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A COMBINED EXPERIMENTAL AND DFT INVESTIGATION OF ISOMERIC HEPARIN DISACCARIDES METAL COMPLEXES

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Motivations :

Why Heparin disaccharides?

Heparin (HP) glycosaminoglycans (GAGs)¹, an anticoagulant drug, are recognized to be a biologically important polysaccharide, and have been **involved in many biological processes** such as blood coagulation, cell-cell and cell-matrix interaction inflammatory processes, cell growth, lipid transport and metabolism.

Why is it important to study the interaction between HP and metal cations?

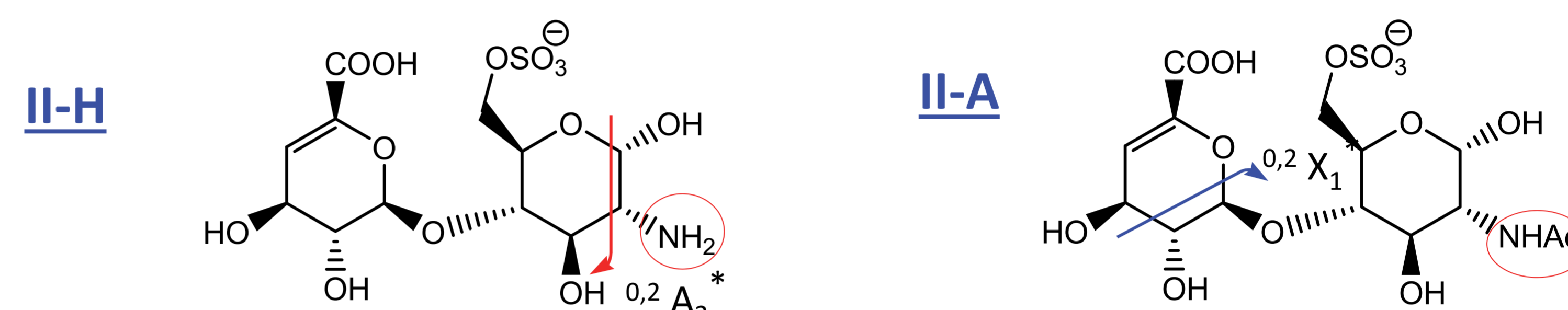
The effect of metal ions on protein-carbohydrate complexes is largely **unknown**. Heparin-biomolecule interaction can be influenced by the binding of metal ions to these complexes². For example, it has been reported that physiological Ca²⁺ **induces conformational changes** in heparin that are necessary for the interaction between the anticoagulant Heparin and Annexin V, a protein proposed to play an important role in the inhibition of blood coagulation³. It is therefore a **Calcium-dependant interaction**.

What is our strategy?

Experimentally our aim was to study (Ca(II-H))⁺ and (Ca(II-A))⁺ complexes by tandem **ESI/MS**. Once generated in the gas phase, ions then undergo a fragmentation process by Collision Induced Dissociation (**CID**). The Ca²⁺ cation induces different conformational changes in both isomers, resulting in **completely different fragmentation pathways**. Theoretically our aim is to explain this Metal-HP interaction by **DFT** calculations and **delineate** mechanisms of dissociation accounting for the experimental data.

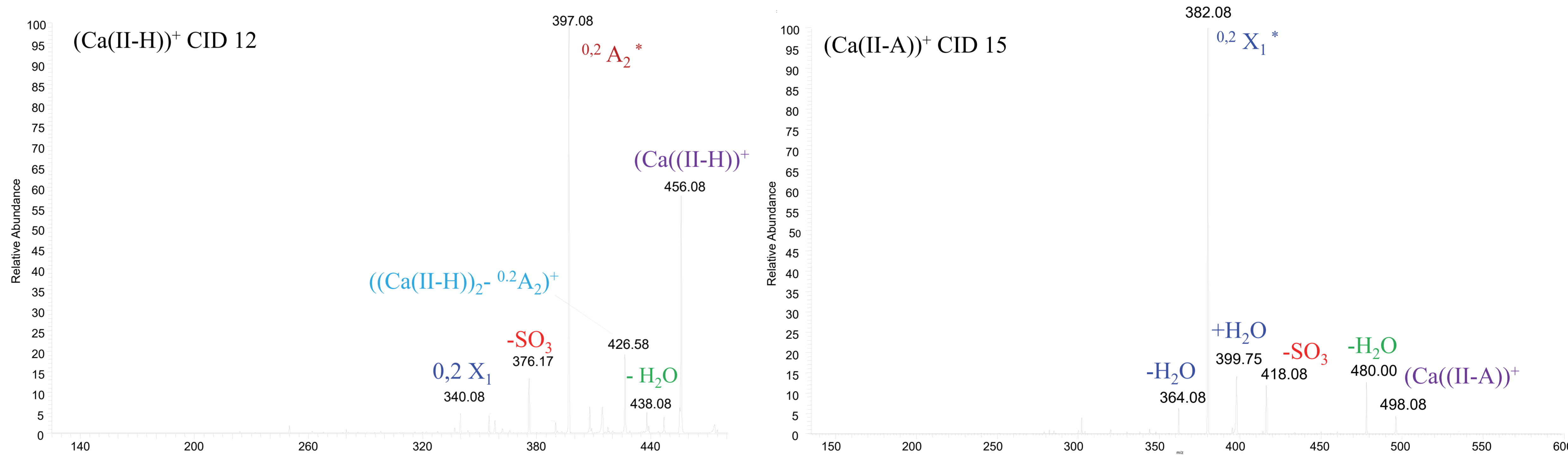
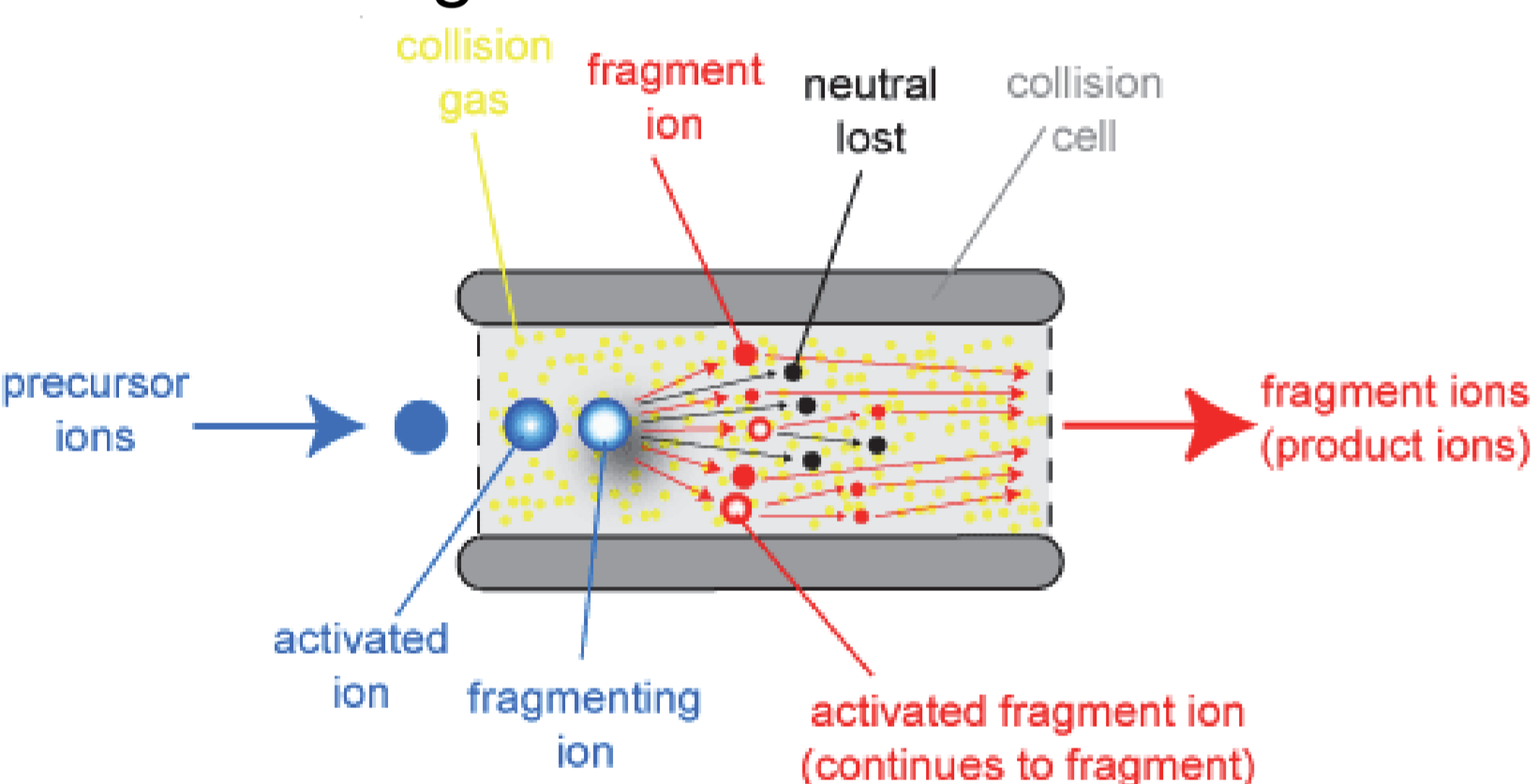
Why II-A and II-H isomers?

Without metal there is **no difference** in the MS/MS spectra of these two isomers. Only ^{0,2}A₂ fragmentation is observed. **With** Ca²⁺ dissociation pattern **changes drastically**. Interaction between Acetyl/Ca²⁺ must be important in the dissociation process.



MS/MS results:

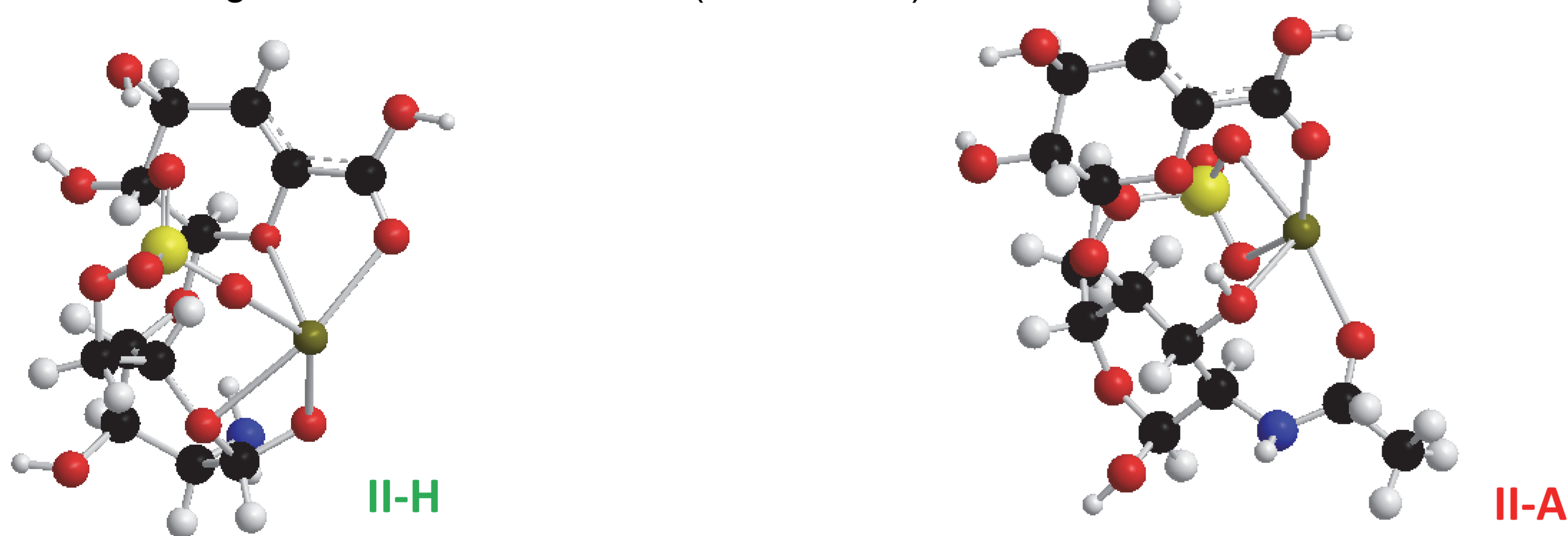
Experiments were carried out on a **LTQ Orbitrap XL** mass spectrometer coupled to an ESI source. Nitrogen gas was used as collision gas.



Computational results:

The geometries were optimized using the density functional theory (DFT) with the **B3LYP** hybrid functional and 6-311G** basis set. Refined relative energies were obtained at the **6-311++G(3df,2p)** level.

Without Ca²⁺ all the calculated 50 conformers, for each disaccharide, are very close in energy (<50 KJ/mol). Nevertheless, when **(Ca(HP))⁺** is formed it is observed an increase in relative energies between conformers (>50KJ/mol).

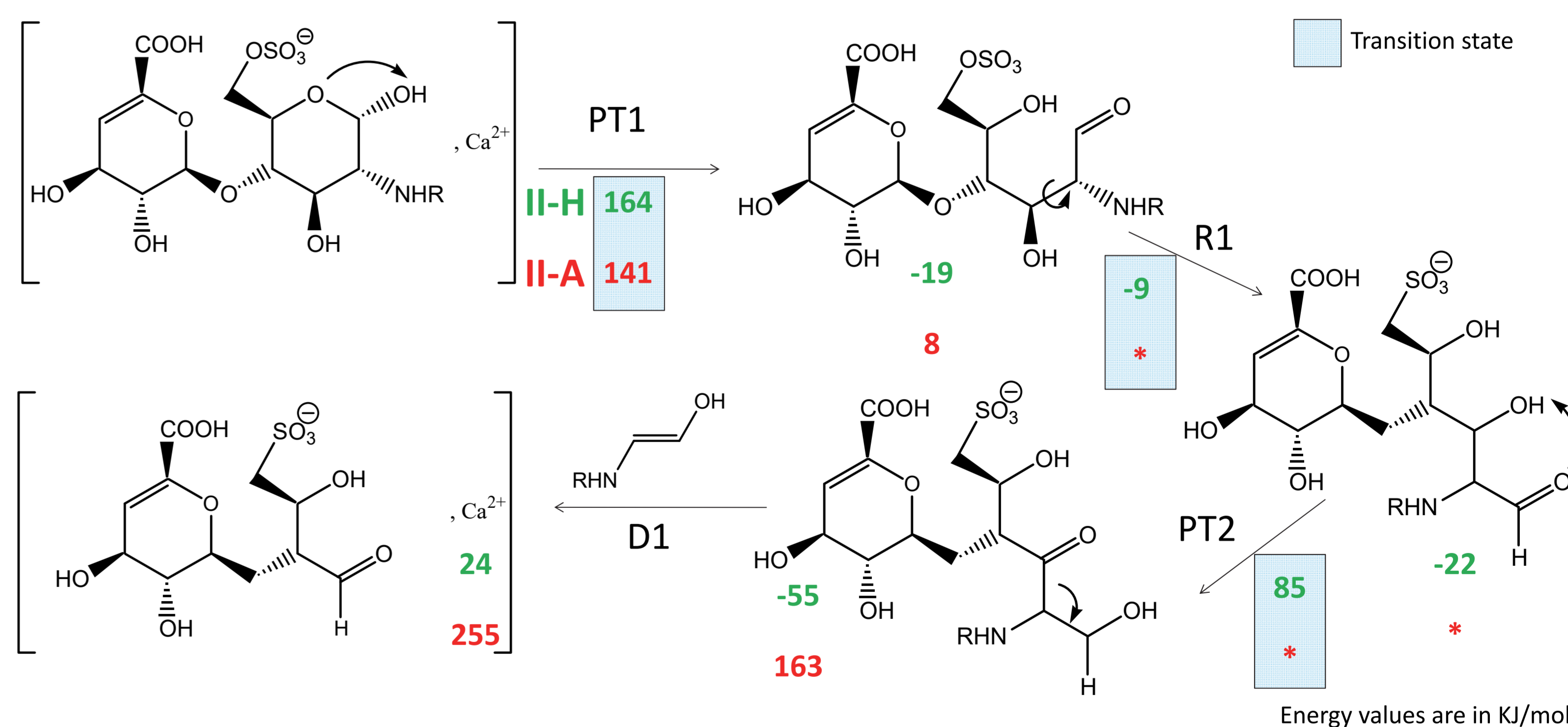


High Binding Energy (BE) values (~1400 KJ/mol) are obtained. As deduced from the conformers calculation and the BE values, the metal complex **stabilizes strongly** one structure. It seems safe to deduce that both sugars lose partially their possibilities to change structurally. **Biologically**, this consideration could be critical in order to explain the **strong interactions** aforementioned. **Analytically**, when (Ca(HP))⁺ is formed, the molecule loses its flexibility due to the fixation structure effect and therefore it is noticed a decrease in the number of fragments.

Choosing the fragmentation pathway

Leary *et al.*⁴ delineates mechanisms of dissociation for isomeric HP without metal based upon **CID** experiments and **H/D** exchange. Another mechanism has been tested in this work but those pathways remain the most favorable ones.

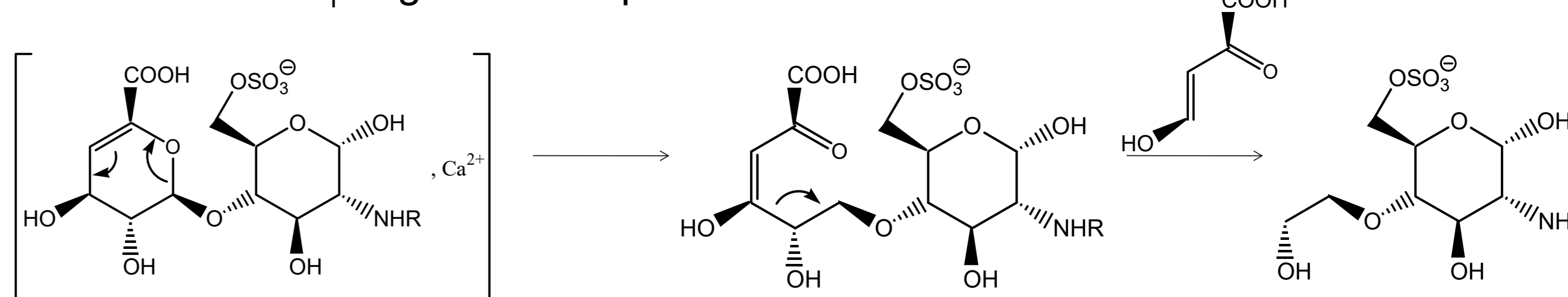
^{0,2}A₂ Dissociation



The acetyl group in II-A **blocks the R1** (Rearrangement) step. Nevertheless, it is still possible to transfer the proton through the acetyl carbonyl group. The energy associated (PT2 barrier) is however bigger (**163 KJ/mol**) than for II-H (**-55 KJ/mol**).

^{0,2}X₁ Dissociation

Starting from the initial structures, and using the dissociation mechanism given by Leary *et al.* shown below, the same methodology will be employed in order to unravel the ^{0,2}X₁ fragmentation pattern.



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4. O.M.Saad, J.A. Leary, *J. Am. Soc. Mass Spectrom*, 15 1274-1286 (2004).