

Hydrolysis of *N,N*-dimethylindole-3-ethaniminium cation, the
oxidized form of the endogenous psychedelic
N,N-dimethyltryptamine

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Details of applied methods 1.

- The time-independent Schrödinger's equation:

$$\hat{H}\Psi = E\Psi \quad (1)$$

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

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

$$\left[\hat{T}_n(\mathbf{R}) + E_i(\mathbf{R}) \right] \Theta_{ik}(\mathbf{R}) = E_{ik} \Theta_{ik}(\mathbf{R}) \quad (3)$$

- In our work we focus on the solution of Equation (2), all calculations were performed using the Gaussian 16 C.01 [2] program package.
- The examined chemical systems contain 31–37 atoms.
- *Ab initio* methods (e.g. MP2, CCSD) found to be extremely time consuming. Therefore, the DFT [3] approach was our choice. $\Delta G_{\text{TS}3_0}^\ddagger = 28.90$

[1] M. Born and J. R. Oppenheimer, *Annalen der Physik*, 1927, **389**, 457–484.

[2] M. J. Frisch, G. W. Trucks and H. B. Schlegel *et al.*, *Gaussian 16, Revision C.01*, 2016, Gaussian, Inc., Wallingford, CT.

[3] Y. Zhao and D. G. Truhlar, *Theoretical Chemistry Accounts: Theory, Computation, and Modeling (Theoretica Chimica Acta)*, 2008, **120**, 215–241.

Details of applied methods 2.

- The M06-2X hybrid functional [4] with the correlation consistent aug-cc-pVDZ, and aug-cc-pVQZ basis sets [5–7] were applied:
 - M06-2X/aug-cc-pVDZ: geometry optimizations (using tight optimization criteria for the structures [8]) were performed to find stationary points on the PES, and harmonic frequency, thermochemical analysis were also carried out $\rightarrow G_{\text{opt,freq}}^{\text{corr}}$
 - M06-2X/aug-cc-pVQZ: single point energy (SPE) calculations $\rightarrow E_{\text{spe}}^{\text{total}}$
- The "SuperFine" integration grid [8] for numerical integrations was used in each computation.
- Implicit solvent model: SMD variation of IEFPCM [9].

[4] Y. Zhao and D. G. Truhlar, *Journal of Chemical Theory and Computation*, 2011, **7**, 669–676.

[5] T. H. Dunning, *Journal of Chemical Physics*, 1989, **90**, 1007–1023.

[6] R. A. Kendall, T. H. Dunning and R. J. Harrison, *Journal of Chemical Physics*, 1992, **96**, 6796–6806.

[7] A. K. Wilson, T. van Mourik and T. H. Dunning, *Journal of Molecular Structure: THEOCHEM*, 1996, **388**, 339–349.

[8] J. B. Foresman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods*, Gaussian, Inc., Wallingford, CT, 3rd edn, 2015.

[9] A. V. Marenich, C. J. Cramer and D. G. Truhlar, *Journal of Physical Chemistry B*, 2009, **113**, 6378–6396.

Details of applied methods 3.

- The total Gibbs free energies were computed as

$$G^{\text{total}} = E_{\text{spe}}^{\text{total}} + G_{\text{opt,freq}}^{\text{corr}}, \quad (4)$$

where $G_{\text{opt,freq}}^{\text{corr}}$ is the Gibbs free energy correction, determined at $T = 36$ °C, and $p = 1$ atm in order to simulate the body environment.

- Knowing the activation barriers (ΔG^\ddagger), the corresponding k reaction rate constants were calculated using the Eyring-Polanyi [10–13] formula:

$$k = \frac{\kappa k_{\text{B}} T}{h} \exp\left(-\frac{\Delta G^\ddagger}{RT}\right) \quad (5)$$

- The lowest k constant is the rate-determining step of the reaction, the corresponding ΔG^\ddagger is the highest activation Gibbs free energy.

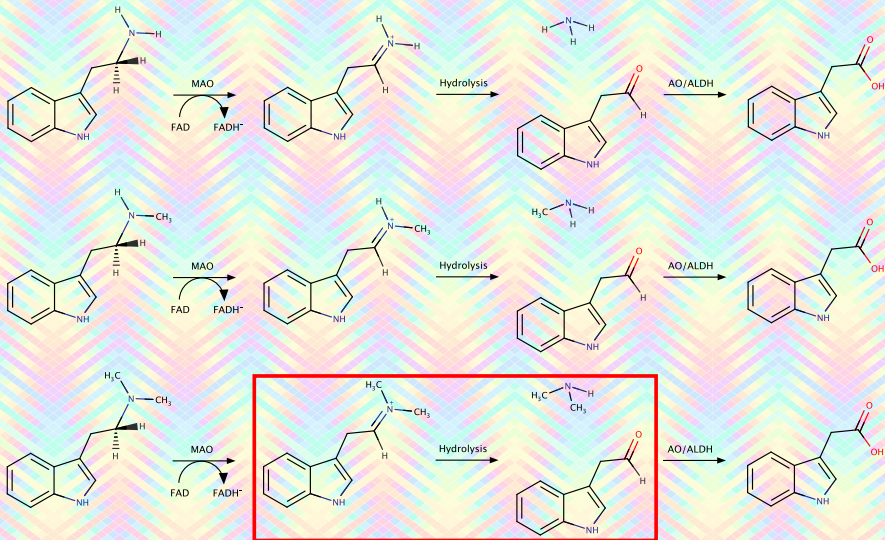
[10] H. Eyring, *The Journal of Chemical Physics*, 1935, **3**, 107–115.

[11] H. Eyring, *Chemical Reviews*, 1935, **17**, 65–67.

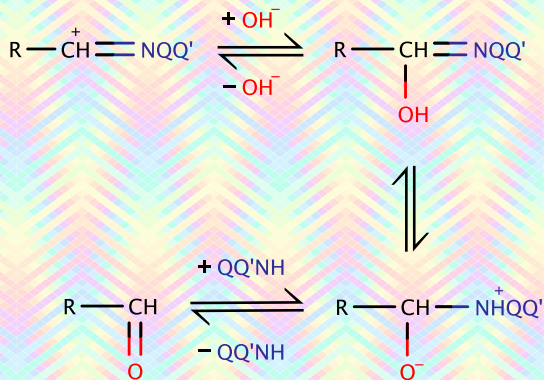
[12] H. Eyring and M. Polanyi, *Zeitschrift für Physikalische Chemie*, 2013, **227**, 1221–1245.

[13] E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Mill Valley, CA, 2nd edn, 2006.

Metabolism of biogenic tryptamines

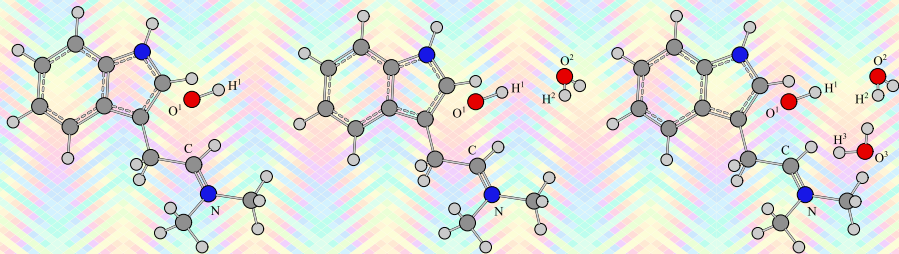


Iminium ion hydrolysis



The examined reaction

- The hydrolysis of *N,N*-dimethylindole-3-ethaniminium cation (imDMT^+) was examined in three different ways:
 - $\text{imDMT}^+ + \text{OH}^-$ (R_0)
 - $\text{imDMT}^+ + \text{OH}^- + \text{H}_2\text{O}$ (R_1)
 - $\text{imDMT}^+ + \text{OH}^- + 2 \text{H}_2\text{O}$ (R_2)

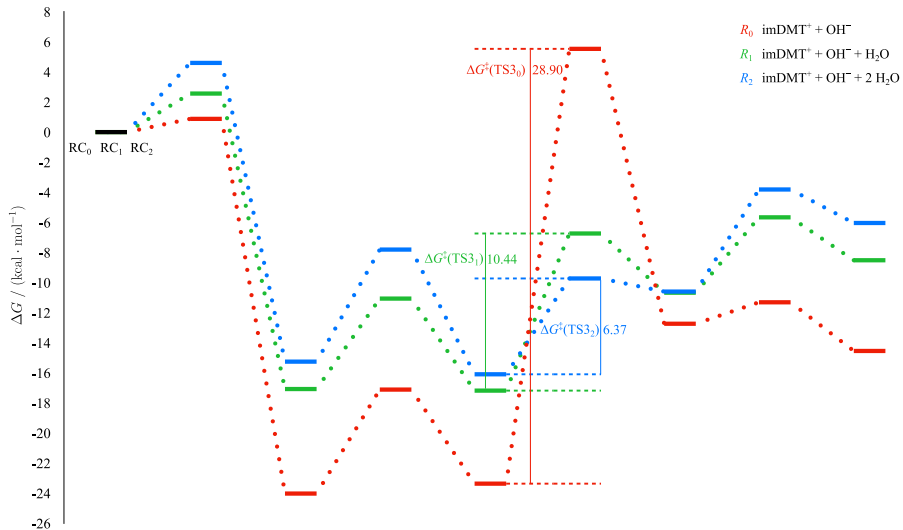


The reaction steps

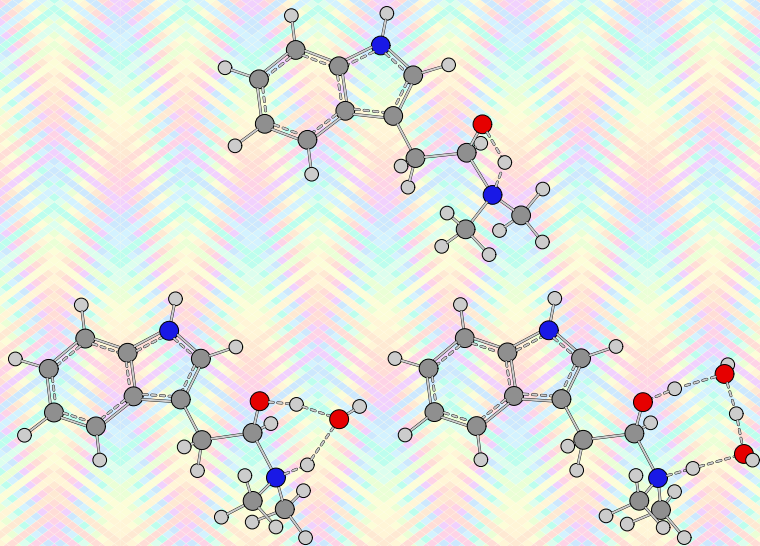
- The overall hydrolysis process includes the following steps:
 - Nucleophilic addition of OH^- on the C atom
 - Inversion of N atom
 - Concerted proton-transfer from ^1O to N \rightarrow rate determining step**
 - Dissociation of the zwitterionic aldehyde-amine (indole-3-acetaldehyde and dimethylamine) adduct

Reaction	ΔG^\ddagger / [kcal mol $^{-1}$]	ΔG^\ddagger / [kJ mol $^{-1}$]	k / [s $^{-1}$]	
R_0	TS1 ₀	0.88	3.68	1.13×10^{12}
	TS2 ₀	6.91	28.92	1.68×10^7
	TS3 ₀	28.90	120.93	4.27×10^{-11}
	TS4 ₀	1.43	5.97	4.11×10^{11}
R_1	TS1 ₁	2.56	10.72	5.07×10^{10}
	TS2 ₁	6.01	25.15	8.82×10^7
	TS3 ₁	10.44	43.70	2.50×10^4
	TS4 ₁	5.01	20.96	5.59×10^8
R_2	TS1 ₂	4.60	19.24	1.19×10^9
	TS2 ₂	7.45	31.17	6.24×10^6
	TS3 ₂	6.37	26.65	4.56×10^7
	TS4 ₂	6.79	28.39	2.12×10^7

Gibbs free energy profile of the reaction.



3D structures of TS3 transition states of the rate determining steps



Conclusions

- The concerted intramolecular proton-transfer step TS3₀ requires the highest activation Gibbs free energy $\Delta G_{\text{TS3}_0}^\ddagger$ in R_0 .
- The addition of one, or two H₂O molecule(s) in R_1 and R_2 opens up the possibility for concerted intermolecular proton-transfers TS3₁, and TS3₂, which decreases the $\Delta G_{\text{TS3}_1}^\ddagger$ and $\Delta G_{\text{TS3}_2}^\ddagger$ activation barriers. The differences of Gibbs free energies compared to TS3₀ are:
 - R_1 : $\delta(\Delta G^\ddagger) = [\Delta G_{\text{TS3}_1}^\ddagger - \Delta G_{\text{TS3}_0}^\ddagger] = 18.46 \text{ kcal} \cdot \text{mol}^{-1}$
 - R_2 : $\delta(\Delta G^\ddagger) = [\Delta G_{\text{TS3}_2}^\ddagger - \Delta G_{\text{TS3}_0}^\ddagger] = 22.53 \text{ kcal} \cdot \text{mol}^{-1}$

😊 Thank you very much for your attention! 😊