OPEN ACCESS Freely available online

Drug Designing: Open Access

Mini Review

Role of DFT in Drug Design: A Mini Review

Khansa Tariq, Iqra Shaheen, Rahila Shaheen*, Adnan Khalil*

Department of Physics, Khwaja Fareed University of Engineering and Information Technology, 64200, Rahim Yar Khan Pakistan

ABSTRACT

Density Functional Theory (DFT) is a Quantum Mechanical Method (QMM) which got great attention and widely used method for drug designing process in the past years. Now it is consider as most competent method for the pharmaceutical studies. DFT is use to describe biological and molecular systems in a very less cost and with high accuracy. Applications of DFT in drug design are discussed in this paper in detail. Overview of importance of DFT in drug design, accuracy and recent role of DFT in COVID-19 has been discussed. The conclusion of all sections has been presented in the end of paper.

Keywords: Density functional theory; Quantum mechanical method; Biological system; Molecular system; Drug design

ABBREVIATION

DFT: Density Functional Theory; QMM: Quantum Mechanical Method; CAMD: Computer Aided Molecular Design; CI: Configuration Interaction; MPn: Moller-Plesset Perturbation Theory; LDA: Local Density Approximation; GGA: Generalized Gradient Approximation; HF: Hatree Fock.

INTRODUCTION

Researchers required much development in the field of medicinal and drug chemistry; experimental methods that were using in drug design are expensive, time consuming and provide limited information. The researchers put their interest in the development of new computational methods in the field of drug design. In biological system when works at quantum mechanical level, there is a need of a method which provides us wide and useful information in limited time. Computer Aided Molecular Design (CAMD) becomes most attractive in drug design process. CAMD used molecular mechanics method to solve the problems in drug design but some deficiencies came in MM method when it is used to study electron based properties. In Hatree-Fock (HF) method [1-4], electron co-relation is excluded and this method is also unable to describe precisely some properties. Configuration Interaction (CI) and Moller-Plesset Perturbation theory (MPn) [5-7] both included electron co-relation but are costly. Density Functional Theory is a Quantum Mechanical Method (QMM) which is considered as one of most efficient and excellent method for drug design process. This computational method is taking less time and least costly as compare to other computational methods. The paper presents the importance of DFT and its applications in drug design. Initially an introduction is made. Next, accuracy of DFT some drug design will be discussed. Some antibiotic drug design for some diseases will be discussed. The whole summary of paper will be discussed at the end.

LITERATURE REVIEW

Density Functional Theory (DFT)

In drug design and medicinal chemistry, DFT is considering as most efficient and significant method. In DFT, firstly we have to determine an important property that is electronic density ρ. By using electronic density ρ, we can determine easily ground energy state and all other properties of molecules [8]. Ground energy state is a function of electronic density ρ which is used to map a function to a value and describe by the equation 1. A functional is expressed by square brackets in equation 1 [9].

$$E0\,[\rho]=V[\rho]+T[\rho]+EXC[\rho] \qquad (1)$$

Correspondence to: Rahila Shaheena, Department of Physics, Khwaja Fareed University of Engineering and Information Technology, 64200, Rahim Yar Khan,Pakistan, E-mail: rahilashaheenkfueit@gmail.com

Adnan Khali, Department of Physics, Khwaja Fareed University of Engineering and Information Technology, 64200, Rahim Yar Khan, Pakistan, E-mail: adnan.khalil@kfueit.edu.pk

Received: 06-Jun-2022, Manuscript No. DDO-22-17762; **Editor assigned:** 10-Jun-2022, Pre-QC No. DDO-22-17762 (PQ); **Reviewed:** 24-Jun-2022, QC No. DDO-22-17763; **Revised:** 01-Jul-2022, Manuscript No. DDO-22-17762(R); **Published:** 08-Jul-2022, DOI: 10.35248/2169-0138.22.11.216

Citation: Tariq K, Shaheen I, Shaheen R, Khalil A (2022) Role of DFT in Drug Design: A Mini Review. Drug Des. 11.216.

The above equation of functional ground energy state E0 [ρ] consists of three terms; first one V[ρ] tells interactions between distribution electrons and interaction of coulomb as well as nuclei and electrons interaction. The second term T[ρ] tells total energy of the system in which Kinetic and potential both included. The last term EXC[ρ] tells the effects of both exchange and correlation i.e., exchange correlation energy. DFT would be accurate method if the third term becomes known as other first two terms are known. This is reason why DFT is considered as approximation method because we use approximation value of EXC [ρ]. There are three types of approximations first one is hybrid functional second one is Local Density Approximation (LDA) and third is Generalized Gradient Approximation (GGA). Functional chooses any one of these approximation and there is no alternate method to enhance the calculations of accuracy of DFT. For each application, individual functional accuracy is calculated. Despite of this fact, DFT method is still most extensively used for the calculation of electronic structures of molecules because of its high efficiency and accuracy. Electron density is used in the replacement of complex wave-function and Schrödinger equation due to which electronic structures of bigger size molecules easily calculated through DFT as compared to other methods i.e., HF, MPn and CI.

DFT study for COVID-19 and common diseases

COVID-19 is horrible pandemic occur in all over the countries. There is not any country that becomes safe from this pandemic. Millions of people have died due to this infection and this directly affects the immunity system of human being. Immunity always plays a vital role to protect us from this pathogenic infection. There are no promising drugs available in drug market to cure the patient from this kind of infection. DFT calculations are considered effective due to its efficiency and accuracy [10]. Studied 20 amino acids by using DFT and found arginine as a best immunity booster. They found amino acids are not toxic and these are used to give energy in body by making cells, protecting cells and others [11]. Studied lethal mutagenesis and tautomers in HIV and Corona virus by using TD-DFT and predicted efficient and precise [12] investigate the ability of four derivatives of ferrocence for anti-corona diseases by using quantum chemical and molecular docking [13,14]. Using DFT calculations to study structural properties of tetrazole and found this highly stable and docking calculation predict that 4-g compound exhibit excellent biological properties and best as anticovid-19 drug. DFT study of new type of compound Co (II), Zn (II) 2-cholorobenzoate with complexes of 3-cyanopyridine found best for anti-corona disease. The materials that are currently used in medicine such as in drug design are discussed in this section [15]. Formed novel compound Vanillin isoniazid (VAN-INH) by cocrystallization process and also formed two others compounds such as VAN-NIC and VAN-INM. These compounds have improved solubility and dissolution rate so that they gave new path for the development and improve the rate of production of natural drug. Vanillin has less bioavailability due its less solubility and it became expensive in medicine, optoelectronics and food application [16]. DFT suggests enediyne drug can be used for anticancer and antitumor. Bleomycin drug properties calculated by using DFT and found as antibiotic drug for cancer treatment. Artemisinin drug is strong antidrug for malaria disease. Derivatives and analogs of nucleic acid base is strongly use as antileukemic drug. A DFT calculation of zinc proteinases shows that this can be used as anticancer, antitumor and for cardiovascular diseases. Amino acids and proteins are strongly use in drug designing system as antibiotic. DFT calculations of sugars got great attention, carbohydrates are important for living organisms. Organic-metals compounds are usually use for antitumor drugs.

DFT accuracy for the analysis of drug properties

DFT accuracy is study in detail for the molecular properties. The accuracy of DFT for the study of diverse molecular properties is limited for specific functional as hybrid functional is consider better than other approaches such as GGA or LDA approaches. An estimated accuracy of DFT for B3LYP is shown in Table 1. Hybrid functional B3LYP is widely used [17,18].

Properties	Estimated accuracy	Recommended calculation of DFT for
Atomization energies	2.2 kcal-mol-1	No
Transition Barriers	1 kcal-mol-1	Yes
Geometry	Bond angle=0.20 Bond length=0.005 Å	Yes
I.E and A.E	0.2 eV	Yes
Metal-ligand bond	4-5 kcal-mol-1	Yes
Ionic, Covalent and H-Bonding	1-2 kcal-mol-1	Yes
Metal reaction pathway transition	5 kcal-mol-1	Yes
Relative energy conformational	1 kcal-mol-1	Yes
Charge transfer, Ion-dipole and interaction of hydro-phobic	1-2 kcal-mol-1	No

Table 1: Estimated DFT accuracy using B3LYP functional for molecular drug properties.

DFT applications in drug design

There are number of applications which are currently discussed using DFT in the study of drug like molecules as well as its properties. DFT has wide importance in field of drug design. Few applications showing the role and importance of DFT are being reviewed.

Modeling of interaction of receptor and drug

DFT is nowadays widely used for drug designing because of its role in studying properties of drugs and also their interaction

with their receptors. Drugs are designed on the basis of their receptors, which bind only specific type of drugs. It is a ligand gated system in which when a drug which is our ligand when binds with its specific receptors on the cell membrane or target cell, specific gates open and drug enters the cell. In order to facilitate this study DFT is widely used. Number of examples is found in previous papers in which interaction of potential target-drug is studied [19-26].

Modeling of organometallic drug

Organometallic drugs are part of biological systems. Their study is being carried out efficiently by DFT. Furthermore, DFT is used to make metal containing system that is used to study inorganic therapeutics. DFT helps to know the structure of drug molecule and drug design. However appropriate method of DFT is essential for studying properties of specific drug [27-38].

Modeling of mechanism of action of drug

Using DFT we become able to replicate the transition state between potential drugs and their receptors. By constructing the transition state, it became easy to decrease the activation barrier by enzymes. For this purpose, we developed mechanism based inhibitors using DFT which serve to replicate the transition state [38]. Also study of neuraminidases aid us in such a development of transition state inhibitors [39-43]. Hence, DFT aided us in understanding drug action mechanism modeling [44,45].

DISCUSSION AND CONCLUSION

Nowadays, DFT is considering a convenient method in drug design. DFT is use to describe biological and molecular systems in a very less cost and with high accuracy. In this paper, we discussed the detail introduction of DFT and applications of DFT in drug design and concluded that DFT helps to know the structure of drug molecule and drug design. The accuracy of DFT for the study of diverse molecular properties is limited for specific functional as hybrid functional is consider better than other approaches such as GGA or LDA approaches. There are three types of approximations first one is hybrid functional second one is Local Density Approximation (LDA) and third is Generalized Gradient Approximation (GGA). Functional chooses any one of these approximation and there is no alternate method to enhance the calculations of accuracy of DFT. In this paper, recent DFT calculations for COVID-19 are discussed. DFT Applications and accuracy for the drug properties are explained.

REFERENCES

1. Hartree DR. The wave mechanics of an atom with a non-Coulomb central field. Part I. Theory and methods. In Mathematical Proceedings of the Cambridge Philosophical Society 1928 (Vol. 24, No. 1, pp. 89-110)
2. Hartree DR. The wave mechanics of an atom with a non-coulomb central field. Part II. Some results and discussion. In Mathematical Proceedings of the Cambridge Philosophical Society 1928 (Vol. 24, No. 1, pp. 111-132). Cambridge University Press.
3. Hartree DR. The wave mechanics of an atom with a non-coulomb central field. part iii. term values and intensities in series in optical spectra. In Mathematical Proceedings of the Cambridge Philosophical Society 1928 (Vol. 24, No. 3, pp. 426-437). Cambridge University Press.
4. Fock V. Näherungsmethode zur Lösung des quantenmechanischen Mehrkörperproblems. Zeitschrift für Physik. 1930 ;61(1):126-48.
5. Møller C, Plesset MS. Note on an approximation treatment for many-electron systems. Phys Rev.1934 ;46(7):618.
6. Slater JC. The theory of complex spectra. Phys Rev. 1929;34(10): 1293.
7. Condon EU. The theory of complex spectra. Phys Rev. 1930;36(7):1121.
8. Hohenberg W. P.; Kohn, Inhomogeneous Electron Gas. Phys. Rev. 1964;136:B864-71.
9. Kohn W, Sham LJ. Self-consistent equations including exchange and correlation effects. Phys Rev. 1965;140(4A): A1133.
10. Singh P, Kumar D, Pal S, Kumari K, Bahadur I. L-amino-acids as immunity booster against COVID-19: DFT, molecular docking and MD simulations. J Mol Struct. 2022 ;1250:131924.
11. Fong C. Lethal mutagenesis and tautomerism in Corona, Covid-19 and HIV viruses: predicting efficacy by TD DFT quantum mechanics.
12. Abbas G, Irfan A, Ahmed I, Al-Zeidaneen FK, Muthu S, Fuhr O, et al. Synthesis and investigation of anti-COVID-19 ability of ferrocene Schiff base derivatives by quantum chemical and molecular docking. J Mol Struc. 2022 ;1253:132242.
13. Devasia J, Chinnam S, Khatana K, Shakya S, Joy F, Rudrapal M, et.al. Synthesis, DFT and In Silico Anti-COVID Evaluation of Novel Tetrazole Analogues. Polycycl Aromat Compd 2022 :1-6.
14. Öztürkkan FE, Özdemir M, Akbaba GB, Sertçelik M, Yalçın B, Necefoğlu H, et al. Synthesis, crystal structure, potential drug properties for Coronavirus of Co (II) and Zn (II) 2-chlorobenzoate with 3-cyanopyridine complexes. J Mol Struct. 2022 ;1250:131825.
15. Ouyang J, Xing X, Zhou L, Zhang C, Heng JY. Cocrystal design of vanillin with amide drugs: Crystal structure determination, solubility enhancement, DFT calculation. Chem Eng Res Des. 2022.
16. Hoffmann M, Rychlewski J. Density functional theory (DFT) and drug design. In Reviews of Modern Quantum Chemistry: A Celebration of the Contributions of Robert G Parr (In 2 Volumes) 2002 (pp. 1767-1803).
17. Becke AD. Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys. 1993;98(492):5648-52.
18. Stephens PJ, Devlin FJ, Chabalowski CF, Frisch MJ. Ab initio calculation of vibrational absorption and circular dichroism spectra using density functional force fields. J Phys Chem. 1994 ; 98(45): 11623-7.
19. Kumar RA, Ikemoto N, Patel DJ. Solution structure of the calicheamicin γ1I-DNA complex. J. Mol Biol. 1997 ;265(2):187-201.
20. Inoue Y, Sugio S, Andzelm J, Nakamura N. A density functional study of the receptor ligand interaction: Stabilization energy in ammonium salt− aromatic interactions. J Phys Chem A. 1998 ;102(3):646-8.
21. Sapse AM, Rothchild R, Lown JW. Semi-empirical, ab initio and molecular modeling studies on the DNA binding of a calicheamicinone-polyamide conjugate. J. Biomol. Struct. 2000 ; 18(3):423-31.
22. de Esch IJ, Timmerman H, Menge WM, Nederkoorn PH. A qualitative model for the histamine H3 receptor explaining agonistic and antagonistic activity simultaneously. Archiv der Pharmazie: Int J Pharm Med Chem. 2000.
23. Mavri J, Hadži D. Modelling of ligand–receptor interactions: Ab-initio and DFT calculations of solvent reaction field effects on

methylated ammonium–π and–acetate complexes. J Mol Struct: Theo chem. 2001;540(1-3):2515.

24. Sulpizi M, Schelling P, Folkers G, Carloni P, Scapozza L. The rational of catalytic activity of herpes simplex virus thymidine kinase: A combined biochemical and quantum chemical study. J Biol Chem. 2001 ;276(24):21692-7.
25. Sulpizi M, Folkers G, Rothlisberger U, Carloni P, Scapozza L. Applications of density functional theory-based methods in medicinal chemistry. Quantitative Structure-Activity Relationships. 2002; 21(2):173-81.
26. Hirokawa S, Imasaka T, Imasaka T. Chlorine substitution pattern, molecular electronic properties, and the nature of the ligand receptor interaction: Quantitative Property: Activity relationships of polychlorinated dibenzofurans. Chem Res Toxicol. 2005;18(2): 232-8.
27. Raber J, Zhu C, Eriksson LA. Activation of anti-cancer drug cisplatin is the activated complex fully aquated? Mol Phy. 2004; 102(23-24):2537-44.
28. Burda JV, Šponer J, Leszczynski J. The interactions of square platinum (II) complexes with guanine and adenine: A quantum-chemical ab initio study of metalated tautomeric forms. J Biol Inorg Chem. 2000; 5(2):178-88.
29. Ballone P, Marchi M. A density functional study of a new family of anticancer drugs: Paclitaxel, taxotere, epothilone, and discodermolide. J Phys Chem. A 1999 ; 103(16):3097-102.
30. Hoffmann M, Rychlewski J. Effects of substituting a OH group by a F atom in D-glucose. Ab initio and DFT analysis. J Am Chem Soc. 2001; 123(10):2308-16.
31. Zubrzycki IZ, Blatch GL. DFT study of a substrate and inhibitors of 1-deoxy-2-xylulose-5-phosphate reductoisomerase–the potential novel target molecule for anti-malaria drug development. J Mol Model. 2001 ;7(10):378-83.
32. Lee HJ, Song JW, Choi YS, Park HM, Lee KB. A theoretical study of conformational properties of N-methyl azapeptide derivatives. J Am Chem Soc. 2002 ; 124(40):11881-93.
33. Jezierska A, Panek J, Ryng S. DFT study of a novel lead structure in the isoxazole heterocyclic system. J Mol Struct. THEOCHEM. 2003 ; 636(1-3):203-14.
34. Flores-Holguín N, Glossman-Mitnik D. CHIH-DFT determination of the molecular structure, infrared and ultraviolet spectra of the antiparasitic drug megazol. J Mol Struct. THEOCHEM. 2004 ;681(1-3):77-82.
35. Gomes JR, Ribeiro da Silva MD, Ribeiro da Silva MA. Solvent and structural effects in the N−H bond homolytic dissociation energy. J Phys Chem. A. 2004 ;108(11):2119-30.
36. Ramalho TC, de Alencastro RB, La-Scalea MA, Figueroa-Villar JD. Theoretical evaluation of adiabatic and vertical electron affinity of some radiosensitizers in solution using FEP, ab initio and DFT methods. Biophys Chem. 2004 ; 110(3):267-79.
37. Ramalho TC, DA Cunha EF, DE Alencastro RB. Theoretical study of adiabatic and vertical electron affinity of radiosensitizers in solution part 2: Analogues of tirapazamine. J Theor Comput Chem. 2004; 3(01):1-3.
38. Schramm VL. Enzymatic transition states and transition state analog design. Annu Rev Biochem. 1998 ; 67(1):693-720.
39. Chong AK, Pegg MS, Taylor NR, von Itzstein M. Evidence for a sialosyl cation transition-state complex in the reaction of sialidase from influenza virus. Eur J Biochem. 1992 ; 207(1):335-43.
40. Taylor G. Sialidases: Structures, biological significance and therapeutic potential. Curr Opin Struct Biol. 1996; 6(6):830-7.
41. Barnes JA, Williams IH. Quantum mechanical/molecular mechanical approaches to transition state structure: mechanism of sialidase action.
42. Thomas A, Jourand D, Bret C, Amara P, Field MJ. Is there a covalent intermediate in the viral neuraminidase reaction? A hybrid potential free-energy study. J Am Chem Soc. 1999 ; 121(41): 9693-702.
43. Ban F, Gauld JW, Boyd RJ. Modeling the action of an antitumor drug: A density functional theory study of the mechanism of tirapazamine. J Am Chem Soc. 2001 ; 123(30):7320-5.
44. Sulpizi 8M, Laio A, VandeVondele J, Cattaneo A, Rothlisberger U, Carloni P. Reaction mechanism of caspases: insights from QM/MM Car–Parrinello simulations. Proteins: Struct Funct Genet. 2003 ; 52(2):212-24.
45. LaPointe SM, Weaver DF. A review of density functional theory quantum mechanics as applied to pharmaceutically relevant systems. Curr Comput-Aid Drug. 2007; 3(4):290-6.