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"Stereoelectronic Umpolung": Converting a p-Donor into a σ-Acceptor via Electron Injection and a Conformational Change

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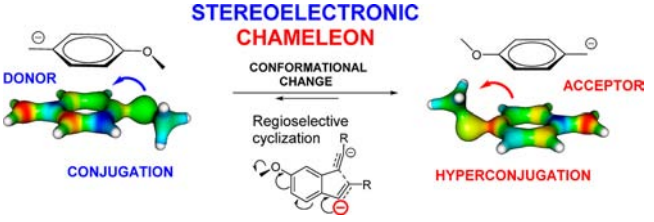
ABSTRACT



The *para*-OMe functional group, usually regarded as a conjugative p-donor, acts as an efficient hyperconjugative σ-acceptor in reductive cycloaromatization reactions. This apparent reversal of electronic properties is associated with a conformational change that aligns the σ^*_{O-C} orbital with the adjacent aromatic system and provides stabilization to the developing negative charge in the TS of the dianionic cyclization of enediynes. The chameleonic character of the OMe group illustrates the important role of negative hyperconjugation in anionic processes.

The utility of electronic substituent effects in organic chemistry is, to a large extent, based on reliable and predictable patterns of electronic behavior, associated with the common functional groups. The donor properties of the OMe group, documented by its σ_{para} (−0.12) and σ_{para}^{+} (−0.78) values, served as a reliable reference in numerous mechanistic studies based on the Hammett analysis. In this work, we will show how a conformational change with the concomitant switch in stereoelectronics can convert this well-known p-donor into a hyperconjugative σ-acceptor capable of controlling the regioselectivity of anionic cycloaromatizations.

Motivation for this work came from studies aimed at a better understanding of electronic effects in cycloaromatization reactions. These reactions provide a versatile platform for testing theoretical concepts related to organic reactivity because they involve concomitant electronic reorganization in two orthogonal π-systems.[1] The most famous of these reactions, the Bergman cyclization,[2] is the key step in the mechanism of biological activity of natural enediyne antibiotics.[3] This process and related reactions[4] continue to find new applications in organic synthesis[5] and materials science.[6]

Due to the poor communication between orthogonal π-systems, remote substituents attached to the out-of-plane aromatic π-system of benzannelated enediynes cannot transmit electronic effects to the developing in-plane σ-radicals in the Bergman cyclization.[7,8] Earlier, we provided computational evidence that analogous substituent

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effects are strongly amplified in reductive cycloaromatizations of enediynes where transition states correspond to the crossing between frontier MOs of different symmetries.[9]

In order to test this theoretical model, we turned to the reductive C_1-C_5 cyclizations of enediynes as a probe of remote substituent effects. Previously, we had unraveled the combination of factors that facilitate this path in comparison the Bergman (C_1-C_6) pathway.[9] Although the thermal version of this process (Schreiner–Pascal cyclization) is difficult,[10] this cyclization can be carried out either via reduction with Li-napthalenide[11] or, for activated enediynes with acceptor substituents, via photoinduced electron transfer (PET).[12] In the latter case, the reaction cascade continues toward the formation of more reduced (indene) products. From a practical perspective, the formal transfer of four H-atoms from the environment doubles the DNA-damaging potential relative to the Bergman cyclization. This process can lead to the ratios of double strand (ds) to single strand (ss) DNA cleavage that rival[13] and exceed[14] those of the natural antibiotic calicheamicin and to pronounced cytotoxicity toward a variety of cancer cell lines.[15]

Conveniently, one can use the *regio*selectivity of the nonsymmetric C_1-C_5 ring closure step as an alternative experimental probe for the remote substituent effects (Figure 1). The comparison of *two alternative reactions of the same reactant* avoids the complications associated with differences in the reduction potentials for enediynes with different substituents.

The seminal study of Whitlock and co-workers[11] found that the Li-naphthalenide-promoted C_1-C_5 cyclization of enediynes proceeds via a dianion (Scheme 1). The evidence included incorporation of two deuterium atoms upon quenching with D_2O and with the need for 2 equiv of the reducing agent for the full enediyne→fulvene conversion. The didehydrofulvene dianion is stable toward further reduction and furnishes fulvene upon quenching with a proton source.

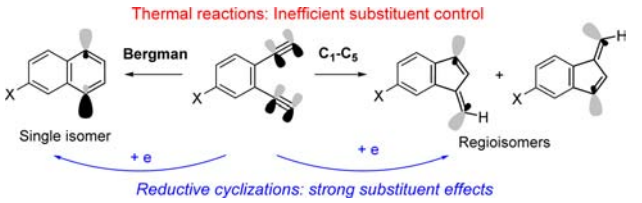
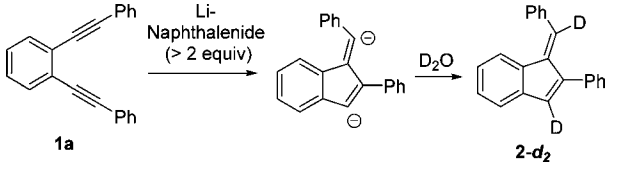


Figure 1. Comparison of thermal and reductive Bergman and C_1-C_5 cycloaromatizations of enediynes.

Scheme 1. Li-Naphthalenide-Mediated C_1-C_5 Cyclization of Enediynes Proceeds via a Dianion



We had reproduced this result and investigated the potential energy surface for this process computationally. This analysis indicated a significant redistribution of electron density in the TS with the most pronounced accumulation of the negative charge at the unsubstituted endocyclic fulvene carbon (Figure 2).

The reasons for this electronic reorganization are twofold: (a) the conversion of delocalized π-anions into a localized endocyclic σ-anion and, to some extent, (b) additional polarization of the exocyclic π-system toward the core with the concomitant increase in the aromatic cyclopentadienyl-anion character of the newly formed five-membered ring. Interestingly, unlike the thermal TS and the anionic reactant and product, the core of the anionic TS is distinctly nonplanar. This nonplanarity assists in the negative charge delocalization by allowing the mixing of "in-plane" and "out-of-plane" orbitals at the MO crossing point (Figure 2).

Due to the observed negative charge accumulation in the ring, one would expect the introduction of acceptor groups at the para position relative to the *endo*cyclic anionic carbon to have the largest stabilizing influence. An acceptor at the exocyclic anionic center is expected to have a lower impact. Donor substituents should have an opposite effect on regioselectivity via selective destabilization of the respective transition states ("Type D" products, Figure 3).

The OMe-substituted enediynes **1b,c** have a higher reduction potential and react with Li-naphthalenide more slowly but display remarkable regioselectivity (Figure 4). Surprisingly, the cyclizations of nonsymmetric enediynes with the OMe group, either at the core or at the terminus, led to the formation of "Type A" products (Figure 3) where the OMe group was in electronic communication with the position of negative charge accumulation in the

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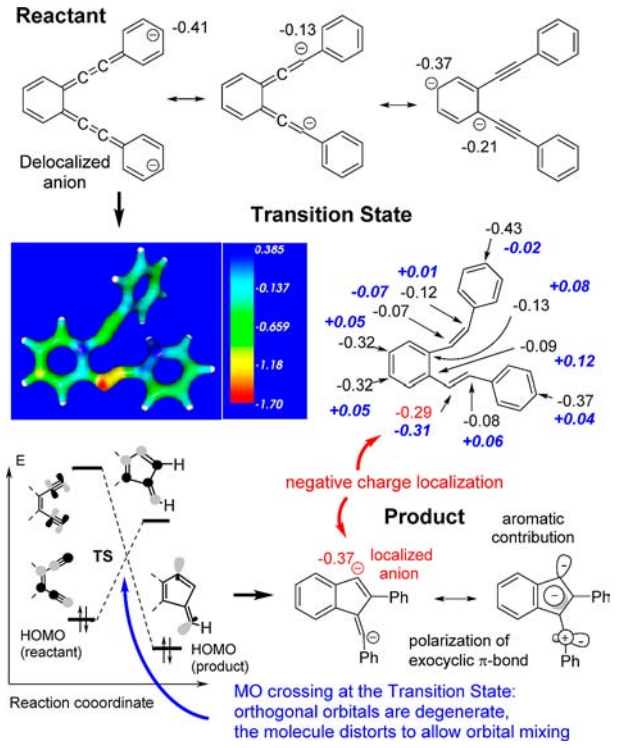

Figure 2. Evolution of electron density during cycloaromatization of the delocalized enediyne dianion into the partially localized benzofulvene dianion is illustrated using selected NBO charges in the reactant, TS, and the product together with ESP of the TS. Changes in charge in the TS relative to the reactant are shown in blue bold italics. Negative and positive values indicate an increase and a decrease in electron density, respectively. The MO diagram illustrates that the TS corresponds to the MO crossing where in-plane and out-of-plane MOs are degenerate. Geometric distortions at this point allow strong orbital mixing.

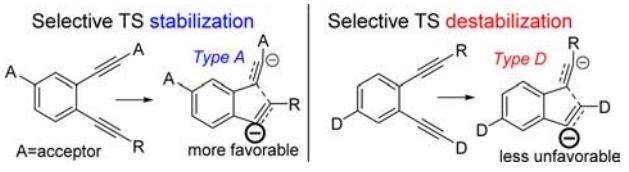

Figure 3. Expected substituent effects on the regioselectivity of the anionic C_1-C_5 ring closure. Site with the largest accumulation of the negative charge in the TS (the endocyclic vinyl carbon of fulvene moiety) is indicated with a larger red circle.

TS! The regioselectivity of cyclizations was determined by HSQC and HMBC spectra as described in the Supporting Information (SI).[16]

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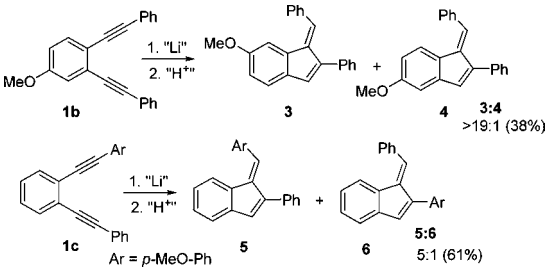

Figure 4. Li naphthalenide-mediated cyclization of enediynes with the core and terminus OMe-substitution.

How can the OMe group, the classic electron donating functionality, act as an anion-stabilizing group? In order to answer this question, we had analyzed the cyclization of enediynes **1b** and **1c** computationally.

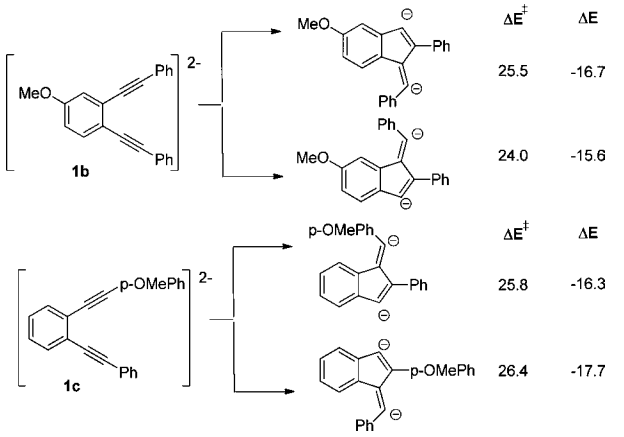

Figure 5. M06-2X/6-31+G** activation barriers and reaction energies of dianionic cyclizations of enediynes **1b** and **1c**.

The calculated activation barriers at the M06-2X/6-31+G** level of theory agree well with the experimental results. For enediyne **1b**, the *p*-OMe group acts as an anion stabilizing substituent leading to an ~1.5 kcal/mol decrease in the activation barrier for the formation of the experimentally preferred regioisomer (Figure 5). The activation barrier for the other isomer formation (25.5 kcal/mol) is identical to that for the parent enediyne **1a**. For enediyne **1c**, the preferred TS does not show additional stabilization, suggesting that the OMe group offers the same stabilization to the reactant and product. On the other hand, the TS for the less favorable isomer formation is slightly raised in energy (26.4 kcal/mol)

Stereoelectronic Switch via Rotation: Trading Conjugation for Hyperconjugation. The explanation for this seemingly anomalous behavior of the OMe group came from the analysis of structures and NBO delocalizing interactions of the calculated transition states.

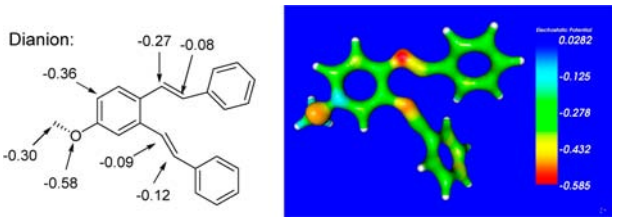

Figure 6. Preferred TS for the cyclization of enediyne **1b**.

The striking difference between the geometries of neutral OMe-substituted enediynes[17] and their anionic forms is the relative orientation of the OMe substituent (Figure 6). The Me group is rotated 90° in both the reactant and in the C_1-C_5 TS. This rotation aligns the O−C bond with the aromatic π-system instead of the usual orientation where the p-type lone pair of oxygen is in resonance with the aromatic core (conformation adopted by the dianionic fulvene product and all species at the neutral PES; see SI for the geometries).

Such a change has profound stereoelectronic consequences. It "inverts" the electronic character of the OMe group converting it from a p-donor to a moderately strong hyperconjugative σ-acceptor.[18] Figure 7 illustrates the generality of such conformational preferences and the associated electronic effects in the benzylic cation, radical, and anion. Such "inversion" is favorable because anionic species benefit from delocalizing interactions with an acceptor but not from the four-electron interactions with the donor.[19]

The acceptor ability of σ_{O-C} bonds plays an important role in several stereoelectronic phenomena such as the gauche effect and anomeric effect.[18] Note, however, that the acceptor ability depends on which end of the other C−O bond participates in the interactions. The acceptor ability at the oxygen end (i.e, that of σ_{O-C} bonds) is lower because σ^*_{C-O} is polarized toward the carbon atom.[20] This work illustrates that, when electron demand is significant and delocalization of the negative charge is needed, the acceptor ability of σ_{O-C} bonds still can be a decisive factor in the observed selectivity.

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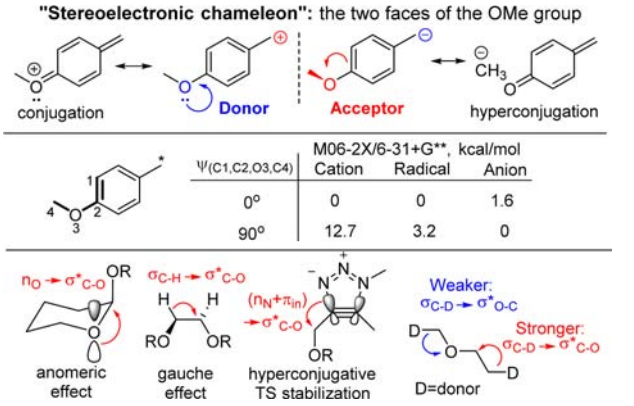

Figure 7. Top and center: contrasting properties of the MeO group as a function of orbital alignment. Bottom left: Stereoelectronic effects based on acceptor ability of σ_{C-O} bonds. Bottom right: Comparison of σ_{C-O} and σ_{O-C} bonds as hyperconjugative acceptors.

In summary, the regioselectivity of the C_1-C_5 cycloaromatization reaction of benzannelated enediynes is efficiently controlled by remote substitution. From a practical point of view, we have found new substitution patterns capable of controlling the regioselectivity of this process.

From the conceptual point of view, our results highlight the "stereoelectronic umpolung" of a common functional group. We have identified a simple conformational change that converts a p-donor into a σ-acceptor in order to assist in accommodating the electronic demand of an electron-rich TS. This interesting finding not only provides an explanation to the counterintuitive experimental selectivity but also suggests that the acceptor ability of the alkoxy groups should be taken into consideration in chemical reactions and processes that involve electron-rich systems. The stereoelectronic character of orbital interactions suggests the possibility of conformational control (gating) in such systems and opens interesting opportunities in the design of molecular electronics, memory, sensors, logical gates, etc.

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Supporting Information Available. Description of computational details, experimental methods, and results. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.