Hole Catalysis of Pericyclic Reactions: How to Activate and Control Oxidant Upconversion in Radical-Cationic Diels-Alder Cycloadditions

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ABSTRACT: In order to use holes as catalysts, the oxidized product should be able to transfer the hole to a fresh reactant. For that, the hole-catalyzed reaction must increase the oxidation potential along the reaction path, i.e., lead to "hole upconversion". If this thermodynamic requirement is satisfied, a hole injected via one-electron oxidation can persist through multiple catalytic cycles and serve as a true catalyst. This work provides guidelines for the rational design of hole-catalyzed Diels-Alder (DA) reactions, the prototypical cycloaddition. After revealing the crucial role of hyperconjugation in the absence of hole upconversion in the parent DA reaction, we show how upconversion can be reactivated by proper substitution. For this purpose, we computationally evaluate the contrasting effects of substituents at the three possible positions in the two reactants. The occurrence and magnitude of hole upconversion depend strongly on the placement and nature of substituents. For example, donors at C1 in 1,3-butadiene shift the reaction to the hole-upconverted regime with an increased oxidation potential of up to 1.0 V. In contrast, hole upconversion in C2-substituted 1,3-butadienes is activated by acceptors with the oxidation potential increase up to 0.54 V. Dienophile substitution results in complex trends because the radical cation can be formed at either the dienophile or the diene. Hole upconversion is always present in the former scenario (up to 0.65 V). Finally, we report interesting stereoelectronic effects that can activate or deactivate upconversion via a conformational change.

INTRODUCTION

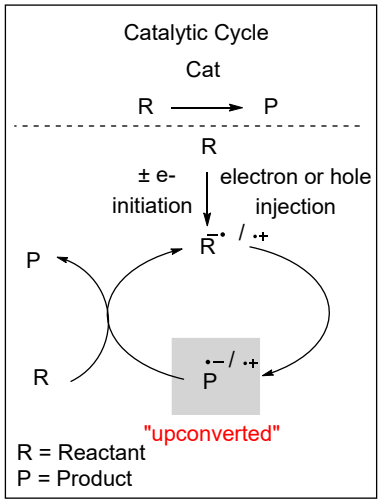
Countless creative catalytic systems are invented by chemists in the constant quest for increasing speed and efficiency of chemical transformations.[1,2] Modern catalytic designs often feature complex molecular architectures that are both elegant and functional. However, there is beauty in simplicity as well. For example, using an electron as a catalyst is appealing, both conceptually and practically. Not only are electrons cheap and abundant but they are also traceless and recyclable, so the use of electrons as catalysts is an inherently green chemical strategy.[3]

Many chemical transformations are made possible by electron transfer as illustrated by the remarkable increase in the applications of electrochemical and photoredox methods in chemistry.[4–8] However, only a small part of electrochemical and photoredox transformations are truly catalyzed by electrons. Instead of reusing a single electron in multiple catalytic cycles (as one would expect for a truly catalytic process), many electron transfer reactions are generally mediated by the constant influx of either electrons or photons. Even if each electron is used with 100% efficiency, a catalyst with a turnover number (TON) of 1 cannot not be considered a great catalyst.

For electrons to behave in a truly catalytic manner, two key conditions must be satisfied; a) one-electron reduction of a reactant should decrease the activation barrier of the target reaction, and b) the product of the electron catalyzed reaction should be a better reductant than the starting material, so that the catalytic electron can be transferred to the new molecule of the neutral starting material and restart the catalytic cycle (Scheme 1). In such a catalytic cycle, the radical ionic intermediate must be "upconverted".

The concept of "upconversion of reductants" or "electron upconversion" is a phenomenon that describes a seeming paradox where a weak reductant is converted into a more potent reductant in a process that is overall thermodynamically favorable.[9] Electron upconversion is useful for selective control in multicomponent reactions.[17–23] Electron upconversion explains a number of remarkable observations of highly efficient catalytic cycles in reductive[17], electrochemical[18–20], and photoredox[21–23] processes. It also provides the conceptual thermodynamic cornerstone for using electrons as catalysts.[3]

Scheme 1. A catalytic cycle illustrating how redox upconversion allows true catalysis with electrons or holes. If the product radical anion is a better reducing agent than the starting radical anion, the catalytic electron is transferred to the fresh molecule of starting material at the end of each catalytic cycle. Analogously, hole-catalysis requires the product radical cation to be a stronger oxidant than the reactant radical cation.



Satisfying the thermodynamic condition for upconversion is not trivial because the increase in the reduction potential is generally associated with thermodynamically unfavorable reactions. In fact, such an increase in the reduction potential may seem "counter-thermodynamic" as electron transfer is exergonic when it converts more oxidizing species into less oxidizing species (Figure 1). However, not *all* exergonic chemical reactions proceed in a direction that lowers the overall redox potential. We defined thermodynamic conditions and the rules for the logical design of reactions that lead to exergonic reductant upconversion without violating the laws of thermodynamics.[9]

One can also extend this concept to "hole upconversion" or "upconversion of oxidants." The general rule is simple: for upconversion to occur, a radical ionic reaction must be thermodynamically less favorable (*less* exergonic) than its neutral counterpart (Figure 2). Furthermore, to benefit from the unconverted energy, the paradoxical prerequisite must be satisfied, i.e., the neutral reaction should be kinetically less favorable than the radical-cationic reaction despite being thermodynamically more favorable. Again, in hole-catalyzed chemical reaction via the hole-upconverted regime, a weak oxidant is converted to a more potent oxidant to continue the chain reaction by oxidizing a fresh molecule of the neutral reactant. Below, we illustrate how a reaction can be simultaneously thermodynamically favorable and increase the oxidation potential.

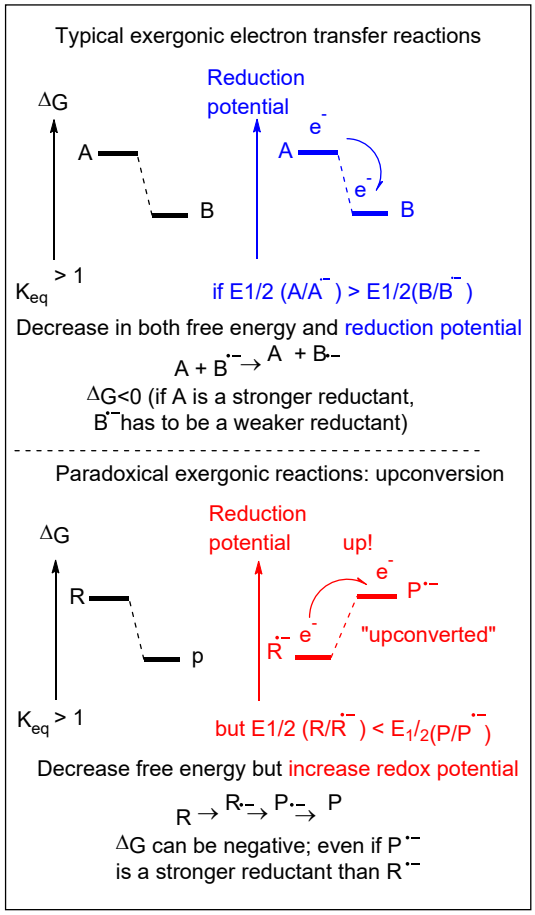


Figure 1. A comparison of standard exergonic reactions (top) vs. unconverted reactions (bottom). Note that the two thermodynamic parameters are measured in units of energy (free energy (ΔG) and reduction potential (E)) change in opposite directions for upconversion.

We will show that the concept of hole upconversion can provide a key to identifying hole catalyzed reactions with a TON > 1, in other words, the transition from chain to non-chain in the Diels – Alder (DA) reaction. Usually, experimental techniques are used to detect hole catalysis in a single electron transfer (SET) oxidation process. For example, chain mechanisms can be revealed if the photochemical quantum yield (Φ) is >1 or when the Faraday efficiency in an electrochemical process is < 1.0 Faraday /mol. Identifying hole upconversion can save time and effort by guiding experimental explorations in new areas of chemistry that are suitable for hole catalysis.

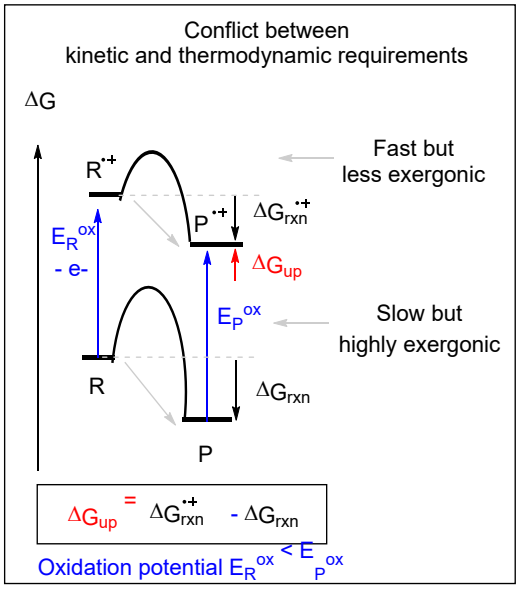
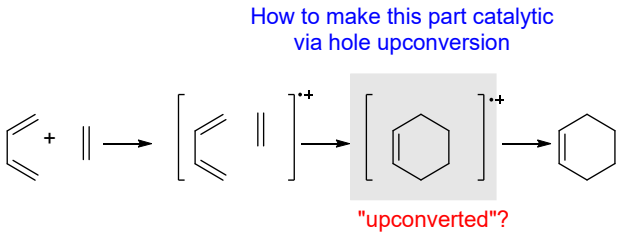


Figure 2. Resolving the conflicting kinetic and thermodynamic requirements to achieve hole upconversion for the design of hole-catalyzed reactions.

In this work, we use our approach and reasonable prediction to analyze the occurrence of hole catalysis in the DA reaction (Scheme 2). Although catalysis by holes in DA and other cycloaddition reactions is well-known[7,24–34], the role of hole upconversion in this prototypical cycloaddition reaction has not been explored. We use computation to systematically evaluate the magnitude of hole upconversion in hole-catalyzed DA reactions. For that purpose, we will explore the role of substituents in both the diene and the dienophile and reveal how the complex interplay of several electronic effects can be analyzed logically and used to activate hole upconversion. Necessary to the analysis, we will for the first time explore the stereoelectronic aspects of hole upconversion revealed by conformational effects in such reactions.

Scheme 2. Can hole upconversion be a general strategy in hole catalyzed DA reactions?



COMPUTATIONAL DETAILS AND METHODS

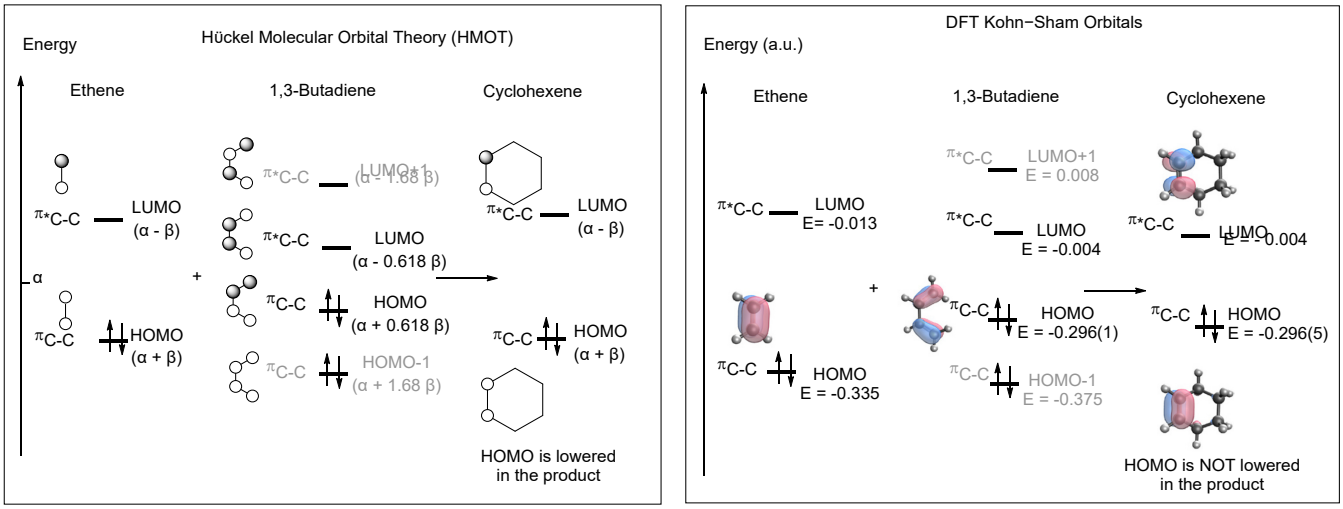
All structures were fully optimized with the (U)M06-2X functional and the 6-311++G(d,p) basis set, with an ultrafine integration grid using Gaussian09[35] program package. The implicit SMD solvation model was used to simulate the effects of nitromethane (CH_3NO_2) throughout the calculated structures. Full geometry optimization with TightOpt convergence criteria was carried out to find stationary points on the potential surfaces. Numerical harmonic frequency calculation was used to obtain thermodynamic quantities and verify all structures as stationary points or transition points. Electronic structures and properties were analyzed by Natural Bond Orbitals (NBO, Version 3.1)[36] package implemented in Gaussian09. All energy is reported in kcal/mol unless specified. NBO are visualized using IQmol version 2.15.[37]

RESULTS AND DISCUSSION

Why to expect hole upconversion in cycloaddition reactions: At first glance, the parent DA reaction appears to be a perfect candidate for hole upconversion as more delocalized diene radical-cation is converted into an alkene radical-cation. For example, the classic Hückel molecular orbital theory (HMOT) quickly reveals that the highest occupied molecular orbital (HOMO) of butadiene/ethylene system is higher than the HOMO of cyclohexene product (Scheme 3). If one uses the Hückel HOMO energies to predict the location of the hole in the radical-cationic version of this reaction, one expects the hole energy to be lowered from a relatively high energy diene HOMO to the lower energy HOMO of cyclohexene. From this perspective, hole upconversion should be possible in the classic [4+2] cycloadditions, because lowering the hole energy transforms the radical cationic product into a more potent oxidant.

However, HMOT considers only π-electrons. On other hand, the DFT Kohn – Sham orbitals, which include *all* electrons, reveal a different picture. According to the DFT analysis, the HOMO of cyclohexene is nearly *isoenergetic* to the HOMO of butadiene. Of course, it is not surprising that excluding all sigma orbitals in HMOT does not capture the full picture. However, the discrepancy is interesting, especially because the small difference between the reactant and the product leaves the question of whether hole upconversion is present in the parent DA reaction. What are the reasons for this discrepancy between the two theoretical models?

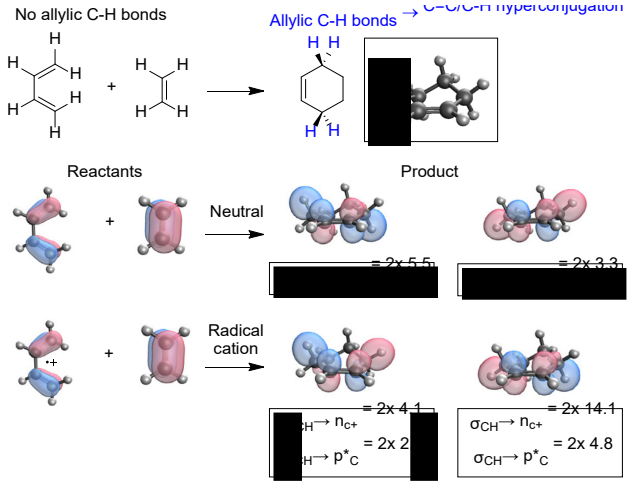
Scheme 3. Left: Diene has a higher energy than HOMO the product (cyclohexene). Within the framework of Hückel analysis (all sigma-orbitals are neglected), upconversion should be present in the DA reaction. Right: Inclusion of all sigma orbitals (i.e., calculations at the M06-2x/D3/6-311++G/ (d, p)/UF), (SMD= nitromethane) level reveal that the HOMO of cyclohexene is nearly isoenergetic to the HOMO of butadiene, leaving the question about hole upconversion in the parent DA reaction open. Note: spectator MOs are excluded in DFT Kohn-Sham Orbitals diagram.



Since HMOT description does not include sigma bonds, this approximation completely neglects hyperconjugation (i.e., the contribution of sigma orbitals to delocalization).[38,39] However, in the present case, the hyperconjugative stabilization in cyclohexene radical cation is much greater than that of the neutral cyclohexene. Furthermore, the π-hole in butadiene radical-cation (Scheme 4) is not stabilized by hyperconjugation because in butadiene there are no allylic C-H bonds which would be aligned with the π-orbitals. On the other hand, cyclohexene has *four* allylic C-H bonds. An interesting consequence is that hyperconjugation noticeably contributes to the exergonicity of the neutral DA reaction. NBO analysis evaluates the donation from the four sigma C-H bonds to the cyclohexene $\pi^*_{C=C}$ orbital ($\sigma_{CH} \rightarrow \pi^*_{cc}$) as 17.6 kcal/ mol. Even more relevant to the present story is the large *increase* in the stabilizing effect of hyperconjugation in the cyclohexene radical cation in comparison to the neutral cyclohexene. This is not surprising because the oxidized π-bond becomes a stronger acceptor than a neutral π-bond. Indeed, the four sigma C-H bonds in the radical-cation contribute much more (~50 kcal/mol) for the hole stabilization. NBO analysis, which considers the one-electron π-bond as a combination of a radical and a cation, provides energies of ~36 and 14 kcal/mol for the $\sigma_{CH} \rightarrow n_{c+}$ and $\sigma_{CH} \rightarrow p^*_C$ interactions, respectively.

Because of the hyperconjugative stabilization discussed above, the radical cationic DA is slightly more exergonic (1.6 kcal/mol) than its neutral counterpart (Scheme 5). Hence, the thermodynamic conditions for hole upconversion are not satisfied in the parent DA reaction. However, because the decrease in oxidation potential is only -1.6 kcal/ mol (0.07 eV), it should be possible to introduce hole upconversion by a suitable choice of additional electronic effects. Furthermore, the calculated activation barrier for the radical cation reaction (5.3 kcal/ mol)[26,40] is much lower than for the neutral (29.7 kcal/mol)[41–43] , therefore, the DA reaction is greatly accelerated by the one-electron oxidation.

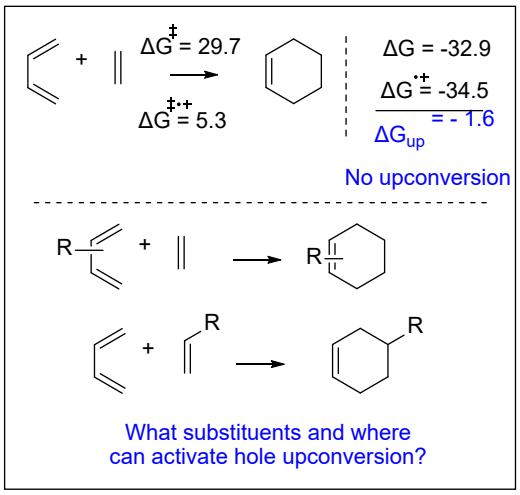
Scheme 4. The danger of underestimating the role of hyperconjugation in DA reactions. NBO energies of hyperconjugative interactions (in kcal/mol) illustrate the greater importance of stabilizing $\sigma_{CH} \rightarrow \pi^*_{C=C}$ donation in cyclohexene radical cation in comparison with neutral cyclohexene.



Since kinetic aspects are very favorable, evaluating the ways to solve the thermodynamic problem and finding the right substituent pattern for activating hole upconversion can greatly expand the synthetic potential of hole-catalyzed DA reactions. To explore this opportunity, we evaluated substituents effects on hole upconversion. We will show that the key to unlocking hole upconversion is in rendering the radical cationic cycloaddition less exergonic. Logically, it can be accomplished in two ways: either

by stabilizing the reactant or by destabilizing the DA product.

Scheme 5. Parent DA reaction is not a candidate for hole upconversion but can the right substituent at the right position activate the upconversion?



The role of substituents. The interplay of stabilizing effects on the radical cationic intermediates of the reactant and product creates a distinct pattern where hole upconversion can be either present or lost. At specific positions on the diene, i.e., first (C1) and second (C2) carbons, or the dienophile, substituents can exert stabilizing or destabilizing effects by influencing the electron distribution via either inductive or delocalizing interactions. We reveal the linear correlations of free energies with substituent Hammett parameters[44,45] (σ^+) for the neutral and radical-cationic DA reactions. The reactivity constant (ρ) slope corresponds to the sensitivity of the system to the substituent. Because the slopes for neutral and radical-cationic reactions are different, the two lines can intersect, leading to the occurrence of "crossover" regions. As the crossover point is approached, the magnitude of the upconversion decreases until it is switched off. These correlations illustrate how to use substituents to activate or deactivate hole upconversion and how to control the magnitude of the upconverted energy.

Substituents at C1 Position: Hole upconversion is activated by a broad range of donors at the C1 position (Figure 3A). Here, the electron donating groups stabilize the initially formed radical cation, but the stabilizing effect is lost in the product radical cation intermediate, where the donor group is not connected to the forming $\pi_{C=C}$ bond. The penalty for the loss in product stabilization renders the radical-cationic DA less exergonic and allows these reactions to satisfy the thermodynamic conditions for upconversion.

The magnitude of the upconverted energy is greatest for the strongest donors (NH_2>OR~OH) and gets smaller as donor ability of the substituent decreases. Furthermore, the upconversion effect disappears as one switches from donor to acceptors. This is not surprising because C1-acceptors destabilize the hole in the reactant but not in the product, thus making the DA reaction more favorable. Although both neutral and radical cationic cycloadditions are made more exergonic by acceptor substitution, the radical cation reaction is significantly more sensitive to the substituent effects. This is well-illustrated by the difference in the ρ values for the correlation with the σ^+ Hammett parameters (-3.1 and -17, respectively). The greater the magnitude of the ρ, the greater the sensitivity to substituent effects. The large difference in the Hammett correlation slopes leads to the cross-over between two regions

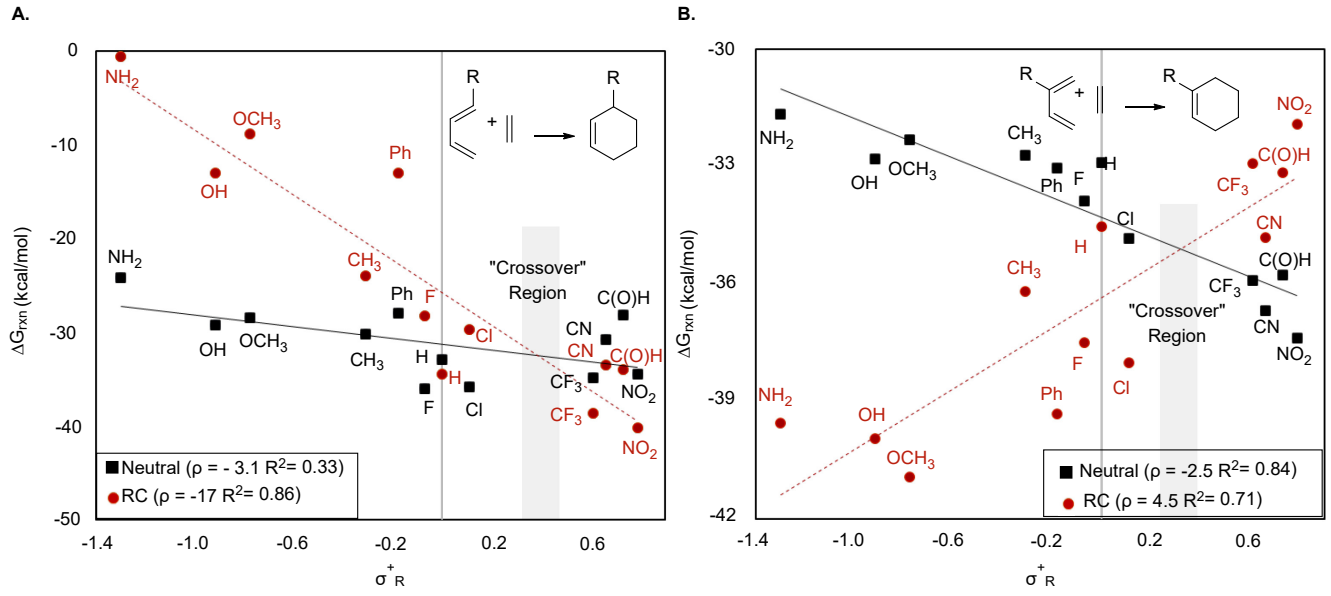


Figure 3. The relationship between free energies for the neutral and radical cation (RC) reaction vs Hammett σ^+ constants (which account for functional group effects for direct resonance stabilization of positive charges) in two families of substituted dienes. A. C1- position: Upconversion is activated by donors. B. C2-substutition: Upconversion is activated by acceptors.

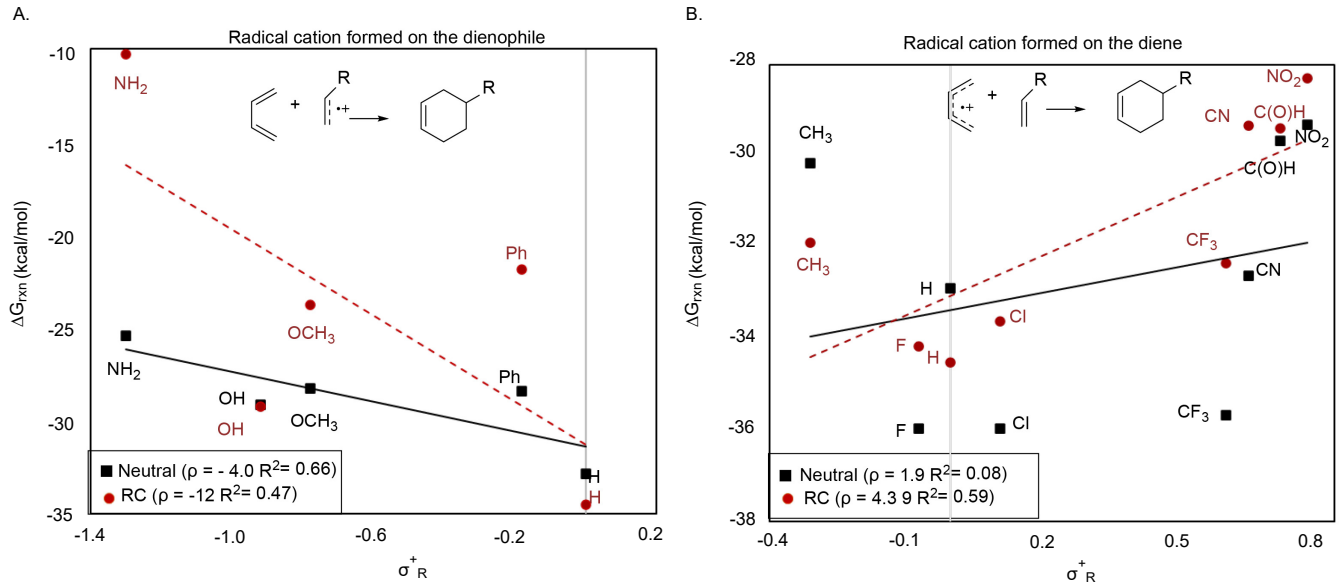


Figure 4. Complex behavior: The radical cation can be formed on the diene for both donors and acceptors. A. When the radical cation is formed on the dienophile, upconversion is almost always activated and only possible with donors (R= H, is parent DA where radical cation is formed on the diene). B. When the radical cation is formed on the diene, acceptors are activating but donors are unpredictable.

i.e., upconversion-active, and upconversion-inactive.

Substituents at C2 Position: Remarkably, the opposite is observed for substituents at the C2 position (Figure 3 B). Although there is no upconversion with donors, upconversion is activated by acceptors. In this situation, both the reactant and product radical cations are stabilized by donor substituents. Hence, the variations in the reaction exergonicity are much smaller than for the C1-substituted dienes. In the reactant, the hole was stabilized by being in the diene moiety. However, as expected, the stabilization is greater in the product where substituent becomes the main source of stabilization for the hole. As a result, the reactivity constant is *positive* and is much smaller in the absolute magnitude than in the previous case (4.5 vs. -17). In this system, hole upconversion is observed after the crossover from donor to acceptor substituents. The origin of this crossover is different from the case of C1-substituted dienes because the neutral DA reaction follows an opposite trend with a negative slope for the Hammett correlation (ρ = -2.5).

Substituents at the dienophile: Lastly, when the substituent is on the dienophile, the results are complex and not easily predictable (Figure 4). Depending on the functional group, the initially formed radical cation can be located on the diene or dienophile. Unless a strong donor substituent is present at the dienophile, the radical cation is formed on the diene. Here, the donor and the acceptor group can lead to upconversion for opposite reasons. For radical cation intermediates formed on the diene, hole upconversion is observed except with R = methyl group (ΔG_{up} -1.7). Since donors or acceptors are not directly attached to the cationic carbon, the reaction systems have relatively low sensitivity to substituent effects in the radical cation reaction (ρ = 4.3) and neutral (ρ = 1.9). If the hole is on the dienophile, upconversion is almost always present, because resonance stabilization of the hole by the substituent is not as strong in the product as in the reactant.

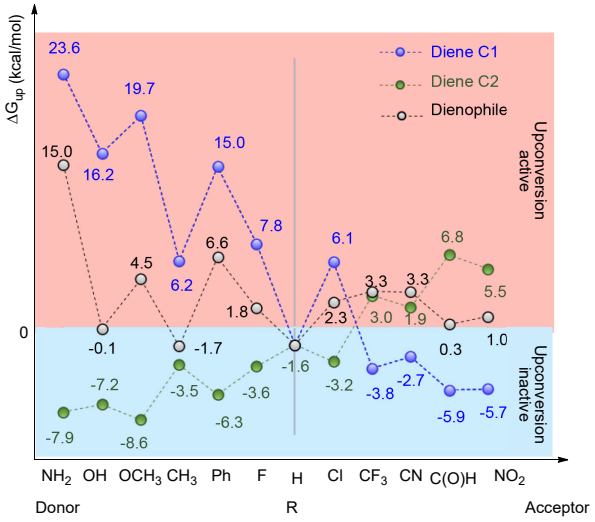


Figure 5. Comparison of free energies of upconversion (ΔG_{up}, kcal/ mol) vs the substitutes in the DA reaction of 1,3-butadiene (C1 and C2) and dienophile. The patterns summarize the position and substituents effects on making the DA a hole catalyzed chain reaction. In other words, where upconversion is active (red - ΔG_{up} >0) or inactive (blue - ΔG_{up} <0)

These models clearly show that it is not merely the presence of a donor or an acceptor that can lead to upconversion, but the appropriate placement of such groups is needed. The patterns summarized in Figure 5 show the effective position and substituents for the making hole catalyzed DA a chain reaction. At all three positions, a noticeable deviation from the trends is when the functional

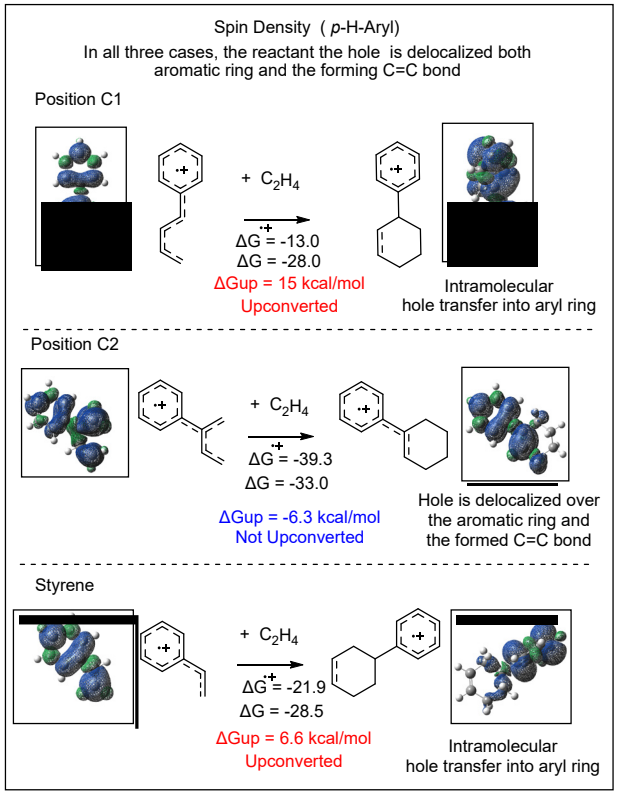
group is phenyl (R = Ph), particularly in the radical cation reaction. In the following section, we analyze the origin of the large deviation in para-substituted aryl compounds.

Substituents "competing for the hole" – cyclization of aryl substituted substrates:

A. Contrasting effects of the Ph group.

As illustrated in Hammett plots (Figure 3 and 4), there is a significant deviation from the correlation based on their σ^+ Hammett values when R = Ph. These deviations illustrate an interesting feature of hole-catalyzed reactions – the location of the hole depends on the nature of the substituent. Sometimes, a substituent can "steal" the hole via rapid intramolecular electron transfer from the reacting functionality (Scheme 6). In this scenario, the role of such substituent changes from secondary to primary. Such behavior was recognized before by Chiba et al, who used it for development of aromatic redox tags strategy in cycloaddition reactions.[29,46] The reactivity of aryl-substituted butadiene provides an example of such behavior as we will illustrate below.

Scheme 6. Spin densities for the aryl radical cation intermediate for reactants and products of the DA reaction: The hole stays with the alkene and aromatic π-system in the reactants but moves to the aromatic system in the case of styrene and position C1 of the products.



According to the data presented in the previous sections, the Ph group leads to hole upconversion at the C1 position of butadiene or at the dienophile (15 and 6.6 kcal/mol, respectively) but not when it is attached at C2 position (-6.3 kcal/mol). In the radical cation reaction, notice how the Ph group steals the hole and switches from secondary to primary in the reactant and product. The hole is delocalized in both the alkene and phenyl moiety in all three reactants but moves to the aromatic ring in the products resulting from 1-phenyl-1,3-butadiene/ethene and butadiene/styrene cyclization. As a result, the stabilizing effect of Ph group is decreased in the product and the upconversion is observed. In contrast, for the product of 2-phenyl-1,3-butadiene/ethene cyclization (i.e., substitution at C2), the spin density is extended to the carbon where the double bond is formed. Consequently, the stabilizing effect is not only preserved but even increased, so the reaction becomes more favorable thermodynamically but at the expense of reduced amount of energy stored by upconversion.

B. Para-substituted aromatic groups at C1 and C2 positions of 1,3-butadiene.

Regardless of donor or acceptor properties, upconversion is always present for the radical-cationic DA reaction of 1-Ar-substituted butadiene where it can reach up to 15 kcal/mol and is never found for the analogous reaction of 2-Ar-substituted butadiene ($\Delta G_{up} \sim$ -10 kcal/mol). Considering that the substituents are not directly attached to the bond-forming carbons (secondary R effects), it is not surprising that ρ values for the neutral reaction is relatively low (ρ = -1.4) compared to the radical cation reaction where substituents effects switch from secondary to primary (ρ = 8.9 for donors and ρ = -8.8 acceptors) at the C1 position (Figure 6). The opposite is observed at the C2 position where substituent effects are consistently secondary. Interestingly, the sensitivity to substituents is larger for the neutral reactions (ρ = -4.3 for donors and ρ = 4.3 acceptors) than for the radical cation reaction (ρ = -0.81).

However, upconversion is never switched off for 1-Ar-butadienes substitution or switched on for 2-Ar-butadienes substitution as the substituent changes. The nature of the aryl group does influence the magnitude of upconversion. For aryl groups at C1, each of the tested para-substituents were found to make the ΔG_{up} smaller. Both donors and acceptors, paradoxically, make the radical-cationic version more exergonic. This interesting behavior almost entirely originates from the effect of substituents on the radical cation reaction and can be explained by intramolecular hole transfer from the diene moiety to the Ar group during the cycloaddition process.[29]

Intramolecular hole transfer only occurs with donors but not with the acceptors (see Supporting Information (SI) -Intramolecular Electron Transfer in *p*-X – Aryl). In the donor substituted 1-Ar-butadiene reactants, the hole is stabilized by both the diene and the donor group. In the product, however, the hole is exclusively localized in the Ar ring where the stabilization of the substituent becomes the primary source and stronger.

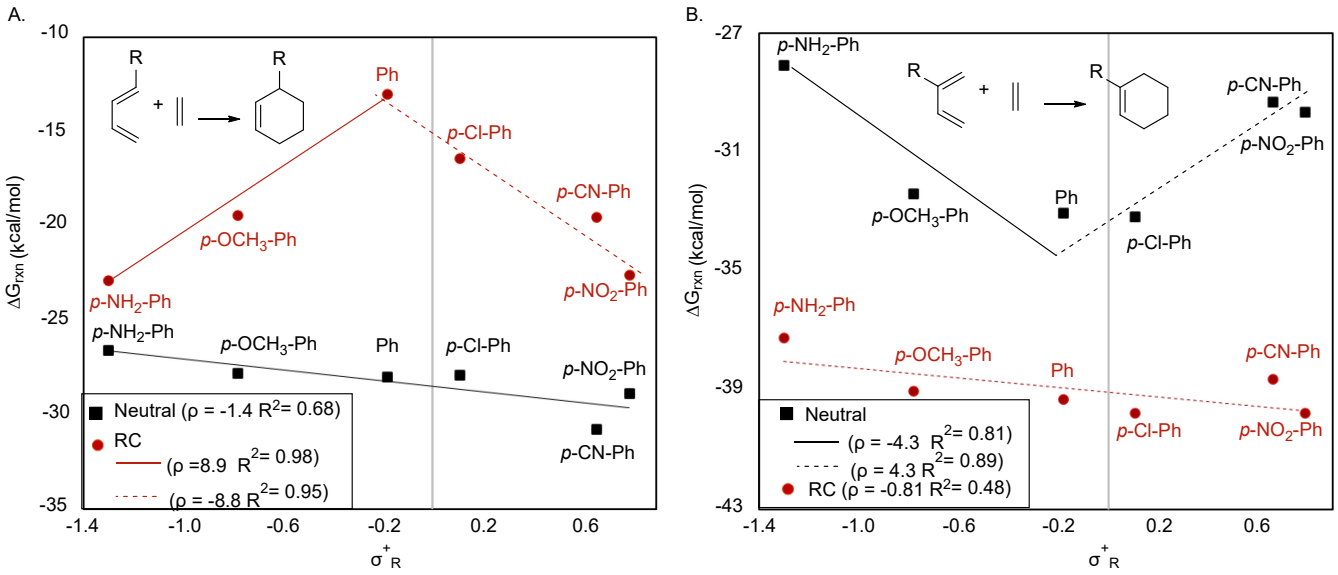


Figure 6. Regardless of the donor/ acceptor properties of the substituent, hole upconversion is: A. Always present for 1-Ar-butadienes, and B. Always lost for 2-Ar-butadienes. Interestingly, both donor and acceptor substituents decrease the magnitude of ΔG_{up} for C1 substitution but increase ΔG_{up} for C2-substitution.

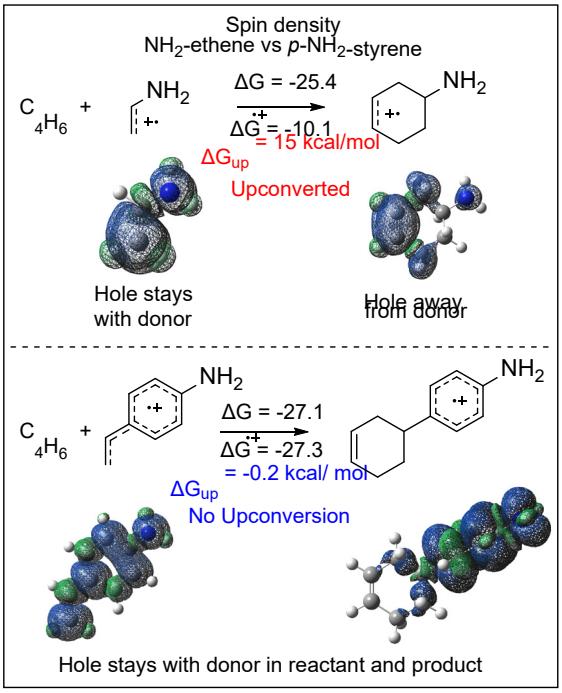
For the acceptor-substituted Ar, the hole does not get transferred to the Ar group but stays in the forming bond of the newly formed cyclohexene ring. This way the hole escapes *destabilization* by the acceptor. Hence, the donor substituents make the radical cationic reaction more exergonic by increasing stabilization whereas the acceptor substituents achieve the same effect by inducing less destabilization. In the neutral reaction, the substituent effects are weak (ρ = -1.4), but both acceptors and donors have opposite effects.

The effect for the Ar groups at the C2 position is also interesting. In contrast, to the above, it originates mostly from the effect on the neutral reaction. Both donors and acceptors make the neutral reaction less exergonic. This can be simply attributed to the diene reactant being more stabilized by conjugation than the cyclohexene product. As a result, neither donors nor acceptors can assist in making hole upconversion likely to occur.

C. Styrene derivatives as dienophiles.

For styrene derivatives, the resulting trends are more predictable and less complex (Figure 7) in comparison with the dienophiles where the same substituents are *directly* attached to the ethene moiety (Figure 3). The observed trends are readily explained by comparing the location of the hole and the possible stabilization by the substituent in the reactant and product. For example, the very low ΔG_{up} in the *p*-NH_2-substituted styrene (-0.2 kcal/mol) seems to contradict the large upconversion observed for aminoethane (ΔG_{up} = 15 kcal/mol). However, this difference is understandable once one notices that the hole stays stabilized by the NH_2 donor in the product of the amino styrene reaction (i.e., stabilization by the donor is not lost), so the effect of the *p*-Ph-NH_2 group on the exergonicity of radical-cationic DA reaction is small (Scheme 7). This is different from the analogous amino ethene reaction where the hole is moved away from the donor in the product.

Scheme 7. For ethene reaction (top) upconversion is present but lost in the styrene reaction (bottom). Notice that the hole stays stabilized by the NH_2 donor in the styrene reaction (i.e., stabilization by the donor is not lost), but in the aminoethane, the hole is moved away from the donor in the product which results in losing stabilization (i.e., the radical-cationic reaction becomes less exergonic).



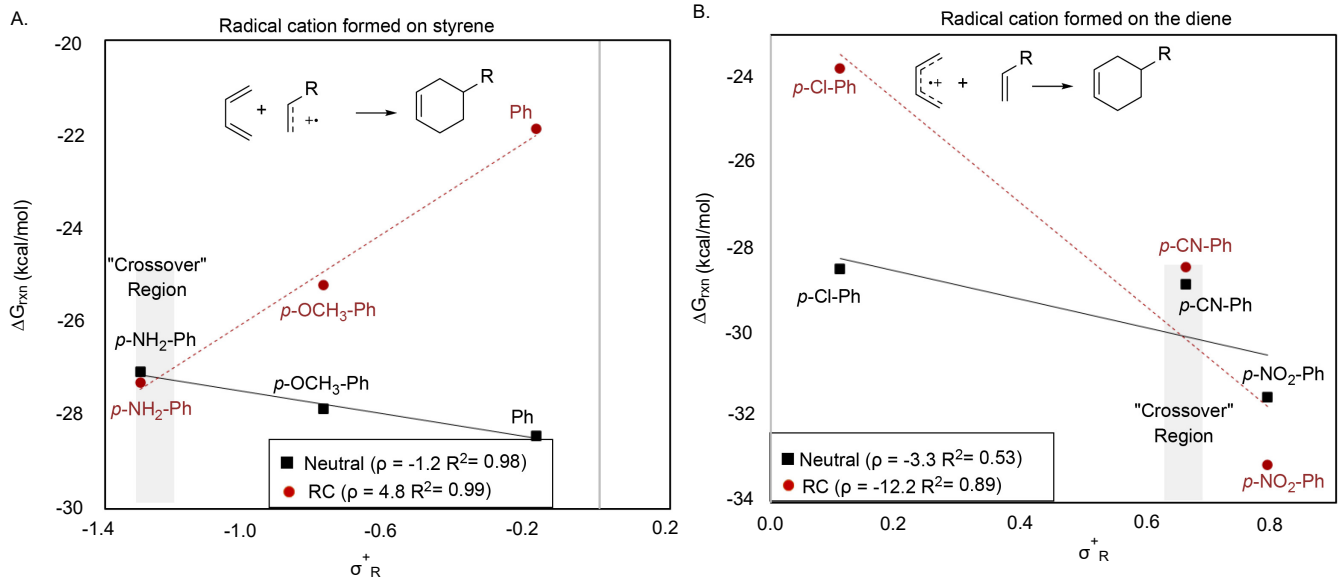


Figure 7. In styrene derivatives, hole upconversion is A. Activated by donors. B. Deactivated by acceptors.

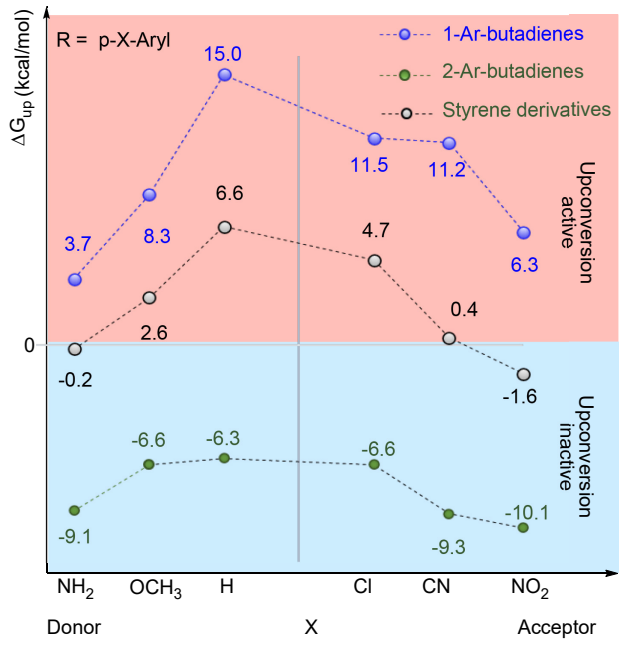


Figure 8. How to control upconversion in the radical cation DA reaction of aryl substituted reactants. Upconversion is active in the red and inactive in the blue part of the energy ranges.

Due to the loss of stabilization, the latter radical cationic reaction becomes less exergonic, which is the right recipe for hole upconversion. As for acceptor-substituted styrene moieties, the hole moves from the double bond conjugated with the acceptor Ar group to the forming π-bond where the effect of the Ar group is lost. The loss of stabilization from the Ar group leads to an increase in cyclization exergonicity. In short, the reaction with strong acceptors (i.e., Ar = *p*-CN-Ph and *p*-NO_2-Ph) is more exergonic.

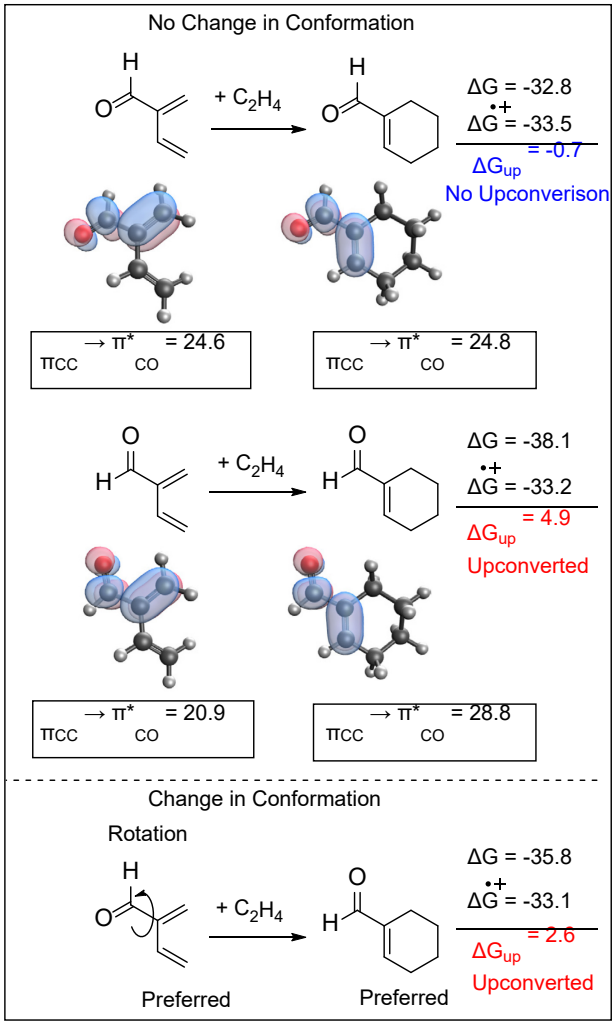
For these substitution patterns, the mere presence of an aryl group on the diene is the determining factor for activating (or deactivating) hole upconversion as there are no crossover regions where the correlations for neutral and radical-cationic reactions would intersect (Figure 8). As for styrene derivatives, the donor and acceptor properties determined the presence of hole upconversion.

So far, our analysis has focused on evaluating the optimal placement and substituent properties. Interestingly, oxygen containing substituents offer an additional level of complexity (but also an additional tool for the control of upconversion!). To understand this, we shift our focus to stereoelectronic effects prominent in oxygen-containing molecules.[47]

Conformational control of upconversion: The stereoelectronic nature of conjugation contributes to the magnitude of upconversion. Conjugative stabilization associated with conformational features was considered for all molecules (See SI Conformation Analysis). This stabilization has a sizeable effect on the magnitude of the upconverted energy and is more apparent in carbonyl derivatives at the C2 position. This example introduces the complexities of additional stereoelectronic effects present in oxygen-containing molecules. The conformational preference of the carbonyl group can change during reaction and this change can control the outcome of upconversion. The preferred conformer puts the C=O bond anti periplanar to the C=C bond in the reactant and product.[36,39,48,49] Because the location of the double bond changes as the result of DA cycloaddition, the C=O bond must rotate to reestablish this favorable conformation.

In such compounds, keeping track of the preferred conformation is essential as different results are obtained for different conformations. For example (Scheme 8), if the product is "frozen" in the conformation that was preferred for the reactant, no hole upconversion is observed (-0.7 kcal/mol). In contrast, starting with the less stable conformation of the reactant that corresponds to the more stable conformation of product leads to considerable upconversion (4.9 kcal/mol). With the assumption that the rotation barrier for the interconversion is sufficiently small, the most experimentally relevant way to evaluate the presence of hole upconversion in conformationally labile reactants requires the most stable conformers of *both* the reactant and the product as this connects the lowest energy regions of the two potential energy surfaces. Such conformationally adjusted analysis leads to upconversion of 2.6 kcal/mol. Other carbonyl derivatives, including carboxylic acid, amide, acyl chloride, and ester, show similar conformational dependence for the magnitude of upconversion.

Scheme 8. NBO analysis of conjugative interactions involved in the conformation dependence of aldehydes.



Correlation with experiments

Of course, mono-substituted reaction systems presented above do not describe all possible scenarios because DA reactions can include multiple substituents. Nevertheless, the conclusion of our approach applies to more complicated reactions performed routinely in the laboratory. Our calculations are close to experimental results as shown in the following examples. Hole upconversion is a straightforward approach for identifying and understanding the key to using holes as true catalysts in several important literature examples.

First reported by Bauld and coworkers is the carefully analyzed benchmark radical cationic DA reactions between trans-anethole and 1,3-butadiene.[24,25] In their original work, it was found that substoichiometric amount of the oxidant (3-5 mol % of tris(4-bromophenyl) aminium hexachloroantimonate) is usually sufficient to assure rapid and complete reaction, clearly indicating that the reaction is catalytic. Although later examples, such as the one shown in Figure 9a, used a greater amount of the oxidant (50%), this was mostly due to partial deactivation of the oxidant by the reaction with the 2,6 -Di-tert-butylpyridine (DTBP) used as a buffer.

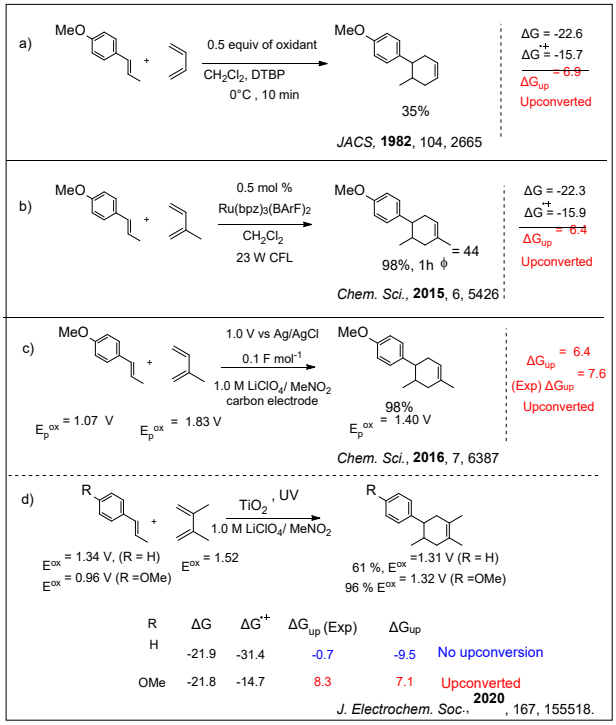


Figure 9. Comparing computational and experimental hole upconversion for electrochemical and photochemical hole-catalyzed DA reactions.

Subsequent important work of Yoon and coworkers revealed that hole-catalysis is observed in photoredox-mediated DA reactions. The quantum yield (Φ= 44) of reaction, i.e., the formation of 44+ molecules of product as the result of absorption of single photon is best explained by suggesting that the reaction is not "photocatalytic" but "electrocatalytic". In other words, the radical-cation of the

product can oxidize the fresh molecule of the neutral reactant, establishing a non-photochemical catalytic chain.[7] Note that the quantum yield provides a convenient method to quickly estimate the average chain length involved in photocatalytic reactions or, in the language of catalysis, to evaluate the TON in hole catalysis (Figure 9b). Chiba[29] and Okada[31] revealed the presence of hole catalysis in true electrochemical processes. For example, 0.1 Faraday/mol of electricity (i.e.., "0.1 moles of holes/moles of product") was enough to achieve nearly full conversion in the DA reaction based on redox tag strategy (Figure 9c).[50] Although the oxidation potentials for the products are not always reported in this field, Okada et al.[31] did measure the oxidation potentials of both reactant and product for the DA reaction shown in Figure 9d. Here, the oxidation potential of the reactant is less than that of the product, which means that the peak potential values satisfy conditions necessary for hole-catalytic process. Because the oxidation peak potential (E_p^{ox}) is a thermodynamic measure of oxidizing power ($\Delta G = nFE_p^{ox}$), increase in the oxidation potential in the product is one of the prerequisites for hole upconversion and hole catalysis. Although the work illustrated in Figure 9d does not provide direct evidence for hole catalysis, do note that once hole upconversion is possible, the yield increases by the factor of >1.5 (from 61 to 96%).

Notice that several of the above examples introduce additional methyl substituents on both reactants. Regardless of the number of substituents, we can use our systematic approach to predict the presence of hole upconversion for such systems. Gratifyingly, the experimental values and computed values are only 1.2 kcal/mol (0.05 eV) different (Figure 9c). Considering that the computational methods do not capture the full complexity of the experimental system (for example, the presence of $LiClO_4$ or TiO_4), such small difference may be fortuitous. In any case, the computational data successfully identifies the presence of hole upconversion in those reaction systems where the radical-cationic Diels-Alder reaction is promoted by sub-stoichiometric amounts of the oxidant.

CONCLUSION

We have outlined the general thermodynamic guidelines for the design of hole-catalyzed DA reactions by evaluating patterns of hole upconversion in this significant cycloaddition reaction. Generally, in reactions involving upconversion, the formation of neutral products from neutral reagents is more exergonic than the radical cation counterpart.

Despite expectations based on the classic Hückel theory, there is no hole upconversion in the parent radical-cationic DA reaction of ethene and butadiene radical cation. This counterintuitive finding is explained by the large hyperconjugative stabilization of the cyclohexene radical cationic product by the four allylic C-H bond donors. This finding illustrates the danger of underestimating the importance of hyperconjugation[24] in chemical reactivity.

The appropriate placement of donors and acceptors on the diene and dienophile can recover upconversion (Figure 10). The magnitude of upconverted energy can be understood by comparing substituent effects on the relative stabilization of the oxidized (radical-cationic) states of reactant and product. The upconversion becomes larger when stronger donors are present at either the C1 position of the butadiene's or at ethene, while strong acceptors at the butadiene's C2 position always activate upconversion and increase its magnitude. Careful analysis is required for substituents at the alkene as radical cations can be formed on either diene or dienophile.

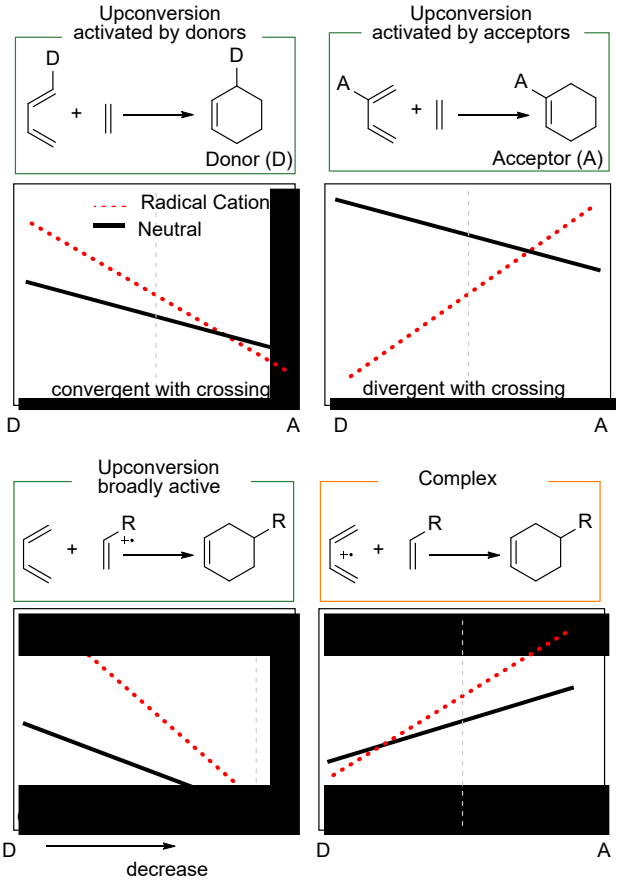


Figure 10. How to stay above the waterline? There are many ways to reach upconversion! The neutral and radical-cationic DA reactions can respond to substituent donor ability in the same way (convergent behavior, i.e., both slopes are either positive or negative) or in the opposite way (divergent behavior, i.e., one of slopes is positive, the other one is negative). Trendlines for the radical cationic DA reactions are shown with dashed lines, for the neutral DA reactions – with solid lines.

Note that there are many possible ways to get to upconversion by using a variety of substitution patterns. However, all of this variety can be understood in a rational way by analyzing the patterns of spin delocalization and stabilization in the radical-cationic reactant and product of DA cycloaddition. Hole upconversion is observed when a radical-cationic reaction stays "above the waterline" relative to the exergonicity of its neutral counterpart.

An interesting stereoelectronic component of upconversion is revealed by conformational effects accompanying the radical-cationic DA reactions of dienes with a carbonyl group at C2. The preferred conformation differs for the radical cation of the reactant and the product, so the cycloaddition step is accompanied by a 180-degree rotation of the "spectator" substituent.

Identifying and understanding the "hole upconversion" processes provides a key to using holes as true catalysts for chain chemical transformations. By understanding the logic of upconversion, we can design reactions where the hole upconversion is activated and true hole-catalyzed pathways are introduced and exploited reliably. We hope that such rational design will help to the development of the burgeoning fields of organic electrochemistry[51–56] and photoredox catalysis.[57,58]

ASSOCIATED CONTENT

Supporting information
The supporting information is available free of charge (PDF)

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NOTES

The authors declare no competing financial interest.

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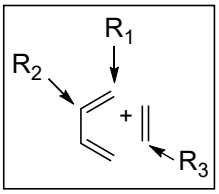
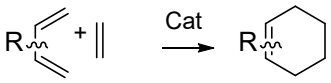
770

"Upconversion" = Hole catalysis



Contrasting effects of R_1,R_2, and R_3

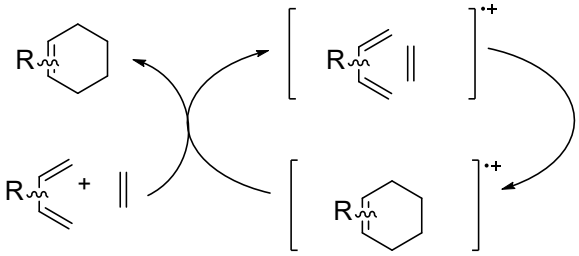
Where to add substituent to activate hole catalysis?



Catalytic cycle for hole catalysis

- e- initiation

hole injection



"upconverted"

$E_{1/2}(S/S^{\bullet+}) < E_{1/2}(P/P^{\bullet+})$

S = Reactant **P** = Product

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