APPENDICES

APPENDIX A: Theoretical Background

The Theory of Quantum Chemical Calculations

1. The Schrödinger Equation

The quantum chemical methods are based on finding solutions to the Schrödinger equation on molecular orbital theory. Quantum mechanics explains how entities like electrons have both particle-like and wave-like characteristics. The time independent Schrödinger equation for a molecule (n-electron and N-nuclei system):

$$H\psi(\vec{r},\vec{R}) = E\psi(\vec{r},\vec{R}) \tag{1}$$

and the Hamiltonian is (in atomic units):

$$H = T + V$$

$$H = -\sum_{i=1}^{N}\frac{1}{2}\nabla_i^2 - \sum_{A=1}^{M}\frac{1}{2M_A}\nabla_A^2 - \sum_{i=1}^{N}\sum_{A=1}^{M}\frac{Z_A}{r_{iA}} + \sum_{i=1}^{N}\sum_{j>i}^{N}\frac{1}{r_{ij}} + \sum_{A=1}^{M}\sum_{B>A}^{M}\frac{Z_A Z_B}{R_{AB}} \tag{2}$$

where T and V are the kinetic and potential energy operators, respectively, which separate out the motion of the nuclei from the motion of the electrons, equation (2) can be rewritten as

$$H = -\sum_{A=1}^{M}\frac{1}{2M_A}\nabla_A^2 + H_{el} \tag{3}$$

This focus on the electronic Hamiltonian, H_{el}, and try to solve the electronic Schrödinger equation in the field of the fixed nuclei. The nuclear-nuclear repulsion term (the final in equation (2)) appears as a constant in H_{el}. Further assume the wave function $\psi(\vec{r},\vec{R})$ to be a product of an electronic and a nuclear part:

$$\psi(\vec{r},\vec{R}) = \psi_{elec}(\vec{r},\vec{R})\psi_{nucl}(\vec{R}) \quad (4)$$

The justification for this is that the electrons are much lighter than the nuclei. This is called the Born-Oppenheimer approximation. The parametric $\vec{R}$ dependence of ψ_{elec} arises since the electron distribution depends implicitly on the particular nuclear arrangement for the system under study. The nuclear wave function, ψ_{nucl}, describes the vibrational, rotational and translational motion of the nuclei. From (1), (3) and (4) can obtain;

$$H\psi(\vec{r},\vec{R}) = H\psi_{elec}(\vec{r},\vec{R})\psi_{nucl}(\vec{R}) = \left(-\sum_{A=1}^{M}\frac{1}{2M_A}\nabla_A^2 + H_{el}\right)\psi_{elec}(\vec{r},\vec{R})\psi_{nucl}(\vec{R})$$

$$= \left(-\sum_{A=1}^{M}\frac{1}{2M_A}\nabla_A^2 + E_{el}\right)\psi_{elec}(\vec{r},\vec{R})\psi_{nucl}(\vec{R}) = E\psi_{elec}(\vec{r},\vec{R})\psi_{nucl}(\vec{R}) = E\psi \quad (5)$$

The electronic wavefunction $\psi_{elec}(\vec{r},\vec{R})$ can be divided out from both sides of equation (5), provided that terms in $\nabla^2\psi_{elec}(\vec{r},\vec{R})$ are small, i.e. the electronic wavefunction changes slowly upon small displacements of the nuclear positions. Thus, if we neglect the influence of the nuclear derivative on the electron wave function (ψ_{el}) (i.e. the nuclei move slowly compared with the electrons) which can separate equation (5) into two equations, an electronic part:

$$H_{el}\psi_{el}(\vec{r},\vec{R}) = E_{el}(\vec{R})\psi_{el}(\vec{r},\vec{R}) \quad (6)$$

where

$$H_{el} = -\sum_{i=1}^{N}\frac{1}{2}\nabla_i^2 - \sum_{i=1}^{N}\sum_{A=1}^{M}\frac{Z_A}{r_{iA}} + \sum_{i=1}^{N}\sum_{j>i}^{N}\frac{1}{r_{ij}} + \sum_{A=1}^{M}\sum_{B>A}^{M}\frac{Z_A Z_B}{R_{AB}} \quad (7)$$

and a nuclear part:

$$H_{nucl}\psi_{nucl}(\vec{R}) = E\psi_{nucl}(\vec{R}) \tag{8}$$

where

$$H_{nucl} = -\sum_{A=1}^{M}\frac{1}{2M_A}\nabla_A^2 + E_{el}(\vec{R}) \tag{9}$$

2. Hartree Fock Theory

An exact solution to the Schrödinger equation is not possible for any but the most trivial molecular systems. However, a number of simplifying assumptions and procedures do make an approximate solution possible for a large range of molecules. To simplify the treatment further, the next step is to assume that the electrons are non-interacting. This implies that (apart from the constant nuclear-nuclear repulsion term) which can rewrite the total n-electron Hamiltonian as a sum of n one-electron Hamiltonians,

$$H_{el} = \sum_{i=1}^{N} h(i) \tag{10}$$

$$h(i) = \left(-\frac{1}{2}\nabla_i^2 - \sum_{A=1}^{M}\frac{Z_A}{r_{iA}}\right) \tag{11}$$

This is clearly an oversimplification, since have neglected the electron-electron repulsion term $\frac{1}{r_{ij}}$. Equation (10) defines the independent particle model. The one-electron Hamiltonians (equation (11)) are termed core-Hamiltonians, since the only interactions included are those between the electrons and the bare nuclei. Including an average interaction term in the $\{h(i)\}$, these become effective one-electron Hamiltonians. As a consequence of equation (10), the total wave function can be rewritten as a product of n single-particle wave functions,

$$\psi(\vec{r}) = \phi_1(\vec{r}_1)\phi_2(\vec{r}_2)...\phi_n(\vec{r}_n) \tag{12}$$

or, take the electron spin into account,

$$\psi = \chi_1(\vec{x}_1)\chi_2(\vec{x}_2)...\chi_n(\vec{x}_n) \tag{13}$$

The spin orbitals $\{\chi_i(\vec{x}_i)\}$ are the products of the spatial orbitals $\phi_i(\vec{r}_i)$ and the spin functions ($\alpha(\omega)$ and $\beta(\omega)$); $\vec{x}_i$ denotes both the space and spin coordinates of electron i. The total independent particle spin-orbital wave function (equation (13)) is called a Hartree-product. This is an eigenfunction of the n-electron model Hamiltonian defined in equation (10), and the corresponding eigenvalue is a sum of the single-particle spin-orbital energies,

$$E_{el} = \sum_{i=1}^{M} \varepsilon_i \tag{14}$$

A further requirement on the state wave function (13) is that it must be anti-symmetric with respect to the interchange of coordinate r (both space and spin) of any two electrons,

$$\left|\psi(\vec{x}_1, \vec{x}_{2,...,} \vec{x}_n)\right|^2 = \left|\psi(\vec{x}_2, \vec{x}_1, ..., \vec{x}_n)\right|^2 \tag{15}$$

$$\psi(\vec{x}_1, \vec{x}_2, ..., \vec{x}_n) = \pm\psi(\vec{x}_2, \vec{x}_1, ..., \vec{x}_n) \tag{16}$$

It is also possible to write equation (16) in terms of a $n \times n$ determinant, a Slater determinant, which has the same antisymmetric properties:

$$\psi = (n!)^{-1/2} \begin{vmatrix} \chi_1(\vec{x}_1) & \chi_2(\vec{x}_1) & \cdots & \chi_n(\vec{x}_1) \\ \chi_1(\vec{x}_2) & \chi_2(\vec{x}_2) & & \\ \cdots & & \cdots & \\ \chi_1(\vec{x}_n) & \chi_2(\vec{x}_n) & \cdots & \chi_n(\vec{x}_n) \end{vmatrix} \tag{17}$$

Which commonly is written like:

$$|\psi\rangle = (n!)^{-1/2} |\chi_1(\vec{x}_1), \chi_2(\vec{x}_2), \ldots, \chi_n(\vec{x}_n)\rangle \tag{18}$$

It can easily be verified that the Slater determinant obeys the Pauli principle, as the determinant then becomes zero. The pre-factor $(n!)^{-1/2}$ is a normalisation constant, and the $\{\chi_i\}$ are assumed orthonormal. By antisym-metrizing the Hartree-product (13) in the form of a Slater determinant (17), that the probability of finding any two electrons at the same point in space (i.e. $\vec{x}_1 = \vec{x}_2$) is zero.

Through the wave functions, the effective potential is generated. This potential allows to refine wave functions, from which a new potential is obtained. The procedure is repeated until a stable, self-consistent solution is reached. Due to the iterative procedure, the initial guess of the wave function, can of course be chosen ad hoc. However, the better the initial guess is, the easier it is to reach a stable solution to the eigenvalue problems in a relatively short computational time, is provided by the variation principle. This can be stated in the following way: Given any approximate wave function, satisfying the correct boundary conditions, the expectation value of the energy obtained by this wave function never lies below the exact energy of the ground state. Expressed in mathematical terms:

$$E_e = \frac{\langle \psi | H_e | \psi \rangle}{\langle \psi | \psi \rangle} \geq E_{exact} \tag{19}$$

A conceptually appealing model for the (trial) wave function of our molecular system, is to regard it as being constructed from molecular orbitals (MO). This

description in analogous to the model used for the atomic orbitals (AO). The MO's, the elements of the wave function determinant, are in turn thought of as being constructed by a Linear Combination of Atomic Orbitals (LCAO),

$$\psi_i^{MO} = \sum_{\mu} c_{\mu i} \phi_{\mu}^{AO} \tag{20}$$

The variational principle leads to following equations describing the molecular orbital expansion coefficients, c_{vi}, derived by Roothaan and by Hall:

$$\sum_{v=1}^{N} \left(F_{\mu v} - \varepsilon_i S_{\mu v}\right) c_{vi} = 0 \quad \mu = 1,2,..., N \tag{21}$$

Equation 21 can be rewritten in matrix form:

$$FC = SC\varepsilon \tag{22}$$

with

$$F_{\mu v} = H_{\mu v}^{core} + \sum_{\lambda\sigma} P_{\lambda\sigma}\left[(\mu v|\lambda\sigma) - \frac{1}{2}(\mu\lambda|v\sigma)\right] \tag{23}$$

$$F_{\mu v} = H_{\mu v}^{core} + G_{\mu v} \tag{24}$$

where $H_{\mu v}^{core}$, core-Hamiltonian matrix, defined as

$$H_{\mu v}^{core} = \int dr_1 \phi_{\mu}^{*}(1) h(1) \phi_v(1) \tag{25}$$

The matrix P is the density matrix or charge- and bond-order matrix,

$$P_{\mu v} = 2\sum_{a}^{N/2} C_{\mu a} C_{va}^{*} \tag{26}$$

The matrix S is the overlap matrix, indicating the overlap between orbitals.

$$S_{\mu\nu} = \int dr_1 \phi_\mu^*(1)\phi_\nu(1) \tag{27}$$

The term $(\mu\nu|\lambda\sigma)$ in Equation 23 signified the two-electron repulsion integrals, defined as

$$(\mu\nu|\lambda\sigma) = \int dr_1 dr_2 \phi_\mu^*(1)\phi_\nu(2) r_{12}^{-1} \phi_\lambda^*(2)\phi_\sigma(2) \tag{28}$$

The (initial) wave function is used to generate an effective potential, which apply this potential in order to refine the coefficient matrix. The modified MO's form the new input in the Roothaan or Pople-Nesbet (1986) equations, and a new potential is generated. The iterative procedure is repeated until convergence is reached, i.e. when the changes in energy and/or charge density in two subsequent iterations are below a pre-set threshold value.

Before a more technical description of the SCF-procedure is presented, first need to define a new transformation matrix X, used for orthogonalisation of the basis set. This orthogonalisation can be either symmetric or canonical. A symmetric orthogonalisation implies that X is formed through the relation

$$X = S^{-1/2} = Us^{-1/2}U^\tau \tag{29}$$

where S is the overlap matrix, U is an unitary matrix which diagonalizes S, and the diagonal matrix of the eigenvalues of S is given by the relations. In the canonical orthogonalisation procedure, X is instead given by

$$X = Us^{-1/2} \tag{30}$$

Consider a new coefficient matrix C' related to the old coefficient matrix C by

$$C' = X^{-1}C, \qquad C = XC' \tag{31}$$

where assumed that X possesses an inverse. Substituting $C = XC'$ into the Roothaan equations gives

$$FXC' = SXC'\varepsilon \tag{32}$$

Multiplying on the left by X^{τ} gives

$$\left(X^{\tau}FX\right)C' = \left(X^{\tau}SX\right)C'\varepsilon \tag{33}$$

if define a new matrix F^{τ} by

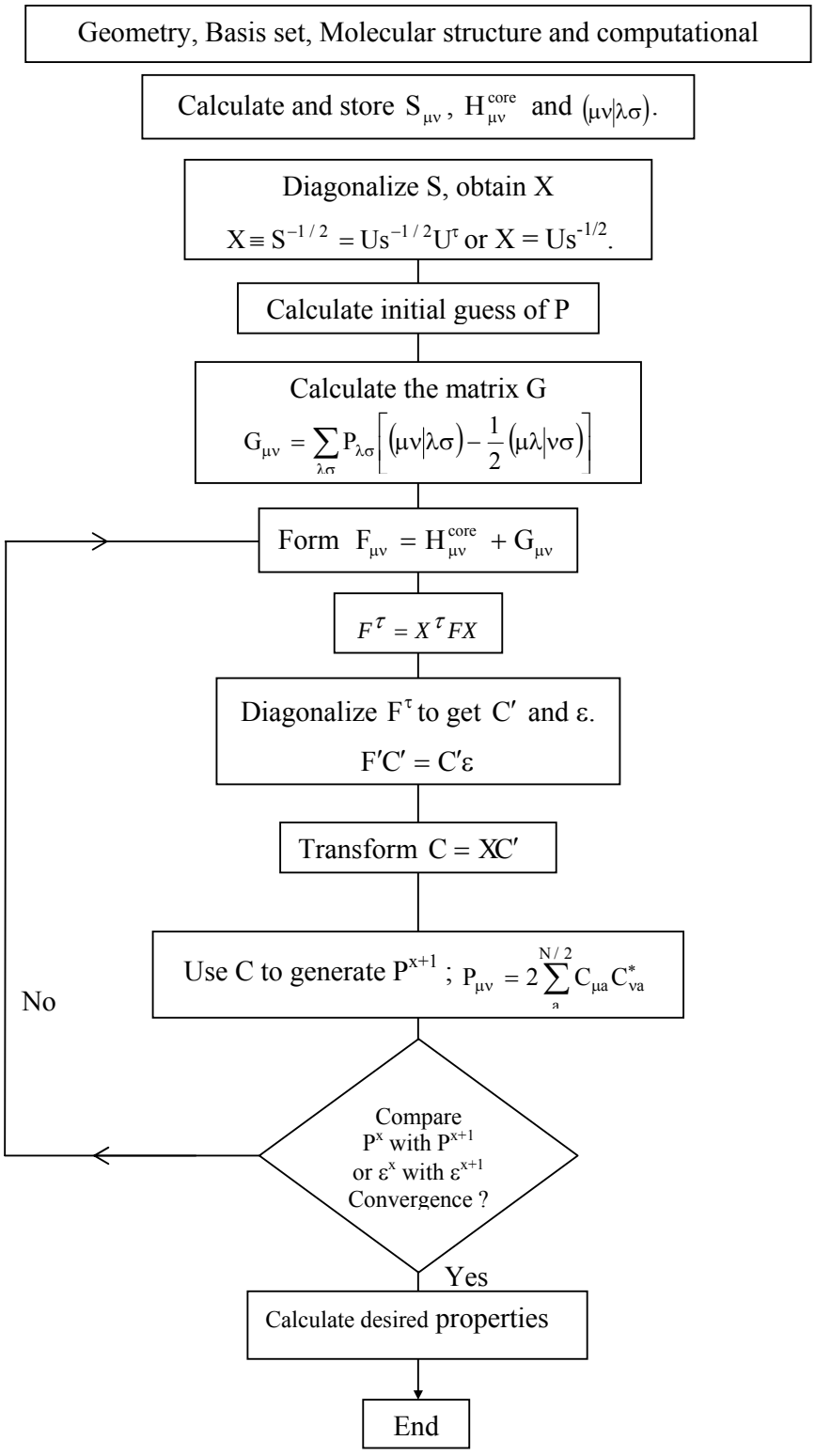
$$F^{\tau} = X^{\tau}FX \tag{34}$$

and use (27),then

$$F'C' = C'\varepsilon \tag{35}$$

The SCF procedure, outlined in Appendix figure I, is as follows

1. Specify a molecule (a set of nuclear coordinates $\{R_A\}$, atomic numbers $\{Z_A\}$, and number of electron N) and a basis set $\{\phi_\mu\}$.
2. Calculate all required molecular integrals, $S_{\mu\nu}$, $H_{\mu\nu}^{core}$ and $(\mu\nu|\lambda\sigma)$.
3. Diagonalize the overlap matrix S and obtain a transformation matrix X from either equation $X \equiv S^{-1/2} = Us^{-1/2}U^\tau$ or $X = Us^{-1/2}$.
4. Obtain a guess at the density matrix P.
5. Calculate the matrix G of equation $F_{\mu\nu} = H_{\mu\nu}^{core} + G_{\mu\nu}$ from the density matrix P and the two-electron integral $(\mu\nu|\lambda\sigma)$.
6. Add G to the core-Hamiltonian to obtain the Fock matrix $F = H^{core} + G$.
7. Calculate the transformed Fork matrix $F^\tau = X^\tau F X$
8. Diagonalize F^τ to obtain C' and ε.
9. Calculate $C = XC'$.
10. Form a new density matrix P from C using $P_{\mu\nu} = 2\sum_a^{N/2} C_{\mu a} C_{\nu a}^*$.
11. Determine whether the procedure has converged, i.e. determine whether the new density matrix of step (10) is the same as the previous density matrix within a specified criterion. If the procedure has not converged, return to step (5) with the new density matrix.
12. If the procedure has converged, then use the resultant solution, represented by C, P, F, etc., to calculate expectation values and other quantities of interest.



Appendix Figure A1 Schematic view of a Hartree-Fock self consistent field calculation.

3. Basis Set

The basis set most commonly used in quantum mechanical calculations are composed of atomic functions. The next approximation involves expressing the molecular orbitals as linear combinations of a pre-defined set of one-electron functions known as basis function. An individual molecular orbitals is defined as:

$$\phi_i = \sum_{\mu=1}^{N} c_{\mu i}\chi_\mu \tag{36}$$

where the coefficients $c_{\mu i}$ are known as molecular orbital expansion coefficients. The basis function $\chi_1 \ldots \chi_N$ are also chosen to be normalized. Gaussian-type atomic functions were used as basis functions. Gaussian functions have the general form

$$g(\alpha, \vec{r}) = cx^n y^m z^l e^{-\alpha r^2} \tag{37}$$

where $\vec{r}$ is of course composed of x, y, and z. α is a constant determining the size (radical extent) of the function. In Gaussian function, $e^{-\alpha r}$ is multiplied by powers (possibly 0) of x, y, and z and a constant for normalization, so that:

$$\int_{\text{allspace}} g^2 = 1 \tag{38}$$

Thus, c depends on α, l, m, and n.

Here are three representative Gaussian functional (s, p_y and d_{xy} types, respectively):

$$g_s(\alpha, \vec{r}) = \left(\frac{2\alpha}{\pi}\right)^{3/4} e^{-\alpha r^2}$$

$$g_y(\alpha, \vec{r}) = \left(\frac{128\alpha^5}{\pi^3}\right)^{1/4} ye^{-\alpha r^2}$$

$$g_{xy}(\alpha, \vec{r}) = \left(\frac{2048\alpha^7}{\pi^3}\right)^{1/4} xye^{-\alpha r^2} \qquad (39)$$

Linear combinations of primitive gaussians like these are used to form the actual basis functions; the latter are called contracted Gaussians and have the form

$$\chi_\mu = \sum_P d_{\mu p} g_p \qquad (40)$$

where the $d_{\mu p}$'s are fixed constants within a given basis set. Note that contracted functions are also normalized in common practice. A few commonly used basis sets are lists as following.

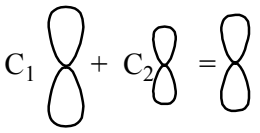
Minimal Basis Sets: Minimal basis sets contain the minimum number of basis functions needed for each atom, as in these examples:

H: 1s

C: 1s, 2s, $2p_x$, $2p_y$, $2p_z$

Minimal basis sets use fixed-size atomic-type orbitals. The STO-3G basis set is a minimal basis set (although it is not the smallest possible basis set). It used three gaussian primitives per basis function, which accounts for the "3G" in its name. "STO" stands for "Slater-type orbitals," and the STO-3G basis set approximates Slater orbitals with gaussian functions.

Split Valence Basis Sets



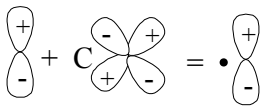
The first way that a basis set can be made larger is to increase the number of basis functions per atom. Split valence basis sets, such as 3-21G and 6-31G, have two (or more) sized of basis function for each valence orbital. For example, hydrogen and carbon are represented as:

H: 1s, 1s'
C: 1s, 2s, 2s', $2p_x$, $2p_y$, $2p_z$, $2p'_x$, $2p'_y$, $2p'_z$

where the primed and unprimed otbitals differ in size.

The double zeta basis sets, such as the Dunning-Huzinaga basis set (D95), form all molecular orbitals from linear combinations of two sized of functions for each atomic orbital. Similarly, triple split valence basis sets, like 6-311G, use three sizes of contracted functions for each orbital-type.

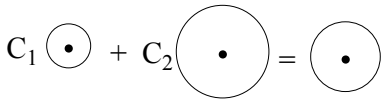
Polarized Basis Sets



Split valence basis sets allow orbitals to change size, but not to change shape. Polarized basis sets remove this limitation by adding orbitals with angular momentum beyond what is required for the ground state to the description of each atom. For example, polarized basis sets add d functions to carbon atoms and f functions to transition metals, and some of them add p functions to hydrogen atoms.

So far, the only polarized basis set 6-31G(d) is used. Its name indicates that it is the 6-31G basis set with d functions added to heavy atoms. This basis set is becoming very common for calculations involving up to medium-sized systems. This basis set is also known as 6-31G*. Another popular polarized basis set is 6-31G(d,p), also known as 6-31G**, which adds p functions to hydrogen atoms in addition to the d functions on heavy atoms.

Diffuse Functions



Diffuse functions are large-size versions of s- and p- type functions (as opposed to the standard valence-size functions) which allow orbitals to occupy a larger region of space. Basis sets with diffuse functions are important for systems where electrons are relatively far from the nucleus: molecules with lone pairs, anions and other systems with significant negative charge, systems in their excited states, systems with low ionization potentials, descriptions of absolute acidities. The 6-31+G(d) basis set is the 6-31G(d) basis set with diffuse functions added to heavy atoms. The double plus version, 6-31++G(d), adds diffuse functions to the hydrogen atoms as well. Diffuse functions on hydrogen atoms seldom make a significant difference in accuracy.

High Angular Momentum Basis Sets

Even larger basis sets are now practical for many systems. Such basis sets add multiple polarization functions per atom to triple zeta basis set. For example, the 6-31G(2d) basis set adds two d functions per heavy atom instead of just one, while the 6-311++G(3df,3pd) basis set contains three sets of valence region functions, diffuse functions on both heavy atoms and hydrogens, and multiple polarization funtions:3 d functions and 1 f function on heavy atoms and 3 p functions and 1 d function on

hydrogen atoms. Such basis sets are useful for describing the interactions between electrons in electron correlation methods.

4. Semi-empirical Calculations

Because both time and storage requirements of an *ab initio* Hartree-Fock calculation increase as the fourth power of the number of basis functions, calculations on large molecules even with the smallest basis sets are apt to be prohibitive. In such situations, the NDDO (neglect of diatomic differential overlap) formalism affords practical methods for calculating the electronic structure of large systems. Here, only one- and two-centre, two-electron integrals are considered, and the Hartree-Fock matrix, consists only of elements for which basis functions μ and ν are on the same atom, and basis functions λ and σ are on another atom. The individual terms are defined below (the sum α is over all other atoms).

$$
\begin{aligned}
F_{\mu\mu} &= H_{\mu\mu}^{core} + \sum_{\nu} P_{\nu\nu}\left[\langle\mu\mu|\ \nu\nu\rangle - \langle\mu\nu|\mu\nu\rangle\right] + \sum_{\delta}\sum_{\lambda}\sum_{\sigma} P_{\lambda\sigma}\langle\mu\mu|\nu\nu\rangle \\
F_{\mu\nu} &= H_{\mu\nu}^{core} + P_{\mu\nu}\left[3\langle\mu\nu|\ \mu\nu\rangle - \langle\mu\mu|\nu\nu\rangle\right] + \sum_{\delta}\sum_{\lambda}\sum_{\sigma} P_{\lambda\sigma}\langle\mu\nu|\lambda\sigma\rangle \\
F_{\rho\lambda} &= \beta_{\rho\lambda} - \frac{1}{2}\sum_{\nu}\sum_{\sigma} P_{\lambda\sigma}\langle\mu\nu|\lambda\sigma\rangle \qquad (41)
\end{aligned}
$$

The elimination of three- and four-centre integrals greatly reduces the time and storage requirements for an NDDO calculation (which now increase as the square of the number of atoms) relative to that for a full Hartree-Fock treatment.

Three levels of NDDO theory are included in *SPARTAN'S SEMI EMPIRICAL* module: MNDO Modified Neglect of Diatomic Overlap

AM1 Austin Method 1

PM3 MNDO Parameterization Method 3

In all of these formalisms, only the valence electrons are considered. The one-electron terms are given by,

$$H_{\mu\nu}^{core} = U_{\mu\nu} - Z_A \sum_{B \neq A} Z_B \langle \mu\nu | \delta\delta \rangle \qquad (42)$$

Here, μ and ν are located on atom A and the summation is over all other atoms. Uνν is related to the binding energy of an electron in atomic orbital ν, and is determined from spectroscopic data. Uνμ is set to zero for $\nu \neq \mu$. The second term in equation 42 represents the attraction on an electron on atom A from the nuclear framework. The two center integral involves only the s function on atom B. Z_A is the charge of atom A without its valence electrons.

All one-centre, two-electron integrals (νν|μμ) and (νμ|νμ) are fitted to spectroscopic data. The two-centre, two-electron repulsion integrals (νμ|λσ) are approximated by classical multipole-multipole charge interactions between atoms A and B. The multipole charge separations within an atom are treated as adjustable parameters, i.e. optimized to fit the experimentally derived one-centre integrals.

The βμλ terms appearing in the Fock matrix (equation 41) are the one-electron, two-centre core resonance integrals and are approximated as,

$$\beta_{\rho\lambda} = \frac{\beta_\rho + \beta_\lambda}{2} S_{\rho\lambda} \qquad (43)$$

where $S_{\alpha\beta}$ is the overlap integral between Slater orbitals α and β, and $\alpha\beta$ and $\beta\alpha$ are adjustable parameters optimized using experimental thermo chemical data for simple molecules. Because all of the adjustable parameters are rooted in experimental data, these methods are known as semi-empirical. As in *ab initio* Hartree-Fock calculations, an SCF procedure is used to converge on a density matrix, and the electronic energy.

The three methods differ only in the core-repulsion terms (they also differ in the detailed parameterization). Core repulsion includes nuclear repulsion and non-valence electron-electron repulsion, which are not explicitly considered in the

calculation of the electronic energy. In the MNDO model, the core repulsion energy is given by,

$$E^{CR} = \sum_{A \neq B} \sum_{B \neq A} Z_A Z_B \langle \delta(A) | \delta(B) \rangle \left(e^{-\sigma_a E_{AB}} + e^{-\sigma_B E_{AB}} \right) \qquad (44)$$

where Rαβ is the internuclear distance and αA and αB are adjustable parameters fit to give the correct empirical behavior. Details are provided in the original papers. MNDO tends to overestimate core repulsion between two atoms at van der Waals distances. For this reason, the AM1 model was developed.

In AM1 a sum of Gaussians is employed to better represent the core repulsion behaviour at van der Waals distances. PM3 uses a similar core repulsion function, but differs in the parameterisation procedure.

One advantage of methods parameterised using experimental data is their implicit inclusion of electron correlation effects. However, dependence on experimental data means that semi-empirical methods would not be expected to perform well on unusual types of molecules for which no data are available from which to construct parameters.

APPENDIX B: Presentation and Proceeding

Poster Presentation

Pongthep Prajongtat, Darinee Sae-Tang, Phronphimon Maitarad, Patchreenart Saparpakorn and Supa Hannongbua. Interaction Energies of Oxaloacetate and Binding Site of Phosphoenolpyruvate Carboxykinase (PEPCK) by MP2 Calculations. The abtract of Pure and Applied Chemistry International Conference (PACCON 2008), Sofitel Centra Grand Bangkok, Bangkok, Thailand, Jan 30-Feb 1 2008.

Interaction Energies of Oxaloacetate and Binding Site of Phosphoenolpyruvate Carboxykinase (PEPCK) by MP2 Calculations

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ABSTRACT

The electronic and structural properties of phosphoenolpyruvate carboxykinase (PEPCK) enzyme complexed with oxaloacetate (OAA) were studied. Surrounding 13 amino acids in the radius of about 7 Å centered at oxaloacetate were selected in this study. Interaction energies between ligand and individual amino acids were calculated at the MP2/6-31G (d, p) level of theory with BSSE correction. The calculated interaction energies of Arg87, His264 and Asp311 were -3.06, -6.23 and -3.40 kcal/mol, respectively. The obtained results showed that Arg87, His264 and Asp311 strongly bind to the ligand via hydrogen bonding interaction.

INTRODUCTION

Hydrazine sulfate can be used for cancer treatment . It can inhibits gluconeogenesis a process synthesizing glucose from non-carbohydrate substance.

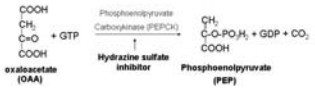


Figure1 Inhibition of one step in gluconeogenesis by hydrazine sulfate

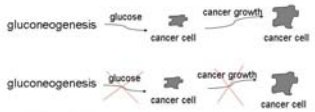


Figure2 Inhibition of gluconeogenesis means that no feeding cancer cells and may stop cancer growth.

RESULTS AND DISCUSSION

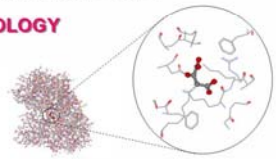
Table1 Interaction energies of oxaloacetate with individual amino acids (in kcal/mol), by MP2/6-31G (d, p) level of theory

Amino acid	Interaction energy (BSSE), kcal/mol
ARG 87	-3.06
GLY 236	-0.32
GLY 237	-0.41
LYS 243	-0.79
LYS 244	1.31
HIS 264	-6.23
SER 286	-1.91
ALA 287	0.08
ASP 311	-3.40
PHE 333	-0.23
GLY 334	0.11
ARG 405	0.82
PHE485	-0.52

CONCLUSION

The obtained results of interaction energies indicated that Arg87, His264 and Asp311 demonstrate stronger interactions than other amino acids.This indication can be explained by hydrogen bond interactions between oxaloacetate and these three amino acids. A further work will be studied on hydrazine sulfate which is a noncompetitive inhibitor of PEPCK.

METHODOLOGY



PEPCK complexed with OAA
(code 2QF1)

Figure3 surrounding 13 amino acids in the radius of about 7 Å centered at OAA were selected in this study.

After adding hydrogen atoms to the structure, PM3 method was used for optimization.

The interaction energies between oxaloacetate and individual amino acids were calculated from the optimized complex structure at the MP2/6-31G (d, p) level with the basis set superposition error (BSSE) correction.

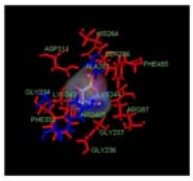


Figure4 Graphical representation of the attractive (red) and repulsive (blue) interactions between OAA and individual amino acids of PEPCK

Figure5 Graphical representation of the hydrogen bonds between OAA and three main amino acids, (1) = 2.46 Å, (2) = 2.69 Å and (3) = 2.53 Å

ACKNOWLEDGMENTS

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The Development and Promotion of Science and Technology Talent Project (DPST)

RESEARCH INTERESTS

- Interaction Energies of Oxaloacetate and Binding Site of Phosphoenolpyruvate Carboxykinase (PEPCK) by MP2 Calculations
- Theoretical Investigation on Inhibition of Gluconeogenesis by Hydrazine Sulfate Used to Treat Cancer Related Cachexia

PROCEEDING

Pongthep Prajongtat, Darinee Sae-Tang, Phronphimon Maitarad, Patchreenart Saparpakorn and Supa Hannongbua. Interaction Energies of Oxaloacetate and Binding Site of Phosphoenolpyruvate Carboxykinase (PEPCK) by MP2 Calculations. In the Proceeding of Pure and Applied Chemistry International Conference (PACCON 2008), Sofitel Centra Grand Bangkok, Bangkok, Thailand, Jan 30-Feb 1 2008.

Interaction Energies of Oxaloacetate and Binding Site of Phosphoenolpyruvate Carboxykinase (PEPCK) by MP2 Calculations

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ABSTRACT

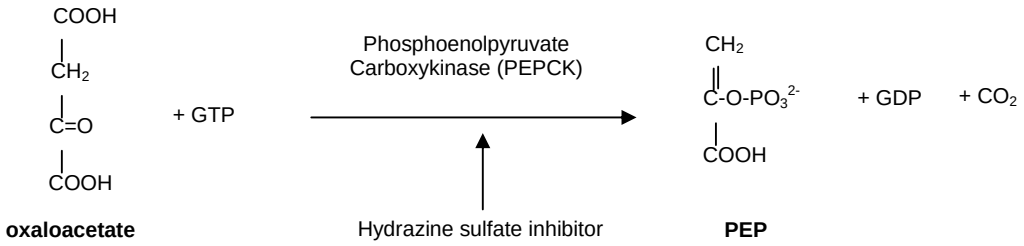
The electronic and structural properties of phosphoenolpyruvate carboxykinase (PEPCK) enzyme complexed with oxaloacetate (OAA) were studied. Surrounding 13 amino acids in the radius of about 7 Å centered at oxaloacetate were selected in this study. Interaction energies between ligand and individual amino acids were calculated at the MP2/6-31G (d, p) level of theory with BSSE correction. The calculated interaction energies of Arg87, His264 and Asp311 were -3.06, -6.23 and -3.40 kcal/mol, respectively. The obtained results showed that Arg87, His264 and Asp311 strongly bind to the ligand via hydrogen bonding interaction.

Keywords : Gluconeogenesis, interaction energy, noncompetitive inhibitor, hydrazine sulfate

1. INTRODUCTION

The conventional treatments for cancer such as chemotherapy and radiation therapy always damage the healthy cells because they can not distinguish between cancer cells and healthy cells. So the unconventional methods for example hydrazine sulfate, green tea, 714-X, essiac and etc. can be used for cancer treatment (1). Hydrazine sulfate which is developed by Dr. Joseph Gold, an American research oncologist now at the Syracuse Cancer Research Institute is the most effective inhibitor that can inhibit gluconeogenesis by blocking the conversion of oxaloacetate to phosphoenolpyruvate (PEP) through phosphoenolpyruvate carboxykinase (PEPCK) inhibition (2, 3). Gluconeogenesis requires a lot of energy for glucose synthesis that the excessive gluconeogenesis is a major determinant of cancer related cachexia. Gold reported that hydrazine sulfate can improve appetite and reduced weight loss (4, 5). In addition, hydrazine sulfate could inhibit tumour growth and increase survival in rats with transplanted tumours (6).

Inhibition of PEPCK enzyme can interfere gluconeogenesis and may be useful in the treatment for cancer related cachexia. In this study we have performed an in-dept modeling analysis of inhibition of PEPCK by hydrazine sulfate



2.COMPUTATIONAL DETAILS

2.1 System studied

The present studies investigate the electronic and structural properties of phosphoenolpyruvate carboxykinase (PEPCK) enzyme complexed with oxaloacetate (OAA). This structure was obtained from protein data bank (code 2QF1). Surrounding 13 amino acids in the radius of about 7 Å centered at oxaloactate were selected in this study. The N and C termini of the residues were capped with an acetyl group (CH_3CO-) and methyl amino group (-$NHCH_3$), respectively. All side chains of Asp, Arg and Lys were assumed to be neutral form. Hydrogen atoms were added to the X-ray structure by using Sybyl7.2 program. However, all heavy atoms of the ligand-binding site complex were fixed at the positions taken from the X-ray protein data bank. The added hydrogen atoms were adjusted to the initial complex structure by the geometry optimization using the PM3 method in the Gaussian 03 program package (7).

2.2 Interaction energies calculations

The interaction energies between oxaloacetate and individual amino acids (defined as X_i) were obtained by the single point energy calculations at the MP2/6-31G(d,p) level of theory with the basis set superposition error (BSSE) correction The interaction energy (INT) is defined as

$$INT_{(OAA\text{-}Xi)} = E_{(OAA\text{-}Xi)} - [E_{(OAA)} + E_{(Xi)}]$$

Where $E_{(OAA\text{-}Xi)}$ is the pair-summed energy of each amino acids X_i with OAA, $E_{(OAA)}$ and $E_{(Xi)}$ are the energies of OAA and individual amino acid, respectively.

3. RESULTS AND DISCUSSION

The calculated interaction energies between oxaloacetate and individual amino acids are given in Table 1. They can be presented by graphical representation in Figure 1. The obtained results show that there are more attractive interactions between oxaloacetate and amino acids surrounding the binding site of the PEPCK enzyme. Because the high interaction energies of Arg87, His264 and Asp311 are -3.06, -6.23 and -3.40 kcal/mol, respectively, these three amino acids are the main contributors in this system. So we focus on the conformation of these three amino acids and oxaloacetate and we found that there are hydrogen bonds occurred. The observable distances of the hydrogen bonds are shown in Table 2 and demonstrated in Figure 2.

Table 1. Interaction energies of oxaloacetate with individual amino acids (X_i) (in kcal/mol),
calculated at the MP2/6-31G (d, p) level of theory

Amino acid	Interaction energy (BSSE), kcal/mol
Arg87	-3.06
Gly236	-0.32
Gly237	-0.41
Lys243	-0.79
Lys244	1.31
His264	-6.23
Ser286	-1.91
Ala287	0.08
Asp311	-3.40
Phe333	-0.23
Gly334	0.11
Arg405	0.82
Phe485	-0.52
Total	-14.55

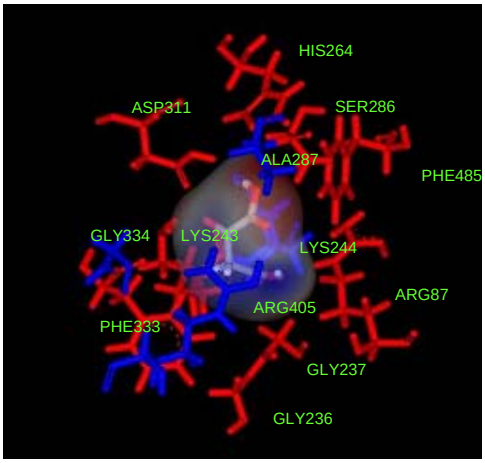


Figure 1. Graphical representation of the attractive (red) and repulsive (blue) interactions between oxaloacetate and individual amino acids (X_i) of PEPCK

Table 2. Hydrogen bond distances* between oxaloacetate and three main amino acids

Amino acids	H---Y distance (Å)
Arg87	2.46
His264	2.69
Asp311	2.53

* defined between H atom and heavy atom (Y) distance

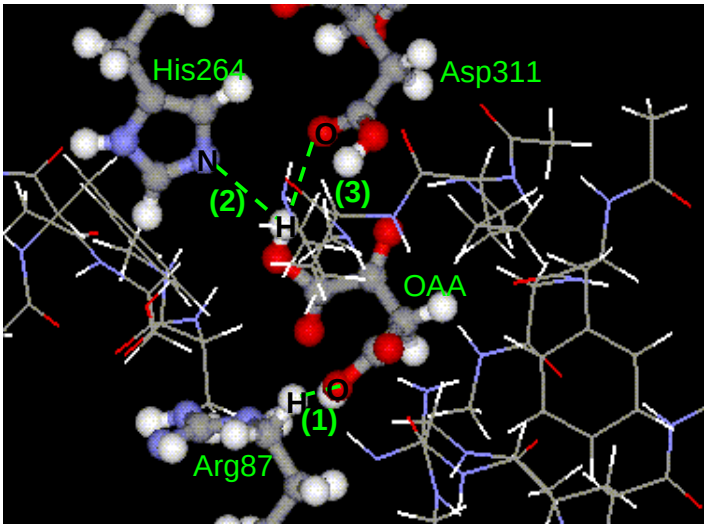


Figure 2. Graphical representation of the hydrogen bonds between oxaloacetate and three main amino acids, (1) = 2.46 Å, (2) = 2.69 Å and (3) = 2.53 Å

Therefore, it is important to note that these hydrogen bond interactions play an important role in the binding of oxaloacetate in the bound PEPCK complex. If we change

some properties of these interactions by using noncompetitive inhibitor, the enzymatic reaction may not occur

4. Conclusions

The total 13 piar-summed energies were used to describe the interaction energy of oxaloacetate and the PEPCK binding site, which is about -14.55 kcal/mol. The obtained results of interaction energies indicated that Arg87, His264 and Asp311 demonstrate stronger interactions than others (-3.06, -6.23 and -3.40 kcal/mol, respectively). These interaction energies were mainly contributed by the hydrogen bonding interaction between oxaloacetate and Arg87, His264, and Asp311. A further work will be studied on hydrazine sulfate which is a noncompetitive inhibitor of PEPCK. This noncompetitive inhibitor should change some properties of the complex between PEPCK and oxaloacetate.

5. Acknowledgments

The Development and Promotion of Science and Technology Talent Project (DPST), Thailand and the Thailand Research Fund (RSA 5080005) are gratefully acknowledged for financial support. Laboratory for Computational and Applied Chemistry (LCAC), KU for providing research facilities.

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