

Abstract

Density functional theory (DFT) using the B3LYP functional was applied to elucidate the molecular properties of the antitumor drug thiotepa and its main metabolite tepa. Aqueous solvent effects were introduced using the conductor-like polarizable continuum model (CPCM). The protocol for calculating the pK_a values obtained with different cavity models was tested on a series of aziridine and phosphoramidate compounds. An efficient computational scheme has been identified that uses the CPCM model of solvation with a universal force field (UFF) cavity. The method has been used to evaluate the basicities of thiotepa and its metabolite. Our calculations show that the basicities of the aziridine moiety of thiotepa and tepa are dramatically reduced compared to free aziridine, indicating that highly acidic media are needed to produce substantial yields of the N-protonated form of the drug. Finally, the mechanisms of reaction of the drug and its metabolite are discussed based on our theoretical results. The calculations reproduce the experimental trends very satisfactorily