

## A Rationale to Describe Ambident Reactivity

**Authors :** David Ryan, Martin Breugst, Turlough Downes, Peter A. Byrne, Gerard P. McGlacken

**Abstract :** An ambident nucleophile is a nucleophile that possesses two or more distinct nucleophilic sites that are linked through resonance and are effectively “in competition” for reaction with an electrophile. Examples include enolates, pyridone anions, and nitrite anions, among many others. Reactions of ambident nucleophiles and electrophiles are extremely prevalent at all levels of organic synthesis. The principle of hard and soft acids and bases (the “HSAB principle”) is most commonly cited in the explanation of selectivities in such reactions. Although this rationale is pervasive in any discussion on ambident reactivity, the HSAB principle has received considerable criticism. As a result, the principle’s supplantation has become an area of active interest in recent years. This project focuses on developing a model for rationalizing ambident reactivity. Presented here is an approach that incorporates computational calculations and experimental kinetic data to construct Gibbs energy profile diagrams. The preferred site of alkylation of nitrite anion with a range of ‘hard’ and ‘soft’ alkylating agents was established by <sup>1</sup>H NMR spectroscopy. Pseudo-first-order rate constants were measured directly by <sup>1</sup>H NMR reaction monitoring, and the corresponding second-order constants and Gibbs energies of activation were derived. These, in combination with computationally derived standard Gibbs energies of reaction, were sufficient to construct Gibbs energy wells. By representing the ambident system as a series of overlapping Gibbs energy wells, a more intuitive picture of ambident reactivity emerges. Here, previously unexplained switches in reactivity in reactions involving closely related electrophiles are elucidated.

**Keywords :** ambident, Gibbs, nucleophile, rates

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