

Reactivity of a Substituted *m*-Benzyne Biradical

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Abstract: Fourier transform ion cyclotron resonance mass spectrometry has been employed to systematically investigate the intrinsic (solvent-free) reactivity of a 1,3-dehydrobenzene (*m*-benzyne) with a pyridinium charge site in the 5-position. The *m*-benzyne was generated by using a combination of ion–molecule reactions and photodissociation and isolated *prior* to examination of its gas-phase reactions. The ionic reaction products and reaction efficiencies (second-order reaction rate constant/collision rate constant) were compared to those measured for the isomeric *o*-benzyne and the analogous phenyl monoradical. The *m*-benzyne yields some of the products formed for the *o*-benzyne but it also reacts via distinct radical pathways characteristic of the corresponding phenyl radical. These radical pathways are not observed for the *o*-benzyne. However, the reaction efficiencies measured for the *m*-benzyne are significantly lower than those measured for the analogous phenyl radical or the isomeric *o*-benzyne. These findings are partially rationalized by the relatively strong coupling (about 21 kcal mol⁻¹) between the two formally unpaired electrons in the *m*-benzyne that hinders radical reactions. On the other hand, the greater distance between the reactive sites in the *m*-benzyne makes alkyl-type addition reactions sterically and energetically less favorable than for the *o*-benzyne.

Introduction

The reactivity of benzyne and other aromatic σ,σ -biradicals has received renewed interest since the discovery that such 1,4-biradicals are likely to be the key intermediates in the biological action of the enediyne group of antitumor antibiotics.¹ However, their high reactivity has thus far prevented the detailed experimental characterization of most of these species. Indeed, out of the three prototypical benzyne, i.e., the *o*-, *m*-, and *p*-benzyne, the reactivity of only the *o*-benzyne can be considered to be well-characterized. Numerous studies² demonstrate that this species readily undergoes addition reactions with electrophilic as well as nucleophilic substrates.

In sharp contrast to the vast amount of literature describing the reactivity of the *o*-benzyne and its derivatives, only a handful of publications³ report results on reactions of *m*-benzyne derivatives. The most conclusive reactivity study on *m*-benzyne derivatives has been carried out by Squires and co-workers.^{3a} This work focused on the gaseous 3,5-dehydrophenyl anion examined in a flowing afterglow apparatus. The carbanionic nature of this biradical anion dominates its reactivity. For example, the reactions with carbon dioxide and carbon disulfide yield two other *m*-benzyne derivatives, the 3,5-dehydrobenzoate (via addition to carbon dioxide) and the 3,5-dehydrothiophenolate (via abstraction of a sulfur atom from carbon disulfide).

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The latter two *m*-benzyne derivatives were found to be unreactive toward all neutral reagents studied, including NO, O₂, and NO₂. The lack of observation of radical-type reactivity for the three *m*-benzyne derivatives was taken as evidence for a singlet electronic ground state,^{3a} in analogy with the parent hydrocarbon ($\Delta E_{S/T} = -21$ kcal mol⁻¹).^{3e}

Fourier transform ion cyclotron resonance mass spectrometry provides a powerful tool for the study of the intrinsic or solvent-free reactivity of many charged radicals and biradicals. This experimental approach allows the isolation (purification) of the radical of interest and the examination of its properties under clean conditions (i.e., in the presence of only the desired ionic and neutral reagents).⁴ The properties of the radical can be studied in great detail, e.g., reaction rate constants, product branching ratios, and various thermochemical parameters are readily determined.⁵ We recently published a preliminary study wherein this approach was used to generate the first known gaseous *m*-benzyne that carries a positively charged substituent.⁶ We report here a systematic comparison of the chemical properties of the *m*-benzyne derivative, its *o*-benzyne isomer, and the analogous phenyl radical.

Experimental Section

All the experiments were performed in an Extrel model FTMS 2001 Fourier transform ion cyclotron resonance mass spectrometer equipped with an Odyssey data station and a SWIFT (Stored Waveform Inverse

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Fourier Transform) cell controller. The instrument⁷ contains a differentially pumped dual cell placed within the pole gap of a 3 T superconducting magnet operated at 2.4–2.9 T. The two sides of the dual cell are separated by a common wall (the conductance limit). Ion transfer between the reaction chambers occurs through a 2 mm hole located in the center of the conductance limit. The three trapping plates were kept at +2 V unless otherwise specified. The nominal base pressure in each side of the dual cell ($<1 \times 10^{-9}$ Torr) was maintained by two turbomolecular pumps (Balzers TPU 330 L/s), each backed with an Alcatel 2012 mechanical pump. The pressure was measured with two ionization gauges, one located on each side of the dual cell. The samples were introduced into the cell at a nominal pressure of approximately 1×10^{-7} Torr by using a heated solids probe, a Varian leak valve, a pulsed valve system (consisting of two General Valve Corporation pulsed valves and a reservoir), or one of two batch inlet systems equipped with an Andonian variable leak valve. The pressure readings were corrected for the sensitivity of the ion gauges toward each neutral reagent^{8a} and for the pressure differential between the cell and the ion gauge, as described previously.^{8b} The latter correction factor was obtained by measuring the rates of reactions with known rate constants involving the neutral molecules of interest.

The precursors to the ions (1,3,5-tribromobenzene for the *m*-benzyne derivative, 1-chloro-3,4-diiodobenzene for the *o*-benzyne derivative, 1,4-dibromo-2-chlorobenzene for the *p*-benzyne derivative, 1-bromo-3-iodobenzene for the monoradical, and iodobenzene for the even-electron ion) were introduced into one side of the dual cell by using a heated solids probe or a variable leak valve and ionized by electron impact. The ionization conditions were optimized for the maximum ion signal for each experiment (typically 15–20 eV electron energy, 70–80 ms beam time, 8–10 μ s emission current). The radical cations were reacted with 3-fluoropyridine (added into the same cell through a batch inlet system) to introduce a pyridinium charge site via replacement of a halogen atom (chlorine, bromine, or iodine atom; 3-fluoropyridine was used instead of pyridine to avoid generation of a product ion with the same mass as that of the reactant ion when a bromine atom is replaced). After an adequate amount of the desired replacement product was formed (typically 0.8–6 s), the ions were transferred into the other side of the dual cell by grounding the conductance limit plate (for 100–150 μ s) and collisionally cooled for about 1 s with the neutral reagent present in that cell. Before the transfer of ions into this cell, however, ions already present due to electron ionization were removed by applying a negative potential (–2 V) to the remote trapping plate of that cell (typically for 10 ms). The product ion obtained upon replacement of a chlorine atom (for the *o*- and *p*-benzyne derivatives) or bromine atom (for the *m*-benzyne derivative and the monoradical) was partially isolated via ejection of the most abundant unwanted ions by using the SWIFT technique.⁹ The radical site(s) were generated by sustained off-resonance irradiated collision-activated dissociation¹⁰ (SORI–CAD) applied for approximately 1 s at a frequency 0.5–1 kHz higher than the cyclotron frequency of the ions, with argon pulsed into the cell to reach a nominal peak pressure of about 1×10^{-5} Torr, or by photodissociation at 266 nm by using a Nd:YAG laser. The ions were collisionally and irradiationally cooled by allowing them to collide for 0.4–1 s with the neutral molecules present in the cell. The desired bi- or monoradical was isolated by using the SWIFT technique and allowed to react with a neutral reagent (at a nominal pressure of 6.0×10^{-8} to 1.4×10^{-7} Torr) for a variable period of time (typically 1–20 s). After reaction, the ions were excited for detection by using “chirp” excitation. All the measured spectra are an average of at least 20 transients and were recorded as 64K data points and subjected to one zero fill prior to Fourier transformation.

Since the reactions studied under the conditions described above

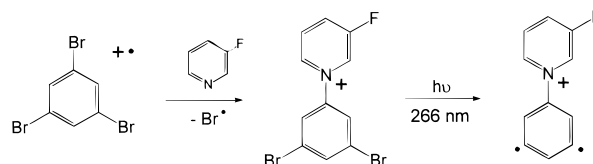
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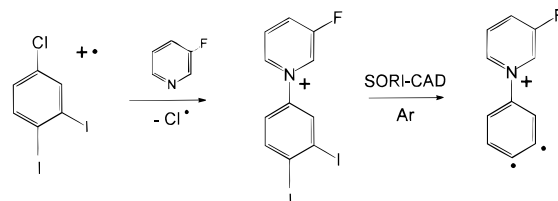
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Scheme 1



Scheme 2



follow pseudo-first-order kinetics, their second-order rate constants (k_{exp}) were obtained from a semilogarithmic plot of the relative abundance of the reactant ion as a function of time. The collision rate constants (k_{coll}) were calculated by using the parametrized trajectory theory.¹¹ The reaction efficiencies are given by $k_{\text{exp}}/k_{\text{coll}}$. The accuracy of the rate constant measurements is estimated to be $\pm 50\%$, while the precision is better than $\pm 10\%$. Primary products were distinguished from secondary products based on their constant relative abundances at short reaction times and, in some cases, isolation of a product ion and examination of its reactivity.

1-Chloro-3,4-diiodobenzene was synthesized from 4-chloroanthranilic acid by conversion of the anthranilic acid to *o*-benzyne in the presence of iodine.¹² All other reagents were obtained commercially and used as received. The purity of each reagent was verified by mass spectrometry and in some instances also by gas chromatography.

Results and Discussion

Generation and Structural Characterization of Charged Benzyne. A method published earlier for the generation^{13,14} of charged phenyl radicals in the gas phase was applied⁶ to the synthesis of charged *o*-, *m*-, and *p*-benzyne biradicals in a dual-cell Fourier transform ion cyclotron resonance mass spectrometer (Schemes 1 and 2; Figure 1). Electron ionization of 1-chloro-3,4-diiodo-, 1,3,5-tribromo-, or 1,4-dibromo-2-chlorobenzene, followed by reaction of the resulting radical cation with 3-fluoropyridine, generates the *N*-(3,4-diiodophenyl)-3-fluoropyridinium, *N*-(3,5-dibromophenyl)-3-fluoropyridinium, or *N*-(2,5-dibromophenyl)-3-fluoropyridinium ion, respectively. Homolytic cleavage of the carbon–bromine bonds by photodissociation or the carbon–iodine bonds by sustained off-resonance irradiated collision-activated dissociation (SORI–CAD¹⁰) yields the desired biradicals. The charged biradicals were isolated by ejecting all unwanted ions from the cell and allowed to react with a neutral reagent for a variable period of time to determine the reaction products and the second-order reaction rate constants (given as reaction efficiencies, i.e., reaction rate constant k_{exp} /collision rate constant k_{coll}).

The structure of the *m*-benzyne derivative was verified by examining its reactivity toward two radical traps, benzyl isocyanide and benzeneselenol. These reagents rapidly transfer $\cdot\text{CN}$ or $\cdot\text{H}$, respectively, to the analogous *N*-(3-dehydrophenyl)-3-fluoropyridinium monoradical. About half of the *m*-benzyne molecules undergo consecutive abstraction of two $\cdot\text{CN}$ groups

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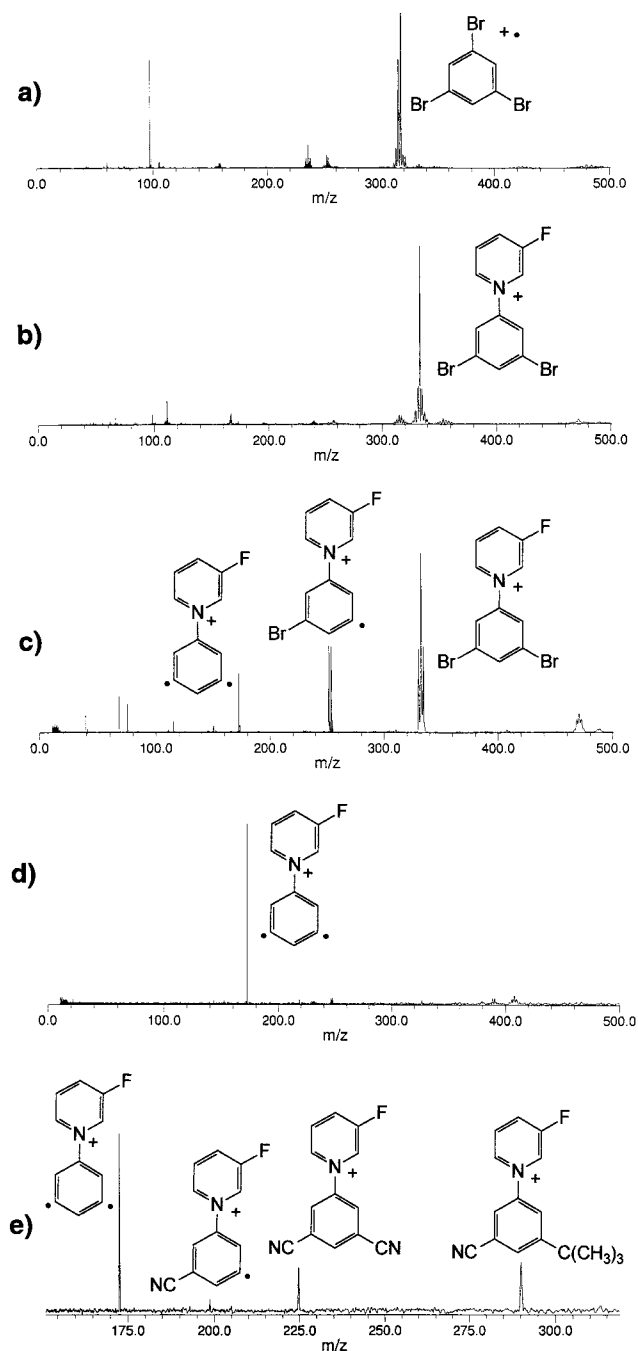


Figure 1. (a) Electron ionization of 1,3,5-tribromobenzene. (b) Reaction of the radical cation of 1,3,5-tribromobenzene (m/z 312 + isotopes) with 3-fluoropyridine yields the N -(3,5-dibromophenyl)-3-fluoropyridinium ion (m/z 330 + isotopes). (c) Photodissociation (266 nm) of the ion of m/z 330 (+ isotopes) results in cleavage of one and two carbon–bromine bonds to yield the N -(3-bromo-5-dehydrophenyl)-3-fluoropyridinium ion (m/z 251 + isotopes) and the N -(3,5-dehydrophenyl)-3-fluoropyridinium ion (m/z 172), respectively. (d) Isolation of the N -(3,5-dehydrophenyl)-3-fluoropyridinium ion (m/z 172). (e) Reaction of this species with benzyl isocyanide for 8 s at 1.2×10^{-7} Torr occurs by $\cdot\text{CN}$ abstraction (to yield an ion of m/z 198), followed by abstraction of another $\cdot\text{CN}$ from a second molecule of benzyl isocyanide (to produce an ion of m/z 224), as well as by addition (to yield an adduct of m/z 289).

from benzyl isocyanide and two $\cdot\text{H}$ atoms from benzeneselenol (the rest of the biradical molecules form a stable addition product that is likely to be covalently bonded, since no such product is formed for the corresponding monoradical or its even-electron analog). These findings demonstrate the presence of two radical

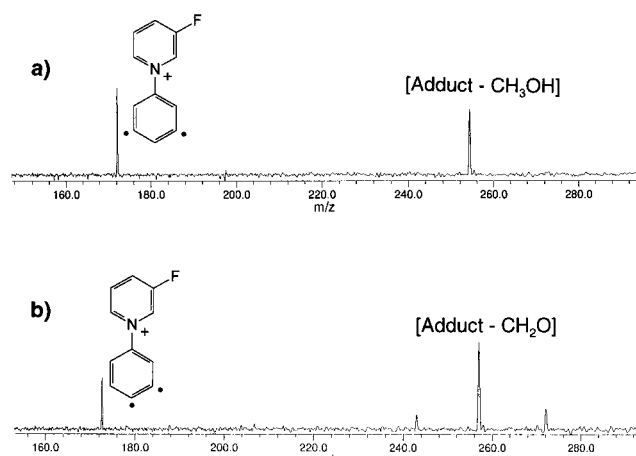


Figure 2. (a) Reaction of the N -(3,5-dehydrophenyl)-3-fluoropyridinium ion (m/z 172) with 2,3-dimethoxy-1,3-butadiene (1.2×10^{-7} Torr) occurs via elimination of methanol from the adduct (to produce an ion of m/z 254; reaction time 4 s). (b) Reaction of the N -(3,4-dehydrophenyl)-3-fluoropyridinium ion (m/z 172) with 2,3-dimethoxy-1,3-butadiene (1.2×10^{-7} Torr) occurs primarily via elimination of formaldehyde from the adduct (to yield an ion of m/z 256; reaction time 2 s).

sites in the reactant ion, i.e., a biradical structure. Analogous ions with no radical sites, e.g., the even-electron N -phenyl-3-fluoropyridinium ion, are unreactive toward both benzeneselenol and benzyl isocyanide.

The *o*-benzyne derivative displays reactivity that is strikingly different from that of the isomeric *m*-benzyne. The *o*-benzyne abstracts HSCH_3 from dimethyl disulfide, while the *meta*-isomer is unreactive toward this reagent. The *o*-benzyne reacts with 2,3-dimethoxy-1,3-butadiene primarily by addition followed by elimination of formaldehyde (Figure 2b), whereas elimination of methanol was observed for the *m*-benzyne (Figure 2a). The observation of pseudo-first-order kinetics for all reactions of both the *o*- and *m*-benzyne species (for examples, see Figure 3) suggests that the ion populations are composed of only one isomer. On the basis of all these results, it is concluded that the *m*-benzyne derivative does not rearrange to the more stable *o*-benzyne, and that the two benzyne likely maintain their structural integrity.

The reactivity of the species thought to be the *p*-benzyne derivative was found to be distinctly different from that of the charged *o*- and *m*-benzyne and the analogous monoradical. Despite the expectation that the *p*-benzyne derivative should undergo radical reactions more readily than the isomeric *m*-benzyne (due to its very small singlet–triplet gap^{3e,16} of about $3.8 \text{ kcal mol}^{-1}$), this species was found to be unreactive toward all the reagents examined. For example, no reaction was observed with *tert*-butyl isocyanide or 2,3-dimethoxy-1,3-butadiene, although both readily react with the *o*- and *m*-isomers and the monoradical. The lack of reactivity toward these radical traps is readily understood if the *p*-benzyne derivative undergoes rapid ring-opening via a reverse Bergman cyclization before bimolecular reactions. This well-documented reaction is exothermic for the unsubstituted *p*-benzyne in solution ($\Delta H = -8.5 \text{ kcal mol}^{-1}$; $E_a = 20 \text{ kcal mol}^{-1}$),¹⁵ and it has been estimated^{17a}

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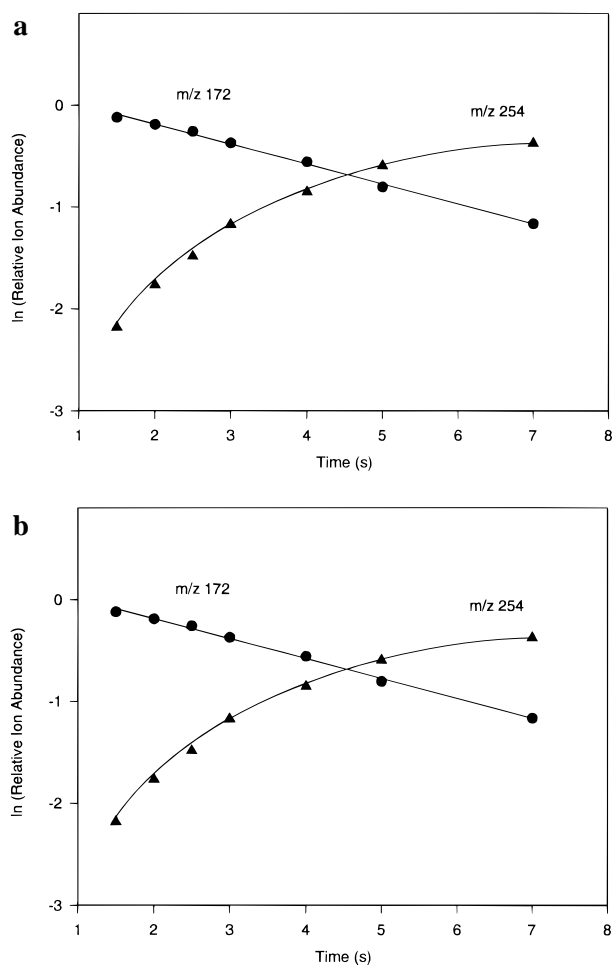


Figure 3. (a) Temporal variation of the ion abundances for the reaction of the *N*-(3,5-dehydrophenyl)-3-fluoropyridinium ion (m/z 172; see Figure 2a) with 2,3-dimethoxy-1,3-butadiene (MW 114; 1.2×10^{-7} Torr). The only reaction observed is elimination of methanol from the adduct to yield an ion of m/z 254. (b) Temporal variation of the ion abundances for the reaction of the *N*-(3,4-dehydrophenyl)-3-fluoropyridinium ion (m/z 172) with *tert*-butyl isocyanide (MW 83; 1.2×10^{-7} Torr). HCN abstraction produces the primary product ion of m/z 199.

computationally to be even more favorable (more exothermic; smaller E_a) for the protonated pyridine analogue (the 2,5-dehydropyridinium ion).

Issues Concerning Singlet/Triplet Gaps of Biradicals. The singlet–triplet gap (or energy difference between the lowest-energy singlet and triplet states, $\Delta E_{S/T}$) of a singlet biradical is thought to affect its ability to undergo radical reactions due to the requirement for partial uncoupling of the biradical electrons in the transition state.¹⁷ Hence, a larger singlet–triplet gap, i.e., a more negative value of $\Delta E_{S/T}$, is expected to lead to a greater barrier and a slower reaction.

The singlet–triplet gaps of the prototypical *o*-, *m*-, and *p*-benzynes have been measured to be 37.5, 21.0, and 3.8 kcal mol⁻¹, respectively.^{3c} Recent computational studies illustrate the dependence of these values on structural changes in the benzynes.¹⁷ Replacement of a CH fragment in the ring by N at a position that is not adjacent to the biradical centers was found to have only a small effect on $\Delta E_{S/T}$ (a change of 4–6 kcal mol⁻¹ is due to unequal mixing of the N lone pair with the bonding and antibonding orbitals of the dehydro centers).¹⁷ A larger effect was predicted for the 2,5-dehydropyridine with N adjacent to one of the biradical centers. At this position, N stabilizes zwitterionic resonance structures and hence lowers

Table 1. Reactions of the *N*-(3,4-Dehydrophenyl)-3-fluoropyridinium Ion

| neutral reagent | reaction observed ^a | branching ratio (%) | reaction efficiency ($k_{\text{exp}}/k_{\text{coll}}$) |
|----------------------------------|--|---------------------|--|
| benzeneselenol | addition | 100 | 0.34 |
| thiophenol | addition | 100 | <i>b</i> |
| tetrahydrofuran | no reaction | | <i>c</i> |
| dimethyl diselenide | addition | 71 | 0.29 |
| dimethyl disulfide | HSeCH ₃ abstraction | 29 | |
| allyl iodide | HSCH ₃ abstraction | 100 | 0.26 |
| <i>tert</i> -butyl isocyanide | no reaction | | <i>c</i> |
| <i>tert</i> -butyl isocyanide | HCN abstraction | 100 | 0.65 |
| benzyl isocyanide | addition | 100 | <i>b</i> |
| di- <i>tert</i> -butyl nitroxide | [addition – C ₄ H ₈ – •CH ₃] | 100 | 0.53 |
| 2,3-dimethoxy-1,3-butadiene | [addition – CH ₂ O] | 71 | 0.45 |
| | [addition – •CH ₃] | 17 | |
| | [addition – C ₂ H ₄ O] | 12 | |
| ethyl 1-propenyl ether | addition | 100 | <i>b</i> |
| furan | addition | 92 | 0.13 |
| | [addition – C ₂ H ₂] | 8 | |
| 2-pyrone | addition | 100 | <i>b</i> |
| benzene | no reaction | | <i>c</i> |
| triethylamine | addition | 42 | 0.47 |
| | [addition – C ₂ H ₄] | 6 | |
| | [addition – 3-fluoropyridine] | 23 | |
| | C ₂ H ₆ abstraction | 15 | |
| | •C ₂ H ₅ abstraction | 8 | |
| | H ₂ abstraction | 6 | |

^a There are no major secondary reactions. ^b Reaction efficiency not measured. ^c A reaction with an efficiency less than 0.001 is too slow to be observed under these conditions.

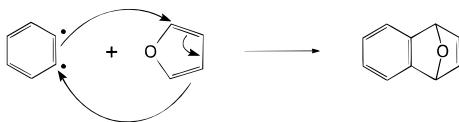
the energy of the singlet relative to that of the triplet state (the value of $\Delta E_{S/T}$ was estimated to be 12 kcal mol⁻¹ more negative than that for *p*-benzyne).^{17b} However, protonation of N was calculated to remove most of the interaction of the N lone pair with the biradical centers.^{17a,c} The $\Delta E_{S/T}$ values of the protonated forms of the dehydropyridines were estimated to be approximately the same as those of the corresponding prototypical (unsubstituted) benzynes.^{17a,c} For example, the 3,5-dehydropyridinium ion was calculated^{17c} to have $\Delta E_{S/T}$ equal to that of the prototypical *m*-benzyne (21 kcal mol⁻¹).

The computational studies¹⁷ discussed above indicate that introduction of a charge directly into the benzyne π -system in the form of a protonated N has little or no effect on the value of $\Delta E_{S/T}$. We conclude that the values of $\Delta E_{S/T}$ for the pyridinium-substituted *o*- and *m*-benzynes discussed here (bi-phenyl-type nonplanar, isolated π -systems) are unlikely to differ from those of the corresponding prototypical benzynes. Hence, the species studied are ground-state singlets with $\Delta E_{S/T}$ values of about –38 and –21 kcal mol⁻¹, respectively. Due to the large singlet–triplet gaps, neither benzyne is expected to readily undergo radical reactions. However, radical reactions of the *m*-benzyne are likely to be associated with lower (although still significant) barriers than those of the isomeric *o*-benzyne.

Reactivity of the *o*-Benzyne Derivative. In general, the charged gaseous *o*-benzyne derivative exhibits reactivity patterns (Table 1) that are analogous to those reported for the prototypical *o*-benzyne in solution (Table 2).² Neither one of these biradicals undergoes radical reactions. Most of the reactions are dominated by formation of a stable addition product. For example, both biradicals readily form a stable adduct with furan (Scheme 3) and thiophenol (Tables 1 and 2). Further, both eliminate ethylene from the adduct formed with triethylamine (Tables 1 and 2; a

Table 2. Solution Reactions of the Neutral *o*-Benzyne Reported in the Literature

| neutral reagent | reaction observed | ref |
|-------------------|---|------------|
| thiophenol | addition | 2a |
| ethyl vinyl ether | addition | 2b |
| furan | addition | 2a, 2c |
| 2-pyrone | [addition - CO ₂] | 2a, 2c |
| benzene | addition | 2a, 2c, 2d |
| triethylamine | [addition - C ₂ H ₄] | 2a, 2c |

Scheme 3

substantial amount of a stable adduct was also observed for the charged *o*-benzyne derivative). Predominant addition reactions have been reported earlier also for the gaseous *o*-benzyne coordinated to metal ions.¹⁸

In some instances, however, the charged *o*-benzyne derivative seemed to be less reactive than the neutral *o*-benzyne. For example, the neutral *o*-benzyne undergoes Diels–Alder addition to benzene in solution (Table 2), while the charged *o*-benzyne is unreactive toward benzene (Table 1). Further, addition followed by elimination of CO₂ was observed upon reaction of the neutral *o*-benzyne with 2-pyrone in solution (Table 2), but the gaseous *o*-benzyne simply adds to this reagent (Table 1). These differences in reactivity between the two *o*-benzynes can be rationalized by considering the different environments wherein they were examined, i.e., solution vs dilute gas phase. First, addition products are not commonly observed in dilute gas phase due to their fast back-dissociation. Further, the formation of the final cycloaddition products from the prototypical *o*-benzyne in solution is likely to be associated with relatively high barriers in many instances (e.g., see the reaction in Scheme 3). A reacting system studied at low pressures (as in this study) cannot overcome barriers that exceed the energy level of the separated reactants (due to the absence of a heat source, solvent). Hence, any barrier over 15–20 kcal mol⁻¹ (typical “solvation” energy available for the gas-phase collision complex) prevents the reaction of the gaseous *o*-benzyne.

The inability of the charged *o*-benzyne derivative to undergo radical reactions was further probed by allowing it to react with benzeneselenol, thiophenol, dimethyl disulfide, dimethyl diselenide, *tert*-butyl isocyanide, allyl iodide, and di-*tert*-butyl nitroxide. Each of these reagents has been demonstrated to react efficiently with charged phenyl radicals in the gas phase.^{6,13,14,19,20} However, the charged *o*-benzyne does not react with these reagents via radical pathways; in each case, either electrophilic addition or no reaction was observed (Table 1). These findings reflect the substantial singlet–triplet gap of the *o*-benzyne ($\Delta E_{ST} \sim -38$ kcal mol⁻¹).

Reactivity of the *m*-Benzyne Derivative. The charged *m*-benzyne derivative reacts very differently from its *o*-benzyne isomer. In addition to addition reactions, the *m*-benzyne undergoes radical reactions typical for analogous phenyl radicals (Tables 1, 3, and 4). However, both types of reactions occur

Table 3. Reactions of the *N*-(3-Dehydrophenyl)-3-fluoropyridinium Ion

| neutral reagent | reaction observed ^a | branching ratio (%) | reaction efficiency ($k_{\text{exp}}/k_{\text{coll}}$) |
|----------------------------------|--|---------------------|--|
| benzeneselenol | H• abstraction | 100 | 0.15 |
| thiophenol | H• abstraction | 83 | 0.03 |
| | addition | 17 | |
| tetrahydrofuran | H• abstraction | 100 | 0.008 |
| dimethyl diselenide | •SeCH ₃ abstraction | 100 | 0.25 |
| dimethyl disulfide | •SCH ₃ abstraction | 100 | 0.05 |
| allyl iodide | I• abstraction | 90 | 0.19 |
| | •C ₃ H ₅ abstraction | 10 | |
| <i>tert</i> -butyl isocyanide | •CN abstraction | 100 | 0.20 |
| benzyl isocyanide | •CN abstraction | 100 | <i>b</i> |
| di- <i>tert</i> -butyl nitroxide | H• abstraction | 2 | 0.38 |
| | O• abstraction | 72 | |
| | OH abstraction (2°) | | |
| | [addition - C ₄ H ₈ - •CH ₃] | 4 | |
| | [addition - •C ₄ H ₉] | 3 | |
| | [addition - C ₄ H ₈] | 19 | |
| 2,3-dimethoxy-1,3-butadiene | [addition - •CH ₃] | 100 | 0.32 |
| benzene | [addition - H• addition] | 25 75 | 0.007 |

^a There are no major secondary reactions unless so indicated (2°).

^b Reaction efficiency not measured.

Table 4. Reactions of the *N*-(3,5-Dehydrophenyl)-3-fluoropyridinium Ion

| neutral reagent | reaction observed ^a | branching ratio (%) | reaction efficiency ($k_{\text{exp}}/k_{\text{coll}}$) |
|----------------------------------|--|---------------------|--|
| benzeneselenol | addition | 37 | 0.01 |
| | H• abstraction | 63 | |
| | 2 × H• abstraction (2°) | | |
| thiophenol | no reaction | | <i>b</i> |
| tetrahydrofuran | no reaction | | <i>b</i> |
| dimethyl diselenide | addition | 100 | 0.01 |
| dimethyl disulfide | no reaction | | <i>b</i> |
| allyl iodide | no reaction | | <i>b</i> |
| <i>tert</i> -butyl isocyanide | HCN abstraction | 51 | 0.11 |
| | •CN abstraction | 33 | |
| | addition | 2 | |
| | [addition - 3-fluoropyridine] | 14 | |
| | 2 × •CN abstraction (2°) | | |
| benzyl isocyanide | addition | 52 | <i>c</i> |
| | •CN abstraction | 48 | |
| | 2 × •CN abstraction (2°) | | |
| di- <i>tert</i> -butyl nitroxide | [addition - C ₄ H ₈ - •CH ₃] | 11 | 0.13 |
| | addition | 37 | |
| | O• abstraction | 52 | |
| 2,3-dimethoxy-1,3-butadiene | [addition - CH ₃ OH] | 100 | 0.15 |
| ethyl 1-propenyl ether | no reaction | | <i>b</i> |
| furan | no reaction | | <i>b</i> |
| 2-pyrone | no reaction | | <i>b</i> |
| benzene | no reaction | | <i>b</i> |
| triethylamine | [addition - 3-fluoropyridine] | 100 | 0.10 |

^a Only the predominant secondary reactions are shown. ^b A reaction with an efficiency less than 0.001 is too slow to be observed under these conditions. ^c Reaction efficiency not measured.

much more slowly than the reactions of the phenyl radical and the isomeric *o*-benzyne. For example, the *m*-benzyne abstracts two hydrogen atoms and adds to benzeneselenol (6:4 ratio) at an efficiency of 0.01 (1% of collisions lead to a reaction; Table 4), while the monoradical abstracts a hydrogen atom an order of magnitude faster (efficiency = 0.15; Table 3), and the *o*-benzyne adds to benzeneselenol at an even faster rate (efficiency = 0.34; Table 1). Further, reaction of the *m*-benzyne

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derivative with *tert*-butyl isocyanide occurs via HCN and CN abstraction at an efficiency of 0.11 (Table 4), while the charged *o*-benzyne abstracts HCN and the monoradical $\cdot\text{CN}$ at much greater efficiencies (0.65 and 0.20, respectively; Tables 1 and 3).

The relatively "tame" nature of the charged *m*-benzyne derivative is further demonstrated by its reaction with nitroxides. Stable nitroxide radicals, such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), are widely used to trap reactive free radicals via addition reactions^{21a-d} that are sometimes followed by N–O bond homolysis (reported^{21e} recently for the 1,4-dehydronaphthalene biradical). The charged *m*-benzyne derivative reacts with di-*tert*-butyl nitroxide by addition as well as oxygen atom abstraction, but at a low efficiency (0.13; Table 4). In contrast, the analogous monoradical abstracts an oxygen atom from this reagent at a significantly greater efficiency (0.38; Table 3) and the charged *o*-benzyne derivative reacts via rapid addition followed by elimination of 2-methylpropene and a methyl radical (efficiency = 0.53; Table 1).

Some of the results described above mirror those obtained by Chen and co-workers¹⁶ and by Roth and co-workers.²² The work carried out by these two groups demonstrates that the rates of some radical reactions of *p*-benzyne derivatives in solution, specifically, hydrogen atom abstraction from various substrates by the 1,4-didehydronaphthalene and 9,10-dehydroanthracene biradicals, are significantly lower than those of the analogous monoradicals. Hence, radical reactions of singlet biradicals of the *p*-benzyne type are hindered by more substantial barriers than those associated with the reactions of the related monoradicals. Even greater barriers are expected for *m*-benzyne derivatives since the smaller distance between the radical sites in these species results in stronger coupling of the formally unpaired electrons. The large singlet–triplet gap leads not only to a greater barrier to radical reactions but also to a lesser thermodynamic driving force. For example, hydrogen atom abstraction from thiophenol by the prototypical (unsubstituted) phenyl radical is exothermic by 31 kcal mol⁻¹,^{3e,23,24} while the same reaction for the prototypical *m*-benzyne is exothermic by only 15 kcal mol⁻¹ (the complete lack of radical reactions for the *o*-benzyne also partially arises from unfavorable thermo-

chemistry: hydrogen atom abstraction from thiophenol by the prototypical *o*-benzyne is endothermic by 0.5 kcal mol⁻¹).^{3e,22,23}

The rate differences observed for the addition reactions of the isomeric *o*- and *m*-benzyne derivatives are also best rationalized by the relative location of the biradical centers, but for a different reason. The substantial π -bonding between the adjacent dehydro centers in *o*-benzynes leads to facile alkyne-type addition reactions² (see Scheme 3 for example). Analogous reactions for *m*-benzynes are not feasible as they would lead to highly strained products.

Finally, it should be noted that the different location of the charged substituent in the isomeric *o*- and *m*-benzyne derivatives is not likely to contribute to their reactivity differences. This is indicated by previous studies¹⁴ on isomeric charged phenyl monoradicals as well as the preceding discussion on the influence of charged groups on the singlet/triplet gaps of biradicals.

Conclusions

An investigation of the chemical properties of a *m*-benzyne derivative in the gas phase has revealed distinct reactivity characteristics that differ from those of the related monoradical and the isomeric *o*-benzyne. The *m*-benzyne undergoes radical reactions and also addition reactions that are characteristic of *o*-benzynes. Despite multiple reaction pathways, the *m*-benzyne is much less reactive than either the isomeric *o*-benzyne or the related monoradical. The reduced radical-type reactivity is rationalized by the strong coupling of the formally unpaired electrons in the *m*-benzyne, which results in a reduced thermodynamic driving force and increased barrier for radical reactions. On the other hand, the greater distance between the reactive centers in the *m*-benzyne hinders alkyne-type addition reactions characteristic of the *o*-benzyne. The influence of various structural features on the reactions of *m*-benzyne is currently under investigation.

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