Understanding the NO detoxification mechanism in truncated hemoglobin N from *M. Tuberculosis:* a QM-MM and classical simulation study.

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Mycobacterium tuberculosis is the causative agent of human tuberculosis. The nitric oxide reaction with oxy-truncated hemoglobin N (trHbN) has been proposed to be responsible for the resistance mechanism by which this microorganism can evade the toxic effects of NO by converting it into the innocuous nitrate. In this work, we explore the molecular basis of the NO detoxification mechanism by using a combination of classical and hybrid quantum-classical (QM-MM) simulation techniques to analyze the ligand migration, ligand binding and chemical reaction steps. Classical molecular dynamics results suggest that trHbN has evolved a dual-path mechanism for migration of O_2 and NO to the heme, to achieve the most efficient NO detoxification. QM-MM calculations indicate that the protein environment enhances strongly the protein oxygen affinity, but is not found to make a significant contribution to the heme moiety catalyzed reaction. Finally, our results show that that trHbN is able to release rapidly the nitrate anion using an eggression pathway other than those used for the entry of both O_2 and NO and that its release is promoted by hydration of the heme cavity. These results provide a detailed understanding of the molecular basis of the NO detoxification mechanism used by trHbN to guarantee an efficient NO detoxification and thus warrant survival of the microorganism under stress conditions.