

## Experimental and Theoretical Characterization of the 3,5-Didehydrobenzoate Anion: A Negatively Charged *meta*-Benzyne

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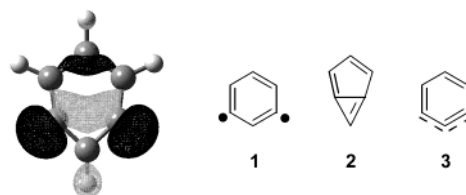
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**Abstract:** A negatively charged analogue of *meta*-benzyne, 3,5-didehydrobenzoate, was synthesized in a Fourier transform ion cyclotron resonance mass spectrometer, and its reactivity was compared to that of the same ion generated previously in a flowing afterglow apparatus and to its positively charged cousin, *N*-(3,5-didehydrophenyl)-3-fluoropyridinium. 3,5-Didehydrobenzoate was found to react as a nucleophile with electrophilic reagents. In contrast, *N*-(3,5-didehydrophenyl)-3-fluoropyridinium does not react with the same electrophilic reagents but reacts instead with nucleophilic reagents. Neither ion is able to abstract hydrogen atoms from typical hydrogen atom donors. The absence of any radical reactivity for these *meta*-benzynes is consistent with predictions that radical reactions of singlet biradicals should be hindered as compared to their monoradical counterparts. High-level calculations predict that the carboxylate moiety does not significantly perturb the singlet–triplet splitting of 3,5-didehydrobenzoate relative to the parent *meta*-benzyne.

### Introduction

*meta*-Benzyne is perhaps the most fundamentally interesting yet least well-understood isomer of the benzyne family, especially regarding its reactivity.<sup>2</sup> The large distance between the radical sites on the aromatic ring in *meta*-benzyne precludes the concerted electrocyclic reactivity observed for *ortho*-benzyne, an important and useful intermediate in synthetic organic chemistry. However, the orientation of the two formally nonbonding orbitals allows the back lobes of the orbitals to overlap (evident in the *meta*-benzyne HOMO, Figure 1). This through-space bonding interaction is substantial and results in *meta*-benzyne having a large preference for a singlet ground state (singlet–triplet splitting of  $-21$  kcal/mol vs  $-38$  kcal/mol for *ortho*-benzyne and  $-4$  kcal/mol for *para*-benzyne, as measured by negative ion photoelectron spectroscopy)<sup>3</sup> and having potentially a bicyclic (**1**, Figure 1) rather than a diradicaloid structure (**2**, Figure 1). Vibrational frequencies obtained from infrared absorption of matrix-isolated *meta*-benzyne<sup>4</sup> and substituted *meta*-benzynes<sup>5,6</sup> and from negative ion photoelec-



**Figure 1.** The highest occupied molecular orbital ( $a_1$  symmetry) of *meta*-benzyne along with three representations of *meta*-benzyne.

tron spectroscopy<sup>3</sup> are consistent with frequencies calculated for the monocyclic structure. On the basis of high-level calculations, Sander and co-workers have concluded that the electronic structure of *meta*-benzyne is best described not by (**1**) or (**2**) but instead by a monocyclic,  $\sigma$ -allylic structure (**3**, Figure 1).<sup>7</sup>

Regardless of whether *meta*-benzyne is formally bicyclic, the large singlet–triplet splitting should hinder radical reactions because a portion of this stabilization energy must be overcome for the biradical electron pair to uncouple during the course of a radical reaction. Experimental and computational work by Chen and co-workers shows that even the small 4 kcal/mol interaction between the biradical electron pair in *para*-benzyne and its analogues severely retards radical reactivity.<sup>8,9</sup> For example, they found that 9,10-didehydroanthracene abstracts

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(1) Johnson & Johnson Pharmaceutical Research & Development, L. L. C., 3210 Merryfield Row, San Diego, CA 92121.

(2) Sander, W. *Acc. Chem. Res.* **1999**, *32*, 669–676.

(3) Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 5279–5290.

(4) Marquardt, R.; Sander, W.; Kraka, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 746–748.

(5) Sander, W.; Exner, M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2285–2290.

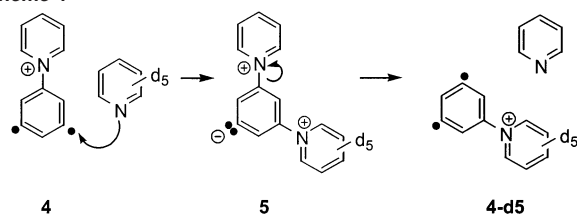
(6) Sander, W.; Bucher, G.; Wandel, H.; Kraka, E.; Cremer, D.; Sheldrick, W. S. *J. Am. Chem. Soc.* **1997**, *119*, 10660–10672.

(7) Winkler, M.; Sander, W. *J. Phys. Chem. A* **2001**, *105*, 10422–10432.

(8) Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896–4903.

(9) Logan, C. F.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 2113–2114.

Scheme 1



hydrogen atoms from alcohols 10–100 times slower than the analogous 9-dehydroanthracene monoradical.<sup>8</sup> Ab initio calculations show that the hydrogen atom abstraction barrier from methanol is 1.5 kcal/mol larger for *para*-benzyl than for the phenyl radical.<sup>9</sup> These observations led to the suggestion that *meta*-benzyl with its larger singlet–triplet splitting should be significantly less reactive than *para*-benzyl and, therefore, a potential substitute for the latter as a more selective warhead in DNA-cleaving antitumor drugs.<sup>10</sup> Despite the therapeutic importance of these biradicals, very little is known about their reactivity because of the difficulties inherent in generating and studying them in condensed phases.

Mass spectrometry is a convenient tool that provides access to highly reactive intermediates in a solvent-free environment. Neutral species can be modeled by attaching a chemically inert charged group to the reactive moiety of interest. This distonic ion approach has been successfully applied to the study of substituent effects on the reactivity of phenyl radicals toward a variety of substrates,<sup>11–14</sup> including biomolecules.<sup>15</sup> Recently, this approach has been utilized to generate charged analogues of *ortho*-, *meta*-,<sup>16</sup> and *para*-benzyl.<sup>17</sup>

Interestingly, the positively charged *meta*-benzyl analogues were often found to undergo net radical reactions at rates similar to those of the corresponding monoradical species – in conflict with Chen’s proposed reactivity paradigm.<sup>18</sup> On the other hand, Squires and co-workers synthesized 3,5-didehydrobenzoate in a flowing afterglow apparatus and demonstrated that this ion is unreactive toward common radical traps (e.g., dimethyl disulfide, allyl iodide, 1,4-cyclohexadiene) that are reactive in the case of some of the positively charged *meta*-benzyl distonic ions.<sup>19</sup> These apparent discrepancies are explained in part in a recent paper where we report that the *meta*-benzyl moiety in the positive ion can react as an electrophile.<sup>20</sup> For example, the *N*-(3,5-didehydrophenyl)pyridinium ion (4, Scheme 1) reacts with perdeuterated pyridine to form a symmetric, dritterionic intermediate (5, Scheme 1) which can fragment via loss of the pyridine to give a distonic *meta*-benzyl with a new charge site. Net radical abstraction products can arise via this nucleo-

philic addition–elimination pathway if the incoming nucleophile can fragment homolytically after addition to the *meta*-benzyl moiety. Such a mechanism circumvents the requirement to uncouple the biradical electron pair and rationalizes the unexpectedly large reaction rates for some of the positively charged *meta*-benzyl analogues.

The 3,5-didehydrobenzoate ion should also react via similar two-electron mechanisms; however, it is likely that the negative charge site perturbs the *meta*-benzyl moiety such that the addition of nucleophilic species (such as dimethyl disulfide and allyl iodide used by Squires and co-workers<sup>19</sup>) is disfavored. In a previous paper, we raised the possibility that 3,5-didehydrobenzoate could react as a nucleophile, possibly reacting with strong electrophiles by charge-site substitution in a manner analogous to the positively charged species.<sup>20</sup> We report here a combined theoretical and FT-ICR experimental examination of the reactivity of 3,5-didehydrobenzoate, a negatively charged analogue of *meta*-benzyl.

## Experimental Section

All of the experiments were performed in an Extrel model FTMS 2001 Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR) equipped with an Odyssey data station and a SWIFT (Stored Waveform Inverse Fourier transform<sup>21</sup>) cell controller. The instrument<sup>22</sup> 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 for positive ions and –2 V for negative ions unless otherwise specified. The normal base pressure in each side of the dual cell (<1 × 10<sup>–9</sup> 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<sup>–7</sup> Torr by using a heated solids probe, a Varian leak valve, a pulsed valve system (consisting of two General Valve Corp. 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<sup>23a</sup> and for the pressure differential between the cell and the ion gauge, as described previously.<sup>23b</sup> The latter correction factor was obtained by measuring the rate of electron transfer to argon cations, a reaction that occurs at collision rate.

All reagents were obtained commercially and used as received. The precursors to the ions (triallyl 1,3,5-benzenetricarboxylate for the negatively charged *meta*-benzyl derivative; 3,5-dinitrobenzoyl chloride and 1,3,5-tribromobenzene for the positively charged *meta*-benzyl derivatives, allyl isophthalate for the negatively charged monoradical, and 1,3-diiodobenzene for the positively charged monoradical) 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 2–3 eV of electron energy for negative ions, 12–20 eV of electron energy for positive ions, 50–80 ms of beam time, and 5–10 μA of emission current). The 3,5-didehydrobenzoate

- (10) Chen, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1478–1480.  
 (11) Heidbrink, J. L.; Ramirez-Arizmendi, L. E.; Thoen, K. K.; Guler, L.; Kenttamaa, H. I. *J. Phys. Chem. A* **2001**, *105*, 7875–7884.  
 (12) Heidbrink, J. L.; Thoen, K. K.; Kenttamaa, H. I. *J. Org. Chem.* **2000**, *65*, 645–651.  
 (13) Tichy, S. E.; Thoen, K. K.; Price, J. M.; Ferra, J. J., Jr.; Petucci, C. J.; Kenttamaa, H. I. *J. Org. Chem.* **2001**, *66*, 2726–2733.  
 (14) Ramirez-Arizmendi, L. E.; Guler, L.; Ferra, J. J.; Thoen, K. K.; Kenttamaa, H. I. *Int. J. Mass Spectrom.* **2001**, *210/211*, 511–520.  
 (15) Petzold, C. J.; Ramirez-Arizmendi, L. E.; Heidbrink, J. L.; Perez, J.; Kenttamaa, H. I. *J. Am. Soc. Mass Spectrom.* **2002**, *13*, 192–194.  
 (16) Thoen, K. K.; Kenttamaa, H. I. *J. Am. Chem. Soc.* **1999**, *121*, 800–805.  
 (17) Amegayibor, F. S.; Nash, J. J.; Lee, A. S.; Thoen, J.; Petzold, C. J.; Kenttamaa, H. I. *J. Am. Chem. Soc.* **2002**, *124*, 12066–12067.  
 (18) Nelson, E. D.; Artau, A.; Price, J. M.; Kenttamaa, H. I. *J. Am. Chem. Soc.* **2000**, *122*, 8781–8782.  
 (19) Hu, J.; Squires, R. R. *J. Am. Chem. Soc.* **1996**, *118*, 5816–5817.  
 (20) Nelson, E. D.; Artau, A.; Price, J. M.; Tichy, S. E.; Jing, L.; Kenttamaa, H. I. *J. Phys. Chem. A* **2001**, *105*, 10155–10168.

- (21) (a) Marshall, A. G.; Wang, T.-C. L.; Ricca, T. L. *J. Am. Chem. Soc.* **1985**, *107*, 7893–7897. (b) Marshall, A. G.; Ricca, T. L.; Wang, T. C.-L. U.S. Patent 4,761,545, 1988.  
 (22) (a) Farrell, J. T., Jr.; Lin, P.; Kenttamaa, H. I. *Anal. Chim. Acta* **1991**, *246*, 227–232. (b) Zeller, L.; Farrell, J. T., Jr.; Vainiotalo, P.; Kenttamaa, H. I. *J. Am. Chem. Soc.* **1992**, *114*, 1205–1214. (c) Kiminkinen, L. K. M.; Stirk, K. G.; Kenttamaa, H. I. *J. Am. Chem. Soc.* **1992**, *114*, 2027–2031.  
 (23) (a) Bartmess, J. E.; Georgiadis, R. M. *Vacuum* **1983**, *33*, 149–153. (b) Stirk, K. M.; Kenttamaa, H. I. *J. Phys. Chem.* **1992**, *96*, 5272–5276.

anion was generated by electron ionization of triallyl 1,3,5-benzenetricarboxylate followed by on-resonance collision-activated dissociation. The *N*-(3,5-didehydrophenyl)pyridinium cation was generated by electron ionization of 3,5-didehydrobenzoyl chloride. Sequential collision-activated dissociations yielded the 3,5-didehydrobenzoyl cation. The 3,5-didehydrobenzoyl cation was allowed to react with pyridine to form the *N*-(3,5-didehydrophenyl)pyridinium cation.<sup>20</sup> 1,3,5-Tribromobenzene was subjected to electron ionization and allowed to react with 3-fluoropyridine to produce the *N*-(3,5-didehydrophenyl)-3-fluoropyridinium ion.<sup>16</sup> Similarly, 1,3-diiodobenzene was subjected to electron ionization and allowed to react with pyridine to form the *N*-(3-didehydrophenyl)pyridinium ion.<sup>24</sup>

The above reactant ions were then transferred from the source cell into the analyzer cell by grounding the conductance limit plate (for 100–150  $\mu$ s). The reactant ions were allowed to cool for about 1 s by emission of infrared light and collisions 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) for positive ions and a positive potential (+2 V) for negative ions to the remote trapping plate of that cell (typically for 10 ms). The radical site(s), excluding that of 3,5-didehydrobenzoate, were generated by sustained off-resonance irradiated collision-activated dissociation<sup>25</sup> (SORI-CAD). The excitation pulse was applied for approximately 1 s at a frequency 0.5–1 kHz higher than the cyclotron frequency of the ions, while argon was pulsed into the cell to reach a nominal peak pressure of about  $1 \times 10^{-5}$  Torr. The ions were cooled by allowing them to undergo IR emission and collide for 0.4–1 s with neutral molecules present in the cell. The desired bi- or monoradical was isolated by using the SWIFT technique<sup>21</sup> and allowed to react with a neutral reagent (at a nominal pressure of  $4.0 \times 10^{-8}$ – $1.2 \times 10^{-7}$  Torr) for a variable period of time (typically 1–20 s). After reaction, the ions were excited for detection by using “chirp” excitation. All of the measured spectra are an average of at least 10 transients and were recorded as 64k data points and subjected to one zero fill prior to Fourier transformation.

Because the reactions studied under the conditions described above follow pseudo-first-order kinetics, their second-order rate constants ( $k_{\text{exp}}$ ) were obtained from a semilogarithmic plot of the relative abundance of the reactant ion as a function of time. The collision rate constants ( $k_{\text{coll}}$ ) were calculated by using a parametrized trajectory theory.<sup>26</sup> The reaction efficiencies are given by  $k_{\text{exp}}/k_{\text{coll}}$ . Primary products were distinguished from secondary products on the basis of their constant relative abundances at short reaction times and, in some cases, isolation of a product ion and examination of its reactivity.

## Theoretical Methods

All didehydrobenzoate geometries were optimized at the density functional (DFT) level of theory with one of three functionals and the augmented, correlation-consistent, polarized, valence-triple- $\zeta$  basis set of Dunning et al. (aug-cc-pVTZ).<sup>27</sup> Two of the functionals were of the “pure”-DFT type; both of these used the gradient-corrected exchange functional of Becke,<sup>28</sup> which was combined with either the gradient-corrected correlation functional of Lee, Yang, and Parr<sup>29</sup> (BLYP) or that of Perdew, Burke, and Wang<sup>30</sup> (BPW91). The third was Becke’s three-parameter exchange-correlation operator which combines exact Hartree–Fock exchange with Slater’s local exchange functional and Becke’s<sup>28</sup> 1988 gradient correction to Slater’s functional and for

correlation employs the gradient-corrected correlation functional of Lee, Yang, and Parr.<sup>29</sup> This combination is denoted B3LYP.<sup>31</sup> Vibrational frequencies and 0 K enthalpy contributions were calculated for all minima at their respective levels of theory and were used unscaled.

Two singlet minima were obtained at the B3LYP level. One was optimized at the restricted level, and the other was optimized at the unrestricted level (i.e., the “wave function” was unstable with respect to spin-symmetry breaking). Broken spin-symmetry BLYP or BPW91 singlet calculations inevitably converged to the restricted minimum during geometry optimization (and the wave functions returned to the restricted solution for that minimum).

Energies at the CASPT2 level<sup>32,33</sup> with the aug-cc-pVTZ basis set were calculated for all DFT geometries. The reference MCSCF wave functions utilized were of the CASSCF<sup>34</sup> variety; 12 electrons were included in the 11-orbital active space constructed from the nine  $\pi$ -orbitals and the two radical orbitals. Some caution must be applied in interpreting the CASPT2 results because this level of theory is known to suffer from a systematic error proportional to the number of unpaired electrons.<sup>35</sup>

Energies for the DFT geometries were also calculated using coupled-cluster theory. Coupled-cluster calculations including single and double excitations and a perturbative estimate for linked triple excitations were carried out for single-configuration reference wave functions expressed in Hartree–Fock orbitals (CCSD(T)<sup>36,37</sup>). Coupled-cluster energies with the aug-cc-pVTZ basis set could not be practically obtained. An improved “hybrid” coupled-cluster energy was arrived at using a composite of CCSD(T) energies with three different basis sets: cc-pVDZ,<sup>27a</sup> aug-cc-pVDZ,<sup>27</sup> and a modified version of cc-pVTZ<sup>27a</sup> in which the d functions on hydrogen and the f functions on heavy atoms were removed. The composite energy was calculated according to

$$E[\text{CCSD(T)/composite}] = E[\text{CCSD(T)/cc-pVDZ}] + \{E[\text{CCSD(T)/aug-cc-pVDZ}] - E[\text{CCSD(T)/cc-pVDZ}]\} + \{E[\text{CCSD(T)/cc-pVTZ}] - E[\text{CCSD(T)/cc-pVDZ}]\} \quad (1)$$

The geometry of the monoradical (3-didehydrobenzoate) was also optimized at the BPW91/cc-pVDZ level for the purpose of calculating <sup>1</sup>H isotropic hyperfine splittings (hfs). The 5-H hfs value was then used to estimate the singlet–triplet (S–T) splitting of 3,5-didehydrobenzoate using a correlation between BPW91/cc-pVDZ calculated hfs values and CASPT2/cc-pVDZ/CASSCF/cc-pVDZ calculated S–T splittings.<sup>38,39</sup> The hfs of the proton attached to C5 was calculated<sup>40</sup> within Gaussian 98 according to

$$a_X = (4\pi/3)\langle S_z \rangle^{-1} g g_X \beta \beta_X \rho(X) \quad (2)$$

where  $g$  is the electronic  $g$  factor,  $\beta$  is the Bohr magneton,  $g_X$  and  $\beta_X$  are the corresponding values for nucleus  $X$ , and  $\rho(X)$  is the Fermi contact integral

- (24) Petzold, C. J.; Nelson, E. D.; Lardin, H. A.; Kenttämää, H. I. *J. Phys. Chem. A* **2002**, *106*, 9767–9775.  
 (25) Gauthier, J. W.; Trautman, T. R.; Jacobson, D. B. *Anal. Chim. Acta* **1991**, *246*, 211–225.  
 (26) Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183–5185.  
 (27) (a) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007–1023. (b) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796–6806.  
 (28) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100.  
 (29) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.  
 (30) Perdew, J. P.; Burke, K.; Wang, Y. *Phys. Rev. B* **1996**, *54*, 16533–16539.

- (31) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.  
 (32) Andersson, K.; Malmqvist, P.-Å.; Roos, B. O.; Sadlej, A. J.; Wolinski, K. *J. Phys. Chem.* **1990**, *94*, 5483–5488.  
 (33) Andersson, K. *Theor. Chim. Acta* **1995**, *91*, 31–46.  
 (34) Roos, B. O.; Taylor, P. R.; Siegbahn, P. E. M. *Chem. Phys.* **1980**, *48*, 157–173.  
 (35) Andersson, K.; Roos, B. O. *Int. J. Quantum Chem.* **1993**, *45*, 591–602.  
 (36) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1982**, *76*, 1910–1918.  
 (37) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479–483.  
 (38) (a) Cramer, C. J.; Squires, R. R. *J. Phys. Chem. A* **1997**, *101*, 9191–9194. (b) Debbert, S. L.; Cramer, C. J. *Int. J. Mass Spectrom.* **2000**, *201*, 1–15; **2000**, *203*, 201.  
 (39) Johnson, W. T. G.; Cramer, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 923–928 and references therein.  
 (40) Lim, M. H.; Worthington, S. E.; Dulles, F. J.; Cramer, C. J. In *Density-Functional Methods in Chemistry*; Laird, B. B., Ross, R. B., Ziegler, T., Eds.; ACS Symposium Series 629; American Chemical Society: Washington, DC, 1996; pp 402–422.

**Table 1.** C3–C5 Distance (Å) for 3,5-Didehydrobenzoate Optimized at Various Levels of Theory

DFT method	triplet	restricted singlet	bss <sup>a</sup> singlet
BLYP	2.357	2.053	
BPW91	2.350	1.991	
B3LYP	2.330	1.930	2.137

<sup>a</sup> Broken spin-symmetry (unrestricted formalism),  $\langle S_z \rangle = 0.42$ .

$$\rho(X) = \sum_{\mu\nu} P_{\mu\nu}^{\alpha-\beta} \phi_{\mu}(\mathbf{R}_X) \phi_{\nu}(\mathbf{R}_X) \quad (3)$$

where  $P^{\alpha-\beta}$  is the BPW91/cc-pVDZ one-electron spin density matrix, and evaluation of the overlap between basis functions  $\phi_{\mu}$  and  $\phi_{\nu}$  is only at the nuclear position,  $\mathbf{R}_X$ .

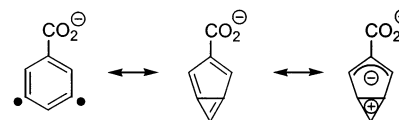
The correlating equation appropriate for *meta*-diradicals is (S–T splitting, kcal/mol) =  $-1.39 \times (\text{H hfs, G}) - 9.48$ .<sup>38,39</sup> To compare to experiment, as opposed to the CASPT2/cc-pVDZ level, a correction of  $-3.0$  kcal/mol was applied to account for the difference between the CASPT2 calculated<sup>38</sup> S–T splitting of *meta*-benzynes ( $-18.0$  kcal/mol) and the experimentally determined<sup>3</sup> value ( $-21.0 \pm 0.3$  kcal/mol).

All calculations were performed with Gaussian 98 (revision A.9)<sup>41</sup> except for the CASPT2 calculations, which were performed with MOLCAS Version 5.<sup>42</sup>

## Results and Discussion

**Computational Characterization of the 3,5-Didehydrobenzoate.** It has been repeatedly shown that the potential energy surfaces of singlet didehydrobenzenes are very flat along the radical–radical separation coordinate when the two dehydro centers are related to one another in a *meta* fashion,<sup>5,6,7,38,39,43,44</sup> and 3,5-didehydrobenzoate is no exception. Thus, as shown in Table 1, the singlet interdehydro distance varies over slightly more than 0.2 Å depending on which DFT functional and formalism is applied. This range is somewhat smaller than that found for *meta*-benzynes itself,<sup>7</sup> possibly because substitution of a carboxylate would be expected to destabilize the diradicalic mesomer that contributes to the singlet valence bond description as the benzyne geometry becomes more bicyclic (Figure 2).<sup>44</sup> The geometry of the triplet state is much less sensitive to the functional, as expected in the absence of any opportunity for  $\sigma$ -bond formation.

To better assess the quality of the different singlet geometries, highly correlated levels of molecular orbital theory were employed, including multireference second-order perturbation

**Figure 2.** Resonance structures contributing to the valence bond description of singlet 3,5-didehydrobenzoate.**Table 2.** Energies (kcal/mol) of Different Singlet 3,5-Didehydrobenzoate Geometries Relative to the UB3LYP Geometry at the CASPT2 and CCSD(T) Levels of Theory

method	geometry			
	B3LYP	BPW91	BLYP	UB3LYP
CASPT2/aug-cc-pVTZ	1.6	1.3	1.0	0.0 <sup>a</sup>
CCSD(T) <sup>b</sup>	1.9	0.4	-0.4	0.0 <sup>c</sup>

<sup>a</sup> Absolute energy ( $E_h$ )  $-418.33952$ . <sup>b</sup> From eq 1. <sup>c</sup> Absolute energy ( $E_h$ )  $-418.17779$ .

theory using a 12-electron/11-orbital complete-active-space reference wave function (CASPT2) and coupled-cluster theory including single, double, and triple excitations estimated perturbatively (CCSD(T)). Single-point energy calculations for the different geometries were compared at these levels of theory (Table 2).

If we assume that the variation in single-point energies is entirely associated with the interdehydro distance, it is apparent that the CASPT2 level favors the longest distance, that is, that from the UB3LYP level, while the CCSD(T) level favors something between the BLYP and UB3LYP distances. As the CASPT2 calculations involve a more complete basis set (including higher angular momentum functions on all atoms), it is likely to be slightly more accurate, but insofar as zero-point vibrational motion along the interdehydro coordinate will be expected to have large amplitude, given the flatness of the surface, the exact location of the potential energy minimum is not of paramount interest in any case. Quite clear, however, is that the restricted B3LYP geometry is of rather poor quality, owing to the tendency for Hartree–Fock exchange, which is included in the functional, to overemphasize bonding interactions between the dehydro positions.<sup>7,43d</sup> This artifactual effect is sufficiently strong in parent *meta*-benzynes that it leads to the erroneous prediction that the molecule is a closed-shell bicyclic system.<sup>7,43d,46</sup>

With respect to the singlet–triplet (S–T) splitting in 3,5-didehydrobenzoate, we do not expect DFT to be particularly accurate on the basis of prior studies of *meta* biradicals.<sup>39,43,44</sup> However, those prior studies have also shown that even though the S–T splittings predicted from the density functional level are poor, the geometries are typically better than those available from, say, multiconfigurational SCF methods. As indicated by the results in Table 3, those same trends hold true here. The DFT methods predict S–T splittings considerably smaller than those from the highly correlated levels of molecular orbital theory. As a separate check on the better reliability of the CASPT2 and CCSD(T) predictions, the correlation established between <sup>1</sup>H hyperfine splittings in aryl radicals and corresponding S–T splittings in didehydroarenes<sup>38,39,44,45</sup> predicts a splitting of  $-18.1$  kcal/mol, in much better agreement with the correlated MO methods as compared to the DFT methods.

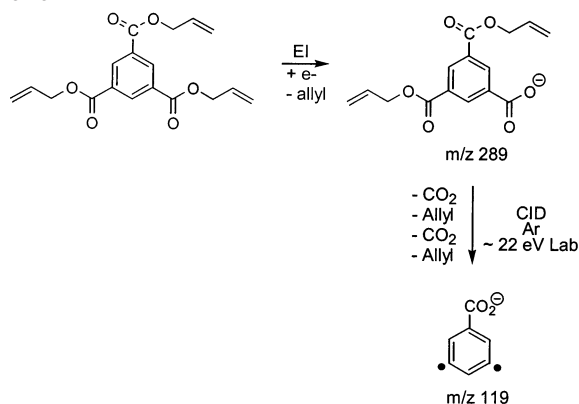
- (41) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.
- (42) Andersson, K.; Barysz, M.; Bernhardsson, A.; Blomberg, M. R. A.; Cooper, D. L.; Fleig, T.; Fülscher, M. P.; de Graaf, C.; Hess, B. A.; Karlström, G.; Lindh, R.; Malmqvist, P.-Å.; Neogrády, P.; Olsen, J.; Roos, B. O.; Sadlej, A. J.; Schütz, M.; Schimmelpennig, B.; Seijo, L.; Serrano-Andrés, L.; Siegbahn, P. E. M.; Ståhring, J.; Thorsteinsson, T.; Velyazov, V.; Widmark, P.-O. Lund University: Sweden, 2000.
- (43) (a) Cramer, C. J.; Nash, J. J.; Squires, R. R. *Chem. Phys. Lett.* **1997**, *277*, 311–320. (b) Kraka, E.; Cremer, D.; Bucher, G.; Wandel, H.; Sander, W. *Chem. Phys. Lett.* **1997**, *268*, 313–320. (c) Cramer, C. J.; Debbert, S. *Chem. Phys. Lett.* **1998**, *287*, 320–326. (d) Kraka, E.; Anglada, J.; Hjerpe, A.; Filatov, M.; Cremer, D. *Chem. Phys. Lett.* **2001**, *348*, 115–125.
- (44) Johnson, W. T. G.; Cramer, C. J. *J. Phys. Org. Chem.* **2001**, *14*, 597–603.

- (45) (a) Squires, R. R.; Cramer, C. J. *J. Phys. Chem. A* **1998**, *102*, 9072–9081. (b) Cramer, C. J.; Thompson, J. J. *J. Phys. Chem. A* **2001**, *105*, 2091–2098.
- (46) (a) Hess, B. A. *Eur. J. Org. Chem.* **2001**, 2185–2189. (b) Hess, B. A. *Chem. Phys. Lett.* **2002**, *352*, 75–78.

**Table 3.** Predicted 3,5-Didehydrobenzoate S–T Splittings ( $H_0$ , kcal/mol)

method <sup>a</sup>	geometry		
	BPW91	BLYP	UB3LYP
BPW91	-12.5		
BLYP		-12.5	
UB3LYP			-9.9
CASPT2	-19.3	-20.0	-20.2
CCSD(T) <sup>b</sup>	-19.6	-20.4	-20.6
hfs <sup>c</sup>	-18.1		

<sup>a</sup> Unless otherwise indicated, the aug-cc-pVTZ basis set was used. Absolute energy ( $E_h$ ) -418.33952. <sup>b</sup> From eq 1. <sup>c</sup> See Theoretical Methods section.

**Scheme 2**

The CASPT2 and CCSD(T) S–T splittings are not particularly sensitive to whether the BLYP or UB3LYP geometry is used. Furthermore, to within the expected error in the theoretical models, the S–T splittings predicted from these levels are identical to that measured for *meta*-benzynes.<sup>3</sup> Thus, theory predicts substitution of a carboxylate moiety at the 1 position in 3,5-didehydrobenzene to have no effect that significantly differentiates between the singlet and triplet states. This observation is in keeping with predictions made in general for 1-substitution effects in 3,5-benzynes.<sup>39,46</sup>

**Generation and Characterization of 3,5-Didehydrobenzoate.** Generation of the *meta*-benzynes anion, 3,5-didehydrobenzoate, was afforded via a two-step ion synthesis within a Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR). The neutral precursor, triallyl 1,3,5-benzenetricarboxylate, was subjected to 2.3 eV dissociative electron ionization to form an ion of  $m/z$  289 (Scheme 2). This product was then subjected to on-resonance collision-activated dissociation (CAD) to form 3,5-didehydrobenzoate ( $m/z$  119). This gas-phase synthesis is similar to that used by Reed and co-workers to generate 3- and 4-didehydrobenzoate ions in an FT-ICR mass spectrometer.<sup>47</sup> All of the reactions of 3,5-didehydrobenzoate were found to obey pseudo-first-order kinetics, which suggests that only one isomer is present in the reactant ion population.

Validation of the structure of the 3,5-didehydrobenzoate anion was accomplished by examining its reactions with a variety of neutral reagents. The 3,5-didehydrobenzoate anion reacts with some substrates by two sequential atom or group abstractions, which indicates that the ion possesses two radical sites. For example, two iodine atoms are abstracted from iodine, and two

bromine atoms are abstracted from carbon tetrabromide. Analogous behavior was reported earlier for the positively charged *N*-(3,5-didehydrophenyl)-3-fluoropyridinium *meta*-benzynes upon reaction with, for example, *tert*-butyl isocyanide where two sequential cyano abstractions are observed.<sup>16</sup>

The corresponding positively and negatively charged monoradicals also undergo the above abstraction reactions, but only one atom/group is abstracted. In addition, these monoradicals react with hydrogen atom donors by hydrogen abstraction<sup>24</sup> and with nitroxides by oxygen abstraction.<sup>48</sup> However, neither 3,5-didehydrobenzoate ion nor *N*-(3,5-didehydrophenyl)-3-fluoropyridinium react with hydrogen atom donors, while 3,5-didehydrobenzoate does not react with di-*tert*-butyl nitroxide. This finding demonstrates that the radical sites in the 3,5-didehydrobenzoate must interact (i.e., the biradical must have a singlet electronic ground state).

In addition, 3,5-didehydrobenzoate reacts with boron trifluoride primarily by addition that is sometimes accompanied by loss of the CO<sub>2</sub> charge site. Subsequent reactions of this product indicate that it retains the *meta*-benzynes moiety (vide infra). This type of charge-site substitution reactivity with retention of the *meta*-benzynes moiety is characteristic of positively charged *meta*-benzynes analogues and suggests that the  $m/z$  119 ion contains an intact carboxylate group and a *meta*-benzynes moiety.<sup>20</sup>

**Reactivity – Radical or Ionic Mechanism?** Just as in the case of positively charged *meta*-benzynes, high level calculations predict that the 3,5-didehydrobenzoate favors a singlet ground state by about 21 kcal/mol. The strong interaction between the odd spins in such singlet biradicals has several important implications on their reactivity. First, for the biradical electron pair to engage in radical reactions, a portion of the singlet stabilization energy must be overcome. The end result is expected to be significantly slower radical reactions due a larger reaction barrier than that for the monoradical. This effect has been demonstrated computationally<sup>9</sup> and experimentally,<sup>8,17,49</sup> for hydrogen abstraction reactions of *para*-benzynes, which has a relatively small singlet–triplet splitting (–3.8 kcal/mol).<sup>3</sup> Second, the overall thermodynamic driving force for a radical abstraction reaction by a biradical is reduced relative to the corresponding monoradical by approximately the amount of bonding interaction between the radical sites.

Despite the evidence that a large singlet–triplet splitting should significantly inhibit radical reactions, positively charged distonic analogues of *meta*-benzynes were found to yield net radical abstraction products at rates approaching those of the corresponding distonic monoradicals.<sup>18,20</sup> A thorough examination of these reactions led to the conclusion that *such radical abstraction products are not the result of a radical mechanism at all*. Instead, the positively charged *meta*-benzynes (and likely *meta*-benzynes itself) can act as electrophiles, producing net radical products via a nucleophilic addition–elimination mechanism (e.g., Scheme 3).

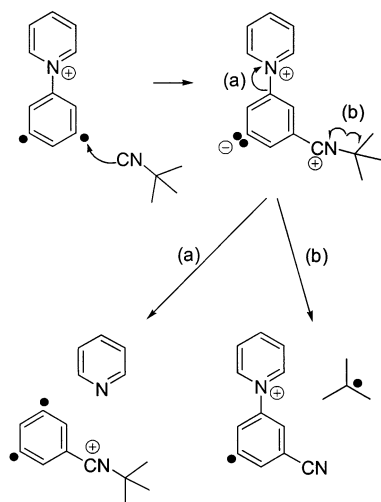
To determine whether 3,5-didehydrobenzoate reacts by an ionic or a radical mechanism, its reactivity was compared with that of the previously examined<sup>24</sup> 3-didehydrobenzoate (Table 4). Just as with the positively charged *meta*-benzynes analogues,

(47) Reed, D. R.; Hare, M.; Kass, S. R. *J. Am. Chem. Soc.* **2000**, *122*, 10689–10696.

(48) Heidbrink, J. L.; Amegayibor, F. S.; Kenttämaa, H. I., submitted.

(49) Roth, W. R.; Hopf, H.; Wasser, T.; Zimmermann, H.; Werner, C. *Liebigs Ann.* **1996**, 1691–1695.

Scheme 3



**Table 4.** Efficiencies<sup>a</sup> and Products<sup>b</sup> of Reactions of *N*-(3,5-Didehydrophenyl)-3-fluoropyridinium, 3,5-Didehydrobenzoate, and 3-Dehydrobenzoate with Electrophilic Reagents

I <sub>2</sub>	I abs 1.0 (2°) I abs Eff = 1.4%	I abs 0.45 (2°) I abs iodide Eff = 87%	I abs 1.0 Eff = 100%
CBr <sub>4</sub>	No Reaction	Br abs 1.00 (2°) Br abs Eff = 25%	Br abs 1.0 Eff = 28%
CBrCl <sub>3</sub>	No Reaction	Br abs 1.00 (2°) Br abs Eff = 6%	Br abs 1.0 Eff = 21%
CHBr <sub>3</sub>	No Reaction	Br abs 1.0 (2°) Br abs Eff = <sup>c</sup>	Br abs 0.76 H abs 0.24 Eff = 16%
CCl <sub>4</sub>	No Reaction	No Reaction	No Reaction
BF <sub>3</sub>	No Reaction	Adduct - CO <sub>2</sub> 0.60 (2°) F <sup>-</sup> transfer Adduct 0.40 Eff = 70%	No Reaction

<sup>a</sup> Reaction efficiencies reported as  $k_{\text{exp}}/k_{\text{collision}} \times 100\%$  (i.e., the percentage of collisions that lead to a reaction). <sup>b</sup> Product branching ratios are given in parentheses. Secondary products (2°), if any were observed, are given underneath the primary product that produced them. <sup>c</sup> Reaction efficiency was too low to be measured accurately.

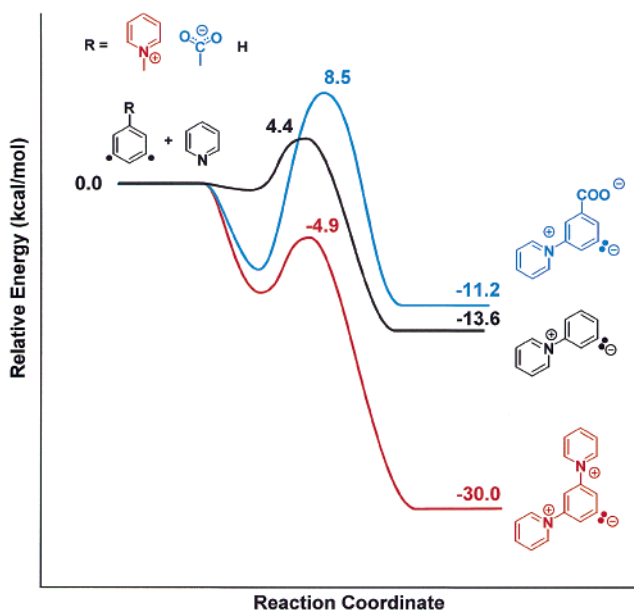
the 3,5-didehydrobenzoate often reacts by net radical abstractions at rates similar to those of its corresponding monoradical. For example, 3,5-didehydrobenzoate and 3-dehydrobenzoate abstract a bromine atom from carbon tetrabromide at nearly identical rates (see Table 4). Similar results were obtained with iodine (iodine atom abstraction) and bromotrichloromethane (bromine atom abstraction). In addition, 3,5-didehydrobenzoate does not react with hydrogen atom donors by hydrogen atom abstraction or with di-*tert*-butyl nitroxide by radical–radical recombination. These data are consistent with a nonradical mechanism.

**Reaction with Nucleophiles.** To determine whether the *meta*-benzyne moiety in 3,5-didehydrobenzoate can react as an electrophile, the distonic ion was allowed to react with a variety of nucleophilic reagents (Table 5). In all cases, no reaction was observed. This is consistent with the work of Squires and co-workers who found that 3,5-didehydrobenzoate did not react with dimethyl disulfide, allyl iodide, or 1,4-cyclohexadiene in their flowing afterglow apparatus (FA).<sup>19</sup> However, these results

**Table 5.** Efficiencies<sup>a</sup> and Products<sup>b</sup> of Reactions of *N*-(3,5-Didehydrophenyl)-3-fluoropyridinium and 3,5-Didehydrobenzoate with Nucleophilic Reagents

pyridine	No reaction	No reaction	substitution 1.0 Eff. = 2.0%
<i>t</i> -butyl isocyanide	No reaction	No reaction	HCN abs 0.53 (2°) adduct CN abs 0.40 (2°) CN abs substitution 0.07 Eff. = 11%
dimethyl disulfide	No reaction	No reaction	SCH <sub>3</sub> abs 1.0 (2°) SCH <sub>3</sub> abs Eff. = 0.05%
1,4-cyclohexadiene	No reaction	No reaction	No reaction
allyl iodide	No reaction	No reaction	No reaction

<sup>a</sup> Reaction efficiencies reported as  $k_{\text{exp}}/k_{\text{collision}} \times 100\%$  (i.e., the percentage of collisions that lead to a reaction). <sup>b</sup> Product branching ratios are given in parentheses. Secondary products (2°), if any were observed, are given underneath the primary product that produced them.

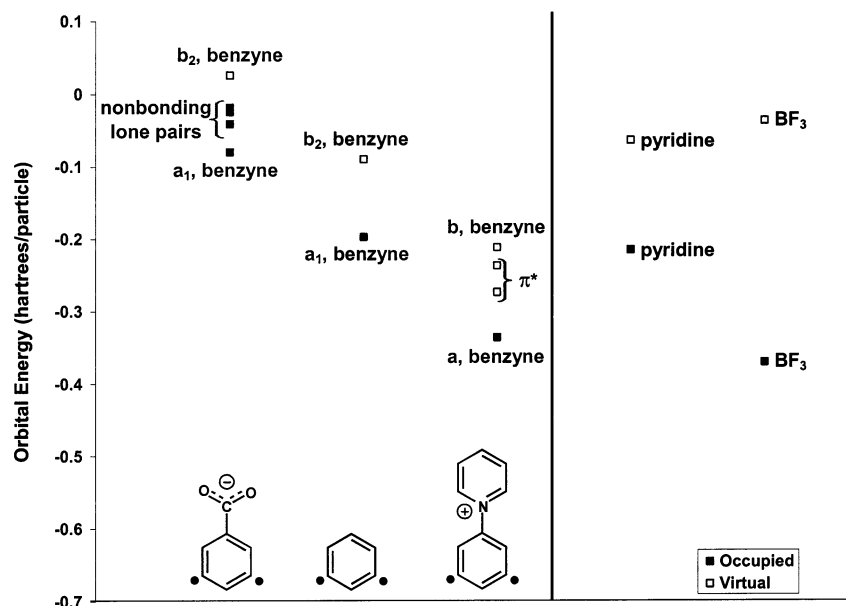


**Figure 3.** BLYP/6-31+G(d) calculated potential energy surfaces for the addition of pyridine to 3,5-didehydrobenzoate, *meta*-benzyne, and *N*-(3,5-didehydrophenyl)pyridinium.

are in sharp contrast with previous studies on *N*-(3,5-didehydrophenyl)-3-fluoropyridinium, a positively charged *meta*-benzyne analogue, which does react with some nucleophilic reagents (Table 5).

The proposed mechanism for the reactions of positively charged *meta*-benzyne distonic ions involves addition of a nucleophile to the *meta*-benzyne moiety and fragmentation of the resulting ditterionic intermediate.<sup>18,20</sup> The intermediate can fragment in two ways which are both evident in the reaction of *N*-(3,5-didehydrophenyl)-3-fluoropyridinium with *tert*-butyl isocyanide (Scheme 3). Heterolytic cleavage of the *N*-phenyl pyridinium bond (Scheme 3, path a) results in substitution of the charge site and formation of a new distonic *meta*-benzyne. Homolytic cleavage of a bond in the incoming nucleophile (Scheme 3, path b) leads to a net cyano radical abstraction albeit via a nonradical mechanism.

The calculated potential energy surfaces for nucleophilic addition of pyridine to *N*-(3,5-didehydrophenyl)pyridinium,



**Figure 4.** BLYP/6-31+G(d) calculated orbital energies of the highest occupied and lowest unoccupied orbitals of 3,5-didehydrobenzoate, *meta*-benzyne, *N*-(3,5-didehydrophenyl)pyridinium, pyridine (a good nucleophile), and boron trifluoride (a strong electrophile).

**Table 6.** BLYP/6-31+G(d) Calculated Dipole Moments for *N*-(3,5-Didehydrophenyl)pyridinium, *meta*-Benzyne, and 3,5-Didehydrobenzoate, and Their Respective Pyridine Addition Products and Transition States

	dipole moment (debye)		
	benzyne	addition TS	pyridine adduct
<i>N</i> -(3,5-didehydrophenyl)pyridinium	4.9	9.8	6.1
<i>meta</i> -benzyne	0.9	5.6	7.0
3,5-didehydrobenzoate	7.5	18.1	16.3

*meta*-benzyne, and 3,5-didehydrobenzoate are shown in Figure 3. For all three systems, addition of pyridine to the *meta*-benzyne moiety is exothermic. However, the reaction barrier for addition to 3,5-didehydrobenzoate is  $\sim 14$  kcal/mol, which is almost 3 times larger than the addition barrier for the positively charged analogue or neutral *meta*-benzyne (5.0 and 4.4 kcal/mol, respectively). Calculations show that for the positively charged and neutral *meta*-benzyne, the addition barrier is controlled primarily by the amount of charge separation in the transition state.<sup>20</sup> The degree to which charge is separated in a molecule may be estimated by the molecular dipole moment. The calculated dipole moments for the benzyne as well as for the pyridine addition transition states and intermediates are summarized in Table 6.<sup>50</sup> The positively charged and neutral benzyne have similar activation energies for pyridine addition and coincidentally have similar increases in dipole moment at their transition states (increases of 4.9 and 4.7 D, respectively). In contrast, the 3,5-didehydrobenzoate not only has a large increase in dipole moment at the transition state (increase of 10.6 D) but also a large absolute dipole moment in the transition state and in the addition product. This considerable charge separation renders nucleophilic addition to 3,5-didehydrobenzoate kinetically unfeasible.

Because addition of pyridine to the *meta*-benzyne moiety necessarily involves donation of electron density from the

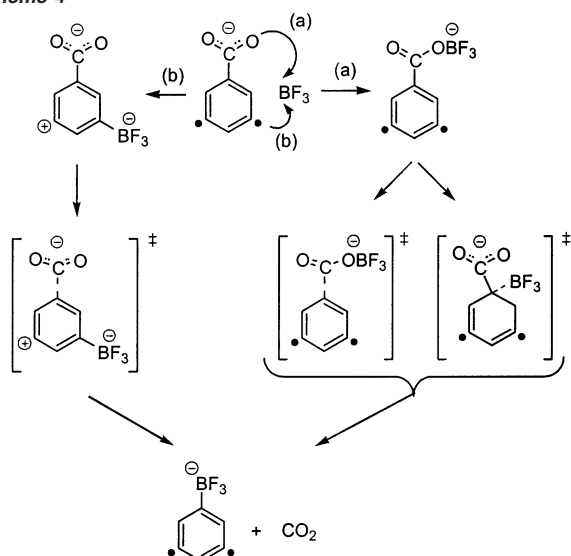
pyridine HOMO (containing the nitrogen lone pair) and the benzyne LUMO (the antisymmetric combination of the non-bonding orbitals containing the radical electrons), the relative energies of these orbitals should also give insight into the reactivity of these distonic *meta*-benzyne. The energies of the relevant orbitals are shown in Figure 4. Addition of a positively charged substituent to *meta*-benzyne lowers the energy of the symmetric (occupied) and antisymmetric (unoccupied) benzyne orbitals. In fact, the antisymmetric “benzyne” orbital of *N*-(3,5-didehydrophenyl)pyridinium is lowered so drastically that its energy is similar to that of the pyridine HOMO. In the case of 3,5-didehydrobenzoate, the carboxylate substituent raises the energy of the LUMO to a such an extent that the energy gap between the benzyne LUMO and pyridine HOMO is large enough to make nucleophilic addition to the benzyne unlikely.

**Reaction with Electrophiles – Boron Trifluoride.** The orbital picture in Figure 4 raises the interesting possibility that the symmetric orbital containing the “biradical” electron pair in 3,5-didehydrobenzoate is raised high enough in energy that it can interact with the LUMO of strongly electrophilic species. Boron trifluoride is a good probe for this type of reactivity because addition of the biradical pair to the empty p-orbital on boron would result in a ditterionic intermediate which could fragment by loss of carbon dioxide to yield a charge-site substitution product (Scheme 4, pathway b). This pathway is analogous to the charge-site substitution mechanism already described for the positively charged *meta*-benzyne analogues. However, both intuition and the calculated highest occupied orbitals of 3,5-didehydrobenzoate (Figure 4) lead one to the conclusion that addition of boron trifluoride to the carboxylate group (Scheme 4, pathway a) to form an “ate” complex should be the thermodynamically preferred pathway.

Reaction between 3,5-didehydrobenzoate and boron trifluoride (Table 4) does indeed produce a charge-site substitution product as well as an addition product (60 and 40% of the product distribution, respectively). The charge-site substitution (CSS) product (3,5-didehydrophenyl)trifluoroborane is still a distonic *meta*-benzyne, and, as such, it should react similarly to the parent

(50) Dipole moments for charged molecules depend on the choice of origin. In this instance, we take as the origin the center of nuclear charge, so the magnitudes of the ionic dipole moments reflect relative electronic polarization in a meaningful way.

Scheme 4

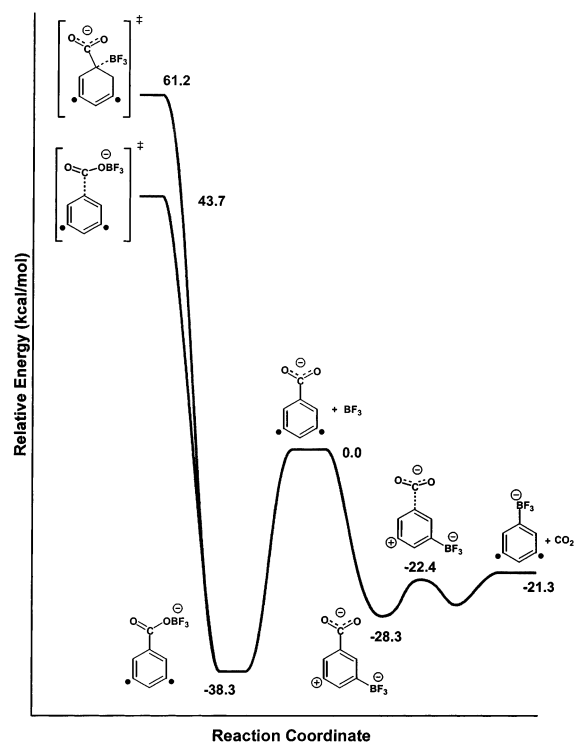


didehydrobenzoate. In fact, the isolated CSS product does react with carbon tetrabromide by the sequential abstraction of two bromine atoms, providing support that the benzyne moiety remains intact.

Experimental evidence also suggests that the (3,5-didehydrophenyl)trifluoroborate is the result of the dritterionic intermediate, despite the fact that the “ate” complex is also certainly formed in the reaction. The *ipso*-substitution mechanism required for the “ate” complex to produce the CSS product (Scheme 4, path a) is unlikely because the simple benzoate ion should be equally suited to react via this mechanism. Instead, only rapid adduct formation was observed in the reaction of benzoate with boron trifluoride. Off-resonance (i.e., low energy) collision-activated dissociation (SORI-CAD) of the benzoate-boron trifluoride adduct produces exclusively the original benzoate ion (via loss of boron trifluoride). In contrast, SORI-CAD of the 3,5-didehydrobenzoate-boron trifluoride adduct produces two fragmentation products – due to loss of boron trifluoride and loss of carbon dioxide in a 3:1 ratio. The former fragmentation product can be rationalized as arising from the “ate” complex; however, the CO<sub>2</sub> loss product can only come easily from either the dritterion or the *ipso*-substitution intermediate.

Density functional theory calculations corroborate the experimental results (Figure 5). Not surprisingly, addition of boron trifluoride to one of the carboxylate oxygens in 3,5-didehydrobenzoate is a barrierless and a significantly exothermic process. More importantly, while boron trifluoride addition to one of the dehydro carbons is about 10 kcal/mol less exothermic than addition to the carboxylate, it is also calculated to proceed without a barrier. Decarboxylation of the dritterion to form the charge-site substitution product occurs with only a moderate energy barrier of about 6 kcal/mol. Both alternate mechanisms for charge-site substitution (direct decarboxylation of the “ate” complex and *ipso*-substitution) are calculated to have significant reaction barriers (>40 kcal/mol higher in energy than the separated reactants) and are therefore not viable pathways.

Theory also predicts that the dritterionic intermediate should possess some degree of phenyl cation character just as the Lewis structure implies. Electrophilic addition of boron trifluoride to both *meta*-benzyne and 3,5-didehydrobenzoate leads to an



**Figure 5.** BLYP/6-31+G(d) calculated potential energy surface for the reaction between 3,5-didehydrobenzoate and boron trifluoride to produce a net charge-site substitution product. The energy minimum on the right (shown without a structure) corresponds to a solvated complex between carbon dioxide and (3,5-didehydrophenyl)trifluoroborate. The energy of this complex was not calculated.

**Table 7.** BLYP/6-31+G(d) Calculated C–C–C Bond Angles around the Dehydro Carbon (C<sub>1</sub>–C<sub>2</sub>–C<sub>3</sub>) in *N*-(3,5-Didehydrophenyl)pyridinium, *meta*-Benzyne, 3,5-Didehydrobenzoate, and Their Respective Boron Trifluoride and Pyridine Addition Products

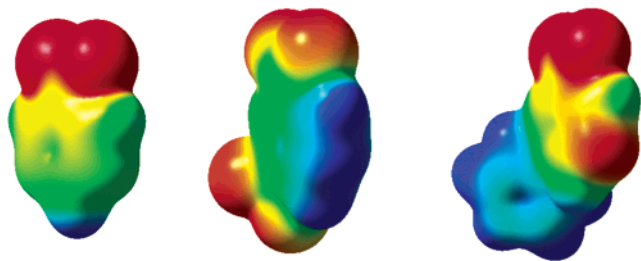
<i>N</i> -(3,5-didehydrophenyl)-pyridinium R = pyridinium	143.3°	<sup>a</sup>	120.3° <sup>c</sup>
<i>m</i> -benzyne R = H	140.1°	144.4° <sup>b</sup>	119.3° <sup>c</sup>
3,5-didehydrobenzoate R = carboxylate	137.3°	141.0° <sup>b</sup>	121.3° <sup>c</sup>

<sup>a</sup> There is no stable BF<sub>3</sub> addition product at BLYP/6-31+G(d). <sup>b</sup> The corresponding angle in the phenyl cation is 146.6°. <sup>c</sup> The corresponding angle in the phenyl anion is 112.2°.

increase in the bond angle at the remaining dehydro carbon (Table 7), suggesting a reduction in electron density. In both cases, the bond angle is close to the corresponding bond angle in the phenyl cation. In contrast, addition of a nucleophile (e.g., pyridine) to the benzyne moiety results in a significant reduction in the bond angle. Electrostatic potential surfaces (Figure 6) of 3,5-didehydrobenzoate and its boron trifluoride and pyridine adducts tell a similar story. Unfortunately, attempts to trap the dritterionic intermediate via ion–molecule reactions with pyridine and several amines (Scheme 5) were not successful, presumably because such an addition leads to greater charge separation and is therefore associated with a significant barrier.

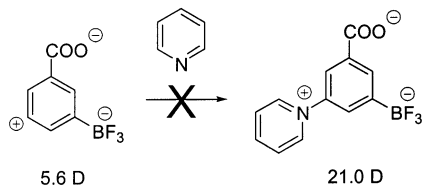
No reaction was observed between boron trifluoride and *N*-(3,5-didehydrophenyl)pyridinium. This is not surprising considering the electron deficiency of the *meta*-benzyne moiety





**Figure 6.** Electrostatic potential energy surfaces (BLYP/6-31+G(d)) for 3,5-didehydrobenzoate (left), its BF<sub>3</sub> adduct (center), and its pyridine adduct (right). The surfaces are calculated at the same electron density and with identical chromatic scales, with red more negative and blue more positive.

**Scheme 5**

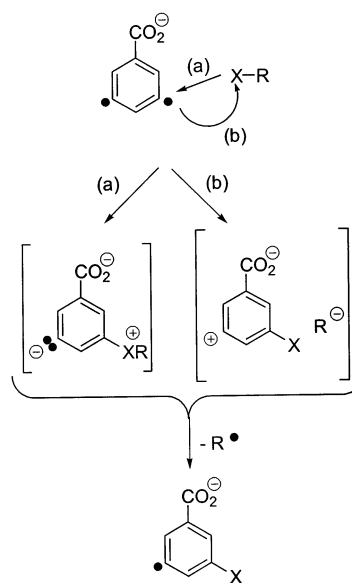


in this dionic ion. In fact, calculations predict a monotonic increase in energy as the boron approaches one of the dehydro carbons. In contrast, boron trifluoride addition to neutral *meta*-benzyne is expected to be exothermic by 5 kcal/mol and to occur without a barrier. The dipole moment of the boron trifluoride adduct to *meta*-benzyne is similar to that of its adduct with pyridine (7.7 and 7.0 D, respectively); however, the latter reaction is almost 3 times more exothermic than the former. The greater thermodynamic stability of the pyridine addition product than the BF<sub>3</sub> addition product is largely the result of the sp<sup>2</sup>-hybridized dehydro carbon being more likely to accept negative rather than positive charge density.

**Reaction with Electrophiles – Halogen Donors.** In the case of the reaction between 3,5-didehydrobenzoate and boron trifluoride, the benzyne moiety almost certainly is involved in a nucleophilic attack on the boron atom. However, the mechanism for halogen abstraction by the negatively charged benzyne is less clear. Several ionic mechanisms are possible, including nucleophilic addition of the halogenated molecule to the benzyne to form a “halonium” intermediate (Scheme 6, path a) and nucleophilic attack on the halogen atom either in a concerted “halophilic” substitution reaction<sup>51</sup> (Scheme 6, path b) or in a stepwise fashion via a hypervalent 10-X-2 “ate” complex.<sup>52</sup>

The experimental data provide some circumstantial evidence that 3,5-didehydrobenzoate reacts as a nucleophile in net halogen atom abstraction reactions. For example, *N*-(3,5-didehydrophenyl)pyridinium is primed to react as an electrophile (Scheme 6, path a) and would be expected to react faster than 3,5-didehydrobenzoate if both benzyne were reacting via this mechanism. However, it does not react with carbon tetrabromide, bromotrichloromethane, or bromoform, while 3,5-didehydrobenzoate sequentially abstracts two bromine atoms from these reagents at varying efficiencies (Table 4). In addition, iodine atom abstraction from iodine occurs at least 30 times more efficiently for 3,5-didehydrobenzoate than for *N*-(3,5-didehydrophenyl)pyridinium.

**Scheme 6**



The reaction with iodine is interesting because this is the only reagent studied that reacts with both the positively and the negatively charged benzyne. Iodine is sufficiently polarizable that it can act as a weak nucleophile and form an iodonium intermediate in reactions with *N*-(3,5-didehydrophenyl)pyridinium. Iodine is also an electrophile that possesses an excellent iodide leaving group for concerted halophilic reactions. In fact, in the reaction of iodine with 3,5-didehydrobenzoate, iodide formation accounts for about one-half of the branching ratio, although this pathway should be about 9 kcal/mol less exothermic than iodine atom abstraction on the basis of the electron affinities of the iodine atom<sup>53</sup> and benzoate radical<sup>54</sup> (3.059 and 3.45 eV, respectively).

The quality of the leaving group should provide some insight into relative reaction rates if halophilic substitution reactions are indeed occurring (Scheme 6, path b). The exothermicity of bromine abstraction from carbon tetrabromide and bromotrichloromethane should be nearly identical on the basis of their literature C–Br bond dissociation energies<sup>55</sup> (56.2 and 55.3 kcal/mol, respectively); however, 3,5-didehydrobenzoate abstracts a bromine atom from carbon tetrabromide 4 times faster than from bromotrichloromethane. Examination of the leaving group gas-phase proton affinity shows that tribromomethyl anion is less basic and therefore should be a better leaving group than trichloromethyl anion (proton affinities of 349.7<sup>56</sup> and 357.6 kcal/mol,<sup>57</sup> respectively). Bromine abstraction from bromoform was also observed; however, the reaction occurs too slowly to measure a reaction efficiency accurately. The poor dibromomethyl anion leaving group (proton affinity of 369.0 kcal/mol)<sup>56</sup> may be at least partially responsible for this slow reaction, although the ~6 kcal/mol reduction in reaction exothermicity (C–Br bond dissociation energy of bromoform is ~62 kcal/mol<sup>58</sup>) is certainly a factor also.

(53) Hanstorp, D.; Gustafsson, M. *J. Phys. B.* **1992**, *25*, 1773.

(54) Fujio, M.; McIver, R. T., Jr.; Taft, R. W. *J. Am. Chem. Soc.* **1981**, *103*, 4017.

(55) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493–532.

(56) Born, M.; Ingemann, S.; Nibbering, N. M. M. *Int. J. Mass Spectrom.* **2000**, *194*, 103–113.

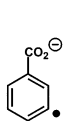
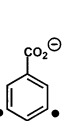
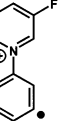
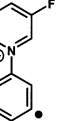
(57) Paulino, J. A.; Squires, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 5573–5580.

(58) Egger, K. W.; Cocks, A. T. *Helv. Chim. Acta* **1973**, *56*, 1516–1536.

(51) For a review of such reactions see: Zefirov, N. S.; Makhon'kov, D. I. *Chem. Rev.* **1982**, *82*, 615–624.

(52) (a) Wiberg, K. B.; Sklenak, S. *J. Org. Chem.* **2000**, *65*, 2014–2021. (b) Cioslowski, J.; Piskorz, P.; Schimeczek, M.; Boche, G. *J. Am. Chem. Soc.* **1998**, *120*, 2612–2615. (c) Boche, G.; Schimeczek, M.; Cioslowski, J.; Piskorz, P. *Eur. J. Org. Chem.* **1998**, 1851–1860.

**Table 8.** Efficiencies<sup>a</sup> and Products<sup>b</sup> of Reactions of 3-Dehydrobenzoate, 3,5-Didehydrobenzoate, *N*-(3-Dehydrophenyl)-3-fluoropyridinium, and *N*-(3,5-Didehydrophenyl)-3-fluoropyridinium with Hydrogen Atom Donors and Di-*tert*-butyl Nitroxide

				
tetrahydrofuran	H abs 1.0 Eff. = 0.2%	No reaction	H abs 1.0 Eff. = 1.0%	No reaction
acetone	H abs 1.0 Eff. ~ 0.003%	No reaction	H abs 1.0 Eff. ~ 0.004%	No reaction
toluene	No reaction	No reaction	Addition <sup>c</sup> 0.85 H abs 0.15 Eff. = 1.3%	
3-chlorophenol		No reaction		
di- <i>tert</i> -butyl nitroxide	O abs 0.58 Addition <sup>d</sup> 0.42  Eff. = 6.8%	No reaction	O abs 0.72 (2°) H abs 0.26 Addition <sup>d</sup> 0.26 H abs 0.02 Eff. = 38%	O abs 0.52 Addition <sup>d</sup> 0.48  Eff. = 13%

<sup>a</sup> Reaction efficiencies reported as  $k_{\text{exp}}/k_{\text{collision}} \times 100\%$  (i.e., the percentage of collisions that lead to a reaction). <sup>b</sup> Product branching ratios are given in parentheses. Secondary products (2°), if any were observed, are given underneath the primary product that produced them. <sup>c</sup> Branching ratio for addition to toluene includes products corresponding to addition followed by loss of hydrogen atom and addition followed by loss of methyl radical. <sup>d</sup> Branching ratio for addition to di-*tert*-butyl nitroxide includes products corresponding to addition followed by loss of isobutene, addition followed by loss of *tert*-butyl radical, and addition followed by loss of isobutene and methyl radical.

**Reaction with Hydrogen Donors and Di-*tert*-butyl Nitroxide.** Hydrogen atom abstraction by *meta*-benzynes can only occur by a radical mechanism, although the transition state for such an abstraction may possess significant hydride or proton transfer character. On the basis of the prediction that singlet biradicals should undergo radical reactions much more slowly than their monoradical counterparts, it is not surprising that neither the positively nor the negatively charged *meta*-benzynes abstracts a hydrogen atom from the hydrogen atom donors studied (Table 8). In most of the cases, the corresponding monoradicals react to yield a hydrogen atom abstraction product albeit with low reaction efficiencies (Table 8).

Certain dialkyl nitroxides are stable free radicals that are used to trap carbon-centered radical species by adduct formation (via a radical–radical recombination reaction).<sup>48,59</sup> Net oxygen atom abstraction is also observed in some instances where homolytic cleavage of the N–O bond occurs in the adduct. For example, the *para*-benzynes 1,4-didehydronaphthalene reacts with the nitroxide TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) by two sequential oxygen atom abstractions to produce 1,4-naphthoquinone.<sup>60</sup> Similar oxygen atom abstraction reactions have been reported for the ion–molecule reactions of positively charged distonic phenyl radicals.<sup>48</sup>

As expected, 3-dehydrobenzoate abstracts an oxygen atom from di-*tert*-butyl nitroxide as does its positively charged monoradical counterpart (Table 8). The positively charged *meta*-benzynes also reacts predominately by oxygen abstraction; however, a comparison of the biradical and monoradical reaction rates casts doubt about whether the reactivity of the biradical is truly radical in nature. The biradical reacts only 4 times less rapidly than the monoradical (taking into account only the rate of oxygen abstraction) which is faster than expected, given the strong coupling between the biradical electron pair in *meta*-

benzynes. It seems more likely on the basis of previous observations of the electrophilic reactivity of *meta*-benzynes that the nucleophilic oxygen of the nitroxide adds to the *meta*-benzynes moiety and subsequent fragmentation of the adduct results in the final observed net radical abstraction product. On the other hand, 3,5-didehydrobenzoate is completely inert toward the nitroxide. The lack of reactivity is evidence of the reduced ability of 3,5-didehydrobenzoate to participate in radical reactions or react as an electrophile.

## Conclusions

High level calculations at the CASPT2 and CCSD(T) levels predict that the carboxylate group does not perturb the singlet–triplet gap of 3,5-didehydrobenzoate relative to *meta*-benzynes. The large singlet–triplet splitting ( $\sim -21$  kcal/mol) calculated for both the 3,5-didehydrobenzoate and the *N*-(3,5-didehydrophenyl)-3-fluoropyridinium has the effect of severely inhibiting the radical reactivity of these *meta*-benzynes as predicted by Chen and co-workers.<sup>10</sup> As a result, neither ion abstracts a hydrogen atom from common hydrogen atom donors. However, the lack of radical reactivity does not mean that the benzyne are generally not reactive.

A positively charged substituent attached to the benzyne (e.g., 3-fluoropyridinium) biases its reactivity toward nucleophilic reagents, while a negatively charged substituent (e.g., carboxylate) has the opposite effect. The 3,5-didehydrobenzoate was found to react as a nucleophile with electrophilic reagents, such as boron trifluoride and halogenated alkanes, while the *N*-(3,5-didehydrophenyl)-3-fluoropyridinium ion does not react at all with these species. In fact, the 3,5-didehydrobenzoate reacts with the strong electrophile boron trifluoride to form a new *meta*-benzynes, (3,5-didehydrophenyl)trifluoroborane, by a charge-site substitution mechanism analogous to that reported earlier for reaction of *N*-(3,5-didehydrophenyl)pyridinium with strong nucleophiles.

It is satisfying that the previous “discrepancy” between the inertness of 3,5-didehydrobenzoate in the FA and the often high reactivity of *N*-(3,5-didehydrophenyl)-3-fluoropyridinium ion in the FT-ICR is not the result of the ion generation method or the type of mass spectrometer used. In fact, the reactivity of 3,5-didehydrobenzoate was found to be similar in both the FT-ICR and the FA. Instead, the difference lies in the inherent nucleophilic/electrophilic reactivity of the benzyne moiety itself. This work, in conjunction with previous studies, indicates that neutral *meta*-benzynes is likely to be ambiphilic, reacting rapidly with both strong nucleophiles and electrophiles.

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**Supporting Information Available:** Optimized geometries, energies, and frequencies for the calculated species (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

(59) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1988**, *53*, 1632–1641.  
(60) Grissom, J. W.; Gunawardena, G. U. *Tetrahedron Lett.* **1995**, *36*, 4951–4954.