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Organic Chemistry: Current Research

Commentary

A Brief Note on Automatic Mapping of Atoms

Seo Jun*

Department of Chemistry, University of Warsaw, Ulju-gun, Ulsan, South Korea

DESCRIPTION

Proton-Coupled Electron Transfers (PCETs) are oxidoreduction mechanisms during which each electron and protons are exchanged, typically in a much combined elementary step. By virtue of transferring an electron and proton, PCET will perform as a non-traditional mechanism for homolytic bond cleavage, formally adding or removing the element of H to or from substrates of interest. PCET mechanisms play a key role in several distinct areas of chemistry and chemical change. For example, biological oxidoreduction (redox) processes like enzymatic C–H oxidation, ribonucleotide reduction, photosynthesis and small-molecule metabolism all involve key PCET steps. PCET is prevalent in inorganic technologies for the interconversion of small molecules like O_2/H_2O, N_2/NH_3, and CO_2/alkanes. Traditionally the use of PCET as a mechanism for bond homolysis in organic synthesis has been less extensively investigated [1]. However, the past decade has witnessed important growth in this area, with organic chemists, a lot of absolutely recognizing the ability of PCET to change the direct generation of radical intermediates from the varied common organic functional groups.

An essential aspect of free radical chemistry is the means by which radical intermediates are generated from closed-shell beginning materials. The homolytic cleavage or formation of C–H and E–H (E=N, O, S) bonds could be a significant approach, as reactive radicals can be accessed directly from readily available beginning materials without the necessity for substrate pre-functionalization. Consequently, homolytic bond activations are powerful artificial strategies, as exemplified by the extensive use of Hydrogen-Atom-Transfer (HAT) reactions within the selective functionalization of open-chain aliphatic C–H bonds [2]. Whereas powerful, the scope of radical generation via HAT is usually restricted thermodynamically by the range of accessible H-atom donors and acceptors. The position of HAT equilibria will be expressed because of the distinctions within the Bond Dissociation Free Energies (BDFEs) of the 2 bonds to hydrogen that are undergoing exchange.

To be energetically favorable, the BDFE of the bond broken in the reactants should be weaker than the BDFE of the bond formed within the product. This presents a major challenge to HAT activation of the many common organic functional groups, which might need either the cleavage of exceptionally strong bonds or the formation of unusual weak bonds, to hydrogen. As an example, the removal of H from the N-H bonds in N-alkyl amides (BDFE≈110 kcal mol) or the O-H bonds in aliphatic alcohols (BDFE≈105 kcal mol-1) necessitates the use an H-atom that forms a good stronger bond to hydrogen.

Consequently, even potent H-atom abstractors, like the iron oxo species of cytochrome P450 enzymes (O–H BDFE≈95 kcal mol-1) are thermodynamically incapable of activating those functional groups. Likewise, the addition of H to an aromatic organic compound generates a neutral ketyl radical with an exceptionally weak O–H bond requiring an H-atom donor with equally low bond strength [3]. However, metal hydrides, which are used as catalytic H donors, typically have complexes with lower bond strengths that tend to evolve H_2. Conceivably, this can be overcome when an unfavorable HAT then includes a quick and irreversible exothermal downhill reaction of the generated radical; however, this is often restricted to specific circumstances. In those limitations, general strategies for the direct HAT activation of the many common functional groups have yet to be reported.

Over the past decade, a set of PCET mechanisms have emerged that address those thermodynamic limitations. Multi-Site Proton-Coupled Electron Transfer (MS-PCET) involves the homolytic cleavage or formation of a C–H or E–H bond by the transfer of an electron and proton to form completely independent reagents. In these MS-PCETs, the electron and proton originate from two separate donors or travel to two distinct acceptors. In observation, this usually involves the use of separate Electron-Transfer (ET) and Proton-Transfer (PT) reagents [4]. For oxidative MS-PCET, the combination of a single-electron oxidizing agent and a Brønsted base will act as a proper H acceptor, whereas the combination of a single-electron reducer and Brønsted acid will act as a proper H donor in reductive MS-PCET reactions. By physically separating the ET and PT reagents, MS-PCET mechanisms can span a far wider thermodynamic range than is possible standard platforms for

Correspondence to: Seo Jun. Department of Chemistry, University of Warsaw, Ulju-gun, Ulsan, South Korea, E-mail: seojun1@cuhk.edu.kr

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HAT (vide infra), enabling stronger formal H-atom acceptors and H-atom donors to be accessed.

MS-PCET offers orthogonal chemoselectivity from what's usually observed *via* HAT. HAT chemoselectivity is ruled primarily by reaction drive, polarity matching effects, and reorganization energies. In oxidative HAT, this usually results in selective homolytic cleavage of the weakest or most well polarity-matched aliphatic C–H bond in a substrate. MS-PCET involving the combined transfer of an electron and proton instead required preorganization of the PT coordinate in a hydrogen-bonding complex between the substrate and base (or acid) before the Electron-Transfer (ET) event [5]. This requirement for non-covalent pre-association permits for the selective homolysis of stronger, polar functional groups within the presence of weaker aliphatic C–H bonds, which are poor hydrogen bond donors. Similarly, through pre-association with an appropriate acid before ET, selective MS-PCET reduction of imines and carbonyl groups can be achieved within the presence of less polar olefins despite a strong thermodynamic bias for C–H bond formation. These features of MS-PCET provide a distinct and general methodology for the catalytic generation of synthetically important free-radical intermediates directly from a wide range of common organic functional groups.

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