Tools for Prediction of pKa Values of Acetylenes: GIAO-NMR Chemical Shifts and Hydrogen Exchange Barriers

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The diversity in acidity among compounds containing a terminal alkyne group indicates that such functional groups can exhibit very different acid-base properties, which can significantly influence a compound's biological activity, chemical stability, and environmental fate [1]. The acidity of terminal alkynes is extremely important in organic chemistry and the pharmaceutical industry. For this reason, we aimed to develop a simple and efficient computational protocol to estimate their pKa values. To this end, we examined various quantum chemical methods by analyzing and testing a collection of compounds with known experimental pKa values. Although standard thermodynamic approaches proved insufficient, we identified two methods we consider reliable: a kinetic approach, based on calculating the proton exchange barriers in terminal alkynes, and a spectroscopic approach, based on the theoretical calculation of ^{1}H NMR chemical shifts. Both methods show a very good correlation with experimental data, confirming their practical value for predicting the acidity of alkynes [2].

Using these approaches, we calculated the pKa values of drugs containing a terminal alkyne group (ethinylestradiol, rasagiline, selegiline, pargyline, 5-ethynyluracil, and erlotinib). The results showed that the predicted pKa values of these compounds vary by as much as 8 to 9 pKa units.

References:

[1] J. Ho, M. L. Coote, *J. Chem. Theory Comput.* **5** (2009) 295–306.

[2] A. J. Kresge, P. Pruszynski, P. J. Stang, B. L. Williamson, *J. Org. Chem.* **56** (1991) 4808-4811.