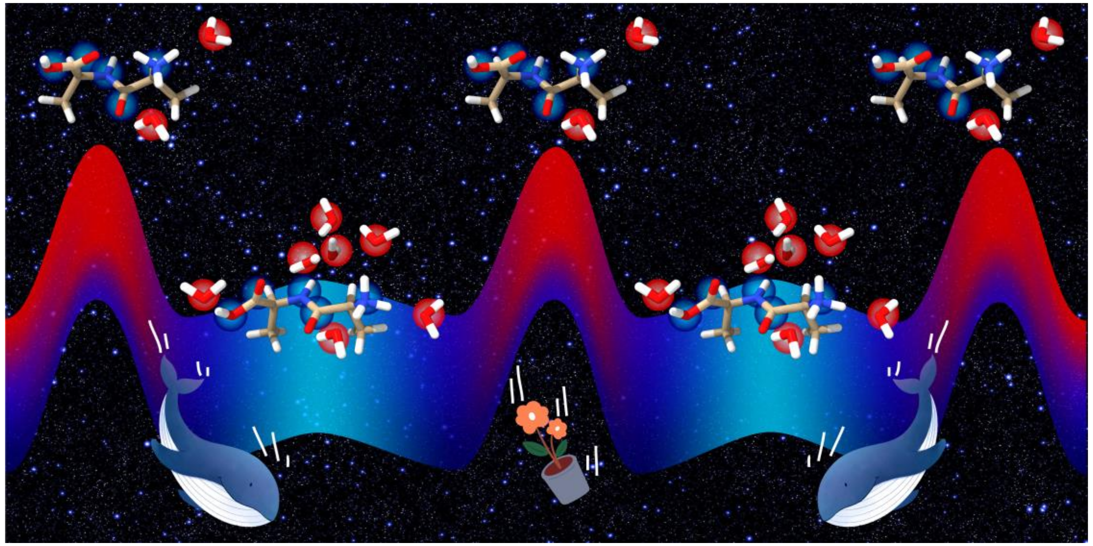
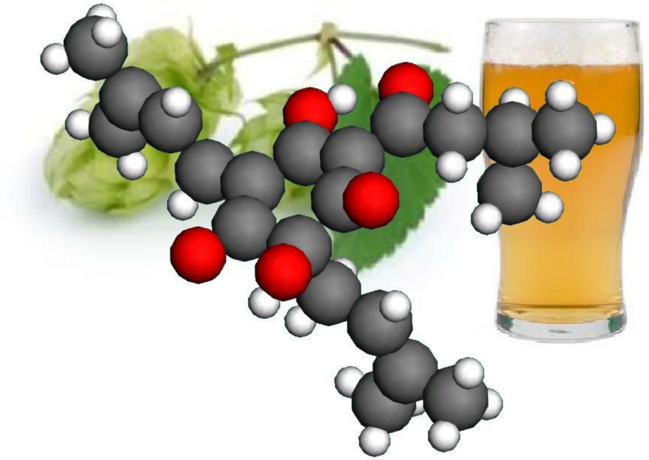
The Hitchhiker's Guide to Dynamic Ion-Solvent Clustering

(…in Differential Mobility Spectrometry)

Christian Ieritano, W. Scott Hopkins

CSC 2024 (Winnipeg)





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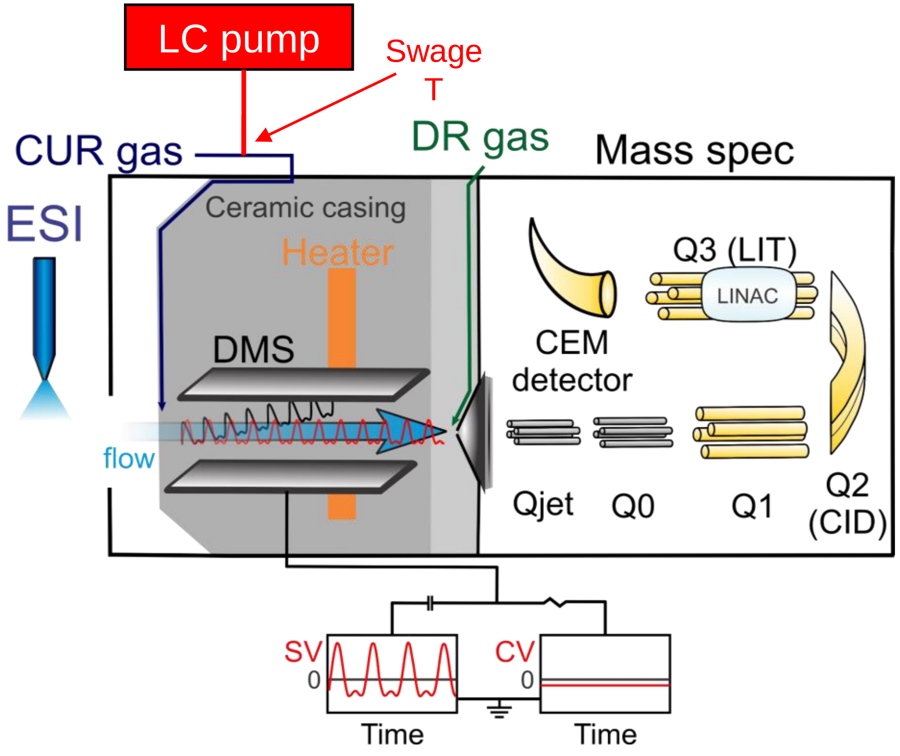
June 3, 2024

What is differential mobility spectrometry (DMS)?

Differential mobility spectrometry (DMS) harnesses the non-linear dependence of an ion's mobility to separate analytes.



At high electric field strengths, an ion's mobility changes non-linearly with the applied field

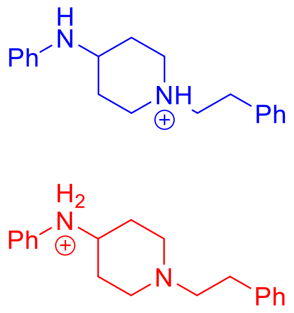
$$\alpha(E) = \frac{K(E) - K(0)}{K(0)} \qquad K = \frac{3}{16}\sqrt{\frac{2\pi}{\mu k_B T}} \cdot \frac{q(1+\alpha)}{N \cdot \Omega(T)}$$

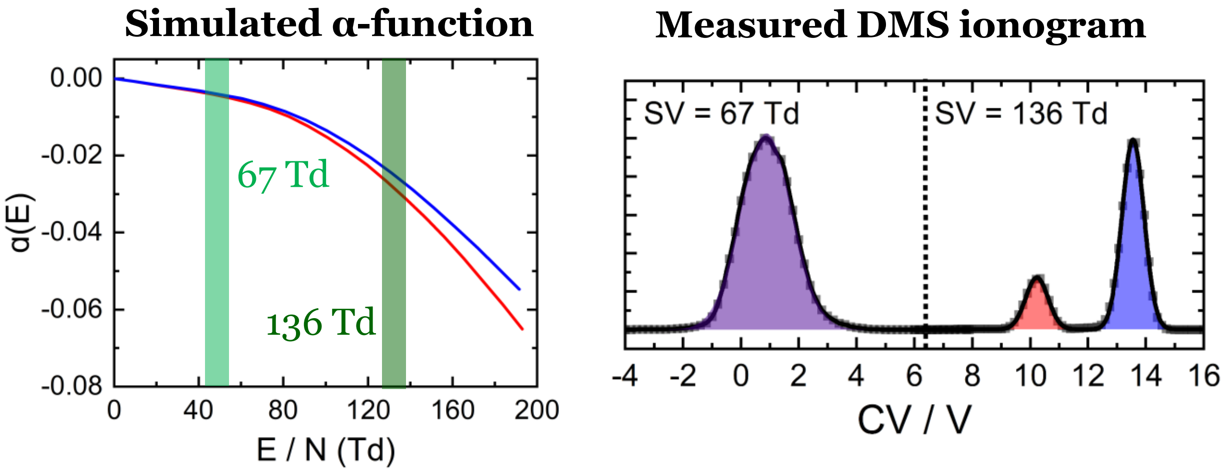
$$T_{eff} = T_{bath} + \frac{M}{3k_b}(KE)^2(1+\beta)$$

MOBCAL-MPI 2.0

Analyst, 2019, **144**, 1660 - 1670.
Analyst, 2023, **148**, 3257-3273.

Example: predicting the DMS separation of prototropic isomers in a pure N_2 environment via MobCal-MPI



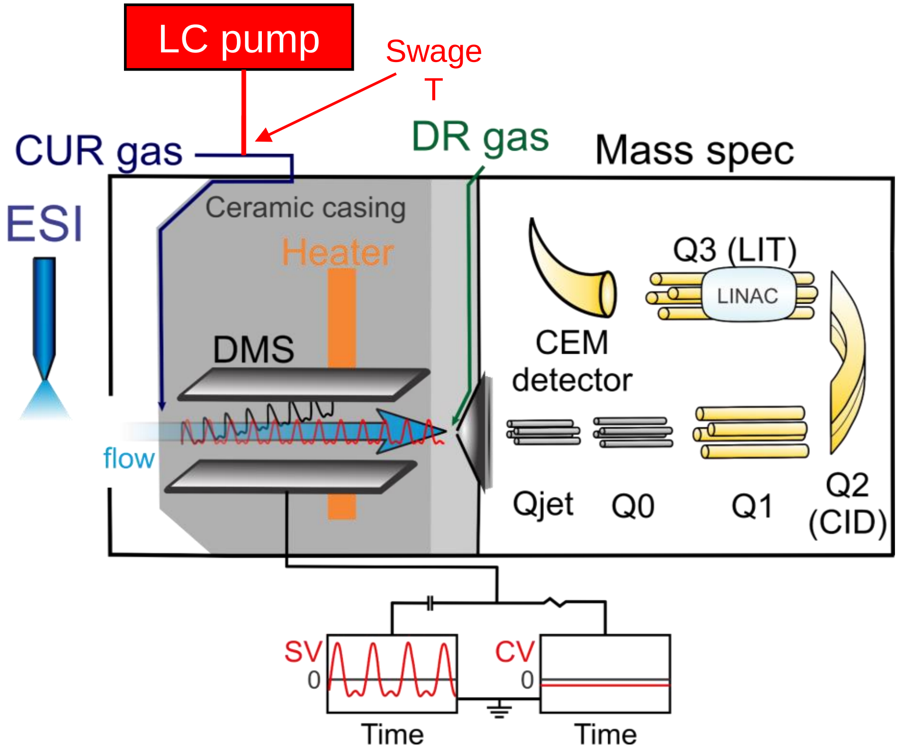


*from geometries and partial charges at ωB97X-D3/Def2-TZVPP

For a specific SV, every analyte will elute from the DMS cell at a characteristic CV related to its alpha function

How does DMS relate to dynamic ion solvation?

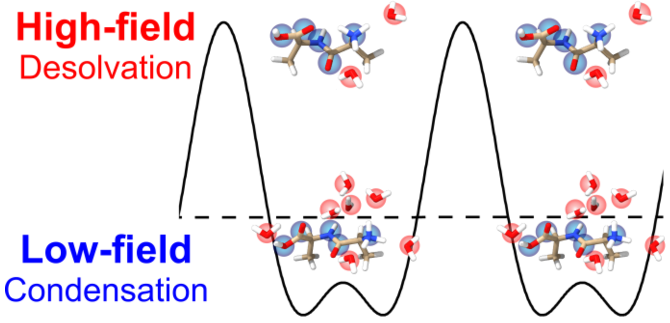
Differential mobility spectrometry (DMS) harnesses the non-linear dependence of an ion’s mobility to separate analytes.



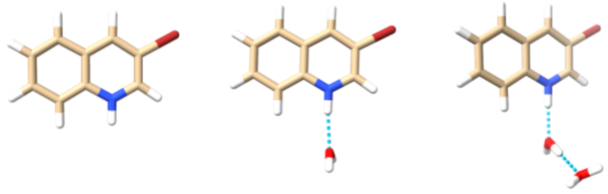
The nature of the SV waveform ensures **dynamic** ion-solvent interactions during DMS transit

Doping the carrier gas with solvent (1.5 mol%) induces dynamic solvation/desolvation cycles

Changes to an ion’s mobility upon microsolvation can be modeled

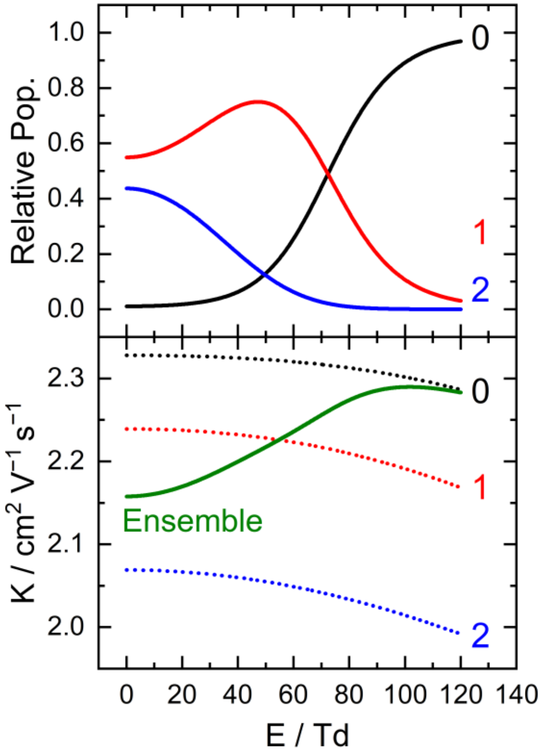


Bare ion **1 H_2O** **2 H_2O**



$$\Delta G_{ass} = (n \cdot G_{H_2O}) + G_{[M+H]^+} - G_{[M+H+n(H_2O)]}$$

$$P_i = P \cdot e^{\frac{\Delta G_{ass_i}(T)}{k_B T}} \qquad P = \frac{1}{\sum_i P_i}$$

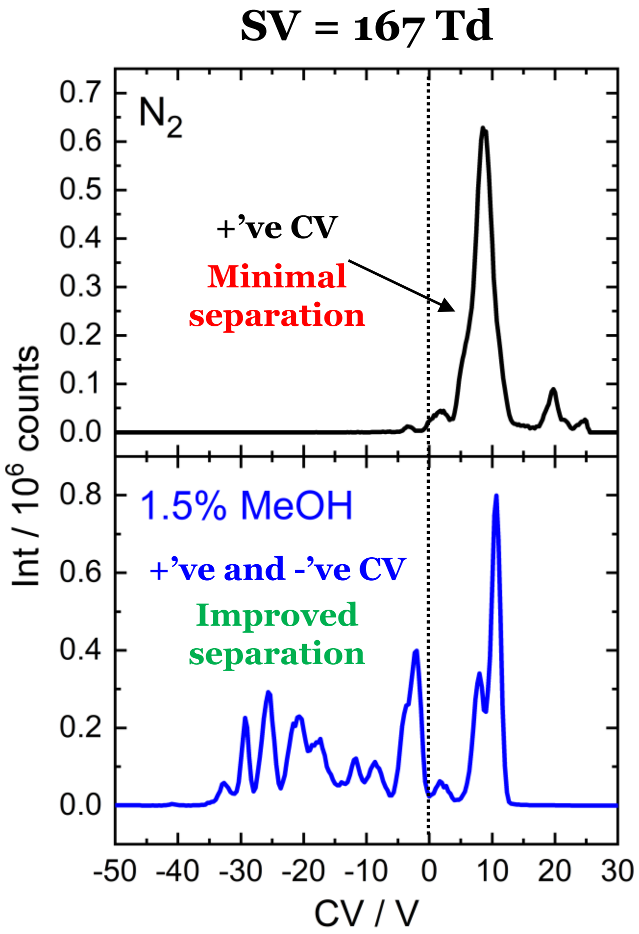


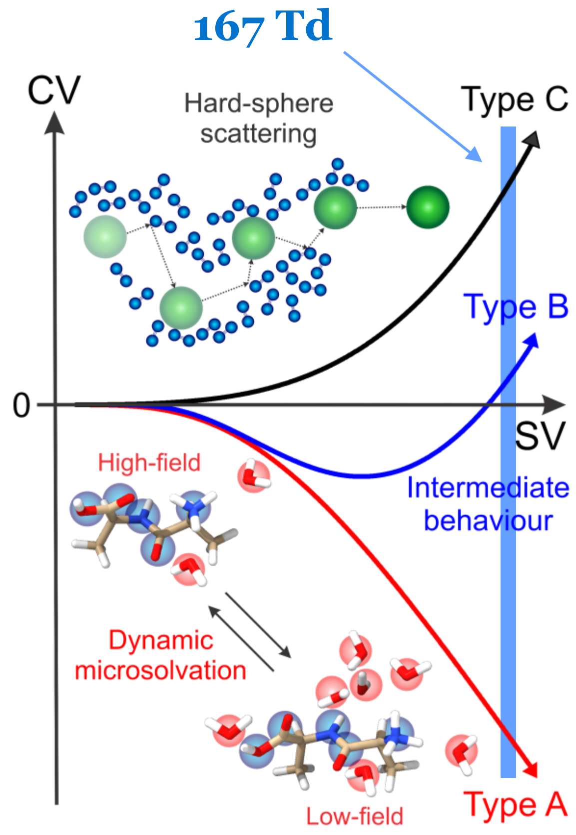
$$K_{ens} = \sum_i P_i \cdot K_i$$

What's so interesting about dynamic ion solvation in DMS?

1. Modifiers enhance separations of complex mixtures

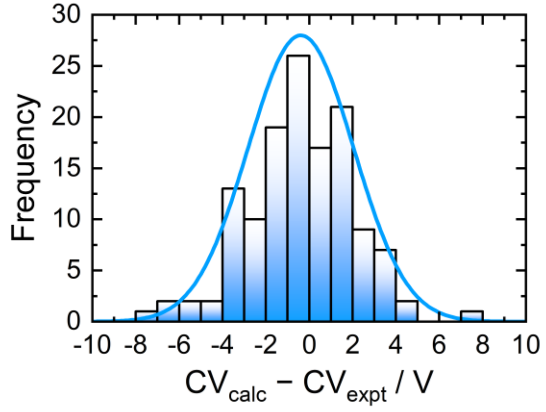
Simultaneous DMS-MS measurements of 60 compounds





2. Understanding dynamic ion-solvent interactions enables predictions of DMS behaviour

From first-principles modelling



J. Am. Soc. Mass Spectrom. 2022, **33**, 535 – 547.

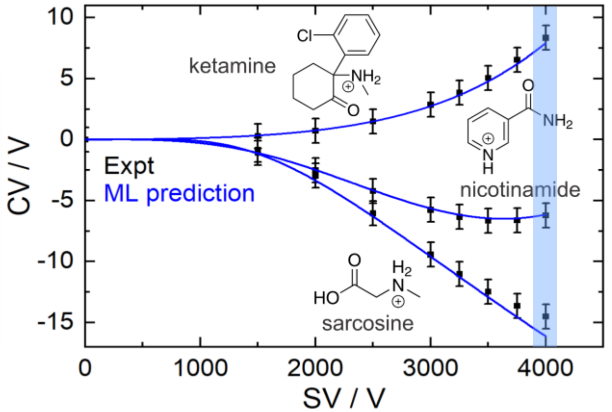
Phys. Chem. Chem. Phys. 2022, **24**, 20594 – 20615.

Analyst. 2023, **148**, 3257 – 3273.

J. Am. Soc. Mass Spectrom. 2023, **34**, 1417 – 1427.

ΔCV_{avg} = -0.4 V at SV = 167 Td

Via machine learning (Random Forest Regression)



Analyst, 2021, **146**, 4737 - 4743.

Anal. Chem., 2021, **93**, 8937 – 8944.

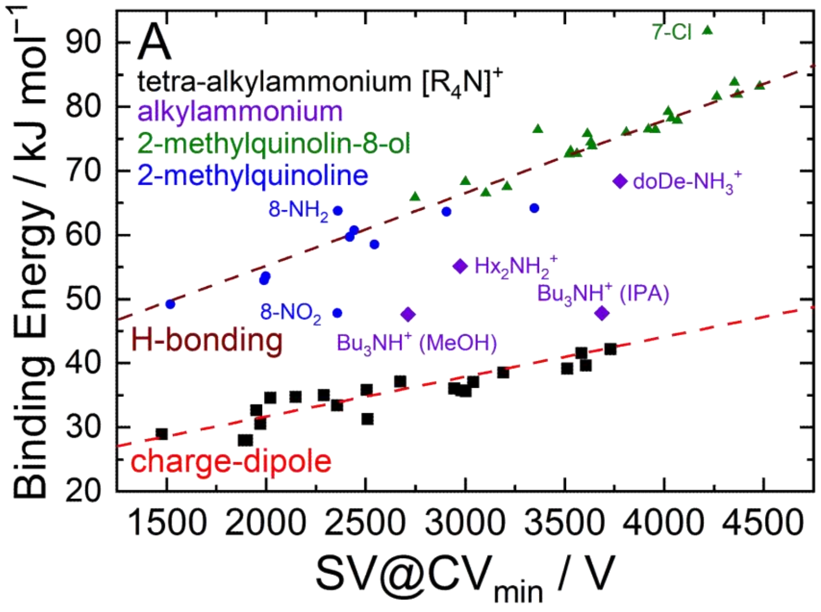
Phys. Chem. Chem. Phys. 2022, **24**, 20594 – 20615.

$|\Delta CV_{avg}|$ = 2.2 V at SV = 167 Td for 300+ compounds!

What's so interesting about dynamic ion solvation in DMS?

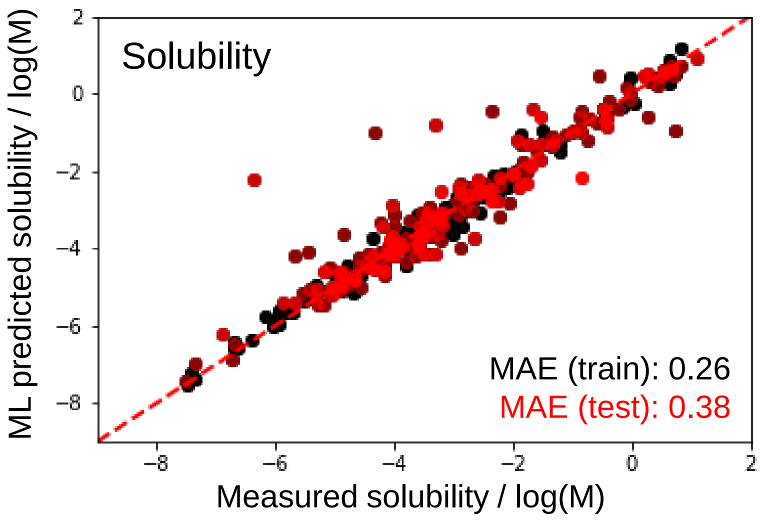
3. Correlating DMS behaviour with solution-phase properties intrinsic to the drug-design process

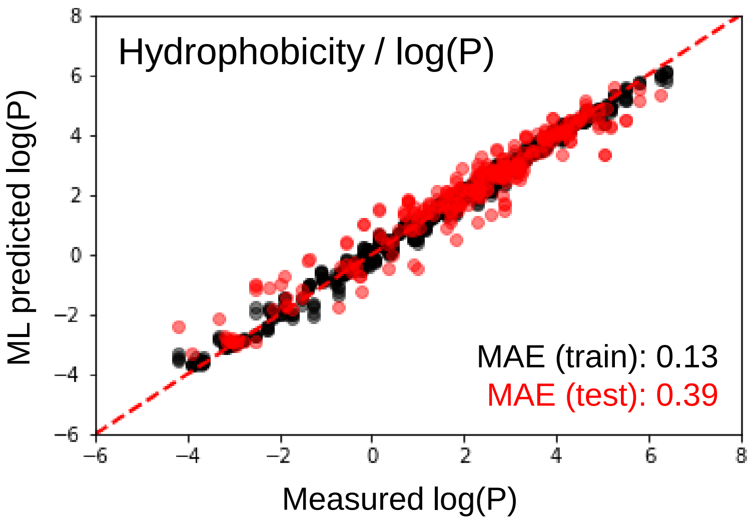
Hypothesis: Dynamic microsolvation processes during an ion's transit in the DMS cell mimics its solution-phase primary solvation shell.



Linear trends observed within identical compound classes for several properties but not amongst different compound classes

Machine learning enables general predictions (5-fold cross validation)





Random forest models trained using only DMS-MS data (SV/CV pairs) acquired in a MeOH modified environment using only nanograms of material.

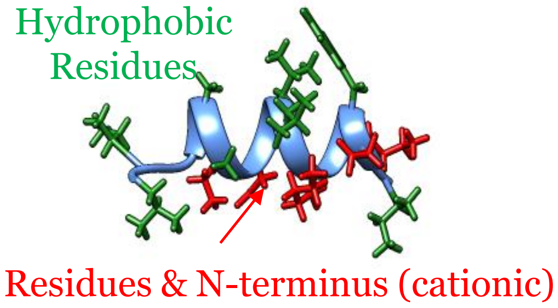
Phys. Chem. Chem. Phys. 2022, **24**, 20594 – 20615.
Anal. Chem. 2023, **95**, 10309 – 10321.

“Ion microsolvation” is more than a buzz word

4. Charge manipulation

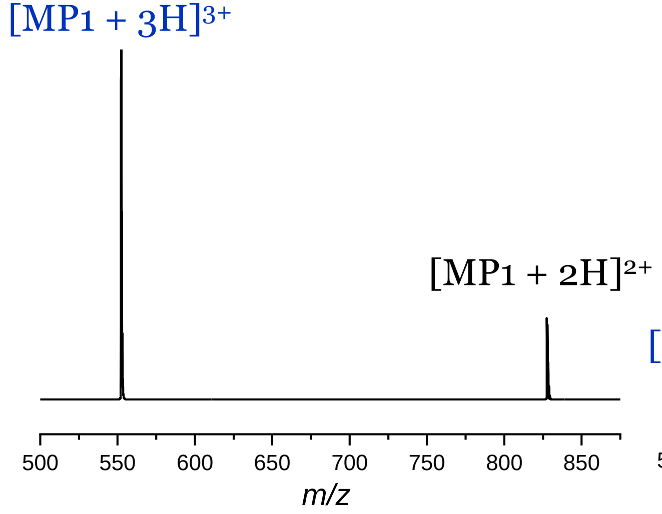
https://phys.org/news/2015-09-brazilian-wasp-venom-cancer-cells.html

Polybia-MP1

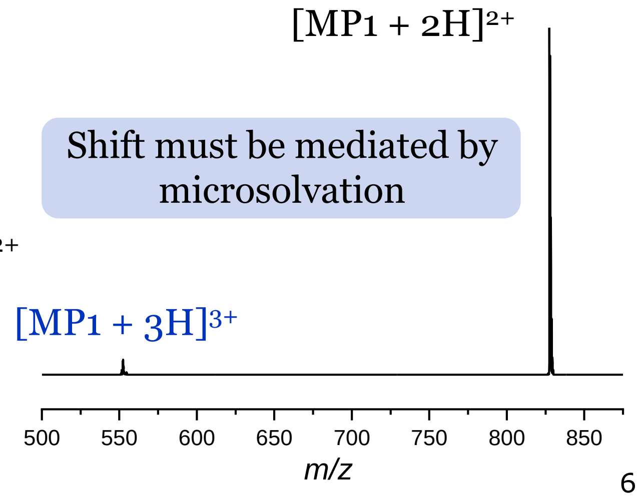


Addition of solvent vapour to the DMS cell alters the charge state distribution of MP1

Dry N_2



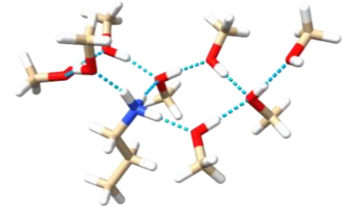
N_2 with 1.5% MeOH



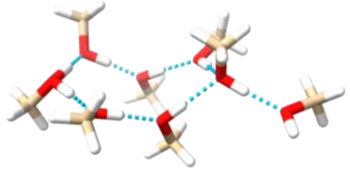
The shift in charge state distribution is likely mediated by microsolvation

Solvation/desolvation processes can induce proton transfer

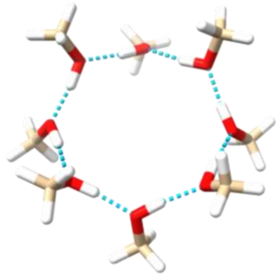
$[PrNH_2 + H + (MeOH)_8]^+$

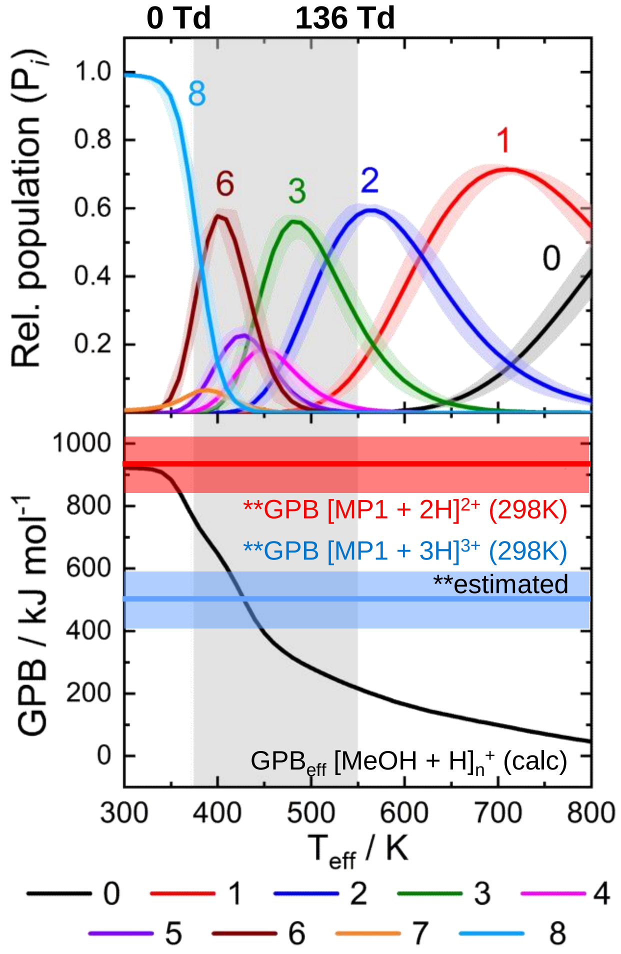


$[(MeOH)_8 + H]^+$



$[(MeOH)_8]$

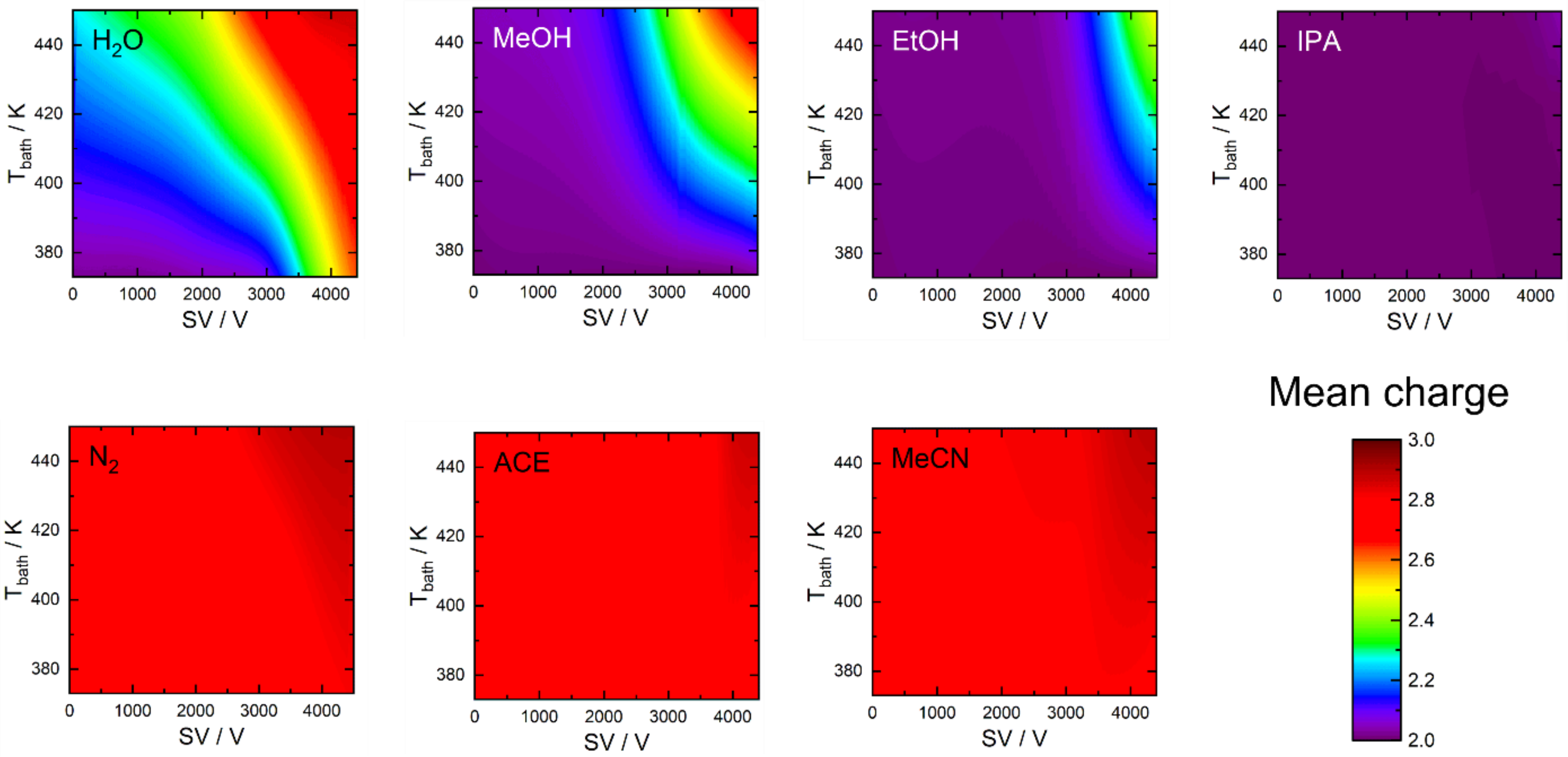




$$GPB_{eff} = \sum_i P_i \cdot GPB_i$$

J. Am. Soc. Mass Spectrom., 2021, 32, 956-968

Microsolvation facilitates ion-solvent proton transfer

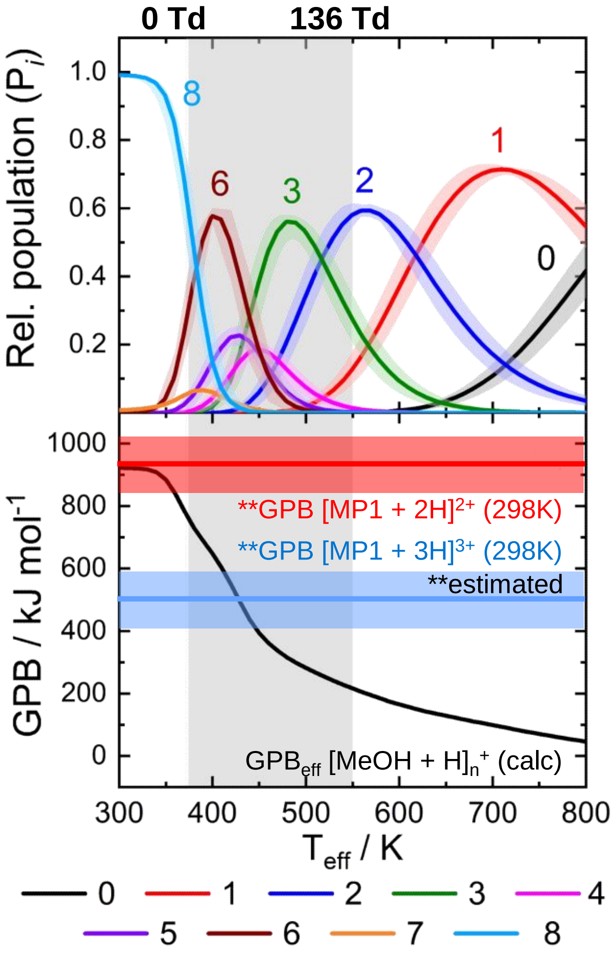


Gas-phase basicity ordering: **ACE** > IPA >**MeCN** > EtOH > MeOH > H_2O

No charge transfer with aprotic modifiers because of inability to form H-bonded networks with high GPB!

Instead, retention of high charge states that otherwise fragment during DMS-transit

The +3 ion re-emerges at high bath gas temperatures and high SV fields



$$GPB_{eff} = \sum_i P_i \cdot GPB_i$$

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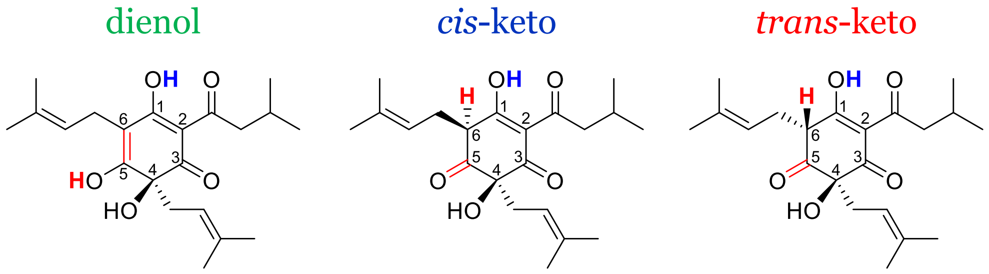
Speaking of proton transfers …

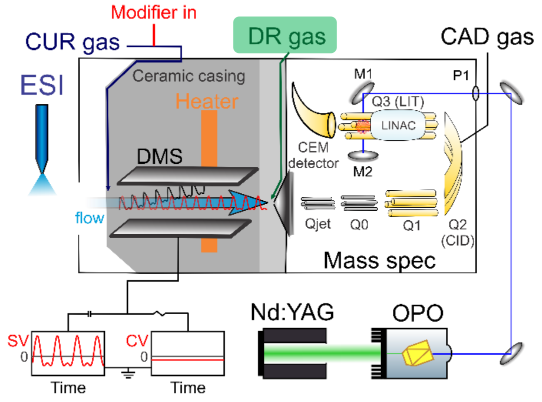
5. Harnessing the separation power of dynamic microsolvation and HDX

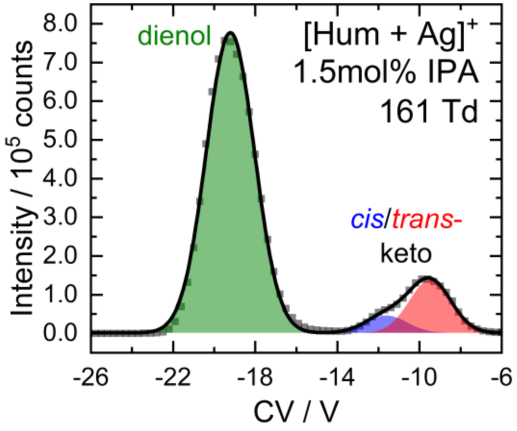
Humulone: A brewer's best friend



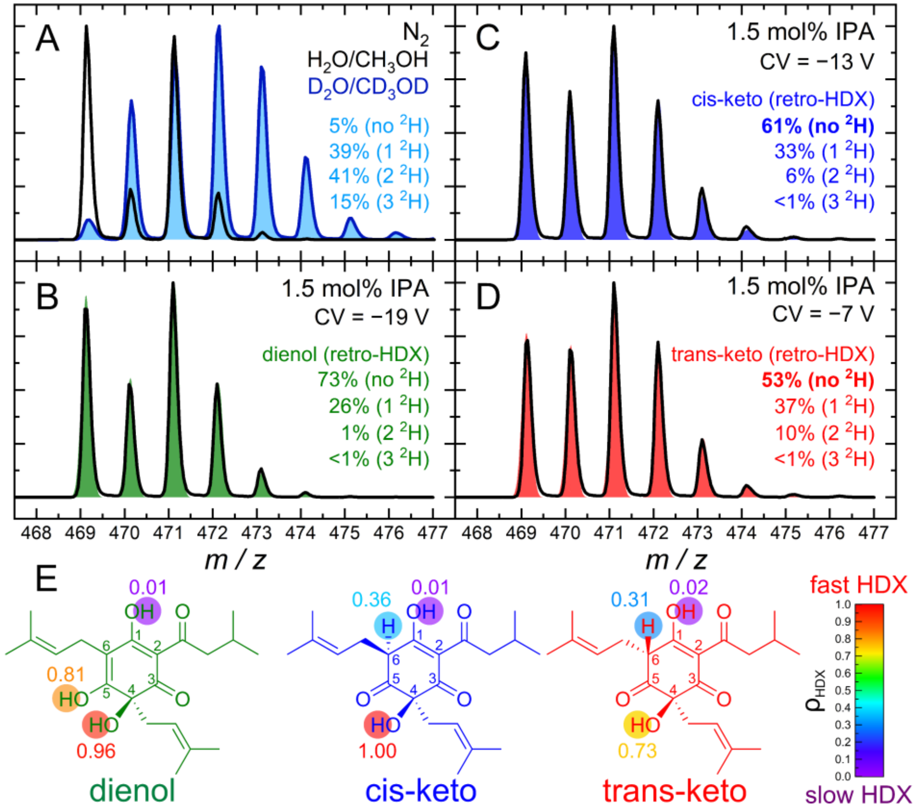
Tautomer resolution requires detection as silver adduct (*i.e.*, $[M + Ag]^+$ **and** 1.5 mol% of IPA doped into the curtain gas.

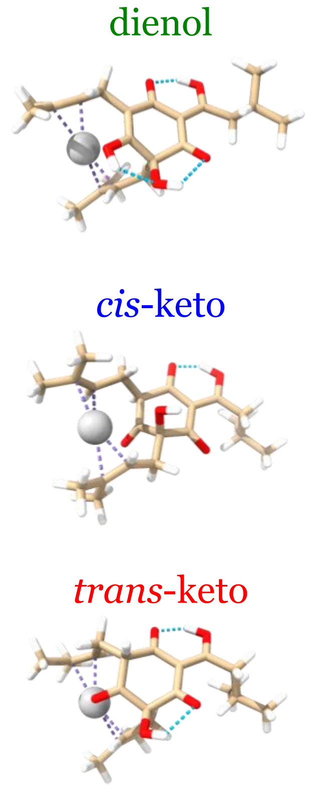
HDX reagent (e.g., D_2O) is bubbled into the DR gas line, but the excess IPA would destroy any HDX reagent by back-exchange





Retro-HDX: Deuterate pre-ESI, then watch back-exchange with protic modifier





HDX events happen only at points of solvent accretion (*i.e.*, the charge site!)

J. Am. Soc. Mass Spectrom., 2023, **34**, 1315 – 1329.

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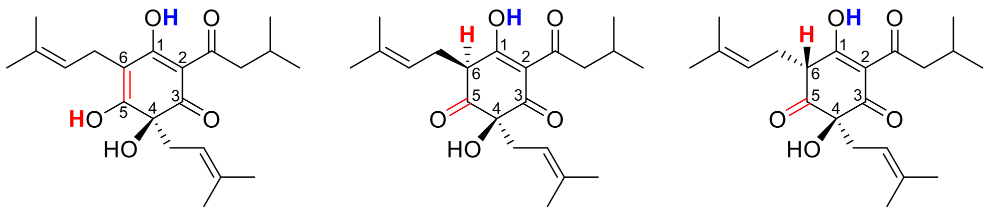
dienol *cis*-keto *trans*-keto



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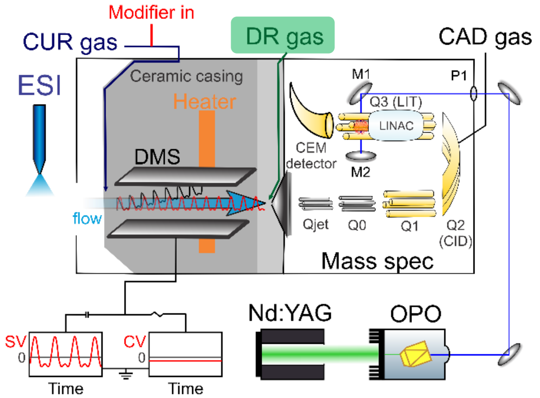
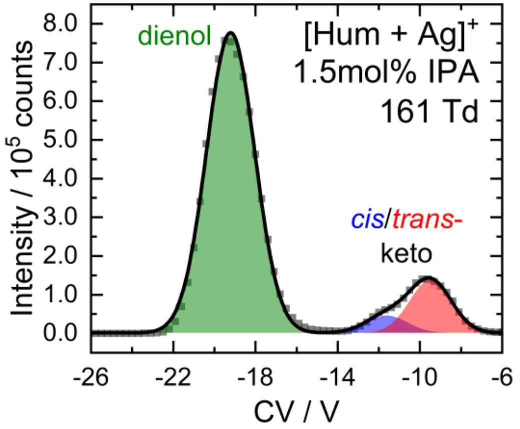
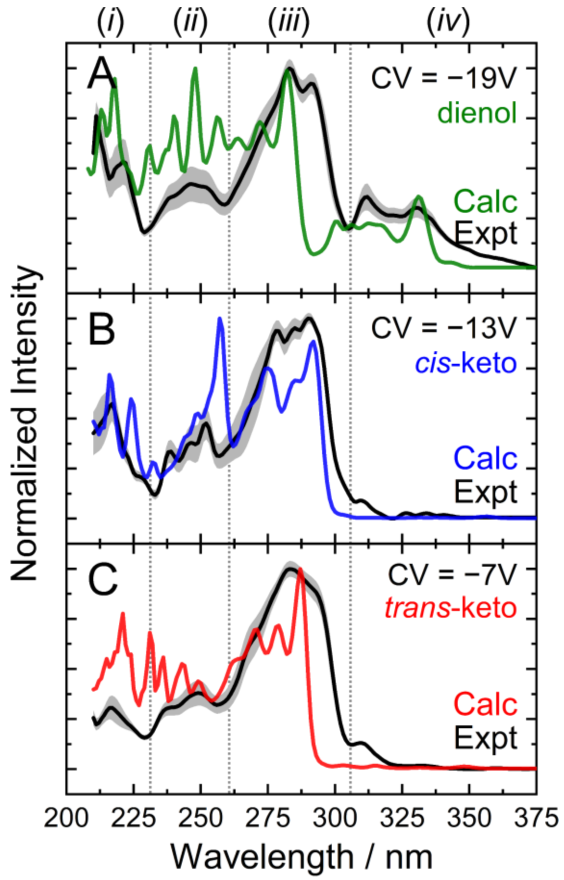
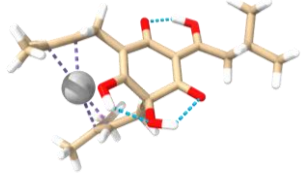




UVPD: DMS-select each tautomer, then interrogate w/ tunable output of the YAG-pumped OPO

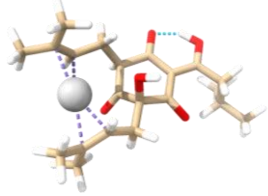


dienol



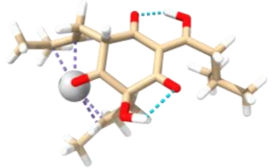
dienol clearly distinguished

cis-keto



…but the keto tautomers are somewhat ambiguous

trans-keto



J. Am. Soc. Mass Spectrom., 2023, **34**, 1315 – 1329.

WaterFEL – A Canadian Free Electron Laser (FEL) Facility

What is an FEL?

Linear accelerator-based light sources provide **tunable, high-power, narrow bandwidth IR light from 20 – 4000 cm^{-1}**

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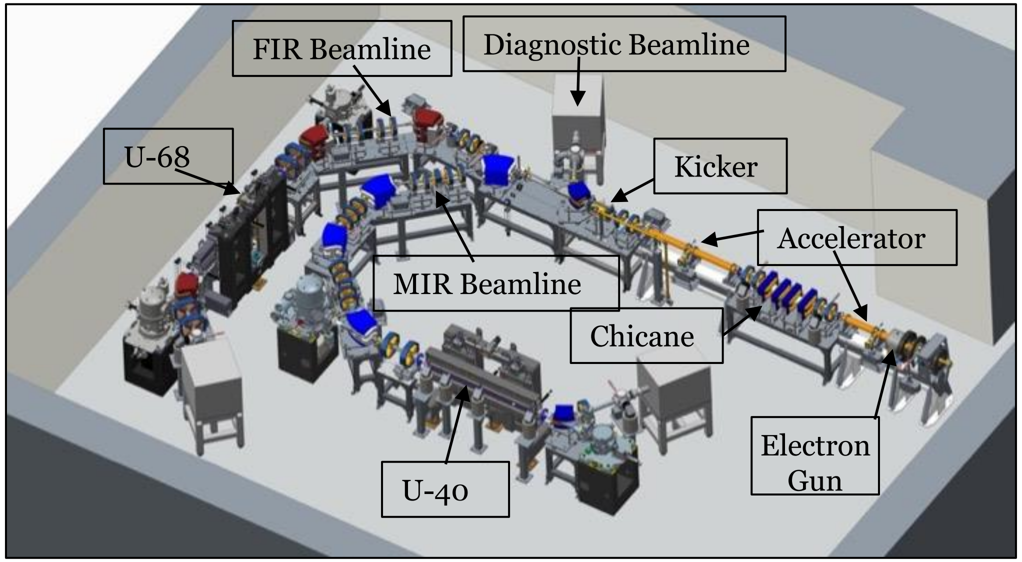
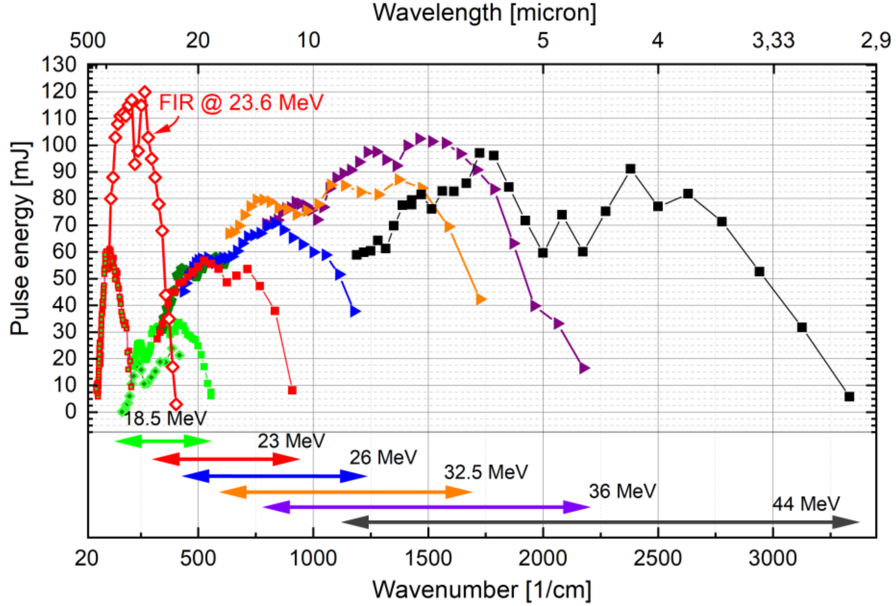


2023 CFI award for $10M to construct a Canadian FEL at the University of Waterloo (UW)

With matching funding from Ontario and additional contributions from UW and other institutions



$\bar{\nu}$ / cm^{-1}	Energy per pulse (mJ; 10 Hz)	Bandwidth ($\Delta\bar{\nu}$ / cm^{-1})
3900*	20 – 30*	± 8.3*
3000	50	± 6.75
2000	60	±5.625
1000	75	±2.25
500	50	±1.125
100	>100	±0.225

*not shown; hot off the presses at FHI!

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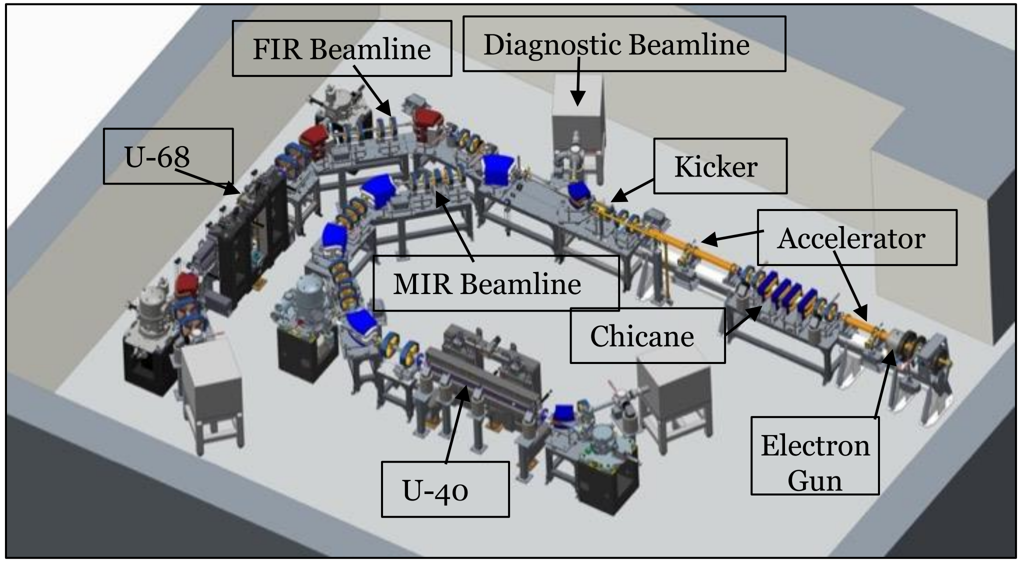

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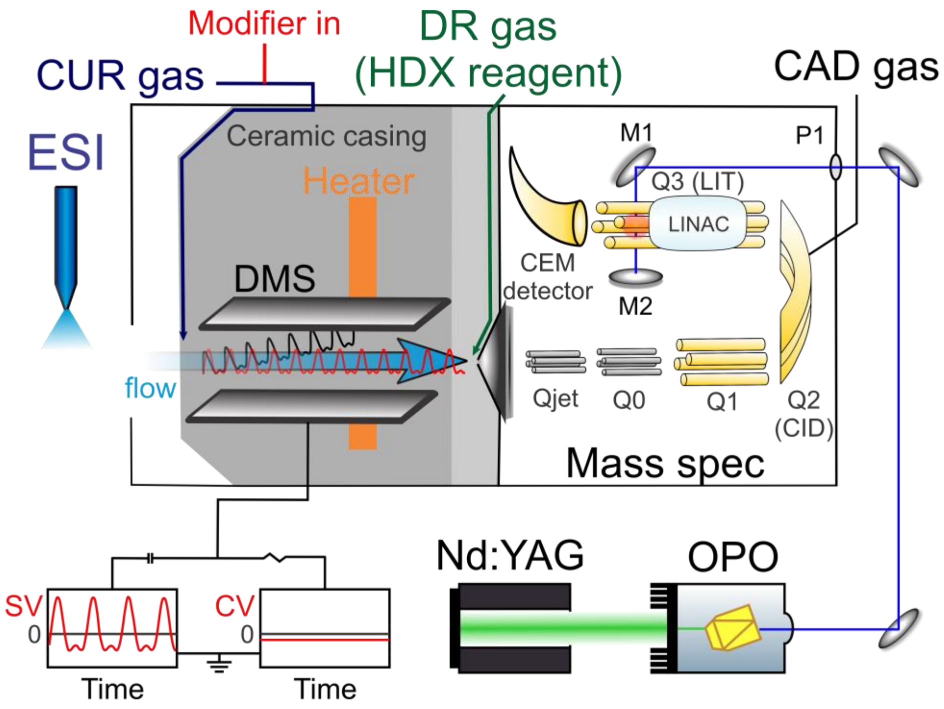
WaterFEL instrumentation



Facility open to the global community, with beam-time being awarded based on merit of proposals

First user proposals for early 2029

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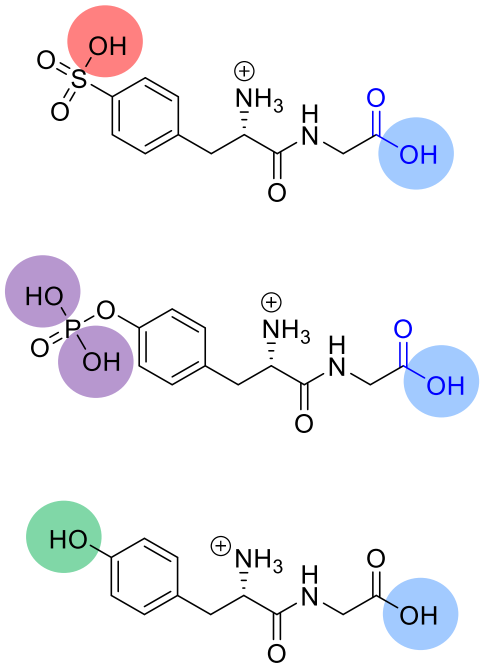
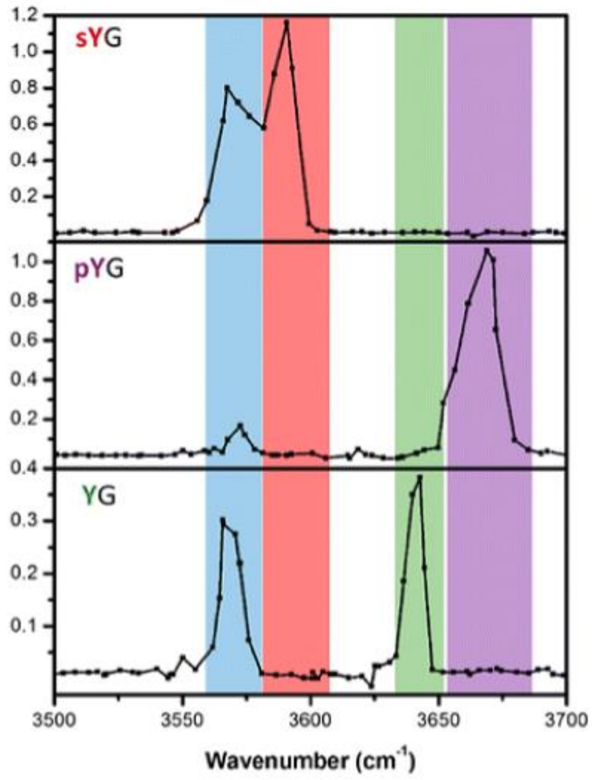
WaterFEL – Some of the many applications

Site-specific information about biological modifications



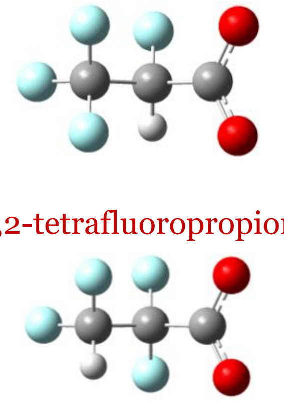


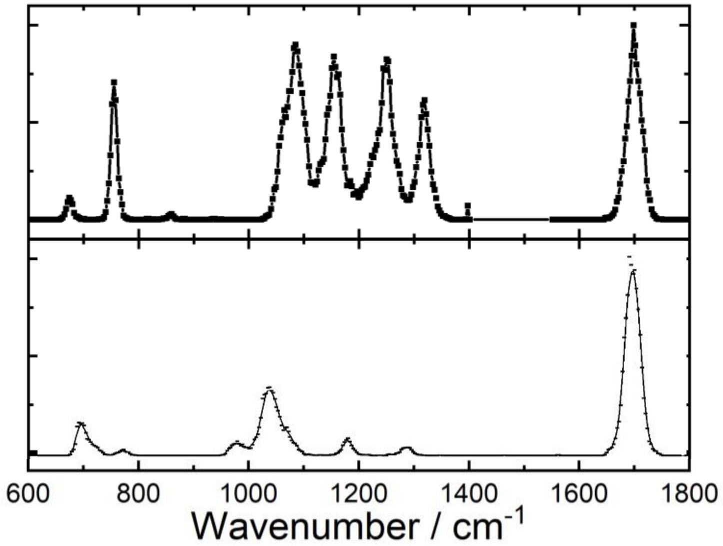
...combined with bottom-up approaches enable sequencing w/ unambiguous PTM assignment

Unambiguous distinction of "indistinguishable" isobars

3,3,3,2-tetrafluoropropionic acid

3,3,2,2-tetrafluoropropionic acid





Arthur Lee

Combine IRMPD and AI for molecular fingerprinting

Tuesday 4:00 – 4:20pm
(IN, MT, PTC) Modern Spectroscopic Approaches for Deciphering Complex Phenomena

Acknowledgements

The Brain Trust

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Dr. Steve Walker
Justine Bissonnette
Chris Ryan
Cailum Steinstra
Patrick Thomas
Arthur Lee

SCIEX Gurus

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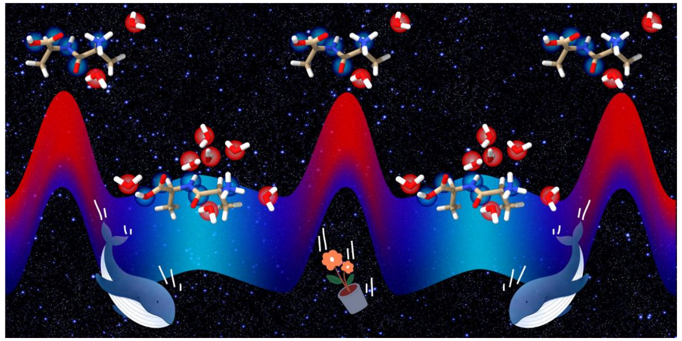
Dr. Brad Schneider
Dr. Mircea Guna

Academic friends

Dr. John Janiszewski (NIH)
Dr. Gilles Goetz (Pfizer)
Dr. Larry Campbell (Bedrock)

For more information on our work, see:



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Phys. Chem. Chem. Phys, 2022, 24, 20594-20615.

Resources and Funding

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Watermine Innovation

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