The importance of methionine and of a Tyr/Asp diad in prenyl transferases and terpene synthases

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Prenyltransfering enzymes are at the basis of the vast isoprenoid natural product diversity. They include, e.g., aromatic prenyl transferases, prenyl diphosphate and terpene synthases, all of which activate an (olig)prenyl diphosphate to form a stabilized prenyl cation reactive intermediate, that after addition to a nucleophile (C=C bond) and deprotonation delivers the product(s). So far, aromatic amino acids have been suggested to stabilize the cation intermediate. In this paper their role is elucidated further, but most importantly, other nucleophilic amino acids, specifically methionine are suggested as additional or alternative aids for cation stabilization. This suggestion is supported by site directed mutagenesis, bioinformatics and modelling studies. In addition, a new catalytic diad composed of Tyr and Asp, represented by a Yx(x)xxD-motif, is identified as important player for deprotonation and proton-relay in intermediates and finalizing deprotonation steps of many prenyl transferring and cyclizing enzymes.