Automated reaction discovery through reactive MD simulations

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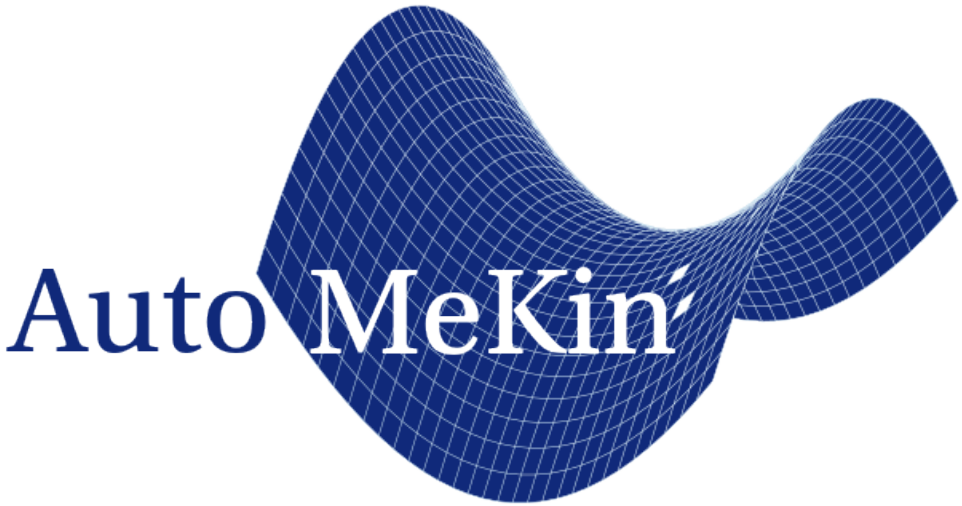
Outline

- ✓ Our method: AutoMeKin
- ✓ Applications

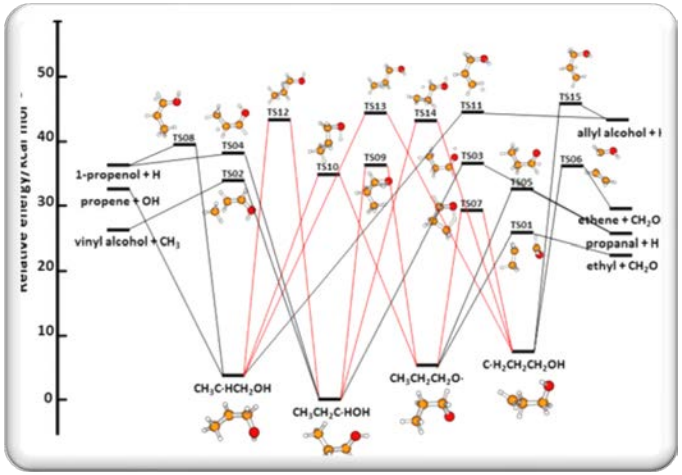


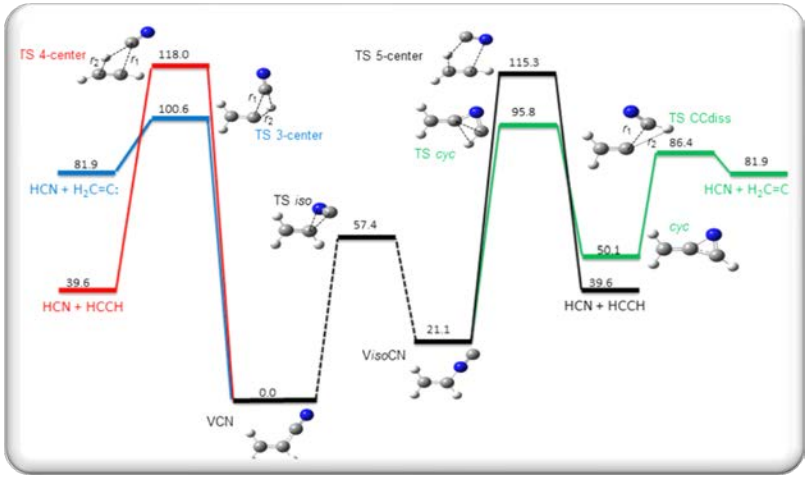
Our method

Complex and/or non-intuitive mechanisms

Manual searches:

- ✓ can be tedious
- ✓ and might overlook unconventional paths



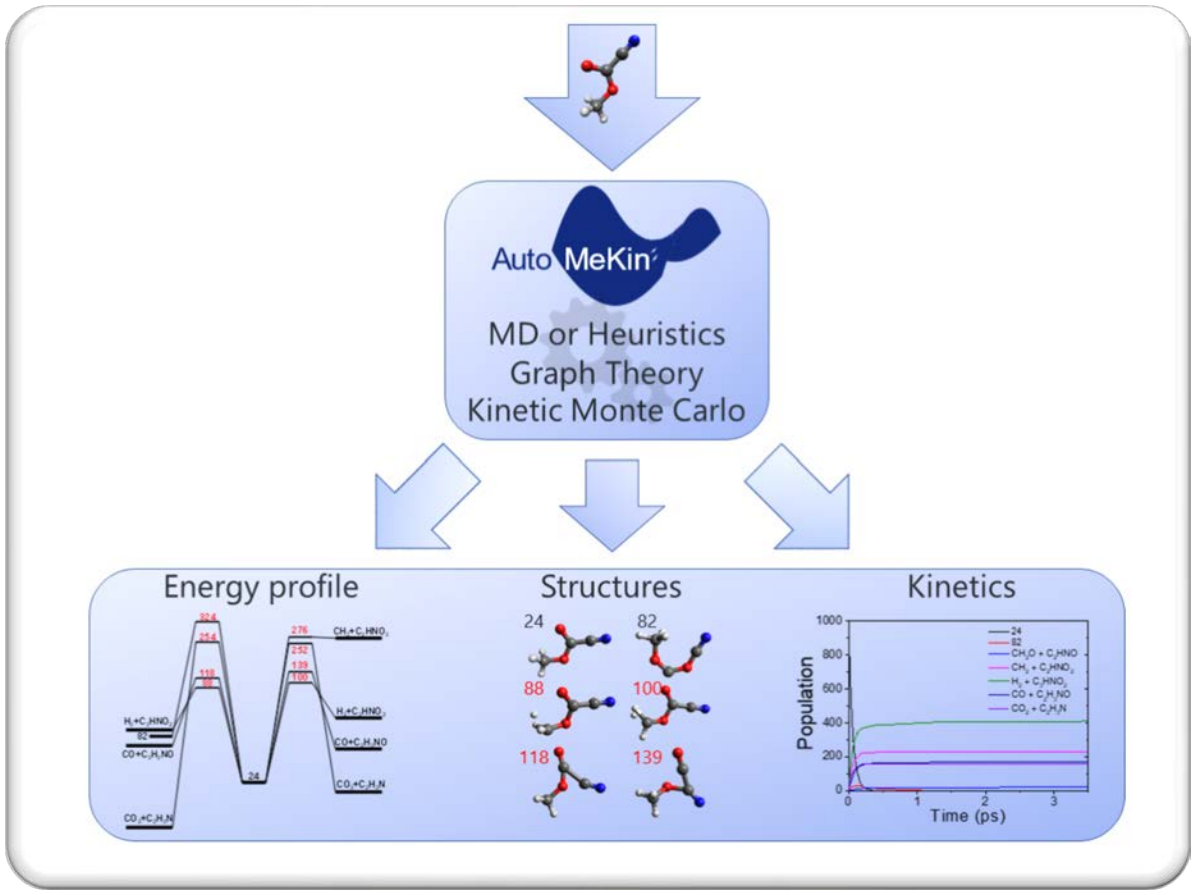


AutoMeKin

J. Comput. Chem. **2015**, *36*, 222

Phys. Chem. Chem. Phys. **2015**,*17*, 14912

J. Comput. Chem. **2021**, *42*, 2036

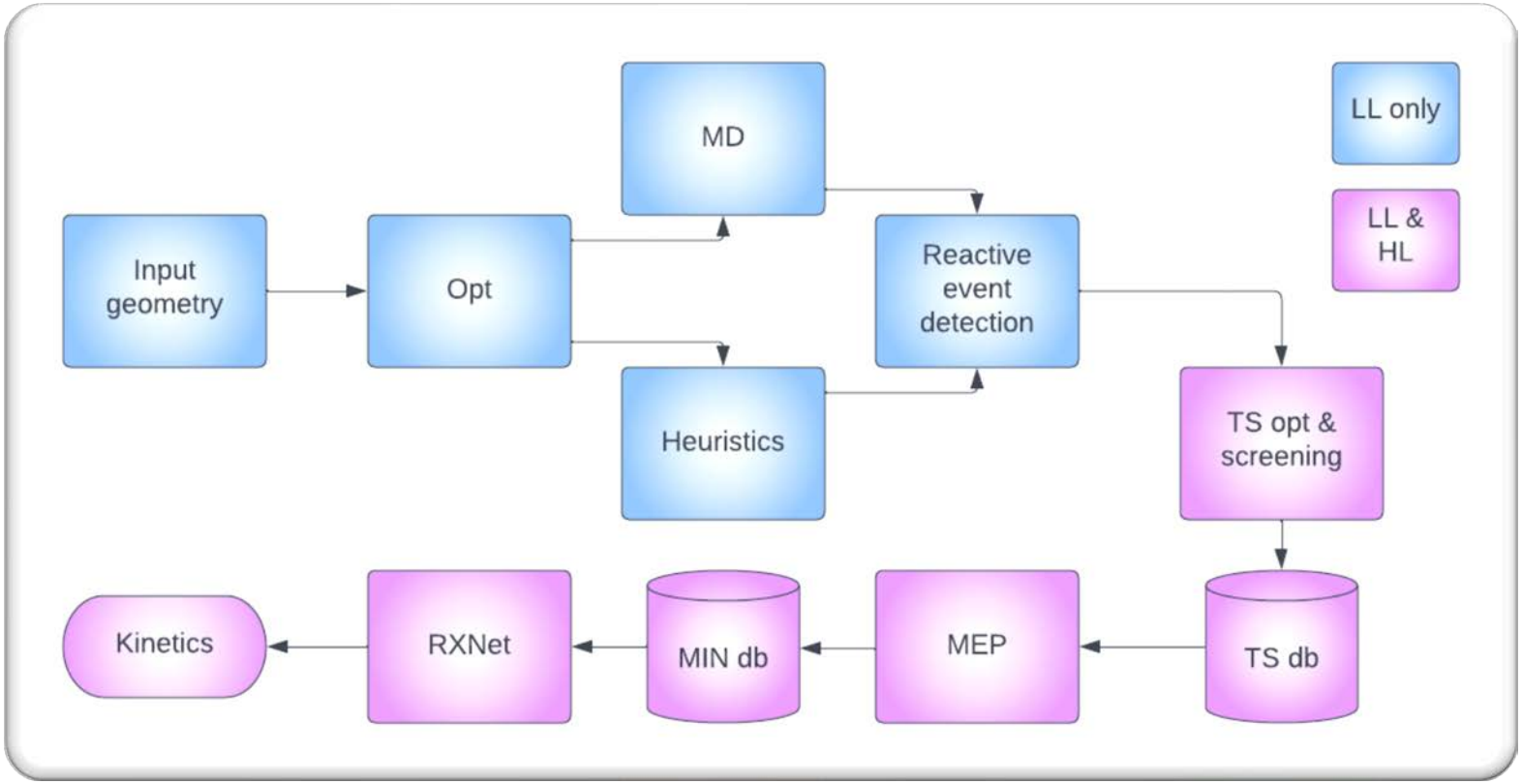


AutoMeKin's pipeline

J. Comput. Chem. **2015**, *36*, 222

Phys. Chem. Chem. Phys. **2015**,*17*, 14912

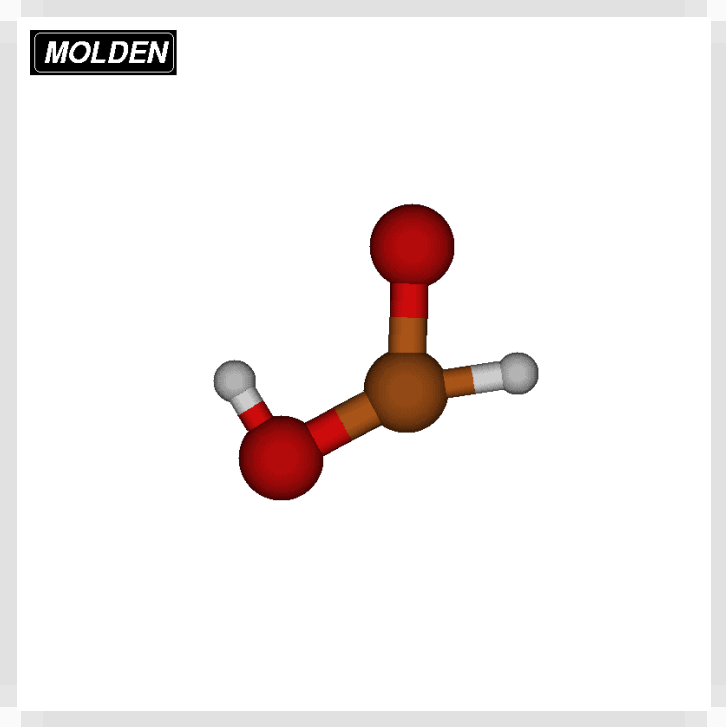
J. Comput. Chem. **2021**, *42*, 2036



Reactive MD simulations I

Phys. Chem. Chem. Phys. **2015**,*17*, 14912

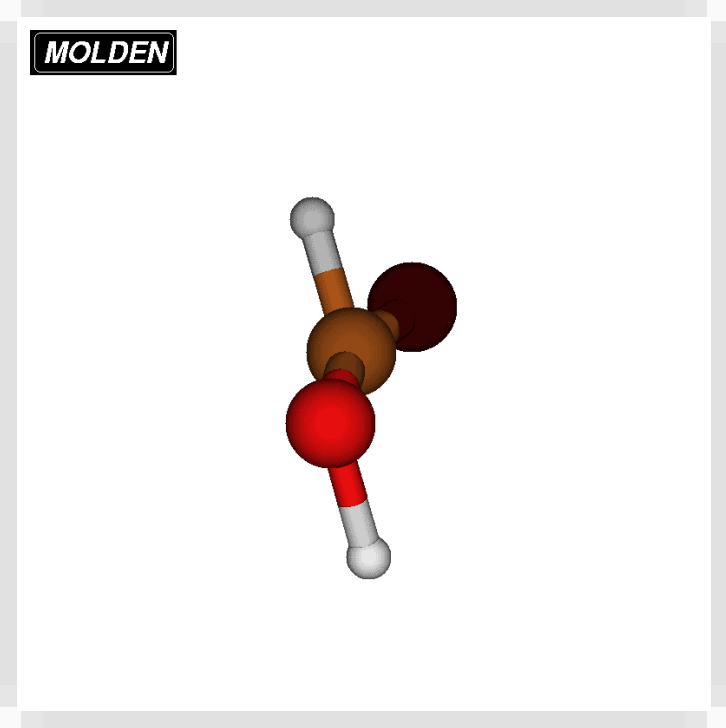
- ✓ Standard MD: high *E* or *T* and short:
- ✓ QCT
- ✓ microcanonical/canonical sampling
- ✓ adaptive energy range
- ✓ movie (210 kcal/mol)



Reactive MD simulations II

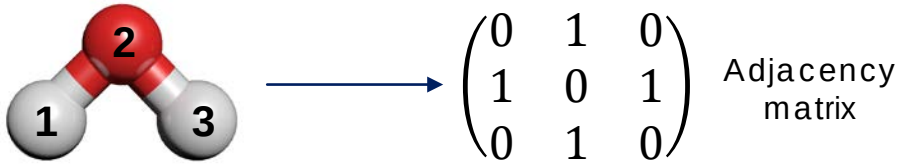
ChemSystemsChem **2020**, *152*, e19002

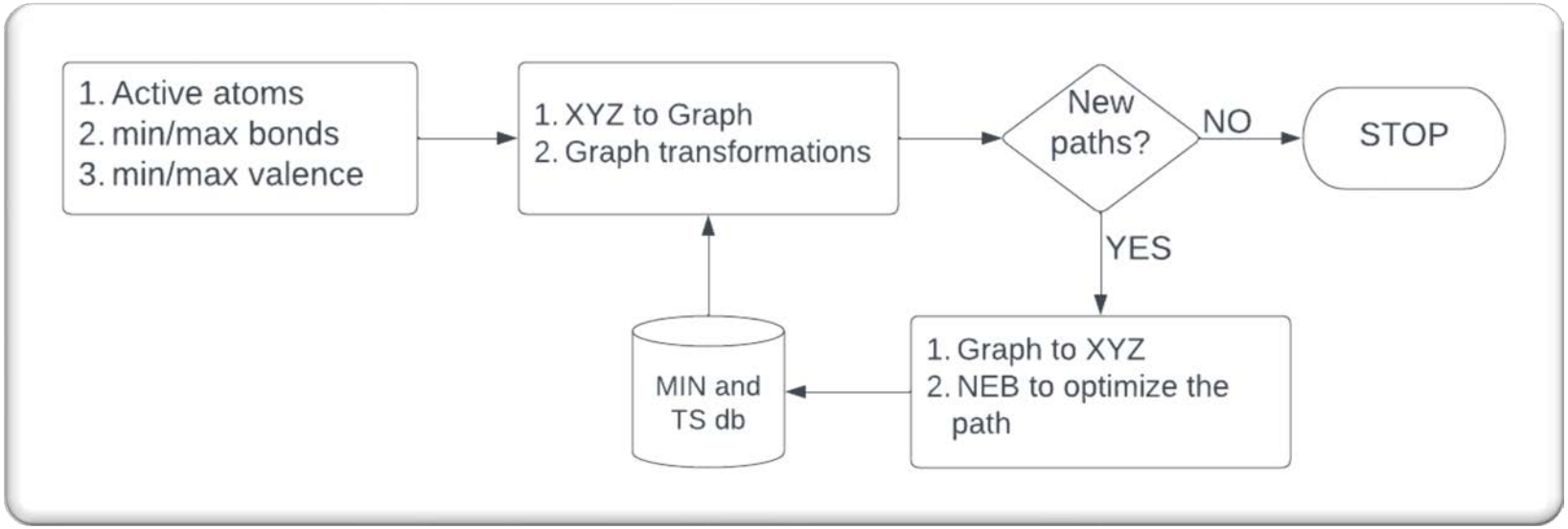
- ✓ Rare-event acceleration method (BXDE):
- ✓ energy boxes
- ✓ more efficient sampling
- ✓ loose coupling via ASE
- ✓ movie: Langevin 1000 K



ChemKnow

J. Comput. Chem. **2021**, *42*, 2036

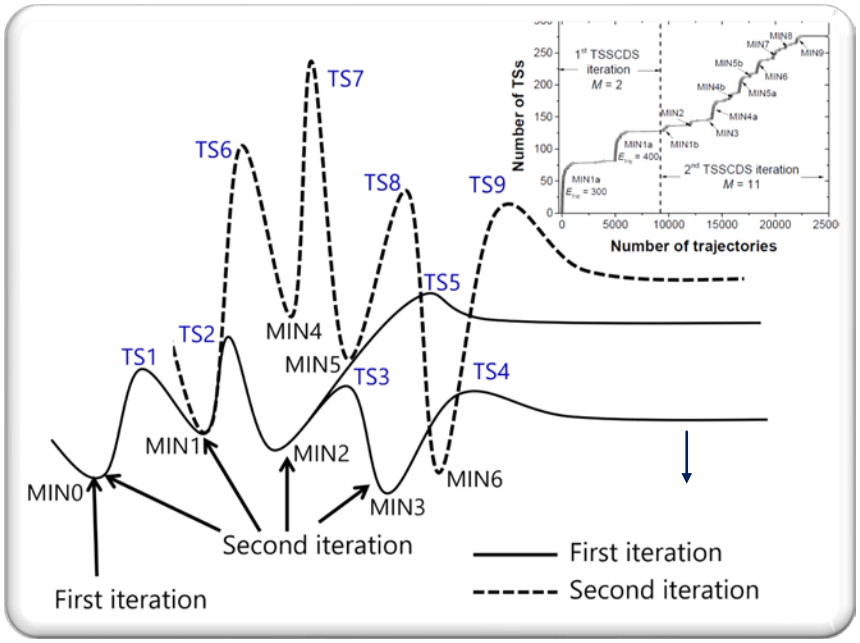




Sampling from multiple minima

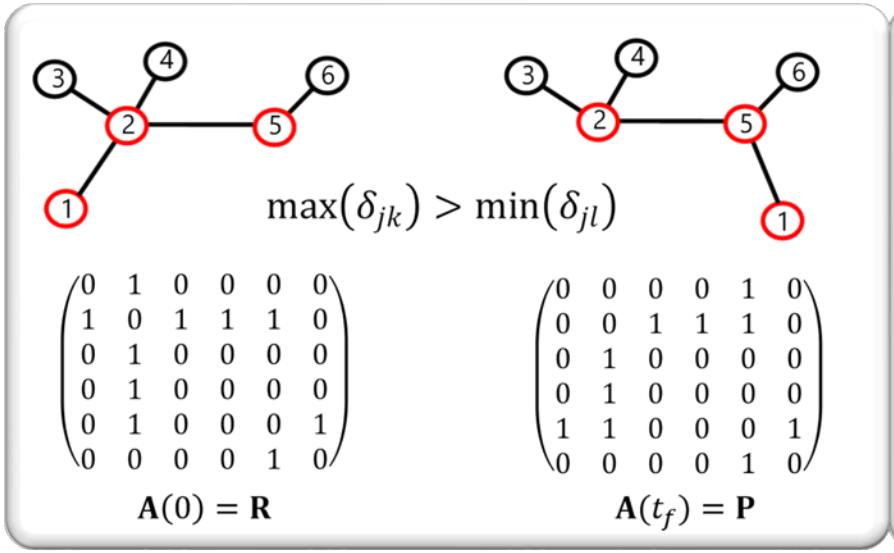
Phys. Chem. Chem. Phys. **2015**,*17*, 14912

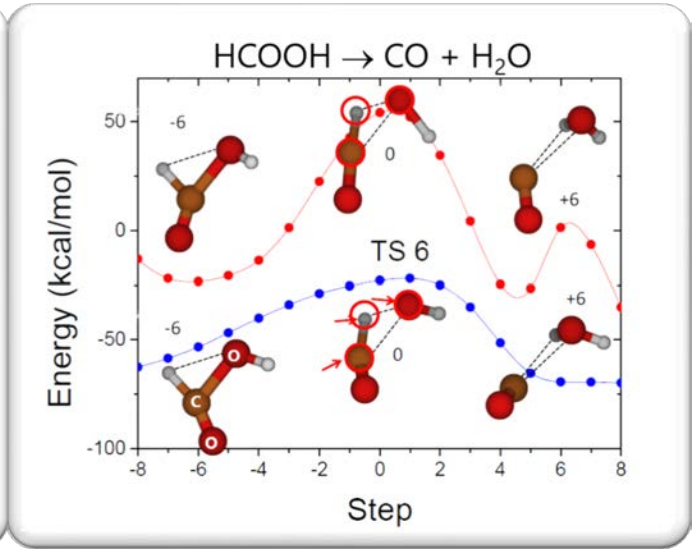
- ✓ Trajectories start from multiple minima



Reactive event detection I: (BBFS)

- ✓ Algorithm based on the adjacency matrix
- ✓ Relaxation of atoms not involved in the reaction



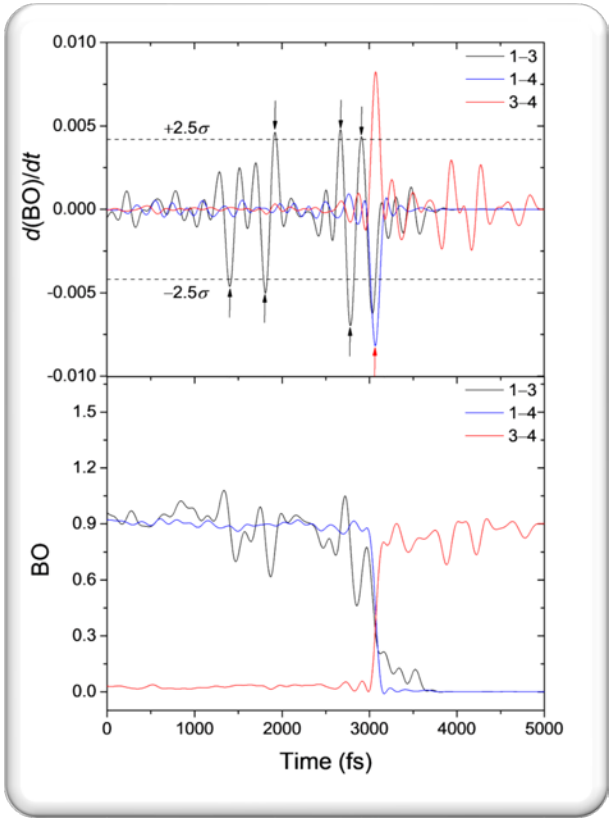


$$a_{ij} = \begin{cases} 1 & \text{if } \delta_{ij} < 1 \\ 0 & \text{otherwise} \end{cases}, \text{ with } \delta_{ij} = \frac{r_{ij}}{r_{ij}^{\text{ref}}}$$

Reactive event detection II: (BOTS)

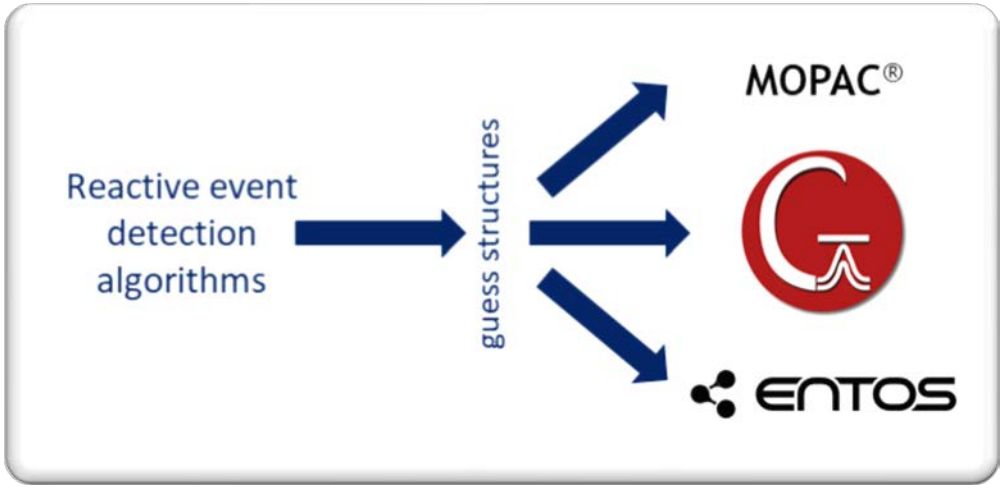
JCTC, **2020**, *16*, 1606

- ✓ Algorithm based on the bond orders
- ✓ Relaxation of atoms not involved in the reaction



Optimization

Single-ended methods: MOPAC, G09, G16, Entos Qcore

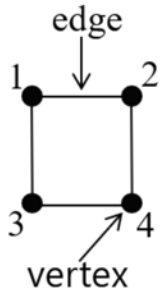


Screening

Molecules, **2018**, *23*, 3156

PRL, **2011**, *107*, 085504

Spectral Graph Theory & SPRINT coordinates



Laplacian $\mathbf{L} = \mathbf{D} - \mathbf{A}$

$$\begin{pmatrix} 2 & -1 & -1 & 0 \\ -1 & 2 & 0 & -1 \\ -1 & 0 & 2 & -1 \\ 0 & -1 & -1 & 2 \end{pmatrix}$$

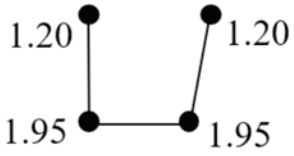
$$\lambda = 0,2,2,4$$

Adjacency

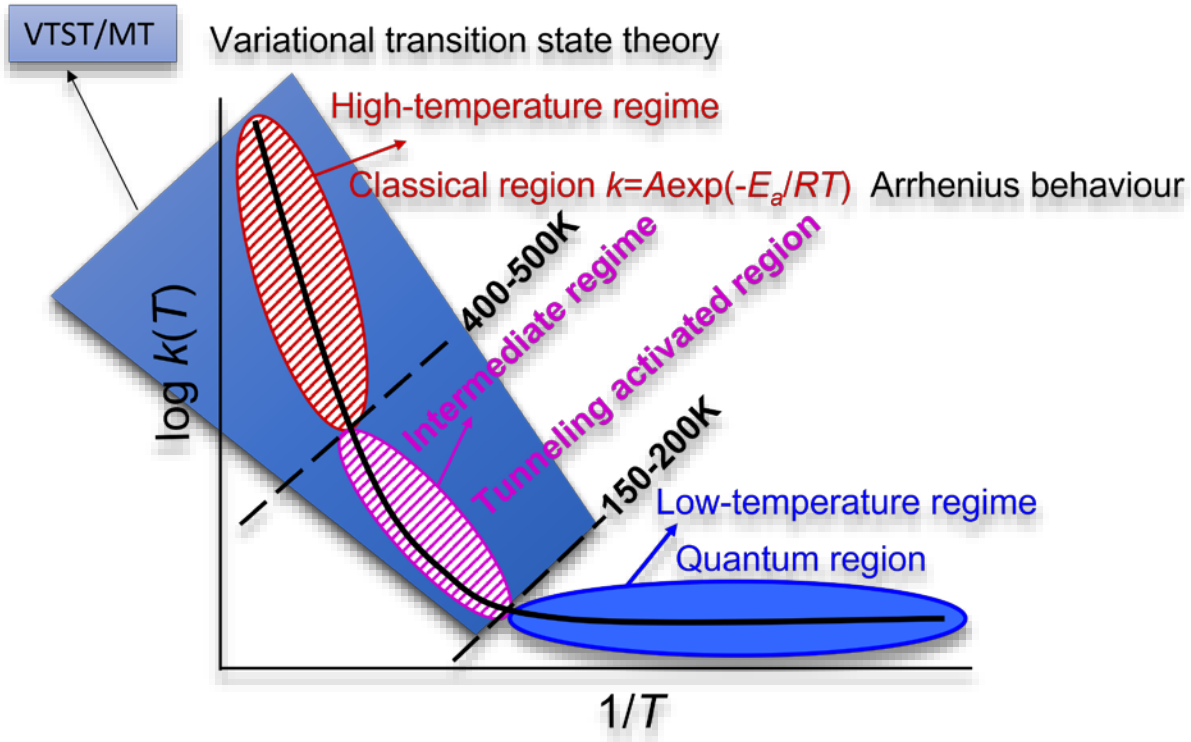
$$\begin{pmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{pmatrix}$$

$$a_{ij} = \frac{1 - (\delta_{ij})^n}{1 - (\delta_{ij})^m}$$

SPRINT Coordinates



$$S_i = \sqrt{N}\lambda^{max}\nu^{max}$$



Basic concepts of chemical kinetics

Basic concepts of chemical kinetics I

Homogeneous reactions (occurring in a single phase).

closed system (in general, gas-phase reactions).

$$aA + bB + \cdots \rightarrow eE + fF + \cdots \qquad (1)$$

a, *b*, ..., *e*, *f*,... stoichiometric coefficients (in general, ν_i)

A, *B*,..., *E*, *F*,... chemical species.

ν_i must ensure mass and charge balance.

Rate of Reaction (*r*)

$$r = \frac{1}{V}\left(\frac{1}{\nu_i}\frac{dn_i}{dt}\right) = \frac{1}{\nu_i}\frac{d[\mathrm{S}_i]}{dt} \qquad \text{constant } V \qquad (2)$$

$$r = -\frac{1}{a}\frac{d[\mathrm{A}]}{dt} = -\frac{1}{b}\frac{d[\mathrm{B}]}{dt} = \cdots = \frac{1}{e}\frac{d[\mathrm{E}]}{dt} = \frac{1}{f}\frac{d[\mathrm{F}]}{dt} = \cdots \qquad (3)$$

$[\mathrm{S}_i]$ molar concentration of species *i*.

Example: $N_2 + 3H_2 \rightarrow 2NH_3$ $\quad r = -\frac{d[\mathrm{N_2}]}{dt} = -\frac{1}{3}\frac{d[\mathrm{H_2}]}{dt} = \frac{1}{2}\frac{d[\mathrm{NH_3}]}{dt}$

Units for *r*: chemical kinetics: M s^{-1} (mol L^{-1} s^{-1}),

chemical dynamics: molecule cm^{-3} s^{-1}

Basic concepts of chemical kinetics II

Rate Law

Relationship between the rate of reaction and the concentrations of species at time t. For many reactions: $\boldsymbol{r = k[A]^{\alpha}[B]^{\beta}\ldots}$

k is the rate constant or rate coefficient. $k = k(T, p)$
$\alpha, \beta, \ldots$ are the orders with respect to species $A, B, \ldots$. The sum $\alpha + \beta + \ldots$ is the overall order.

Examples:

$2N_2O_5 \rightarrow 4NO_2 + O_2$ $\quad r = k[N_2O_5]$

$2NO + O_2 \rightarrow 2NO_2$ $\quad r = k[NO_2]^2[O_2]$

$H_2 + Br_2 \rightarrow 2HBr$ $\quad r = \frac{k[H_2][Br_2]^{1/2}}{1+j[HBr]/[Br_2]}$

In general, rate laws cannot be deduced from the reaction stoichiometry; they must be determined experimentally (or predicted by simulations).

Basic concepts of chemical kinetics III

Reaction Mechanisms

Collection of coupled steps involving chemical transformations of molecular species. The different steps are called elementary reactions.

A complex (or composite) reaction is formed by two or more elementary steps. Most chemical reactions are complex.

Example: $2N_2O_5(g) \rightarrow 4NO_2(g) + O_2(g)$ $\qquad r = k[N_2O_5]$

1. $N_2O_5 \rightleftharpoons NO_2 + NO_3$
2. $NO_2 + NO_3 \rightarrow NO + O_2 + NO_2$
3. $NO + N_2O_5 \rightarrow NO_2 + NO_2 + NO_2$

The molecularity is the number of molecules that react in an elementary reaction.

Unimolecular reaction	A → products	$-\frac{d[A]}{dt} = k[A]$
Bimolecular reaction	A + B → products	$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A][B]$
	2A → products	$-\frac{1}{2}\frac{d[A]}{dt} = k[A]^2$

Basic concepts of chemical kinetics IV

Differential Rate Equations (DREs)

For a given reaction mechanism, we may write the (coupled) differential rate equations (aka Chemical Master Equation). From these equations, we may predict the rate law (not always) and the time evolution of the populations of all the chemical species involved in the mechanism.

Example: $2N_2O_5(g) \rightarrow 4NO_2(g) + O_2(g)$

1. $N_2O_5 \rightleftharpoons NO_2 + NO_3$
2. $NO_2 + NO_3 \rightarrow NO + O_2 + NO_2$
3. $NO + N_2O_5 \rightarrow NO_2 + NO_2 + NO_2$

$$\frac{d[N_2O_5]}{dt} = -k_1[N_2O_5] + k_{-1}[NO_2][NO_3] - k_3[NO][N_2O_5]$$

$$\frac{d[NO_2]}{dt} = k_1[N_2O_5] - k_{-1}[NO_2][NO_3] + 3k_3[NO][N_2O_5]$$

$$\frac{d[NO_3]}{dt} = k_1[N_2O_5] - (k_{-1}+k_2)[NO_2][NO_3]$$

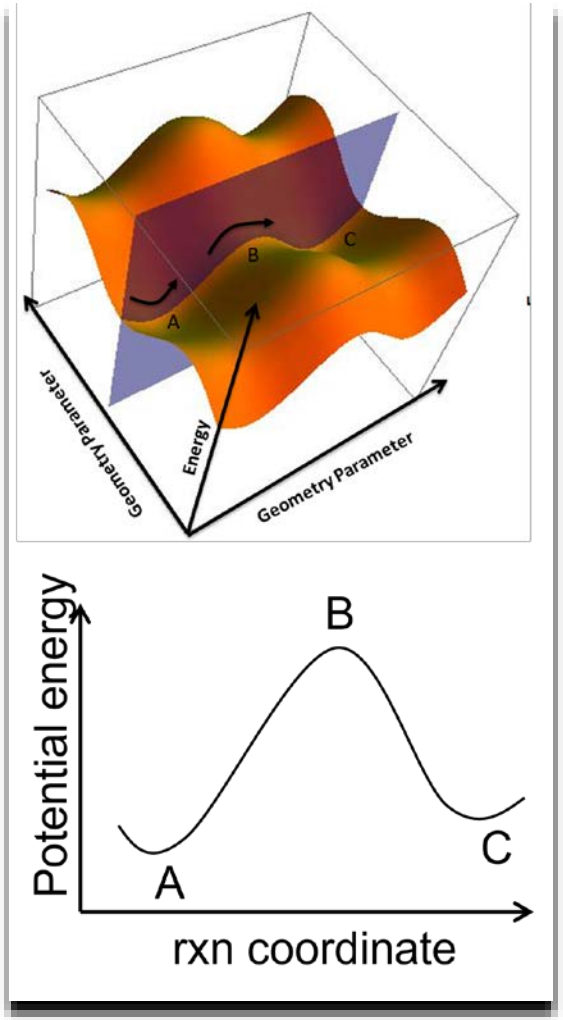
$$\frac{d[NO]}{dt} = k_2[NO_2][NO_3] - k_3[NO][N_2O_5]$$

$$\frac{d[O_2]}{dt} = k_2[NO_2][NO_3]$$

Solution of the DREs: Analytical, numerical integration, KMC

Basic concepts of chemical kinetics V

In terms of PESs, an elementary step involves motion across a single barrier



Basic concepts of chemical kinetics VI

Important points of the PES: Those in which the gradient is zero (stationary points).

Minima or equilibrium geometries: All the eigenvalues of the Hessian are positive.

- ✓ Global: Lowest potential energy of the PES.
- ✓ Local: A point with the lowest potential in a given region.
- ✓ Reactive intermediate: Metastable local minimum.
- ✓ Conformers: The set of local minima that can be interconverted by rotations about single bonds.

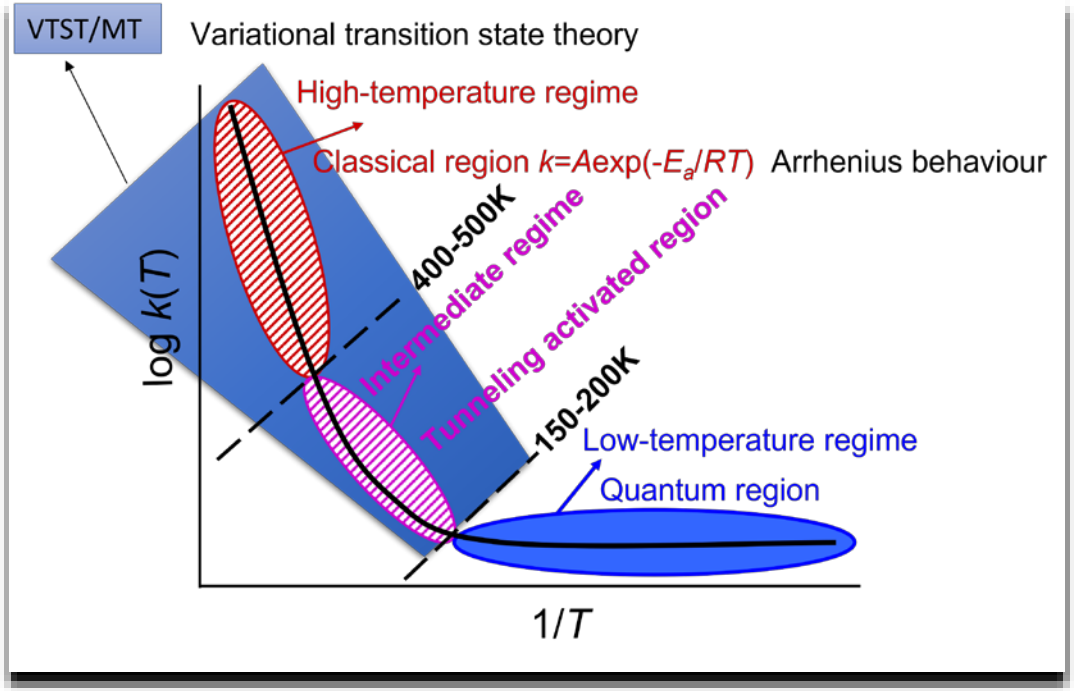
Saddle points: One or more eigenvalues of the Hessian are negative.

- ✓ First order: Only one of the eigenvalues is negative.
- ✓ Second order: Two eigenvalues are negative.
- ✓ Transition state (TS): First order saddle point relevant for the study of a chemical reaction.

Note: the Hessian is the matrix of second derivatives of the potential with respect to the coordinates (also called force constant matrix).

Basic concepts of chemical kinetics VII

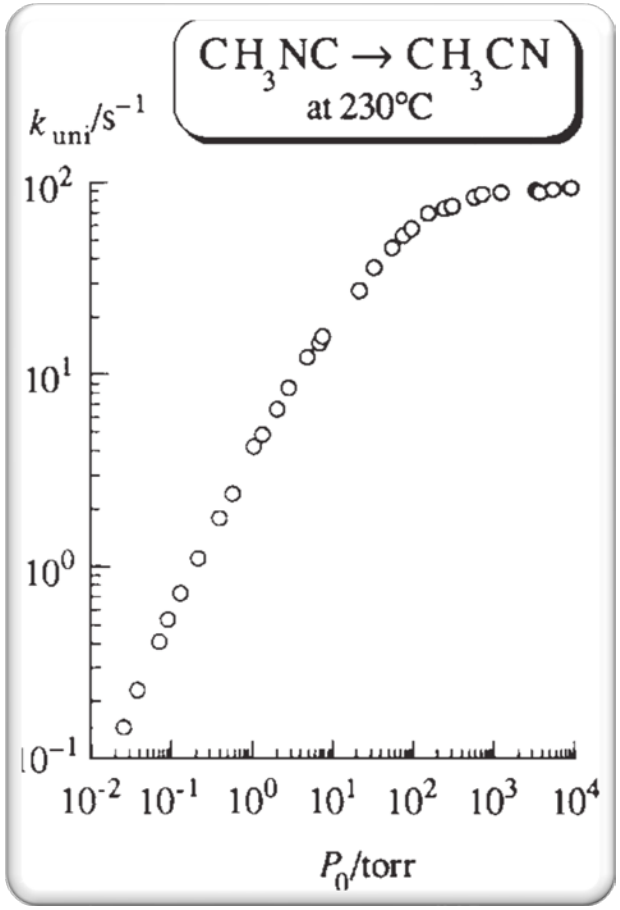
Dependence of k on T



Basic concepts of chemical kinetics VIII

Dependence of k on p

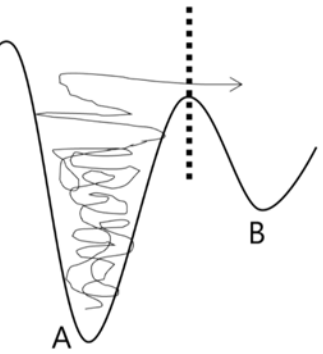
In general, only important for gas-phase unimolecular reactions



Kinetics module in AutoMeKin I

TST/RRKM

$$k(T) = \sigma \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}}$$

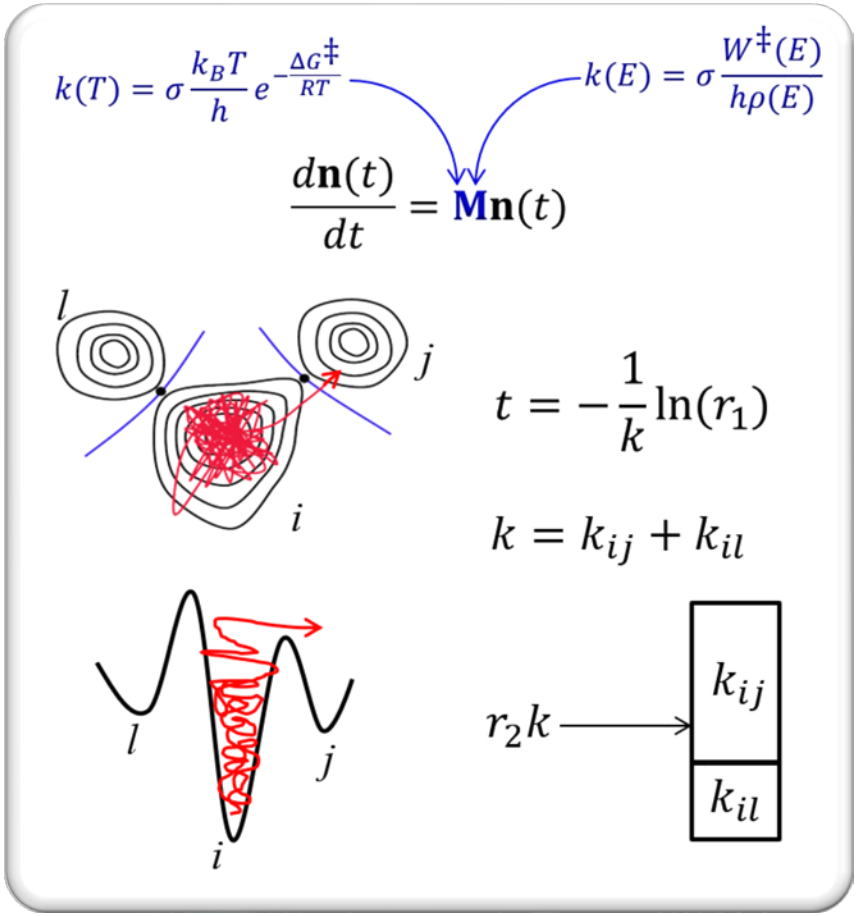


$$k(E) = \sigma \frac{W^{\ddagger}(E)}{h\rho(E)}$$

TST	RRKM
Boltzmann distribution	Fast IVR
The TS is not re-crossed	
The reaction follows the IRC	
The nuclei behave according to classical mechanics	

Kinetics module in AutoMeKin II

Chemical Master Equation: KMC



Computer program

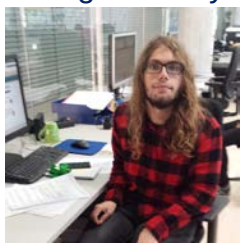
AutoMeKin2021: J. Comput. Chem., **2021**, *42*, 2036

https://rxnkin.usc.es/index.php/AutoMeKin

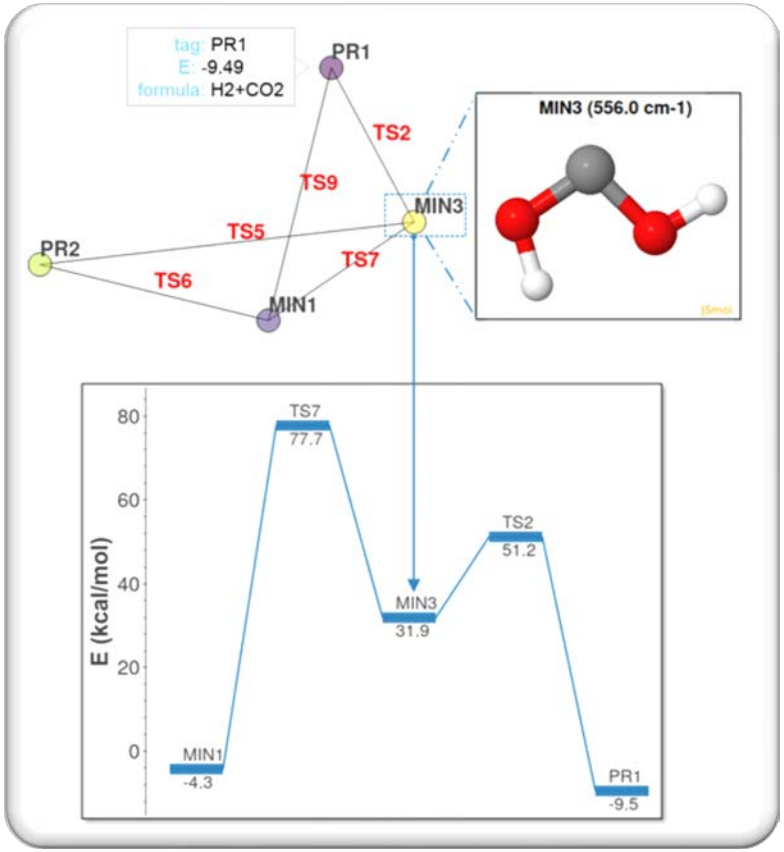
amk_tools: ACS Physical Chemistry Au **2022,** *2,* 225

Carles Bo

Diego Garay



Moisés Alvarez

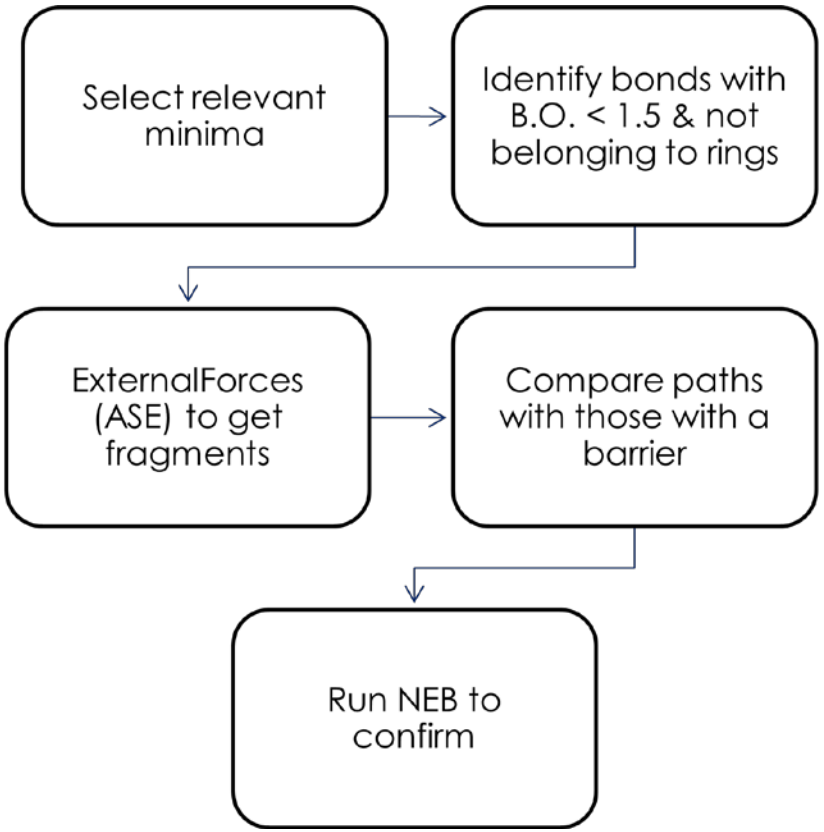


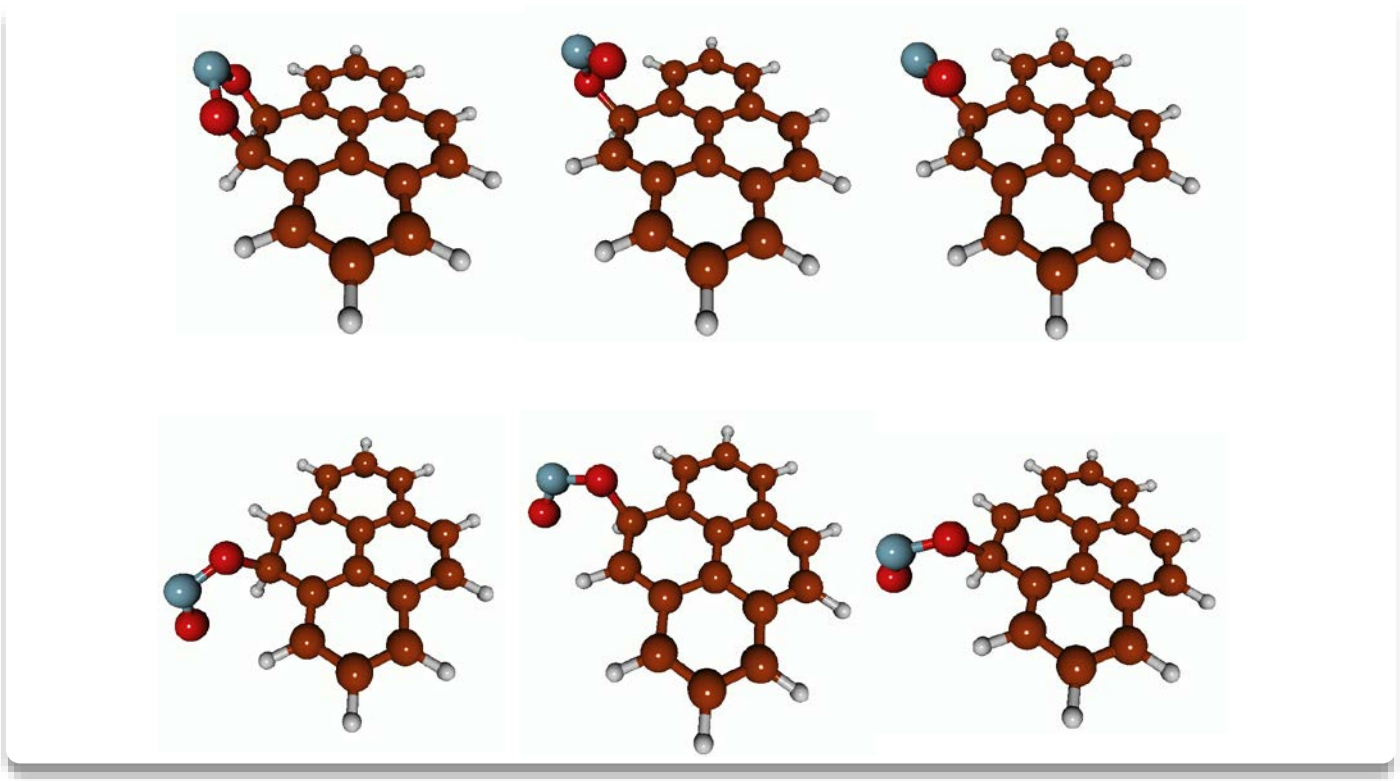
Computer program

AutoMeKin2021: J. Comput. Chem., **2021**, *42*, 2036

https://rxnkin.usc.es/index.php/AutoMeKin

Barrierless rxns: ACS Physical Chemistry Au **2022,** *2,* 225





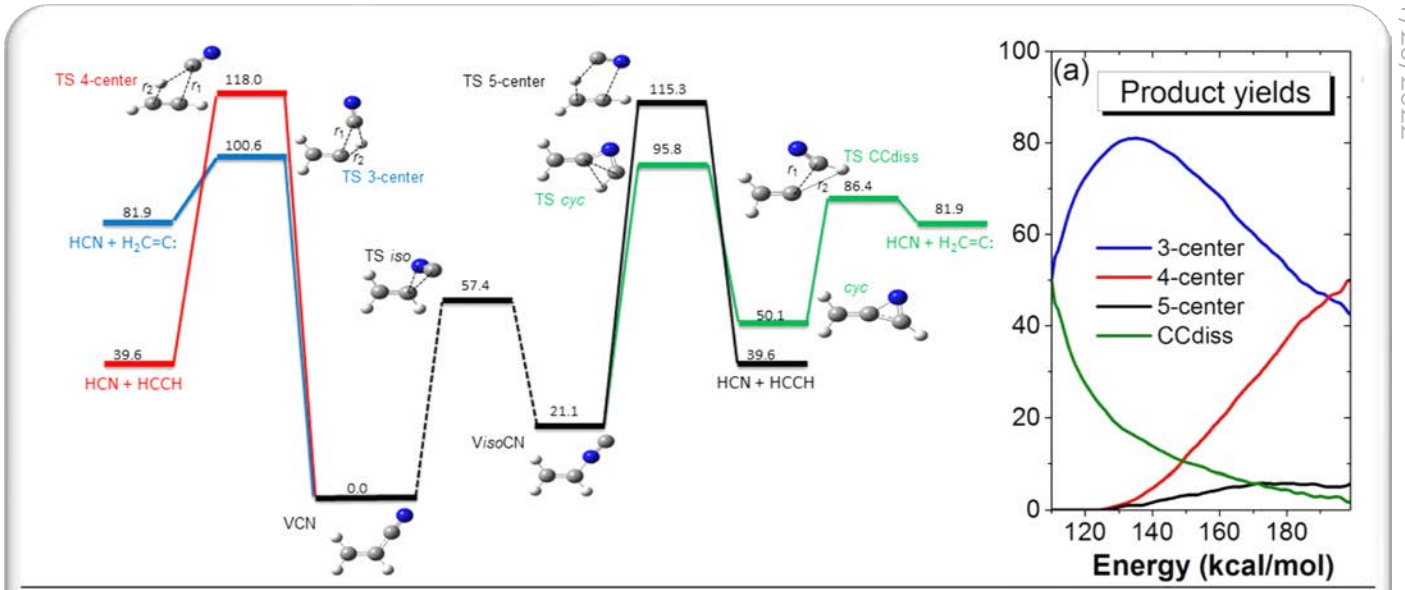
Applications

System	Reference
Fragmentation of indole	ACS Phys Chem Au **2022** (accepted)
Digylcine and dialanine	JCTC **2021**, *17*, 5556
Photoisomerization of a charged styryl dye	J. Am. Soc. Mass. Spectrom. **2021**, *32*, 2842
Formation mechanisms of formaldehyde in cold astrophysical regions	A&A **2021**, *656*, A148
Fragmentation of octaazapentalene	Monatsh Chem. **2021**, *152*, 421
Syngas oxy-combustión in supercritical CO_2	J. CO2 Util **2021**, *49*, 101554
Electron-transfer-induced cleaveage in Tryptophan	JPCA **2021**, *125*, 2324
Cycloaddition of cyclic nitrone	Tetrahedron **2020**, *76*, 130764
Ozonolysis of α-pinene	ChemSystemsChem **2020**, *152*, e19002.
vdW interactions	IJQC **2019**, *119*, e26008
Fragmentation of L-Cysteine	JPCA **2019**, *123*, 3685
Thermal decomposition of 1-propanol	JPCA **2018**, *122*, 4790
Tetrahydrofuran oxidation	Combust Flame **2018**, *191*, 252
Photolysis of methyl cyanoformate	ApJ **2017**, *849*, 15
Hydroformylation of ethylene	Chem. Sci. **2017**, *8*, 3843
Fragmentation of protonated uracil	PCCP **2016**, *18*, 22712
Photolysis of acryloyl chloride	PCCP **2016**, *18*, 5019
Photolysis of propenal	PCCP **2015**, *17*, 14912
HCN elimination from vinyl cyanide	PCCP, **2015**, *17*, 6948

Systems studied so far

HCN elimination from vinyl cyanide

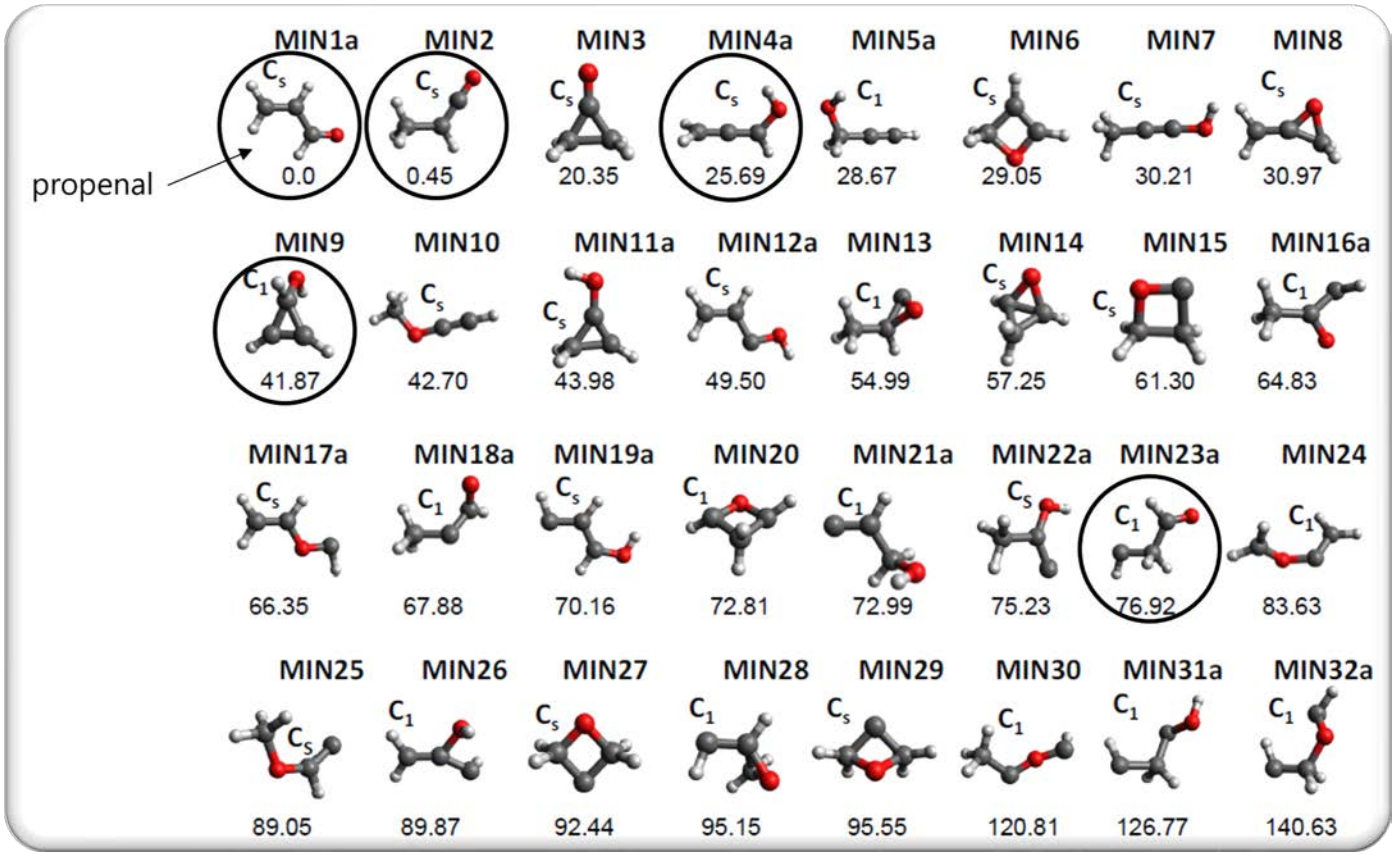
PCCP **2015**, *17*, 6948



Products	Exp	AutoMeKin
Vinylidene	77	79
Acetylene	23	21

Photolysis of propenal

PCCP **2015**, *17*, 14912
JCP **2011**, *134*, 044309

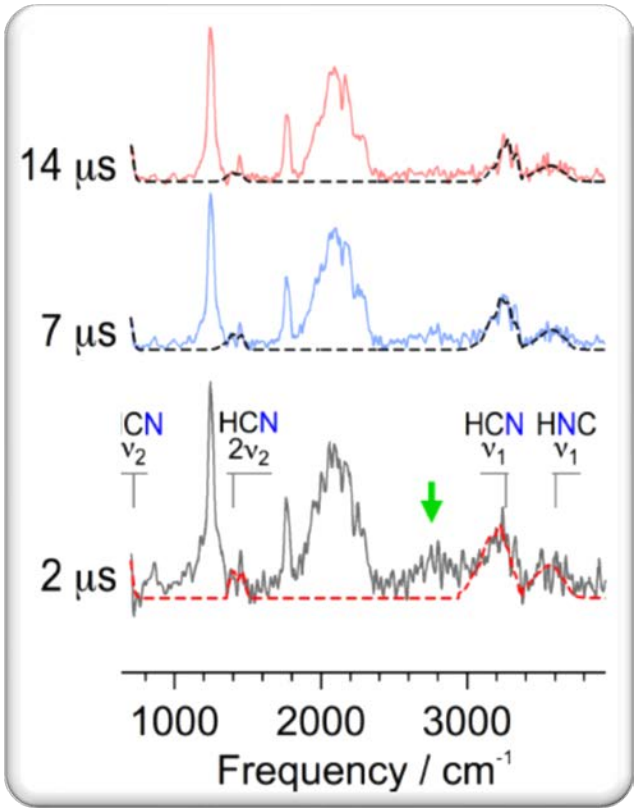


CCSD(T)/6-311+G(3df,2p)//B3LYP/6-311G(d,p)

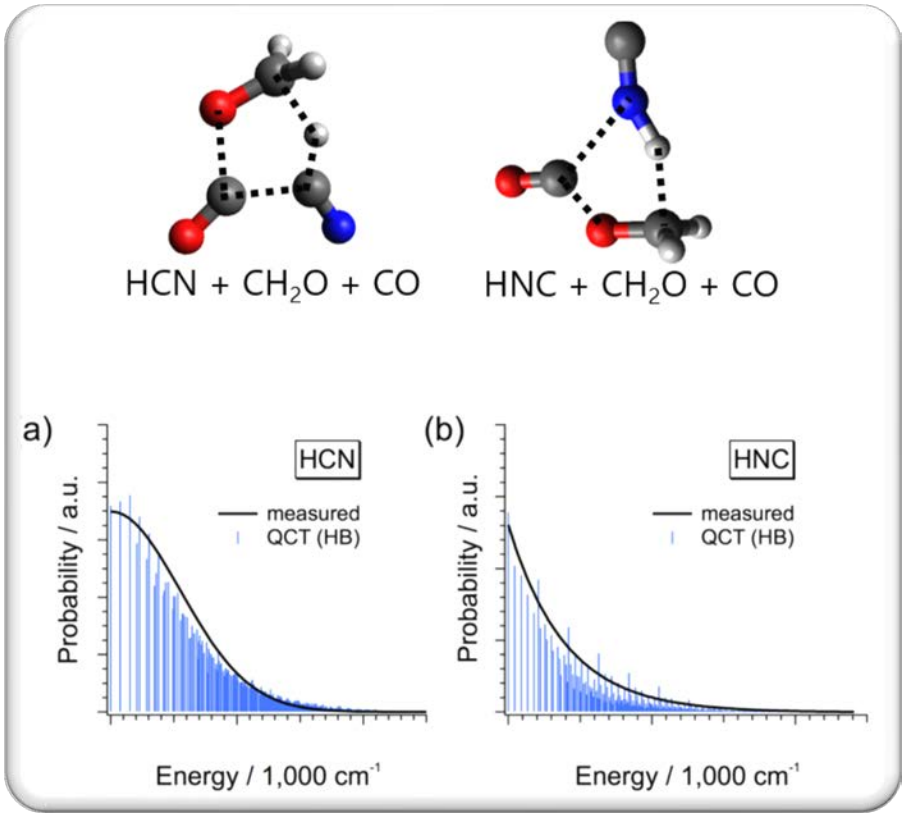
Photolysis of methyl cyanoformate

ApJ. **2017**, *849*, 15

Time-resolved IR spectra
Evidence of
HCN(HNC) formation



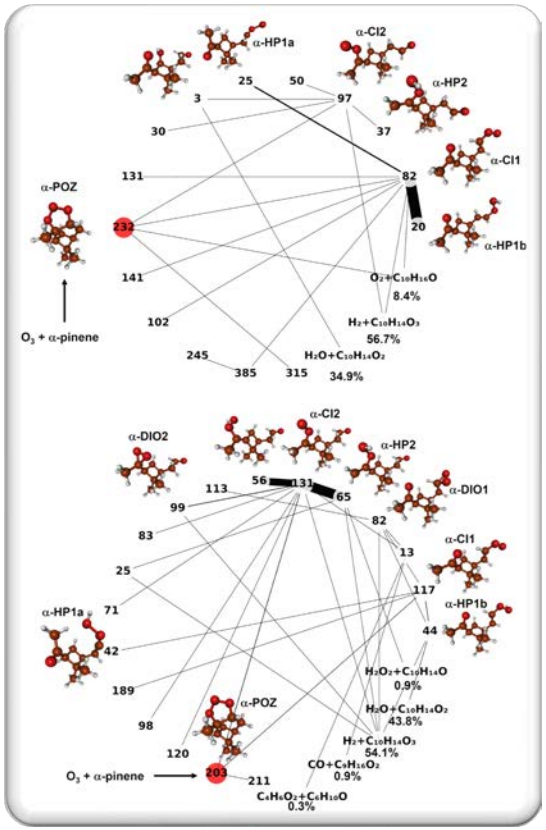
AutoMeKin & QCT
Top: AutoMeKin's TSs
Bottom: Vibrational distros



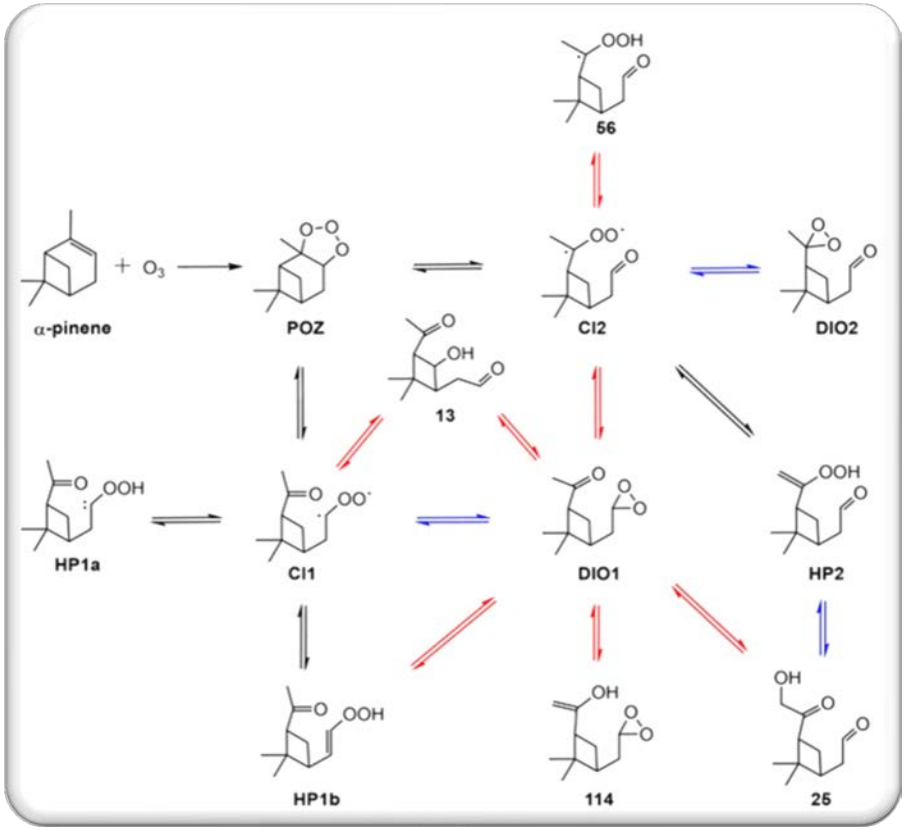
Ozonolysis of α-pinene

ChemSystemsChem **2020**, *152*, e19002

Reaction networks
Top: stdMD
Bottom: BXDE



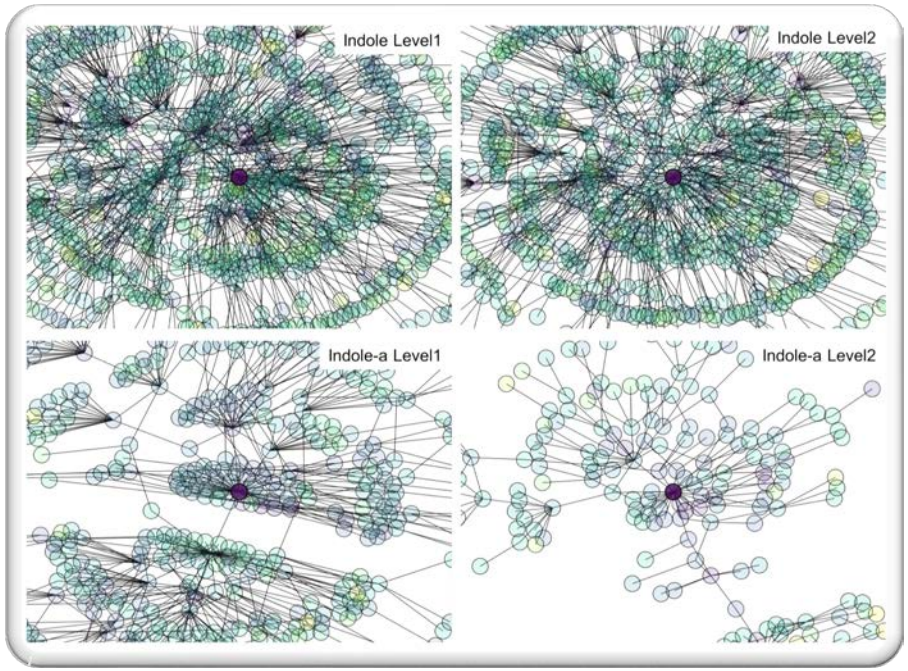
Mechanism
Blue: stdMD & BXDE
Red: Only BXDE



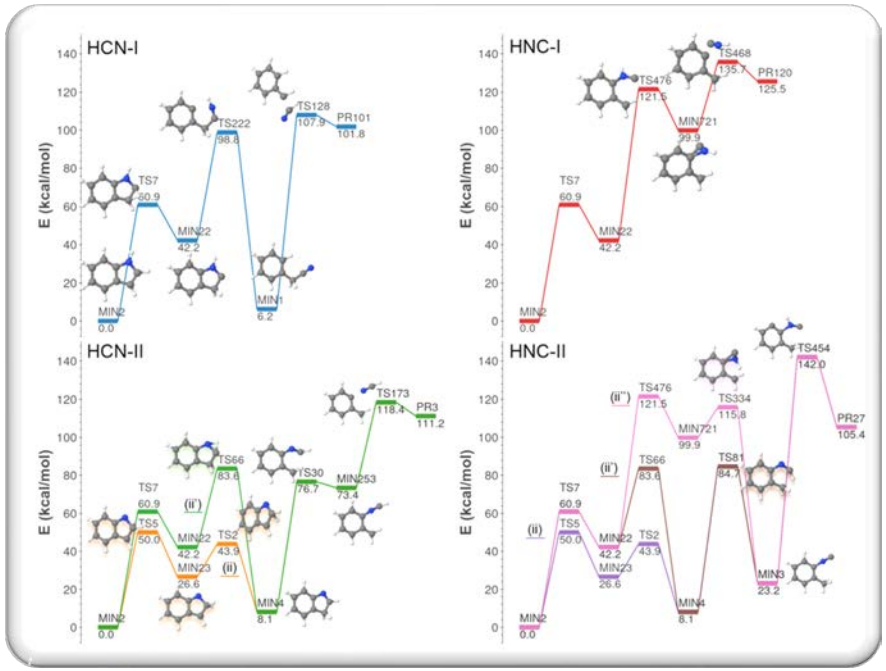
Unimolecular decomposition of indole I

ACS Physical Chemistry Au **2022,** *2,* 225

Reaction network



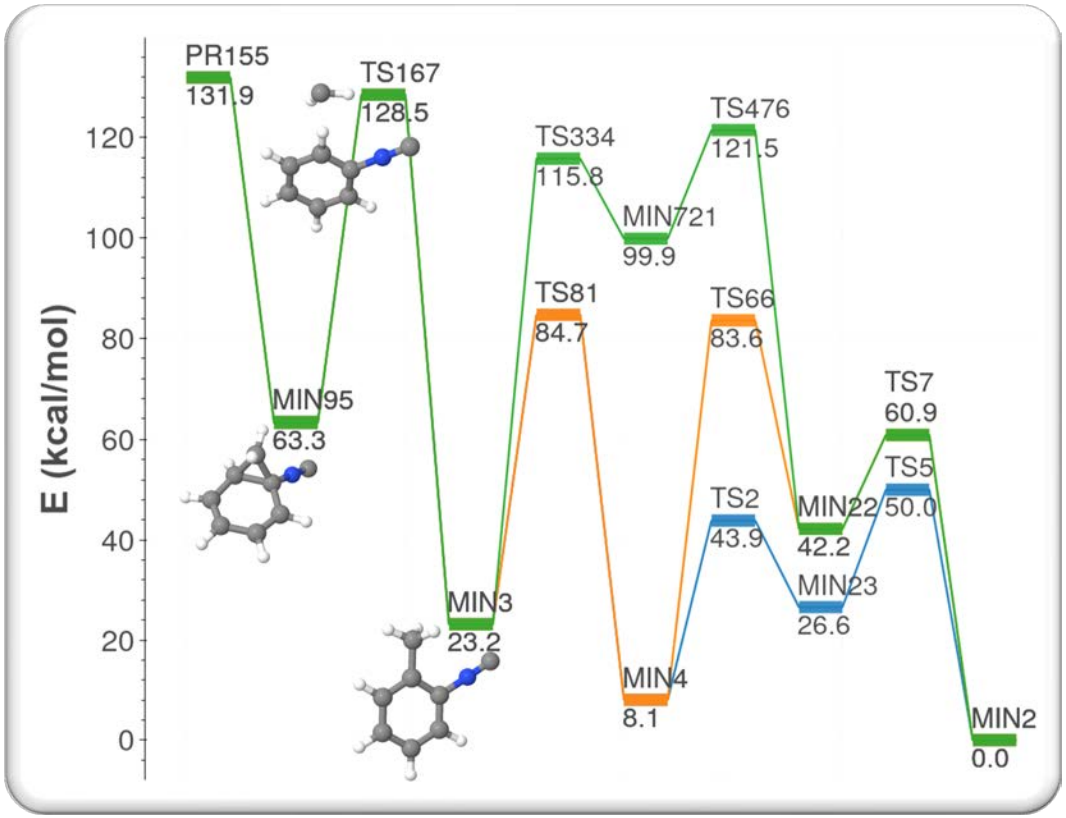
HCN elimination paths



Unimolecular decomposition of indole II

ACS Physical Chemistry Au **2022,** *2,* 225

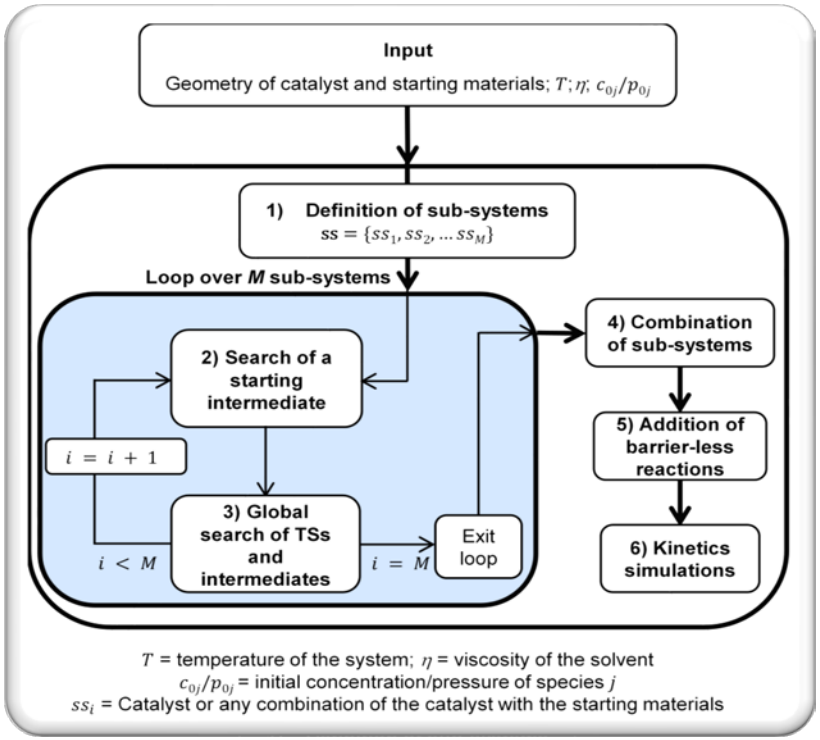
Astrochemistry: Formation of indole from methelene (CH_2) and phenyl isocyanide (C_6H_5CN) in the ISM



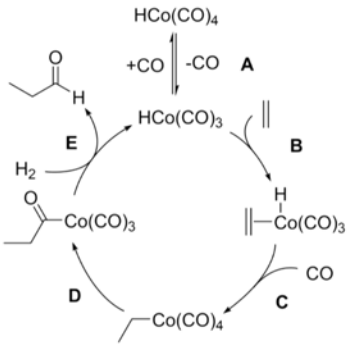
Hydroformylation of ethylene I

Chem. Sci. **2017**, *8*, 3843

Workflow



Initial conditions



Heck and Breslow mechanism

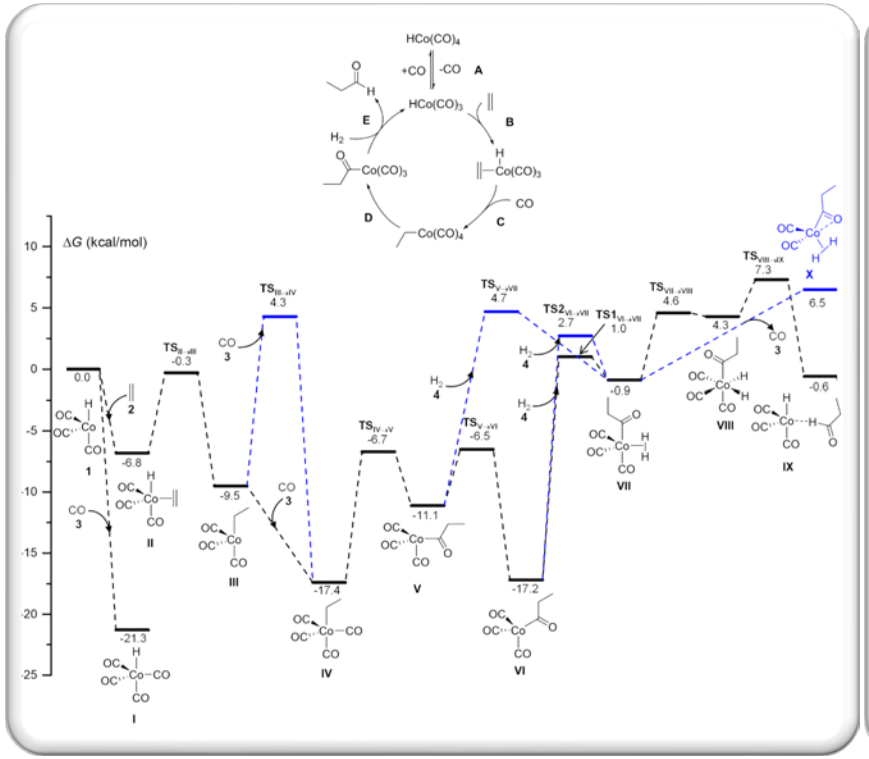
Input

Catalyst and starting materials: $HCo(CO)_3$ (**1**), ethylene (2), CO (**3**) and H_2 (**4**)
Temperature: 423 K
Solvent: Toluene ($\eta = 2.09 \times 10^{-4}$ Pa s)
$c_{0,cat}$=0.0004-0.02 M
$c_{0,eth}$=0.04-2 M
p_0=1-60 bar CO and H_2

Hydroformylation of ethylene II

Chem. Sci. **2017**, *8*, 3843

Reaction mechanism

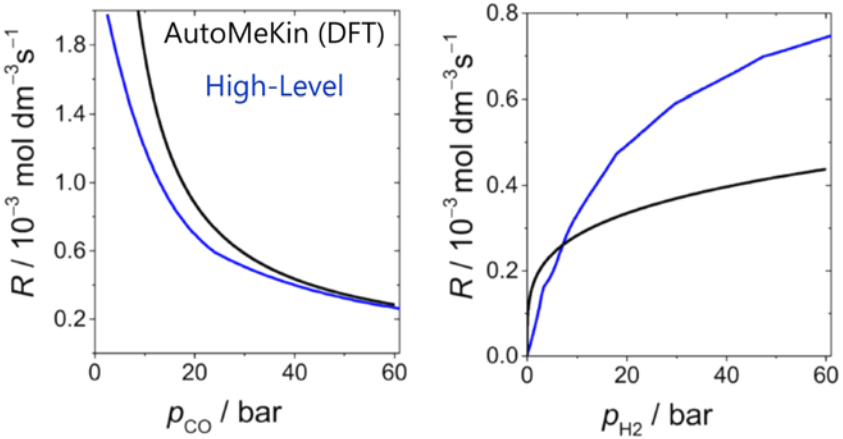


Rate law

$$R_{\text{exp}} = k\frac{[\text{H}_2]^{0.6}[\text{CO}][\text{cat}]^{0.8}[\text{alkene}]}{(1+K[\text{CO}])^2}$$

$$R_{\text{High-Level}} = k\frac{[\text{H}_2]^{0.5}[\text{cat}]^{0.5}[\text{alkene}]}{[\text{CO}]}$$

$$R_{\text{AutoMeKin}} = k\frac{[\text{H}_2]^{0.4}[\text{cat}]^{0.5}[\text{alkene}]}{1+a_1[\text{CO}]+a_2[\text{CO}]^2}$$



vdW interactions

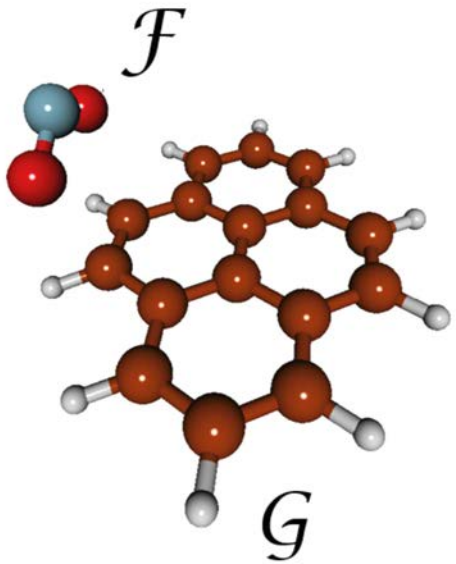
Int. J. Quantum Chem. **2019**, *119*, e26008

New A matrix

$\mathbf{F}$: Molecule $\mathcal{F}$

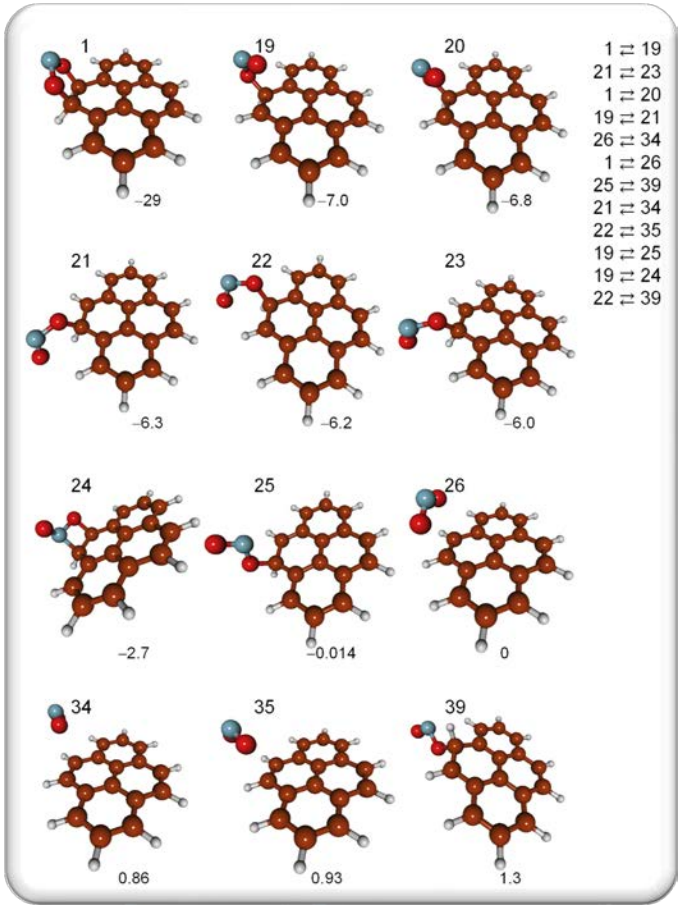
$\mathbf{G}$: Molecule $\mathcal{G}$

$$\mathbf{A} = \begin{pmatrix} \mathbf{F} & \mathbf{FG} \\ \mathbf{FG} & \mathbf{G} \end{pmatrix}$$



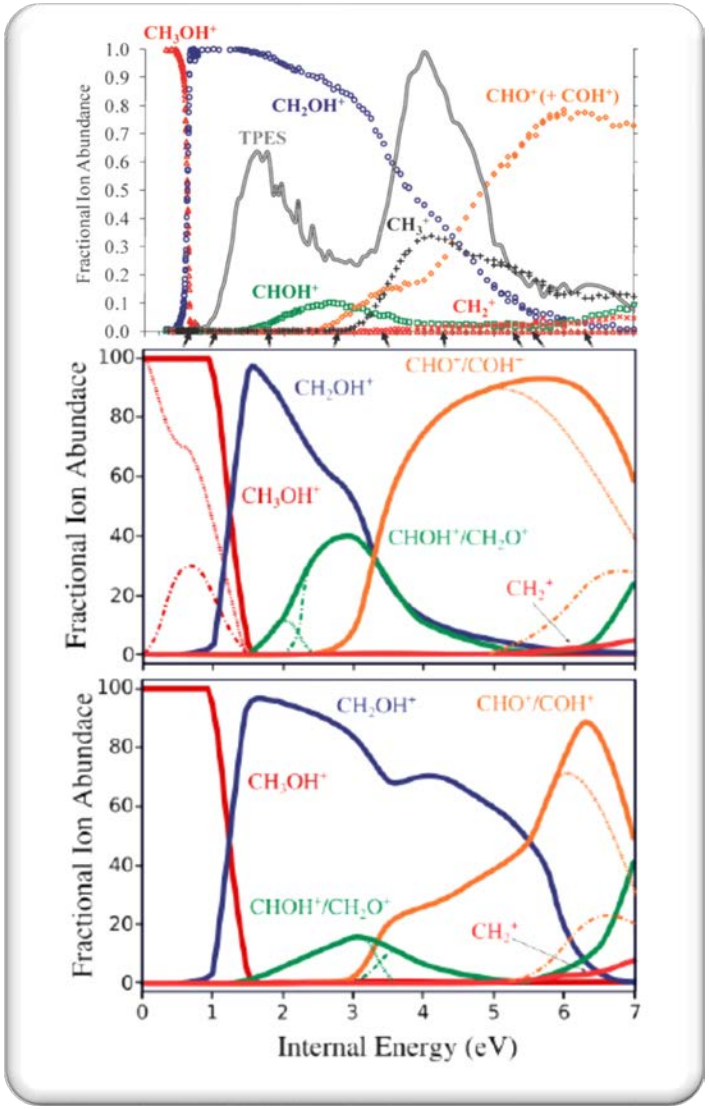
NO_2-pyrene

Most stable minimum-energy structures



Interface with M3C

Simulation of dissociative photoionization



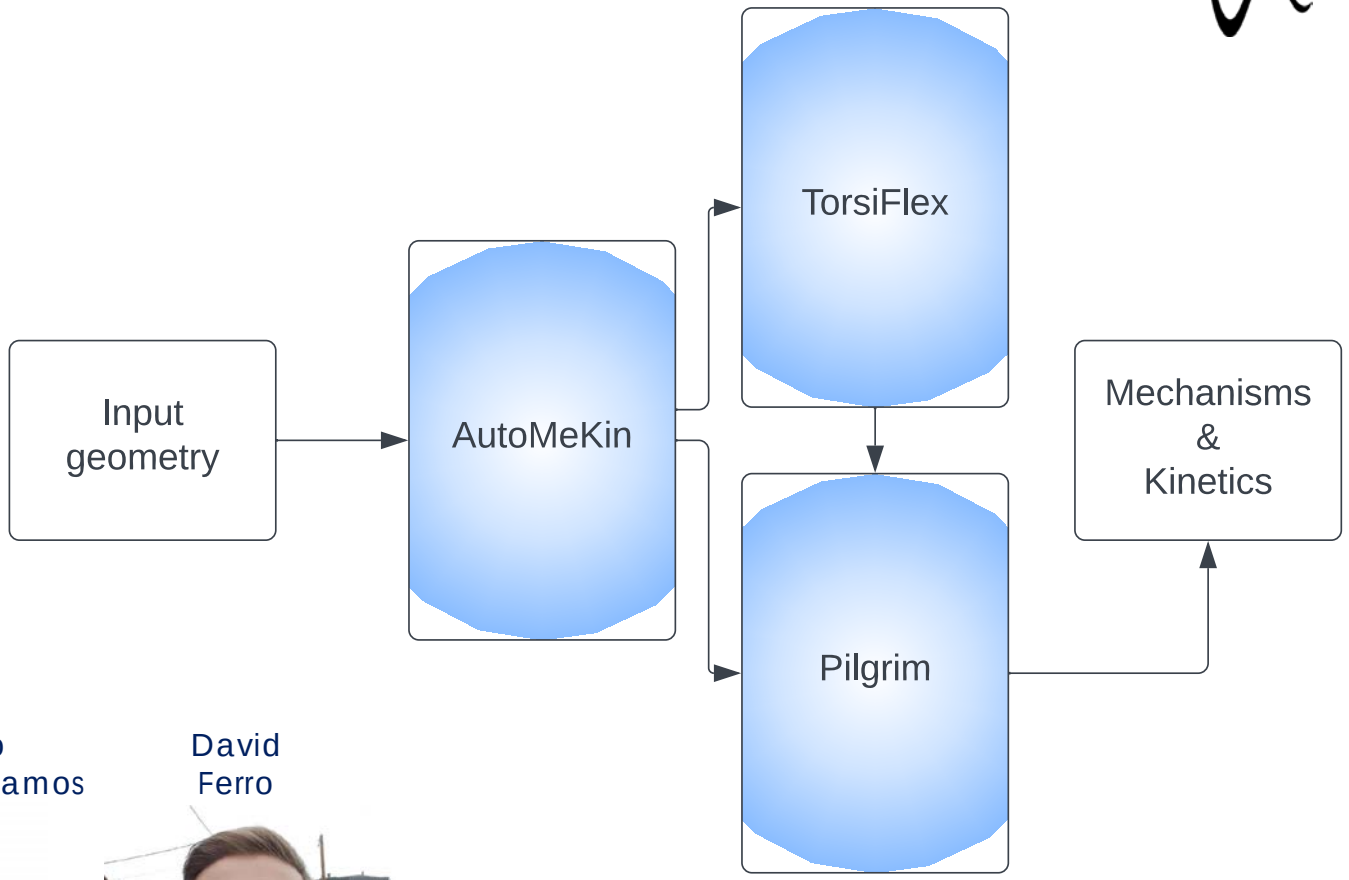
Exp

M3C

M3C+AutoMeKin

Nestor Aguirre

Interface with the Cathedral package



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https://github.com/cathedralpkg

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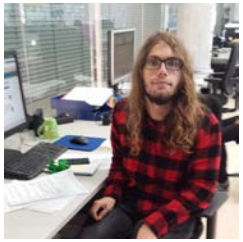

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