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# Generation of Arylnitrenium Ions by Nitro-Reduction and Gas-Phase Synthesis of *N*-Heterocycles

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Nitro-reduction by the vinyl halide radical cation  $\text{CH}_2 = \text{CH-X}^{\cdot+}$  ( $\text{X} = \text{Cl}$  or  $\text{Br}$ ) converts nitroaromatics into aryl nitrenium ions, significant intermediates in carcinogenesis, and the present study reports on the scope and regioselectivity of this versatile reaction. The reaction is general for different kinds of substituted nitroaromatics; *para/meta* substituents have little effect on the reaction while *ortho* substituents result in low yields of aryl nitrenium ions. The phenyl nitrenium ion  $\text{PhNH}^+$  can be generated by chemical ionization (CI) of nitrobenzene using 1,2-dichloroethane as the reagent gas or by atmospheric pressure chemical ionization (APCI) of 1,2-dichloroethane solution doped with nitrobenzene. The chemical reactivities of the aryl nitrenium ions include one-step ion/molecule reactions with nucleophiles ethyl vinyl ether and 1,3-dioxolanes, respectively, involving the direct formation of new C–N bonds and synthesis of indole and benzomorpholine derivatives. The indole formation reaction parallels known condensed phase chemistry, while the concise morpholine-forming reaction remains to be sought in solution. The combination of collision-induced dissociation (CID) with novel ion/molecule reactions should provide a selective method for the detection of explosives such as TNT, RDX and HMX in mixtures using mass spectrometry. In addition to the reduction of the nitro group, reduction of methyl phenyl sulfone  $\text{PhS(O)}_2\text{Me}$  to the thioanisole radical cation  $\text{PhSMe}^{\cdot+}$  occurs using the same chemical ionization reagent 1,2-dichloroethane. This probably involves an analogous reduction reaction by the reagent ion  $\text{CH}_2 = \text{CH-Cl}^{\cdot+}$ . (J Am Soc Mass Spectrom 2004, 15, 1675–1688) © 2004 American Society for Mass Spectrometry

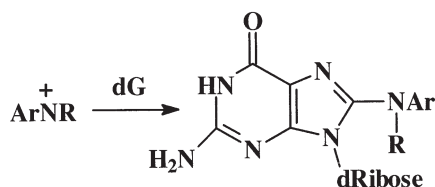
Nitrenium ions  $\text{RR}'\text{N}^+$ , a family of reactive intermediates characterized by a divalent nitrogen and a formal positive charge, are involved in a variety of organic reactions [1–3] and have also been implicated as ultimate carcinogens produced in the course of aromatic amine metabolism [4–7]. When aromatic amines are oxidatively converted to highly reactive aryl nitrenium ions  $\text{ArNR}^+$ , the elusive aryl nitrenium ions attack DNA *in vivo* to form amination adducts as the first step in a reaction sequence that may lead to carcinogenic mutation. Because of this relevance, the chemistry of nitrenium ions has received increasing attention [8–10]. It is known that in solution, aryl nitrenium ions  $\text{ArNH}^+$  react with nucleophiles (e.g.,  $\text{N}_3^-$ ,  $\text{Cl}^-$ ,  $\text{H}_2\text{O}$ ,  $\text{ROH}$ ) at the aromatic ring rather than at nitrogen, indicating that aryl nitrenium ions possess significant iminocyclohexadienyl cation character [11–15]. However, in the case of deoxyguanosine as

the nucleophile, aryl nitrenium ions react predominantly at the external nitrogen to yield the  $\text{C}_8$ -adduct (Scheme 1) [9]. Calculations have been performed to rationalize the complex regiochemistry of the interactions of nitrenium ions and nucleic acid bases [16]. Reactions of phenyl nitrenium ions with benzene and halobenzenes in the gas phase have been investigated by Kenttämä and coworkers using FT-ICR mass spectrometry [17]. While fluorobenzene forms exclusively an addition product, chlorobenzene also undergoes a halogen substitution reaction. Adduct formation of the isolated phenyl nitrenium ion with deoxyguanosine has also been observed in the gas phase [17].

Abramovitch et al. [18, 19], Takeuchi et al. [20, 21], and Falvey and coworkers [15, 22, 23] reported the generation of various nitrenium ions by the photolysis of *N*-aminopyridinium salts through heterolytic scission of the N–N bond (Scheme 2, eq 1) while McClelland [24, 25] observed the formation of aryl nitrenium ions from the hydrolysis of nitrene, generated by the photolysis of aryl azides (Scheme 2, eq 2). Aryl nitrenium ions can also be produced through hydrolysis of hydroxamic acid esters such as *N*-(sulfonatoxy)-*N*-

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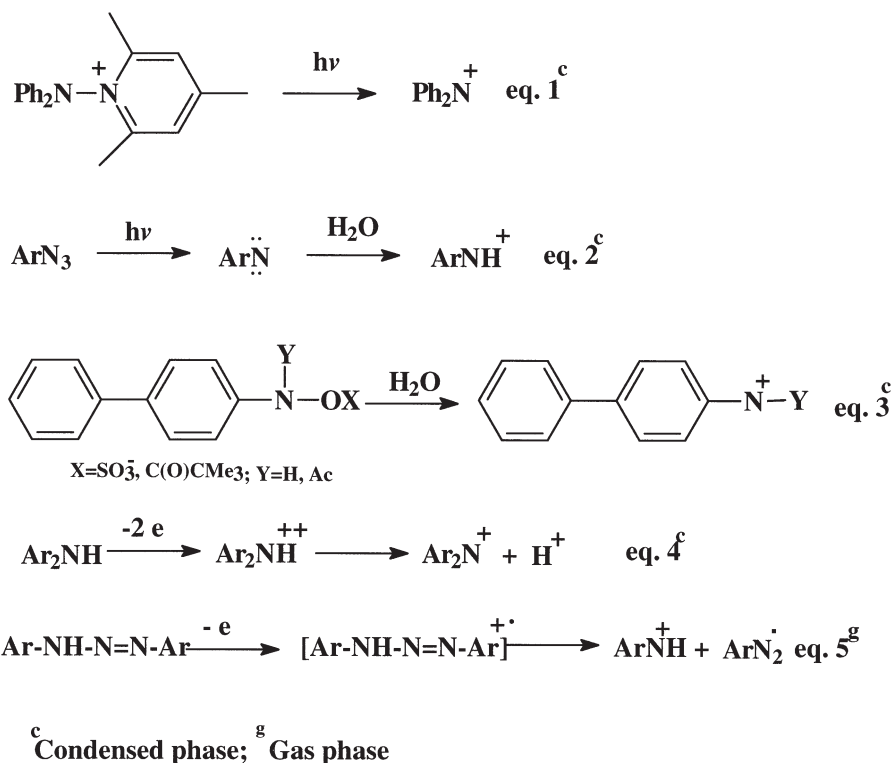


Scheme 1

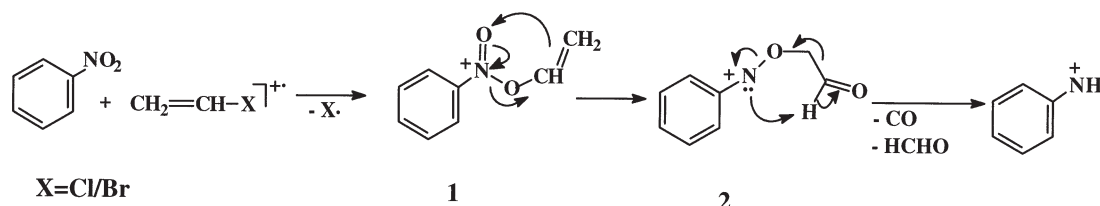
acetyl-4-biphenylamine (Scheme 2, eq 3) [26]. Diaryl derivatives  $\text{Ar}_2\text{N}^+$  have been obtained electrochemically via two electron oxidation and deprotonation of the corresponding amines in acetonitrile (Scheme 2, eq 4) [27, 28]. The loss of  $\text{N}_2$  upon protonation of phenyl azides in the gas phase has been reported to produce phenylnitrenium ions  $\text{PhNH}^+$  [29]. A previous study from this laboratory showed that electron ionization of diazoaminobenzene yields phenylnitrenium ions (Scheme 2, eq 5) [30].

Recently, we reported a simple new method for generation of the phenylnitrenium ion  $\text{PhNH}^+$  from

1,2-dichloroethane or vinyl bromide chemical ionization (CI) of nitrobenzene in the mass spectrometer, involving a novel reduction reaction of nitrobenzene by the vinyl halide radical cation  $\text{CH}_2 = \text{CH-X}^+$  ( $\text{X} = \text{Cl}$  or  $\text{Br}$ ) [31]. The reaction proceeds by vinylation of nitrobenzene followed by the exclusive fragmentation via a five-membered-ring Cope-like rearrangement to form the phenylnitrenium ions (Scheme 3). The present study further investigates the scope of this chemical ionization method for the generation of arylnitrenium ions and the regioselectivity of this reduction reaction by the vinyl halide radical cation. The analogous reduction of aromatic sulfones by vinyl chloride radical cation has also been explored. In addition, gas phase one-step syntheses of biologically important *N*-heterocycles, indole and benzomorpholine derivatives, from various reactive arylnitrenium ions have been examined, including the reaction mechanism. The potential applications of these characteristic reactions to the selective detection of explosives are also discussed.

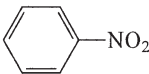
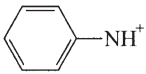
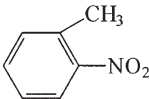
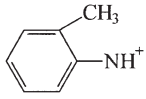
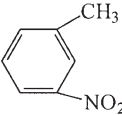
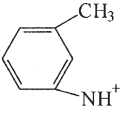
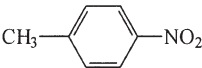

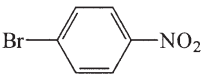
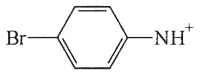
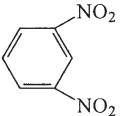
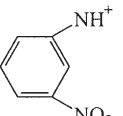
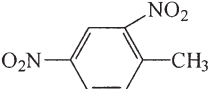
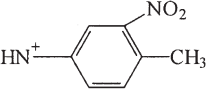
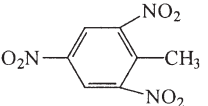
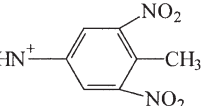
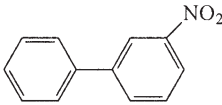
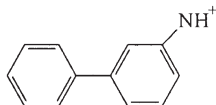
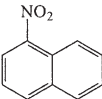
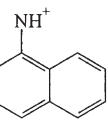
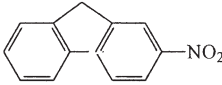
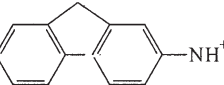
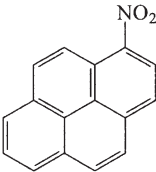
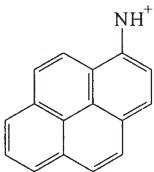


Scheme 2

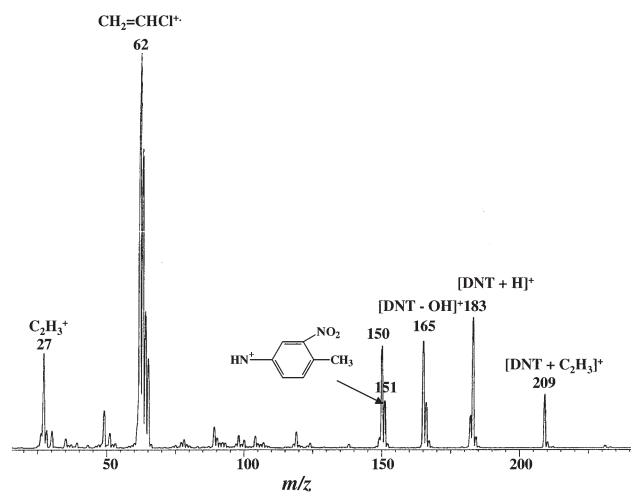


Scheme 3

**Table 1.** Chemical ionization of nitroaromatics using 1,2-dichloroethane as the reagent gas

Neutral compounds		Preferred structure	Generated arylnitrenium ions	
			<i>m/z</i>	<i>m/z</i> of its fragment ions
Nitrobenzene			92	39, 65
2-Nitrotoluene			106 <sup>a</sup>	30, 77, 78, 79
3-Nitrotoluene			106	79
4-Nitrotoluene			106	39, 51, 65, 79
4-Bromo-1-nitrobenzene			170	91, 143
1,3-Dinitrobenzene (DNB)			137	52, 54, 79, 91
2,4-Dinitrotoluene (DNT)			151	93, 104, 105
2,4,6-Trinitrotoluene (TNT)			196	66, 80, 91, 92, 121, 138, 150
3-Nitrobiphenyl			168	141
1-Nitronaphthalene			142 <sup>a</sup>	115
2-Nitrofluorene			180 <sup>a</sup>	82, 153
1-Nitropyrene			216 <sup>a</sup>	188, 189

<sup>a</sup>Low abundance.



**Figure 1.** Chemical ionization mass spectrum of 2,4-dinitrotoluene using 1,2-dichloroethane as the reagent gas. The reagent ion  $\text{CH}_2 = \text{CHCl}^+$  appears at  $m/z$  62.

## Experimental

Experiments were carried out using a Finnigan TSQ-70 and a TSQ 700 triple quadrupole mass spectrometer (ThermoFinnigan, San Jose, CA) fitted with conventional CI and an APCI ionization sources, respectively. Ion/molecule reactions were performed by mass selection of precursor ions in Q1, reaction with neutral reagent in Q2 and mass analysis using Q3 to monitor product ions. The collision energy, given as the voltage difference between the ion source and the collision quadrupole, was nominally 0 eV for ion/molecule reactions and either 3 or 10 eV for CID. All compounds were commercially available and used without further purification except the standard compound benzomorpholine.

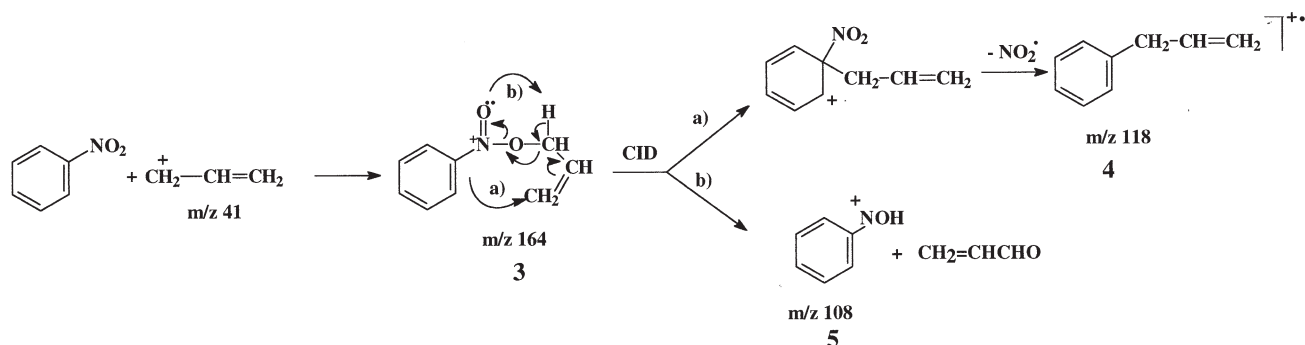
Density functional theory calculations (DFT) using B3LYP and 6-31G(d) basis sets were carried out with the Gaussian 98 program package [32] at the Purdue University Computing Center (PUCC) to obtain optimized geometries and energies. Harmonic vibrational frequencies were calculated at the B3LYP/6-31G(d) level to characterize the stationary points and to obtain the zero-point vibrational energies, which were scaled by a

factor of 0.96 and incorporated in the final total energy calculations. Hartree-Fock calculations were carried out with the Gaussian 2003 program [33].

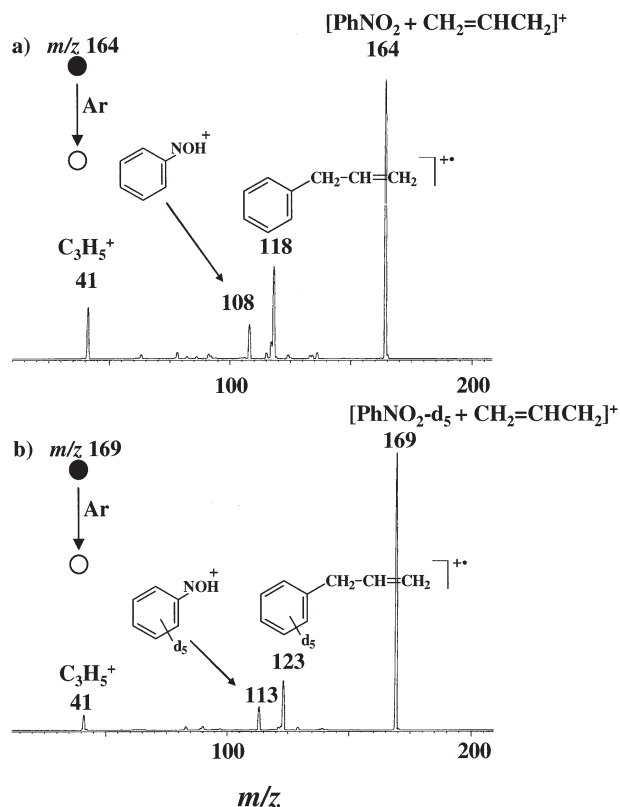
## Results and Discussion

### Generation of Arylnitrenium Ions by Nitro-Reduction

A previous report [31] showed that chemical ionization of nitrobenzene  $\text{PhNO}_2$  using 1,2-dichloroethane  $\text{CH}_2\text{ClCH}_2\text{Cl}$  or vinyl bromide  $\text{CH}_2 = \text{CH} - \text{Br}$  as the reagent gas (yielding  $\text{CH}_2 = \text{CHCl}^+$  or  $\text{CH}_2 = \text{CHBr}^+$  as the reagent ion) gives rise to phenylnitrenium ion  $\text{PhNH}^+$  ( $m/z$  92) presumably from the intermediate vinylated nitrobenzene  $[\text{PhNO}_2 + \text{C}_2\text{H}_3]^+$  ( $m/z$  150). The latter ion exclusively fragments into the phenylnitrenium ion upon CID. The chemical ionization process for the generation of phenylnitrenium ion involves the reduction of nitrobenzene by vinyl halide radical cation  $\text{CH}_2 = \text{CHX}^+$  ( $\text{X} = \text{Cl}$  or  $\text{Br}$ ), as confirmed by the ion/molecule reaction of the isolated ion  $\text{CH}_2 = \text{CHX}^+$  ( $\text{X} = \text{Cl}$  or  $\text{Br}$ ) with nitrobenzene. In the present study, chemical ionization of nitroaromatic compounds including 2-nitrotoluene, 3-nitrotoluene, 1-nitronaphthalene, and 3-nitrobiphenyl was carried out using 1,2-dichloroethane as the reagent gas. Corresponding reduced products, aryl nitrenium ions  $\text{ArNH}^+$ , have been observed both in the CI mass spectra and the CID MS/MS spectra of their precursors, the vinylated ions  $[\text{ArNO}_2 + \text{C}_2\text{H}_3]^+$ . The experimental results as well as previously reported data [31] are summarized in Table 1. Figure 1 shows the CI mass spectrum of 2,4-dinitrotoluene using 1,2-dichloroethane as the reagent gas as an example, in which the corresponding aryl nitrenium ion and the intact vinylated adduct appear at  $m/z$  151 and 209, respectively. Ion of  $m/z$  150 in Figure 1 might be 4-methyl-3-nitrophenylnitrene radical cation, which fragments into ions of  $m/z$  92 and 104. It can be seen that the chemical ionization method for the generation of aryl nitrenium ions is quite general and the reduction reaction is feasible for various substituted nitroaromatics, including mono-, di- and trisubstituted nitrobenzenes and nitropolyaromatics. However, compared

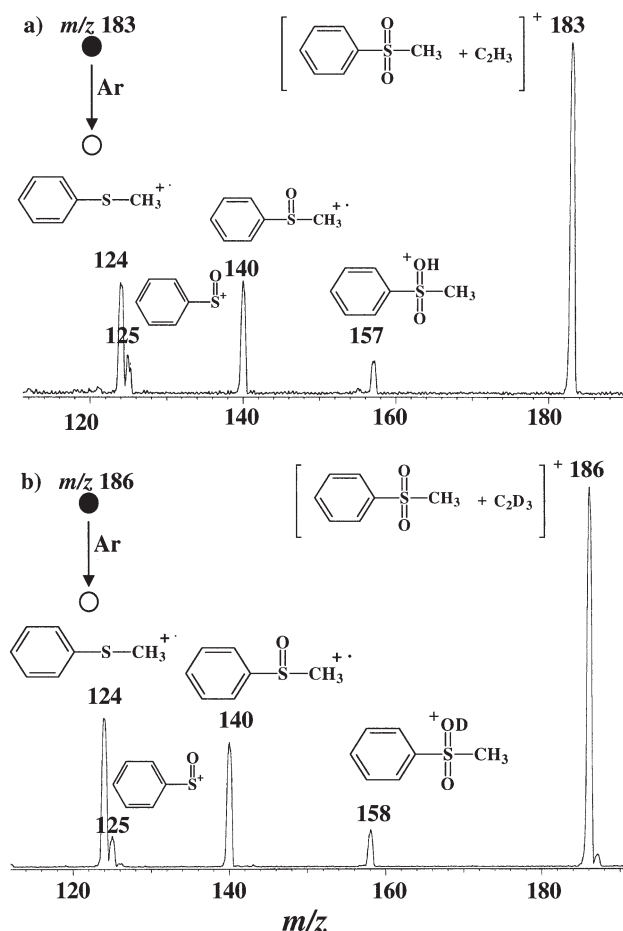


**Scheme 4**

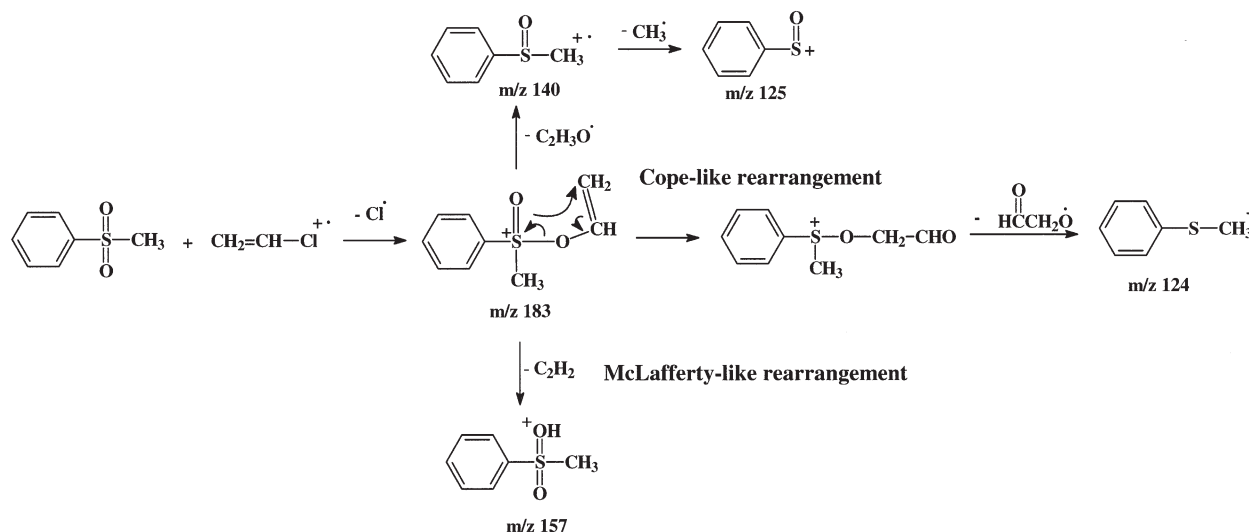


**Figure 2.** CID product ion MS/MS spectra of allyl adduct ions: (a)  $[\text{PhNO}_2 + \text{CH}_2 = \text{CHCH}_2]^+$  ( $m/z$  164) and (b)  $[\text{PhNO}_2\text{-d}_5 + \text{CH}_2 = \text{CHCH}_2]^+$  ( $m/z$  169) using argon as target at nominal 3 eV collision energy.

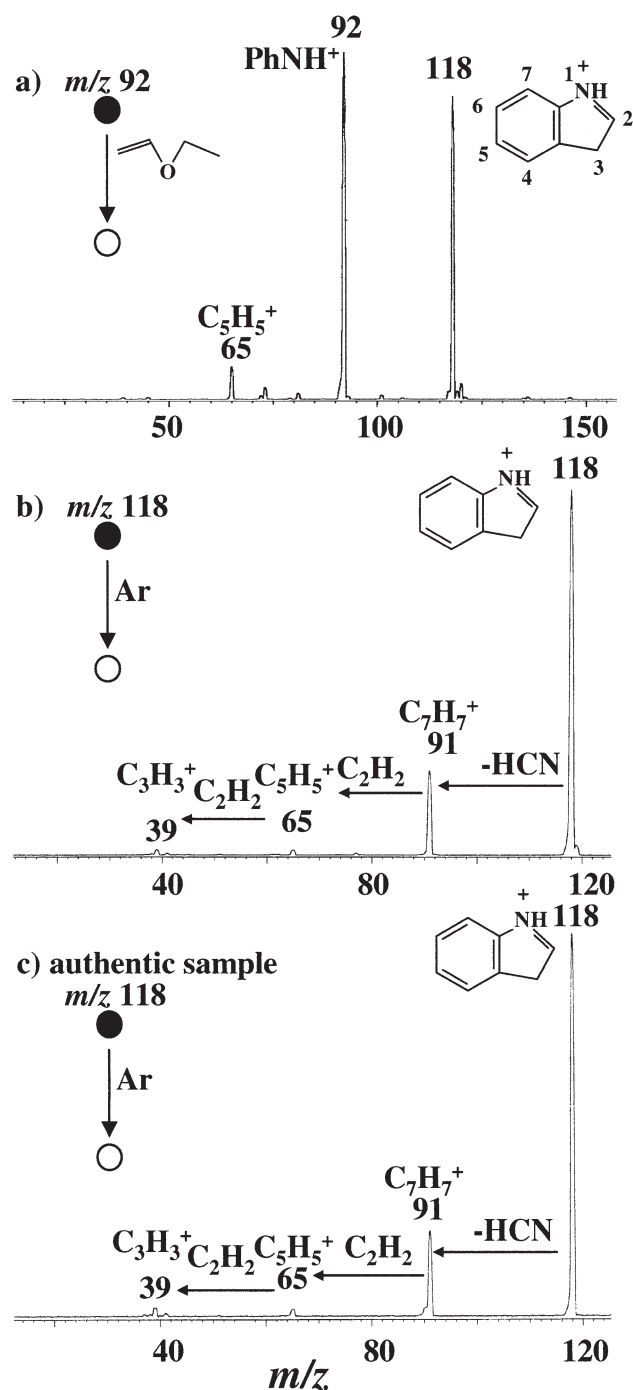
with substituted nitrobenzenes, nitropolyaromatics such as 1-nitronaphthalene, 2-nitrofluorene, and 1-nitropyrene, give lower yields of aryl nitrenium ions. Also, it can be seen from Table 1 that the position of substituents in the nitroaromatics affects the efficiency of generation of aryl nitrenium ions. For instance, com-



**Figure 3.** CID product ion MS/MS spectra of vinyl adduct ions: (a)  $[\text{PhS}(\text{O})_2\text{Me} + \text{C}_2\text{H}_3]^+$  ( $m/z$  183) and (b)  $[\text{PhS}(\text{O})_2\text{Me} + \text{C}_2\text{D}_3]^+$  ( $m/z$  186) using argon as target at nominal 10 eV collision energy.



**Scheme 5**



**Figure 4.** (a) Product ion mass spectrum showing ion/molecule reactions of the phenylnitrenium ion  $\text{PhNH}^+$  ( $m/z$  92) with ethyl vinyl ether. The protonated indole ion ( $m/z$  118) is the main product. (b) CID product ion MS/MS spectrum of the product ion at  $m/z$  118 generated from the ionization of a mixture of nitrobenzene, vinyl bromide, and ethyl vinyl ether and (c) CID product ion MS/MS spectrum of protonated indole ( $m/z$  118) generated by CI of authentic indole using isobutane as the reagent gas. Spectra b and c are identical.

pared with 3-nitrotoluene and 4-nitrotoluene, 2-nitrotoluene gave a very weak peak of 2-methyl phenylnitrenium ion, indicating that the *ortho*-substituted group reduces the yield of the aryl nitrenium ions while *meta*-

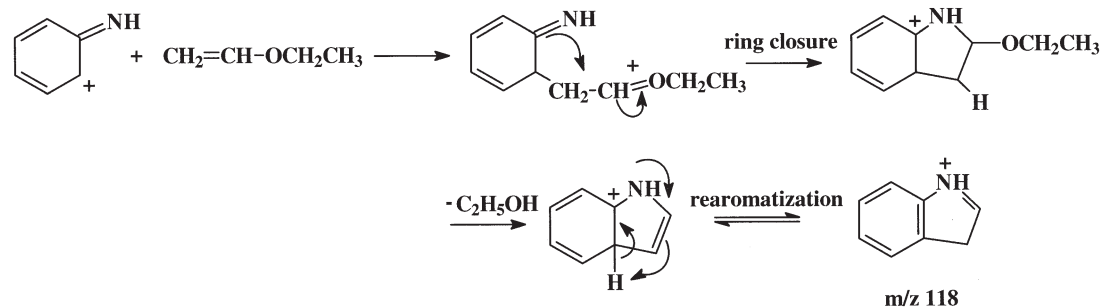
and *para*-substitution has little effect. For nitroaromatic compounds such as 4-bromo-1-nitrobenzene, 1,3-dinitrobenzene (DNB), 2,4-dinitrotoluene (DNT), 2,4,6-trinitrotoluene (TNT), and 3-nitrobiphenyl, which have at least one nitro group without adjacent substituents, the yields of nitrenium ions are relatively high. The effect of neighboring groups suggests that the predominant structure of the formed nitrenium ion from multiply nitro-substituted compounds like DNT might be 4-methyl-3-nitrophenylnitrenium ion rather than 2-methyl-3-nitrophenylnitrenium ion. This important regioselectivity can be explained as the result of an *ortho* steric effect which prevents the vinylation of substrates by the vinyl halide radical cation, the first key step in the reaction. On the basis of this hypothesis, the most likely structures of the generated aryl nitrenium ions are included in Table 1 as well. A common loss of neutral HCN (or HNC) was observed upon CID of all of the aryl nitrenium ions except those with additional nitro substituents, such as 4-methyl-3-nitrophenylnitrenium ion which displays an alternative fragmentation by loss of  $\text{NO}_2$ .

Interestingly, when  $\text{PhNO}_2^+$  was mass-selected and allowed to react with  $\text{CH}_2 = \text{CHCl}$ , i.e., when the charges on the two reagents in the above CI experiment were reversed, phenylnitrenium ion  $\text{PhNH}^+$  was again observed. However, since no neutral gas reagent  $\text{CH}_2 = \text{CHCl}$  was used during the corresponding CI experiment on nitrobenzene using  $\text{CH}_2\text{ClCH}_2\text{Cl}$  as the reagent, the generation of phenylnitrenium ion  $\text{PhNH}^+$  in this ion/molecule reaction can not be the result of a direct reaction between radical cation  $\text{PhNO}_2^{\cdot+}$  and  $\text{CH}_2 = \text{CHCl}$ . Instead it must be due to the reaction of the charge exchange product  $\text{CH}_2 = \text{CHCl}^{\cdot+}$  with  $\text{PhNO}_2$ , as proposed earlier [31].

Compared with the previously reported methods for the generation of nitrenium ions discussed in the Introduction, the advantage for the method reported here is that the intrinsic chemical reactivity of aryl nitrenium ions can be explored easily in the gas phase using mass spectrometry, as demonstrated below. When a mixture of 1,2-dichloroethane and nitrobenzene (120:1 by volume) was ionized by positive ion APCI in a commercial instrument TSQ 700 without any modification, the phenylnitrenium ion  $\text{PhNH}^+$  ( $m/z$  92) was formed. This example of an ion/molecule reaction occurring under atmospheric pressure [34] extends the scope of the method for the generation of aryl nitrenium ions, since larger and heavier molecular substrates can be introduced using APCI compared to conventional CI.

In the case of the prototype nitro-reduction reaction, we propose a five-member-ring Cope-like rearrangement mechanism converting the ion 1 to form 2 (Scheme 3). An analogous Cope-like rearrangement (Scheme 4, pathway a) reported from this laboratory in 1976 occurs during the fragmentation of allylated nitrobenzene 3 [ $\text{PhNO}_2 + \text{CH}_2 = \text{CH-CH}_2$ ] $^+$  ( $m/z$  164) and forms the allyl-substituted benzene radical cation 4 ( $m/z$



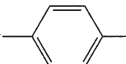
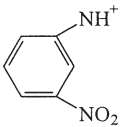
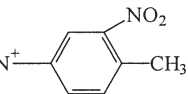
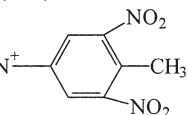


Scheme 6

118) [35]. When this experiment was repeated recently using the triple quadrupole instrument, an additional rearrangement (pathway b) was observed to produce the protonated nitrosobenzene 5 ( $m/z$  108) by loss of the  $\alpha,\beta$ -unsaturated aldehyde, acrolein  $\text{CH}_2 = \text{CHCHO}$ . The low-energy CID (nominal 3 eV) of [nitrobenzene +  $\text{C}_3\text{H}_5$ ] $^+$  ( $m/z$  164) generated by chemical ionization of nitrobenzene using allyl bromide as the reagent gas, gives rise to rearrangement ions of  $m/z$  108 and 118

(Figure 2a). Correspondingly, the low-energy collision (3 eV) of [nitrobenzene- $\text{d}_5$  +  $\text{C}_3\text{H}_5$ ] $^+$  ( $m/z$  169) generated by chemical ionization of nitrobenzene- $\text{d}_5$  using allyl bromide as the reagent gas forms the isotopologue ions of  $m/z$  113 and 123 (Figure 2b). Upon higher-energy collisions, i.e., 10 eV, both the ions 4 and 5 generated by rearrangement disappeared and only the allyl cation  $\text{CH}_2 = \text{CH-CH}_2^+$  ( $m/z$  41) could be seen. This result is consistent with the well-known generalization that

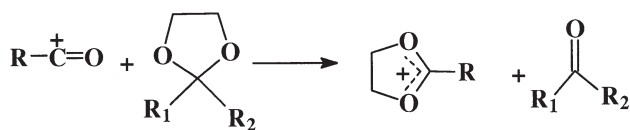
**Table 2.** Major ionic products of ion/molecule reactions between aryl nitrenium (or vinylated ions) and ethyl vinyl ether

Reagent ions ( $m/z$ )	Products, $m/z$ (relative abundance) <sup>a</sup>				
	Protonated indole derivatives	Proton transfer	Ethyl transfer	Adduct	Other ions
PhNH $^+$ (92)	118 (100)	73 (5)	101 (2)	- <sup>b</sup>	65(10), 81(2), 120(5)
Br-  NH $^+$ (170)	196 (36)	73 (34)	101 (35)	242 (3)	72(22), 117(39), 118(46), 164(47), 171(100), 186(36), 214(20)
 NH $^+$ (137)	163 (19)	73 (31)	101 (33)	-	72(40), 91(16), 107(20), 117(100), 146(26), 165(17), 218(9)
HN $^+$ -  (151)	177 (62)	73 (46)	101 (100)	223 (15)	93(71), 131(35), 149(40), 249(39)
HN $^+$ -  (196)	222 (9)	73 (39)	101 (100)	268 (11)	80(12), 136(12), 150(15)
[PhNO $_2$ + $\text{C}_2\text{H}_3$ ] $^+$ (150)	118 (100)	73 (5)	101 (4)	222 (3)	65(8), 92(88), 176(13)
[4-BrPhNO $_2$ + $\text{C}_2\text{H}_3$ ] $^+$ (228)	196 (67)	73 (11)	101 (23)	300 (65)	117(100), 118(77), 163(86), 170(62), 196(67), 254(83)
[DNB + $\text{C}_2\text{H}_3$ ] $^+$ (195)	163 (17)	73 (44)	101 (43)	- <sup>b</sup>	72(21), 117(100), 137(76), 208(18), 221(79)
[DNT + $\text{C}_2\text{H}_3$ ] $^+$ (209)	177 (41)	73 (45)	101 (72)	281 (81)	93(100), 117(31), 131(51), 151(67), 233(71)
[TNT + $\text{C}_2\text{H}_3$ ] $^+$ (254)	222 (7)	73 (49)	101 (16)	326 (43)	267(24), 196(100), 280(49)

<sup>a</sup>Percentage abundance relative to the base peak, excluding the reagent ion.

<sup>b</sup>Not observed.





Scheme 7

high-energy collisions favor simple cleavage over rearrangements.

### Reduction of Methyl Phenyl Sulfone to Give the Thioanisole Radical Cation

The remarkable nitro reduction has been extended to methyl phenyl sulfone  $\text{PhS(O)}_2\text{Me}$ , an aromatic sulfone. Chemical ionization of methyl phenyl sulfone  $\text{PhS(O)}_2\text{Me}$  using 1,2-dichloroethane as the reagent gas, forms thioanisole radical cation  $\text{PhSMe}^+$  ( $m/z$  124) and CID of this ion yields the same fragment ions of  $m/z$  47, 65, 78, 91, and 109 as that of the molecular ion from authentic methyl phenyl sulfide by electron ionization (EI), confirming its structure. Formation of the thioanisole radical cation ( $\text{PhSMe}^+$ ,  $m/z$  124) probably involves the reduction of methyl phenyl sulfone by vinyl chloride radical cation  $\text{CH}_2 = \text{CHCl}^+$ , analogously to the case of nitrobenzene. In parallel with the nitro-reduction, vinylated methyl phenyl sulfone [ $\text{PhS(O)}_2\text{Me} + \text{C}_2\text{H}_3$ ] $^+$  ( $m/z$  183) was also observed in 1,2-dichloroethane chemical ionization of methyl phenyl sulfone,  $\text{PhS(O)}_2\text{Me}$ . As displayed in Figure 3a, the ion of  $m/z$  183 yields upon CID to yield the protonated methyl phenyl sulfone cation  $\text{PhS(O)(OH)Me}^+$  ( $m/z$  157) by loss of acetylene, the methyl phenyl sulfoxide radical cation ( $\text{PhS(O)Me}^+$ ,  $m/z$  140) by loss of  $\text{C}_2\text{H}_3\text{O}^+$  radical and the

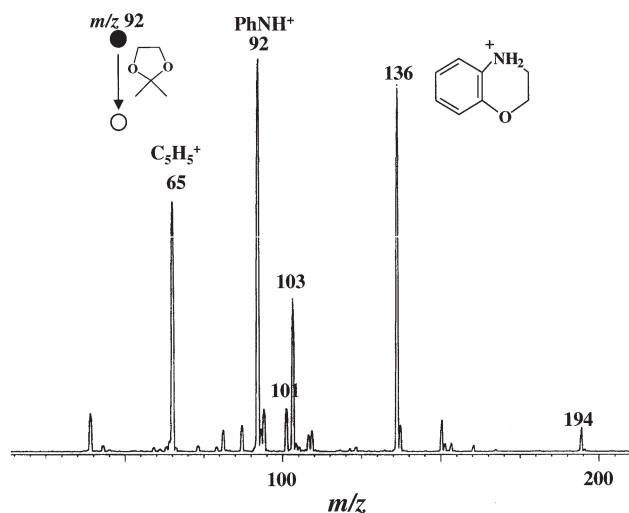
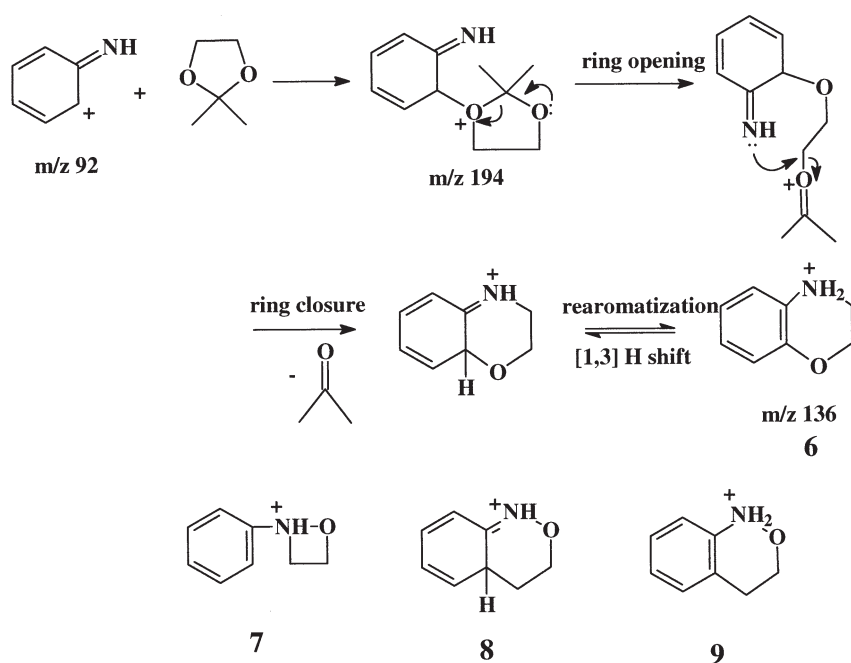


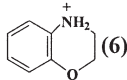
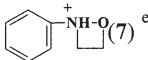
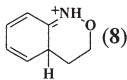
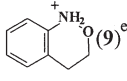
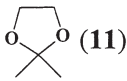
Figure 5. Product ion mass spectrum showing ion/molecule reactions of the phenylnitrenium ion  $\text{PhNH}^+$  ( $m/z$  92) with 2,2-dimethyl-1,3-dioxolane.

thioanisole radical cation ( $\text{PhSMe}^+$ ,  $m/z$  124). The fragment ion  $\text{PhS}^+(\text{O})$  ( $m/z$  125) arises from secondary fragmentation of  $\text{PhS(O)Me}^+$  ( $m/z$  140) by loss of  $\text{CH}_3$ . The structural assignment of these fragment ions was confirmed by CID of the deuterated vinylated methyl phenyl sulfone ion [ $\text{PhS(O)}_2\text{Me} + \text{C}_2\text{D}_3$ ] $^+$  ( $m/z$  186) generated by the chemical ionization of methyl phenyl sulfone  $\text{PhS(O)}_2\text{Me}$  using 1,2-dichloroethane- $\text{d}_4$  as the reagent gas (Figure 3b). Scheme 5 suggests a mechanism of formation of the thioanisole radical cation in chemical ionization. First, vinylation of methyl phenyl sulfone occurs by loss of chlorine from the vinyl chloride radical cation to form the vinylated methyl phenyl



Scheme 8

**Table 3.** B3LYP/6-31G(d) calculated energies of molecules and cations

Species	E (Hartrees <sup>a</sup> )	ZPE <sup>b</sup>	Corrected energies <sup>c</sup>	ΔE (kcal/mol)
 (6)	−440.5931071	0.173546	−440.42650	— <sup>d</sup>
 (7) <sup>e</sup>	—	—	—	—
 (8)	−440.528923	0.170383	−440.36536	—
 (9) <sup>e</sup>	—	—	—	—
PhNH <sup>+</sup> (10)	−286.6702715	0.105611	−286.56888	—
 (11)	−346.9884299	0.148979	−346.84541	—
CH <sub>3</sub> COCH <sub>3</sub> (12)	−193.1556946	0.084072	−193.07499	—
(6 + 12) - (10 + 11)	—	—	—	−54.7

<sup>a</sup>1 Hartree = 627.51 kcal/mol.<sup>b</sup>Uncorrected.<sup>c</sup>Calculated as E + ZPE × 0.96.<sup>d</sup>Not applied.<sup>e</sup>Unstable species.

sulfone ion [PhS(O)<sub>2</sub>Me + C<sub>2</sub>H<sub>3</sub>]<sup>+</sup> (*m/z* 183). Besides a McLafferty-type rearrangement and the direct cleavage to form the ion PhS(O)(OH)Me<sup>+</sup> (*m/z* 157) and PhS(O)Me<sup>+</sup> (*m/z* 140), respectively, the precursor ion of *m/z* 183 undergoes a five-membered ring Cope-like rearrangement followed by a cleavage of the S–O bond to yield the ion PhSMe<sup>+</sup> of *m/z* 124, a process similar to the key step involved in the nitro-reduction mechanism mentioned above. Overall, this reduction of methyl phenyl sulfone by vinyl chloride radical cation forms the thioanisole radical cation via loss of two oxygen atoms while the net oxidation number of sulfur changes from +2 in methyl phenyl sulfone to −1 in PhSMe<sup>+</sup>. Calculations (Gaussian 2003 HF/3-21 + G) show that this reaction is highly exothermic (by 120.6 kcal/mol). Additional experimental results show that 1,2-dichloroethane chemical ionization of methyl benzenesulfinate PhS(O)OMe failed to form the deoxygenated product ion PhSMe<sup>+</sup>, consistent with the proposed mechanism in indicating that the reduction reaction requires two adjacent double bonds (S–O or N–O) in reactants like nitrobenzene and methyl phenyl sulfone.

### Synthesis of N-Heterocycles Using Arylnitrenium Ions

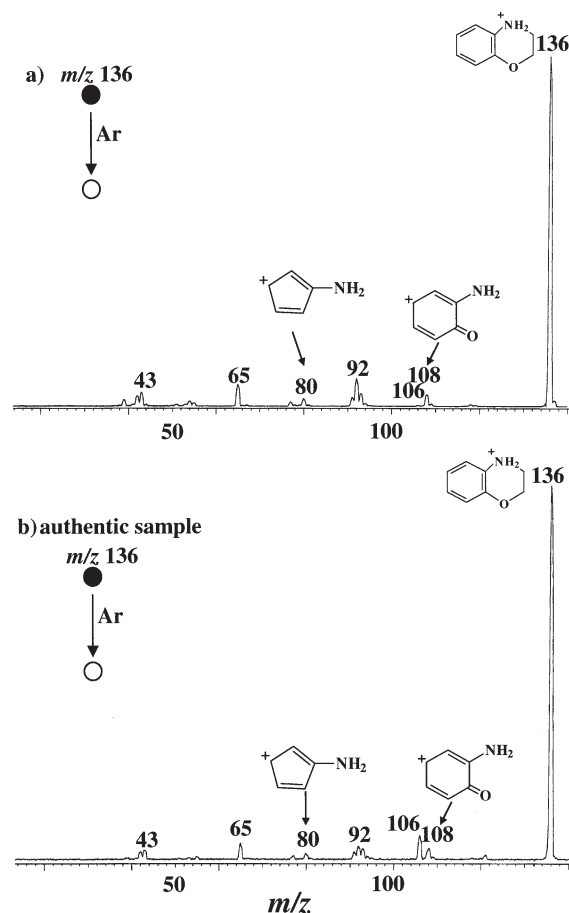
**Indole synthesis.** Indole ring system, present in many natural products, in pharmaceuticals, and in agro-

chemicals, exhibits important biological activity. For this reason, there is a continuing quest for efficient synthetic methods of construction of this heterocycle system. However, classical methods such as the Fisher [36], Gassman [37], and Nenitzescu [38] procedures usually require highly functionalized starting materials which are not easily available. A gas-phase Fischer indole synthesis via acid-catalyzed elimination of NH<sub>3</sub> from protonated phenylhydrazones was reported from this laboratory [39]. With phenylnitrenium ion PhNH<sup>+</sup> (*m/z* 92) in hand, the indole ring can be easily constructed in a one-step synthesis. Figure 4a shows the product ion mass spectrum of the ion/molecule reaction between phenylnitrenium ions PhNH<sup>+</sup> (*m/z* 92) and ethyl vinyl ether. The major product ion at *m/z* 118 was identified as the protonated indole. (Note that protonation occurs preferentially at the C3 atom) [40]. Evidence for this identification was obtained by comparing the CID spectrum of the product ion with that of the protonated authentic indole (Figure 4b and c). The fragment ion at *m/z* 91 was formed by the loss of HCN from the protonated indole (*m/z* 118) upon collision and it can further dissociate into ions at *m/z* 65 and 39 by consecutive losses of acetylene molecules. This result exactly parallels the condensed-phase study of McClelland et al. [41] in which they found that 4-biphenylnitrenium ion reacts with ethyl vinyl ether to yield 5-phenylindole using a laser flash photolysis (LFP)

technique, providing another example [39, 42–45] of the fact that ion/molecule reactions can bridge the gas phase/condensed phase gap. A mechanism for the formation of the protonated indole is proposed in Scheme 6. Initially the phenylnitrenium ion  $\text{PhNH}^+$  shown in the iminocyclohexadienyl cation form [11–15] gives an addition product with ethyl vinyl ether in Markovnikov fashion. The subsequent ring closure followed by the elimination of ethanol and re-aromatization gives rise to the protonated indole ( $m/z$  118). Note that the new C–N bond is formed during this ion/molecule reaction.

Ion/molecule reactions of ethyl vinyl ether with 4-bromophenylnitrenium ion ( $m/z$  170), 3-nitrophenylnitrenium ion ( $m/z$  137), 4-methyl-3-nitrophenylnitrenium ion ( $m/z$  151), 4-methyl-3,5-dinitrophenylnitrenium ion ( $m/z$  196) generated from 1,2-dichloroethane CI of 4-bromo-1-nitrobenzene, 1,3-dinitrobenzene, 2,4-dinitrotoluene, and 2,4,6-trinitrotoluene (TNT), respectively, were also examined and the results are summarized in Table 2. All of the corresponding indole products were generated from these arylnitrenium ions. The major competitive reactions are proton transfer and ethyl transfer to give the protonated and ethylated ions of ethyl vinyl ether.


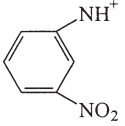
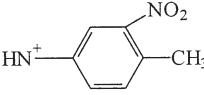
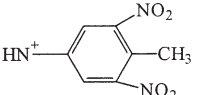
**Benzomorpholine synthesis.** Benzomorpholine, 3,4-dihydro-2H-1,4-benzoxazine, is a constituent of many naturally occurring substances [46]. Various benzoxazine derivatives have shown interesting pharmacological activities, e.g., anticancer [47], antiemetic [48], antitubercular [49], and antirheumatic properties [50]. It is therefore important to seek new simple routes for the synthesis of benzomorpholine. An earlier study [51] from this laboratory reported that arenesulfonylium cation  $\text{PhS}^+$  can undergo the Eberlin reaction with 2,2-dimethyl-1,3-dioxolane, a cyclic ketal and form a characteristic four-membered cyclic product, 2-aryl-1,2-oxathietan-2-ium ion (the prototype Eberlin reaction [52–55] is the gas-phase transacetalization of acylium ions  $\text{RCO}^+$  by cyclic acetals or ketals, as shown in Scheme 7). The reaction proceeds through transfer of an oxirane  $\text{CH}_2\text{CH}_2\text{O}$  moiety, the protection group of 2,2-dimethyl-1,3-dioxolane, to the arenesulfonylium cation  $\text{PhS}^+$  with release of neutral acetone. The reactive electrophile, phenylnitrenium ion  $\text{PhNH}^+$  ( $m/z$  92) is structurally similar to arenesulfonylium cation  $\text{PhS}^+$  and its reaction with cyclic acetals and ketals has been also performed. Figure 5 illustrates the product ion mass spectrum of the ion/molecule reaction between phenylnitrenium ions  $\text{PhNH}^+$  ( $m/z$  92) and 2,2-dimethyl-1,3-dioxolane. A highly abundant peak ( $m/z$  136) is observed, which corresponds to the Eberlin reaction product with a mass/charge increment of 44 in comparison to the reactant  $\text{PhNH}^+$  ( $m/z$  92). Other product ions,  $m/z$  101 and 103, due to hydride abstraction and proton transfer reaction of 2,2-dimethyl-1,3-dioxolane are observed as the main competitive reactions. Simi-



**Figure 6.** CID product ion MS/MS spectra of: (a) the product ion of  $m/z$  136 generated from the ionization of a mixture of nitrobenzene, vinyl bromide, and 2,2-dimethyl-1,3-dioxolane and (b) the protonated benzomorpholine ( $m/z$  136) generated by CI of authentic benzomorpholine sample using isobutane as the reagent gas.

larly,  $\text{PhND}^+$  ( $m/z$  93) reacts with 2,2-dimethyl-1,3-dioxolane to yield the corresponding Eberlin product ion of  $m/z$  137. In Eberlin reactions, reactant ions are generally required to have a Lewis acidic site that can participate in electrophilic addition and a Lewis basic site that can promote nucleophilic ring-closure [56]. Based on this rule, the most likely product ion structure and mechanism for the Eberlin reaction is proposed in Scheme 8. Initially, the simple adduct ( $m/z$  194, Figure 5) of the phenylnitrenium ion  $\text{PhNH}^+$  and neutral 2,2-dimethyl-1,3-dioxolane is formed. Electrophilic addition takes place at the *ortho*-carbon in the aromatic ring rather than the nitrogen of the phenylnitrenium ion, just as the case for the reaction of phenylnitrenium ion with ethyl vinyl ether. Subsequently, a ring opening/recyclization process occurs to release the neutral acetone, followed by re-aromatization via a 1,3-hydrogen shift to yield a *N*-heterocycle product, the protonated benzomorpholine 6. Overall, transfer of an oxirane  $\text{CH}_2\text{CH}_2\text{O}$  moiety, the protection group of the 2,2-dimethyl-1,3-dioxolane, onto the phenylnitrenium

**Table 4.** Major ionic products of the Eberlin reaction of arylnitrenium ions (or vinylated ions) and cyclic acetals (or ketals)

Reactants		Products, <i>m/z</i> (relative abundance) <sup>a</sup>			
Ions ( <i>m/z</i> )	Neutrals	Eberlin reaction product	Proton transfer and hydride abstraction	Adduct	Other ions
PhNH <sup>+</sup> (92)	2,2-dimethyl-1,3-dioxolane	136 (100)	103(41),101(12)	194 (7)	39(11),65(69),150(9)
	4-methyl-1,3-dioxolane	150 (7)	89(17),87(100)	180 (24)	39(8), 65(53), 122(10), 162(8), 177(9)
	1,3-dioxolane	136 (4)	75(5), 73(100)	166 (30)	65(16), 106(11), 148(12)
	1,3-dioxane	150 (15)	89(15),87(30)	180 (100)	39(7), 65(34), 145(9), 162(19), 177(3)
PhND <sup>+</sup> (93)	2,2-dimethyl-1,3-dioxolane	137 (91)	103(47), 101(14)	195 (26)	39(13), 65(100), 110(38), 136(55), 151(27)
 (170)	2,2-dimethyl-1,3-dioxolane	214 (46)	103(57), 101(16)	272 (14)	91(32), 143(29), 175(40), 254(100)
 (137)	2,2-dimethyl-1,3-dioxolane	181 (49)	103(100), 101(22)	239 (4)	79(14), 84(11), 91(36), 175(39), 204(21), 221(49)
 (151)	2,2-dimethyl-1,3-dioxolane	195 (10)	103(100), 101(4)	253 (40)	93(37), 207(7)
 (196)	2,2-dimethyl-1,3-dioxolane	240 (18)	103(100), 101(10)	- <sup>b</sup>	59(16), 108(12), 121(14), 138(23), 150(14)
[PhNO <sub>2</sub> + C <sub>2</sub> H <sub>3</sub> ] <sup>+</sup> (150)	2,2-dimethyl-1,3-dioxolane	136 (63)	103(9), 101(6)	-	65(13), 92(100), 194(3)
[4-BrPhNO <sub>2</sub> + C <sub>2</sub> H <sub>3</sub> ] <sup>+</sup> (228)	2,2-dimethyl-1,3-dioxolane	214 (16)	103(39), 101(11)	-	91(9), 170(65), 175(19), 254(100), 272(12)
[DNB + C <sub>2</sub> H <sub>3</sub> ] <sup>+</sup> (195)	2,2-dimethyl-1,3-dioxolane	181 (13)	103(14), 101(4)	-	137(100), 173(5), 175(10), 204(5), 221(16), 279(3)
[DNT + C <sub>2</sub> H <sub>3</sub> ] <sup>+</sup> (209)	2,2-dimethyl-1,3-dioxolane	195 (9)	103(100), 101(3)	-	93(25), 151(23), 226(22), 253(23)
[TNT + C <sub>2</sub> H <sub>3</sub> ] <sup>+</sup> (254)	2,2-dimethyl-1,3-dioxolane	240 (4)	103(100), 101(2)	-	104(7), 138(6), 150(5), 196(42), 298(2)

<sup>a</sup>Percentage abundance relative to the base peak, excluding the reagent ion.<sup>b</sup>Not observed

ion PhNH<sup>+</sup> occur with a total exothermicity is 54.7 kcal/mol in terms of density functional theory (DFT) calculations (Table 3). The adduct ion of *m/z* 194 mainly fragments into protonated benzomorpholine (*m/z* 136) and phenylnitrenium ion (*m/z* 92) upon CID. It suggests that the adduct ion (*m/z* 194) is the intermediate for the Eberlin reaction, in good agreement with the proposed mechanism. Calculations also show that the protonated benzomorpholine **6** is more stable than other likely structures such as **7**, **8**, and **9**, listed in Scheme 8. This result was confirmed by the comparison of CID spectrum of the product ion (*m/z* 136) with protonated authentic benzomorpholine (Figure 6a and b). The two CID spectra are very similar except for the relative abundance of the peak at *m/z* 106 which could be due to the impurity in the authentic benzomorpholine sample. The ion

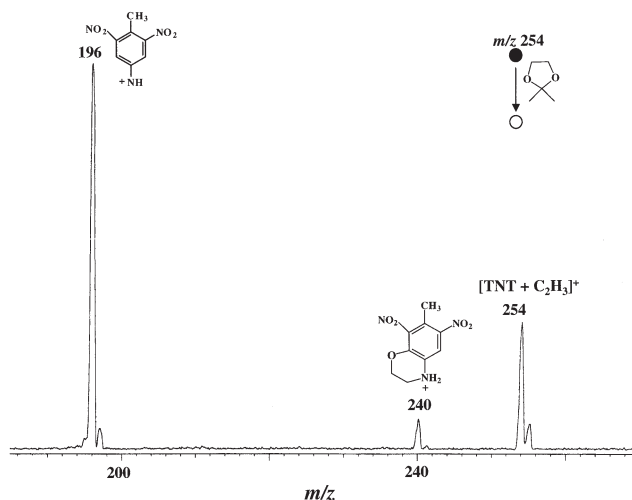
of *m/z* 80 could be formed from the further dissociation of the characteristic ion at *m/z* 108 by loss of CO.

When 4-methyl-1,3-dioxolane was used as collision gas instead of 2,2-dimethyl-1,3-dioxolane, the expected transfer of CH(CH<sub>3</sub>)CH<sub>2</sub>O took place, demonstrating the occurrence of an Eberlin-type reaction. The lower abundance of the product ion (*m/z* 150) in the case of 4-methyl-1,3-dioxolane indicates that the steric effect of the methyl group in 4-methyl-1,3-dioxolane reduces the reaction yield [54]. Cyclic acetals such as 1,3-dioxolane and 1,3-dioxane were found to undergo Eberlin-like reactions with phenylnitrenium ions as well. Additional arylnitrenium ions, 4-bromophenylnitrenium ion (*m/z* 170), 3-nitrophenylnitrenium ion (*m/z* 137), 4-methyl-3-nitrophenylnitrenium ion (*m/z* 151) and 4-methyl-3,5-dinitrophenylnitrenium ion (*m/z* 196) were also studied.

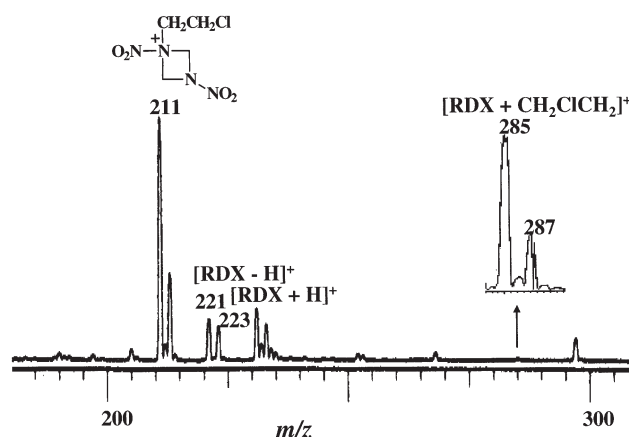
nylnitrenium ( $m/z$  196), were also found to react with 2,2-dimethyl-1,3-dioxolane to form the corresponding ionic morpholine products and the results are summarized in Table 3. The major involved competitive reactions are proton transfer and hydrogen abstraction to give the protonated and deprotonated ions of 2,2-dimethyl-1,3-dioxolane, respectively. The gas-phase Eberlin reactions of aryl nitrenium ions in the synthesis of benzomorpholines suggest that the analogous concise reaction in the condensed phase might exist, just as the indole synthesis discussed above.

### Application to Explosives Monitoring

Employing CID to cause fragmentation of analytes ions followed by reaction of fragment ions—ion/molecule reactions after collision-induced dissociation—represents a general strategy for identifying classes of compounds with high selectivity [57, 58, 59]. As mentioned before, the vinylated nitroaromatic ions easily fragment into aryl nitrenium ions. Thus the ion/molecule reactions of the vinylated nitroaromatics such as  $[\text{PhNO}_2 + \text{C}_2\text{H}_3]^+$  ( $m/z$  150),  $[\text{4-BrPhNO}_2 + \text{C}_2\text{H}_3]^+$  ( $m/z$  228),  $[\text{DNB} + \text{C}_2\text{H}_3]^+$  ( $m/z$  195),  $[\text{DNT} + \text{C}_2\text{H}_3]^+$  ( $m/z$  209), and  $[\text{TNT} + \text{C}_2\text{H}_3]^+$  ( $m/z$  254) were carried out with both ethyl vinyl ether and 2,2-dimethyl-1,3-dioxolane. As expected, both ionic indole and morpholine products were observed, as a result of the fact that the vinylated ions  $[\text{ArNO}_2 + \text{C}_2\text{H}_3]^+$  fragment to yield aryl nitrenium ions  $\text{ArNH}^+$  prior to the reactions (Tables 2 and 4). Figure 7 displays the ion/molecule reaction of the vinylated TNT ion  $[\text{TNT} + \text{C}_2\text{H}_3]^+$  ( $m/z$  254) with 2,2-dimethyl-1,3-dioxolane, both the aryl nitrenium ion ( $m/z$  196) and the Eberlin reaction product ion ( $m/z$  240) are observed. The formation of two characteristic products ( $m/z$  196 and 240) facilitates the allocation of this characteristic ion/molecule reaction and selective detection of TNT in mixtures using mass spectrometry.



**Figure 7.** Product ion mass spectrum showing ion/molecule reactions of the vinylated TNT  $[\text{TNT} + \text{C}_2\text{H}_3]^+$  ( $m/z$  254) with 2,2-dimethyl-1,3-dioxolane.



**Figure 8.** Chemical ionization mass spectrum of RDX using 1,2-dichloroethane as the reagent gas. 1-Chloroethyl-1,3-dinitro-1,3-diazacyclobutane cation  $[\text{RDX} + \text{CH}_2\text{ClCH}_2 - \text{CH}_2\text{NNO}_2]^+$  ( $m/z$  211) was observed.

etry. The selectivity stems from the combination of the unique fragmentation behavior and the diagnostic products of the Eberlin-like reaction. Also, the reaction of vinylated TNT with ethyl vinyl ether to form specific indole derivatives provides additional characteristic ion/molecule reactions for the detection of TNT [59, 60].

Two non-aromatic explosive compounds, 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX) and 1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane (HMX), have also been investigated by 1,2-dichloroethane chemical ionization. Unlike nitrobenzene, the analogous aryl nitrenium ions were not formed, probably due to the lack of resonance stabilization of the aromatic ring. However, the ring contraction of the adduct ion  $[\text{RDX} + \text{CH}_2\text{ClCH}_2]^+$  ( $m/z$  285) occurs to give rise to the characteristic 1-chloroethyl-1,3-dinitro-1,3-diazacyclobutane cation  $[\text{RDX} + \text{CH}_2\text{ClCH}_2 - \text{CH}_2\text{NNO}_2]^+$  ( $m/z$  211) by loss of  $\text{CH}_2\text{NNO}_2$  (Figure 8). In addition, the abundance of the ion of  $m/z$  211 is much higher than that of the deprotonated or protonated RDX ions. Similarly,  $[\text{HMX} + \text{CH}_2\text{ClCH}_2 - \text{CH}_2\text{NNO}_2]^+$  ( $m/z$  285) was also observed in the CI spectrum of HMX. Therefore, the selective chemical ionization by 1,2-dichloroethane will be potentially useful for the detection of RDX and HMX with increased selectivity and sensitivity.

### Conclusions

The nitro-reduction reaction by the vinyl halide radical cation  $\text{CH}_2 = \text{CH-X}^{\cdot+}$  ( $\text{X} = \text{Cl}, \text{Br}$ ) is general and particularly selective to nitro groups which do not have adjacent substituents. The reduction has been extended to methyl phenyl sulfone, in which the aromatic sulfone losses two oxygen atoms to form the thioanisole radical cation via a Cope-like rearrangement. The investigation of the reactivity of generated aryl nitrenium ions provides concise routes to the synthesis of biologically important *N*-heterocycles such as the protonated indole and benzomorpholine derivatives, involving new C–N



bond formation. Chemical ionization of RDX and HMX using 1,2-dichloroethane as the reagent gas was found to yield characteristic ions  $[\text{RDX} + \text{CH}_2\text{ClCH}_2 - \text{CH}_2\text{NNO}_2]^+$  ( $m/z$  211) and  $[\text{HMX} + \text{CH}_2\text{ClCH}_2 - \text{CH}_2\text{NNO}_2]^+$  ( $m/z$  285), respectively. These new findings might provide a selective method for the detection of explosives like TNT, RDX and HMX in mixtures.

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## References

- Gassman, P. G. Nitrenium Ions. *Acc. Chem. Res.* **1970**, *3*, 26.
- Fishbein, J. C.; McClelland, R. A. Azide Ion Trapping of the Intermediate in the Bamberger Rearrangement. Lifetime of a Free Nitrenium Ion in Aqueous Solution. *J. Am. Chem. Soc.* **1987**, *109*, 2824.
- McClelland, R. A. Flash Photolysis Generation and Reactivities of Carbenium Ions and Nitrenium Ions. *Tetrahedron* **1996**, *52*, 6823.
- Scribner, J. D.; Naimy, N. K. Adducts between the Carcinogen 2-Acetamidophenanthrene and Adenine and Guanine of DNA. *Cancer Res.* **1975**, *35*, 1416.
- Miller, J. A. Carcinogenesis by Chemicals: An Overview—G. H. A. Clowes Memorial Lecture. *Cancer Res.* **1970**, *30*, 559.
- Moonen, H. J. J.; Briede, J. J.; Van Maanen, J. M. S.; Kleinjans, J. C. S.; De Kok, T. M. C. M. Generation of Free Radicals and Induction of DNA Adducts by Activation of Heterocyclic Aromatic Amines via Different Metabolic Pathways in Vitro. *Mol. Carcinogen.* **2002**, *35*, 196.
- Hatcher, J. F.; Swaminathan, S. Identification of *N*-(Deoxyguanosin-8-Yl)-4-Azobiphenyl by  $^{32}\text{P}$ -Postlabeling Analyses of DNA in Human Uroepithelial Cells Exposed to Proximate Metabolites of the Environmental Carcinogen 4-Aminobiphenyl. *Environ. Mol. Mutagen.* **2002**, *39*, 314.
- Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; Swanegan, L. A. Reactivity Patterns of *N*-Arylnitrenium Ions: Lack of Correlation with  $\text{S}^+$ . *J. Am. Chem. Soc.* **1994**, *116*, 11626.
- Novak, M.; Kennedy, S. A. Selective Trapping of *N*-Acetyl-*N*-(4-Biphenyl)Nitrenium and *N*-Acetyl-*N*-(2-Fluorenyl)Nitrenium Ions by 2'-Deoxyguanosine in Aqueous Solution. *J. Am. Chem. Soc.* **1995**, *117*, 574.
- Novak, M.; Toth, K.; Rajagopal, S.; Brooks, M.; Hott, L. L.; Moslener, M. Reactivity and Selectivity of the *N*-Acetyl-Glu-P-1, *N*-Acetyl-Glu-P-2, *N*-Acetyl-Meiqx, and *N*-Acetyl-Iqx Nitrenium Ions: Comparison to Carbocyclic *N*-Arylnitrenium Ions. *J. Am. Chem. Soc.* **2002**, *124*, 7972.
- Srivastava, S.; Toscano, J. P.; Moran, R. J.; Falvey, D. E. Experimental Confirmation of the Iminocyclohexadienyl Cation-Like Structure of Arylnitrenium Ions: Time-Resolved IR Studies of Diphenylnitrenium Ion. *J. Am. Chem. Soc.* **1997**, *119*, 11552.
- Gassman, P. G.; Campbell, G. A. Mechanism of the Chlorination of Anilines and Related Aromatic Amines. Involvement of Nitrenium Ions. *J. Am. Chem. Soc.* **1971**, *93*, 2567.
- Gassman, P. G.; Campbell, G. A.; Frederick, R. C. Chemistry of Nitrenium Ions. XXI. Nucleophilic Aromatic Substitution of Anilines via Aryl Nitrenium Ions (Anilenium Ions). *J. Am. Chem. Soc.* **1972**, *94*, 3884.
- Ren, D.; McClelland, R. A. Carbocation-Like Reactivity Patterns in *X'*-Substituted-4-Biphenylnitrenium Ions. *Can. J. Chem.* **1998**, *76*, 78.
- Srivastava, S.; Ruane, P. H.; Toscano, J. P.; Sullivan, M. B.; Cramer, C. J.; Chiapperino, D.; Reed, E. C.; Falvey, D. E. Structures of Reactive Nitrenium Ions: Time-Resolved Infrared Laser Flash Photolysis and Computational Studies of Substituted *N*-Methyl-*N*-Arylnitrenium Ions. *J. Am. Chem. Soc.* **2000**, *122*, 8271.
- Parks, J. M.; Ford, G. P.; Cramer, C. J. Quantum Chemical Characterization of the Reactions of Guanine with the Phenylnitrenium Ion. *J. Org. Chem.* **2001**, *66*, 8997.
- Campbell, J. L.; Kenttämää, H. I. Reactions of the Phenylnitrenium Ion in the Gas Phase: Observing Electronic Reactivity Leading to Carcinogenic Activity, unpublished results.
- Abramovitch, R. A.; Evertz, K.; Huttner, G.; Gibson, H. J.; Weems, H. G. Thermolysis of 1-(*N*-Acetyl-*N*-Arylamino)-2,4,6-Triphenylpyridinium Tetrafluoroborates: A New Source of Arylnitrenium Ions. *J. Chem. Soc. Chem. Commun.* **1988**, *4*, 325.
- Abramovitch, R. A.; Shi, Q. Photolytic Generation of *N*-Arylnitrenium Ions under Neutral Conditions: Synthesis of Polycyclic Lactams. *Heterocycles* **1994**, *37*, 1463.
- Takeuchi, H.; Hayakawa, S.; Murai, H. Singlet Stabilization of Parent Nitrenium Ion. *J. Chem. Soc. Chem. Commun.* **1988**, *19*, 1287.
- Takeuchi, H.; Hayakawa, S.; Tanahashi, T.; Kobayashi, A.; Adachi, T.; Higuchi, D. Novel Generation of Parent, Alkyl, Dialkyl, and Alicyclic Nitrenium Ions in Photolyses of Pyridinium, Quinolinium, Bipyridinium, and Phenanthroline Salts and Aromatic *N*-Substitution by Nitrenium Ions. *J. Chem. Soc. Perkin 2* **1991**, *6*, 847.
- Srivastava, S.; Kercher, M.; Falvey, D. E. On the Solution Chemistry of Parent Nitrenium Ion  $\text{NH}^{2+}$ : The Role of the Singlet and Triplet States in Its Reactions with Water, Methanol, and Hydrocarbons. *J. Org. Chem.* **1999**, *64*, 5853.
- Moran, R. J.; Falvey, D. E. Photogenerated Diarylnitrenium Ions: Laser Flash Photolysis and Product Studies on Diphenylnitrenium Ion Generated from Photolysis of 1-(*N,N*-Diphenylamino)Pyridinium Ions. *J. Am. Chem. Soc.* **1996**, *118*, 8965.
- McClelland, R. A.; Davidse, P. A.; Hadzialic, G. Electron-Deficient Strong Bases. Generation of the 4-Biphenyl- and 2-Fluorenylnitrenium Ions by Nitrene Protonation in Water. *J. Am. Chem. Soc.* **1995**, *117*, 4173.
- McClelland, R. A.; Ahmad, A.; Dicks, A. P.; Licence, V. E. Spectroscopic Characterization of the Initial C8 Intermediate in the Reaction of the 2-Fluorenylnitrenium Ion with 2'-Deoxyguanosine. *J. Am. Chem. Soc.* **1999**, *121*, 3303.
- Kennedy, S. A.; Novak, M.; Kolb, B. A. Reactions of Ester Derivatives of Carcinogenic *N*-(4-Biphenyl)Hydroxylamine and the Corresponding Hydroxamic Acid with Purine Nucleosides. *J. Am. Chem. Soc.* **1997**, *119*, 7654.
- Svanholm, U.; Parker, V. D. Chemistry of the Dianisylnitrenium Ion. Stable Protonated Nitrenium Ions. *J. Am. Chem. Soc.* **1974**, *96*, 1234.
- Serve, D. Chemistry of Electrogenerated Diarylnitrenium Ions. Absorption Spectra of Stable Protonated Nitrenium Ions. *J. Am. Chem. Soc.* **1975**, *97*, 432.
- Attina, M.; Cacace, F.; Petris, G. D. Gas Phase Protonation of Alkyl and Phenyl Azides. *Int. J. Mass Spectrom. Ion Processes* **1989**, *90*, 263.
- Kasthurikrishnan, N.; Cooks, R. G.; Thompson, M. J. Sampling of Aryldiazonium, Anilino, and Aryl Radicals by Membrane Introduction Mass Spectrometry: Thermolysis of Aromatic Diazoamino Compounds. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 234.

31. Chen, H.; Zheng, X.; Yang, P.; Cooks, R. G. Reduction of Nitroaromatics to Arylnitrenium Ions by Vinyl Halide Cations. *Chem. Commun.* **2004**, 6, 688.
32. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; 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.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A7*; Gaussian, Inc., Pittsburgh, PA, 1998.
34. Sabino, A. A.; Meurer, E. C.; Eberlin, M. N. Ionic Transacetalization with Acylium Ions: A Class-Selective and Structurally Diagnostic Reaction for Cyclic Acetals Performed under Unique Electrospray and Atmospheric Pressure Chemical Ionization In-Source Ion-Molecule Reaction Conditions. *Anal. Chem.* **2003**, 75, 4701.
35. Kruger, T. L.; Flammang, R.; Litton, J. F.; Cooks, R. G. Protonation, Ethylation, and Allylation of Substituted Nitrobenzenes in the Gas Phase. A Study by Ion Kinetic Energy Spectrometry and Chemical Ionization. *Tetrahedron Lett.* **1976**, 50, 4555.
36. Robinson, B. Studies on the Fischer Indole Synthesis. *Chem. Rev.* **1969**, 69, 227.
37. Gassman, P. G.; Bergen, T. J. V.; Gilbert, D. P.; Cue, B. W. General Method for the Synthesis of Indoles. *J. Am. Chem. Soc.* **1974**, 96, 5495.
38. Granik, V. G.; Lyubchanskaya, V. M.; Mukhanova, T. I. Nenitzescu Reaction. *Khimiko-Farmatsevticheskii Zhurnal* **1993**, 27, 37.
39. Glish, G. L.; Cooks, R. G. The Fischer Indole Synthesis and Pinacol Rearrangement in the Mass Spectrometer. *J. Am. Chem. Soc.* **1978**, 100, 6720.
40. Sindona, G.; Uccella, N.; Stahl, D. Reaction Mechanisms of Gaseous Organic Ions. Part 22. Structure and Reactivity of Protonated Indole in the Gas Phase by MS/MS. *Int. J. Mass Spectrom. Ion Processes* **1985**, 63, 49.
41. McClelland, R. A.; Kahley, M. J.; Davidse, P. A. Reactivity of the 4-Biphenyl and 2-Fluorenylnitrenium Ions with Heterocyclic and Carbon Nucleophiles. *J. Phys. Org. Chem.* **1996**, 9, 355.
42. Blanksby, S. J.; Bowie, J. H. Construction of Interstellar Cumulenes and Heterocumulenes: Mass Spectrometric Studies. *Mass Spectrom. Rev.* **1999**, 18, 131.
43. Burns, T. D.; Spence, T. G.; Mooney, M. A.; Posey, L. A. Electrospray Ionization of Divalent Transition Metal Ion Bipyridine Complexes: Spectroscopic Evidence for Preparation of Solution Analogs in the Gas Phase. *Chem. Phys. Lett.* **1996**, 258, 669.
44. Depuy, C. H. Understanding Organic Gas-Phase Anion Molecule Reactions. *J. Org. Chem.* **2002**, 67, 2393.
45. Johlman, C. L.; White, R. L.; Sawyer, D. T.; Wilkins, C. L. Gas-Phase Hydrolysis of Phenyl Acetate and Phenyl Benzoate by Superoxide Ion. *J. Am. Chem. Soc.* **1983**, 105, 2091.
46. Sainsbury, M. Oxazines, Thiazines and Their Benzoderivatives in Comprehensive Heterocyclic Chemistry. **1984**, 3, 995.
47. Sugimoto, Y.; Otani, T.; Oie, S.; Wierzba, K.; Yamada, Y. Mechanism of Action of a New Macromolecular Antitumor Antibiotic, C-1027. *J. Antibiot.* **1990**, 43, 417.
48. Fukuda, T.; Setoguchi, M.; Inaba, K.; Shoji, H.; Tahara, T. The Antiemetic Profile of Y-25130, a New Selective 5-HT<sub>3</sub> Receptor Antagonist. *Eur. J. Pharmacol.* **1991**, 196, 299.
49. Hirata, T.; Saito, H.; Tomioka, H.; Sato, K.; Jidoi, J.; Hosoe, K.; Hidaka, T. In Vitro and in Vivo Activities of the Benzoxazinorifamycin Krm-1648 Against Mycobacterium tuberculosis. *Antimicrob. Agents Chemother.* **1995**, 39, 2295.
50. Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamoto, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.; Yano, K.; Kuroti, T. Antirheumatic Agents: Novel Methotrexate Derivatives Bearing a Benzoxazine or Benzothiazine Moiety. *J. Med. Chem.* **1997**, 40, 105.
51. Zheng, X.; Tao, W. A.; Cooks, R. G. Eberlin Reaction of Arenesulfonylium Cations with Cyclic Acetals and Ketals: Ring Contraction and Cycloreversion. *J. Chem. Soc. Perkin 2* **2001**, 3, 350.
52. Eberlin, M. N.; Cooks, R. G. Gas-Phase Oxirane to Acylium Ions on Reaction with 1,3-Dioxolanes Elucidated by Tandem and Triple Stage Mass Spectrometric Experiments. *Org. Mass Spectrom.* **1993**, 28, 679.
53. Wang, F.; Ma, S.; Tao, W. A.; Cooks, R. G. Replacement of C–O by P–O in Cyclic Acetals and Ketals. *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 386.
54. Tao, W. A.; Zheng, X.; Cooks, R. G. Synthesis of B,N,O-Containing Heterocycles via Eberlin Reaction of Dimethylamino Borinium Ion with Cyclic Acetals and Ketals. *J. Mass Spectrom.* **2000**, 35, 1215.
55. Chen, H.; Zheng, X.; Cooks, R. G. Ketalization of Phosphonium Ions by 1,4-Dioxane: Selective Detection of the Chemical Warfare Agent Simulant Dmmp in Mixtures Using Ion/Molecule Reactions. *J. Am. Soc. Mass Spectrom.* **2003**, 14, 182–188.
56. Cooks, R. G. The Eberlin Reaction: Ionic Transacetalization in the Gas Phase, unpublished results.
57. Colorado, A.; Brodbelt, J. Class-Selective Collisionally Activated Dissociation/Ion-Molecule Reactions of 4-Quinolone Antibiotics. *Anal. Chem.* **1994**, 66, 2330.
58. Brodbelt, J. Analytical Applications of Ion/Molecule Reactions. *Mass Spectrom. Rev.* **1997**, 16, 91.
59. Meurer, E. C.; Chen, H.; Riter, L. S.; Cotte-Rodriguez, I.; Eberlin, M. N.; Cooks, R. G. Gas-Phase Reactions for Selective Detection of the Explosives TNT and RDX. *Chem. Commun.* **2004**, 1, 40.
60. Chen, H.; Chen, H.; Cooks, R. G. Meisenheimer Complexes Bonded at Carbon and at Oxygen in the Gas Phase. *J. Am. Soc. Mass Spectrom.* **2004**, 15, 998–1004.