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Instantaneous pKa assessment from molecular dynamics simulations

We demonstrate the application of our innovative ‘instantaneous pK’ approach to the molecular dynamics simulation of crystallite models exposed to an acidic solvent environment. For this, the bulk solution properties pH and pK are scrutinized into local aspects and effectively characterized for individual molecules of crystal faces, edges and steps, respectively. To illustrate this concept, we introduce two prototype cases: the acid-induced dissociation of i) calcite and ii) carbamazepine (CBZ, form III) drugs. We find acid-induced calcite dissociation follows a rather intuitive mechanism, namely the protonation of crystal edges/steps leading to ion-by-ion dissociation of HCO3− and Ca2+ species into water. In contrast, our simulations of CBZ solvation at pH = 3 and pH = 2, respectively, reveal a more complex dissolution behavior. The molecular crystals were found to accommodate a substantial degree of CBZ protonation without drug release to the solvent. Instead, the crystallite edges and corners are re-arranged in favor of a surprisingly stable core–shell structure, featuring a CBZ core and a mixed CBZ/CBZH shell of +0.005 and +0.03 C m−2 surface charge at pH = 3 and pH = 2, respectively. The resulting crystallite models are persistent and even more drastic acidity is needed to enable actual dissociation of CBZH into water.

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