

Can a Computer Predict Organic Reactions ?

- *ab initio* molecular dynamics simulation -

<AT THE BEGINNING>

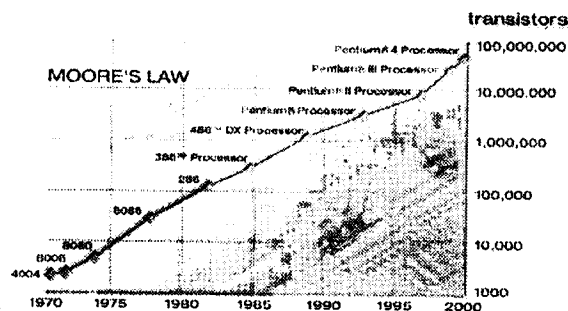
Recently, drastic progress of computational performance and programs allows us to handle very fast computer easily, even in personal use. With the acute development of CPU power, some new methods of computational chemistry, which is not applicable once ago due to demanding heavy calculation cost, become feasible.

One of the most promising methods is

"*ab initio* molecular dynamics (AIMD) simulation".

It will be very powerful tool for description of dynamics of chemical reaction etc., which is impossible to express by classical methods.

Today I focus on recent mechanistic study using AIMD simulation.



G. Moore (Intel) predicted that the number of transistors per square inch on IC had doubled every year since the IC was invented. This trend would continue for the foreseeable future. In subsequent years, the pace slowed down a bit, but data density has doubled approximately every 18 months.

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- ~ Contents ~
1. Introduction and background
 2. Ab initio MD for small reaction system (H.Yamatoka, M.Aida)
 3. Ab initio MD for transition metal catalysis (R.J.Meier)
- Appendix
-

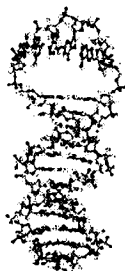
1. Introduction and Background

▷ Two classical approach in computational chemistry

Molecular Mechanics (MM) Simulation

- \$ Molecular dynamics (MD)
- \$ Monte Carlo (MC)
- \$ Molecular mechanics (MM)

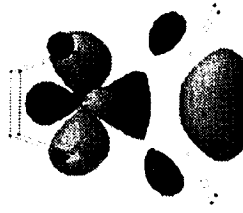
- > Description of **nucleus, molecule, macrosystem** behavior
(Structural optimization, dynamics observation ...)
- > **Newton's motion of equation**
empirical force field representing interatomic interaction
- > **Low-cost calculation**
- > **Time-dependent dynamics** could be examined with MD method
- > Usually ignores the behavior of electron



Molecular Orbital (MO) Calculation

- \$ empirical, semi-empirical
- \$ ab initio, DFT

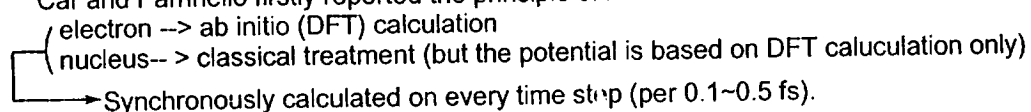
- > Description of **electronic state**
(Electron density, frontier orbital interaction ...)
- > **Schrödinger wave equation**
electronic interaction
- > **Relatively expensive**
for precise, quantitative expression
- > Only **static state** could be expressed
- > **Transition state** (bond forming/breaking) is expressible



Ab initio molecular dynamics simulation

▷ Ab initio molecular dynamics ... ?

Car and Parrinello firstly reported the principle of AIMD method in 1985.



<Features>

Merit : Both electron state and dynamics are described *under non-zero temperature*

→ Most promising method for computational mechanistic study

The reaction pathway assumption is *not always required*.

→ Possibility of finding alternative reaction pathway.

Demerit : *highly CPU power-demanding*

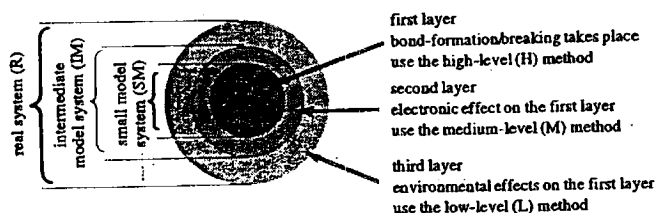
→ (System scale is limited to small size
Time scale is rather short span (~ 10ps)) ----- will be improved in the future.

<For large system application...>

(e.g. Chemical reaction in solvent
biomolecule (protein, enzyme, etc), metal clusters
Transition metal catalysis (of course, selectivity discussion is one of major interests)
Surface, solid, heterogeneous system)

Calculation-cost reduction is inevitable to finish calculation in reasonable span.

- QM/MM hybrid, ONIOM



- Linear-Scaling

- pseudopotential core approximation etc...

Reviews for Yamataka/Aida's work

ファルマシア. 2004, 40, 111-115

Bull. Chem. Soc. Jpn. 2002, 75, 2555-2569

Reviews for Meier's work

J. Mol. Catal. A 2000, 160, 189-197

Chem. Soc. Rev. 2003, 32, 151-157

Other representative review of introduction/application of AIMD simulation

Computing in Science & Engineering 2003, 36-44

Acc. Chem. Res. 2002, 35, 455-464

QSAR 2002, 21, 119-127

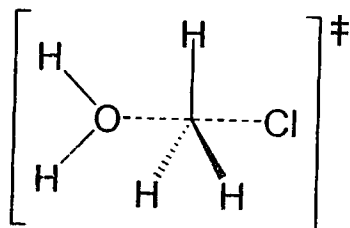
2. Ab initio MD for small reaction system

Chem. Phys. Lett. 1998, 292, 474-480

Ab initio molecular dynamics simulations on the hydrolysis of methyl chloride with explicit consideration of three water molecules

Misako Aida **, Hiroshi Yamataka *, Michel Dupuis *

▷ Model Reaction : Hydrolysis of CH₃Cl (S_N2- type)



This transition state model is not proper.
Solvent effect is completely ignored.

(Nu(H₂O) proton is transferred by solvent network.
L (Cl) is solvated and stabilized.)

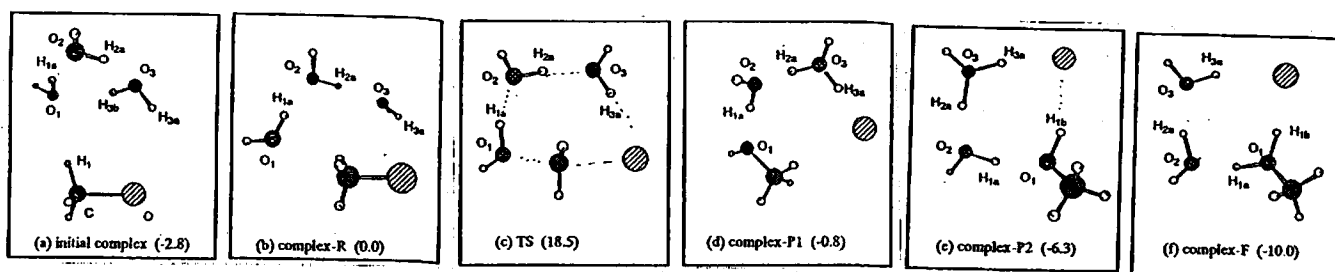


> In this report, n=3 model is adopted.

(their previous MO study shows...
- n=13 is enough to reproduce various experimental factors.
- n= 3 is minimum model that shows hydrogen-bonding network, proton shuttle behavior.)

▷ Calculation

Step 1 : Minimize energy of stationary structures



> HF / 6-31G level.

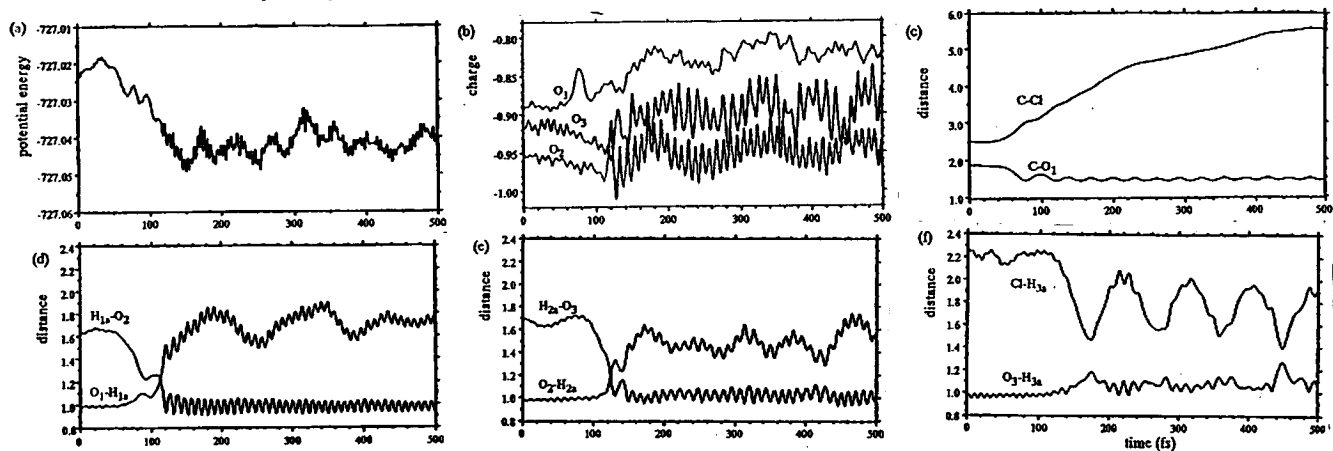
> IRC pathway was also calculated. → TS(c) connects complex-R(b) and complex-P1(d)

Step 2 : Ab initio MD simulations @298K (9 trajectories)

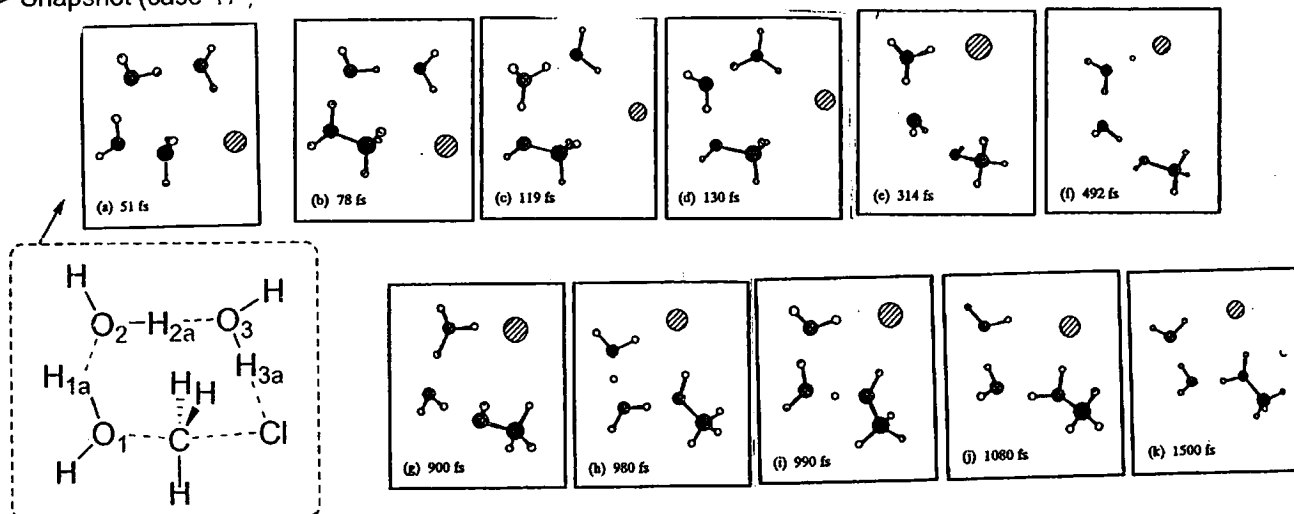
> Simulation was started from TS(c), with different initial velocity following Maxwell-Boltzmann distribution.

→ 3 / 9 : go back to reactant complex-R(b)
6 / 9 : proceed to product states.

> Behavior of one trajectory toward product state (case-1)

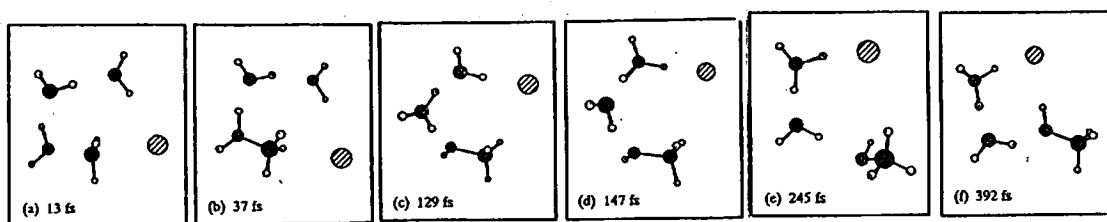


> Snapshot (case-1)



@~130 fs : complex-P1 → @~500 fs : complex-P2 → @~1100fs : complex-F

> Snapshot (case-2)

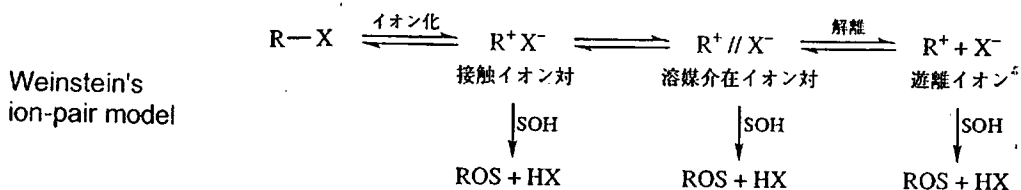


@~140 fs : complex-P1 → @~390 fs : complex-P2



Dynamic simulation might give different product that predicted by IRC analysis.

▷ Model Reaction : Hydrolysis of ^tBuCl (S_N1- type)



Also important to deal with large amount of solvent molecule around the ion pair.

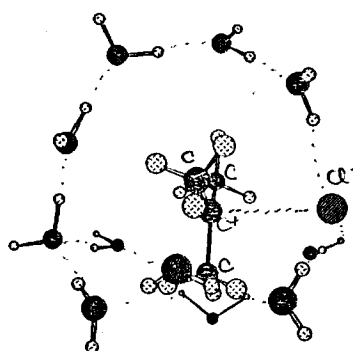
↓
QM/MM method

▷ Calculation

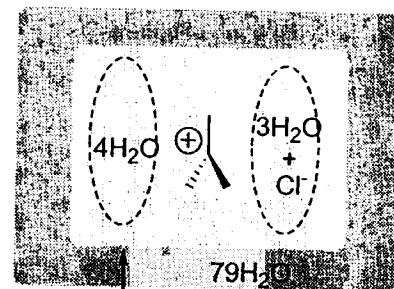
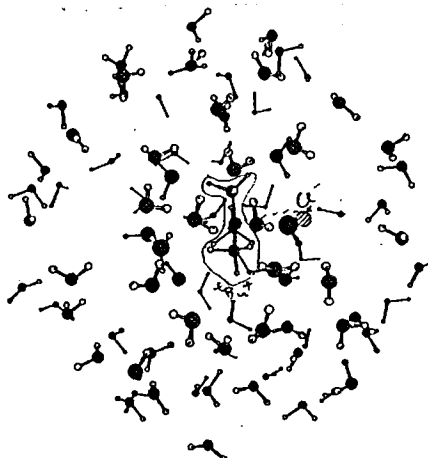
Step 1 : Optimization of local minimum structure of contact ion pair

<model for reaction center>
^tBuCl + 10H₂O (HF/3-21G level)

<model for whole reaction system>



add
bulk water
molecules



QM region (HF/3-21G)

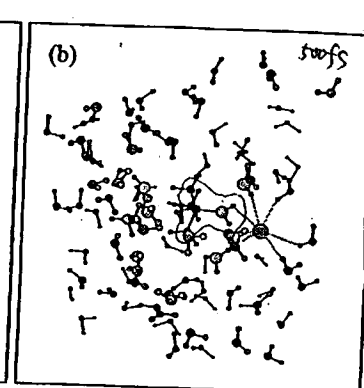
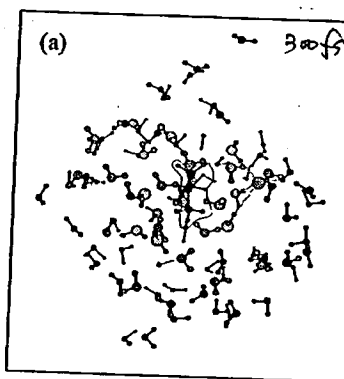
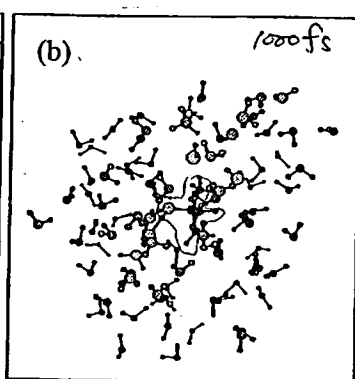
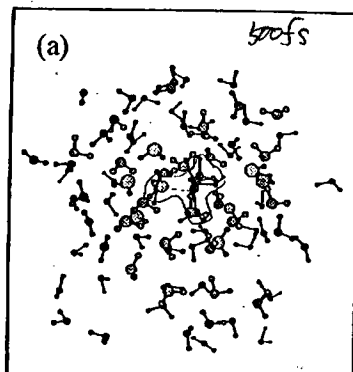
MM region (TIP3P)

Step 2 : QM/MM-MD simulation (14 trajectories)

5 / 14 : go back to reactant

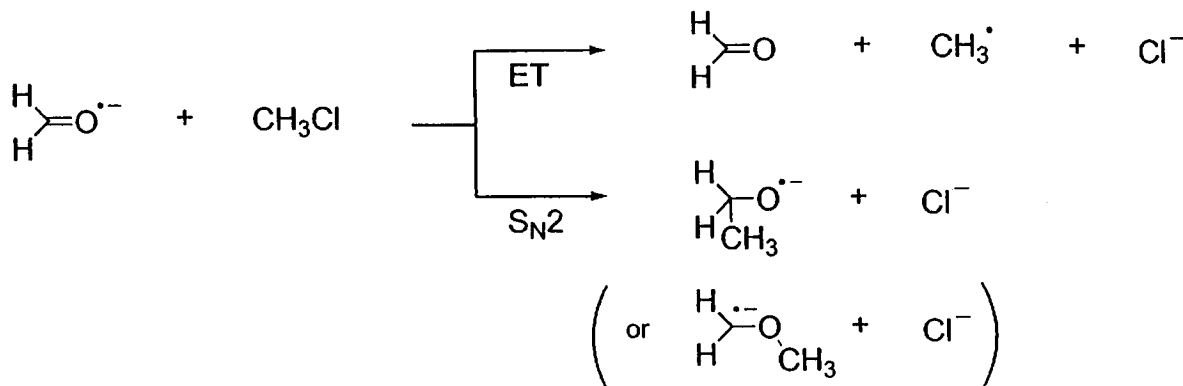
6 / 14 : inversion S_N1

3 / 14 : retention S_N1



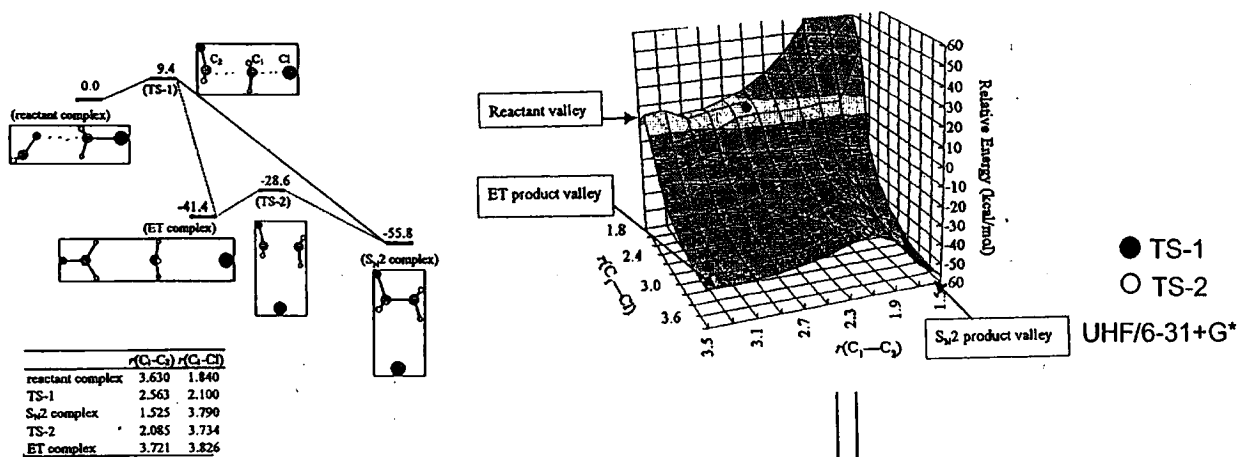
Borderline reaction ... the reaction proceeds via a region mechanistically intermediate between two extremes, usually very difficult to investigate by simple experimental methods.

▷ Model Reaction : S_N2 / ET competition reaction



▷ Calculation

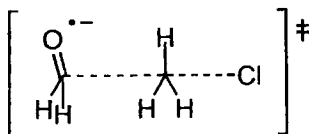
Step 1 : Energy optimization of stationary state and calculation of PES & IRC



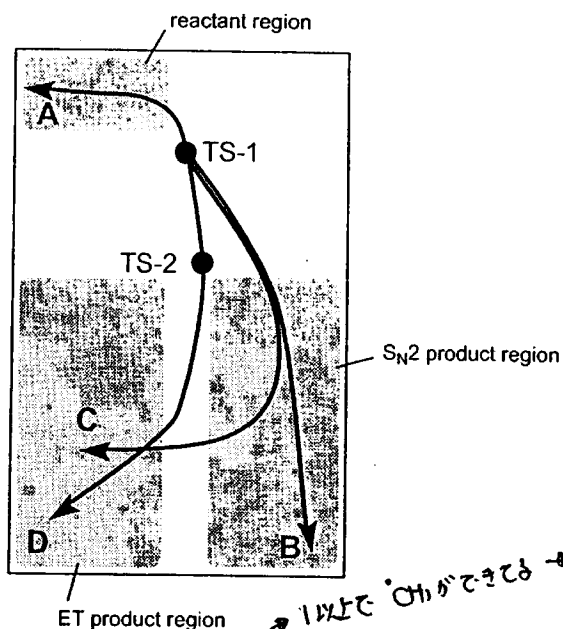
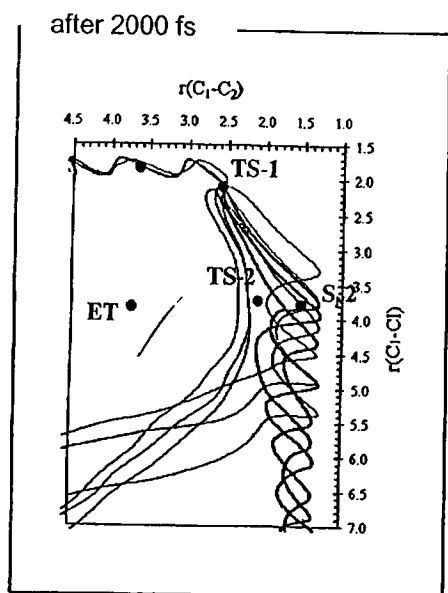
UHF/6-31+G*

IRC analysis predicts that product should be S_N2-type.

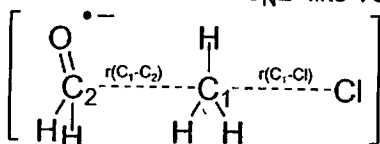
TS-1 : S_N2-like TS



Step 2 : Ab initio MD simulation @ 298K (50 trajectories)

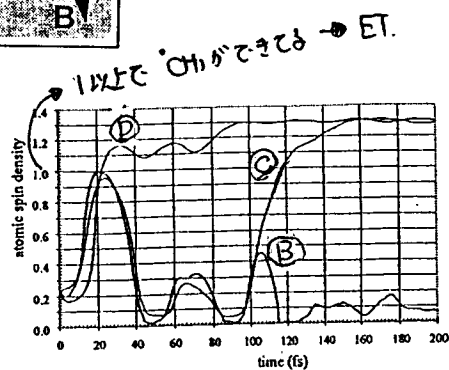


> Simulation starts from S_{N2} -like TS(TS-1).

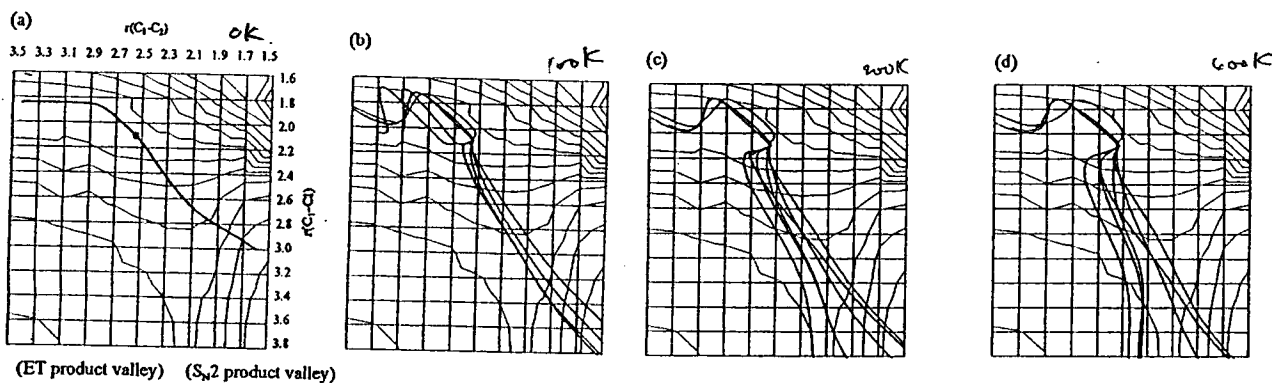


	A	B	C	D
τ^a	Reactant	S_{N2}	S_{N2} then ET	ET directly
50	12	36	0	3
2000	12	32	4	3
∞	12	31	5	3

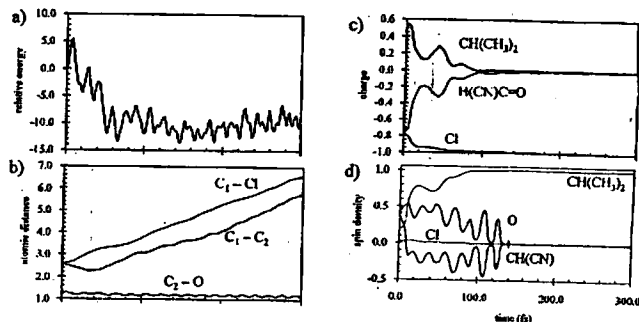
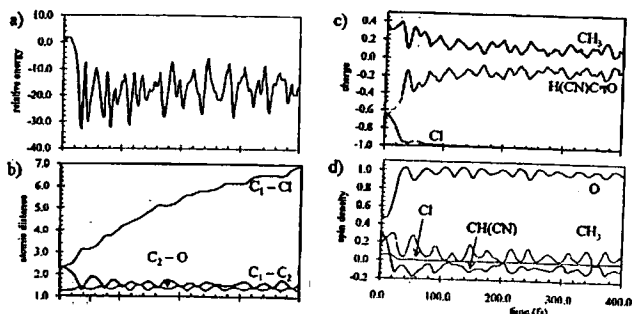
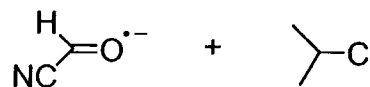
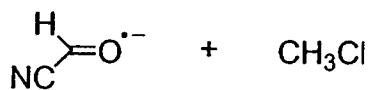
a) The relaxation time used in the simulations.



Step 3 : Temperature effect



Step 4 : Substrate effect (UHF/6-31+G* ; @298K)



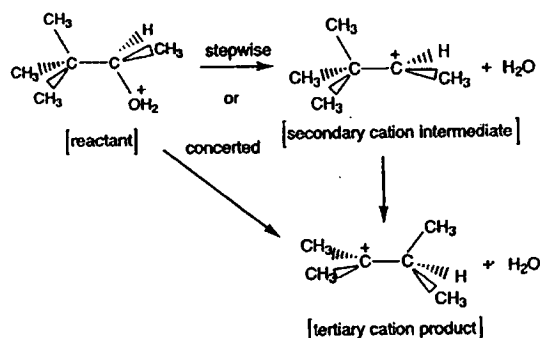
Product is all S_{N2} type.

Product is all ET type.
But product is all S_{N2} type @100K.

Dynamics-Driven Reaction Pathway in an Intramolecular Rearrangement

Salai Cheettu Ammal,¹ Hiroshi Yamataka,^{1*} Misako Aida,^{2*} Michel Dupuis^{3*}

▷ Model Reaction : Wagner-Meerwein rearrangement



Kinetic isotope effect

ab initio MO calculation (HF, MP2, B3LYP)

concentrated, single TS is suggested.

▷ Calculation

Step 1 : Energy optimization of stationary state and calculation of PES & IRC

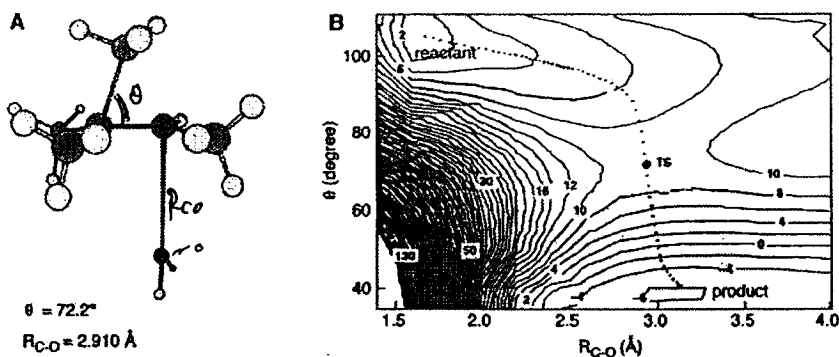
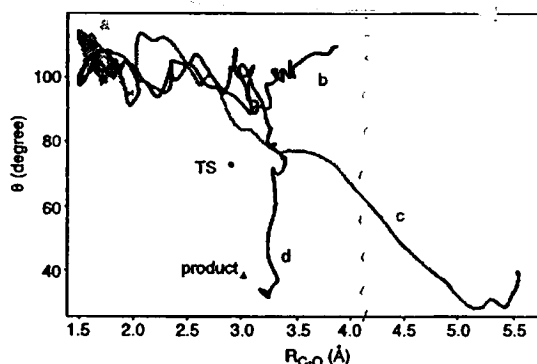


Fig. 1. (A) Gas phase TS structure and (B) potential energy contour map for the pinacolyl-OH₂⁺ rearrangement calculated at HF/6-31G*. The numbers are the potential energy (kcal mol⁻¹) relative to the reactant. The dotted line is the IRC path.

IRC analysis also shows concerted pathway, only single TS.

Step 2 : Ab initio MD simulation (50 trajectories ; HF/6-31G*)

Fig. 2. Four different types of trajectories observed in the simulations. (a) Trajectories that stayed in the reactant region, (b) those that gave the secondary carbocation intermediate, (c) those that gave the rearranged product in a concerted manner, and (d) those that gave the rearranged product in a stepwise manner.



> starts from reactant species

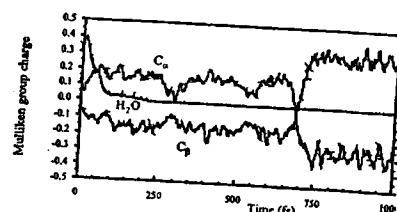
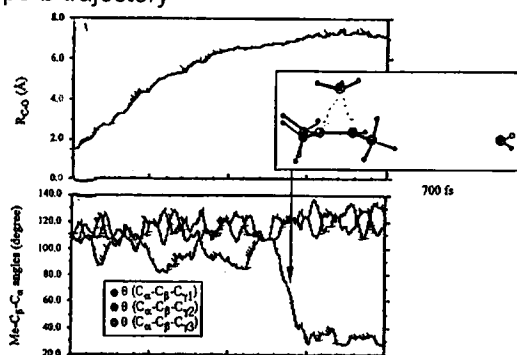
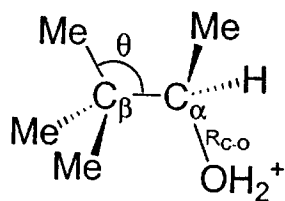
@ 400K after 500 fs

a(28/50) : back to reactant
 b(20/50) : secondary carbocation
 c(1/50) : product via concerted path
 d(1/50) : product via stepwise path

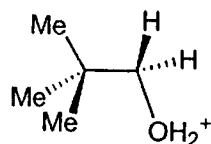
> longer simulation was carried out for type-b trajectories

7/20 : rearrangement
 8/20 : stay in secondary-carbocation region
 5/20 : back to reactant

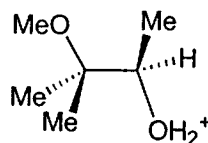
> Behavior example of type-b trajectory



Step 3 : Substrate effect (@400K; HF/6-31G*)

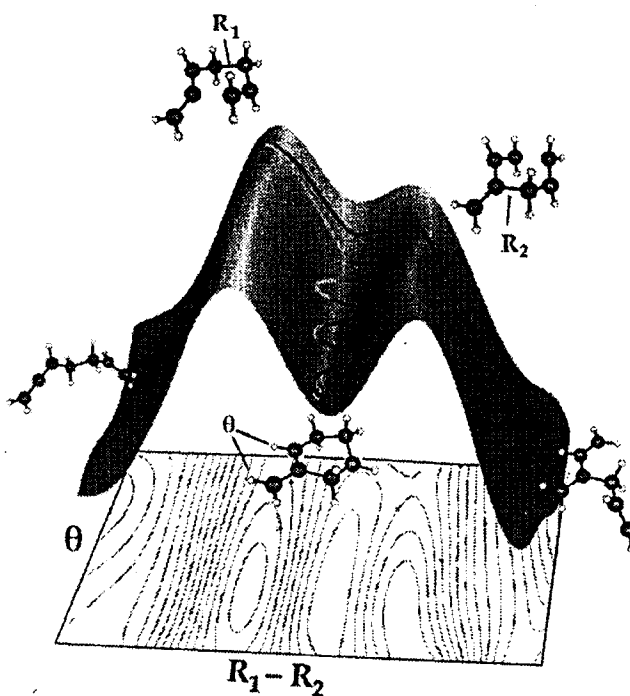


⇒ concerted path only



⇒ concerted path only

Ab initio MD simulation has a great possibility for discovery of new pathway.



3. Ab initio MD for transition metal catalysis

J. Am. Chem. Soc. 1994, 116, 7274-7281

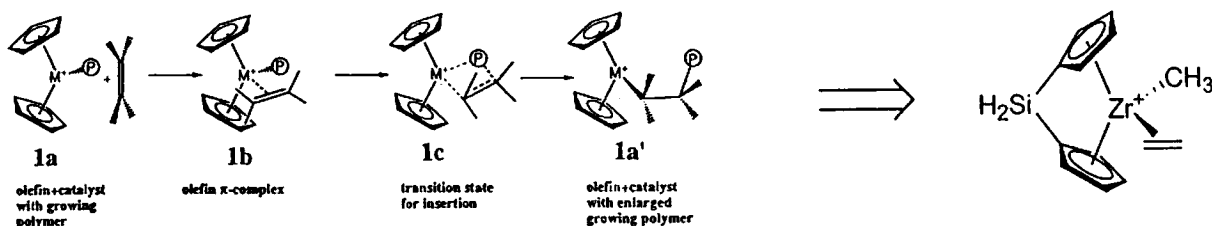
Ab Initio Molecular Dynamics Study of Metallocene-Catalyzed Ethylene Polymerization

First report of utilization of ab initio MD simulation to mechanistic study on transition metal catalysis

Robert J. Meier,¹ Gerard H. J. van Doremaele,¹ Simona Iarlori,¹ and Francesco Buda²

▶ Model Reaction : Alkene insertion on olefin polymerization catalysis

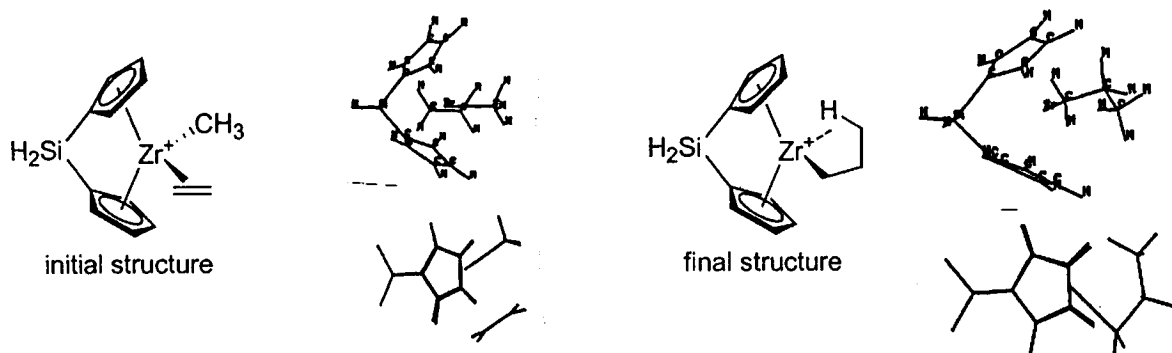
-proposed mechanism-



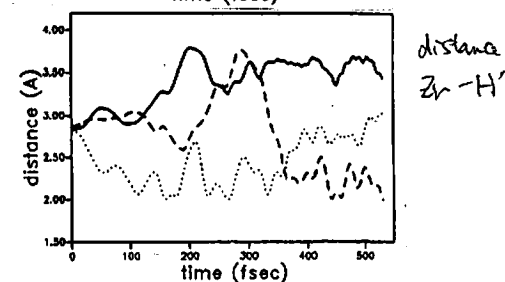
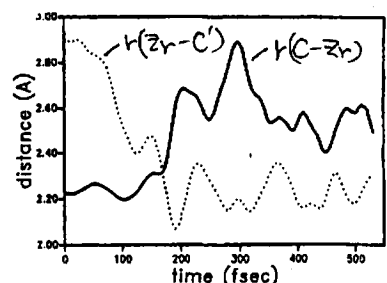
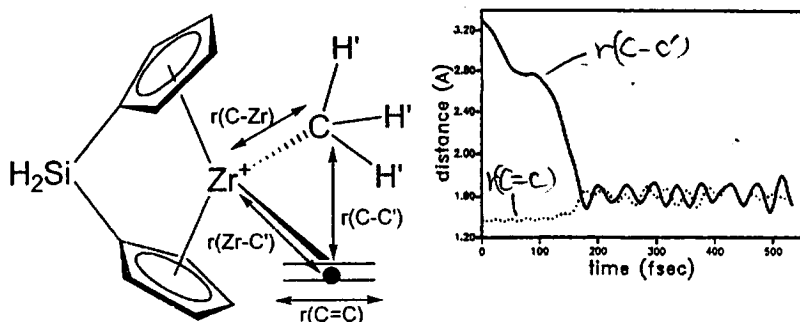
▶ Calculation

Step 1 : Energy optimization of stationary state

> Structure is optimized based on Car-Parrinello AIMD method (DFT level)



Step 2 : Ab initio MD @ 400K (DFT level)



70~170 fs : insertion occurred.
unexpectedly fast! → because of initial structure choice?

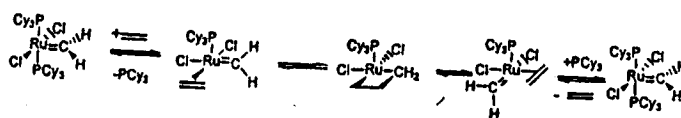
100 fs~: distance between one of H' and Zr is $< 2.5 \text{ \AA}$ → γ -agostic interaction is observed.

HOMO transfer is observed during insertion step.

Zr-C bond (initial state) → one of Cp ring (170fs) → propyl α -carbon (final state)

► Model Reaction : Ru-catalyzed olefin metathesis

<Proposed mechanism by Grubbs>



~ keypoint of Grubbs' proposal ~

\$ activity : bisphosphine complex << monophosphine complex
bulkier phosphine favor the ligand dissociation.

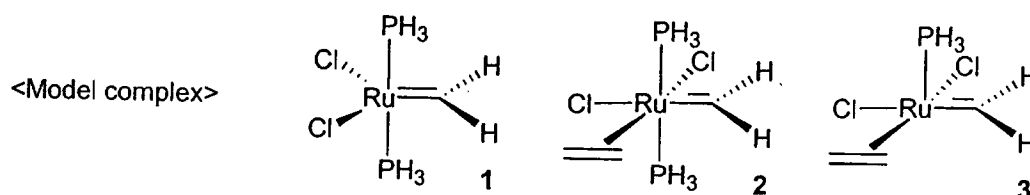
bisphosphine complex has weak metathesis activity

\$ ethylene coordination site is cis to carbene

\$ R=CH₂ bond should rotate 90° in order to react with ethylene

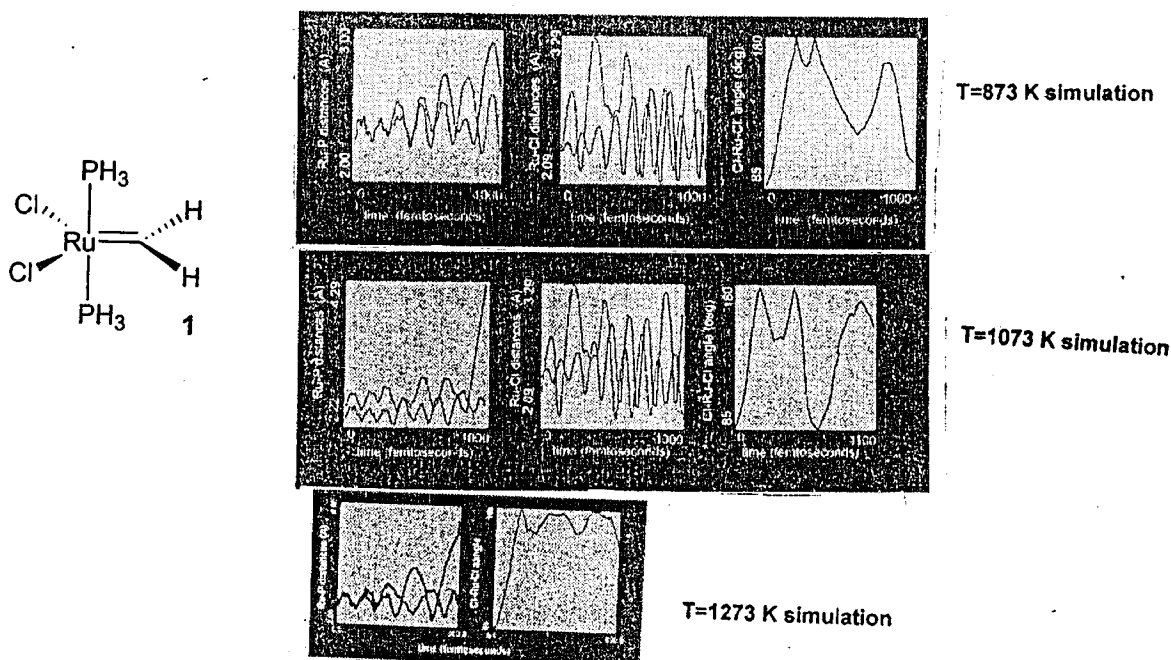
► Calculation

Step 1 : Energy optimization of initial state → carried out in DFT level.



Step 2 : Ab initio MD simulation of complex 1 under high temperature

In this study, simulation is carried out under relatively high temperature condition.
→ To express the molecular behavior at the high-end tail of Maxwell-Boltzmann distribution.

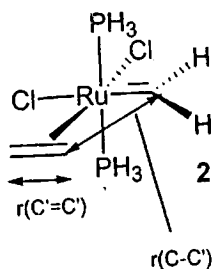


T= 1073K, 1273K : one of Ru-P length become >4Å at ~1000fs
→ one PH₃ ligand dissociated under high temp. condition.

During the simulation, Ru=CH₂ double bond easily rotated.

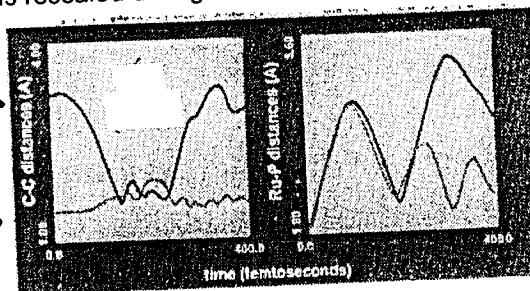
Step 3 : Ab initio MD simulation of complex 2

In these studies, initial molecular energy is concentrated in the form of Ru-P bond compression.
 → For selective bond activation. Atomic velocity is rescaled during first femtoseconds to limit whole energy.

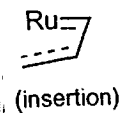


$T=400 \pm 40K$

$r(C-C) \rightarrow$
 $r(C=C) \rightarrow$

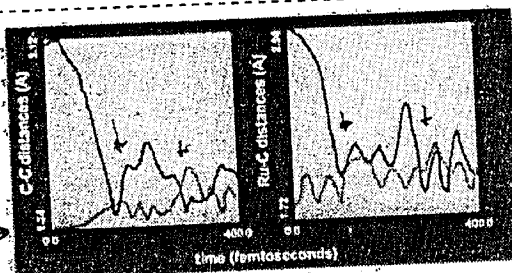


@~130fs

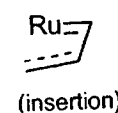


$T=400 \pm 250K$

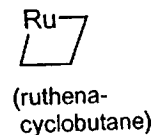
$r(C-C) \rightarrow$
 $r(C=C) \rightarrow$



@~130fs

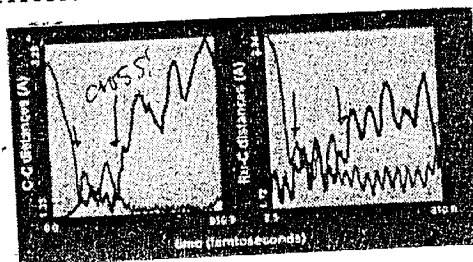


@~300fs

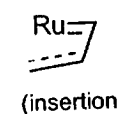


$T=400 \pm 500K$

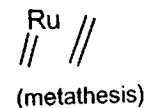
$r(C-O) \rightarrow$
 $r(C=C) \rightarrow$



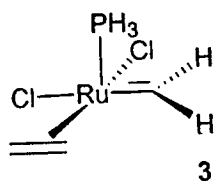
@~150fs



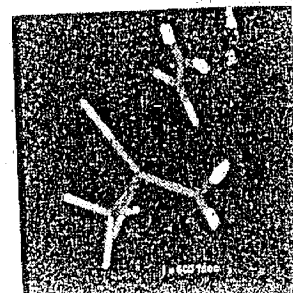
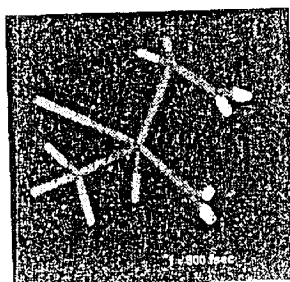
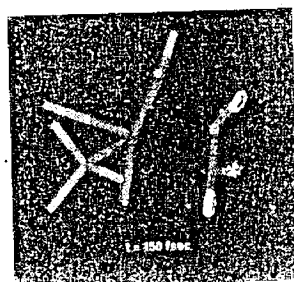
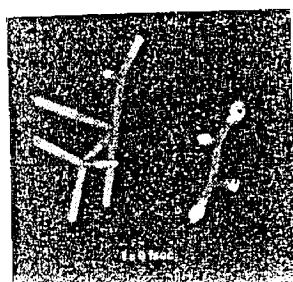
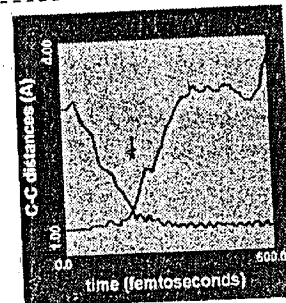
@~350fs



Step 4 : Ab initio MD simulation of complex 3



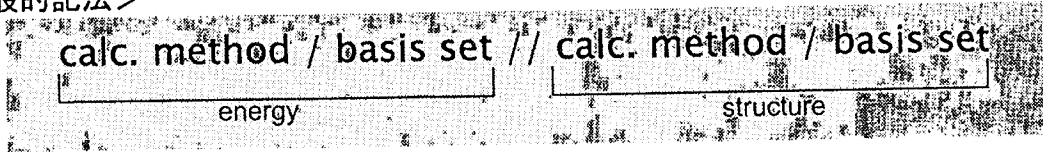
initial $T=0K$ (Ru-P bond is compressed)



Appendix

▷ QM calculation

<一般的記法>



(例) MP4 / 6-311G(3df,2dp) // RHF / 6-31G(d,p)

⇒ 6-31G(d,p)基底を用いたRestricted HF法により構造を決定
得られた構造を基に、6-311G(3df,2dp)基底を用いたMP4法によりエネルギーを計算

<計算に要する相対コスト>

approximation	reliability	size dependency	no. of non-H atoms
<i>ab initio MO methods</i>			
CCSD(T)/QZDP	quantitative (ca. 2 kcal mol ⁻¹)	N ⁶	several
MP2/DZP	semi-quantitative	N ⁴	ca. 50
DFT(B3LYP)/DZP	semi-quantitative	N ³	ca. 200
HF/DZ	qualitative	N ³	ca. 400
<i>semi-empirical MO methods</i>			
AM1, PM3, MNDO	semi-qualitative	N ⁽²⁻³⁾	1000s
<i>classical force field methods</i>			
Amber, Charmm, MM3	semi-qualitative	N ⁽¹⁻²⁾	ca. 10 ⁵

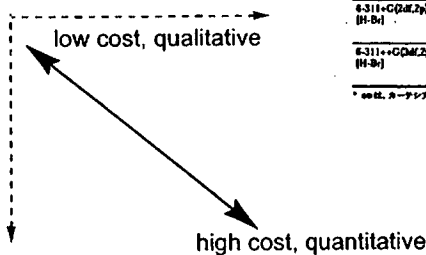
N = 基底関数の数
(∞ 電子数)

<汎用基底関数系>

基底関数系	電子数 →					全CI
	RHF	MP2	MP3	MP4	CCSD(T)	
最小 STO-3G						
スプリットバレンス 3-21G						
分層関数 6-31G(d)						
6-31G(4p)						
diffuse関数 6-311+G(4p)						
高次元基底関数 6-311+G(2df,2dp)						
6-311+G(2df,2dp)						
	RHF 関数					Schrödinger 方程式

基底関数系 (適用可能な原子) 記述	基底関数の数 第一関数の原子 基底関数	デフォルト の関数型*
STO-3G [H-X]	最小基底系 (精度を犠牲にして、計算時間を速く を要した)。3-21G でも大きすぎるような系に 対して、定性的な結果を求める時に用いる。	5 1 6D
3-21G [H-X]	スプリットバレンス系。原子関数ごとに二つの関 数を置くので、精度をよりよく表現でき る。6-31G が大きすぎるような系に対して用い る。	9 2 6D
6-31G(d) [H-C]	基底関数に分層関数を加える。中層関数から大きな の基底関数と対応している。この基底系 は、大成分のd関数を用いる。	15 2 6D 7F
6-31G(4p) [H-C]	基底関数にも分層関数を加える。基底関数に なるような場合 (例えば、基底エネルギー) や 定性的に精度の高いエネルギーを求める計算に 用いる。	15 5 6D 7F
6-31+G(d) [H-C]	分層関数に加える。孤立電子を持つ系やフ ン、自由状態に置換。	19 2 6D 7F
6-31+G(4p) [H-C]	上の基底系に基底のp関数を加える。6-31G(4p) の基底系を用いる時は、diffuse関数が必要。	19 5 6D 7F
6-311+G(4p) [H-Br]	split-valued 基底関数関数を6-31+G(4p)に追加する (二つのp関数とp関数)。もう一つは付くと水 素原子にもdiffuse関数を加えることになる。	22 6 5D 7F
6-311+G(2df,2dp) [H-Br]	二層のd関数(diffuse関数)を基底関数に加え、一 層のp関数を基底系に加える。	27 6 5D 7F
6-311+G(2df,2dp) [H-Br]	二層のd関数と一層のdiffuse関数ととも に)を基底関数に、二層のp関数を基底系に加 える。	24 9 5D 7F
6-311+G(2df,2dp) [H-Br]	diffuse関数に加えて、三層のd関数と一層の関 数を基底系に、二層のp関数と一層のd関数を 基底系に加える。	39 15 5D 7F

* 6Dは、s-p軌道の内成分のd関数、5Dは7Fは、d関数とdiffuse関数のd関数とdiffuse関数を意味する。



▷ Potential energy surface / Intrinsic reaction coordinate

PES (ポテンシャルエネルギー面)

反応座標(RC)の変化に対応する系のエネルギー変化をプロットしたもの。
実際は多次元だが、反応に密接に関わる結合の距離や角度だけを変数にし、
見やすいように2次元もしくは3次元にプロットすることが多い。

IRC (極限的反応座標)

反応システムがPESの上を極微小のエネルギー変化を受けて
進んだときに通る反応経路。最もポテンシャルエネルギーの低い谷間を通る道のり。
遷移状態(TS)はIRCに沿った方向に対してはエネルギーの極大点だが
他の方向に対しては全てエネルギー極小点になっている。(PESの鞍点がTSになる)

