Optimized Programs and Methods Required for the Computational Study of Beta Blockers

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Abstract:

This study was designed to estimate the optimized conditions for the computational study of quantum characteristics of beta blockers. Carvedilol was selected as a representative of beta blockers. Optimized energies and bonds lengths were measured using different methods including PM3, HF and DFT. A comparison has been made between Gaussian and GAMESS programs. The difference in optimized energy values, and the approaching of the bonds angle to the optimal values were studied. The results showed that Gaussian software showed higher priority than GAMESS software, which can be observed from the differences in the optimized energy values and the approaching of the bonds angles to the optimal values. The obtained results will be depended on all subsequent studies. IR spectroscopic data were employed to select the most appropriate method. Three different methods (PM3, HF and DFT) have been used to measure IR, then compared with experimental values of carvedilol. DFT method showed an advantage over the other methods. Based on all above, DFT (B3LYP/6-311G) has been recommended in the computational chemistry calculations study for carvedilol and resemble beta blockers.

Key words: Beta Blockers, Gaussian software, GAMESS software, DFT, HF, PM3, Computational chemistry
Introduction:

β-adrenergic antagonist or β-adrenoceptor antagonists are chemical substance that have the ability to block the action of endogenous catecholamine such as adrenaline and noradrenalin upon β-adrenergic receptor, resulting in modifying the sympathetic nervous system activity [1]. They were introduce in the 1960s, and widely used since that in the treatment of cardiac disease and hypertension.

The different pharmacokinetic and pharmacodynamics properties of beta blockers classified these drugs into selective or nonselective on the β1 or β2 receptor and whether they do or not have the intrinsic sympathetic activity. Beta blockers with selective properties for the β1 receptor would bind to the cardiac receptor, whereas a nonselective beta blocker would bind to both β1 (cardiac) and β2 (vascular, bronchial smooth muscle and metabolic) receptor. [2]

Although Beta –blocker are similar in this competitive antagonistic action on beta-adrenoreceptors (β1, β2 and β3), but they differ in their intrinsic sympathomimetic activity (ISA), receptor selectivity, vasodilating properties and metabolism and drug half-life. The receptor specificity also affect the mechanism of the anti-hypertensive mechanism of beta blockers [3]

Carvedilol CRV (±)-1-(carbazol-4-yloxy)-3-((2-(o-methoxy-phenoxy)ethyl)oxy)-2-propanol is a racemic lipophilic aryloxypropanolamine. Noncardioselective β-adrenergic blocking agent with blocking activity against α1- and ß-adrenergic receptors.

It is considered as an effective treatment for mild and moderate congestive heart failure [4]. The vasodilatation which result from blocking of α 1-receptors, significantly decreases systemic blood pressure, pulmonary capillary wedge pressure and pulmonary artery pressure. While reduction in the heart rate and increasing in diastolic filling time are all considered as an outcomes of blocking of β-receptors. The combined effects of blocking both α- and β-adrenergic receptors also have an impact by reducing the myocardial oxygen consumption. [5]

COMPUTATIONAL METHODOLOGY:

A general formula was suggested for beta blockers Figure (4-1), in order to Facilitate reviewing of results, where: X= carbazole in carvedilol , naphthalene in propranolol and phenyl acetamide in atenolol (or one of there derivitives ) Y= alkyl catechol (catechol amine – NH group ) in carvedilol and often an isopropyl group in propranolol and atenolol
DFT theory is based on the electron density by using electron density associated with the correct Hamiltonian operator the energy of the system can be completely described. Density Functional Theory is emanating from solving the time independent Schrodinger Equation for the electrons of molecular systems as a function of the positions of the nuclei. The premise behind the density functional theory is that the energy of a molecule can be determined from the electron density instead of a wave function [6].

Semiempirical may be defined as involving assumptions, approximation, or generalization designed to simplify calculation or to yield a result in accord with observation. Thus the semiempirical method of quantum chemistry start out from the ab initio formalism and then introduce rather drastic assumptions to speed up the calculations. [7]

Semiempirical quantum chemistry attempts to address two limitations, namely slow speed and low accuracy, of the Hartree-Fock calculation by omitting or parameterizing certain integrals based on experimental data, such as ionization energies of atoms, or dipole moments of molecules. As a result, semiempirical methods are very fast, applicable to large molecules, and may give accurate results when applied to molecules that are similar to the molecules used for parameterization. On the downside, accuracy of semiempirical methods is erratic on many systems. [8]

Parametric Method 3, PM3 uses a Hamiltonian that is very similar to the AM1 Hamiltonian but the parameterization strategy is different. While AM1 was parameterized largely based on a small number of atomic data, PM3 is parameterized to reproduce a large number of molecular properties. In some sense, chemistry gave way to statistics with the PM3 model. Different parameterization, and slightly different treatment of nuclear repulsion allow PM3 to treat hydrogen bonds rather well but it amplifies non-physical hydrogen-hydrogen attractions in other cases. The accuracy of thermochemical predictions with PM3 is slightly better than that of AM1. The PM3 model has been widely used for rapid estimation of molecular properties and has been recently extended to include many elements, including some transition metals. [9]
Two highly productive approaches to solution of the electronic Schrodinger equation have arisen over the past 50 years. Wave function-based approaches expand the electronic wave function as a sum of Slater determinants, the orbitals and coefficients of which are optimized by various numerical procedures. Hartree–Fock theory is the simplest method of this type, involving optimization of a single determinant; however, its usefulness is limited because of complete neglect of electron correlation. The second class of theoretical approaches are based on density functional theory (DFT), which, following the Hohenberg–Kohn theorem, mandates expression of the total energy of the system as a functional of the electron density[10].

**Calculations Programs.**

**Gaussian 03 Software:**

Gaussian is an electronic structure modeling software application, it is arguably the most-used computational quantum-chemistry program. It does electronic-structure calculations and standard quantum chemical calculations.

Gaussian is a general purpose ab initio electronic structure package that is capable of computing energies, geometries, vibrational frequencies, transition states, reaction paths, excited states and a variety of properties based on various uncorrelated and correlated wave functions. Gaussian is used by chemists, chemical engineers, biochemists, physicists and others for research in established and emerging areas of chemical interest. [11]

Starting from the basic laws of quantum mechanics, Gaussian predicts the energies, molecular structures, and vibrational frequencies of molecular systems, along with numerous molecular properties derived from these basic computation types. It can be used to study molecules and reactions under a wide range of conditions, including both stable species and compounds which are difficult or impossible to observe experimentally such as short-lived intermediates and transition structures. [12]

**GAMESS Software:**

GAMESS is a computational chemistry software program that stands for General Atomic and Molecular Electronic Structure System. GAMESS is a program for ab initio molecular quantum chemistry. Briefly, GAMESS can perform a number of general computational chemistry calculations, including Hartree–Fock, density functional theory (DFT), generalized valence bond (GVB), Nuclear gradients are available, for automatic geometry optimization, transition state searches, or reaction path following. Computation of the energy hessian permits prediction of vibrational frequencies, with IR or Raman intensities. Solvent effects may be modeled by the discrete Effective Fragment potentials, or continuum models such as the Polarizable Continuum Model [13].

**Results and Discussion**

**Optimal Software Selection**

For the main compound Carvedilol Figure (2), a comparison has been occurred between Gaussian software and GAMESS software using different approximation methods included PM3, HF, DFT.
DFT with a hybrid functional B3LYP is widely used to study biological and pharmacological system [14]. So it will depend. Factors undergone comparison was, Optimized energy, bond length and bond angles, Table (1), (2)

![Figure (2) Optimized structure of Carvedilol](image)

Table (1): Carvedilol Optimized energy calculated by different methods and softwares

| Software | Optimized energy/ Kcal .Mol⁻¹ |
|----------|-------------------------------|
|          | PM3              | HF/6-311G         | DFT/B3LYP         |
| Gaussian | 815663.26         | 835863.41         | 841197.08         |
| GAMEES   | 811342.242        | 835861.176        | 840689.835        |

The convergence between HF and DFT method is clearly noted from the above result, with a clear preference for gaussian software.

Most prominent note is the Higher diffraction on the Optimized energy values calculated by PM3. This may be due to that The majority of semiempirical methods are based on the neglect of differential diatomic overlap (NDDO) approximation, which ignores a large number of two-electron integrals and assumes experimentally derived parameters for others[15][16].

Semiempirical calculations are much faster than their ab initio counterparts. [17][18] Their results, however, can be very wrong if the molecule being computed is not similar enough to the molecules in the database used in parametrizing the method[19][20].
Among the most used semiempirical methods are MINDO, MNDO, AM1, PM3 and SAM1. The semiempirical methods have afforded vast information for practical application [21] [22]. It is also noted that Optimized energy calculated by HF and DFT method is Very close , likewise with preference for gaussian software.

HF (ab initio) methods are based on the electronic wave function ,while DFT focusing on the electron density. HF theory accounts for electron-electron interactions only, including the quantum mechanical exchange term but lacking the electron correlation. A popular way to overcome the neglect of electron correlation effects in HF theory can be found in the DFT framework. The computational effort required by common,DFT calculations is similar to that for HF calculations, whereas the accuracy of DFT is much better than that of HF theory [23][24].

As observed from all of above results gaussian software showed priority than GAMEES software, which noted from the difference in Optimized energy values in all methods and the Approaching of the bonds angle to the optimal values , so it will be depeneded in all subscuent studies.
Table (2): Carvedilol bonds length and bonds angle calculated by different methods & softwares

| Software | Gaussian | GAMEES |
|----------|----------|--------|
| Method   | Property |
| PM3      | O(1)-C(2) 1.427 | 1.474 |
| HF/6-311G| C(2)-C(3) 1.547 | 1.518 |
| DFT B3LYP/6-311G | 1.458 | 1.547 |
| PM3      | O7-H(8) 0.948 | 0.982 |
| HF/6-311G| C(3)-C(4) 1.541 | 1.524 |
| DFT B3LYP/6-311G | 1.548 | 1.533 |
| Optimal  | B.L/A° O(7)-H(8) 0.948 | 0.982 |
|          | C(3)-O(7) 1.415 | 1.452 |
|          | C(2)-C(3) 1.547 | 1.547 |
|          | B.A/° X-O(1)-C(2) | 114.21 |
|          | O(1)-C(2)-C(3) 108.23 | 110.91 |
|          | C(2)-C(3)-O(7) | 111.09 | 102.86 |
|          | C(3)-O(7)-H(8) 106.56 | 113.65 |
|          | C(3)-C(4)-N(5) | 110.48 | 112.14 |
|          | C(4)-N(5)-H(6) 109.81 | 111.38 |
|          | H(6)-N(5)-Y 109.66 | 111.98 |

B.L/A°: Bond length and angle

Table (3) : DFT vibration frequencies and IR absorption intensities for Carvedilol molecule

| Description      | DFT | Experimental |
|------------------|-----|--------------|
| N-H str. (amine) | 3336.24 | 14.173 | 3343.34 | |
| O-H str. (hydroxyl) | 2918.78 | 48.427 | 2923.68 | |
| C-H str.          | 2836.09 | 60.073 | 2842.60 | |
| C-O str.          | 1094.99 | 90.01  | 1097.31 | |

Determination of Optimal Approximation Method:
From the previous study, DFT method showed an advantage over the other methods. To make sure, I.R spectroscopic data was employed to select the most appropriate method, where I.R spectrum was measured by PM3, HF, DFT method, Figure (3) and compared with experimental values of carvedilol. Table (3)

Figure (3): D, showed the peaks 3343.34 cm⁻¹ (N-H, stretching), 2923.68 cm⁻¹ (O-H, stretching), 2842.60 cm⁻¹ (C-H, stretching) and 1097.31 cm⁻¹ (C-O, stretching). These peaks can be considered as characteristic peaks of carvedilol and were not affected and prominently observed in IR spectra[25].

Table (3): DFT vibration frequencies and IR absorption intensities for Carvedilol molecule

Based on all above, DFT (B3LYP/6-311G) has been adopted in the determination of Optimized energy and all properties of the pharmaceutical compound under consideration.
Figure (3): I.R spectrum of carvedilol determined by A:PM3, B: HF, C:DFT, [D:experimental][25][26]
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