



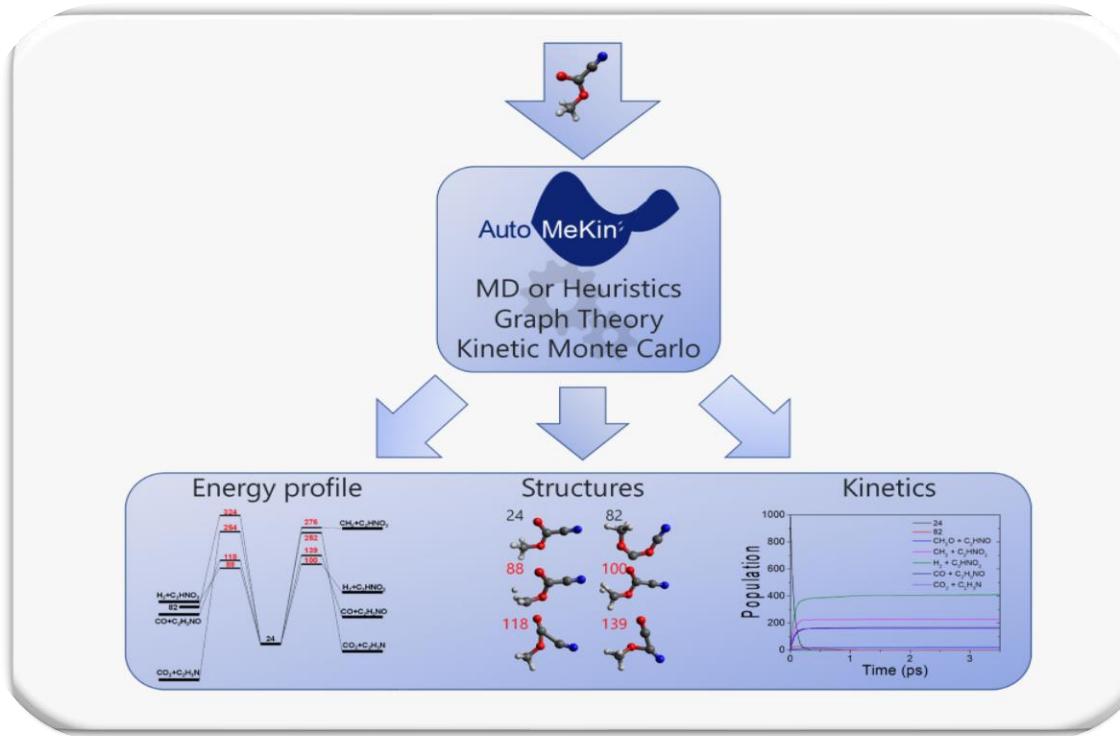
Automated Reaction Discovery using MD Simulations

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Department of Physical Chemistry
University of Santiago de Compostela
SPAIN





AutoMeKin (Automated Mechanisms and Kinetics)



FULL PAPER

WWW.C-CHEM.ORG

Journal of
**COMPUTATIONAL
CHEMISTRY**

An Automated Method to Find Transition States Using
Chemical Dynamics Simulations

Emilio Martínez-Núñez*

PCCP

PAPER



Cite this: *Phys. Chem. Chem. Phys.*
2015, 17, 14912



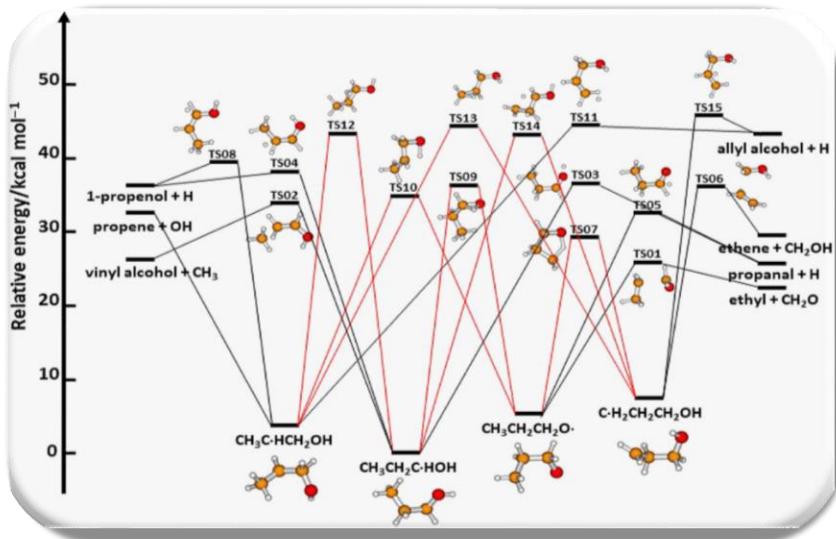
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An automated transition state search using
classical trajectories initialized at multiple
minima†

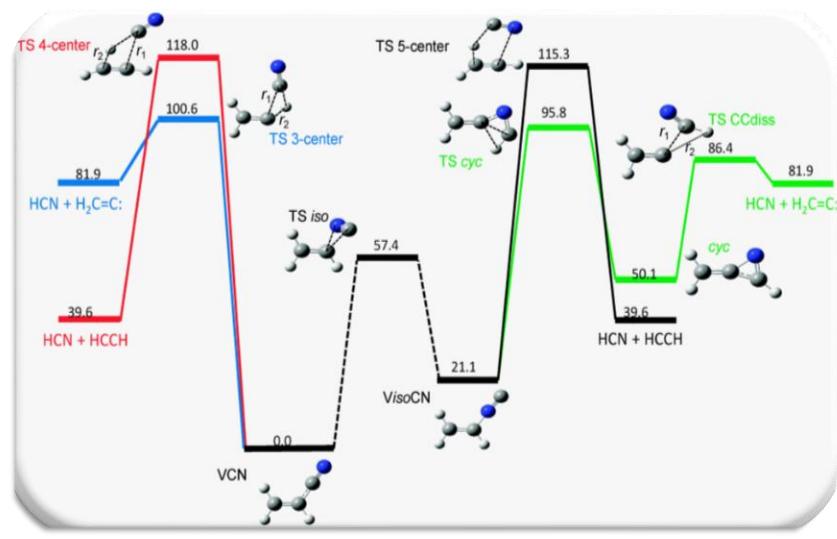
Emilio Martínez-Núñez



AutoMeKin: Motivation

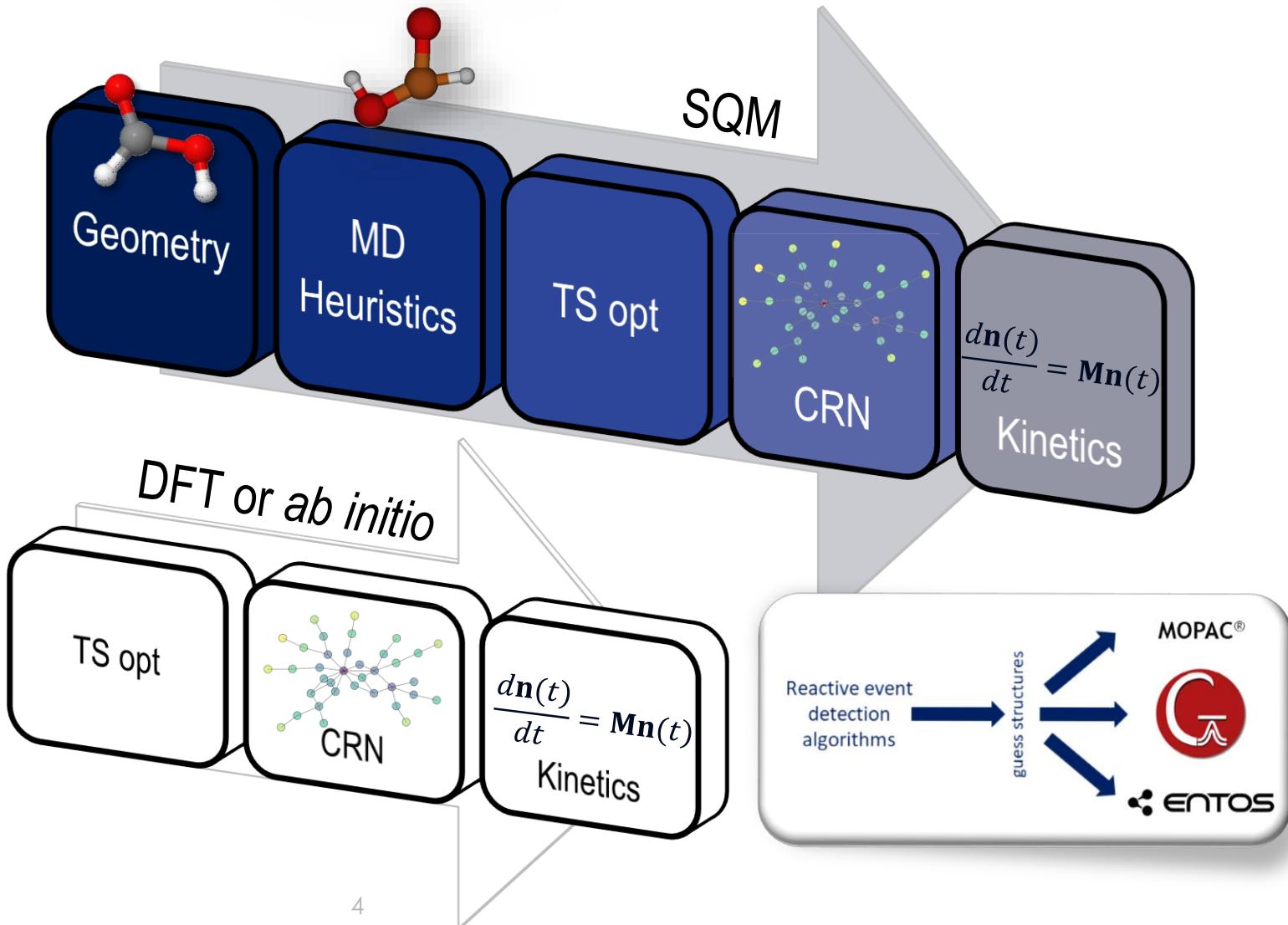


Manual search is not efficient



Possible non-intuitive pathways

AutoMeKin: Workflow





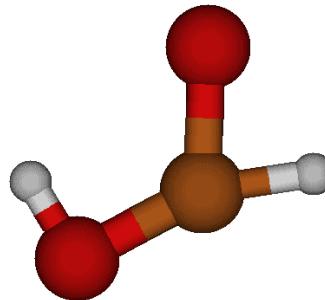
MD simulations

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

MOLDEN



MD simulations

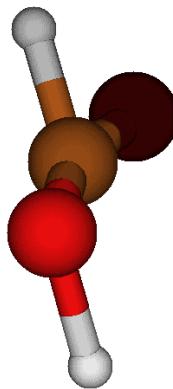
ChemSystemsChem 2020, 152, e19002

Rare-event acceleration

method (BXDE):

- ✓ Energy boxes
- ✓ More efficient sampling
- ✓ Loose coupling via ASE
- ✓ Movie: Langevin 1000 K

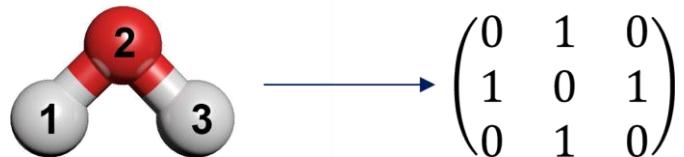
MOLDEN



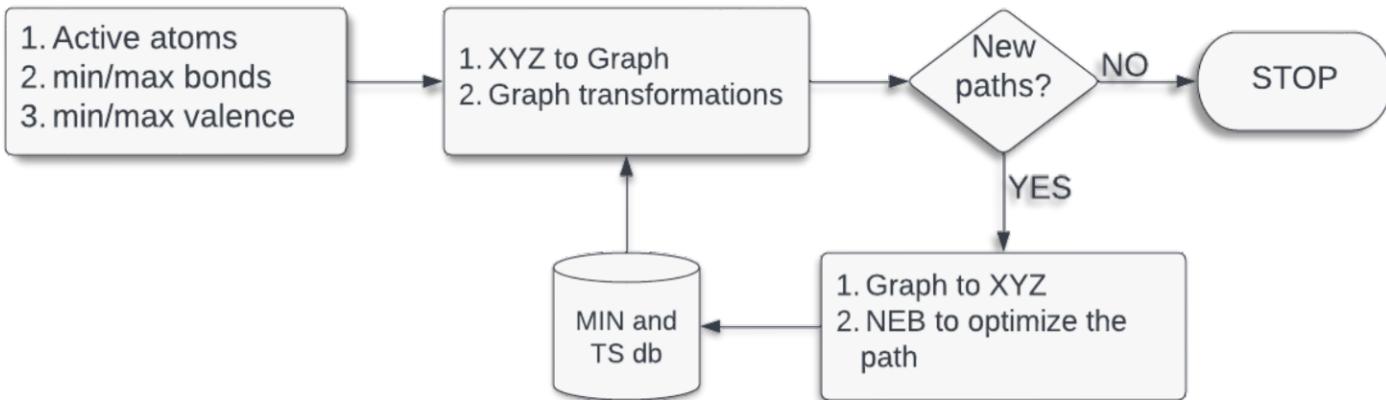


ChemKnow module

J Comput. Chem. 2021, 42, 2036



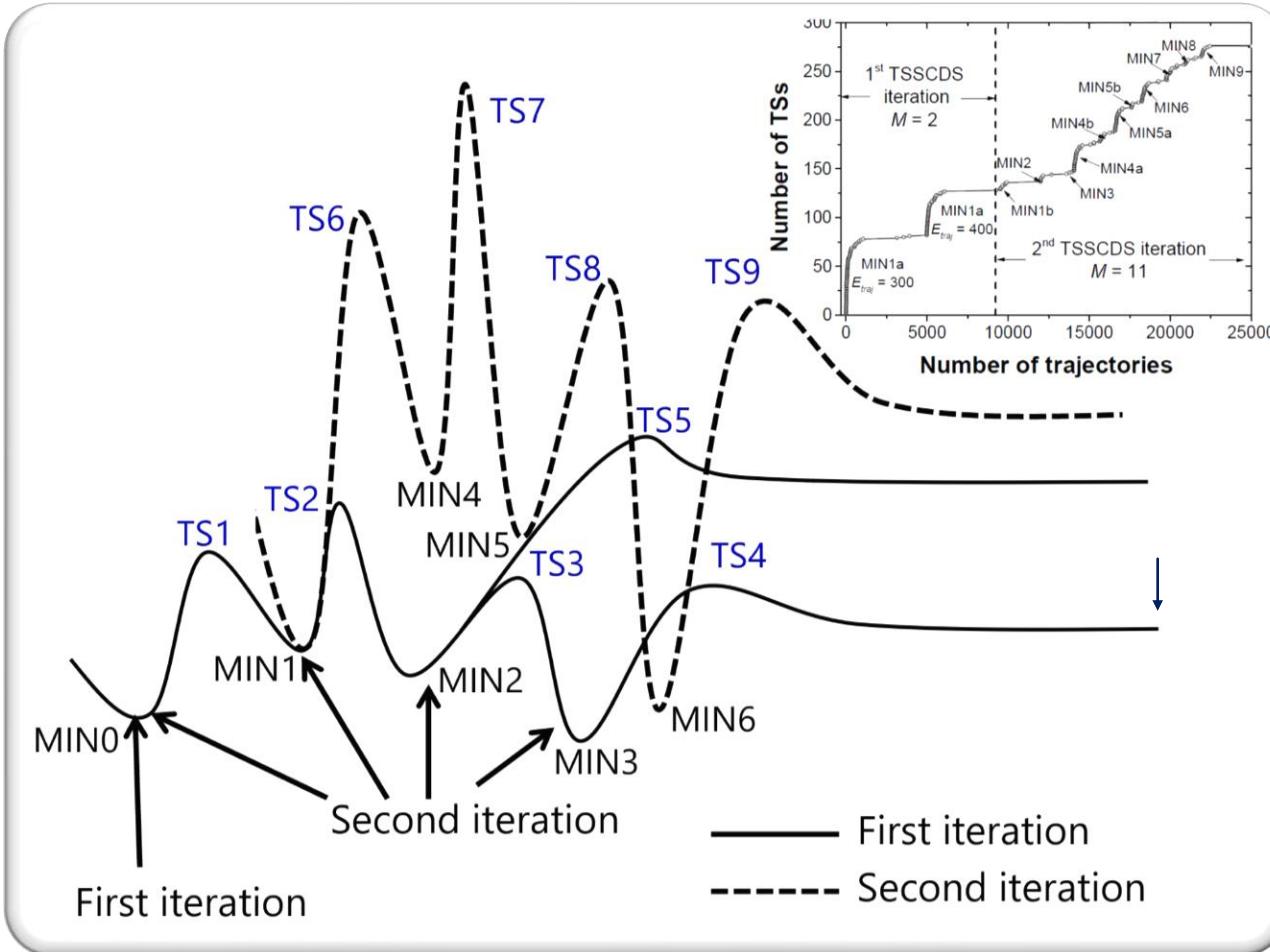
Graph space



Workflow

Sampling from multiple minima

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



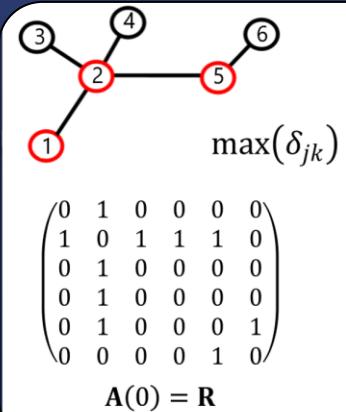


Graph Theory

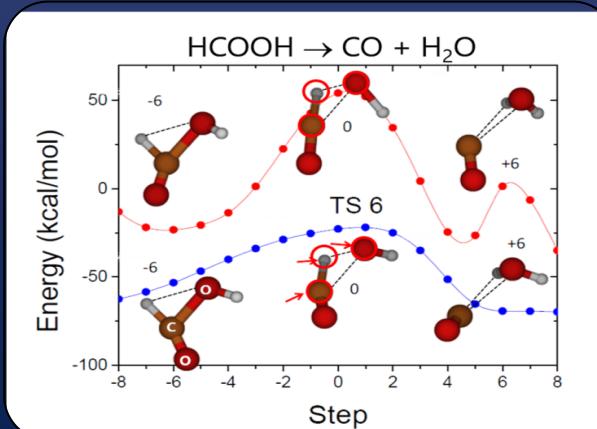
J Comput. Chem. 2015, 36, 222

Detecting Transition States

Graph-based detection step



Relaxation step



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

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

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

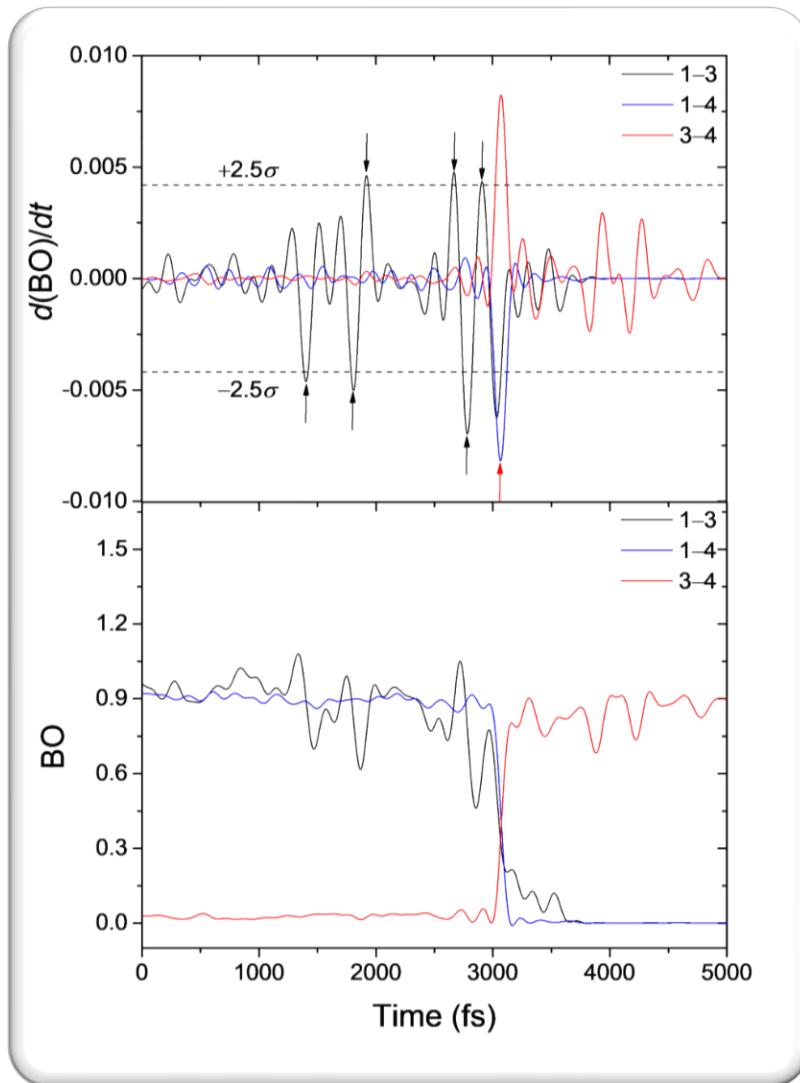
Multiple minima
Spectral Graph Theory

- ✓ Compare structures
- ✓ Degree of fragmentation



Event detection: Bond orders

JCTC, 2020, 16, 1606





Basic concepts of chemical kinetics

Homogeneous reactions (occurring in a single phase).

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



Rate of Reaction (r)

$$r = \frac{1}{V} \left(\frac{1}{\nu_i} \frac{dn_i}{dt} \right) = \frac{1}{\nu_i} \frac{d[S_i]}{dt} \quad \text{constant } V \quad (2)$$

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

Example: $\text{N}_2 + 3\text{H}_2 \rightarrow 2\text{NH}_3 \quad r = -\frac{d[\text{N}_2]}{dt} = -\frac{1}{3} \frac{d[\text{H}_2]}{dt} = \frac{1}{2} \frac{d[\text{NH}_3]}{dt}$

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

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

Basic concepts of chemical kinetics

Rate Law

For many reactions: $r = k[A]^\alpha[B]^\beta\dots$

k is the *rate coefficient*. $k = k(T, p)$
 α, β, \dots are the *orders* with respect to species A, B, \dots .

Examples:



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

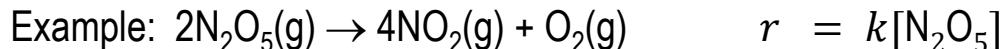


Basic concepts of chemical kinetics

Reaction Mechanisms

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

A *complex reaction* is formed by two or more elementary steps.



1. $\text{N}_2\text{O}_5 \rightleftharpoons \text{NO}_2 + \text{NO}_3$
2. $\text{NO}_2 + \text{NO}_3 \rightarrow \text{NO} + \text{O}_2 + \text{NO}_2$
3. $\text{NO} + \text{N}_2\text{O}_5 \rightarrow \text{NO}_2 + \text{NO}_2 + \text{NO}_2$

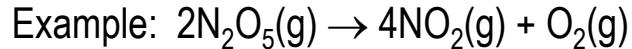
The *molecularity* is the number of molecules that react in an elementary reaction.



Basic concepts of chemical kinetics

Differential Rate Equations (DREs)

For a given reaction mechanism, we may write the (coupled) differential rate equations (aka Chemical Master Equation).



1. $\text{N}_2\text{O}_5 \rightleftharpoons \text{NO}_2 + \text{NO}_3$
2. $\text{NO}_2 + \text{NO}_3 \rightarrow \text{NO} + \text{O}_2 + \text{NO}_2$
3. $\text{NO} + \text{N}_2\text{O}_5 \rightarrow \text{NO}_2 + \text{NO}_2 + \text{NO}_2$

$$\frac{d[\text{N}_2\text{O}_5]}{dt} = -k_1[\text{N}_2\text{O}_5] + k_{-1}[\text{NO}_2][\text{NO}_3] - k_3[\text{NO}][\text{N}_2\text{O}_5]$$

$$\frac{d[\text{NO}_2]}{dt} = k_1[\text{N}_2\text{O}_5] - k_{-1}[\text{NO}_2][\text{NO}_3] + 3k_3[\text{NO}][\text{N}_2\text{O}_5]$$

$$\frac{d[\text{NO}_3]}{dt} = k_1[\text{N}_2\text{O}_5] - (k_{-1} + k_2)[\text{NO}_2][\text{NO}_3]$$

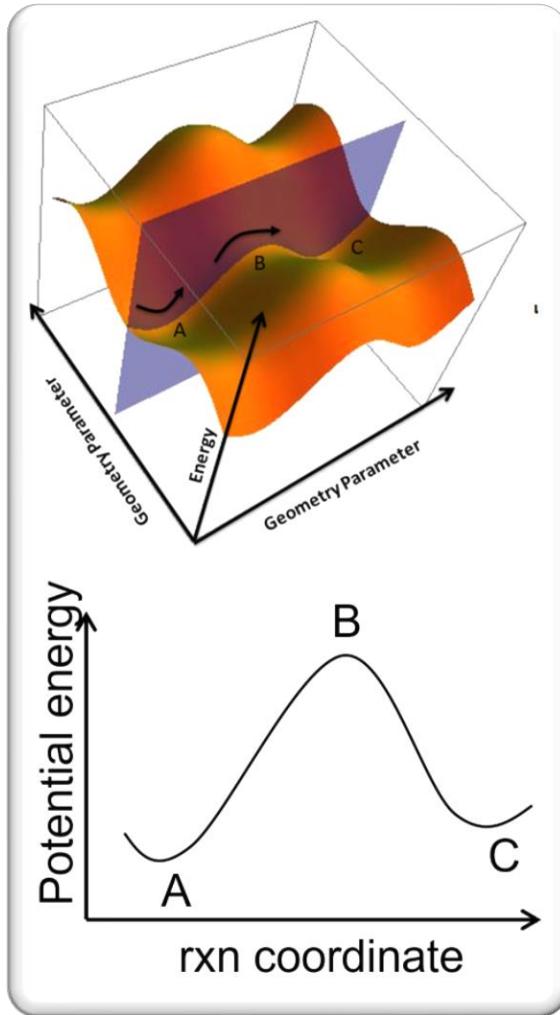
$$\frac{d[\text{NO}]}{dt} = k_2[\text{NO}_2][\text{NO}_3] - k_3[\text{NO}][\text{N}_2\text{O}_5]$$

$$\frac{d[\text{O}_2]}{dt} = k_2[\text{NO}_2][\text{NO}_3]$$

Solution of the DREs: Analytical, numerical integration, KMC

Basic concepts of chemical kinetics

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

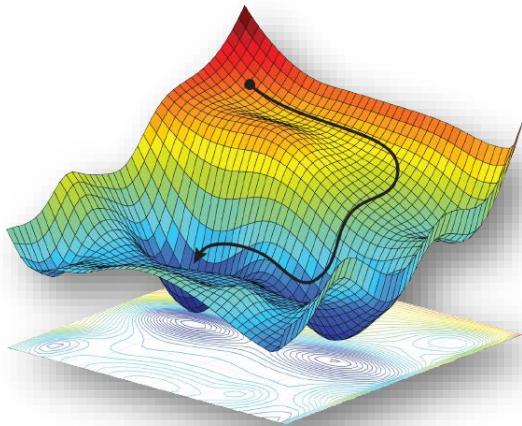


Basic concepts of chemical kinetics

Important points of the PES

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

Global, local, reactive intermediates, conformers



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

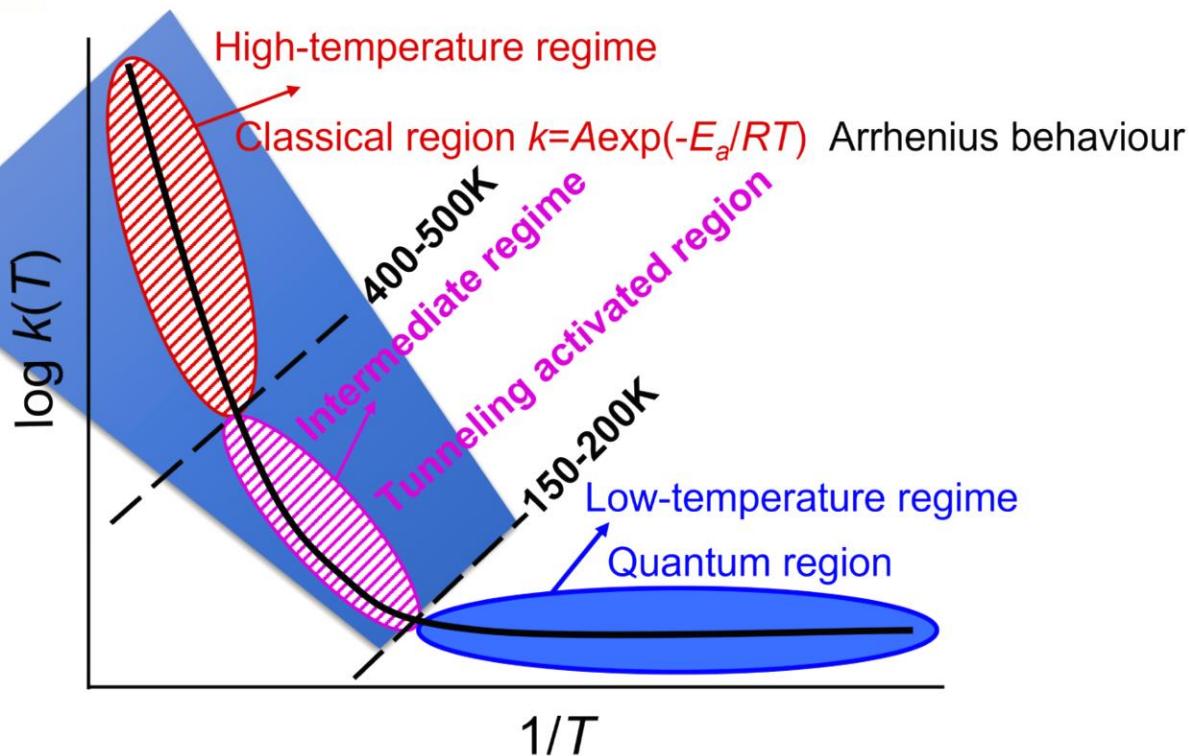
First order, second order, transition state

Basic concepts of chemical kinetics

Dependence of k on T

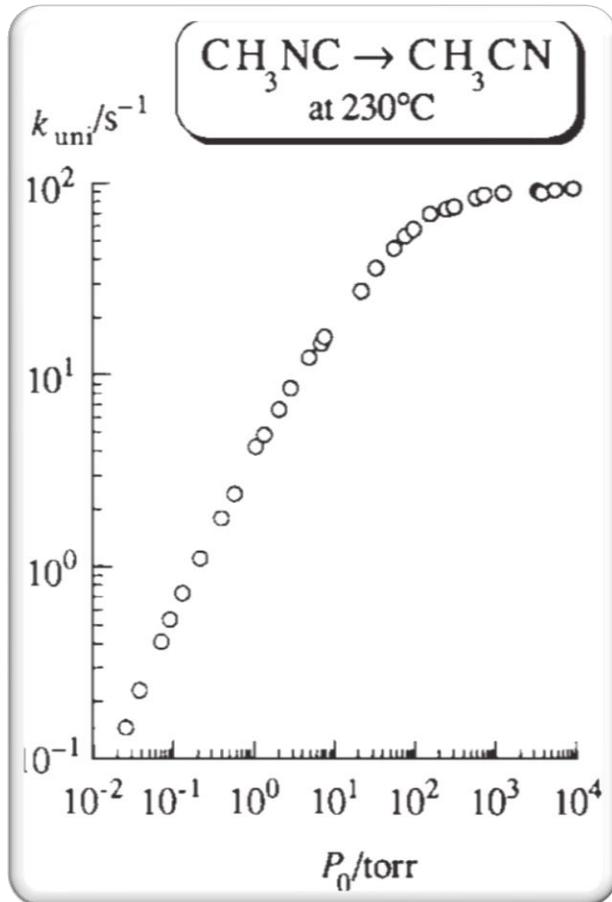
VTST/MT

Variational transition state theory



Basic concepts of chemical kinetics

Dependence of k on P





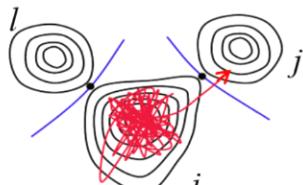
Semi-automated kinetics

Automated

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

$$\frac{d\mathbf{n}(t)}{dt} = \mathbf{M}\mathbf{n}(t)$$

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



$$t = -\frac{1}{k} \ln(r_1)$$

$$k = k_{ij} + k_{il}$$

$$r_2 k \longrightarrow \begin{array}{|c|} \hline k_{ij} \\ \hline k_{il} \\ \hline \end{array}$$

Not automated

Pilgrim: A thermal rate constant calculator and a chemical kinetics simulator

David Ferro-Costas ^a, Donald G. Truhlar ^b, Antonio Fernández-Ramos ^{a,*}

^a Centro Singular de Investigación en Química Biológica e Materiales Moleculares (CQUS), Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

^b Department of Chemical Theory Center, and Minnesota Supercomputing Center, University of Minnesota, 207 Pleasant Street SE, Minneapolis, MN 55455-0431, USA

$$\gamma_j^{\text{CVT/SCT}} = \Gamma_j^{\text{CVT}} \kappa_j^{\text{CVT/SCT}}$$

$$\Gamma_j^{\text{CVT}}(T) = \frac{Q_{\text{rv},j}^{\text{GT}}(T, s_\star^{\text{CVT}})}{Q_{\text{rv},j}^\ddagger(T)} e^{-[\beta \Delta U_j(s_\star^{\text{CVT}})]}$$

$$\kappa^{\text{SAG}} = \frac{\beta \int_0^\infty dE \exp(-\beta E) P^{\text{SAG}}(E)}{\exp(-\beta V^{\text{AG}})}$$



Last version (2021_rev1135)

ACS Phys. Chem. Au **2022**, 2, 225

Web server. GitHub & Sylabs.
amk_tools

- ✓ Carles Bo & Diego Garay (ICIQ)
- ✓ Command line & Interactive HTML

Diego Garay



Carles Bo



Load vibrations Normal modes ▾ To clipboard (Click an element)

Reaction network visualization

MIN82 Locate molecule Show profile Molec. filter 85.05 Energy filter

JSmol



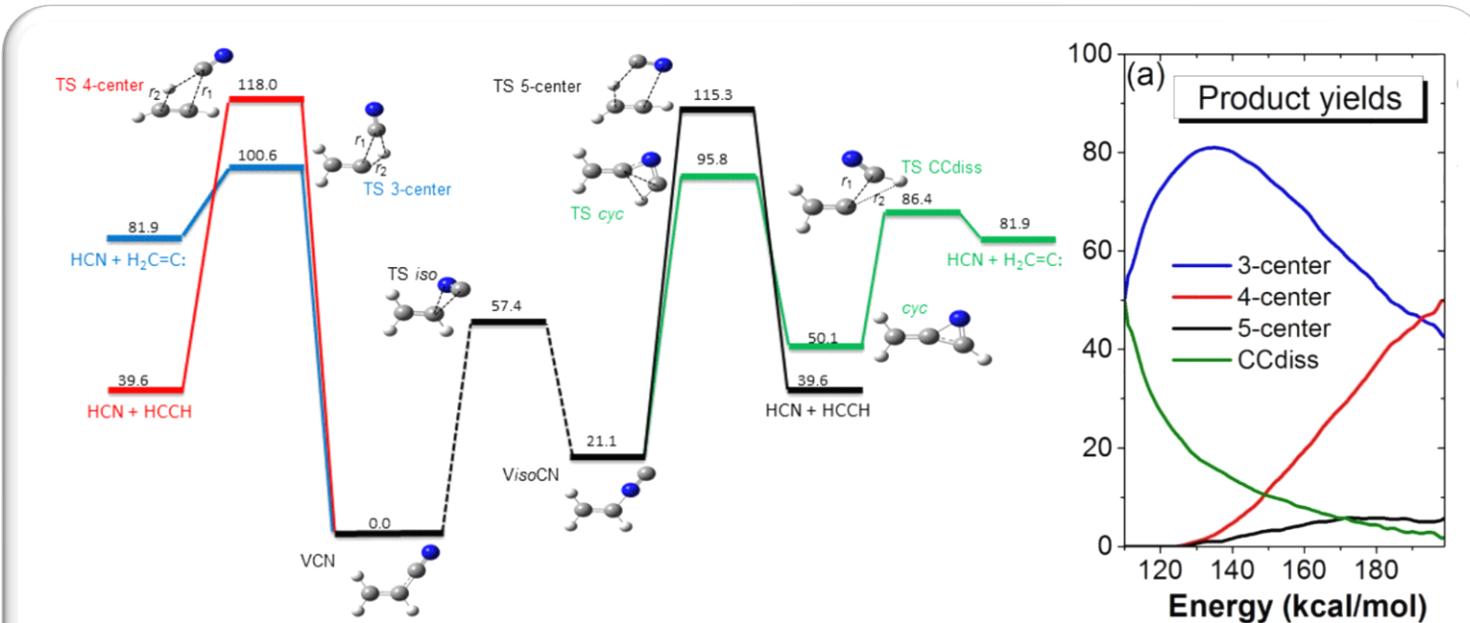
AutoMeKin: Applications

System	Reference
Pyrolysis of isoprene	Combust. Flame 2022 , 242, 112206
Fragmentation of indole	ACS Phys. Chem. Au 2022 , 2, 225
Diglycine and dialanine	JCTC 2021 , 17, 5556
Photoisomerization of a charged styryl dye	J. Am. Soc. Mass. Spectrom. 2021 , 32, 284
Formation of formaldehyde in cold astrophysical regions	A&A 2021 , 656, A148
Fragmentation of octaazapentalene	Monatsh Chem. 2021 , 152, 421
Syngas oxy-combustion in supercritical CO ₂	J. CO ₂ Util 2021 , 49, 101554
Electron-transfer-induced cleavage 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

- ✓ Atmospheric chemistry.
- ✓ Astrochemistry.
- ✓ Non-covalent interactions.
- ✓ Homogeneous catalysis.

HCN elimination from vinyl cyanide

PCCP 2015, 17, 6948

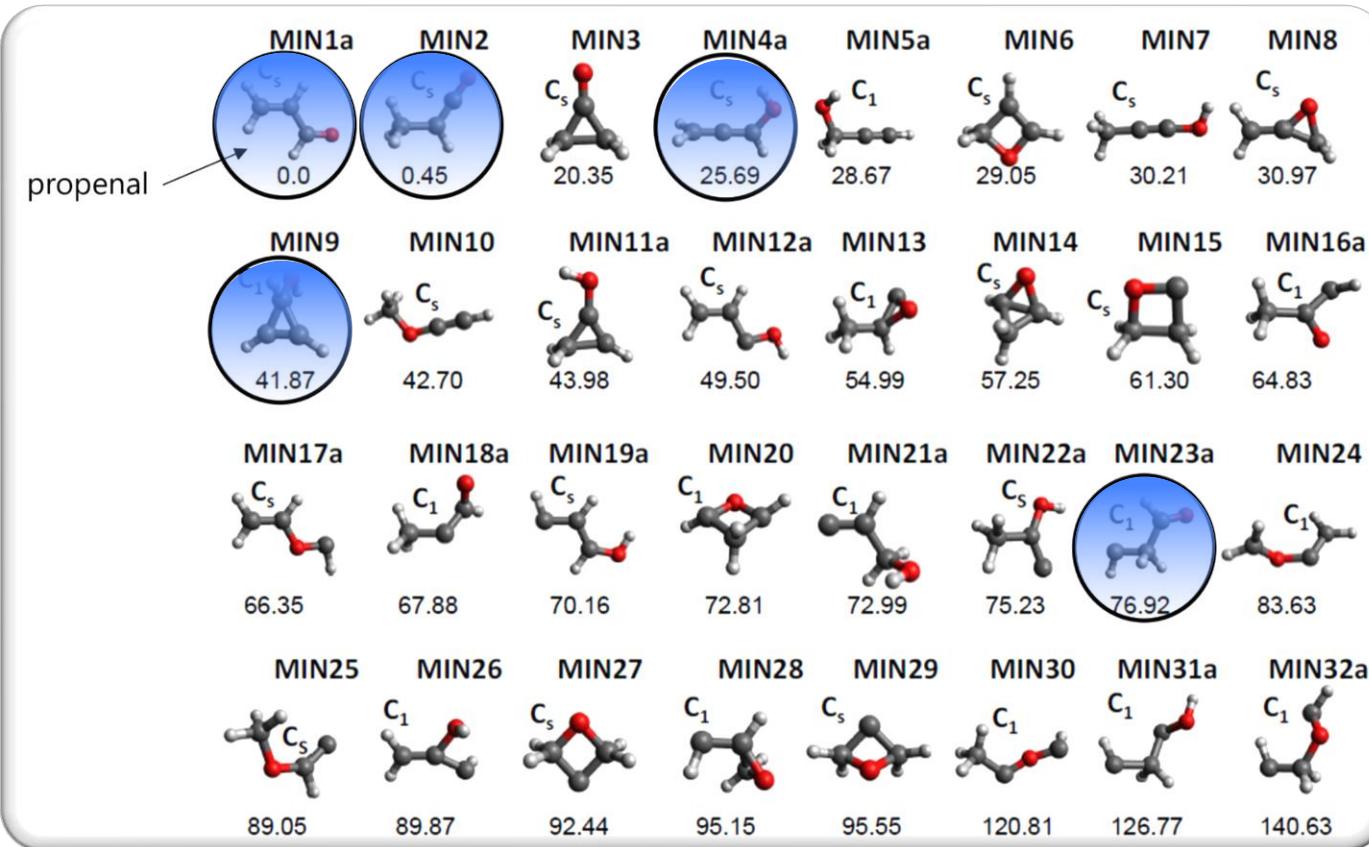


Products	Exp	AutoMeKin
Vinylidene	77	79
Acetylene	23	21



Isomers of propenal

PCCP 2015, 17, 14912



Dimerization of C₆₀

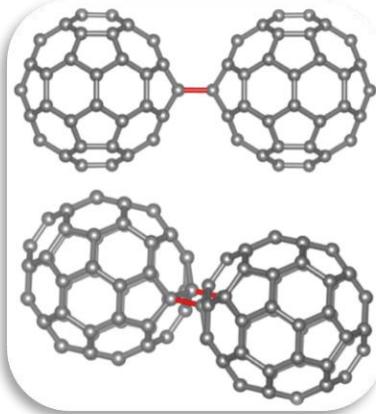
C₆₀+C₆₀ molecular bonding revisited and expanded

Jorge Laranjeira,^{1,*} Karol Strutyński,² Leonel Marques,¹ Emilio Martínez-Núñez,³ and Manuel Melle-Franco^{2,†}

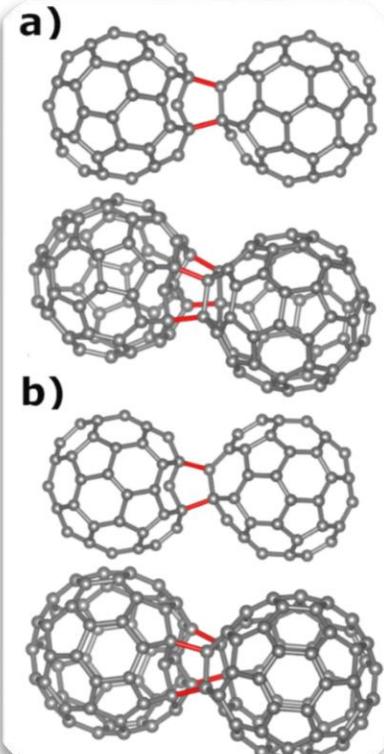
¹Departamento de Física and CICECO, Universidade de Aveiro, 3810-193 Aveiro, Portugal

²Departamento de Química and CICECO, Universidade de Aveiro, 3810-193 Aveiro, Portugal

³Departamento de Química Física, Universidade de Santiago de Compostela, 15782, Santiago de Compostela, Spain



- ✓ DFT with dispersion
- ✓ Known dimers from 12 to 41
- ✓ 2 ns high-energy MD with AutoMeKin



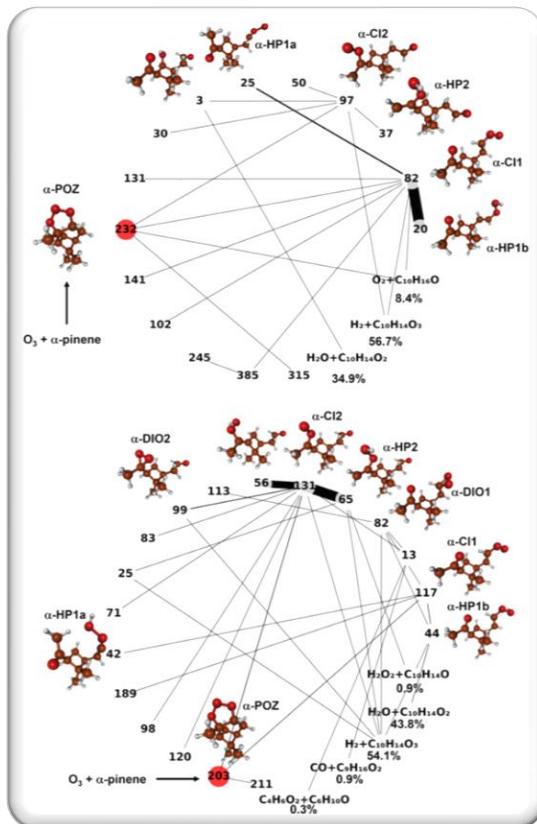
Ozonolysis of α -pinene

ChemSystemsChem 2020, 152, e19002

Reaction networks

Top: stdMD

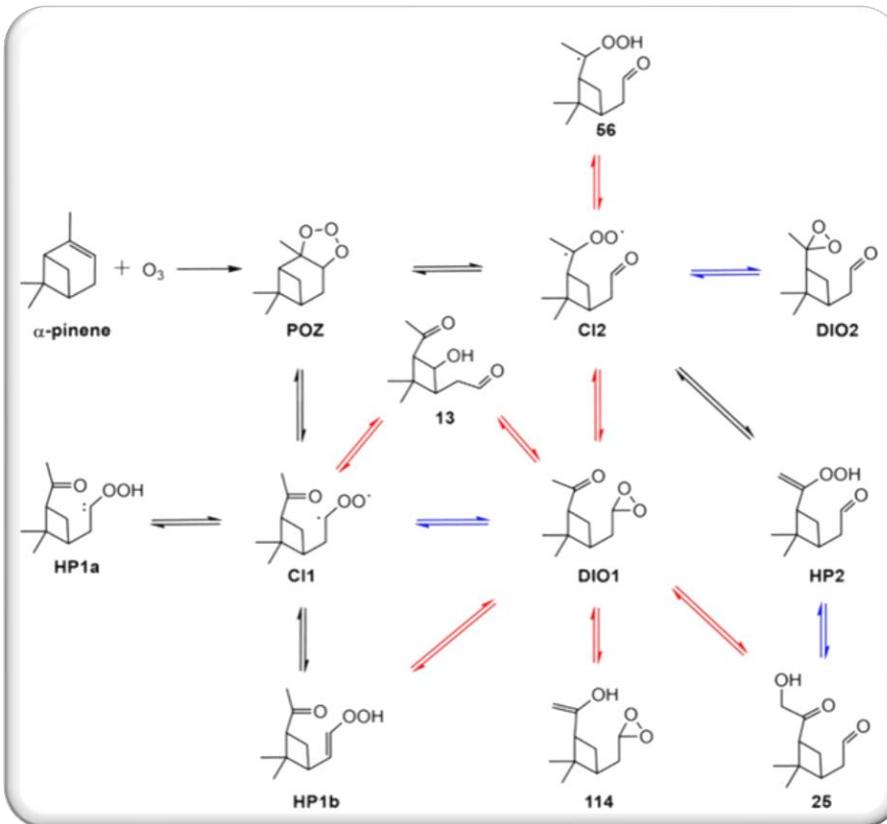
Bottom: BXDE



Mechanism

stdMD & BXDE

Only BXDE

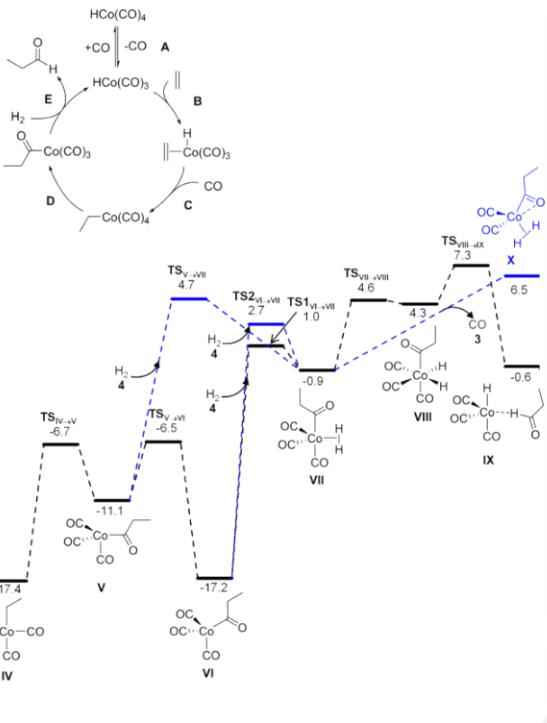




Hydroformylation of ethylene

Chem. Sci. 2017, 8, 3843

Reaction mechanism

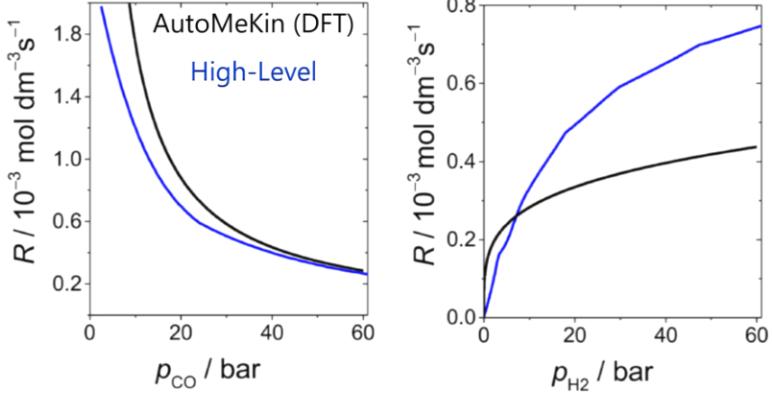


Rate law

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

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

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

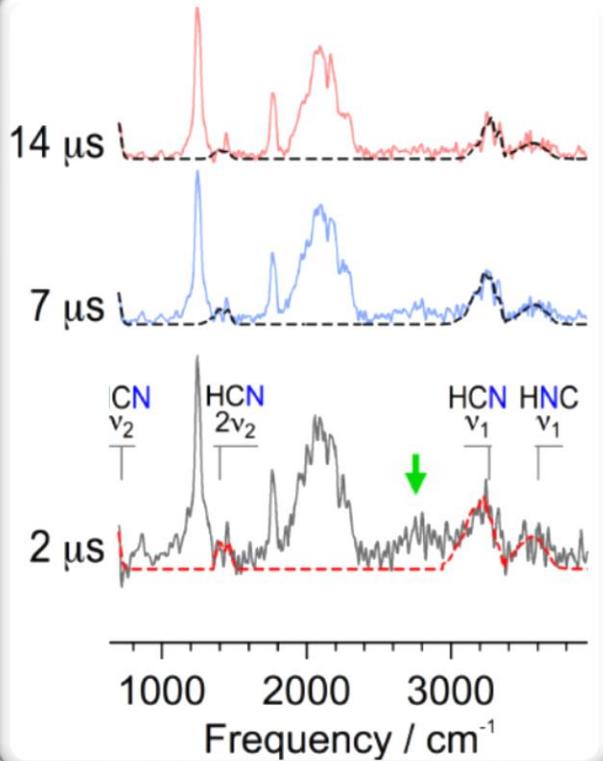




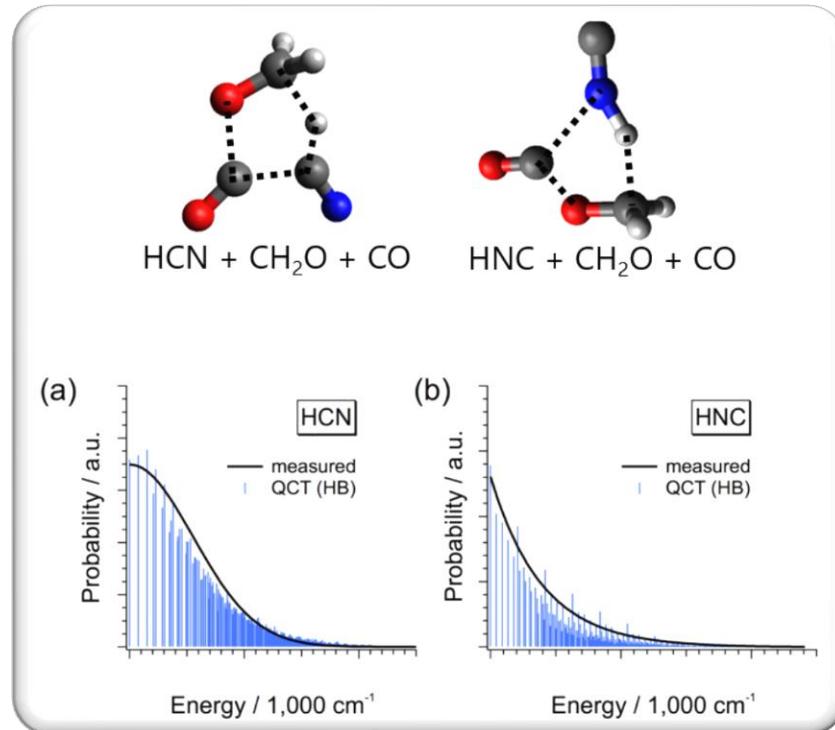
Photolysis of methyl cyanoformate

ApJ. 2017, 849, 15

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

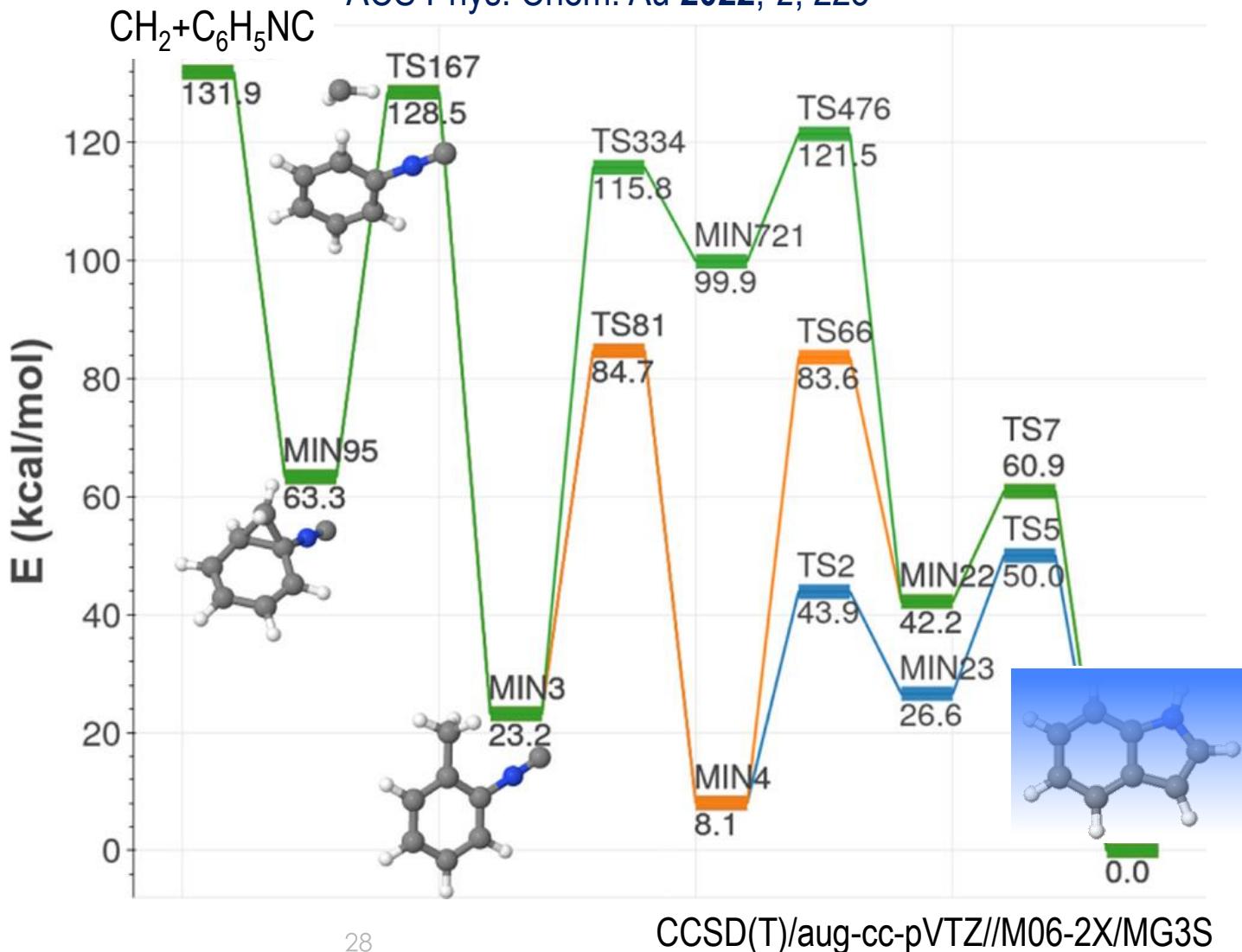


AutoMeKin & QCT TSs & Vibrational distros



Formation of indole in the ISM

ACS Phys. Chem. Au 2022, 2, 225



Formation of cyanoketene in the ISM

Toward the Detection of Cyanoketene in the Interstellar Medium:
New Hints from Quantum Chemistry and Rotational Spectroscopy

Bernardo Ballotta,* Tainah D. Marforio, Sergio Rampino, Emilio Martínez-Núñez, Vincenzo Barone, Mattia Melosso, Andrea Bottoni, and Luca Dore*

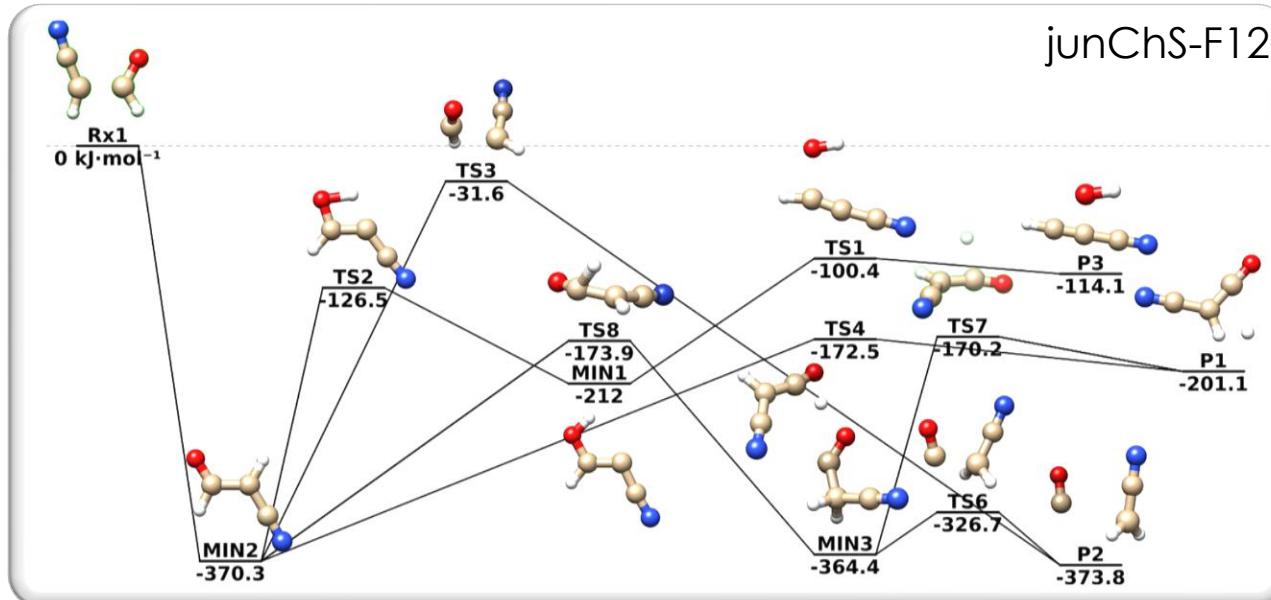


Cite This: ACS Earth Space Chem. 2023, 7, 1172–1180



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Reaction mechanisms

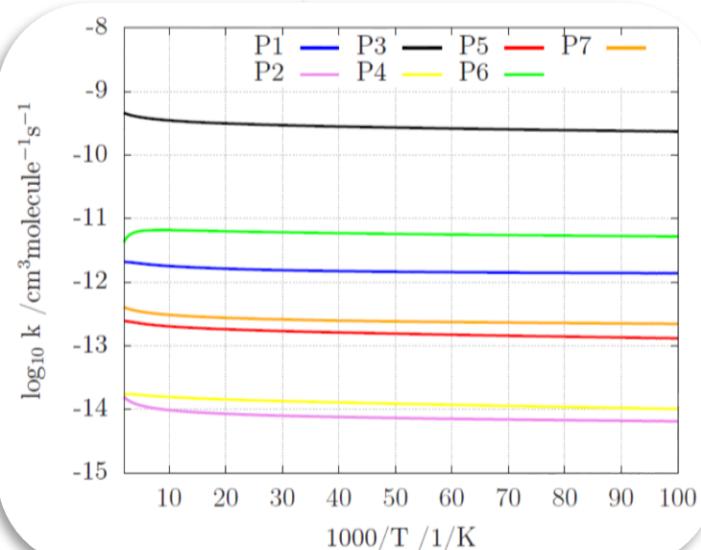
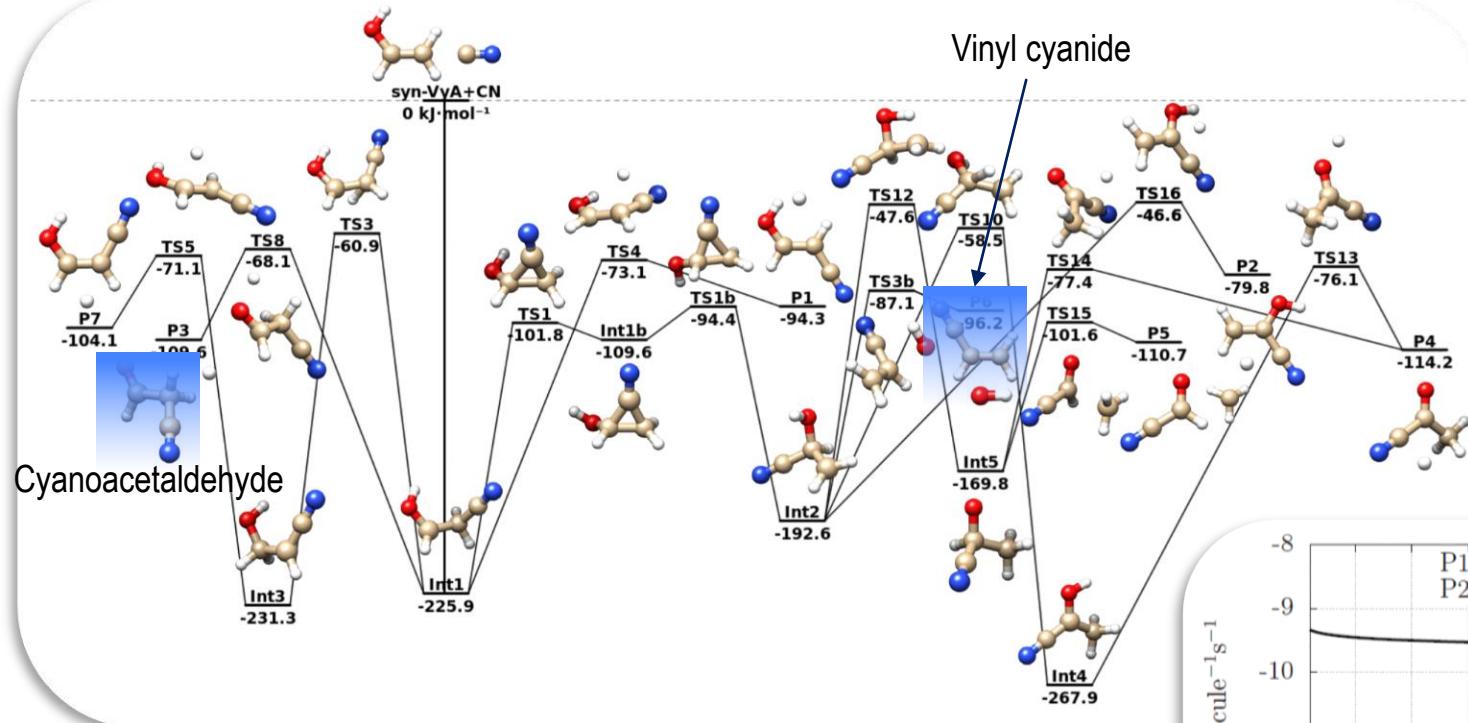


Product abundances

10-600 K: P1 > P2 > P3

Cyanide + vinyl alcohol in the ISM

PCCP (*submitted*)

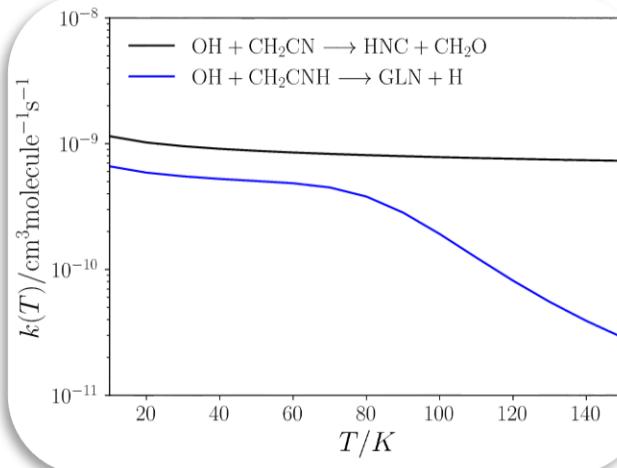
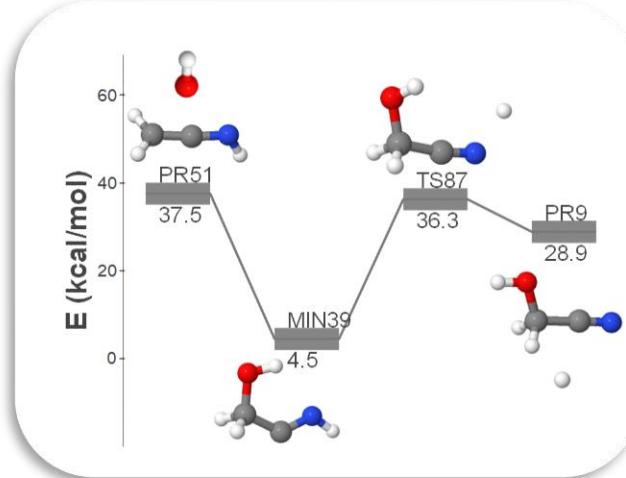
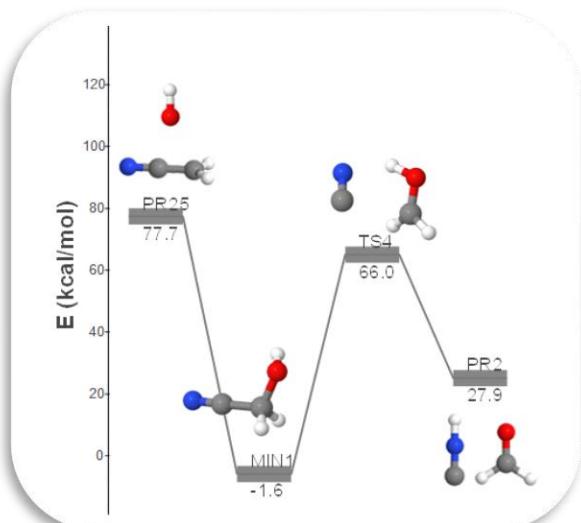


Formation of glycolonitrile in the ISM

PCCP (*submitted*)

	GLN		GLN-H	
	SQM	DFT	SQM	DFT
Average shortest path length	3.6 (3.9)	3.1 (3.3)	3.8 (4.8)	3.6 (4.1)
Average clustering coefficient	0.15 (0.03)	0.16 (0.06)	0.13 (0.02)	0.15 (0.03)

ω B97XD/Def2-TZVPP





vdW interactions

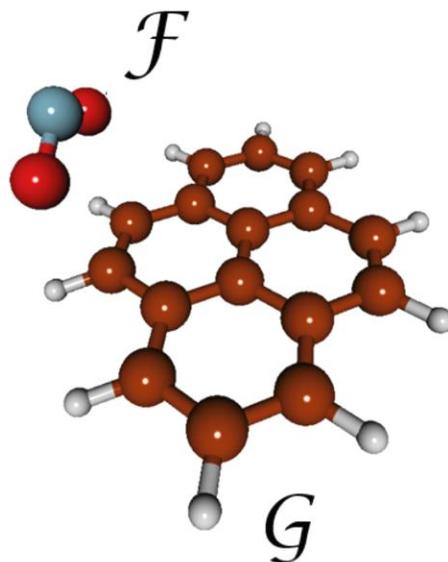
Int. J. Quantum Chem. 2019, 119, e26008

New A matrix

F: Molecule F

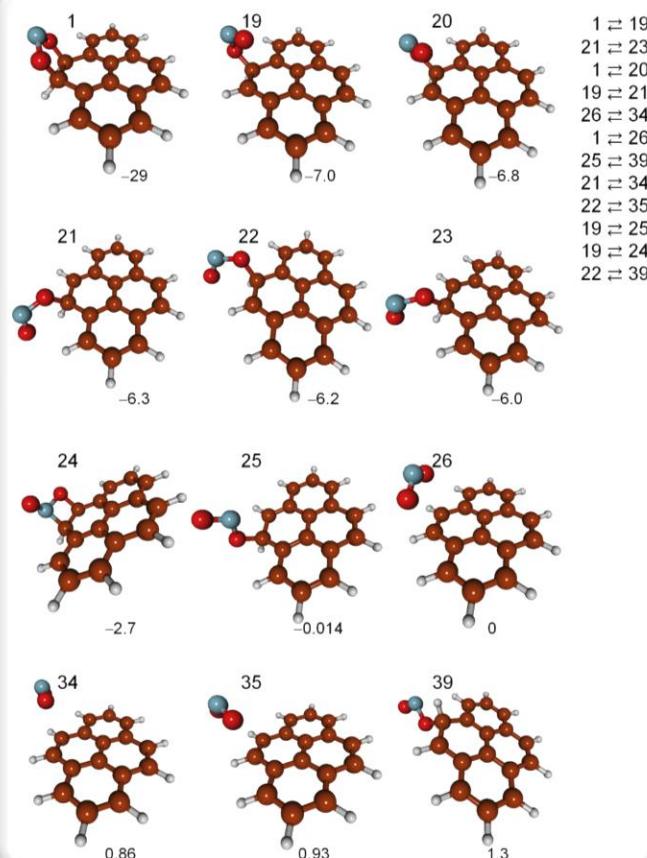
G: Molecule G

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



NO₂-pyrene

Most stable minimum-energy
structures

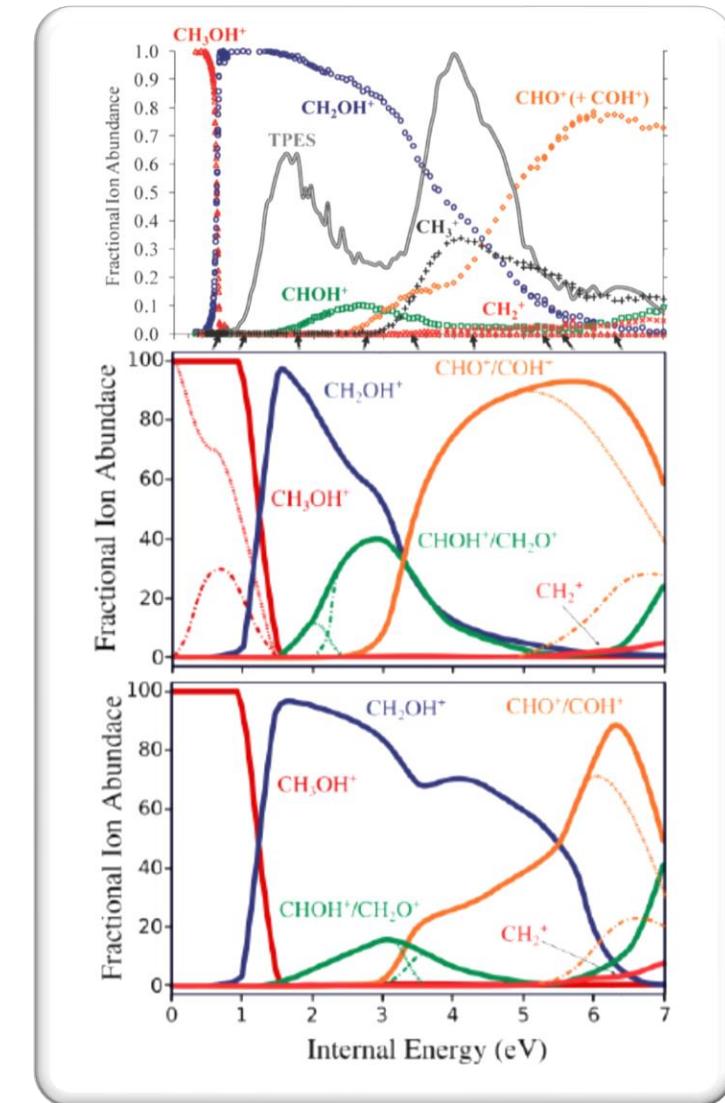




Dissociative photoionization



Néstor Aguirre



Exp

M3C

M3C+AutoMeKin

Integration within the Cathedral package

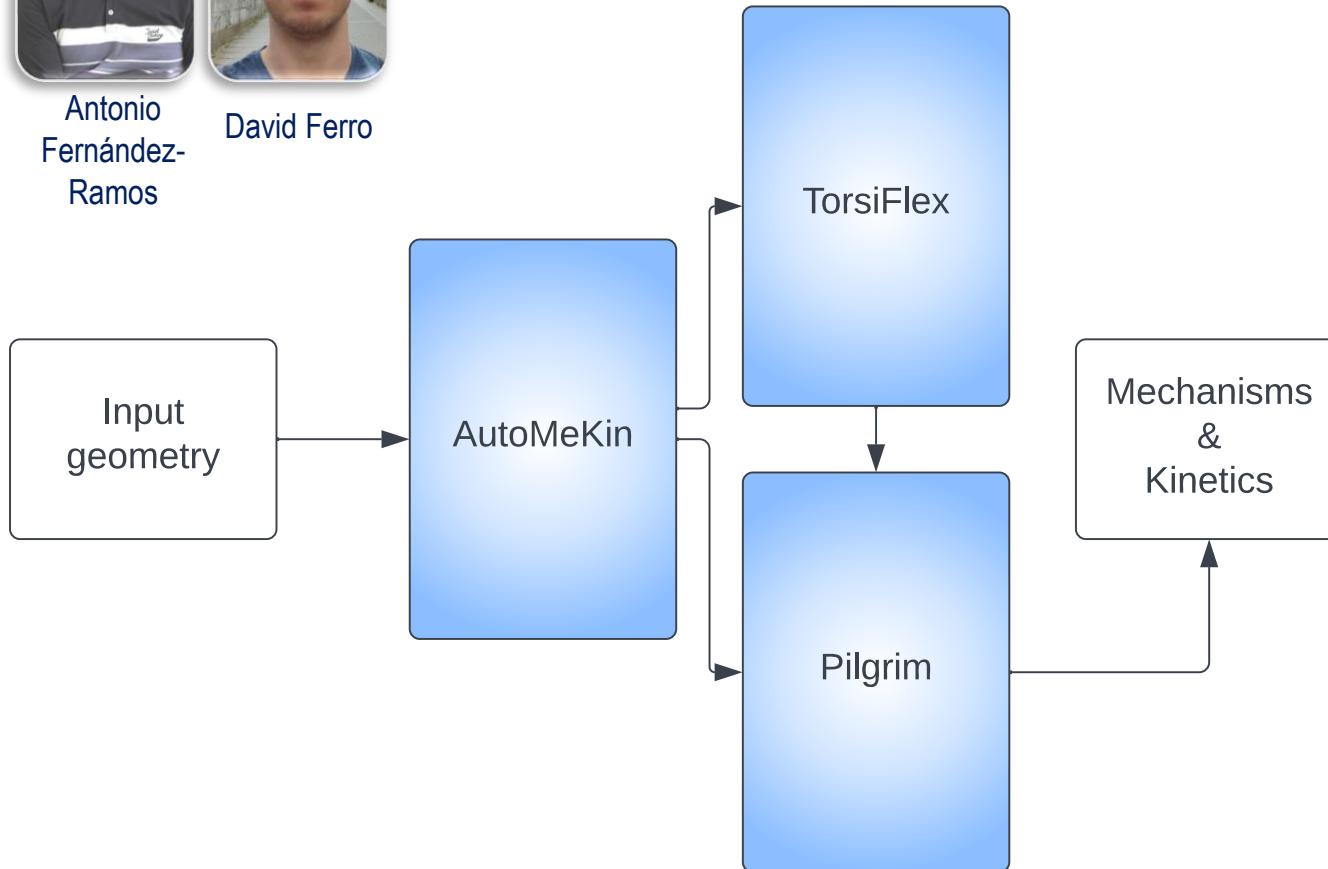


Antonio
Fernández-
Ramos



David Ferro

<https://github.com/cathedralpkg>





Thank you



George Barnes



Carles Bo



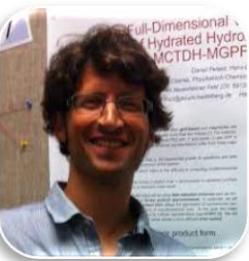
Diego Garay



Dave Glowacki



Sabine Kopec



Dani Peláez



Aurelio Rodríguez



Roberto Rodríguez



Robin Shannon



Pablo Tahoces



Saulo Vázquez