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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, Thomas Delhayé, Erell Froger, Yves Gimbert, Axel Raux, et al.. Proposition of optimization strategies in collision energies on QTOF and Orbitrap instruments to perform comparable CID-MS-MS spectra in metabolomics. 39^{ème} Journées Françaises de Spectrométrie de Masse (SFSM 2023), Sep 2023, Marseille, France. 2023. hal-04328759

HAL Id: hal-04328759

<https://hal.science/hal-04328759v1>

Submitted on 7 Dec 2023

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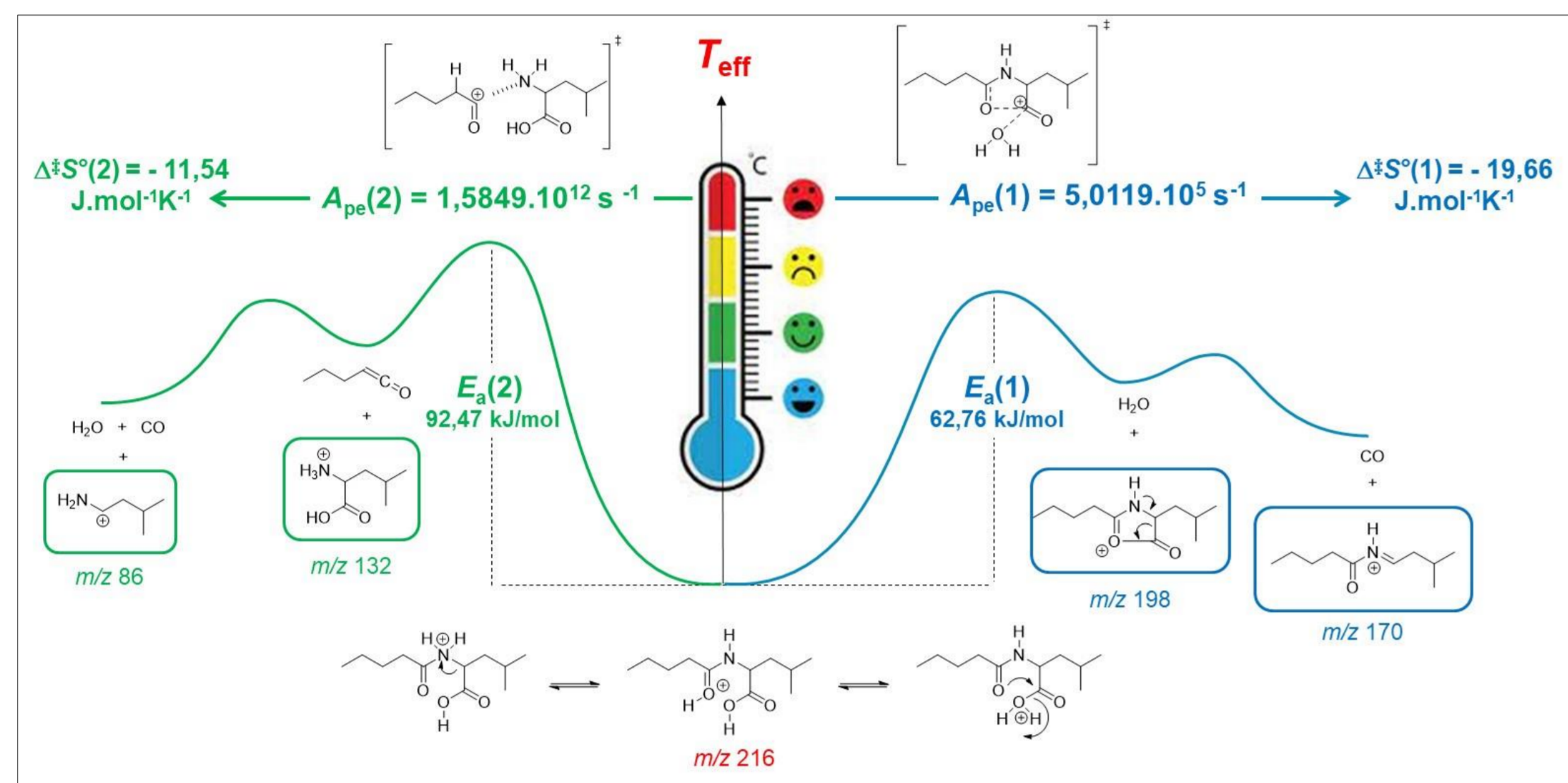
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Structural identification of biomarkers is an important step in the workflow and metabolomic. The recognition strategies for characterizing the metabolite involve comparisons of fragmentation mass spectra obtained with MS-MS peak lists available on 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.

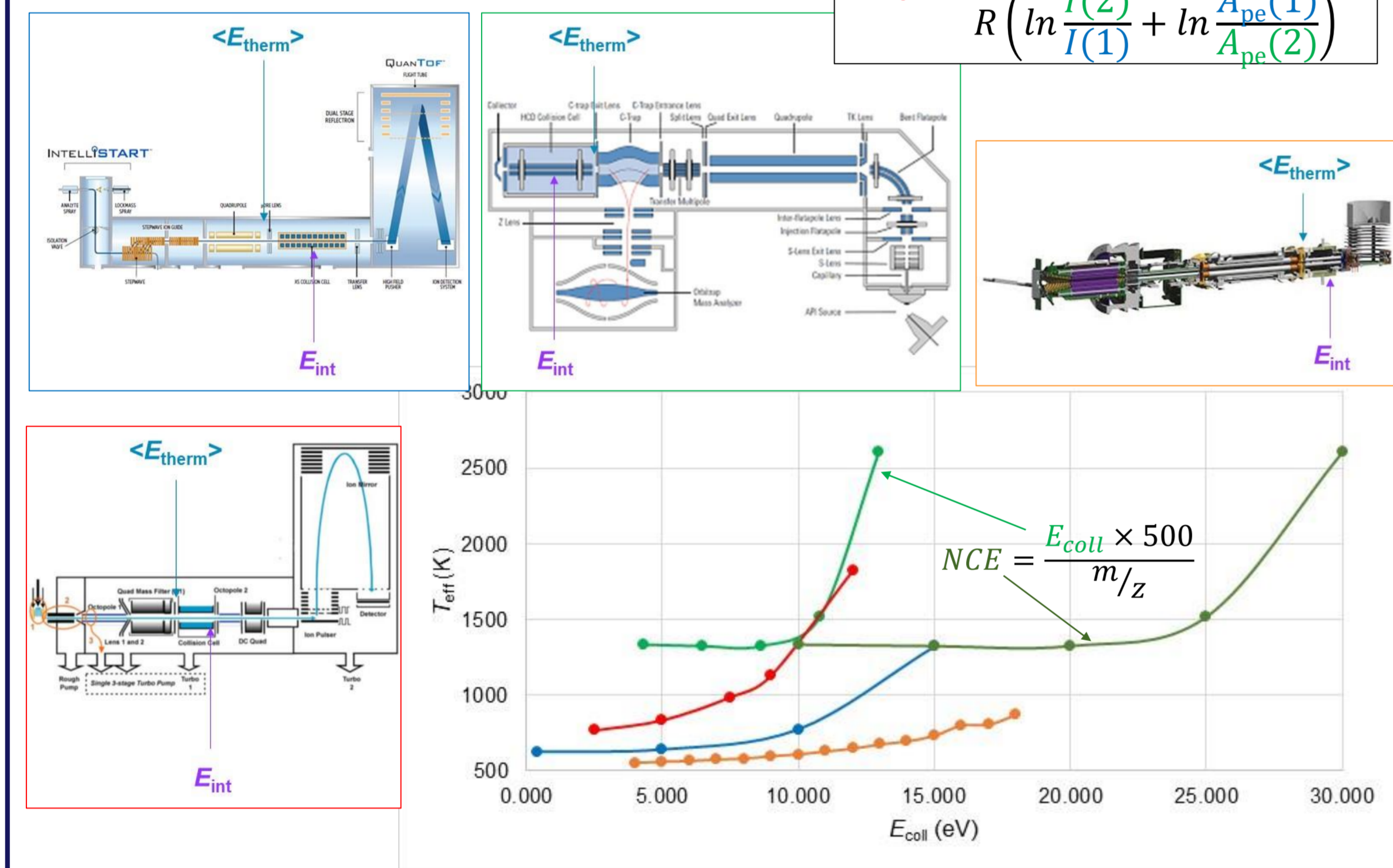
The thermal extrapolation method for the effective temperatures and internal energies of activated ions [1]

Protonated valeryl leucine used as thermometer ion

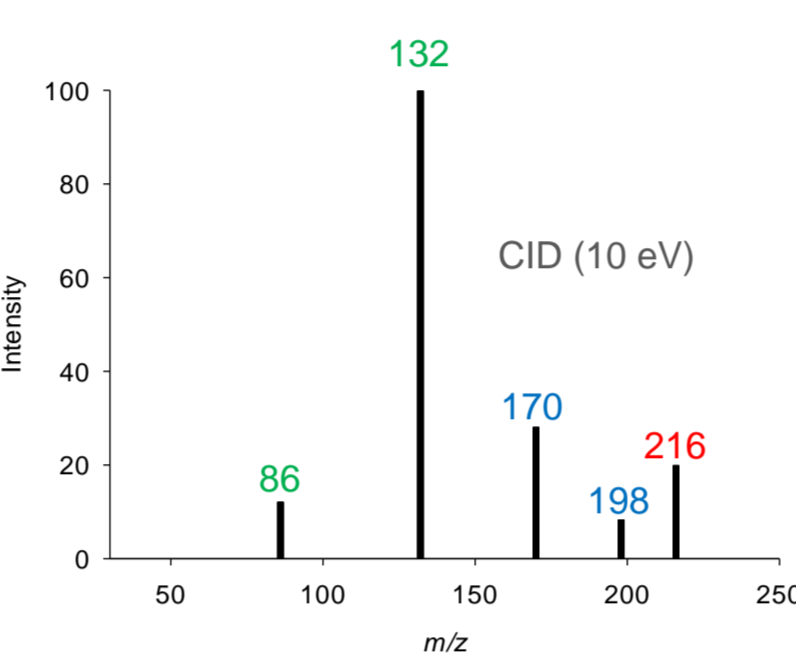


Effective Temperature of m/z 216 ions

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



Xevo G2 XS QTOF Waters



Theory

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

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

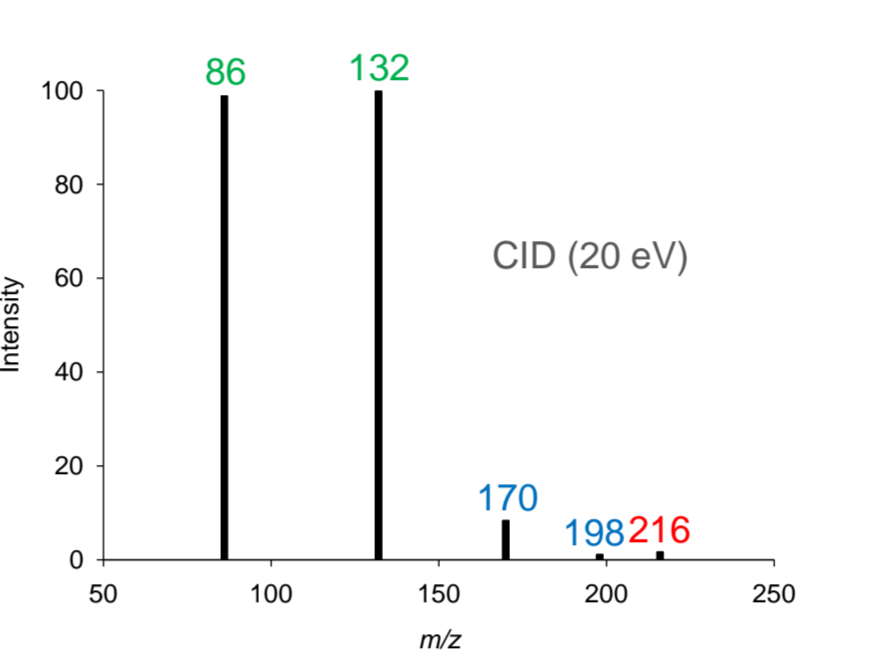
Frequency file

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

Center of Mass Energy

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

QExactive Q-Orbitrap Thermo



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

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

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

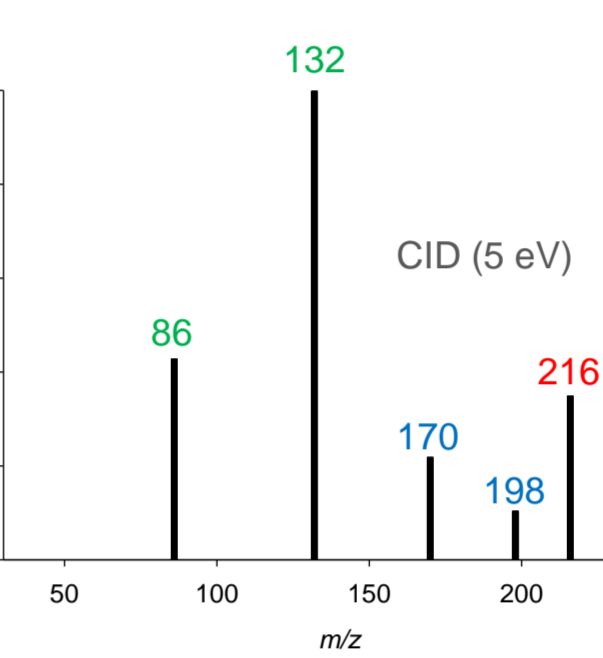
E_{int} (eV)	$E_{deposited}$ (eV)	E_{coll} (eV)	Efficiency (%)
1.69	1.27	6	21
1.76	1.34	5	27
2.50	2.08	10	21
6.05	5.63	15	38
89.82	89.40	20	447

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

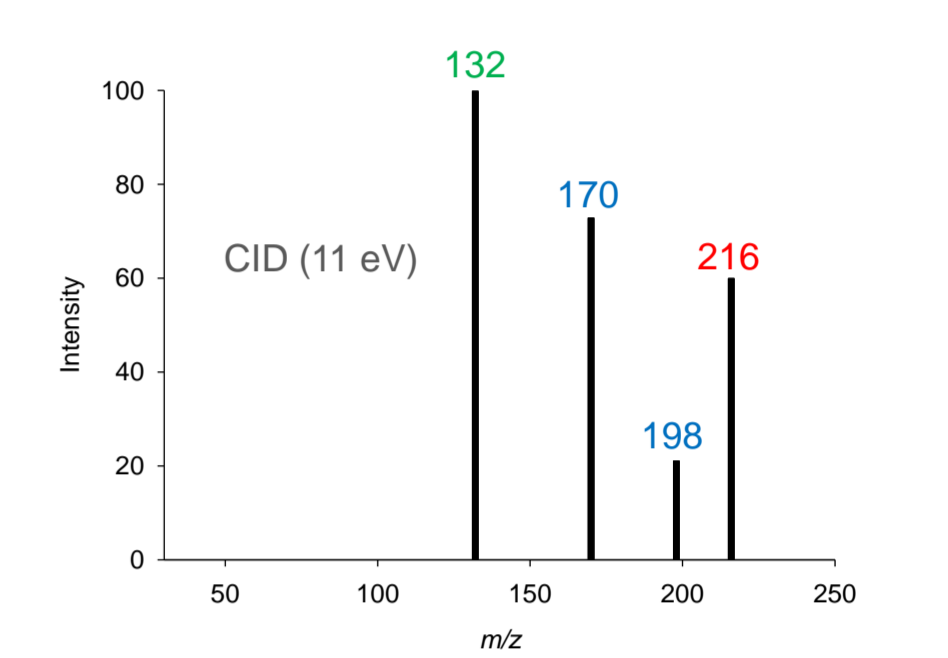
E_{int} (eV)	$E_{deposited}$ (eV)	E_{coll} (eV)	Efficiency (%)
1.39	0.97	6	16
1.47	1.05	8	13
1.60	1.18	10	12
1.79	1.37	12	11
2.03	1.61	14	12
2.62	2.20	16	14

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

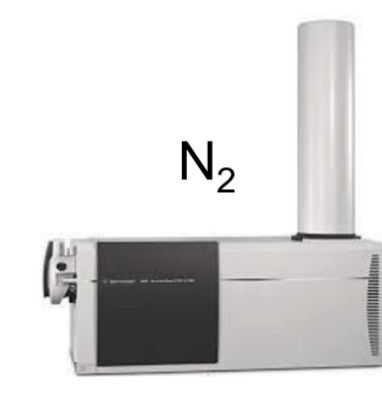
QTOF Agilent 6530



QTOF timsTOF PRO 2 Bruker



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



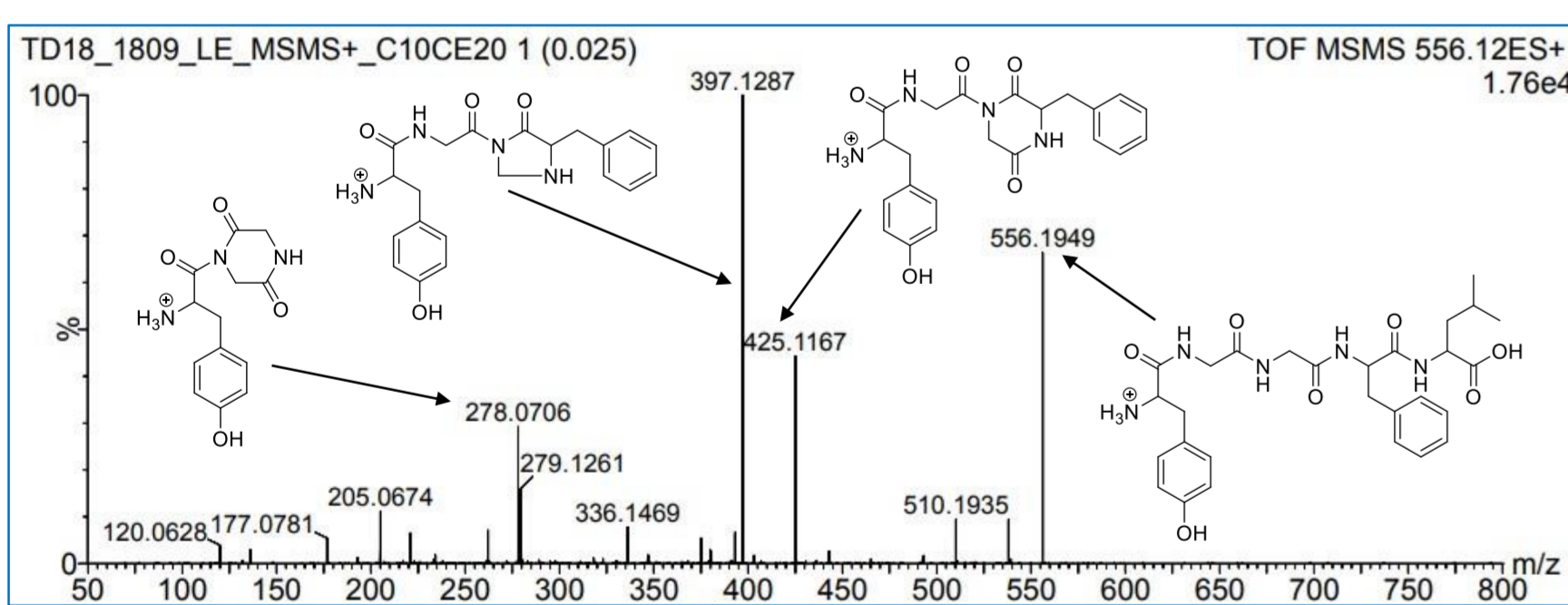
E_{cm} (eV)	15% E_{cm} (eV)	Nb collisions
0.94	0.14	9
0.78	0.12	11
1.56	0.23	9
2.34	0.35	16
3.13	0.47	191



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]⁺ m/z 556 (QqTOF Waters) E_{coll} = 20 eV

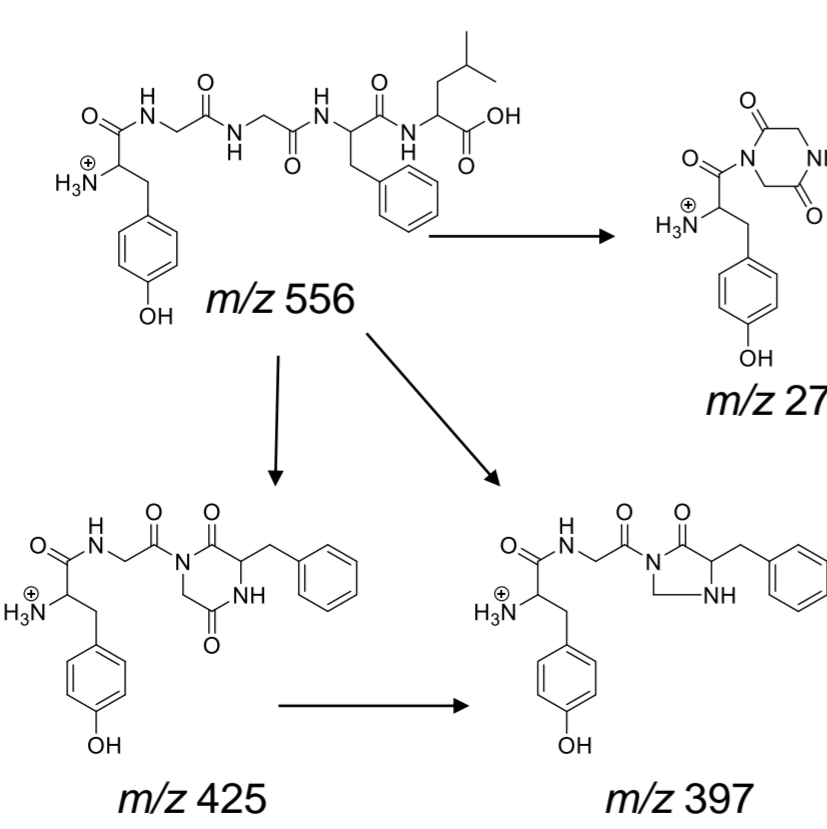
Experimental Survival Yields at different E_{coll} values

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

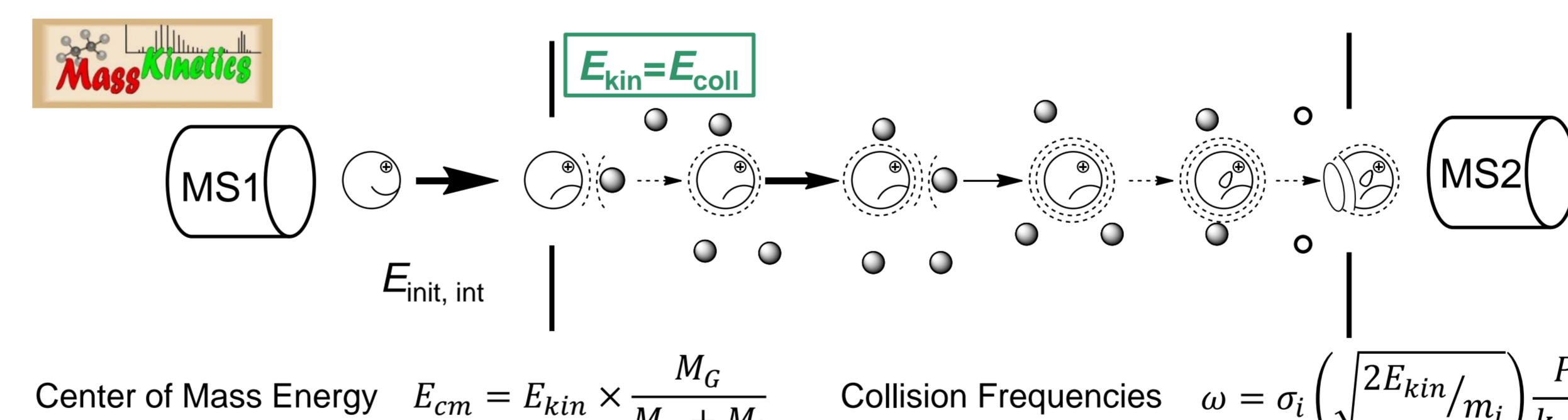
Thermochemistry of protonated leucine enkephaline fragmentation [4]

Fragmentations	E ₀ (eV)	Log(A)	CCS (Å ²)	η
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[§]

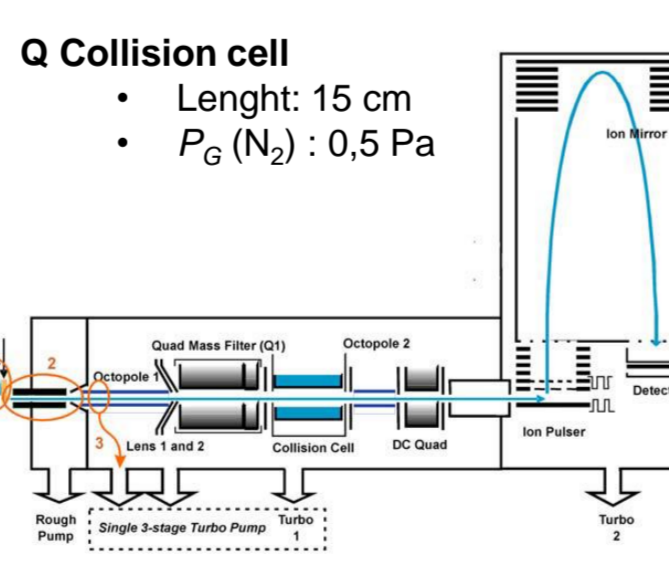
$$P(E_{Therm}) = \frac{\rho(E_{int}) \exp(-E_{int}/k_B T)}{\int_0^\infty \rho(E_{int}) \exp(-E_{int}/k_B T)}$$

Reaction by RRKM theory[§]

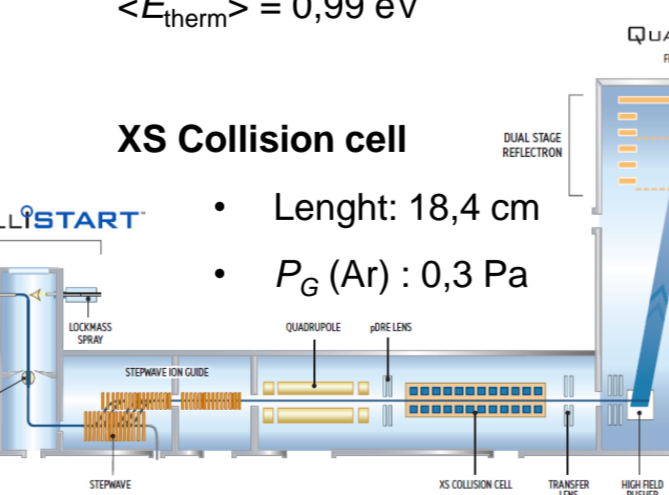
$$k^{i,j}(E_{int}) = \frac{\sigma N^\ddagger(E_{int} - E_0)}{h \rho(E_{int})}$$

Modelling of mass spectrometer parameters

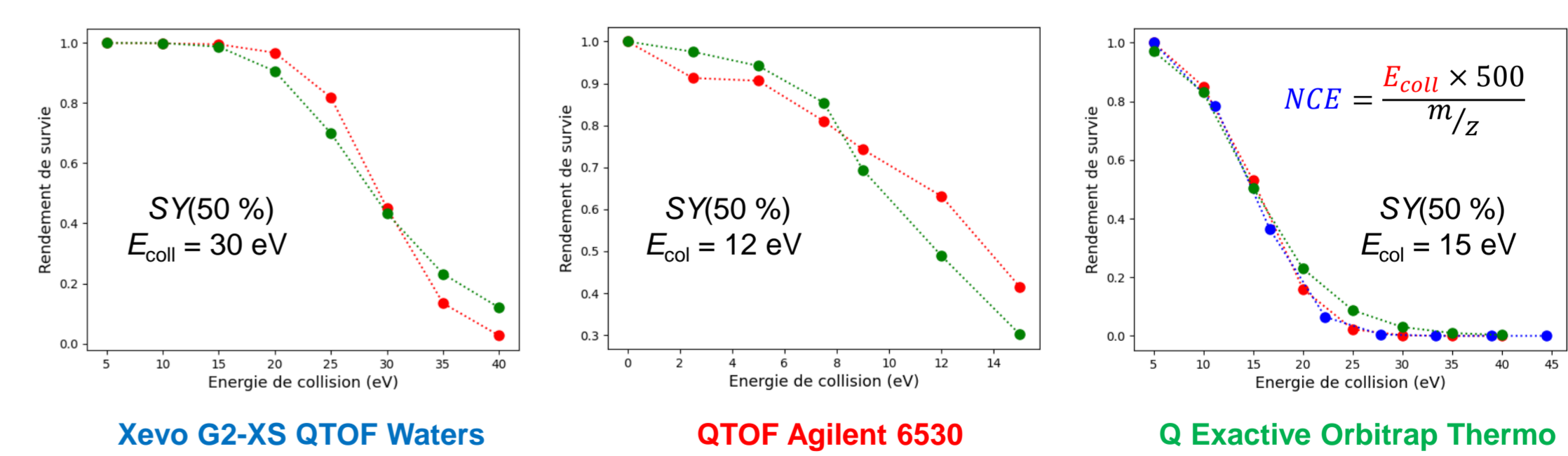
P_{therm}(m/z 556) at 293 K + 2.7 eV
<E_{therm}> = 0,99 + 2,7 = 3,69 eV (596 K)



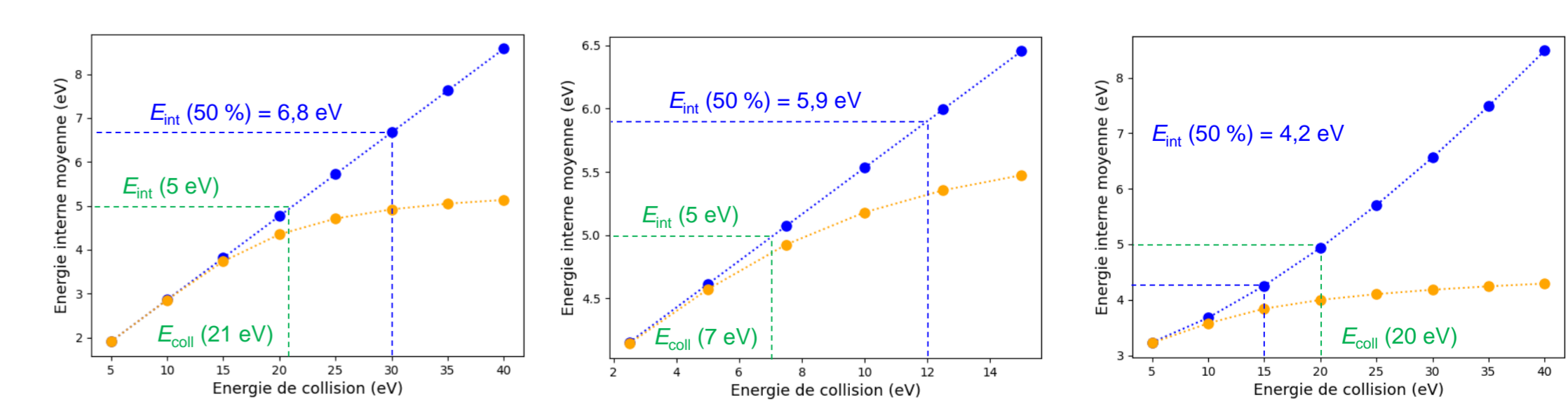
P_{therm}(m/z 556) at 293 K
<E_{therm}> = 0,99 eV



SY(Exp) vs SY(Theo) considering fragmentations (E₀ values)



E_{int} of non-fragmented ions vs E_{int} of activated ions (E₀ = 10 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.

Acknowledgements : FEDER funds, Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation, région Bretagne, département d'Ille et Vilaine et Rennes Métropole (CPER MATECOM 2015-2020 and CyMoCoD 2021-2026).

