

Extending Views of Catalysis: Quantum Entatic State/Rack Mechanism for Catalysis by Solvent Environments

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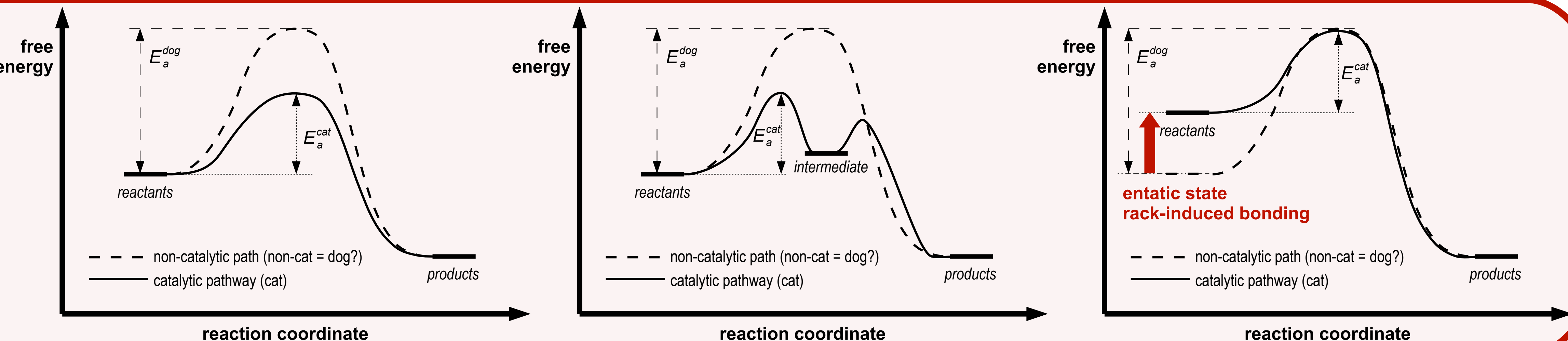
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Introduction

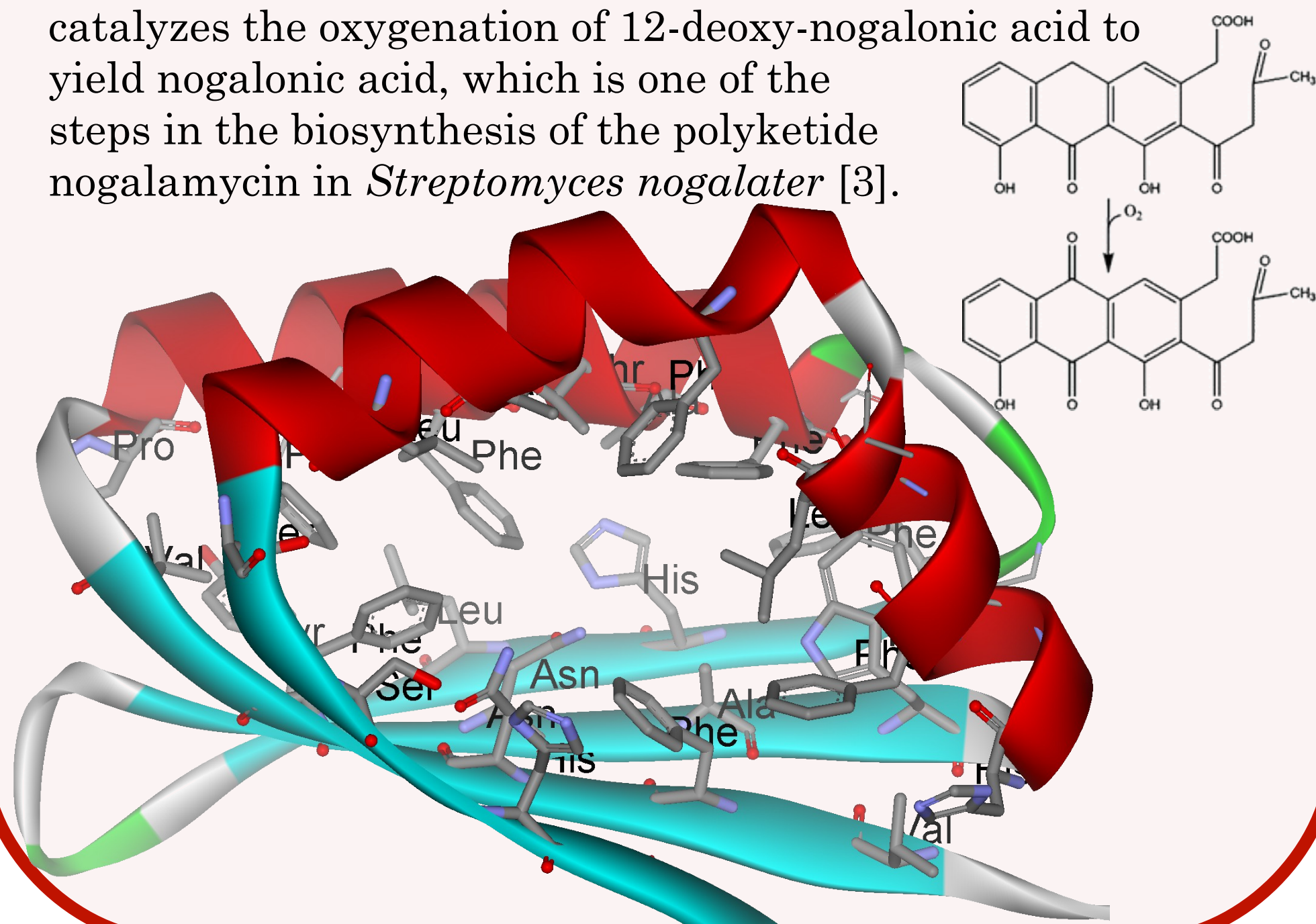
Three common ways a catalyst may function are (i) the lowering of the activation barrier (E_a), (ii) the opening up new reaction pathways with new intermediate(s) and reduced activation barriers, and (iii) activation of reactants by steric strain toward reactivity.

The latter is known as 'entatic state' [1] achieved through 'rack-induced bonding' [2] that occurs when the pre-shaped active site destabilizes the reactants, thus lowers activation barrier.



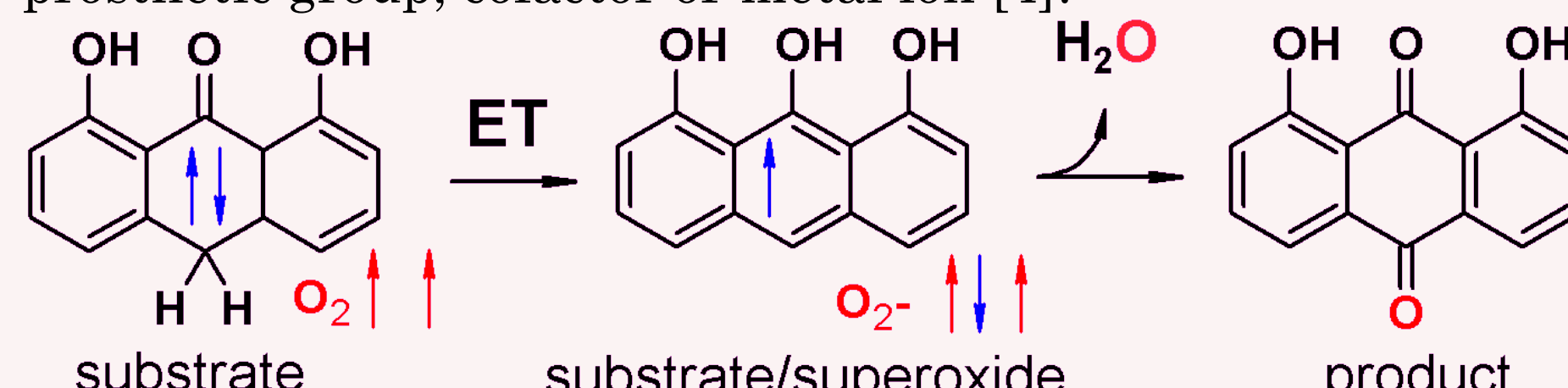
Inspiration from ...

The 12-deoxy-nogalonic acid monooxygenase (NMO or SnoaB) catalyzes the oxygenation of 12-deoxy-nogalonic acid to yield nogalonic acid, which is one of the steps in the biosynthesis of the polyketide nogalamycin in *Streptomyces nogalater* [3].



The Challenge is to Rationalize ...

... how NMO, as member of a family of small cofactor-free oxygenases, carries out oxygenation reactions without any prosthetic group, cofactor or metal ion [4]!

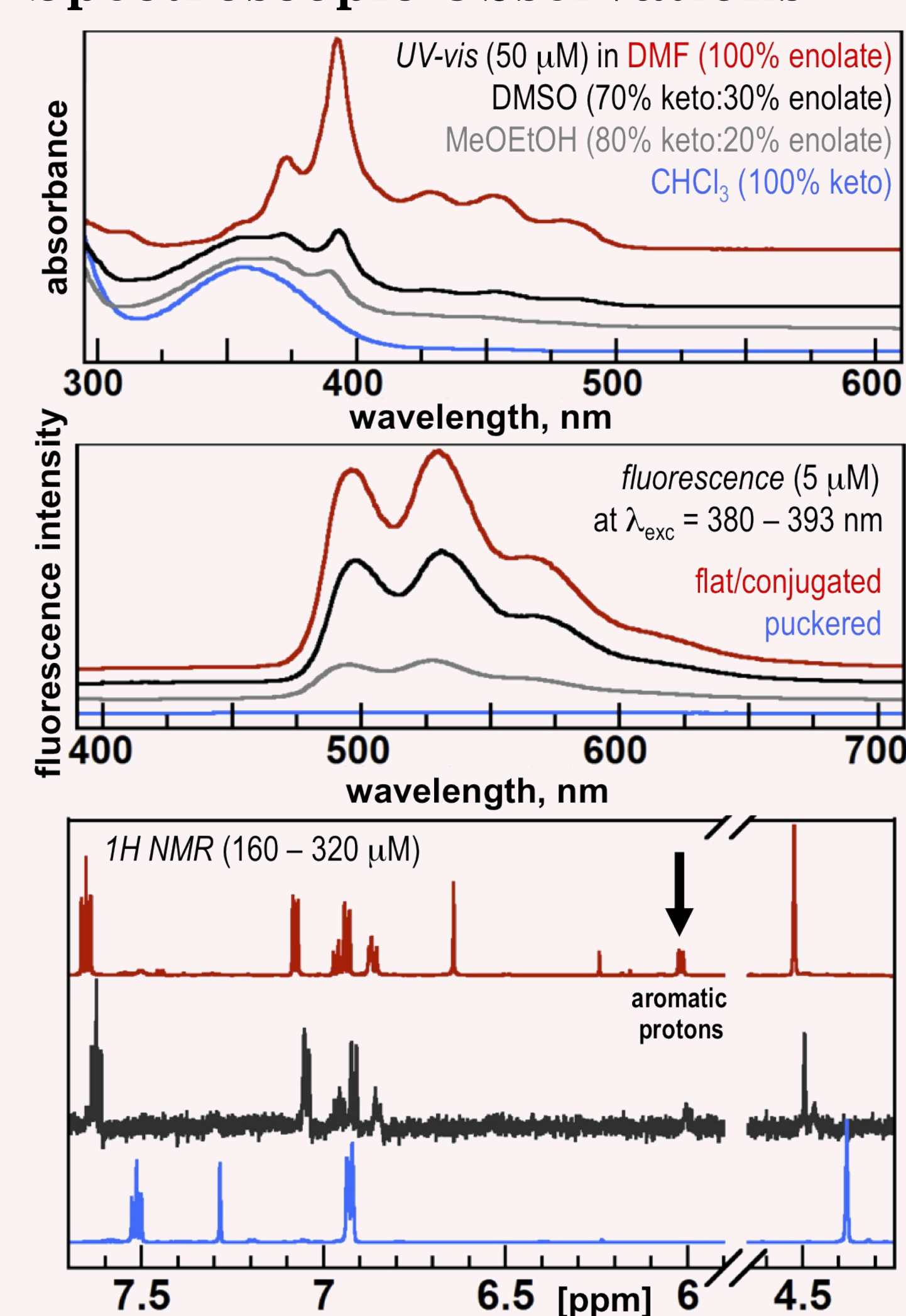


in benzene and CHCl_3 no reactivity for 24 and 48 hr, respectively (despite good O_2 solubility, ≈ 7 mM)

in DMSO $t_{1/2} > 8$ hr
in water $t_{1/2} > 4$ hr (pH = 8.0, but $>50\%$ dimerization side-product)
in DMF $t_{1/2} = 2.9$ hr ($\text{pK}_a = 9.28 \pm 0.07$, 100% oxygenation product)
in MeOEtOH $t_{1/2} = 0.5$ hr

in NMO enzyme at pH = 9.8 $t_{1/2} < 5$ sec ($\text{pK}_a = 7.15 \pm 0.09$)
pH = 6.3 $t_{1/2} < 6$ min

Spectroscopic Observations

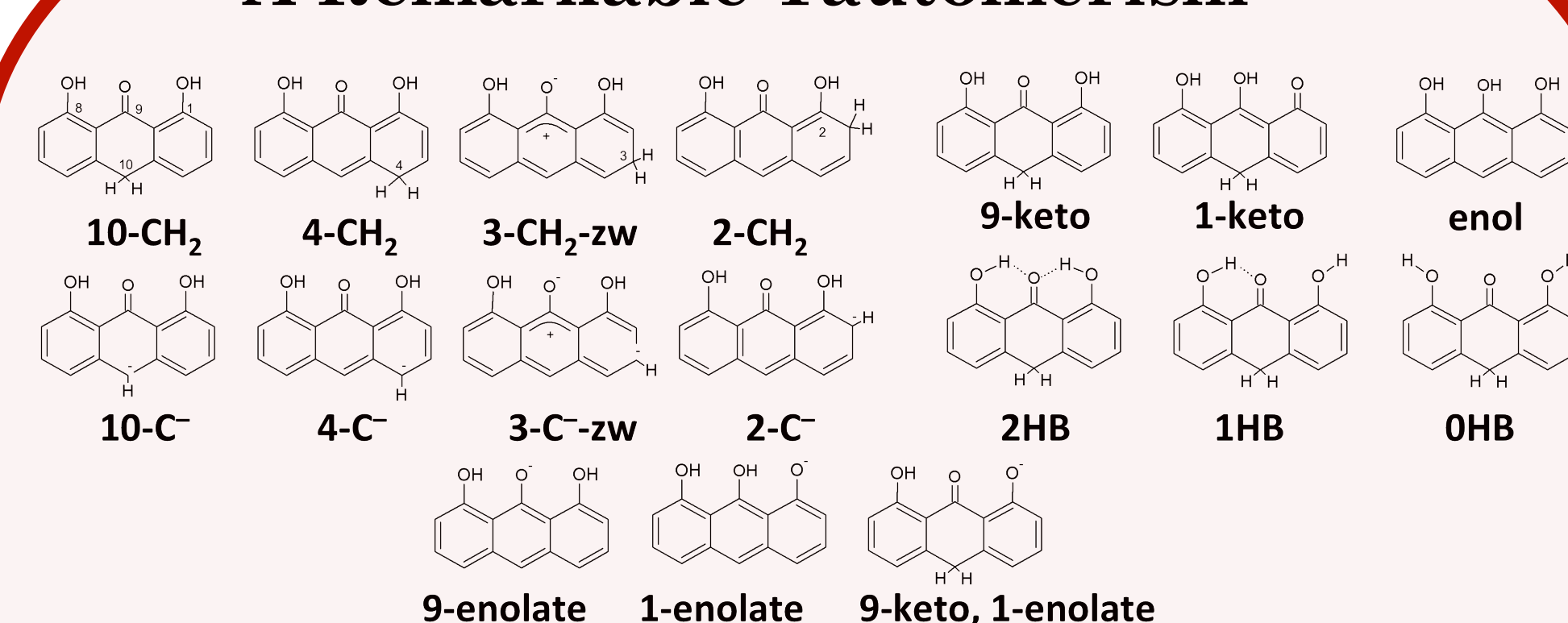


- spontaneous shift from keto to enolate forms as a function of solvent environment
- remarkably strong neat solvent/solute interactions, concentration dependency
- poor correlation of reactivity/speciation solely with solvent dielectric constant
- importance of H-bonding acceptor/donor and zwitterionic character, π/π stacking
- substrate-/ O_2 - radical pair formation is facilitated by ion-pairing of enolate-/protonated solvent

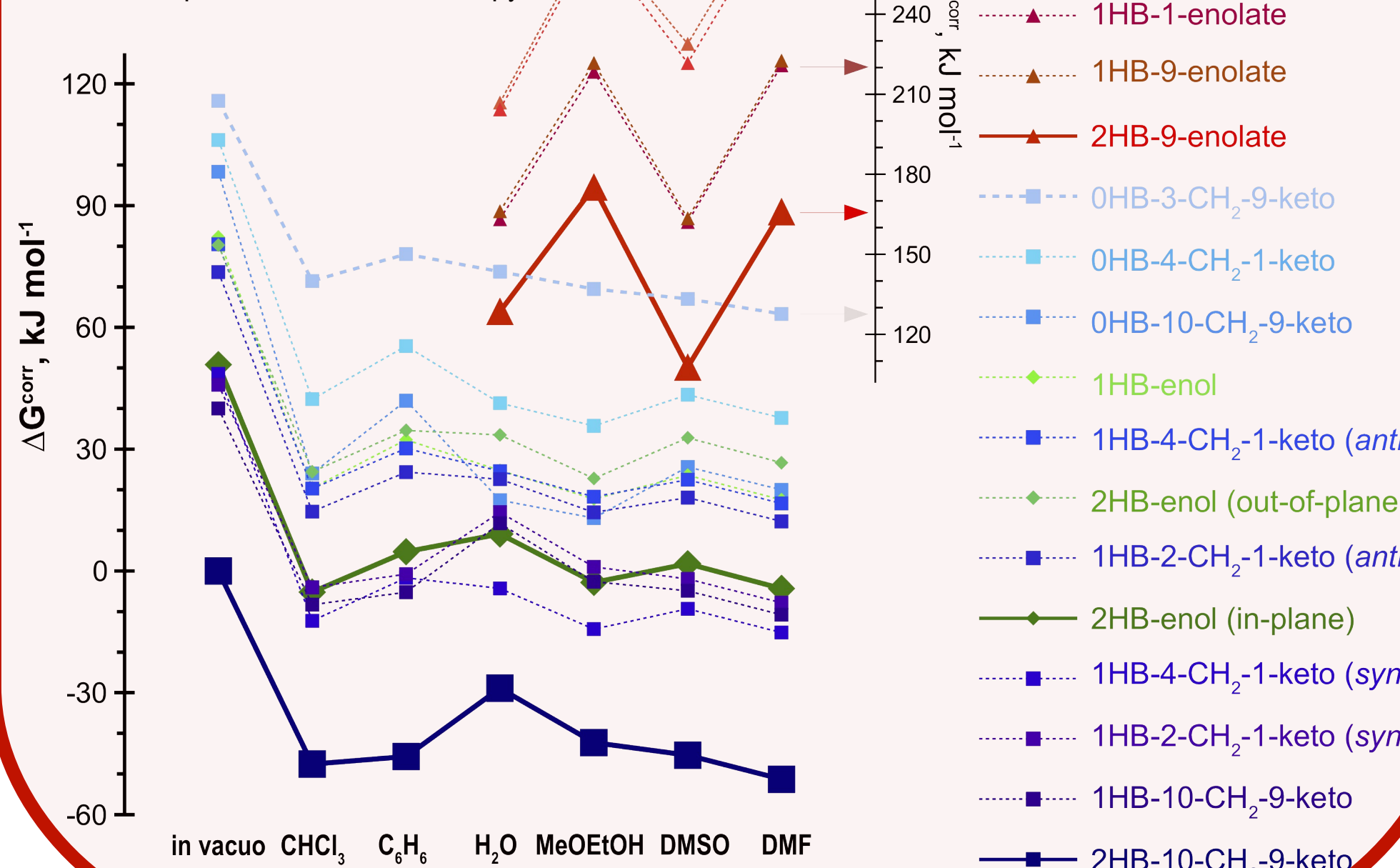
When in doubt ...

... please, visit your local theoretician!

A Remarkable Tautomerism

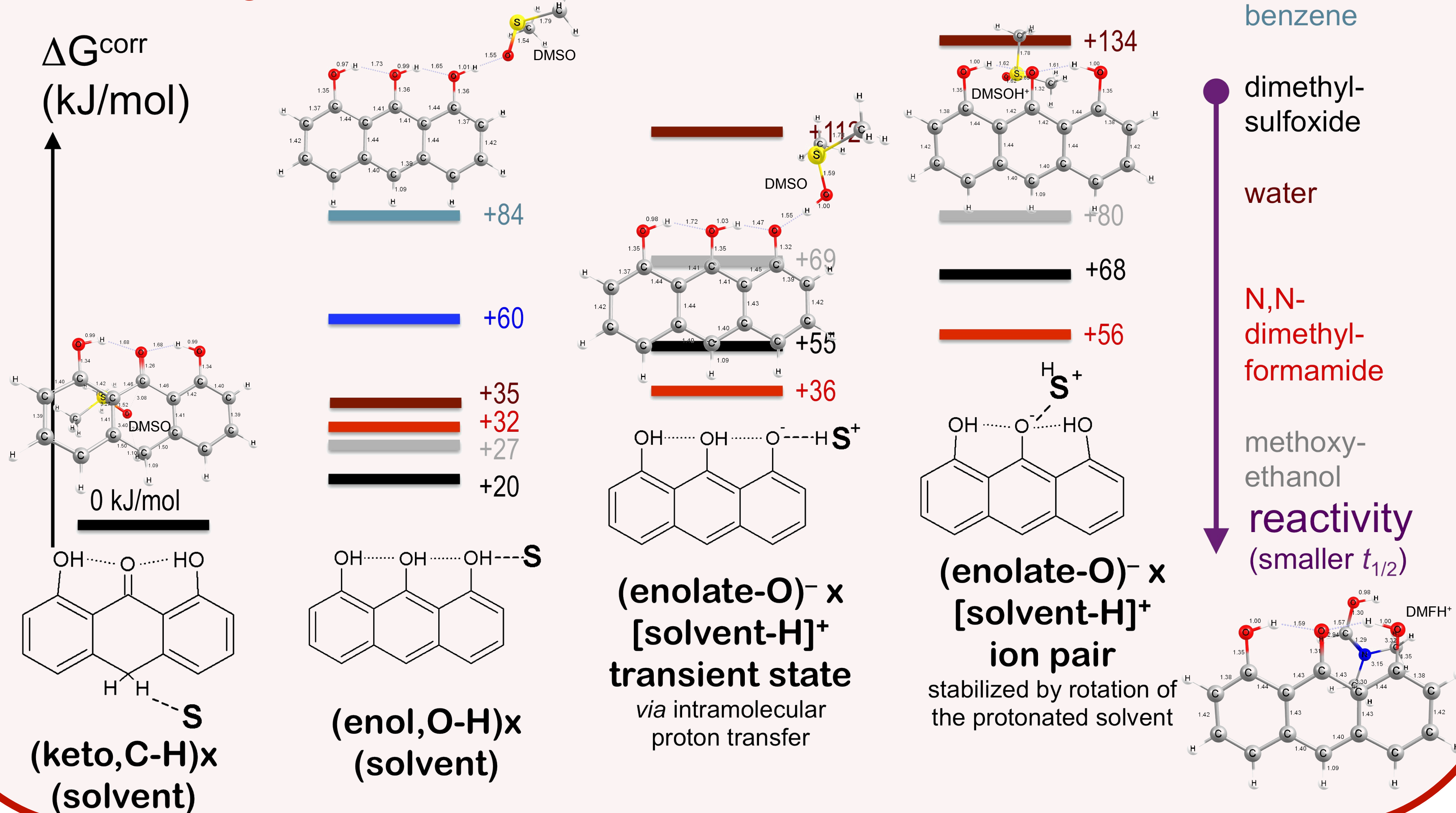


ΔG^{corr} values were calculated at MN15/6-611++G**/SMD level of theory [5] by considering Whitesides' [6] 'free-volume' condensed phase translational entropy.



'QUANTUM' ENTATIC STATE/RACK MECHANISM

'rack-induced bonding' is due to electronic and electrostatic interactions, and not from steric bulk!



Relevance

The evolution of composition (chemical/biological) and structure (morphology/molecular/atomic) are central to Emergence-of-Life research. It has well established tools and methodologies. It has already been provided essential insights *via* phylogenetic analysis (composition), molecular fossils in structural biology (protein folds, prosthetic groups). The focus on **Cofactor-free Catalysis** provides us with an opportunity to evaluate on how chemical/biological function may have emerged with or without being constrained by a specific composition or structure. While not without some pitfalls, chemical and physical changes as confined by geology, physics, chemistry, and biology allow for incorporation benign factors, such as non-innocent solvent micro-environments to guide our thinking and imagination along the evolutionary path of the emergence of the building blocks of life.

COMPOSITION

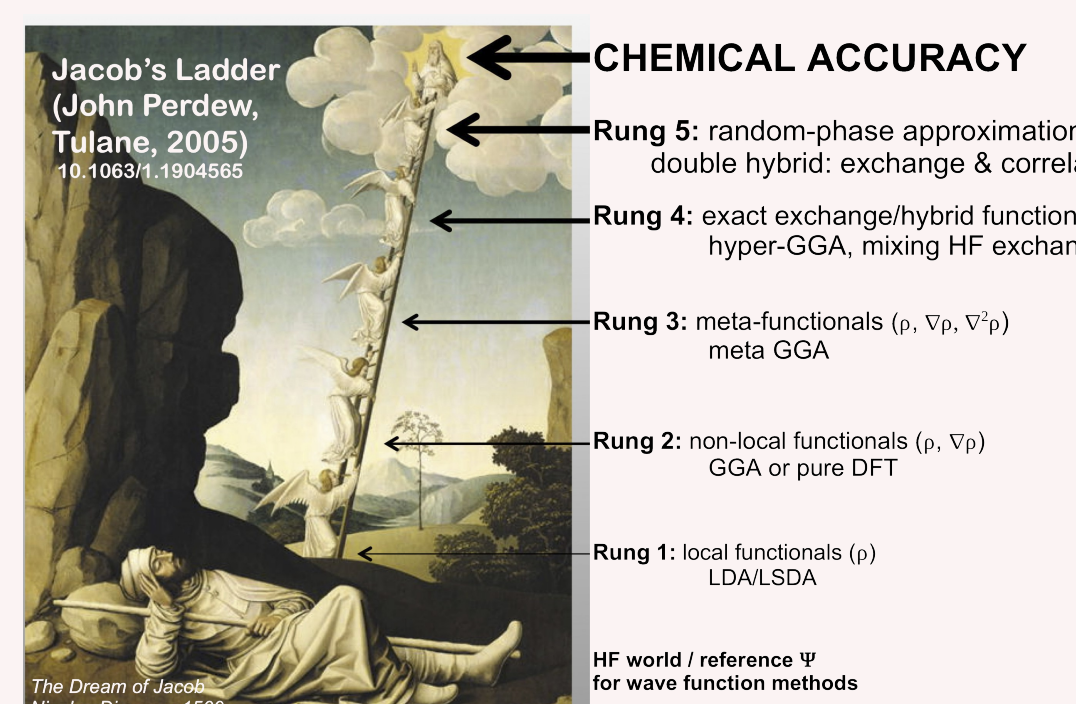
EVOLUTION

FUNCTION

Critical: Level of Theory

Root mean square errors in tautomerisation enthalpies for 1HB-9-keto, 2HB-enol, 1HB-enol, 0HB-9-keto isomers. The reference level for this study is CBS-QB3 [7]

Rung 2:	BP86 15.0 kJ/mol	Rung 3:	TPSS 15.5 kJ/mol
	BLYP 9.8 kJ/mol		revTPSS 16.3 kJ/mol
	PBE 14.2 kJ/mol		M06L 11.6 kJ/mol
Rung 4:	B3LYP 8.2 kJ/mol	Rung 5:	MN15 4.0 kJ/mol
	camB3LYP 14.2 kJ/mol		
	camB3LYP+GB3J 13.1 kJ/mol		
	omegaB97XD 14.3 kJ/mol		



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Acknowledgements

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