Computational Methods for Predicting the pK_a of Terminal Alkynes

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The acid dissociation constant (pK_a) is among the most widely used physicochemical properties of molecules, as it is essential for understanding their chemical behavior in various environments. This is particularly true in aqueous solutions, where ionization significantly influences molecular interactions and reactivity. pK_a influences the pharmacokinetic profiles of drugs, including their absorption, distribution, metabolism, and excretion. It is also an important consideration in the design of drug excipients, delivery systems, and formulation vehicles [1]. One of the important chemical processes affected by the pK_a of alkynes is deuterium labelling. This process enables the synthesis of deuterated terminal alkynes, which are valuable intermediates used in a wide range of applications across biotechnology, medicinal chemistry, analytical chemistry, pharmaceutical and the agrochemical industry [2].

Although many experimental techniques exist for determining the pK_a of molecules—such as potentiometric titration, fluorometry, calorimetry, voltammetry and nuclear magnetic resonance—there is little data on computational methods that offer both speed and high accuracy [1b]. In this study, we used density functional theory (DFT) methods in the Gaussian software package, installed on the "Supek" supercomputer, to evaluate and compare several computational strategies for predicting the pK_a of terminal alkynes. These included thermodynamic cycles, isodesmic reaction schemes, GIAO-NMR chemical shifts, and hydrogen exchange barrier calculations.

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