



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

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Elise Dumont, Raymond Grüber, Eric Girard, Nicolas Giraud, Olivier Maury. An intensive GPU--based screening of complexa9on energies towards Lanthanides--driven crystallogenesis. 15ieme Rencontre de Chimistes Théoriciens Francophones, Jun 2016, Lyon, France. hal-02061561

HAL Id: hal-02061561

<https://hal.science/hal-02061561>

Submitted on 8 Mar 2019

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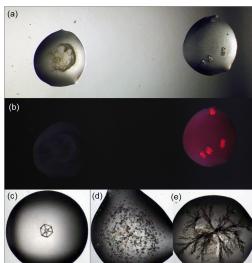
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An intensive GPU-based screening of complexation energies towards Lanthanides-driven crystallogenesis

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

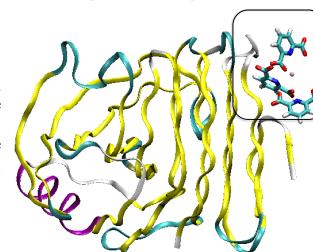
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Context: interactions lanthanides-protein ruling out crystallization



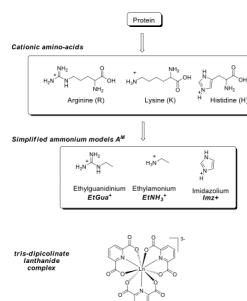
Some beautiful crystals...

(a,b) Crystallization of EcAcrB alone (right) and in the presence of $[\text{Eu}(\text{DPA})_3]^{3-}$ (left) under 315 nm irradiation (b). Auto-crystallisation of $[\text{Eu}(\text{DPA})_3]^{3-}$ in the presence of a protein and (c) high NaCl concentration ($>0.8\text{M}$), (d) Ca^{2+} salts and (e) Mg^{2+} .

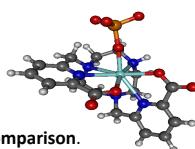


Underlying ΔG ...

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



Which Ln complexes ?



Complexes such as $[\text{Y}(\text{dpa})_3]^{3-}$ and FR39 (pattern)

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

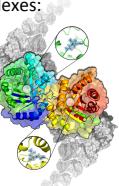
But we need to go from ΔE (PCCP 2013 for aliphatic models) to ΔG ...

An efficient GPU screening

Amber 2015
Reference Manual
(Covers Amber14 and Amber15)

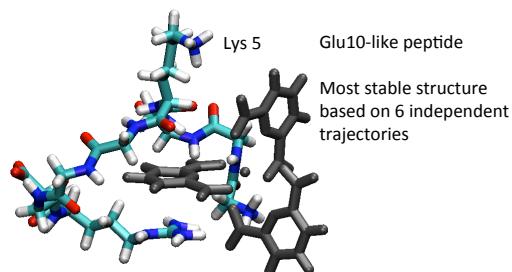
Mainly electrostatic-driven, with cationic (+1) or anionic (-3) complexes:
which amino acids develop a second-shell coordination ?

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

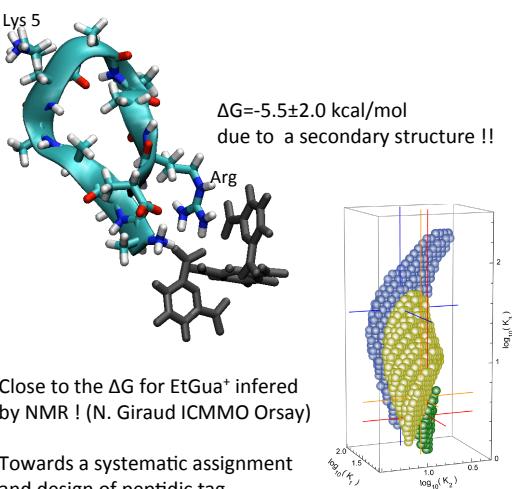


QM/MM-MD scheme towards the evaluation of interaction where the metallic center is directly involved

A screening on model decapeptides



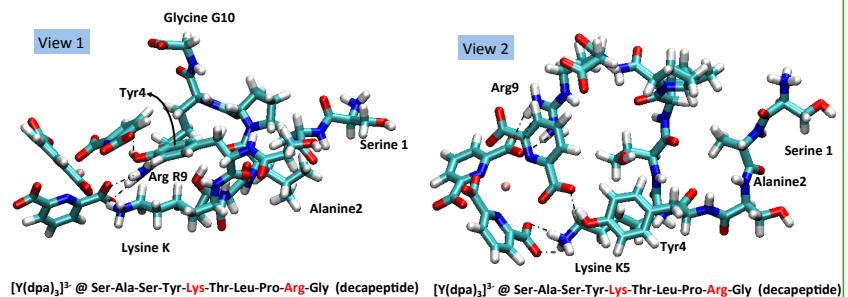
$\Delta G = -26.0 \pm 4.3 \text{ kcal/mol}$, as Gly10 «wraps» itself around $[\text{Y}(\text{dpa})_3]^{3-}$ hence a very strong complexation (>SASY)



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

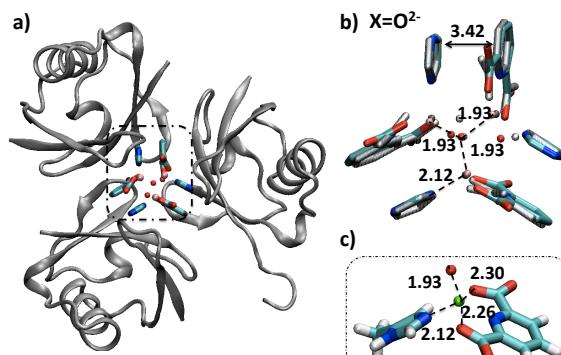
Towards a systematic assignment and design of peptidic tag.

Predicting structures of $\text{Ln}(\text{DPA})_3 @ \text{SASY}$



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_3COO^-	-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 O^{2-} (RMSD=0.402). c) Typical coordination around one zinc center.

