Evidence for Radical Cations in Linked Mechanisms of *N*,*N*-Dialkyl Aromatic Amine Nitration and Nitrosative Dealkylation

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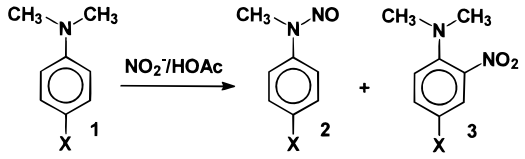
Abstract: *N*,*N*-Dialkyl aromatic amines react rapidly with nitrous acid to competitively produce a nitrosamine and a nitro compound. The mechanism of nitro compound formation involves a reaction of an amine radical cation with NO_2, while the nitrosamine is produced by two competing pathways, one of which involves *N*-α-CH deprotonation of a radical cation with subsequent oxidative generation of an imminium ion, and the other of which occurs through NOH elimination of a nitrosammonium ion ($R_3N-N{=}O^+$). All three pathways are linked through the reversible homolysis of $R_3N-N{=}O^+$ to NO and a radical cation.

Introduction

Much of the recent organic chemistry of nitrous acid has been focused on the possible inadvertent formation of potentially carcinogenic *N*-nitroso compounds such as nitrosamines. Indeed, we were recently led to consider the possible formation of nitrosamines from esters of *p*-*N*,*N*-dialkylbenzoic acid, which are used commercially as sun-blocking agents, among other things.[1,2] Prior work in our laboratory and those of others raised significant questions, however, regarding the ability of *N*,*N*-dialkyl aromatic amines to nitrosate sufficiently fast to produce significant quantities of nitrosamines at ambient temperatures.[3,4] Most, but certainly not all, tertiary aliphatic amines react too slowly with nitrous acid at 25 °C to produce significant quantities (0.1%) of nitrosamines.[3,4] The nitrosative dealkylation of triethylamine, typical of many tertiary amines, can be estimated to be 6.7×10^{-7} M^{-1} s^{-1} at 25 °C,[5] but is too slow for measurement at this temperature.[3,4] For simple amines, the rate of nitrosamine formation only competes with the thermal decomposition of HNO_2 at temperatures above 50−60 °C. The low nitrosation rates of simple aliphatic tertiary amines are due, in part, to their high basicity and protonation under acidic conditions required for the generation of nitrosating agents. While *N*,*N*-dialkylanilines are much less basic than triethylamine, their rapid nitrosative dealkylation was not anticipated. A review of the early literature, however, reveals that *N*,*N*-dialkyl aromatic amines are both nitrosatively dealkylated and nitrated by nitrous acid,[6,7] but the kinetics and mechanisms of these transformations have not been reported. We found that ethyl 4-(dimethylamino)benzoate (**1**, X = CO_2Et) reacts with HNO_2 in HOAc to form large quantities of ethyl 4-methylnitrosaminobenzoate (**2**, X = CO_2Et) and smaller amounts of ethyl 4-(dimethylamino)-2-nitrobenzoate (**3**, X = CO_2Et) in less than an hour at 25 °C (Scheme 1).[1,2] This qualitative finding naturally led us to ask if nitrosamine formation in this system was occurring by a mechanism different than elucidated for the nitrosation of trialkyl tertiary amines (Scheme 2, path A).[3,4]

Scheme 1



The mechanism and kinetics of nitrosative dealkylation of trialkyl tertiary amines have been investigated.[3,4] A key marker of this mechanistic pathway, shown as path A (**1** → **4** → **8** → **2**) in Scheme 2, is the formation of 0.5 mol of N_2O for every mole of nitrosamine formed. We have identified other structural features of tertiary amines which render them highly reactive toward nitrosative dealkylation and demonstrated that they occur by different mechanisms than that shown in path A of Scheme 2, but none of these would appear to be applicable to the reactions of *N*,*N*-dialkyl anilines.[8−14] Our preliminary investigations of the nitrosation of **1** (X = CO_2Et) showed that the

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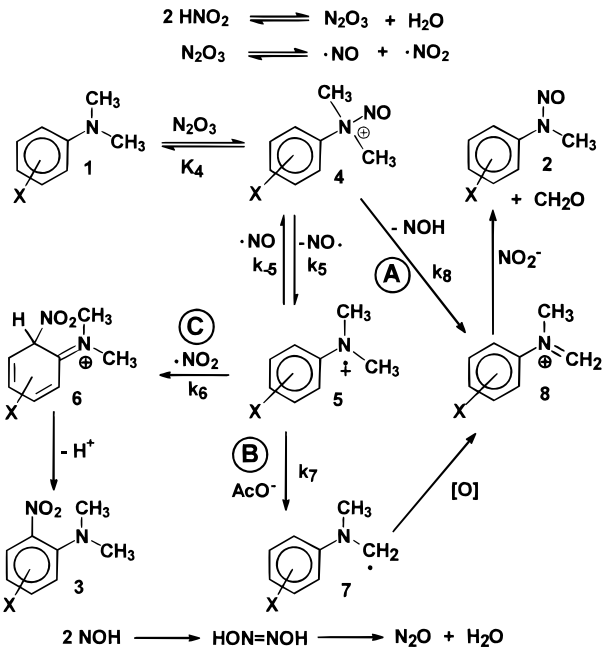
Scheme 2



relative yields of nitrosamine and nitro compound vary significantly with relatively minor changes in reaction conditions. These data suggested the operation of facile mechanistic switching and led us to consider a possible role for radical cation intermediates in the nitrosation chemistry of these aromatic amines.

Radical cations have been shown to be intermediates in the nitrous acid-catalyzed HNO_3 nitration of *N*,*N*-dialkyl aromatic amines and other aromatic compounds.[15−21] The relatively facile one-electron oxidation of aromatic amines also has led Colona et al. to propose the involvement of radical cations in nitrosative *N*-dealkylations of aromatic amines.[22] This group reported the ipso (p) and o-nitration of a group of *p*-substituted-*N*,*N*-dimethylanilines by nitrite in HOAc.[22] In two cases nitrosative demethylation was also observed. On the basis of their earlier work, they proposed that the nitration occurred through radical recombination of NO with radical cation followed by oxidation to the nitro compound, and that demethylation also occurred through a radical cation by an unspecified process. Verardo et al. observed the formation of nitro compounds, nitrosamines, and other substances when aromatic tertiary amines were heated with nitrite esters at reflux,[23] and proposed that nitro compound formation arose from the reaction of a radical cation with NO_2, but gave no direct role to radical cations in nitrosamine formation. These observations, and our own findings regarding the unexpectedly high reactivity of **1** (X = CO_2Et) toward nitrosative dealkylation, called for a more thorough investigation of the possible role of radical cations in the nitrous acid chemistry of *N*,*N*-dialkyl tertiary amines.

Overview

To improve the readability of this paper, we present here an overview of the mechanistic hypothesis that has arisen from this work. This is shown in Scheme 2. We propose that all reactions proceed through the reversible formation of a nitrosammonium ion **4**, which either suffers reversible homolysis to generate NO and radical cation **5** or loses NOH ultimately to give a nitrosamine (path A) by the established mechanism.[3,4] The radical cation **5** either reacts with NO_2 to give the nitro compound **3** (path C), loses a proton from the *N*-bound alkyl group to eventually produce a nitrosamine (path B), a new mechanism of nitrosative dealkylation, or reacts with NO to regenerate **4**.

In the presentation of the data and the attending discussion we will first show that nitration by nitrous acid in this system involves a radical cation. We will then show that nitrosamine formation occurs by more than one mechanism, and will present data consistent with the existence of a radical cation pathway, which competes with path A (NOH elimination). We present data supporting the hypothesis that the homolysis of the nitrosammonium ion is reversible, and that this equilibrium links nitrosamine and nitro compound formation in such a way that minor changes in reaction conditions and substrate structure change the pathway taken.

General Characteristics of the Transformation

The reactions of p-substituted-*N*,*N*-dialkylanilines were studied under several different nitrosating conditions resulting from the additon of concentrated aqueous sodium nitrite to either glacial acetic acid (HOAc) or 60% HOAc/H_2O buffered to pH 3.8 with NaOAc. (Even though some transformations produce the nitro compound **3** as the major product, we will use the term nitrosating agent in connection with the reagent nitrous acid, regardless of the nature of the products generated.) The literature suggests that the principal nitrosating agent under these conditions is N_2O_3.[24] Its initial steady state concentration is significantly higher in HOAc than in buffer. Nitrosations in HOAc occur more rapidly, but significant amounts of N_2O_3 are lost due to reversible homolysis to NO_2 and NO, followed by escape of the volatile gases. Accordingly, some transformations were examined in closed systems with no headspace above the liquid.

In a typical nitrosation, *N*,*N*-dimethyl-4-chloroaniline **1** (X = Cl) (0.23 mM) was reacted with $NaNO_2$ (0.69mM) in 60% HOAc buffer at pH 3.8 at 21 °C. The reaction was complete in 90 min with the production of the nitrosamine **2** (X = Cl) **(**83%) and the nitro compound **3** (X = Cl) (10%). Under similar conditions the ratio of the nitro compound to nitrosamine (**3/2** X = Cl) increased linearly as the initial [NO_2^-] to [amine] ratio increased. For example, the ratio **3/2** (X = Cl) was 0.6 with a 3× excess of NO_2^- but increased to 2.8 with a 15× excess. While this system appeared to be well behaved, other reaction variables can change the relative product composition. We have made numerous observations and a sample of these data are provided in Table 1. The following conclusions can be made: (1) The ratio of **3/2** was much greater when the reaction was conducted in glacial HOAc. (2) The Cl-substituted compound not only reacted more rapidly than the CO_2Et-substituted derivative but the ratio of **3/2** was also much greater. (3)

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Table 1. Variation of the **3/2** Ratio with Reaction Conditions for the Nitrosation of **1**[a]

run	X	$[NO_2]_o$	$[Am]_o$	solv	time	% rxn	**3/2**	% **2**
1	Cl	0.69	.25	buffer	78	96	0.15	82
2	Cl	3.3	1.1	HOAc	3	98	6.3	13
3	Cl	1	1.1	HOAc	3	65	1.7	24
4[b]	Cl	2.6	0.23	buffer	6	38	1.4	13
5	Cl	2.6	0.23	buffer	6.2	30	2.3	8.1
6	CO_2Et	67	6.7	HOAc	47	81	0.3	65
7	CO_2Et	18	6.9	buffer	50	48	0.03	31
8[b]	CO_2Et	27	2.7	buffer	61	52	0.12	46
9	CO_2Et	27	2.7	buffer	61	53	0.07	49

[a] General notes: concentrations are in mM; buffer is 60% HOAc/H_2O with NaOAc at pH 3.8; HOAc is glacial acetic acid; times are in min; unless noted specifically reactions were open to the atmosphere. [b] Without headspace.

Table 2. The Effect of Added Gases on Product Ratios from the Nitrosation of **1**

gas	% rxn	% **2**	% **3**	**3/2**
N_2	52	26	24	0.9
NO	76	49	24	0.5
O_2	97	15	75	5

Regardless of the ring substituent or the solvent, the **3/2** ratio increased with $[NO_2^-]$. (4) When reactions were conducted without headspace in closed vessels, the **3/2** ratio was greater regardless of the ring substituent. In the case of the nitrosation of **1** (X = CO_2Et) the product ratio was seen to change over the course of runs in HOAc. For example, the ratio of **3/2** (X = CO_2Et) changed smoothly, from 0.23 at 11% reaction to 0.12 at 63% reaction.

As may be expected from the headspace studies, reaction of **1** (X = Cl) in HOAc with a 10× $[NO_2^-]$ excess in the presence of added gases change the **3/2** ratio dramatically. In these experiments, a HOAc solution of **1** was run through a set of freeze−thaw cycles under vacuum to remove residual gases. The headspace above the liquid was then saturated with either N_2, NO, or O_2,, and a 10× excess of concentrated aqueous sodium nitrite was introduced by syringe. The product yields are given in Table 2. Addition of NO increased the yield of nitrosamine **2** (X = Cl) while addition of O_2 markedly increased the relative and absolute quantity of nitro compound **3** (X = Cl).

The nature of *N*-alkyl substituents can also alter the **3/2** ratio. Deuteration of the methyl groups bound to N increases the relative amount of nitro compound (vide infra). *N*-Cyclopropyl-*N*-methyl-4-chloro- or 4-carboethoxyaniline react with HNO_2 in HOAc to give only the nitrosamine **2** and no detectable amount of nitro compound. This phenomenon was seen for all compounds bearing a cyclpropyl group on N.[25]

Kinetic data for nitrosation of **1** (X = Cl or CO_2Et) are reported in Table 3. Reactions were followed by determining the concentrations of the amine, nitrosamine, and nitro compound by HPLC as a function of time. The rate data given in Table 3 are for the disappearance of the amine. Rate constants are the average of two to three determinations derived from linear regression of ln([amine]) vs time at nitrite concentrations 3- to 10-fold greater than that of the amine (pseudo first order). Good linearity was observed in all cases. The order in NO_2^- was determined only for **1** (X = Cl) in buffer by plotting log(k_{obs}) vs log($[NO_2^-]$) for runs where the $[NO_2^-]_0$ was varied giving a nitrite order of 0.97 ± 0.08 for this substrate. Second-order rate constants were calculated for all runs but, given the reaction complexity and the mechanistic switching observed for some substrates bearing the CO_2Et substitutent, we do not know the nitrite order for this substrate.

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The Mechanism of Nitro Compound Formation

To our knowledge, the mechanism of nitrous acid nitration has not been the object of a modern study, but a closely related transformation, the nitrous acid-catalyzed nitration by HNO_3 of relatively electron rich aromatic substrates, has been carefully examined. While the work in this area has been reviewed by several authors who have made seminal contributions,[15−21] the reader's attention is directed to a short review by Ridd,[15] who presented strong evidence for the mechanism shown in Scheme 3.[26−30]

In Ridd's work, and also in this paper, NO^+ is used to represent the various species which are effective NO^+ donors. The key transformation is the oxidation of the aniline to a radical cation by NO^+ (eq 1). The nitronium ion or a related species is then seen to oxidize the NO produced back to NO^+ with the formation of NO_2. Reaction of the radical cation with NO_2 then leads to the formation of the nitro compound. This mechanism is based on kinetics, ^{15}N CIDNP NMR data, product studies, electrochemical data, and ESR experiments.[15,26−30] Related work on other aromatic substrates by Kochi,[18] Eberson and Radner,[16,17] and Moodie et al.[20,21] present similar mechanisms. We show here that a closely related mechanism is responsible for nitration by HNO_2.

No NO_3^- and hence NO_2^+ are present in our reaction media, ruling out conventional electrophilic aromatic nitration. Moreover, it has been demonstrated with several substrates that nitration by nitrosating agents occurs much more rapidly than conventional HNO_3 acid-catalyzed nitration of aromatic amines and leads to a different regiochemistry.[31] It has been assumed that the nitro compounds arise in nitrosation reactions by C-nitrosation followed by oxidation.[15,22,31,32] To test this hypothesis, we sought the synthesis of 4-chloro-2-nitroso-*N*,*N*-dimethylaniline. Despite numerous attempts we were unable to prepare this compound and, surprisingly, 2-nitroso-*N*,*N*-dialkylanilines appear to be unknown. We then examined the possible oxidation of 4-nitroso-*N*,*N*-dimethylyaniline under the conditions in which **3** was produced in high yield. The C-nitroso compound was recovered unchanged under conditions where the consumption of **1** (X = Cl) by nitrosating agents was complete. These data provide strong evidence that **3** (X = Cl) was not being produced in our system by the oxidation of a C-nitroso compound.

Key evidence for the intermediacy of an amine radical cation in the nitrous acid-catalyzed nitration of *N*,*N*-dimethyl-*p*-toluidine by $H^{15}NO_3$ involved the Ridd group's observation of enhanced emission in the ^{15}N CIDNP NMR spectra of 4-methyl-2-nitro-*N*,*N*-dimethylaniline.[27,30] To determine whether a radical was involved in the production of **3** we nitrosated **1** with Na-$^{15}NO_2$ and the ^{15}N-NMR spectra were recorded as a function

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Table 3. Rates of Amine Disappearance upon Nitrosation

run	*T*, °C	compd[a]	10^4k_{obs}[b]	$[NO_2^-]$[c]	$[NO_2^-]/[Am]$	$100k_{2nd}$[d]	solvent
1	21	Cl	6.6 ± 0.2	0.69	2.8	96 ± 3	buffer[e]
2	21	Cl (D_6)	1.51 ± 0.08	0.69	3.2	22 ± 1	buffer
3	30	CO_2Et	4.4 ± 0.2	20.8	3	2.1 ± 0.1	buffer
4	30	CO_2Et (D_6)	1.18 ± 0.04	23.5	3	0.50 ± 0.02	buffer
5	30	CO_2Et	6.0 ± 0.2	67	10	0.89 ± 0.03	HOAc[f]
6	30	CO_2Et (D_6)	2.50 ± 0.04	67	10	0.373 ± 0.006	HOAc

[a] *p*-Substituted *N*,*N*-dimethylanilines **1**; (D_6) = $N(CD_3)_2$. [b] Pseudo first order rate constant (s^{-1}). [c] mM. [d] 2nd order rate constant calculated by dividing k_{obs} by $[NO_2^-]$ (s^{-1} M^{-1}). [e] 60% aqueous HOAc buffered to pH 3.8 with NaOAc (1.66 M). [f] Glacial acetic acid.

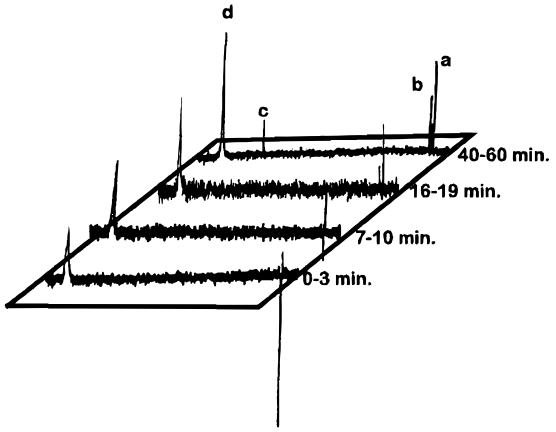
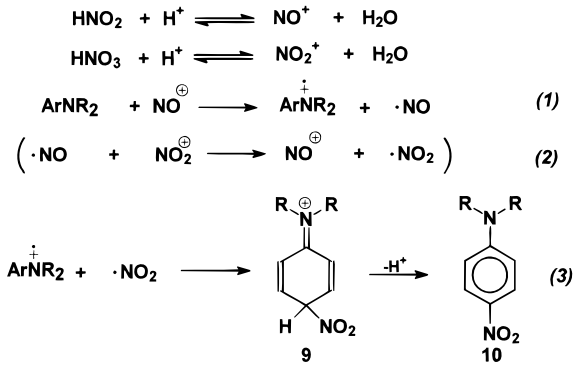


Figure 1. ^{15}N-NMR CIDNP spectra for the reaction of $Na^{15}NO_2$ with **1** (X = Cl) in D_4-HOAc. Spectra were accumulated over the time intervals shown following the addition of $Na^{15}NO_2$ in D_2O. Line assignments: a, $Ph^{15}NO_2$ standard; b, **3** (X = Cl) ; c, **2** (X = Cl); d, $H^{15}NO_2$. For each trace the line intensities should be compared to that of the nitrobenzene standard because of computer manipulation of graphical data for presentation purposes.

Scheme 3



of time. To enhance sensitivity, higher concentrations ([**1**(X = Cl)] = 0.04 M and $[NO_2^-]$ = 0.30 M in D_4-HOAc) had to be employed than those used in the kinetics experiments. ^{1}H NMR spectra were recorded under the same conditions to verify the reaction rate, course, and product identity. The ^{1}H NMR spectra showed no evidence for the formation of an ipso (para) intermediate, as was observed by Giffney and Ridd[27] in the nitration of *N*,*N*-dimethyl-*p*-toluidine. ^{15}N-NMR spectra were accumulated over the intervals shown in Figure 1 after $Na^{15}NO_2$ addition. The spectra at the first two time intervals show a strong but diminishing emission signal for the nitro group of **3** (X = Cl). In the latter time runs the emission signal has disappeared and only the normal absorption peak of the product nitro signal was observed.

Our CIDNP data were analogous to those obtained by the Ridd group[29,30] and an analogous application of the Kaptein equation,[33] modified for ^{15}N,[34] led to a similar conclusion.[35] Reaction of an amine radical cation with NO_2 to generate **6** (Scheme 2) is completely consistent with the observed CIDNP emission. We propose that the mechanism of nitration by nitrous acid is adequately represented by the transformations depicted in path C of Scheme 2 (**1** → **4** → **5** → **6** → **3**). The radical cation **5** is proposed to arise through the homolysis of the nitrosammonium ion **4** (vide infra), but could be produced by an equivalent set of transformations involving oxidation by N_2O_3, another NO^+ donor, or NO_2. Under our conditions, NO_2 is generated through the well-known facile homolysis of N_2O_3. The reaction of **5** with NO_2 generates the familiar nitration intermediate **6**, which rapidly deprotonates to generate **3**.

This mechanistic hypothesis is supported by several other pieces of data. The fact that the ^{15}N CIDNP evolved over the same time frame as the production of the nitro compound, as independently measured by ^{1}H NMR, provides evidence that the amine radical cation is on the reaction path to the nitro compound and that the CIDNP does not result from some minor side reaction. While the rate of disappearance of **1** (X = Cl) is first order in $[NO_2^-]$, the ratio of nitro compound to nitrosamine **3**/**2** (X = Cl) increased linearly with increasing $[NO_2^-]$, suggesting that nitro compound formation is second order in $[NO_2^-]$. Rate determining formation of the radical cation **5** followed by a more rapid reaction of it with NO_2, as shown in Scheme 2, would meet this requirement. Other observations which support the proposed mechanism include the fact that the **3**/**2** (X = Cl) ratio increased when the reaction was conducted in a closed vial without headspace (compare entries 4 with 5 and 8 with 9 in Table 1). These conditions retained the volatile NO_2 and increased its reaction with the radical cation. Similarly, the saturation of the system with O_2 increased the concentration of NO_2 through the oxidation of NO and increased the formation of the nitro compound (Table 2).

When one of the N-bound substituents is capable of a reaction that rapidly transforms the radical cation, no nitro compound is produced. Neither 4-chloro-*N*-cyclopropyl-*N*-methylaniline nor any other *N*-cyclopropyl-*N*-alkylaniline examined by us produced any nitro compound upon reaction with HNO_2.[25] The sole amine derived product in these reactions is the nitrosamine **2** (Scheme 4). It is well-known that the generation of radicals at atoms attached to the cyclopropyl group results in ring opening. This process is so fast as to preclude the possibility of NO_2/amine radical cation combination at the aromatic ring.

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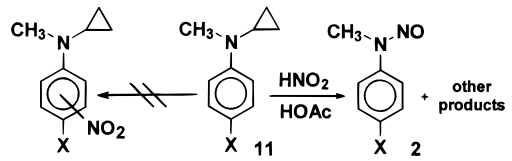
(35) The Kaptein equation modified for ^{15}N is $\Gamma = -\mu\epsilon\Delta g a_N$, where μ is positive for F-radical pairs formed by diffusion, ϵ is positive for product formation from geminate collapse of these radicals (NO_2 and **5** (X = Cl)), $\Delta g = g_{NO_2} - g_{rad.cat}$ is negative (g_{NO_2} = 2.000 and $g_{rad.cat}$ can be estimated to be close to 2.0032, the value for the radical cation derived from *N*,*N*-dimethyl-*p*-toluidine[30]), and a_N for NO_2 is negative,[30] giving Γ = −(emission).

Table 4. Products and Yields from Reactions of Radical Cations and Controls

run	substrate	reactant	% rxn[a]	% 2	other products
1	**1** (X = $N(CH_3)_2$)	NO_2^- /HOAc	97	31	**12** (59%), **13** (7%)
2	**5** (X = $N(CH_3)_2$)	NO_2^- /H_2O	99	74	**12** (4%), **13** (2%)
3	**5** (X = $N(CH_3)_2$)	NO/H_2O	89	58	**12** (12%), **13** (3%)

[a] Percent reaction determined by measuring the amount of unreacted amine recovered.

Scheme 4

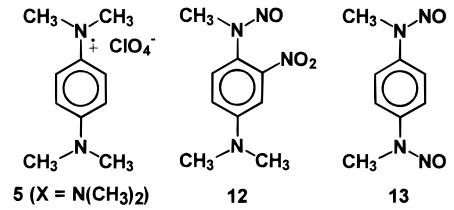


These data and those discussed above are completely consistent with the mechanism of nitro compound formation (path C) in Scheme 2.

Model Radical Cation Reactions

While the mechanism for nitro compound formation appears secure within the framework of data and literature precedent provided, several questions remained. Why do we apparently see no products arising from the combination or recombination of NO with the amine radical cation? Is it possible that NO_2^- reacts with the radical cation to produce a nitro compound? To answer these questions we prepared amine radical cations and examined their transformations with NO, NO_2, and NO_2^-. In each case control reactions involving the parent amine also were carried out. The reactions of radical cations derived from either **1** (X = Cl or X = $N(CH_3)_2$, *N*,*N*,*N*′,*N*′-tetramethyl-1,4-benzendiamine, the precursor of Wurster's blue) have been examined. Because of its greater stability, more reliable quantitative data were obtained from the transformations of Wurster's blue, although those from the more reactive radical cation derived from **1** (X = Cl) were similar, but have been omitted from Table 4.

Aqueous solutions of purified Wurster's blue **5** (X = $N(CH_3)_2$) reacted with both $NaNO_2$ and NO resulted in predominant formation of the nitrosamine **2** (X = $N(CH_3)_2$) (Table 4, runs 2 and 3). The major product from the reaction of NO_2 with **5** (X = $N(CH_3)_2$) (CH_3CN, 10 min) was the nitro-nitrosamine **12** with much smaller amounts of **13**. However,



reaction of **1** (X = $N(CH_3)_2$) with NO_2 under similar conditions (30 min) resulted in the formation of **2** (X = $N(CH_3)_2$) as the major product with minor amounts of **13.** The predominant formation of **12** from the reaction of Wurster's blue with NO_2 supports the mechanism proposed for nitro compound formation. Subsequent oxidation of the resulting amine and reaction with the accumulating reduction product (NO_2^- or HNO_2) leads to nitrosamine formation. In the case of the reaction of the parent amine (**1**, X = $N(CH_3)_2$) with NO_2, the primary reaction was an oxidation producing **5** and NO_2^-. The relative quantity of NO_2 was significantly reduced at the expense of NO_2^- formation and the predominant reaction was nitrosamine formation as was observed in the reaction of **5** with NO_2^-.

These model transformations demonstrate the following: (1) Neither NO nor NO_2^- is reactive toward the amines. (2) NO_2^- does not react with these radical cations to produce significant quantities of nitro compounds, especially when compared to the nitrous acid nitrosations (Table 4, run 1). (3) The major product from reactions of the radical cations with either NO or NO_2^- is the nitrosamine. (4) NO_2 reacts with both radical cations and their parent amines, blurring somewhat the distinctions between the transformations, but supporting the hypothesis that NO_2 can both oxidize the amine to a radical cation and react with the latter to produce a nitro compound. We discuss the mechanisms of these transformations further below. Although every attempt was made to keep these systems free of O_2, it is difficult to avoid some contamination and we believe that the small relative yields of the nitro compound in the Wurster's blue transformation with NO (Table 4, run 3) likely resulted from production of NO_2 by the oxidation of NO.

Evidence for More than One Mechanism of Nitrosamine Formation

The data presented so far provide strong evidence that nitro compound formation in these systems involves a radical cation intermediate. Several pieces of data also implicate a role for radical cations in the mechanisms of nitrosamine formation. These include the finding that *N*-cyclpropyl-*N*-alkylanilines only give nitrosamines upon reaction with HNO_2, and the observation that the model radical cations react with NO_2^- or NO to produce nitrosamines as the major products. In seeking to determine whether more than one mechanistic pathway was giving rise to nitrosamine formation in these reactions, we examined the ratio of **2** (X = Cl) to N_2O produced in the nitrous acid transformations. The mechanism given in path A of Scheme 2 predicts that 2 mol of nitrosamine should be produced for every mole of N_2O. The production of N_2O in the nitrosation of tribenzylamine had been confirmed,[3] but no studies have been carried out to verify the predicted product ratio. We reasoned that competition from another mechanism of nitrosamine formation would either eliminate N_2O formation or significantly increase the **2** (X = Cl)/N_2O ratio.

Quantitation of N_2O Production. To test this hypothesis we developed a method for quantitating the amount of N_2O produced in the nitrosation of **1** (X = Cl, CO_2Et) as a function of reaction conditions. N_2O was determined by sampling the headspace above stirred reaction mixtures and quantifying by GC. Immediately after the gas sampling, the nitrosamine yield was determined by HPLC. The data are given in Table 5. To ensure sensitivity in the N_2O determinations most of the reactions were run to near completion, but this condition also produces limitations in the interpretation of the data because of the possibility of mechanistic switching during the course of the run. Nevertheless, it is evident that nitrosamine/N_2O ratios as high as 9.5 were observed in some cases, clearly indicating the operation of more than one mechanism of nitrosamine formation. From these data it can be seen that the fraction of nitrosamine (frad) produced by a radical cation pathway was a function of the initial reactant concentrations, the solvent, the substituent, and, in glacial acetic acid, added base in the form of sodium acetate (run 3).

Table 5. Nitrosamine/N_2O Ratios as a Function of Conditions and Substrate for the Nitrosation of **1**

run[a]	X	[Am][b]	[NO_2^-][b]	solv	ratio[c]	frad[d]	% **2**	**3/2**	% rxn
1	Cl	0.052	0.157	HOAc	2.00	0.00	11.8	7.39	99
2	Cl	0.052	0.052	HOAc	2.00	0.00	24.1	1.70	65
3	Cl	0.052	0.052	HOAc[e]	4.44	0.55	28.8	1.56	74
4	Cl	0.012	0.037	buffer	9.52	0.79	43.5	1.29	100
5	Cl	0.024	0.037	buffer	4.65	0.57	54.9	0.79	98
6	Cl	0.034	0.037	buffer	3.70	0.46	32.0	0.43	46
7	Cl	0.052	0.037	buffer	3.33	0.40	26.9	0.30	35
8	Cl	0.052	0.157	buffer	2.17	0.08	42.9	1.22	95
9	Cl	0.012	0.095	buffer	2.00	0.00	34.6	1.86	99
10	CO_2Et	0.050	0.152	HOAc	2.47	0.19	40.5	1.48	100
11	CO_2Et	0.050	0.152	buffer	2.00	0.00	29.9	0.11	33
12	CO_2Et	0.012	0.037	buffer	4.76	0.58	32.3	0.08	35

[a] Each entry is the average of four to five separate determinations. [b] Concentrations are in M. [c] Molar ratio of nitrosamine **2** to N_2O. [d] Fraction of the nitrosamine being produced by a pathway (presumed to involve a radical cation) other than that involving the coproduction of N_2O. [e] NaOAc added (1.52 M).

Table 6. Kinetic Deuterium Isotope Effects on Amine Nitrosation Rates and Rates of Product Formation

	X	amine	nitrosamine	nitro
1[a]	pCl[c]	4.38 ± 0.08	6.98 ± 0.25	0.43 ± 0.03
2[a]	pCO_2Et[c]	3.69 ± 0.09	3.84 ± 0.13	0.28 ± 0.01
3[b]	pCO_2Et[d]	2.39 ± 0.04	7.47 ± 0.12	0.42 ± 0.05

[a] In buffer. [b] In glacial acetic acid. [c] $T = 21$ °C. [d] $T = 30$ °C.

Deuterium Kinetic Isotope Effects. To gain more information regarding the nature of the dealkylation step which gives rise to the nitrosamine, we prepared the perdeuteriomethyl isotopomers of **1** (X = Cl, CO_2Et) and measured their nitrosation rates. Rate constants are reported in Table 3 and k_H/k_D values are presented in Table 6, including k_H/k_D values for the amine nitrosation, nitrosamine formation, and nitro compound formation. Rate constants for the disappearance of the respective amines were determined as discussed above. The k_H/k_D values obtained for the nitrosamine and the nitro compound were estimated from plots of $\ln([\text{amine}]_0 - [Z])$ vs t, where [Z] = [nitrosamine] or [nitro compound], respectively. Errors were estimated from the standard deviation of the slope, obtained by linear regression, for each kinetic run and were propagated in k_H/k_D. All plots were well behaved except for several of the nitro compounds. Isotope effects of less than one exhibited for the formation of **3** (X = Cl, CO_2Et) clearly reflect the mechanistic switching that occurs upon deuterium substitution. The deuterated compounds show an enhanced rate of nitro compound formation.

A deuterium isotope effect of 3.5 (80 °C) has been determined previously for the nitrosative dealkylation of tribenzylamine by means of intramolecular competition.[3] While the values of k_H/k_D measured for amine disappearance shown in Table 6 are in this range, our other data, as well as the change in isotope effects for the formation of the nitrosamine (X = CO_2Et) with solvent change, suggest that steps involving C−H bond breakage may not be the sole contributors to k_{obs}. The k_H/k_D for nitrosamine formation from **1** (X = Cl) in buffer or **1** (X = CO_2Et) in HOAc are significant, as expected for processes in which the breakage of a C−H bond occurs through a well-centered transition state.

Discussion

We propose that the data presented above argue for linked competitive mechanisms of nitration and nitrosative dealkylation by two different pathways: one, the classical mechanism, involves NOH elimination (**1** → **4** → **8** → **2**, path A of Scheme 2),[3,4] and another, described here for the first time, occurs through the deprotonation of a radical cation (**1** → **4** → **5** → **7** → **8** → **2**, path B of Scheme 2). A better understanding of the evidence and arguments which support our hypotheses is facilitated by consideration of the rate equation (eq 4) derived

$$-\frac{d[\text{Am}]}{dt} = \frac{K_4[\text{Am}][N_2O_3]}{[NO_2^-]}\left\{k_8 + \frac{k_5k_7[Y^-] + k_5k_6[NO_2]}{k_{-5}[NO] + k_6[NO_2] + k_7[Y^-]}\right\} \quad (4)$$

from the mechanistic scaffold presented in Scheme 2. The derivation required several important assumptions: (1) Steady-state conditions were assumed for both the nitrosammonium ion **4** and the radical cation **5**. (2) The radical **7** and the imminium ion **8** were presumed to be rapidly oxidized and converted to the nitrosamine, respectively. (3) Hydrolysis of the nitrosammonium ion **4** to **1** was presumed to be more rapid than its other transformations.[4] And (4) the major base (Y^-) involved in the deprotonation of the radical cation **5** was AcO^-. The latter assumption will hold under the buffer conditions used here, and when $[NO_2^-] \gg [\text{Am}]$, but will break down if that condition is not met and would thus invalidate eq 4. The kinetic measurements of the nitrosation of **1** (X = Cl) were carried out under high acetate concentrations ($[AcO^-] = [Y^-]$). As a result, terms containing k_7 in eq 4 may be large in comparison to summed components ($k_7[Y^-] \gg k_6[NO_2]$ and $k_7[Y^-] \gg k_{-5}[NO]$). Under these constraints it can be shown that eq 4 reduces to eq 5, where K_a is the dissociation constant for AmH^+, K_2 is the

$$-\frac{d[\text{Am}]}{dt} = \frac{K_4(k_8 + k_5)[\text{Am}][N_2O_3]}{[NO_2^-]} = \frac{K_aK_3K_4(k_8 + k_5)[\text{Am}]_T[NO_2^-][H^+]^2}{K_2^2([H^+] + K_a)} \quad (5)$$

dissociation constant of HNO_2, K_3 is the equilibrium constant for the formation of N_2O_3 from HNO_2, and $[\text{Am}]_T$ is the total amine concentration. With these simplifications in eq 4, eq 5, which shows a first-order dependence on both $[NO_2^-]$ and $[\text{Am}]_T$, is in agreement with our experimental observations. Nevertheless, eq 4 is a useful tool in understanding the mechanistic switching observed under some of the experimental conditions used in this work.

We show the radical cation **5** to arise through *reversible homolysis* of the nitrosammonium ion **4**, a process first considered prior to the advent of modern mechanistic tools,[36] but as stated before **5** could be produced by other processes. The key step is the recombination of **5** with NO to regenerate the nitrosammonium ion **4**, a hypothesis that successfully accounts for the mechanistic switching we observe and ties numerous experimental observations together in a comprehensible format. Our evidence in support of the reversible homolysis comes from three sources: (1) Independently generated radical cations reacted with NO in H_2O to give nitrosamines. These transformations are well rationalized as occurring through the nitrosammonium ion **4** as depicted in Scheme 2. Competitive hydrolysis of **4** provides the HNO_2 or NO_2^- required for the conversion of the imminium ion to the nitrosamine. (2) As shown in Table 2, addition of NO nearly

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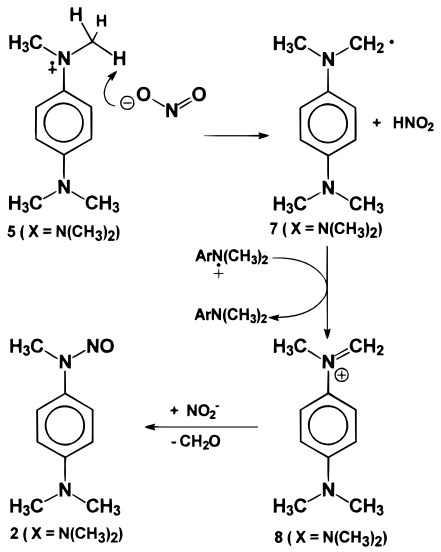
doubled the nitrosamine yield compared to the control, while the addition of O_2 decreased the nitrosamine yield, but increased the production of **3** (X = Cl). Here, NO reacted with **5** to generate **4** from which the nitrosamine is produced through the classical path (A), or was oxidized to NO_2 by O_2, decreasing the extent of the back reaction but increasing the amount of NO_2 and thereby the rate of nitro compound formation through **5** as is predicted by the rate equation. (3) Careful studies of the mechanisms of both secondary arylamine nitrosation and diazonium ion formation from some primary arylamines present strong evidence for the reaction of NO with the corresponding amine radical cations to produce nitrosammonium ions from which subsequent transformations occur.[37,38]

A priori, there are two reasonable mechanisms for the conversion of the radical cation **5** to the imminium ion **8**: (1) deprotonation to a radical **7**, which is rapidly oxidized to the imminium ion **8**, or (2) hydrogen atom abstraction to produce the imminium ion directly. Our data, considered in the light of literature precedent, are in best agreement with path 1. A significant deuterium isotope effect is observed for nitrosamine formation in two cases (Table 6, entries 1 and 3). In the first case, the conditions are the same for which we observed 80% of nitrosamine formation to be occurring by a pathway other than NOH elimination, as determined from the N_2O/nitrosamine yield data (Table 5, entry 4). Under these conditions a $k_H/k_D = 7$ is observed for the rate of nitrosamine formation, a value consistent with deprotonation of the radical cation.[39,40] The resulting radical **7** will be oxidized rapidly[39,40] in the nitrosation media to the imminium ion **8**. Dinnocenzo et al.[39] and Parker and Tilset[40] have independently shown that the α-C−H of aromatic amine radical cations are significantly acidic. Parker and Tilset[40] determined a pK_a of 9 for **5** (X = Cl)**,** and Dinnocenzo et al. have measured k_H/k_D values of 7−8 for the deprotonation rates of similar radical cations,[39] although such effects are certain to be a function of both the ring substituent and the base strength. Thus, literature precedent on the properties of aromatic amine radical cations supports our hypothesis that the radical cation is being deprotonated. Reference to Scheme 2 and eq 4, however, shows that isotope effects on k_{obs} occur through changes in the magnitudes of k_7 and k_8, which appear in summed terms. Moreover, k_7 appears in both the numerator and denominator of eq 4, and changes in its magnitude resulting from deuterium substitution will be modulated by concentration changes. The lower values of k_H/k_D for amine disappearance (Table 6) compared to nitrosamine formation are manifestations of these effects.

Additional support for these postulates is found in the data of Table 5. Although the reaction of **1** (X = Cl) was too rapid for convenient kinetic studies and hence k_H/k_D determinations in HOAc, comparison of runs 2 and 3 (Table 5) shows that the percent of nitrosamine formation occurring by the radical pathway is increased from 0 to 55% merely through the inclusion of 0.5 M NaOAc in the reaction media. The data of Table 5 also show that the fraction of the radical pathway to the nitrosamine is increased by changing the solvent form HOAc to buffer, where the concentration of the base necessary for deprotonation reactions of **5** (X = Cl) is necessarily greater. Under these conditions (runs 4−7) the participation of the radical cation pathway is greatest when the $[NO_2^-]_0/[amine]_0$ ratio is greatest. It is unclear, without further work, why and how the fraction of the radical pathway depends so on the initial reactant concentrations. A limitation of the current work is that the nitrosamine/N_2O ratios were observed, in most cases, over the whole reaction and could be distorted by the occurrence of mechanistic switching resulting from reactant concentration changes during a given run.

Scheme 5



This analysis also helps clarify how the reaction of Wurster's blue with NO_2^- in H_2O gives nitrosamine. In this case, NO_2^- acts at first principally as a base to deprotonate the radical cation **5** (X = $N(CH_3)_2$) and generate a radical **7** (X = $N(CH_3)_2$), (Scheme 5). Precedent exists for the oxidation of similar radicals to imminium ions by radical cations.[39] Thus, the oxidation of **7** (X = $N(CH_3)_2$) to the imminium ion **8** (X = $N(CH_3)_2$) by **5** (X = $N(CH_3)_2$) leads ultimately to the nitrosamine **2** (X = $N(CH_3)_2$) by known pathways.

Our data show that mechanistic switching occurs in response factors other than changes in the magnitude of rate constants arising from deuterium substitution. An increase in any concentration found in the denominator of the second term of eq 4 could reduce the overall magnitude of that term and the participation of the radical cation pathways compared to NOH elimination (k_8, path A). As discussed above, addition of acetate ion to glacial acetic acid significantly increases the proportion of the nitrosamine which is produced through the radical cation pathway from the nitrosation of **1** (X = Cl). Inspection of data from runs 1−8 of Table 5 for the nitrosation of **1** (X = Cl) in either glacial acetic acid or buffer shows that the extent of nitrosamine formation through the radical cation pathway is greater in the more basic buffer media where the concentration of $Y^- = AcO^-$ is large. In glacial acetic acid, because of the low H_2O concentration, the concentrations of N_2O_3 and its homolysis products, NO and NO_2, will be higher, and will increase the magnitude of the denominator of the second term of eq 4, also reducing the participation of the radical cation pathway to **2**.

It is also apparent that a change in the ring substitutent significantly influences the nature of these transformations. Amines containing the CO_2Et substituent exhibited smaller relative yields of nitro compound and nitrosamine formation through a radical cation path. While a more complete understanding of the influence of ring substituents and other reaction variables on the mechanistic pathways must await additional experiments, a few preliminary conclusions can be drawn and

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are well supported by the literature of amine radical cation chemistry. The rate of amine radical cation formation in these reactions will parallel their oxidation potential: X = $(CH_3)_2N$ ≫ Cl > CO_2Et.[40] On the other hand, the C−H acidity (and probable deprotonation rates) of their resulting radical cations will exhibit the opposite substituent effect. Thus, k_5 is expected to be significantly less when X = CO_2Et and the path involving NOH loss may predominate. When a radical cation is produced from an amine bearing the CO_2Et substituent, however, it is likely to be rapidly deprotonated, resulting in nitrosamine formation at the expense of the nitro compound formation (see run 12 Table 5).

Conclusions

Our investigation of an apparently simple transformation, known since the earliest days of organic chemistry, shows that the mechanisms of nitrosamine formation and nitro compound generation from a *N*,*N*-dialkylaromatic amine and nitrous acid are mechanistically linked. Much of the chemistry of nitrosating agents with *N*-alkyl tertiary aromatic amines presented in the literature, including that of Colona et al.,[22] is well rationalized by our mechanistic scaffold in which the reversible formation aromatic amine radical cation from a nitrosammonium ion plays a key role. Mechanistic changes, and as a result product distributions, are influenced by subtle changes in concentrations and reactant structure. From the perspective of human health and safety, it is significant that nitrosamines arise rapidly, at low concentrations from the reaction of acidic nitrite with *N*,*N*-dialkylaromatic amines. The greater nitrosation reactivity of these amines in comparison to trialkylamines is likely a manifestation of both their lower basicity and lower oxidation potentials, but the relative significance of the latter factor remains to be determined. Few studies of the carcinogenicity of aromatic nitrosamines have been conducted. Methylphenylnitrosamine is a potent carcinogen.[42] It is likely that nitrosamine formation rates and nitrosamine carcinogenicity levels are significantly influenced by the nature of both the ring and *N*-substituents. Until more work is done to clarify these determinants, steps should be taken to prevent the formation of nitrosamines in commercial intermediates or formulations containing *N*,*N*-dialkylaromatic amines.

Experimental Section

Instrumentation. Melting points were obtained on a Thomas-Hoover capillary tube apparatus and are not corrected. ^{1}H, ^{13}C NMR, and ^{15}N NMR were recorded on either a Joel FX-90Q (90 MHz for ^{1}H), Nicolet NT (300 MHz for ^{1}H and 75 MHz for ^{13}C), or Bruker AMX 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C, and 51 MHz for ^{15}N). Gas chromatography was done on a Hewlett-Packard 5890 series gas chromatograph equipped with a Flame ionization or thermal energy analyzer (TEA model 502) detectors with a SPB-1 (0.25 mm × 30 m) fused silica capillary column. GC-mass spectral analyses were performed on a Hewlett-Packard 5970 mass selective detector with a 20 M SPB5 capillary column and controlled with a Hewlett-Packard 59970 Chemstation computer. For analyses of nitrous oxide a Gowmac series 550 thermal conductivity detector (TCD) equipped with a 9 ft. × 1/8 in. stainless steel column packed with Poropak Q (80−100 mesh) was used. High-pressure liquid chromatography (HPLC) was performed with a Waters Maxima 820 system controller, a Waters model 490 programmable multiwavelength detector, a Waters model 710B Wisp autosampler, and two Waters model 510 pumps. The columns used for HPLC analyses were Zorbax Rx-C8 (4.6 mm × 25 cm) and Zorbax ODS−C18 (4.6 mm × 25 cm). IR spectra were recorded on Nicolet-FTIR 20DXB. UV data were obtained with a HP84 52A diode array spectrophotometer. Elemental analyses were done by Desert Analytics.

Materials. Solvents used for HPLC were of Fisher Optima grade and were filtered before use. Solvents used for flash chromatography and moisture sensitive reactions were purchased from Fisher Scientific and purified. Tetrahydrofuran was dried over calcium hydride and distilled from lithium aluminum hydride. Methylene chloride was washed with concentrated sulfuric acid, water, and saturated potassium carbonate, predried over calcium sulfate, and distilled over calcium hydride or phosphorus pentoxide. Acetonitrile was distilled over calcium hydride. Hexane was distilled over anhydrous sodium sulfate. All solvents were stored over molecular sieves. NO, N_2O, and NO_2 were purchased from Matheson. NO was purified by passing it through solid KOH and anhydrous $CaCl_2$. All other common reagents were purified by normal procedures, when required.

Synthesis of Known Amines and Nitrosamines. Unless noted specifically below, known compounds were prepared by published procedures or slight modifications thereof. NMR and other characteristic data are given in the Supporting Information. Formanilides were reduced to the corresponding *N*-methylanilines by the method similar to that of Brown and Heim.[42] **Compounds:** 4-Chloroformanilide,[43] *N*-methyl-4-chloroaniline,[44] *N*,*N*′-diformyl-*p*-phenylenediamine,[45] *N*-nitroso-*N*-methyl-4-chloroaniline[46] (**2** X = Cl), *N*,*N*′-dinitroso-*N*,*N*′-dimethyl-*p*-phenylenediamine[47] (**13**), *N*,*N*-dimethyl-4-chloroaniline[48] (prepared by a modification of the method of Borsch and Hassid[49]), *N*,*N*,*N*′,*N*′-tetramethyl-2-nitro-*p*-phenylenediamine[50] (**3**, X = $N(CH_3)_2$), and 4-chloro-2-nitrodimethylaniline[51] (**3**, X = Cl).

Nitrosation of *N*,*N*,*N*′-Trimethyl-*p*-phenylenediamine and Separation of the Products by Chromatography. According to Loeppky et al.[10] isopropyl nitrite was added dropwise to the stirring *N*,*N*,*N*′-trimethyl-*p*-phenylenediamine (0.45 g, 3 mmol) at 0−5 °C. The reaction was allowed to warm to 20 °C. After 1 h, the excess isopropyl nitrite was removed in vacuo and the resulting solid was subjected to flash column chromatography (7:3 hexane:ethyl acetate over silica gel). Two major fractions were collected. **Fraction 1: *N*′-nitroso-*N*,*N*,*N*′-trimethyl-*p*-phenylenediamine (2, X = $N(CH_3)_2$)**; mp 95−98 °C (lit.[52] mp 98−99 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.34 (d, 2H), 6.77−6.75 (d, 2H), 3.42 (s, 3H), 2.99 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.86, 131.93, 121.04, 112.42, 40.54, 32.44. **Fraction 2: *N*′-Nitroso-*N*,*N*,*N*′-trimethyl-3-nitro-*p*-phenylenediamine (12)**; mp 84−86 °C (lit.[53] mp 87 °C); ^{1}H NMR (500 MHz, CDCl3) δ 7.88 (d, 1H), 7.68 (dd, 1H), 7.14 (d, 1H), 3.43 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 145.10, 138.03, 132.55, 124.39, 118.99, 117.18, 42.39, 31.43.

***N*,*N*-(D_6)-Dimethyl-4-chloroaniline (1D_6, X = Cl)**. To a cooled (−78 °C), stirred dry THF (50 mL) solution of 4-chloroaniline (2.0 g, 16 mmol) under N_2 was added, dropwise, a 2.5 M solution of *n*-BuLi (13 mL, 33 mmol) in THF. After the mixture was stirred for 30 min, a solution of CD_3I (1.5 mL, 23.6 mmol) in THF (2 mL) was added, stirring was then continued for 3 h at −78 °C and the mixture was allowed to warm to room temperature and then stirred for an additional 12 h. Ethanol (50 mL) was added and the resulting mixture was extracted with ether (4 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product (2.4 g) was subjected to column chromatography on silica gel (16:1 hexane:ether) to give 0.51 g of the deuterium compound in 20% yield. Recrystallization from ethanol yielded 0.22 g of a white solid; mp 32−34 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−6.65 (dd, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.20, 128.75, 121.26, 113.50,

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39.60 (m, $J = 20.5$ Hz). HRMS (EI) calcd for $C_8H_4D_6N^{35}Cl$ 161.0872, found 161.0873.

Ethyl 4-((D$_6$)-Dimethylamino)benzoate (1, X = CO$_2$Et; D$_6$). A dry 100 mL, three-necked round-bottomed flask equipped with a magnetic stirrer and N_2 balloon was charged with *p*-carboethoxyaniline (0.44 g, 2.6 mmol) in CH_3CN (25 mL). Deuterated formaldehyde (D_2O, 98%, 20% solution in D_2O, 6.0 mL, 35.3 mmol) and deuterated sodium cyanoborohydride ($NaBD_3CN$) (0.51 g, 7.7 mmol) were added in succession to the stirring solution of the amine. After the mixture was stirred for 10 min, glacial HOAc (2 mL) was added dropwise, then stirring was continued for 2 h followed by the addition of HOAc (1 mL) and continued stirring for 13 h. The solvent was removed in vacuo, and 10% NaOH was added. The resulting aqueous mixture was extracted with ether (3 × 25 mL), and the ether extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield 418.3 mg (80.8% yield) of a white solid which was recrystallized from ethanol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90−6.63 (dd, 4H), 4.34 (q, 2H), 1.36 (t, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.99, 153.24, 131.14, 117.21, 110.54, 60.04, 39.18 (m, 20.9 Hz), 14.43. HRMS (EI): calcd for $C_{11}H_9D_6NO_2$ 199.1471, found 199.1478.

***N*-Methyl-*N*-cyclopropyl-4-chloroaniline (11).** According to the two-step procedure described by Kang and Kim,[54] in a dry flask under N_2, 2.0 g (14.12 mmol) of *N*-methyl-4-chloroaniline, 3.5 g (21.18 mmol) of 1-ethoxy-1-bromocyclopropane, and 2.14 g (21.18 mmol) of triethylamine were all dissolved in 7 mL of dry CH_2Cl_2. The mixture was allowed to reflux while being stirred for 46 h. After dilution with 30 mL of CH_2Cl_2, the mixture was rinsed successively with 2 × 20 mL of H_2O and 20 mL of brine. The aqueous washes were back extracted with 20 mL of CH_2Cl_2. The two organic layers were combined, dried over anhydrous $MgSO_4$, filteredm and tripped of solvent. The resulting residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to give the *N*-methyl-*N*-(1-ethoxycyclopropyl)-4-chloroaniline as a colorless oil in 67% yield (74% corrected), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (dt, 2H, $J = 3.3$, 9.2 Hz), 6.91 (dt, 2H, $J = 3.3$, 9.2 Hz), 3.51 (q, 2H, $J = 7.0$ Hz), 3.06 (s, 3H), 1.22 (br. s, 2H), 1.11 (t, 3H, $J = 7.0$ Hz), 0.90 (br. d, 2H, $J = 1.9$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.2, 128.48, 122.49, 114.69, 75.09, 62.24, 37.94, 16.42, 15.42.

In a dry flask equipped with a stirring bar and a rubber septa, 671 mg (17.73 mmol) of $NaBH_4$ were suspended in 15 mL of dry THF. The solution was cooled to 0 °C and 2.66 g (17.73 mmol) of $BF_3{\cdot}Et_2O$ was added via a syringe under N_2 atmosphere. The mixture was stirred at 0 °C for 45 min, and 2.0 g (8.86 mmol) of *N*-methyl-*N*-(1-ethoxycyclopropyl)-4-chloroaniline dissolved in 3 mL of dry THF was added dropwise via a gastight syringe. The mixture was allowed to warm slowly to room temperature and stirring was continued for an additional 6 h. The reaction was carefully quenched with water and extracted in 40 mL of diethyl ether followed by washing with 3 × 20 mL of H_2O and 1 × 20 mL of brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatographic purification (3% ethyl acetate in hexanes) afforded the desired product as a colorless oil in 89% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dt, 2H, $J = 3.3$, 9.2 Hz), 6.9 (dt, 2H, $J = 3.3$, 9.2 Hz), 2.94 (s, 3H), 2.53 (m, 1H), 0.81 (m, 2H), 0.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.39, 128.54, 122.19, 114.80, 39.07, 33.30, 9.07; IR (neat) 3086 w, 3045 w, 3008 w, 2939 w, 2878 w, 2817 w, 1599 m, 1497 s, 1456 w, 1360 m, 1336 m, 1308 w, 1306 w, 1267 w, 1236 w, 1184 w, 1116 m, 1097 w, 1025 w, 998 w, 963 w, 814 s, 734 m cm^{-1}. Anal. Calcd for $C_{10}H_{12}ClN$: C, 66.11; H, 6.66; N, 7.71. Found: C, 66.29; H, 6.52; N, 7.58

Nitrosation Reactions. (a) Nitrosation of *N*,*N*-Dimethyl-4-chloroaniline (1, X = Cl). The general procedure for the nitrosation of **1** involved its dissolution in an acidic solvent, either glacial HOAc or 60% aqueous HOAc containing sodium acetate (1.66 M), followed by dropwise addition of a three molar excess of aqueous $NaNO_2$ solution. The reaction was allowed to stir for 30 min, neutralized with saturated K_2CO_3 solution, and extracted with ether (4 × 25 mL), and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and analyzed by GC-FID and HPLC utilizing nitrobenzene as an internal standard.

(b) Nitrosation of 1 under No Headspace Conditions. In a typical procedure, a series of 12 mL vials containing a mini stir bar were charged with 10 mL of a standard stock buffer solution (pH = 3.8, 1.66 M NaOAC in 60% HOAc) containing the amine **1** (X = Cl or CO_2Et) and nitrobenzene as an internal standard. The vials were crimp sealed with a Teflon-backed rubber seal and equilibrated at 21 °C for 20 min prior to the addition of 2 mL of a standard solution of aqueous $NaNO_2$. In the case of **1** (X = Cl) the mixture was 0.23 mM in amine and 2.3 mM in NO_2^- (see Table 1). The reaction mixture was stirred for 6 min and the entire contents of each vial quenched by addition of 20% K_2CO_3 solution (7 mL). The aqueous layer was extracted with ether (5 × 1 mL) and analyzed by HPLC.

(c) Nitrosation of 1 (X = Cl) under Headspace Conditions. A procedure identical to that described above was utilized except that the headspace above the liquid was covered with N_2 which permitted ample space for gas−liquid equilibration.

(d) Nitrosation of 1 (X = Cl) in the Presence of Added NO. A 100 mL, three-necked flask was charged with **1** (X = Cl) (0.50 g, 0.32 mmol) in HOAc (10 mL) and attached to a vacuum manifold. To a 10 mL, two-necked flask was added 1 mL of 0.37 M $NaNO_2$ solution in water. The contents of both flasks were subjected to 4 freeze−thaw degassing cycles. After bringing the solutions to room temperature purified NO gas was introduced into the vacuum manifold until atmospheric pressure was attained. The equilibration was repeated. The nitrite was transferred into the amine solution with a cannula under NO gas and NO gas was introduced until a pressure of 1 atm was reached. The reaction mixture was stirred for 40 min and the excess NO was removed. The reaction flask was detached from the manifold and the quantitation standard nitrobenzene (0.018 g, 0.15 mmol) was added in ether. The reaction was quenched by addition of 30% K_2CO_3 solution (125 mL) and extracted with ether (3 × 40 mL), dried over Na_2SO_4, filtered, concentrated in vacuo, and subjected to chromatographic analysis. The products of the reaction of **2** and **3** were identified by their mass spectral data and comparison of GC retention times with those of authentic standards. HPLC analysis was used for determination of product yields.

(e) Nitrosation of 1 (X = Cl) under N_2. The nitrosation reaction was done exactly as above except it was done under a N_2 atmosphere.

Nitrosation of 1 (X = Cl) in the Presence of Added O_2. The reaction was carried out as described for that carried out in an NO atmosphere except that NO was replaced with O_2.

Identification and Quantification of N_2O and Nitrosamines as Products in the Nitrosation of 1 (X = Cl or CO_2Et). Calibration: A calibration curve was constructed by determining the amount of N_2O produced in the headspace from the introduction of 0.1 mL of a 0.39 M solution of NaN_3, 0.8 mL of H_2O, and 0.1 mL of a 1.2 M solution of $NaNO_2$ into 20 mL contained in a 100 mL, three-necked flask fitted with a stirrer, a control valve, and a leveling bulb filled with water. After 15−25 min, and adjustment to atmospheric pressure, the headspace above the solution was sampled by use of a 5 mL gastight syringe and analyzed by GC-TCD. The above procedure was repeated at a minimum of five different concentrations of NaN_3. A plot of the concentration of NaN_3 (N_2O) against the peak height of N_2O was linear. Calibration was performed each time before conducting the nitrosation reaction. **Analyses:** The amines were subjected to nitrosation under typical nitrosating conditions, which involves their dissolution in an acidic solvent and addition of saturated $NaNO_2$. The reaction was allowed to proceed typically for 15−30 min. The gaseous species evolved in the reaction and contained in the headspace above the solution were sampled with the help of a 5 mL gastight syringe and analyzed for N_2O by GC-TCD in the manner described above. Immediately after the gas sampling, the reaction mixture was worked up by addition of a 30% K_2CO_3 solution (125 mL) followed by extraction with ether (4 × 25 mL), dried over Na_2SO_4, and analyzed by HPLC. Nitrosamines were quantitated by HPLC by using our standard methodology. All products were identified by comparison of retention times with authentic standards.

(f) Nitrosation of *N*-Cyclopropyl-*N*-methyl-4-chloroaniline (11,

(54) Kang, J.; Kim, K. S. *J. Chem. Soc., Chem. Commun.* **1987**, 897−898.

X = Cl). With use of the standard nitrosation procedure, 500 mg (2.75 mmol) of *N*-cyclopropyl-*N*-methyl-4-chloroaniline was nitrosated in 6 mL of glacial HOAc with 380 mg (5.51 mmol) of $NaNO_2$ dissolved in 2 mL of H_2O. The resulting reddish residue was purified by flash column chromatography (10% ethyl acetate in hexane) to give *N*-methyl-*N*-nitroso-4-chloroaniline as a yellow crystalline solid in 61% yield as the sole benzenoid product (97% by HPLC analysis before purification).

Kinetic Studies of Nitrosation. In a typical procedure, a 12 mL reaction vial containing a mini stir bar was charged with 10 mL of standard stock solution consisting of 0.214 mM *N*,*N*-dimethyl-4-chloroaniline (**1**, X = Cl) and 0.235 mM nitrobenzene in buffer of pH 3.8−3.9 (27.2 g of NaOAc in 200 mL of 60% aqueous HOAc) and stabilized in a constant-temperature bath at 21 °C before the addition of 1.8 mL of 0.0275 M aqueous $NaNO_2$ solution. The reaction mixture was stirred, and at regular intervals 1 mL aliquots were withdrawn and quenched with 30% K_2CO_3 (5 mL) solution. The aqueous layer was extracted with ether (5 × 1 mL) and analyzed by HPLC. The concentrations of the various components were determined with the internal standard method.

Measurement of Rate Constants k_H and k_D To Determine Isotope Effects in the Nitrosation of Ethyl 4-(Dimethylamino)benzoate (1, X = CO_2Et). A small reaction vial was charged with ethyl 4-(dimethylamino)benzoate (0.016 g, 0.083 mmol) and the internal standard ethyl 4-(benzylnitrosamino)benzoate (0.0075 g, 0.026 mmol) in 10 mL of buffer of pH 3.8−3.9 (1.66 M NaOAc in 60% aqueous HOAc). The reaction vial was stabilized in a constant-temperature bath at 30 °C before the addition of 2 mL of a 0.13 M aqueous $NaNO_2$ solution. The reaction mixture was stirred and at regular time intervals, 1 mL aliquots were withdrawn and quenched with 30% K_2CO_3 (5 mL) solution. The aqueous layer was extracted with ether (5 × 1 mL) and analyzed by HPLC. Similarly, the D_6 isotopomer was nitrosated under identical conditions and the rate constant determined.

^{1}H NMR Studies in Preparation for ^{15}N CIDNP. The nitrosation of **1** (X = Cl) was followed by ^{1}H NMR spectroscopy at 25 °C with use of a Bruker AMX 500 spectrometer. In a typical procedure, 0.5 mL of a D_4-acetic acid solution of 0.07 M **1** (X = Cl) and 0.017 M nitromethane (internal standard) was introduced into a 5 mm spin tube and 0.35 mL of a 0.71 M solution of $NaNO_2$ in D_2O was added. The extent of the reaction was calculated from the percentage of unreacted starting material. The concentration of the starting amine was determined from the integration value of the signal for the *N*,*N*-dimethyl protons of the amine **1** and the methyl proton of the internal standard.

^{15}N NMR CIDNP Studies. The studies involving ^{15}N NMR spectroscopy were carried out at 25 °C with a Bruker AMX 500 spectrometer. The concentrations of the reagents were the same as those used in the corresponding ^{1}H NMR experiment except that the internal standard used was ^{15}N labeled nitrobenzene (0.029 g, 0.23 mmol). The spectra were measured at various intervals, using a pulse angle of 30 and a pulse delay of 0.2 s. The identity and the ^{15}N NMR shifts of the various peaks obtained during the nitrosation reaction are as follows: δ −5.42, "NO^+"; −9.31, nitrobenzene; −8.03, *N*,*N*-dimethyl-4-chloro-2-nitroaniline; 160.16, *N-nitroso-N*-methyl-4-chloroaniline; 201.37, NO_2^-. Shifts are referenced to CH_3NO_2 as an external standard (δ = 0).

Nitrosation of *N*,*N*,*N*′,*N*′-Tetramethyl-*p*-phenylenediamine. To a stirred, glacial HOAc (10 mL) solution of the amine (0.057 g, 0.35 mmol) and phenetole (internal standard) (0.099 g, 0.81 mmol) was added a 1.4 M solution of $NaNO_2$ (1 mL, 1.4 mmol) in water. The reaction mixture was stirred for 1 h prior to quenching the solution with 30% K_2CO_3 (5 mL) solution. The aqueous solution was extracted with CH_2Cl_2 (3 × 25 mL), dried over Na_2SO_4, filtered, and subjected to chromatographic analysis. The initial identity of the products of nitrosation was established from their mass spectral data and their presence confirmed by comparison of their GC retention time with those of authentic standards. HPLC analysis was used to determine product yields.

Reaction of Wurster's Blue Perchlorate with Sodium Nitrite in Water. A stock solution (10 mL each, 2.6 mM) of Wurster's blue perchlorate[53] was added to two separate vials containing a mini-stir bar. To the stirring solutions of the perchlorate was added 0.04 mL of a 3.3 M solution of $NaNO_2$. The reaction in one vial was allowed to proceed for 5 min and the other 40 min. At the end of the reaction time, phenetole (0.018 g, 0.14 mmol) was added and the reaction mixture was quenched by addition of a 30% K_2CO_3 solution (10 mL) and a few drops of 10% $FeSO_4$. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL), dried over Na_2SO_4, filtered, and subjected to chromatographic analysis. The products of the reaction were identified by their mass spectral data and comparison of GC retention times with those of authentic standards. HPLC analysis was used to determine product yields.

Reaction of Wurster's Blue Perchlorate with Nitric Oxide Gas (NO). A 50 mL 0.1 mM solution of Wurster's blue perchlorate was placed in a 100 mL, three-necked flask. Two necks of the flask were closed with a subaseal stopper. After attachment to the vacuum manifold, the contents of the flask were degassed by several freeze−thaw degassing cycles. NO gas, which was purified by passing through solid KOH and anhydrous $CaCl_2$, was introduced into the evacuated manifold until atmospheric pressure was attained. The valve to the reaction flask was closed and the excess gas was removed. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The unreacted NO was removed and N_2 was allowed into the system until atmospheric pressure was attained. Phenetole (0.04 g, 0.44 mmol), which served as an internal standard, was added and the reaction mixture quenched by addition of 30% K_2CO_3 solution (10 mL) and 10% $FeSO_4$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL), dried over Na_2SO_4, filtered, concentrated in vacuo, and subjected to chromatographic analysis. The products of the reaction were identified by their mass spectral data and comparison of GC retention times with those of authentic standards. HPLC analysis was used to determine product yields.

The Reaction of *N*,*N*,*N*′,*N*′-Tetramethylphenylenediamine with NO in Acetonitrile. A 100 mL, three-necked flask was charged with the amine (0.021 g, 0.13 mmol), phenetole (0.042 g, 0.35 mmol), and anhydrous CH_3CN (50 mL). The solution was subjected to reaction with NO under conditions identical with those described above for Wurster's blue perchlorate. The workup procedure was the same, except that no $FeSO_4$ was added. Unreacted starting material was recovered after workup.

Reaction of Wurster's Blue Perchlorate with Nitrogen Dioxide (NO_2). To a stirred CH_3CN (10 mL) solution of Wurster's blue perchlorate (0.027 g, 0.10 mmol) was added liquid NO_2 (0.01 g, 0.22 mmol) by use of a syringe. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was quenched by the addition of water and a few drops of 10% $FeSO_4$. The aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL), dried over Na_2SO_4, filtered, and subjected to chromatographic analysis. The products of the reaction were the nitrosamine **13** and the nitrosonitro compound **12**, which were identified by their mass spectral data and comparison of their HPLC retention time with those of authentic standards.

Reaction of *N*,*N*,*N*′,*N*′-Tetramethylphenylenediamine with NO_2. To a stirred CH_3CN (10 mL) or CH_2Cl_2 (10 mL) solution of the amine (0.033 g, 0.20 mmol) was added liquid NO_2 (0.02 g, 0.44 mmol), and the reaction was stirred for 30 min. At the end of 30 min, the reaction mixture was analyzed by HPLC and GC-MS. The products for the reaction in CH_3CN were the nitrosamine **2** (X = $N(CH_3)_2$) and the di-*N*-nitroso compound **13**.

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Supporting Information Available: Plots of (1) Concentrations of **1**−**3** (X = Cl) from the nitrosation of **1** (X = Cl), (2) first-order treatment of data for **1** (X = Cl) from the same experiment, (3) log (k_{obs}) vs log ([NO_2^-]) for nitrosation of **1** (X = Cl), (4) the ratio of **3/2** (X = Cl) vs [NO_2^-], and (5) NMR and physical data for all known compounds used in this work (2 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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