



TECHNION

Dana Research Group

Fundamental and Applied Chemical Kinetics

**Quantitative *in-silico* kinetic predictions
of API degradation**

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Acknowledgments

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Prof. William H. Green, MIT

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All RMG, ARC, and T3's developers



The grand question of this talk:

Can we **quantitatively predict**
the degradation of API molecules?

Our Goal:

Develop an **automated** self-improving software to **predict and explain**
free-radical oxidative stability and model solution degradation kinetics of APIs

Talk Outline

- **Methodology**
- The Radical “Soup” in API Stress Testing
- Case Studies
- Outlook and Perspective

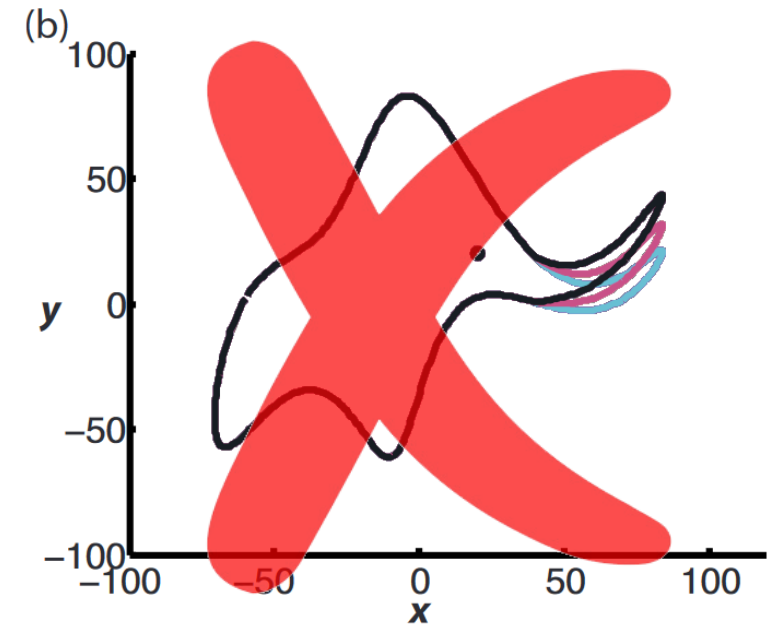
Predictive Chemical Kinetic Modeling

Overarching goal:

Predict the time-evolution of a chemical system given known initial conditions.

John von Neumann famously said:

With four parameters I can fit an elephant,
and with five I can make him wiggle his trunk.



We are **not fitting**, but rather **predicting**.

Predictive Chemical Kinetic Modeling

Why do we want predictive chemistry?

Predictive Science:

Accurate predictions **show we understand** the system, not just waving hands.

Understand important systems, **esp. if not practical to perform experiments**.

Predictive Design and System Optimization:

Develop **new products and processes** on the computer rather than trial and error.

Chemical Discovery:

Can we **predict new types of reactions**, never discovered before?

Predictive Chemical Kinetic Modeling

Required
Parameters



Experimentally
Available
Parameters

Luckily, **computational chemistry**

has already advanced to the stage where it has quantitative predictive capability for reaction rates of complex species



Predictive Chemical Kinetic Modeling



Massachusetts
Institute of
Technology



Reaction Mechanism Generator

What do we need to generate a kinetic model?

all (significant?) **intermediate species**

all (significant?) **reactions**

all **reaction rate coefficients**



Predictive Chemical Kinetic Modeling

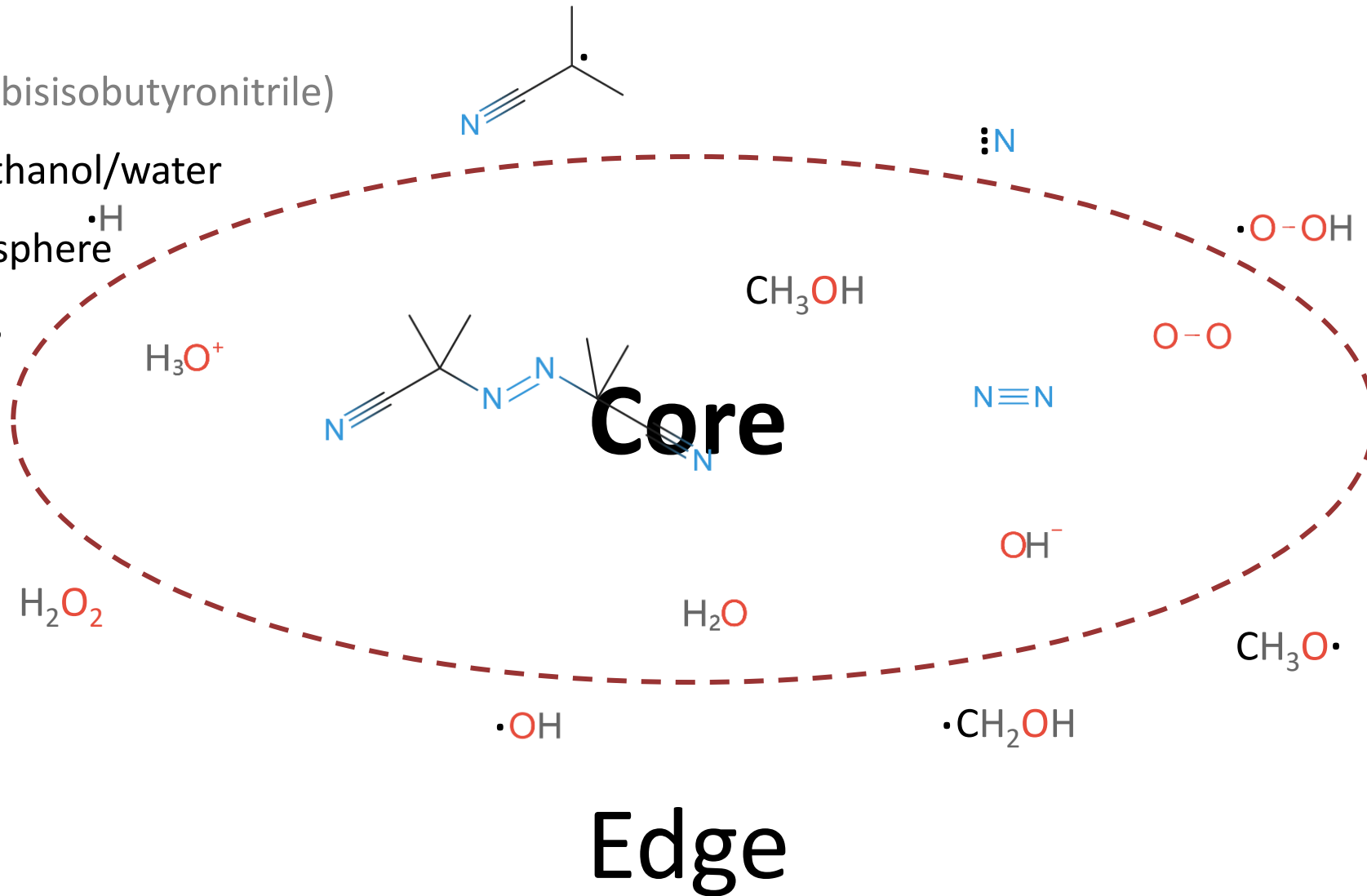
Conditions:

5.0 mM AIBN (azobisisobutyronitrile)

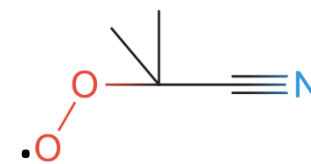
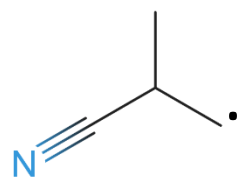
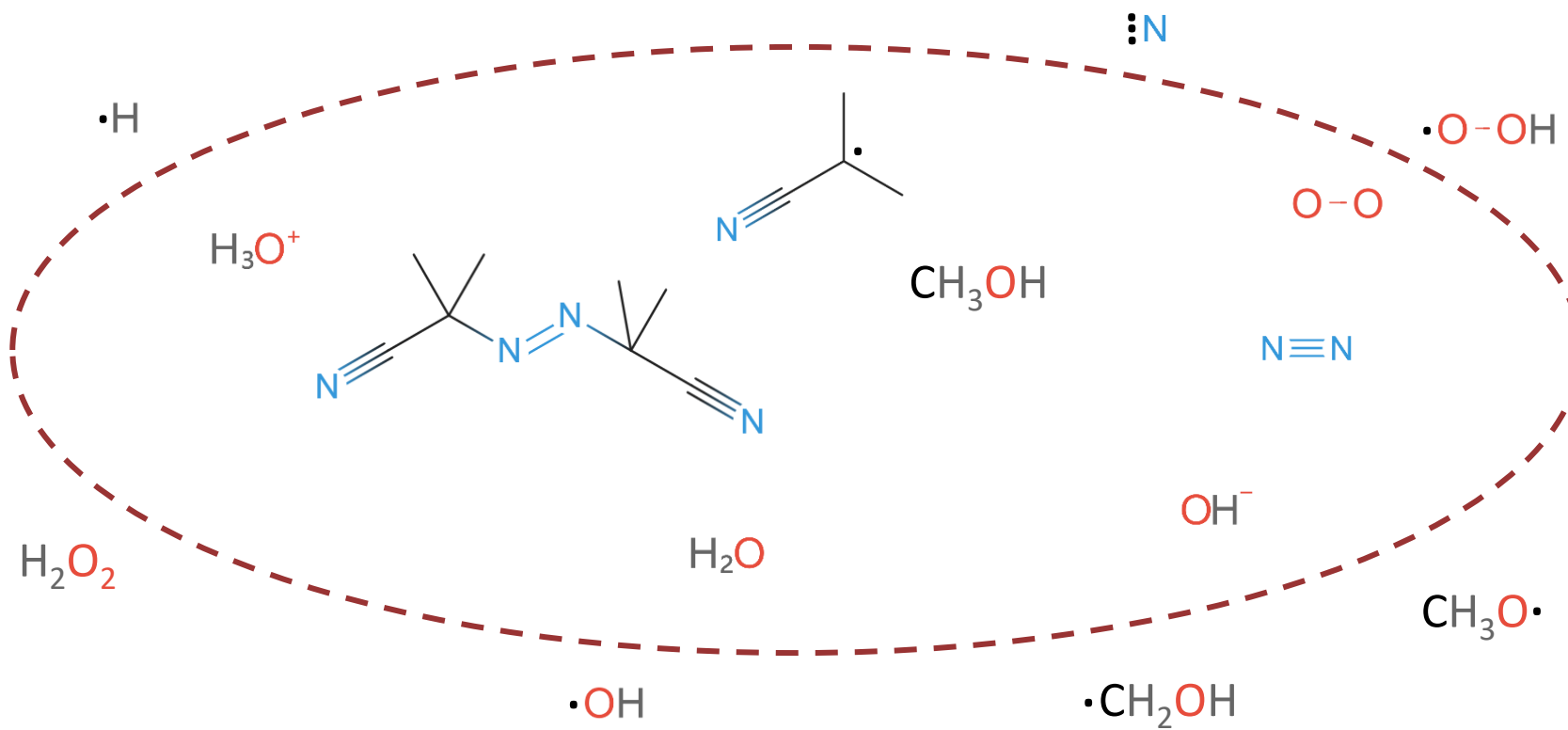
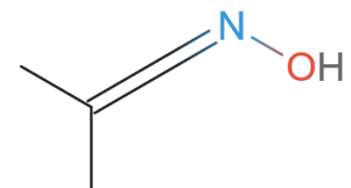
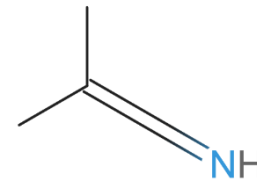
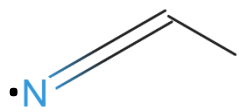
in 50/50 (v/v) methanol/water

open to the atmosphere

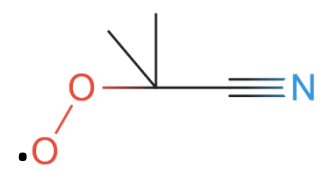
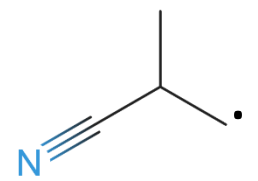
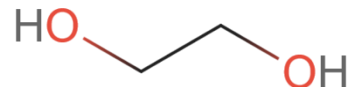
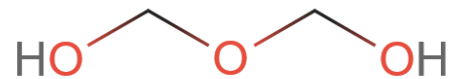
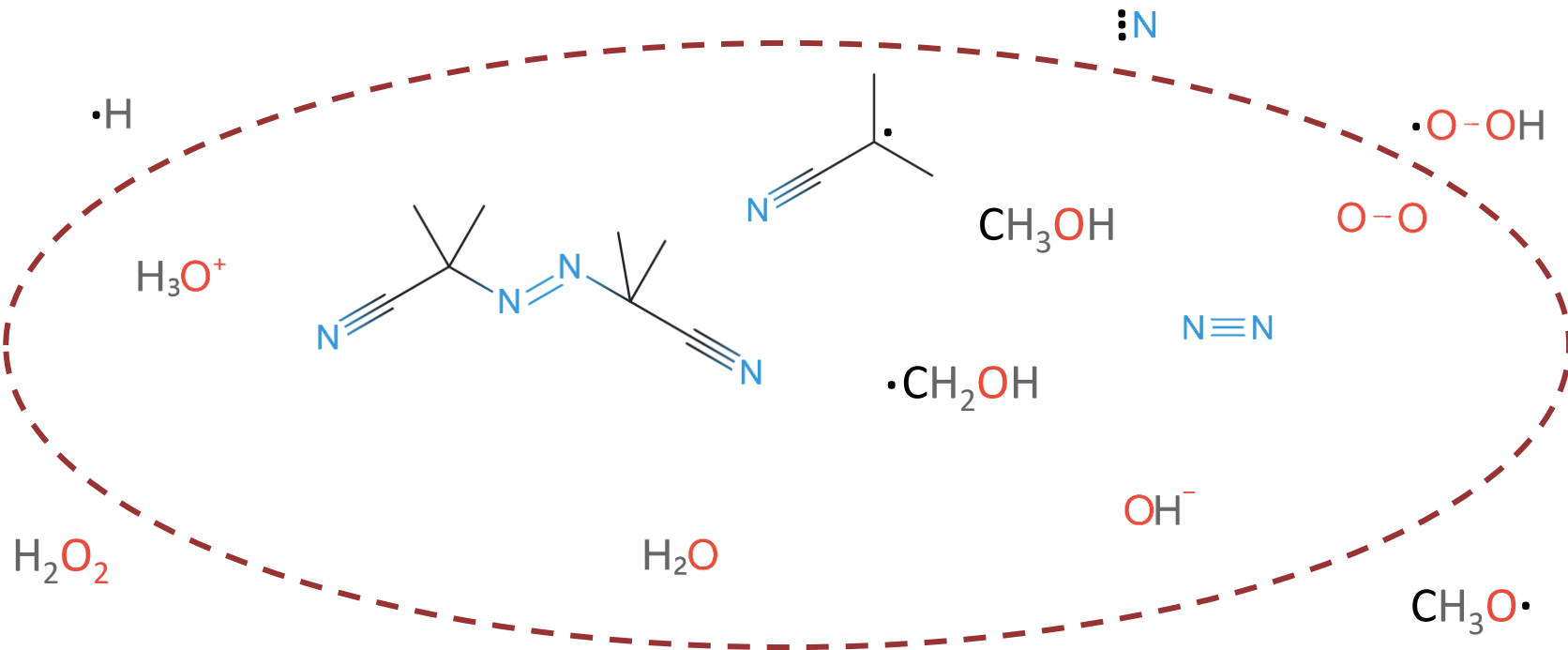
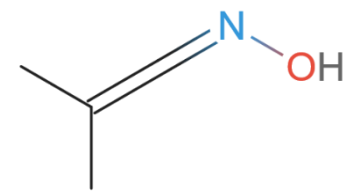
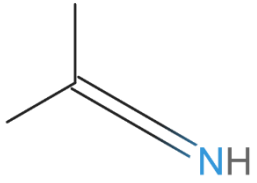
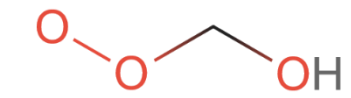
T = 40°C, 72 hours

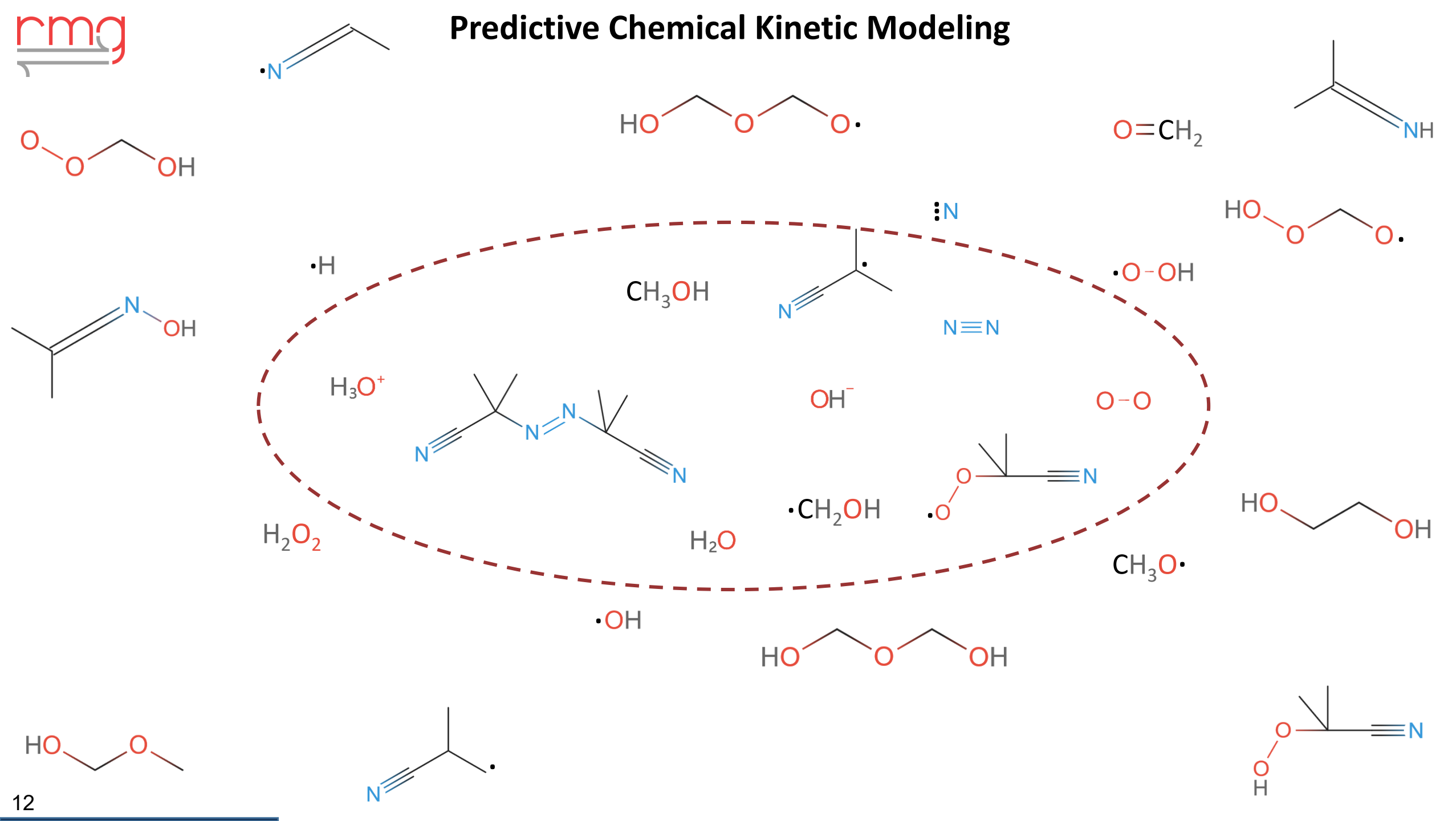


Predictive Chemical Kinetic Modeling

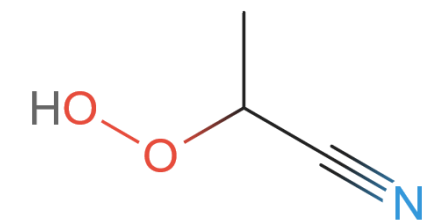
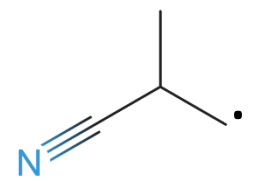
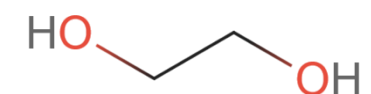
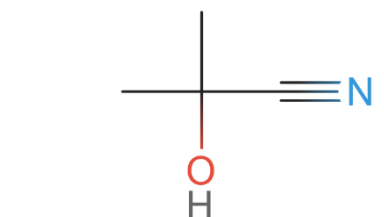
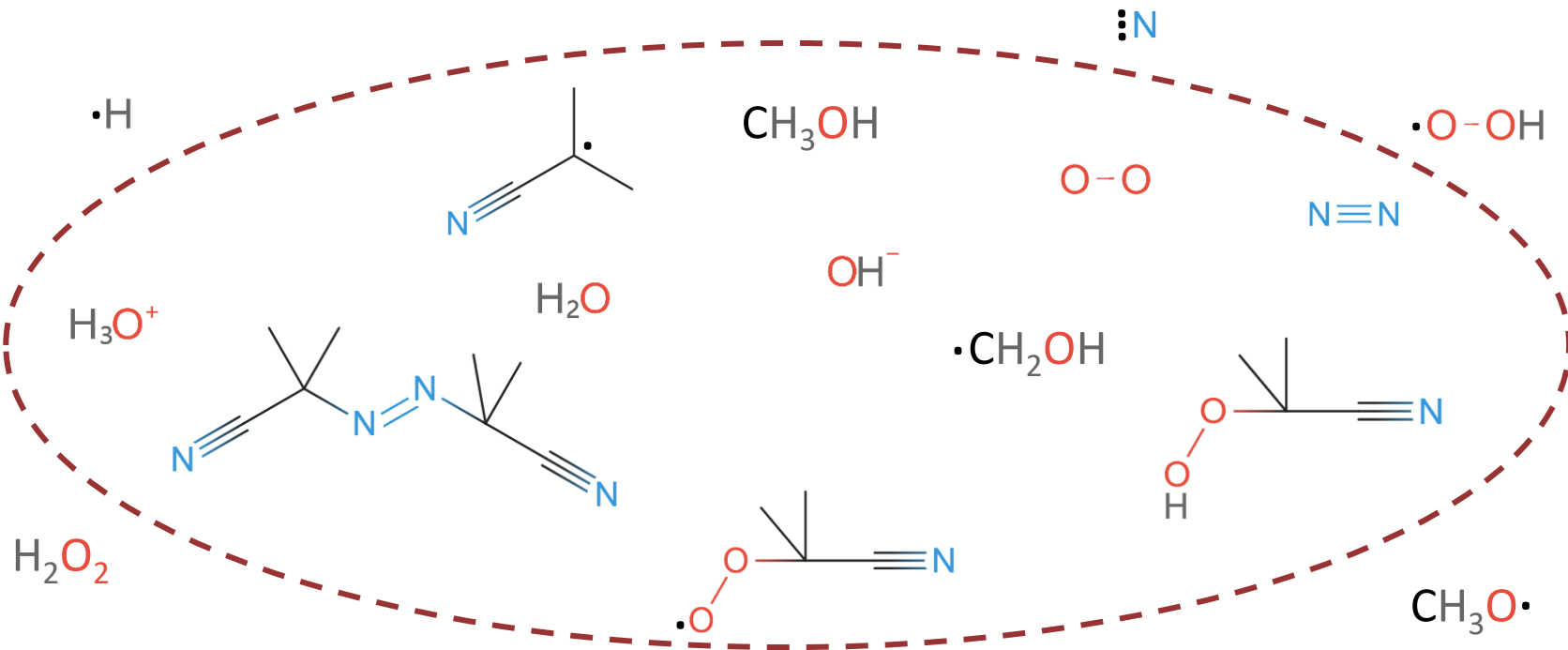
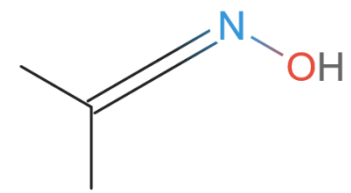
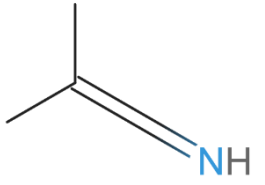
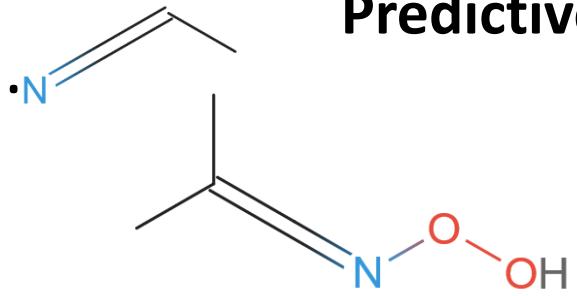
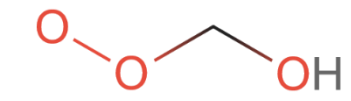


Predictive Chemical Kinetic Modeling

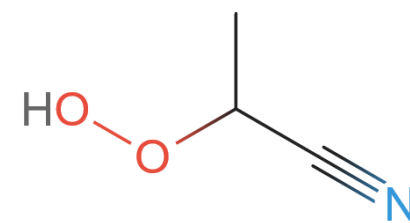
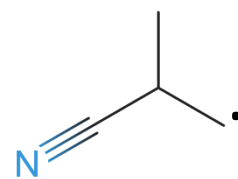
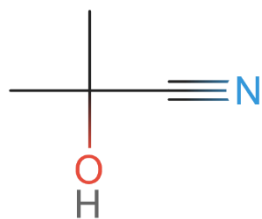
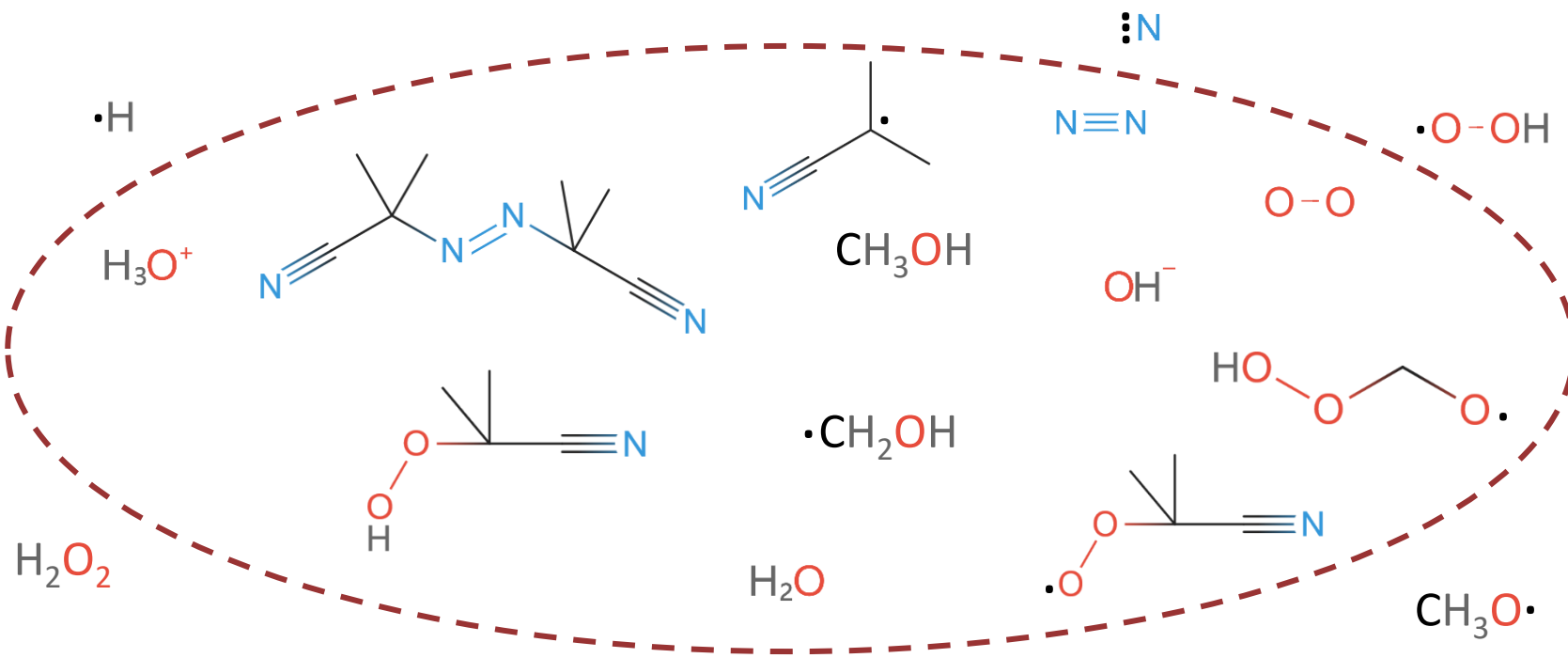
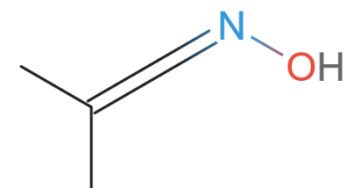
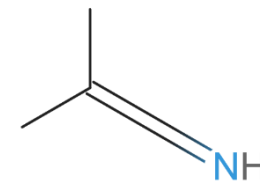
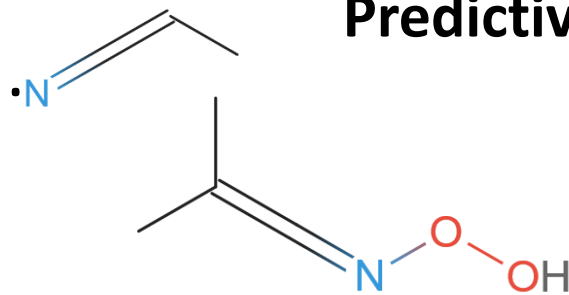
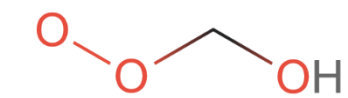




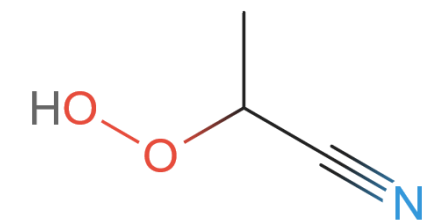
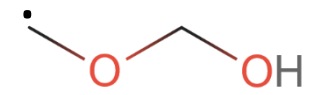
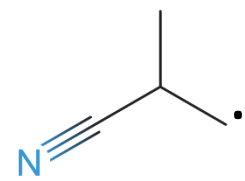
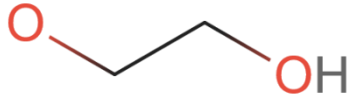
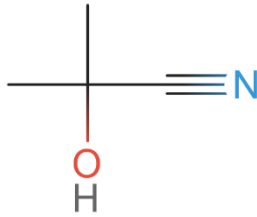
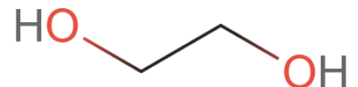
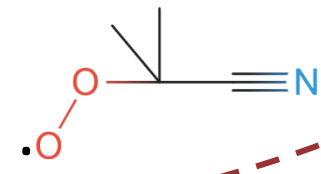
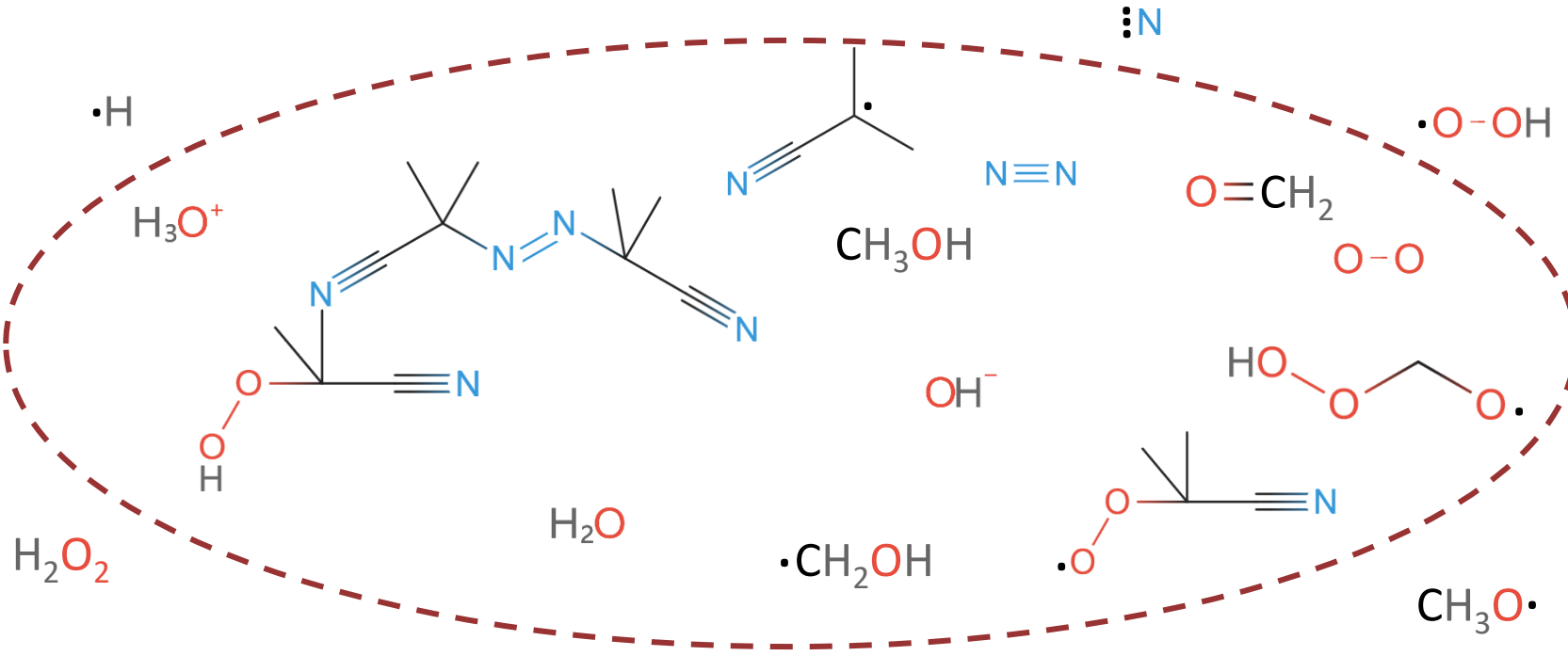
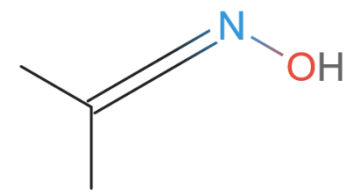
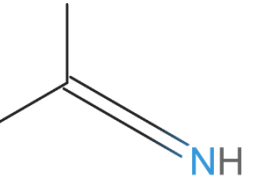
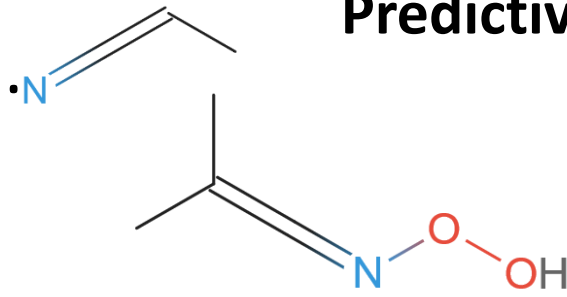
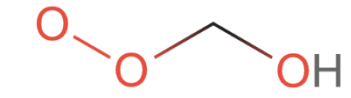
Predictive Chemical Kinetic Modeling



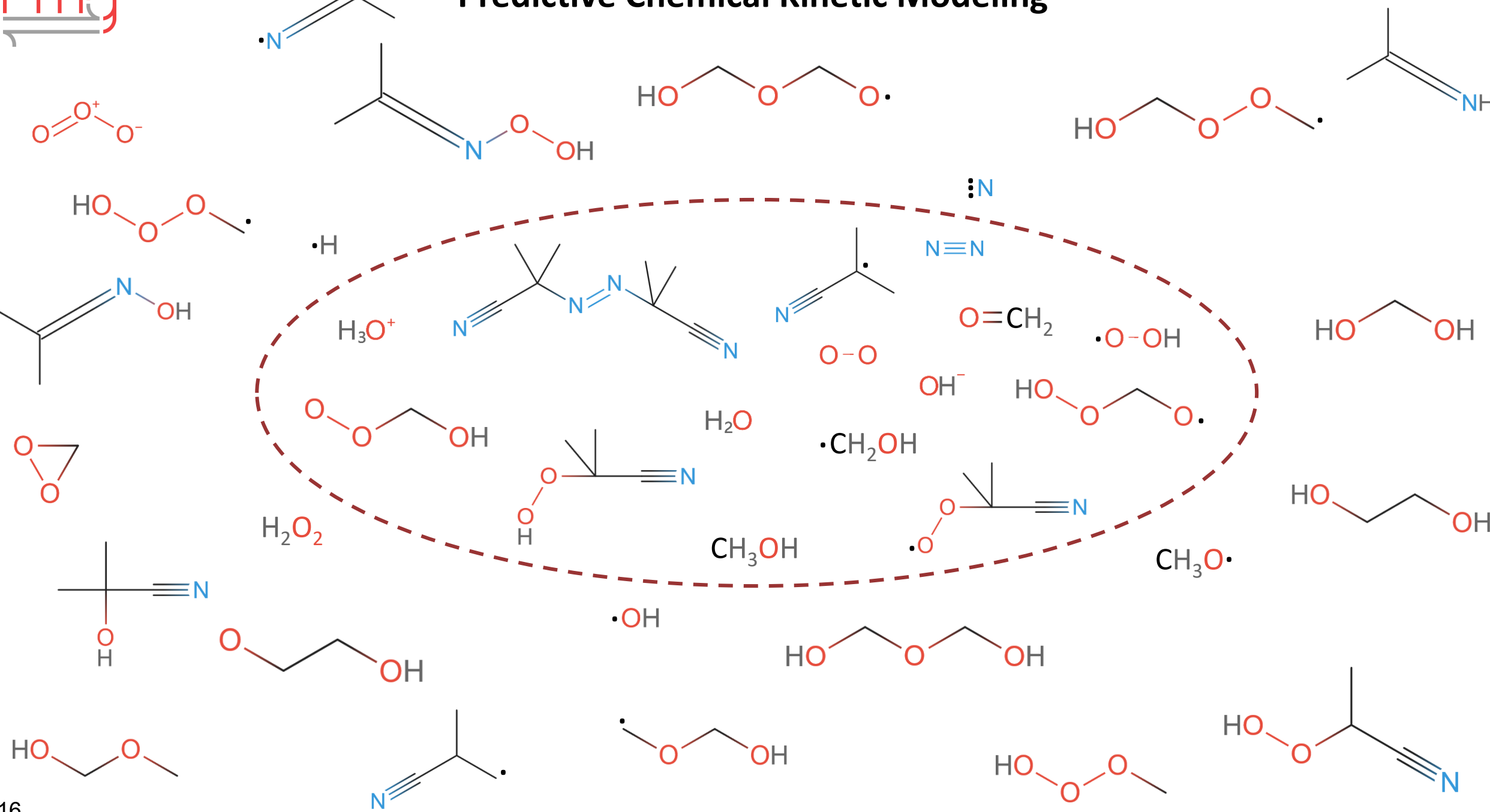
Predictive Chemical Kinetic Modeling

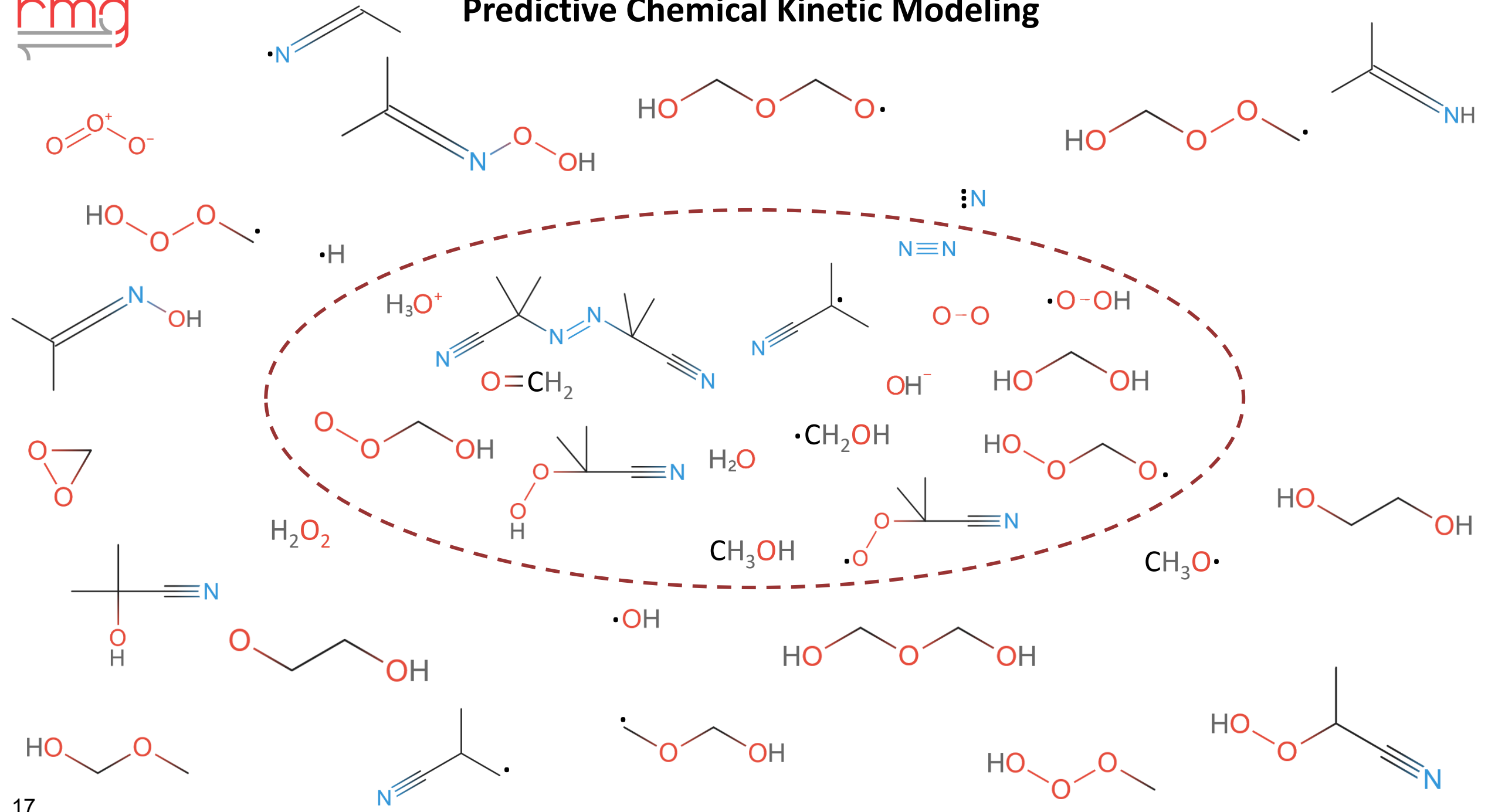


Predictive Chemical Kinetic Modeling

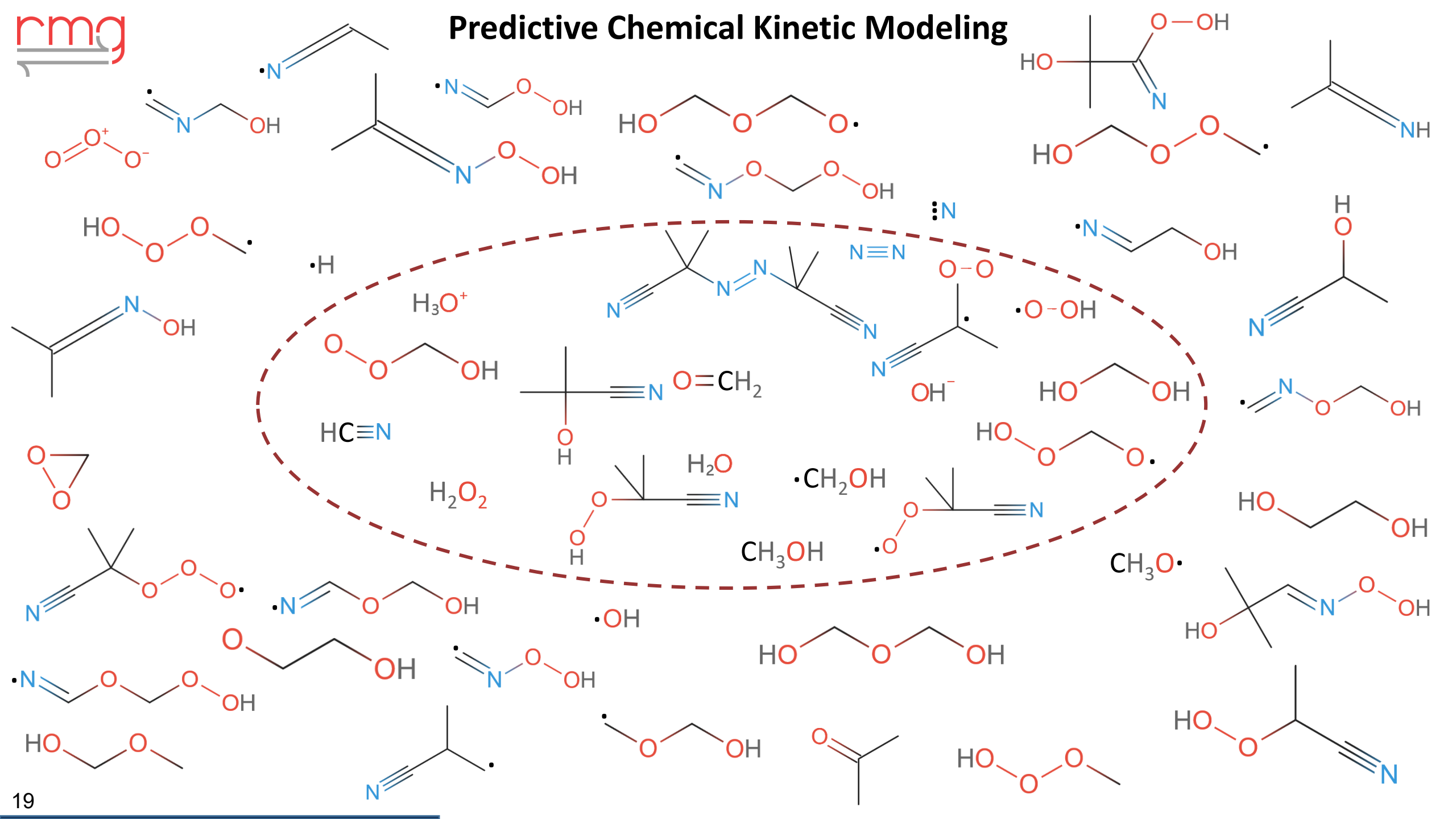


Predictive Chemical Kinetic Modeling

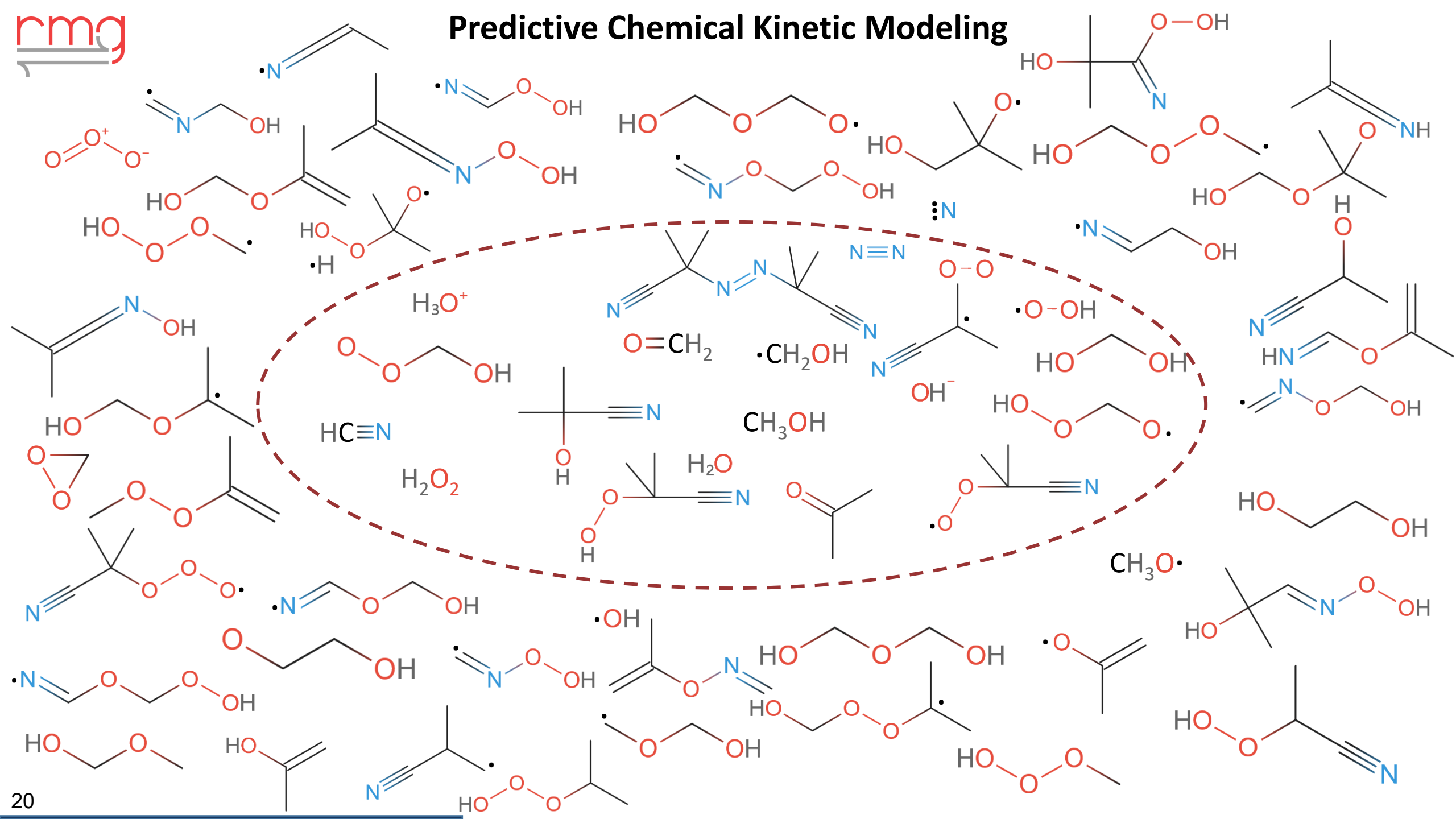




Predictive Chemical Kinetic Modeling



Predictive Chemical Kinetic Modeling





• • •
Core:

27 Species, 94 Reactions

Core + Edge: 240 Species, 1586 Reactions

(tolerance = 1%; termination time = 72 hours; execution time = 2 hours)

Where are the data (kinetics and thermochemistry) coming from?



Where are the data (kinetics and thermochemistry) coming from?

Existing “libraries” in RMG’s database:

Compiled literature values, or own computations / measurements

Estimations:

Group- / Tree- / ML- based data estimations

Ab-initio (e.g., DFT / WF):

Complementary quantum chemical computations for selected model parameters



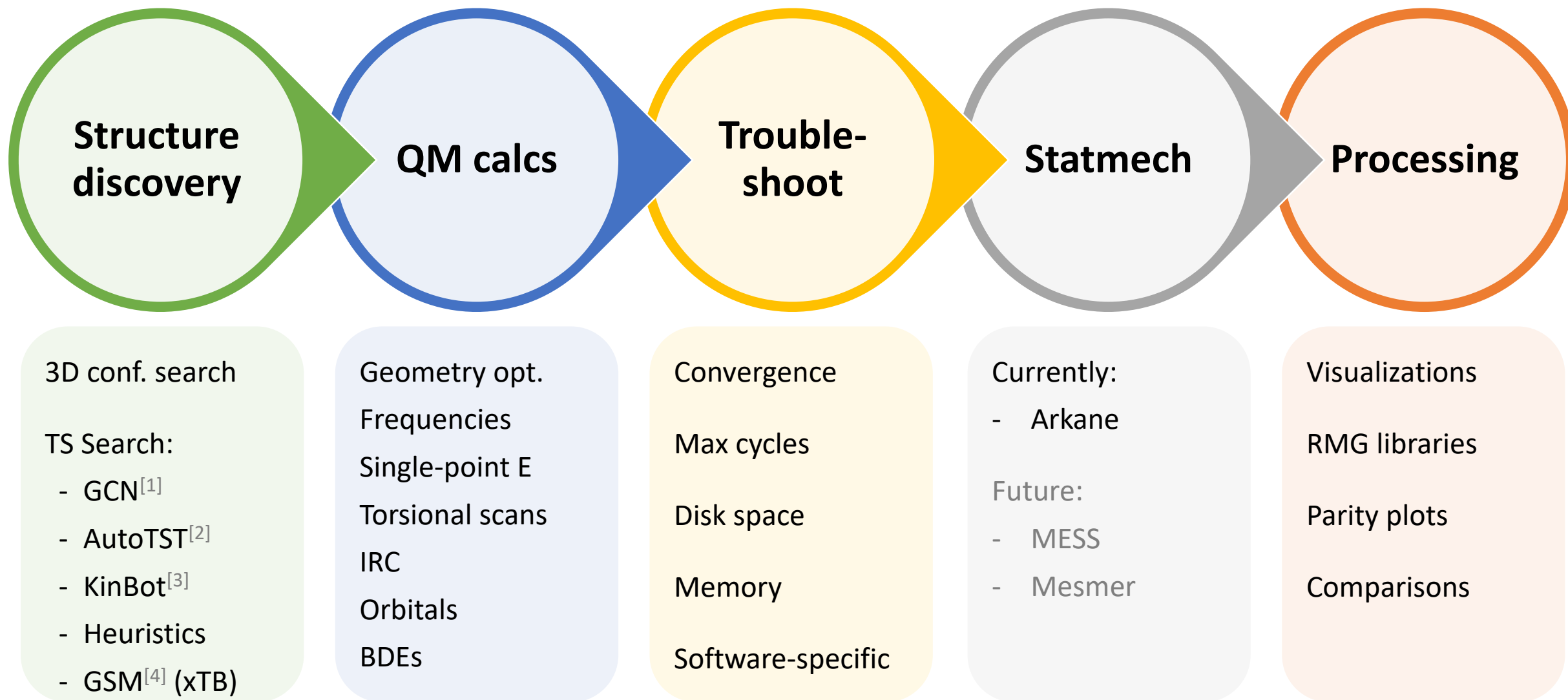
Predictive Chemical Kinetic Modeling

Need high-quality automated ab-initio thermo-kinetic computations

Introducing the **Automated Rate Calculator (ARC)** software tool:



ARC's mission is to provide the community a **well-documented, extensible** codebase for automatically calculating **species thermochemistry** and high-pressure limit **reaction rate coefficients**.



[1] L. Pattanaik et al., Phys. Chem. Chem. Phys. 2020, 22, 23618.

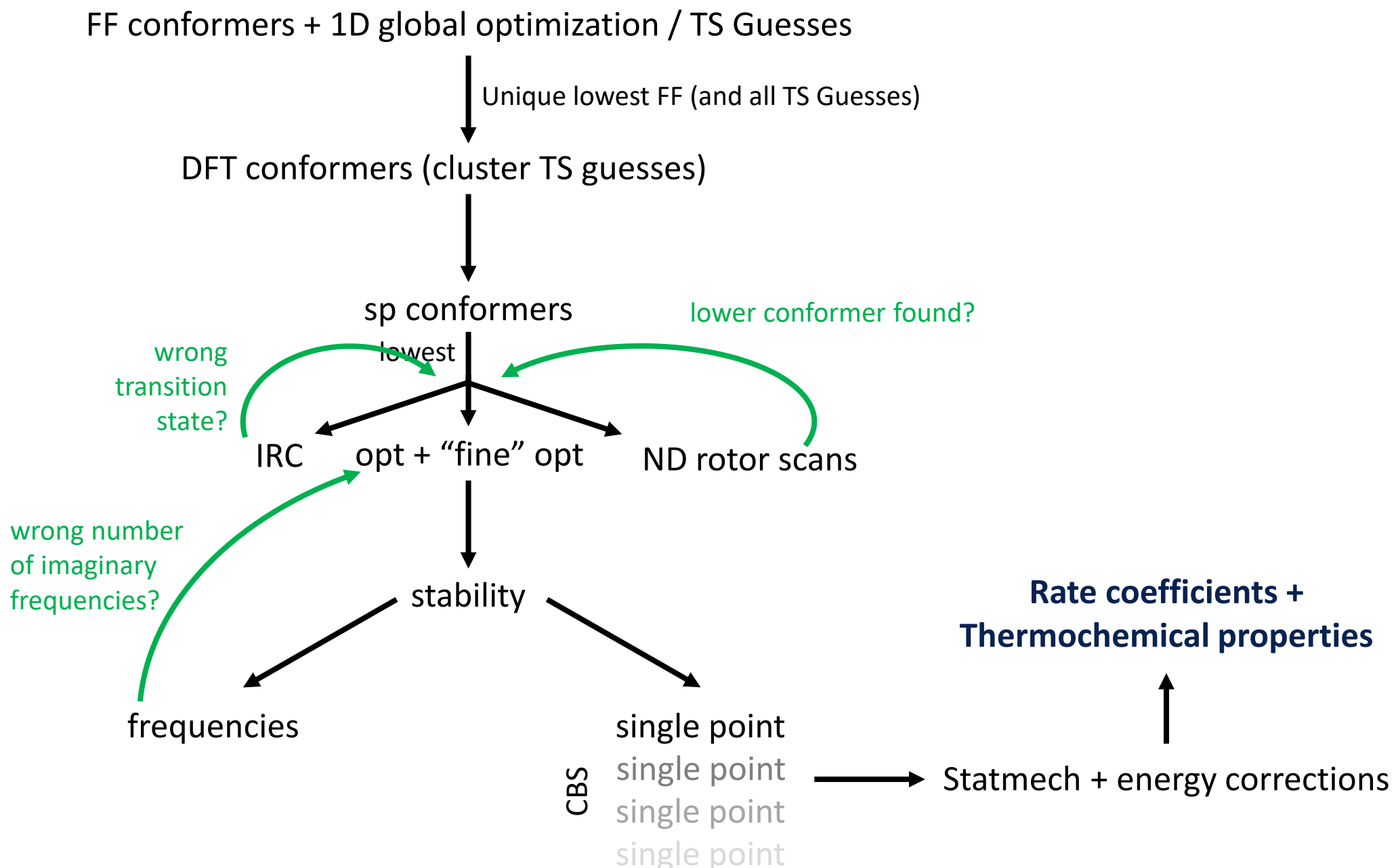
[3] R. Van de Vijver, J. Zador, Comp. Phys. Comm. 2020, 248, 106947.

[2] P.L. Bhoorasingh et al., J. Phys. Chem. A 2017, 121, 6896.

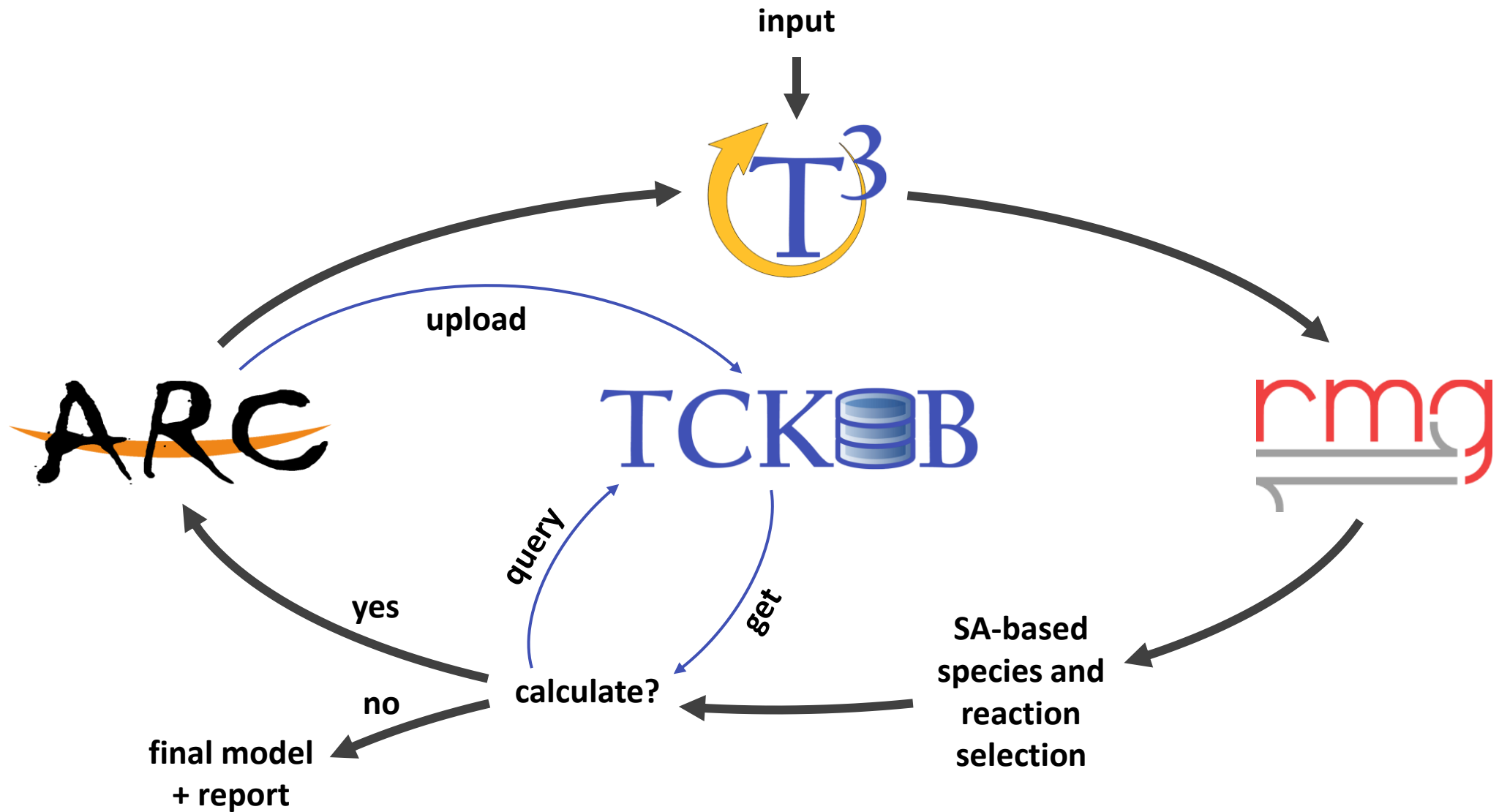
[4] P.M. Zimmerman, J. Chem. Phys. 2013, 138, 184102.

Predictive Chemical Kinetic Modeling

Various job and server troubleshooting techniques



Predictive Chemical Kinetic Modeling



T3: github.com/ReactionMechanismGenerator/T3

ARC: github.com/ReactionMechanismGenerator/ARC

RMG: github.com/ReactionMechanismGenerator/RMG-Py

TCKDB: github.com/TCKDB/TCKDB

Talk Outline

- **Methodology**
 - The Radical “Soup” in API Stress Testing
 - Case Studies
 - Outlook and Perspective
-

Talk Outline

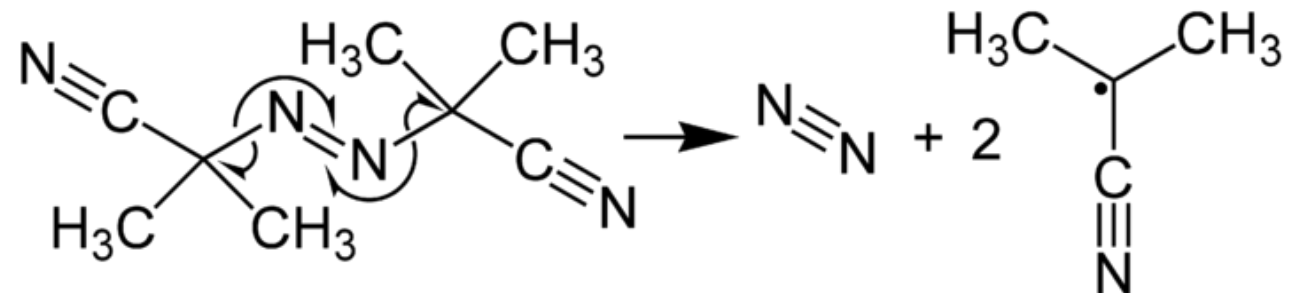
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The Radical “Soup” in API Stress Testing

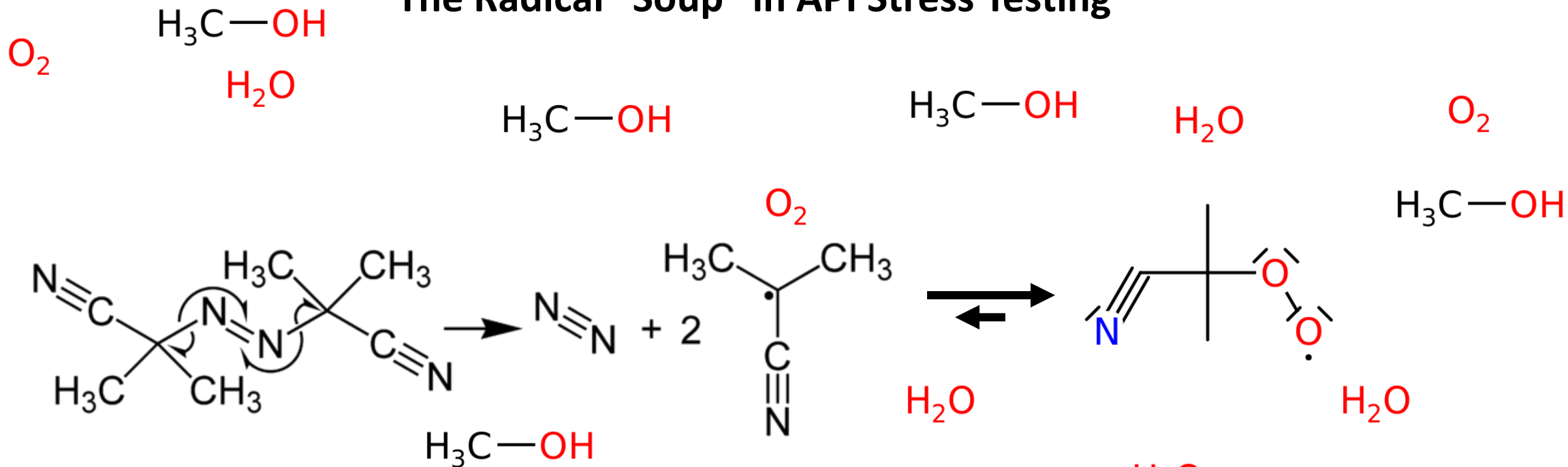
Three types of oxidative stress testing are commonly used:

1. Using **hydrogen peroxide** to cover nucleophilic-electrophilic oxidations,
2. Using **azoalkanes** to cover **free-radical oxidation** (autoxidation), and
3. Using **transition metals** to cover single electron transfer oxidations.

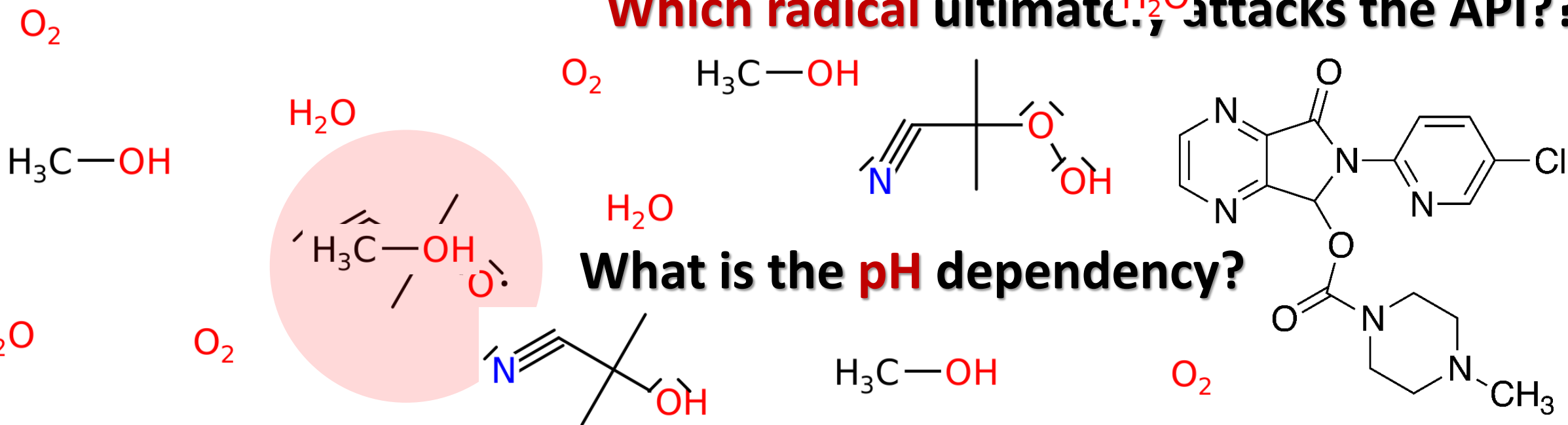
AIBN (azobisisobutyronitrile)



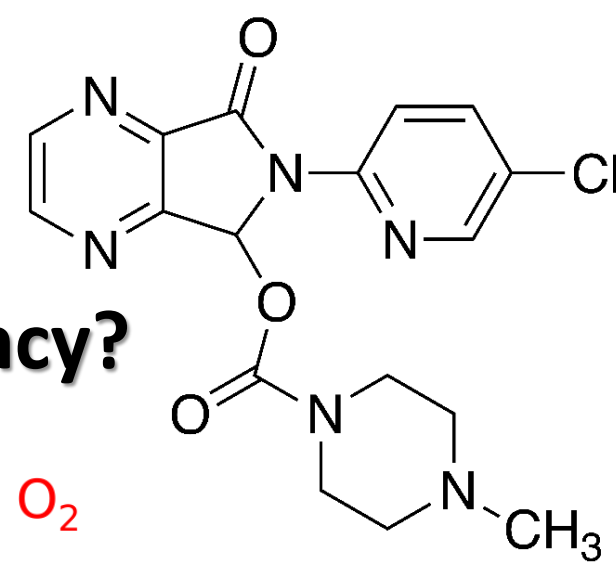
The Radical "Soup" in API Stress Testing



Which radical ultimately attacks the API?

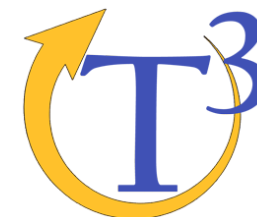


What is the pH dependency?



The Radical “Soup” in API Stress Testing

The model was automatically generated and refined using:



Initial conditions:

5.0 mM AIBN, 12.05 mg/L N₂ (const.), 7.45 mg/L O₂ (const.)

in a water/methanol co-solvent system of 50/50 (v/v)

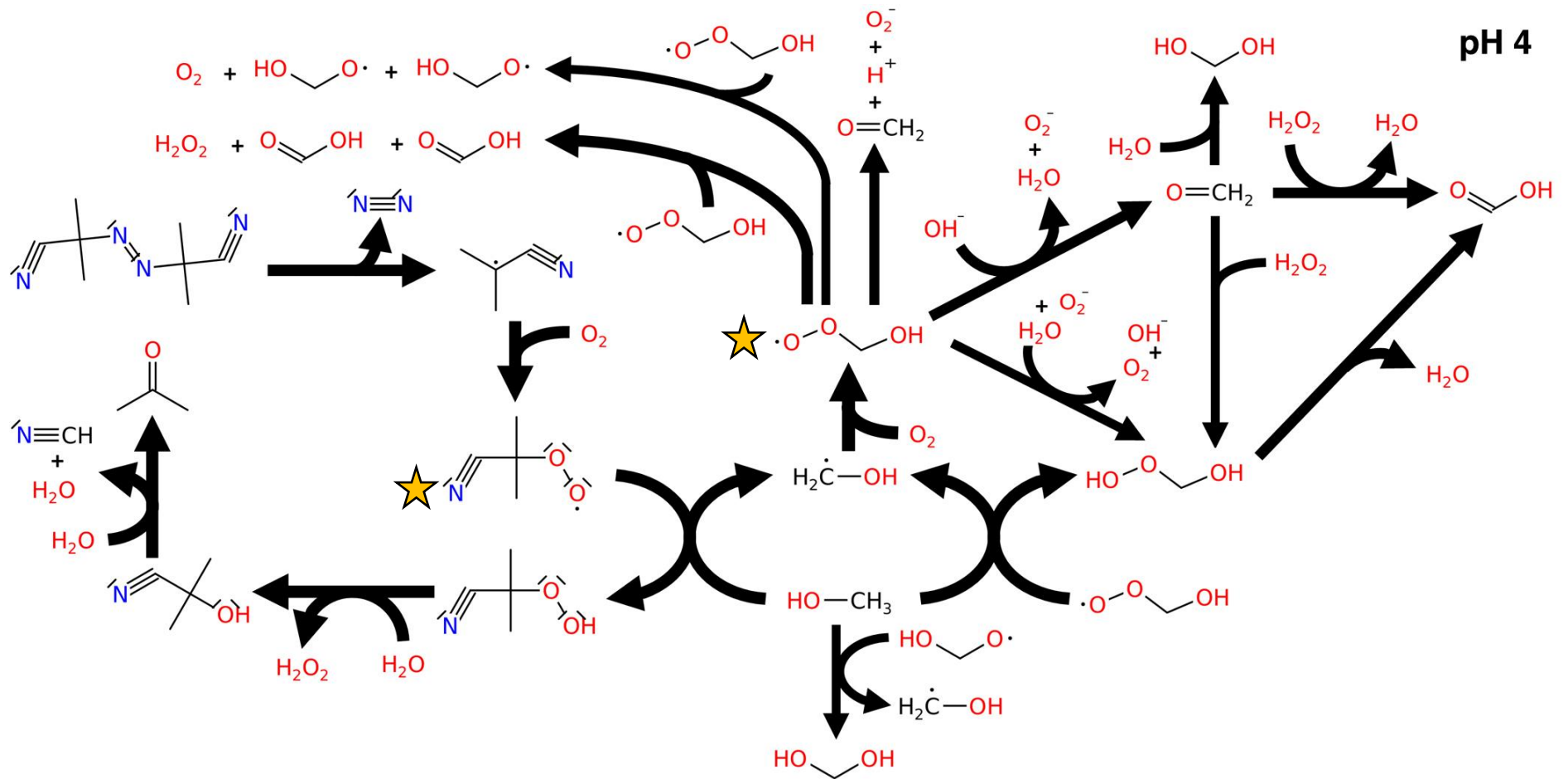
at 40° C, 1 atm

The model consisted of 27 species and 94 elementary reactions.

Parameters were refined using [DLPNO-CCSD\(T\)/Def2-TZVP//ωB97X-D/Def2-TZVP](#) with solvation corrections

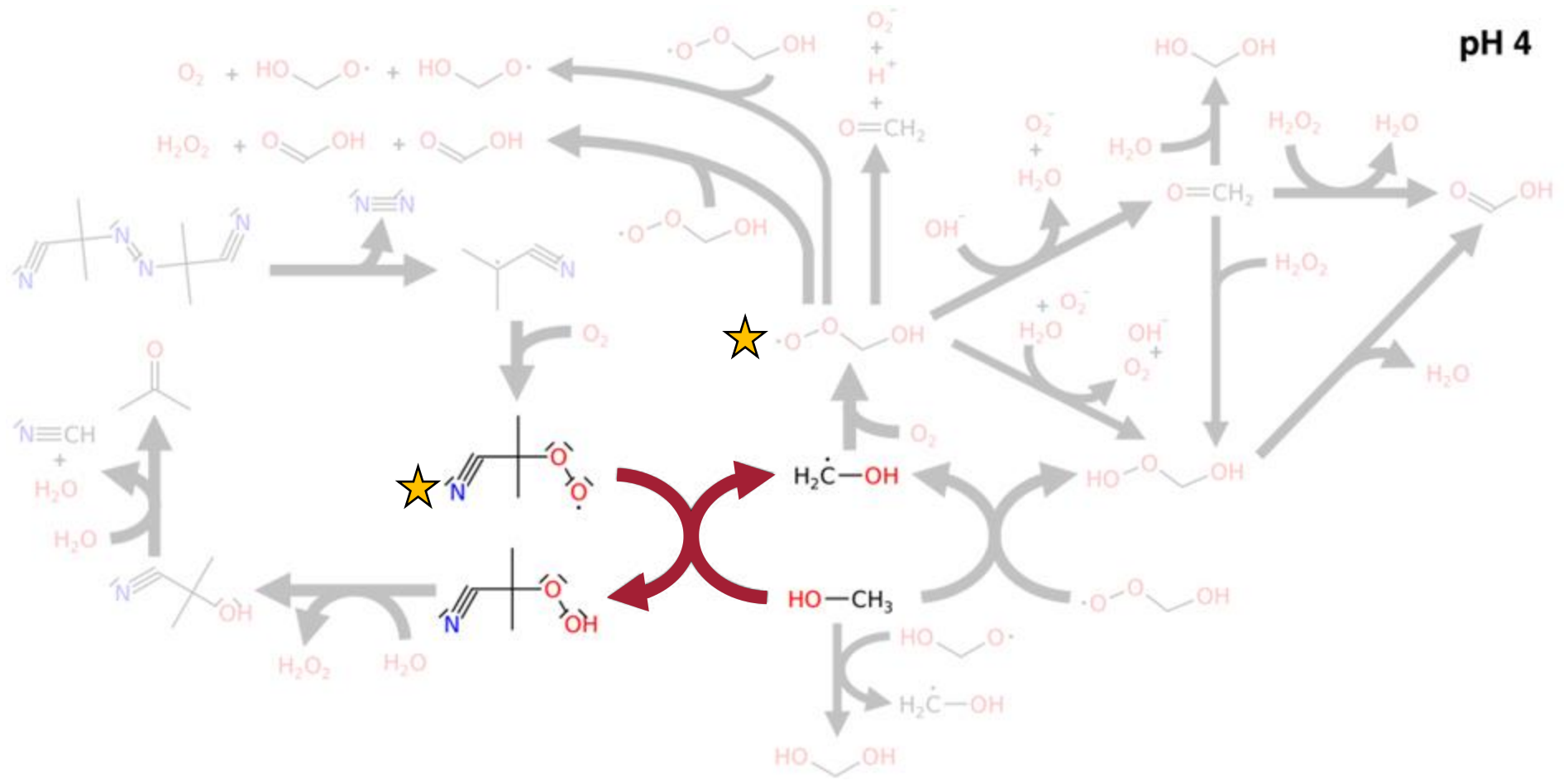
The Radical "Soup" in API Stress Testing

Major reaction pathways at 24 hours:



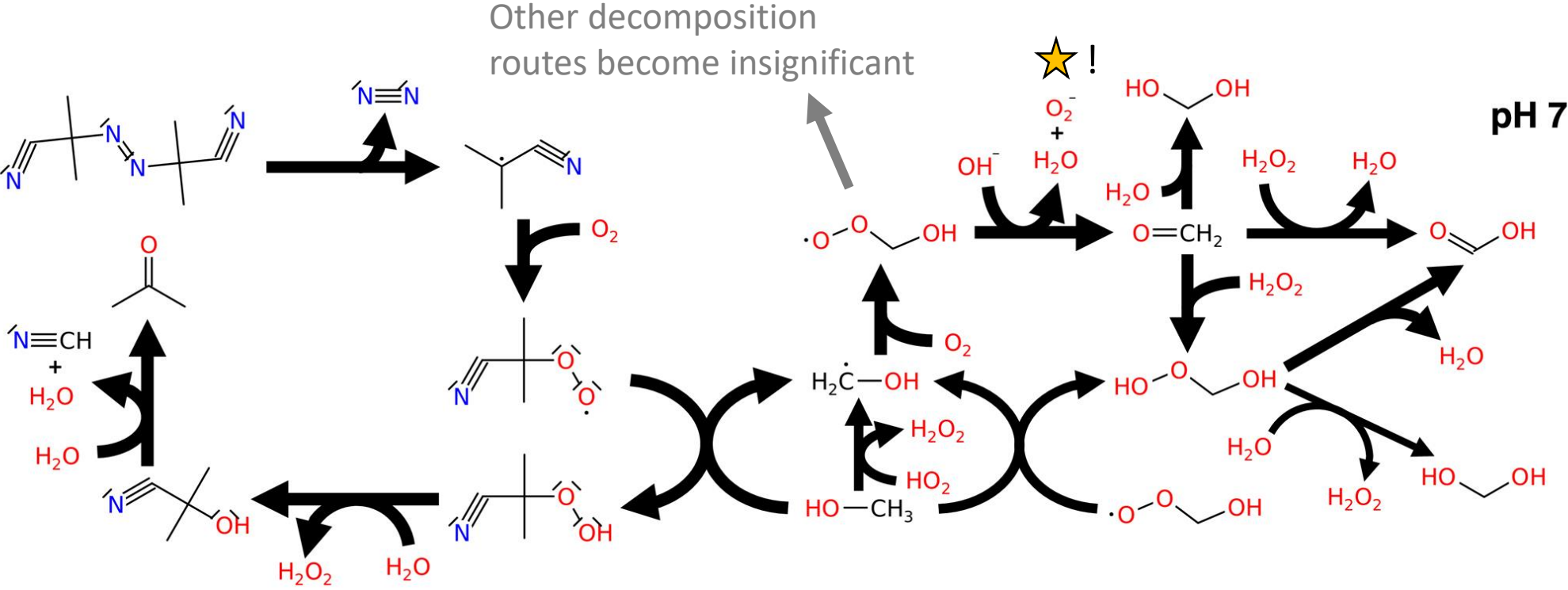
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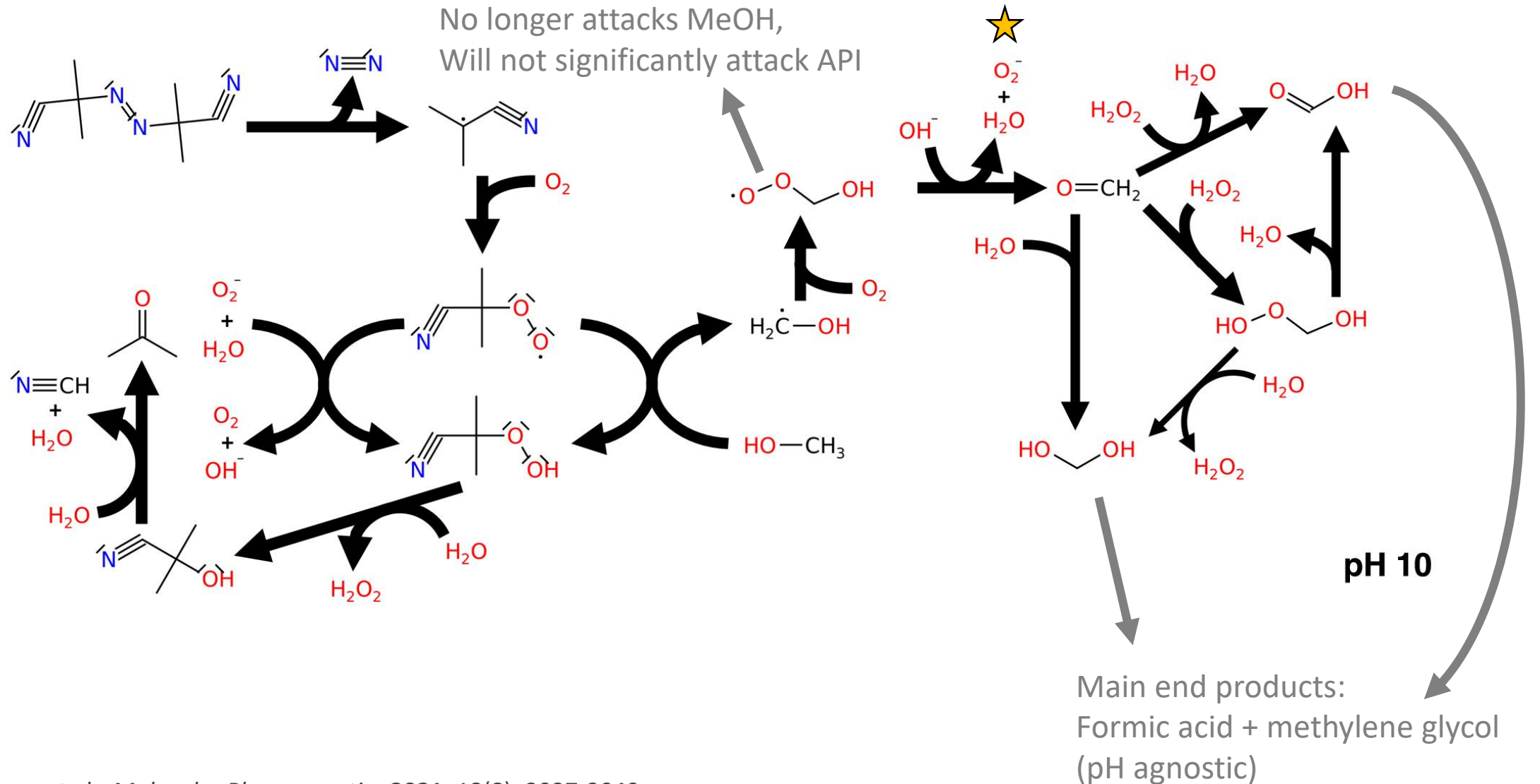
The Radical "Soup" in API Stress Testing

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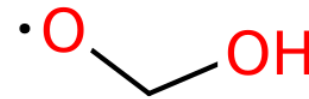
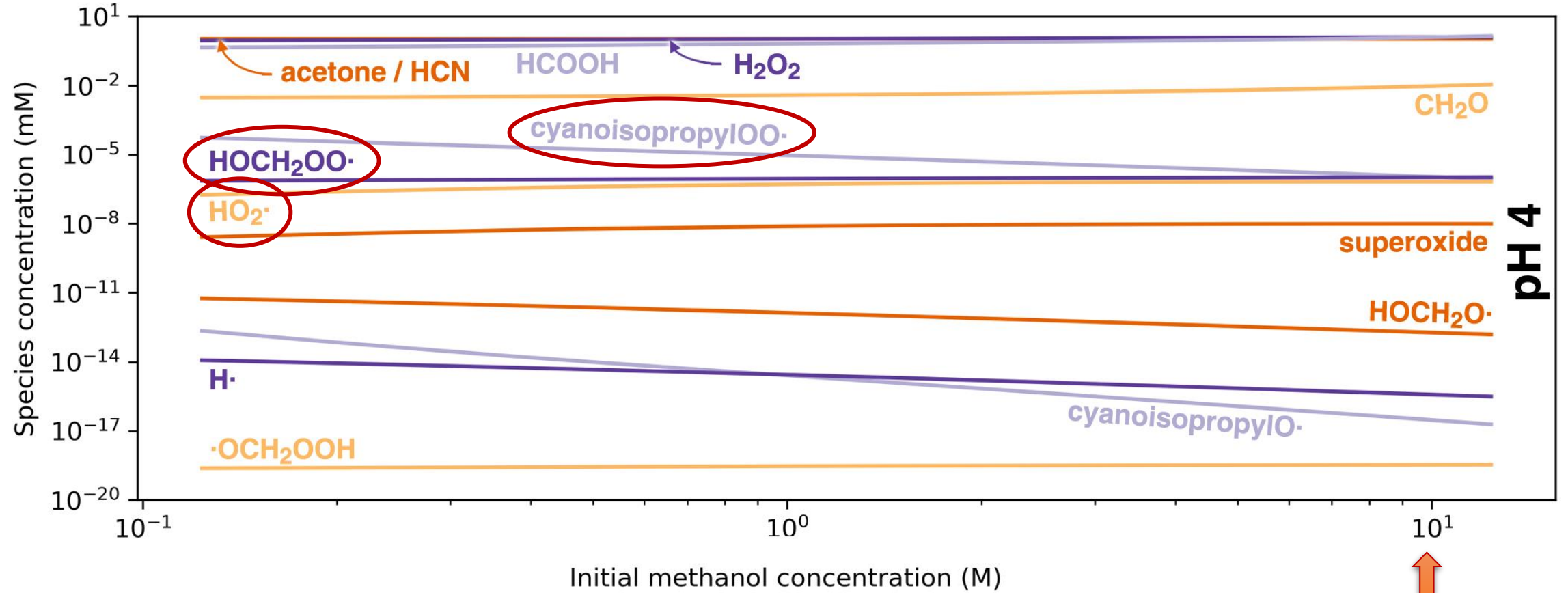
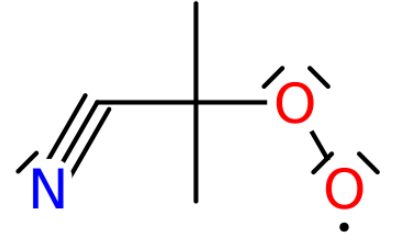
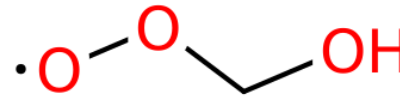
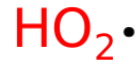
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Major reaction pathways at 24 hours:



The Radical "Soup" in API Stress Testing

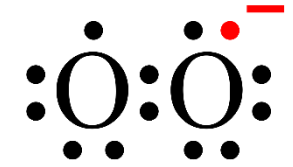
Species concentrations at 72 hours:



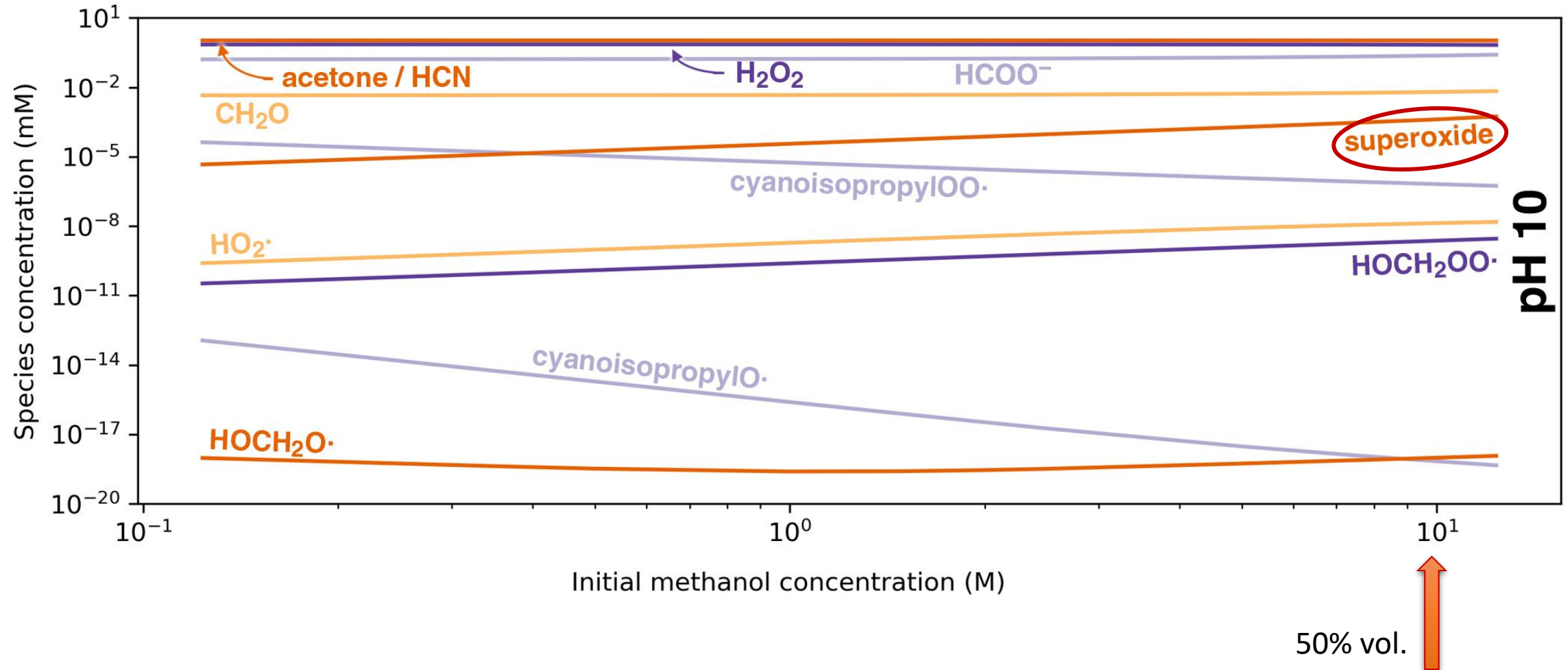
50% vol.



The Radical "Soup" in API Stress Testing



Species concentrations at 72 hours:



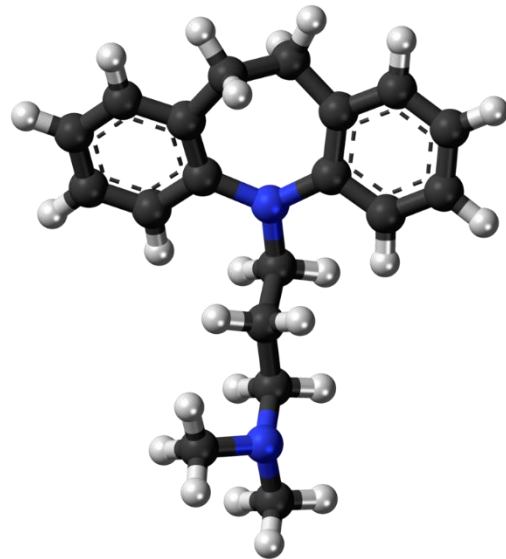
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Case Study 1: Imipramine Oxidation



Case Study 1: Imipramine Oxidation

Imipramine

Mainly used in the treatment of depression.

Also effective in treating anxiety and panic disorder.

Initial conditions:

1.96 mM API

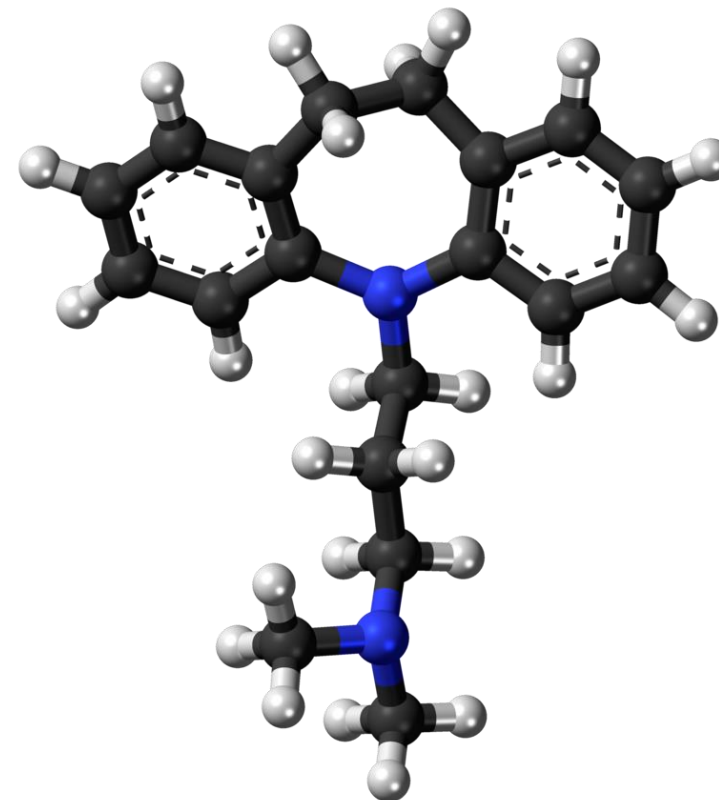
Open system

50/50 (v/v) methanol/0.2 M carbonate buffer

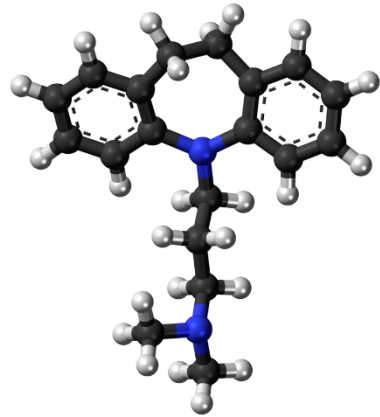
pH 11 (pKa 9.5)

at 40° C

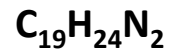
72 hours (3 days)



Case Study 1: Imipramine Oxidation



Imipramine



Important questions

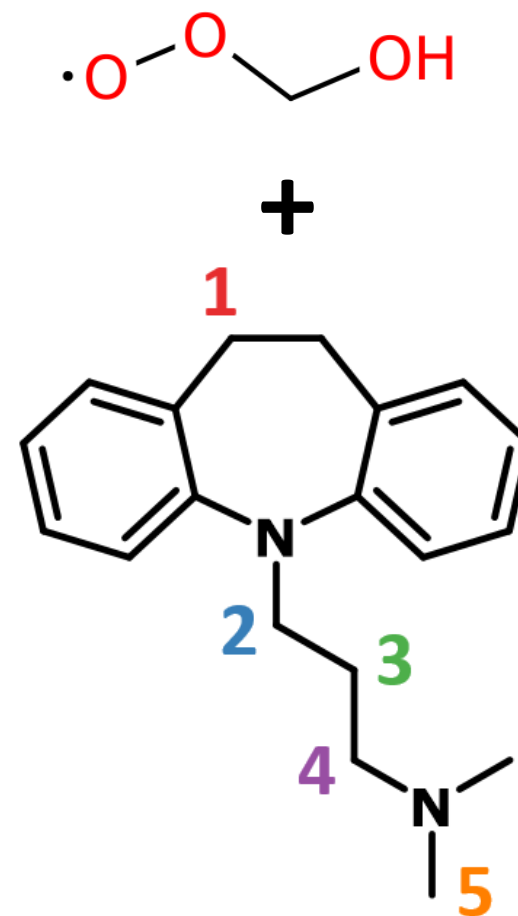
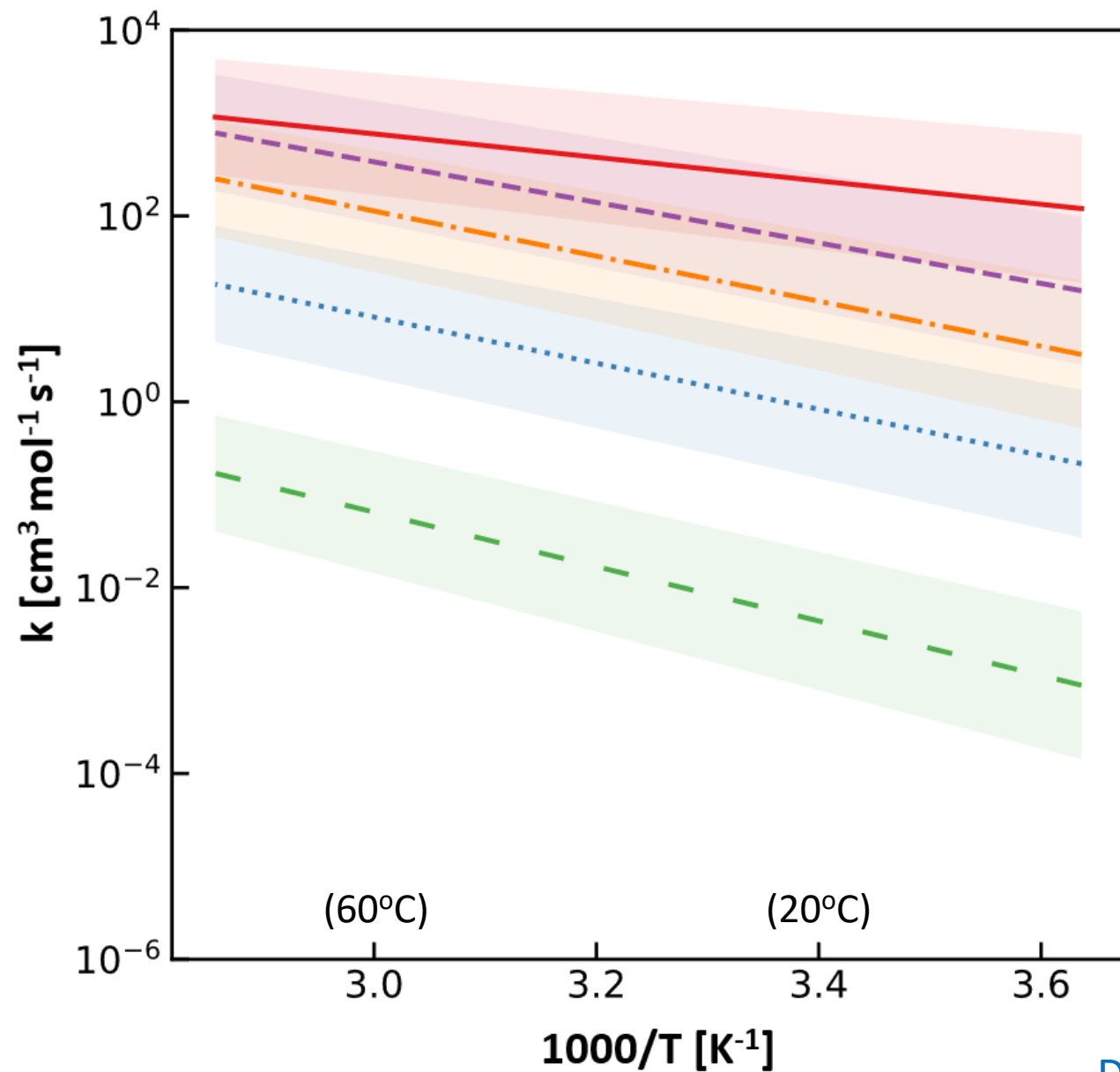
Which **sites** are more susceptible to radical oxidation?

What are the major **degradation pathways** and their kinetics?

What are the chemical structures of stable **degradants**?

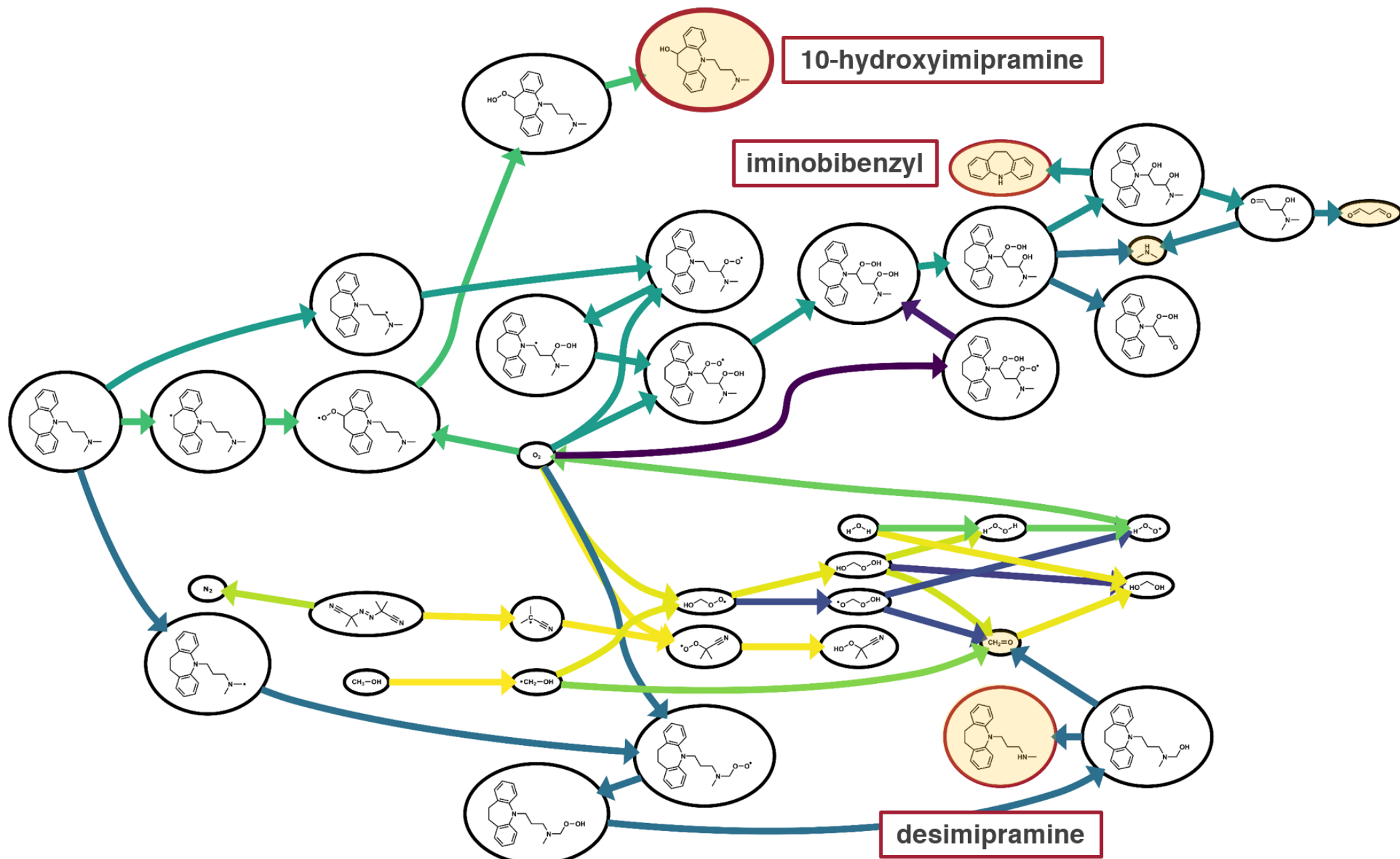
What are the relative **concentrations** of major degradants?

Case Study 1: Imipramine Oxidation

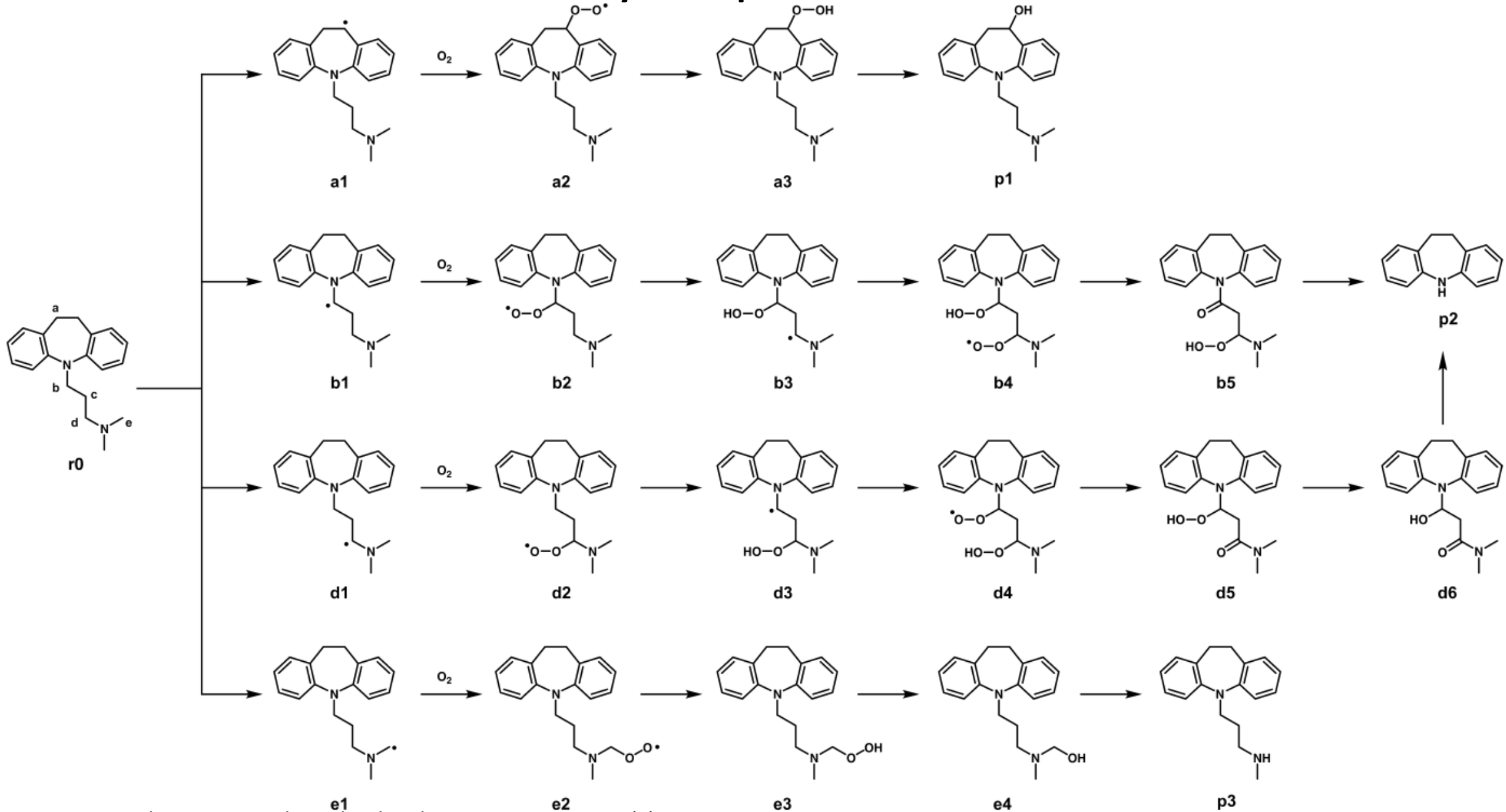


DLPNO-CCSD(T)/Def2-TZVP// ω B97X-D/Def2-TZVP

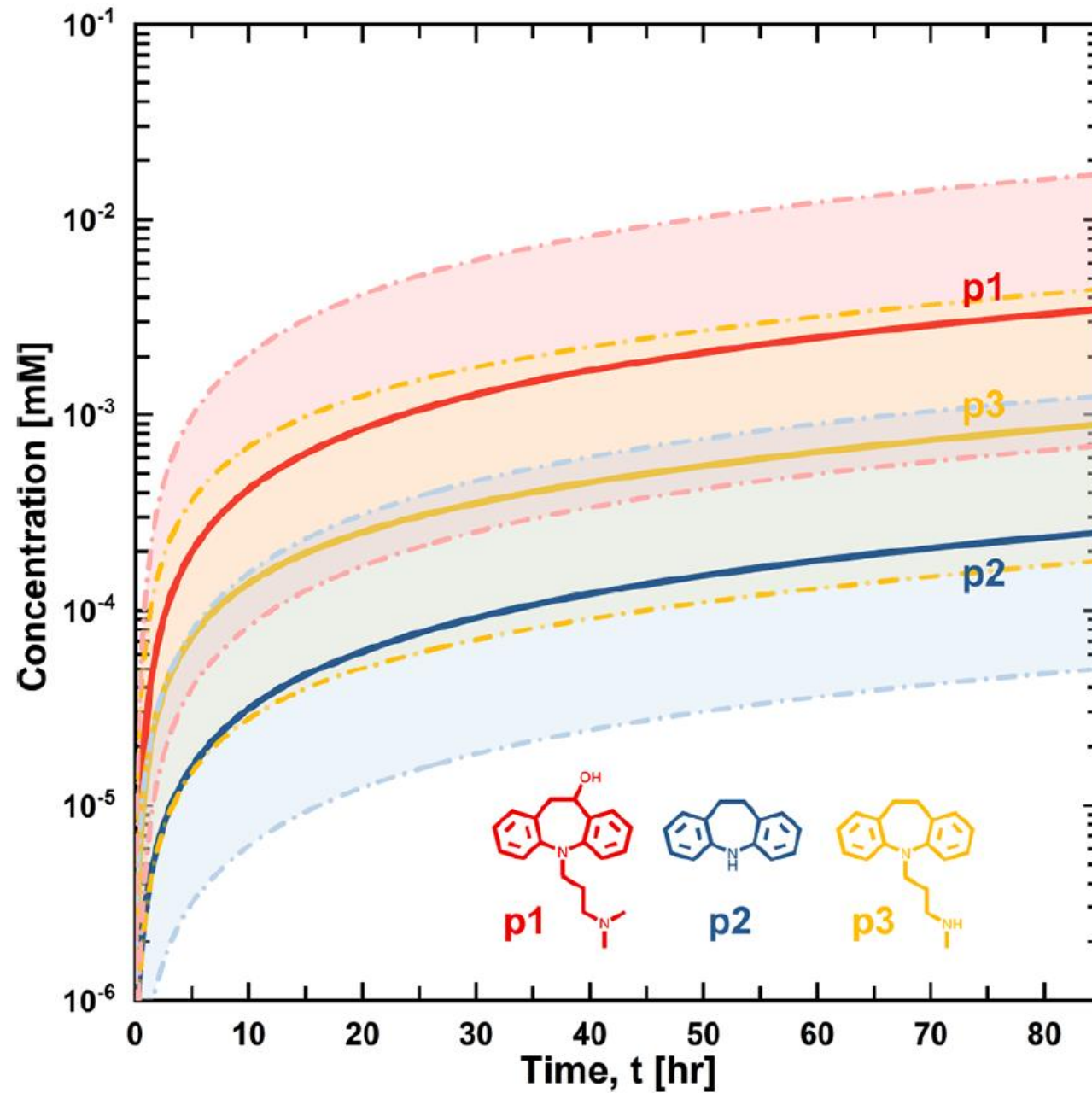
Case Study 1: Imipramine Oxidation



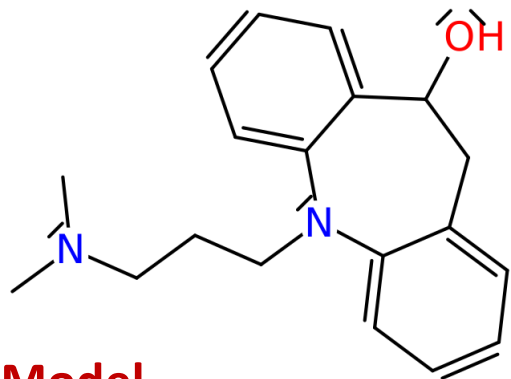
Case Study 1: Imipramine Oxidation



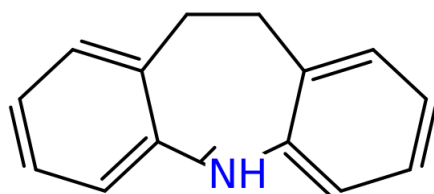
Case Study 1: Imipramine Oxidation



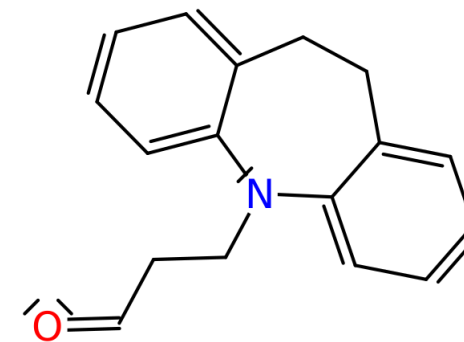
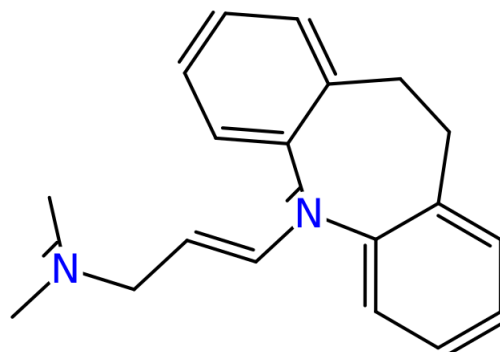
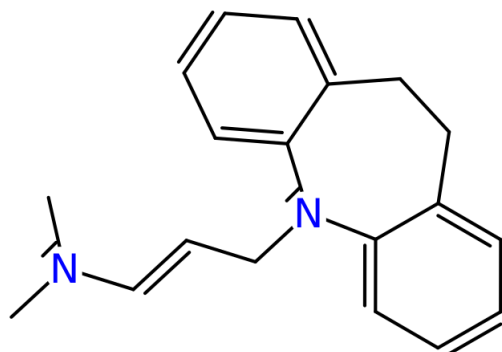
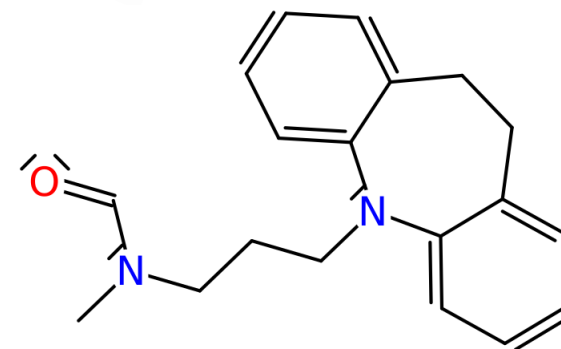
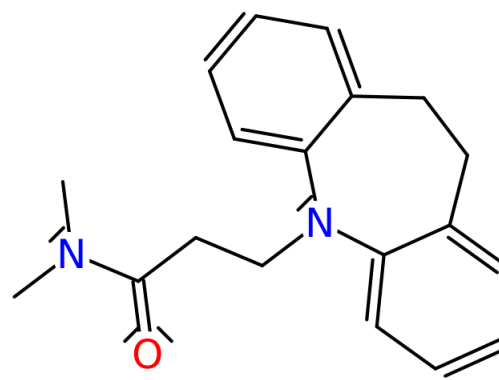
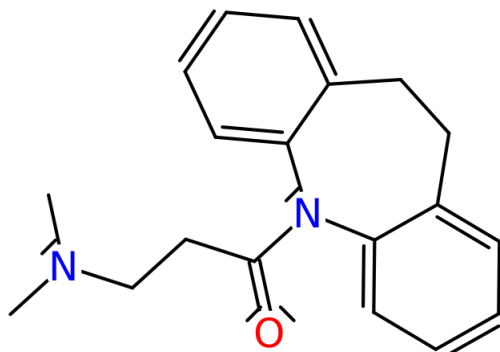
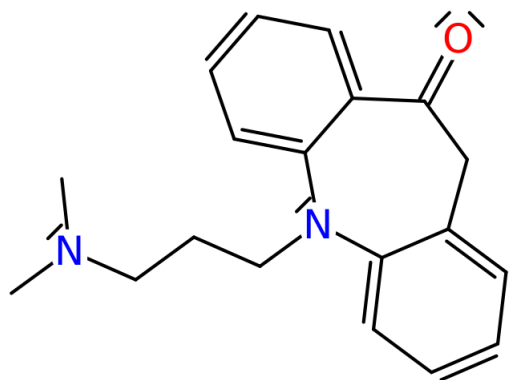
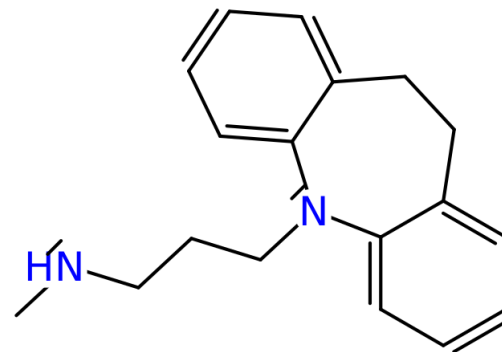
Case Study 1: Imipramine Oxidation



Model



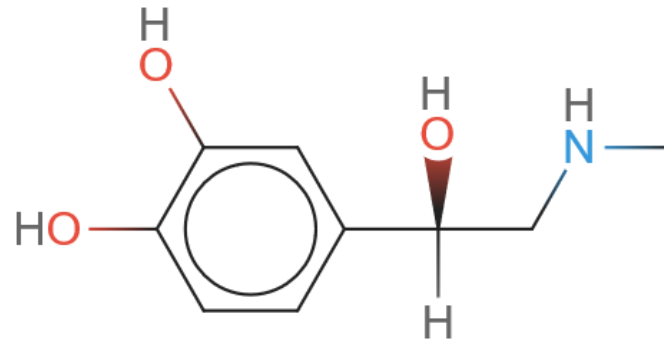
Experiment



Zeneth ("Very Likely" prediction)

Case Study 2: Adrenaline Thermolysis

Case Study 2: Adrenaline Thermolysis



Initial conditions:

10 µg/mL API

Closed system

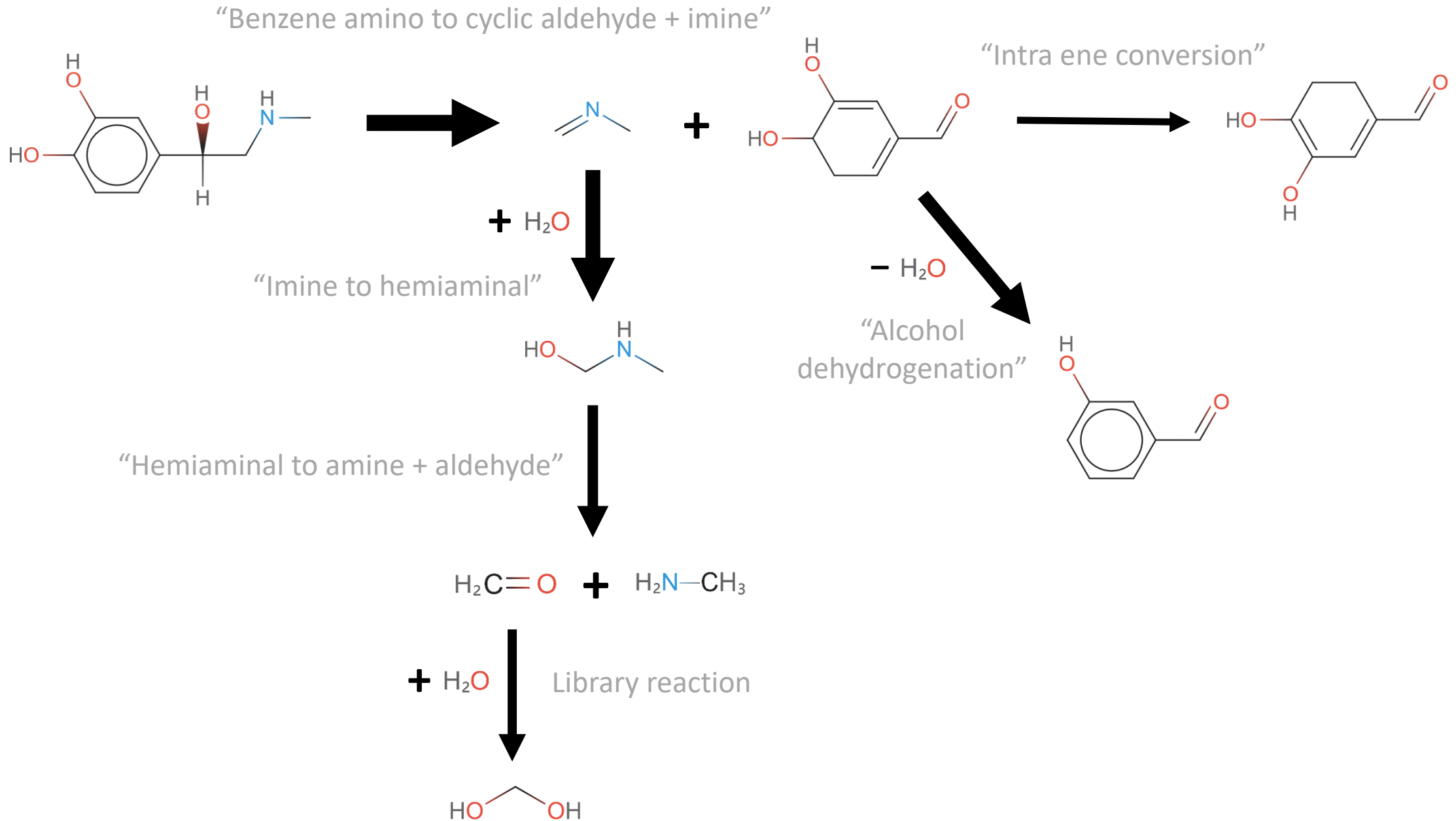
10/90 (v/v) acetonitrile / aqueous buffer

pH 1 (adrenaline shown to be most stable at pH 2.5 – 4.5)

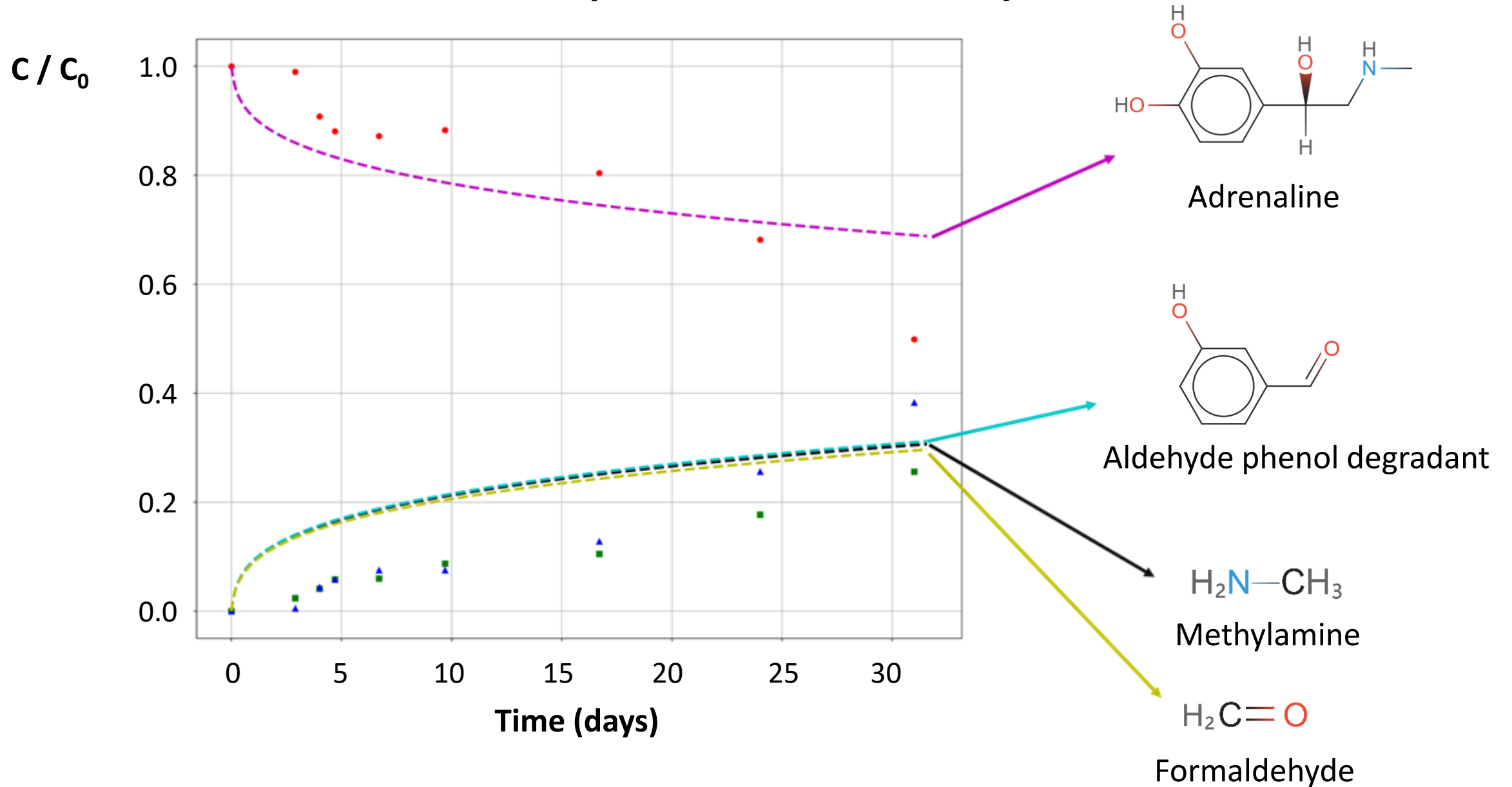
at 80° C

800 hours (~33 days)

Case Study 2: Adrenaline Thermolysis



Case Study 2: Adrenaline Thermolysis



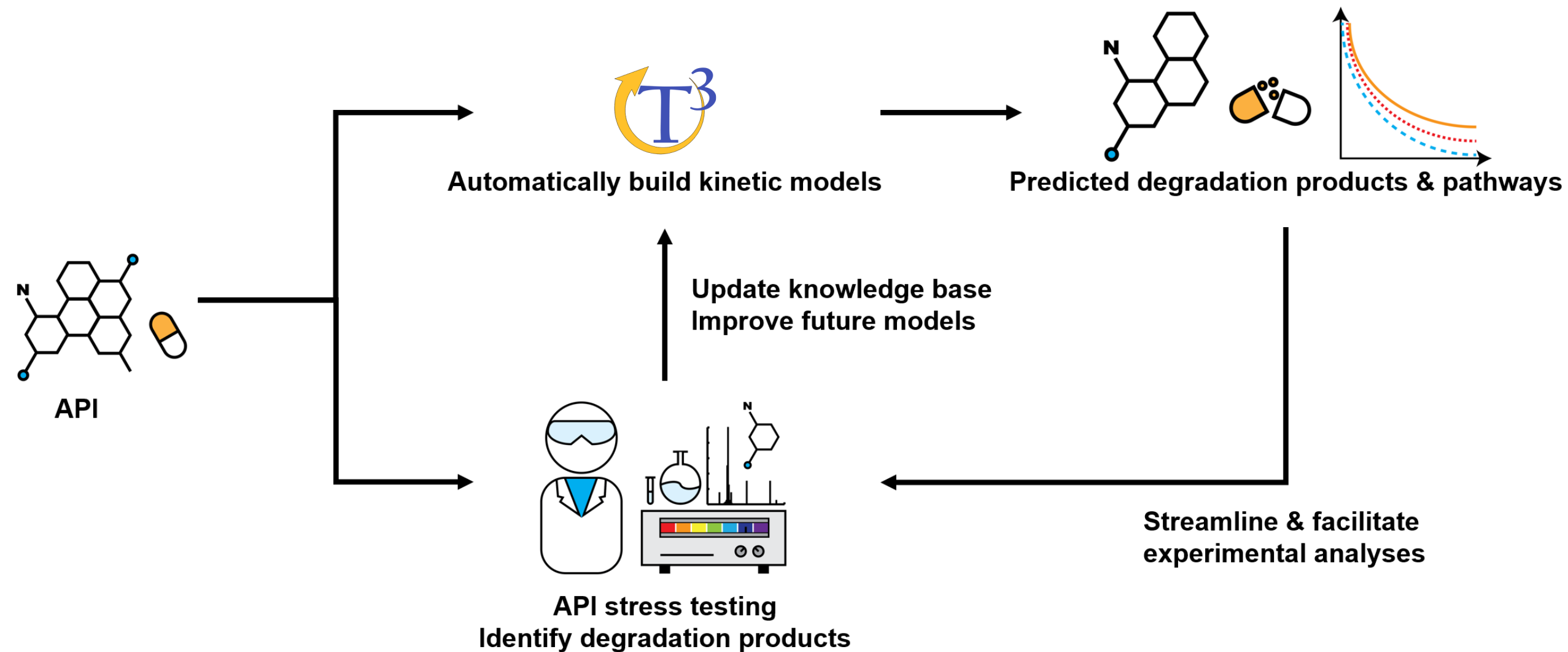
Talk Outline

- Methodology
 - The Radical “Soup” in API Stress Testing
 - **Case Studies**
 - Outlook and Perspective
-

Talk Outline

- Methodology
 - The Radical “Soup” in API Stress Testing
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-

Outlook and Perspective



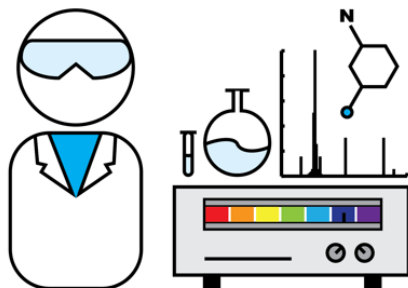
Outlook and Perspective

What can we do with predictive chemical kinetic models?

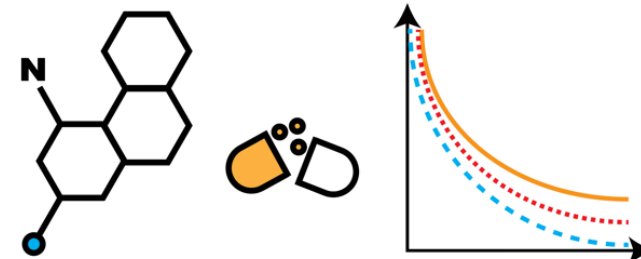
1. Assist experimental stress testing in **standard preparations** and **result corroboration**



API



API stress testing
Identify degradation products



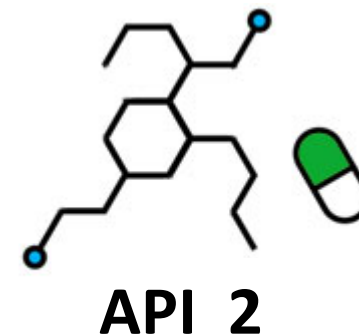
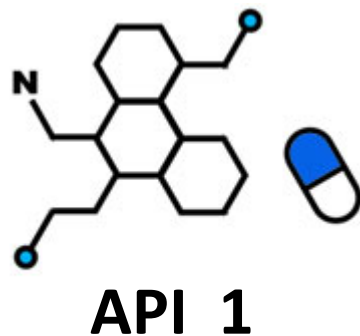
Predicted degradation products & pathways

Outlook and Perspective

What can we do with predictive chemical kinetic models?

1. Assist experimental stress testing in **standard preparations** and **result corroboration**

2. **Compare** the chemical stability of candidate API molecules with a similar biological function



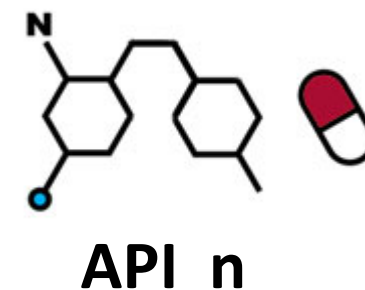
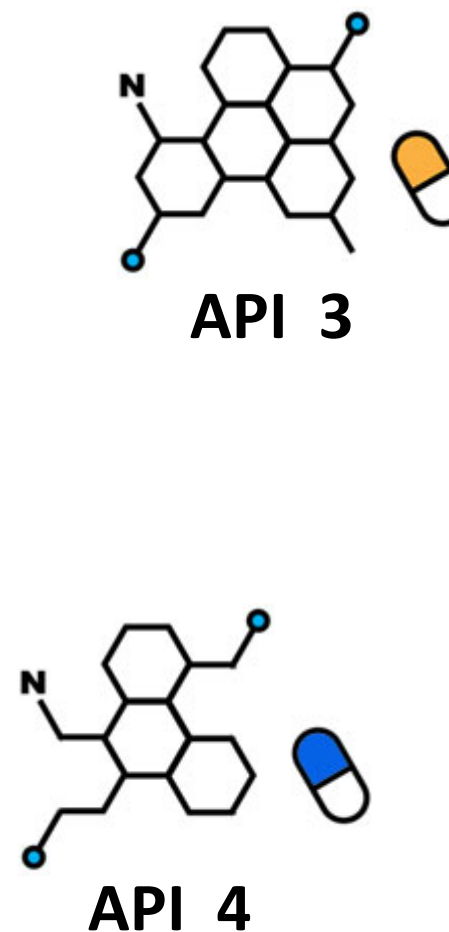
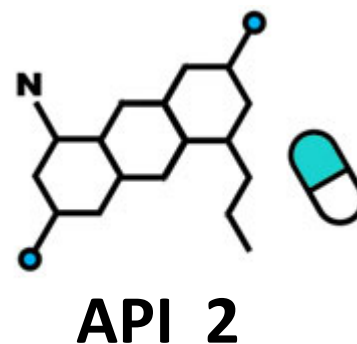
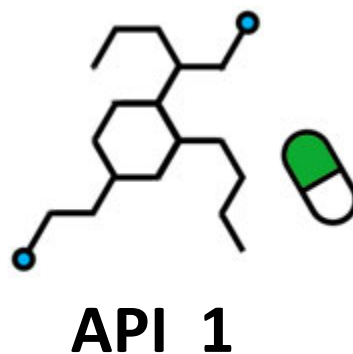
Outlook and Perspective

What can we do with predictive chemical kinetic models?

1. Assist experimental stress testing in **standard preparations** and **result corroboration**

2. **Compare** the chemical stability of candidate API molecules with a similar biological function

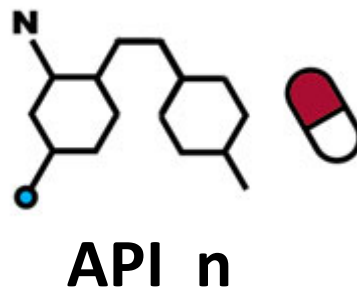
3. **Screen** many API molecules using a low level of theory




Outlook and Perspective

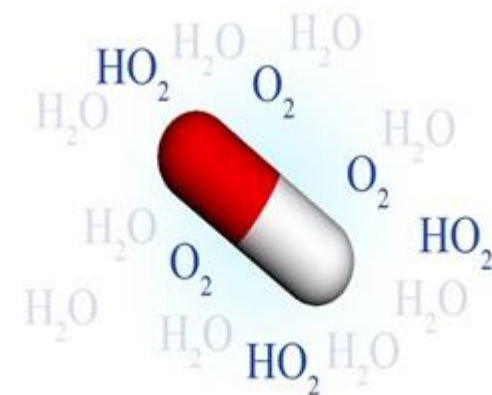
What can we do with predictive chemical kinetic models?

1. Assist experimental stress testing in **standard preparations** and **result corroboration**
2. **Compare** the chemical stability of candidate API molecules with a similar biological function
3. **Screen** many API molecules using a low level of theory



Remaining Challenges

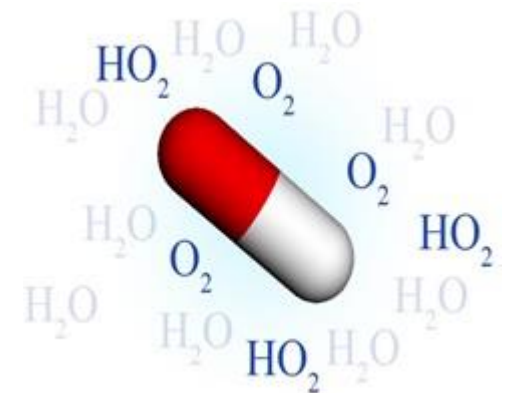
- Improve the **prediction power** of the tools (i.e., add and train reaction “families”)
- Improve automated lowest-energy **3D conformer** identification considering solvation effects
- Improve **automated quantum-chemical computation** schemes
- Add important features: **chirality** preservation, **pH-dependent $k(T)$** , predict **pKa(s)** and consider **protonation states**, automate **solvation correction schemes** (COSMO-RS + Turbomol)
- Develop a **high-level module** to automate the entire process (*“one ring to rule them all”*) 
- Apply the self-improving tool for new APIs with **various chemical motifs**
- Validate against generated **experimental data** (seeking collaborations)

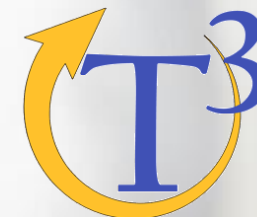


Summary

- Developed an **automated scheme** to predict API degradation
- Showed what the prominent radicals in the **“Soup”** system are, and their pH dependency
- Presented the **first detailed kinetic model** of an API degradation
- Successfully **modeled the degradation of selected APIs** (imipramine, adrenaline)
- We’re developing an **ecosystem of software tools** and a **novel platform-technology**

Looking for partners capable of performing experimental API degradation studies who would like to have a front-row seat in developing, directing, and supporting a novel technological tool.





**Quantitative *in-silico* kinetic predictions
of API degradation**

Asst. Prof. Alon Grinberg Dana

Department of Chemical Engineering
Technion – Israel Institute of Technology

alon@technion.ac.il



ARC supports a variety of
electronic structure software



What ARC Does – Servers



SSH

S1



SSH

S2



What ARC Does – Servers



S1



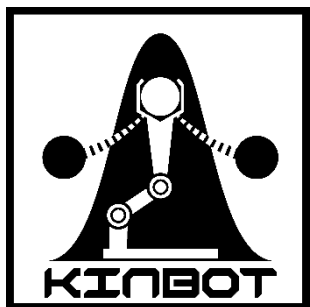
SSH

S2

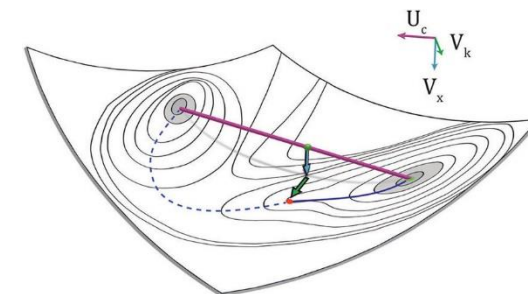
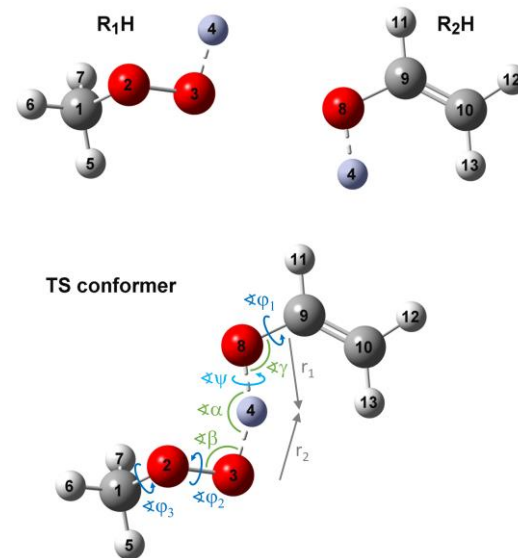
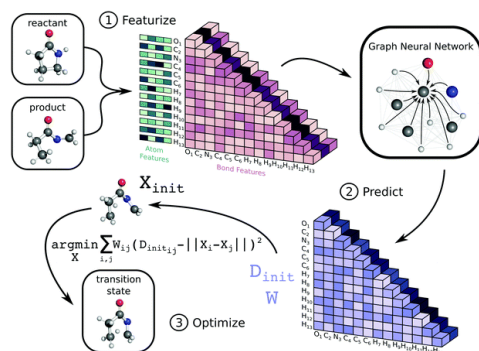


What ARC Does – TS Searches

Alongside the technical challenges, the most significant scientific challenge it to **attain a reasonable TS geometry guess**



Auto
TST



KinBot: R. Van de Vijver, J. Zádor, *Comp. Phys. Comm.* **2020**, 248, 106947

AutoTST: N.D. Harms, C.E. Underkoffler, R.H. West, *ChemRxiv* **2020**, 10.26434/chemrxiv.13277870.v2

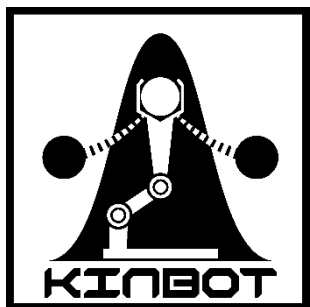
GCN: L. Pattanaik, J.B. Ingraham, C.A. Grambow, W.H. Green, *Phys. Chem. Chem. Phys.* **2020**, 22, 2361823626

ARC: A. Grinberg Dana et al., In Preparation

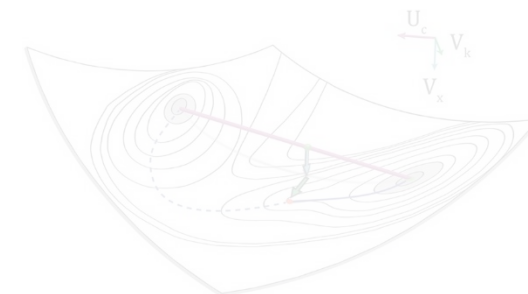
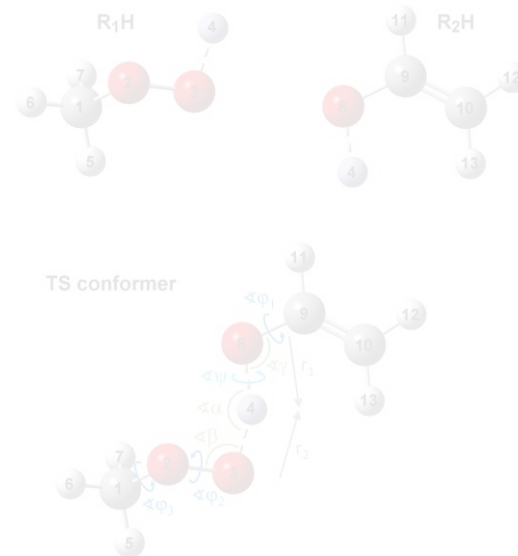
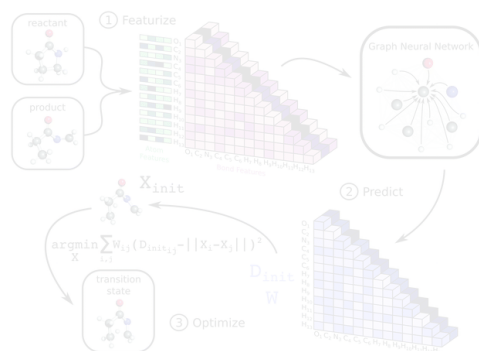
GSM: P. Zimmerman, *J. Chem. Theory Comput.* 2013, 9(7), 3043-3050

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Auto
TST



KinBot supports >30 unimolecular reaction families

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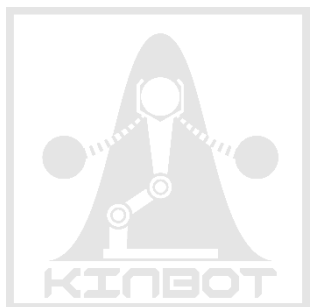
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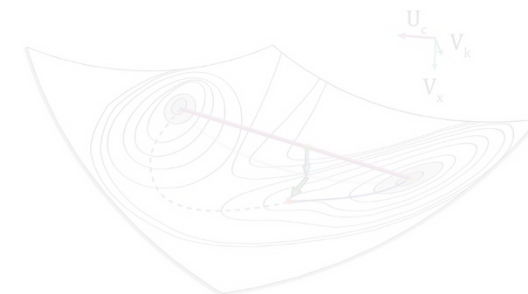
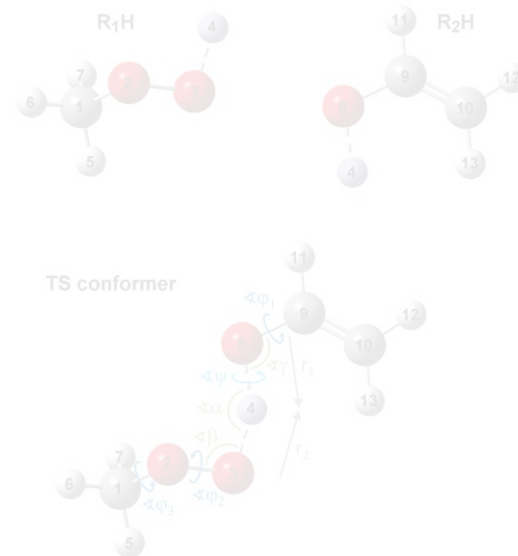
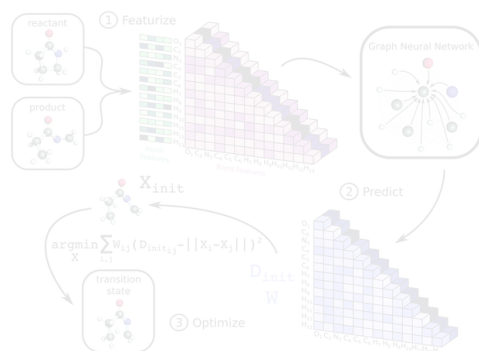
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What ARC Does – TS Searches

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Auto
TST



AutoTST supports the hydrogen abstraction, disproportionation and intra-H migration reaction families

KinBot: R. Van de Vijver, J. Zádor, *Comp. Phys. Comm.* **2020**, 248, 106947

AutoTST: N.D. Harms, C.E. Underkoffler, R.H. West, *ChemRxiv* **2020**, 10.26434/chemrxiv.13277870.v2

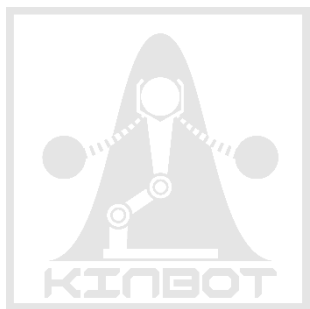
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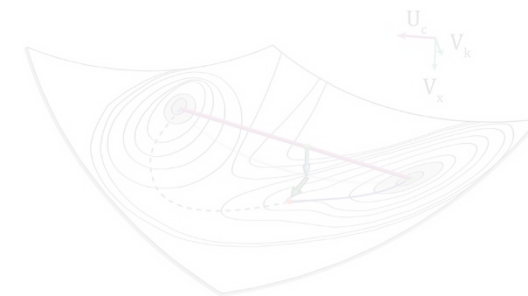
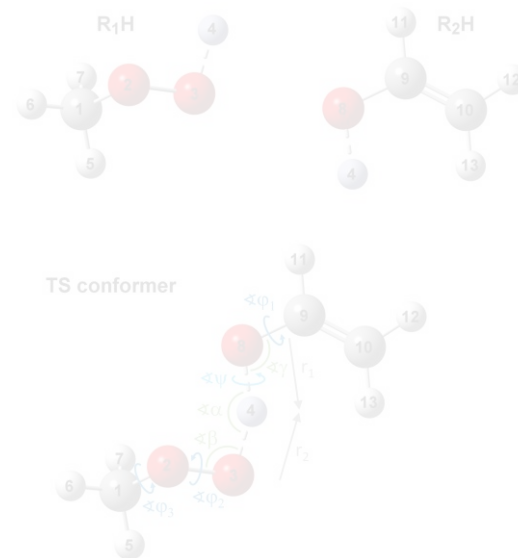
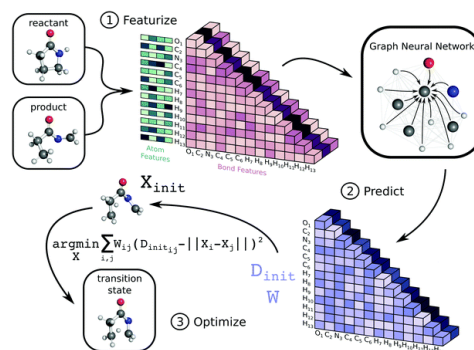
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Auto
TST



GCN (graph convolutional network) supports isomerization reactions

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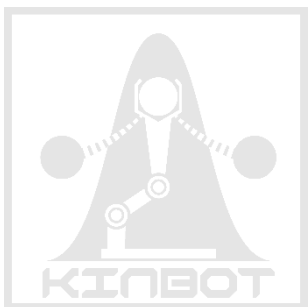
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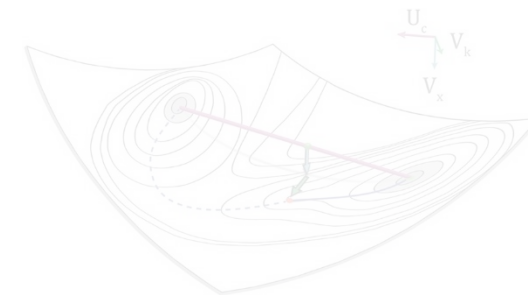
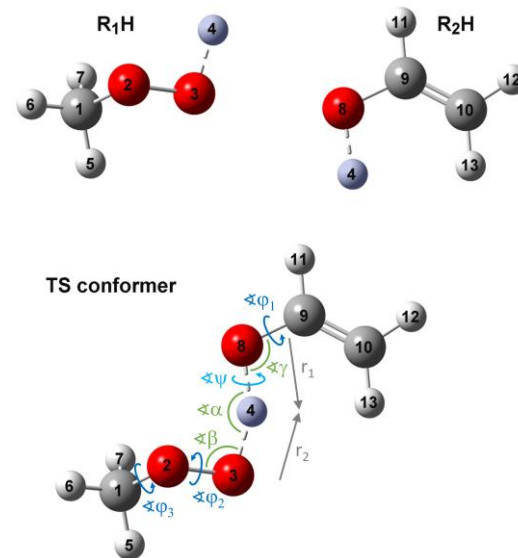
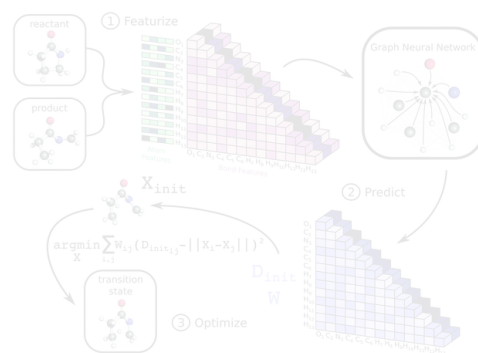
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TST



ARC's heuristics currently only support hydrogen abstraction reactions

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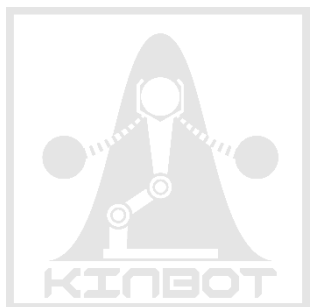
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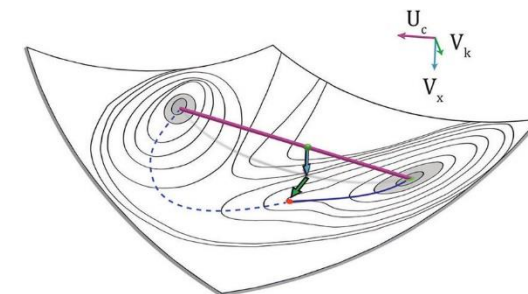
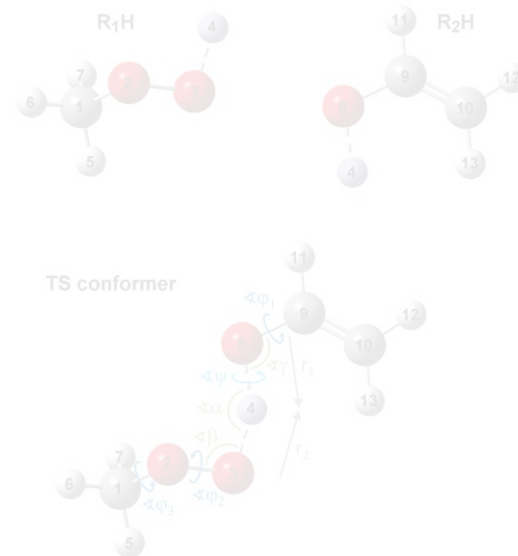
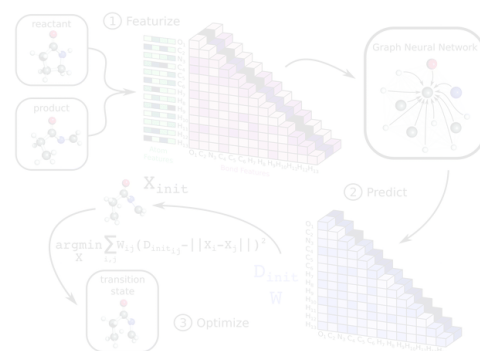
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What ARC Does – TS Searches

Alongside the technical challenges, the most significant scientific challenge it to **attain a reasonable TS geometry guess**



Auto
TST



GSM (growing string method) is applicable for all reaction families

KinBot: R. Van de Vijver, J. Zádor, *Comp. Phys. Comm.* **2020**, 248, 106947

AutoTST: N.D. Harms, C.E. Underkoffler, R.H. West, *ChemRxiv* **2020**, 10.26434/chemrxiv.13277870.v2

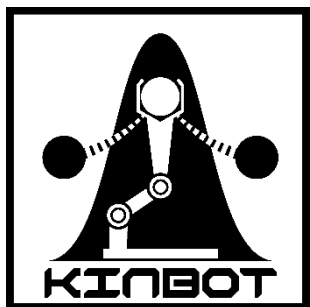
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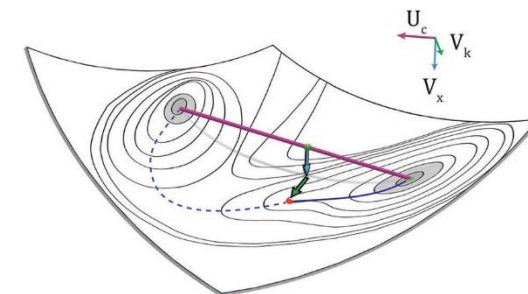
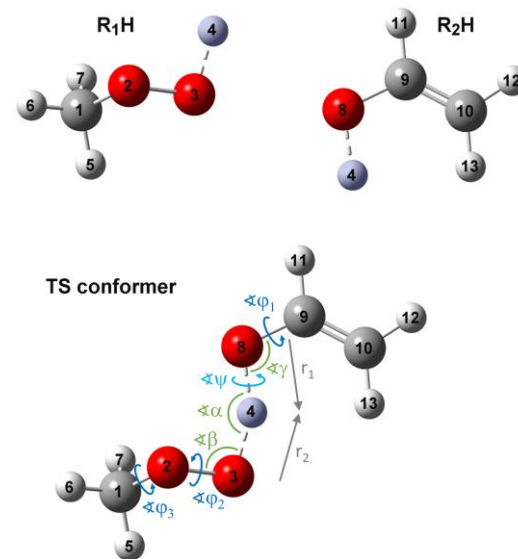
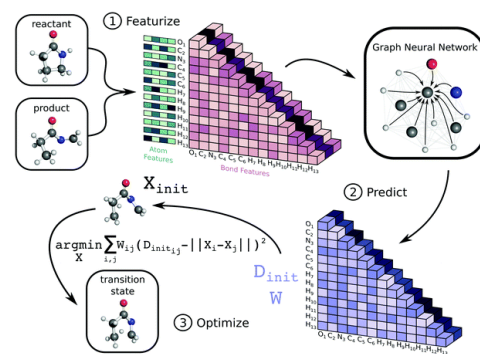
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What ARC Does – TS Searches

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Auto
TST



Additional TS Search “Adapters” are constantly being added to ARC

KinBot: R. Van de Vijver, J. Zádor, *Comp. Phys. Comm.* **2020**, 248, 106947

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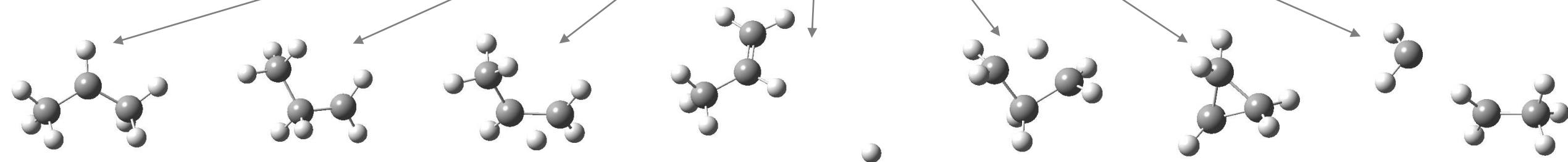
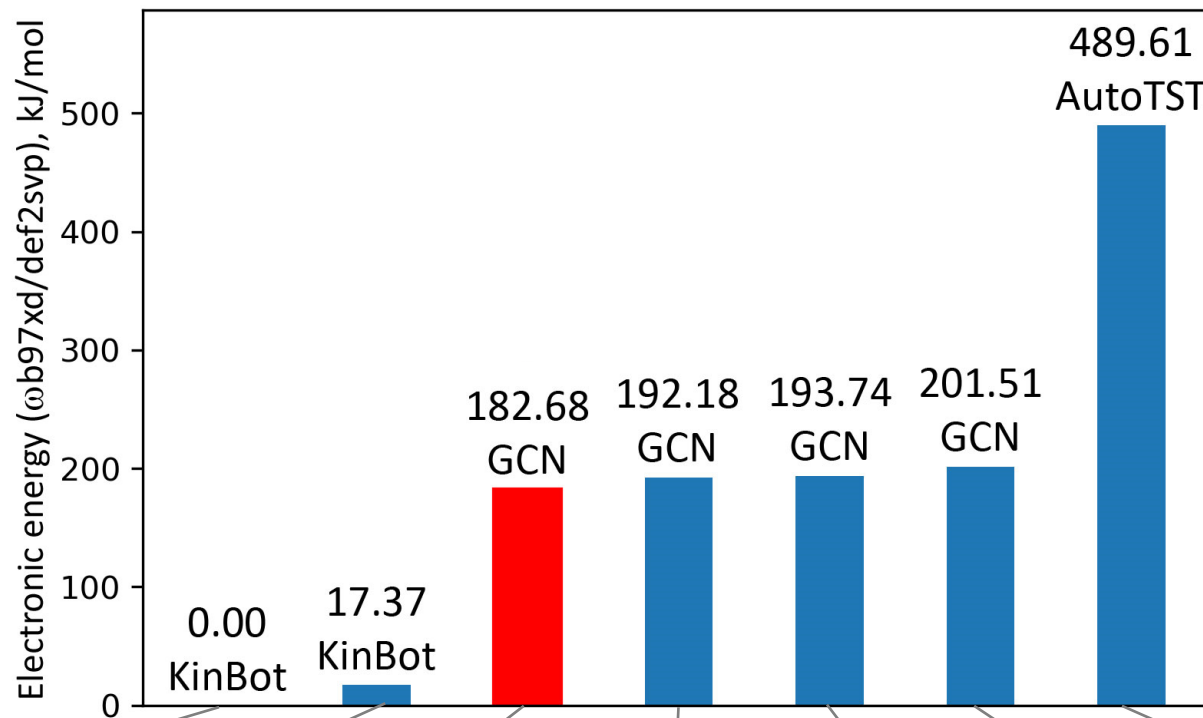
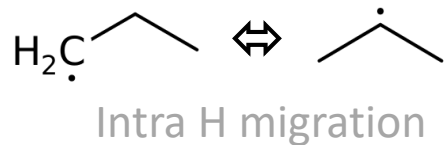
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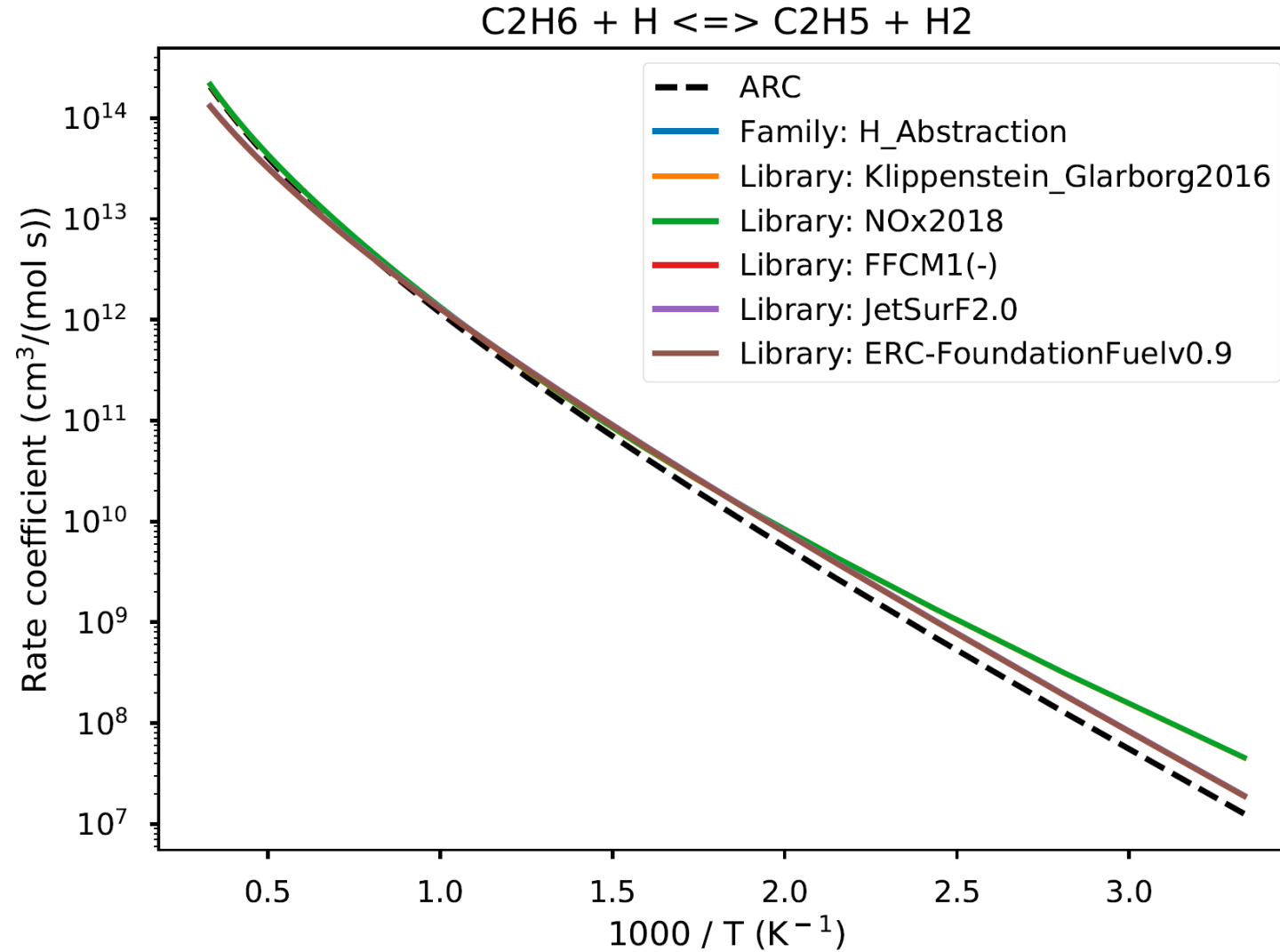
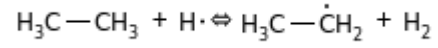
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What ARC Does – TS Searches

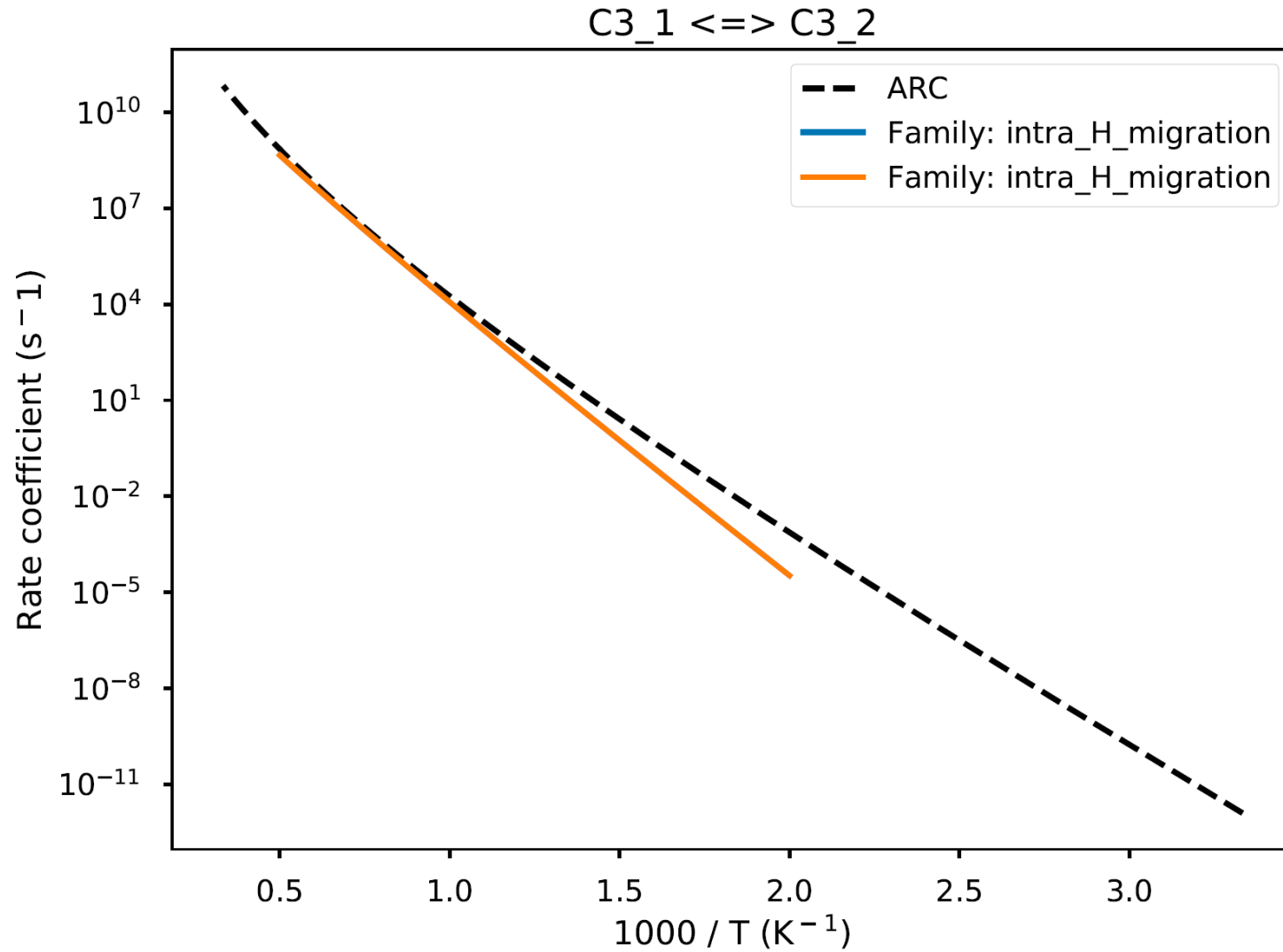
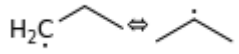
ARC generates a TS comparison figure for each reaction, which is often insightful



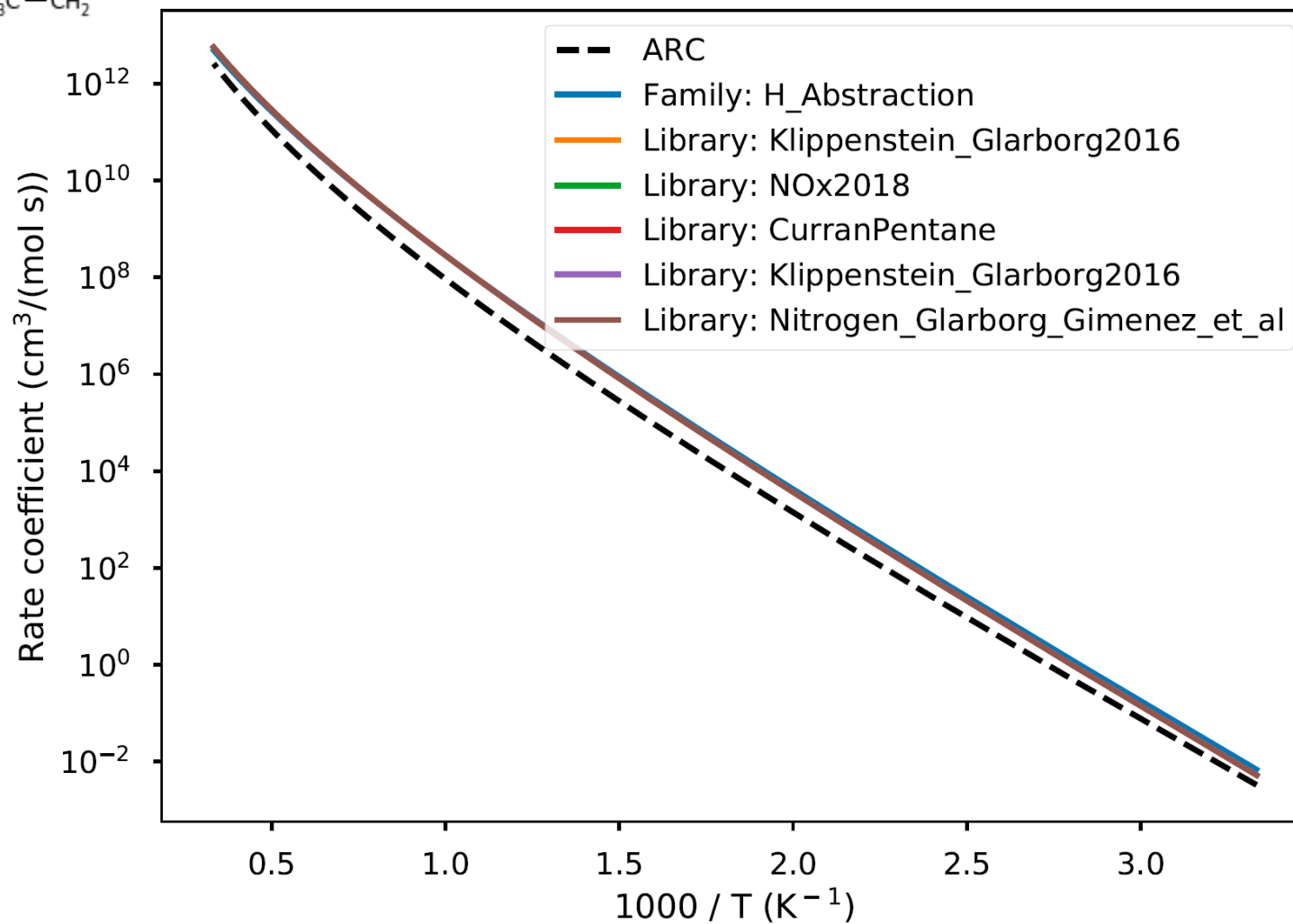
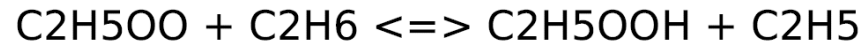
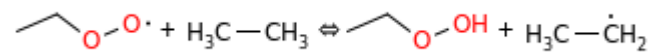
Chemical Kinetics – A Suite of Software Tools (ARC)



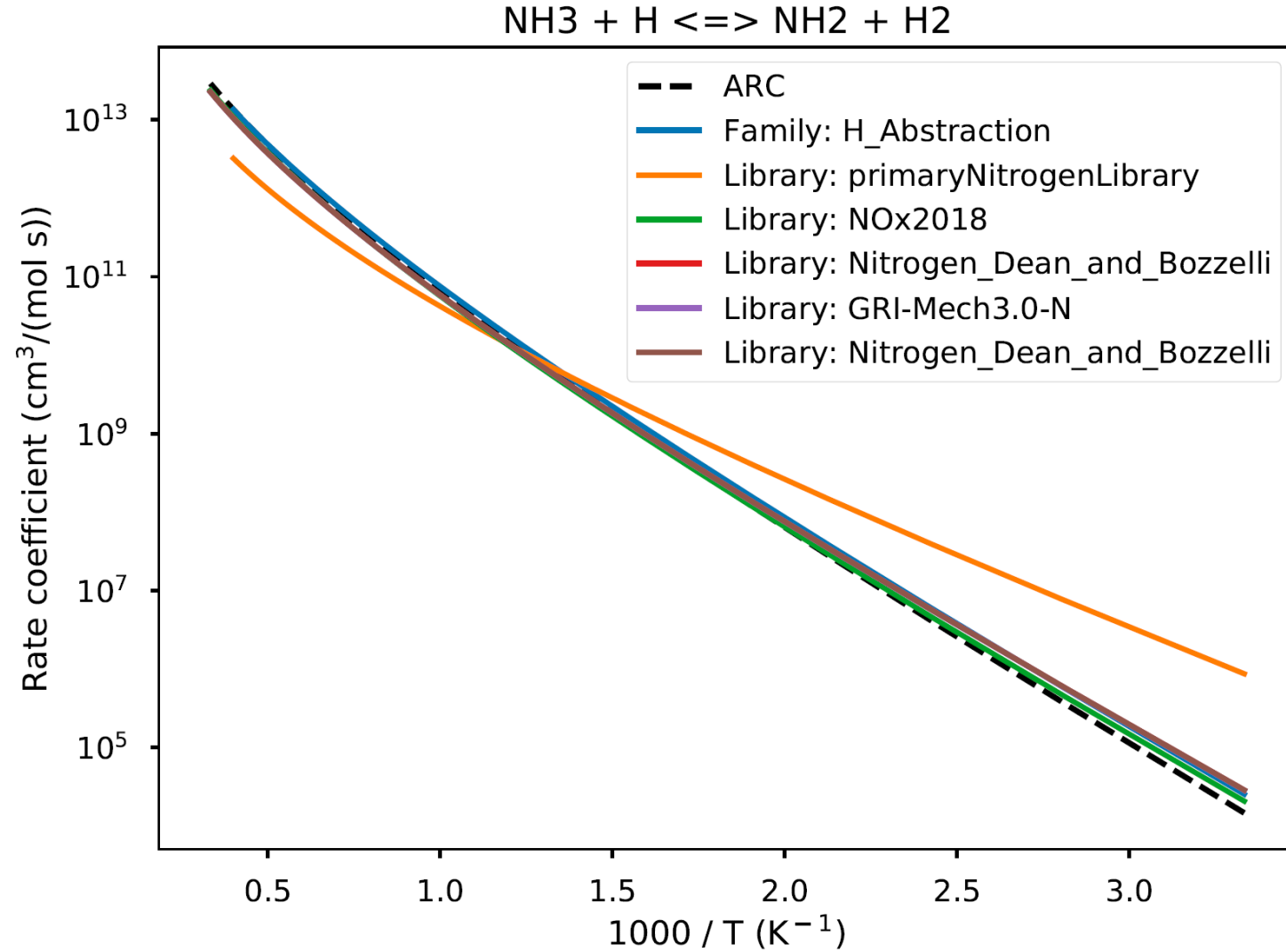
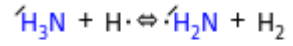
Chemical Kinetics – A Suite of Software Tools (ARC)



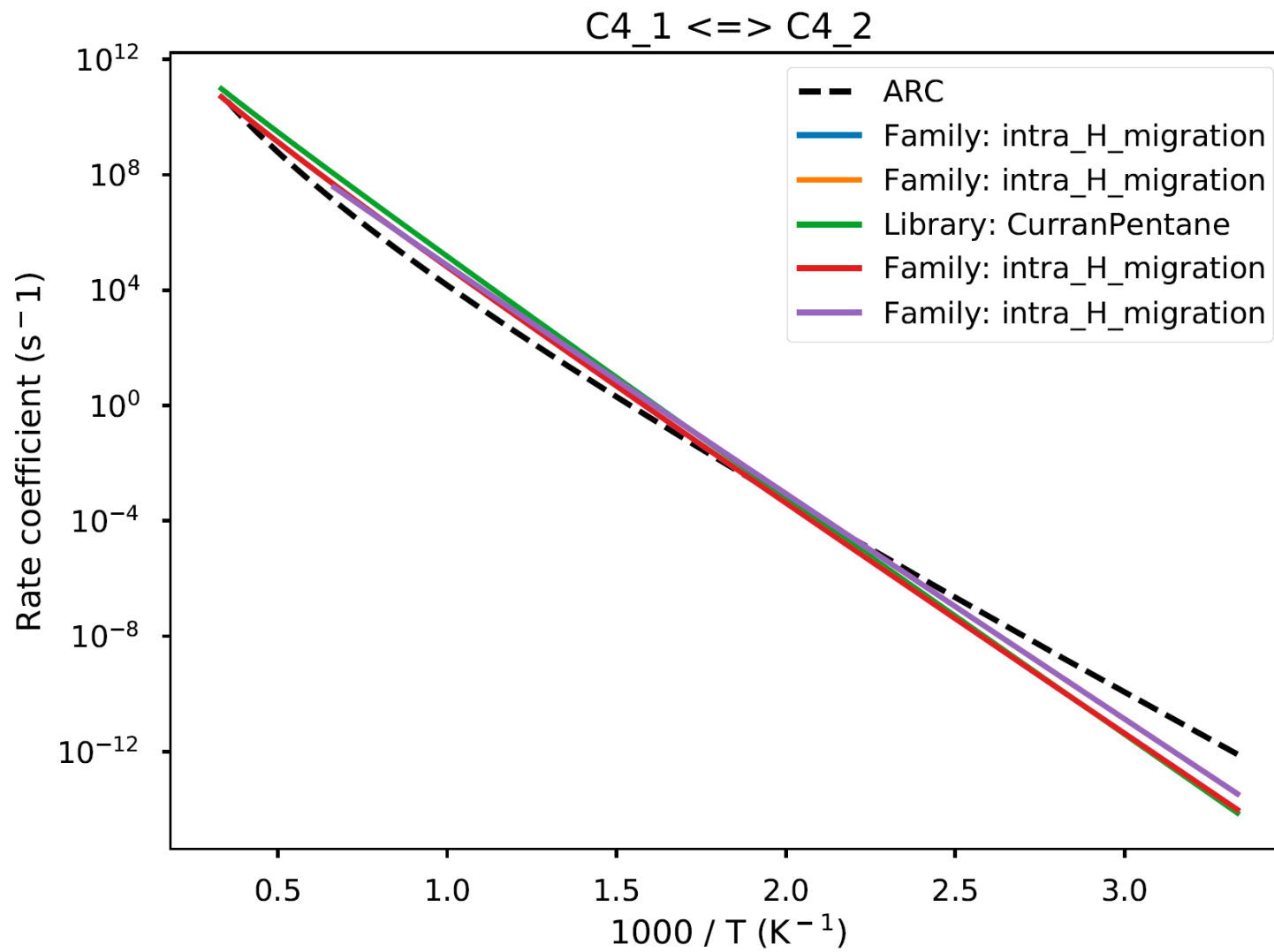
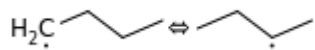
Chemical Kinetics – A Suite of Software Tools (ARC)



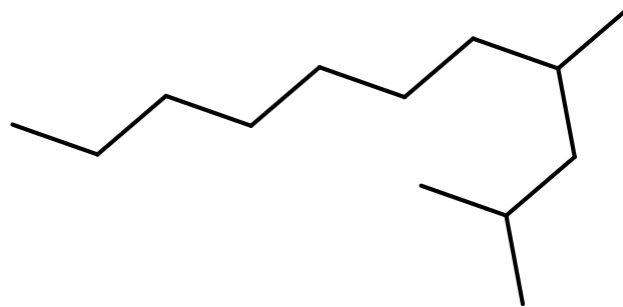
Chemical Kinetics – A Suite of Software Tools (ARC)



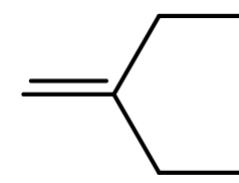
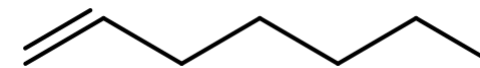
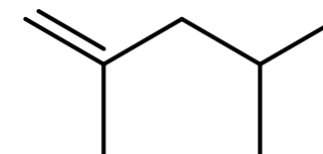
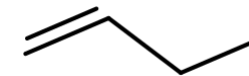
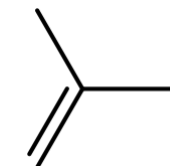
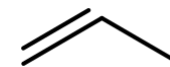
Chemical Kinetics – A Suite of Software Tools (ARC)



Scramjet Propulsion

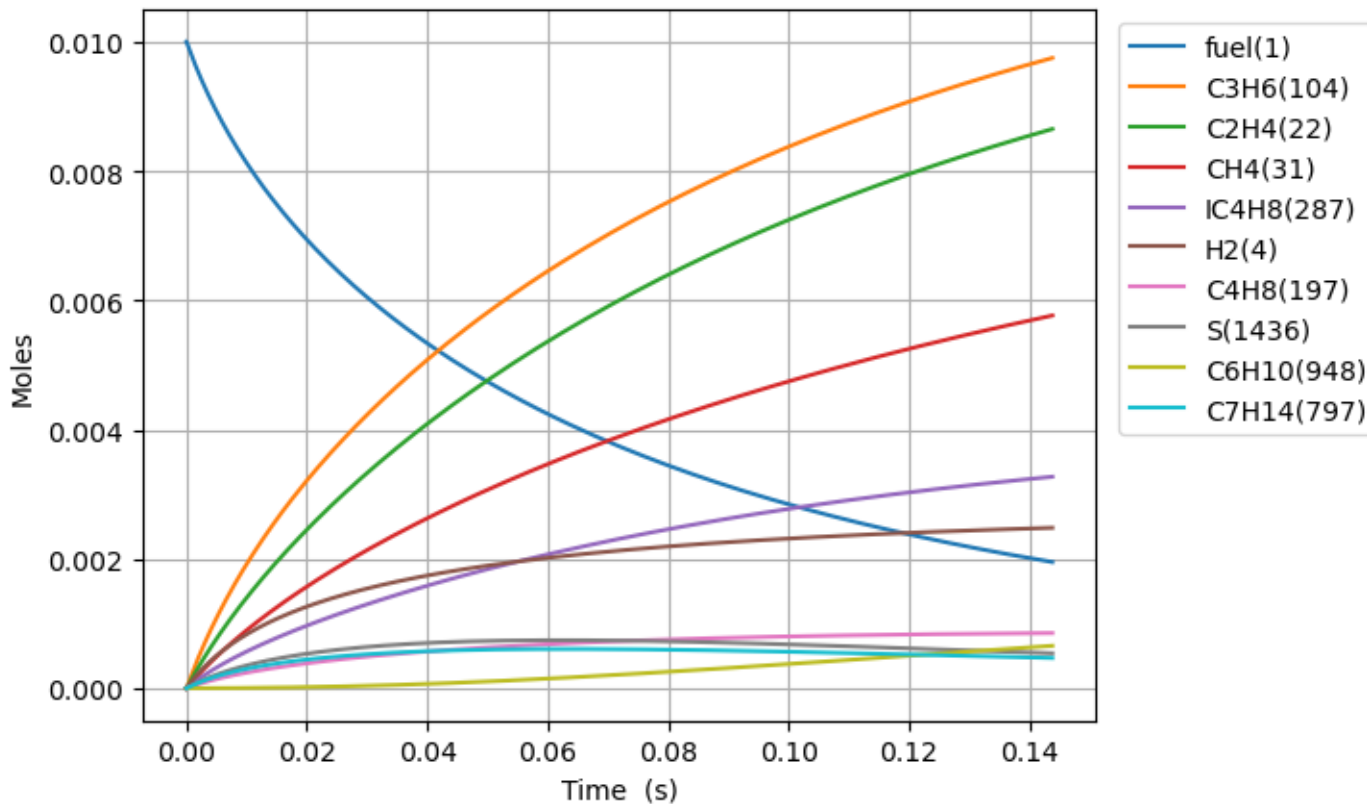


2,4-dimethylundecane (C₁₃H₂₈)

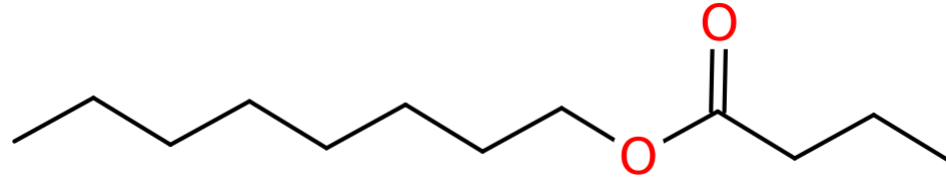


1000 K (727°C)

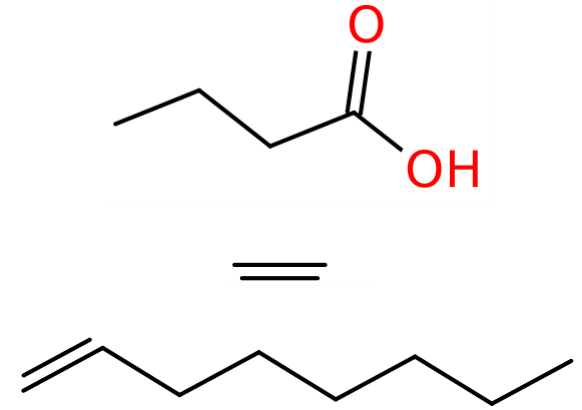
25 bar



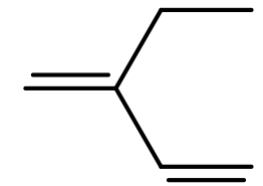
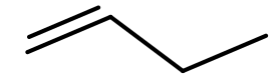
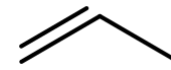
Scramjet Propulsion



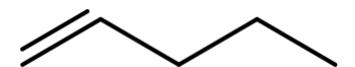
octyl butanoate ($C_{12}O_2H_{24}$)



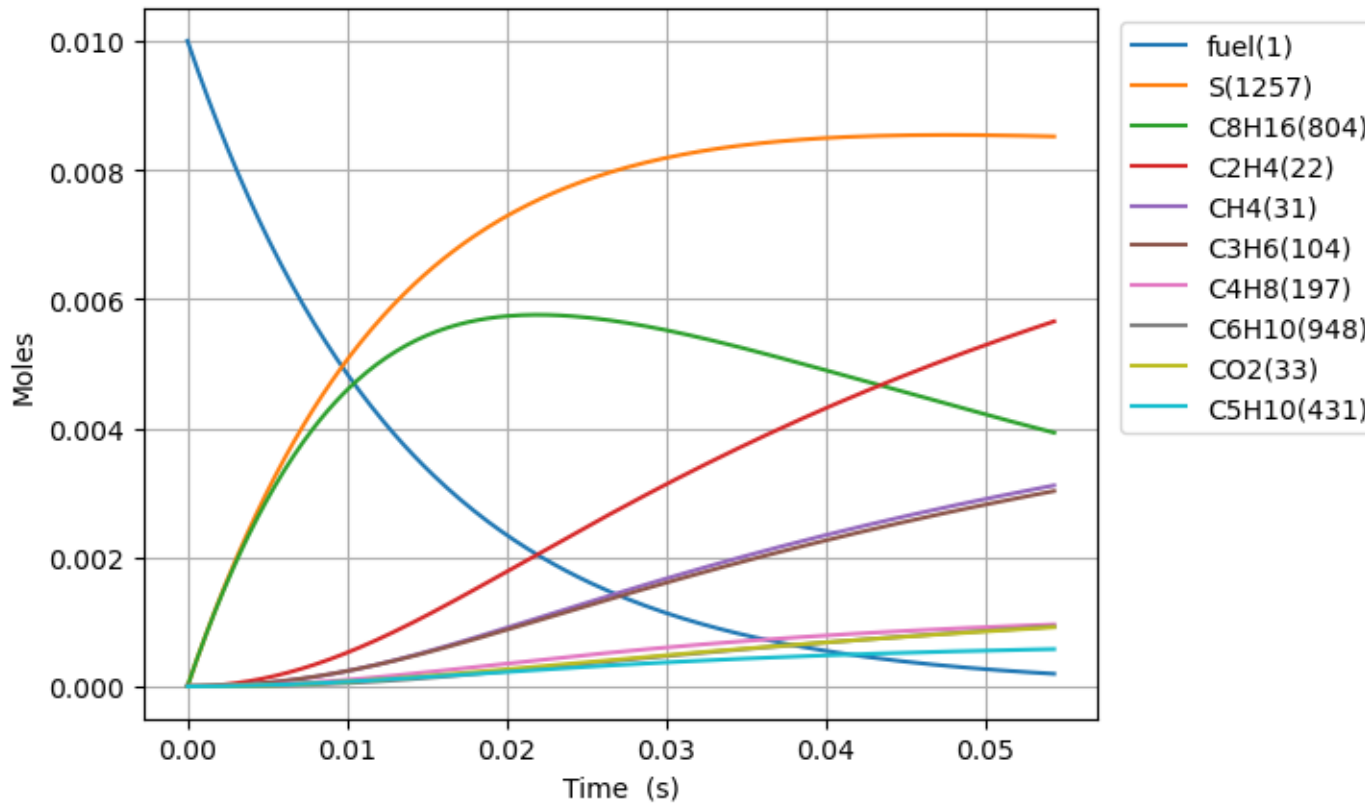
CH_4



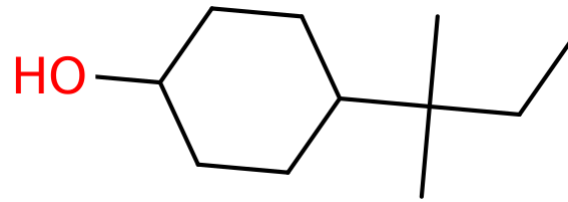
CO_2



1000 K (727°C)
25 bar



Scramjet Propulsion



4-tert-amylcyclohexanol ($C_{11}OH_{22}$)

1000 K (727°C)
25 bar

