Automated Reaction-Route Searching Program

GRRM 1.00

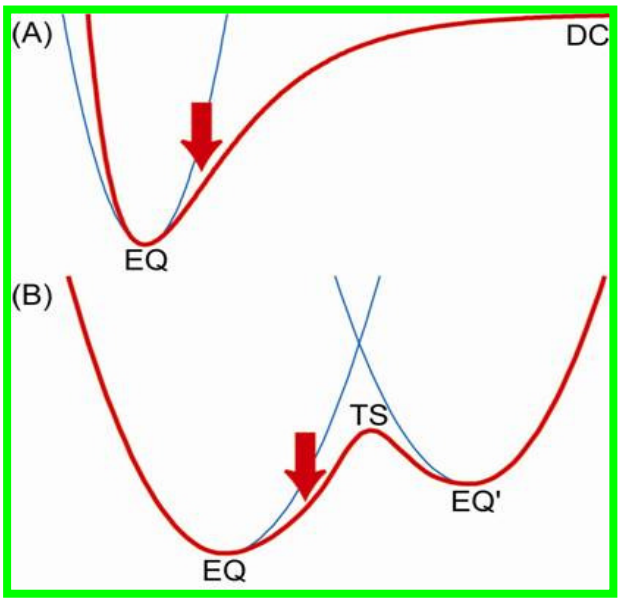
Unexplored Chemistry and a Compass in the Chemical World

Chemistry is a wonderful world with lots of unexplored materials, which is producible from ca. one hundred kinds of chemical elements. More than thirty millions of compounds have already been known, and now two millions of new chemical compounds are produced annually. Invention and discovery of chemical reactions among compounds have extensively been made by chemists.

Eighty years ago, when quantum mechanics was discovered, all problems in chemistry seemed to be insolvable. Equations for chemical problems are so complex that many theoreticians had abandoned to solve the problems at that time. However, some theoretical chemists had continually made efforts to improve approximation techniques solving chemical problems until many problems could have been solved effectively by means of electronic computers and computational techniques. By virtue of recent developments, the range of quantum chemical treatments has rapidly been widened so that we are now able to apply them to various chemical problems.

A theoretical technique based on quantum chemical calculations has made it possible to determine a stable geometrical structure and its energy in good accuracy for a chemical system without experiments. This is called “structure-optimization”, which can be used by anyone in nowadays. However, it requires an initial guess, which should be made on the basis of our experience or chemical intuition. Since no general method exists to find out suitable initial guesses, one cannot avoid try-and-errors before one finally obtains some valuable conclusions such as new compounds or new chemical reaction pathways. It follows that a global search of isomers and reaction pathways among them has never been accomplished except for very small systems not larger than a four atom system. It has been an unexplored summit to perform a global search of isomers and inter-conversion reaction pathways among them for a chemical system composed of more than four atoms.

Aiming at such an unexplored summit, the scaled hypersphere search (**SHS**) method has been developed by Ohno and Maeda (**Chem. Phys. Lett. 384, 277 (2004)**). This method has made it possible for the first time to discover reaction networks connecting various isomers with the same chemical formula, starting from an arbitrary isomer structure. An automatic search has become possible via one-after-another algorithm tracing each reaction pathway around every equilibrium structure to disclose conversion pathways to other isomers as well as reaction routes into dissociation.



In every reaction route, the potential energy curve cannot avoid downward distortion with respect to the harmonic potential (Anharmonic Downward Distortion: ADD) on going from the reactant to the product. Namely, every chemical reaction goes along the ADD. This propensity can be denoted as the ***quantum principle of chemical reactions*** (**J. Phys. Chem. A 110, 8933 (2006)**). By noting this principle, the SHS method enables us for the first time to trace reaction pathways after discovering initial parts of reaction channels around an equilibrium structure. Like the points of a compass indicating North-and-South even on the ocean without signposts, the direction of the maximal ADD has been discovered to behave as "the compass in the chemical world" indicating the right reaction route how to get to the product.

The Quantum Principle of Chemical Reactions

In either case (**A**) where chemical bond dissociation occurs from an equilibrium structure (**EQ**) or case (**B**) where chemical bond reorganization into another equilibrium structure of **EQ'** occurs via a transition structure (**TS**), anharmonic downward distortion (**ADD**) from the blue curve to the red curve happens on the potential energy surface, associated with the reaction process going.

The maximal direction of **ADD** is a signpost of the chemical reaction route to behave as a compass searching unknown reactions.

Traditional theories of chemical reactions, such as Bell-Evans-Polanyi principle (1936), Frontier electron theory by Fukui (1952), Hammond postulate (1955), Woodward Hoffmann rule (1969), and Marcus formula (1968), utilize simple models. All of these famous theories cannot directly cope with the precise quantum mechanical potential energy surfaces which may involve a number of summits, valleys, and mountain passes.

In recent decades, reliability of quantum chemical calculations has been improved considerably to enable us to obtain potential energies in good chemical accuracy. Prediction and analysis based on quantum chemistry have been expected to be promising for various chemical problems even in the outside ranges of the traditional theories.

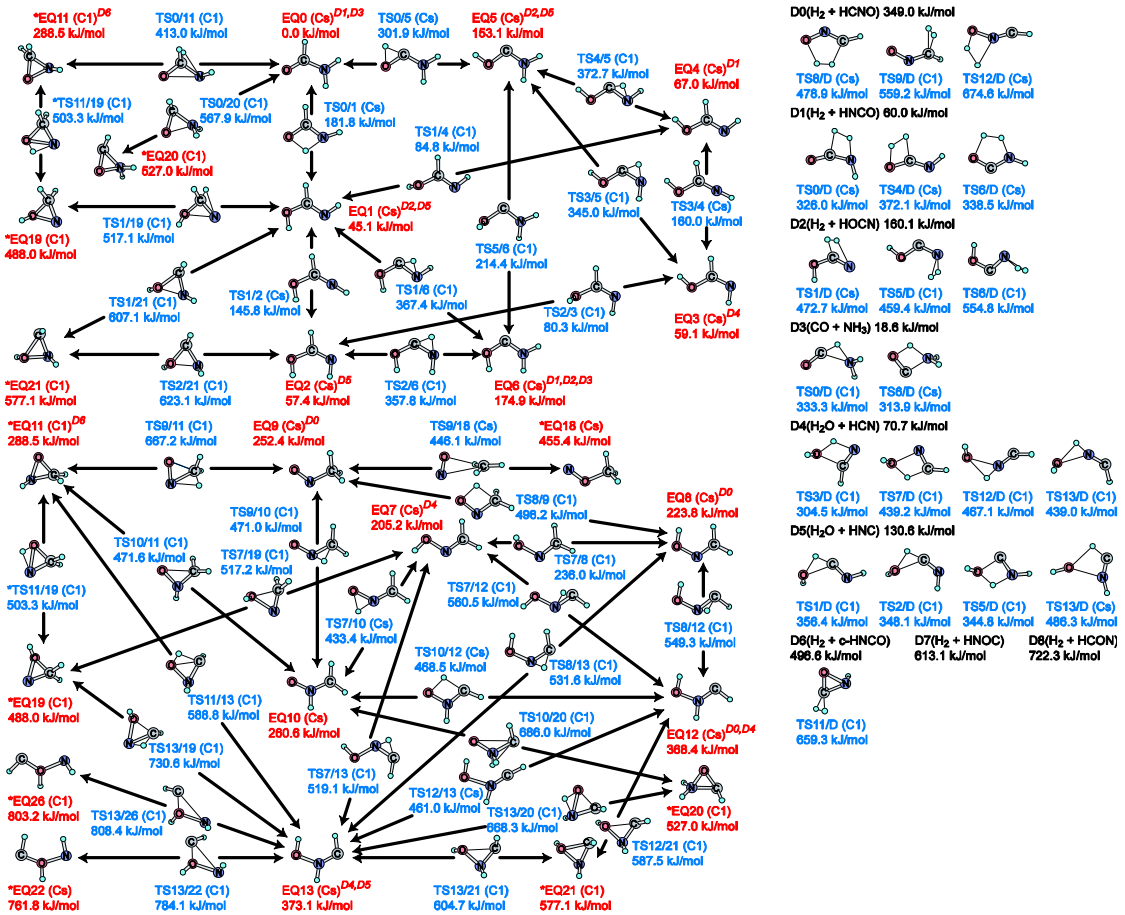
The Quantum Principle of Chemical Reaction noting anharmonic downward distortion of the potential has enabled us for the first time to make an automated search of chemical reactions based on quantum chemical calculations, and it provides a compass to explore unknown chemical world and to give us valuable means to solve longstanding problems.

GRRM ?

- *GRRM* 1.00 is the first program in the world making it possible to search Global Reaction Route Map (**GRRM**) in an automatic way based on quantum chemical calculations.
- *GRRM* 1.00 automatically searches isomers of a given chemical formula and isomerization pathways connecting the isomers.
- *GRRM* 1.00 determines transition structures (**TS**) on the reaction path and also calculates intrinsic reaction coordinates (**IRC**), normal modes, and imaginary frequencies for **TS**.

Power of GRRM

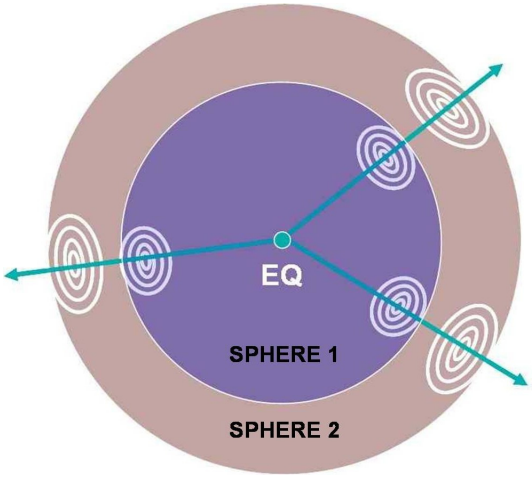
- *GRRM* 1.00 opens the doorway to unknown chemical world to enable us to make an automated search of unexplored novel compounds and new reaction routes.
- *GRRM* 1.00 discovers novel compounds and new reaction routes very efficiently by the SHS method using closed sphere surfaces based on the Quantum Principle of the Chemical Reactions, whereas a fine-toothcomb approach fails in vain even after billions of years.
- *GRRM* 1.00 gives new strategies for problems of energies and environments; it enables us to find an ideal reaction route without byproducts or loss of resources (***Atom Economy***), since finding a decomposition route of an aimed compound leads to discovery of a synthetic route in the opposite direction.
- *GRRM* 1.00 can be used automatically to know chemical species of the specified chemical formula and reaction routes connecting them by anyone without experiences and intuition.



Global reaction route map for CH_3NO (partly abbreviated for the space)

Breakthrough for Reaction Route Exploration !
Scaled Hypersphere Search (SHS) Method

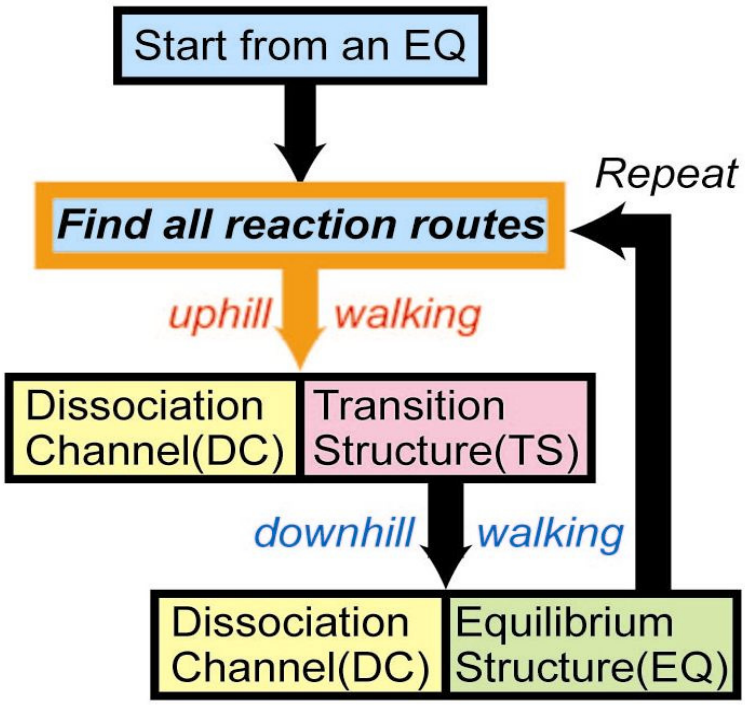
- Why an automated search of global reaction route maps (**GRRM**) has been unable? This is because there has been no algorithm to find and follow reaction paths from an equilibrium structure (**EQ**) upward to a transition structure (**TS**) or a dissociation structure (**DC**) automatically. *GRRM* 1.00 has realized an automated search of **GRRM** based on the scaled hypersphere search (**SHS**) method by Ohno and Maeda.
- How the **SHS** method can automatically find reaction paths starting from an equilibrium structure? It has become possible by the "**Quantum Principle of Chemical Reactions**". When we look into tendencies of the potential energy in chemical reactions, the potential around an equilibrium structure always shows a downward distortion from the parabolic shape of the harmonic potential. Namely, an anharmonic downward distortion (**ADD**) of the potential always happens, associated with chemical reactions. This is the principle of chemical reactions, and it follows that maximal directions of **ADD** have a function of a **compass** indicating reaction pathways. This principle has made it possible for the first time to trace reaction pathways from equilibrium structures by chasing maximal directions of **ADD**.
- The **SHS** method efficiently finds maximal directions of **ADD** indicating pathways of chemical reactions. It is not a right way to find the lowest direction of the potential for searching maxima of **ADD,** which inevitably leads to the coordinate along the lowest frequency normal mode to become unsuccessful in finding maxima of **ADD**. In principle, anhamonicity of the potential can be determined from differentiation coefficients higher than the second order. Higher order derivatives are, however, too expensive to obtain for determination of maxima of ADD. The **SHS** method treats all normal coordinates equivalently with using scaled normal coordinates canceling the difference of the frequencies. If the potential is purely harmonic, energies on the hypersphere surface at the same distance of the equilibrium point in the scaled normal coordinates definitely become constant everywhere. Real energy values on the hypersphere may differ depending on the extent of anharmonicity of the directions. Thus, energy minima on the hypersphere correspond to the maxima of ADD, and it follows that reaction pathways existing around the equilibrium structure can be found successively.



Scaled Hypersphere Search (SHS) Method

By tracing each energy minimum on the scaled hypersphere surface, reaction pathways around an equilibrium point (**EQ**) can be discovered.

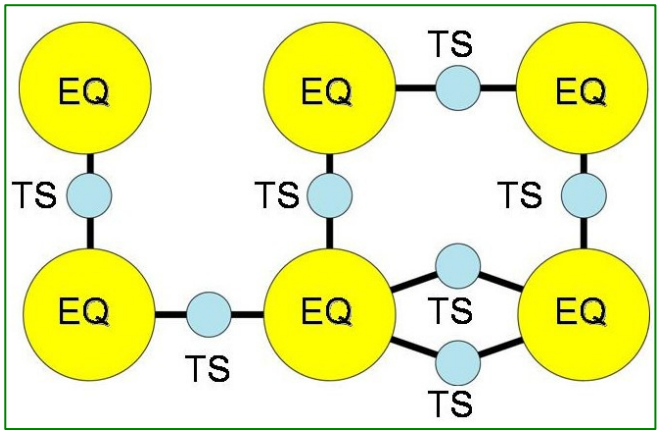
- In the **SHS** method, finding maxima on a closed surface has made it possible for the first time to discover reaction pathways starting from a compound automatically. This closed surface is a finite area described by cyclic variables of angles, which enables the **SHS** method to grasp efficiently the reaction pathways going though the closed surface from the inside to the outside.



The **SHS Algorithm** searching reaction pathways.

- ***GRRM*** **1.00** has solved the long standing problem finding reaction pathways by introduction of a special technique determining all energy minima on the hypersphere (maxima of **ADD**). Finding a structure at an energy minimum can easily be made in conventional quantum chemical calculations, while it has been almost impossible to determine all minima, even if the area is limited on the finite hypersphere surface. The iterative optimization- elimination (**IOE**) technique proposed by Maeda and Ohno (**J. Phys. Chem. A 109, 5742 (2005)**) has overcome this difficulty. Unknown minima can be discovered one after another by the conventional minimization technique after canceling each minimum when it is once found.
- The **IOE** technique, which has been developed in association with the **SHS** method, has a very powerful function in addition.

ADD indicating directions of reactions may be overlapped, when they nearly coincide in the same spatial region. In the worst cases, overlapped pathways do not show independent maxima, but they exhibit displaced maxima with some shoulders. Even in such difficult situations, the **IOE** technique can find out hidden pathways involved in overlapped cases by eliminating each pathway when it is once found. This procedure is very similar to the deconvolution technique, which is very powerful to disclose individual components of spectral peaks from heavily overlapped spectra.



One-after-another search of reaction pathways in the **SHS** method.

GRRM **1.00** equips with this powerful technique decomposing heavily overlapped ADD into individual components to discover every reaction pathway separately.

Examples of GRRM 1.00 *applications*

Global Reaction Route Mapping of a given chemical composition

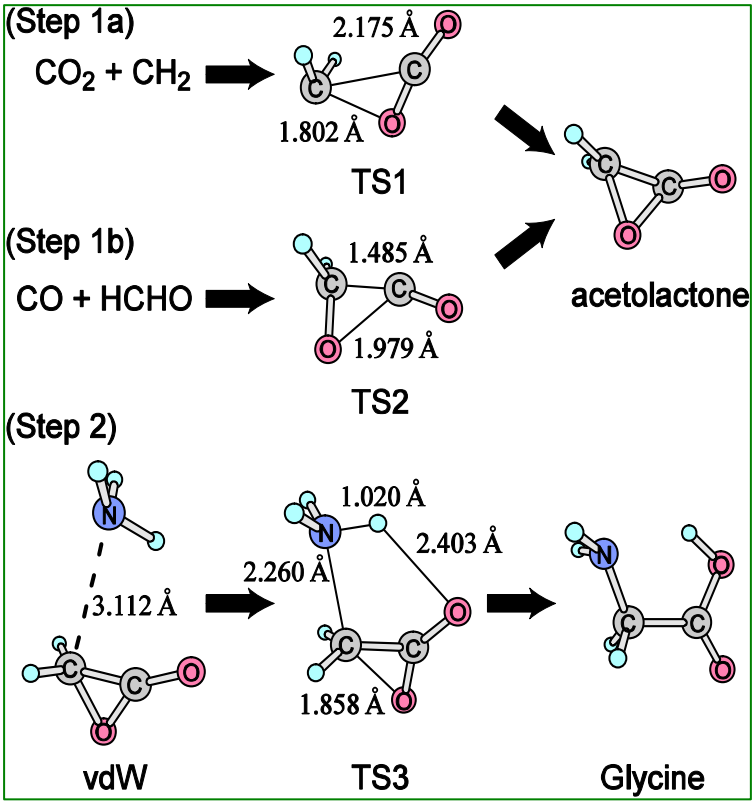
- An automated global search of reaction pathways is made one-after-another by a novel algorithm tracing anharmonic downward distortion (**ADD**) of the potential based on the quantum principle of chemical reactions.
- An automated search for isomers of a given chemical composition is made.
- An automated search for reaction pathways among isomers is made.
- An automated search for dissociation pathways and synthetic pathways is made.

Example: Global Reaction Route Map for CH_3NO

- ***GRRM* 1.00** can be used for finding unexpected new reaction routes by application of global reaction route mapping.
- ***GRRM* 1.00** automatically obtains basic data for making a world atlas of reaction networks for a given chemical formula. (A graphic software is required for obtaining a real figure.)

Reaction design for energy/environment problems aiming at complete Atom Economy

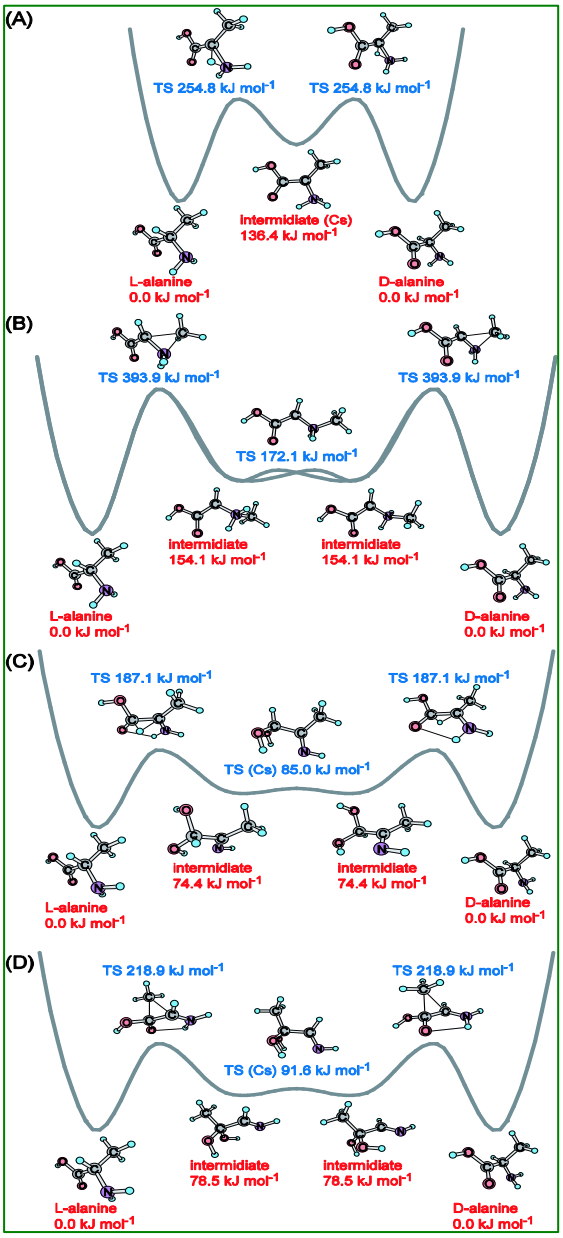
- Efficient use of reactant materials for obtaining target products, ideally with no byproducts, is called **Atom Economy**.
- ***GRRM* 1.00** can be used to design an ideal synthetic route to accomplish perfect **Atom Economy** by complete use of reactant materials without loss.
- Design of reactions producing target compounds from reactant molecules with no loss is also useful for the study of molecular evolution on the earth or in the universe.



New synthetic routes of Glycine

An application of the SHS method to the simplest amino acid molecule of (**Glycine**) $C_2H_5NO_2$ has provided us new synthetic routes. First, a dissociation channel yielding an ammonia molecule NH_3 was found. Second, two dissociation routes producing ($CO_2 + CH_2$) and ($CO + HCHO$) were found. It follows that reverse routes of these dissociation channels were discovered as two new synthetic routes with no byproducts.

Step 1a+2 : $(CO_2+CH_2)+NH_3$
Step 1b+2 : $(CO+HCHO)+NH_3$

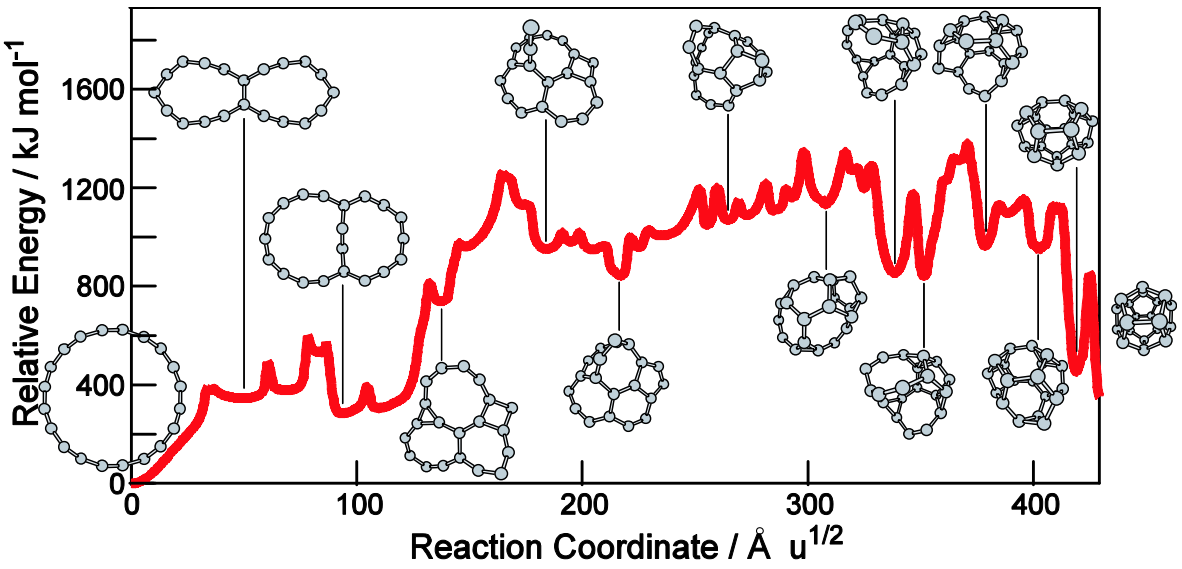


Design of D-L conversion pathways of optical isomers with chirality.

- Most natural amino acids related to life are **L**-types. Therefore, the **D**-type glutamic acid does not provide good taste.
- Whether isomerization from one chiral isomer to the other is possible or not has been unknown. In the left figure, ***GRRM* 1.00** has shown for the first time that **D-L** conversion pathways exist for alanine, the most basic optically active amino acid molecules.
- No direct conversion pathway via only one transition structure (**TS**) exits between **D**-and **L**-isomers of alanine. This is an important finding concerning with the vital stability of amino acid molecules.
- Between **D**- and **L**-isomers of alanine, four conversion routes have been discovered, (**A**) a route via a planar intermediate without chirality, (**B**) a route via an intermediate with helical chirality, and (**C**) (**D**) two routes via an intermediate with axial chirality.
- ***GRRM* 1.00** creates valuable information of new reaction routes, which is useful for selective synthesis or deactivation of optical isomers.

Exploration of Intermediates in Multi-step Reaction and Design/Explanation of Pathways.

- ***GRRM* 1.00** can be used to find out multi-step pathways and intermediates.
- An example below demonstrates a series of multi-step pathways connecting a single ring and a fullerene of C_{20} clusters.



GRRM 1.00 is the first computer program based on the **SHS** algorithm for an automated exploration of chemical reaction pathways by utilizing energies obtained from solutions of $H\Psi = E\Psi$.

GRRM 1.00 copes with long standing fundamental problems in chemistry by automated exploration of chemical reaction pathways.

- *GRRM* 1.00 **automatically explores unknown isomers.**
- *GRRM* 1.00 **automatically explores unknown synthetic routes.**
- *GRRM* 1.00 **automatically explores unknown dissociation channels.**

GRRM 1.00 develops an unexplored world of chemistry by elucidating unknown chemical reaction networks.

- *GRRM* 1.00 **is useful for production of the Atlas for the chemical world.**
- *GRRM* 1.00 **is useful for design of new chemical compounds and reactions.**
- *GRRM* 1.00 **is useful for designing new tactics for energy/environment problems.**
- *GRRM* 1.00 **is useful for elucidation of catalysis and design of new catalysts.**

GRRM 1.00 is an epoch-making program of potential analyses for the following problems.

- **Normal coordinate analysis** Normal coordinate calculations can be made at arbitrary structures. Optionally, enthalpy and Gibbs energies can also be obtained.
- **Optimization of equilibrium structures** Equilibrium structures can be optimized by **SIRFO** and **BFGS** methods.
- **Optimization of transition structures** Transition structures can be optimized by **SIRFO** and **Bofill's** methods.
- **IRC search** **IRC** can be traced by **Page** and **McIver** methods.
- **GRRM search** Global reaction route mapping (**GRRM**) can be made for the potential surface of a given chemical formula. Starting from an equilibrium structure, automated search of dissociation and isomerization can be performed to explore **GRRM** corresponding to the Atlas of chemical reaction routes. Optionally, exploration of reaction routes can be made for the limited region around a particular structure.
- **One step TS search** An efficient search of the reaction pathway connecting a reactant and a product can be made to determine the transition structure (**TS**). This procedure can be done automatically without initial guess, and this technique is much more rapid and applicable than any other methods, such as the **NEB** method.
- **Intermediate search** Intermediates between a pair of isomers can be found, even if they are far apart. The **SHS** method in the hypersphere-contraction-mode enables us to explore multi-step reaction pathways, even if they amount to several tens of steps.

Program Package & Requirement for GRRM 1.00

GRRM 1.00 utilizes energies obtained by **Gaussian03**.

GRRM 1.00, a 64-bit or a 32-bit version, can be used under a Linux/Unix environment.

GRRM 1.00 can be used for research and education, after application to the following address by E-mail. ohnok@m.tohoku.ac.jp