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

Abstract

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The monoamine oxidase (MAO) is a flavoenzyme[1–6] , which performs the oxidation of monoamine neurotransmitters such as serotonin, dopamine, norepinephrine, and their structurally related neuromodulator compounds, usually called "trace amines" (TAs) referring to their lower concentration compared to the main neurotransmitters.[7–9] The latter group includes tryptamine (T), and phenylethylamine (PEA) as well as their derivatives. They have not received too much scientific interest before the discovery of G protein coupled human trace amine associated receptors (TAARs).[10–14] The irregularities of TA levels has been linked to numerous mental disorders like schizophrenia, major depression, bipolar disorder, anxiety, attention deficit hyperactivity disorder (ADHD), and substance abuse disorders.[8,9,15] The MAO has two isoforms, MAO-A and MAO-B. Their primary structure (sequence of amino acids) share around 70% identity, but their distribution in tissues and their selectivity to substrates is different.[3,5,6,16–18] MAOs have crucial role in the breakdown/inactivation of monoamine compounds in the body, therefore they responsible for the regulation their levels.

A compound belonging to the TA group, *N*,*N*-dimethyltryptamine (DMT) is a naturally occurring serotonergic indole alkaloid, which has profound psychedelic (mind-altering) effects on the human psyche.[19–24] Lately, it has been discovered, that DMT is a natural ligand of sigma-1 receptors and it has important role in tissue protection, regeneration, and immunity.[25] *In vitro* experiments revealed that DMT shows potent protective effects against hypoxia.[29]

We have investigated the metabolism of DMT with monoamine oxidase A enzyme using multilayer QM:MM quantum chemical calculations.[30] The MAO converts DMT into a positively charged iminium ion form, namely *N*,*N*-dimethylindole-3-ethaniminium cation ($imDMT^+$).

In order to examine the metabolism process of endogenous DMT further, we decided to study the hydrolysis of $imDMT^+$ in detail, which resulting indole-3-acetaldehyde (IAL) and dimethylamine. Three different systems (or reaction paths) were examined, which include the $imDMT^+$ cation and one OH^- ion with zero (R_0), one (R_1), and two H_2O molecules (R_2) respectively. The largest, 2 H_2O containing system is shown in Figure 1. Our results demonstrate that the presence of water molecule(s) open the possibility for an intermolecular proton transfer in the third step of the reaction (Figure 2) and dramatically reduces the corresponding barriers (R_1,R_2) compared to the intramolecular (R_0) case.

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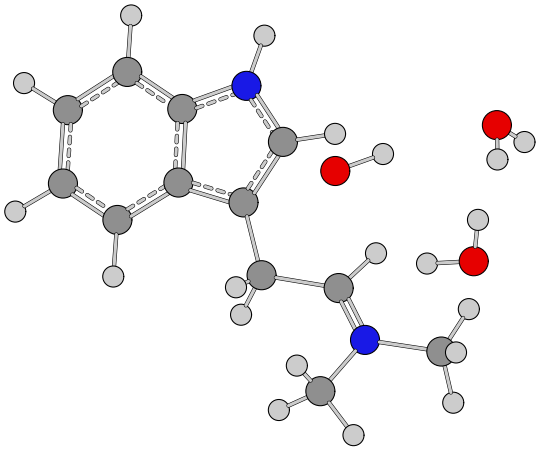

Figure 1

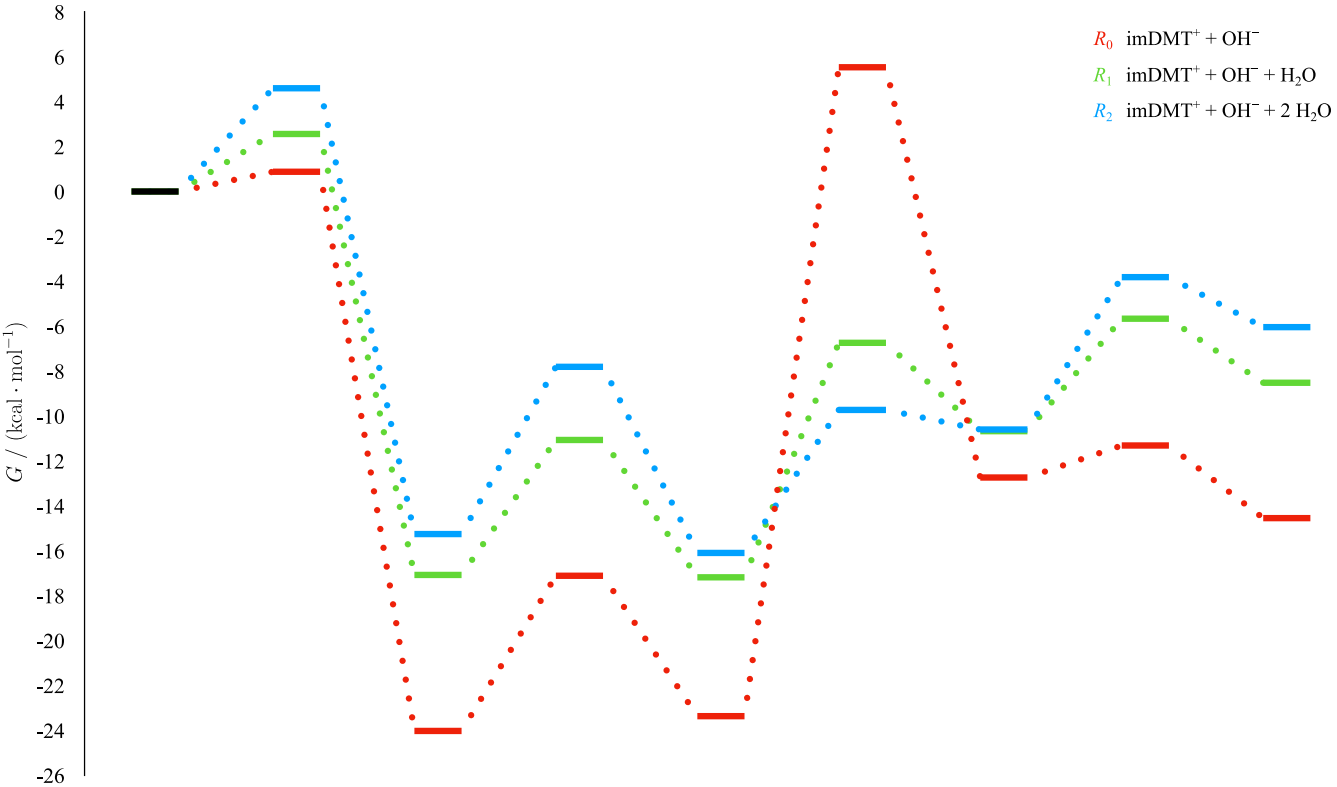

Figure 2

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