



An intensive GPU--based screening of complexa9on energies towards Lanthanides--driven crystallogenesis

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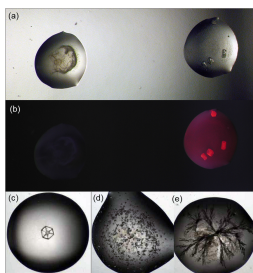
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An intensive GPU-based screening of complexation energies towards Lanthanides-driven crystallogenes

Elise Dumont¹, Raymond Grüber, Eric Girard², Nicolas Giraud³, Olivier Maury¹

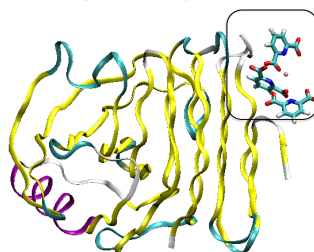
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Context: interactions lanthanides-protein ruling out crystallization



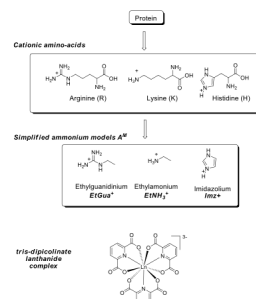
Some beautiful crystals...

(a,b) Crystallization of EcAcrB alone (right) and in the presence of [Eu(DPA)₃]³⁻ (left) under 315 nm irradiation (b). Auto-crystallization of [Eu(DPA)₃]³⁻ in the presence of a protein and (c) high NaCl concentration (>0.8M), (d) Ca²⁺ salts and (e) Mg²⁺.



Underlying ΔG...

Proximal residues involved
Inter/intra-protein
interaction ?
Protein « shape »
(hydrophobic patch) ?

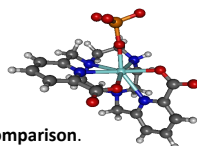


Which Ln complexes ?

Complexes such as [Y(dpa)₃]³⁻ and FR39 (pattern)

Modelling can get insights and provide a **same-footing comparison**.
This approach can be benchmarked against sophisticated NMR models.

But we need to go from ΔE (PCCP 2013 for aliphatic models) to ΔG...



An efficient GPU screening

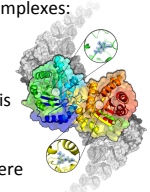
Mainly electrostatic-driven, with cationic (+1) or anionic (-3) complexes:
which amino acids develop a second-shell coordination ?

Classical MD: Amber/ff14 + parametrization of the Ln complex
GPU-timing : 100ns in two days for a decapeptide + post-analysis MMPBSA.

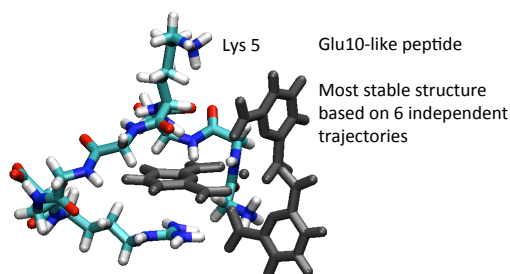
QM/MM-MD scheme towards the evaluation of interaction where the metallic center is directly involved

Amber 2015
Reference Manual

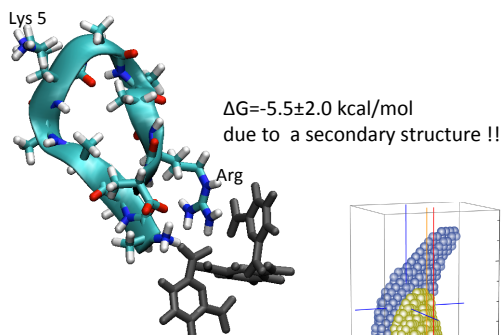
(Covers Amber and AmberTools)



A screening on model decapeptides

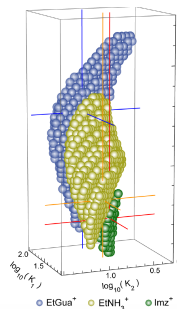


ΔG = -26.0 ± 4.3 kcal/mol, as Gly10 « wraps » itself around [Y(dpa)₃]³⁻ hence a very strong complexation (>SASY)

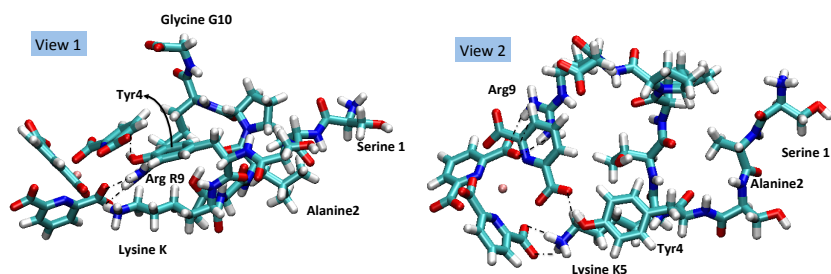


Close to the ΔG for EtGua⁺ inferred by NMR ! (N. Giraud ICMO Orsay)

Towards a systematic assignment and design of peptidic tag.



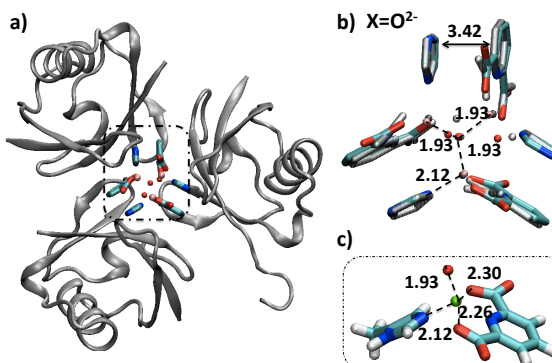
Predicting structures of Ln(DPA)₃@SASY



[Y(dpa)₃]³⁻ @ Ser-Ala-Ser-Tyr-Lys-Thr-Leu-Pro-Arg-Gly (decapeptide) [Y(dpa)₃]³⁻ @ Ser-Ala-Ser-Tyr-Lys-Thr-Leu-Pro-Arg-Gly (decapeptide)

On-going NMR measurements with NMR to assess our values.

Pitfalls: Zinc-containing enzymes and competing anions...



Anion	ΔE (FR39)
NO ₃ ⁻	2,7
Cl ⁻	-1,5
CH ₃ COO ⁻	-5,2
SO ₄ ²⁻	-8,2
HPO ₄ ²⁻	-14,2
F ⁻	-21,3
HO ⁻	-24,2
PO ₄ ³⁻	-26,6

Figure 2. a) Cartoon representations of the ubiquitin trimer, with the central Zn cluster surrounded in a round box b) superimposed geometries of the X-ray (grey) vs. DFT (color) optimized coordinates for the cluster with a central oxygen O²⁻ (RMSD=0.402). c) Typical coordination around one zinc center.