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## Proposition of optimization strategies in collision energies on QTOF and Orbitrap instruments to perform comparable CID-MS-MS spectra in metabolomics

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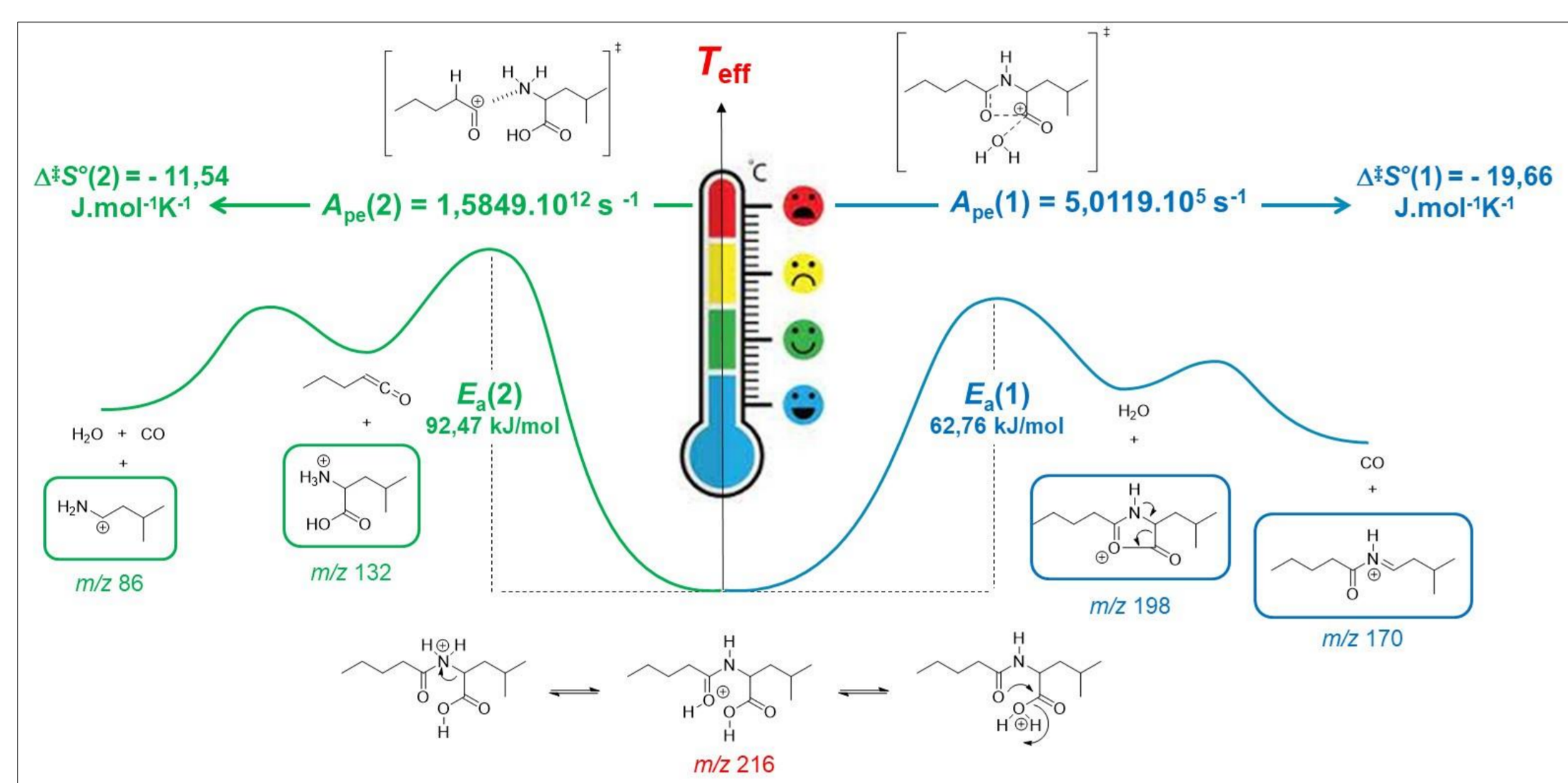
David Rondeau,<sup>1</sup> Thomas Delhaye,<sup>1</sup> Erell Froger,<sup>1</sup> Yves Gimbert,<sup>2</sup> Axel Raux,<sup>3</sup> Yann Guitton,<sup>3</sup> Pierre Le Pogam-Alluard,<sup>4</sup> Myriam Le Roch,<sup>5</sup> Marylène Chollet-Krugler<sup>5</sup>

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Structural identification of biomarkers is an important step in the workflow and metabolomic. The recognition strategies for characterizing the metabolite involve comparisons of fragmentation mass spectra obtained with MS-MS peak lists available on different MS-MS databases (METLIN, HMDB...) or via the interrogations of web-based mass spectrometry ecosystems using molecular networks. However, collision-Induced Dissociation (CID) spectra are function of the internal energy imparted in the precursor ion during the activation process. For increasing the similarity index, it could be interesting to propose strategies for calibrating the CID-MS-MS spectra in internal energy. Such an approach has been initiated in a consortium regrouping different mass spectrometry laboratories. Two strategies have been work out at this purpose.

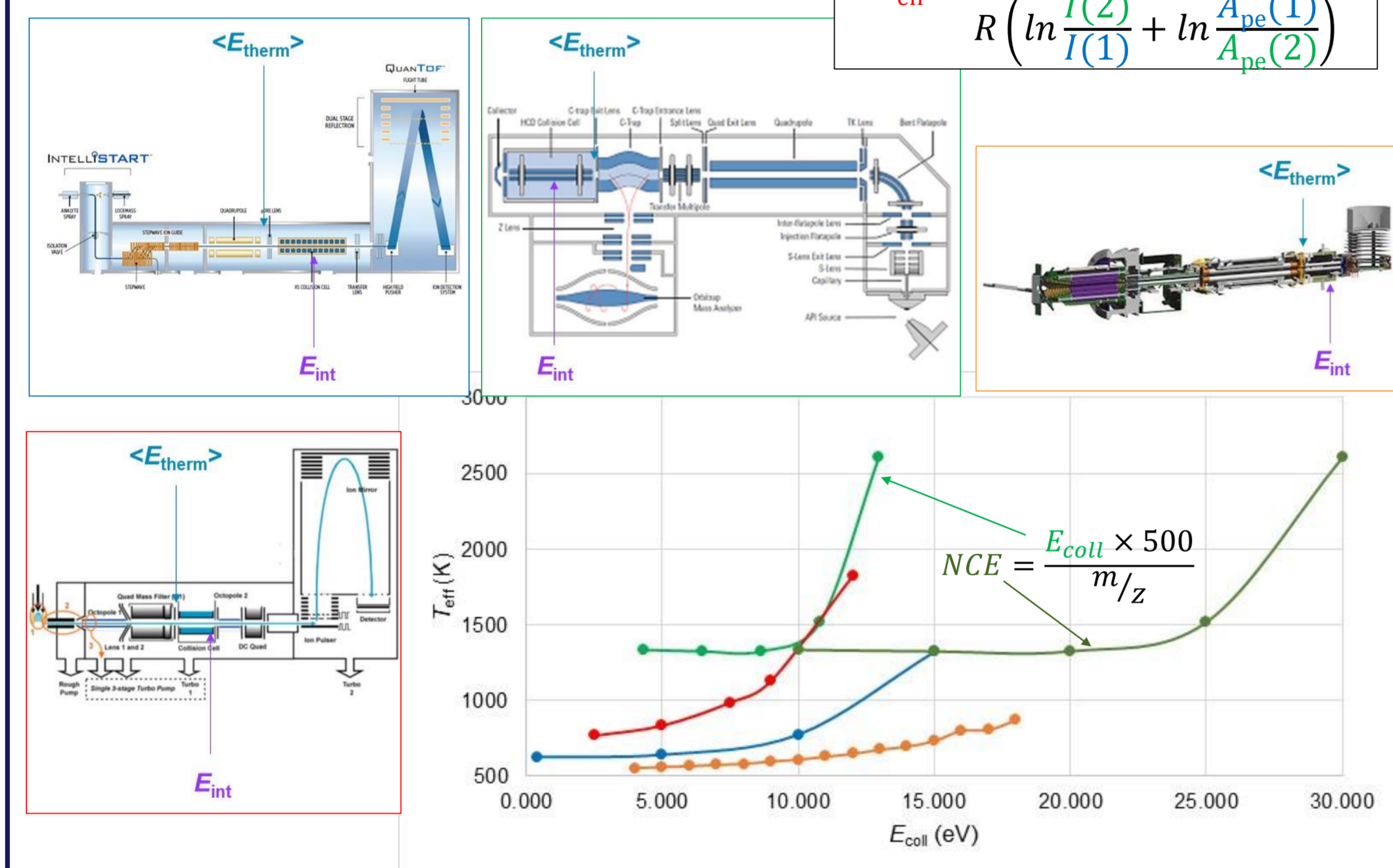
## The thermal extrapolation method for the effective temperatures and internal energies of activated ions [1]

Protonated valeryl leucine used as thermometer ion

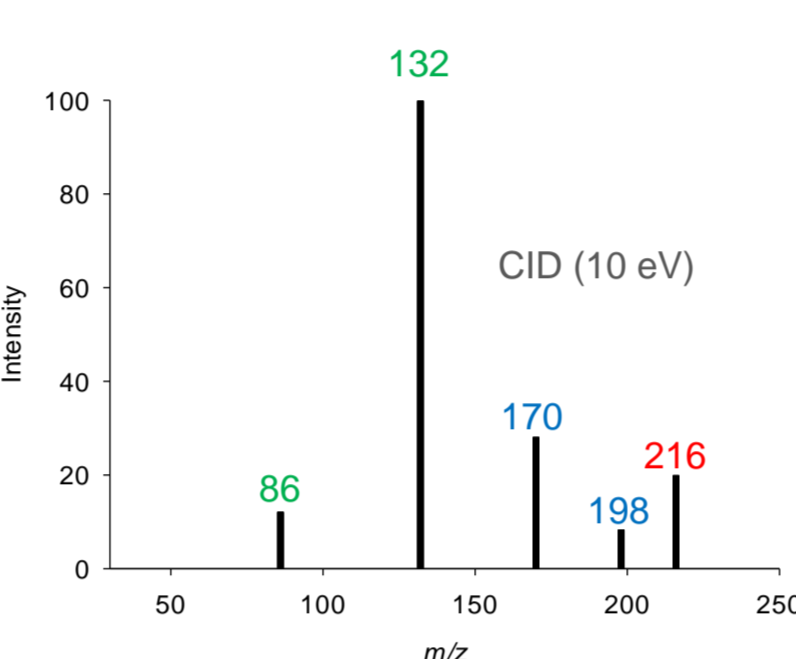


Effective Temperature of m/z 216 ions

$$T_{eff} = \frac{E_a(1) - E_a(2)}{R \left( \ln \frac{I(2)}{I(1)} + \ln \frac{A_{pe}(1)}{A_{pe}(2)} \right)}$$

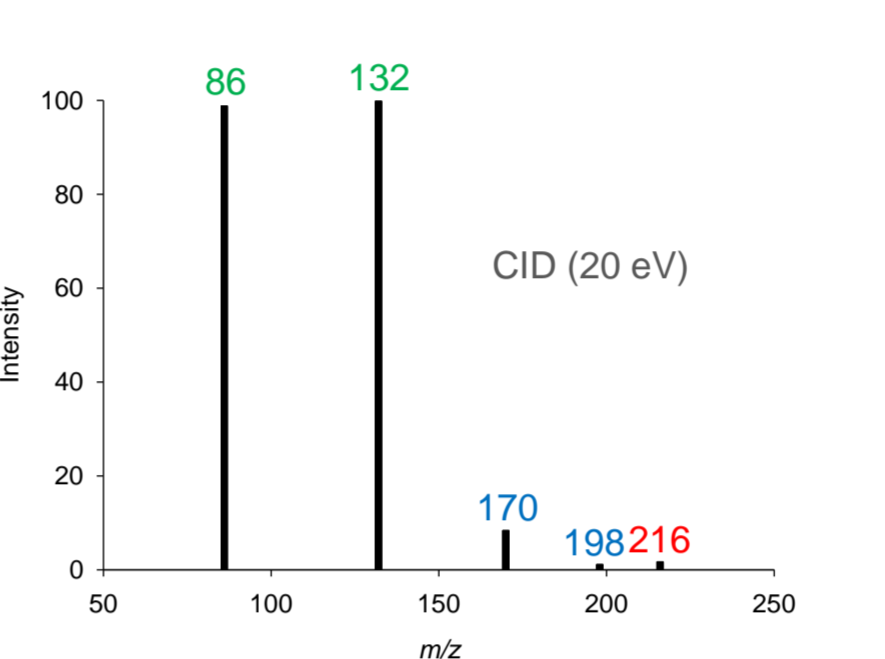


Xevo G2 XS QTOF Waters

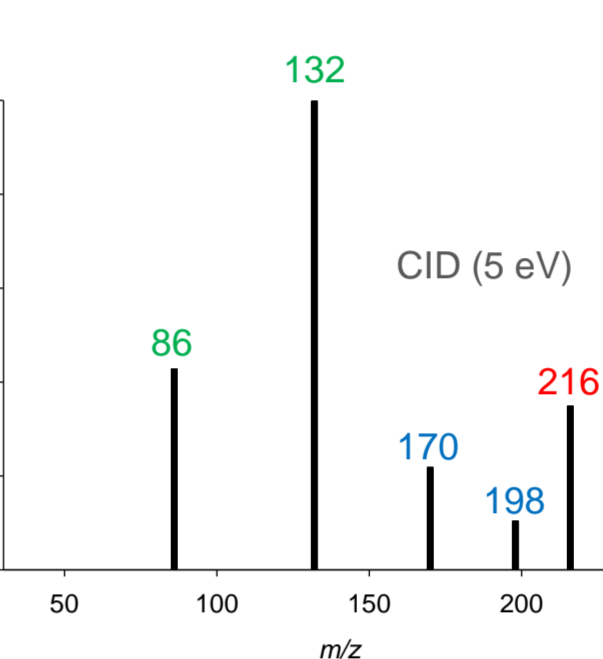


Theory

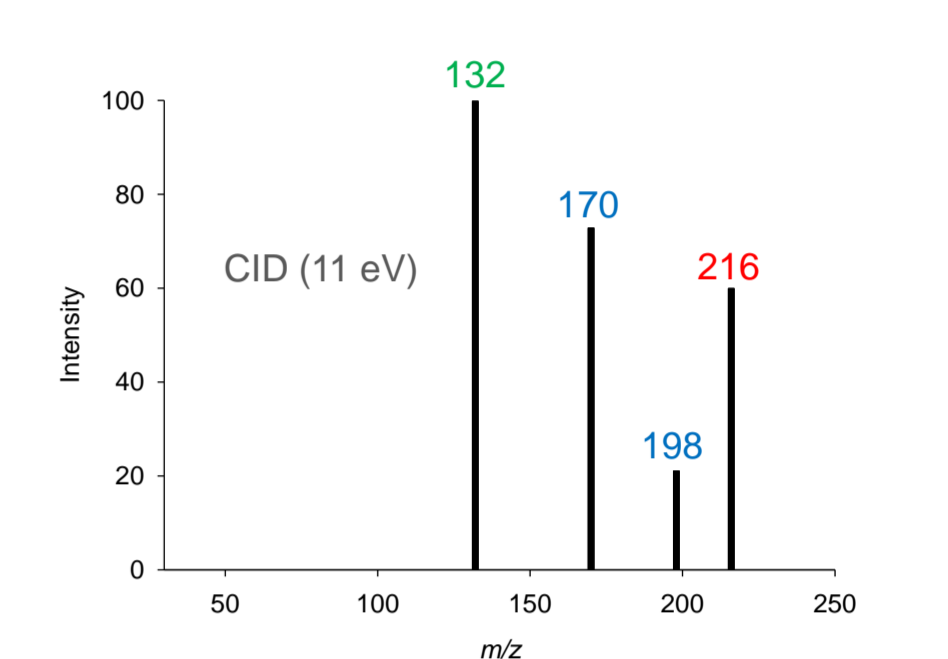
QExactive Q-Orbitrap Thermo



QTOF Agilent 6530



QTOF timsTOF PRO 2 Bruker

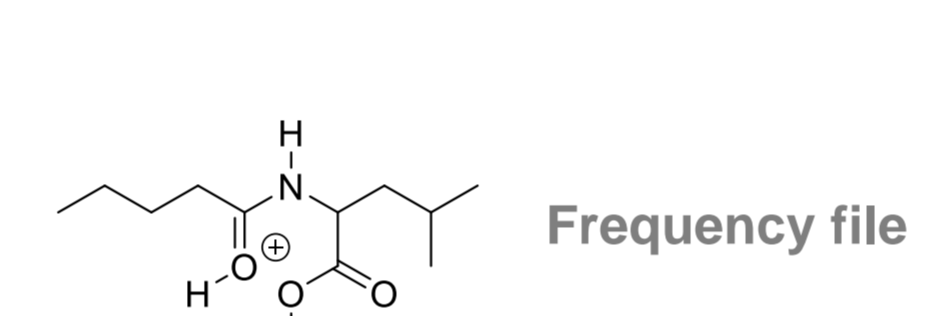


Efficiency of Energy Deposition :  $\langle E_{deposited} \rangle = \langle E_{int} \rangle - \langle E_{therm} \rangle$

Thermal Energy  $\langle E_{therm} \rangle = \sum_{i=1}^s \frac{h\nu_i}{\exp(h\nu_i/k_B T)}$

$$\langle E_{therm} \rangle = 0,42 \text{ eV for a mass spectrometer temperature of } 298 \text{ K}$$

Frequency file



Internal Energy  $\langle E_{int} \rangle = \sum_{i=1}^s \frac{h\nu_i}{\exp(h\nu_i/k_B T_{eff})}$

$$\langle E_{int} \rangle = \sum_{i=1}^s \frac{h\nu_i}{\exp(h\nu_i/k_B T_{eff})}$$

Center of Mass Energy

$$E_{cm} = E_{coll} \times \frac{M_{Gaz}}{M_{Gaz} + M_{ion}}$$

$E_{int}$ (eV)	$E_{deposited}$ (eV)	NCE(%)	$E_{coll}$ (eV)	Efficiency (%)
6.15	5.73	10	4.32	133
6.07	5.65	15	6.48	87
6.07	5.65	20	8.64	65
7.50	7.08	25	10.80	66
16.30	15.88	30	12.96	123
91.25	90.83	35	15.12	601

$E_{coll} \rightarrow E_{int} \sim 70\%$

$E_{int}$ (eV)	$E_{deposited}$ (eV)	$E_{coll}$ (eV)	Efficiency (%)
2.43	2.01	2.5	80
2.81	2.39	5.0	48
3.75	3.33	7.5	44
4.70	4.28	9.0	48
9.85	9.43	12.0	79

$E_{coll} \rightarrow E_{int} \sim 50\%$

$E_{int}$ (eV)	$E_{deposited}$ (eV)	$E_{coll}$ (eV)	Efficiency (%)
1.69	1.27	6	21
1.76	1.34	5	27
2.50	2.08	10	21
6.05	5.63	15	38
89.82	89.40	20	447

$E_{coll} \rightarrow E_{int} \sim 30\%$

$E_{int}$ (eV)	$E_{deposited}$ (eV)	$E_{coll}$ (eV)	Efficiency (%)
1.39	0.97	6	16
1.47	1.05	8	13
1.60	1.18	10	12
1.79	1.37	12	11
2.03	1.61	14	12
2.62	2.20	16	14

$E_{coll} \rightarrow E_{int} \sim 10\%$



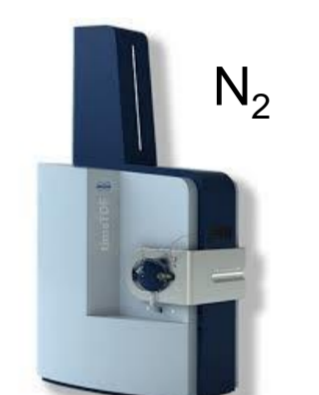
$E_{cm}$ (eV)	15% $E_{cm}$ (eV)	Nb collisions
0.50	0.07	77
0.74	0.11	51
0.99	0.15	38
1.24	0.19	38
1.49	0.22	71
1.74	0.26	349



$E_{cm}$ (eV)	15% $E_{cm}$ (eV)	Nb collisions
0.29	0.04	47
0.57	0.09	28
0.86	0.13	26
1.03	0.15	28
1.38	0.21	46



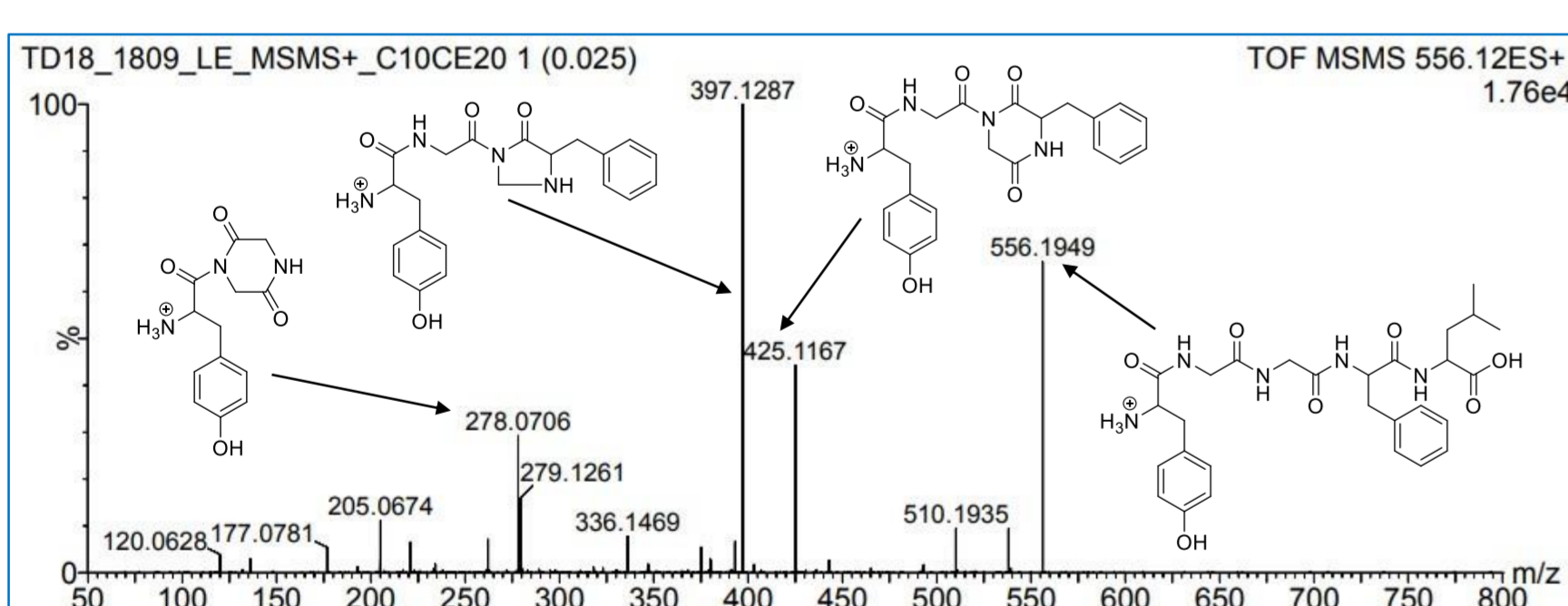
$E_{cm}$ (eV)	15% $E_{cm}$ (eV)	Nb collisions
0.94	0.14	9
0.78	0.12	11
1.56	0.23	9
2.34	0.35	16
3.13	0.47	191



$E_{cm}$ (eV)	15% $E_{cm}$ (eV)	Nb collisions
0.69	0.10	9
0.92	0.14	8
1.15	0.17	7
1.38	0.21	7
1.61	0.24	7
1.84	0.27	8

## The ion behavior modelling method considering the collision activation conditions using RRKM theory [2,3]

Protonated leucine enkephaline used as thermometer ion



CID-MSMS spectrum of [M+H]<sup>+</sup> m/z 556 (QqTOF Waters)  $E_{coll} = 20 \text{ eV}$

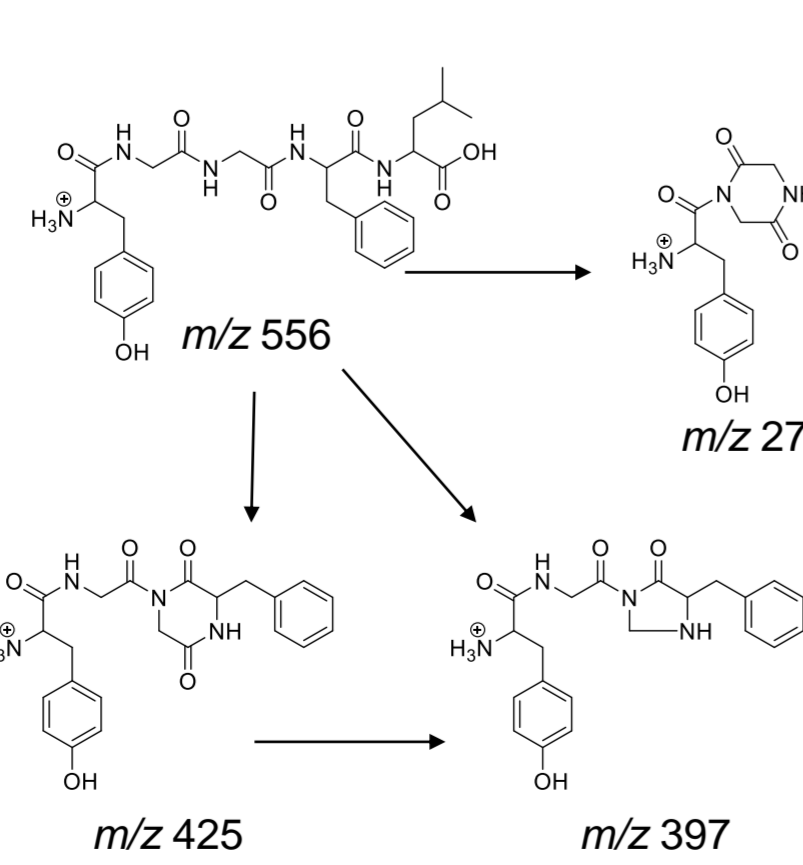
Experimental Survival Yields at different  $E_{coll}$  values

$$SY(Exp) = \left( \frac{I_{P^+}}{I_{P^+} + \sum_{i=1}^n I_{F^+}} \right) = \frac{I_{m/z(556)}}{I_{m/z(556)} + I_{m/z(425)} + I_{m/z(397)} + I_{m/z(278)}$$

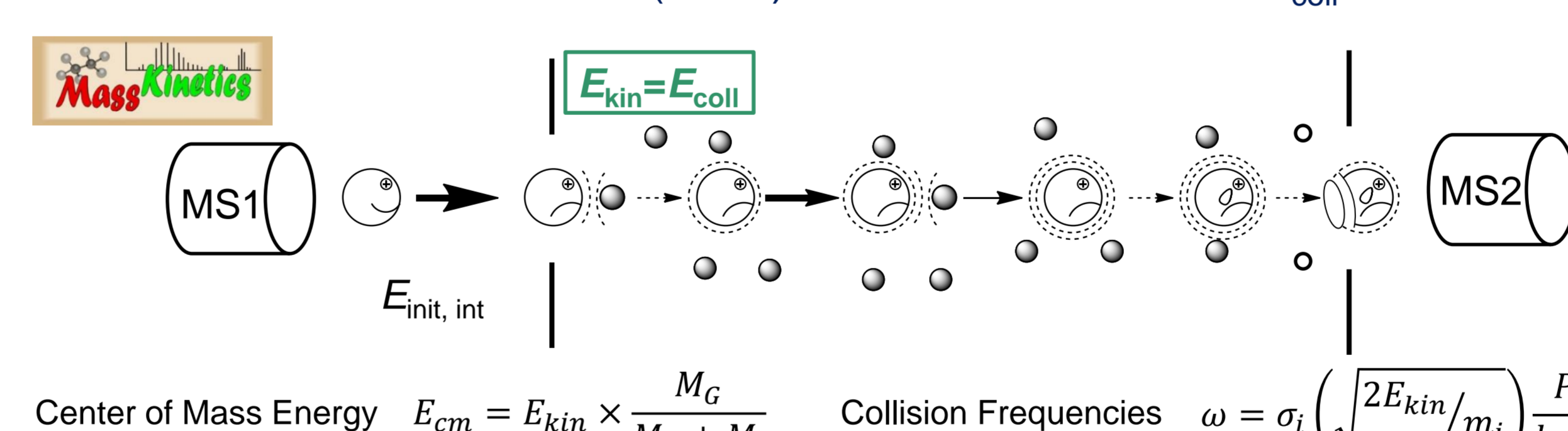
Thermochemistry of protonated leucine enkephaline fragmentation [4]

Fragmentations	$E_0$ (eV)	Log(A)	CCS (Å <sup>2</sup> )	$\eta$
556 → 425	1.19	10.5	162	0.128
556 → 397	1.24	10.5	162	0.128
556 → 278	1.24	10.5	162	0.128
425 → 397	1.14	11	162	0.1285

Full optimization of geometries was performed using the B3LYP density functional,34 with the basis set 6-31+G(d,p). Frequency and energy calculations were done at this level



Theoretical Survival Yields SY(Theo) calculated at different  $E_{coll}$  values

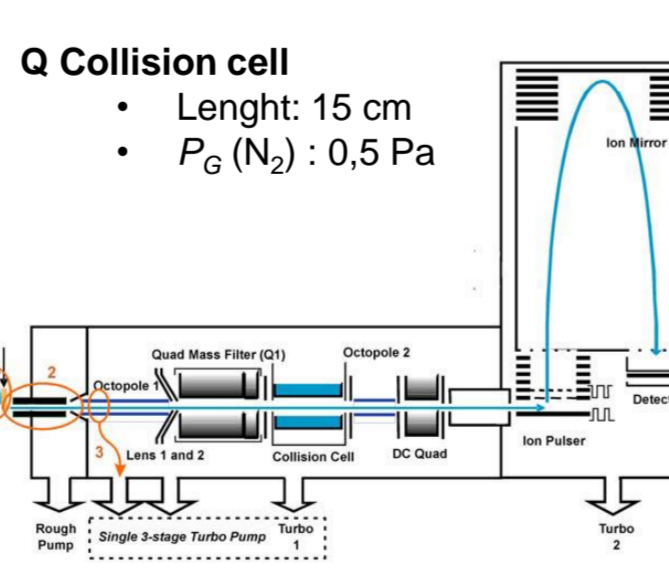


Initial Internal Energy Distribution  $P(E_{Therm}) = \frac{\rho(E_{int}) \exp(-E_{int}/k_B T)}{\int_0^\infty \rho(E_{int}) \exp(-E_{int}/k_B T)}$

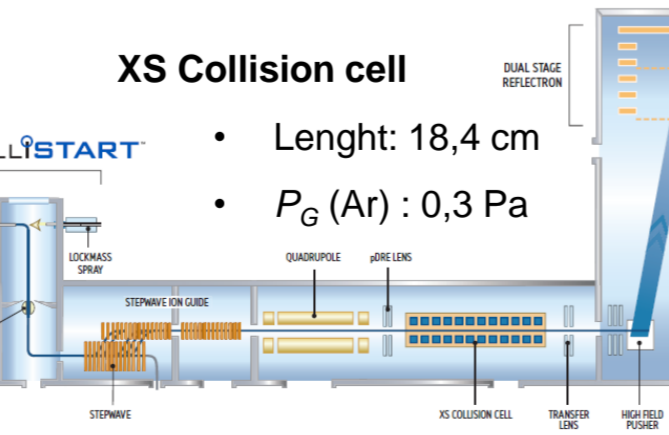
$$k^{i,j}(E_{int}) = \frac{\sigma N^\ddagger(E_{int} - E_0)}{h \rho(E_{int})}$$

Modelling of mass spectrometer parameters

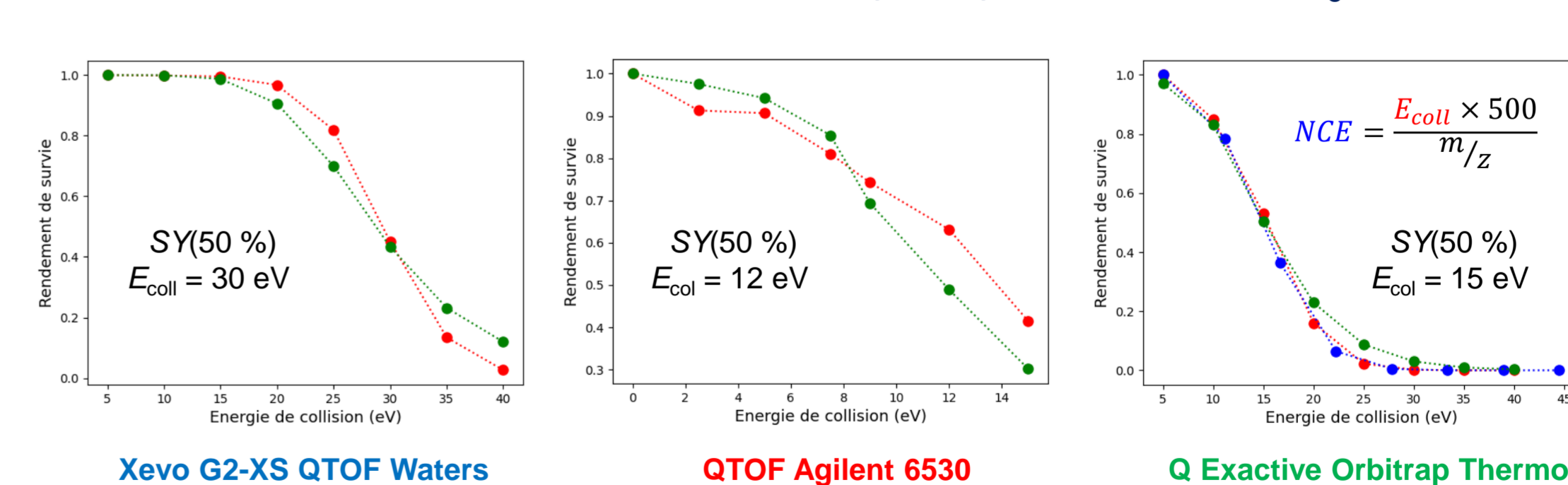
$P_{therm}(m/z 556)$  at 293 K + 2.7 eV  
 $\langle E_{therm} \rangle = 0,99 + 2,7 = 3,69 \text{ eV (596 K)}$



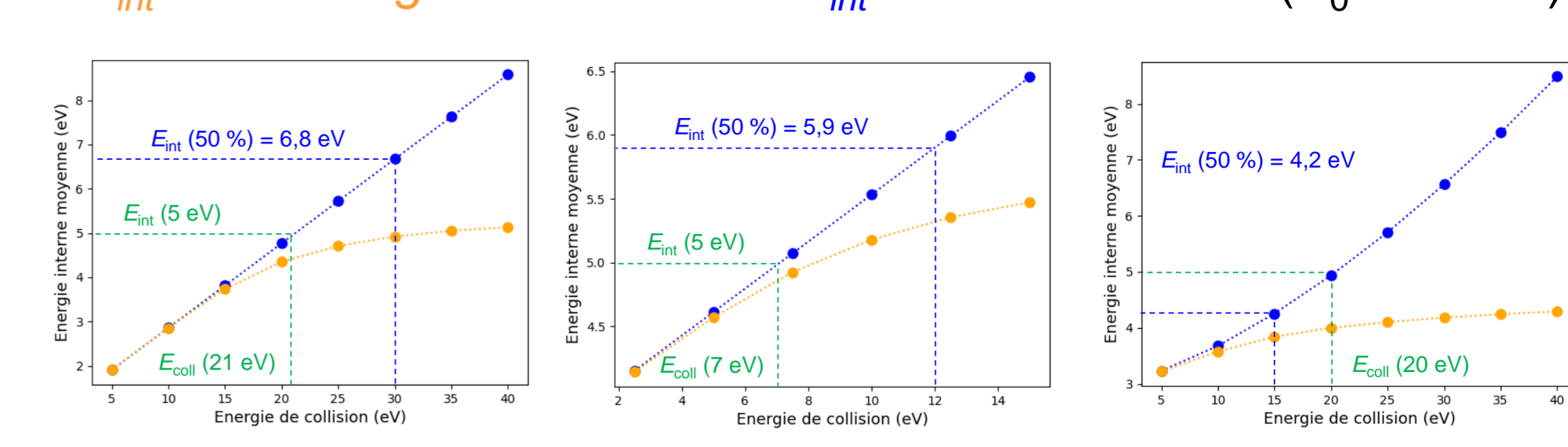
$P_{therm}(m/z 556)$  at 293 K  
 $\langle E_{therm} \rangle = 0,99 \text{ eV}$



SY(Exp) vs SY(Theo) considering fragmentations ( $E_0$  values)



$E_{int}$  of non-fragmented ions vs  $E_{int}$  of activated ions ( $E_0 = 10 \text{ eV}$ )



### References :

- [1] M. Meot-Ner (Mautner), A. Somogyi. *Int. J. Mass Spectrom.* 2007, **263**, 346-356.
- [2] L. Drahos, K. Vékey. *J. Mass Spectrom.* 2001, **36**, 237-263.
- [3] D. Rondeau, L. Drahos, K. Vékey. *Rapid Commun. Mass Spectrom.* 2014, **28**, 1273-1284.
- [4] J. Sztáray, A. Memboeuf, L. Drahos, K. Vékey. *Mass Spectrom. Rev.* 2011, **30**, 298- 320.

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