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The driving force for the acylation of β-lactam antibiotics by L,D-transpeptidase from Mycobacterium tuberculosis: Molecular dynamics and Quantum mechanics/molecular mechanics (QM/MM) study

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Abstract
β-lactam antibiotics, which are used to treat infectious diseases (tuberculosis), are currently the most effective class of antibiotics. This study focused on the chemical reactivity of five- and six-membered ring systems attached to the β-lactam ring. A partially constrained Molecular dynamics for 20 ns was performed on the precomplex system. The last snapshots from the final 5 ns were used as starting structures for the unconstrained ONIOM TS calculations. The ring strain energy (RSE), force constant (FC) of amide (C—N), acylation transition states and second-order perturbation stabilization energies of 13 basic structural units of β-lactam derivatives were computed using the M06-2X and G3/B3LYP multistep method. In the ring strain calculations, an isodesmic reaction scheme was used to obtain the total energies. RSE is relatively greater in the five-(1a-2c) compared to the six-membered ring systems except for 4b, which gives a RSE that is comparable to five-membered ring lactams. These variations were also observed in the calculated inter-atomic amide bond distances (C—N), which is why the six-membered ring lactams C—N bond are more rigid than those with five-membered ring lactams. The calculated ΔG# values from the acylation reaction of the lactams (involving the S—H group of the cysteine active residue from L,D transpeptidase 2) revealed a faster rate of C—N cleavage in the five-membered ring lactams especially in the 1-2 derivative (17.58 kcal mol-1). This observation is also reflected in the calculated amide bond force constant (1.26 mDyn/A) indicating a weaker bond strength, suggesting that electronic factors (delocalization) play more role on reactivity β-lactam ring, than ring strain.
The Centre for high Performance computing (CHPC, www.chpc.ac.za) provided the computational resources (CPUs) for this work. Drawing allocation from CHEM0808 workspace (Lustre file system) on Lengau Cluster. The Gaussian09 (D01) program was used to execute the jobs. 24 cores, 1node and 48:00 hours wall time were used. Also, AMBER 14 was used for the MD studies with mpirun -np 72 -machinefile, walltime=48:00hours and ncpus=24

Keywords: β-lactam antibiotics; Transition state (TS); Ring strain energy (RSE); Force constant (FC), Activation energy.

References

1. Novak, I., and Chua, P. J. (2006) Computational study of pharmacophores: β-Lactams, The Journal of Physical Chemistry A 110, 10521-10524.
2. Zhanel, G. G., Lawrence, C. K., Adam, H., Schweizer, F., Zelenitsky, S., Zhanel, M., Lagacé-Wiens, P. R., Walkty, A., Denisuik, A., and Golden, A. J. D. (2018) Imipenem–relebactam and meropenem–vaborbactam: two novel carbapenem-β-lactamase inhibitor combinations, 78, 65-98.
3. Vreven, T., Byun, K. S., Komáromi, I., Dapprich, S., Montgomery Jr, J. A., Morokuma, K., and Frisch, M. J. (2006) Combining quantum mechanics methods with molecular mechanics methods in ONIOM, Journal of chemical theory and computation 2, 815-826.
4. Boonsri, P., Kuno, M., and Hannongbua, S. (2011) Key interactions of the mutant HIV-1 reverse transcriptase/efavirenz: an evidence obtained from ONIOM method, MedChemComm 2, 1181-1187.
5. Patet, R. E., Caratzoulas, S., and Vlachos, D. G. (2016) Adsorption in zeolites using mechanically embedded ONIOM clusters, Physical Chemistry Chemical Physics 18, 26094-26106.

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