Ligand-Induced Conformational and Volume Changes of Hsp90αN Protein

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Introduction

Voids and cavities of the native protein structure play a major role in protein stability against pressure-induced unfolding. The change in protein volume upon unfolding is defined as: $\boldsymbol{\Delta V = (\delta \Delta G / \delta P)_T}$ [1]. The protein volume changes could also be a consequence of the protein-ligand binding. Here we report our insights on calculating volumetric parameters of several protein structures. One apo (1UYL) and three holo (4EGK, 2YI7, 2YI6) PDB structures of Hsp90α N-terminal domain were used in this study. We demonstrate that there is a relatively large shift of alpha carbon ($\mathbf{C}\alpha$) atoms that belong to the lid of Hsp90αN protein when it binds radicicol - a tight-binding inhibitor of sub-nanomolar affinity. Our calculations of the void volume change in the vicinity of the lid show that radicicol (4EGK) makes the largest impact on this change, while ICPD47 (2YI7) and ICPD62 (2YI6) exhibit little or no impact at all. These findings contribute to the knowledge, which is necessary to reveal the mechanism of protein volume change uppon ligand binding.

Objective

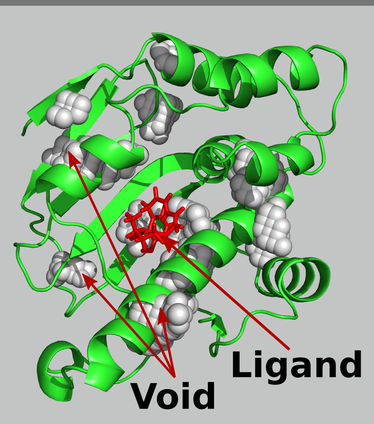

Figure 1: Radicicol and Hsp90αN complex.

Key research questions

- How does a ligand affect conformation of the Hsp90αN protein.
- How large is the geometrical volume change of the voids in protein structure uppon ligand binding.

Methods

- Preparation:
  - Firstly, ligand molecules are removed from the structure.
  - The ends of the amino acid sequences are cut to be the same for all proteins.
  - Finally all structures are aligned by minimizing root-mean-square-distance between $\mathbf{C}\alpha$ atoms.
- Analysis:
  - Using MDTraj [2] the shift of $\mathbf{C}\alpha$ atoms between apo and holo structures is calculated.
  - Using McVol [3] all voids belonging to protein are detected by roling a 1.3 Å radius probe around a protein.
  - McVol algorithm calculates the volume of the voids.

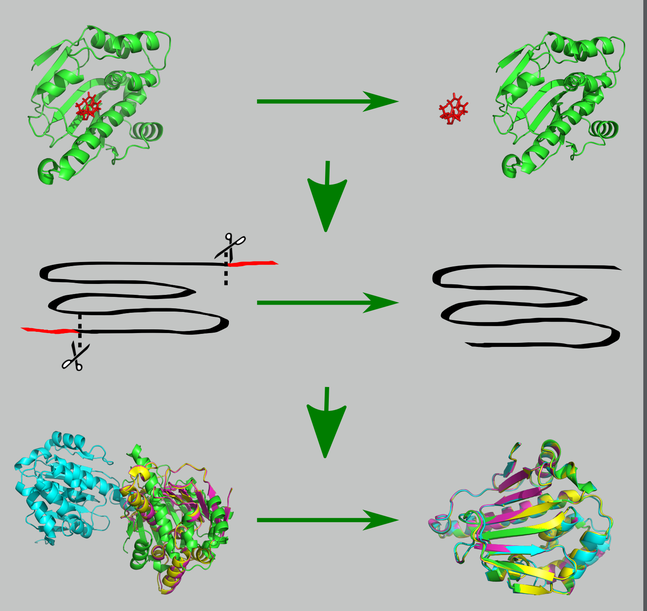

Figure 2: Protein structures preparation sequence.

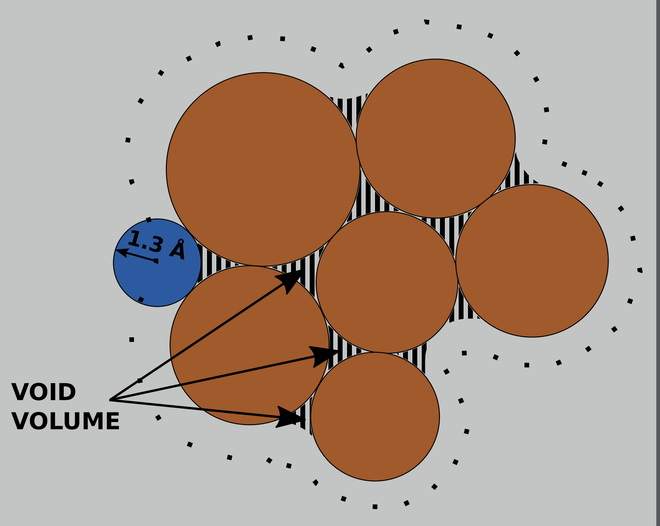

Figure 3: McVol algorithm ilustration: 1.3 Å radius probe is rolled around the protein.

Results: Figure

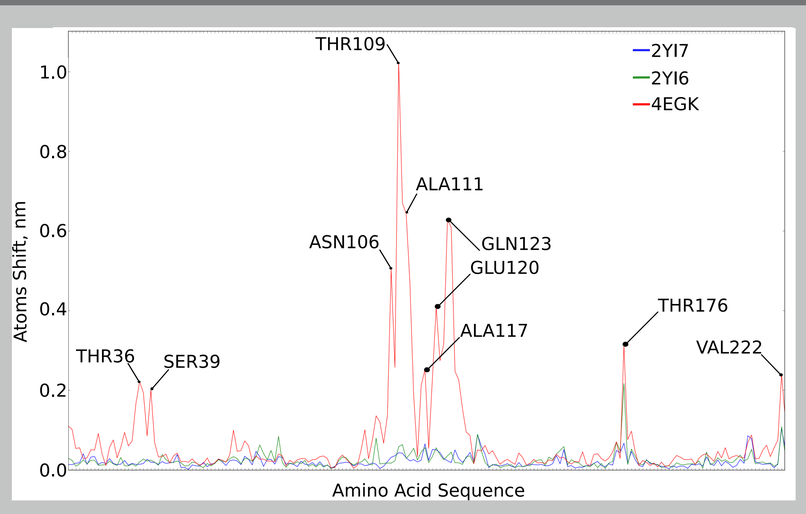

Figure 4: Protein $\mathbf{C}\alpha$ shift when radicicol (4EGK), ICPD47 (2YI7) or ICPD62 (2YI6) is binded to the Hsp90αN. Values are obtained by subtracting distances between apo and holo $\mathbf{C}\alpha$ atoms. PDB codes are given in parentheses.

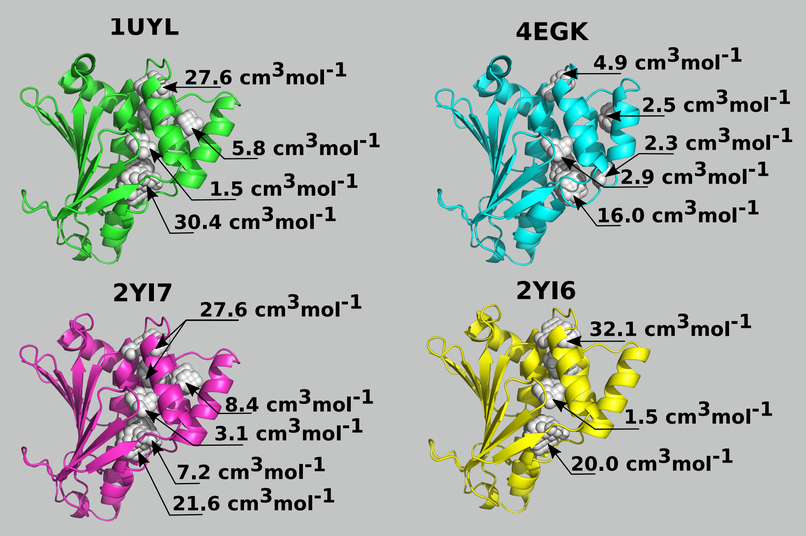

Figure 5: Volume of the voids in conformationally active region of the protein when different ligands are present.

Results: Table

Protein ID	Ligand ID	$K_{d_{intr}}$, nM	V_{void}, $\mathrm{cm^3mol^{-1}}$	ΔV_{void}, $\mathrm{cm^3mol^{-1}}$
1UYL	-	-	65.3	-
4EGK	RDC	0.04	28.6	-36.7
2YI7	ICPD47	1.1	67.9	2.6
2YI6	ICPD62	2	55.1	-10.2

Table 1: Void volumes of Hsp90αN in complex with radicicol (4EGK), ICPD47 (2YI7) & ICPD62 (2YI6) compounds.

Conclusion

- Large conformational changes caused by the radicicol binding to the protein, leads to the larger change of the void volume in the vicinity of the "lid".

References

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