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Italiadomani
PIANO NAZIONALE
DI RIPRESA E RESILIENZA

Theoretical and Spectroscopic analysis of Gold(I) Cysteine and Selenocysteine Complexes

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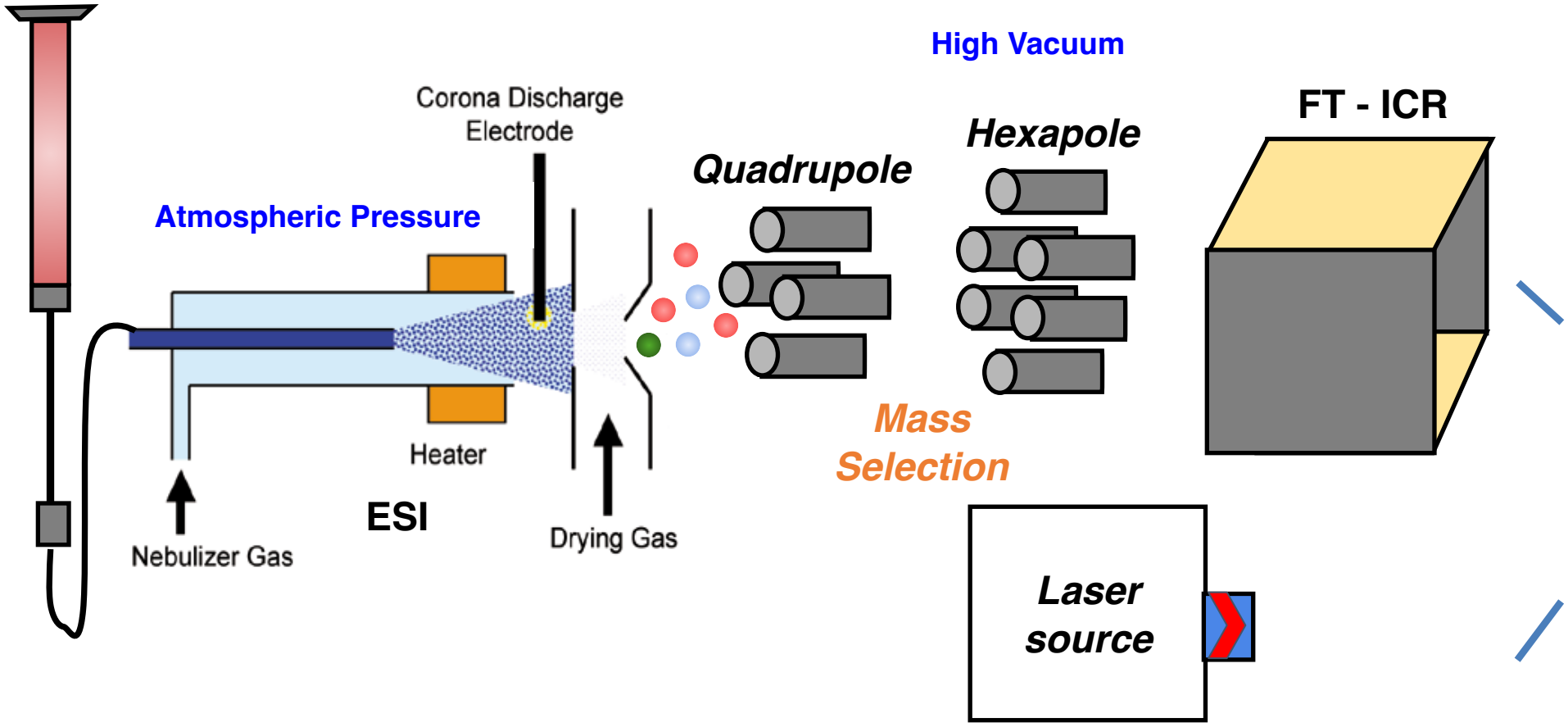

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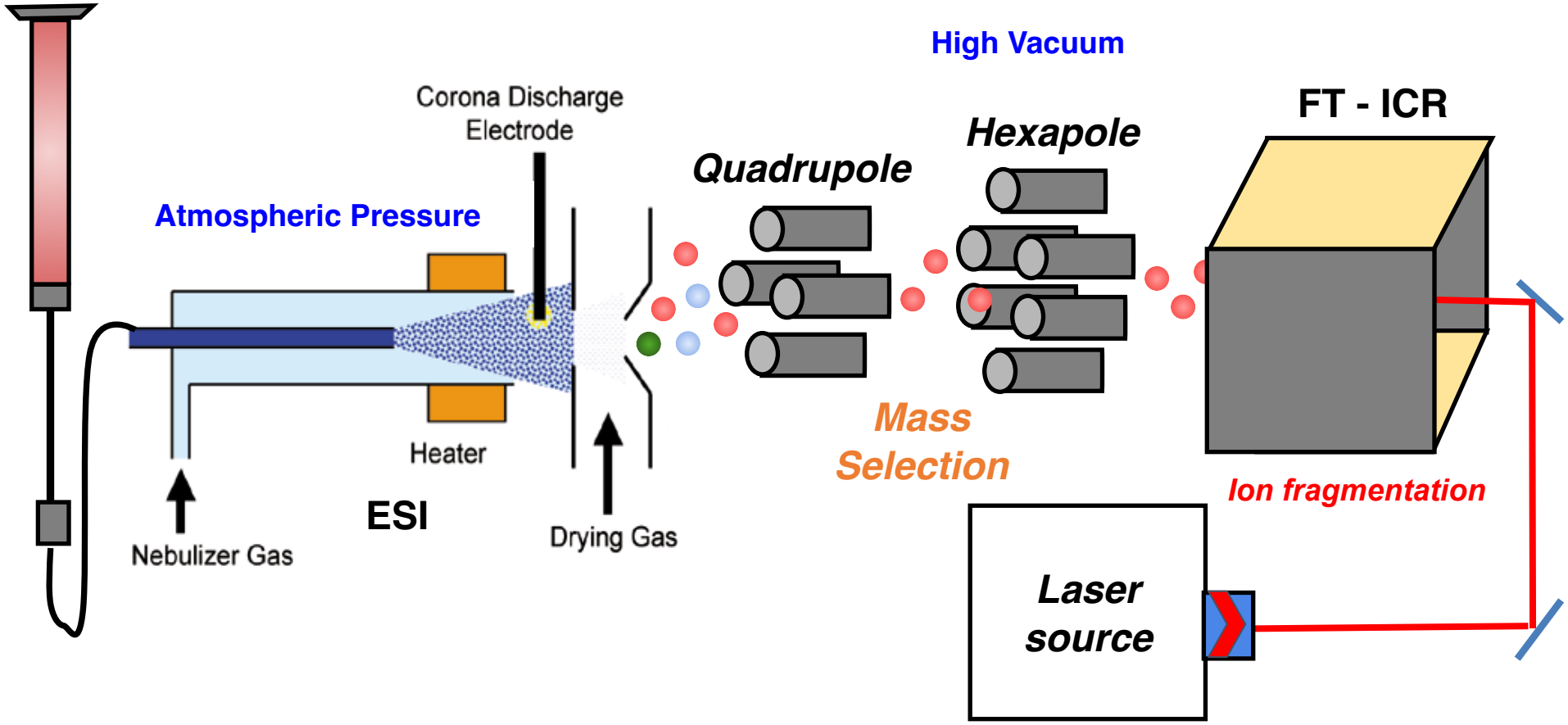

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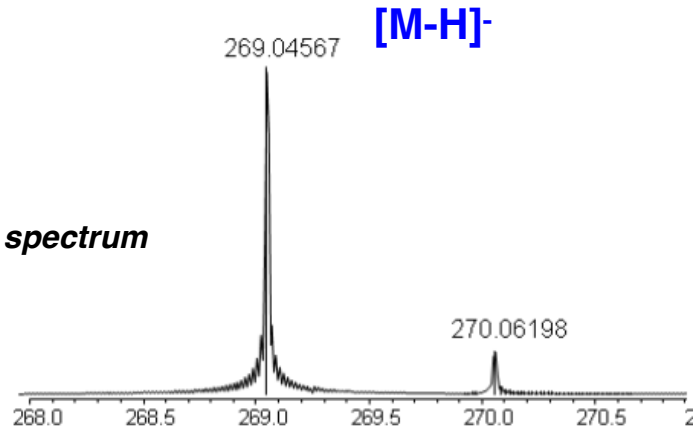

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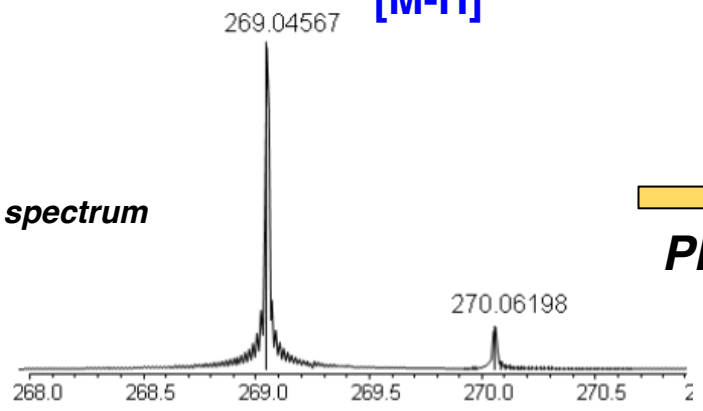

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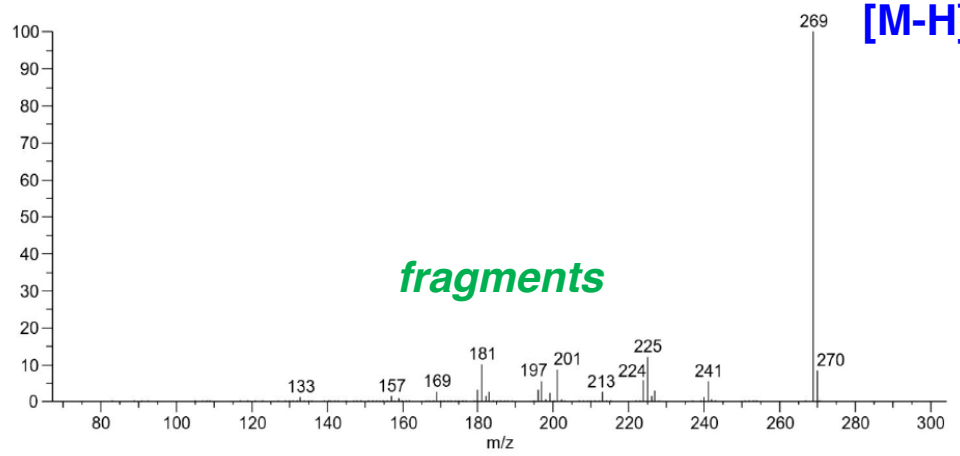

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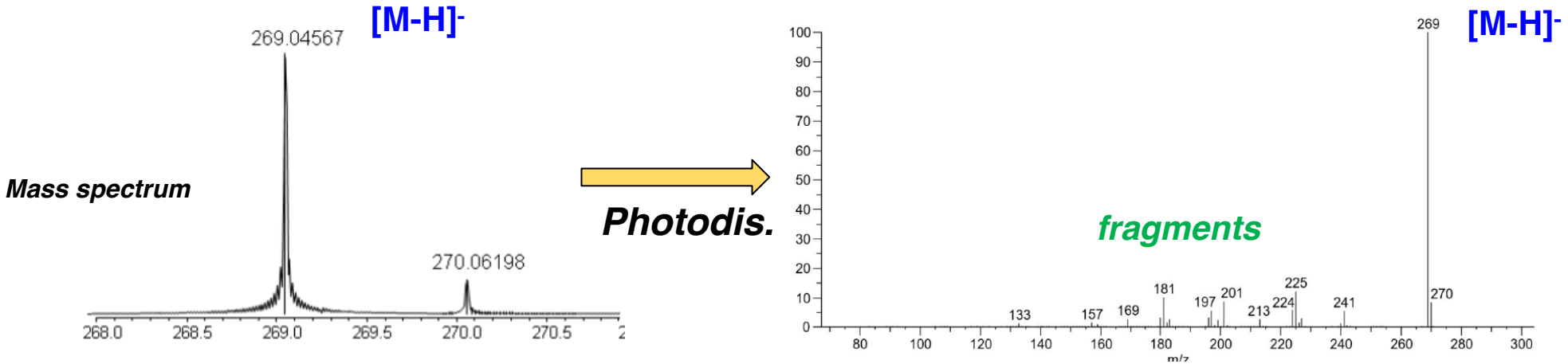
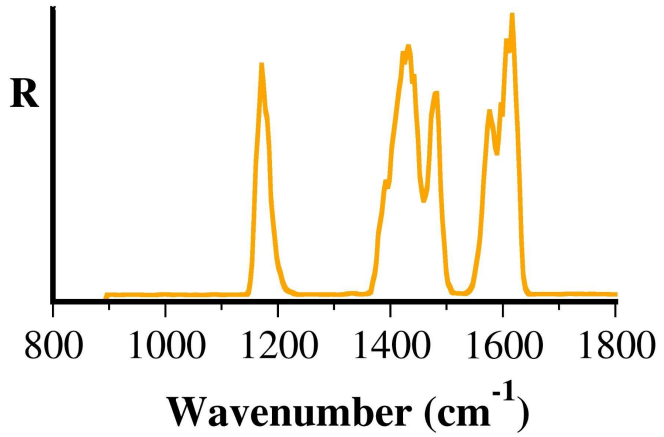


$$R = -\log[I_{parent} / (I_{parent} + \Sigma I_{fragment})]$$



IRMPD spectrum of the finger print region

Computational procedure

1) Conformational search of the most stable isomers and conformers.

2) Geometry optimization with standard computational method (e.g. B3LYP/6-311+G**) and benchmark of DFT functionals.

3) Geometry optimization and calculations of harmonic frequencies with best functionals and the highest basis set.

4) Application of scaling factor that that depends on the level of theory and wavelength region that is considered.

5) For some systems, to reach a satisfactory accuracy it is necessary to include the anharmonic vibrational corrections, with increase of computational burden.

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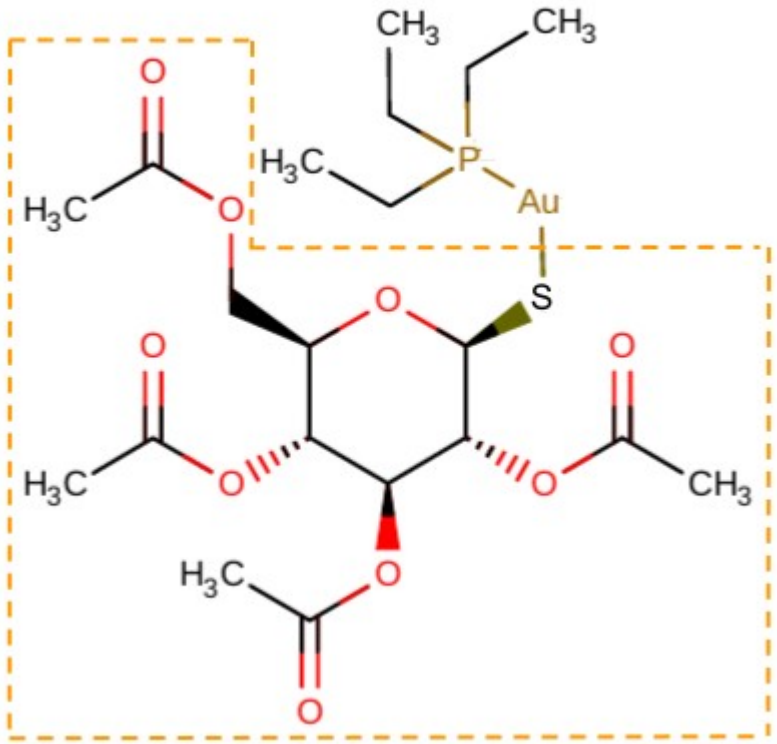
Auronofin and Gold(I) complexes with Cys and Sec



Auranofin (AF), approved in 1985 for the treatment of rheumatoid arthritis

AF and related complexes favour binding cysteine (Cys) and selenocysteine (Sec) residues contained in proteins like albumin, the proteasome system, the NF-κB protein complex and thioredoxin reductase (TrxR).

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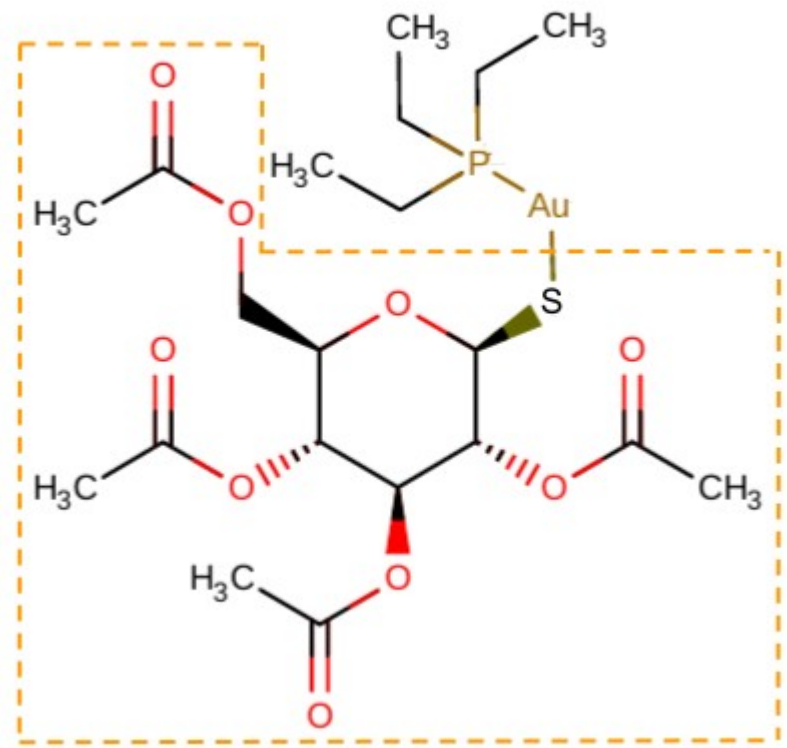

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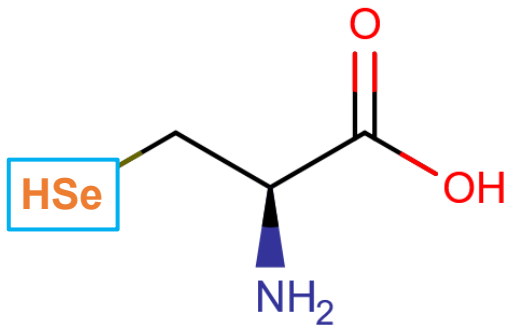
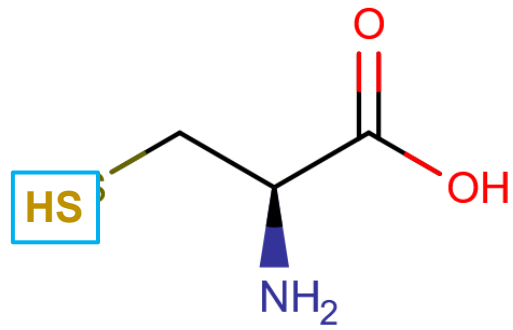


Sec



Cys

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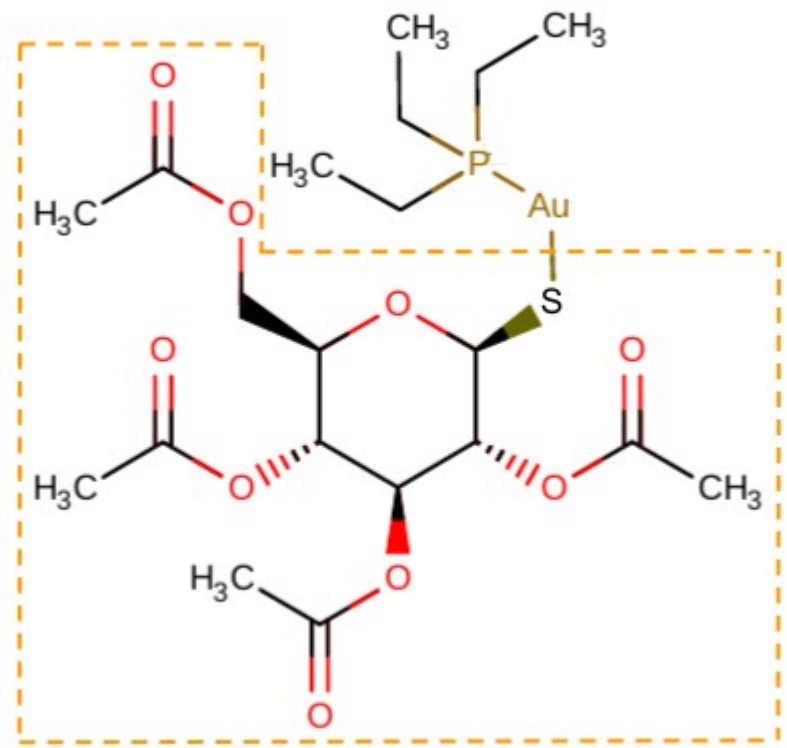

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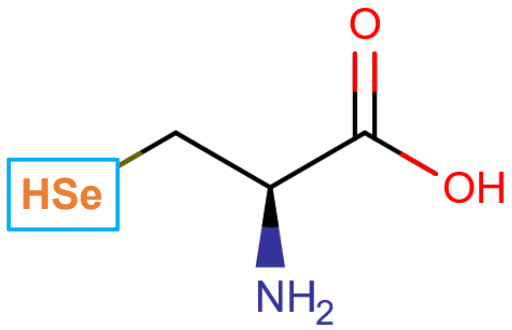

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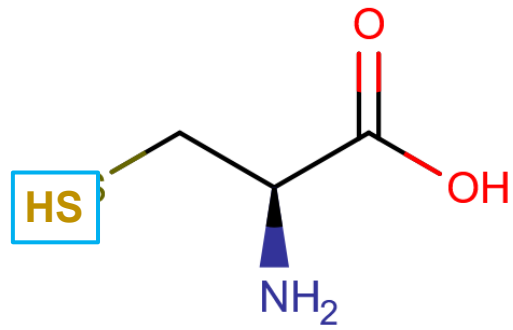

Cys

AF

$[(Et_3P)AuSec]^+$

$[(Et_3P)AuCys]^+$

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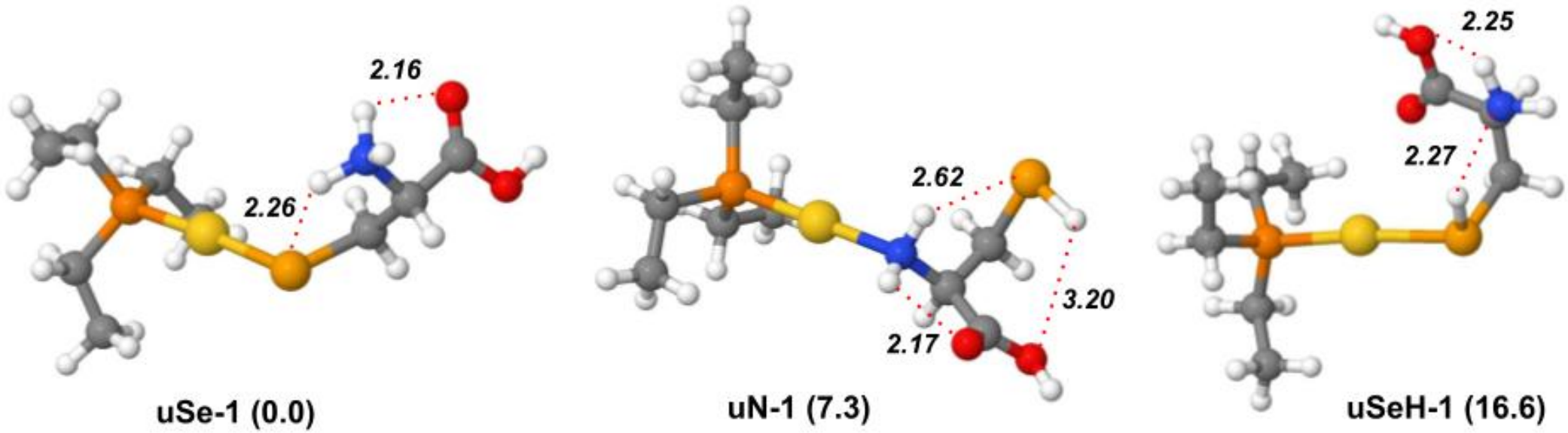
Results - IRMPD spectroscopy and structure of $[(Et_3P)AuSec]^+$



Optimized geometries of the most stable isomers and conformers of the $[(Et_3P)AuSec]^+$ ion, computed in **gas phase** at the **B3LYP/BS1** level of theory. Free energy values relative to **uSe-1** are reported in parenthesis in kJ mol^{-1}. Hydrogen bond distances (Å) are indicated by red dotted lines.

BS1: 6-311+G(2df,pd) for H, C, N and O atoms, 6-311+G(3df) for P and Se, and the LANL2TZ-f pseudopotential for Au.

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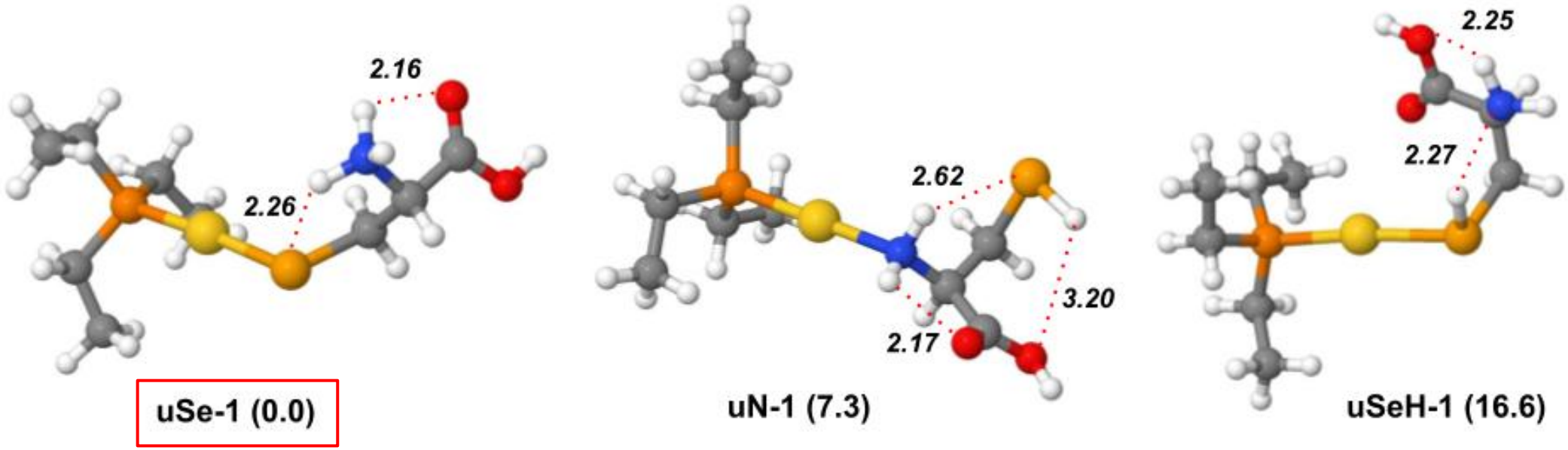

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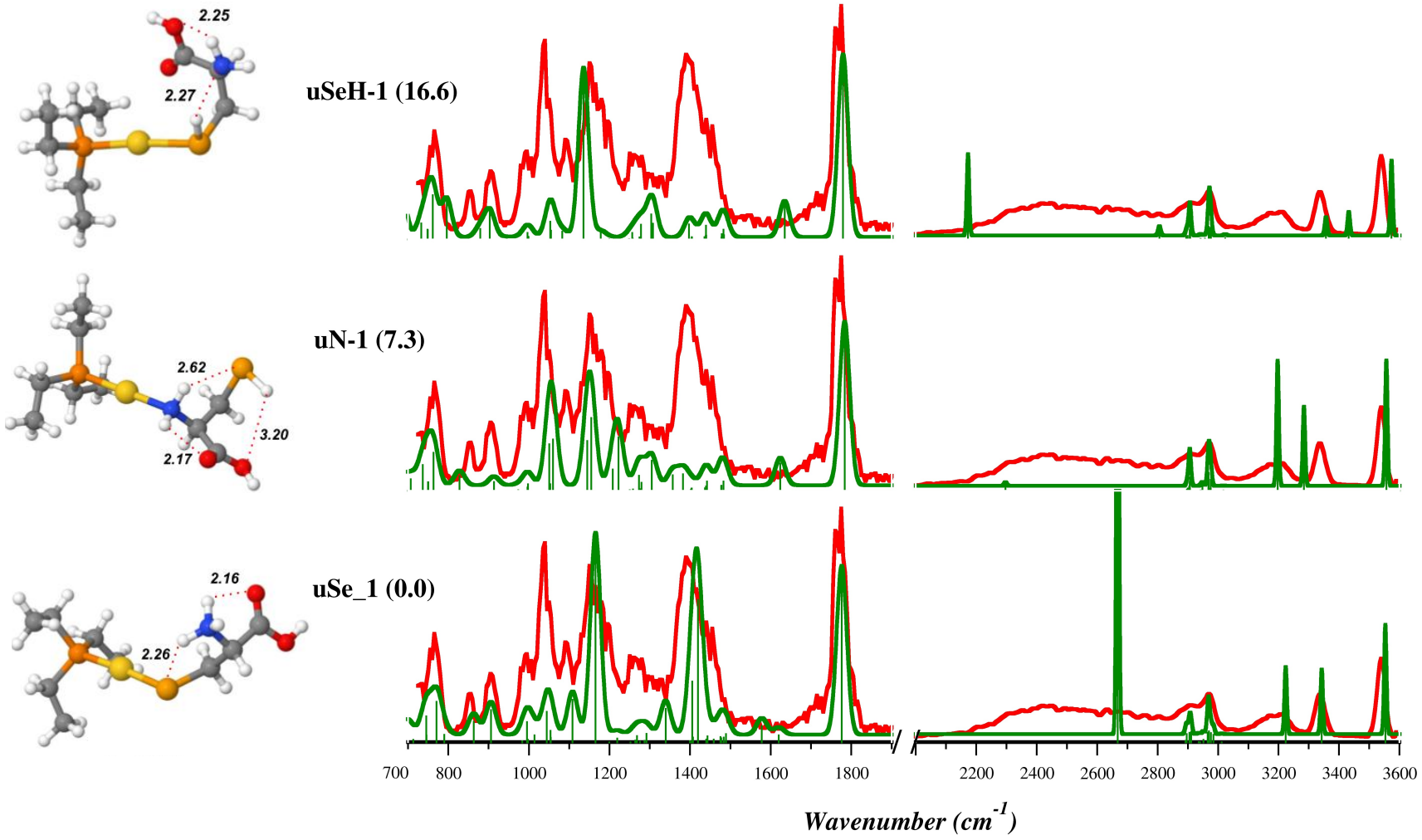

Lvl of theory: B3LYP/BS1
Scaling factors: 0.985 (700–2000 cm^{-1}) and 0.955 (2000–3800 cm^{-1}).

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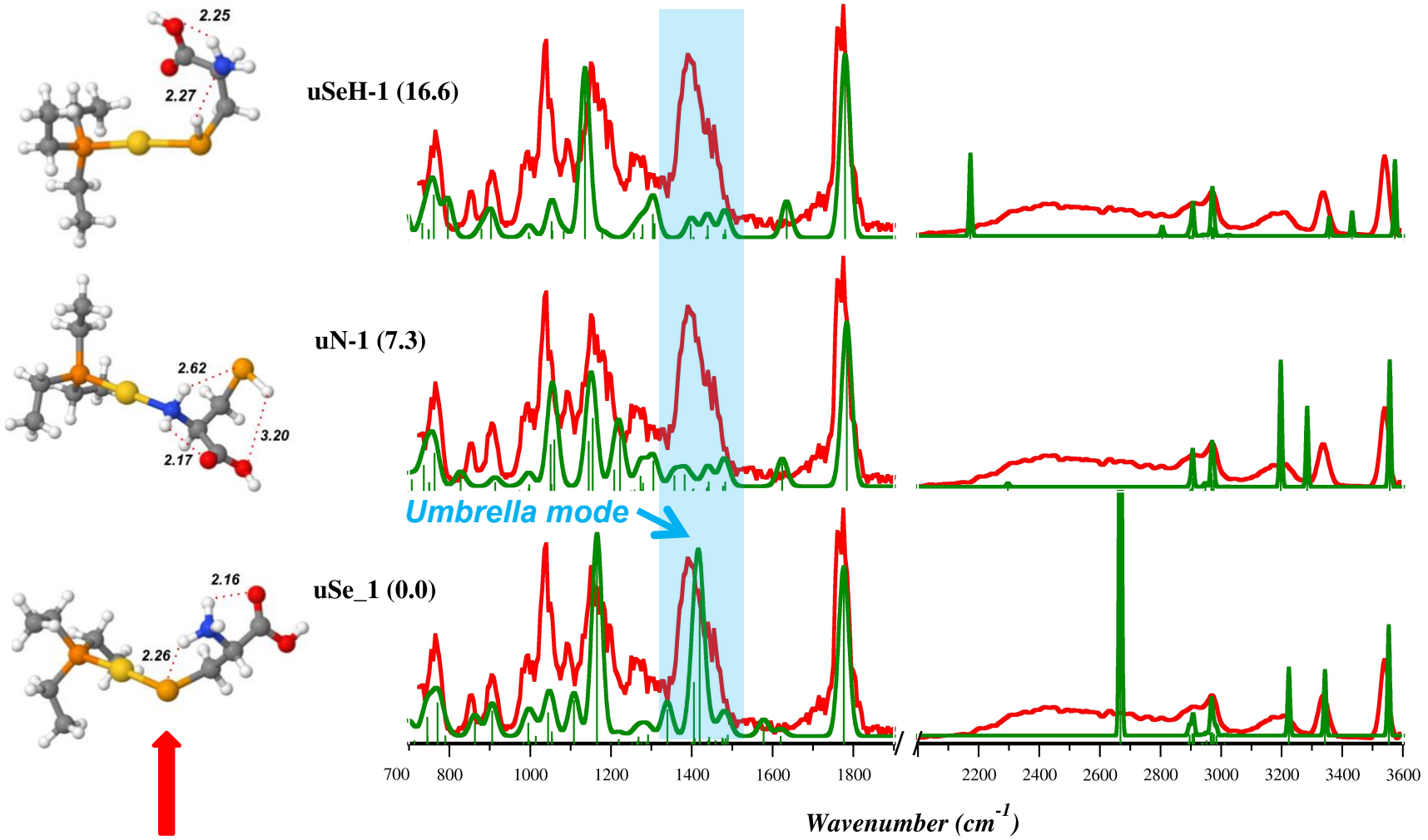

The most abundant species in the ion population is the zwitterionic uSe isomer (Se^-, NH_3^+), characterized by the presence of a ***protonated amino group****, whose associated* ***umbrella mode*** *gives rise to a* ***highly diagnostic band*** *in the structural assignment.*

Lvl of theory: B3LYP/BS1
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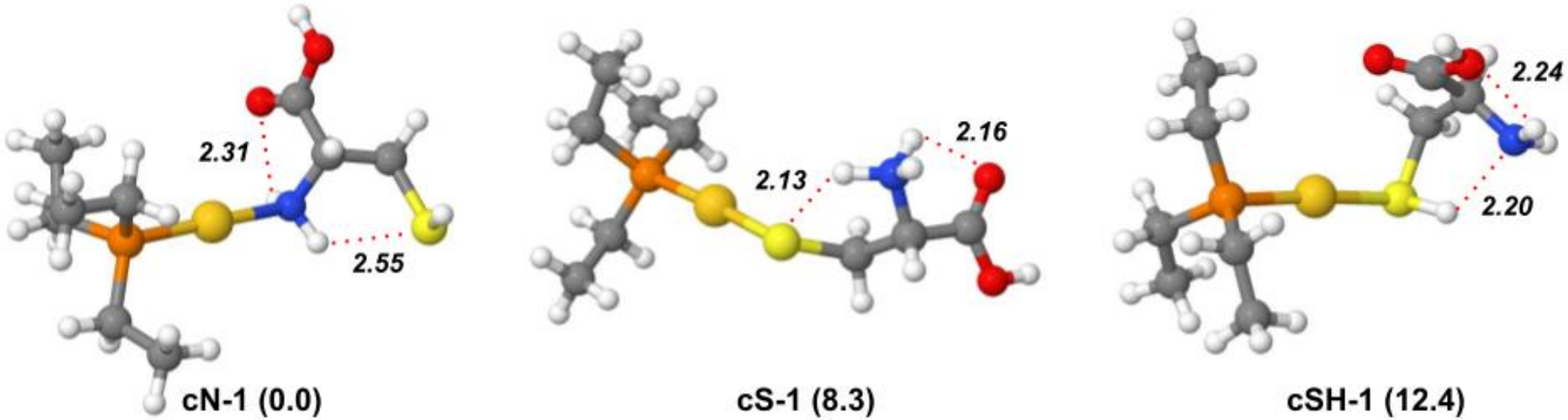
Results - IRMPD spectroscopy and structure of $[(Et_3P)AuCys]^+$



Optimized geometries of the most stable isomers and conformers of the $[(Et_3P)AuCys]^+$ ion, computed in **gas phase** at the **B3LYP/BS1** level of theory. Free energy values relative to **cN-1** are reported in parenthesis in kJ mol^{-1}. Hydrogen bond distances (Å) are indicated by red dotted lines.

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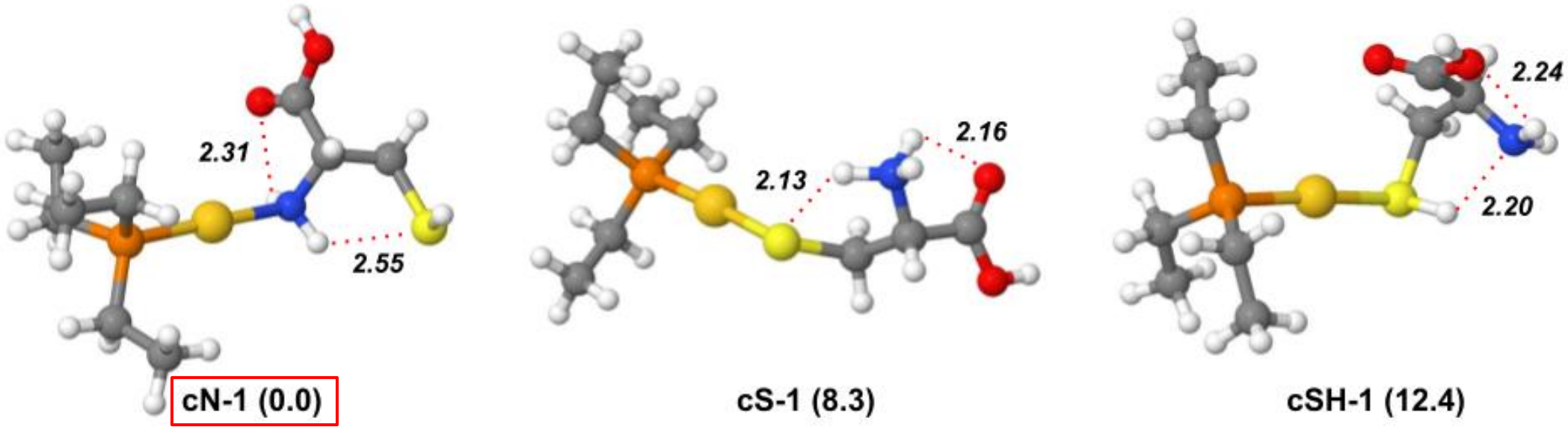

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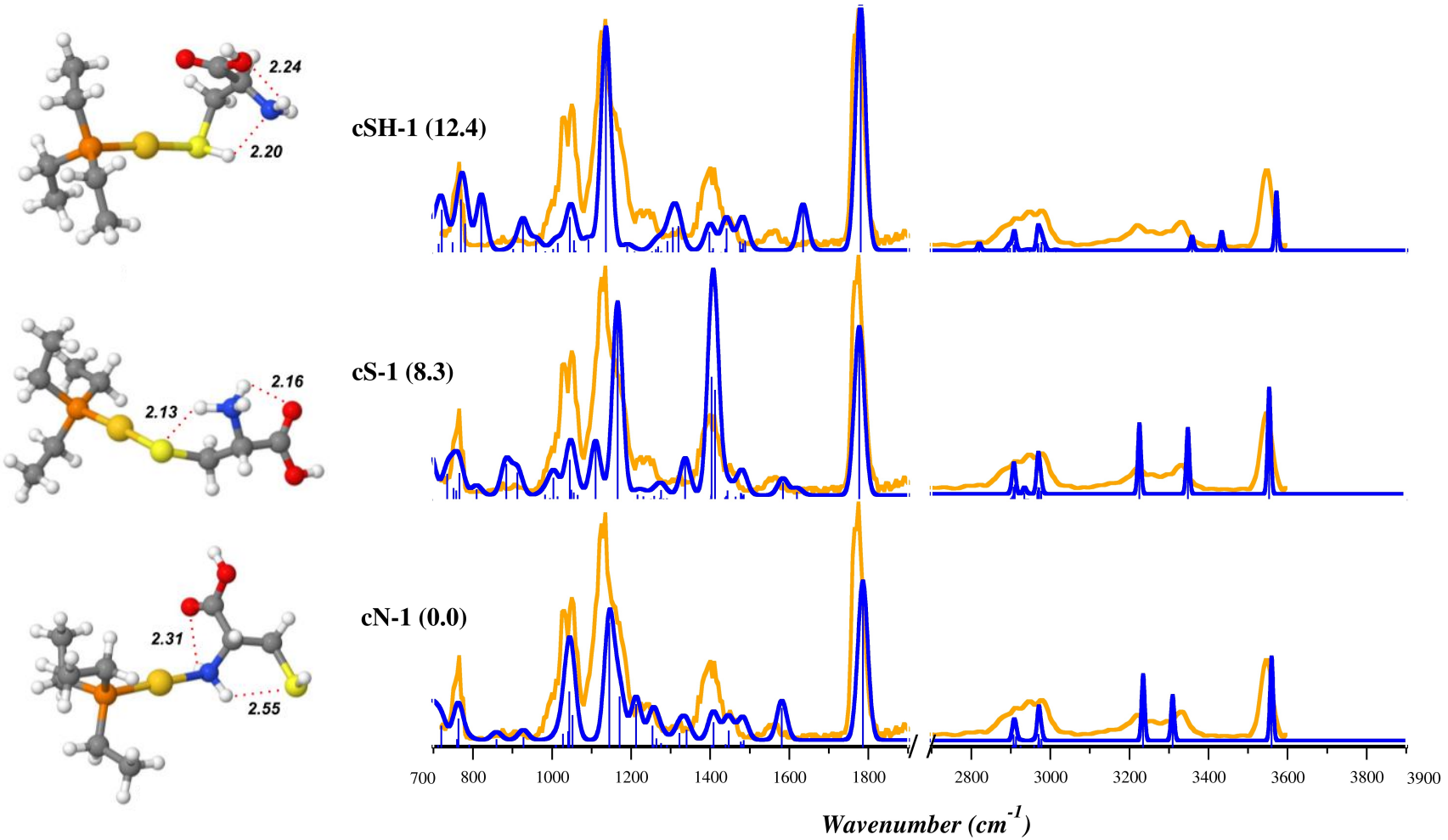

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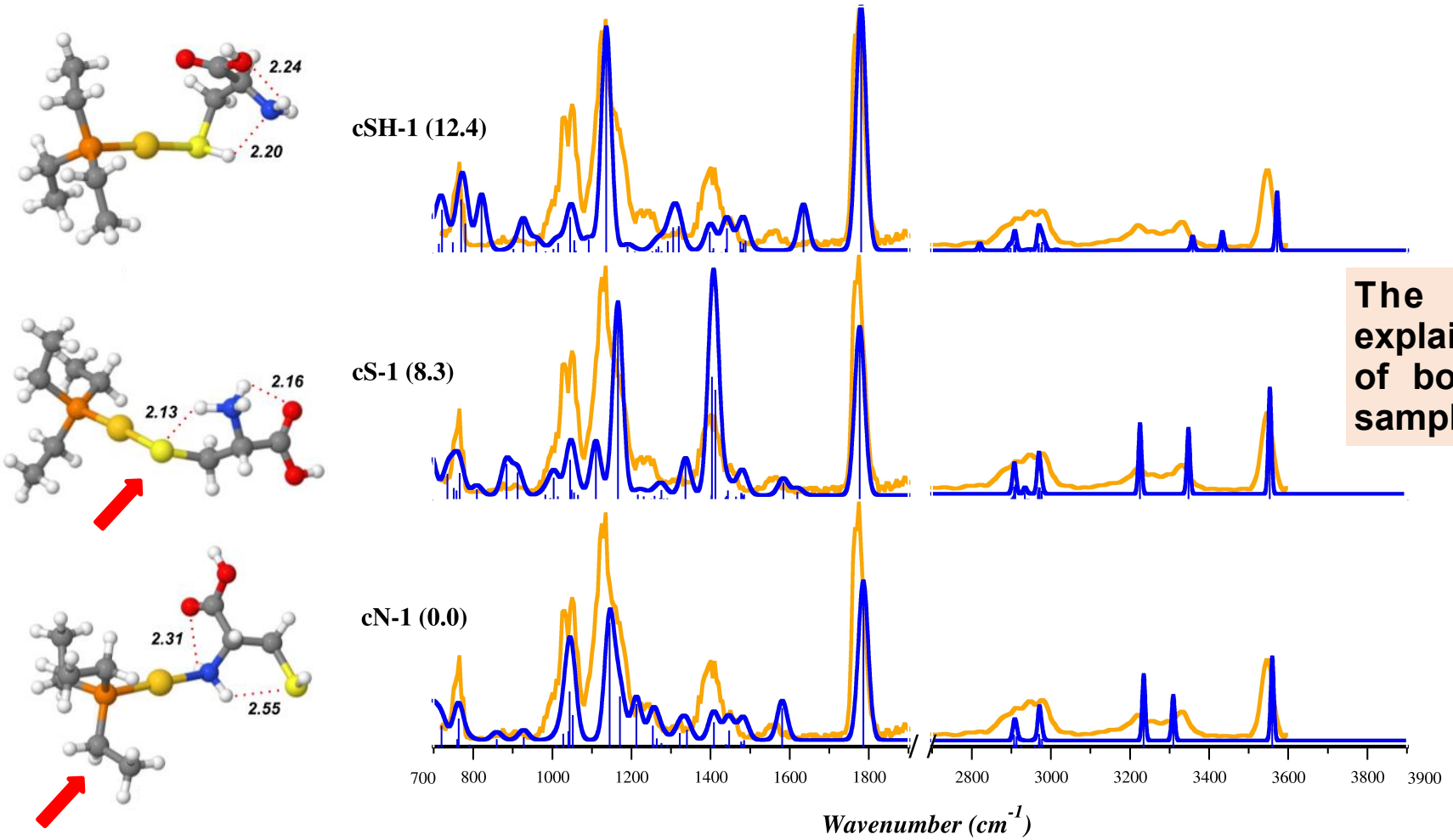

The experimental envelope can be explained considering the contributions of both cS-1 and cN-1 isomers to the sampled ion population.

Lvl of theory: B3LYP/BS1
Scaling factors: 0.985 (700–2000 cm^{-1}) and 0.955 (2000–3800 cm^{-1}).

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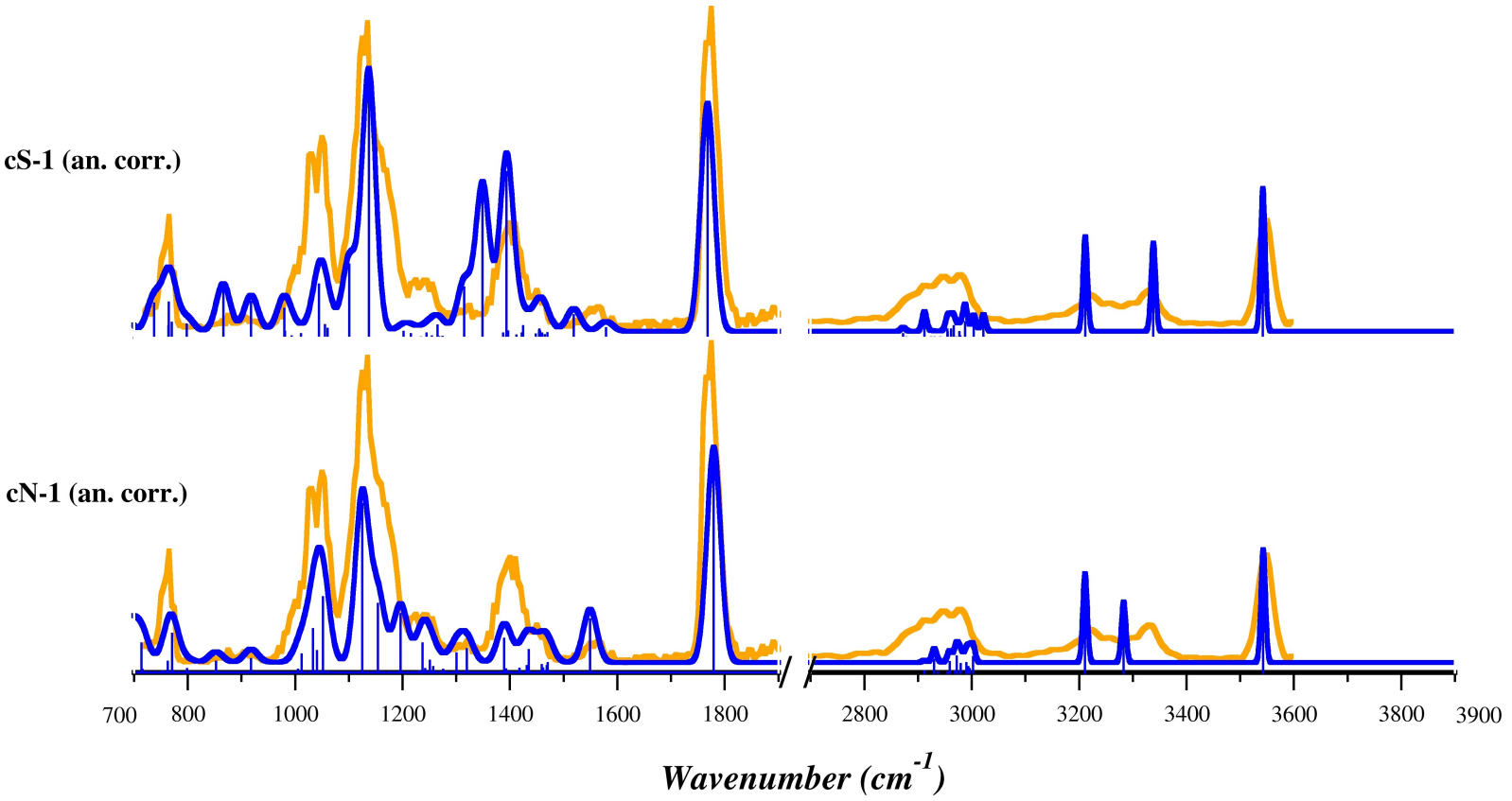

$\nu^{hybrid} = \nu^{harm}$ (B3LYP/BS1) + $\Delta\nu^{anharm}$ (B3LYP/6-311+G(d,p)/LANL2DZ)

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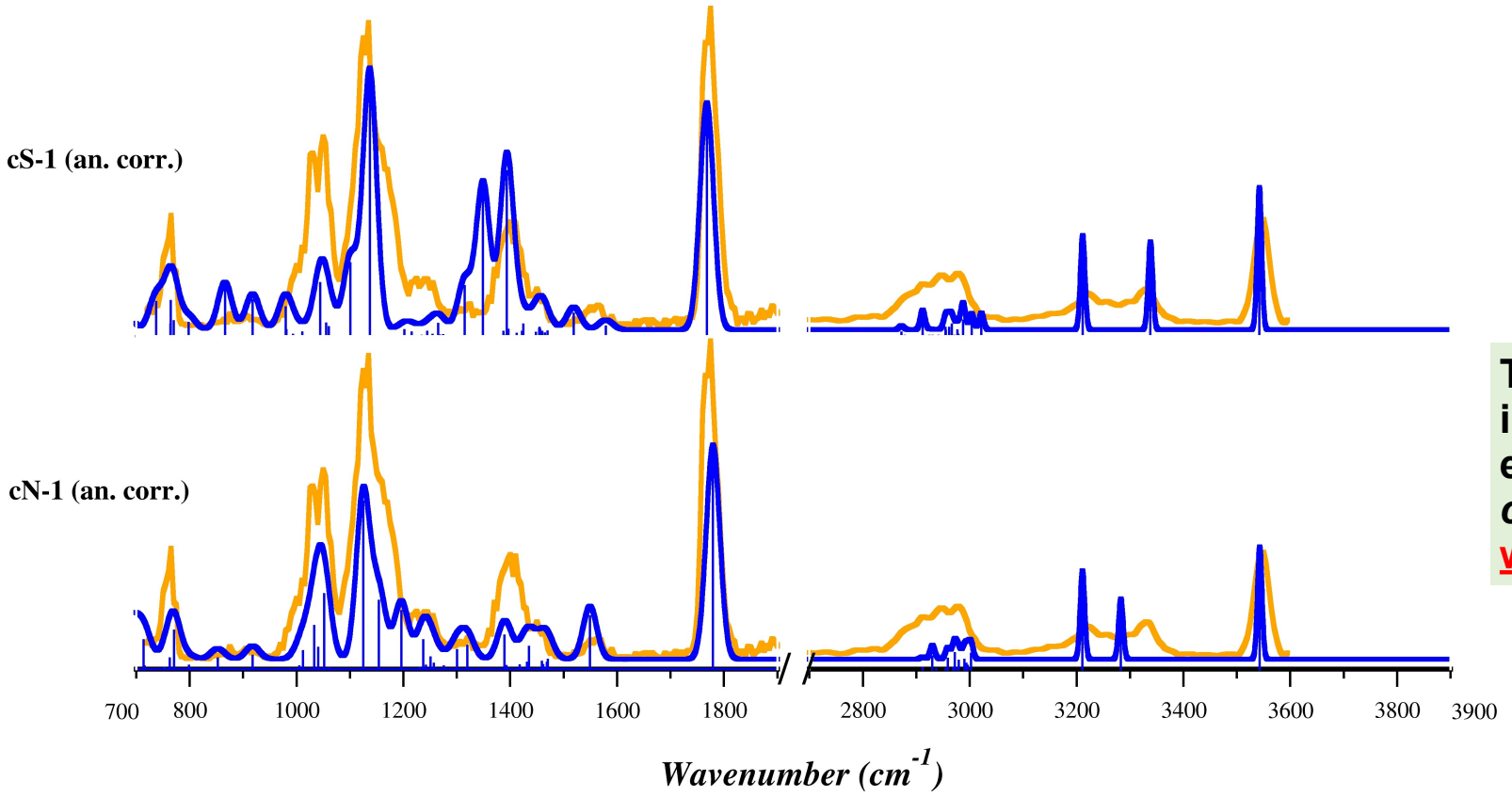

The anharmonic corrections significantly improve the correspondence with the experimental spectrum for both *cN-1* and *cS-1*, allowing band attribution without applying any scaling factors.

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Results - IRMPD spectroscopy and structure of $[(Et_3P)AuCys]^+$

Relative free energy values (kJ mol^{-1}) ***of cN-1*** *and* ***cS-1*** *computed in solution (methanol and water) using the* ***CPCM*** *and* ***Onsager methods****.*

$[(Et_3P)AuCys]^+$ Isomer	Gas	Relative free energy - CPCM		
		Methanol	Water	Relative averaged energy (methanol and water)
cN-1	0	0	0.7	0.0 [a]
cS-1	8.3	1.4	0	0.4 [a]
$[(Et_3P)AuCys]^+$ Isomer	**ε = 1 (Gas phase)**	**Relative free energy - Onsager Method**		
		ε = 32.61 (Methanol)	**ε = 78.36 (Water)**	**ε = 55.49 [b] (water-methanol mixture 50:50)**
cN-1	0	0.0	0.0	0.0
cS-1	8.3	3.5	3.2	3.3

[a] Free energy value computed as [G(methanol) + G(water)/2] to estimate the relative free energies in a water-methanol mixture (50:50).
[b] Hypothetical dielectric constant of a water-methanol mixture (50:50) computed as [ε(methanol) + ε(water)]/2],

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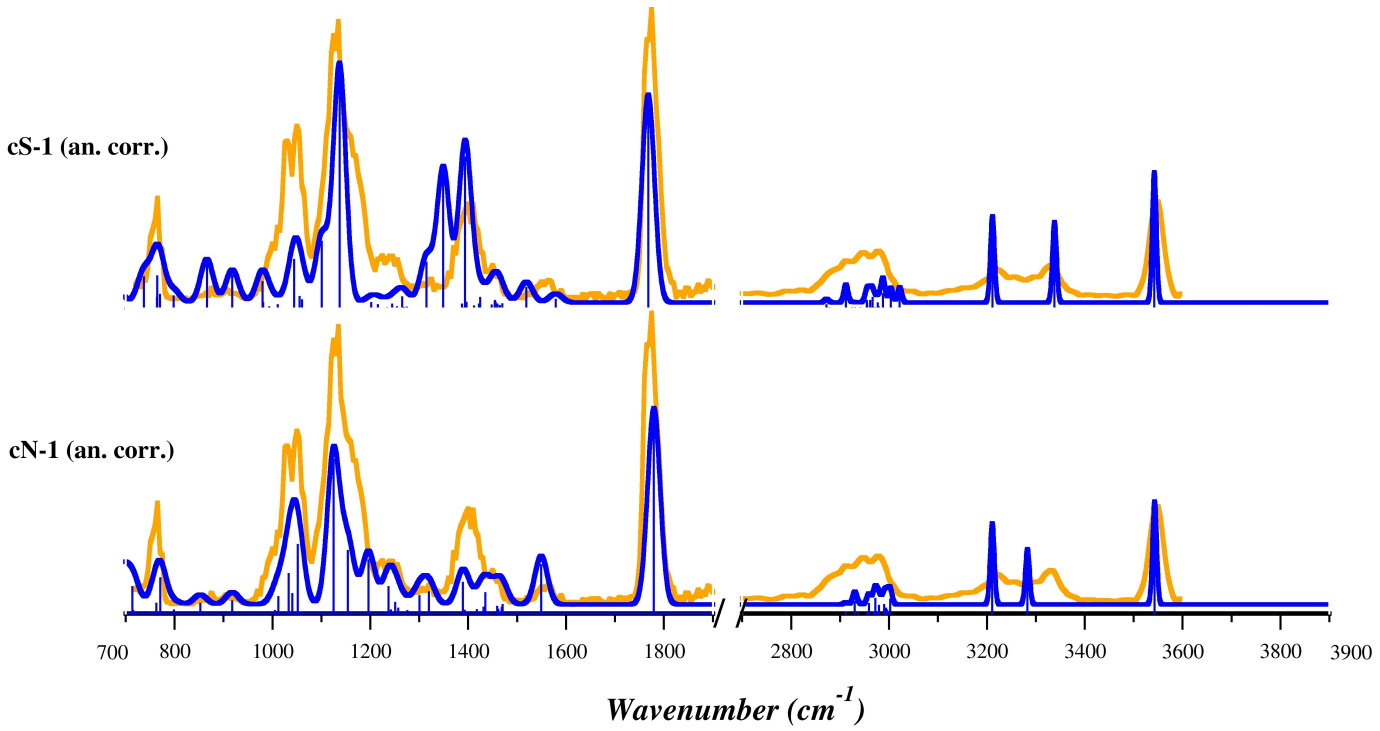

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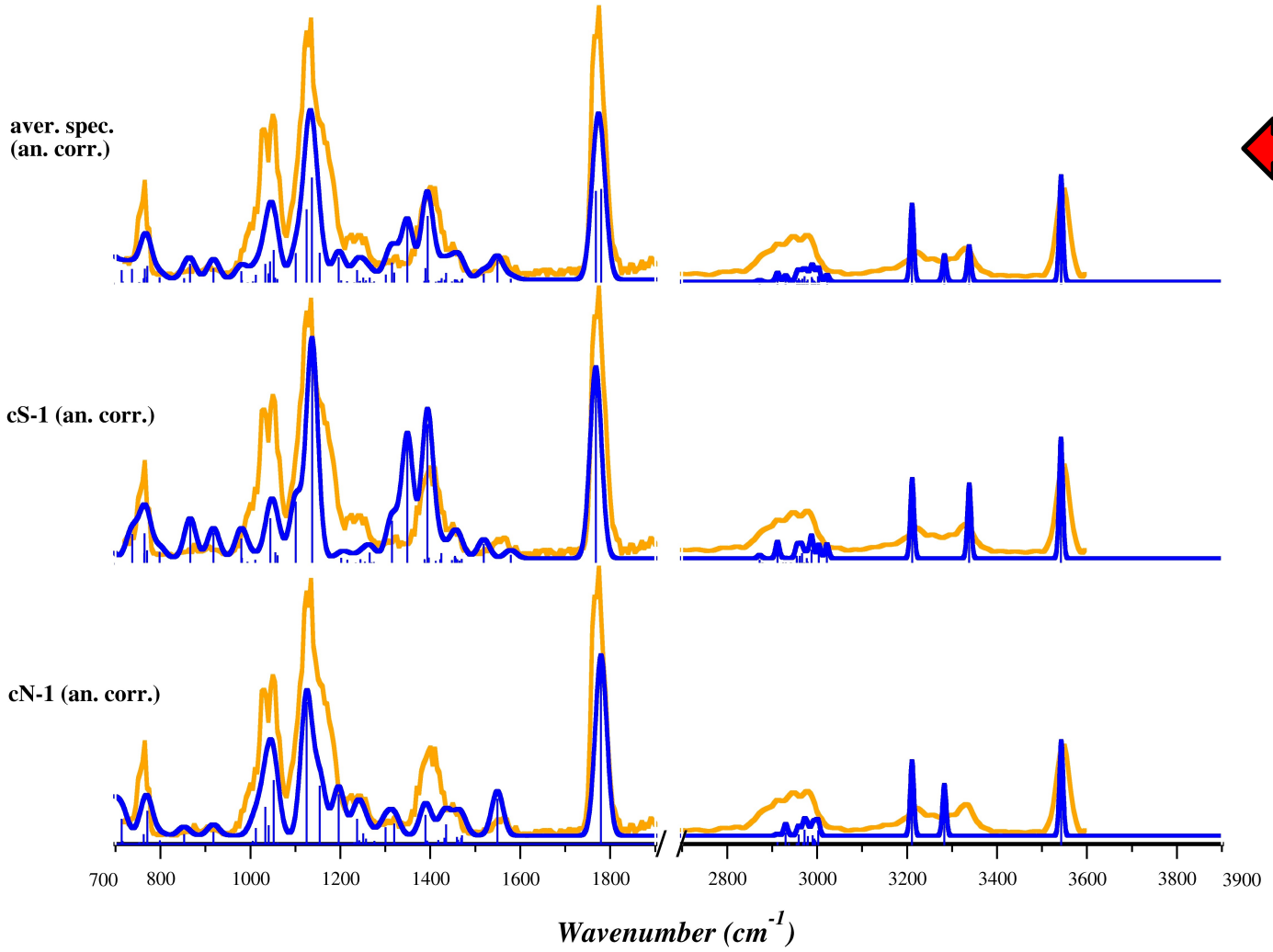

Anharmonic averaged spectrum

cN-1 : cS-1 = 68 : 32

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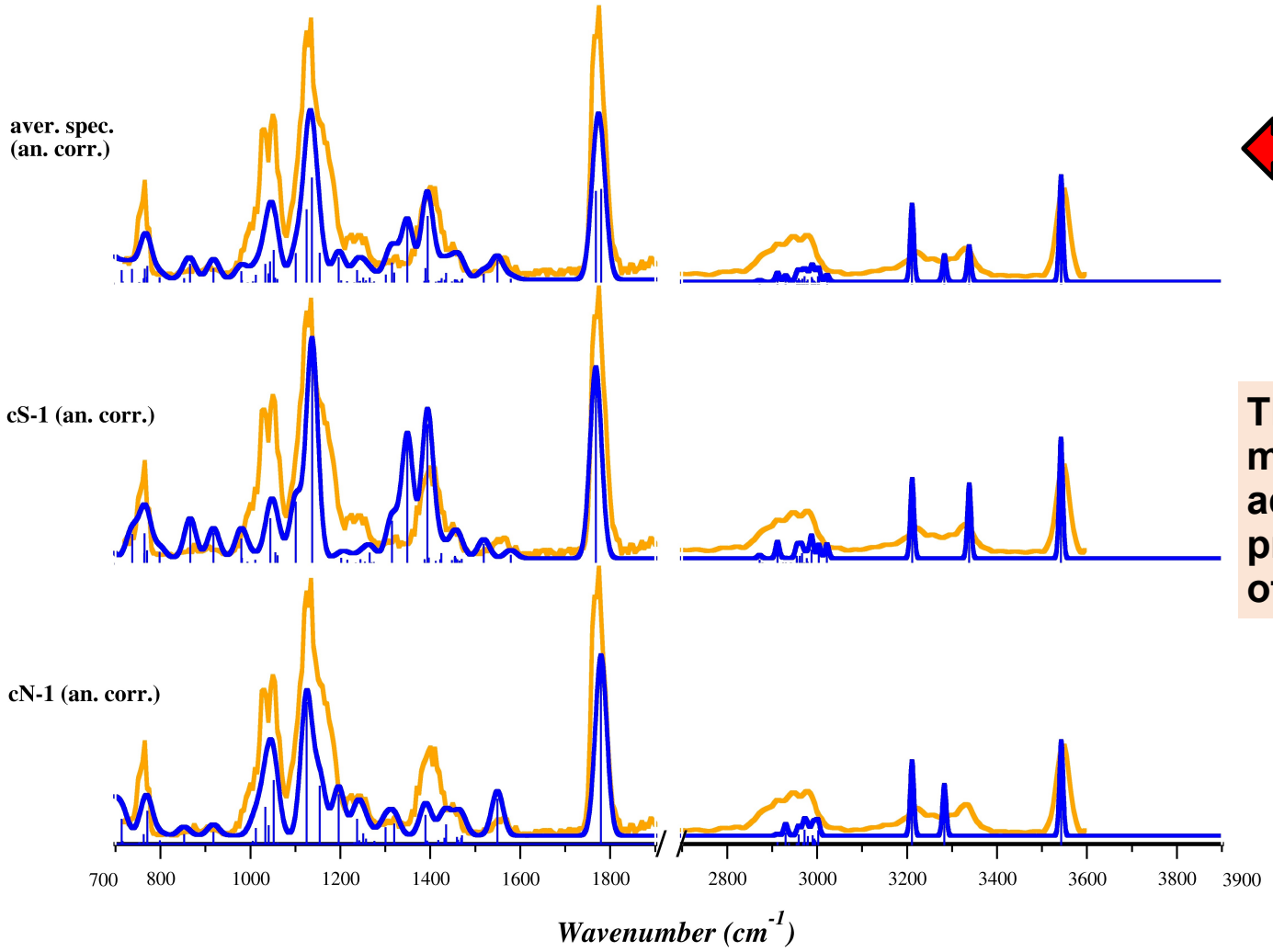

Anharmonic averaged spectrum

cN-1 : cS-1 = 68 : 32

The anharmonic spectrum for a 68:32 ratio (accurately matching the experimental spectrum) provides an additional indication that both isomers, cN and cS, are present in the sampled ion population, with an excess of cN.

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Conclusions

$[(Et_3P)AuSec]^+$ complex is well simulated by the theoretical spectrum of the lowest energy Se-bound isomer, in agreement with the strong tendency of gold(I) to bind soft nucleophiles.

The assayed ion population of $[(Et_3P)AuCys]^+$ complex is found to be composed of both N- and S-bound isomers. The relative amount of the two isomers is likely related to their mutual stability in the condensed phase, which may be drastically modified by the solvent dielectric constant.
This interesting result highlights the possibility of targeting different nucleophilic functions with gold-containing complexes depending on the dielectric constant of the medium.

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Prof. L. Storchi, Prof. C. Coletti, and Prof. N. Re

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Università "La Sapienza" of Rome

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Grazie per l'attenzione

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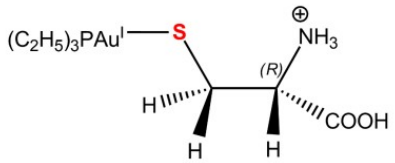
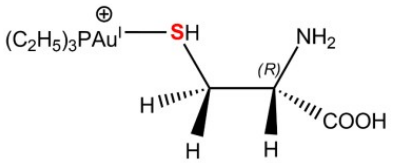
2D structures of A) $[(Et_3P)AuCys]^+$ and B) $[(Et_3P)AuSec]^+$ isomers investigated in this study

A)

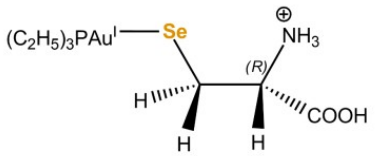


cS

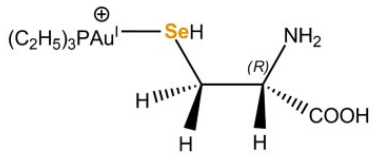


cSH

B)



uSe



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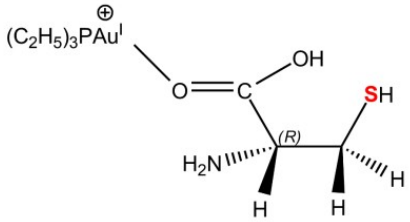
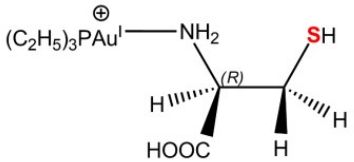
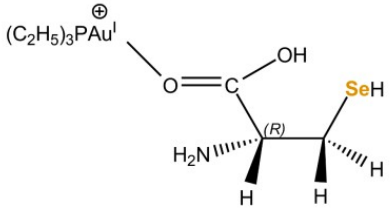


cCOOH



cN



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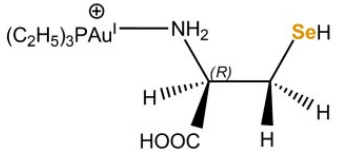
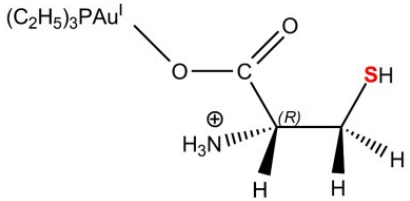
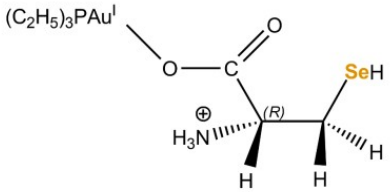


uN



cCOO



uCOO