Supplementary data

A QM/MM Evaluation of the Missing Step in the Reduction Mechanism of HMG-CoA by Human HMG-CoA Reductase

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In this paper we have used NADPH parameters developed and published in [1].

The neutral His405 System			
Atoms	**$q_{Reactants}$**	**q_{TS}**	**$q_{Products}$**
HIS405-N	-0.1752	-0.1630	-0.1663
GLU98-O1	-0.5029	-0.5092	-0.6065
GLU98-O2	-0.1589	-0.1550	-0.6297
GLU98-C	0.5631	0.5791	0.5765
MEV815-O	-0.4814	-0.6135	-0.2935
MEV815-C	0.4652	0.3207	0.2181
NADPH818-C	-0.0904	-0.1107	0.0571

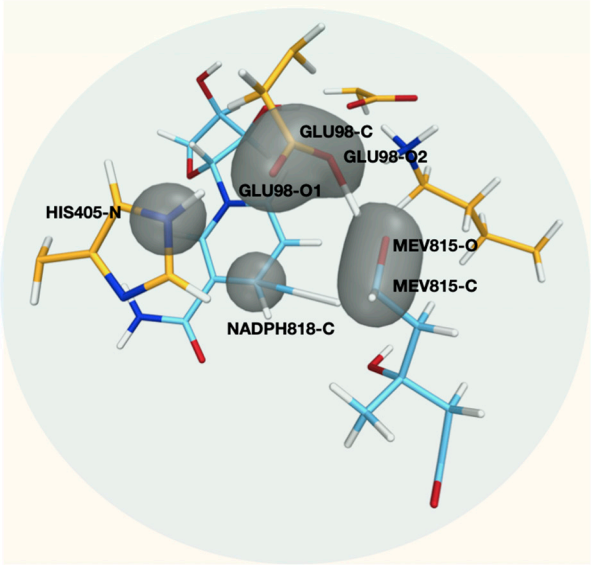

Figure S1 The mulliken charges for each atom involved in the reaction mechanism for *The Neutral His405 System* (left) with a corresponding optimized structure of the products (right).

The cationic His405 System			
Atoms	$q_{Reactants}$	q_{TS}	$q_{Products}$
HIS405-N	-0.5456	-0.5437	-0.4971
GLU98-O1	-0.5472	-0.5703	-0.6409
GLU98-O2	-0.5711	-0.5831	-0.5260
GLU98-C	0.6033	0.6031	0.6031
MEV815-O	-0.4687	-0.5967	-0.7357
MEV815-C	0.3008	0.1095	-0.0225
NADPH818-C	-0.3199	-0.2985	-0.1005

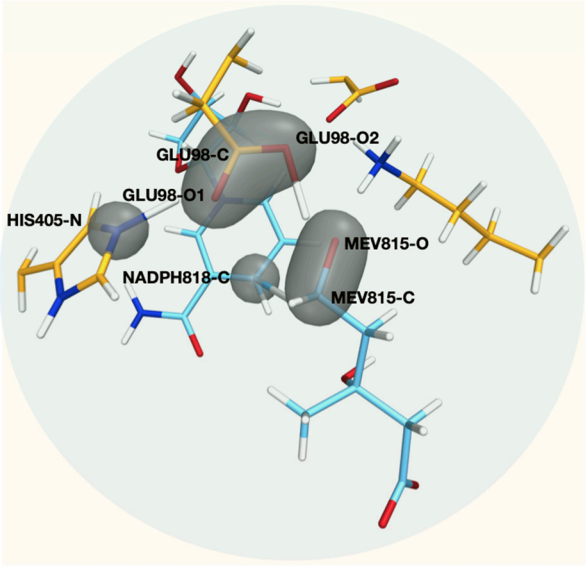

Figure S2 The mulliken charges for each atom involved in the reaction mechanism for *The Cationic His405 System* (left) with a corresponding optimized structure of the products (right).

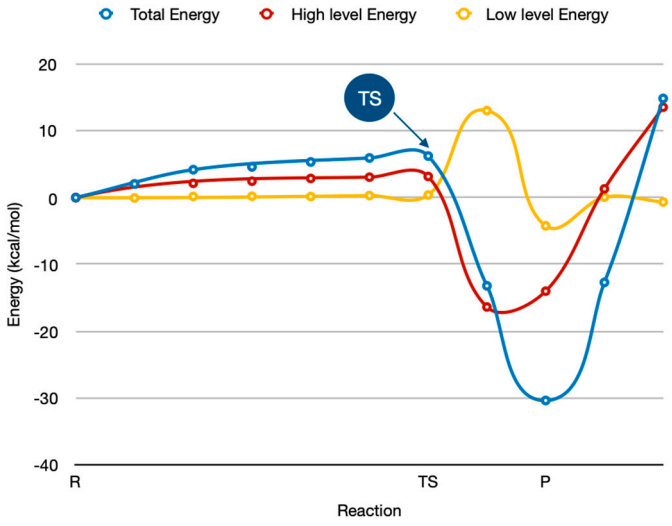

Figure S3 The linear scan of *The Natural His405 System*. The distance was decreased from 2.99 to 2.19 *Å* with a 0.5 *Å* increment, after which another linear scan was done with a decrease of the distance with the increments of 0.01 *Å*.

References:

[1] Cummins PL, Ramnarayan K, Singh UC, Gready JE, Molecular-dynamics free-energy perturbation study on the relative affinities of the binding of reduced and oxidized NADP to dihydrofolate-reductase, Journal of the American Chemical Society 1991, 113, 8247.