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Protonated Nitro Group as a Gas-Phase Electrophile: Experimental and Theoretical Study of the Cyclization of *o*- Nitrodiphenyl Ethers, Amines, and Sulfides

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Abstract

A novel gas-phase electrophilic cyclization, initiated by the protonation of a nitro group, occurs for 2-nitrophenyl phenyl ether and for the analogous sulfide and amine, leading to heterocyclic intermediates in each case. Subsequently, the cyclic intermediates dissociate via two pathways: (1) unusual step-wise eliminations of two OH radicals to afford heterocyclic cations, [phenoxazine – H]⁺, [phenothiazine – H]⁺ and [phenazine + H]⁺, and (2) expulsion of H₂O, to yield a heterocyclic ketone, followed by loss of CO. The proposed structures of the gas-phase product ions and reaction mechanisms are supported by chemical substitution, deuterium labeling, accurate mass measurements at high mass resolving power, product-ion mass spectra obtained by tandem mass spectrometry, mass spectra of reference compounds, and molecular orbital calculations. Using a mass spectrometer as a reaction vessel, we demonstrate that, upon protonation, a nitro group becomes an electrophile and participates in cyclization reactions in the gas-phase.

Introduction

Electrophilic cyclization reactions to give novel heterocycles by simultaneous removal of small molecules are fascinating and potentially useful synthetic processes [1]. Cyclodehydrations of

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aromatic mono carboxylic acids, induced by polyphosphoric acid as a dehydrating agent have been routinely used to synthesize cyclic ketones [2,3]. These reactions are viewed to be intramolecular Friedel-Crafts acylations that occur by electrophilic mechanisms, for which a variety of acids have been used for effecting the cyclizations [4]. The question we ask in this research is “do aromatic nitro compounds also undergo intramolecular cyclizations catalyzed by strong acids?” This could occur if the nitro group becomes an electrophile upon protonation. The only example, to our knowledge, is the cyclization of 4'-chloro-2-nitro-*N*-phenyl aniline in concentrated sulfuric acid to yield 2-chloro phenazine at 180 °C and 2-chloro phenazine-10-oxide at low temperatures [5].

In addition to answering the above question, we wish to demonstrate that cyclizations and rearrangements of protonated molecules can be productively studied in the gas-phase by using mass spectrometric methods and theoretical calculations. Additionally, we seek to determine the mechanisms under solvent-free conditions because the mechanisms of these reactions are not well known. Investigations in the absence of solvent employ ideal conditions for understanding energetics and intrinsic mechanisms of reactions at the molecular level [6,7]. Fast atom bombardment (FAB), chemical ionization (CI) and electrospray ionization (ESI) readily generate protonated molecules or $[M + H]^+$ ions, and well established mass spectrometric methods for ion chemistry, reveal the properties of and the mechanisms for the reactions of protonated molecules in the absence of a solvent. The acid-catalyzed rearrangement of allyl phenyl ether, using chemical ionization (CI) mass spectrometry, is one example of the utility of mass spectrometry in this area [8]. A recent report by Cooks and coworkers [9] on the reduction of nitro aromatic compounds to aryl nitrenium ions in the gas-phase by radical cations of vinyl halides demonstrate that ‘gas-phase synthetic chemistry’ remains of current interest. Cycloaddition reactions involving ion-molecule reactions in the gas phase and comparison to reactions in solution are the subjects of a recent review [10]. These and other examples show the utility of a mass spectrometer as a “reaction vessel” for investigating gas-phase reactions of potential synthetic utility [11–14]. The gas-phase cyclizations of the radical cations of several disubstituted aromatic compounds led to the discovery of new methods [15,16] for the synthesis of heterocyclic compounds. An additional example, characterized recently by us, is the gas-phase cyclization of protonated *N*-[2-(benzoyloxy) phenyl]-benzamide, which closely resembles the acid-catalyzed cyclization of the same molecule in solution [17].

There is also increasing interest for developing methods for the synthesis of phenoxazine and phenothiazine derivatives owing to applications in drug development [18,19], chemical analysis [20], and synthesis, as indicated by a patent in 2006 [21].

Another motivation for this study is the unusual successive expulsions of two OH radicals, a process that also occurs for protonated *meso*-tetraphenylporphyrins, having a nitro group in the β -pyrrolic position [22,23]. The mechanism of that reaction, however, is not known.

A study of the gas-phase reactions of protonated 2-nitrophenyl aryl ethers and the analogous sulfides and amines occurring in a mass spectrometer and modeled by theoretical calculations should provide important insight into the prospects for gas-phase cyclizations that may be important for designing synthetic processes and for understanding the double OH radical loss. To carry out such a study, we selected 2-nitrophenyl-aryl ethers, **1** to **3**, 2-nitrophenyl-aryl sulfides, **5** to **7**, and 2-nitrophenyl-aryl amines **9** to **12** as suitable model compounds to investigate potential cyclization as promoted by a protonated nitro group serving as an electrophile (Table 1). Studies of compounds **4**, **8** and **13**, the *para* nitro isomers, serve as necessary control experiments.

Experimental Methods

Synthesis

Ethers **1** to **4** were synthesized by the Ullmann diaryl etherification procedures [24–26]. The diaryl ethers obtained were purified by column chromatography on silica gel by using *n*-hexane as eluent. Sulfides **5** to **8** were synthesized from appropriate sodium thiophenoxide and chloronitrobenzene as reported previously [27] and purified by recrystallisation from ethanol. Amines **10** to **12** were synthesized from appropriate chloronitrobenzene and toluidine, as previously reported [5,28]. The amines were purified by column chromatography on silica gel by using a 1:9 mixture of chloroform and hexane as eluent. Amines **9**, **13**, phenoxazine, phenazine and phenazine-5-oxide were purchased from Aldrich Chemical Co (St. Louis, MO) and phenoxazine was acetylated to obtain *N*-acetylphenoxazine. Phenoxazine was *N*-acetylated by acetic anhydride prior to introduction to the mass spectrometer. The structures of all compounds were consistent on the basis of ¹H-NMR, IR, and mass spectra with previously-reported data (See Supplementary Material for spectra of compounds **1** and **5**).

Mass spectrometry

The protonated molecules were generated by FAB, CI and ESI methods and the radical cations by EI. The FAB, CI and EI experiments were conducted on a VG ZAB-T four-sector mass spectrometer of BEBE design [29]. MS1 is a standard high-resolving power, double-focusing mass spectrometer (ZAB) of reverse geometry. MS2 possesses a prototype Mattauch-Herzog-type design, incorporating a standard magnet and a planar electrostatic analyzer having an inhomogeneous electric field, followed by single-point and array detectors. For FAB analysis, samples were dissolved in methanol, and a 1 μL aliquot was loaded on the probe along with 1 μL of the matrix, 3-nitrobenzyl alcohol (3-NBA). A Cs⁺ ion gun operated at 30 keV was used to desorb the ions, which were accelerated to 8 kV. Samples were introduced through direct-probe insertion for EI and CI experiments, and the ions were accelerated to 8 kV. For CI experiments, methane was used to generate the CI reagent ions and produce [M + H]⁺ ions.

The dissociation of the precursor ion, by either metastable-ion (MI) or high-energy (4 keV) collisionally activated dissociation (CAD) with helium as collision gas, was studied in the third field-free region. Sufficient helium gas was added to the collision cell to decrease the main-beam intensity by 30%. Both MS1 and MS2 of the mass spectrometer were operated at a mass resolving power of 1000. Typically 10–20 scans were signal averaged for each spectrum. Data acquisition and workup were accomplished by using a VAX 3100 work-station equipped with OPUS software.

The ESI experiments, both MS and low-energy CAD (MS/MS), were conducted by using a Micromass Q-ToF-*Ultima* instrument operated in the positive-ion mode. The needle voltage was 3 kV, and the cone voltage was 90 V. The temperatures of the source block and for desolvation were 90 and 150 °C, respectively. The samples were dissolved in 1:1 mixture of acetonitrile and water and introduced by direct infusion at a flow rate of 10 μL/min. All parameters (i.e., aperture to the TOF, transport voltage, offset voltages) were optimized to achieve maximum sensitivity and a mass resolving power of 15,000 ('W' mode, full width at half maximum).

The CAD experiments on ESI-produced ions were carried out by mass selecting the precursor ion by using the quadrupole analyzer, and the product ions were recorded using the time-of-flight analyzer operating at a mass resolving power of 15000 ('w' mode). The energies for colliding the ions under study were of the order of 7 to 9 eV with argon as target gas admitted to the collision hexapole. The accurate masses of the product ions were determined using the precursor ion as an internal mass standard.

Low-energy ESI-CAD(MS^3) experiments (low-energy CA) was performed on Finnigan LCQ Classic or Advantage ion-trap mass spectrometers. The samples, dissolved in 1:1 mixture of acetonitrile and water, were introduced by direct infusion at a flow rate of 10 μ L/min.

On all instruments, CA was carried out under multiple-collision conditions, a consideration, particularly true for low-energy CA, giving rise to multiple-generation product ions. In addition, ions generated by FAB and CI have much greater internal energy than the same ions generated by ESI. Together, this gives rise to some variability in the obtained MS/MS spectra, particularly at m/z below 100 since such ions likely represent a second or greater generation from the precursor.

To track fragmentation pathways, $[M + D]^+$ ions were generated and subjected to low-and energy-CAD. By FAB, this involved desorption from D_2O -exchanged 3-NBA as matrix. By CI, $[M + D]^+$ ions were generated using CD_4 as reagent gas. For ESI, ions were generated from 1:1 acetonitrile/ D_2O mixtures.

Theoretical Calculations

Proposed reaction mechanisms with consequent structures of intermediates and the heats of formation/reaction were evaluated and calculated by molecular modeling of the precursor ions, proposed intermediates, and products. Owing to the large size of the ions, the initial survey calculations were performed by using the PM3 [30,31] semi-empirical algorithm, which was obtained as part of the Spartan '02 for Linux package (Wavefunction, Inc.). The starting points of the investigation were the protonated ions of compounds **1**, **5** and **9** [3], to which we limited the calculations.

Second stage calculations were by density functional theory (DFT), which required less computational overhead than formal ab initio methods and yet incorporated dynamic correlation, had little spin contamination [32–24], and usually performed adequately giving proper geometries, energies, and frequencies [35]. DFT was part of the Gaussian 98 or Gaussian 03 suites (Gaussian, Inc.) [36–38]

Minima and transition states were optimized to the DFT level of B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d,p), confirmed by vibrational frequency analysis, and scaled zero-point and thermal-energy corrections for standard temperature and pressure were applied [39]. Connections of transition states were confirmed by projection of the normal variable associated with the imaginary frequency or by path calculations. The heats of formation or reaction are reported as enthalpies relative to the ion that represents the starting point for the mechanistic scheme. It must be noted that these calculations yield information about the potential-energy surface, but ultimately fragmentation patterns are determined by kinetic processes.

For fragmentation processes that involve the loss of an OH radical from an even-electron precursor ion, we employed multiconfiguration SCF calculations, specifically, CASSCF(6,8)/6-31G(d,p), which is included in the Gaussian 03 suite [38]. Transition states and minima were confirmed by vibrational frequency calculations and thermal energy corrections were scaled and applied [39].

Results and discussions

Experimental Observations

2-Nitrophenyl-phenyl ether—FAB of 2-nitrophenyl phenyl ether (**1**) (Fig. 1) affords the protonated molecule, $[M + H]^+$ of m/z 216 and source-generated fragment ions of m/z 215, 199, 198, 182, 170, and lower m/z . The abundant m/z 182 fragment ion (74%) is formed by consecutive elimination of two OH radicals, whereas, the m/z 199 and 198 ions arise by the

loss of an OH radical and H₂O, respectively. The m/z 170 ion may be either $[M + H - NO_2]^+$ or $[M + H - H_2O - CO]^+$. Under metastable-ion (MI) and high-energy collisional activation (Fig. 2), the $[M + H]^+$ ion (**1** in Table 2) yields the same series of fragment ions (e.g., those of m/z 199, 198, 182, and 170) and additional fragments at m/z 139, 122 (base) and at lower m/z . The m/z 182 ion's relative abundance increases considerably compared to that of the m/z 199 ion in CAD vs. MI, strongly suggesting that the former ion forms step-wise from the protonated molecule. The loss of the first OH, however, does not necessarily require the presence of the nitro group at the *ortho* position; the *para* nitro isomer $[M + H]^+$ (**4**) dissociates via the loss of OH to produce an ion of m/z 199 but undergoes no losses of H₂O or a second OH radical (Table 2). Moreover, protonated methyl substituted analogs, 2-nitrophenyl-4-methylphenyl ether (**2**) and 2-nitrophenyl-2-methylphenyl ether (**3**) decompose metastably or via high-energy collisional activation to give a similar series of fragment ions: m/z 213 – OH radical), 212 (– H₂O), 196 (2x –OH radicals), 184, and 122 (Table 2).

When protonation is by FAB, the source-produced $[M + H - OH]^+$ is overlapped by the ¹³C isotopomer of the $[M - OH]^+$ ion. This occurs because the molecular radical cation of **1** is relatively abundant (36% of the $[M + H]^+$ abundance) and also undergoes facile loss of OH [40]. Protonation of the ethers by either ESI or methane CI avoids the problem because no molecular radical cations are produced.

CAD of ESI-produced ions also yields m/z 199, 198, 182, 170, and 122 (Fig. 3). The m/z 198 ion's relative abundance is greater than that of the m/z 199 ion as is the case for CI-MI (or CAD) but not for MI or CAD of FAB-produced ions, indicating that the loss of H₂O is the major and more energetically favorable process (Table 2). The accurate masses of the fragments produced in CAD of ESI-produced ions agree well with the calculated values, supporting the proposed eliminations (Table 3). Accurate-mass measurement reveals an elemental composition of C₁₁H₈NO for the m/z 170 ion, indicating that its origin is loss of CO from the $[M + H - H_2O]^+$ ion and not loss of NO₂ from the $[M + H]^+$ ion. (There is no detectable CO loss from the $[M + H]^+$ ion). In addition, the collisionally generated m/z 198 ion from **1** (ESI-MS³ experiment) shows that this $[M + H - H_2O]^+$ ion expels CO to yield only the m/z 170 fragment, strongly suggesting that the ion is a protonated cyclic ketone (Scheme 1). Similarly, accurate-mass measurements of the m/z 184 fragments from the protonated methyl analog (**2** and **3**) show that these arise also by CO losses from the corresponding $[M + H - H_2O]^+$ ions. Accurate mass measurement of the m/z 122 fragment confirms its composition as C₆H₄NO₂⁺, likely the 2-NO-cyclohexyldienone cation that likely arises by loss of phenol via an acyclic mechanism.

We propose that the fragment ion of m/z 182, generated by the step-wise elimination of two OH radicals, has a heterocyclic structure. The CAD spectra of the FAB-produced m/z 182 ion from **1** and of the m/z 182 fragment ion formed by the EI-induced loss of the acetyl radical from *N*-acetyl phenoxazine are very similar (Figures 4a and 4b); the fragment formed by loss of acetyl is a reference for the $[M - 2OH]^+$ ion. The spectra, identical except for a minor m/z 90 ion, are evidence that the m/z 182 ion produced by the elimination of two OH radicals from the $[M + H]^+$ ion of **1** is the $[M - H]^+$ ion from phenoxazine and thus has a cyclic structure (Scheme 1). We do not consider the difference in abundance of the m/z 90 ion as significant since this ion represents at least a second-generation product ion owing to the multiple-collision conditions used in CA (**Experimental**) and substantive differences in precursor ion preparation in these experiments.

Given that the fragment ions $[M + H - H_2O]^+$ and $[M + H - 2OH]^+$ have heterocyclic structures, the $[M + H]^+$ ions of the *ortho* isomers likely undergo ring closure prior to fragmentation (Scheme 1). We propose that protonation of a NO₂ oxygen converts the nitrogen to an electrophile capable of attacking the 2'-position. The resulting cyclic intermediates decompose

by two channels: (1) the elimination of an OH radical followed by a second OH radical and (2) the expulsion of H₂O followed by CO.

2-Nitrophenyl-phenyl Sulfide and Amine—To understand the scope of this electrophilic cyclization, we examined the fragmentations of *ortho* nitro sulfides **5–7** and amines **9–12**, analogs that replace the O bridge with S or NH. The collisionally induced fragmentations of the [M + H]⁺ ions of *ortho*-nitro sulfides **5–7** and amines **9–12** (Table 2) indicate two important fragmentation pathways analogous to those of the ethers **1–3**: one involving consecutive losses of two OH radicals to afford [M + H - OH]⁺ and [M + H - 2OH]⁺, and the second featuring the step-wise elimination of H₂O and CO to yield [M + H - H₂O]⁺ and [M + H - H₂O - CO]⁺, respectively. The collisionally produced fragments from the ESI-generated [M + H]⁺ ions of the sulfide **5** and amine **9** (Figs. 3b and 3c) have accurate masses that support the proposed eliminations of OH, H₂O, 2x OH, and (H₂O + CO) (Table 3). The relative abundances indicate that H₂O loss is the more dominant process, induced not only by collisional activation of the ESI-produced ions but also for the metastable and collisionally activated ions formed by CI, as similarly found for the ether-derived ions. FAB-produced [M + H]⁺ ions, however, fragment both metastably and upon collisional activation to give more highly abundant [M + H - OH]⁺ ions. The relative abundance of the [M + H - 2OH]⁺ (of *m/z* 198) formed by the consecutive losses of two OH radicals, however, is low for the sulfide owing to competition with other dissociation channels (loss of NOH and SH), as revealed by the CAD of the [M + H - OH]⁺ ion. We note that in the product-ion (MS/MS) spectra for the sulfides, the most dominant fragmentation processes involve sulfur chemistry, specifically O transfer to sulfur, and not the cyclization process implied to give the high-mass fragment ions. We will not consider these competing fragmentation processes further.

Evidence that the reaction is specific for *ortho* isomers is the lack of collisionally produced [M + H - 2OH]⁺, [M + H - H₂O]⁺ and [M + H - H₂O - CO]⁺ ions of the *para* nitro isomers **4**, **8**, and **13**, irrespective of the method of ionization (Table 2) and fragmentation. Furthermore, the FAB-generated [M + D]⁺ ions of compounds **1**, **5**, and **9** (3-nitrobenzyl alcohol-OD as matrix) show losses, upon CA, of both OH and OD radicals such that both [M + D - (OH + OD)]⁺ and [M + D - (OH + OH)]⁺ ions are produced nearly equally. CI with methane-d₄ as reagent gas gives a similar result. The eliminations of OH radical and H₂O split into OH radical, OD radical and H₂O, and HDO losses, indicating that both fragmentation pathways involve H/D mixing, and the extent of mixing is approximately 1:1.

Moreover, the CAD mass spectra of collisionally generated [M + H - H₂O]⁺ ions (*m/z* 214) from sulfide **5**, as obtained by ESI-MS³ experiments, undergo only expulsion of CO, a property analogous to that of the ether (**1**), suggesting a protonated cyclic ketone structure for the fragments (Scheme 1). The collisionally produced [M + H - H₂O]⁺ ions (*m/z* 197) from the amine (**9**) yield two fragment ions [of *m/z* 180 (100%) and 169 (8%)], indicating expulsions of an OH radical and CO, respectively. Therefore, the [M + H - H₂O]⁺ ion from the amine **9**, may exist as a mixture of two isomeric structures: one that eliminates an OH radical and a second that loses CO. EI of 1-hydroxyphenazine [41] gives precedent as it shows an abundant (60%) [M - CO]⁺ fragment, and CAD [42] of the ESI-produced [M + H]⁺ of 5-methyl-1-hydroxyphenazine shows abundant fragments formed by CH₃ and CO losses, suggesting that CO loss is a characteristic fragmentation of protonated 1-hydroxyphenazines. The OH radical loss channel is certainly due to the bridging NH moiety having an additional active hydrogen compared to O and S. Repeating the ESI experiment for compound **9** by dissolving it in a 1:1 mixture of acetonitrile and D₂O, we generated [2-nitrodiphenyl amine-N-d + D]⁺, (the [M - H + 2D]⁺ ion, *m/z* 217). Low-energy collisional activation shows that the ion eliminates H₂O [*m/z* 199 (82%)], HDO [*m/z* 198 (100%)] and D₂O [*m/z* 197 (14%)], evidence that the original N-H hydrogen is involved, in part, in the H₂O loss. An MS³ experiment shows that the *m/z* 198 ion fragments by expelling OH and OD to give ions of *m/z* 181 (100%) and 180 (12%)

in addition to losing CO to give an m/z 170 fragment (8%). After the loss of HDO, the remaining D is unavailable for further loss.

In addition, the CAD mass spectrum of the $[M + H - 2OH]^+$ (m/z 181) produced upon CI of **9** (Fig. 5b) is virtually identical to that of the protonated phenazine (Fig. 5a), supporting a cyclic product. To confirm the heterocyclic structure for the $[M + H - H_2O - OH]^+$ ion from **9**, we compared the CAD mass spectra of the ion of m/z 180 obtained as a fragment ion upon FAB of compound **9** (Fig 6a) with that of the radical cation of phenazine obtained by EI (Fig. 6b). The two mass spectra are also virtually identical, indicating that the ion of m/z 180 has indeed the phenazine radical cation structure.

Given that the $[M + H - H_2O]^+$ and $[M + H - 2OH]^+$ from the amine and sulfide, in addition to ether, precursors have heterocyclic structures, the $[M + H]^+$ ions of these *ortho* isomers also undergo ring closure (Scheme 1). Protonation of the NO₂ oxygens again converts the nitrogen to an electrophile, promoting a cyclization via electrophilic attack at the 2'-position. As for the ether compounds, the cyclized intermediate ions dissociate either by elimination of an OH radical followed by a second OH radical or by the expulsion of H₂O followed by CO.

Theoretical calculations: proposed mechanism of cyclization

We undertook theoretical calculations to aid in the elucidation of mechanisms of cyclization and fragmentation that are the focus of this study. We explored the protonation, cyclization and subsequent fragmentation of protonated 2-nitrophenyl phenyl ether (**1**), sulfide (**5**) and amine (**9**). Protonation of the nitro-group oxygen indeed makes the nitrogen an electrophile and 2'-attachment is the first step in cyclization, forming a tricyclic core from which the low-mass groups are eliminated, resulting in the proposed cyclic product ions. The results, shown in Schemes 2(a–d), represent routes with lowest transition state barriers among many alternatives; and the calculated relative enthalpies are summarized in Tables 4(a,b).

Calculations reveal that the lowest-energy protonation sites, forming the initial $[M + H]^+$ ions, are on one of the oxygen atoms of the nitro group for **1** and **5** (ether and sulfide, **M₁**), and on the bridging amine nitrogen for **9** (**M_{1N}**, Scheme 2a). In the most stable configurations of the protonated molecule, the phenyl rings are canted relative to each other, and the proton participates in a hydrogen bond with the bridging moiety for **1** and **9**. Only a low-energy barrier (52 kJ/mol) separates the NH and NO₂ protonation sites for amine **9**. At internal energies below the rearrangement threshold (< 100 kJ/mol), the nitro-protonated ions can assume an array of rotational isomers, separated by mainly low-energy barriers of which only those linked to the proposed electrophilic cyclization are shown. Central are **M_{1a}** and **M_{1b}**, the latter of which forms a cyclic structure **M₂**, via electrophilic substitution with the protonated nitro group acting as the electrophile. Ion **M_{1a}** of **9** can lose H₂O, consistent with the enhanced water loss observed for the amines (Table 2), and ultimately forms the cyclic product **P_{1a}**. This water loss should be competitive with cyclization because the more entropically favorable transition state for loss, **TS_{1P}**, vs. cyclization, **TS₂**, compensates for its greater energetic barrier (16 kJ/mol difference, Table 4b). Besides cyclization, **M_{1b}** can transfer a proton through **M_{1c}** to the 2'-position on the phenyl ring (to form **M₂₀**). At the 2'-position, the 'labeled' and 'unlabeled' protons can interchange via structures **M_{1b}**, **M_{1c}**, and **M₂₀**, essentially inverting the 'label' pattern and leading to a process whereby two OH groups or an OH and OD are lost in an observed ratio of ~ 1:1. Additional proton transfers, such as to 3' position via **TS₂₀**, are less competitive because **TS₂₀** presents a greater energetic barrier than **TS_{1b}** or **TS_{1c}** and hence would make only minor contribution to H scrambling.

Ion **M_{1b}** is also the starting point for a fragmentation mechanism that gives rise to the m/z 122 ion as the most abundant fragment in the ether **1–3** CA spectra. The mechanism commences with OH transfer from the N of nitro group to C1' on the opposite phenyl ring. Cleavage of the

C1'-O ether bond results in phenol loss and the m/z 122 fragment. The results are also consistent with $[M + D]^+$ deuterium fate. The highest barrier is the first transition state, an OH transfer, and is ~ 60 kJ/mol higher (Supplemental Material) than TS_{2a} (rate limiting step) and more entropically favorable than TS_2 (cyclization step). This coupled with the energy available in the system by CA and/or ion preparation proves sufficient to drive the fragmentation. In contrast, the analogous fragmentation yielding the m/z 121 ion from amine **9** is not observed under any conditions we employed. Here the transition state for OH transfer is ~ 90 kJ/mol greater than TS_{2a} , and it would compete unfavorably with the already described water loss from M_{1a} , which has similar entropic constraints and a lower transition state barrier of ~ 75 kJ/mol greater than that for TS_{2a} . However, the analogous transition state barrier from M_{1b} of sulfide **5** is ~ 45 kJ/mol higher than TS_{2b} , and the analogous m/z 138 fragment is found in high-energy CA spectra only. In the sulfide case, this alternate fragmentation pathway must compete with lower energy rearrangements that involve O transfer from the N of the nitro group to the S.

The 4-nitro analogs, **4**, **8** and **13** of **1**, **5**, and **9**, respectively, lose predominantly (solely for ether **4** and sulfide **8**) the hydroxyl radical. The analogous process from M_{1a} , yielding the uncyclized radical cation P_{10} , an $[M + H - OH]^+$, requires more energy than the greatest barriers involving cyclization (> 50 kJ/mol difference, Tables 4a, 4b). Nevertheless, the homolytic cleavage involved in OH radical loss would be more entropically favorable than the constrained transition state for cyclization, TS_2 ; thus, some P_{10} would be likely formed. We explored the potential-energy surface for routes to convert P_{10} , via cyclization, to P_{12} and discovered even greater energetic barriers (> 250 kJ/mol). Thus, any P_{10} formed would be uncompetitive in generating a second OH radical loss.

The initial, cyclized $[M + H]^+$ ion, M_2 , can be transformed into a large array of possible rearrangement products by means of reversible H and OH transfers. The most energetically and mechanistically feasible set of such rearrangements along with resultant product ions comprise the core of the proposed mechanisms (Scheme 2b). The resulting best route involves the sequential conversion of M_2 to M_8 (Scheme 3 – 'red' route). On this reaction path, the rate-limiting step would correspond to crossing TS_{2a} . The most stable intermediate ions are, in order of stability, M_5 , M_7 and M_8 . Of interest is M_5 because, unlike the other cyclic $[M + H]^+$ ions except M_4 , M_5 has no transition state for loss of H_2O . As a consequence, we propose that most OH radical loss proceeds from this intermediate. The production of $[M + H - OH]^+$, P_{12} , from M_5 requires less energy than passing over the previous transition state, TS_4 ; hence there would be sufficient available energy to drive the first loss of OH radical (Tables 4a, 4b, Scheme 3). In addition, we performed CASSCF type calculations on M_5 and transition states for OH radical loss from even-electron M_5 : $TS(M_5-P_{12})$ and $TS(M_5-P_{13})$ yielding P_{12} and P_{13} , respectively (Table 4c). The results indicate, although direct comparison is not possible, that the reverse activation energy for the loss process is small for amine **9** and sulfide **5** and moderate for ether **1** cases.

Additional available energy from CA of P_{12} or P_{13} , or carried over from ionization of the precursor, drives the loss of a second OH radical yielding $[M + H - 2(OH)]^+$ ion P_{14} , which has the experimentally verified structure of the $[M - H]^+$ phenoxazine or the $[M + H]^+$ of phenacene ion from ether **1** and amine **9**, respectively. Reverse activation energy associated with loss of OH radical from P_{12} or P_{13} (ether **1**) is minimal (≤ 3 kJ/mol) and small for the other P_{13} cases (≤ 15 kJ/mol, Tables 4a, 4b). These results are reasonable given that loss of OH from P_{12} entails only N-OH bond cleavage, whereas, loss from P_{13} involves ring relaxation to planarity with concomitant re-establishment of aromaticity. From P_{12} , the OH radical loss would involve a simple homolytic bond cleavage, and the entropic factors in the transition states would be favorable to cleavage.

Intermediate $[M + H]^+$ ions **M**₇ and **M**₈ can readily lose H₂O by transition states **TS**_{7a} and **TS**₈, respectively, to yield $[M + H - H_2O]^+$ ions, **P**₂ and **P**_{2c}, respectively (Scheme 2c), the latter with reverse activation energy ≥ 300 kJ/mol (Scheme 3, Table 4b). The product $[M + H - H_2O]^+$ ion, **P**_{2c}, is a substituted, protonated cyclic ketone, which can extrude CO to form the second-generation product ion, $[M + H - (H_2O + CO)]^+$, **P**₆ (Scheme 2c). The substantial energy available in the formation of **P**_{2c} and neutral H₂O is sufficient to drive the CO-loss process, which is highly endothermic relative to **P**_{2c}.

In addition, the intermediates from **M**₁ of the amine (X = NH; **9**) present additional pathways for the elimination of H₂O owing to the presence of a second active H, located on the amine N. Of particular interest are such pathways that originate from intermediate $[M + H]^+$ ions, **M**₄ and **M**₅ (Scheme 2d). For all cases (**1**, **5** or **9**), intermediates **M**₄ and **M**₅ can reversibly generate other intermediate ions, **M**₁₀, **M**₁₁ and **M**₁₂, which eliminate H₂O, via transition states, **TS**_{11a} and **TS**₁₂ forming the product $[M + H - H_2O]^+$ ion **P**₂ (Table 4). The presence of the N-H in amine **9** opens two additional, more facile routes of H₂O loss, via transition states **TS**₁₀ and **TS**_{11b}. Furthermore, the $[M + H - H_2O]^+$ product ion **P**_{2b} can undergo an OH radical loss to yield a second-generation $[M + H - H_2O - OH]^+ \cdot$ product ion **P**₁₆, which is a major product ion and has the structure of the phenacene radical cation, as experimentally verified.

The results of molecular orbital calculations thus substantiate the experimental observation that, upon protonation, the ether (**1**), sulfide (**5**) and amine (**9**) undergo cyclization by attack of an electrophilic nitro group followed by fragmentation yielding heterocyclic product ions.

Conclusion

2-Nitrophenyl phenyl ether, amine, sulfide, and their substituted analogs undergo protonation at one of the oxygen atoms of the nitro group, converting it to an electrophile and promoting cyclization. The cyclization may be considered to be an intramolecular electrophilic substitution. The competitive eliminations of the OH radical and H₂O, the latter the major process, occur from the resulting cyclic structure of the protonated molecule. The loss of a second OH radical from the $[M + H - OH]^+$ ions generates fragment ions whose structures are [phenoxazine - H]⁺ and [phenazine + H]⁺ ions from the ether and amine, respectively. The $[M + H - H_2O]^+$ ions dissociate via loss of CO. Theoretical calculations predict and experiments verify that a fraction of the $[M + H - H_2O]^+$ ions possess protonated heterocyclic ketone structures (phenoxazine-1-one, phenothiazine-1-one, and 10*H*-phenazine-1-one, protonated on carbonyl oxygen, from the ether, sulfide and amine, respectively). Owing to the presence of a second active hydrogen as NH in the amine, the $[M + H - H_2O]^+$ ions possess an additional structure (N- hydroxyphenazine cation), which can lose an OH radical. The reaction in which a protonated nitro group participates in a gas-phase electrophilic cyclization is unusual but may be general.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Mass spectrum of FAB-produced 2-nitrophenyl phenyl ether from a matrix of 3-nitrobenzyl alcohol.

Figure 2.
The CAD mass spectrum of $[M + H]^+$ (m/z 216) ions of the ether **1** produced by FAB.

Figure 3. CAD mass spectra of ESI-produced $[M + H]^+$ of (a) 2-nitrophenyl phenyl ether, **1**, (b) 2-nitrophenyl phenyl sulfide, **5**, and (c) 2-nitrodiphenyl amine, **9**.

Figure 4. CAD mass spectra of the ions of m/z 182 produced from (a) *N*-acetyl phenoxazine by EI, (b) compound **1** by FAB.

Figure 5.

The CAD mass spectrum of (a) the $[M + H]^+$ ions of phenazine, produced by methane CI and (b) the fragment ion of m/z 181 from **9**. In both mass spectra the most abundant fragment is the m/z 180 ion due to H-radical loss (not shown).

Figure 6. The CAD mass spectra of the (a) fragment ion of m/z 180 from **9** produced by FAB, and (b) the phenazine radical cation produced by EI.

Scheme 2.

Scheme 2a. Proposed mechanism of initial cyclization of protonated precursors. In structure **M₁**, the bridging heteroatom is shown as Y (either O, S). Structures **M_{1N}**, **P₁** and **P_{1a}** are specific for the amine, and the bridging moiety is NH, which becomes N as shown after loss of H₂O. For all other structures, the bridging atom is depicted as X referring to O, S, or NH. The protonating H(D) and its fate in the proposed mechanisms is shown by bold **H**.

Scheme 2b. Proposed rearrangement of cyclized intermediates (X = O, **1**; S, **5**; NH, **9**). The protonating H(D) and its fate in the proposed mechanisms is shown by bold **H**.

Scheme 2c. Proposed mechanism: Loss of H₂O and CO (X = O, **1**; S, **5**; NH, **9**). The protonating H(D) and its fate in the proposed mechanisms is shown by bold **H**.

Scheme 2d. Proposed mechanism: Loss of H₂O (X = O, **1**; S, **5**; NH, **9**). The protonating H(D) and its fate in the proposed mechanisms is shown by bold **H**.

Scheme 3.

Relative enthalpies of reaction paths from protonated precursor to H₂O loss (ether **1**).
Most favorable reaction path indicated in red from data in Schemes 2a and 2b.

R	R ₁	R ₂	R ₃	
NO ₂	H	H	H	
NO ₂	H	H	CH ₃	
NO ₂	H	CH ₃	H	
H	NO ₂	H	H	
NO ₂	H	H	H	
NO ₂	Cl	H	H	
NO ₂	Cl	H	CH ₃	
H	NO ₂	H	H	
NO ₂	H	H	H	
NO ₂	H	H	CH ₃	
NO ₂	H	H	Cl	
NO ₂	Cl	H	CH ₃	
H	NO ₂	H	H

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R₃R₂R₁

R

Phenazine

Table 2

Partial MI and CAD mass spectra of $[M + H]^+$ ions of compounds 1–13.

Compd	Spectrum	$[M + H]^+$	$[M + H - OH]^+$	$[M + H - 2OH]^+$	$[M + H - H_2O]^+$	$[M + H - H_2O - CO]^+$	$[M + H - H_2O - OH]^+$
[*] 1	FAB-MI	<i>m/z</i> 216	<i>m/z</i> 199 (60)	<i>m/z</i> 182 (9)	<i>m/z</i> 198(40)	<i>m/z</i> 170 (8)	nd
	FAB-CAD		(14)	(25)	(10)	(12)	
	CI-MI		(32)	(34)	(50)	(12)	
	CI-CAD		(8)	(54)	(14)	(10)	
	ESI-CAD		(1)	(5)	(4)	(9)	
[*] 2	FAB-MI	<i>m/z</i> 230	<i>m/z</i> 213 (30)	<i>m/z</i> 196(60)	<i>m/z</i> 212 (28)	<i>m/z</i> 184 (24)	nd
	FAB-CAD		(16)	(34)	(18)	(15)	
	ESI-CAD		(8)	(8)	(20)	(45)	
[*] 3	FAB-MI	<i>m/z</i> 230	<i>m/z</i> 213(60)	<i>m/z</i> 196(11)	<i>m/z</i> 212 (30)	<i>m/z</i> 184 (70)	nd
	FAB-CAD		(40)	(75)	(37)	(24)	
4	FAB-MI	<i>m/z</i> 216	<i>m/z</i> 199(100)	nd	nd	nd	nd
	FAB-CAD		(100)				
^{**} 5	FAB-MI	<i>m/z</i> 232	<i>m/z</i> 215(24)	<i>m/z</i> 198(<1)	<i>m/z</i> 214(30)	<i>m/z</i> 186(4)	nd
	FAB-CAD		(22)	(5)	(22)	(10)	
	CI-MI		(45)	(9)	(80)	(18)	
	ESI-CAD		(30)	nd	(28)	(15)	
6	ESI-CAD	<i>m/z</i> 266	249(10)	nd	248 (7)	220 (20)	nd
7	ESI-CAD	<i>m/z</i> 280	263(20)	nd	262 (12)	234 (15)	nd
8	ESI-CAD	<i>m/z</i> 232	<i>m/z</i> 215(100)	nd	nd	nd	nd
9	FAB-MI	<i>m/z</i> 215	<i>m/z</i> 198 (40)	<i>m/z</i> 181 (1)	<i>m/z</i> 197(100)	<i>m/z</i> 169 (8)	<i>m/z</i> 180(30)
	FAB-CAD		(22)	(44)	(63)	(18)	(100)
	ESI-CAD		(10)	(2)	(36)	(10)	(100)

Compd	Spectrum	[M + H] ⁺	[M + H - OH] ⁺	[M + H - 2OH] ⁺	[M + H - H ₂ O] ⁺	[M + H - H ₂ O - CO] ⁺	[M + H - H ₂ O - OH] ⁺
10	ESI-CAD	<i>m/z</i> 229	212(2)	195(1)	211(55)	<i>m/z</i> 183(4)	194(100)
11	ESI-CAD	<i>m/z</i> 249	232(2)	215(1)	231(48)	<i>m/z</i> 203(4)	214(100)
12	ESI-CAD	<i>m/z</i> 263	246(2)	229(1)	245(50)	<i>m/z</i> 217(3)	228(100)
13	FAB-MI	<i>m/z</i> 215	<i>m/z</i> 198 (100)	nd	(8)	***169 (32)	nd
	ESI-CAD		(100)	nd	nd	(5) ([M+H-NO ₂])	nd

Numbers in parenthesis are relative abundances. 'nd' is "not detected."

*

For **1**, **2** and **3** the base peak corresponds to ion of *m/z* 122.

**

Other major fragment ions: 184(70), 168(30, -SO₂), 167(80, -SO₂H), 154(20, -SO₂H), 125(55), 123(50), 109(100) (abundances by CI-CAD, present in ESI-CAD).

This ion is formed by the loss of NO₂ as determined by accurate-mass data.

Table 3
Measured accurate masses of fragment ions generated by ESI-CAD of the $[M + H]^+$ ions of compounds **1**, **2**, **5**, and **9**.

Compd.	$[M + H - OH]^+$	$[M + H - 2OH]^+$	$[M + H - H_2O]^+$	$[M + H - H_2O - CO]^+$	$[M + H - H_2O - OH]^+$
1	199.0629 (199.0633)	182.0605 (182.0606)	198.0556 (198.0555)	170.0605 (170.0606)	nd
2	213.0790 (213.0790)	196.0760 (196.0762)	212.0713 (212.0712)	184.0760 (184.0762)	nd
5	215.0406 (215.0405)	nd (too weak)	214.0322 (214.0326)	186.0378 (186.0377)	nd
9	198.0794 (198.0793)	181.0753 (181.0765)	197.0713 (197.0715)	169.0769 (169.0766)	180.0681 (180.0687)

The figures in parentheses are the calculated masses; 'nd' is "not detected."

Table 4

Table 4a. Calculated relative enthalpies of formation/reaction for minima (M _n) and products(P _n).									
Ether				Amine			Sulfide		
Label	Corrected H (hartree)	Δ^2H_f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)	Corrected H (hartree)	Δ^2H_f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)	Corrected H (hartree)	Δ^2H_f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)
M ₁	-743.358934	0		-723.494657	0		-1066.331648	0	
M _{1N}									
M _{1a}	-743.355136	10		-723.491686	8		-1066.337664	-16	
M _{1b}	-743.345825	34		-723.482744	31		-1066.327682	10	
M _{1c}	-743.341280	46		-723.473933	54		-1066.323497	21	
M ₂	-743.310115	128		-723.455569	103		-1066.290294	109	
M ₃	-743.367842	-23		-723.496232	-4		-1066.338871	-19	
M _{3a}	-743.360378	-4		-723.502694	-21		-1066.338416	-18	
M ₄	-743.349328	25		-723.473405	56		-1066.318530	34	
M ₅	-743.399508	-107		-723.525801	-82		-1066.375042	-114	
M ₆	-743.376461	-46		-723.525404	-81		-1066.357764	-69	
M ₇	-743.394643	-94		-723.530669	-95		-1066.375325	-115	
M ₈	-743.387746	-76		-723.530677	-95		-1066.362888	-82	
M ₉	-743.357563	4		-723.491156	9		-1066.330769	2	
M ₁₀	-743.372129	-35		-723.527211	-85		-1066.356341	-65	
M ₁₁	-743.392743	-89		-723.545818	-134		-1066.373135	-109	
M ₁₂	-743.381495	-59		-723.508195	-36		-1066.350715	-50	
M ₂₀	-743.342224	44		-723.482230	33		-1066.323172	22	
P ₁				-647.022730		98			
P _{1a}				-647.061244		-3			
P ₂	-666.994251		-184	-647.137723		-204	-989.971277		-195
P _{2a}				-647.077595		-46			
P _{2b}				-647.123193		-166			
P _{2c}	-667.044390	0	-316	-647.187647	0	-335	-990.026939	0	-341
P ₃	-667.024236	53	-263	-647.165248	59	-277	-990.010251	44	-298

Table 4a. Calculated relative enthalpies of formation/reaction for minima (M_n) and products(P_n).

Ether				Amine			Sulfide		
Label	Corrected H (hartree)	Δ^2H_f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)	Corrected H (hartree)	Δ^2H_f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)	Corrected H (hartree)	Δ^2H_f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)
P ₄	-666.946695	256	-59	-647.089781	257	-78	-989.930999	252	-89
P ₅	-666.958962	224	-91	Unstable			-989.944869	215	-126
P ₆	-553.660068	107	-208	-533.809718	91	-245	-876.649406	90	-252
P ₁₀	-667.527630		209	-647.666391		201	-990.510437		183
P ₁₂	-667.585613		57	-647.727074		42	-990.566620		35
P ₁₃	-667.578464		76	-647.708675		90	-990.554754		66
P ₁₄	-591.793723		163	-571.943217		127	-914.775204		140
P ₁₆				-571.275457		86			
CO	-113.343442			-113.343442			-113.343442		
H ₂ O	-76.434736			-76.434736			-76.434736		
OH	-75.751594			-75.751594			-75.751594		

Table 4b. Calculated relative enthalpies of formation and reaction for transition states (TS_n).

Ether				Amine				Sulfide			
Label	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ^2H_{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _f (kJ/mol)
TS ₁	-743.341879	45					-1066.324028	20			
TS _{1N}				-723.474889	52						
*TS _{1a}	-743.344310	38		-723.460744	89		-1066.316363	40			
TS _{1b}	-743.336431	59		-723.473304	56		-1066.319564	32			
TS _{1c}	-743.333015	68		-723.466113	75		-1066.312759	50			
TS _{1P}				-723.437185	151						
TS ₂	-743.306609	137		-723.446371	127		-1066.286323	119			
TS _{2a}	-743.301510	151		-723.443181	135		-1066.276715	144			
TS _{2b}	-743.293281	172		-723.434954	157		-1066.270580	160			
TS _{2c}	-743.284250	196		-723.426320	179		-1066.265103	175			

Table 4b. Calculated relative enthalpies of formation and reaction for transition states (TS_n).

Label	Ether			Amine			Sulfide		
	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ ² H _{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ ² H _{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ ² H _{rxn} (kJ/mol)
TS ₃	-743.317117	110		-723.443083	135		-1066.277729	142	
TS _{3a}	-743.290181	181		-723.431837	165		-1066.264095	177	
TS _{3b}	-743.284245	196		-723.432148	164		-1066.274762	149	
TS ₄	-743.335455	62		-723.461566	87		-1066.310871	55	
TS _{4a}	-743.338308	54		-723.466560	74		-1066.310739	55	
TS _{4b}	-743.334995	63		-723.457884	97		-1066.305079	70	
TS ₅	-743.352924	16		-723.495205	-1		-1066.327800	10	
TS _{5a}	-743.343142	41		-723.485711	23		-1066.318557	34	
TS ₆	-743.341417	46		-723.485618	24		-1066.321591	26	
TS ₇	-743.353990	13		-723.488173	17		-1066.333354	-4	
TS _{7a}	-743.376454	-46		-723.515934	-56		-1066.356194	-64	
TS ₈	-743.358101	2		-723.496523	-5		-1066.329571	5	
TS ₉	-743.344824	37		-723.488411	16		-1066.324106	20	
TS ₁₀				-723.490741	10				
TS ₁₁	v743.326458	85		-723.486342	22		-1066.312588	50	
TS _{11a}	-743.317173	110		-723.462775	84		-1066.300270	82	
TS _{11b}				-723.504126	-25				
TS ₁₂	-743.322582	95		-723.454395	106		-1066.289184	111	
-TS ₂₀	-743.309080	131		-723.439424	145		-1066.290125	109	
TS _{P1a}				-647.017670		111			
TS _{P2a}				-647.054342		15			
TS _{P2c}	-667.010467	89	-226	-647.157396	79	-256	-990.001318	67	-274
TS _{P3}	-666.939173	276	-39	-647.088958	259	-76	-989.924112	270	-71
TS _{P4}	-666.947099	255	-60	-647.087111	264	-71	-989.932270	249	-93
TS _{P4a}	-666.943594	265	-51	-647.084631	270	-65	-989.929000	257	-84
TS _{P5}	-666.949680	249	-67		335		-989.936737	237	-105
TS _{P12}	-667.545655	162		-647.693584		130	-990.525604		143

Table 4b. Calculated relative enthalpies of formation and reaction for transition states (TS_n).

Ether				Amine				Sulfide				
Label	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ ² H _{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ ² H _{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ ² H _{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _f (kJ/mol)	Δ ² H _{rxn} (kJ/mol)
TS _{P13}	-667.544448		165	-647.689655		140	-990.520935		155			

Table 4c. Calculated relative enthalpies of formation/reaction for OH loss from M₅.

Ether				Amine			Sulfide		
Label	Corrected H (hartree)	Delta; ² H _r (kJ/mol)	Δ ² H _{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _r (kJ/mol)	Δ ² H _{rxn} (kJ/mol)	Corrected H (hartree)	Delta; ² H _r (kJ/mol)	Δ ² H _{rxn} (kJ/mol)
M ₅	-738.852246		0	-719.016800		0	-1061.477464		0
TS(M ₅ -P12)	-738.779567	191		-718.971955	118		-1061.423827	141	
TS(M ₅ -P ₁₃)	-738.781760	185		-718.956252	159		-1061.417007	159	
P ₁₂ -M ₅			164			124			149
P ₁₃ -M ₅			182			172			180

Enthalpies of reaction (Δ²H_{rxn}) include contributions from concomitant H₂O, OH radical, and CO losses.

* Values of **TS1a** for amine were calculated at level: B3LYP/6-311+G(2d,p)/MP2/6-31G(d,p).

Enthalpies of formation(ΔH_f) are reported relative to **M5** in this table only.

Enthalpies of reaction (Δ²H_{rxn}) include contributions from concomitant OH radical loss.

Values for **M5**, **TS(M5-P12)**, and **TS(M5-P13)** were calculated/optimized by: CASSCF(6,8)/6-31G(d,p).

Enthalpies of reaction (ΔH_{rxn}) for **P12-M5** and **P13-M5**, including OH loss, are derived from Tables 4(a,b) which were calculated by: B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d,p).