Structure and Stability of Different Tautomers of Some Antibiotics

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Abstract

Antibiotics are among the most commonly prescribed medications and represent one of the most widely used drugs, essential for treating various bacterial infections. However, these molecules adopt different tautomeric conformations in the cellular environment. Therefore, understanding tautomerism in antibiotics is crucial for their recognition by receptors and the design of more effective antibiotics. In this study, a systematic conformational analysis of 23 Food and Drug Administration-approved (FDA) antibiotics of different classes is performed by using an accurate dispersion-corrected density functional theory and an implicit solvation model to treat the biological aqueous environment. This procedure helped to identify about 105 tautomeric conformations of these antibiotics. It is found that Doxycycline favours three degenerate tautomeric conformations, while others exhibited a single distinct energetically favourable tautomeric conformation. The second most tautomers of these molecules are found to be ~14-18 kcal/mol less stable than their most stable counterparts, and therefore, they may rarely populate cells. Thus, it is expected that this study will help elucidate the mechanisms of antibiotic recognition by receptors and aid in the future design of robust antibiotics.

Keywords: Antibiotics, Density functional theory (DFT), Conformations, Tautomers, Drug Design.