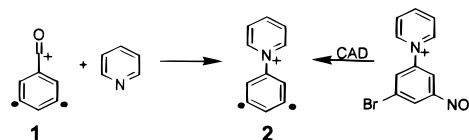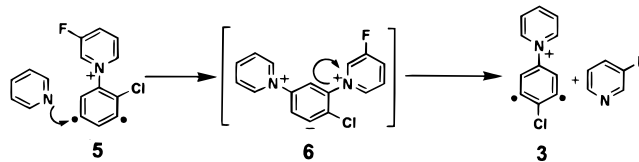# *m*-Benzyne Reacts as an Electrophile

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1,3-Didehydrobenzene, or *m*-benzyne, is the least understood of the three benzynes. To date, very little has been reported about its chemical reactivity.[1] The bulk of what is known has been provided by mass spectrometric studies of *m*-benzynes with chemically inert charged moieties (e.g., 3,5-didehydrobenzoate anion[2] and *N*-(3,5-didehydrophenyl)-3-fluoropyridinium cation[3]). Since such species bear a net charge, they allow the power and versatility of mass spectrometry to be applied to their study. Examinations of such *m*-benzyne derivatives reveal them to be generally less reactive than related phenyl radicals.[2,3] Decreased radical reactivity has also been reported for *p*-benzyne.[4,5] This was attributed to the singlet ground-state multiplicity of the biradical (i.e., the barriers to radical reactions are augmented by the need to "uncouple" the biradical electron pair during reaction).[6] Despite the relatively small singlet−triplet gap of *p*-benzyne (ΔE_{ST} = −3.8 kcal/mol),[7] the energetic penalty for uncoupling the biradical electrons has been reported to slow reactions by one to several orders of magnitude.[4,5] It is likely that *m*-benzyne, whose singlet preference is much stronger (ΔE_{ST} = −21 kcal/mol),[7] will suffer far more extreme inhibition to free radical reactivity. While this appears to be generally true for charged *m*-benzynes, some free-radical-type reactions have been found to occur at rates only slightly less than those of phenyl radical analogs.[3] For example, the *N*-(3,5-didehydrophenyl)-3-fluoropyridinium ion reacts with *tert*-butyl isocyanide by CN abstraction at one-third of the rate measured for the analogous monoradical ion. Such a small rate difference between *m*-benzyne and phenyl radical analogs conflicts with the paradigm[6] of biradical reactivity based on studies of *p*-benzyne. We report here new observations on the reactions of charged *m*-benzynes that demonstrate the ability of the *m*-benzyne moiety to react as an electrophile. This reactivity is shown to be the likely origin of some of the previously reported[3] net-radical reactions. It also provides a context that helps to reconcile previous reports of *m*-benzyne reactivity with current understanding of the effect of the singlet−triplet gap on the reactions of biradicals.

Examination of the gas-phase reactions of several charged *m*-benzynes with various nucleophiles in a Fourier-transform ion cyclotron resonance mass spectrometer revealed facile substitution reactions that are not observed for monoradical counterparts. For example, the 3,5-didehydrobenzoyl cation[8] (**1**) reacts with pyridine by replacement of CO (Scheme 1). The resultant product ion was found to display reactivity identical to that of the *N*-(3,5-didehydrophenyl)pyridinium ion (**2**) generated previously,[3] indicating that the *m*-benzyne moiety is conserved in the substitution process. This unexpected reactivity is indicative of previously

(1) Sander, W. *Acc. Chem. Res.* **1999**, *32*, 669−676.
(2) Hu, J.; Squires, R. R. *J. Am. Chem. Soc.* **1996**, *118*, 5816−5817.
(3) Thoen, K. K.; Kenttämaa, H. I. *J. Am. Chem. Soc.* **1999**, *121*, 800−805.
(4) Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896−4903.
(5) Roth, W. R.; Hopf, H.; Wasser, T. Zimmermann, H.; Werner, C. *Liebigs Ann.* **1996**, 1691−1695.
(6) Logan, C. F.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 2113−2114.
(7) Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 5279−5290.
(8) Ion **1** was generated by collision-activated dissociation (CAD) of the 3,5-dinitrobenzoyl cation produced by 20 eV electron ionization of 3,5-dinitrobenzoyl chloride in an FT-ICR mass spectrometer. Experiments were conducted as described in ref 3.
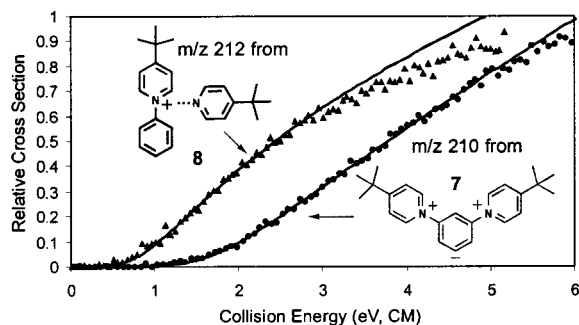
Scheme 1

Scheme 2

undescribed aspects of *m*-benzyne reactivity, and was undertaken as the central theme of this research.

The study of several reacting systems demonstrates that the CO-substitution observed for **1** is quite general. It not only occurs for strong nucleophiles (triethylamine, dimethyl sulfide) but also for weaker ones (ethanol, tetrahydrofuran). Furthermore, the substitution products themselves can undergo substitution by stronger nucleophiles, and a general hierarchy of substitution of a stronger nucleophile for a weaker one exists. For example, 3-fluoropyridine can be replaced by pyridine, which can in turn be replaced by triethylamine. These findings are consistent with the fact that the substitution reaction is effectively the transfer of a Lewis acid (the 3,5-dehydrophenyl cation[9,10]) between two Lewis bases. This reactivity requires the presence of the *m*-benzyne moiety; substitution is not observed for analogous monoradicals or even-electron species (i.e., the 3-dehydrobenzoyl and benzoyl cations).

Although the reactions discussed above appear at first glance to involve *ipso*-substitution, reactions of the *N*-(4-chloro-3,5-didehydrophenyl)pyridinium (**3**) and its *2*-chloro isomer[11] (**4**, not shown) reveal that, in fact, the nucleophilic attack occurs at the *meta*-position. These 2- and 4-chloro isomers can be unambiguously distinguished based on their reaction with *tert*-butyl isocyanide. The 4-chloro-substituted ion **3** yields the *N*-(3-cyano-4,5-didehydrophenyl)pyridinium ion as the major product (Cl is lost in the reaction). This pathway is not observed for the 2-chloro isomer **4** which instead reacts almost exclusively by HCN abstraction. These findings provide a tool for determining the regiochemistry of nucleophilic attack on these species. The *N*-(2-chloro-3,5-didehydrophenyl)-3-fluoropyridinium ion (**5**) was reacted with pyridine to yield a chlorine-substituted *N*-(3,5-didehydrophenyl)pyridinium product ion. This product is expected to be **4** if *ipso*-substitution occurs. However, the product ion does not react like **4** but like its isomer, **3**. It is concluded that the site of the initial nucleophilic attack is not the *ipso*- but the *meta*-position. A proposed mechanism for the reaction is shown in Scheme 2.

The most intriguing facet of the proposed mechanism is the bis(pyridinium)phenide intermediate (**6**). The unsubstituted analog (no chlorine) is predicted (B3LYP/6-31+G(d) + ZPVE) to correspond to a potential energy minimum that resides 31 kcal/mol below the separated reactants, pyridine and *N*-(3,5-didehydrophenyl)pyridinium ion (**2**). The intermediate has C_2 symmetry, a positive charge distributed equally between the two pyridinium moieties, and a strongly localized negative charge at the phenide moiety.

(9) Nelson, E. D.; Kenttämaa, H. I. Submitted for publication.
(10) Schleyer, P. V.; Jiao, H. J.; Glukhovtsev, M. N.; Chandrasekhar, J.; Kraka, E. *J. Am. Chem. Soc.* **1994**, *116*, 10129−10134.
(11) These ions were generated using the method of ref 3.

Figure 1. Relative cross-sections measured for CAD of **7** and **8** as a function of center-of-mass (CM) collision energy. The loss of 4-*tert*-butylpyridine was monitored. The data were collected at various argon pressures and extrapolated to zero target gas pressure. The solid lines are calculated fits of the data (ref 13).

The possibility of a metastable bis(pyridinium)phenide intermediate inspired us to attempt to trap this unusual species to long-term stability. Such a trapping of the intermediate was achieved in the reaction of the *N*-(3,5-didehydrophenyl)-4-*tert*-butylpyridinium ion with 4-*tert*-butylpyridine. This substitution reaction is thermoneutral and the intermediate (**7**) possesses a large number of vibrational modes, which lead to a sufficiently long lifetime for **7** to stabilize by irradiation of IR light. However, this trapping of the intermediate to stability occurs only very slowly over hundreds of collisions, during which many identity substitution reactions presumably take place. Energy-resolved collision-activated dissociation (CAD) experiments carried out in a flowing afterglow−triple quadrupole apparatus[12] using the procedures developed by Armentrout et al.[13] revealed a threshold of 1.38 eV (31.8 kcal/mol) for 4-*tert*-butylpyridine loss from **7**, in good agreement with theory (vide supra).[14] In contrast, a much lower threshold of 0.81 eV was measured for the equivalent loss of 4-*tert*-butylpyridine from the cluster of 4-*tert*-butylpyridine and the *N*-phenyl-4-*tert*-butylpyridinium ion (**8**). This finding suggests that the bonding in **7** is weakly covalent rather than electrostatic in nature.

Ion **7** was also observed to exhibit chemical reactivity consistent with the proposed presence of the phenide moiety. Though possessing a net positive charge, this ion reacts with the electrophiles carbon dioxide and boron trifluoride to form covalently bonded adducts, reactivities also observed for the phenide anion.[15] *Such nucleophilic addition reactivity, while common for negative ions, is extremely unusual for positive ions*, and hence structurally revealing.

(12) Marinelli, P. J.; Paulino, J. A.; Sunderlin, L. S.; Wenthold, P. G.; Poutsma, J. C.; Squires, R. R. *Int. J. Mass Spectrom. Ion Processes* **1994**, *130*, 89−105.

(13) Rodgers, M. T.; Ervin, K. M.; Armentrout, P. B. *J. Chem. Phys.* **1997**, *106*, 4499−4508.

(14) Ion **7** was generated in the flowing afterglow−triple quadrupole apparatus by electron ionization of 3,5-dinitrobenzoyl chloride to form the 3,5-didehydrophenyl cation (see ref 9 for more discussion of this ion and its reactivity). Reaction of this species with 4-*tert*-butylpyridine forms the *N*-(3,5-dehydrophenyl)-4-*tert*-butylpyridinium ion which reacts further to form the bis(4-*tert*-butylpyridinium)phenide cation.

(15) (a) Bierbaum, V. M.; DePuy, C. H.; Shapiro, R. H. *J. Am. Chem. Soc.* **1977**, *99*, 5800−5802. (b) Hill, B. T.; Poutsma, J. C.; Chyall, L. J.; Hu, J.; Squires, R. R. *J. Am. Soc. Mass Spectrom.* **1999**, *10*, 896−906.

Scheme 3
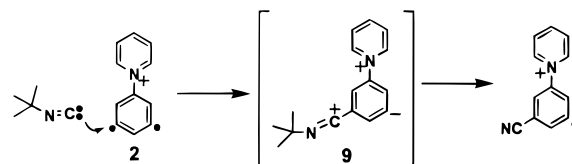
The above finding of facile nucleophilic addition to *m*-benzyne analogs provokes a reexamination of some of the previously reported radical-type reactions. For example, the *N*-(3,5-dehydrophenyl)pyridinium ion (**2**) reacts with *tert*-butyl and benzyl isocyanides by CN abstraction, reactivity qualitatively similar to that of the neutral free radicals[16] and charge-substituted mono-radical cations.[3] However, since the isocyanides are basic species (e.g., the proton affinity of *tert*-butyl isocyanide is 208.1 kcal/mol, between those of pyrrole and ammonia[17]), they would also be expected to add to the *m*-benzyne moiety in a facile manner. Indeed, the analogous *m*-benzyne with a less nucleophilic 3-fluoropyridine charge site reacts with *tert*-butyl isocyanide to produce a small amount of charge site substitution (14%), demonstrating that addition has indeed taken place. When a yet less nucleophilic charge site is present (e.g., tetrahydrofuran, dimethyl sulfide, diethyl ether), substitution is the only reaction observed. These findings suggest that the isocyanides may add also to the *m*-benzyne moiety of **2** (Scheme 3), although the substitution reaction is endothermic in this case. Indeed, addition by *tert*-butyl isocyanide is calculated to be 39 kcal/mol exothermic (B3LYP/6-31+G(d) + ZPVE). Under these circumstances, the addition intermediate (**9**) provides a route to a CN abstraction via a bond cleavage in the isocyanide moiety to form *tert*-butyl radical (Scheme 3). Since the rate-limiting step of this mechanism involves a nucleophilic addition to, rather than a radical abstraction by the *m*-benzyne moiety, the singlet ground state of the reactant ion does not impede the reaction.

The above findings have implications for the reactivity pathways accessible to *m*-benzyne itself. For example, the addition of pyridine to *m*-benzyne is calculated (B3LYP/6-31+G(d) + ZPVE) to be exothermic by 13 kcal/mol and to have only a moderate barrier (8 kcal/mol). Lacking a leaving group, this species cannot undergo substitution reactions. However, such a zwitterionic intermediate can be subject to fragmentation, rearrangement, or further reactions.

(16) Kim, S. S.; Yang, K. W.; Lee, C. S. *J. Org. Chem.* **1996**, *61*, 4827−4829.

(17) Lias, S. G. Ionization Energy Evaluation. In *NIST Chemistry WebBook*; NIST Standard Reference Database Number 69; Mallard, W. G., Linstrom, P. J., Eds.; March 1998; National Institute of Standards and Technology: Gaithersburg MD, 20899 (http://webbook.nist.gov).