

# Theoretical Estimation of the Aqueous pK<sub>a</sub>s of Thiols

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**Abstract.** The ionization state of a compound under different conditions is an important parameter influencing the compound's activity as a drug, metabolite, pollutant, or otherwise bioactive agent. Sulfhydryl compounds (thiols) tend to be considerably more acidic than their hydroxyl (alcohol) analogs. In this report quantum chemical approaches previously used for the estimation of the aqueous pK<sub>a</sub>s of alcohols are applied to the estimation of the acidities of thiols. Acidity estimates obtained from the general-purpose SPARC calculational program [Hilal, Karickhoff, and Carreira, *Quant. Struct.-Act. Relat.* **14**, 348 (1995)] have been employed as a benchmark. Quantum chemical calculations were performed using both the semiempirical RM1 method and the density functional theory B3LYP/6-31+G\* method. The effectiveness of the SM5.4 and SM8 solvent models in estimating the aqueous-phase acidities was also examined.

Keywords: Thiols, pK<sub>a</sub>, acidities, QSAR, DFT, RM1

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