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The Catalytic Mechanism of Activation by Glutamyl-tRNA Synthetase; A QM-Cluster Study.
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Aminoacyl-tRNA synthetases (aaRS's) are ubiquitous ancient enzymes that have central roles in a range of biological processes including viral assembly, inflammation and cell death.\textsuperscript{1-3} They are perhaps most well known for their role in protein synthesis.\textsuperscript{3} However, glutamyl-tRNA synthetase is unique in that it also plays a critical role in the biosynthesis of chlorophyll.\textsuperscript{4,5} More specifically, it catalyses the aminoacylation of its cognate tRNA via two half-reactions.\textsuperscript{6} In the first glutamate is activated by reacting with ATP to give the aminoacyl-adenylate. In the second half-reaction the latter is then reacted with its cognate tRNA, resulting in transfer of the aminoacyl fragment onto the tRNA moiety. This overall process is further complicated by the fact that it appears that all 3 reactants, ATP, glutamate and the cognate tRNA are required for the first half-reaction.\textsuperscript{7} That is, the reaction of ATP with glutamate, within the enzymes active site, can not occur without tRNA also being present.\textsuperscript{8} How the tRNA may modify the enzyme, or participate in the reaction is unclear. Using computational chemistry, we have modeled the activation of glutamate by Glutamyl-tRNA synthetase, with and without the presence of the tRNA moiety. Particularly, atomistic-level insights have been gained using a quantum mechanical-chemical cluster (QM-cluster)-based computational approach. Some recent key findings of our studies will be presented.\textsuperscript{9,10}
(3) Safro, M. G.; Moor, N. A. Mol. Biol. 2009, 43, 211-222.