Quantum chemical investigation on the metabolism of the endogenous psychedelic N,N-dimethyltryptamine molecule by the monoamine oxidase A enzyme

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Introduction. Using the Born-Oppenheimer approximation.

- The time-independent Schrödinger's equation:

$$\hat{H}\Psi = E\Psi \tag{1}$$

- Using the Born–Oppenheimer approximation [1,2] the motion of electrons and nuclei are separated and can be solved independently:

$$\hat{H}_e(\underline{\mathbf{r}}, \underline{\mathbf{R}})\Phi_i(\underline{\mathbf{r}}, \underline{\mathbf{R}}) = E_i(\underline{\mathbf{R}})\Phi_i(\underline{\mathbf{r}}, \underline{\mathbf{R}}) \tag{2}$$

$$\left[\hat{T}_{\mathrm{n}}(\underline{\mathbf{R}}) + E_i(\underline{\mathbf{R}})\right] \Theta_{ik}(\underline{\mathbf{R}}) = E_{ik}\,\Theta_{ik}(\underline{\mathbf{R}}) \tag{3}$$

- In our work we focuses on the Eq. (2)
- DFT [3] methods can be used for large scale-systems.

[1] M. Born, J. R. Oppenheimer, Ann. Phys., **1927**, 389, 457.
[2] E. Kapuy E., F. Török, Az atomok és molekulák kvantumelmélete, Akadémiai Kiadó, Budapest, **1975**.
[3] Y. Zhao and D. G. Truhlar, Theoretical Chemistry Accounts: Theory, Computation, and Modeling (Theoretica Chimica Acta), **2008**, 120, 215–241.

Introduction. The ONIOM (QM:MM) approach

- Enzymes are large-scale systems. Let's use the DFT methods. → ϟϟϟ
  - The system is too large (thousand of atoms).
  - What can we do?
- ONIOM [4] approach: combining other levels of theory.
  - Divide the system in 2 (or more) parts
  - The most important atoms
    → QM level
  - Rest of the system
    → MM [5] level (classical force fields)

[4] L. W. Chung, W. M. C. Sameera, R. Ramozzi, A. J. Page, M. Hatanaka, G. P. Petrova, T. V. Harris, X. Li, Z. Ke, F. Liu, H.-B. Li, L. Ding and K. Morokuma, Chemical Reviews, **2015**, 115, 5678–5796.
[5] A. K. Rappe, C. J. Casewit, K. S. Colwell, W. A. Goddard and W. M. Skiff, Journal of the American Chemical Society, **1992**, 114, 10024–10035.

Introduction. Exploring the Potential Energy (hyper)Surface (PES) of the system.

- Searching of chemically relevant species:
  - reactants
  - transition states
  - intermediates?
  - products
- Finding critical points of the PES by optimization algorithms.:
  - Local minimum points (reactants, intermediates, products),
  - 1st order saddle points (transition states).
- Determining $\Delta E^{\ddagger}$, (or $\Delta G^{\ddagger}$ values) and the corresponding k reaction rate constants.

$$k = \frac{\kappa k_B T}{h} \exp\left(- \frac{\Delta G^{\ddagger}}{RT} \right) \tag{4}$$

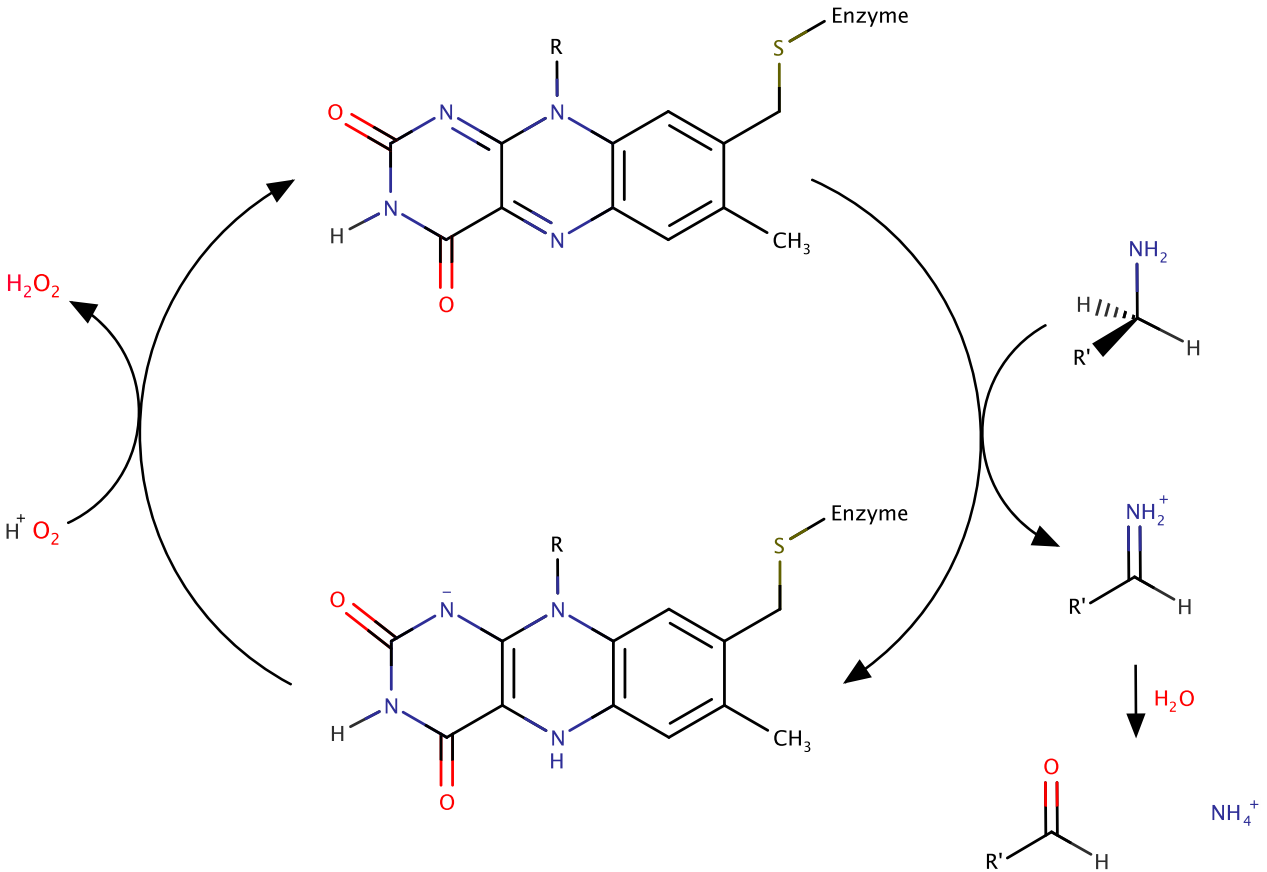
- The lowest k constant is the rate-determining step of the reaction, the corresponding $\Delta G^{\ddagger}$ is the highest activation Gibbs free energy.

Introduction. Choice of the system

- The enzyme: monoamine oxidase (MAO)
  - It has two isoforms. MAO-A (in this research we focus on A type) and MAO-B. They share about 70% structural identity.
  - catalyses the oxidation of various monoamine neurotransmitters (serotonin, dopamine, etc.), trace amine and regulates their levels
  - irregular activities of MAO link to psychiatric and neurological disorders
- The ligand: N,N-dimethyltryptamine (DMT), and its primary amine analogue tryptamine (T)
  - Powerful psychedelic substance. It is usually regarded as „the spirit" molecule. [6] Therapeutic potentials: antidepressant, anxiolytic. [7]
  - It is biogenic, the human body contains it in trace levels
  - It has a role in immunity, tissue protection and inflammatory responses, alleviating damage caused by hypoxia states. [8]

[6] R. Strassman, DMT: the spirit molecule: a doctor's revolutionary research into the biology of near-death and mystical experiences, Park Street Press, **2001**.
[7] R. G. dos Santos, F. L. Osorio, J. A. S. Crippa, J. Riba, A. W. Zuardi and J. E. C. Hallak, Therapeutic Advances in Psychopharmacology, **2016**, 6, 193–213.
[8] E. Frecska, A. Szabo, M. J. Winkelman, L. E. Luna and D. J. McKenna, Journal of Neural Transmission, **2013**, 120, 1295– 1303.

Introduction. How MAO works?



Results. Calculated of protonation states of ligands

- The acid dissociation constant:

$$K_{\mathrm{a}} = \frac{[\mathrm{A}^-][\mathrm{H}^+]}{[\mathrm{AH}]}$$

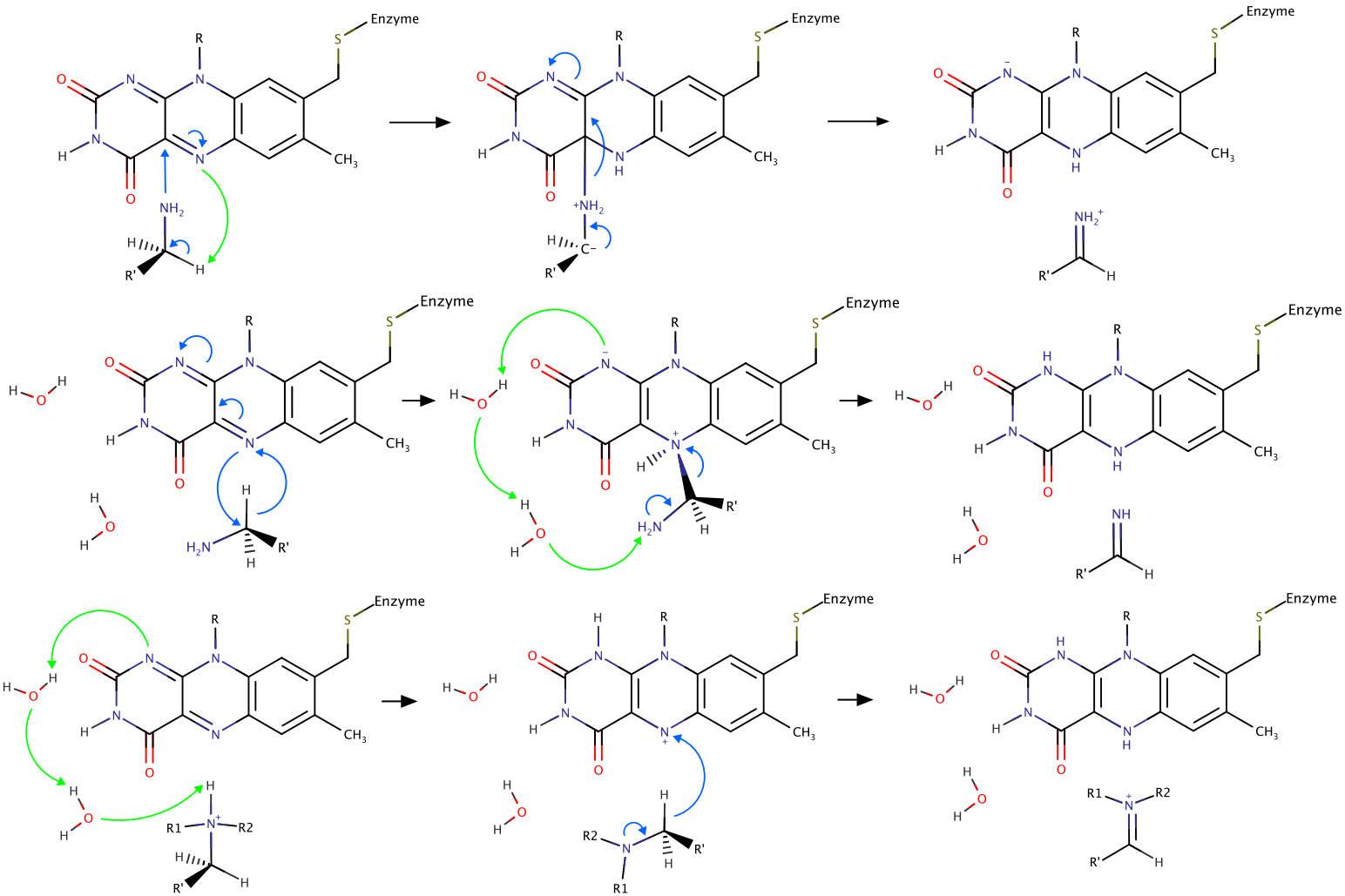
$$\mathrm{p}K_{\mathrm{a}} = -\log_{10} K_{\mathrm{a}}$$

- Estimated distribution of BH^+ (TH^+, DMTH^+) protonated and B (T, DMT) neutral form of substrates:

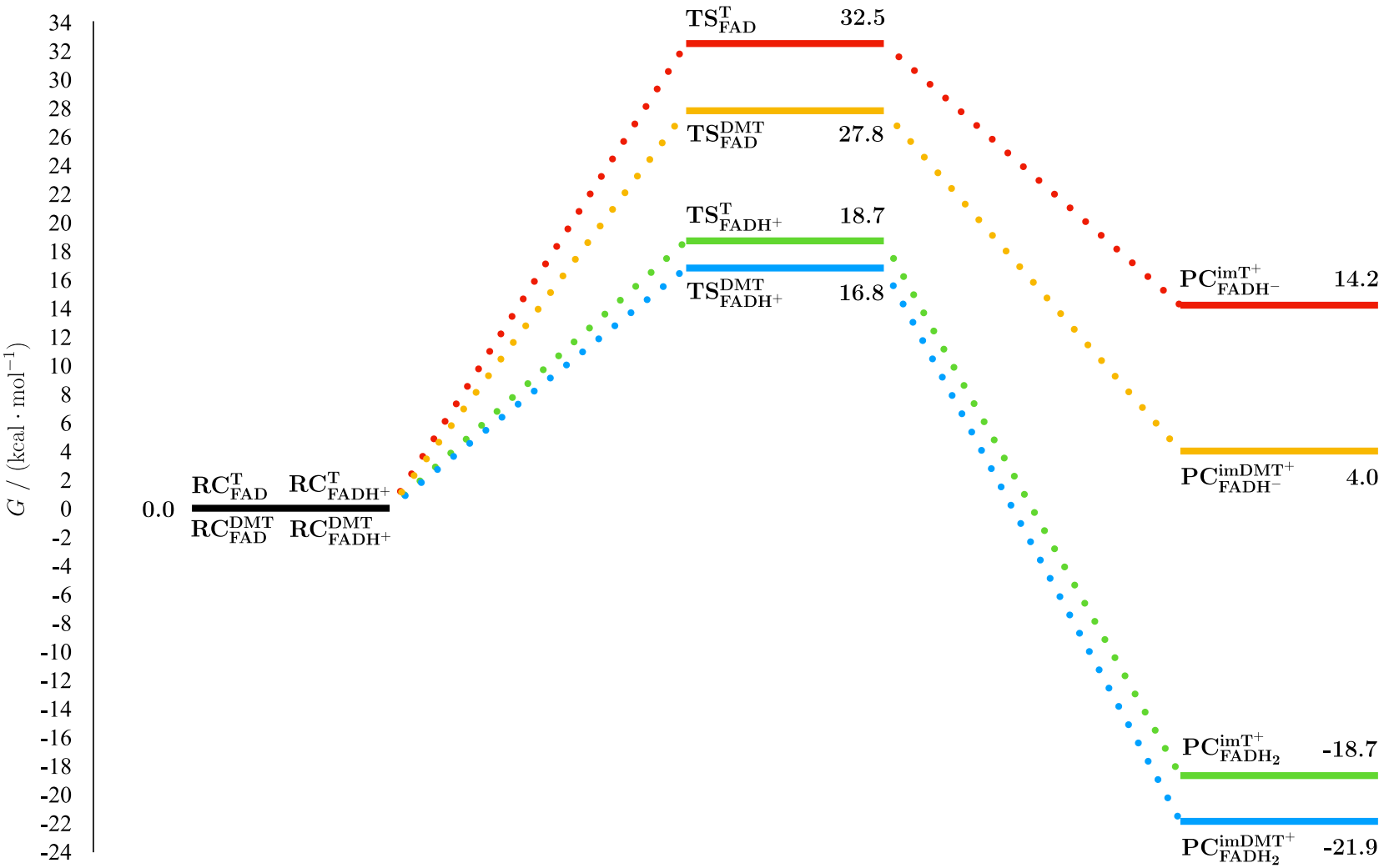
Ligand	$\mathrm{p}K_{\mathrm{a}}^{\mathrm{exp}}$	$\mathrm{p}K_{\mathrm{a}}^{\mathrm{calc}}$	$\frac{\mathrm{B\text{-}H}^+}{\mathrm{B}} \cdot 100\%$
T	10.2	9.42	$\approx 99 - 100\%$
DMT	8.68	9.24	$\approx 94 - 99\%$

- The protonated form of the substrates are dominant in average body pH (7.4) and temperature (36 °C). They should be concerned in the mechanism.

Results. A new mechanistic proposal (3rd scheme)



Results. Computing the activation barriers.



Conclusions.

- The activation Gibbs free energies are lower for DMT compared to T in both cases (FAD, $FADH^+$).
- The $FADH^+$ cofactor decreases the barrier for T and DMT as well:
  - In case of tryptamine $\delta(\Delta G^{\ddagger}) = 13.8\ \text{kcal} \cdot \text{mol}^{-1}$
  - For dimethyltryptamine $\delta(\Delta G^{\ddagger}) = 11.0\ \text{kcal} \cdot \text{mol}^{-1}$
- Our suggested unusual $FADH^+$ coenzyme nearly decreases the $\Delta G^{\ddagger}$ by 2-folds compared to FAD.

Proposal for future investigations.

- Elucidate the possibility of $FADH^+$ formation.
  $\rightarrow$ very expensive calculations.
- What is the final product of MAO catalysed oxidation of amines?
  - Positively charged iminium cation:
    $\rightarrow$ In the case of tertiary DMT it is the only possibility.
  - Neutral imine or iminium cation?
    $\rightarrow$ For primary T is it depends on the FAD or $FADH^+$ state of the co-enzyme.
    $\rightarrow$ In the former case (FAD) neutral imine is the preferred one.
    $\rightarrow$ In the latter case ($FADH^+$) the iminium species are the only option.

Thank you very much for your attention!