QM/MM modelling of the hydrolytic activity of *Trypanosoma cruzi trans*-Sialidase and *Trypanosoma rangeli* Sialidase

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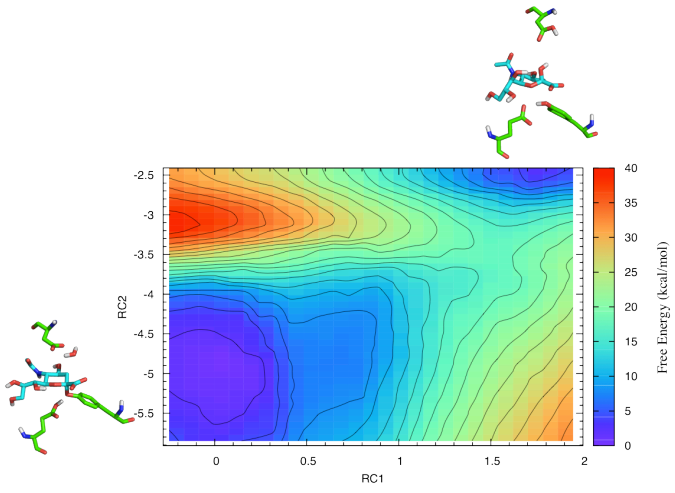
Chagas disease, also known as American trypanosomiasis, is a lethal, chronic disease that currently affects more than 20 million people in Central and South America (1).The protozoan parasite *Trypanosoma cruzi* is the causative agent of Chagas disease and was identified in Brazil by Carlos Chagas in 1909 (2). The *trans*-Sialidase from *T.cruzi* (TcTS) is a crucial enzyme for the infection of this parasite: sialic acids from the host are transferred to the cell surface glycoproteins of the trypanosome and provide the ability to evade the immune system (3, 4). On the other hand, *Trypanosoma rangeli* Sialidase (TrSA), which shares 70% sequence identity with TcTS, is a strict hydrolase and shows no trans-sialidase activity. TcTS and TrSA represent therefore an excellent model to understand the determinants of their catalytic mechanism. Advances in computer power, force field development and simulation methodologies applied to the study of catalytic mechanisms of enzymes have led to a maturity in the field that enables theoretical results to fill in some of the missing features that the experimental tools cannot provide. By means of combined quantum mechanics-molecular mechanics (QM/MM) calculations and Umbrella Sampling simulations, we were able to investigate with atomic detail the hydrolysis activities of TcTS and TrSA and compute the free energy profiles of the reactions. These results, together with our previous computational investigations, shed light into the catalytic mechanism of sialidases and can contribute to design new drugs for the treatment of Chagas disease (5).



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