Xu Z; Haro JM; Li B and Jones JW (2021) Lithium Hydroxide Hydrolysis Combined with MALDI TOF Mass Spectrometry for Rapid Sphingolipid Detection. J. Am. Soc. Mass Spectrom 32 (1), 289–300. [PubMed: 33124427]

[13] Tran, A, I., Monreal, A,.Moskovets, E,. Aguilar, H & Jones, J. (2022). Rapid detection of viral envelope using lithium adducts and AP-MALDI high-resolution mass spectrometry. Journal of the American Society for mass Spectrometry, 32 (9), 2322-2333

[14] Foresman, J. B., & Frisch, A. (1996). Exploring chemistry with electronic structure methods 2nd Ed. Pittsburgh, PA. *Gaussian, Inc*., USA

[15] Stewart J. P and Stewart A. C .(2023). A semiempirical method optimized for modeling proteins. Journal of Molecular Modeling 29:284

[16] Stewart, J. P (1989) Optimization of parameters for semiempirical methods I. method. *J. Comput Chem*. 10, 209

[17] Stewart, J. P (1989) Optimization of parameters for semiempirical methods II. application. *J. Comput Chem*. 10, 221

[18] Stewart, J. P (1989) Optimization of parameters for semiempirical methods IV: extension of MNDO, AM1 and PM3 to more main group elements. *Mol Model. 10, 155-164*

[19] Thiel. W., (2000) Semiempirical methods, modern methods and Algorithms of Quantum Chemistry. NIC,3, 261-283.

[20] Paquet, E and Viktor. H. L (2018) Computational Methods for Ab Initio Molecular Dynamics. Advances in Chemistry, vol. 2018, Article ID 9839641, 14 pages, 2018.

[21] Lewars, Errol. G., (2003) Computational chemistry, Introduction to the theory and applications of molecular and quantum mechanics. Kluwer Academic Publishers, Secaucus, NJ, USA.

[22] Dewar, M.J.S., Jie, C., Yu, J. 1993. *Tetrahedron, 49, 3003*

[23] Holder, A. J., Dennington, R. D., and Jie, C. (1994). *Tetrahedron, 50, 627* https://doi.org/10.1155/2018/9839641

[24] Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, Jr., J. A., Peralta, J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R. L., Morokuma, K., Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö., Foresman, J. B., Ortiz, J. V.,

Cioslowski, J., Fox, D. (2009). *J.: Gaussian 09, Revision A.1. Gaussian, Inc*. Wallingford CT

[25] Vanommeslaeghe, K.; Hatcher, E.; Acharya, C.; Kundu, S.; Zhong, S.; Shim, J.; Darian, E.; Guvench, O.; Lopes, P.; Vorobyov, I.; Mackerell, A. D., Jr. *(2010)Journal of Computational Chemistry, 31 (4), 671-690CODEN: JCCHDD; ISSN:0192-8651. (John Wiley & Sons, Inc.)*

[26] Pham, H.T., Maccarone. A.T., Cample. J.L., Mitchell. T.W., Blanksby. S.J. 2013: Ozone-Induced Dissociation of conjugated Lipids reveals significant reaction rate enhancements and characteristic odd-electron product ions. *J. Am. Soc. Mass Spectrom*. 24,286-296

[27] IUPAC-IUB (1978) Commission on Biochemical Nomenclature. Biochem. J. 171, 21-35