Rearrangements

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Exploring Diradical Chemistry: A Carbon-Centered Radical May Act as either an Anion or Electrophile through an Orbital Isomer**

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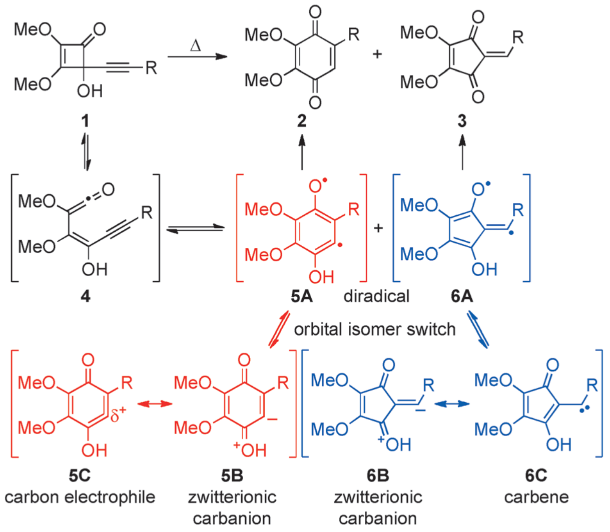
Abstract: *Diradical intermediates, formed by thermolysis of alkynylcyclobutenones, can display radical, anion, or electrophilic character because of the existence of an orbital isomer with zwitterionic and cyclohexatrienone character. Our realization that water, alcohols, and certain substituents can induce the switch provides new opportunities in synthesis. For example, it can be used to shut down radical pathways and to give access to aryl carbonates and tetrasubstituted quinones.*

In the vast majority of pericyclic reactions, the number of bonds formed is equal to the number of bonds broken such that the reactivity state of the starting material(s), for example, anion, radical, closed-shell neutral etc., is mirrored in the product(s) formed. However, for a small subset of electrocyclization reactions this generalization does not hold true, as it is possible for two π-bonds to interact with the creation of a single σ-bond and two radical centers.[1] This means of entry into the curious world of diradical chemistry is typified by the Bergman cyclization,[2] where an enediyne is transformed into a *p*-benzyne intermediate through the action of heat or light.

Many related processes take closed-shell molecules and transform them into reactive diradical intermediates. These include the Garratt–Braverman,[3] Hopf,[4] Moore,[5] Myers–Saito,[6] Schreiner–Pascal,[7] Schmittel,[8] and Wang[9] cyclization reactions. Alabugin et al. have recently summarized the fascinating chemistry such processes unlock,[1] and pay special attention to the relationship existing between diradical and zwitterionic forms of a given intermediate.[10] In Moore's thermochemical rearrangement of alkynylcyclobutenones such as **1**, two diradical intermediates **5A** and **6A** can be formed from the transient vinylketene **4** (Scheme 1).[5] However, through transfer of an electron from the π-system to the SOMO in the plane of the σ-framework, orbital isomers with zwitterionic (e.g. **5B**) and/or carbenic character (e.g. **6B**/**C**) can be accessed.[11,12] Thus, in principle it is possible for the carbon-radical center in **5A** to display reactivity characteristic of an anion (**5B**) or an electrophile (**5C**), while in **6** it can additionally exhibit carbene-type character (**6C**).



Scheme 1. A prototypical alkynylcyclobutenone rearrangement showing the diradical intermediates and their orbital isomers.

Herein we demonstrate, for the first time, that all three modes of reactivity are available to intermediates akin to **5**. Of particular note is a recognition that the nature of the orbital isomer formed is largely determined by its local environment and by changing this it is possible to effect a switch between its diradical (**5A**) and zwitterionic/cyclohexatrienone (**5B**/**C**) forms.

We first became aware of the significance of the zwitterionic orbital isomer **5B** during an attempt to use Moore's alkynylcyclobutenone rearrangement in target synthesis (Scheme 2).[13] Our plan was to transform the cyclobutenone **7** into the bicyclic quinone **9** through capture of the aryl radical (**11A**) by the proximal alkene.[14] Indeed, when a 1,4-dioxane solution of **7** was heated at 150°C under continuous flow,[15] the anticipated product **9** was given in modest yield (60%) together with the quinone **8** (30%).

Consideration of this outcome led us to wonder if we could exploit the deuterium-isotope effect to bias the reaction in favor of cyclization over hydrogen-atom abstraction. We reasoned that deuterium-atom abstraction from [D]-**11A**

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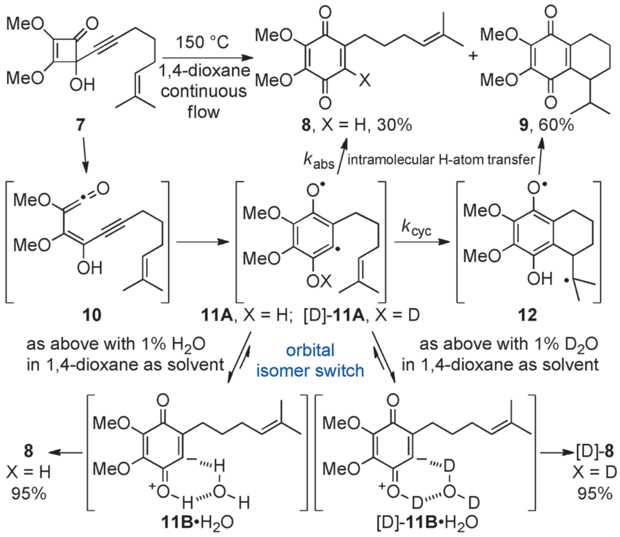


Scheme 2. An orbital isomer switch promoted by water (or D_2O) diverts the course of the reaction towards the quinone **8** (or [D]-**8**).

would be much slower than hydrogen-atom abstraction from **11A** (k_{abs}), but the rate of cyclization leading to **9** (k_{cyc}) would be unchanged. Thus, it should be possible to increase the yield of **9** through the simple use of D_2O as a cosolvent for the reaction (Scheme 2).[16] The outcome of that experiment was as unexpected as it was remarkable. Instead of promoting the radical cyclization pathway, it shut it down! Indeed, the only product given was [D]-**8** in 98% yield upon isolation. A similar switch to **8** was observed when the thermolysis was conducted in aqueous 1,4-dioxane.

In the context of radical chemistry these results made no sense. However, by invoking the zwitterionic orbital isomer **11B**, one could envision a rapid O to C proton transfer catalyzed by water (or D_2O). To test that hypothesis, we modelled the reaction using DFT calculations [at the UB3LYP/6-311G(d,p) level].[17,18] In line with the work of others,[19] our analysis gave a ΔE value for the diradical **13A** and it was 4.1 kcal mol^{-1} lower than that for the zwitterionic isomer **13B** (see Figure 1 and the Supporting Information). However, when water was included in the calculations the relative stabilities reversed, with **13B**·H_2O now favored over **13A** + H_2O by 11.9 kcal mol^{-1}. Importantly, **13B**·H_2O showed no spin contamination, thus confirming its closed-shell character.

From these and related calculations it was clear that the availability of two hydrogen bonds between water and **13B** was the trigger for the orbital isomer switch. Calculations also showed that **13B**·H_2O would collapse to the quinone **14**·H_2O through a near spontaneous proton transfer (Figure 1). Experimentally, we were able to confirm the importance of hydrogen bonding with the thermolysis of the MOM ether **15** in 1,4-dioxane and 1,4-dioxane containing 1% H_2O. As expected, protection of the hydroxy group shut down the aforementioned proton-transfer relay. As a consequence, reactions in 1,4-dioxane and aqueous 1,4-dioxane both proceeded via the diradical intermediate **17A** to give benzopyran **16** in 70% yield (Scheme 3).[14d]

Another point of interest revealed by these calculations relates to the favored geometries of the orbital isomers of **13**, geometries which were markedly different. The diradical isomer **13A** had a near-planar geometry, as expected for an arene. In contrast, the six-membered ring in **13B** and **13B**·H_2O had a pronounced pucker (Figure 2), thus indicating significant cyclohexatrienone character (**13C**). From this observation we concluded that it might be possible for **13** to act as an electrophile, thus exposing a third mode of reactivity as yet unrecognized.

To test that hypothesis we examined the reactivity of the diradical intermediate **19A** computationally. Pleasingly, calculations revealed a low-energy cyclization pathway leading

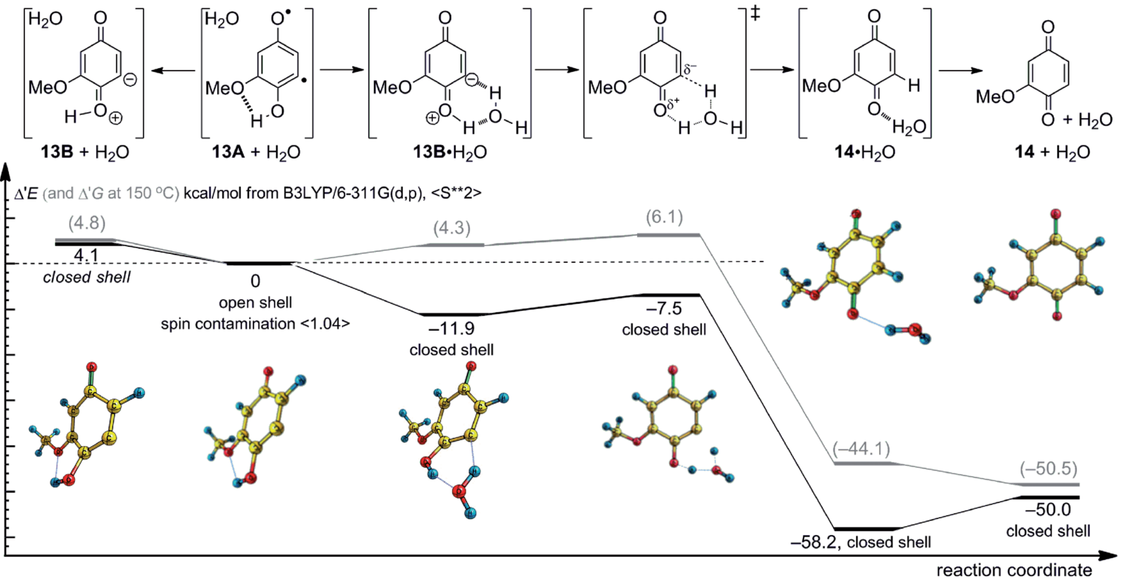
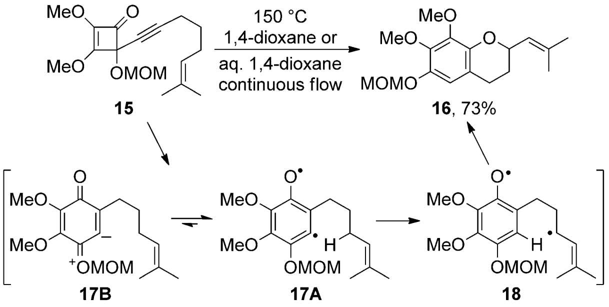
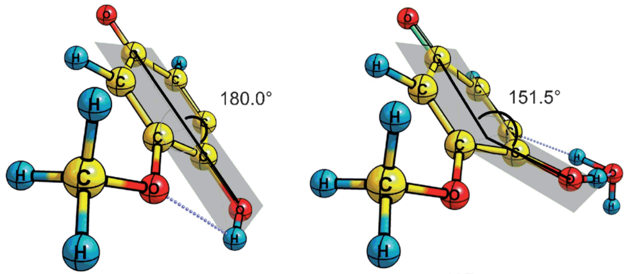


Figure 1. A computational study reveals an orbital isomer switch triggered by water.



Scheme 3. Influence of OH protection on the reaction course. MOM = methoxymethyl.



13A **13B•H_2O**

Figure 2. Planarity in diradical **13A** contrasts with the pronounced puckering observed for the zwitterion **13B**·H_2O.

to the zwitterion **20** (Figure 3). Importantly, a puckered, closed-shell transition state was indicated, consistent with the reaction proceeding via orbital isomer **19B/C** (Scheme 4 and Figure 3). Experimental evidence for the pathway was provided by the thermolysis of the alkynylcyclobutenone acetate **21** in 1,4-dioxane containing 1 % H_2O, and it led to a 1:1 mixture of the acetates **22** and **23** in near quantitative yield (Scheme 5).[20] This unprecedented rearrangement provided compelling evidence for the intermediacy of the zwitterion **26** and, by implication, the dual zwitterionic/cyclohexatrieneone character of the orbital isomer **25B/C**.

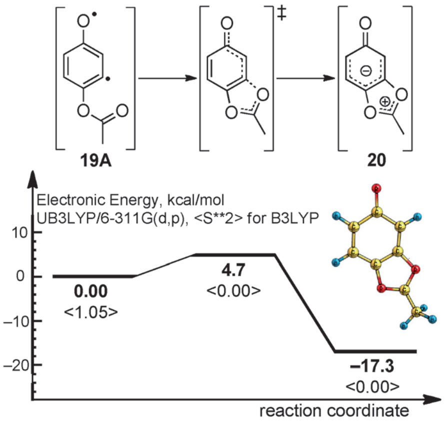
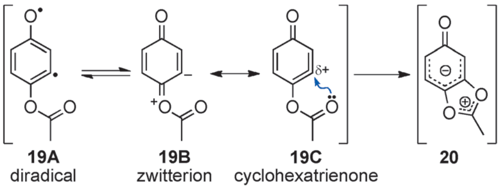
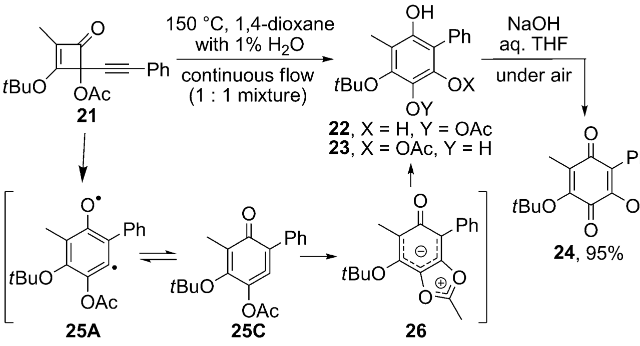


Figure 3. A computational study of the reactivity of the diradical **19A**.



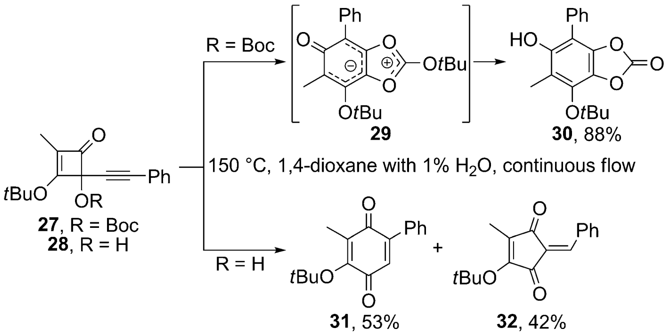
Scheme 4. A computational study predicts the cyclization of the acetate **19** into zwitterion **20** via a closed-shell transition state.



Scheme 5. Experimental evidence that the closed-shell orbital isomer of **25** exhibits cyclohexatrieneone character.

From a synthetic perspective, the method provides rapid and efficient access to tetrasubstituted quinones, as saponification of the crude reaction mixture with NaOH under air gave **24** in high yield (Scheme 5). It can also be used to access catechol carbonates in high yield through the corresponding Boc ester, for example, **27**→[**29**]→**30** (Scheme 6). The efficiency of both of these reactions is striking, given that thermolysis of the free alcohol from which they were derived, **28**, yields a 5:4 mixture of the quinone **31** and cyclopentenedione **32**.[20]

In conclusion, our study of the alkynylcyclobutenone rearrangement has shed new light on the curious world of diradical chemistry. Our demonstration that the reactive carbon center in a diradical intermediate may simultaneously act as a radical, an anion, and an electrophile through its orbital isomers is especially noteworthy. Similarly, our realization that water and, by analogy alcohols, can induce an orbital isomer switch from a diradical intermediate to a zwitterion is an important finding as it provides new opportunities in synthesis and helps to explain why many of these "unimolecular" processes often display a concentration



Scheme 6. A new route to catechol carbonates and the influence of alcohol protection on the course of the reaction. Boc = *tert*-butoxycarbonyl.

dependence and are prone to variance from experiment to experiment.[14c,i,j] It also has implications in the biological sphere, where compounds collapsing to diradical intermediates are among the most potent anticancer agents uncovered to date.[21]

Keywords: density functional calculations · flow chemistry · radicals · rearrangements · small ring systems

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