Review paper on computational QSAR studies on potent tuberculosis Drugs

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Introduction

Quinones are widely found naturally existing composites that have been known since ancient times as pigments and medicines. p-Benzoquinone was prepared some 170 years ago in the earliest era of chemical synthesis in Liebig's laboratory as a result of oxidation of quinic acid with MnO2 and H2SO4. Since then a rich chemistry involving complexes, oxidation-reduction reactions, photochemical processes, polymeric materials, and synthetic transformations of these compounds has been revealed and developed. Ortho and para isomers of quinones have claimed numerous applications in various fields and hence has been widely studied, but the meta isomer has been the subject of extensive discussions since it formally is missing a bond and is an avatar of the so-called non-Kekule´ species [1-2]. Of these quinone compounds, only the p-isomer has a measured heat of formation, and its value is well established. No literature reports on the enthalpy of formation of o- and m-benzoquinone or any of their substituted derivatives have appeared despite extensive efforts to fully characterize these species.

Quinones are organic compounds that are derived from aromatic compounds such as benzene or naphthalene by conversion of an even number of –CH= groups into –C=O groups with any necessary rearrangement of double bonds, resulting in a fully conjugated cyclic dione structure. These compounds along with a very large no. of derivatives constitute the class which plays pivotal role in various important biological functions, health and industry. A few structural examples of quinines are as below

oquinone   p-quinone   naphthoquinone   anthraquinone
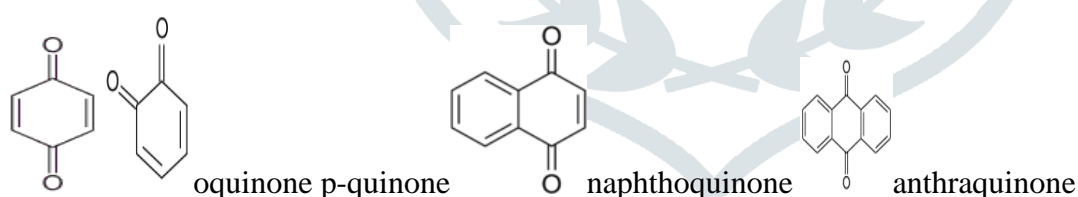
Quinones are found in flowering plants, fungi including lichens, bacteria and arthropods. Nonetheless it could be synthesized chemically by oxidation of phenols [3], hydroquinone [4], Oxidative demethylation of dimethoxy-benzoquinone [5], and precursor method [6] etc.

Applications of benzoquinones:

Throughout history, several references were found about pharmaceutical use of naturally occurring quinines. Streptonigrin is natural quinine with antitumor and antibiotic activity [7]. Kingston and co-workers [8] have isolated two new benzoquinones 2-methoxy-6-heptyl-1, 4-benzoquinone and 2-methoxy-6-pentyl-1, 4-benzoquinone from the leaves of Miconia lepidota present in Surinam forests.

Recently Sansom et al. [9] has isolated an antiproliferative bis-prenylated quinone,5-[1,1-dimethylprop-2-enyl-2-[3-methylbut-2-enyl]cyclohexa-2,5-diene-1,4-dione from the New Zealand brown alga Perithalia capillaries. This compound inhibited superoxide production by human neutrophils in vitro and was also reported to inhibit proliferation of HL60 cells.

Polyanoquinones A and B were used in Taiwan as tonic drugs from years. Heliotropiquinone A and B were used as antifungal, antibacterial [10]. 2-chloro-5-methoxy-3-methyl-cyclohexa-2, 5-diene-1, 4, dione and xylariaquinone were used as antimalarial [11]. Sesquiterepine [12] quinines were used as antiviral, antimicrobial and cyto-toxics.

Other uses:

The reduction of quinone to the corresponding dihydroxy form is an important derivative. In acidic solution, p-benzoquinone is reduced reversibly to hydroquinone. The so-called quinhydrone electrode, containing equimolar solution of quinone and hydroquinone, is used to determine hydrogen ion concentrations [13] depending on the oxidation-reduction reactions. Hydroquinone and its derivatives are used in photographic dye chemicals [14], in medicine, as an antioxidant [15], and in paints, varnishes, and motor fuels and oils. Hydroquinone and certain derivatives are also used as polymerization inhibitors to tie up free radicals by direct reacting with peroxy-free radicals. P-benzoquinone is used as a fungicide and to make dyes and other agrochemicals. It is also an inhibitor especially for vinyl monomers and unsaturated polyester resins, and cross-linking agent [16].

Alopecuquinone and its derivatives are used as analgesic drugs [17], thiaplidiaquinone A and thiaplidiaquinone B are used as antitumor drugs [18]. 2 methoxy-6-pentyl benzoquinone, 2 methoxy-6-heptyl benzoquinone and 2 methoxy-6-benzyl benzoquinone are used as insect antifeedents and antineoplastics [19].

Semi- Empirical methods

Markovic et al. [25] studied the electronic absorption spectra of physcion, aloe emoedin and chrysophynol. The calculation of electronic transition energies intensities using ZINDO/S semi empirical method showed that planar structure had the deepest local minimum in above said molecular. According to the experimental data available in literature, physcion spectrum consisted of 4 strong absorption bands which are matched quite satisfactory by results of ZINDO/s implementations. In case of aloemeedin, optimized geometry predicted that most stable ground state structure of molecular allowed the formation of 2 IHBs which is also matched good by ZINDO/s results.

Pang et al. [26] presented a combines QM/MM study that can be used to assign key resonances in the FTIR spectrum of tryptophan tryptophyl quinone [TTQ] in the TTQ-dependent quinoprotein aromatic amine dehydrogenase [AADH]. It is shown that consideration of the cofactor alone is not sufficient to identify correctly the experimentally observed resonances-inclusion of the protein is required for this. However, to

enable accurate peak assignment, a stepwise approach is needed that builds up increasing levels of complexity from a simple system. Their study is very useful in predicting the spectroscopic changes during the interconversion of intermediates in the reductive half reaction catalyzed by AADH.

Well resolved far-infrared spectra of 1,4-benzoquinone, 1,4-naphthoquinone, and 9, 10-anthraquinonein polycrystalline form have been measured with terahertz time domain spectroscopy at room temperature by Min et al[27]. In this work, they measured three para-quinones, namely 1, 4-benzoquinone, 1, 4-naphthoquinone, and 9, 10-anthraquinone, in the frequency range from 0.3 THz to 2.0 THz with THz-TDS at room temperature. The frequency-dependent power absorption, index of refraction, and complex dielectric function of these quinones were calculated. Theoretical calculation with semi empirical AM1, Hartree-Fock [HF], and density functional theory [DFT] was carried out to analyze the vibrational frequencies of p-quinones. Observed THz responses were attributed to intermolecular vibrational modes mediated by hydrogen bonds comparisons of experimental and calculated data showed that results produced by DFT study at B3LYP/6-311G level gave better simulation.

The performance of 2,5-dialkoxy-1,4-benzoquinone derivatives was investigated for their use as active materials in rechargeable lithium batteries by Masaru et al.[28]. These derivatives show stepwise two-electron redox behavior in cyclic voltammetry. Positive-electrodes that contained these materials showed the high capacities at the initial discharge process. Among the dialkoxy benzoquinone derivatives they tested, methoxy derivative [DMBQ] showed the highest capacity voltage of 2.6 V vs. Li+/Li. This study also showed that the electrochemical properties of 1, 4-benzoquinone derivatives can be adjusted by some chemical modifications. The battery performance of the dialkoxy benzoquinone changed depending on the experimental conditions, including the composition of the electrolyte solution and the amount of conductive additives. It may be possible to realize further improvements in capacity and cycle-life performance by optimizing the cell composition.

Song et al. [29] carried out an exhaustive DFT and ab initio hartree-fock studies on the structural parameters and chemical reactivity of all the free radicals generated by benzoquinones and hydroquinone. The free radicals of hydroquinone were found to be more reactive than free radicals of quinone.

Bangal et al. [30] studied the proton coupled charge transfer in the formation of charge transfer complexes between 1, 4-benzoquinone and 2,6-dimethoxyphenol by DFT-B3LYP/6-311G[d,p]level. In this study they found that the strength of the charge transfer complex formation ability depended on the HOMO-LUMO energy gap which in turn was influenced by the H-bond formation.

Tormenta el al.[31] carried out theoretical analysis of the relative stability of endo, exo Diels-Alder adducts formed by the reaction between cyclopentadiene and 1,4- benzoquinone. The energies of both endo and exo adducts were obtained at CBS-Q level of theory, which showed that endo adduct is more stable than exo. Electronic structure analysis indicated that the attractive delocalization interaction predominates over the steric repulsive interaction in endo adducts.

Sunoj et al. [32] reported the substituent effects of retro Diels-Alder reaction in benzoquinones. A study was carried out on the retro Diels-Alder reaction of cycloadducts formed between substituted cyclopentadiene and p-benzoquinone based on the hybrid HF-DFT method.in this study they found that endo adducts are more stable.

Many well-known quinones such as p- chloranil, dichloro, dicyano-p-benzoquinone [DDQ] and tetracyano-p-benzoquinone have strong power of oxidation and have been extensively used as oxidants in organic synthesis. The Hydride affinity of quinones is measure of their oxidizing power.Based on this principle Zhu et al. [33] predicted the hybrid affinities of a variety of eighty quinone in DMSO solution to prepare many useful organic oxidants.

Khan and Khan [34] have presented the quantitative structure and activity relationship studies employing calculation of electronic, hydrophobic, structural and topological parameters of the compounds. In particular, electronic parameters were considered important in the establishment of quantitative structure and activity relationship models and were helpful to quantify different types of intermolecular and intramolecular interactions, as these interactions were usually responsible for properties of biological systems. The hydroxy substituted quinones and their derivatives were of considerable practical importance in the field of biology and pharmacology, as prominent family of pharmaceutically active and biologically relevant chromophores. Hydroxy naphthoquinone derivatives, in particular, have shown inhibitory effect on DNA topoisomerase-I and antiproliferative activity and cytotoxic activity. They have generated the molecular electronic descriptors like the energies of HOMO and LUMO, dipole moment , ionization potentials, heat of formation, total energy ET , electronic energy Eel, electronic transition energies and IHB strengths for the hydroxy derivatives of series of quinones by optimizing their geometries using the semi empirical and ab initio molecular modelling method. The model starts with the computation of the energy minimum geometries of the individual molecular systems by minimizing the energy with respect to all geometrical coordinates, without imposing any geometrical constraint using the semi empirical quantum mechanical AM1 or the ZINDO/1 method. The optimized geometries so obtained were then used as initial input structure for geometry optimizations using the ab initio calculations at HF level employing basis sets selected depending on the accuracy required. The strengths of the IHBs were calculated by performing the optimization of Molecular Modelling for Generation of Structural and Molecular Electronic Descriptors the geometry for various conformers of the molecular systems using the semi empirical AM1 and the ZINDO/1 methods. In this study, the electronic and geometrical descriptors for the ligands were calculated using the quantum mechanical semi empirical and ab initio methods that can be directly used for QSAR studies of the ligand-protein interactions.

Combined experimental and theoretical study of tetramethoxy-p-benzoquinone [TMQ] was carried out by Bonnard et al. [35]. In carbonate-based electrolytes, electrochemical behaviour of TMQ was characterized by a reversible insertion process located at approximately 2.85 V vs. Li+/Li0. This relatively high potential reactivity, coupled computational methodologies in the field of organic electrode materials, lead to complement these experimental data with theoretical studies performed using density functional theory [DFT]. Single crystals of TMQ were synthesized and thoroughly characterized showing that this quinonic species crystallised in the P21/n space group. The experimental crystal structure of TMQ was then used to assess various DFT methods. The structural features and vibrational spectra were thus predicted by using as a whole five common density functional [PBE, LDA, revPBE, PBEsol, B3PW91] with and without a semi-empirical correction to account for the van der Waals interactions using Grimme's [DFT-D2] scheme. The most reliable combination of the DFT functional and the explicit dispersion correction was chosen to study the Li-intercalated molecular crystal [LiTMQ] with the view of identifying Li insertion sites. A very close agreement with the experiment was found for the average voltage by using the most stable relaxed hypothetical LiTMQ structure. A comparison of vibrational spectra gained either for TMQ molecule and its dimer in gas phase or through periodic calculation was undertaken with respect to the experimentally measured. Among several modes of interaction, most energetically stable mode was found to exhibit no indication of structural instability. The most favourable site for lithium insertion site is found to be a slightly distorted square planar site. This study highlighted the important role of packing forces in vibrational modes.

Nawar and aziz [36] have performed single-electrode tests on several quinone/hydroquinone redox couples, achieving current densities exceeding 500 mA/cm2, which is acceptable for use in energy applications. They fabricated a full cell using para-benzoquinone at the positive electrode against a commercial fuel cell hydrogen electrode separated by a Nafion membrane and evaluated its performance in galvanic mode, where it reached current densities as high as 150 mA/cm2. The results from these studies indicate that the quinone/hydroquinone redox couple is a promising candidate for use in redox flow batteries.

Quinones and their derivatives appear to be promising candidates as they offer low cost, low toxicity, and high reversibility in electrochemical reactions. Quinones were already ubiquitously found in nature, as they play an active role in oxygen-evolving photosynthesis as part of the electron-transport chain in photosystem II. The design of a fuel cell based on the quinone-hydroquinone redox couple would be an important step towards the realization of regenerative flow batteries based on small organic molecules.

Baik accomplished the reactivity and stability studies on benzoquinone methides by ab initio calculations[37]. The relative stabilization energies of differently substituted benzoquinone methides were calculated at the B3LYP/6-31G//B3LYP/6-31G* level by means of isodomic equation shown as:

$R^1 ; R^2$ = H, Me, ^{t}Bu
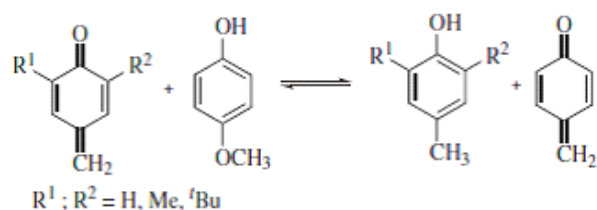
The outcome of theoretical analysis revealed that the symmetrically hindered benzoquinones methides were found to be more stable due to effective hyper conjugation of the dialkyl groups with the ring.

Tsutsui [38] performed theoretical calculations on silyl substituted benzoquinones to investigate the structure and properties. Geometry optimization and vibrational frequency calculations were done at B3LYP/6-31G* level while the SPE calculation were carried out at MP2/6-311+G [2d, p] level. The HOMO and LUMO shifted to higher energies as the no. of silyl groups increased and vibrational frequencies shifted to lower frequencies. The LUMO energy levels were quantitatively proportional to the first half wave reduction potentials.

Nayak et al [39] synthesised 9 noval NQ derivatives and tested their activity against tuberculosis. These derivatives are found to be more active than the standard Tb drug rifampicin.

Pongsri et al [40] prepared a new series of substituted derivatives of 2- hydroxy-1,4 naphthoquinone and tested their activity against Tb. 2 compounds 2-hydroxy-3-((pyridine-2-ylamino)methyl) NQ and 2-hydroxy-3-((2-hydroxyphenyl)(pyridine-2-ylamino)methyl) NQ were found significantly active.

Hazara et al [41] studied the effect of diospyrin and its derivatives on drug efflux pumping and found 4 compounds active with ciprofloxacin.

Mital et al [42] have synthesized a new series of naphthoquinone derivatives and 5 compounds are found to be active against Tb. These are 6-(1,4-dioxo-1,4-dihydro-naphthlene-2-yl)pyridine-2-carboxylic acid methyl ester, 2-(4- acetyl-1-methyl-1h-pyrrol-2-yl) NQ, 2-(3-(4- methyl-piperazin-1-yl)-3-oxoopropylsulphanyl)NQ, 2-(1-acetyl-1h-indol-3-yl)NQ and 3-(1,4-dioxo-1,4-dihydro-naphthlene-2-ylsulphanyl)-propionic acid ethyl ester

Sharma et al [43] studied 7-methyljuglone derivatives to be active against Tb. They applied multiple linear regression analysis on these compounds and suggested that substitution of group at R1 and R3 position on naphthoquinone ring with hydrophobic nature and low bulkiness are favourable for antitubercular activity.

Objectives of the proposed study:

1. Optimization of geometry: finding energetically most favoured geometry of the naphthoquinone derivatives reported in [38] – [41] by using semi empirical method.

2. The heat of formation of the most favoured geometry will be calculated using the semi empirical calculations with the help of Hartree-fock calculations. The energies of the highly occupied and the lowest unoccupied molecular orbitals will be calculated to find the energy band gap of the molecular system. The dipole moment of the various transitions and the Mullikan charges associated with states will be analyzed.

3. A comparison of the structural parameters calculated using various methods:

The calculated parameters will be compared to the experimental data of the naphthoquinone derivatives to decrease the errors occurred during the optimization of the system.

4. The influence of the derivatives added to the basic structure will be analyzed.

5. Decrease in the prediction error

Methodology:

- Data set and data pre-treatment

Experimental values of various electronic parameters will be taken from literature. First step will be encoding the structural features of molecules which were named descriptors .The successful application of the quantum mechanical methods needs to have a proper description of variance between individual descriptor within a set of compounds. The error in the calculated descriptor value must be significantly lower than the real variance of that descriptor.

- Descriptor selection and model development:

The calculated descriptor values will be analyzed with the help of various computational models i.e. algorithms and iterative sequences.

Then a proper criterion will be set for evaluation of credibility of each computational model used.

- Comparison of experimental and calculated data

- Drawing conclusions

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