JST Basic Research Programs

C R E S T

(Core Research for Evolutional Science and Technology)

Annual Report for Research Work in the fiscal year 2006

Research Area :

High Performance Computing for Multi-scale and Multi-physics Phenomena

Research Theme

A program system with hierarchical quantum chemical methods for accurate calculations of biological molecules

Name of Research Director, Belonging and Title:

Seiichiro Ten-no, Nagoya university, Associate Professor

§1. Outline of Research Work

Based on highly accurate ab initio theory, we are developing novel computational methods for biological molecules with quantum mechanical (QM/QM) and molecular mechanical (QM/MM) hierarchies. Reliable and robust simulation techniques granted by the studies of low scaling and novel wave function methods along with the cultivation of new molecular properties will provide the bases of modern science and technology which enable us to study electronic states, dynamics, and inspections of properties transcending the limitation of a field.

§2. Content of Research Work

The project is focused on the five core subjects; 1) fundamental scaling, 2) novel wave function methods, 3) biological probes, 4) dynamics, and 5) installation, as explained in the following. (the name of a head in each section is underlined)

1) Fundamental Scaling [Koch, Ten-no, Sugita]

The section aims at improving the fundamental scaling of quantum chemical calculations. As the computational costs in the usual ab initio methods increase as 4-7th power in molecular size, circumventing the steep barriers is crucial in the project.

Koch has implemented a new Cholesky decomposition which is specifically oriented to the exchange integrals. The new method enables us to treat very large molecules at HF or hybrid DFT with exact exchange. Dr. Jung and Ten-no (in cooperation with Choi and Sugita) have developed a novel QM/MM method based on the generalized hybrid orbitals (GHO) with fractional occupation numbers in auxiliary orbitals. The GHO energy and its gradient are made available in the GELLAN program package. The methods will be utilized in the calculations of excited states and QM/MM dynamics simulations under protein environments.

2) Novel wavefunction methods [Ten-no, Nakano, Hada, Koch]

Novel wavefunction methods oriented to biological molecules are developed. The subject involves the construction of QM/QM hierarchies, multi-reference methods, and relativistic quantum chemistry.

Koch, Boman, and Ten-no have developed QM/QM hierarchical methods. It is shown that the choice of the perturbation spanned by active atomic orbitals leads to preferable results within the SCF-MP2 hybrid method. Based on the Hamiltonian partitioning, the QM/QM program will be extended to the CCSD-MP2 and CCSD-CC2 hierarchical methods. The latter makes it possible to calculate accurate excitation energies of large molecules.

Nakano and his group members have developed a program that optimizes molecular orbital coefficients as well as the configuration interaction (CI) coefficients, on the basis of the formalism and algorithm proposed in 2005. In addition, they implemented a complete active space self-consistent field (CAS-SCF) program into GELLAN. CAS-SCF is a most frequently used

version of the MC-SCF method. They also developed a new efficient program of the multiconfigurational perturbation theory (MC-QDPT) using an algorithm with Hamiltonian matrix elements. This program is 2-10 times more efficient than our previous program based on the diagrammatic algorithm. The new algorithm is also effective for the relativistic version of MC-QDPT, as well as non-relativistic MC-QDPT. The program is going to be implemented into GELLAN in 2007. Using the above methods, Nakano et al. have studied (1) molecular and electronic structures of hybrid-phosphorus-containing porphyrin, (2) electronic excited states of linear merocyanines, (3) excitation spectra of heavy-atom-containing complexes, etc. They clarified (1) the substituent effect for the B and Q absorption bands of hybrid-phosphorus-containing porphyrin, (2) the novel size-dependence of the absorption wave length and the electronic states for the linear morocyanines, and (3) the details of the d-d excitation spectra of some complexes including platinum atom.

Hada and coworkers developed a computer code of the relativistic quantum-chemical calculations based on the finite-order Foldy-Woutheysen (IOFW) transformation. It was confirmed that the calculations are equivalent in energy to the 1-electron Dirac calculations. They applied the IOFW method incorporated with some relativistically corrected 2-electron terms to many electron molecules containing heavy and super-heavy elements. They found that the lowest-order Breit-Pauli 2-electron terms breaks down in heavy elements, while the 1^{st}-order free-particle FW 2-electron terms are accurate in energy even in super-heavy elements.

3) Biological probes [Hada, Fujii, Koch]

Spectroscopic proves useful in biological materials are explored both from computational and experimental points of view.

(1) Magnetic Properties (Hada)

(a)CD spectra

Hada and coworkers calculated CD spectra of chalcogen and dichalcogen compounds (chalcogen = S, Se, Te) by the SAC and SAC-CI methods. The results reproduced adequately some empirical rules such as C_2-rule, quadrant-rule, and the trends of chalcogens. Using these calculated results, they made clear assignments of observed peaks, some of which were different from the experimentally suggested assignments. Relativistic effects of CD spectra were significant in case of Te compounds.

(b)MCD spectra

They also calculated magnetic CD spectra of halogen compounds. The relativistic effects were essentially important in both the peak positions and peak strengths.

(c)Molecular Magnetizability

Hada developed the time-dependent generalized unrestricted Hartree-Fock (TGUHF) method and

calculated the molecular magnetizabilities of XH_2 (X=O, S, Se, Te) and some open-shell molecules. The diamagentic part of magnetizability was affected by the scalar relativistic terms due to the orbital shrink, while the paramagnetic part was affected by the spin-dependent term due to the spin-orbit interaction.

(2) Analyses of Metal Complexes in Biological Systems (Hada)

(a) Drastic changes in paramagnetic C-13 NMR chemical shifts of Fe-bounded small molecules located in various biological environments were observed experimentally. These chemical shifts were well reproduced from the electron spin densities calculated by the SAC-CI method. The side-chains on the porphyrin ring made the porphyrin ring ruffled and therefore this ruffled ring affected significantly the electron spin density and then the C-13 chemical shifts.

(b)The C-13 NMR spectra of CO bounded to metal of Imidazole-matal complexes (metal = Cr^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}) were investigated. The C-13 chemical shifts were explained reasonably by the d-d* transition mechanism which has been proposed previously for metal chemical shifts.

(c)The chemical reaction mechanisms in metabolism of heme were analyzed using a model porphyrin compound. We calculated the electron-attached states of this model compound including the ground and excited states. We found that the electron-transfer occurs by changing molecular structure and it makes the reaction proceed to the next step.

(3) Structural and functional relationship of copper proteins and copper complexes (Fujii)

Fujii has carried out ^{63}Cu NMR spectroscopic studies of copper(I) complexes with various N-donor tridentate ligands. He found that when CO is bound the above tridentate copper(I) complexes, the ^{63}Cu NMR signals become much sharper and show a large downfield shift, compared to those for the corresponding acetonitrile complexes. Temperature dependence of ^{63}Cu NMR signals for these copper(I) complexes show that a quadrupole relaxation process is much more significant to their ^{63}Cu NMR line widths than a ligand exchange process. The findings indicate that CO complexation make ^{63}Cu NMR spectroscopy much more useful for Cu(I) chemistry.

4) Dynamics [Nakano, Sugita, Yamato]

Interfaces between electronic structure theory and molecular simulations are constructed.

Yamato has studied the signal transduction of photoreceptor proteins. The peak in the solar spectral intensity at ground level occurs in the visible region (at 500 nm), where human vision has maximal sensitivity, determined by the optical property of the visual pigment. In general living organism adapt to a diverse range of environments by modulating the optical absorption spectra upon mutations via the protein-chromophore interaction. For example, the λ_{max} of different visual pigments cover a broad range of wavelength from 360 to 560 nm.

Various theoretical studies have been carried out on the spectral tuning mechanism of photosensory receptors. The theoretical prediction of the λ_{max} is a challenging problem for number of reasons: (a) the complexity of the system (b) involvement of the electronic excited state, and (c)

the existence of multiple minium energy conformations. To overcome these difficulties, we developed a self-consistent hierarchical approach, called the Multi-Layer Self-Consistent Molecular Orbital (MLSCMO) method. By using this method, we found a linear correlation between the theoretically predicted shifts and experimentally observed absorption spectra for various mutants of photoactive yellow protein, a small photosensory receptor. Excitation energies of mutants were evaluated by the combination of the high level ab initio calculation for the chromophore inside and the low level ab initio calculation for the surrounding protein environment. Importantly, the electronic states of these two regions were treated both as variables and they are solved consistently to each other. The protein-chromophore interaction has been accurately reproduced by this method.

Yamato has also reported a theoretical/computational analysis of the energy flow relevant to the long-range intramolecular crosstalk between different regions in a photosensory receptor, photoactive yellow protein (PYP). To analyze the energy flow in atomic detail, we derived a theoretical expression for the interresidue energy conductivity in terms of the time-correlation function of the interatomic energy flux. The values of energy conductivities were numerically evaluated by using a long molecular dynamics simulation trajectory of the PYP molecule in the aqueous solution environment. As a result, we detected several pathways for energy transfer relevant for the long-range intramolecular signalling of PYP.

Sugita studied the effect of phosphorylation on the conformation of phospholamban (PLN), which regulates the functions of the calcium pump in sarcoplasmic reticulum. By performing simulations of phosphorylated PLN (pPLN) and unphosphorylated PLN (PLN) in solution, he showed that pPLN is more flexible than PLN, forming weak salt bridges with the phosphorylation site. The result agrees with the structural data obtained with fluorescence resonance electron transfer (FRET) and nuclear magnetic resonance (NMR).

5) Installation [Ten-no, Nakano, Koch]

Computational methods developed in the research project will be collectively installed in the hierarchical quantum chemistry package, GELLAN.

In addition to the above-mentioned developments, the MP2-F12 method, various coupled-cluster models, molecular integrals for energy derivatives were implemented into the GELLAN program in 2006.

§3. Formation of Research Work

1. Nagoya university (Information Science)

Director: Seiichiro Ten-no

Items of Research:

- Supervise the development of the GELLAN program package
- Hybrid coupled-cluster methods (in collaboration with the NTNU group)
- Novel QM/MM methods (with the groups in the Nagoya university (phys), the university of Tokyo, and Kyungbuk University)

2. Kyusyu university

Main Research Collaborator: Haruyuki Nakano

- The development of the contracted multiconfigurational (MC) self-consistent field (SCF) / configuration interaction (CI) method, the merit of which is that the number of electron configurations scales linearly with the system size, and highly accurate multiconfigurational quasi-degenerate perturbation theory using the contracted MC-SCF/CI reference functions.
- The implementation of ab initio direct dynamics, especially the direct CASVB dynamics that can hold clear valence bond resonance structure picture.
- The algorism and program development of the above-mentioned (1 and 2) methods, and implementation into the GELLAN program.

3. Norwegian University of Science and Technology (NTNU, Norway)

Main Research Collaborator: Henrik Koch

- Reduced scaling methods with compact representations of excitation operators in MP2/CC2/CCSD(T) making use of the scarcity of the electron repulsion integrals and the Cholesky decomposition technique.
- Development of fast linear response theories for excited states of biological molecules.

4. Tokyo Metropolitan University

Main Research Collaborator: Masahiko Hada

- Development of a new method for calculating the NMR and MCD spectra of molecules containing heavy elements, based on the relativistic IOFW theory incorporated with the energy-gradient method and the perturbation term of a magnetic field.
- The electronic and NMR spectra of metal-porphyrins in heme-proteins and various chemical environments of biological systems.
- Analysis of NMR chemical shift and metabolism reaction in a model system of metal-enzymes and especially a Cu-imidazole system.

5. Nagoya University (Physics)

Main Research Collaborator: Takehisa Yamato

- Generating statistical ensemble of photoreceptor proteins by molecular dynamics simulation.
- Study of the excited state and photochemical properties of large photoactive proteins by the multiconfigurational self-consistent field theory.

6. University of Tokyo

Main Research Collaborator: Yuji Sugita

- QM/MM methodologies for chemical reactions occurred in proteins (in collaboration with the Nagoya university group). In the method, the reaction centers of proteins are treated by quantum chemical methods, whereas the rest of the proteins and solvents are simulated by classical MD simulations.
- Simulation of a whole reaction cycle of an enzyme by the QM/MM MD simulations for better understanding of biochemical functions of enzymes.

7. Kyungbuk University (Korea)

Main Research Collaborator: Cheol H. Choi

- Acceleration of the Fock matrix engine by FMM
- Development of CGDMS and novel SCF method with a quadratic convergence.
- QM/MM and QM/QFMM methods (in collaboration with Nagoya university)

8. Natural Institute of Natural Sciences

Main Research Collaborator: Hiroshi Fujii

- The group is studying structure-function relationship of metalloproteins from multi-nuclear NMR spectroscopy to develop new NMR methodology for studying protein function.
- To get more insight into ^{63}Cu NMR spectroscopy, they prepare model complexes of copper metalloproteins and measure ^{63}Cu NMR spectra of these complexes.
- To develop new methodology, they also try to use ^{17}O NMR spectroscopy. They will apply ^{17}O NMR spectroscopy for metalloproteins and their model complexes and examine its applicability.

§4. Publication of Research Results

（4－1） Publication of Thesis (The original Work)

① Number of Publications (0 times-Domestic, 25 times-International)

② Detailed Information of Thesis

1. S. Ten-no, “Recent advances in explicitly correlated electronic structure theory using short-range correlation factors” In: E. A. G. Armour, J. Franz, J. Tennyson (Ed) Explicitly Correlated Wavefunctions, Collaborative Computational Project on Continuum States of Atoms and Molecules (CCP2), Daresbury (2006)
2. W. Klopper, F. R. Manby, S. Ten-no, and E. F. Valeev, “R12 methods in explicitly correlated molecular electronic structure theory”, Int. Rev. Phys. Chem., 25 427-468 (2006)
3. S. Ten-no, "New implementation of second-order Moeller-Plesset perturbation theory with an analytic Slater-type geminal", *J. Chem. Phys.*, **126** 014108 (12pages) (2007)
4. M. Nakagaki, E. Nishi, K. Sakota, H. Nakano, H. Sekiya, “A model two-dimensional potential for internal rotation of 9-methylanthracene studied by electronic spectroscopy and DFT calculations”, Chem. Phys. 328, 190-196 (2006)
5. Y. Matano, T. Nakabuchi, T. Miyajima, H. Imahori, and H. Nakano, “Synthesis of Hybrid Phosphorus-Containing Porphyrin”, Org. Lett. 8, 5713-5716 (2006)
6. H. Nakano, “Multireference Perturbation Theory with Four-Component General Multiconfigurational Reference Functions”, Lecture Notes on Computer and Computational Sciences, **7**, 931-934 (2006)
7. Y. Watanabe, H. Nakano, and H. Tatewaki, “The effect of removing the no-virtual-pair approximation on the correlation energy of the He isoelectronic sequence”, J. Chem. Phys. in press
8. van der Avoird, T. B. Pedersen, G. S. F. Dhont, B. Fernández and H. Koch, “Ab initio potential energy surface end rovibrational states of the HCN-HCL complex”, J. Chem. Phys. 124, 204315 (2006)
9. F. Aquilante, T. B. Pedersen, A. Sánchez de Meras and H. Koch, “Fast non-iterative orbital localization for large molecules”, J. Chem. Phys. 125, 174101 (2006)
10. G. Cuesta, T. B. Pedersen, H. Koch and A. Sánchez de Meras, “Carbon nanorings: A challenge to theoretical chemistry”, Chem. Phys. Chem. 7, 2503-2507 (2006)
11. J. Seino, Y. Honda, M. Hada, H. Nakatsuji, “SAC and SAC-CI Calculations of Excitation and Circular Dichroism Spectra of Linear-Chain and Cyclic Dichalcogens”, *J. Phys. Chem.* 110(33), 10053 – 10062 (2006)
12. T. Yoshizawa and M. Hada, “Calculations of Frequency-Dependent Molecular Magnetizabilities with Quasi- Relativistic Time-Dependent Generalized Unrestricted Hartree-Fock Method”, *J. Comp. Chem.* 28(4), 740-747 (2007)
13. Y. Honda, M. Hada, M. Ehara, and H. Nakatsuji, “Ground and Excited States of Singlet, Cation Doublet, and Anion Doublet States of o-Benzoquinone: A Theoretical Study”, *J. Phys. Chem. A*, in press (2007)

14. T. Yamato, T. Ishikura, T. Kakitani, K. Kawaguchi, H. Watanabe, “Spectral tuning of photoactive yellow protein”, *Photochemistry and Photobiology*, in press.
15. K. Kawaguchi, T. Yamato, “Theoretical prediction of optical absorption peaks for photosensory receptor mutants”, *Chem. Phys. Lett.* 430 386-390 (2006)
16. T. Ishikura, T. Yamato, “Energy transfer pathways relevant for long-range intramolecular signaling of photosensory protein revealed by microscopic energy conductivity analysis”, *Chem. Phys. Lett.* 432 533-537 (2006)
17. H. Nishioka, T. Yamato, T. Kakitani, “Temperature dependence of the inelastic tunneling”, *Molecular Simulation* 32 727-734 (2006)
18. Sugita Y, “Miyashita N, Yoda T, Ikeguchi M, and Toyoshima C: Structural Changes in the Cytoplasmic Domain of Phospholamban by Phosphorylation at Ser16: A Molecular Dynamics Study”, Biochemistry 45, 11752-11761 (2006)
19. Manik Kumer Ghosh, Cheol Ho Choi, “The initial mechanisms of Al2O3 atomic layer deposition on OH/Si(1 0 0)-2×1 surface by tri-methylaluminum and water”, Chemical Physics Letters 426 (2006) 365–369
20. Masato Kujime, Takuya Kurahashi, Masaaki Tomura, and Hiroshi Fujii , “^{63}Cu NMR Spectroscopy of Copper(I) Complexes with Various Tridentate Ligands: CO as a Useful ^{63}Cu NMR Probe for Sharpening ^{63}Cu NMR Signals and Analyzing the Electronic Donor Effect of a Ligand”, *Inorg. Chem.* 46, 541-551 (2007)
21. Takuya Kurahashi, Kenji Oda, Manabu Sugimoto, Takashi Ogura, and Hiroshi Fujii, “A Trigonal-Bipyramidal Geometry Induced by an External Water Ligand in a Sterically Hindered Iron Salen Complex, Related to the Active Site of Protocatechuate 3,4-Dioxygenase”, *Inorg. Chem,* 45, 7709-7721 (2006)
22. Hiroshi Fujii and Tadashi Yoshida , “^{13}C and ^{15}N NMR Studies of Iron-Bound Cyanides of Heme proteins and related model complexes: Sensitive Probe for Detecting Hydrogen Bonding Interactions at the Proximal and Distal Sides”, Inorg. Chem. 45, 6816-6827 (2006)
23. Atsunari Tanaka, Hiro Nakamura, Yoshitsugu Shiro, and Hiroshi Fujii, “Roles of the heme distal residues of FixL in O_2 sensing: A single convergent structure of the heme moiety is relevant to the down-regulation of kinase activity”, *Biochemistry 45*, 2515-2523 (2006)
24. Hiroshi Fujii, Takuya Kurahashi, Takehiko Tosha, Tetsuhiko Yoshimura and Teizo Kitagawa , “^{17}O NMR Study of Oxo Metalloporphyrin Complexes: Correlation with Electronic Structure of M=O Moiety”, J. Inorg. Biochem. 100, 533-541 (2006)
25. Masato Kujime and Hiroshi Fujii, “Spectroscopic Characterization of Reaction Intermediates in Nitrite Reduction of Copper(I) Nitrite Complex as a Reaction Model for Copper Nitrite Reductase”, *Angew. Chemie. Int. Ed. 45*, 1089-1092 (2006)

（4－2） Patent Application

① Cumulative Number

1) Patent Applications in the fiscal year 2006 (Domestic- 0 Cases, Oversea- 0 Cases)

2) Cumulative number of Patent Applications for the research period of CREST
(Domestic- 0 Cases, Oversea- 0 Cases)