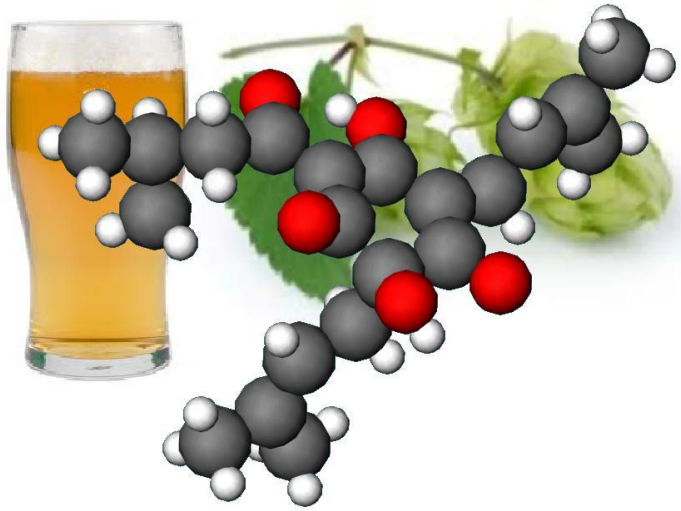
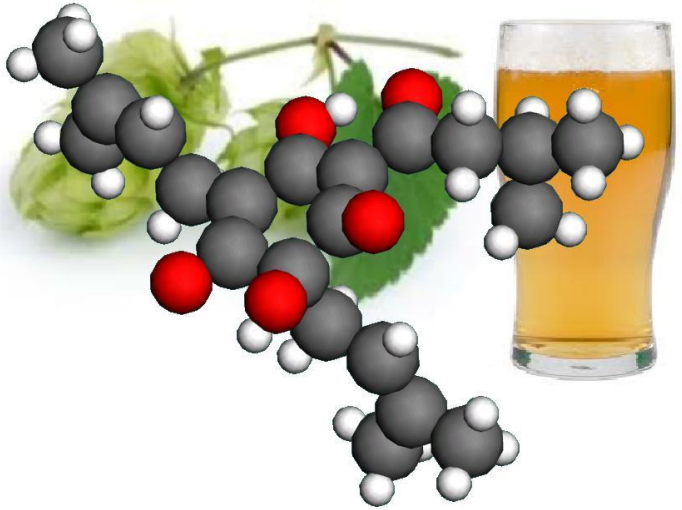
Kinetic vs Thermodynamic Control within Differential Mobility Spectrometry

An Unexpected Observation from Alpha-Acids found in Brewing Hops





Christian Ieritano, Alexander Haack, W. Scott Hopkins

ISIMS 2022
Memphis, TN

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The best discoveries in science are self-motivated

What compounds are present in your favourite foods/beverages? Are there isomeric forms of them to characterize by DMS?

https://advancedmixology.com/blogs/art-of-mixology/why-use-different-beer-glasses

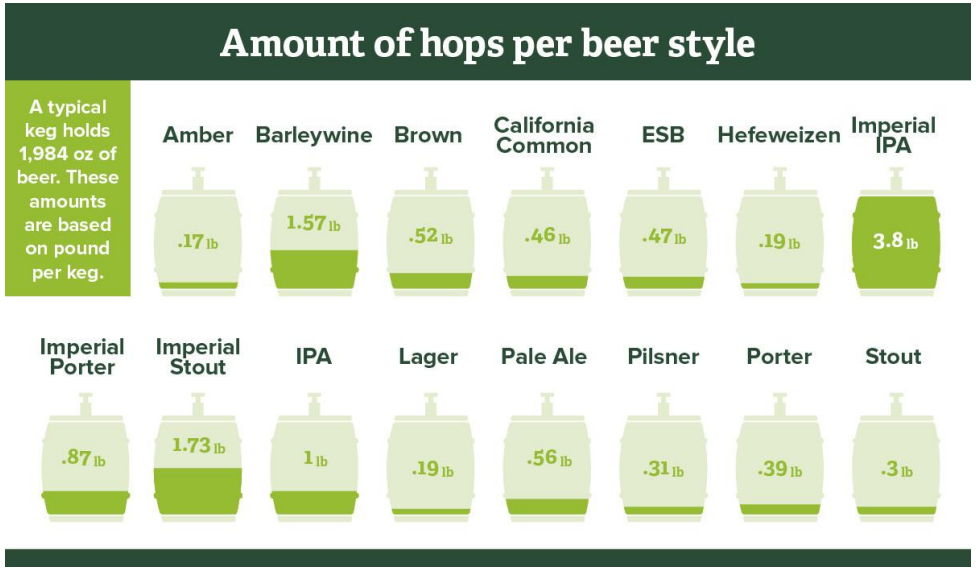
Many types of beer
(and we drink them all)

...sometimes too much

https://beerconnoisseur.com/articles/too-many-beer-styles

Why are hops so important?

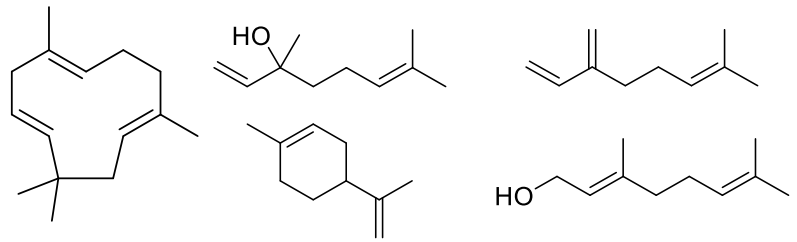
What compounds are present in your favourite foods/beverages? Are there isomeric forms of them to characterize by DMS?



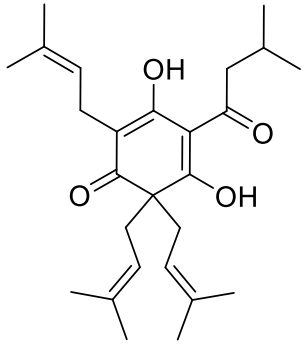
https://www.usahops.org/enthusiasts/brewing.html

Aromas and antimicrobial/antibacterial activity

Terpenes/terpenoids

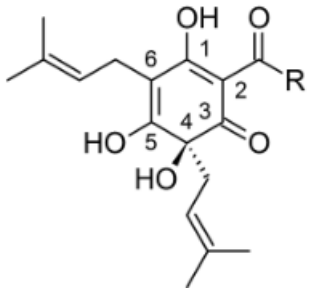


Beta-acids (Lupulones)



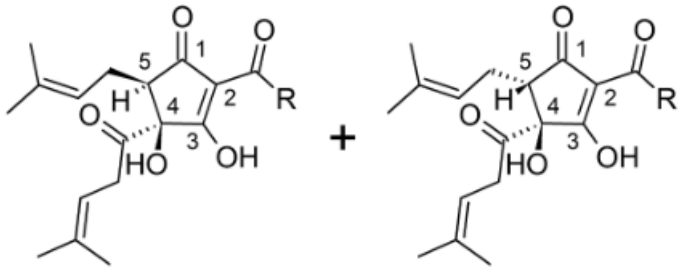
Bitter flavours to counter the sweet malt

Alpha-acids



Humulone

Iso-Alpha-acids

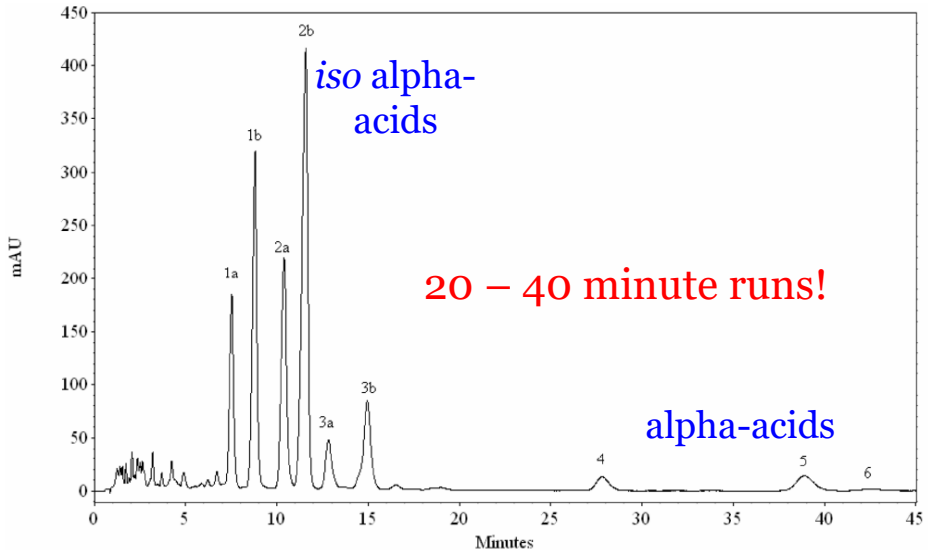


cis-isohumulone trans-isohumulone

Brewers care about hop components in their beer!

What compounds are present in your favourite foods/beverages? Are there isomeric forms of them to characterize by DMS?

LC-UV or LC-MS-MS seems to be the method of choice for (alpha acid analysis

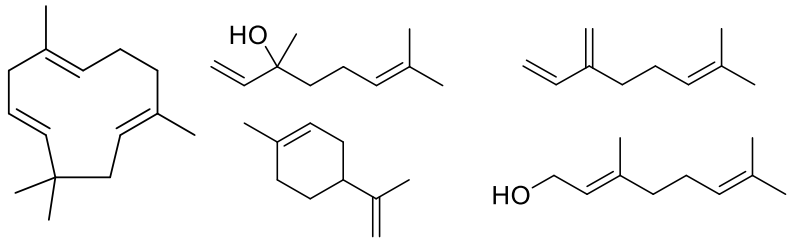


J. Agric. Food. Chem. 2009, 57, 4, 1172 – 1182.

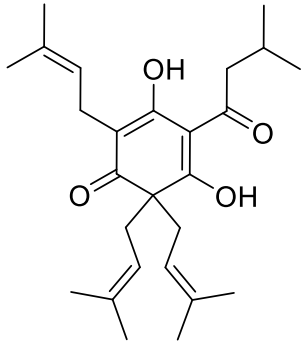
To date, no one has used IMS to quantitate hop components in beer

Aromas and antimicrobial/antibacterial activity

Terpenes/terpenoids

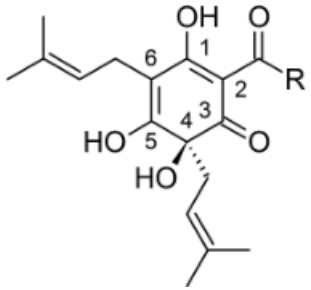


Beta-acids (Lupulones)



Bitter flavours to counter the sweet malt

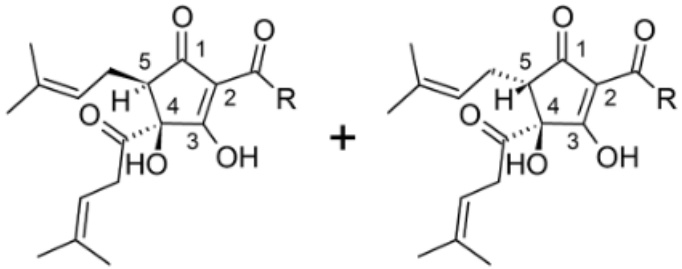
Alpha-acids



Humulone

isomerization

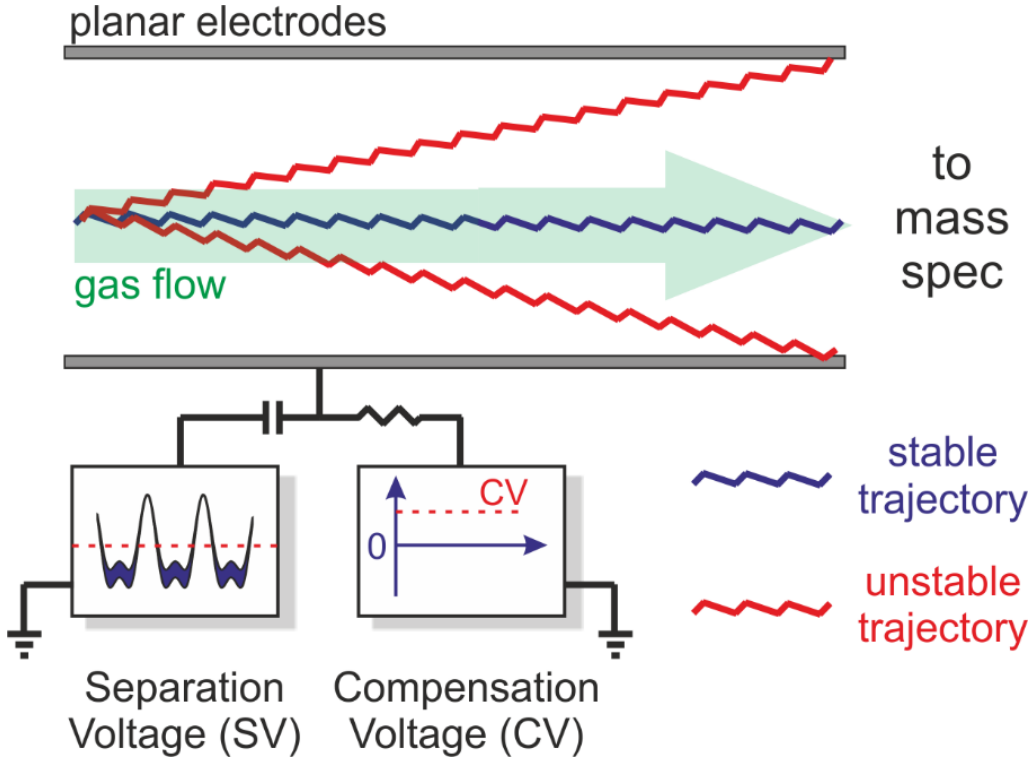
Iso-Alpha-acids



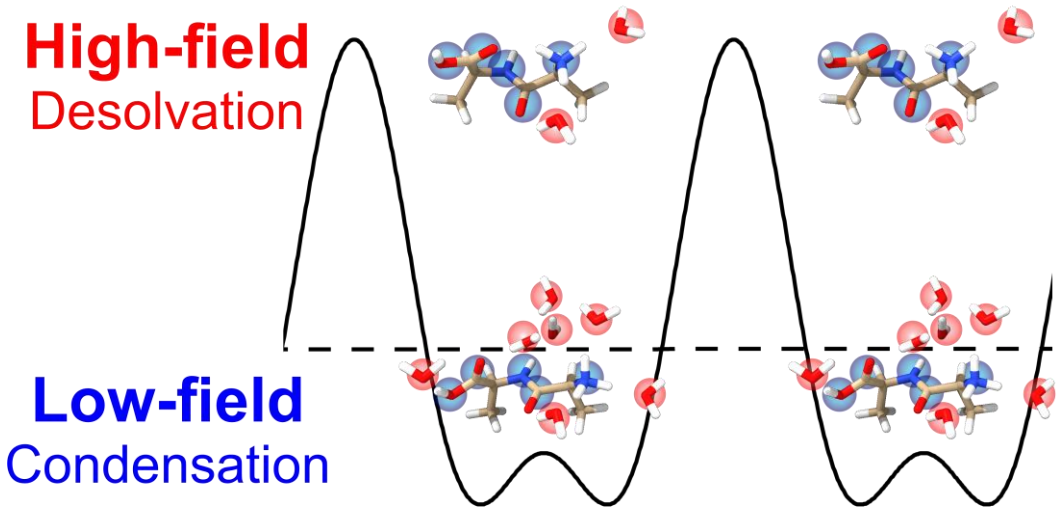
cis-isohumulone trans-isohumulone

What is Differential Mobility Spectrometry (DMS)?

Differential mobility spectrometry (DMS) is a non-linear form of ion-mobility spectrometry



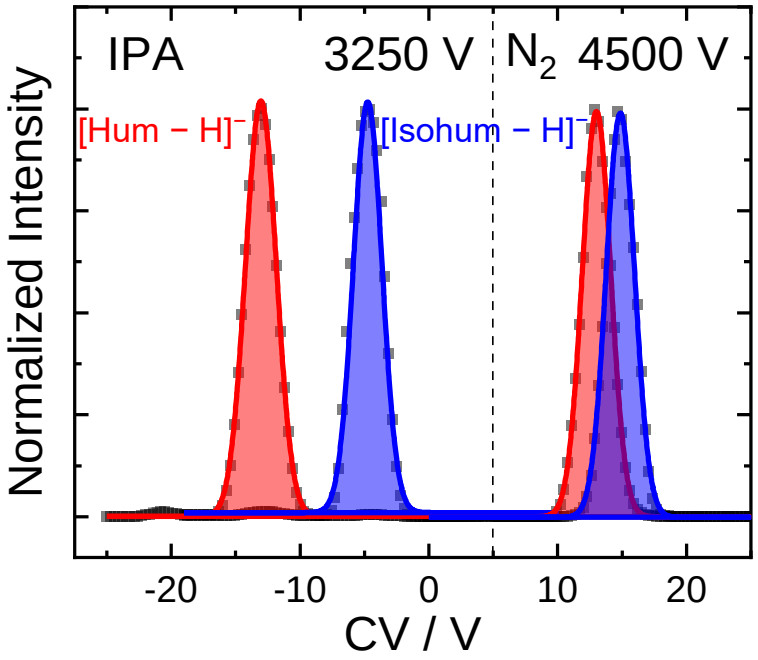
For beer analysis, isopropyl alcohol (IPA) as a modifier is the obvious choice



DMS environments seeded with solvent vapour create a dynamic microsolvation environment

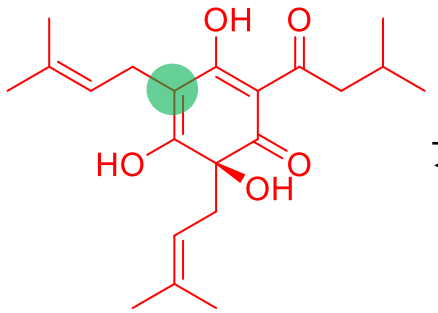
Mol. Phys. **2015**, 113, 3151–3158.

Humulone/Isohumulone is separated by DMS, but …

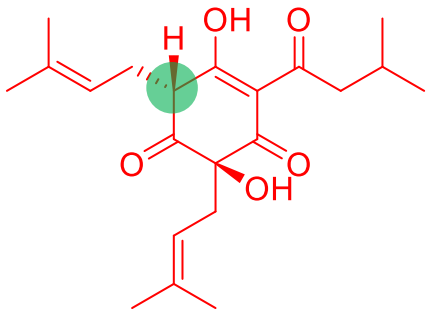


Humulone is separated from **isohumulone** in IPA at SV = 3250V

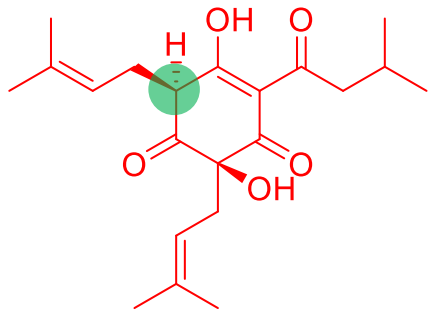
Humulone (enol)



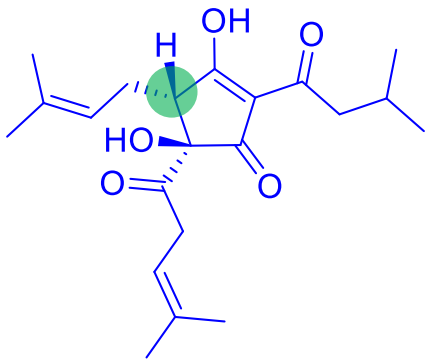
Humulone (trans keto)



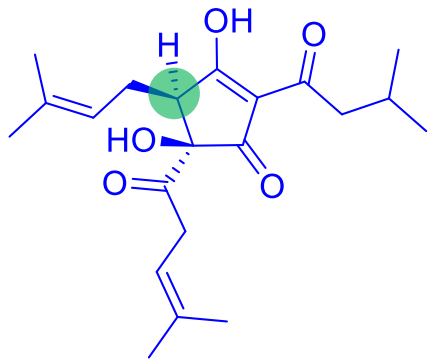
Humulone (cis keto)



trans isohumulone



cis isohumulone



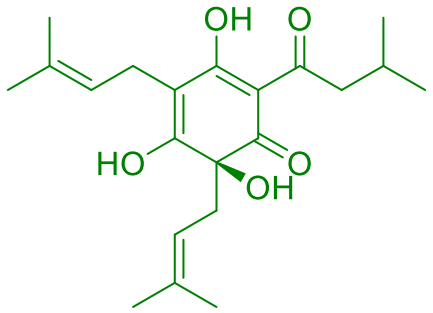
Where is the cis/trans keto form of humulone?

We need to look at things in positive mode for that!

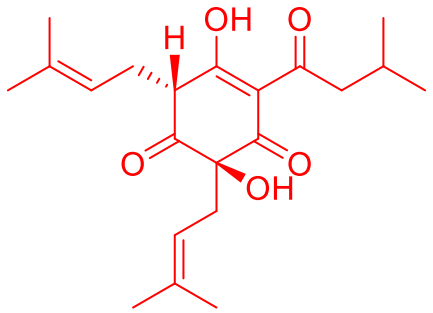
Giving tautomers the best chance to be resolved

We need something that will drive **changes to the olefin containing side-chain** (isoamyl)

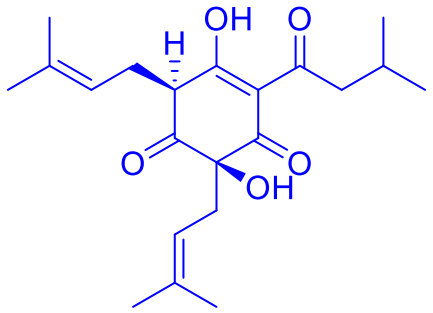
enol



trans keto

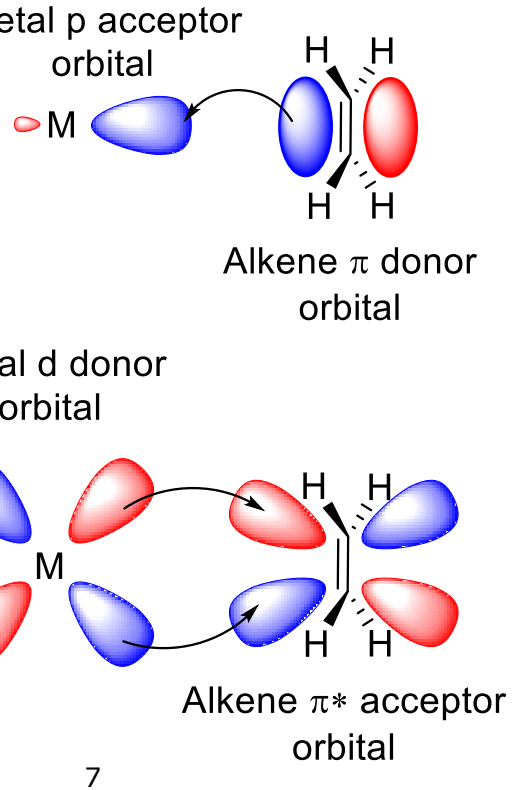


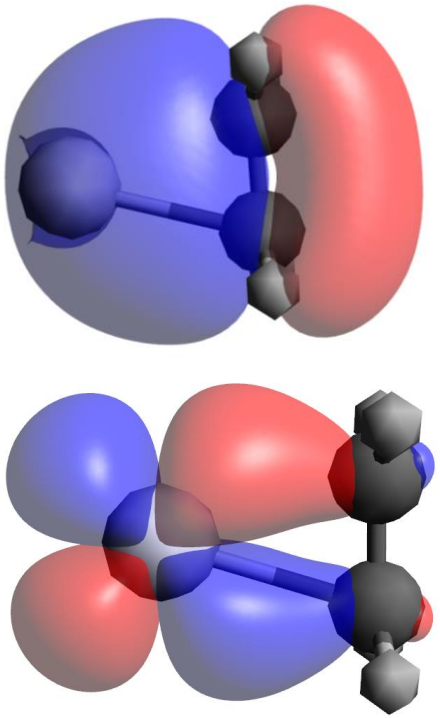
cis keto



Silver cations are the poster child for accepting pi-electrons

Ag^{+} $3d^{10}4p^{0}$





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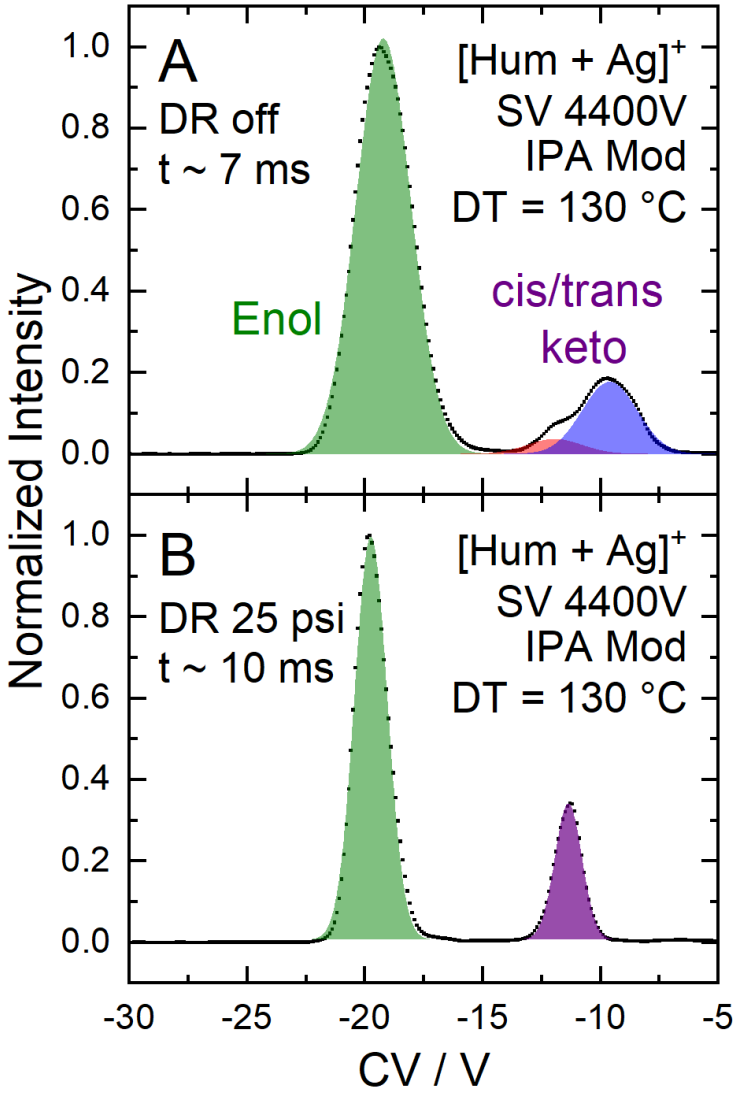
Clear tautomer separation of [Hum + Ag]$^+$ with IPA modifier

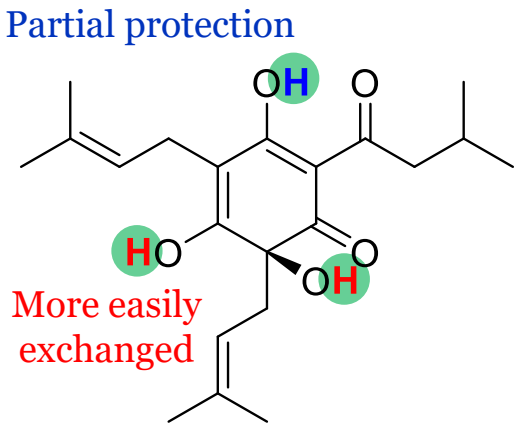


"Retro" HDX

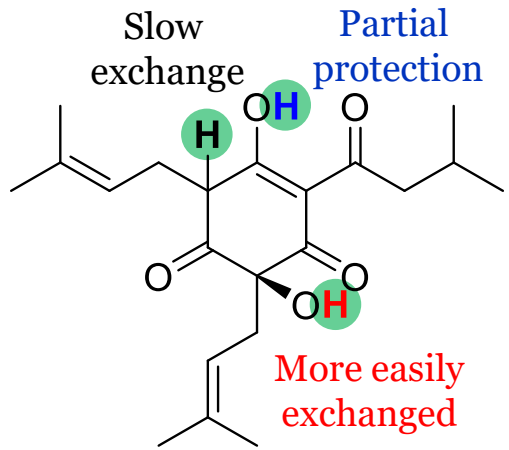
Can't use deuterating reagents when the DMS cell is filled with IPA (protic)

Mix humulone in D_2O/CD_3OD to "pre-deuterate," then watch it back exchange with the IPA modifier

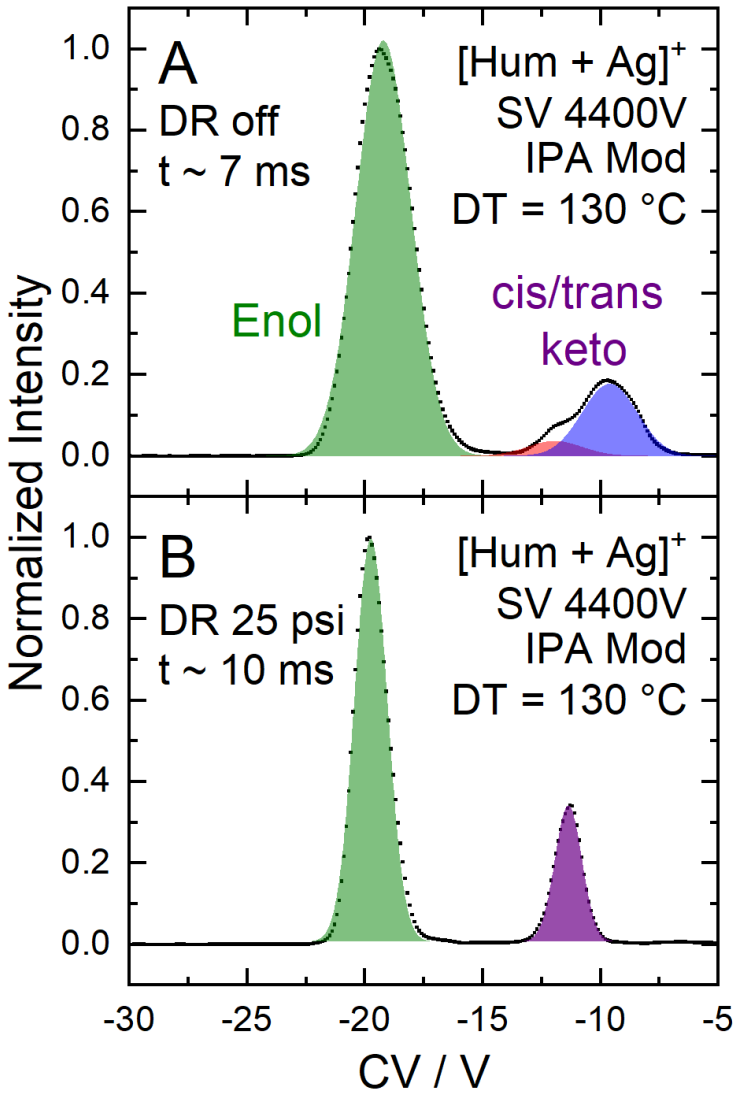
Humulone (Enol)

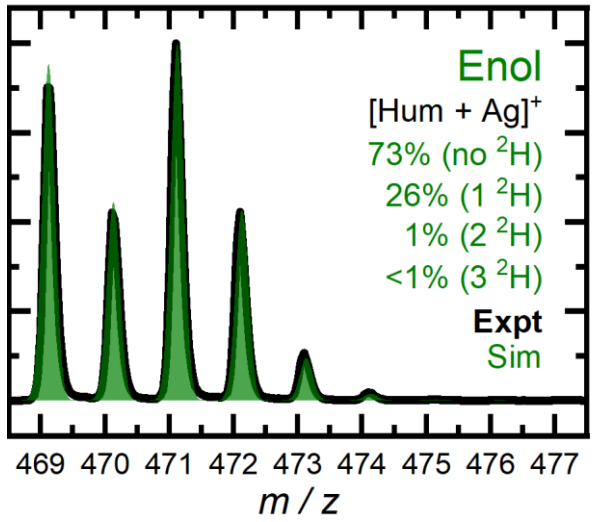


Humulone (Keto)



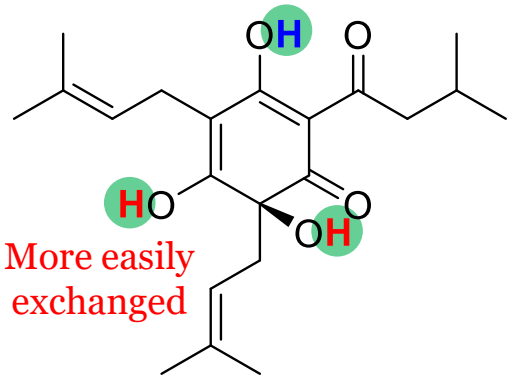
Clear tautomer separation of [Hum + Ag]$^+$ with IPA modifier





Humulone (Enol)

Partial protection

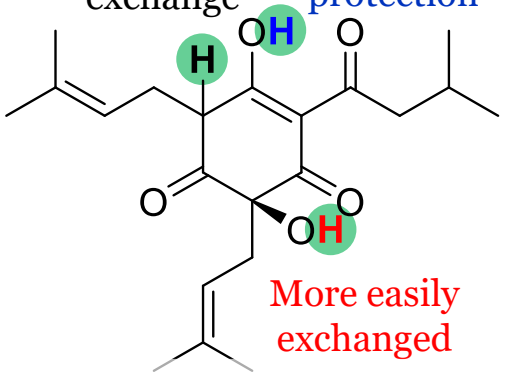


More easily exchanged

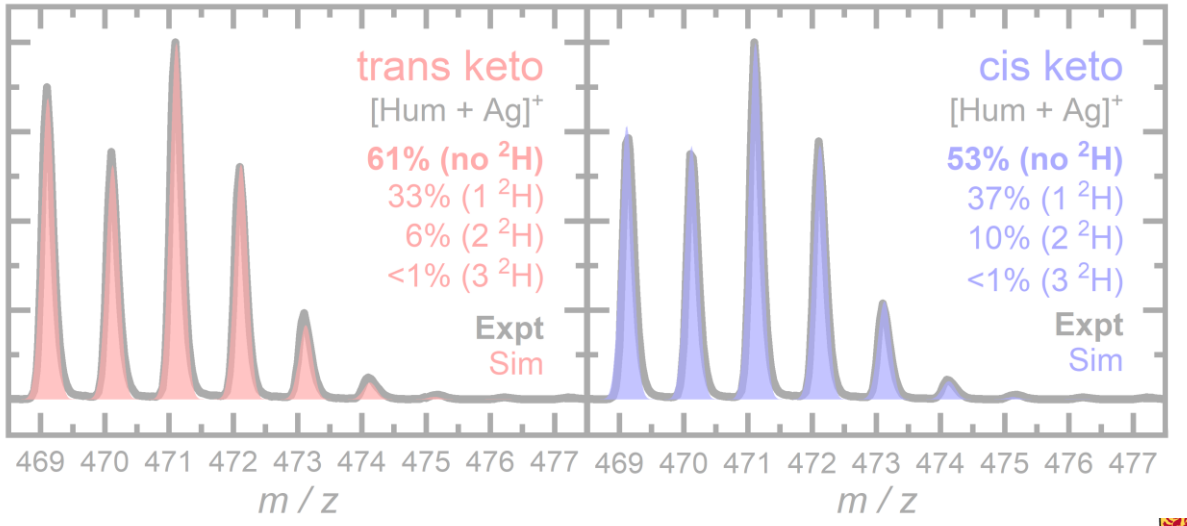
Humulone (Keto)

Slow exchange

Partial protection



More easily exchanged

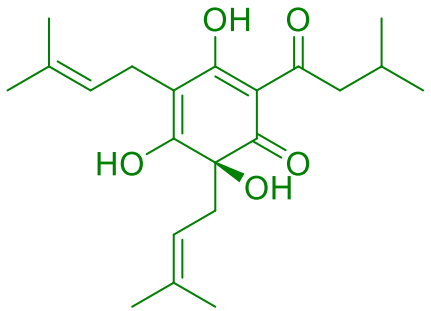


*tentative cis/trans assignments

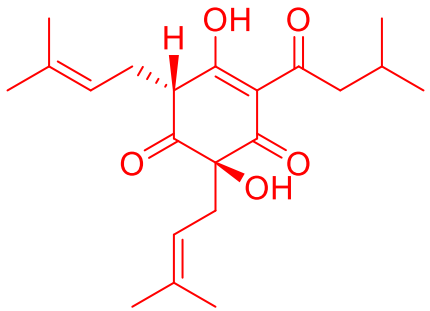
cis keto **exchanges less** compared to trans keto. Different structural motifs?

Time for some modelling and additional characterization!

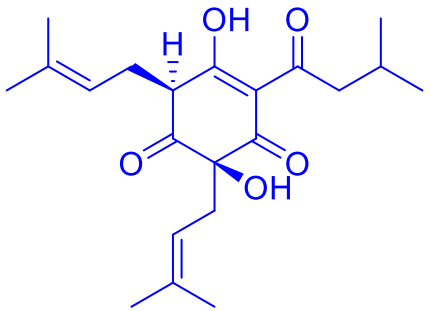
enol



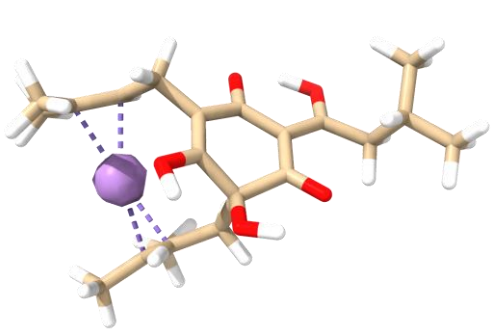
trans keto

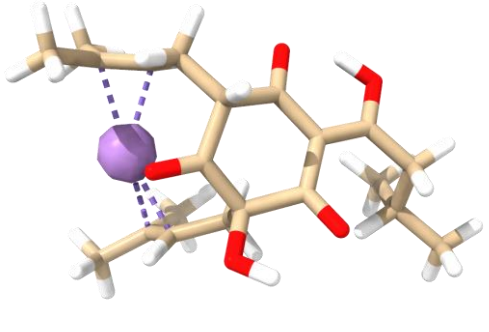


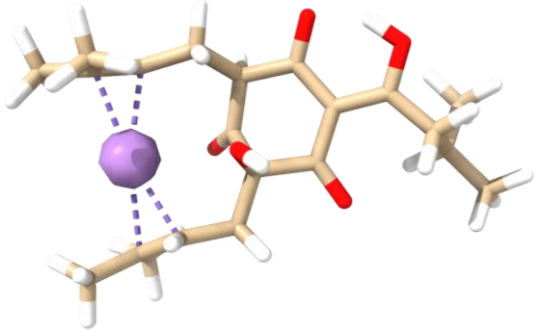
cis keto



Lowest energy configurations

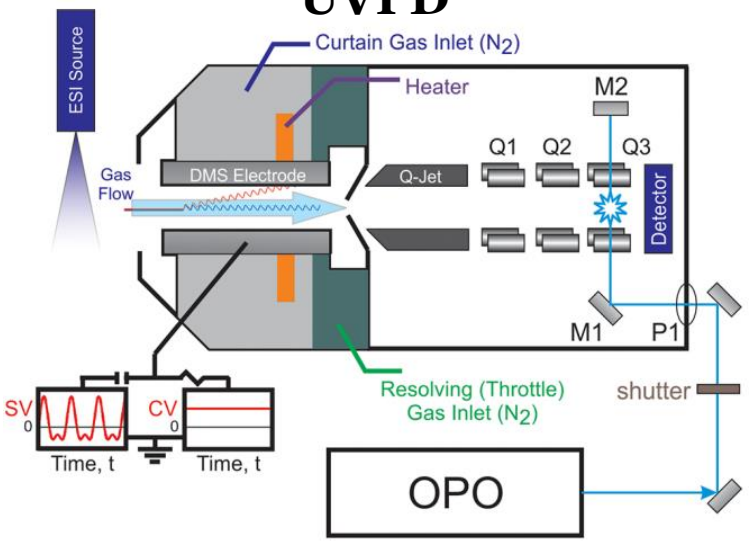




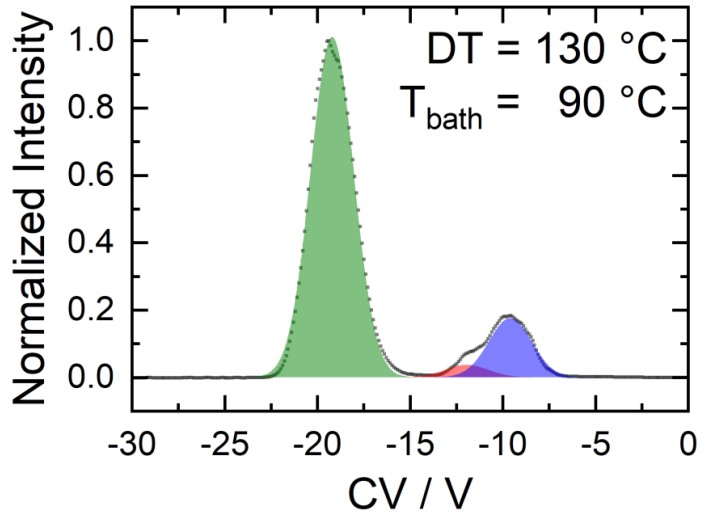


DLPNO-CCSD(T)/Def2-TZVPP//ωB97X-D3/Def2-TZVPP
TD-DFT at ωB97X-D3/Def2-TZVPP yields calculated UV spectra

UVPD

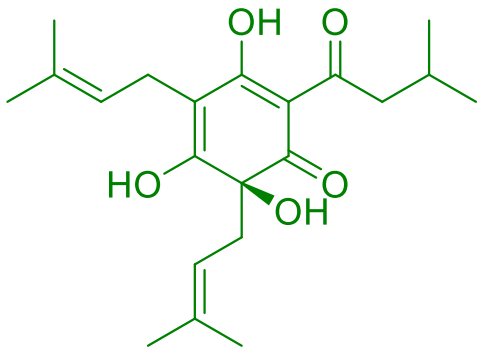


J. Am. Soc. Mass Spectrom. 2020, 31, 2, 405-410.

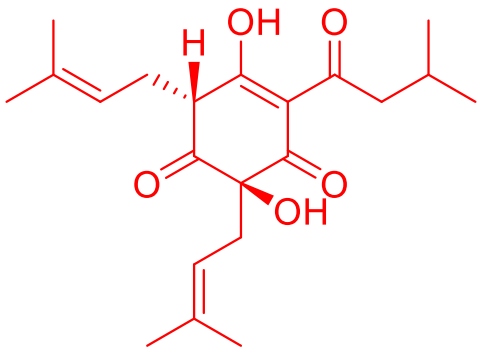


Time for some modelling and additional characterization!

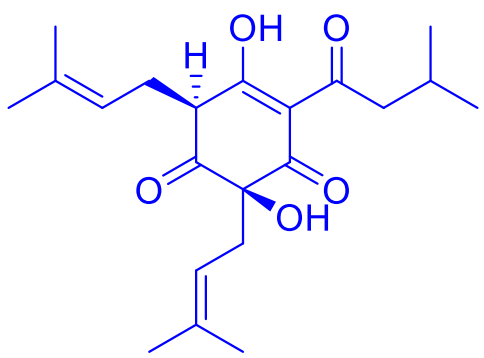
enol

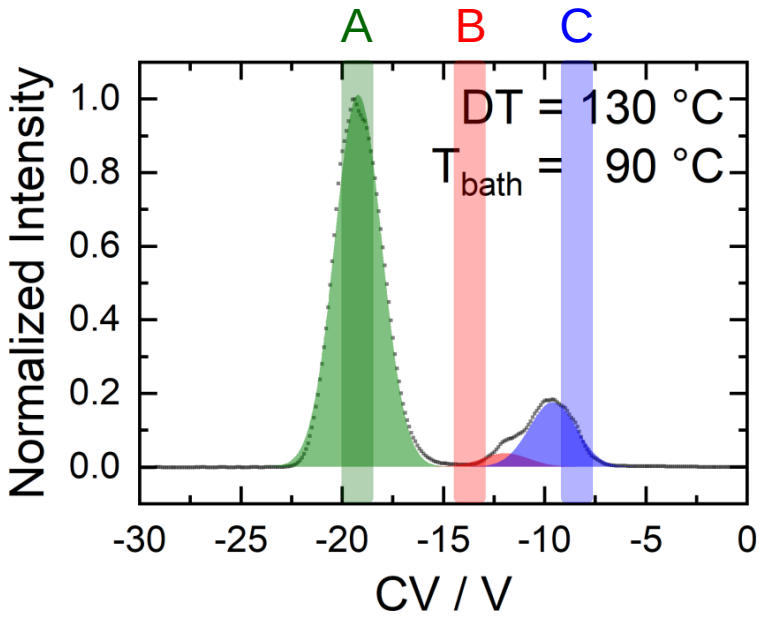


trans keto



cis keto

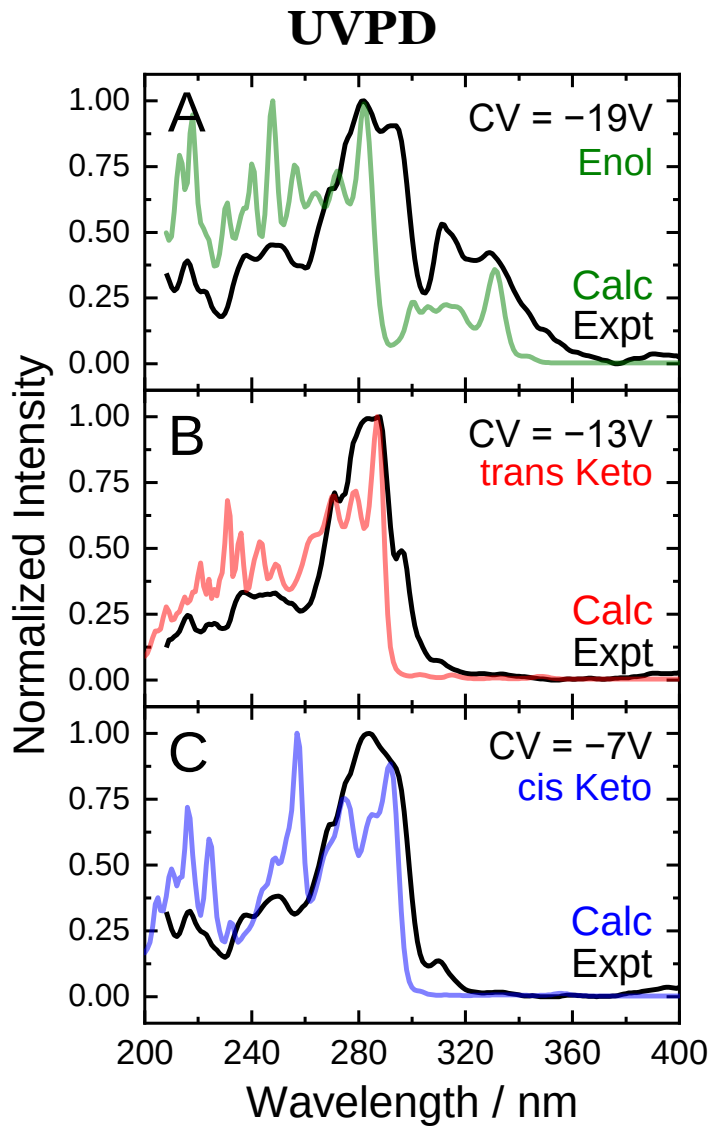




*tentative cis/trans keto assignments

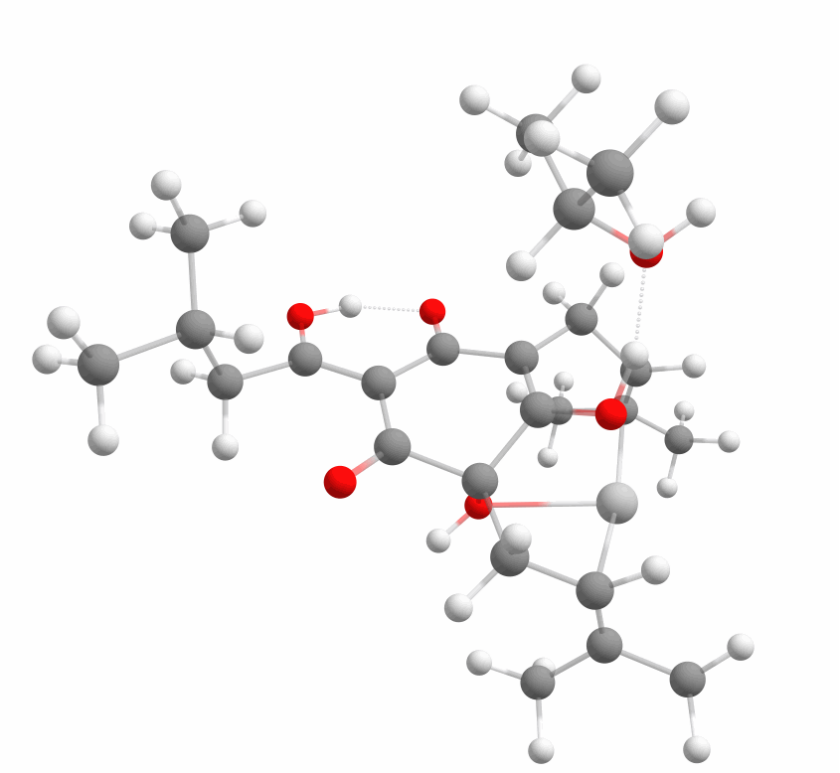
We need a rigorous way to assign cis/trans species

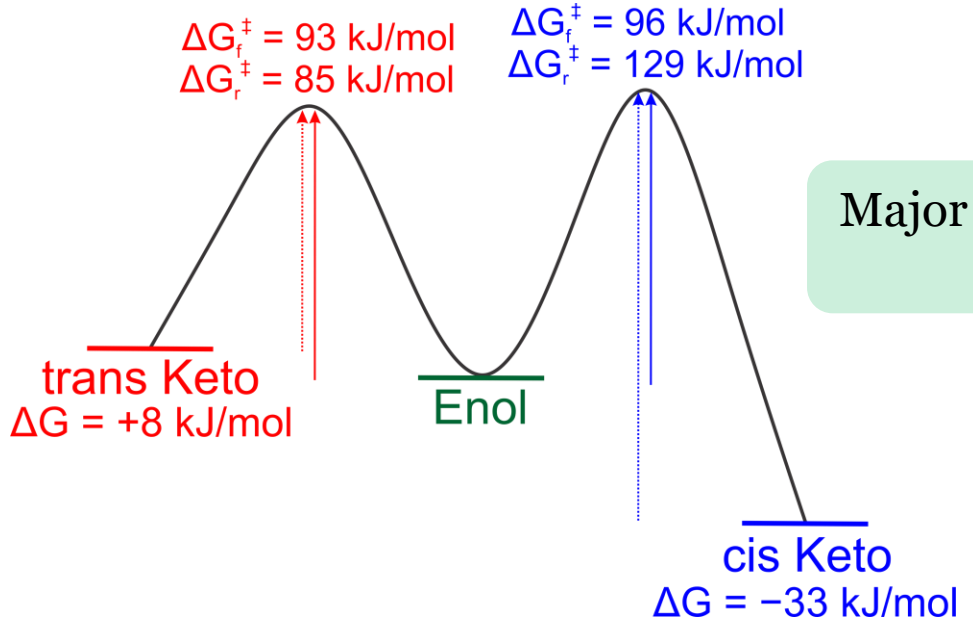
How are we seeing tautomers in the first place?



Hypothesis: dynamic solvation mediates tautomerization

Find transition states where IPA shuttles a proton between the enol form and the cis/trans Keto forms





Major implication of **1-way reversibility**!

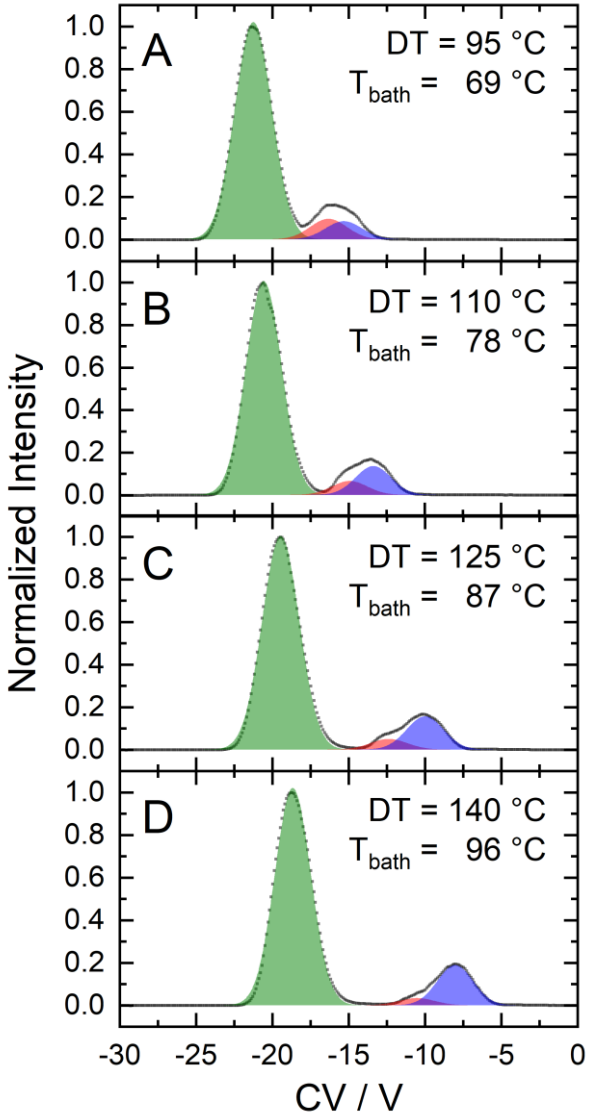
Kinetic product | **Thermodynamic product**

trans keto ⇄ *enol* → *cis keto*

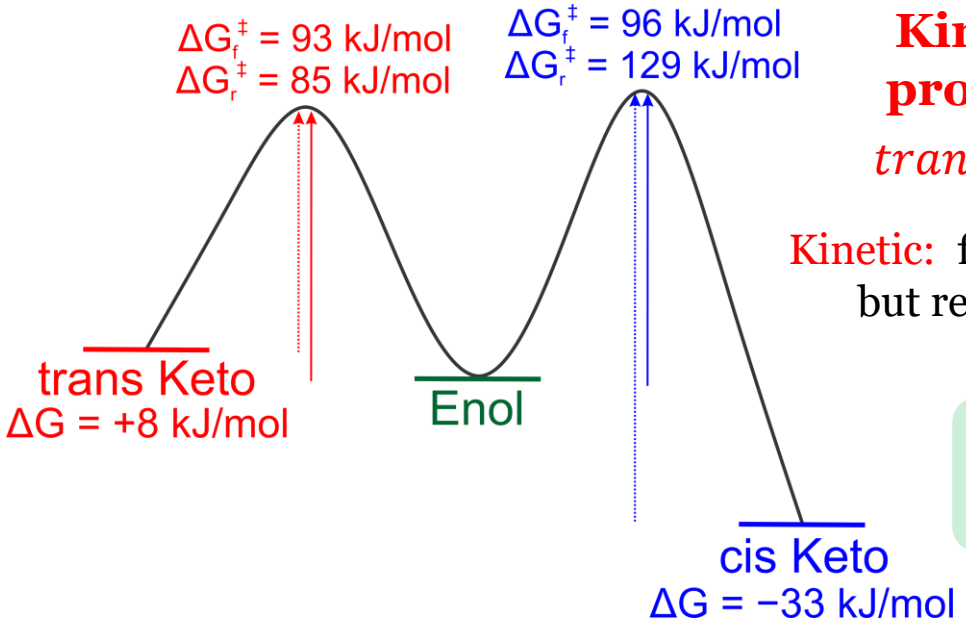
Kinetic: forms faster but reversibly

Thermodynamic: forms slower but "irreversibly"

Hypothesis: dynamic solvation mediates tautomerization



If we increase the T_{eff} of the ion, we can change the reaction kinetics such that the kinetic isomer can revert to back to the enol and "irreversibly" form the thermodynamic isomer



Kinetic product

Thermodynamic product

trans keto ⇄ *enol* → *cis keto*

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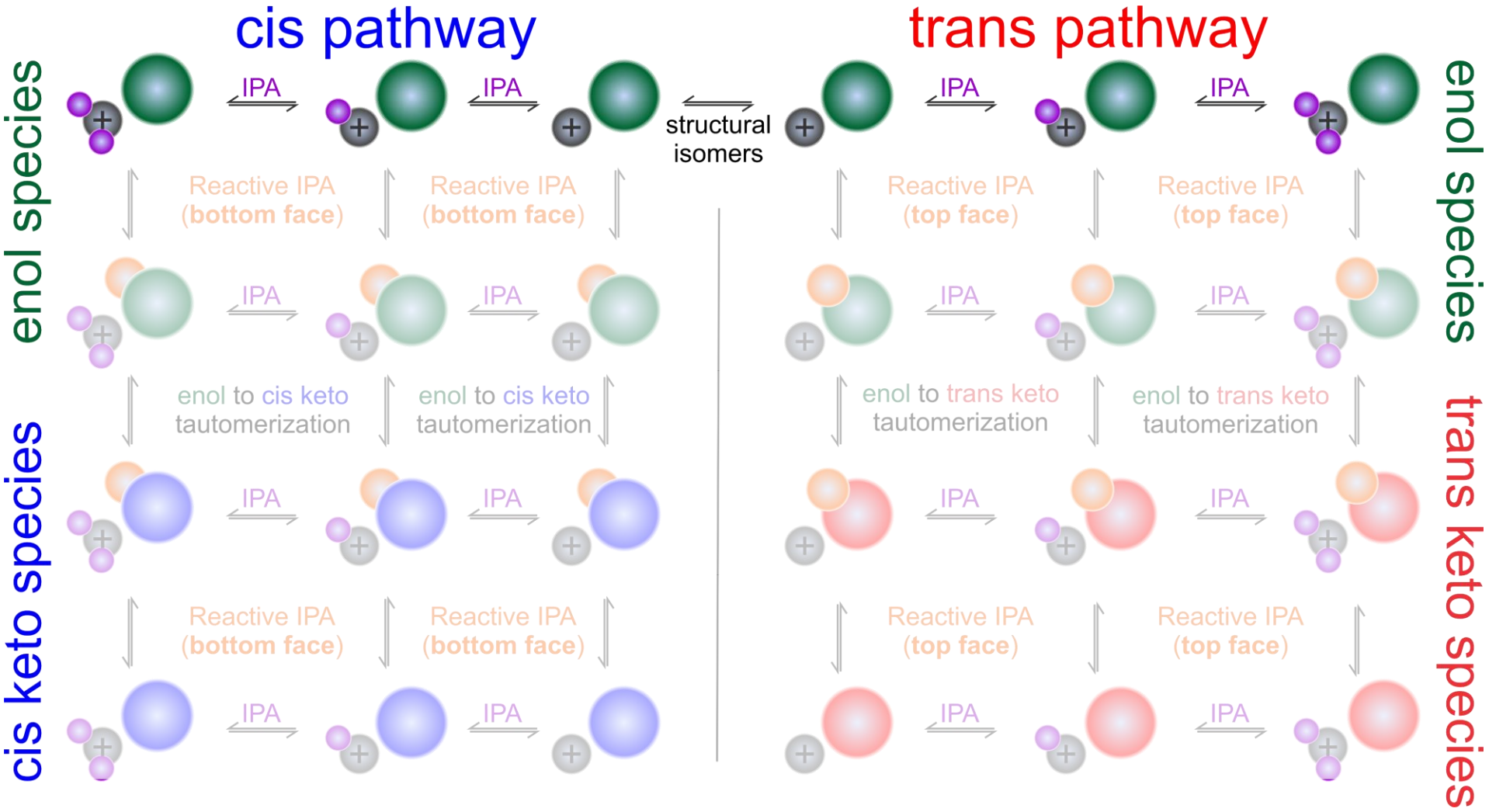
Major implication of **1-way reversibility**!

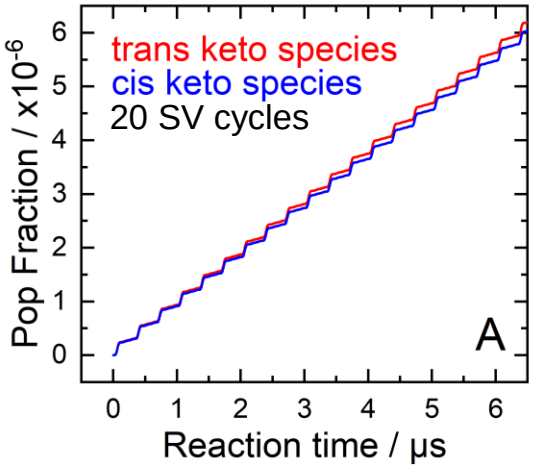
But is this how the chemistry happens in the DMS cell?

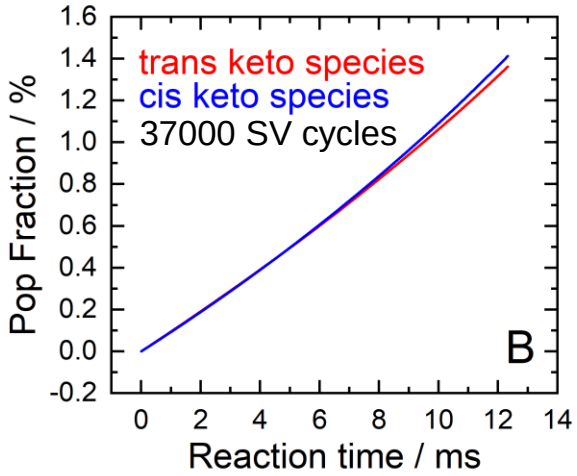


So where do we go from here?

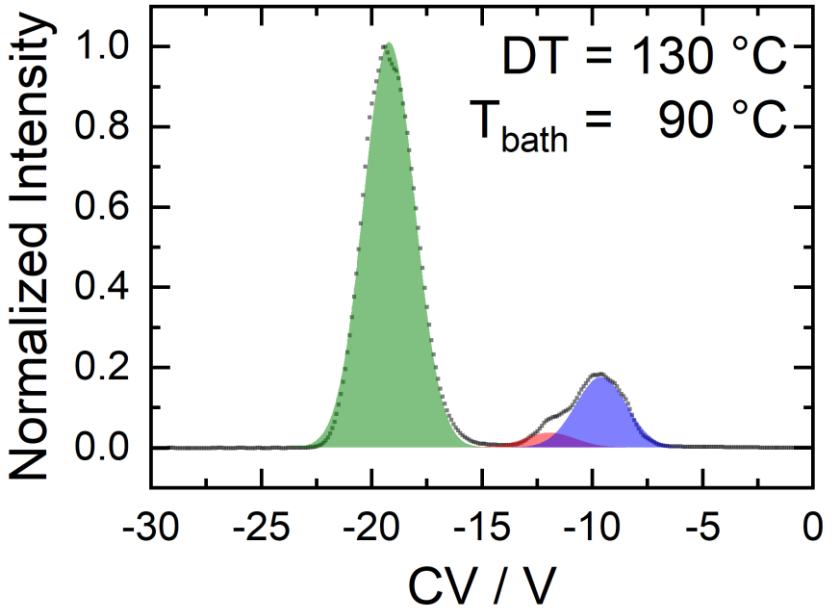
Kinetics model is incomplete – missing a few key minima and transitions states.

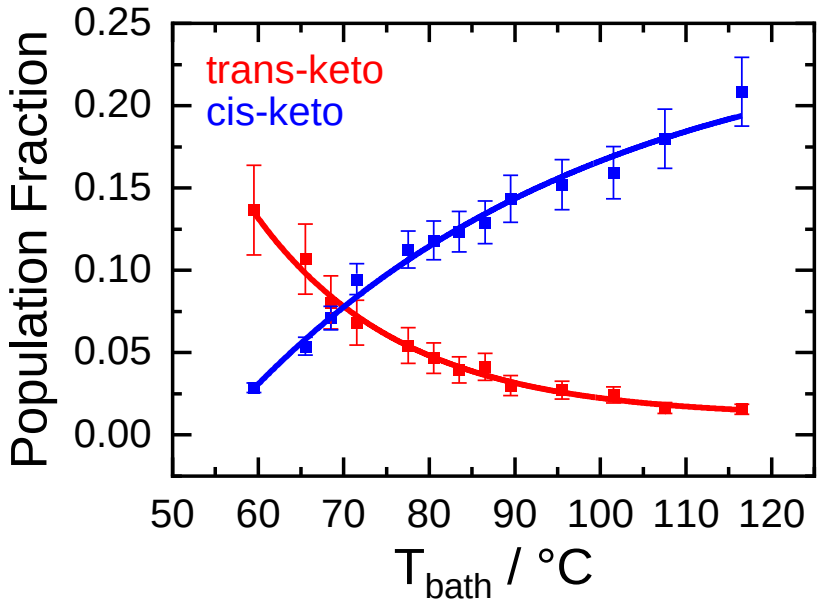
Preliminary results





Preliminary modelling results agree with experiment, supporting the kinetic vs. thermodynamic hypothesis





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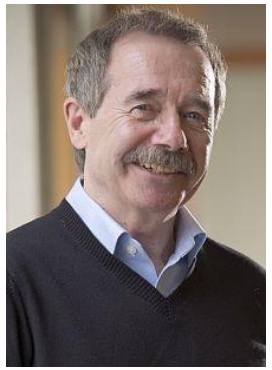
Prof. W. Scott Hopkins



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