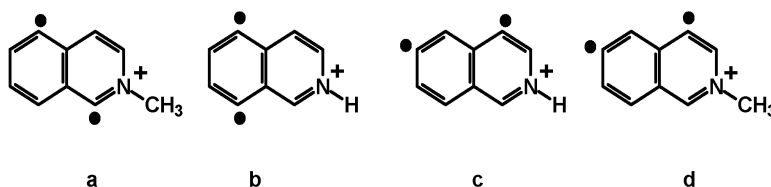


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Radical Reactions of Didehydroarenes with a 1,4-Relationship

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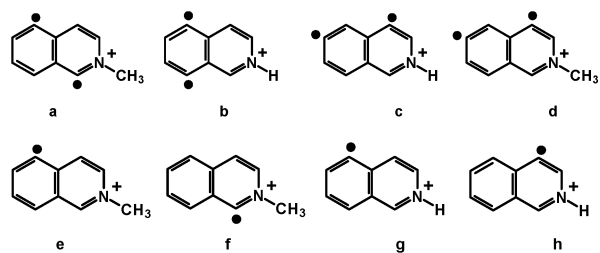
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Reactivity studies for organic biradicals are hindered by the high reactivities and short lifetimes of these species in solution.¹ For example, very little is known about the reaction kinetics and selectivities of aromatic σ,σ -biradicals (“didehydroarenes” or “arynes”), and even less is known about the factors that control their reactivity.¹ However, such information is highly desirable because some didehydroarenes, particularly those with a 1,4-relationship, play a key role in the biological action of antitumor antibiotics.¹ The few studies that have been carried out on reaction kinetics of *para*-benzynes (1,4-didehydrobenzenes) indicate that these species react at substantially lower rates than analogous monoradicals.^{2–5} This rate decrease has been suggested to result from the energetic cost associated with partially uncoupling the (singlet) biradical electrons in the transition state of a radical reaction, which causes a loss of some of the stabilization arising from spin–spin interactions.^{3,4} However, the generally accepted reactivity-controlling role of the singlet–triplet (S–T) gap for benzynes was questioned recently in a computational study.⁶ Clearly, more experimental data are needed to address this issue. Here, we report the generation of three novel didehydroarenes, *N*-methyl-1,5-didehydroisoquinolinium ion (**a**), 4,6-didehydroisoquinolinium ion (**c**), and *N*-methyl-4,6-didehydroisoquinolinium ion (**d**), and the first direct comparison of the reactivities of didehydroarenes with a 1,4-relationship (including the recently reported² 5,8-didehydroisoquinolinium ion (**b**); Scheme 1). This study leads to the conclusion that electronic effects due to the S–T gap can be offset by polar effects in these radical reactions.

The biradicals, **a–d**, and some analogous monoradicals (**e–h**; Scheme 1) were generated from iodo-, nitro-, or dinitro precursors (synthesized using known methods,⁷ or obtained commercially) in a Finnigan dual-cell Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer.⁸ After proton or methyl cation attachment via CH₃OH or CH₃I chemical ionization, respectively, the ionized precursors were transferred from one cell into the other where the radical site(s) were generated via homolytic bond cleavage(s) caused by collision-activated dissociation with argon, as described previously.^{8–11} The isolated monoradicals and biradicals were allowed to react with common atom- and group-donors for variable periods of time. The second-order reaction rate constants (k_{exp}) and the reaction efficiencies ($k_{\text{exp}}/k_{\text{coll}}$) were determined as described in the literature.^{9–12} Previous studies on related monoradicals and biradicals suggest that the species studied here are likely to be stable toward isomerization.^{8–11} This was confirmed by examining structurally diagnostic radical reactions (e.g., transfer of CH₃S- or CN-groups to radical sites from dimethyl disulfide¹³ and *tert*-butyl isocyanide,¹⁴ respectively).

The S–T gaps of the biradicals **a–d** were calculated at the CASPT2/cc-pVDZ//UBPW91/cc-pVDZ + ZPVE level of theory at 298 K to be –8.9, –5.5, –0.7, and –0.7 kcal/mol, respectively. These values are similar to those calculated¹⁵ for the analogous didehydronaphthalenes (–7.8, –5.6, –1.6, and –1.6 kcal/mol, respectively; CASPT2/cc-pVDZ/MCSCF(12,12)/cc-pVDZ + ZPVE).

Scheme 1



Therefore, the presence of a protonated or methylated nitrogen atom in the aromatic ring system does not appear to significantly perturb the spin–spin interactions in these molecules.

The biradicals **a–d** yield reaction products analogous to those obtained for the related monoradicals **e–h**. For example, all of these species react by abstraction of one or two H atoms from tetrahydrofuran, CH₃S groups from dimethyl disulfide, CN groups from *tert*-butyl isocyanide, and I atoms from allyl iodide. These reactions are quite different from the addition/elimination reactions reported previously for substituted 1,2- and 1,3-didehydroarenes.^{8,11} Thus, didehydroarenes with a 1,4-relationship appear to react exclusively as radicals, as predicted by the S–T gap reactivity paradigm.

However, the determination of the reaction efficiencies for the biradicals yielded unexpected results. The reaction efficiencies for **a–d** with tetrahydrofuran are 8%, 0.007%, 26%, and 19%, respectively. Thus, biradical **a**, which has a S–T gap that is 3.4 kcal/mol *greater* than that of biradical **b** (and which also may suffer from steric hindrance), reacts about 3 orders of magnitude *faster* than biradical **b**! It should be noted that these reactions go to completion with constant product branching ratios and that H atom abstraction by **a** is calculated to be about 2 kcal/mol less exothermic than by **b** (CASPT2/cc-pVDZ//UBPW91/cc-pVDZ + ZPVE). Clearly, *the reactivity ordering for the biradicals (b ≪ a < d < c) is in conflict with that predicted by the S–T gap reactivity paradigm (a < b < c ≈ d; this is also the reaction exothermicity ordering)*. The results for the other reactions studied also conflict with the S–T gap reactivity paradigm. For example, the reaction efficiencies of the reactions with dimethyl disulfide are 18%, 10%, 59%, and 27% for **a–d**, respectively (**b < a < d < c**). Moreover, a comparison of these reaction efficiencies with those of the analogous monoradicals, **e–h**, shows that biradicals **a**, **b**, and **d** react more slowly than the monoradicals, but that biradical **c** reacts at a similar rate (reaction efficiencies with dimethyl disulfide: 26% for **e** and 58% for **f** (analogues of **a**), 48% for **g** (analogue of **b**), and 59% for **h** (analogue of **c** and **d**)). This result, in particular, conflicts with the S–T gap reactivity paradigm in two ways. First, **c** does not show any reduction in rate, although some might be expected based on the need to partially uncouple the (singlet) biradical electrons in the transition state. Second, the S–T gaps for **c** and **d** are similar, but **c** reacts with a substantially greater efficiency. All of these observations indicate that the S–T gap is not the only parameter that affects the reaction rates of the biradicals studied here.

It seems likely that the barrier for radical abstraction by a biradical is affected by some of the same parameters that control the reactivity of analogous monoradicals. Our previous studies on substituted, positively charged aryl radicals demonstrated that the transition state energies, and consequently the reaction efficiencies, depend on the electrophilicities of the radicals.¹⁰ Hence, polarization of the transition state appears to be a rate-controlling factor for the reactions of these aryl radicals, as it is for reactions of polar neutral radicals.¹⁶ Calculated electron affinities (EA; the energy released upon attachment of an electron to a radical site) for the mono- and biradicals studied here provide information about the extent of this barrier-lowering effect (adiabatic and diabatic EAs show the same trends). For example, the lower efficiency measured for the reaction of monoradical **g** than of monoradical **h** with dimethyl disulfide (48% and 59%, respectively), tetrahydrofuran (8% and 28%, respectively), and allyl iodide (36% and 49%, respectively) can be interpreted to be a result of the much lower electrophilicity of **g** than **h** (EA_v: **g**, 5.04 eV; **h**, 5.72 eV; UBLYP/aug-cc-pVDZ//UBLYP/cc-pVDZ).

Even though polar effects have been shown to play an important role in the reactions of aryl radicals, nearly nothing is currently known about how these effects impact the reactivity of biradicals. The only arynes for which EAs have been measured are the three benzyne (the adiabatic EAs for 1,2-, 1,3-, and 1,4-didehydrobenzene are 0.564, 0.852, and 1.265 eV, respectively),¹⁷ and, for these molecules, the EA decreases as the S–T gap increases (–37.5, –21.0, and –3.8 kcal/mol,¹⁷ respectively). The vertical EAs for **a–d** were calculated at the UBLYP/aug-cc-pVDZ//UBLYP/cc-pVDZ level of theory to be 6.18, 5.73, 5.99, and 5.82 eV, respectively. For these biradicals, the EAs do not correlate with the S–T gaps as they do for the three benzyne. Further, each biradical has a calculated EA that is greater than that of its monoradical analogues (**b**, 5.73 eV vs **g**, 5.04 eV; **c**, 5.99 eV vs **h**, 5.72 eV; **d**, 5.82 eV vs **h**, 5.72 eV; and **a**, 6.18 eV vs **f**, 6.14 eV). These results suggest that most of the anions of these biradicals are stabilized, relative to those of the monoradicals, due to odd spin and charge delocalization. It is noteworthy that a similar effect has been observed¹⁷ for 1,4-didehydrobenzene, which has an EA that is 0.17 eV greater than that of phenyl radical¹⁸ (1.096 eV).

For three of the four biradicals studied here, the reaction efficiency ordering parallels the EA ordering (**b** < **d** < **c**). Biradicals **c** and **d** have S–T gaps of a similar magnitude; therefore, any major differences in reactivity between these two biradicals should result from differences in polar effects. The significant differences in the reaction efficiencies observed for **c** and **d** (dimethyl disulfide, 59% and 27%; tetrahydrofuran, 26% and 19%; *tert*-butylisocyanide, 94% and 64%, respectively), despite only a 0.17 eV difference in EA, clearly illustrate the importance of polar effects in these reactions. It is also noteworthy that a simple structural change, such as replacement of a proton with a methyl group on the nitrogen atom, causes a major change in reactivity for these biradicals. A comparison of the reaction efficiencies of **b** and **d** (dimethyl disulfide, 10% and 27%; tetrahydrofuran, 0.007% and 19%; *tert*-butylisocyanide, 46% and 64%, respectively) shows that the S–T gap (–5.5 and –0.7 kcal/mol for **b** and **d**, respectively) can also have a major influence on the reactivities of species that have similar EAs (5.73 and 5.82 eV for **b** and **d**, respectively). Biradical **a** has the largest EA but also the largest S–T gap. These two opposing, reactivity-controlling parameters seem to largely offset each other, as evidenced by the moderate reactivity of **a** that is similar to that observed for **d** which has a low EA and a small S–T gap (dimethyl disulfide, 19% and 27%; *tert*-butyl isocyanide, 61% and 64%, for **a** and **d**, respectively).

It is worth noting that only the H-atom abstraction reaction occurs via a simple radical substitution mechanism. All of the other reactions almost certainly involve a stepwise mechanism with the formation of an intermediate.^{13,14,19} It is remarkable that the reactivity ordering of the biradicals is the same for all of these reactions, despite the mechanistic differences.

In conclusion, the height of the barrier for radical abstraction by didehydroarenes that have a 1,4-relationship appears to depend on at least two factors: the S–T gap and polar effects. Any predictions of relative biradical reactivity based on the S–T gap reactivity paradigm^{3,4} will only be valid when the polarities of the reacting systems are the same. Even small differences in the electrophilicities of didehydroarenes can completely reverse the reactivity ordering that would be predicted on the basis of their S–T gaps. Further, biradicals with a greater EA than analogous monoradicals are expected to be more sensitive to polar effects. Therefore, some biradicals may be even more reactive toward radical abstraction than their monoradical analogues. Finally, this work demonstrates that simple structural modifications that influence the polarity, but not the electronic structure, can be used to “tune” the reactivities of didehydroarenes.

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Supporting Information Available: Reaction efficiencies and product branching ratios (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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