Understanding the role of H-bonds in the stability of molecular glue–induced ternary complexes

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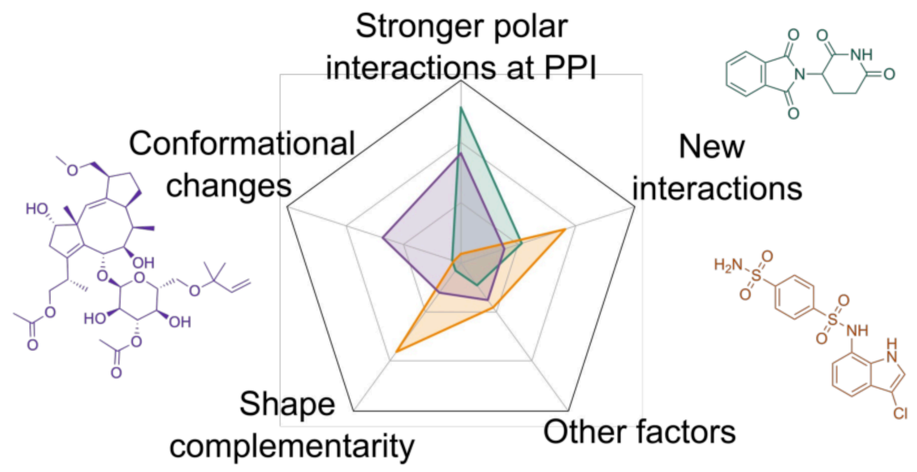
Abstract

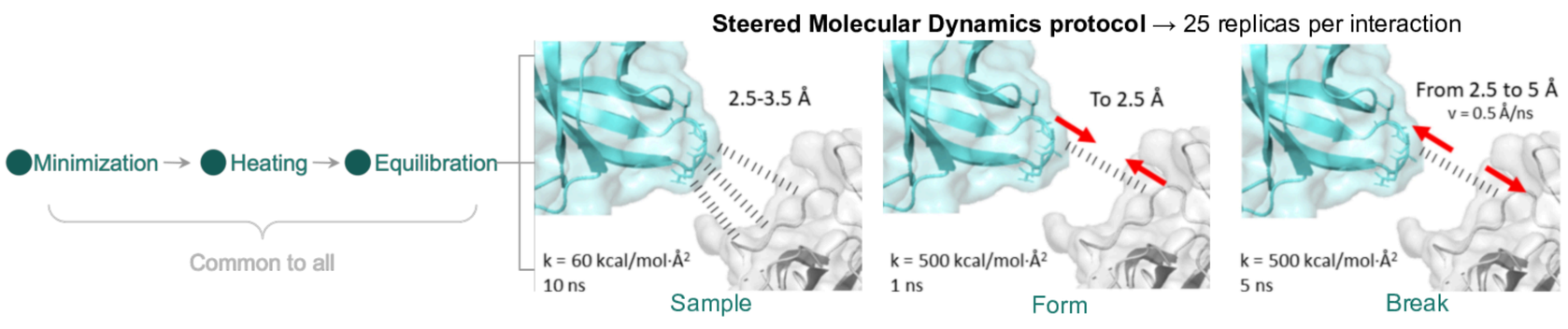
Protein-protein interaction (PPI) networks play a central role in many biological processes and thus the possibility of modulating them using small molecules offers several biomedical and biotechnological opportunities.[1,2] Molecular glues (MGs) are small molecules that bind to a PPI interface and stabilize the complex. Oftentimes, MGs present no measurable affinity to at least one of the proteins involved in the ternary complex[3,4], and the molecular bases for their action are not completely understood. We previously reported a significant correlation between protein-protein hydrogen bond robustness and the stability of the lenalidomide–induced CRBN–CK1α complex.[5]

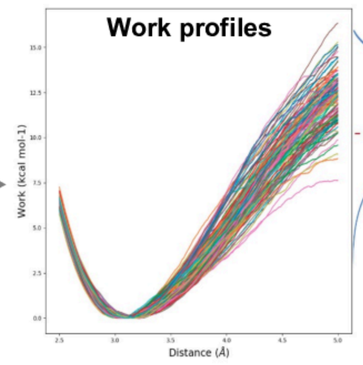
In this work, we demonstrate that this relationship is not unique for that system but rather represents a reproducible physicochemical phenomenon underlying the mechanism of action of chemically diverse MGs, including additional IMiDs and Fusicoccin A.[6] Our results shed light into a vaguely understood phenomenon and pave the way for the development of new computational methods that enable the rational design of molecular glues.



Methods

Steered Molecular Dynamics protocol → 25 replicas per interaction





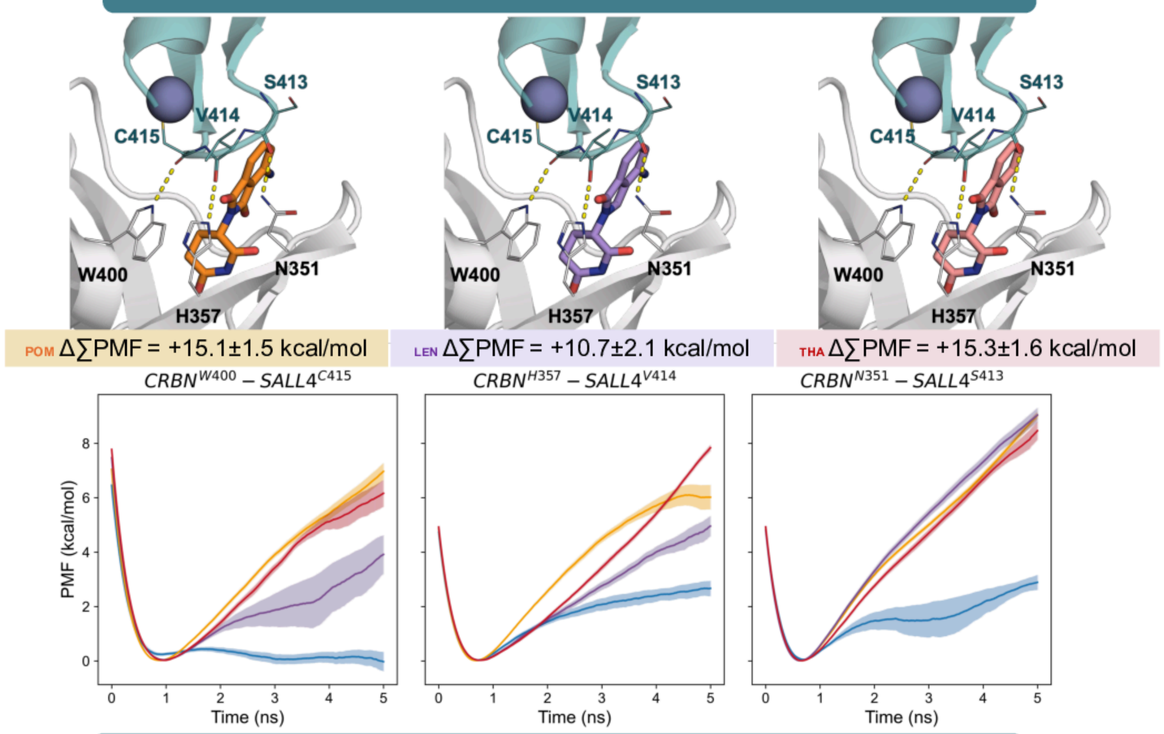
Jarzynski's equality

$$e^{-\Delta G/k_B T} = \langle e^{-W_i/k_B T} \rangle$$

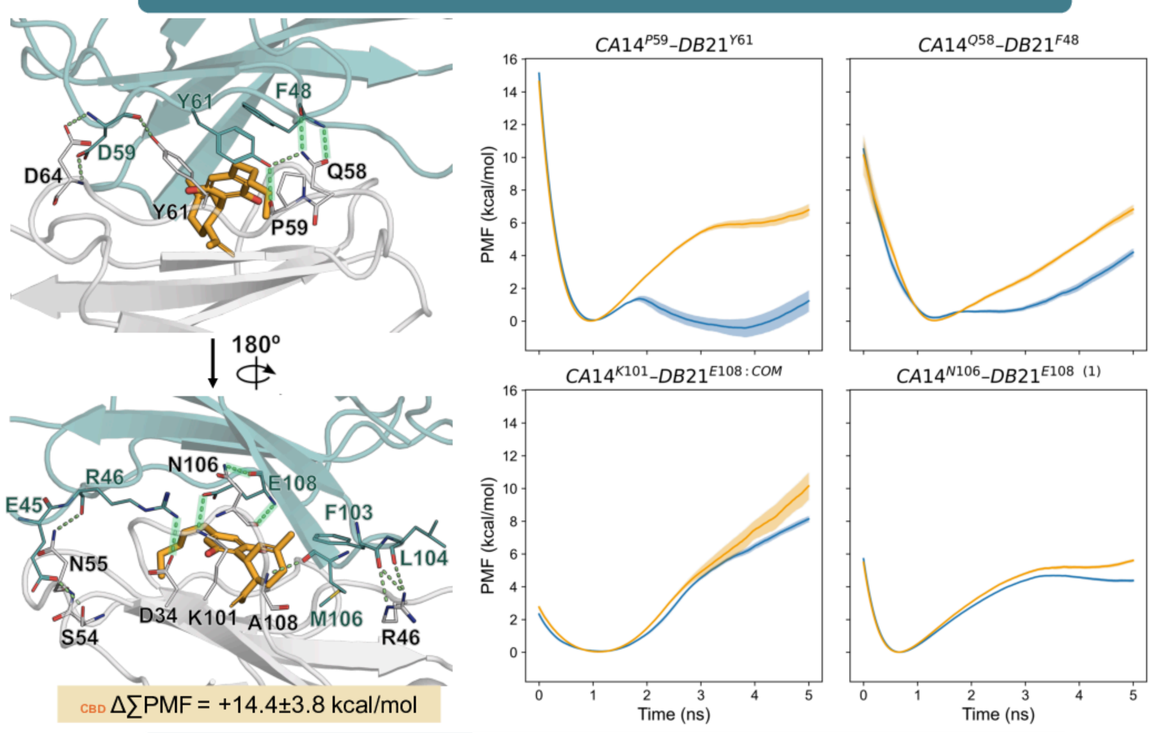
$$\Delta G = -k_B T ln \sum_{i=1}^{N} \frac{e^{-W_i/k_B T}}{N}$$

Results

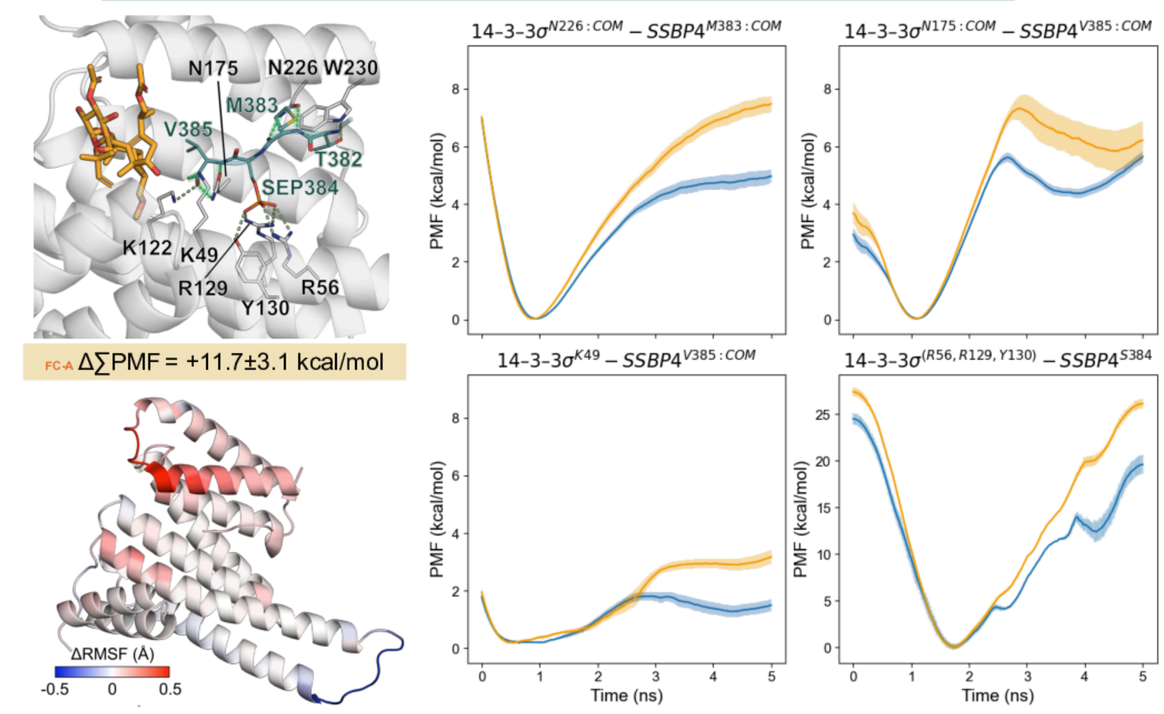
CRBN–SALL4–IMiDs



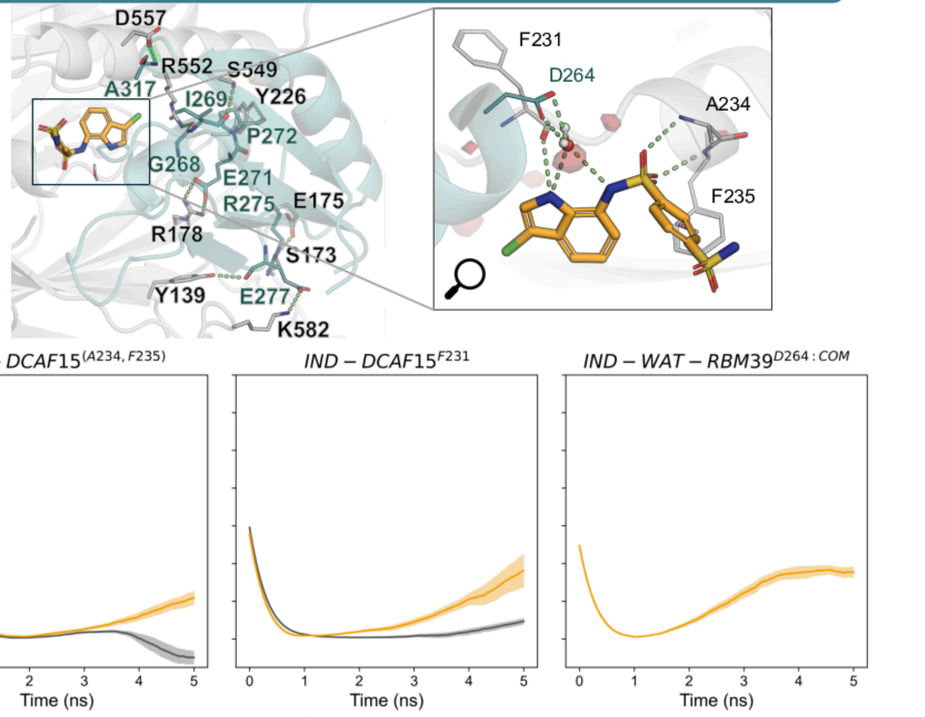
CA14–DB21–CBD



14-3-3σ–SSBP4–FC-A



DCAF15–RBM39–Indisulam



Conclusions

- Steered Molecular Dynamics (SMD) provide a fast way to explore the strength of polar interactions at protein-protein interfaces
- The strengthening of the polar interactions at the PPI induced by molecular glues is observed for structurally unrelated ternary complexes
- Multiple glues induce a water shielding effect in the complex, and the combined PMF is in qualitative agreement with the experimental data
- The cooperativity of Indisulam-induced ternary complex does not rely on the strengthening of the polar interactions at the PPI upon molecular glue binding

References

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Acknowledgements

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