Letter

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Gas Phase Oxidation of Nicotine by OH Radicals: Kinetics, Mechanisms and Formation of HNCO

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ABSTRACT

Cigarette smoke is recognized as having harmful health effects for the smoker and for people breathing second-hand smoke. In an atmospheric chemistry context however, little is known about the fate of organic nitrogen compounds present in cigarette smoke. Indeed, the atmospheric oxidation of nicotine, a major nitrogen-containing component of cigarette smoke, by OH radicals has yet to be investigated. We report the first rate coefficient measurement between OH and nicotine to be \((8.38 \pm 0.28) \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}\) at \(298 \pm 3 \text{ K}\). We use an online proton-transfer-reaction mass spectrometer (PTR-MS) to quantify nicotine’s oxidation products, including formamide and isocyanic acid (HNCO). We present the first evidence that HNCO is formed from
nicotine’s gas phase oxidation and we highlight the potential for this toxic molecule to be an indoor air pollutant after smoking has ended. Mechanistic pathways for the oxidation of nicotine by OH radicals were investigated by theoretical calculations at the M06-2X level of theory and we find that there are many competitive H-abstraction sites on nicotine. Our findings suggest that the atmospheric removal of nicotine by OH radicals may compete with surface deposition and air exchange, and may be a source of HNCO in indoor air.

INTRODUCTION

Smoking has well-documented negative health consequences for populations worldwide, including cancer, pulmonary diseases and cardiovascular diseases.\(^1\) Exposure pathways of concern include mainstream smoke, inhaled by the smoker, sidestream smoke (or second-hand smoke), inhaled in the presence of a smoker, and third-hand smoke, inhaled near surfaces previously exposed to cigarette smoke.\(^2\) Both mainstream and sidestream smoking increase cardiovascular disease risk by promoting atherosclerosis and blood clot formation.\(^1\) Nicotine is the major organic nitrogen compound emitted from burning tobacco cigarettes. It can be present at levels up to 3 mg per cigarette depending on the cigarette brand, and thus may account for \(\sim1.5\%\) of a cigarette’s...
weight. Nicotine is a known health hazard and causes addiction, but is also used as a therapeutic for Parkinson and Alzheimer’s diseases. The atmospheric fate of nicotine has been assumed to be governed by its deposition to surfaces. Based on the current literature, gas-phase nicotine is expected to be rapidly removed by sorption to indoor surfaces, and re-emitted during ventilation, leading to third hand smoke exposure and to concentrations up to ~10% of those observed during the smoking phase indoors. Nicotine adsorption rate coefficients to surfaces in an indoor environment range from 1.5 – 6 hours\(^{-1}\) and 95-99% is reported to be partitioned to the sorbed phase at equilibrium. Nicotine’s heterogeneous oxidation by ozone has been previously studied at high ozone levels and found to proceed on timescales of a week or so. Surprisingly, its rate coefficient with OH radicals has yet to be reported. Nicotine’s gas phase oxidation may compete with deposition and air exchange rates in indoor environments despite expected lower concentrations of OH radicals indoor (~5 × 10\(^5\) molec cm\(^{-3}\)) compared to outdoor air (~2 × 10\(^6\) molec cm\(^{-3}\)). In an outdoor context, nicotine emissions may be increasing through regulations requiring smokers to smoke outside, in which case nicotine may be oxidized in a higher OH radical concentration environment. In addition, electronic cigarettes generate fewer particles, allowing nicotine to partition and/or remain in the gas phase.

Sidestream smoke and nicotine exposure are of concern, but the aging of both the smoke and nicotine may also have negative health and environmental impacts. Nicotine has been found to contribute significantly (with yields of 4-9%) to the formation of secondary organic aerosol (SOA) through reaction with ozone. SOA formation has also been observed by sorbed nicotine from cellulose, cotton and paper surfaces reacting with ozone in the presence of NO\(_x\) and varying RH. In addition, residual nicotine from tobacco smoke sorbed to indoor surfaces may react with...
ambient nitrous acid (HONO) to form carcinogenic tobacco-specific nitrosamines.\textsuperscript{15} These recent studies raise concerns about exposure to tobacco smoke residue, through second- and third-hand smoke.

In an effort to contribute to the growing knowledge of cigarette smoke from an atmospheric chemistry perspective, we provide the first measurement of nicotine’s rate coefficient with OH radicals at room temperature. Also, for the first time, we quantify formamide and HNCO as oxidation products of this alkaloid and further support nicotine’s oxidation mechanism with DFT calculations. The observations of HNCO formation are especially important given this compound’s recognized toxicity. HNCO is known to cause carbamylation which may subsequently lead to illnesses like rheumatoid arthritis, cataracts and cardiovascular diseases.\textsuperscript{16-19} HNCO has also recently been measured in ambient air at concentrations up to 1 ppb, high enough to be of health concern.\textsuperscript{20} The fast gas phase loss kinetics of nicotine and the formation of toxic products contribute to our understanding of the fate of cigarette smoke and to the production of secondary pollutants, especially in an indoor environment.

MATERIALS AND METHODS

1. Kinetic and product study of nicotine

The kinetics of nicotine OH oxidation were studied using a quadrupole proton-transfer-reaction mass spectrometer (PTR-MS) (Ionicon Analytik GmbH, Innsbruck Austria)\textsuperscript{21} connected to a 1 m\textsuperscript{3} Teflon FEP film (American Durafilm) bag (Ingeniven) and mounted on a Teflon-coated frame, with no fan. The chamber is also surrounded by 24 UVB lamps (Microlites Scientific) centered at 310 nm used to photolyse hydrogen peroxide as the OH radical source. The signals of the
compounds of interest were normalized to the H$_3^{18}$O$^+$ ion, m/z 21. Experiments were conducted under dry (< 1 %) and NO$_x$-free conditions (see SI for further details).

For the calibration of the PTR-MS, known volumes of a 0.7 M aqueous solution of nicotine (Sigma-Aldrich, > 99% purity) were injected into the chamber through a glass tube connection. A flow of pure air from an AADCO 737-series generator passed through the glass tube adding nicotine to the chamber in mixing ratios up to ~700 ppbv. Nicotine was monitored at its protonated molecular ion at m/z 163, and had a linear calibration (Figure S1), a sensitivity of 2 ncps/ppbv (calculated using Equation S1)$^{21}$ and a LOD of 2.0 ppbv (3σ). Furthermore, the m/z 44 and m/z 46 PTR-MS signals were assigned to HNCO and formamide. Calibration details of the products are detailed in the SI.

A typical oxidation experiment used 1,3,5-trimethylbenzene (TMB) (Sigma-Aldrich, 98%) as the reference compound for the relative rate kinetics, detected by the PTR-MS at m/z 121.$^{22}$ An aqueous solution of 30 % hydrogen peroxide bubbled into the chamber generated OH radicals upon UVB light exposure. The hydrogen peroxide was continuously injected inside the chamber to ensure a steady state concentration of OH radicals and thus pseudo-first order kinetics (see Figure S3). The OH radical concentration was ~ 10$^7$ molec cm$^{-3}$, estimated by the decay of the reference compound. Refer to the SI for the details on control experiments conducted.

2. Theoretical method

To investigate the mechanism of the gas-phase reaction of nicotine with OH radicals, computational DFT methods were employed using the Gaussian 09 code.$^{23}$ Structures of the reactants and transition states were optimized using the M06-2X density functional method with the 6-311G+(d,p) basis set.$^{24}$ The energies reported are 0 K enthalpies and are calculated from the
sum of the electronic energy and the zero point energy. Optimized geometries are provided in the SI.

The transition state energy represents the energy difference between the transition state and the sum of the reactants’ energies. The assumption is that the energy of the pre-complex formation of nicotine with OH radicals does not affect the rate of the reaction, i.e. we report transition state energy relative to the energy of the reactants as an indication of whether the mechanism is likely to occur readily.

RESULTS AND DISCUSSION

1. Kinetics results

The rate coefficient for nicotine’s gas phase reaction with OH radicals was measured using the relative rate kinetics method. Nicotine was detected in the chamber, but required the use of hundreds of ppbv for quantifiable decays. Compared to our previous experience with gas phase amines, the chamber did not require prior conditioning for a reproducible nicotine signal to be observed (see nicotine signal in Figure S3). Plotting the natural logarithm of the decay of nicotine as a function of the natural logarithm of the decay of the reference compound as in Figure 1 yields a linear regression in which the slope represents the ratio of the nicotine’s rate coefficient to TMB’s rate coefficient. Figure 1 represents the data and fit from a single experiment, and the experiment was performed in triplicate. Based on TMB’s previously reported room temperature rate coefficient of \((5.73 \pm 0.53) \times 10^{-11}\) cm\(^3\) molec\(^{-1}\) s\(^{-1}\), we convert each regression to its corresponding rate coefficient for nicotine. The average of these triplicate rate coefficients leads to a value of \((8.38 \pm 0.28) \times 10^{-11}\) cm\(^3\) molec\(^{-1}\) s\(^{-1}\) for nicotine + OH radicals at 298 ± 3 K where the standard deviation represents the variability between experiments. Since the precision between
replicated experiments is good (3%), the uncertainty for nicotine’s rate coefficient is dominated by the uncertainty in TMB’s rate coefficient, leading to an overall uncertainty closer to 10%. If we assume an indoor environment with an OH radical concentration as high as $5 \times 10^5$ molec cm$^{-3}$, nicotine would have a lifetime of 6.6 hours (or longer with lower averaged OH concentrations), and a shorter lifetime outdoors where OH concentrations are expected to be higher during the daytime.

The room temperature rate coefficient measured for nicotine can be compared to other amines’ reactivity towards OH radicals. Indeed, the majority of alkylamines have rate coefficients between $6-9 \times 10^{-11}$ cm$^3$ molec$^{-1}$ s$^{-1}$. The rate coefficient of heterogeneous nicotine with gas phase ozone has been reported to be $0.035 \pm 0.015$ min$^{-1}$ in the presence of 245 ppmv of ozone. This rate coefficient is not directly transferable to the gas phase, but leads us to believe that the atmospheric oxidation of nicotine will be dominated by OH radicals rather than by ozone.

Concerns over whether the nicotine decay observed was occurring in the gas phase versus on the wall/particle surface are justified. However, we argue that the majority of the decay was occurring in the gas phase during the first hour of oxidation. First, the decay rate of nicotine in a flushing control experiment matched the purging rate of the chamber, suggesting minimal desorption from the wall (Figure S2). Second, particle formation is inevitable during oxidation, but the exponential decay of nicotine and TMB in Figure S3 and their linear relationship in Figure 1 indicates that nicotine does not have an additional and/or growing sink as the experiment progresses. Further discussion is included in the SI.

The fate of gas phase nicotine in a typical indoor environment depends on its deposition to surfaces, the air exchange rate of the room/building and its chemical reactivity. Studies have previously suggested that the majority of nicotine is removed via deposition, and may later
revolatilize.\textsuperscript{7,8,14} Air exchange rates in residential homes range between 0.05 – 5 h\textsuperscript{-1}.\textsuperscript{32} Our results suggest that chemical reactivity with OH radicals may compete with ventilation for removal in particularly well-sealed buildings with low air exchange rates. The gas phase reactivity of nicotine will also apply to deposited molecules that repartition to the gas phase.

![Graph](image-url)

**Figure 1:** Plot of the natural logarithm of the decay of nicotine against the natural logarithm of the decay of the reference compound TMB. Each point was taken at ~ 5 s intervals by the PTR-MS and the linear regression is represented as the black line. The nicotine decay plotted here was taken from 0.08 – 1.2 h from Figure S3A. (See SI for further details on this regression.)

2. **Product study**

Nicotine reacts quickly in the presence of OH radicals and so identifying its oxidation products is important to better assess its health and environmental impact in the context of cigarette smoke. Figure 2 depicts the evolution of nicotine and its nitrogenated products as a function of time, measured by the PTR-MS. The major oxidation products containing nitrogen that could be confidently assigned were formamide and HNCO. If we assume that all the nicotine injected was
oxidized, we can report lower limit yields of 5% for both formamide and HNCO after 2 h of photo-oxidation. The yield of formamide is similar to measured yields from other amines like monoethanolamine (MEA). We note that these yields are likely lower limits since the products do appear to continue growing after the disappearance of nicotine (Figure S4). We also add that these yields are not directly transferable to the real atmosphere as we operate in a NOx-free environment. The production of HNCO from nicotine’s photo-oxidation was also confirmed by appending an acetate reagent ion chemical ionization mass spectrometer to the chamber, an instrument described by Borduas et al., which does not have interferences at HNCO’s molecular ion. Despite uncertainties in HNCO quantification (detailed in the SI), the observation of HNCO production from nicotine photo-oxidation is important, and may contribute to the negative health effects observed with smoking tobacco cigarettes.

By plotting the mixing ratios of formamide and HNCO over time as a function of the decaying nicotine mixing ratio (Figure S5), it is clear that these compounds are not first order generation products. In fact, the exponential curve in Figure S5 suggests they are at least second or third generation products, implying a complex mechanism of formation. Recent studies have shown that HNCO is the major product of formamide photo-oxidation, yet HNCO must have other sources based on the early onset of its production during the nicotine’s oxidation (see Figures 2 and S4). A similar conclusion was also made by Link et al. in their study of photo-oxidation of diesel exhaust. Furthermore, Roberts et al. detected high levels of HNCO from cigarette smoke in a preliminary study. Our study extends Roberts et al.’s observation; even after smoking has ended, there are secondary sources of HNCO, at least from nicotine, with important implications for indoor air quality. HNCO’s dominant ambient atmospheric fate is to partition to the aqueous phase,
where it may have lifetimes from hours to months depending on pH, but yet unknown lifetimes in the indoor environment.

Finally, the signal at m/z 42 was assigned to acetonitrile and detected with a yield of ~ 1 %.

Acetonitrile is typically known as a biomass tracer in ambient air and is expected to be formed from the oxidation of organic nitrogen.

Figure 2: The evolution of nicotine and its oxidation products upon exposure to OH radicals. The m/z with their assignments are m/z 163 (nicotine), m/z 44 (isocyanic acid), m/z 46 (formamide), and m/z 42 (acetonitrile). See also Figure S4.

3. Mechanism of oxidation

To explore the mechanism of oxidation of nicotine, as well as to gain insight into the first-generation oxidation products, we employ computational chemistry to calculate the transition state energies of nicotine + OH radicals relative to the energies of the reactants. Nicotine’s benzylic C–H bond, the most electron rich bond of the molecule, is likely to be the most reactive towards OH (Figure 3 and Figure S6). Its abstraction has been observed as the primary pathway in
nicotine’s aqueous phase oxidation. We calculate a nicotine-OH radical pre-complex at – 3.6 kcal mol$^{-1}$ below the entrance energies of the reactants with a transition state only 0.4 kcal mol$^{-1}$ above the energy of the pre-complex (Figure 3). These energies translate to a facile C–H abstraction and are consistent with the large rate coefficient we measured.

Nonetheless, there exist fourteen C–H bonds (nine of them unique) in nicotine which could react with OH radicals, in addition to potential OH-addition sites on the pyridine ring. To identify which C–H abstraction governs nicotine’s reactivity, we iteratively calculated each C–H bond’s transition state energy. These results are presented in Figure S6 and in the inset of Figure 3 and suggest that many C–H abstraction mechanisms are competitive for reaction with OH radicals.

Thus, the oxidation mechanisms of nicotine appear to be complex and occur at several C–H abstraction sites (in blue in the inset of Figure 3). Furthermore, we highlight unique reactivity on nicotine’s pyridine ring where the OH addition mechanism is deactivated (see SI and Figure S7).

It becomes difficult to assign a single mechanistic pathway for the production of formamide and HNCO. We estimate that at least two closed-shell intermediates are likely prior to formamide production based on calculations of subsequent reactions of the benzylic radical product (not shown). We also cannot differentiate if the nitrogen in formamide originates from the N–CH$_3$ group or the pyridine ring N. Further studies with isotopically labelled nitrogen might help in elucidating and differentiating mechanisms leading to formamide and HNCO.
Figure 3: Theoretical energy diagram for nicotine + OH. Energies are 0 K enthalpies in kcal mol$^{-1}$, at the M06-2X level of theory and 6-311G+(d,p) basis set. Inset: lowest transition state energies for the C−H bond abstraction and OH addition mechanism. Likely reaction sites are colored in blue and unlikely reaction mechanisms are colored in red. Also see Figure S3.

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Author Contributions
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**ASSOCIATED CONTENT**

Supporting Information Available: Detailed information on control experiments, theoretical results and optimized geometries.

**REFERENCES**

References


