

# Aromatic Substitution Reactions between Ionized Benzene Derivatives and Neutral Methyl Isocyanide

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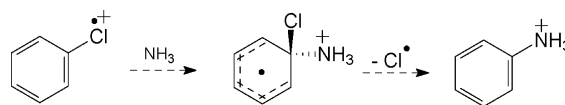
Aromatic substitution reactions of selected ionized benzenes derivatives (chlorobenzene, nitrobenzene, dimethylphthalates) and phenoxy cation using neutral methyl isocyanide as a nucleophile are shown to efficiently occur in the gas phase. Nitrilium ions are produced in high abundance during these processes. These reactions have been performed in the hexapole collision cell of a large-scale hybrid tandem mass spectrometer. Computed 298 K enthalpy diagrams at the B3LYP/6-31+G(d,p) level of theory confirm the exothermic formation of the *N*-methylbenzonitrilium ions starting with ionized chloro- and nitrobenzene molecular ions. In this last case, two other exothermic processes are also detected: (i) an oxygen atom transfer yielding ionized nitrosobenzene and neutral methyl isocyanate and (ii) a loss of carbon monoxide from the ion/molecule reaction product generated when metastably generated phenoxy cations (produced in the hexapole collision cell) react with methyl isocyanide. Using extended theoretical calculations, several reaction pathways have been derived. The behavior of the three isomeric dimethyl phthalates has been investigated in the same way.

## Introduction

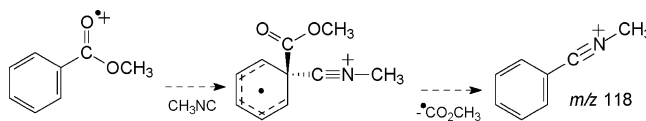
Nucleophilic aromatic substitution reactions are expected to easily occur if the nucleophile reacts with an electron-deficient aromatic compound. Obviously, an efficient way to activate the aromatic substrate is to ionize the molecule, for example, by electron removal. Thus, ion/molecule reactions involving a cationic aromatic substrate and a neutral nucleophile are expected to easily give rise to this kind of substitution reaction. Evidence for cationic aromatic substitution reaction in the gas phase has been presented in the recent years.<sup>1–8</sup> Previous studies were essentially devoted to reactions between ionized halobenzene and ammonia either into photoionized van der Waals complexes<sup>1–4</sup> or by a bimolecular process in a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer.<sup>5–7</sup> It was concluded from these studies that chloro-, bromo- and iodo-benzene radical cations react with ammonia in an ipso substitution reaction to yield anilinium ions. From a mechanistic point of view, the reactions have been interpreted by an addition–elimination process involving the passage through a  $\sigma$ -complex intermediate as illustrated in Scheme 1 in the case of chlorobenzene. It is noteworthy that recent gas phase experiments corroborated this view by identifying these reactions intermediates from their photodissociation IR spectra both in the positive<sup>9</sup> and in the negative<sup>10</sup> ion modes.

Beside these thorough but limited studies, a need for the finding of other examples of nucleophilic aromatic substitution reactions is consequently evident in order to have a more general picture of this type of reaction and to provide new insight into its mechanism. In this context, we have recently shown that, in

## SCHEME 1: Displacement of the Chlorine Atom from Ionized Chlorobenzene by Ammonia



## SCHEME 2: Displacement of a Methoxycarbonyl Radical from Ionized Methyl Benzoate by Methyl Isocyanide Involving an ipso Approach<sup>8</sup>



the gas phase, methyl isocyanide,  $\text{CH}_3\text{NC}$ , is an efficient nucleophilic reagent toward cationic substrates.<sup>11–19</sup> This is the result of its high ionization energy (11.24 eV) and its relatively low proton affinity (839 kJ mol<sup>−1</sup>),<sup>20</sup> which prevent charge and proton exchange processes, respectively. Moreover, the high dipole moment of  $\text{CH}_3\text{NC}$  (3.85 D)<sup>21</sup> favors its association with charged species and consequently increases its reaction efficiency. During these previous investigations, we observed that ionized methyl benzoate reacts with neutral methyl isocyanide producing abundant benzonitrilium ions,  $\text{CH}_3-\text{N}^+\equiv\text{C}-\text{C}_6\text{H}_5$  ( $m/z$  118) by elimination of the original methoxycarbonyl group.<sup>11,12</sup> Using molecular orbital calculations, the mechanism of the reaction has been demonstrated to occur following the two step process depicted in Scheme 2.<sup>8</sup> In addition to the  $m/z$  118 formation resulting from an ipso attack of methyl isocyanide, the competitive formation of  $m/z$  176 ions has been also interpreted by aromatic substitution reaction involving ortho, meta, or para approaches.

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It may be added that, in these substitution processes, where the key step is the addition of the nucleophile, the resulting  $\sigma$ -complex is generally highly stabilized with respect to the reactants. In gas-phase experiments under low pressure, it follows that an energetically excited intermediate is formed and further fragmentation reactions of this species are consequently allowed. Loss of a ring substituent results in the nucleophilic substitution reaction, but other processes are obviously possible, particularly if the stabilization energy of the complex is important. An example is provided by the formation of  $m/z$  162 ions from reaction of ionized methyl benzoate with neutral methyl isocyanide, which has been shown to involve exclusively the methyl group of the  $\text{COOCH}_3$  moiety.<sup>12</sup> It has been demonstrated that this complicated reaction involves significant rearrangements that are only possible because of the large stabilization of the initially produced  $\sigma$ -complex.<sup>8</sup>

The goal of the present study is to extend our knowledge of the gas-phase aromatic substitution reaction by studying several ion/molecule reactions involving neutral methyl isocyanide as the nucleophile. We report here mass spectrometry experiments using a hybrid multisector tandem mass spectrometer. Interpretation of the results was completed by density functional theory molecular orbital calculations at the B3LYP/6-31+G(d,p) level. The chosen benzenic derivatives were chloro- and nitrobenzenes since they bring efficient electron-withdrawing substituents and disubstituted methyl benzoates because of the particularly rich and thoroughly described chemistry of ionized methyl benzoate itself with methyl isocyanide.<sup>8</sup>

## Experimental Section

The spectra were recorded on a hybrid tandem mass spectrometer (Micromass AutoSpec 6F, Manchester) combining six sectors of  $\text{cE}_1\text{B}_1\text{cE}_2\text{cE}_3\text{B}_2\text{cE}_4$  geometry ( $\text{E}_i$  stands for electric sector,  $\text{B}_i$  for magnetic sector, and c for conventional collision cells). Typical conditions already reported elsewhere<sup>22,23</sup> were 70 eV electron energy, 200  $\mu\text{A}$  trap current in the EI mode, 1 mA emission current in the CI mode, and 8 kV accelerating voltage. Recently, an rf-only hexapole collision cell ( $\text{H}_{\text{cell}}$ ) has been installed inside the six-sector instrument between  $\text{E}_2$  and  $\text{E}_3$ , replacing an rf-only quadrupole collision cell installed about ten years ago.<sup>24</sup> This cell is longer (182 mm) and presents better focusing properties over a wider mass range resulting overall in a very significant gain in sensitivity. Moreover, a Pirani gauge has also been fitted allowing accurate measurement of the vacuum within the hexapole. Typically, the pressures used were in the  $10^{-3}$  to  $10^{-4}$  Torr range and were adjusted (and reproduced) using a Negretti needle valve. The cell allows, *inter alia*, the study of associative ion/molecule reactions.<sup>24</sup> Briefly, the experiments utilizing the hexapole consist of the selection of a beam of fast ions (8 keV) with the three first sectors ( $\text{E}_1\text{B}_1\text{E}_2$ ), the deceleration of these ions to approximately 5 eV kinetic energy, which is the voltage difference between the accelerating voltage and the floating voltage applied to the hexapole. Accurate control of this voltage is critical for maximizing the ion beam intensity and is defined by a 10-turn potentiometer, the same for the rf-voltage applied to the hexapole rods. The interaction between the ions and the reagent gas is thereafter realized in the  $\text{H}_{\text{cell}}$  and, after reacceleration at 8 keV, all the ions generated in the hexapole are separated and mass measured by scanning the field of the second magnet. The high energy collisional activation (CA) spectra of mass-selected ions generated in the  $\text{H}_{\text{cell}}$  can be recorded by scanning the field of  $\text{E}_4$  after selection of the ions with  $\text{E}_3$  and  $\text{B}_2$  and collisional activation in the last collision cell.

**TABLE 1: Total Energies and Enthalpies (Hartree) Calculated at the B3LYP/6-31+G(d,p) Level**

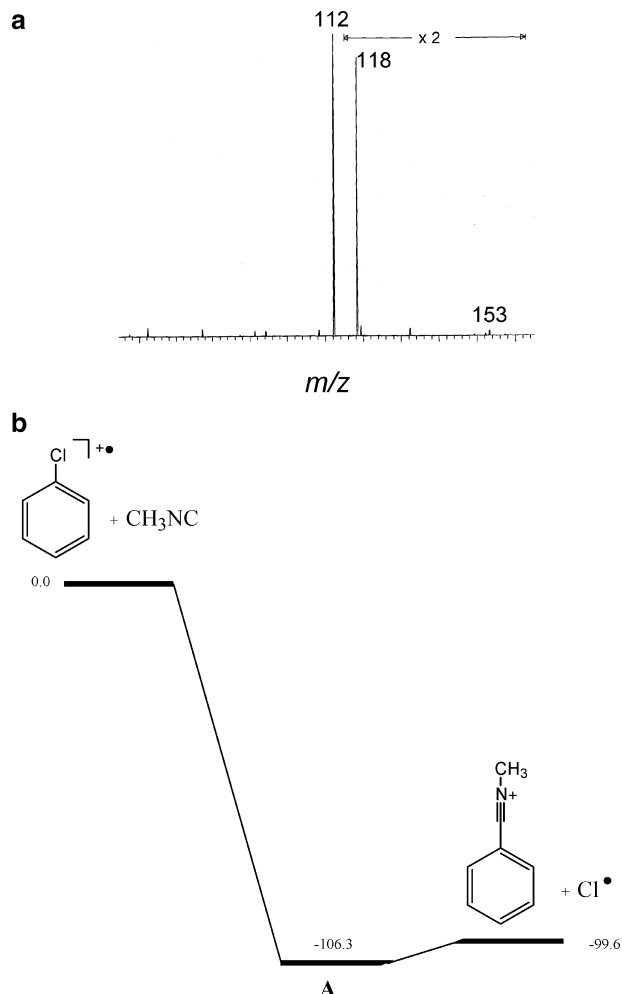
structure	$E_0^\circ$	$H_0^\circ$	$H_{298}^\circ$
$\text{C}_6\text{H}_5\text{Cl}^{++}$	-691.138 299	-691.447 755	-691.441 039
$\text{CH}_3\text{NC}$	-132.730 165	-132.684 910	-132.680 179
$\text{CH}_3\text{NCC}_6\text{H}_5^+$	-364.171 580	-364.032 646	-364.023 231
$\text{Cl}^+$	-460.138 299	-460.138 299	-460.135 940
A: $\text{CH}_3\text{NCC}_6\text{H}_5 \cdots \text{Cl}^{++}$	-824.311 766	-824.172 748	-824.161 724
$\text{C}_6\text{H}_5\text{NO}_2^{++}(\text{di\acute{e}dre } 55^\circ)$	-436.419 722	-436.319 964	-436.311 215
$\text{NO}_2^+$	-205.083 887	-205.075 104	-205.071 224
$\text{C}_6\text{H}_5\text{NO}^{++}$	-361.265 578	-361.167 786	-361.160 636
$\text{CH}_3\text{NCO}$	-208.001 582	-207.951 015	-207.945 333
B: $\text{CH}_3\text{NCC}_6\text{H}_5 \cdots \text{ONO}^{++}$		-569.110 632	-569.096 023
C: $\text{C}_6\text{H}_5\text{NO} \cdots \text{CH}_3\text{NCO}^{++}$		-569.135 622	-569.121 349
$\text{C}_6\text{H}_5\text{O}^+(\text{phenoxy})$	-306.533 853	-306.441 745	-306.435 178
$\text{D}_{\text{oxo}}$	-439.357 102	-439.214 669	-439.204 036
$\text{D}_{\text{ortho}}$	-439.348 009	-439.206 471	-439.195 808
$\text{D}_{\text{ortho}}'$	-439.320 905	-439.181 342	-439.170 203
$\text{D}_{\text{para}}$	-439.338 064	-439.196 593	-439.186 851
$\text{D}_{\text{meta}}$	-439.266 868	-439.127 832	-439.116 812
E	-439.379 783	-439.236 276	-439.226 144
$\text{E/F}_c$	-439.290 226	-439.155 889	-439.145 815
CO	-113.317 323	-113.312 306	-113.309 001
$\text{C}_6\text{H}_5^+$	-231.274 643	-231.189 804	-231.183 973
$\text{F}_a$	-326.097 064	-325.960 769	-325.953 122
$\text{F}_b$	-326.081 650	-325.945 440	-325.937 797
$\text{F}_c$	-326.069 893	-325.934 399	-325.926 720
$\text{F}_d$	-326.016 787	-325.882 136	-325.874 571
$\text{F}_e$	-326.014 101	-325.881 592	-325.873 580
$\text{F}_f$	-326.010 456	-325.879 160	-325.870 211
$\text{F}_g$	-326.033 898	-325.902 465	-325.893 384
G	-439.300 504	-439.160 249	-439.149 413
$\text{CH}_2=\text{NH}$	-94.640 612	-94.600 672	-94.596 807
$\text{c-C}_5\text{H}_5^+$	-193.163 328	-193.083 741	-193.078 283
$\text{DMP}^{++}$	-687.700 953	-687.516 058	-687.501 862
$\text{orthoCNMB}^+$	-592.065 506	-591.883 770	-591.869 926
$\text{DMiP}^{++}$	-687.713 211	-687.529 547	-687.514 571
$\text{metaCNMB}^+$	-592.059 107	-591.877 616	-591.864 530
$\text{DMtP}^{++}$	-687.714 768	-687.530 973	-687.516 044
$\text{paraCNMB}^+$	-592.057 247	-591.875 794	-591.862 720
$\text{CH}_3\text{OCO}^+$	-228.413 832	-228.364 902	-228.359 142
$\text{C}_6\text{H}_5\text{NCO}^{++}$	-399.442 165	-399.338 972	-399.330 775
$\text{C}_6\text{H}_5\text{OCN}^{++}$	-399.369 494	-399.267 576	-399.259 274
$\text{CH}_3^+$	-39.847 335	-39.817 522	-39.813 527

Methyl isocyanide was prepared according a literature procedure,<sup>25</sup> and the other compounds were commercially available (Aldrich) and were used without any further purification.

Quantum chemical calculations were carried out using the Gaussian 03 set of programs<sup>26</sup> within the density functional theory. Geometry optimizations of the stationary points and the corresponding transition structures connecting the relevant equilibrium structures were conducted at the B3LYP/6-31+G(d,p) level of theory. Vibrational frequencies were calculated at this level using the harmonic oscillator approximation. The identity of local minima and transition structures were determined by the absence or presence of only one negative value, respectively. Second, unscaled B3LYP/6-31+G(d,p) frequencies were used to compute zero-point vibrational energies and vibrational contributions to 298 K enthalpies. As underlined in a previous study,<sup>8</sup> the errors on enthalpies computed at this level of theory rarely exceed 5–10  $\text{kJ mol}^{-1}$ . This energy range may thus provide an estimate of the accuracy expected on the present data. The computational results are gathered in Table 1. All energetic data are given in Hartree (total energies and enthalpies) or in  $\text{kJ mol}^{-1}$  (relative energies and enthalpies, 1 hartree = 2625.5  $\text{kJ mol}^{-1}$ ).

## Results and Discussion

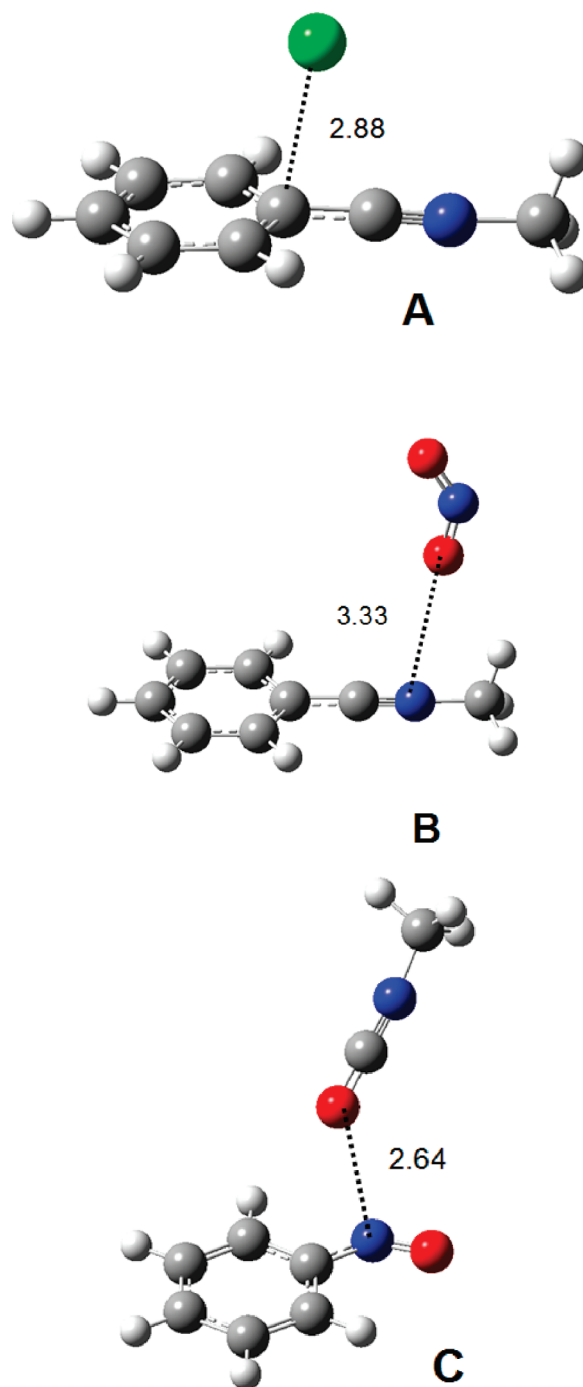
The following compounds, chlorobenzene, nitrobenzene, and three isomeric dimethyl phthalates, have been submitted to 70 eV electron ionization and, after mass selection of the resulting



**Figure 1.** (a) Ion/molecule reactions of mass-selected chlorobenzene ions ( $m/z$  112) with methyl isocyanide; (b) computed 298 K enthalpy diagram ( $\text{kJ mol}^{-1}$ ) for the nucleophilic aromatic substitution reaction of ionized chlorobenzene with methyl isocyanide.

molecular ions, allowed to interact with neutral methyl isocyanide within the rf-only hexapole collision cell as described in the experimental part.

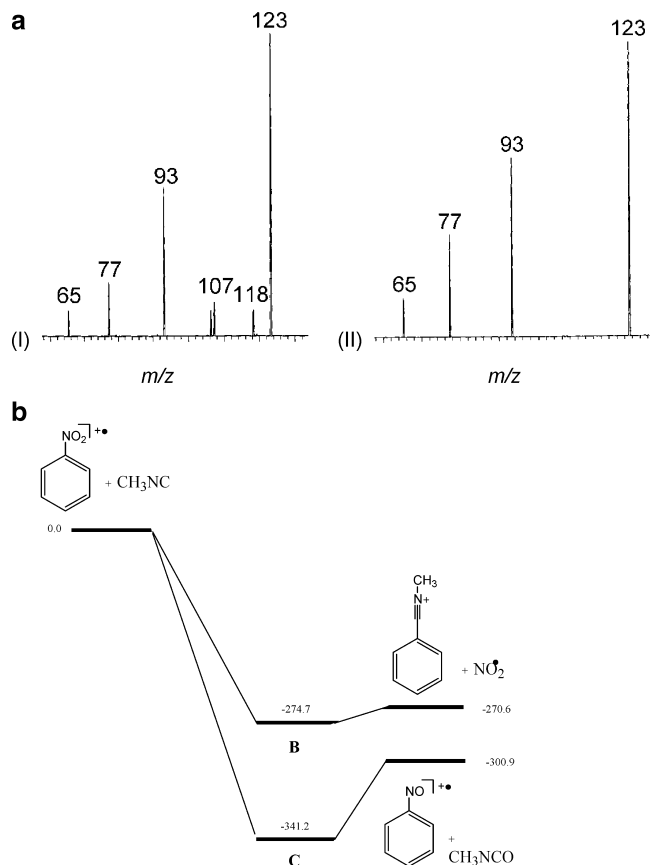
**Chlorobenzene Radical Cation.** In relation with the reported reaction<sup>1,2,4–6</sup> of the chlorobenzene molecular ion with ammonia, we have investigated the products resulting from ion/molecule reactions between mass analyzed chlorobenzene ion,  $\text{C}_6\text{H}_5^{35}\text{Cl}^+$ , and methyl isocyanide. As observed in the mass spectrum presented in Figure 1a, an adduct ion  $[\text{C}_6\text{H}_5^{35}\text{Cl}, \text{CH}_3\text{NC}]^{++}$  is detected at  $m/z$  153, with a very low intensity however. The major process corresponds to the substitution of the chlorine atom and leads to  $m/z$  118 ions,  $[\text{C}_6\text{H}_5, \text{CH}_3\text{NC}]^+$ . The structural and thermochemical aspects of this very clean reaction were explored by DFT calculations. The results are summarized in Figure 1b. Formation of the *N*-methyl benzonitrilium ion occurs via a classical nucleophilic aromatic substitution reaction involving an intermediate complex A. As presented in Figure 2, this latter complex is clearly a  $\sigma$ -complex between *N*-methyl benzonitrilium ion and a chlorine atom since the heavy atom skeleton is fully planar except for the chlorine atom that lies in a plane perpendicular to the benzene ring and has a distance of 2.88 Å from the carbon C(1). The stabilization enthalpy of complex A, with respect to the reactants  $\text{C}_6\text{H}_5^{35}\text{Cl}^+ + \text{CH}_3\text{NC}$ , is 106 kJ mol<sup>−1</sup>. The loose character of the  $\text{C}\cdots\text{Cl}$  interaction in A is illustrated by its low dissociation enthalpy toward  $\text{C}_6\text{H}_5\text{CNCH}_3^+ + \text{Cl}^\bullet$  (6 kJ mol<sup>−1</sup>). The overall substitution



**Figure 2.** Nucleophilic aromatic substitution reaction between ionized substituted benzene (chlorobenzene/nitrobenzene) and neutral methyl isocyanide: optimized structure of the intermediate ion/neutral complexes, see text for more details.

reaction is calculated to be exothermic by 100 kJ mol<sup>−1</sup>. It may be noted that the approach of the two reactants—ionized chlorobenzene and methylisocyanide—may produce several encounter complexes, the most stable of which being complex A. Ion-neutral complex of the type  $[\text{C}_6\text{H}_5\text{Cl}\cdots\text{NCCH}_3]^+$  has been also located but was found to be less stable than A by 70 kJ mol<sup>−1</sup> in the 298 K enthalpy scale.

**Nitrobenzene Radical Cation.** Replacement of the halogen atom on the aromatic ring by another electron-withdrawing substituent such as the nitro group was expected to similarly induce aromatic substitution reaction. The interaction between ionized nitrobenzene and  $\text{CH}_3\text{NC}$  induces a particularly rich

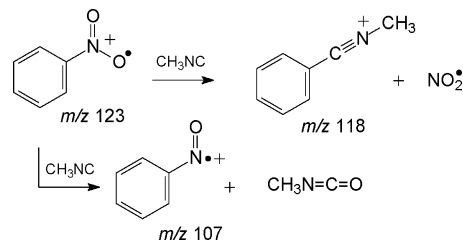


**Figure 3.** (a) Interaction between mass-selected nitrobenzene molecular ions ( $m/z$  123) with methyl isocyanide (I) or with argon(II) in the hexapole collision cell; (b) computed 298 K enthalpy diagram ( $\text{kJ mol}^{-1}$ ) for the nucleophilic aromatic substitution reaction of ionized nitrobenzene with methyl isocyanide.

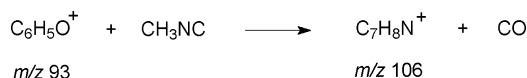
chemistry. Ionized nitrobenzene ( $m/z$  123) indeed reacts with methyl isocyanide to produce  $m/z$  118 ions formally corresponding to the substitution of the nitro radical by the isonitrile moiety (Figure 3a(I)). The major ions observed in the spectrum are, however, detected at  $m/z$  93, 77, and 65. These ions unambiguously originate from spontaneous and collision-induced dissociation reactions of the nitrobenzene molecular ions,  $m/z$  123, as evidenced by the spectrum shown in Figure 3a(II), which corresponds to pure dissociation of  $m/z$  123 ions induced by collisions with argon in the hexapole cell. Indeed, it is well-known that ionized nitrobenzene dissociate by competitive losses of  $\text{NO}^{\bullet}$  ( $m/z$  93) and  $\text{NO}_2^{\bullet}$  ( $m/z$  77),<sup>27</sup> with the former phenoxy cation expelling carbon monoxide to produce  $m/z$  65 ions. Beside these obvious ion/molecule or fragmentation processes, other efficient reactions appear to be responsible of the signals observed at  $m/z$  107 and 106.

Indeed, the formation of  $m/z$  107 ions formally corresponds to an oxygen atom transfer to the isonitrile molecule producing ionized nitrosobenzene ( $\text{C}_6\text{H}_5\text{NO}^+$ ), and probably neutral methyl isocyanate ( $\text{CH}_3\text{N}=\text{C}=\text{O}$ ) (Scheme 3). This charge localization is in agreement with the relative ionization energies (8.09 eV for nitrosobenzene and 10.67 eV for methyl isocyanate) reported in the literature.<sup>20</sup> The CA spectrum of the  $m/z$  107 ions (not shown) also confirms the  $m/z$  107 structural assignment. The mechanistic proposal summarized in Scheme 3 has been analyzed by DFT calculations (Figure 3b). It is found that the approaches of the  $\text{CH}_3\text{NC}$  molecule either on the carbon C(1) or on one of the oxygen atoms of ionized nitrobenzene lead to two different complexes **B** and **C**, see Figure 2. Concerning

### SCHEME 3: Ion/Molecule Reactions of Ionized Nitrobenzene with Methyl Isocyanide



### SCHEME 4: Ion/Molecule Reactions between Mass-Selected Phenoxy Cation and Methyl Isocyanide



the nucleophilic aromatic substitution reaction, the ipso attack on C(1) results in a covalent C(1)–CNCH<sub>3</sub> bond formation. Thus, complex **B** consists of a *N*-methyl benzonitrilium ion and a nitro radical. Its most stable form involves a favorable interaction between the nitrogen of the ion and one oxygen of the radical ( $\text{N}\cdots\text{O}$  distance of 3.33 Å, see Figure 2). As revealed in Figure 3b, complex **B** is more stable than the reactants by 274.7  $\text{kJ mol}^{-1}$  but is situated only 4  $\text{kJ mol}^{-1}$  below the products  $\text{C}_6\text{H}_5\text{CNCH}_3^+ + \text{NO}_2^{\bullet}$ . This situation is consequently comparable to that described above for complex **A** that is also involved as intermediate during an aromatic substitution reaction (see Figure 3b). The approach of  $\text{CH}_3\text{NC}$  on an oxygen atom of ionized nitrobenzene leads to the very stable ion/neutral adduct **C**. This structure is characterized by a  $\text{N}\cdots\text{OCNCH}_3$  distance of 2.64 Å, see Figure 2. This favorable binding is enhanced by the occurrence of another electrostatic interaction between the oxygen of the  $\text{OCNCH}_3$  moiety and an ortho hydrogen of ionized nitrosobenzene ( $\text{H}\cdots\text{OCNCH}_3$  distance of 2.56 Å). As a consequence the stabilization energy of **C** with respect to its components,  $\text{C}_6\text{H}_5\text{NO}^+ + \text{OCNCH}_3$ , is relatively important (40  $\text{kJ mol}^{-1}$ , see Figure 3b).

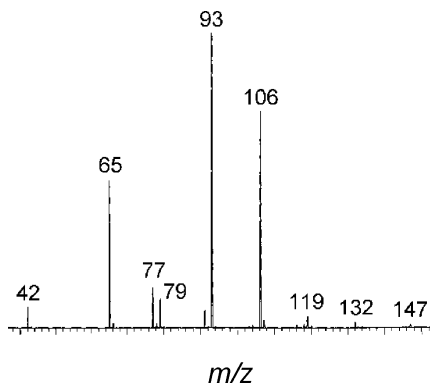
The last, unexpected, peak appearing at  $m/z$  106 in Figure 3a(I) cannot be ascribed to an ion/molecule reaction of the  $m/z$  123 ions or to a consecutive hydrogen atom loss from the  $m/z$  107 ions. In fact, it is found that these ions are due to a reaction of the metastably generated  $m/z$  93 ions with methyl isocyanide. This peculiar reaction will be detailed in the following paragraph.

**Phenoxy Cation.** The efficiency of the formation of the  $m/z$  106 ions by ion/molecule reaction between the phenoxy cation and  $\text{CH}_3\text{NC}$  (Scheme 4) is particularly high as confirmed by the reaction of a pure beam of mass-selected  $m/z$  93 ions generated by dissociative ionization of nitrobenzene with methyl isocyanide (Figure 4).

A careful analysis of the CA data of  $m/z$  106 ions first deserves some comments. The high energy CA spectrum of  $m/z$  106 ions formed by reaction between  $m/z$  93 ions (from ionized nitrobenzene) and  $\text{CH}_3\text{NC}$  is shown in Figure 5(I). Surprisingly, the base peak is observed at  $m/z$  77, followed by  $m/z$  51, suggesting the occurrence of a monosubstituted benzenic structure. Accordingly, such a process is likely to correspond to a reaction yielding the phenyl cation ( $m/z$  77) together with neutral formaldehyde (29 u). Other, minor, but significant peaks at  $m/z$  91 and 65 are also worthy of note since they correspond to a loss of 15 u from  $m/z$  106 for the former and to successive losses of 15 u and 26 u, or a direct elimination of 41 u, for the latter.

Several cation structures corresponding to  $\text{C}_7\text{H}_8\text{N}^+$  composition may be envisaged (Scheme 5). Only few mass spec-



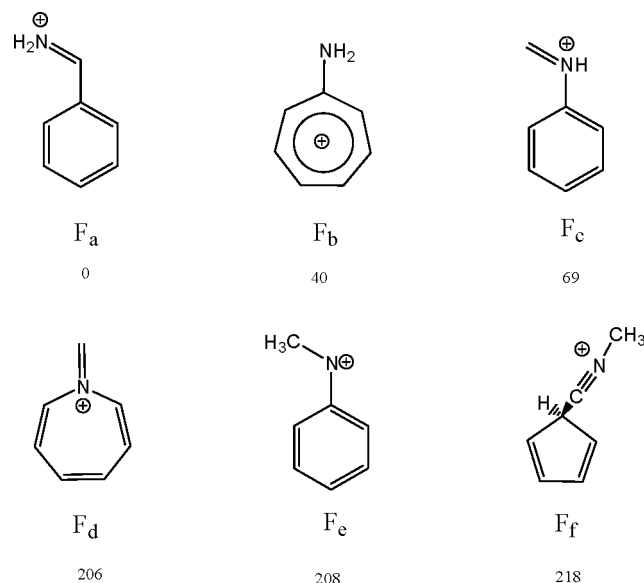


**Figure 4.** Ion/molecule reactions of  $m/z$  93 ions produced by dissociative ionization of nitrobenzene (loss of  $\text{NO}^{\bullet}$ ) and methyl isocyanide.

trometry studies have been devoted to these species. In particular,  $\text{C}_7\text{H}_8\text{N}^+$  generated by dissociative ionization ( $\text{H}^{\bullet}$  loss) of benzylamine and *N*-methylaniline have been analyzed and, based on energetics and metastable ion spectra, it has been proposed that aminotropylium ions **F<sub>b</sub>** are formed at threshold from ionized benzylamine.<sup>28</sup> In the same study, formation of *N*-phenyl methaniminium ions **F<sub>c</sub>** is proposed to occur from ionized *N*-methylaniline (Scheme 5). We examined the  $\text{C}_7\text{H}_8\text{N}^+$  ions obtained from dissociative ionization of *N*-methylaniline. As observed in Figure 5(II), a collisional activation spectrum very similar to that reported in Figure 5(I) is obtained. Small differences are nevertheless noticeable in the  $m/z$  65 and  $m/z$  91 regions. Consequently, at first sight, the  $\text{C}_7\text{H}_8\text{N}^+$  species produced by ion/molecule reaction between phenoxy cation and methyl isocyanide present the same CA spectrum as the methaniminium ions **F<sub>c</sub>**. The marginal discrepancies in the  $m/z$  65 and  $m/z$  91 regions may be interpreted by the coexistence of a small amount of other structure(s). In line with this possibility, we note that ions **F<sub>e</sub>** and **F<sub>f</sub>** are possible candidates since their structures a priori allow direct methyl or  $\text{CH}_3\text{NC}$  eliminations and may consequently explain the presence of  $m/z$  91 and 65 peaks.

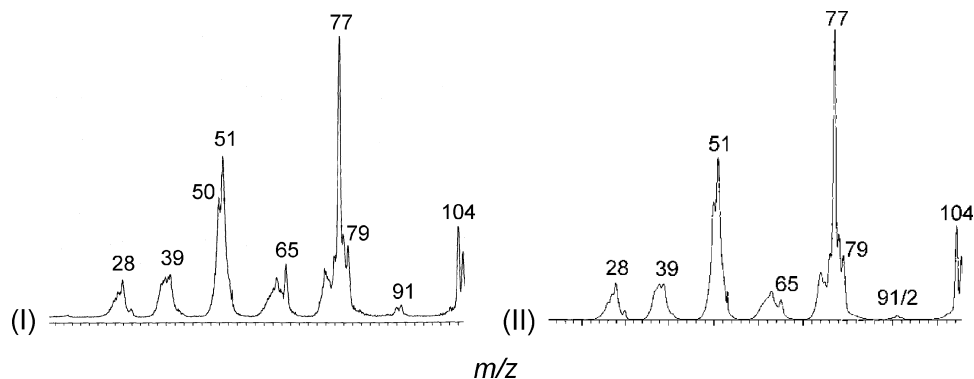
Molecular orbital calculations were undertaken to shed some light on these questions, particularly by examination of several  $\text{C}_7\text{H}_8\text{N}^+$  ions structures and encounter complexes between the phenoxy cation and neutral methyl isocyanide. Relative 298 K enthalpies of the six considered  $\text{C}_7\text{H}_8\text{N}^+$  ions are indicated under each structure in Scheme 5. It appears clearly that, if no energy barrier separates reactant and products, formation of **F<sub>c</sub>** is highly favored with respect to

**SCHEME 5:** Selected  $\text{C}_7\text{H}_8\text{N}^+$  Structures and Calculated Relative 298 K Enthalpies ( $\text{kJ mol}^{-1}$ )

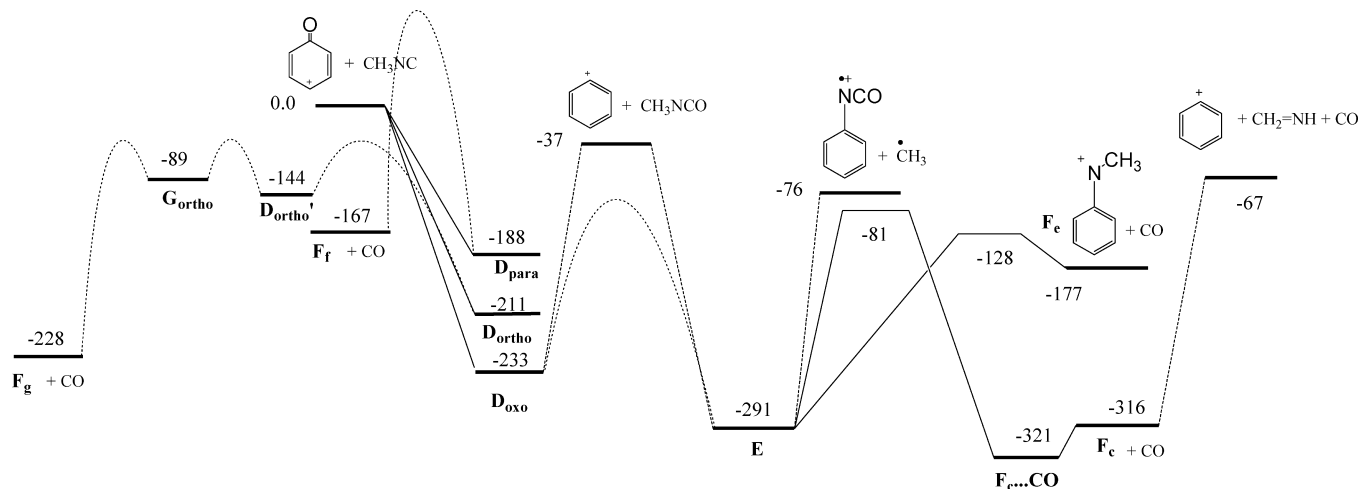


**F<sub>e</sub>** and **F<sub>f</sub>**. It is also interesting to note that structure **F<sub>a</sub>** is more stable than its tropylium-like homologue **F<sub>b</sub>** by 40  $\text{kJ mol}^{-1}$ . This is in contrast with the stability order of the benzyl/tropylium  $\text{C}_7\text{H}_7^+$  ions system, where the latter is ca. 30  $\text{kJ mol}^{-1}$  more stable than the former.<sup>29</sup> It renders also questionable the formation of **F<sub>b</sub>**, rather than **F<sub>a</sub>**, by dissociation of ionized benzylamine of low internal energy.<sup>28</sup>

As exemplified in Figure 6, approach of methyl isocyanide on the phenoxy cation may produce four covalent adducts **D<sub>para</sub>**, **D<sub>meta</sub>**, **D<sub>ortho</sub>**, and **D<sub>oxo</sub>** (see also Scheme 6a). B3LYP/6-31+G(d,p) computations reveal that **D<sub>para</sub>**, **D<sub>ortho</sub>**, and **D<sub>oxo</sub>** are stabilized by 190–235  $\text{kJ/mol}$  related to the starting reagents and that, as expected, **D<sub>meta</sub>**, is by far the least stable and for this reason will not be mentioned thereafter (see Figure 6 and Scheme 6a). Starting from the more stable oxo derivative, a simple reaction path may be imagined to produce methaniminium ions **F<sub>c</sub>** after CO loss (Scheme 6b). It consists of a shift of the  $\text{CH}_3\text{NCO}$  moiety with respect to the phenyl cation. This reaction is possible within an ion neutral complex between  $\text{C}_6\text{H}_5^+$  and  $\text{CH}_3\text{NCO}$ , the product of the simple  $\text{C}_6\text{H}_5\cdots\text{OC}$  bond elongation from **D<sub>oxo</sub>**. Reorientation of the  $\text{CH}_3\text{NCO}$  moiety allows the formation of a  $\text{C}_6\text{H}_5\cdots\text{N}$  bond in order to produce ion **E** (Scheme 6b). Ion neutral complex reactions are not expected to pass through a transition structure whose energy is above the energy level of the



**Figure 5.** High energy CA spectra (nitrogen) of the  $m/z$  106 ions generated by (I) ion/molecule reaction between  $m/z$  93 ions (from ionized nitrobenzene) and methyl isocyanide and (II) dissociative ionization of *N*-methylaniline (hydrogen atom loss).



**Figure 6.** Computed 298 K enthalpy diagram ( $\text{kJ mol}^{-1}$ ) associated to the formation of ions  $m/z$  106 from reaction of the phenoxy ion with methyl isocyanide.

components of the complex. In the present case (see Figure 6), the 298 K enthalpy level of the separated components of the complex,  $\text{C}_6\text{H}_5^+ + \text{CH}_3\text{NCO}$ , is below that of the reactants  $\text{C}_6\text{H}_5\text{O}^+ + \text{CH}_3\text{NC}$  by  $37 \text{ kJ mol}^{-1}$ . This means that the overall process  $\text{C}_6\text{H}_5\text{O}^+ + \text{CH}_3\text{NC} \rightarrow \text{E}$  is allowed to occur. Interestingly enough, structure **E** is strongly stabilized since it is even more stable than **D<sub>oxo</sub>** by more than  $50 \text{ kJ mol}^{-1}$  (see Figure 6 for the corresponding energy diagram). Note also that the fact that  $\text{C}_6\text{H}_5^+ + \text{CH}_3\text{NCO}$  are situated below the reactant explains the observation of a peak  $m/z$  77 in Figure 4.

From ion **E**, loss of carbon monoxide may occur either directly, thus giving  $m/z$  106 ion of structure **F<sub>e</sub>**, or with assistance of a 1,2-hydride ion shift leading to the more stable  $m/z$  106 iminium ion **F<sub>c</sub>**, see Scheme 6b. Note that the most stable form of ion **E** corresponds to a perpendicular arrangement of the  $\text{CH}_3\text{NCO}$  moiety with respect to the phenyl ring whereas in structure **F<sub>e</sub>** all the heavy atoms lies in the same plane, thus the CO loss from **E** is accompanied by a CNC rotation and passage by a transition structure situated above the separated products. The calculated reverse potential energy barrier ( $\text{F}_e + \text{CO} \rightarrow \text{E}$ ) is equal to no less than  $49 \text{ kJ mol}^{-1}$  at the B3LYP/6-31+G(d,p) level (Figure 6). The concerted reaction  $\text{E} \rightarrow \text{F}_c + \text{CO}$  has been similarly examined. During this exploration, we locate an ion/neutral complex [**F<sub>c</sub>**...CO], which may be produced prior to the CO loss. This species is more stable than **F<sub>c</sub>** + CO by  $5 \text{ kJ mol}^{-1}$ . Reaction  $\text{E} \rightarrow \text{F}_c + \text{CO}$  may be seen as a **F<sub>e</sub>**  $\rightarrow$  **F<sub>c</sub>** isomerization by 1,2-H shift, occurring inside a ion/neutral complex. The transition structure energy of this process is situated  $81 \text{ kJ mol}^{-1}$  below the phenoxy cation and methyl isocyanide reactants: the concerted reaction  $\text{E} \rightarrow \text{F}_c + \text{CO}$  is consequently theoretically allowed to occur from ion/molecule reaction between phenoxy cation and methyl isocyanide. Interestingly, the production of **F<sub>c</sub>** ions is then largely favored, and this is in agreement with the similarity between the CA spectrum of the ion/molecule reaction products (Figure 5(I)) and the reference CA spectrum (Figure 5(II)). Nevertheless, *N*-methyl phenylnitrenium cations **F<sub>e</sub>** are also likely to be partly generated. Their presence in the  $m/z$  106 ion beam coming out of the hexapole cell could explain the presence of a more intense  $m/z$  65 signal in the CA spectrum presented in Figure 5(I). Indeed, upon collisional activation, phenylnitrenium ions suffer from decomposition, leading to  $m/z$  65,  $\text{C}_5\text{H}_5^+$  cations.<sup>30</sup> Interestingly, the loss of

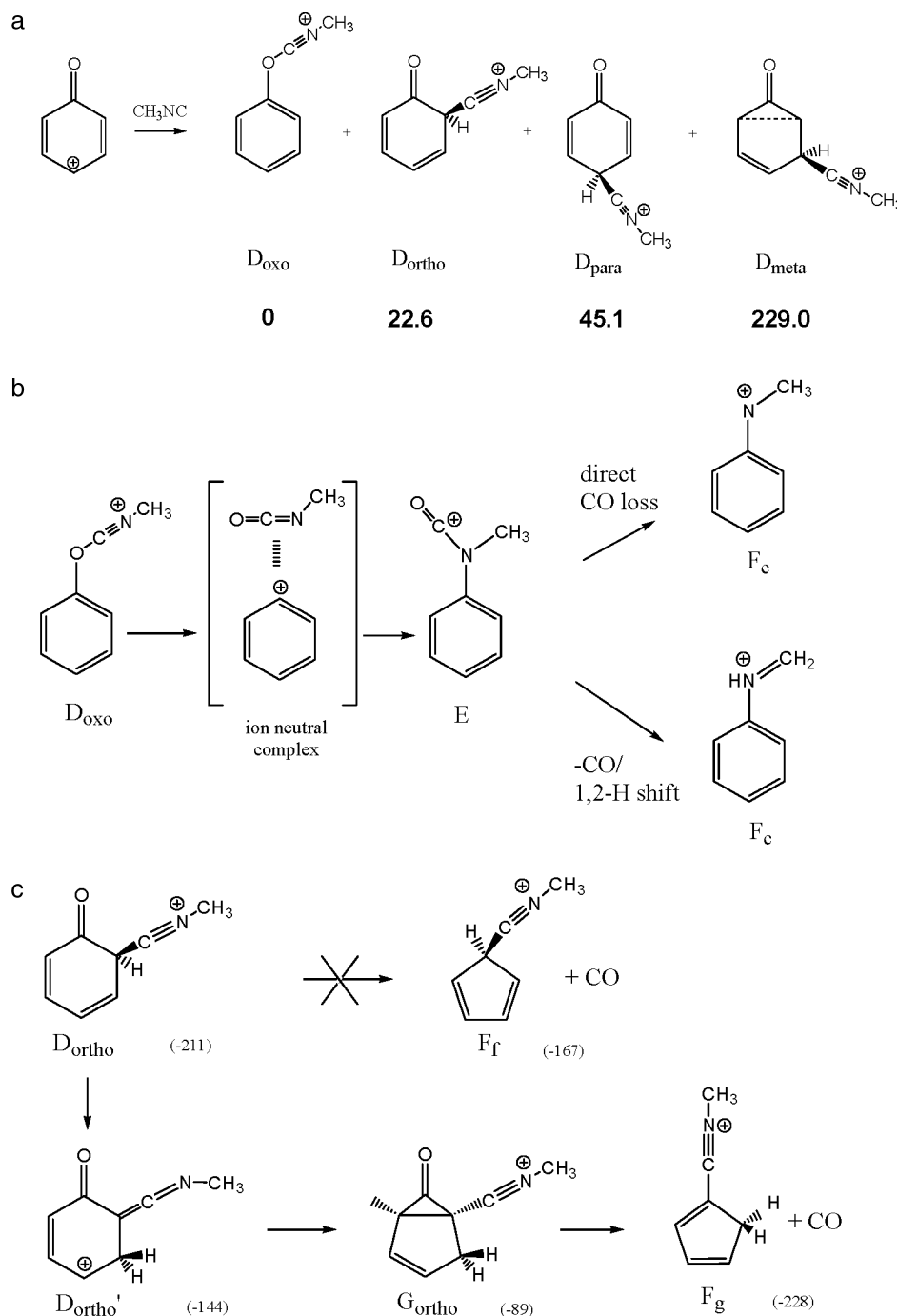
neutral formimine from **F<sub>e</sub>** cations, leading to the phenyl cations detected at  $m/z$  77, also remains an overall exothermic process related to the starting partners, namely, neutral methyl isocyanide and the phenoxy cation (Figure 6). In other words, the  $m/z$  77 signal detected among the ion/molecule reaction products, see Figure 4, can also arise from **F<sub>e</sub>** in addition to the direct decomposition of **D<sub>oxo</sub>**, see Figure 6.

Starting now from **D<sub>para</sub>** or **D<sub>ortho</sub>**, possibilities of CO loss involving ring-opening/ring closure may be devised. We investigated the reactions routes starting from the most stable **D<sub>ortho</sub>** ion (Scheme 6c). In order to test these possibilities, we first explored the direct **D<sub>ortho</sub>**  $\rightarrow$  **F<sub>f</sub>** + CO route by shortening the C(2)...C(6) distance. Indeed, the presence of **F<sub>f</sub>** cations among the ion/molecule reaction products can also be envisaged since those ions are likely to decompose upon collisional activation by loss of a methyl radical. However, all our attempts involved the passage by structures situated more than  $80 \text{ kJ mol}^{-1}$  above the reactants, namely, methyl isocyanide and phenoxy cation. We thus examined a reaction path initiated by a 1,2 hydrogen migration on the phenyl ring and found that formation of the stable isomeric form **D<sub>ortho'</sub>** may be allowed to occur, see Scheme 6c. A ring closure to form **G<sub>ortho</sub>** followed by a CO loss may ultimately give rise to ion **F<sub>g</sub>**. Note that the so obtained cations are likely to isomerize into ion **F<sub>f</sub>** by 1,2-hydride ion migration, thus opening the route to dissociations by methyl or methylisocyanide losses upon collisional activation of the  $m/z$  106 cations (Figure 5(I)).

**Dimethyl Terephthalate, Isophthalate, and Phthalate Radical Cations.** As mentioned in the Introduction, ionized methyl benzoate was found to react with methyl isocyanide by two nucleophilic aromatic substitution reactions and by a more complicated process also initiated by the formation of a  $\sigma$ -complex.<sup>8</sup> Basically, when interacting with neutral methyl isocyanide, ionized methyl benzoate suffers from formal competitive substitution reactions of a hydrogen atom, a methyl radical or the  $\text{CH}_3\text{OCO}$  radical by methyl isocyanide. Such reactions were theoretically studied and the reaction mechanisms were proposed.<sup>8</sup> In the context of the present paper, it seems of interest to investigate the behavior of the disubstituted molecular ions with methyl isocyanide in order to gain further information regarding the substituent effects on nucleophilic aromatic substitution reaction.

Figure 7(I) shows the quite complex mass spectrum of the ions generated in the hexapole collision cell when a beam of

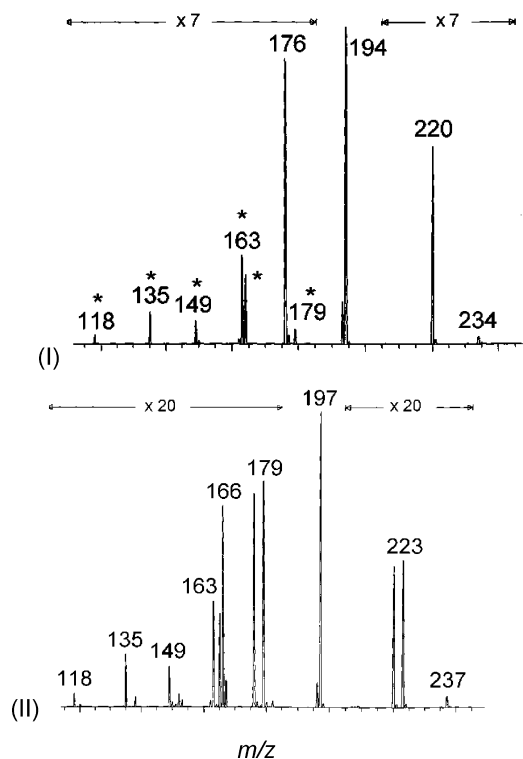
**SCHEME 6: Reorientation of the  $\text{CH}_3\text{NCO}$  Moiety to Produce Ion E. (a) Direct Interaction between the Phenoxy Cation and Neutral Isocyanide: selected structures and calculated relative 298 K enthalpies ( $\text{kJ mol}^{-1}$ ). (b) Carbon monoxide loss from  $\text{D}_{\text{oxo}}$  intermediate cation on the way to the  $m/z$  106 cations. (c) Carbon monoxide loss from  $\text{D}_{\text{ortho}}$  intermediate cation on the way to the  $m/z$  106 cations**



decelerated dimethyl isophthalate ions ( $m/z$  194) interacts with neutral methyl isocyanide. Most of the ions produced are those already observed without any collision/reagent gas in the cell, namely  $m/z$  118, 135, 149, 150, 163, 164, and 179.<sup>32</sup> All those ions arise from metastable decompositions, among them we studied in details the formaldehyde loss.<sup>32</sup> The ion/molecule reaction products are consequently identified at  $m/z$  176 (MeOCO radical loss), 220 (methyl radical loss) and 234 (hydrogen atom loss) and formally correspond to ions obtained by MeOCO radical loss, methyl radical loss and hydrogen atom loss from the encounter complex, respectively. Upon labeling with deuterium atoms on one of the methyl groups (Figure 7(II)),

the observation of the peak at  $m/z$  237 clearly indicates that the lost hydrogen atom from the encounter species arises again from the ring and not from the methyl groups. The 1:1 doublets at  $m/z$  220/223 and at  $m/z$  176/179, respectively, confirm that the lost methyl from the encounter complex arises exclusively from the ester functions and that methyl isocyanide thus displaces one ester function in a radical cation mediated aromatic substitution reaction. Such a behavior is totally similar to the substitution reaction observed when ionized methyl benzoate reacts with neutral methyl isocyanide.<sup>8</sup>

The ion/molecule reactions of the isomeric dimethyl terephthalate and dimethyl phthalate are presented in Figure

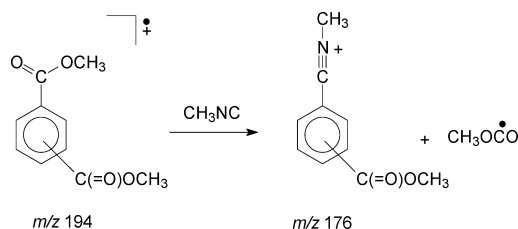


**Figure 7.** Ion/molecule reactions of the dimethyl isophthalate ( $m/z$  194) molecular ions with methyl isocyanide (I) and the same reactions with an isotopologue ( $m/z$  197, II). \* Metastably generated ions.

8. Again, the metastably generated ions first deserve to be identified. The unimolecular decompositions of ionized dimethyl terephthalate correspond to losses of a hydrogen atom ( $m/z$  193), a methyl group ( $m/z$  179), a  $\text{CH}_3\text{O}$  radical ( $m/z$  163), and a  $\text{C}_2\text{H}_3\text{O}_2$  ( $m/z$  135). Again, we thoroughly investigated the methyl radical loss and we identified protonated 5-carboxyphthalide as the fragment ion.<sup>33</sup> As far as metastable ionized dimethylphthalate is concerned, we recently demonstrated that the methoxyl radical loss affords oxygen methylated phthalic anhydride at  $m/z$  163.<sup>31</sup>

On the basis of the results obtained in the case of ionized dimethyl isophthalate, we can then expect to observe the three competitive reactions, namely the  $\text{H}^\bullet$ ,  $\text{CH}_3^\bullet$ , and  $\text{CH}_3\text{OCO}^\bullet$  radical substitutions at  $m/z$  234, 220, and 176. From the direct comparison between Figures 7(I), 8(I), and 8(II), it is apparent that the relative abundances of those ion/molecule reaction products are highly sensitive to the substitution pattern. In particular, the methyl radical substitution reaction ( $m/z$  220 signal) is found significantly increased in the isophthalate

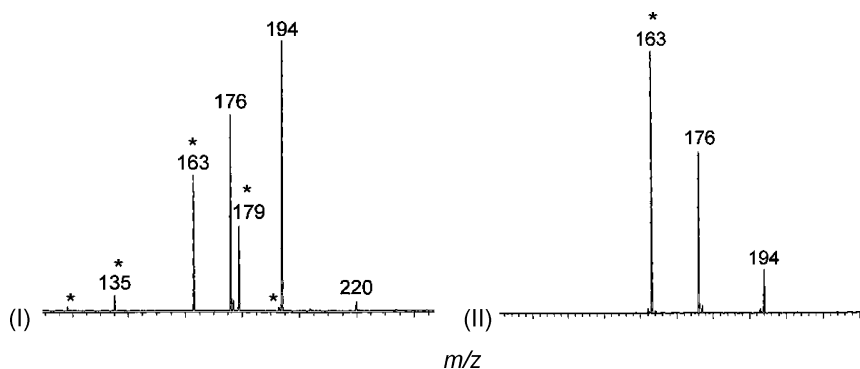
**SCHEME 7: Nucleophilic Aromatic Substitution of  $\text{CH}_3\text{OCO}$  Radical by Methyl Isocyanide When Reacting Ionized Dimethyl Phthalate, Dimethyl Isophthalate, and Dimethyl Terephthalate with Neutral Methyl Isocyanide**



case (40%, Figure 7(I)), considerably reduced in intensity for the terephthalate ions (4.6%, Figure 8(I)) and almost disappearing for the phthalate molecular cations (0.3%, Figure 8(II)). In the same vein, the hydrogen atom substitution is only detected in the case of the isophthalate isomer. Thermochemistry of the aromatic substitution reactions has been investigated by DFT calculation (Table 1). It is found that the exothermicity of the dominant  $\text{CH}_3\text{OCO}$  radical substitution reactions leading to nitrilium ions (see Scheme 7) increases in the order terephthalate (para) < isophthalate (meta) < phthalate (ortho) ( $-67$ ,  $-76$ , and  $-123$   $\text{kJ mol}^{-1}$ , respectively). It is noteworthy that this evolution roughly parallels the increases in intensity of the  $m/z$  176 peaks in Figure 8.

**Conclusion**

Substituted with appropriate leaving groups, ionized aromatic compounds undergo easily a radical cation mediated substitution reaction with methyl isocyanide as the nucleophile. These reactions have been performed in the hexapole collision cell of a large scale hybrid tandem mass spectrometer. Computed 298 K enthalpy diagrams at the B3LYP/6-31+G(d,p) level of theory fully support the experimental results and confirm the exothermic formation of the *N*-methylbenzonitrilium ions starting with ionized chloro- and nitrobenzene molecular ions. In this last case, two other exothermic processes are also detected: (i) an oxygen atom transfer yielding ionized nitrosobenzene and neutral methyl isocyanate and (ii) a loss of carbon monoxide from the ion/molecule reaction product of metastably generated phenoxy cations (produced in the hexapole collision cell) with methyl isocyanide. Using extended theoretical calculations, several reaction pathways have been investigated. Substituent effects were also approached and the associative ion/molecule reactions involving neutral methyl isocyanide and dimethyl



**Figure 8.** Reactions of dimethyl terephthalate (I) and dimethyl phthalate (II) molecular ions ( $m/z$  194) with methyl isocyanide. \* Metastably generated ions.



phthalate molecular ions or its two regioisomers were investigated.

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