Réactivité en phase gazeuse de bio-molécules par dynamique moléculaire

III^{eme} Journée de Simulations Numériques en Chimie à Paris Sud
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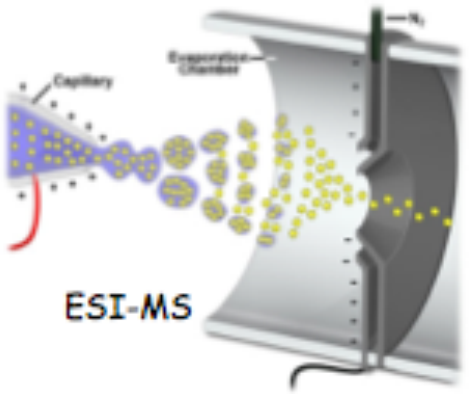
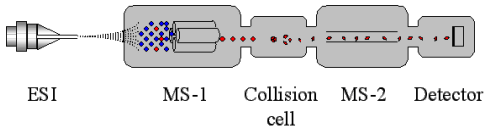
Riccardo Spezia
Laboratoire Analyse et Modélisation pour la Biologie et l'Environnement
UMR 8587 CNRS
Université d'Evry Val d'Essonne

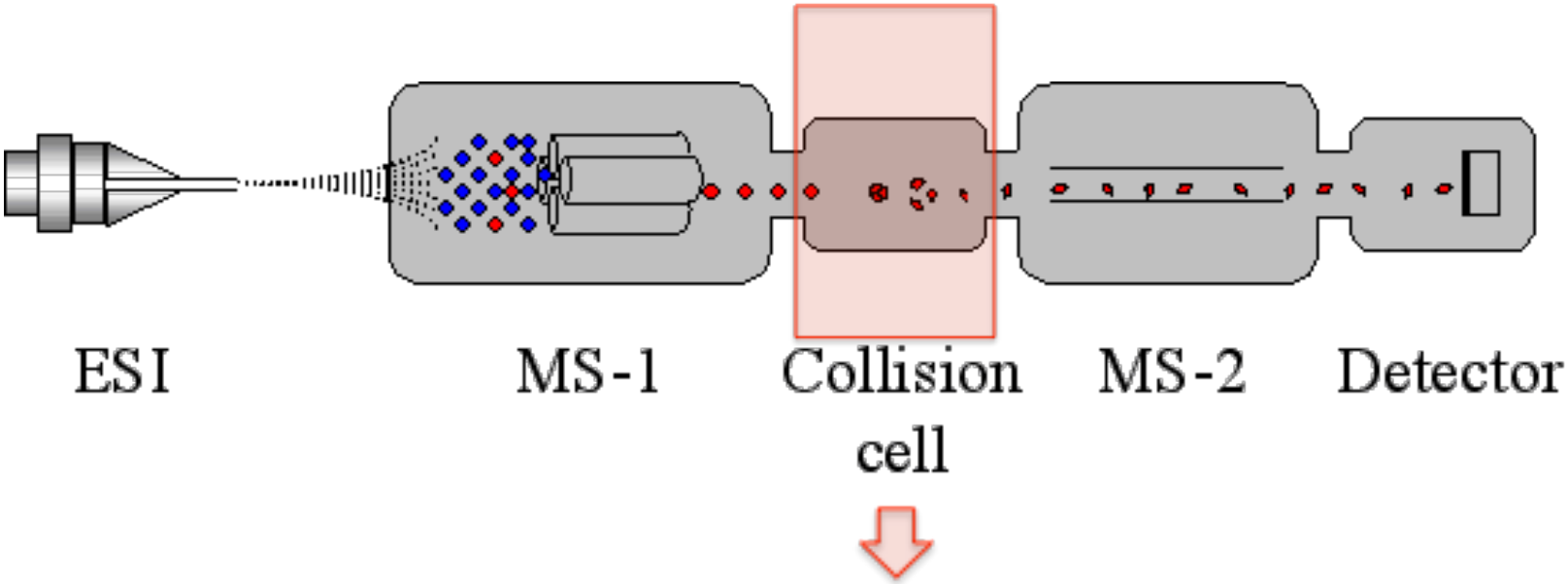
ESI-MS/MS

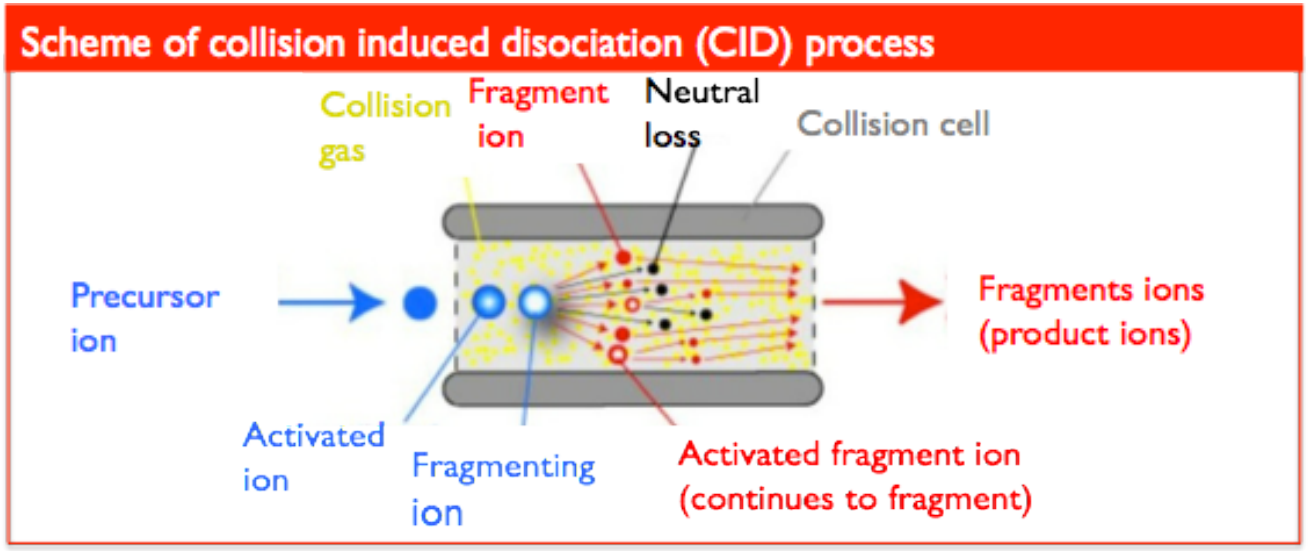
- ✓ Electrospray (ESI): soft ionization technique (John Fenn Nobel Prize 2002)
- ✓ Mass Spectrometry: from m/z exact knowledge of composition, but nothing about structure
- ✓ MS/MS: collision induced dissociation (CID) to have information on chemical reactivity of fragments
- ✓ Used initially in fundamental studies, now extended to analysis in many fields: doping detection, proteomics, metallomics ...
- ✓ ... but fundamental questions (especially for complex structures) are often still unanswered



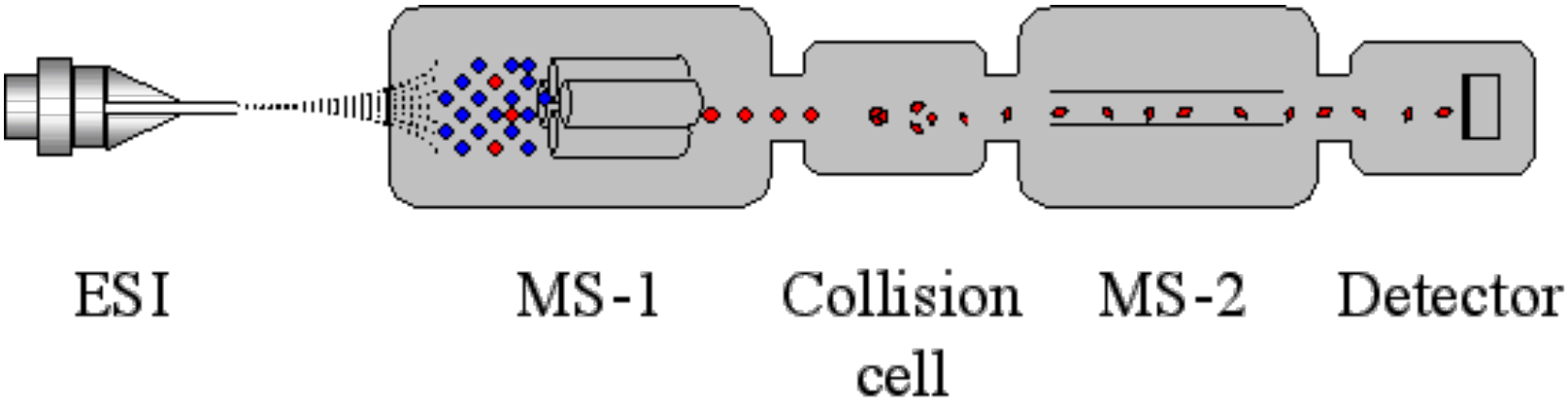


Collision Induced Dissociation



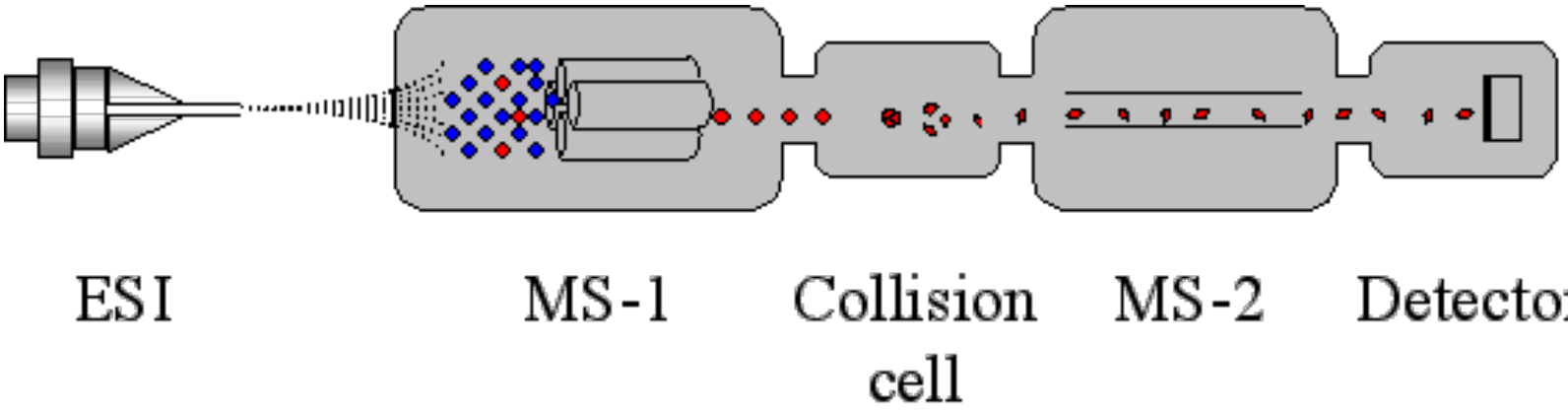


ESI-MS/MS



- ✓ what is the evaporation mechanism?
- ✓ what is (are) the structure(s) in gas phase?
- ✓ what are the CID structures and mechanisms?

ESI-MS/MS



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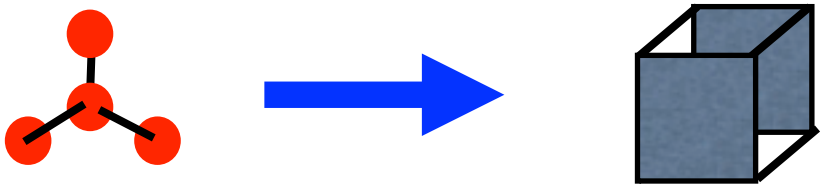
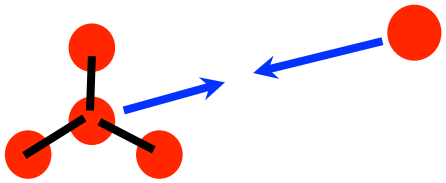
Collision-Induced Dissociation (CID)

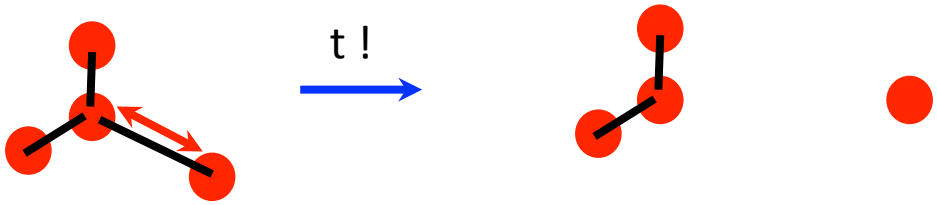
- ✓ Ions obtained by MS, we select a given m/z ratio, then we have a given species
- ✓ Ions can be accelerated by electric fields (low energy) and this translational energy can be tuned



- ✓ Ions enter in the collision room where they find an inert gas such that translational to rovibrational energy transfer is induced (single collision limit)



- ✓ Ions are vibrationally activated and they can dissociate



Molecular “Crash Test”

- ✓ Fragments are the fingerprint of molecules (analytical application)
- ✓ Information on weak/strong points of the molecules: information on chemical bonds and interactions (e.g. metal-molecule complexes)
- ✓ Appearance of fragments as a function of collision energy: information on mechanisms

Fundamental Questions

What are the mechanisms of these reactions?

RRKM, non-RRKM, rotational activation, IVR, shattering

Do dynamics follow the minimum energy path on potential energy surface?

is it possible to have different dissociation pathways and different activations of them?

Can we obtain MS/MS spectra only from calculations?

Fragmentation products independently on experiments

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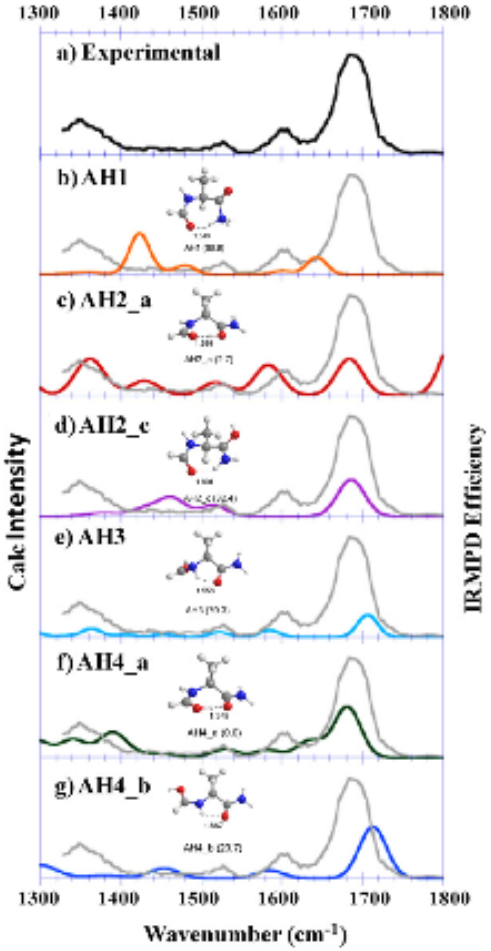
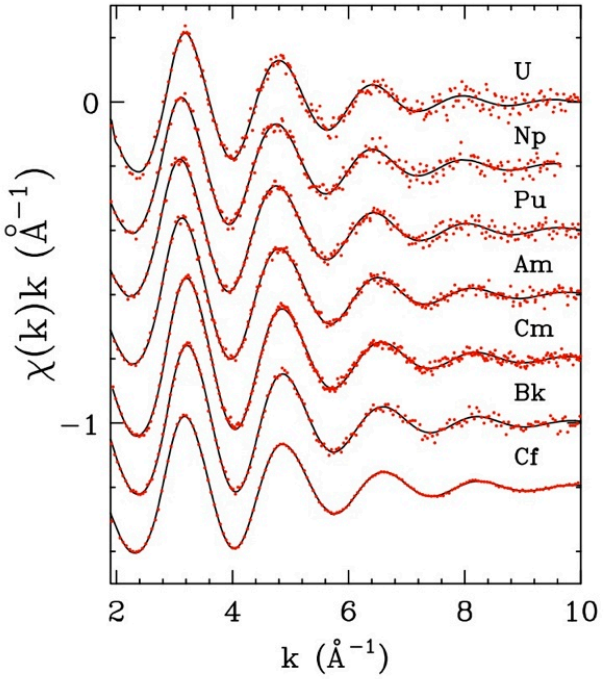
Fragmentation products independently on experiments

Computing spectra

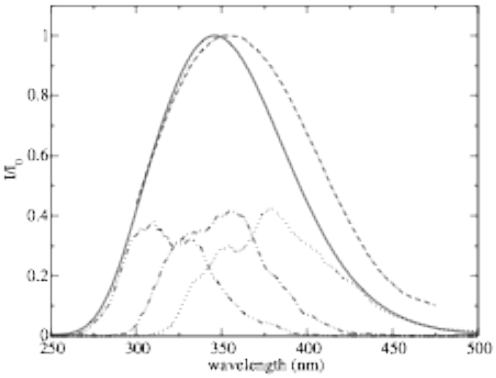
vibrational



EXAFS

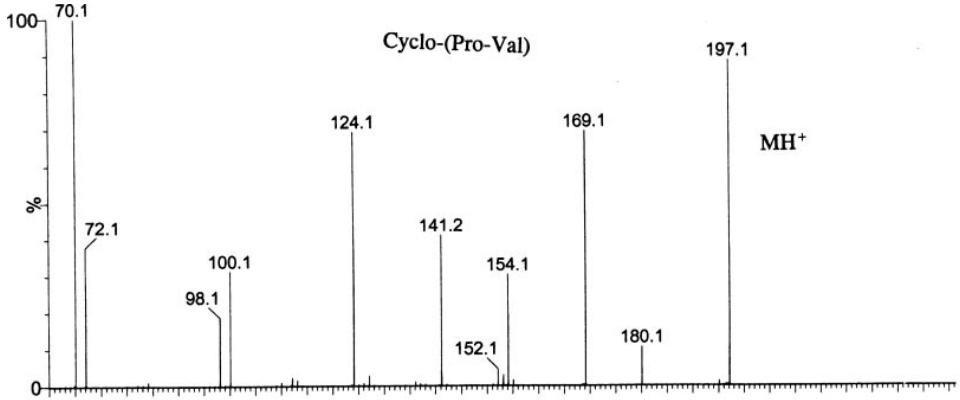


UV-VIS

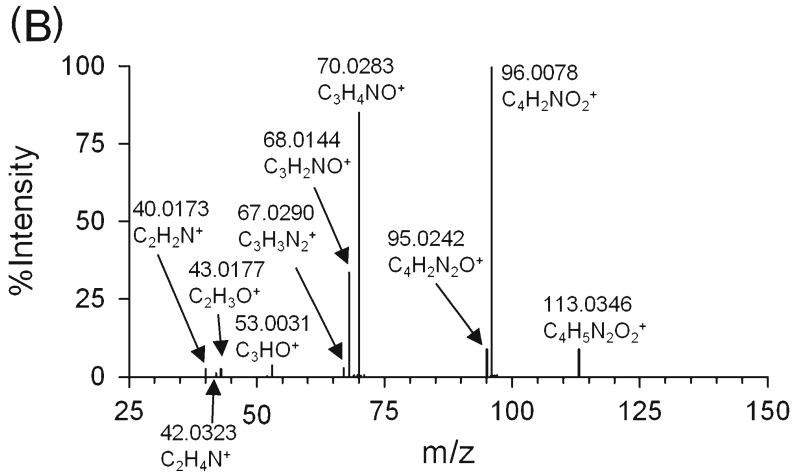


IR, Raman, NMR, EPR ... calculations are able to provide a theoretical spectrum

and for MS/MS?



Harrison, Mass Spect. Rev., 2009, 28, 640– 654



Beach and Gabryelski. J.Am.Soc.Mass Spectrom 2012, 23:858

Quantum chemistry calculations are often used to understand peaks observed (PES analysis + RRKM)

But how obtain them before/without experiments?

Chemical Dynamics Simulations

$$F(X) = -\nabla U(X) = M\dot{V}(t)$$

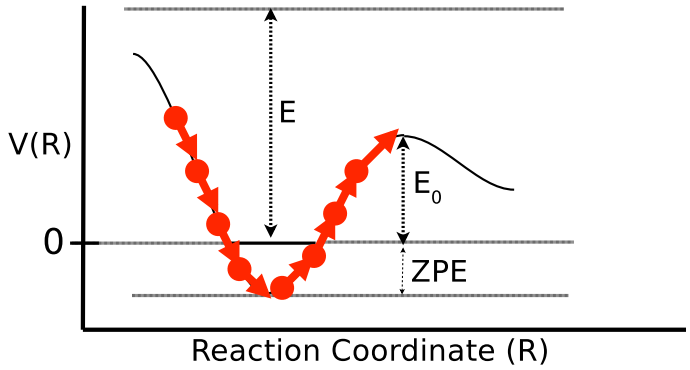
Born-Oppenheimer dynamics : each step solving TISE $\mathcal{H}\Psi = E\Psi$

or more in general getting U as a function of the atomic position.

Velocity Verlet to integrate numerically the equations of motion

$$\mathbf{r}(t+\delta t) = \mathbf{r}(t) + \delta t\mathbf{v}(t) + \frac{1}{2}\delta t^2\mathbf{a}(t)$$

$$\mathbf{v}(t+\delta t) = \mathbf{v}(t) + \frac{1}{2}\delta t[\mathbf{a}(t) + \mathbf{a}(t+\delta t)]$$



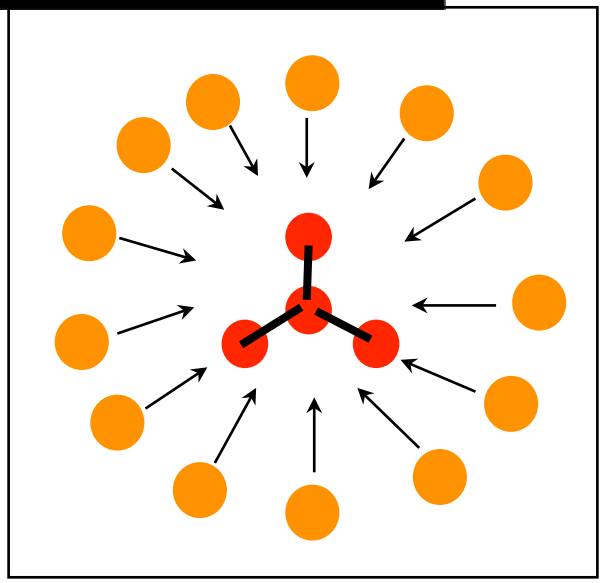
reactive trajectory

Simulation of CID process: fast time scale

Chemical dynamics simulations

An ensemble of trajectories is needed to correctly describe the phenomenon

Ion-projectile orientation is not unique, we need statistics



Initial conditions

Normal modes Boltzmann sampling for vibrational degrees of freedom + 3/2 RT on rotational modes.
Ion-projectile relative energy

Code

VENUS for initial conditions and MD, coupled with Gaussian and Mopac
Hase et al. QCPE 1996, 16, 671

Interaction potential

$$V = V_{ion} + V_{Ar-ion}$$

DFT, MP2, AM1, PM3

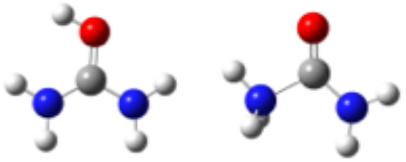
$$V_{Ar-ion} = \sum_i A e^{-br_i} + \frac{c}{r_i^9}$$

Simulation details

200-300 trajectories (DFT or MP2)
5000-10000 trajectories (AM1 or PM3)
Tuning collision energy

Systems

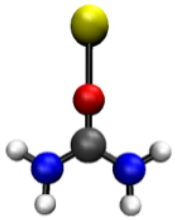
$HUrea^+$



RS, J.-.YSalpin, M.-P.Gaigeot, W.L.Hase and K.Song, J.Phys.Chem.A, 113, 13853 (2009)

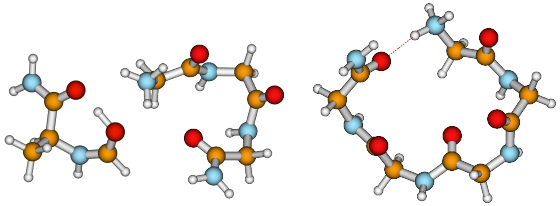
Y.Jeanvoine, M.-P.Gaigeot, W.L.Hase, K.Song and RS, Int.J.Mass Spectrom, 308, 289-298 (2011)

Doubly charged: Ca^{2+}-Urea, Ca^{2+}-formamide; Sr^{2+}-formamide



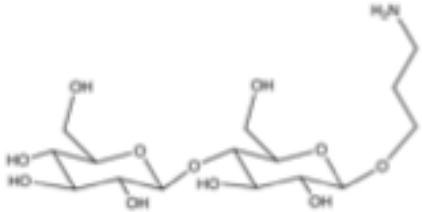
R.Spezia, A.Cimas, M.-P.Gaigeot, J.-Y.Salpin, K.Song and W.L.Hase. Phys. Chem. Chem. Phys. 14, 11724 – 11736 (2012).
A.Martin-Somer, M.-P.Gaigeot, M.Yanez and R.Spezia. Phys. Chem. Chem. Phys. 16, 14813-14825 (2014).

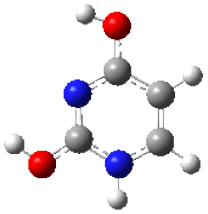
$(peptidesH)^+$



D.Ortiz, P.Martin-Gago, A.Riera, K.Song, J.-Y.Salpin and RS. Int. J. Mass Spectrom. 335, 33-44 (2013).

Carbohydrates, uracil ...

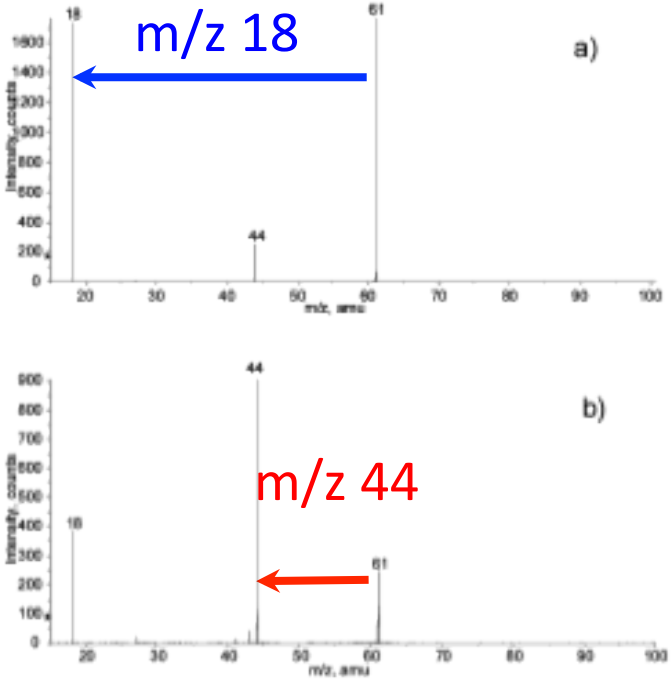




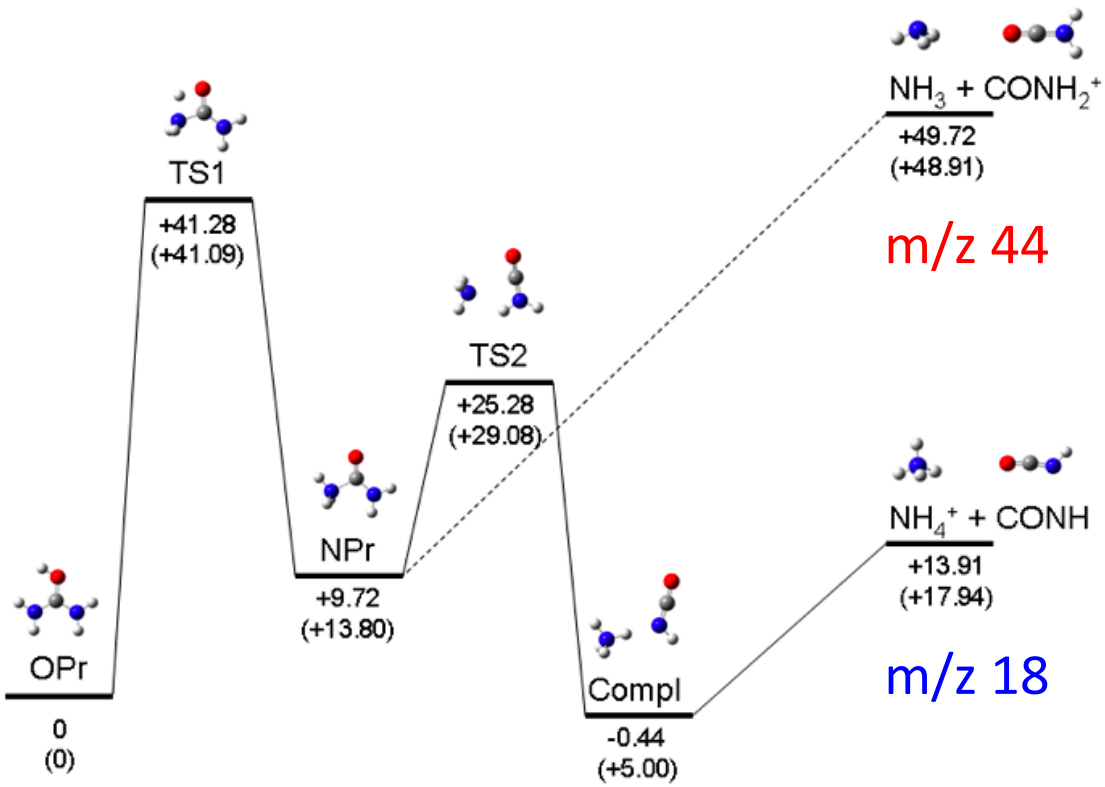
D.Ortiz, J.-Y.Salpin, K.Song and R.Spezia. Int. J. Mass Spectrom. 358, 25-35 (2014).

UreaH$^+$ PES

$CONH + NH_4^+$



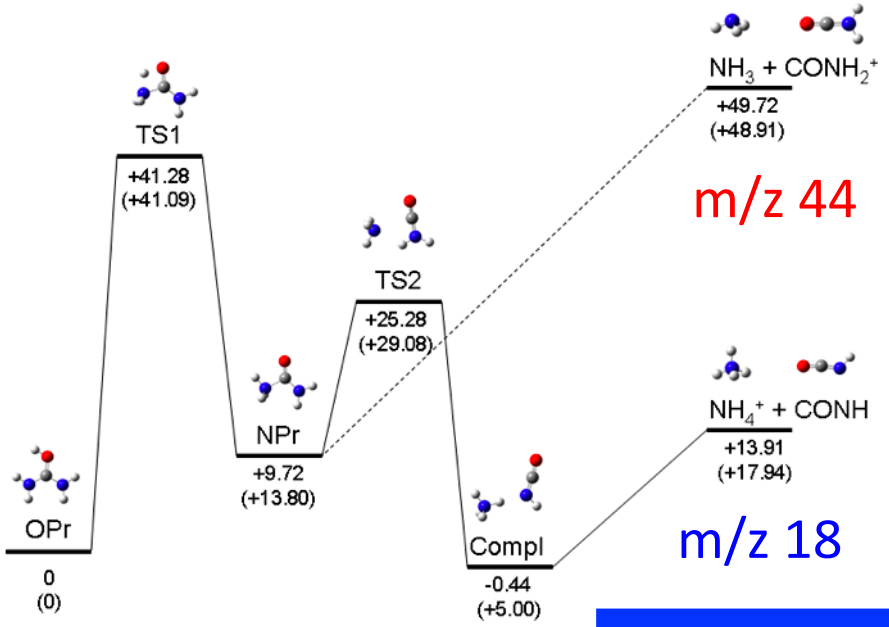
$CONH_2^+ + NH_3$



How can we obtain both low and high energy structures?

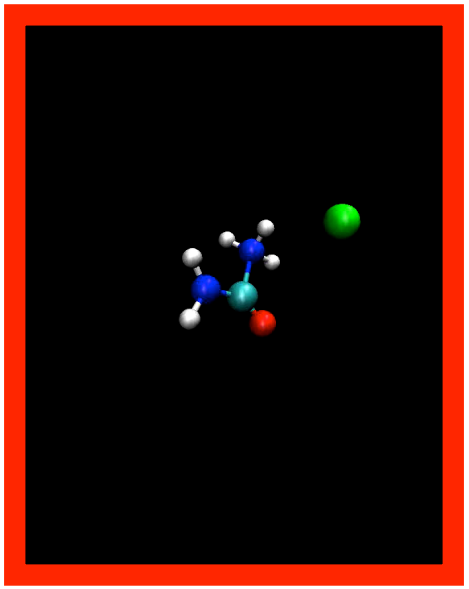
calculated at MP2/6-31g* and MP2/aug-cc-pVTZ level, energies in kcal/mol

UreaH$^+$ PES

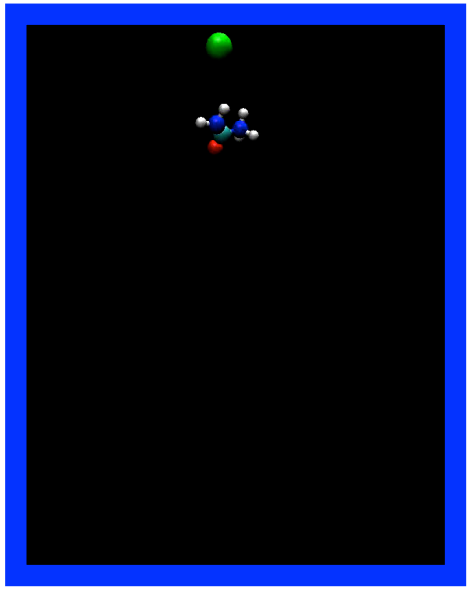


m/z 44

m/z 18



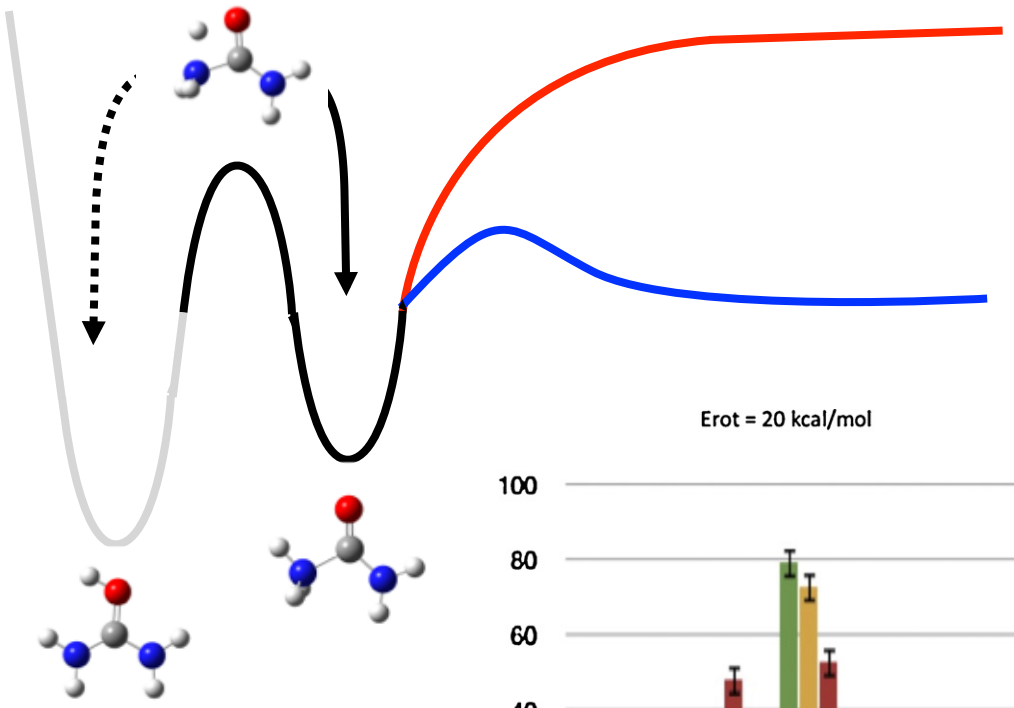
shattering



energy flow

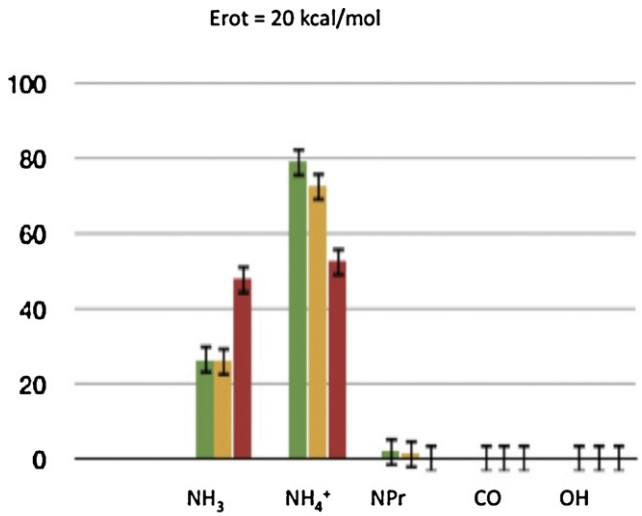
MP2 chemical dynamics

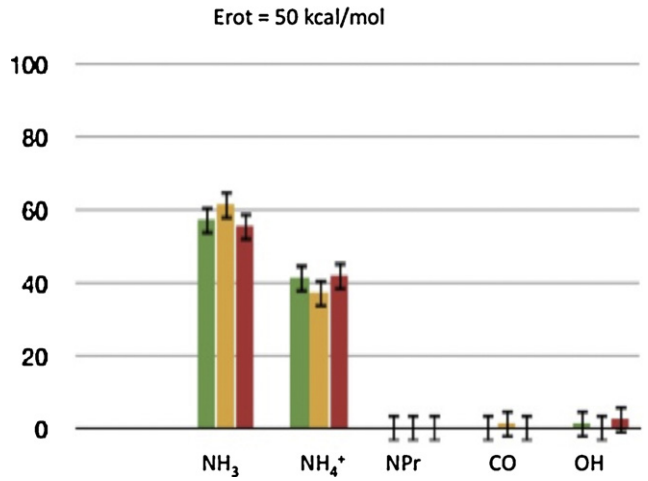
Dynamics from activated TS



$NH_2CO^+ + NH_3$

$CONH + NH_4^+$

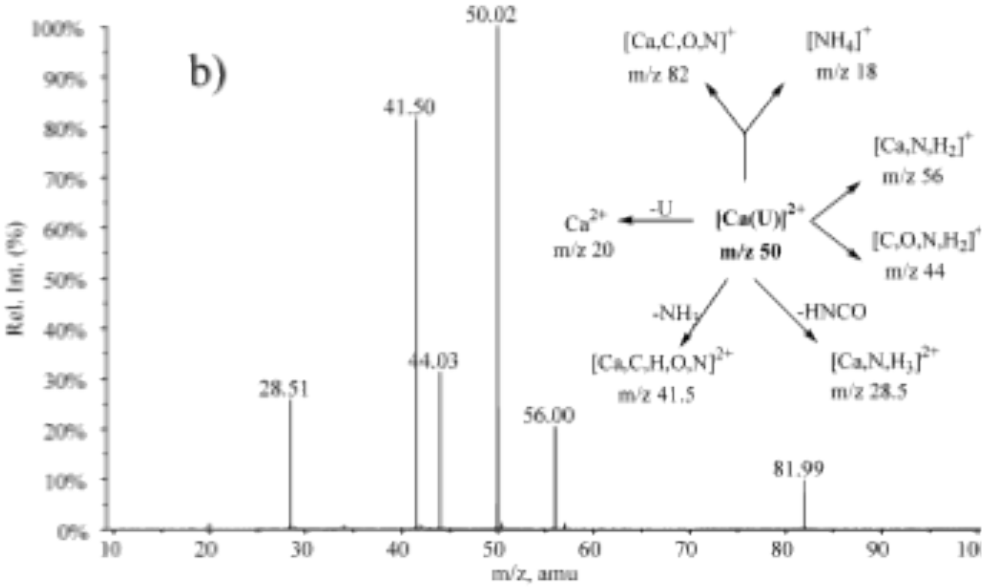




Rotational activation guides the fragmentation pathway towards high energy products

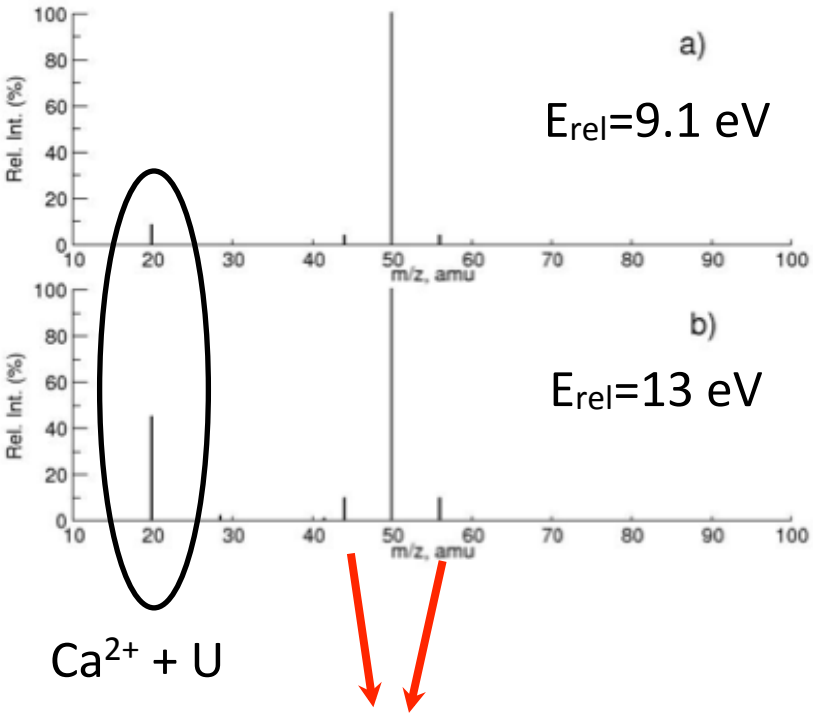
Ca^{2+}/Urea

Experiments



Corral et al. *J. Phys. Chem. A* **2004,** *108,* 10080-10088

Theoretical MS/MS

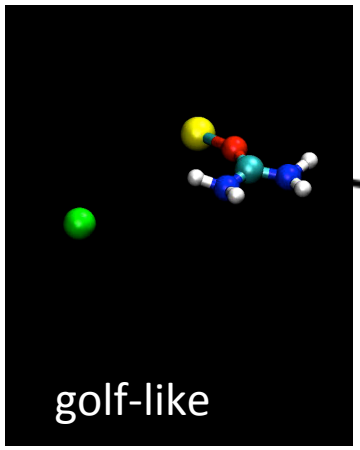


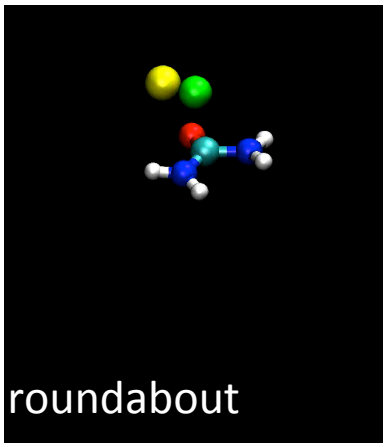
MP2 chemical dynamics

Fragmentation mechanisms

Neutral loss

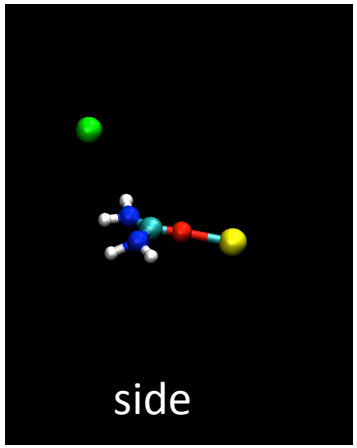
Coulomb explosion

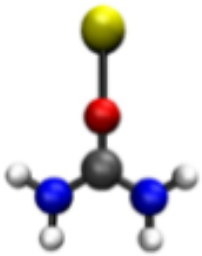


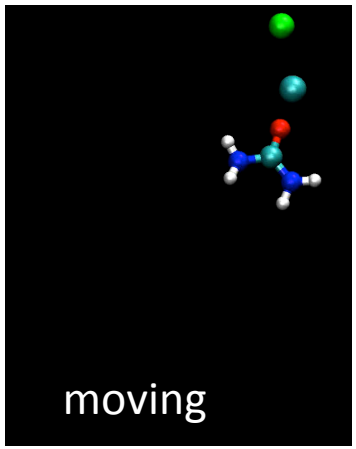


~300 fs

~1000 fs

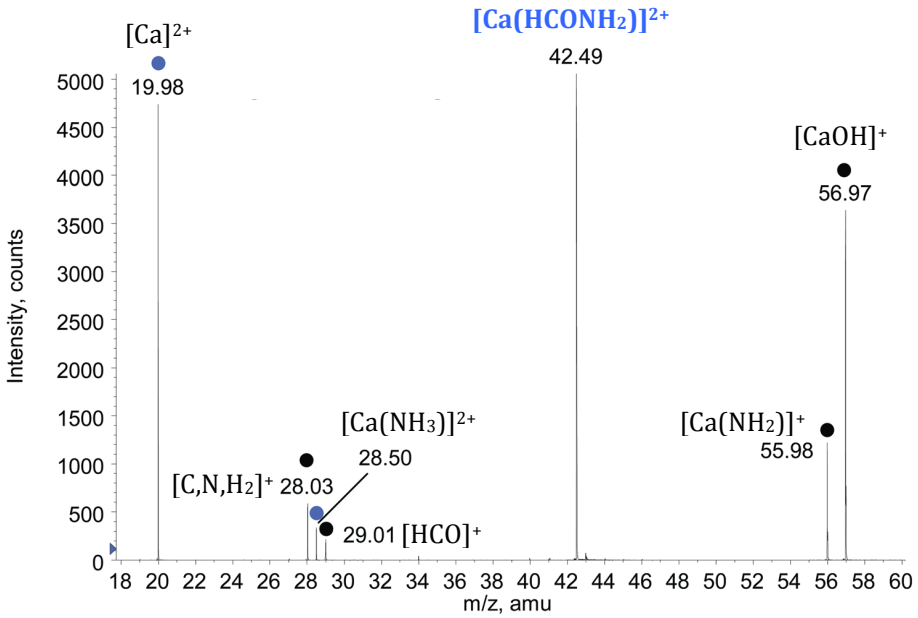




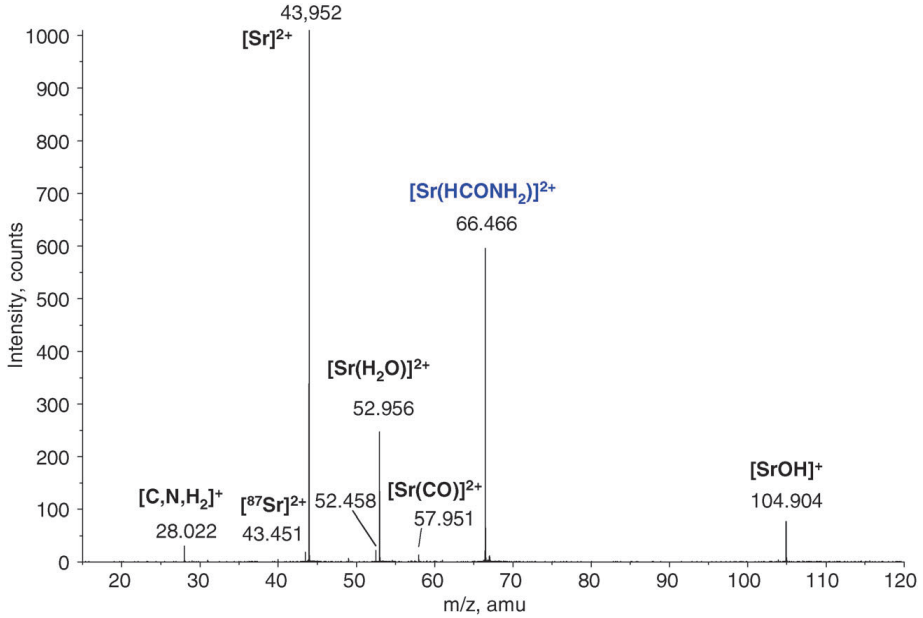


Ca^{2+} and Sr^{2+} with formamide

$[Ca(formamide)]^{2+}$

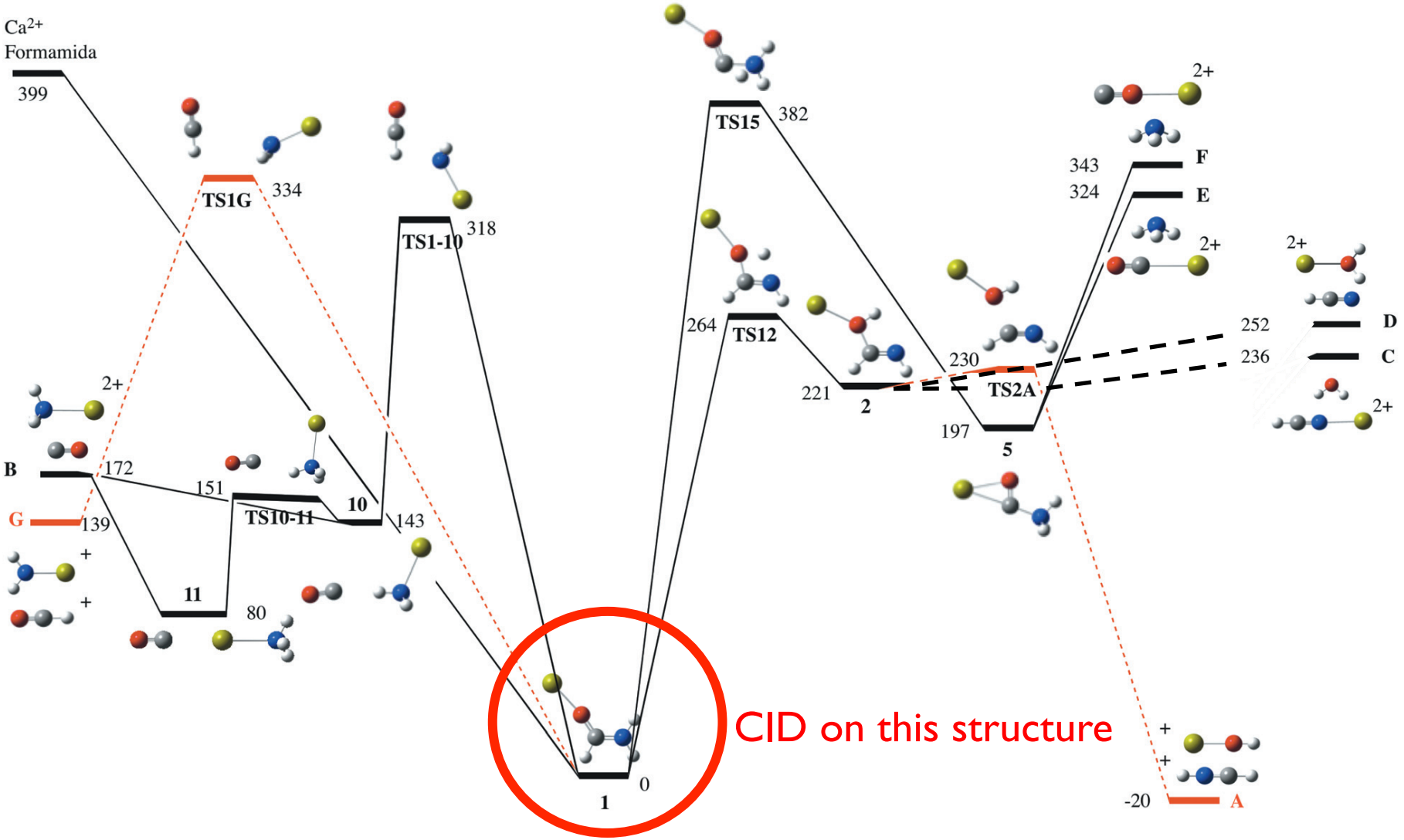


$[Sr(formamide)]^{2+}$



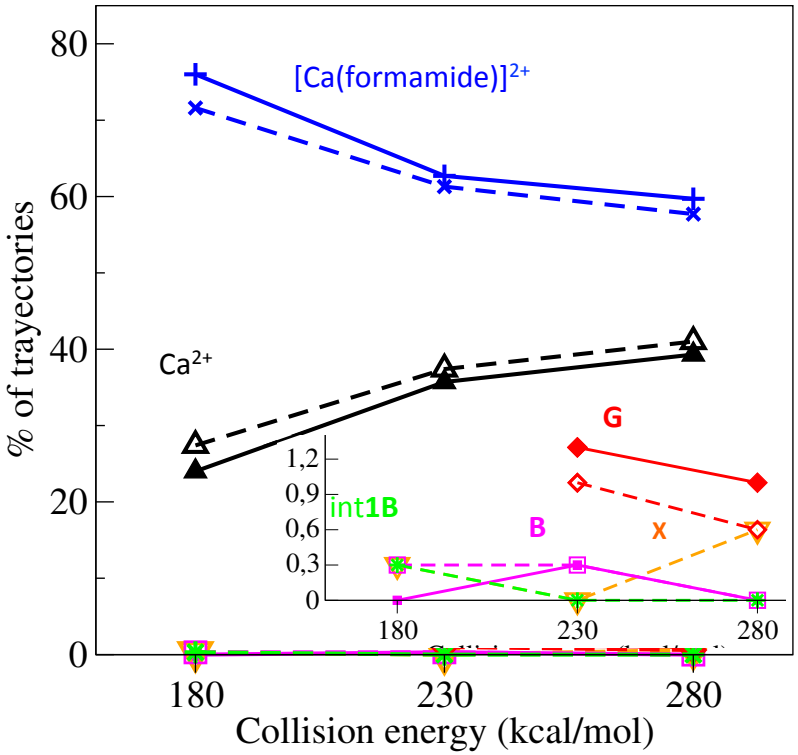
Eizaguirre et al. *Org.Biomol.Chem.*,**2012**, 10,7552

Potential Energy Surface



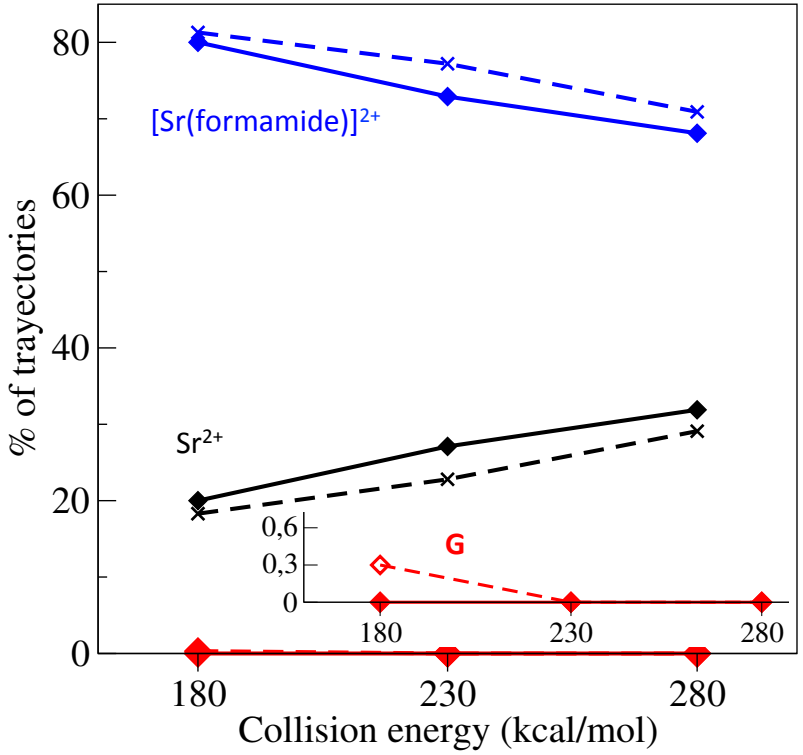
Eizaguirre et al. *Org.Biomol.Chem.*,**2012**, 10,7552

Reaction products



G96LYP/6-31G(d) ——

BLYP/6-31G(d) - - - -



G96LYP/6-31G(d) ——

G96LYP/6-31+G(d,p) - - - -

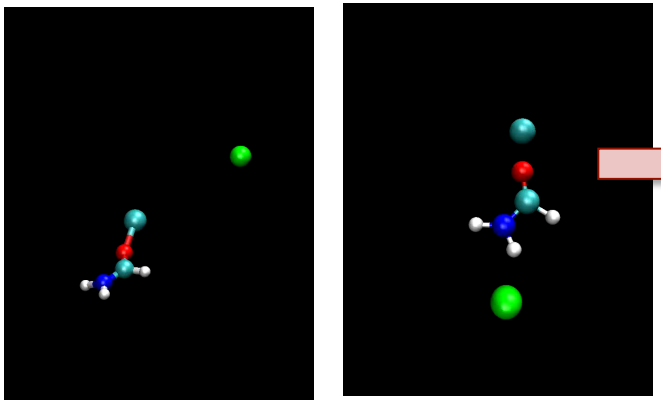
Martin-Somer, Gaigeot, Yanez, Spezia. J. Phys. Chem. A in press

Bridging time gap

Combining molecular dynamics
with
statistical theory

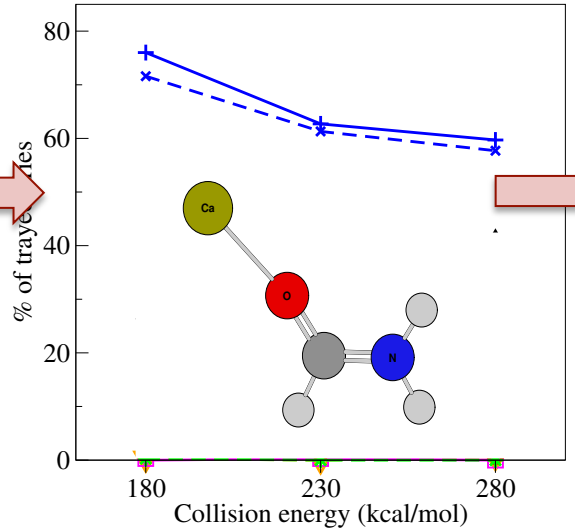
Dynamics & RRKM

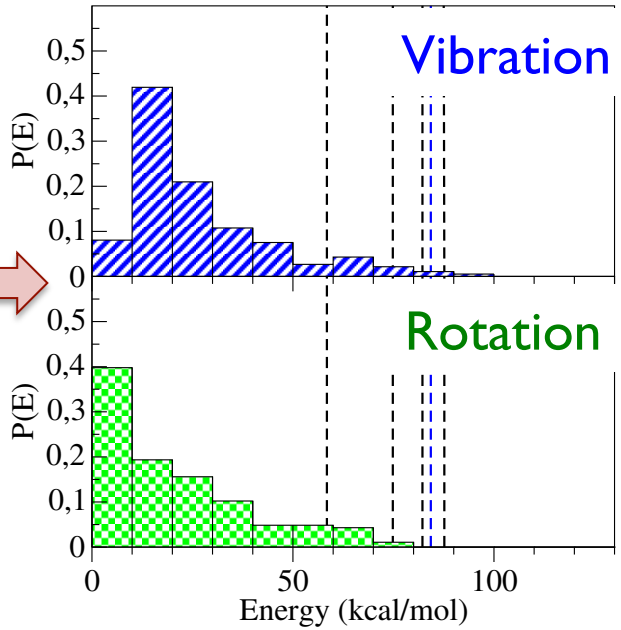
Direct Dynamics Simulations



G96LYP/6-31G(d)

Non-reactives





Energy distribution

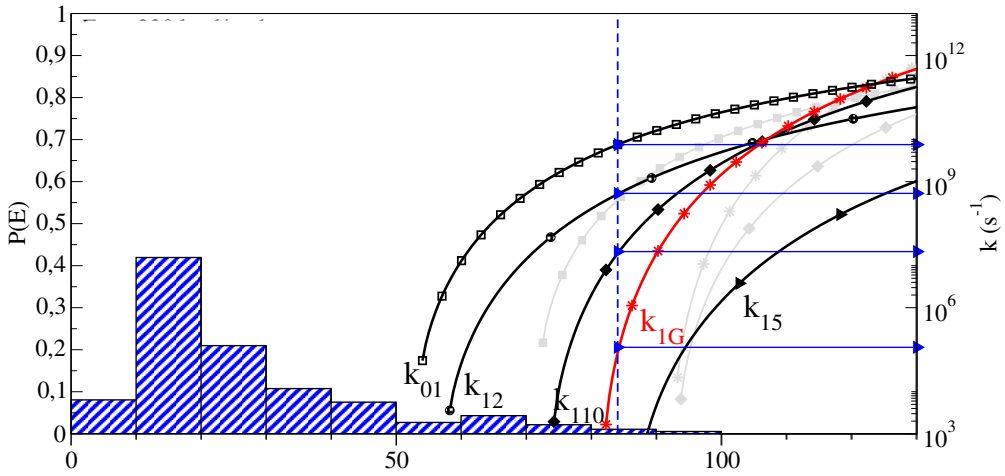
RRKM analysis

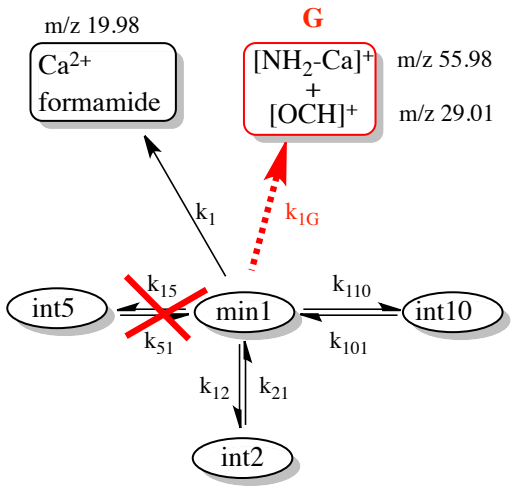
Reaction rate constant

Martin-Somer, Gaigeot, Yanez, Spezia. Phys. Chem. Chem. Phys. 16, 14813-14825 (2014).

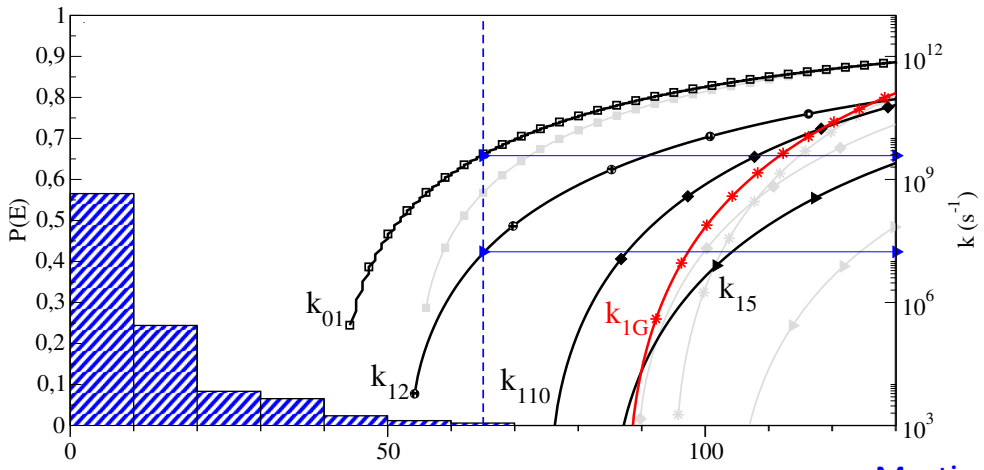
Statistical limit reactivity

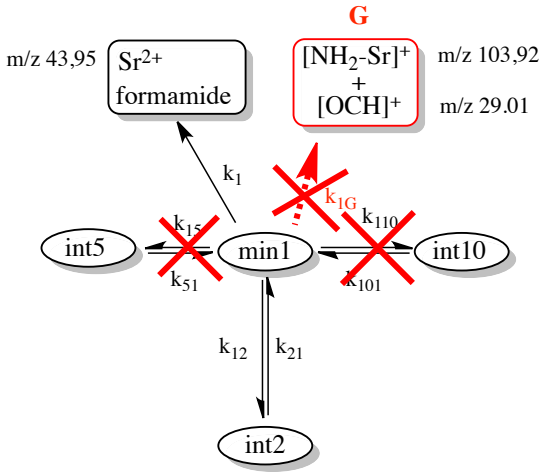
$Ca(formamide)^{2+}$





$Sr(formamide)^{2+}$

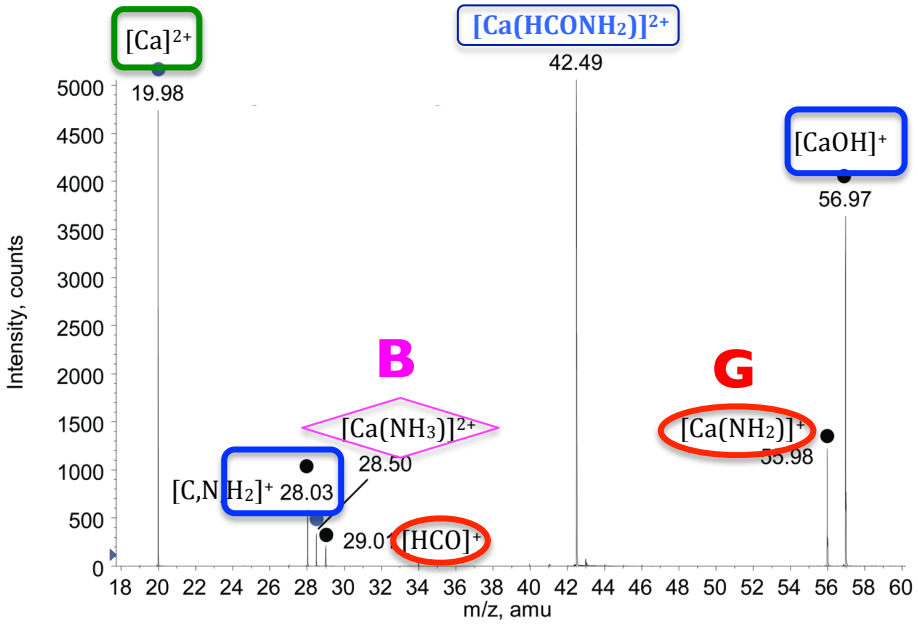




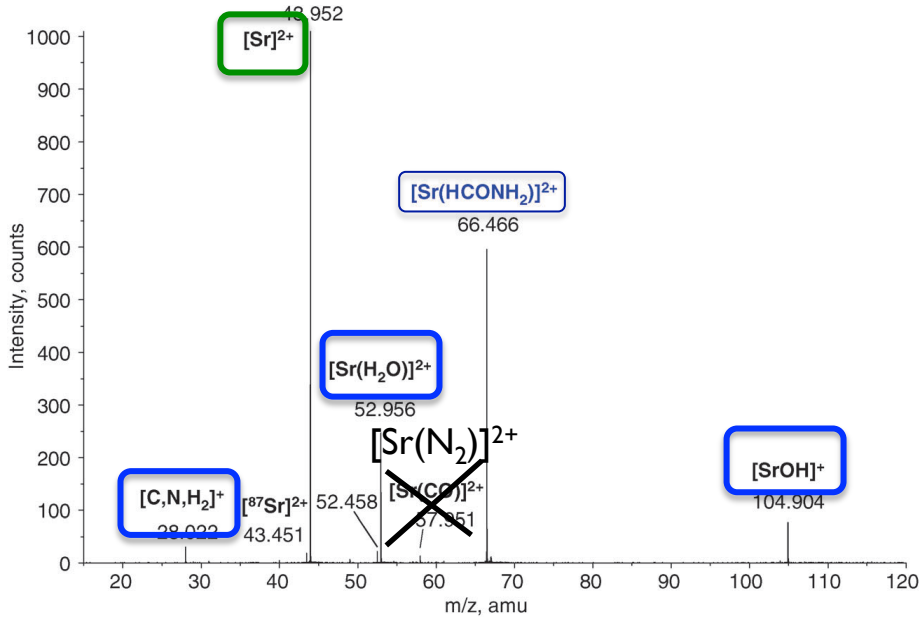
Martin-Somer, Gaigeot, Yanez, Spezia. J. Phys. Chem. A in press

CID experiments and simulations

[Ca(formamide)]$^{2+}$



[Sr(formamide)]$^{2+}$



from direct dynamics

from integrated RRKM

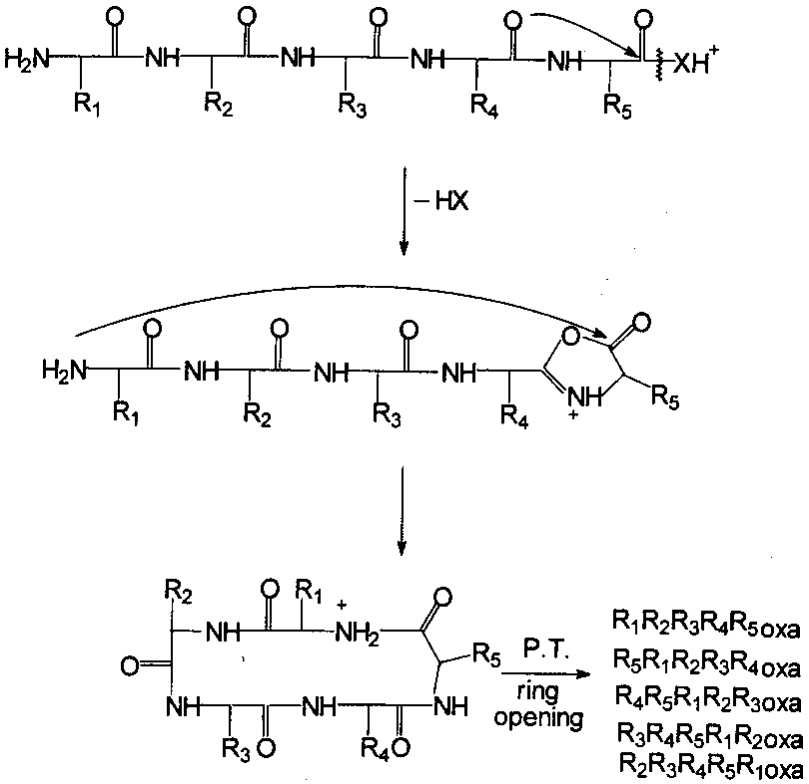
from direct dynamics & RRKM

from integrated RRKM

from integrated RRKM

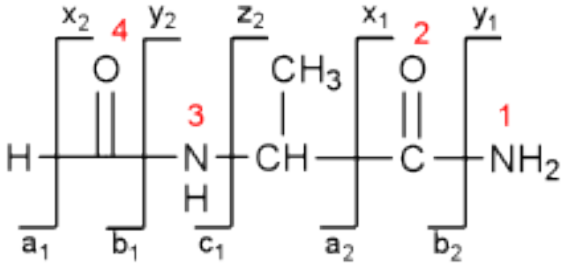
CID of peptides

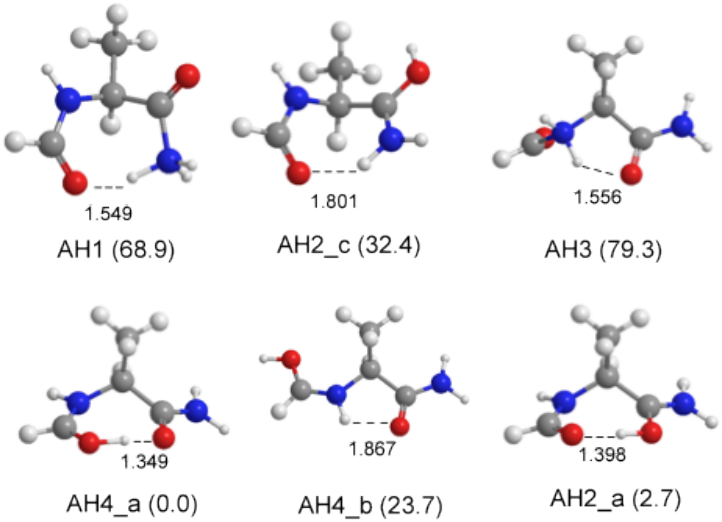
- ✓ Semi-empirical methods (PM3, AM1) for intramolecular potential
- ✓ Application to puzzling MS/MS experiments
- ✓ Insights into fragmentation mechanisms (e.g. cyclization)



Harrison, Mass Spect. Rev., 2009, 28, 640– 654

Peptide model

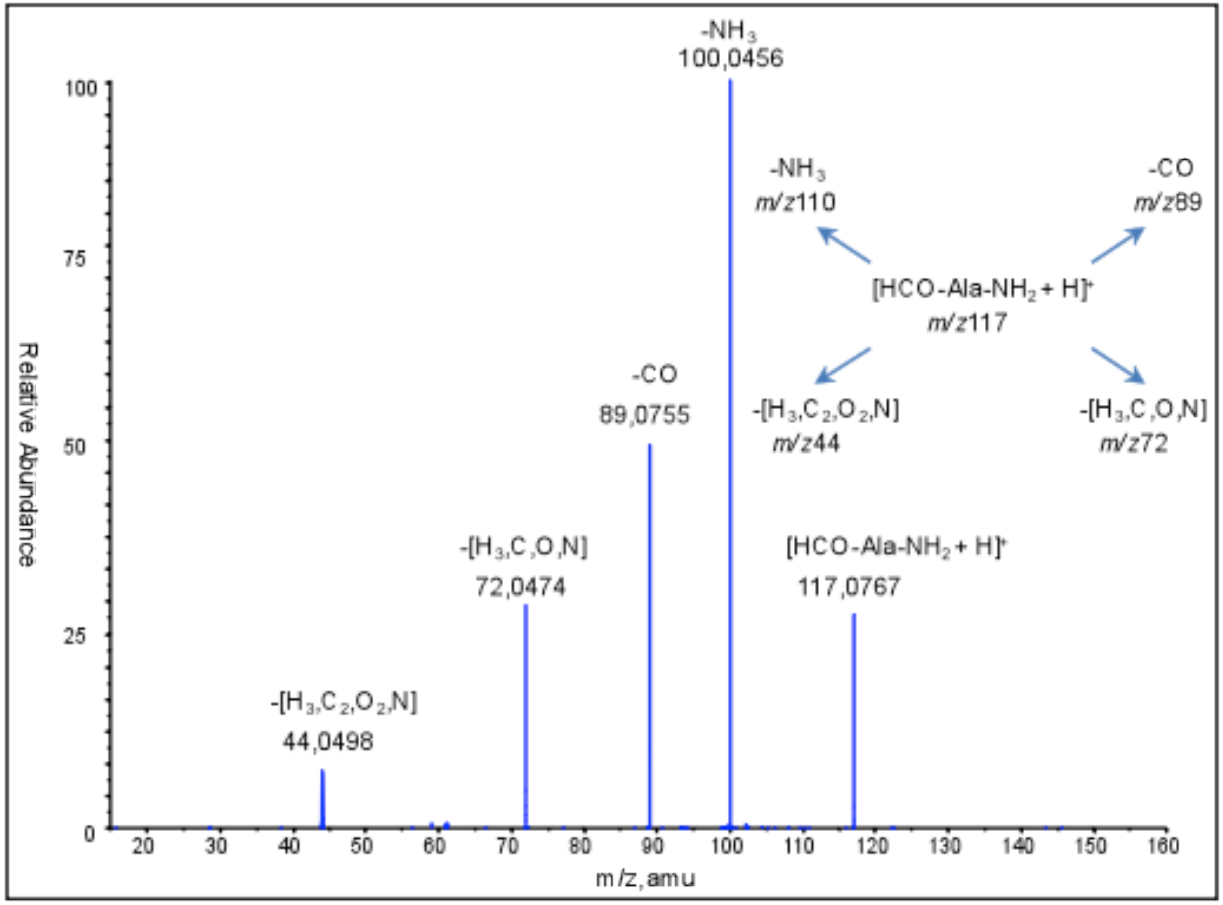




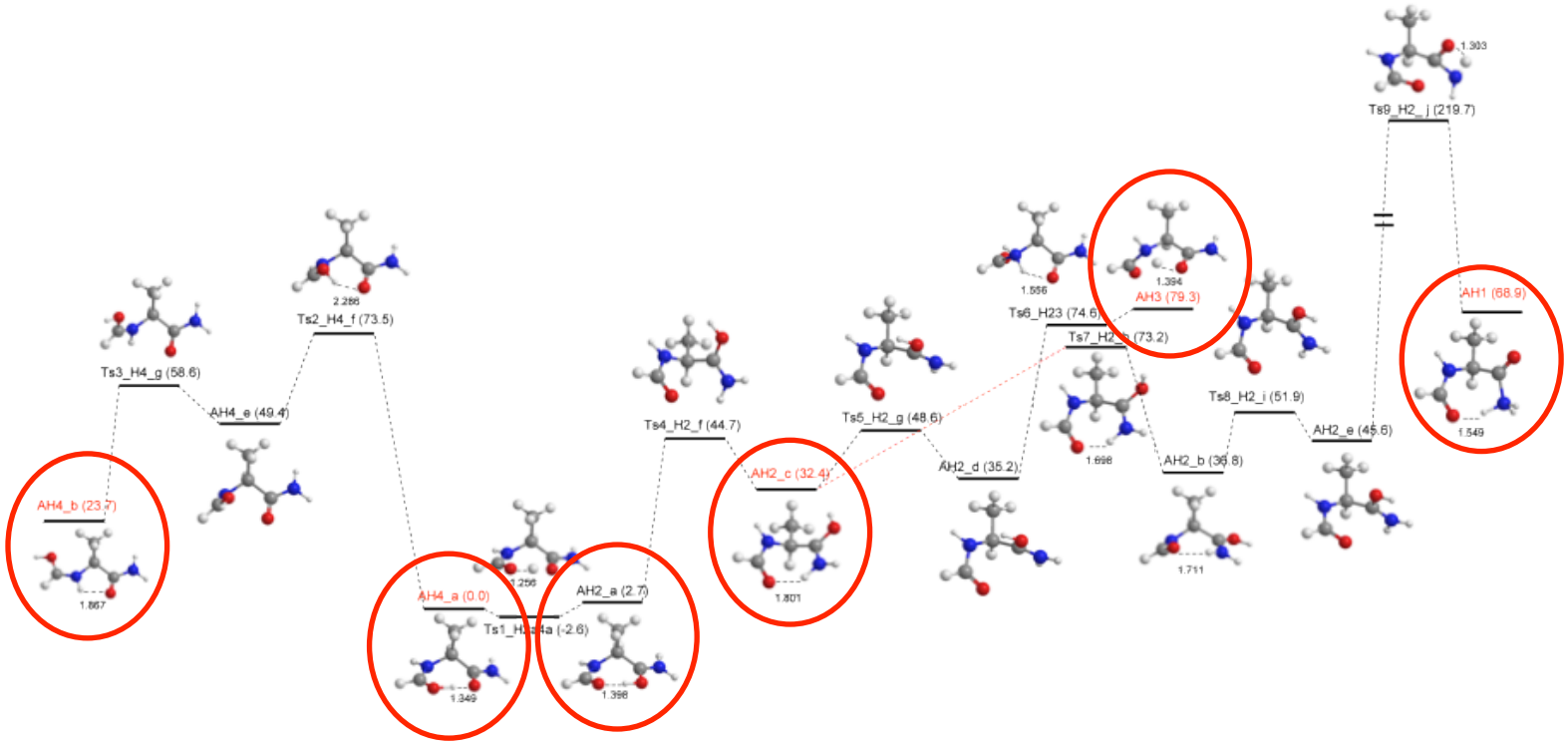
Direct dynamics starting from each isomer and then re-weighted following Boltzmann distribution

~5000 trajectory for each initial structure
PM3/MM up to 10 ps

Experimental MS/MS



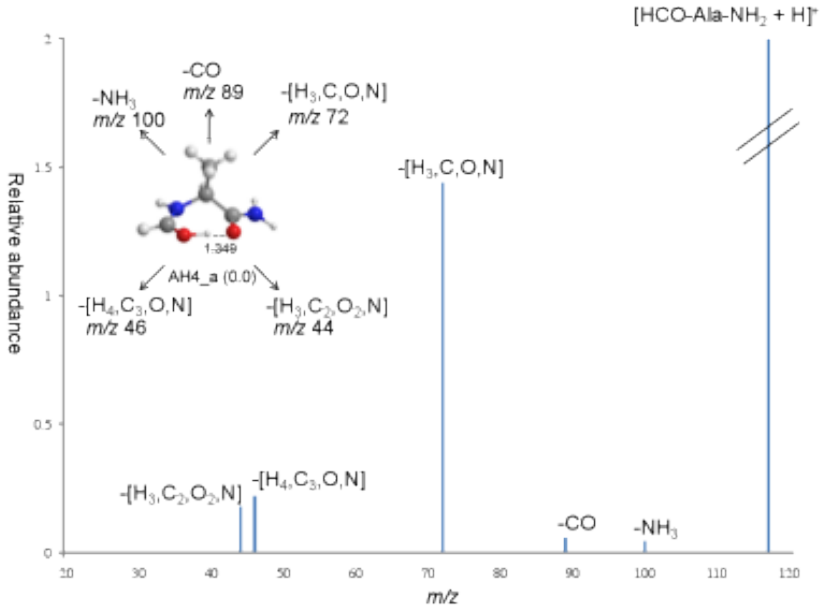
Partial PES

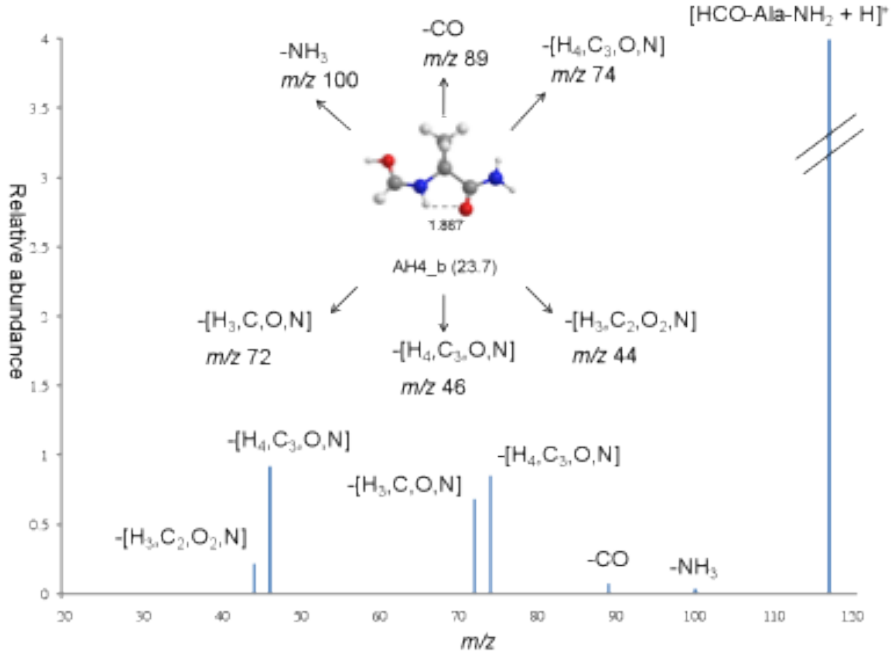


Different minima where the proton is on different basic sites (mobile proton model)

Theoretical CID

Reaction probability depends mainly on protonation site (isomer) and not on structure (conformer)



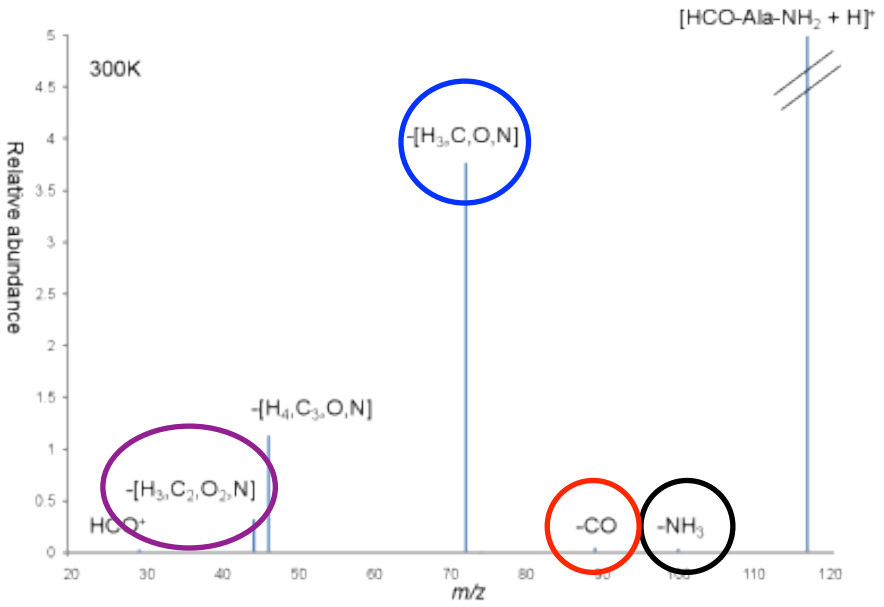


CID spectra of same isomers are quantitatively different but not qualitatively

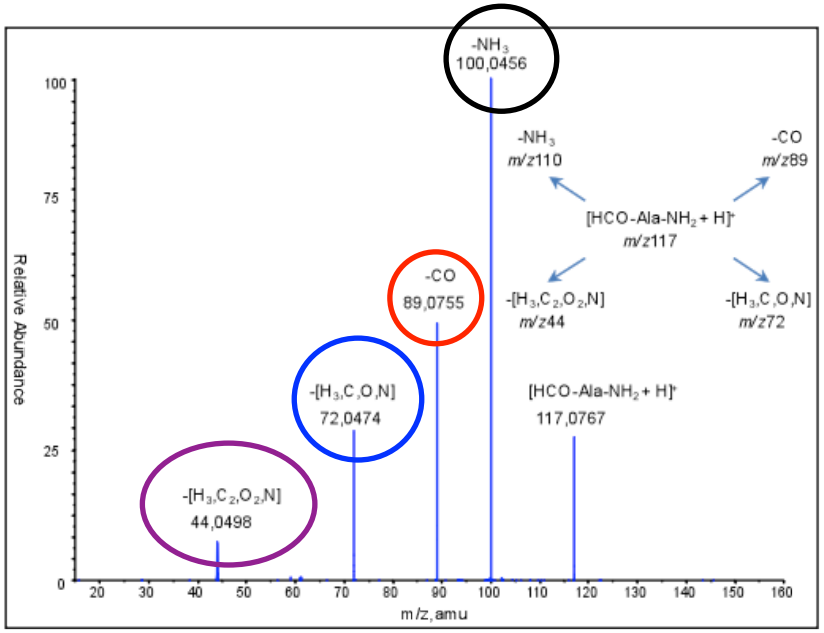
Each isomer is mainly responsible for the appearence of a peak

PM3 chemical dynamics

Theoretical vs Experimental CID



Boltzmann weighted



Experimental

Intensities can depend on the limited simulation time-length

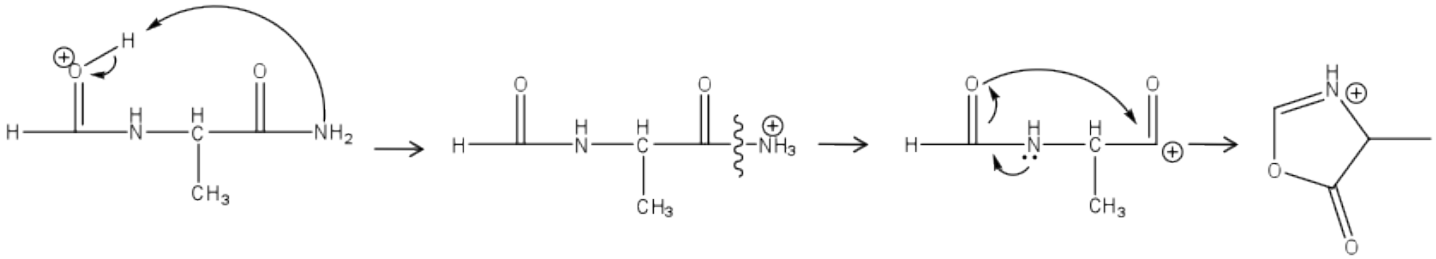
- e.g. NH_3 or CO loss

Unexpected peaks:

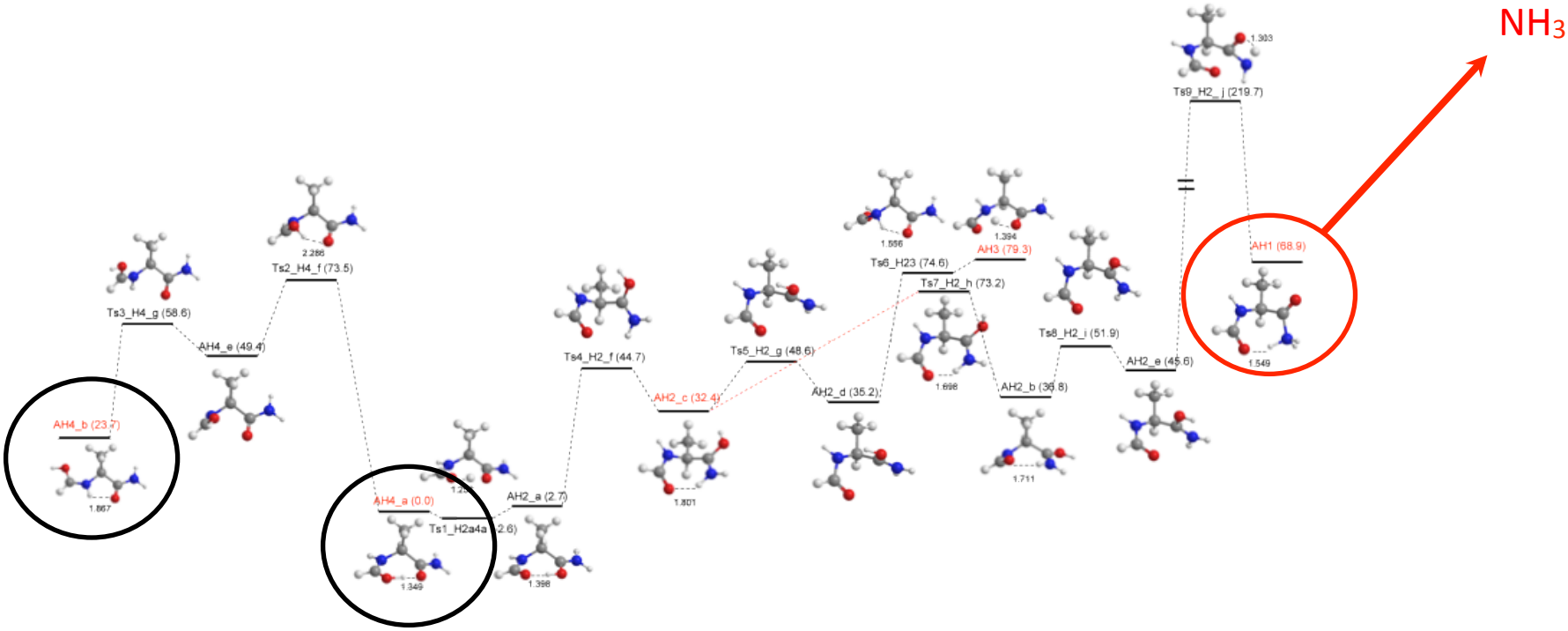
(i) PM3? DFT simulations on most stable isomer confirm them

(ii) They can probably further fragmentate

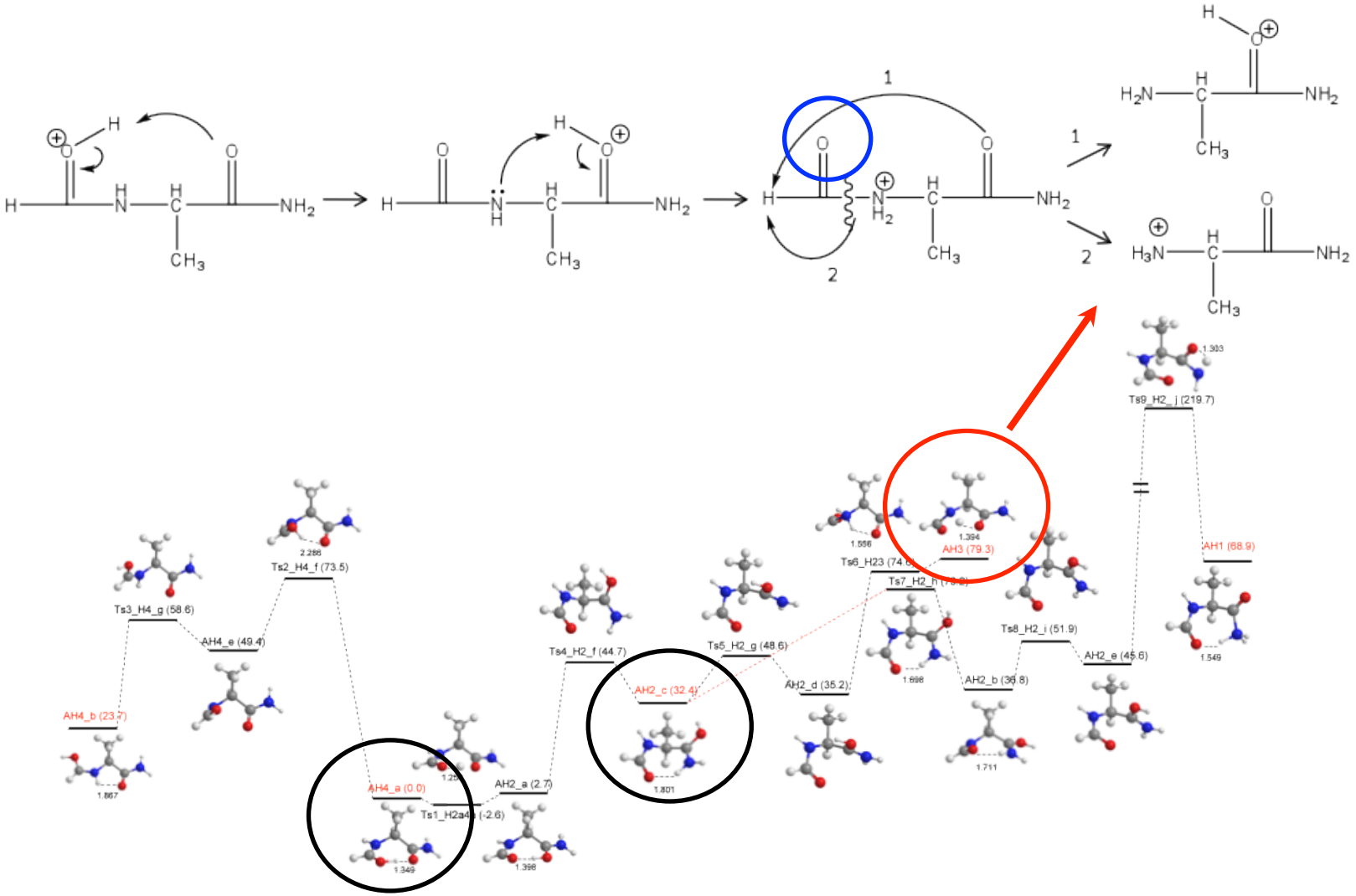
NH_3 loss pathway



oxazolone ring!

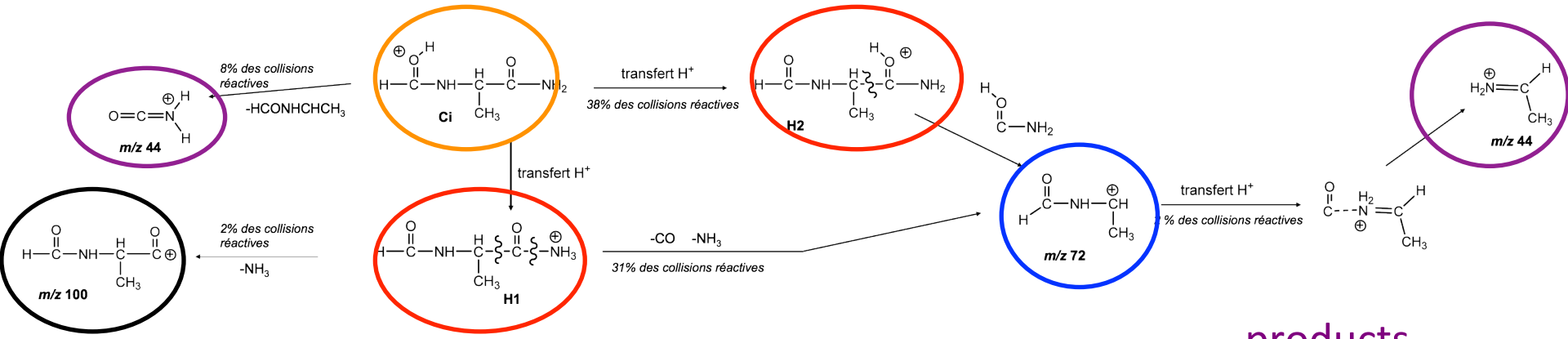


CO loss pathway

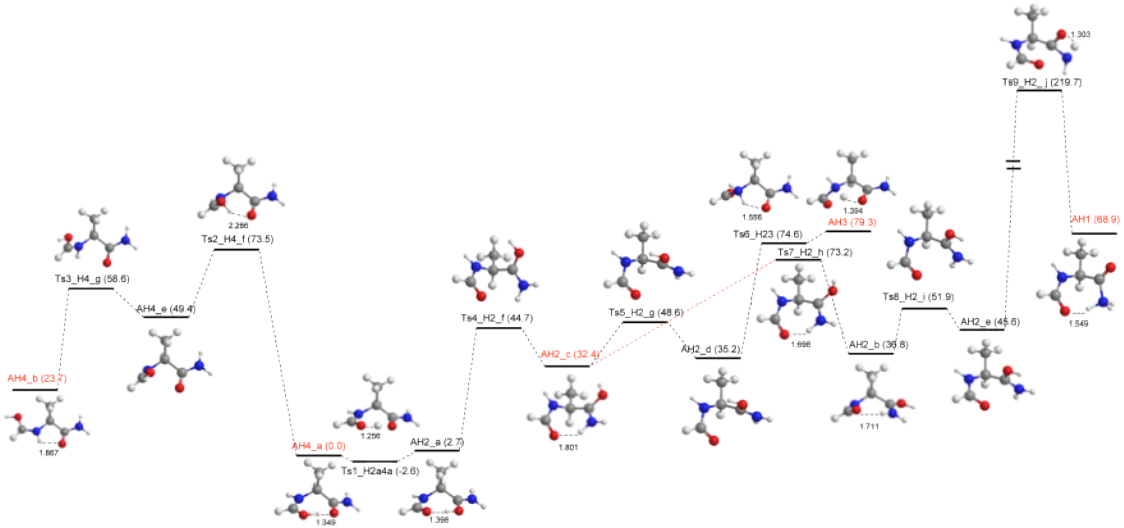


Isotope labelling experiments confirm this picture ...

Fragmentation Pathways Overview



Most stable isomer → other isomers → products products products



D.Ortiz, P.Martin-Gago, A.Riera, K.Song, J.-Y.Salpin and R.Spezia.. Int. J. Mass Spectrom. 335, 33-44 (2013).

TO b OR NOT TO b: THE ONGOING SAGA OF PEPTIDE b IONS

Alex G. Harrison*
Department of Chemistry, University of Toronto, Toronto, Canada

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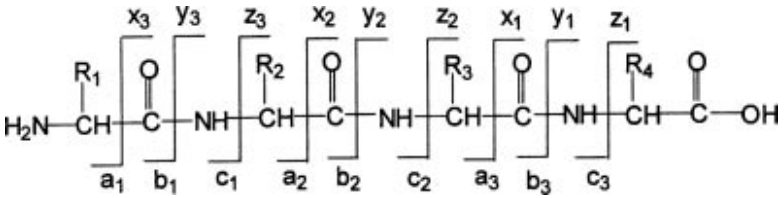
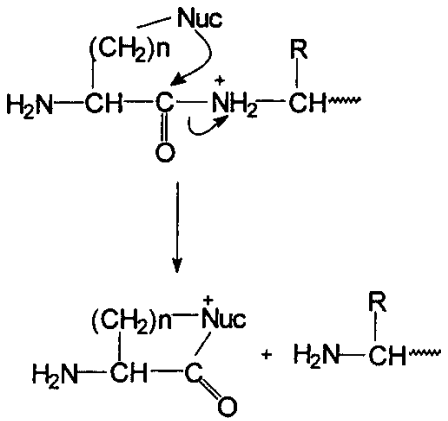
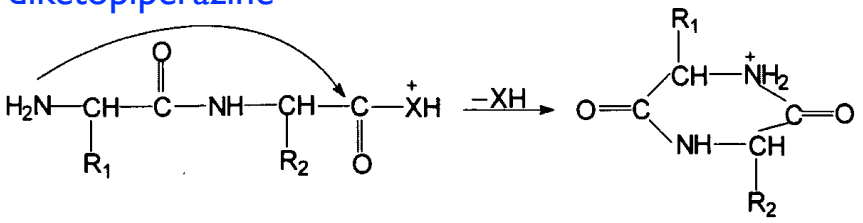
Mass Spectrometry Reviews, **2009**, *28*, 640–654



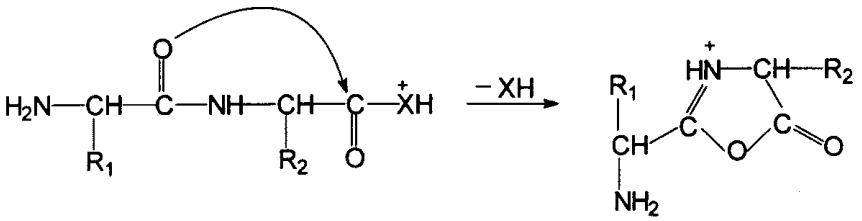


breaking at b/y bond and then a nucleophilic attack

diketopiperazine



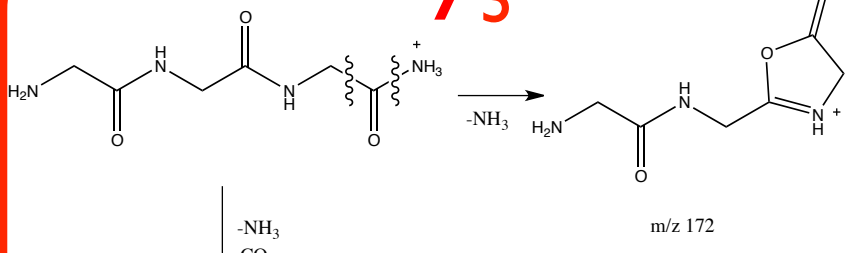
oxazolone

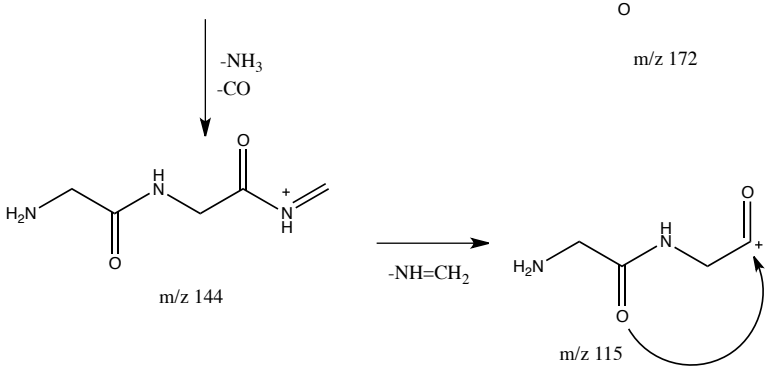


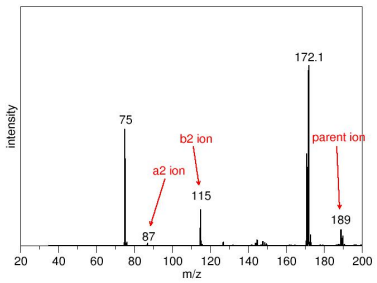
... and ...

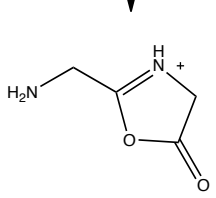
CID of peptides

Gly_3H^+

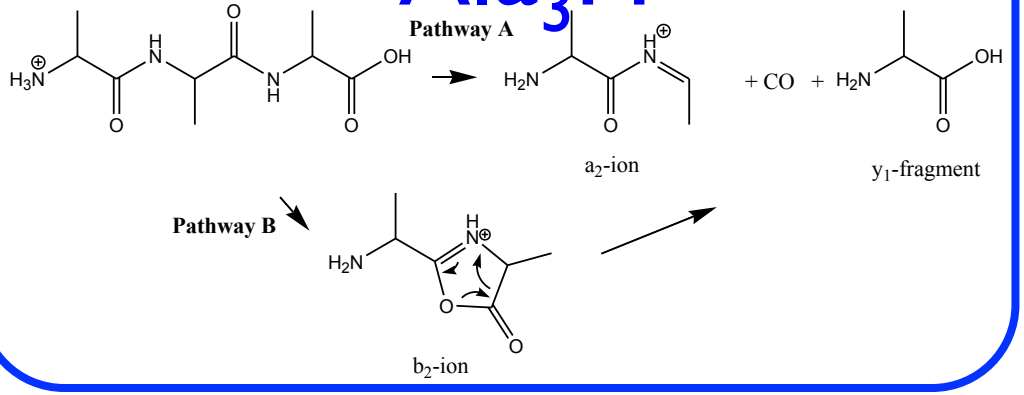




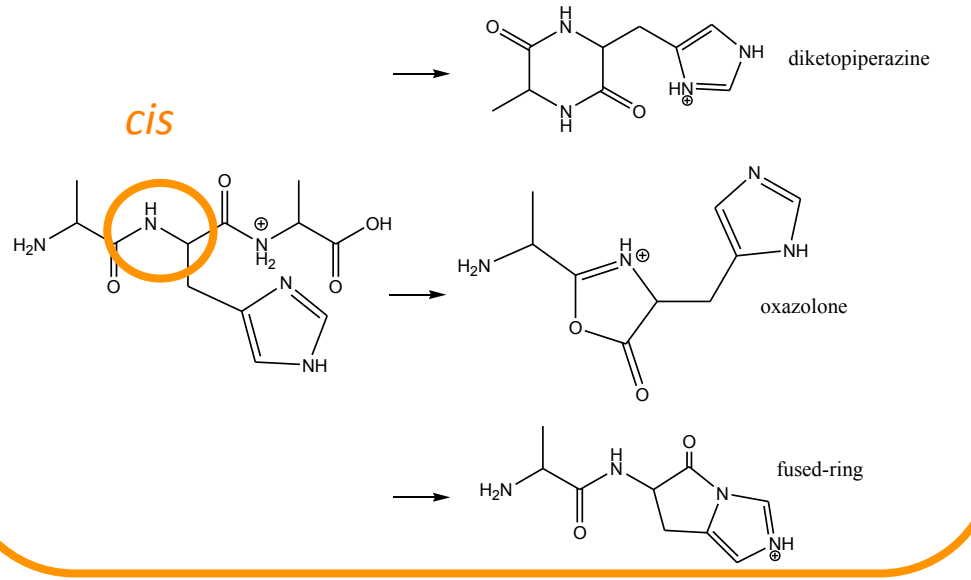




Ala_3H^+



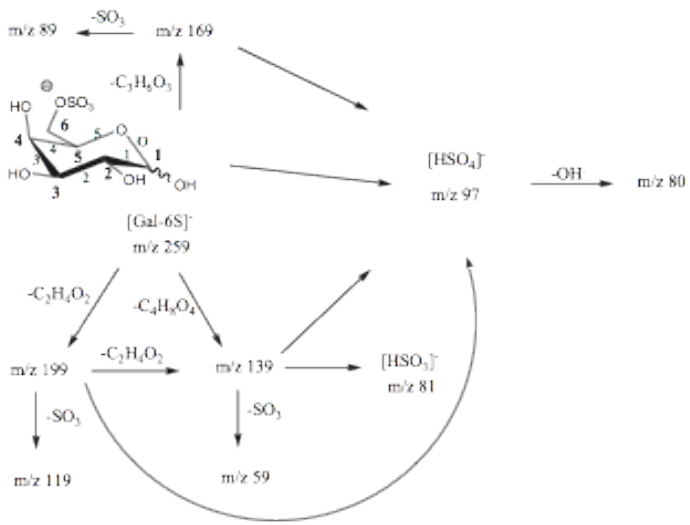
$AlaHistAlaH^+$

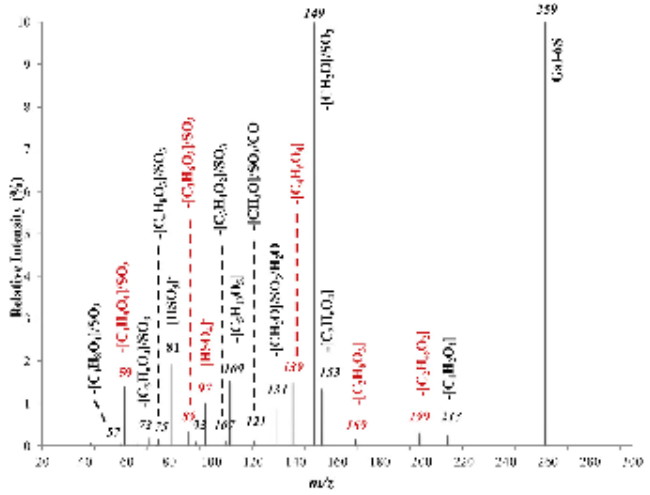


R.Spezia, J.Martens, J.Oomens, K.Song.Submitted (2014)
D.Ortiz, M.-P.Gaigeot, A.Cimas, R.Spezia, J.Oomens. In preparation

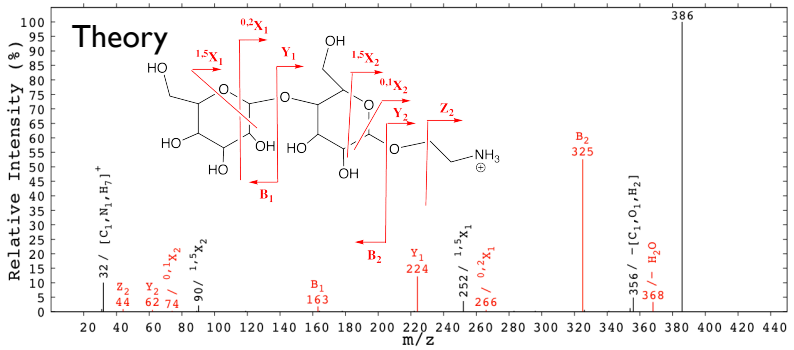
CID of carbohydrates

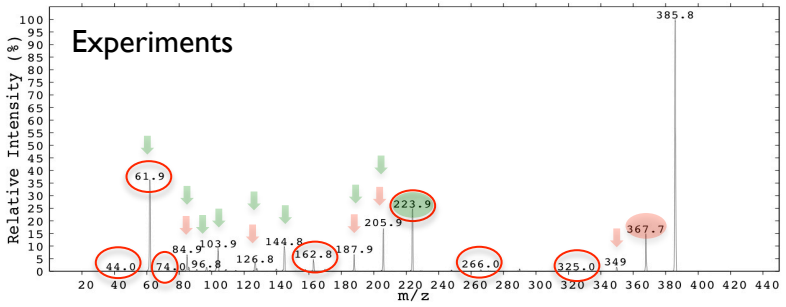
galactose-6-sulfate





cellobiose

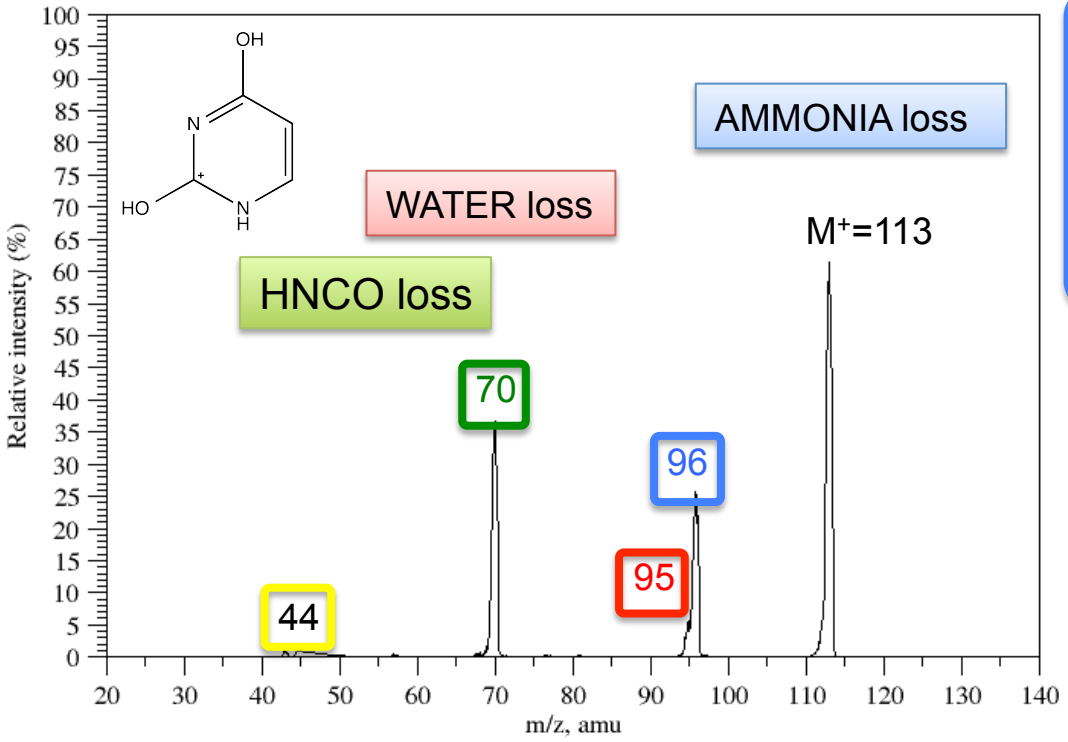


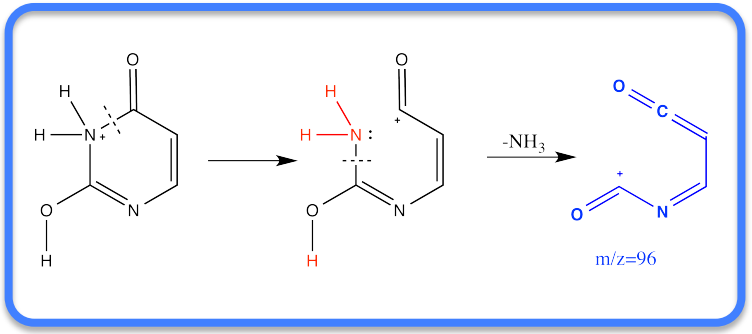


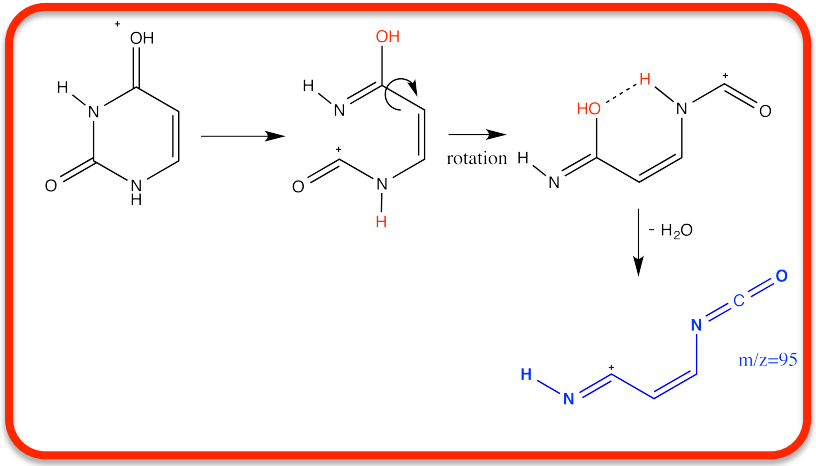
PM3 chemical dynamics

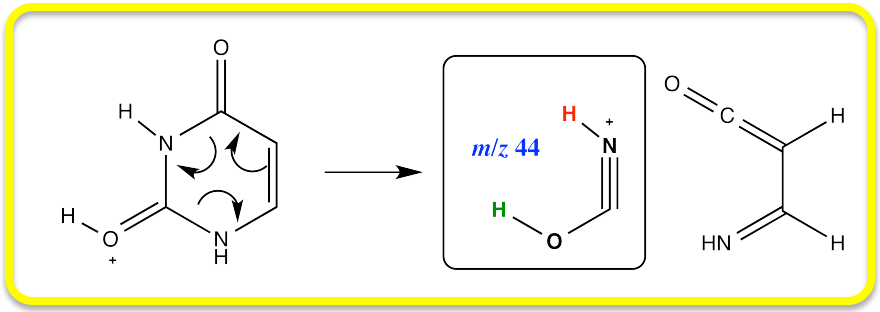
D.Ortiz, J.-Y.Salpin, K.Song and R.Spezia. Int. J. Mass Spectrom. 358, 25-35 (2014).

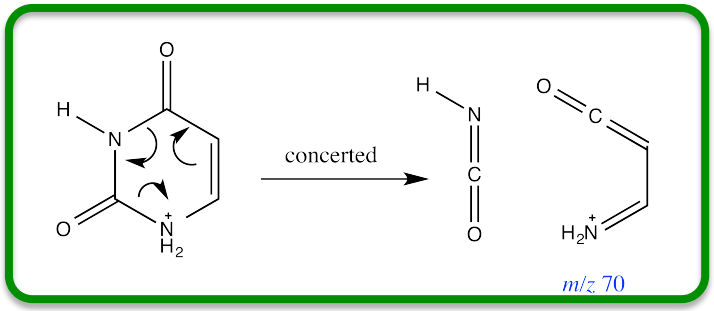
CID of uracil



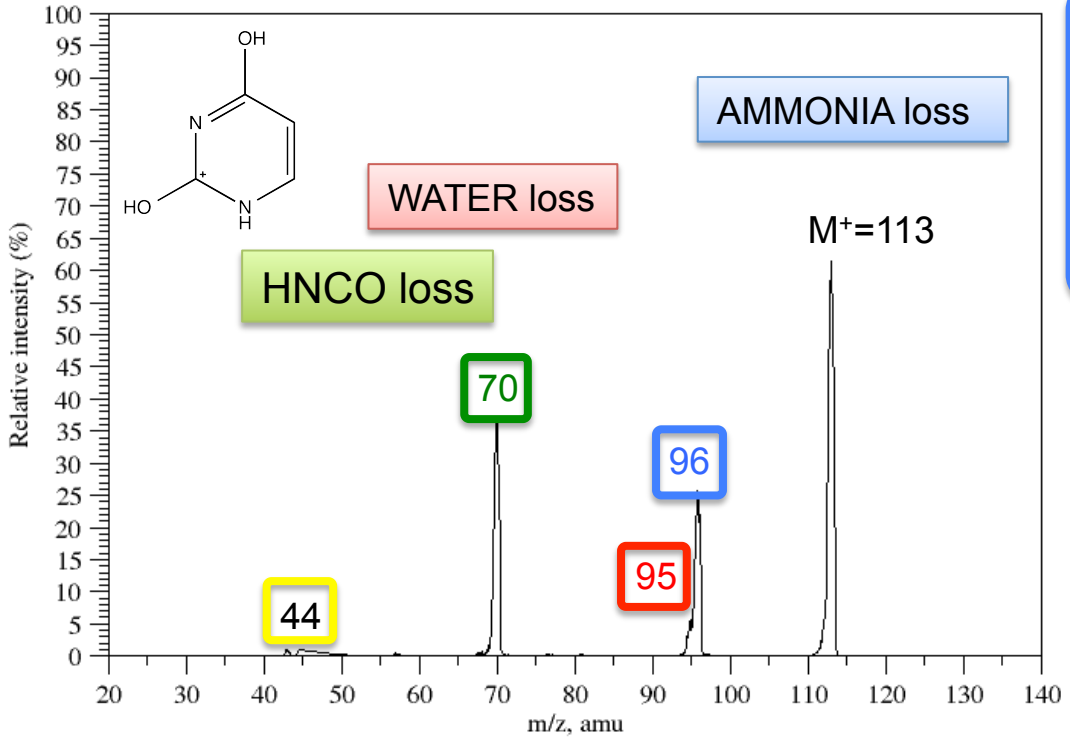


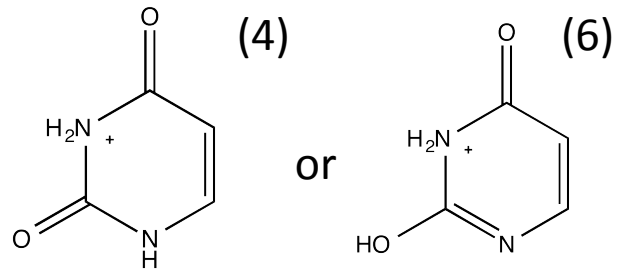


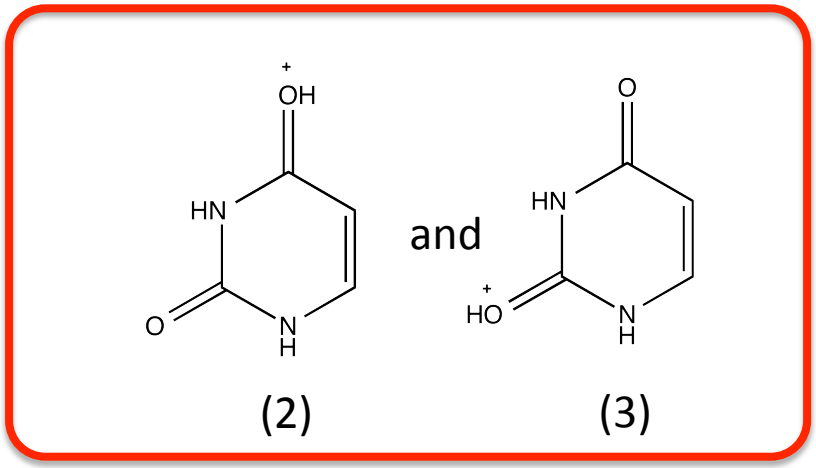


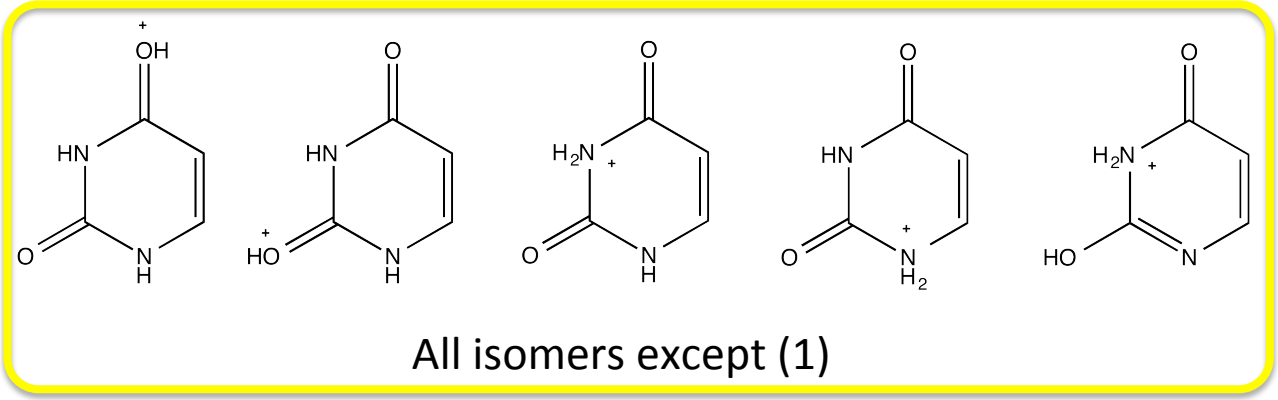


CID of uracil









All isomers

(2), (3) and (4) COMPLETE SPECTRUM

Th MS/MS: flow chart

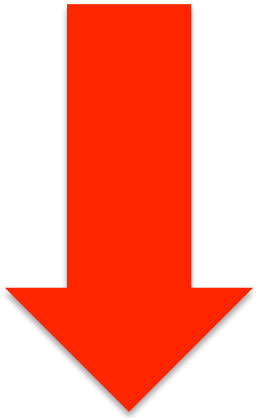
1) Find the most reliable initial structures
2) Do chemical dynamics of CID to obtain reaction pathways and energy transfer
3) Use chemical dynamics to improve the knowledge of PES and eventually re-evaluate the reaction products
4) Use energy transfer and RRKM to obtain information on reactivity at longer time scales

Conclusions

- ✓ Direct Dynamics can provide detailed information on CID processes
- ✓ Energy transfer, isomer reactivity, fragmentation mechanisms
- ✓ Direct relationship with experimental observations
- ✓ Rotational energy can play an important role
- ✓ Dynamics: reaction pathways regulated by dynamical properties
- ✓ High energy structures can be dynamically accessible
- ✓ Theoretical MS/MS … not far from it!!

Perspectives

- ✓ Systematic study of poly-peptides (function of length, residues etc ...)
- ✓ Extent to other systems (e.g. carbohydrates, steroids, DNA bases etc ...)
- ✓ Other methods besides AM1/PM3 for bigger systems
- ✓ Go beyond Newton's dynamics
- ✓ ...

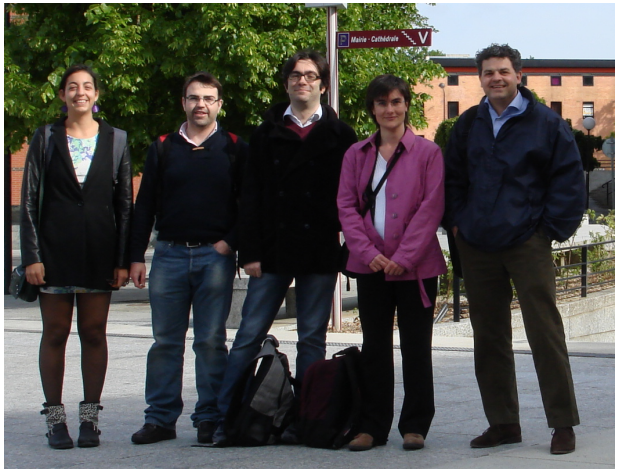


Theoretical Mass Spectrometry

ANR International (NSF): DynBioReact
(coll. W.L..Hase, Texas Tech University)

1PhD (september 2015)
1Post-Doc

Acknowledgments



EVRY

A.Eizaguirre, E.Rossich-Molina, A.Martin-Somer, A.Cimas, Y.Jeanvoine, M.-P.Gaigeot

W.L.Hase Texas Tech

K.Song KNUE

M.Yanez UAM

D.Ortiz, J.Y.Salpin LAMBE, Evry

J.Martens, J.Oomens Felix/Nijmegen

D.Urban, G.Doisneau, Y.Bourdeaux, J.-M.Beau ICMMO, Orsay

GENCI consortium for computing time (IDRIS/CINES/CCRT)

twitter

@riccardosp

http://www.lambe.univ-evry.fr/rspezia

riccardo.spezia@univ-evry.fr

1 Post-Doc
1 PhD (starting september 2015)

ANR International project: DynBioReact
(coll. W.L. Hase, Texas Tech University, USA)

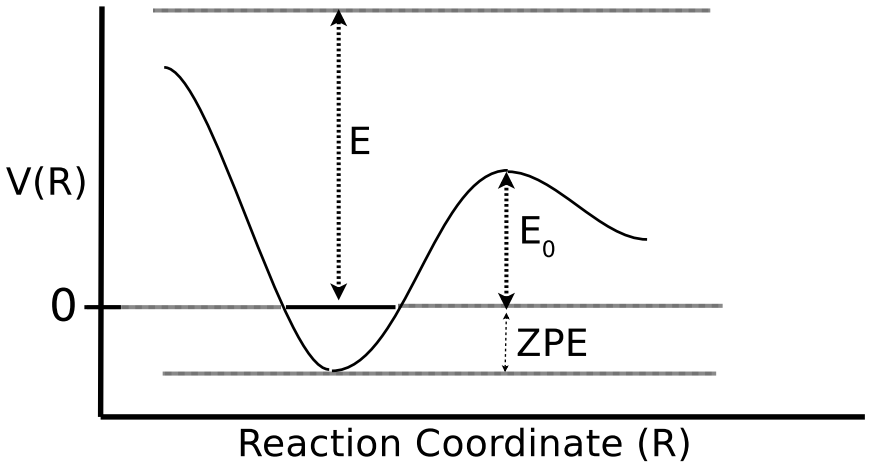
http://www.lambe.univ-evry.fr/rspezia
riccardo.spezia@univ-evry.fr

1PhD (september 2015)
1Post-Doc

Theoretical Mass Spectrometry

ANR International (NSF): DynBioReact
(coll. W.L..Hase, Texas Tech University)

Unimolecular reaction



Energy given to a molecule in the gas phase (isolated) in order to react.

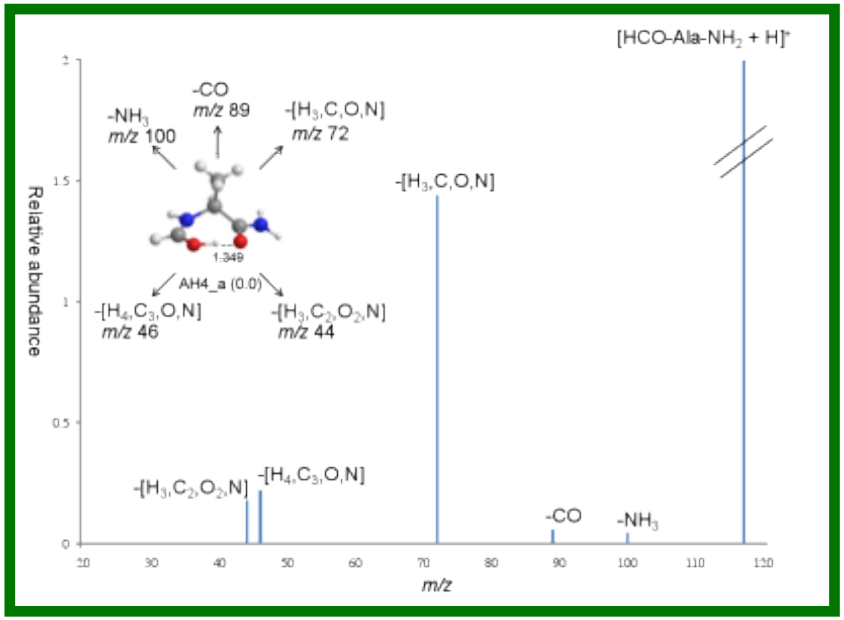
Different way to provide energy : collision, laser, electron ...

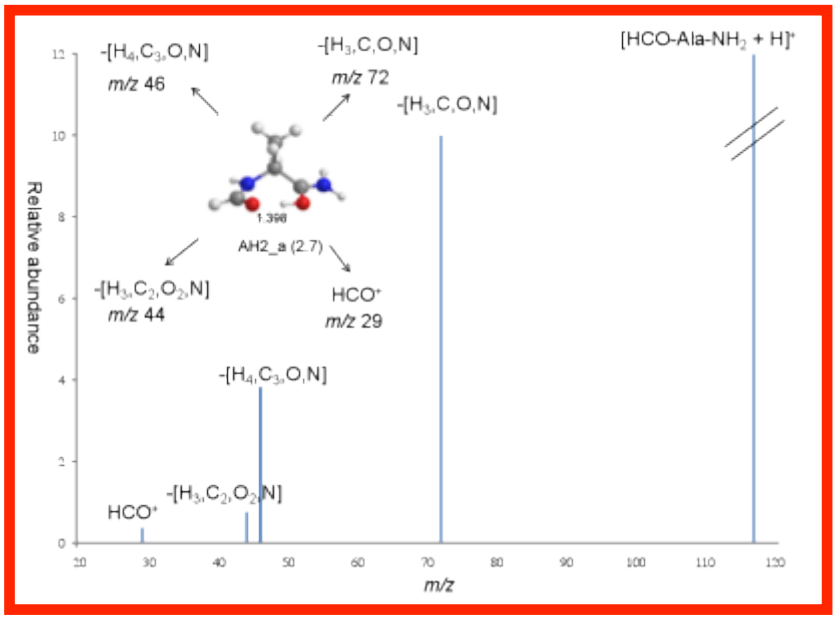
Energy is conserved (no coupling with a bath)

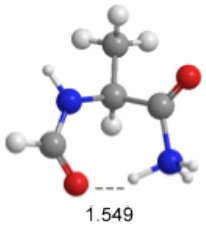
To react the system has to pass the transition state

Reaction can be statistical (slow, microcanonical equilibrium) or non-statistical (fast)

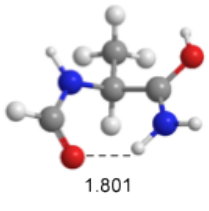
Theoretical CID



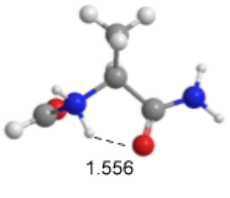




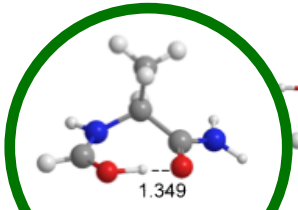
AH1 (68.9)



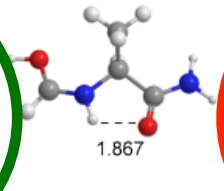
AH2_c (32.4)



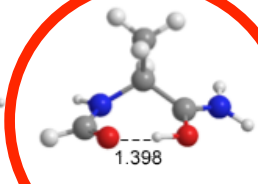
AH3 (79.3)



AH4_a (0.0)



AH4_b (23.7)



AH2_a (2.7)

Theoretical CID