Quantum Signature of Chemical Bond-Breaking in Force Field Based Molecular Potentials

Rejwan Ali
Department of Medicine, Icahn School of Medicine, New York, New York
The Story of “Modern Physics” from the Past 20th Century as described by famous former Soviet physicist Lev Dau Landau => The Big Bang for Quantum Chemistry

Landau’s famous log scale for physicists

Physics Community (estimated by the number of APS members)

Niels Bohr
Werner Heisenberg
Paul Dirac
Wolfgang Pauli
Albert Einstein

\[ \log (\approx 55000) = 4.74 \]
\[ \log (4) = 0.602 \]
\[ \log (\text{UNIQUE}) = 0 \]
Paul Dirac’s statement after his famous relativistic Schrödinger equation

“The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble.”


THEORETICAL CHEMISTRY IS A SPIN-OFF FROM PHYSICS!
Eventual Tunneling of Quantum Theory in Bio-medicine

• Before the advent of digital computer, in pre- and post-World War II era, theorists had spend a significant fraction of their entire career span just to solve ground state energy of a rather small molecule using newly inaugurated quantum techniques by paper and pencil. Several well-known quantum calculation methods had been developed over the decades:
  • Hartree/Fock Method (first introduced in 1920s)
  • Moller/Plesset Perturbation Theory (first introduced in 1930s)
  • Density Functional Theory (first introduced in 1960s)
• By the 1960’s and onwards, with usher of transistorized digital computer age, the field took new leap towards implementation of quantum mechanics based algorithms and correlate the computational results to experimental molecular spectroscopy.
• Visualizing immense future potential for drug molecule applications, in 1990’s pharmaceutical giants, like Merck, GSK started R&D in the new subfield of computational quantum & molecular mechanics in drug development and ligand/protein interaction modelling.
BEFORE 1990s
Researcher’s relied upon traditional methods for drug development

1960s
Digital Computers Age materialized semi-empirical methods/Ab-Initio Theory (AM1, HF)

Since 1990s
Pharmaceutical industries routinely using computational QM tools for drug design.

1990s-Present
QM tools are powerful enough for results on larger and complex molecules. Routine use of force field for macro-molecules in super-computer.

Pre/Post WWII
Theorists study only very small molecules with paper-pencil methods.
Before Covid-19 Pandemic Bio-medical Research was Significantly Focusing on the Menace of Alzheimer’s Disease (AD) to Global and US Population

• In United States 5.3 million people are suffering from AD.
• Third leading cause of death after heart disease and cancer.
• No immediate remedy to improve the scenario.
• FDA has few approved drugs to mitigate the symptoms:
  Donepezil
  Galantamine
  Rivastigmine
  Memantine
Our Initial Research Projects

Donepezil, Rivastigmine and Galantamine bind and inhibit Acetylcholinesterase (AChE), a widely known enzyme involved in AD while Memantine binds to NMDA receptor to inhibit AD process via another mechanism.

Our research is focused on implementing Computational Quantum Mechanics to understand the energetics and origin of drug-related and spectroscopic properties of the molecules as revealed under QM tools.
HOMO and LUMO Orbitals and Energy Gap

- HOMO => Highest Occupied Molecular Orbital
- LUMO => Lowest Unoccupied Molecular Orbital
- HOMO-LUMO Energy Gap => Expressed in eV or Hartree and correlated with drug softness, hardness and chemical potential.

Computations have been performed via DFT and HF methods. Pople type basis function implemented which is based on following generic type orbitals =>

\[
\psi_{\xi,n,l,m}(r, \theta, \phi) = NY_{l,m}(\theta, \phi)r^{2n-2-l}e^{-\xi r^2}
\]

\[
\psi_{\xi,l_x,l_y,l_z}(x, y, z) = N x^{l_x} y^{l_y} z^{l_z} e^{-\xi r^2}
\]

\( l_x, l_y, l_z \) determine the type of orbital

\[ + \ \ \ \ \ \ \ \ \ \ \ = 6-31G^* \]

d-function is added to the \( p \) orbital
Fig.1. HOMO-LUMO orbital energy and electrostatic potential map of donepezil computed by DFT wB97X/6-31*G basis.
Fig.2. HOMO-LUMO orbital energy and electrostatic potential map of galantamine computed by DFT wB97X/6-31*G basis.
Fig. 3. HOMO-LUMO orbital energy and electrostatic potential map of rivastigmine computed by DFT wB97X/6-31*G basis.
Fig. 4. HOMO-LUMO orbital energy and electrostatic potential map of memantine computed by DFT wB97X/6-31*G basis.
Fig. 5. HOMO-LUMO ENERGY gap comparison via different semi-empirical and ab initio techniques implementing Spartan 16 (left) and Gaussian 16 (right) versions.
Fig. 6. 2D ligand interaction map of donepezil with AChE in X-ray structure (left) and ionization map of donepezil for transition state in water (right) computed via AM1 method.
Fig. 7. 2D ligand interaction map of galantamine with AChE in X-ray structure (left) and ionization map of galantamine for transition state in water (right) computed via AM1 method.
Fig. 8. Experimental and Computational $^1$H NMR of donepezil computed via DFT wB97X/6-31*G basis.
Fig. 9. Experimental and Computational $^1$H NMR of galantamine computed via DFT wb97X/6-31*G basis.
Fig. 10. Experimental and Computational $^1$H NMR of rivastigmine computed via DFT wB97X/6-31*G basis.
Fig. 11. Experimental and Computational $^1$H NMR of memantine computed via DFT wB97X/6-31*G basis.
Molecular Dynamics of Rivastigmine bound AChE => Can’t Explain the Mystery of Rivastigmine Break-up as Revealed in the X-ray Structure
Terms in Molecular Mechanics Force Field

We have carried out dihedral potential scan on the C=O bond of rivastigmine that links the two broken moieties as found in PDB crystal.

\[
E_{\text{pair}} = \sum_{\text{bonds}} K_r (r - r_{eq})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\varepsilon R_{ij}} \right]
\]
HARD-BONDED and SOFT-BONDED Terms in Molecular Mechanics Force Field

Force field of BONDED and NON-BONDED terms are connecting the atoms by a topology of network and in fact, NON-BONDED terms do link the atoms at longer geometrical distance and in practical simulations the terms are artificially truncated at 10-12 Å to save computational time; all the force field terms including traditional non-bonded terms basically a representation connectivity of atoms in a bonded topology.
Fig. 12. Torsion energy profile around –CO- bond of rivastigmine linking NAP and Carbamyle moieties.
Fig. 13. Torsion energy profile around –CO- bond of rivastigmine linking NAP and Carbamyle moieties.
Observation of quantum signature in rivastigmine chemical bond break-up and quantum energetics, spectral studies of anti-Alzheimer inhibitors

M Rejwan Ali\textsuperscript{a} and Mihaly Mezei\textsuperscript{b}

\textsuperscript{a}Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, \textsuperscript{b}Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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**ABSTRACT**

Semi-empirical calculations on the torsion potential for dihedral angle of rivastigmine linking NAP and Carbamyle moieties consistently show regions of several discontinuities and a cusp indicating molecular instability and eventual break-up of rivastigmine observed in the X-ray structure. The phenomena can be explained both by definition of large classical force or quantum nature of chemical bond break-up. Also, to better understand the molecular properties and quantum energetics of the inhibitor molecules, we have performed several ab initio based calculations on all four inhibitors at equilibrium geometry, in ground state and gas phase using the density functional theory level wb97X/6-31G* and HF/6-31G*. A number of properties like computational vibrational (IR), Raman and nuclear magnetic resonance (NMR) spectra as well as HOMO and LUMO orbital energies at optimized geometries have been computed by SPARTAN16 and Gaussian16 utilities. Also, the thermodynamic and QSAR properties of the inhibitors have been assessed and compared by a number of different semi-quantum, Hartree-Fock and density functional methods. The theoretical NMR and IR spectra have been benchmarked against experimental spectrum to compare and assess suitability of the computational methodologies and basis set levels for the calculations.

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**KEYWORDS**

Density functional theory (DFT); Hartree-Fock methods (HF); equilibrium and transition states geometries; quantum signature; torsional potential energy
1. In principle the observed quantum feature should not be just limited only in case of torsion potential, rather should appear in other force field or other MM potentials as a function of translational or rotational degree of freedom between nuclei.

2. Does the hypothesis work in case for other dissociative molecules? If so then in protein environment the methods can provide lot more detailed information about drug action via intermediate transition energy states and chemical bond-breaking mechanism.
The Answer is Yes! The Singularity Signature in Molecular Mechanics Potential is Indeed Controlled via Quantum Mechanics as to be reported in upcoming paper.

*Quantum Signature of H-bond Breaking in the Torsion Potential of Water Dimer*
Why the observations here are so significant?

1. Current Molecular Dynamics Simulations has limitations in capturing bond-breaking mechanisms events which are inherent shortcomings of the schemes. Just improving sampling methods in phase space will not be sufficient to overcome the limitations.

2. The findings here will open up new research of “FRACTURE FORCE FIELD/FRACTURE MOLECULAR MECHANICS” at interface of quantum mechanics and molecular mechanics based potential to explore chemical bond breaking mechanism processes.

3. In the experimental frontier, this findings should have footprints in single molecule force spectroscopy and other reaction-based laser spectroscopy.
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Questions ?