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Communication

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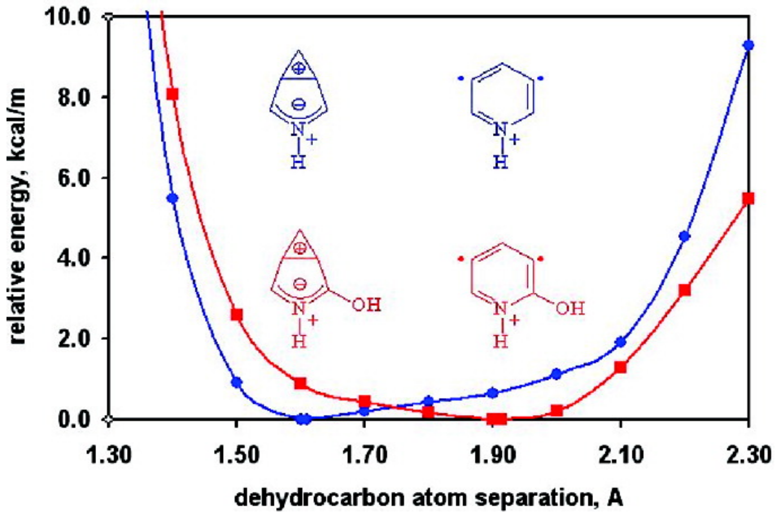

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Demonstration of Tunable Reactivity for *meta*-Benzynes

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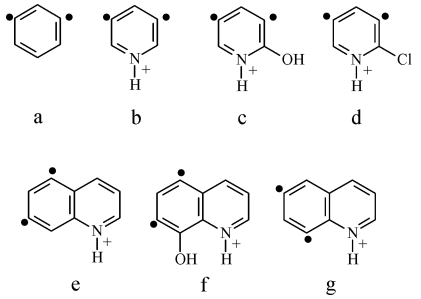
Aromatic σ,σ-biradicals have attracted much attention since the discovery that 1,4-arynes formed by Bergman cyclization are the biologically active intermediates of the enediyne class of antitumor antibiotics.[1,2] This type of biradical can cleave double-stranded DNA via abstraction of H atoms from each DNA strand. To facilitate the design of better antitumor drugs, computations have been employed to explore the factors (e.g., radical site separation, substituents, heteroatoms, charge) that might control the reactivity of naturally (1,4-) as well as non-naturally (1,3-) occurring arynes.[1,3,4] Unfortunately, these predictions are virtually impossible to experimentally verify because of the short lifetimes of such biradicals in solution. Here, we report both computational and experimental gas-phase results that demonstrate unambiguously that appropriate substituents can be used to "tune" the reactivity of 1,3-arynes from mildly carbocationic to aggressively radical-like.

meta-Benzyne (**a**, Scheme 1) has been conclusively shown to have a biradical structure rather than a bicyclic structure.[5] However, the formal radical sites have a substantial degree of stabilizing, "back-lobe" orbital interaction, which results in a relatively short dehydrocarbon atom separation (ca. 2.0 Å)[6a] and a large energy difference between the singlet ground state and the first excited triplet state (i.e., S−T gap = −21.0 kcal/mol).[7] The large S−T gap, which is characteristic of 1,3-arynes, has been predicted[3] and demonstrated[8,9] to hinder radical reactions (e.g., H atom abstraction) of these species, presumably because of a need[3,10] to partially uncouple the biradical electrons in the transition state of such reactions. To avoid this energetically costly uncoupling, 1,3-arynes tend to undergo nucleophilic or electrophilic addition reactions.[8,11] The rates of these reactions are controlled by the barrier for the initial ionic addition step, which is loosely related to the electrophilicity/nucleophilicity of the reagent, as well as the electron affinity (EA)/ionization energy of the biradical.

Scheme 1



Replacing C-5 in a with an NH^+ group (**b**) permits mass spectrometric examination of the biradical and its derivatives. This modification has been predicted[4b] to have only a minor influence on the S−T gap. (U)BLYP/cc-pVDZ calculations[6] for **a** indicate that the (singlet state) potential energy surface for the dehydrocarbon atom separation is very flat. The corresponding (U)BLYP/cc-pVDZ surfaces for **b**−**d** (Figure 1) are also very flat. However, **b** and **d** are predicted to have a substantially smaller dehydrocarbon atom separation than that of either **a** or **c**.[12,13]

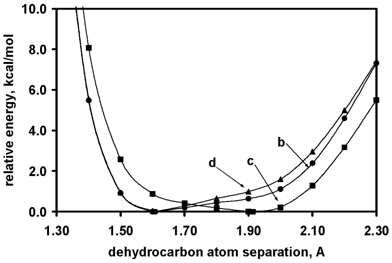
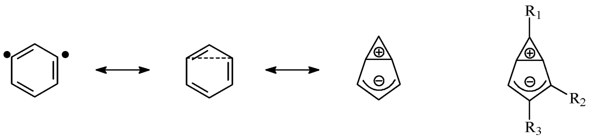


Figure 1. Relative energy versus dehydrocarbon atom separation for **b**−**d**.

Scheme 2



Such geometric changes for singlet *meta*-benzynes have been rationalized[4] by considering the (de)stabilizing effects of heteroatoms/substituents on zwitterionic resonance structures that contribute to the valence bond description of these molecules (Scheme 2). Substituting $C-R_3$ with the electron-withdrawing NH^+ group (**b**) stabilizes the allyl anion part of the molecule, which is predicted to shorten the dehydrocarbon atom distance from ca. 2.0 Å (**a**)[6] to 1.6 Å (**b**, Figure 1). Substituting **b** (S−T gap = −16.3 kcal/mol[14]) at R_2 with an OH group (**c**; S−T gap = −14.1 kcal/mol[14]) should destabilize the allyl anion part of the molecule due to the unfavorable π,π interactions with the O lone pair. Thus, biradical **c** is predicted to have a dehydrocarbon atom separation of ca. 1.9 Å (Figure 1). Substitution of **b** at R_2 with Cl (**d**; S−T gap = −14.4 kcal/mol[14]) should destabilize the zwitterionic resonance structure less than OH because Cl is a much less powerful π donor than OH (but like OH, it is σ-withdrawing). Indeed, biradical **d** is predicted to have a dehydrocarbon atom separation similar to that of **b** (ca. 1.6 Å; Figure 1). Therefore, even though the S−T gaps and EAs (6.30, 6.50, and 6.59 eV, respectively[15]) of **b**−**d** are similar, their structural differences may lead to very different reactivities; that is, biradicals **b** and **d** might undergo electrophilic addition reactions, while **c** may display reactivity that is more radical-like.

A well-known[8,9,11,16] method was used to study the reaction kinetics of **b**−**g** in a dual-cell Fourier-transform ion cyclotron resonance mass spectrometer. Their precursors, 3,5-diiodo-, 2-hydroxy-3,5-diiodo-,[17] and 2-chloro-3,5-dinitropyridines, as well as 5,7-dinitro-,[18] 8-hydroxy-5,7-diiodo-, and 6,8-dinitroquinolines,[19]

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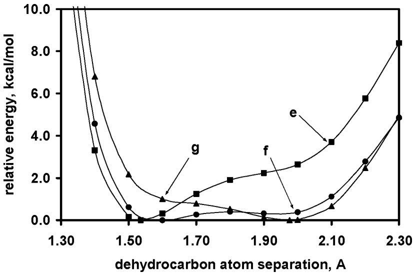

Figure 2. Relative energy versus dehydrocarbon atom separation for **e**−**g**.

respectively, were protonated via CH_3OH chemical ionization in one cell of a Finnigan[20] or Extrel[11] dual-cell FT-ICR. The radical sites were generated in the other cell by collision-activated dissociation of iodine atoms or nitro groups, isolated, and allowed to react with reagents for variable periods of time to determine the second-order reaction rate constants (k_{exp}) and reaction efficiencies (eff = $k_{exp}/k_{collision}$). The structures of the biradicals were confirmed by using well-established, structurally diagnostic reactions.[8,9,11,16]

Gas-phase experiments demonstrate that **b** reacts rapidly with the nucleophiles dimethyl disulfide and *tert*-butyl isocyanide (CH_3S and HCN abstraction eff = 53 and 84%, respectively), as predicted.[11] In fact, these reactions are as fast as those of the corresponding monoradical, 3-dehydropyridinium ion. However, radical reactions occur much more slowly for **b** than for the monoradical; H and I atom abstraction from tetrahydrofuran (THF) and allyl iodide, respectively, occur at eff = 0.7 and 10% for **b** and 38 and 76% for the monoradical.[11]

The OH-substituted biradical **c** abstracts a H atom from THF (eff = 30%) substantially faster than **b**. This reaction is nearly as fast as that for the monoradical discussed above. I atom abstraction from allyl iodide also occurs at a remarkably high rate (eff = 32%). Clearly, OH substitution has converted this *meta*-benzyne from an electrophile (**b**) into a highly reactive (bi)radical (**c**). The reactivity observed for the Cl-substituted biradical, **d**, is also consistent with the theoretical predictions. For example, H atom abstraction from THF (eff = 3.0%) occurs much more slowly for **d** than for **c** despite its greater EA.[21]

Interestingly, addition of an OH group at C-8 in **e** (Scheme 1) has the same effect as for **b**, although **e** is generally less reactive than **b** because of its lower EA (5.26 eV[15]). Biradical **e** does not react with either THF or allyl iodide, and it reacts only slowly with dimethyl disulfide (CH_3S abstraction; eff = 0.2%) and *tert*-butyl isocyanide (HCN abstraction; eff = 11%), although an analogous monoradical (5-dehydroquinolinium ion) reacts rapidly with all of these reagents (eff = 12, 32, 49, and 70%, respectively). This reactivity is consistent with the small dehydrocarbon atom separation (ca. 1.6 Å; Figure 2) and the relatively large S−T gap (−16.7 kcal/mol[14]) predicted for **e**. Substitution at C-8 with an OH group (**f**, Scheme 1) decreases the S−T gap (−11.1 kcal/mol[14]) and increases the EA (5.62 eV[15]) but does not significantly change the dehydrocarbon atom separation for the minimum energy structure (Figure 2). However, OH substitution drastically flattens the potential energy surface so that there is only about a 0.4 kcal/mol difference in energy between structures where the dehydrocarbon atom separation is either 1.6 or 2.0 Å (Figure 2). Thus, **f** should be highly fluxional. This is reflected in its reactivity. Biradical **f** is significantly more reactive than **e**, and it does indeed show radical reactivity; H and I atom abstraction from THF and allyl iodide, respectively, occurs at eff = 1.2 and 5.9%. Finally, biradical **g**, which has an S−T gap (−15.4 kcal/mol[14]) that is almost identical to that of **e**, but a much greater dehydrocarbon atom separation (ca. 2.0 Å; Figure 2**)**, also shows the expected radical reactivity. This biradical undergoes H and I atom abstraction from THF and allyl iodide even faster than **f** (eff = 4.0 and 9.4%, respectively), despite a larger S−T gap and a smaller EA (5.48 vs 5.62 eV).[15]

In summary, we have demonstrated that the reactivity of 1,3-arynes can be "tuned" from electrophilic to radical-like by adding substituents that destabilize a zwitterionic resonance structure (Scheme 2). While these substituent effects can result from either inductive or π interactions, we believe that the latter has a greater influence on the structures of *meta*-benzynes. Thus, selecting π-accepting substituents (e.g., CHO, CN) for R_1 and/or π-donating ones (e.g., OH, NH_2) for R_2 is likely to increase the radical reactivity of *meta*-benzynes.

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(13) For b, the CCSD(T)/cc-pVTZ/(U)BLYP/cc-pVDZ surface is very similar to the (U)BLYP/cc-pVDZ//(U)BLYP/cc-pVDZ surface.

(14) CASPT2/cc-pVDZ//(U)BLYP/cc-pVDZ level of theory.

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