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Factors Controlling Reactivity in the Hydrogen Atom Transfer and Radical Addition Steps of a Radical Relay Cascade

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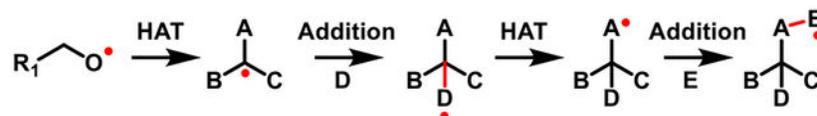
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Abstract

DFT exploration of 1,5- and 1,6-hydrogen atom transfers (HAT), radical addition, and relay to alkene is reported. The reactivity of 1,5- and 1,6-HAT are similar. We also explored reactions involving a multiple radical transferring process. Initially generated radicals undergo a multiple HAT process to form multiple bonds in a “relay” fashion, provided by exquisitely balanced rates.

Graphical Abstract



The hydrogen atom transfer (HAT) reaction transfers a radical center from the original site to a distal position.¹ Although the newly generated radical species is less reactive than the original one, a new bond can now be formed at the distal position, if the lifetime is sufficient for a subsequent addition reaction. One of the earliest examples of a HAT reaction is the Hofmann–Löffler–Freitag reaction,² in which the initial nitrogen based radical, generated via photolytic homolysis of the N–Cl bond such as in (i), undergoes an intramolecular HAT process to relay the radical to a carbon center (Scheme 1) that subsequently reacts with the amine generated to give (ii). In the Norrish Type II reaction,³ a carbonyl such as in (iii) excited to an $n-\pi^*$ state undergoes rapid intramolecular HAT to abstract a γ -hydrogen to produce a 1,4-biradical as the primary photoproduct. The resulting 1,4-biradical then undergoes subsequent reactions of intra-molecular radical recombination [Yang cyclization to generate (iv)] and/or β -cleavage (Norrish Type II).

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02023.

General computational methods; energetics of all computed species; Cartesian coordinates of all computed species; references to computational program (PDF)

The authors declare no competing financial interest.

The most common synthetic applications of HAT involve 1,5- and 1,6-HAT reactions, wherein the newly generated radical-bearing atoms are in a 1,5- and 1,6-relationship respectively with the original radical centers.⁴ Smith et al. recently reported a new synthetic application of the 1,5- and 1,6-HAT process in which an initial alkoxy radical (vi) was generated from a *N*-alkoxyphthalimide (v) via photoredox catalysis (Scheme 1). Upon HAT, the resulting carbon radical (vii), stabilized by either a dioxanyl or a dithianyl group, further engages in radical additions to electrophiles.⁵ This radical “relay” reaction permits remote C–H functionalization and was employed in the total synthesis of (±)-danshenspiroketallactone (x). The originally generated oxy radical reacts in an energetic cascade with a series of electrophiles to generate multiple bonds in a single-flask operation. This work demonstrated the synthetic potential of a radical cascade reaction.⁶

Previously we reported computational studies of intramolecular 1,5- and 1,6-HAT reactions that demonstrate that the 1,5-HAT process is in general more feasible than the 1,6-HAT process.⁷ That is, a six-membered cyclic transition state is both thermodynamically more stable than a seven-membered cyclic transition state and entropically more favored. *Ab initio* calculations of the intramolecular HAT reactions of butan-1-oxyl and pentan-1-oxyl radicals at the MP2/6–31G(d)//UHF/3–21G level demonstrated that the 1,5-HAT possessed a 19.9 kcal/mol energy barrier, and the barrier of the 1,6-HAT was 21.7 kcal/mol.⁴ This 1.8 kcal/mol free energy difference was introduced not from enthalpy ($\Delta H^\ddagger = -0.7$ kcal/mol) but from entropy ($\Delta S^\ddagger = 8.3$ eu, corresponding to 2.5 kcal/mol at rt).⁴ Development of DFT methods have now provided an opportunity to reinvestigate the 1,5- and 1,6-HAT process at a more superior computational level and to provide new mechanistic insights.

The structures of the butan-1-oxyl radical (**1**) and pentan-1-oxyl radical (**2**) were optimized using the DFT method at the uM062X(D3)/6–311++G(2d,p)//uM062X(D3)/6–31G(d) level (Scheme 2).⁸ Each corresponding reactive conformation (**2** and **6**) led to an intramolecular HAT cyclic transition state (**TS1** and **TS2**) to generate a primary carbon radical (**4** and **8**). The energy barriers (11.4 and 11.7 kcal/mol) for the HAT processes are significantly lower compared to our previous calculations.

We found that activation enthalpies and entropies of 1,5- and 1,6-HAT transition states are similar to each other. Seven-membered transition states generally possess more low energy conformations than six-membered transition states, but the seven-membered cyclic transition state of the HAT process possesses almost the same free energy as the six-membered cyclic transition state.

With this principle in mind, we continued our investigations by introducing either a dioxolanyl (**9a** and **9b**) or a dithiolanyl (**9c** and **9d**) as the radical stabilizing group at the HAT destination (Scheme 3). Not surprisingly, the resulting dioxolanyl (**11a** and **11b**) and dithiolanyl (**11c** and **11d**) radicals in both 1,5- and 1,6-HAT processes have significant thermodynamic preferences. Interestingly, both the 1,5- and 1,6-HAT are also kinetically more facile than those without the radical stabilizing groups (see Scheme 2), as can be demonstrated by their low free energy barriers [see **TS3** (a–d), Scheme 3]. This result is due to the radical stabilization effect of the dioxolanyl and dithiolanyl groups, and also to the

Thorpe–Ingold effect that stabilizes the cyclic conformations, which together resulted in a lower barrier compared with the previous examples (see Scheme 2).

The second relay step (a.k.a. radical addition onto the electrophile) was also investigated. Upon introduction of an allyl sulfone electrophile **12** (Scheme 3), the dioxolanyl (**11a** and **11b**) and dithiolanyl (**11c** and **11d**) radicals underwent conjugate addition followed by an α -fragmentation/elimination of **13** to generate the corresponding allylic substituted products **14** and a sulfonyl radical **15**. The radical addition step for dioxolanyl radicals proceeded with a free energy barrier of only 9.6 (**TS4a**, 1,5-HAT) or 8.5 (**TS4b**, 1,6-HAT) kcal/mol, which is comparable to the barrier of the HAT process (7.0 kcal/mol for 1,5-HAT and 7.8 kcal/mol for 1,6-HAT). However, the free energy barrier for the radical addition steps of the dithiolanyl radicals were significantly higher [12.9 kcal/mol for the 1,5-HAT (**TS4c**) and 13.6 kcal/mol for the 1,6-HAT (**TS4d**)], with the conjugate addition step now determining the rate of the overall reaction. This higher energy barrier explains in part why a dithiolane substrate resulted in a lower yield in the experiments. The increased reaction barrier of the second step is likely due to the stability of a dithiolanyl radical. The final α -fragmentation/elimination is in equilibrium, and depending on reaction conditions this might permit a further cascade reaction to occur. This proved to be the case as it was possible to introduce multiple relay steps after the initial HAT, as demonstrated in the original report.⁵

In the following example (Scheme 4) upon the first radical addition that generates tertiary radical **18a**, the tertiary radical undergoes a 1,6-HAT to transport the single electron to the benzylic position of **19**, followed by adding to the second equivalent of **12**. An elimination then occurs that leads to a double addition adduct **20** in 56% overall yield after oxidation.⁵ We have now investigated this relay process computationally. Upon generation of benzylalkoxy radical **16**, a facile 1,5-HAT (**TS5**, 5.9 kcal/mol, Scheme 5) generates benzylic radical **17**. Addition to the radical acceptor **12** leads to **18a** that is in equilibrium with **18b**. **18a** undergoes a seven-membered 1,6-HAT transition state (**TS7**) and then generates a benzylic radical (**19**). Final addition of another equivalent of **12** followed by α -fragmentation furnishes the final product **20b**. The 1,6-HAT process is now the rate-limiting step (16.8 kcal/mol free energy barrier) in this “energetic cascade”. The multiple migration of the original radical from oxy- to dithiolanyl-, β -sulfonyl-, benzyl-, β -sulfonyl-, and finally sulfonyl- are accompanied by bond relocation.

In summary, 1,5- and 1,6-HAT reactions have been further investigated using DFT methods and as shown have similar reactivity. Importantly, installation of radical stabilizing groups leads to the generation of a multiple-stage process involving multiple chemical bond formations. In order to achieve this energetic cascade, electrophiles must be selected in a manner that a radical can be generated at a new position upon each transfer without being quenched. Via this concept, multiple bond construction can be achieved in a single-flask in a “relay” manner, to facilitate the construction of complex molecular structures.

Supplementary Material

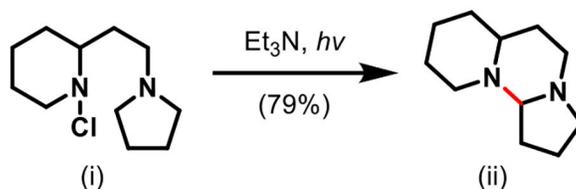
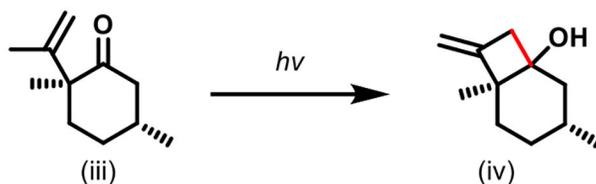
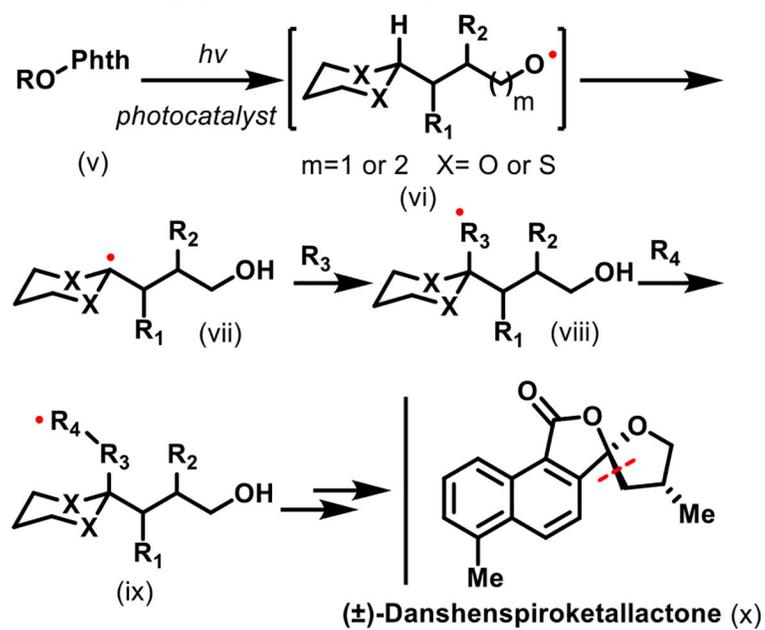
Refer to Web version on PubMed Central for supplementary material.

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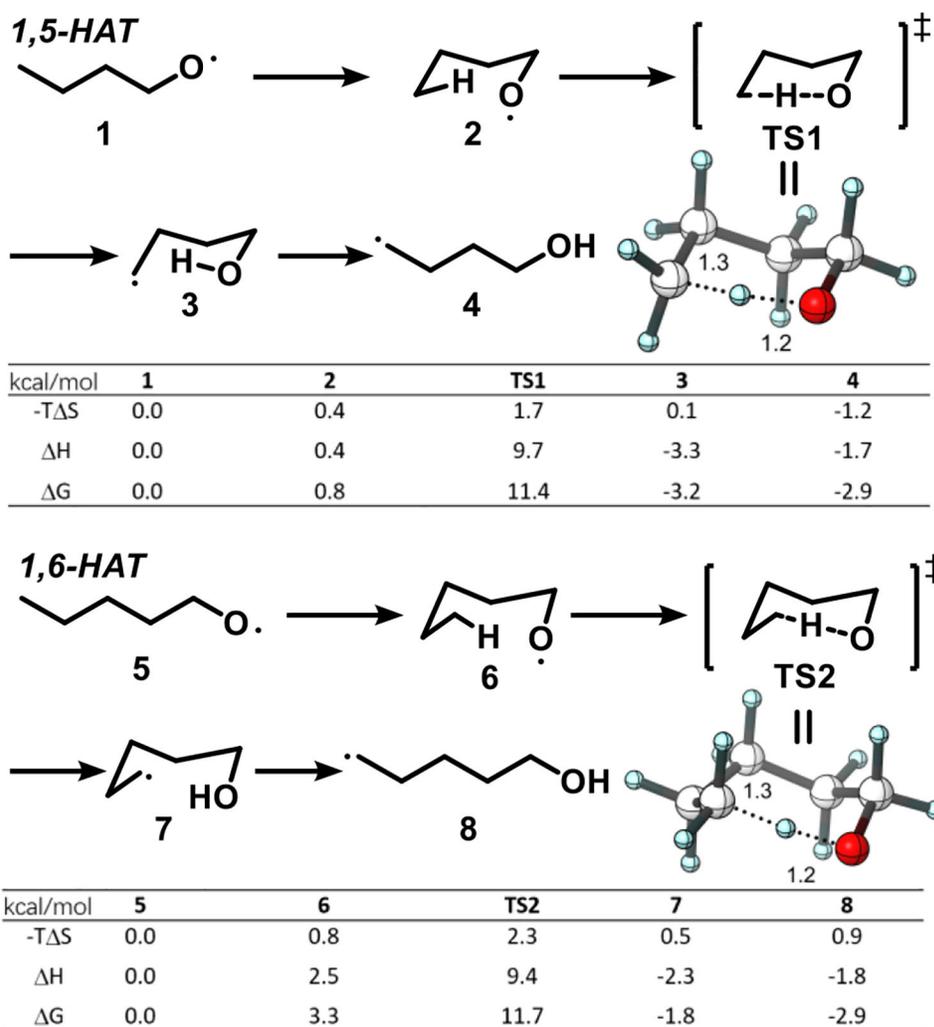
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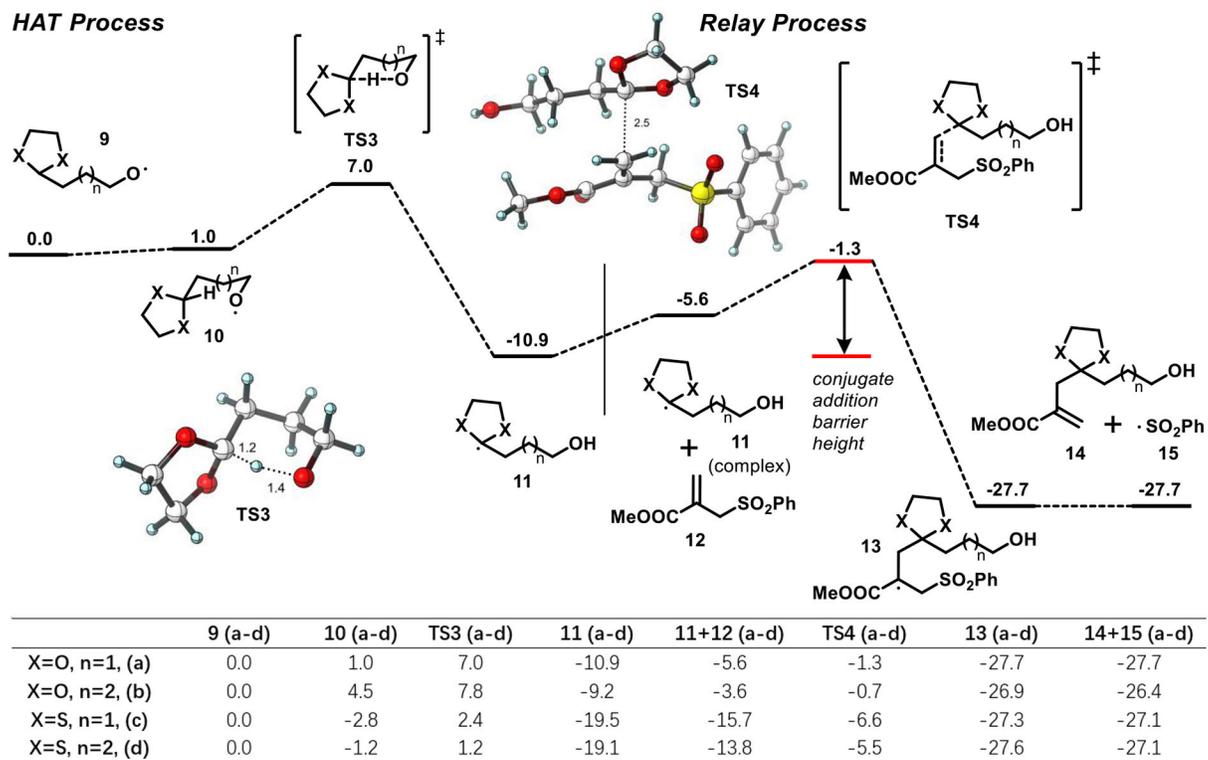
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Hofmann-Löffler-Freytag reaction example**Norrish reaction - type II example****Radical Relay (Smith et al., 2019)**

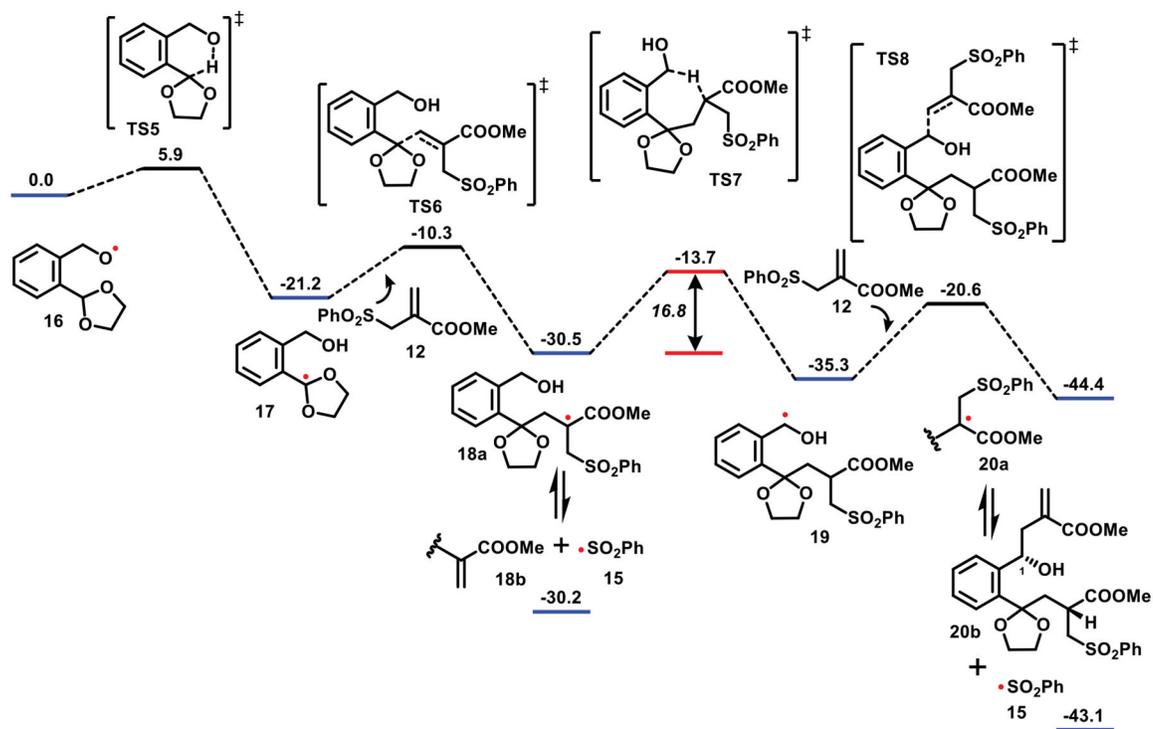
Scheme 1.
Demonstration of Intramolecular HAT Reactions



Scheme 2.
Energetics of HAT Reactions Using DFT Methods

**Scheme 3.**

Free Energy Profile (298 K, 1 atm) of the Radical Relay Reactions



Scheme 5.
Free Energy Profile for the Quadruple-Relay Process (298 K, 1 atm)