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Reduction of nitroaromatics to arylnitrenium ions by vinyl halide cations†

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The title reduction of nitroaromatics $ArNO_2$ by vinyl halide radical cations $CH_2{=}CH{-}X^{+\cdot}$ (X = Cl or Br) to form arylnitrenium ions $ArNH^+$ involves a change in oxidation number of nitrogen from +3 to −1. This novel reaction provides a new route for the generation of arylnitrenium ions, a highly selective method for the detection of explosives in mixtures, and offers clues to the carcinogenic activity of nitroaromatics *in vivo*.

Because arylnitrenium ions $ArNH^+$ have been implicated as ultimate carcinogens due to the formation of amination adducts with DNA,[1] their chemistry is receiving considerable attention.[2] The generation of nitrenium ions by the photolysis of *N*-aminopyridinium salts[3] and arylazides[4] and by hydrolysis of hydroxamic acid esters[5] has been reported. We report a novel reduction reaction of nitroaromatics by the vinyl halide radical cation to form arylnitrenium ions $ArNH^+$.

Fig. 1a displays the products of the ion/molecule reactions of nitrobenzene with the isolated vinyl chloride radical cation $CH_2{=}CH{-}^{35}Cl^{+\cdot}$ (*m*/*z* 62) generated *via* electron impact of 1,2-dichloroethane CH_2ClCH_2Cl. In addition to the vinyl cation $C_2H_3^+$ (*m*/*z* 27), nitrosobenzene radical cation $PhNO^{+\cdot}$ (*m*/*z* 107), nitrobenzene radical cation $PhNO_2^{+\cdot}$ (*m*/*z* 123) and the protonated nitrobenzene cation $PhNO_2H^+$ (*m*/*z* 124), product ions appear at *m*/*z* 92 and *m*/*z* 150 are identified as the phenylnitrenium ion $PhNH^+$ and vinylated nitrobenzene $[PhNO_2 + C_2H_3]^+$, respectively. These assignments are supported by the fact that the corresponding deuterated phenylnitrenium ion $PhND^+$ (*m*/*z* 93) and deuterated vinylated nitrobenzene $[PhNO_2 + C_2D_3]^+$ (*m*/*z* 153) were formed in the ion/molecule reaction of nitrobenzene with the deuterated vinyl chloride radical cation $CD_2{=}CD{-}^{35}Cl^{+\cdot}$ (*m*/*z* 65) generated *via* electron impact of deuterated 1,2-dichloroethane CD_2ClCD_2Cl (Fig. 1b). It is also found that these two ions, $PhNH^+$ (*m*/*z* 92) and $[PhNO_2 + C_2H_3]^+$ (*m*/*z* 150), are produced by chemical ionization (CI) of nitrobenzene using 1,2-dichloroethane as the reagent gas, showing that the CI process involves the reaction of nitrobenzene and the vinyl chloride radical cation. Interestingly, the isotopomeric ions $[PhNO_2 + C_2H_3]^+$ (*m*/*z* 150) and $[PhNO_2 + C_2D_3]^+$ (*m*/*z* 153) fragment exclusively upon collision-induced dissociation (CID) into phenylnitrenium ion $PhNH^+$ (*m*/*z* 92) and deuterated phenylnitrenium ion $PhND^+$ (*m*/*z* 93), respectively, suggesting that the vinylated nitrobenzene ion $[PhNO_2 + C_2H_3]^+$ is the precursor of the phenylnitrenium ion $PhNH^+$. This assumption, as well as the structure of the phenylnitrenium ion, is confirmed by the fact that another isotopomeric vinylated ion $[PhNO_2\text{-}d_5 + C_2H_3]^+$ (*m*/*z* 155) fragments into the corresponding benzene-ring-deuterated phenylnitrenium ion $Ph(d_5)NH^+$ (*m*/*z* 97) in which the benzene ring is conserved. However, to our surprise, the reaction of nitrobenzene with the isolated vinyl cation $C_2H_3^+$ (*m*/*z* 27) failed to give the product of vinylated nitrobenzene ions $[PhNO_2 + C_2H_3]^+$ (*m*/*z* 150). Ion *m*/*z* 91 in Fig. 1a and 1b might be $C_6H_5N^{+\cdot}$, the phenylnitrene[6] as it fragments into an ion of *m*/*z* 64 by loss of HCN upon CID. Both CID of phenylnitrenium ions $PhNH^+$(*m*/*z* 92) and $PhND^+$ (*m*/*z* 93) give the same product ions of *m*/*z* 65 and 39 *via* consecutive loss of hydrogen cyanide HCN/deuterium cyanide DCN and acetylene C_2H_2, which also confirms the structure of the phenylnitrenium ions $PhNH^+$.

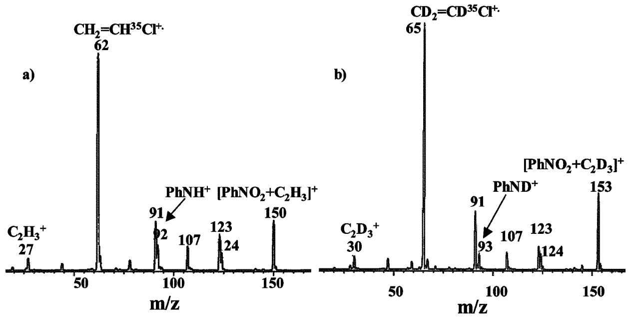
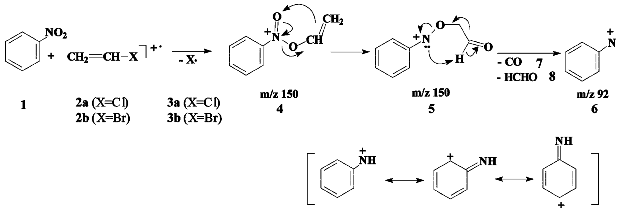


Fig. 1 Tandem mass spectra showing the products of ion/molecule reactions of nitrobenzene with a) $CH_2{=}CH{-}^{35}Cl^{+\cdot}$ (*m*/*z* 62) and b) $CD_2{=}CD{-}^{35}Cl^{+\cdot}$ (*m*/*z* 65) at nominally zero kinetic energy.

A mechanism is proposed for the formation of the phenylnitrenium ion $PhNH^+$ (*m*/*z* 92) in the reaction of nitrobenzene with vinyl chloride radical cation $CH_2{=}CH{-}Cl^{+\cdot}$ (Scheme 1). Ion $CH_2{=}CH{-}Cl^{+\cdot}$ first attacks neutral nitrobenzene to produce the adduct cation **4** (*m*/*z* 150) with loss of chlorine radical; the substituted group C_2H_3 in **4** is assumed to bind at the electronegative oxygen.[7] Then, ion **4** undergoes a five-membered-ring Cope-like rearrangement to form the *O*-acetaldehydylnitrosobenzene cation **5**. Density function theory (DFT) calculations at the level B3LYP/6-31G(d) suggest that ion **5** is more stable than ion **4** by 22.9 kcal mol^{-1} in the gas phase and probably represents the actual structure of the vinylated nitrobenzene ions $[PhNO_2 + C_2H_3]^+$ (*m*/*z* 150). Ion **5** undergoes an intramolecular hydride transfer and the loss of carbon monoxide CO and formaldehyde HCHO to yield the phenylnitrenium ion $PhNH^+$. Overall this remarkable ion/molecule reaction involves the reduction of nitrobenzene with loss of two oxygen atoms while the oxidation number of nitrogen changes from +3 in nitrobenzene to −1 in the phenylnitrenium ion. The net nitro reduction reaction shown in Scheme 1 (X = Cl) is exothermic by 26.7 kcal mol^{-1} which is much less than 90.8 kcal mol^{-1} for the assumed ion/molecule reaction of nitrobenzene with bare vinyl cation forming the phenylnitrenium ion. This calculated result accounts for the failure to observe the latter reaction. It is too exothermic for free vinyl cation to form stable vinylated nitrobenzene ions $[PhNO_2 + C_2H_3]^+$ (*m*/*z* 150) and therefore phenylnitrenium ions with nitrobenzene. By contrast, because loss of chlorine removes excess energy, $CH_2{=}CH{-}Cl^{+\cdot}$ can undergo bond-forming reactions with nitrobenzene. Similarly, the ion/molecule reaction of nitrobenzene with $CH_2{=}CH{-}^{79}Br^{+\cdot}$ (*m*/*z* 106) generated by electron impact of vinyl bromide $CH_2{=}CH{-}Br$ also



Scheme 1

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† Electronic Supplementary Information (ESI) available: supplementary spectra and B3LYP/6-31G(d) optimized geometry and energy of molecules and ions. See http://www.rsc.org/suppdata/cc/b3/b314713d/

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produces the ion $[PhNO_2 + C_2H_3]^+$ (*m/z* 150) and the phenylnitrenium ion $PhNH^+$ (*m/z* 92) as the reduced nitrobenzene product.

With phenylnitrenium ion $PhNH^+$ (*m/z* 92) in hand, the reactivity of this elusive species can be explored. Both n-propanol and benzene yielded adducts with the phenylnitrenium ions $PhNH^+$ (*m/z* 92), a result in agreement with previous reports.[8] In addition, it is found that the ion/molecule reaction between phenylnitrenium ions $PhNH^+$ (*m/z* 92) and ethyl vinyl ether yields the protonated indole (*m/z* 118) which fragments upon CID into ions at *m/z* 39, 65 and 91, the same products observed for the protonated authentic indole. This result exactly parallels McClelland *et al.*'s work[9] in which 4-biphenylnitrenium ion reacts with ethyl vinyl ether to yield 5-phenylindole in solution, providing another example[10] of the fact that ion/molecule reactions can provide valuable information on solution phase reactivity. In addition, the result further confirms the structure of phenylnitrenium ion $PhNH^+$.

This novel nitroreduction by the vinyl halide radical cation has been extended to substituted nitrobenzenes such as 4-nitrotoluene, 4-bromo-1-nitrobenzene, 1,3-dinitrobenzene, 2,4-dinitrotoluene and 2,4,6-trinitrotoluene (TNT). The corresponding arylnitrenium ions have been produced both in the 1,2-dichloroethane CI mass spectra and the CID MS/MS spectra of their vinylated ions (see ESI†). The novel and characteristic ion/molecule reaction uncovered in this work can be used for the selective detection of explosives like TNT in mixtures using tandem mass spectrometry. As a demonstration, a mixture of ethyl isovalerate, 2,4-dimethyl-3-hexanone and TNT was ionized using 1,2-dichloroethane as the reagent gas (Fig. 2a shows the CI spectrum). A neutral gain MS/MS scan[11] can be used as an effective method of identifying the presence of compounds bearing functional groups in a complex mixture. The experiment was carried out using benzene as the collision gas in Q2 at nominally zero kinetic energy and Q3 was scanned to record product ions at the same rate as Q1 scan. Because vinylated nitroaromatic ions can undergo characteristic fragmentation by loss of neutral CO and HCHO (neutral loss of 58 mass units) to form arylnitrenium ions subsequently yielding an adduct with benzene (neutral gain of 78 mass units), the net mass gain for the vinylated nitroaromatic ions is 20 mass units. The neutral gain MS/MS scans recorded using a mass/charge offset of 20 Da for the mixture show only the peak of the vinylated TNT ion, $[TNT + C_2H_3]^+$ (*m/z* 254, Fig. 2b). The high selectivity stems from the fact that only nitroaromatics can undergo this characteristic reaction sequence. The detection limit and analytical performance of this method are under investigation.

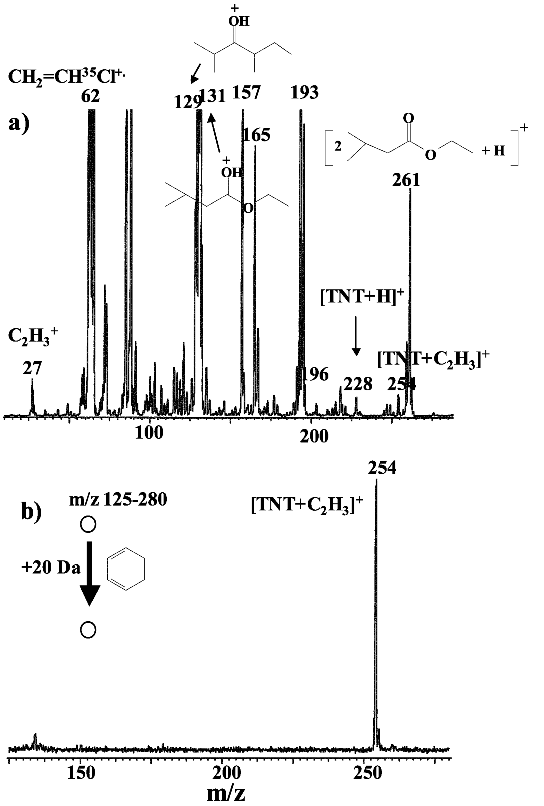

Fig. 2 a) 1,2-Dichloroethane CI mass spectrum of a mixture of ethyl isovalerate, 2,4-dimethyl-3-hexanone and TNT; ions at 157, 165 and 193 correspond to $C_2H_3^+$, $^{35}Cl^+$ and $CH_2{}^{35}ClCH_2^+$ adducts of ethyl isovalerate, respectively. b) Constant neutral gain MS/MS spectrum.

Additional experimental results reveal that CID fragmentation of the vinylated ions of two cancer-suspect agents, 2-nitrofluorene and 1-nitropyrene, produce the corresponding arylnitrenium ions (*m/z* 180 and 216), in spite of the low abundance of the precursor ions. Given the fact that arylnitrenium ions have been implicated in damage of DNA *in vivo* by forming covalently-bound adducts, the generation of arylnitrenium ion $ArNH^+$ from nitroaromatics $ArNO_2$ by this simple nitroreduction reaction indicates the possibility that the carcinogenic mechanism of nitroaromatics involves arylnitrenium ions, similar to that proposed for aromatic amines.[1]

In summary, this work reports a novel "one-pot" gas-phase nitroreduction of nitroaromatics by the vinyl halide radical cation which provides a new method to form arylnitrenium ions $ArNH^+$. This reaction is also demonstrated to be valuable for the highly selective detection of nitroaromatics such as the explosive TNT in mixtures and it is postulated that a related process might be responsible for the carcinogenic activity of nitroaromatics *in vivo*.

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