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An Alternative Mechanism of Tryptophan Metabolism? DFT Study on A Missing Piece in Our Understanding of Heme Chemistry

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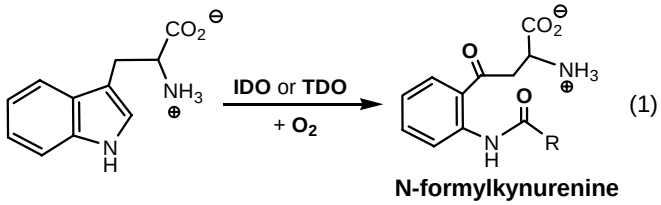
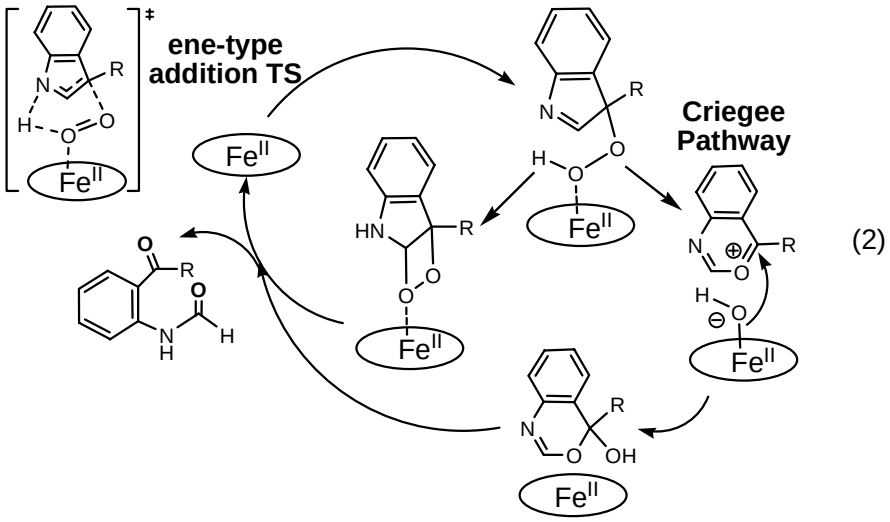
Indoleamine 2, 3-dioxygenase (IDO) and tryptophan 2, 3-dioxygenase (TDO) are unique heme-containing dioxygenases, which involve oxidative cleavage of the pyrrole ring of indoleamines and incorporate two oxygen atoms of oxygen molecule to give N-formylkynurenine derivatives (Eq. 1). Very recently, three crystal structures of IDO and TDO have been obtained [1]. Two mechanistic pathways (ene-type addition of the dioxygen coupled with proton transfer, followed by either the formation of dioxetane or Criegee rearrangement) were proposed (Eq. 2). B3LYP calculations have been performed to elucidate the reaction mechanism of tryptophan metabolism. The proposed concert ene-type addition transition state is calculated to be high in energy. Instead, direct distal oxygen attack to both C2 and C3 positions of the indole (via ionic or radical pathway) are computed to be energetically favorable. In addition, the proposed Criegee rearrangement pathway is found to require a very high barrier (~ 49 kcal/mol) for the model compound, due to the absence of a very strong electron-donating substituent of the indole. Such rearrangement transition state could not be located for the heme-indole complex, and ring opening of epoxide transition state are obtained instead. Alternative pathways derived from the calculations will be presented.





Reference: (1) (a) Sugimoto, H., Oda, S.-I., Otsuki, T., Hino, T., Yoshida, T., Shiro, Y. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 2611. (b) Zhang, Y., Kang, S. A., Mukherjee, T., Bale, S., Crane, B. R., Begley, T. P., Ealick, S. E. *Biochemistry* **2007**, *46*, 145. (c) Forouhar, E., Anderson, J. L. R., Mowat, C. G., Vorobiev, S. M., Hussain, A., Abashidze, M., Bruckmann, C., Thackray, S. J., Seetharaman, J., Tucker, T., Xiao, R., Ma, L.-C., Zhao, L., Acton, T. M., Montelione, G. T., Chapman, S. K., Tong, L. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 473.