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Chemical Properties of a *para*-Benzyne

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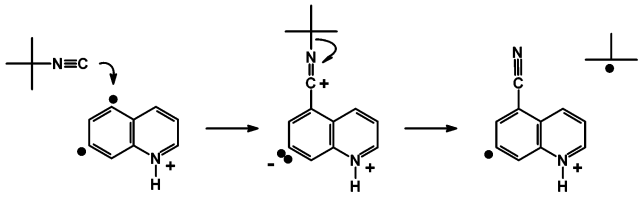
The ability to predict and control the outcome of chemical and biological reactions frequently requires knowledge of the key reaction intermediates. Didehydroarenes (arynes) and their derivatives are reaction intermediates that have been scrutinized for over 50 years.[1] The recent identification of the crucial role of 1,4-didehydroarenes in the biological action of the enediyne antitumor drugs has led to a renewed interest in the properties of this type of aromatic σ,σ-biradical.[2] These biradicals, formed from Bergman cyclization in biological systems, can abstract a H atom from a sugar moiety in each strand of a double-helix DNA, which leads to DNA cleavage and eventually cell death.

Understanding the factors that control the reactivity of aromatic biradicals formed from drugs would clearly be beneficial for the rational design of synthetic nonhydrolytic DNA cleavage agents. Unfortunately, reactivity studies of didehydroarenes in solution (or even unambiguous demonstration of their existence) are a challenge due to their high reactivities and short lifetimes.[1] In fact, solution studies have led to an in-depth chemical characterization of only one member of this family of reaction intermediates: 1,2-didehydrobenzene and its derivatives (*ortho*-benzynes).

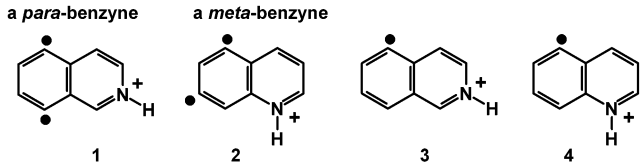
Many of the issues that complicate solution studies of highly reactive molecules are less problematic in the gas phase. Indeed, many exceedingly reactive ionic species have been investigated in detail by mass spectrometric techniques. These techniques can be extended to reactive neutral molecules via ions that contain the reactive group of interest and a chemically inert charged group for mass spectrometric manipulation ("distonic ion approach").[3] One benefit associated with such experiments is that intrinsic (solvent-free) properties can be determined which provides information that is crucial for the understanding of reactivity in any environment.

We recently employed the above approach to chemically characterize several 1,3-didehydroarenes (*meta*-benzynes).[3] These studies demonstrated that this type of reaction intermediate does not undergo radical reactions but instead undergoes electrophilic or nucleophilic addition/elimination reactions, depending on the polarity of the biradical (Scheme 1). The inability of *meta*-benzynes to undergo radical reactions can be understood on the basis of the studies by Chen[4] and Roth[5] in 1996 for H-atom abstraction reactions of *para*-benzyne and 9,10-didehydroanthracene in solution. The observation of substantially lower reaction rates for the biradicals than for the corresponding monoradicals was rationalized on the basis of the electronic structure of the *para*-benzyne. The decreased radical reactivity was proposed to result from the need to partially uncouple the biradical electrons in the transition state.[6] Hence, part of the energy splitting between the singlet ground state and the lowest-energy triplet state (the singlet−triplet (S−T) gap; for *para*-benzyne, −3.8 kcal/mol[7]) was suggested[6] to appear as an energy increment in the reaction barrier, and high reaction barriers would therefore be predicted for biradicals with large S−T gaps. For example, the H-atom abstraction ability of a *meta*-benzyne, which has a S−T gap of about −21 kcal/mol,[7] is expected to be substantially poorer than that of an analogous para benzyne. Indeed, it has been shown that the *meta*-benzyne moiety tends to avoid the costly uncoupling of the biradical electrons in its reactions by favoring nucleophilic or electrophilic addition to yield zwitterionic intermediates.[3] The rates of these reactions are controlled by the barrier to the initial ionic addition step, which is loosely related to the basicity/electrophilicity of the attacking reagent.[3]

Scheme 1



Scheme 2



To the best of our knowledge, the reactivity-controlling role of the S−T gap for singlet didehydrobenzenes has been generally accepted by the scientific community, despite a paucity of experimental data for such species. Here, we describe the first gas-phase reactivity studies for a *para*-benzyne, the 5,8-didehydroisoquinolinium ion (**1**), and the first direct comparison of the reaction kinetics for a *meta*- and a *para*-benzyne (Scheme 2). The results are contrasted with those obtained for two related monoradicals, the 5-dehydroisoquinolinium ion (**3**) and the 5-dehydroquinolinium ion (**4**).

The biradical precursors, 5,8-dinitroisoquinoline and 5,7-dinitroquinoline (synthesized by known methods[8]), and the monoradical precursors, 5-nitroquinoline and 5-nitroisoquinoline (Sigma−Aldrich), were protonated via CH_3OH-chemical ionization in one cell of a Finnigan dual-cell Fourier transform ion cyclotron resonance mass spectrometer and transferred into the other cell. The radical site(s) were generated and the radicals isolated via published methods.[3,9−11] The isolated mono- and biradicals were allowed to react with reagents for variable periods of time. The second-order reaction rate constants (k_{exp}) and the reaction efficiencies (k_{exp}/k_{coll})[12] were determined as described[3,9−11] previously.

There is a significant amount of evidence in the literature suggesting that the mono- and biradicals studied here should be stable with respect to isomerization.[3,9−11] Indeed, all of the reactions of **1**−**4** follow pseudo-first-order kinetics, which suggests that the radical populations are isomerically pure. The number of radical

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sites in each species was verified by using dimethyl disulfide[13] and *tert*-butyl isocyanide.[14] These reagents are known to transfer a CH_3S or CN group, respectively, to each radical site in positively charged dehydroarenes.[9,11,13,14] Sequential transfer of two CH_3S or CN groups was observed for the biradicals (transfer of HCN also occurs), whereas transfer of one CH_3S or CN group was observed for the monoradicals. The presence of two radical sites in the *para*-benzyne and the fact that the benzyne population reacts to completion via radical abstractions rules out the possibility of complete or partial rearrangement to an enediyne. Further, isomerization of either biradical to an ortho isomer seems unlikely on the basis of the lack of reactivity of these species toward furan—a reagent that is known to add (rapidly) to neutral and charged *ortho*-benzynes.[11]

The S−T gaps calculated for the *para*- (**1**) and *meta*-benzynes (**2**) at the CASPT2/cc-pVDZ//MCSCF(12,12)/cc-pVDZ + ZPE level of theory at 298 K are −5.4 and −17.5 kcal/mol, respectively. The large gap calculated for **2** is typical for a *meta*-benzyne[1c,7,15,16] and indicates a strong interaction between the formally unpaired electrons due to through-space orbital overlap. The S−T gap calculated for **2** is of the same magnitude as that calculated[16] for the analogous 1,3-didehydronaphthalene (−17.2 kcal/mol; same level of theory). As expected,[15c] the presence of a protonated nitrogen atom in the naphthalene ring of **2** does not significantly perturb the relevant orbital interaction. Similarly, the magnitude of the S−T gap (−5.4 kcal/mol) calculated for **1** is typical for neutral *para*-benzynes[1c,7,15,16] which have destabilizing through-space orbital overlap but stabilizing through-bond spin−spin interaction (the S−T gap calculated[16] for 1,4-didehydronaphthalene is −5.6 kcal/mol).

The *para*- and *meta*-benzynes yield the same major products with similar branching ratios upon reaction with all of the reagents studied, including *tert*-butyl isocyanide (CN (∼5%) and HCN (∼95%) abstraction), dimethyl disulfide (CH_3S abstraction), 2,3-dimethoxy-1,3-butadiene (addition accompanied by the loss of CH_3-OH), 3-fluoropyridine (adduct formation), and tributyltin hydride (minor H-atom abstraction; major addition, sometimes accompanied by the loss of C_4H_9). Most of the same products were also observed for the monoradicals. However, we have shown that for **2**, most of these products are not formed by a radical pathway but rather by a nucleophilic addition/elimination mechanism (Scheme 1).[3] Many of the reactions of **1** can conceivably occur via either a nucleophilic addition/elimination mechanism or a radical mechanism, depending on which mechanism has a lower barrier.

All but one of the reactions of the *para*-benzyne **1** (efficiencies for *tert*-butyl isocyanide, dimethyl disulfide, and 2,3-dimethoxy-1,3-butadiene are 39, 12, and 19%, respectively; 19% efficiency means that 19 collisions in 100 lead to a reaction) occur substantially faster than those of the meta isomer (12, 0.2, and 3%, respectively), but all of the reactions of both biradicals are considerably slower than those of the monoradicals (the efficiencies for **3** and **4** are 75, 48, and 37%; and 74, 52, and 45%, respectively). The only exceptions to the above are reactions with 3-fluoropyridine. This reagent is relatively unreactive toward electrophilic (*meta*-benzyne) as well as radical (monoradicals) addition. However, both types of addition were found to occur at greater efficiencies (coincidentally, both 3%) than the reaction of the *para*-benzyne (0.9%).[17] This observation suggests that the *para*-benzyne is a poorer electrophile than its *meta*-isomer and also that it is a less reactive radical than the monoradicals (adduct relaxation by light emission is expected to be equally fast for these structurally similar molecules). Therefore, the other reactions of **1** discussed above are probably best characterized as radical reactions.

An examination of the effect of the magnitude of the S−T gap on the reaction efficiencies of the *meta*- and *para*-benzynes and the monoradicals is not meaningful unless all reactions occur by the same mechanism. This is true for H-atom transfer. Exclusive H-atom transfer (or no reaction) was observed between all of the mono- and biradicals and tetrahydrofuran. The monoradicals **3** and **4** react with moderate efficiencies (8 and 13%, respectively). However, the *para*-benzyne **1** reacts extremely slowly (0.007%) and the *meta*-benzyne **2** not at all. Similarly, H-atom abstraction from tributyltin hydride occurs rapidly for the monoradicals (35 and 40%) but slowly for the *para*-benzyne and even more slowly for the *meta*-benzyne (the efficiencies are 1% and 0.2%, respectively; major addition products are also formed). These results are indeed entirely consistent with the S−T gap reactivity model.

In conclusion, the rates measured for all of the different types of radical reactions of the *para*- (**1**) and *meta*-benzyne (**2**), and their monoradical analogues (**3** and **4**), are qualitatively consistent with the S−T gap reactivity paradigm,[6] although the extent of S−T gap control appears to depend on the type of reaction. However, this is of little practical consequence for the *meta*-benzyne whose reactions tend not to occur via radical mechanisms. The results obtained here, together with those reported earlier for *ortho*- and *meta*-benzynes,[11] indicate that the preference for ionic reactivity increases in the order *para*- < *meta*- < *ortho*-. Unambiguous demonstration of nonradical reactivity for the *para*-benzyne, and an in-depth examination of the competition between the two reaction pathways, remain as our future goals.

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