

Synthesis and Characterization of Aromatic Biradicals in the Gas Phase: A *meta*-Benzyne with an Inert Positively Charged Substituent and Its *ortho*- and *para*-Isomers

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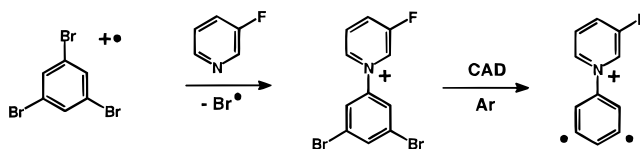
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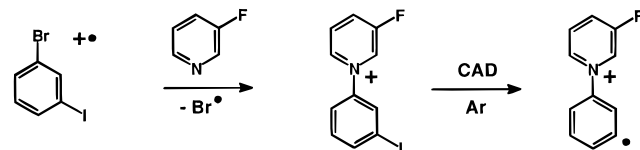
Aromatic biradicals have been the subject of renewed interest since the discovery of their key role in the action of the powerful enediyne antitumor antibiotics.¹ Obviously, knowledge concerning the factors that control the reactivity of these species toward different substrates would be invaluable in the modification and design of DNA-cleaving drugs. However, the high reactivity of organic biradicals makes experimental studies of many of these species difficult. Squires and Hu recently reported the generation of three gaseous negatively charged *meta*-benzynes, the 3,5-dehydrophenyl anion, the 3,5-dehydrobenzoate, and the 3,5-dehydrothiophenolate biradical anion.² The complete lack of radical-type reactivity of these *distonic biradical anions*² was taken as evidence for singlet ground states. We describe herein a general experimental approach for the study of gaseous aromatic biradicals based on mass spectrometric manipulation^{3,4} of the biradicals via a *chemically inert positively charged substituent*. This approach was used to form and isolate (purify) a *meta*-benzyne biradical (a *distonic biradical cation*), to demonstrate that this species is distinct from its *ortho*- and *para*-isomers, and to examine its reactivity toward different neutral reagents in the gas phase.

All experiments described here were carried out using a dual-cell Fourier-transform ion cyclotron resonance mass spectrometer (Extrel Model 2001 FT/MS).^{3–7} The precursor of the *meta*-benzyne, 1,3,5-tribromobenzene, was ionized by electron impact in one side of the dual-cell reaction chamber. *ipso*-Substitution⁸ of a bromine atom in the radical cation of 1,3,5-tribromobenzene with 3-fluoropyridine yields the *N*-(3,5-dibromophenyl)-3-fluoropyridinium ion (Scheme 1). 3-Fluoropyridine was used instead of pyridine to avoid generation of a product ion with the same mass value as that of the reactant ion (pyridine and ⁷⁹Br have the same nominal mass). After transfer into the other side of the dual cell, the *N*-(3,5-dibromophenyl)-3-fluoropyridinium ion was subjected to sustained off-resonance irradiated collision-activated dissociation⁹ (SORI-CAD) using an argon target or to photodissociation (at 266 nm by using a Nd-YAG laser) to induce homolytic cleavage of both remaining carbon–bromine bonds, thus producing the *N*-(3,5-dehydrophenyl)-3-fluoropyridinium biradical ion (a *meta*-benzyne biradical; Scheme 1). Earlier studies have revealed that isomeric *ortho*-, *meta*-, and *para*-monoradicals generated by using this approach are stable toward isomerization, and that the pyridinium charge

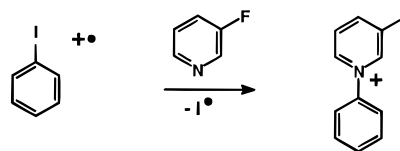
Scheme 1



Scheme 2



Scheme 3



site is chemically inert and merely serves as a handle for mass spectrometric manipulation.^{3–5}

The *meta*-benzyne biradical was isolated by ejecting unwanted ions from the cell and reacted with various neutral reagents for variable periods of time. The second-order reaction rate constants (k_{reaction}) were determined and the reaction efficiencies ($k_{\text{reaction}}/k_{\text{collision}}$) derived as described previously for monoradicals.^{4,5} The observed reactivity was compared to that of the analogous monoradical, the *N*-(3-dehydrophenyl)-3-fluoropyridinium ion, the even-electron *N*-phenyl-3-fluoropyridinium ion, and the isomeric *ortho*- and *para*-benzyne biradicals, *N*-(3,4-dehydrophenyl)- and *N*-(2,5-dehydrophenyl)-3-fluoropyridinium biradical ions. These four ions were generated from 1-bromo-3-iodobenzene (Scheme 2), iodobenzene (Scheme 3), 1-chloro-3,4-diiodobenzene,¹⁰ and 1-chloro-2,5-dibromobenzene, respectively, by using the same general approach employed to generate the *m*-benzyne biradical (replacement of a bromine, iodine, or chlorine atom followed by cleavage of iodine or bromine atoms). Interaction of the (di)halobenzene radical cations with 3-fluoropyridine leads to competitive substitution of each halogen atom. The desired precursor ion (containing either bromine or iodine atoms) was selected from the product mixture for further reactions.

The *meta*-benzyne biradical ion yields distinctly different products from those reported earlier for other gaseous even- and odd-electron organic cations. For example, the biradical reacts slowly with dimethyl diselenide by forming an ion with the *m/z* value corresponding to an adduct (the reaction efficiency is 1%, *i.e.*, 1% of the collisions lead to a reaction). However, conventional radical cations generally react with this reagent by facile electron transfer.^{11,12} On the other hand, *distonic radical cations* (ionized biradicals, zwitterions, and ylides),¹³ including charged phenyl radicals,^{3–5} typically react with this reagent by $\cdot\text{SeCH}_3$ abstraction. For example, the *N*-(3-dehydrophenyl)-3-fluoropyridinium ion, a monoradical, shows exclusive $\cdot\text{SeCH}_3$ abstraction (the reaction efficiency¹² is 25%). Related even-electron cations, including the *N*-phenyl-3-fluoropyridinium ion, are unreactive toward this reagent.

(10) (a) Friedman, L.; Logullo, F. M. *J. Org. Chem.* **1969**, *34*, 3089. (b) Perry, R. J.; Turner, S. R. *J. Org. Chem.* **1991**, *56*, 6573.

(11) Beasley, B. J.; Smith, R. L.; Kenttämäa, H. I. *J. Mass Spectrom.* **1995**, *30*, 384.

(12) Thoen, K. K.; Beasley, B. J.; Smith, R. L.; Kenttämäa, H. I. *J. Am. Chem. Soc.* **1996**, *118*, 1245.

(13) (a) Yates, B. F.; Bouma, W. J.; Radom, L. *J. Am. Chem. Soc.* **1984**, *106*, 5805. (b) Yates, B. F.; Bouma, W. J.; Radom, L. *Tetrahedron* **1986**, *42*, 6225.

(1) See for example: (a) Nicolaou, K. C.; Dai, W. M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Pratiel, G.; Bernadou, J.; Meunier, B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 746.

(2) Hu, J.; Squires, R. R. *J. Am. Chem. Soc.* **1996**, *118*, 5816.

(3) Smith, R. L.; Kenttämäa, H. I. *J. Am. Chem. Soc.* **1995**, *117*, 1393.

(4) Thoen, K. K.; Smith, R. L.; Nousiainen, J.; Nelson, E. D.; Kenttämäa, H. I. *J. Am. Chem. Soc.* **1996**, *118*, 8669.

(5) Li, R.; Smith, R. L.; Kenttämäa, H. I. *J. Am. Chem. Soc.* **1996**, *118*, 5056.

(6) Stirk, K. M.; Smith, R. L.; Orlowski, J. C.; Kenttämäa, H. I. *Rapid Commun. Mass Spectrom.* **1993**, *7*, 392.

(7) Zeller, L.; Farrell, J., Jr.; Vainiotalo, P.; Kenttämäa, H. I. *J. Am. Chem. Soc.* **1992**, *114*, 1205.

(8) (a) Thölman, D.; Grützmaier, H.-F. *J. Am. Chem. Soc.* **1991**, *113*, 3281. (b) Thölman, D.; Grützmaier, H.-F. *Org. Mass Spectrom.* **1989**, *24*, 439.

(9) Gauthier, J. W.; Trautman, T. R.; Jacobson, D. B. *Anal. Chim. Acta* **1991**, *246*, 211.

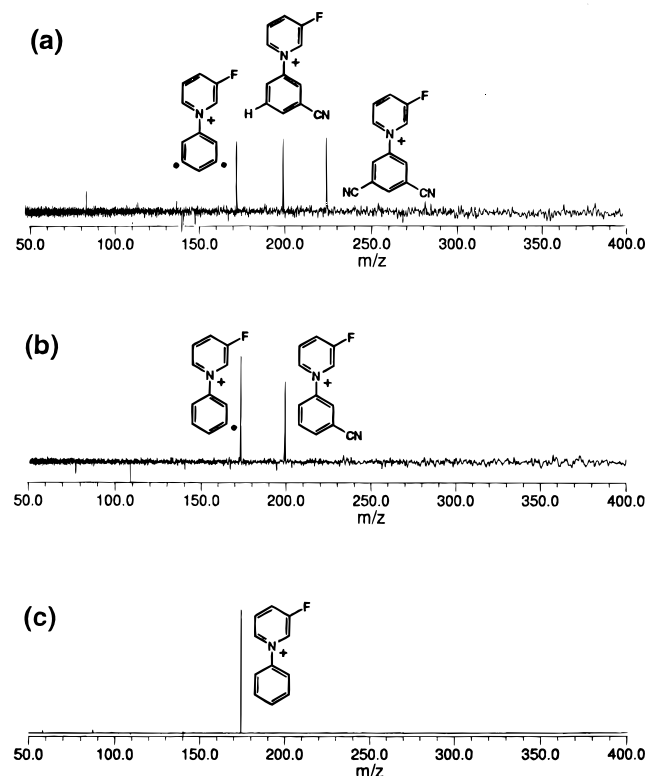


Figure 1. (a) Reaction of the *N*-(3,5-dehydrophenyl)-3-fluoropyridinium biradical ion (m/z 172) for 3 s with *tert*-butyl isocyanide (1.8×10^{-7} Torr). Product ions arising from HCN (m/z 199) and two CN abstractions (m/z 224) are visible. (b) Reaction of the *N*-(3-dehydrophenyl)-3-fluoropyridinium radical ion (m/z 173) for 2 s with *tert*-butyl isocyanide (1.0×10^{-7} torr). A product ion arising from CN abstraction (m/z 199) is formed. (c) The *N*-phenyl-3-fluoropyridinium ion (m/z 174) does not yield observable products after interaction for 10 s with *tert*-butyl isocyanide (0.9×10^{-7} Torr).

Similar results were obtained upon examination of other reactions. For example, the *meta*-benzyne biradical reacts with *tert*-butyl isocyanide to yield the ions arising from HCN abstraction and sequential abstraction of two CN groups (Figure 1a; the reaction efficiency is about 11%). In contrast, the analogous monoradical reacts by CN abstraction¹⁴ (Figure 1b; the reaction efficiency is 21%) while the even-electron ion is unreactive (Figure 1c). Further, the *meta*-benzyne biradical reacts with 2,3-dimethoxy-1,3-butadiene by addition with subsequent elimination of methanol while the monoradical adds to the diene and loses a methyl radical. The even-electron analogue is unreactive toward this reagent.

In each of the cases discussed above, the reactivity of the *meta*-benzyne biradical is *distinctly different* from that observed for its monoradical and even-electron analogues. In some cases, bifunctional reactivity is observed (*e.g.*, abstraction of two CN groups from *tert*-butyl isocyanide; abstraction of two H-atoms

from benzeneselenol; see discussion below). These reactivity characteristics provide strong evidence in support of the indicated biradical reactant structure. Further support is obtained from the observation of different products for the isomeric *ortho*- and *para*-biradical ions. For example, the *ortho*-isomer reacts with dimethyl diselenide by a facile abstraction of CH_3SeH as well as adduct formation. In sharp contrast, the *meta*-isomer reacts by slow and exclusive adduct formation (the reaction efficiencies of the *meta*- and *ortho*-isomers are 1% and 29%, respectively). Further, the *ortho*-benzyne biradical reacts with *tert*-butyl isocyanide by exclusive HCN abstraction (65% efficiency) while the *meta*-isomer also abstracts CN groups. The *para*-isomer does not yield observable products. Finally, the *ortho*-benzyne biradical reacts with 2,3-dimethoxy-1,3-butadiene by predominant addition accompanied by loss of formaldehyde while the *meta*-isomer eliminates methanol. These findings demonstrate that the *meta*-benzyne biradical ion is stable toward rearrangement to its *ortho*- and/or *para*-isomers.

Allyl iodide and benzeneselenol are efficient spin traps that react with radicals by transfer of an iodine atom and a hydrogen atom, respectively. As expected, these reactions occur readily for the *N*-(3-dehydrophenyl)-3-fluoropyridinium monoradical.^{3–5} In sharp contrast, the *meta*-benzyne biradical is unreactive toward allyl iodide and reacts only very slowly with benzeneselenol (consecutive abstraction of two H-atoms and adduct formation occur at about 1% reaction efficiency). This observation is consistent with the singlet electronic ground state of this species (analogous to the neutral and anionic *meta*-benzynes^{2,15}). Singlet biradicals are generally expected to be poor at hydrogen atom abstraction because of partial loss in the transition state of the singlet stabilization energy due to spin–spin interaction. In support of this expectation, the 9,10-dehydroanthracene biradical used as a model for the *para*-benzyne-type biradicals was recently demonstrated¹⁶ to undergo hydrogen atom abstraction in solution significantly slower (by 2 orders of magnitude) than the phenyl radical. This finding was rationalized by computational studies that indicate a greater barrier for hydrogen atom abstraction by the unsubstituted *para*-benzyne than by the phenyl radical.^{16,17} The extra energetic increment was proposed to correlate with the singlet–triplet splitting of the biradical.^{16,17} The greater singlet–triplet splitting¹⁵ of *m*-benzyne compared to that of *para*-benzyne (17 *vs* 2 kcal mol) is likely to make the former biradical even less reactive in atom abstraction reactions.

In summary, a general approach has been developed for the examination of the intrinsic chemical properties of gaseous aromatic biradicals with a chemically inert positively charged substituent. This approach was used to generate a *meta*-benzyne distonic biradical cation and to examine its chemical properties. The results obtained provide further evidence in support of the expected lower reactivity of *meta*-benzyne singlet biradicals relative to that of phenyl radicals in atom abstraction reactions. This experimental approach is currently being utilized in studies of various xylene and phenyl biradicals and triradicals.

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(14) Li, R.; Hu, J.; Hill, B. T.; Squires, R. R.; Kenttämaa, H. I. Manuscript in preparation.

(15) For example, see: (a) Nicolaides, A.; Borden, T. *J. Am. Chem. Soc.* **1993**, *115*, 11951. (b) Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11958. (c) Wenthold, P. G.; Hu, J.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 6961. (d) Wenthold, P. G.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 6401.

(16) Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896.

(17) Logan, C. F.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 2113.