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The mechanistic origin of regiochemical changes in the nitrosative *N*-dealkylation of *N*,*N*-dialkyl aromatic amines†

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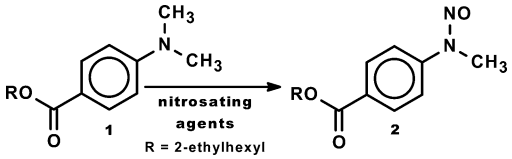
The regioselectivity of the nitrous acid mediated dealkylation of 4-substituted-*N*-ethyl-*N*-methylanilines is a function of the acidity of the reaction mixture. At high acidity deethylation predominates, whereas demethylation is the predominant reaction in nitrosamine formation at pH 2 and above. In some cases the regioselectivity of nitrosative dealkylation changes as the run proceeds. Through the use of the corresponding 4-nitroaniline as the primary substrate, CIDNP, kinetics, kinetic deuterium isotope effects and other transformations involving nitrosations with NO_2 or $NOBF_4$ in aprotic solvents, a new mechanism of tertiary amine nitrosation has been deduced and proposed to explain regioselective deethylation. The mechanism involves the oxidation of the substrate to the amine radical cation by NO^+. This is followed by the abstraction of a hydrogen atom from the carbon adjacent to the amine nitrogen by NO_2 to produce an iminium ion which reacts further to produce the corresponding aldehyde and the nitrosamine. Depending upon the acidity, this process competes with three other mechanistic pathways, two of which give the nitrosamine through the iminium ion, and one leads to the formation of C-nitro compounds. The competing pathways to nitrosamine formation involve NOH elimination from a nitrosammonium ion and deprotonation of the radical cation to give an α-amino radical which rapidly oxidized to the iminium ion. Predominant, but not highly regioselective demethylation occurs by these pathways. Nitro compound formation principally arises from the reaction of NO_2 with the radical cation followed by deprotonation, but also occurs by *para* C-nitrosation followed by oxidation.

Introduction

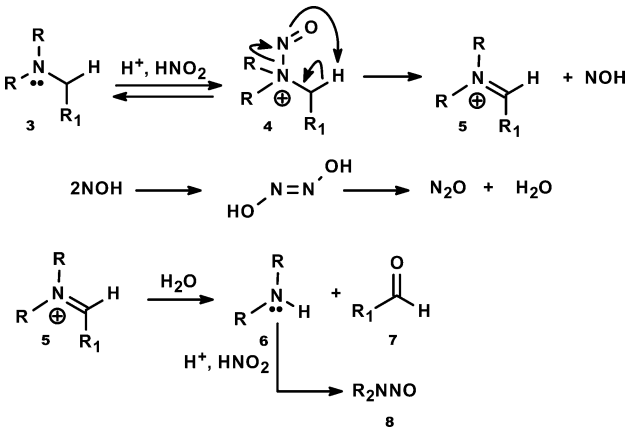
Numerous nitrosamines have been shown to be carcinogenic at low doses in laboratory animals.[1,2] They have been found in foods, drugs, tobacco and tobacco smoke, cosmetics, personal care formulations, rubber products, metalworking fluids, and many other materials to which humans are exposed.[3] Often they are formed from nitrosating agents of uncertain origin, by chemical processes which are poorly understood.[4] Nitrosamines and other DNA damaging compounds can also be formed by endogenous, unsuspected nitrosation transformations in humans.[5] In order to better understand the chemistry underlying the formation of 2-ethylhexyl 4-*N*-nitrosomethylaminobenzoate **2** from 2-ethylhexyl 4-*N*,*N*-dimethylaminobenzoate (Padimate-O) **1** (see Scheme 1), a common sunscreen ingredient, during its production and formulation, we initiated an investigation of rates and mechanisms of *N*,*N*-dialkylaromatic amine nitrosation.[6] In the course of this work we discovered that regiochemistry of nitrosative dealkylation of unsymmetrical dialkylaromatic amines, *N*-ethyl-*N*-methyl-4-carboethoxyaniline, for example, sometimes changed during a run.[7] As an illustration, by following the acidic nitrosation of this amine by HPLC we found, under certain conditions, that initially *N*-demethylation occurred and then after a short time *N*-deethylation became dominant. The factors, and the mechanistic changes which give rise to this unexpected chemistry and the regiochemistry of *N*,*N*-dialkylaromatic amine nitrosative dealkylation are the subject of this paper. In all but a few cases, a change in the regiochemistry of a transformation involves a change in mechanism, which often involves altered rates of reaction. An understanding of the factors which affect the rates and mechanisms of tertiary amine nitrosation, particularly as they relate to changes in structure or reaction conditions, are important in preventing or limiting human exposure to potentially carcinogenic nitrosamines.

† Electronic supplementary information (ESI) available: Explanations of CIDNP, and additional experimental details for kinetics experiments, syntheses of several known compounds, and N_2O determinations. See http://www.rsc.org/suppdata/ob/b4/b418457b/



Scheme 1 Nitrosation of Padimate-O.

The most prominent mechanism of tertiary amine nitrosation, here designated as Mechanism A, is shown in Scheme 2.[8,9] It involves the reversible *N*-nitrosation of the substrate (**3**→**4**) followed by the elimination of NOH to give an iminium ion **5**. The hydrolysis of the latter and the nitrosation of the resultant secondary amine **6** lead to the nitrosamine **8**. A distinguishing feature of this process is the formation of N_2O, which arises from NOH as shown. The transformation is perceived to proceed by the *syn* cyclic elimination of NOH, a process which results in the conformational eclipsing of the substituents on N and those on the carbon from which the H is being eliminated. Thus the pathway which conformationally leads



Scheme 2 Mechanism A: NOH elimination.

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to the lesser "crowding" of the transition state is perceived to control the regiochemistry of the transformation. This concept is well supported by a number of intramolecular competition experiments. The transformation proceeds predominantly by cleavage of the least sterically hindered substituent from N.[8]

$$H^+ + NO_2^- \overset{K_N}{\rightleftharpoons} HNO_2 \quad (1)$$

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O \quad (2)$$

$$N_2O_3 \rightleftharpoons NO + NO_2 \quad (3)$$

$$HNO_2 + H^+ \overset{K_d}{\rightleftharpoons} NO^+ + H_2O \quad (4)$$

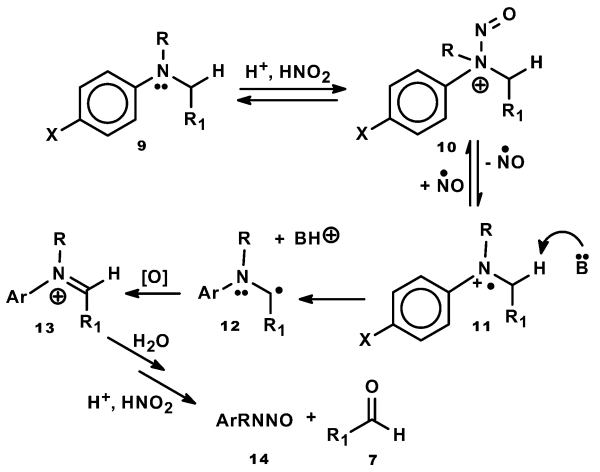
Our investigation of the mechanisms of *N*,*N*-dialkylaromatic amine **9** nitrosation revealed that nitrosamines were also competitively arising by at least one pathway which does not generate N_2O as a co-product.[10] In this case an aromatic nitro compound is formed as a reaction by-product. The nitrosamine/nitro compound ratio could be manipulated by changes in reaction conditions and we determined that there was a linkage in the paths leading to these products. The pertinent "nitrous acid chemistry" is given in eqns. (1)–(4). Extensive investigation involving ^{15}N-CIDNP NMR, kinetics, deuterium isotope effects, transformations employing a confined headspace and/or added NO, NO_2, O_2, or N_2, and reactions of prepared aromatic amine radical cations with NO, NO_2, and NO_2^-, led us to propose that this chemistry was occurring through a radical cation intermediate **11** (Mechanism B, Scheme 3).[10,11] The radical cation forms reversibly from the nitrosammonium ion **10**. Deprotonation to **12** followed by rapid oxidation results in the generation of the iminium ion **13**, which gives the nitrosamine **14** by the same pathway as Mechanism A. Thus mechanisms A and B differ only in the way in which the iminium ion is formed. This difference could, of course, result in differences in the regioselectivity of *N*-dealkylation. In related work, we demonstrated that the nitrosation of *N*-alkyl-*N*-cyclopropyl aromatic amines resulted in exclusive cleavage of the cyclopropyl substituent from nitrogen, a transformation which is indicative of the intermediacy of amine radical cations.[11] Other than this, however, we did not define the regiochemistry of *N*-alkyl cleavage by Mechanism B. As stated above, the regiochemistry of cleavage was sometimes found to vary as the run proceeded, and in other experiments we determined that nitrosamine formation by Mechanisms A and B were always competing to variable extents depending upon reaction conditions and substrates. In almost all cases, however, at the end of the run, the nitrosamine which resulted from cleavage of the least sterically hindered group from N predominated.

Verardo *et al.* have developed a preparative method for the production of nitrosamines from dialkyl aromatic amines by heating the tertiary amine with 4 equivalents of butyl nitrite, one equivalent of H_2O and 0.1 equivalent of NH_4Cl at reflux in an inert atmosphere. This process avoids the production of significant quantities of nitro compound and exhibits a regioselectivity for *N*-dealkylation of 74–100%.[12] Except for benzyl which is selectively cleaved, the smaller alkyl group is selectively removed just as it is in the nitrous acid nitrosative dealkylations. However, the mechanism of the transformation under the Verardo conditions does not appear to be known.[12,13] On the other hand, Hodgson and Nicholson reported in 1941 that the major nitrosamine arising from the reaction of *N*-ethyl-*N*-methyl-4-nitroaniline **15** with sodium nitrite in concentrated HCl is *N*-methyl-*N*-nitroso-4-nitroaniline **17** (deethylation favored).[14] Verardo *et al.* reported that the nitrosation of **15** under their conditions resulted in 74% demethylation.[12] Verardo *et al.* used modern analytical instrumentation, which, of course, Hodgson and Nicholson did not have at their disposal.

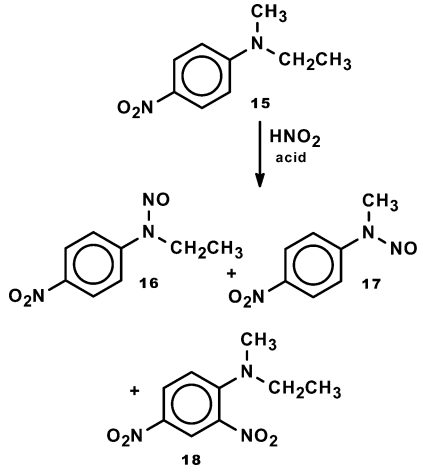
Because of this, we initially sought to verify the early workers reported regioselectivity as a starting point toward understanding why we occasionally observed alterations in the regioselectivity of nitrosative *N*,*N*-dialkyl aromatic amine dealkylation, and how these changes may relate to the regiochemical proclivities of mechanistic paths A and B, the latter of which was unknown at the inception of this research. We report here that within the limits of our experimentation (*i.e.* demethylation *vs.* deethylation) that Mechanism B proceeds with preferential cleavage of the less substituted group from N, as does Mechanism A. Regioselectivity, however is linked to the acidity of the reaction media. Deethylation is overwhelmingly preferred at high acid strength. We propose that this results from the incursion of another radical cation mediated mechanism where the α-hydrogen atom of the *N*-alkyl substituent is removed by H-atom abstraction rather than mild base induced deprotonation (Mechanism B).

Results and discussion

Preliminary experiments showed that the nitrosation of *N*-ethyl-*N*-methyl-4-nitroaniline **15** (see Scheme 4) with 5 eq. of $NaNO_2$ in 50% HCl, the conditions utilized by Hodgson and Nicholson, resulted in preferred deethylation to give **17** in preference to **16** as they had reported.[14] On the other hand, nitrosation of the same amine in glacial or aqueous acetic acid, conditions frequently used in our work, resulted in preferred demethylation. As a result we examined the regiochemistry of this transformation more carefully as a function of acidity. The data of Table 1 clearly show that the preference for deethylation increases with acidity of the medium. The % deethylation (% deEt) in Table 1 and elsewhere in this presentation is given on a per hydrogen atom basis and has been corrected for the differing number



Scheme 3 Mechanism B: deprotonation of radical cation.



Scheme 4

Table 1 The effect of acidity on the regiochemistry of nitrosative dealkylation of *N*-ethyl-*N*-methyl-4-nitroaniline **15**

Run[a]	pH/H_o	% deEt[b,c,d]	Acid mixture
1	2	28.6	75% HOAc–2.7% $HClO_4$–0.7 M NaOAc
2	1.5	41.2	75% HOAc
3	1.1	33.3	75% HOAc–0.2 M NaCl
4	0.3	63.0	75% HOAc–5% $HClO_4$/0.8 M NaOAc
5	−0.2	75.6	75% HOAc–1 M HCl
6	−0.5	81.8	75% HOAc–5% $HClO_4$/0.7 M NaOAc
7	−0.7	84.8	1.1 M HCl
8	−0.8	87.8	75% HOAc–5% $HClO_4$

[a] $[\mathbf{15}]_i = 11.5$ mM, $[NaNO_2]_i = 0.115$ M, 36 min reaction time, 23 °C. [b] deethylation [c] corrected for the number of CH_3 *vs.* CH_2 α-H-atoms. [d] Extents (%) of reaction varied and *N*-ethyl-*N*-methyl-2,4-dinitroaniline **18** was also a product in runs 4–8.

of α-H on Et *vs.* Me. The effect produced by changes in acid strength on the regiochemistry of *N*-dealkylation is remarkable and, to the extent of our knowledge, unprecedented in this kind of chemistry. Since all reactions were stopped at 36 min., the acidity of the mixture did affect the extent of the reaction, which increased from around 4% (runs 1–4) at lower acidity to 70–90% (runs 5,6, and 8). Thus, with the exception of the run in 1.1 M HCl (all other runs utilized 75% HOAc as a base "solvent"), increased acidity also increased reaction rate. These experiments utilized various acid counter ions, OAc^-, Cl^-, and ClO_4^-, not only to manipulate the acidity of the mixture but to determine whether they had any dramatic effect on the reaction regiochemistry. While we did not systematically pursue the question because the primary experimental determinant of regiochemistry appeared to be acidity, the only effect noted is seen in a comparison of runs 2 and 3 where the addition of 0.2 M Cl^- to 75% HOAc decreased the pH but decreased the % deEt by 8% instead of increasing it, as we observed for other increases in acidity. No other significant counter ion effects were observed.

As they are in other nitrosative dealkylation reactions,[8,10] aldehydes are produced from the cleaved alkyl groups under the high acid conditions which give rise to preferential deethylation (3.6 M H_2SO_4 in 90% acetic acid). Formaldehyde and acetaldehyde, determined as their 2,4-dinitrophenyl hydrazones (DNPs), are the respective products of methyl *vs.* ethyl cleavage. After accounting for the extraction efficiency of DNPs under the reaction conditions, the yields of the aldehydes and nitrosamines were: **17**, 45.7 ± 3.3%, CH_3CHO 43.4 ± 3.2%, **16** 12.7 ± 1.7%, CH_2O 11.7 ± 1.5%. These data show that the loss of the alkyl group can be quantitatively accounted for in the corresponding aldehyde products.

In our prior work we showed that the contributions of mechanistic paths A and B could be distinguished by comparing the nitrosamines yields to the N_2O yields.[10] Pathway A produces 0.5 mole of N_2O for every mole of nitrosamine, while N_2O is not a product of nitrosamine production by Mechanism B. As a result we next sought to use this technique to determine how the contribution of Mechanism A changed as the acidity of the mixture was increased. Using a previously developed calibrated procedure, N_2O yields were determined by measuring the headspace N_2O concentration by GC equipped with an electron capture detector.[10] Nitrosamine yields were determined by HPLC. The data are given in Table 2. The contribution of Mechanism A decreases significantly as the acidity of the reaction mixture is increased, and, as seen already, the % deEt increases with acidity. These transformations were conducted in 75% HOAc and HCl was added to increase the acidity. A comparison of runs 3 and 4 (Table 2) shows that halving the substrate concentration makes little difference to the % deEt. It is important to note that run 5 was done with the deuterated substrate *N*-(1′1′-D_2-ethyl)-*N*-methyl-4-nitroaniline (**15-D_2**). As expected, deuteration at the ethyl group results in some mechanistic switching and a decrease in the % deEt under the same conditions (run 4).

The data presented so far indicate that a different mechanism of nitrosative dealkylation is responsible for the increased % deEt with increased acidity of the reaction media. While it may be tempting to ascribe this to the sole incursion of mechanism B, literature data on the regiochemistry of *N*-dealkylation of chemically or electrochemically generated aromatic amine radical cations are inconsistent with such a supposition. These transformations result in the preferential, but not exclusive removal of the least substituted alkyl group from N by a process which involves α-deprotonation of the radical cation by a weak base through a process akin to that shown in Scheme 3, Mechanism B.

The resulting radical is rapidly oxidized to the iminium ion. In order to determine the regiochemical *N*-dealkylation preference for the radical cation derived from **15** under various conditions, we examined the nature of the products arising from both chemical and electrochemical oxidation of the parent amine under various conditions. The data are given Table 3. The

Table 2 Comparison of nitrosamine and N_2O yields with acidity for the nitrosation the of **15**

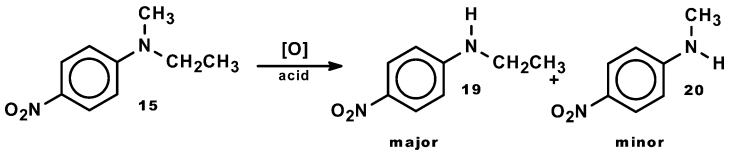
Run	Acid in 75% HOAc	$[\mathbf{15}]/mM_i$	Rxn. time/min	% N_2O	% **17**	% **16**	% rxn[a]	% deEt	% Mechanism A[b]
1	none	11.5	36	0.7 ± 0.1	0.6 ± 0.1	1.2 ± 0.2	3.6 ± 0.2	42.9	80 ± 7
2	0.1 M HCl	11.5	36	2.9 ± 0.2	7.7 ± 0.2	4.0 ± 0.2	32.4 ± 1.0	74.3	50 ± 4
3	1.0 M HCl	11.5	36	1.2 ± 0.6	14.6 ± 1.4	4.5 ± 0.4	71.1 ± 2.3	83.0	13 ± 1
4	1.0 M HCl	5.9	21	0.6 ± 0.1	10.7 ± 0.8	3.2 ± 0.4	39.5 ± 2.8	83.4	9 ± 1
5[c]	1.0 M HCl	5.9	21	0.5 ± 0.1	2.2 ± 0.2	2.8 ± 0.1	24.2 ± 3.7	54.1	19 ± 1

[a] Total conversion of starting material into products. The unlisted product is **18**. [b] Percent of nitrosamine formed by Mechanism A = 200[N_2O]/([**16**] + [**17**])%. [c] Data for the nitrosation of the deuterated substrate *N*-(1′1′-D_2-ethyl)-*N*-methyl-4-nitroaniline (**15-D_2**).

Table 3 Product distribution from the oxidation of *N*-ethyl-*N*-methyl-4-nitroaniline **15**

Oxidation method[a]	Solvent	[**20**]/[**19**]	% deEt[b]	% rxn
$Ce(NH_4)_2(NO_3)_6$	75% HOAc	0.18	21.3	15.5
$Ce(NH_4)_2(NO_3)_6$	75% HOAc–5% $HClO_4$–0.8 M NaOAc	0.33	33.1	6.6
$Ce(NH_4)_2(NO_3)_6$	75% HOAc–5% $HClO_4$	0.32	32.4	1.6
Electrochemical	75% HOAc	0.3	31.0	3.4
Electrochemical	75% HOAc–5% $HClO_4$	0.36	35.1	0.6
Electrochemical	Acetonitrile–$NaBF_4$ (sat.)	0.54	44.8	0.94

[a] $[\mathbf{15}]_i = 2.6$ mM. [b] Corrected for the number of H atoms on the respective substituents.



Scheme 5

oxidations were conducted as described in the Experimental section and amines were analyzed by HPLC.

All of the oxidation processes listed in Table 3 are known to proceed by one electron loss followed by deprotonation of the α-carbon of the alkyl group.[15–17] These hydrogen atoms are relatively acidic, depending upon the aromatic ring substituent.[18,19] The resulting carbon free radical **12** suffers a second one electron oxidation to generate the iminium ion **13**, which hydrolyses in the media to give one of the secondary amines (Scheme 5, **19** or **20**). The data show, in concert with literature precedent, that demethylation is preferred regardless of the acidity of the reaction media.[19] Thus this pathway cannot be leading to the regiochemical preference for deethylation which we observe at high acidity. This does not mean, however, that aromatic amine radical cations are not involved in the reaction leading to preferred deethylation. In order to test for the possible involvement of aromatic amine radical cations, and to gain more information on the pathway to preferred deethylation we performed a number of experiments.

^{15}N CIDNP NMR experiments

Hodgson and Nicholson investigated the nitrosation of *N*-ethyl-*N*-methylaniline **21** (see Scheme 6).[14] After repeating the nitrosation of **21** under the conditions described in the original literature report (50% HCl, 5 equivalents $NaNO_2$), we separated six products by flash column chromatography and identified them, by GC-MS and ^{1}H NMR. All of the compounds are known. As can be seen from the yields given in Scheme 6, determined by HPLC after a reaction time of 4.5 hours, the major products are the nitro compounds **15** and **23**. Our material balance is 93%. As shown in Scheme 4, nitrosation of **15** gives the nitrosamines **16** and **17** and the dinitro compound **18**. Nitrosation of the C-nitroso compound **22** results in its oxidation to **15** and thence conversion to **16–18**. There is extensive literature precedent for the conversion of *p*-nitrosoanilines to their nitro derivatives under nitrosating conditions,[20] although this is probably not the major pathway to **15, 23**, or **18**. We have previously demonstrated that aromatic *o*-nitro compounds arise in reactions of 4-substituted aromatic amines by radical cation–NO_2 recombination.[10] Several recent reports support our conclusions.[21–25] We have shown, as suspected by Hodgson and Nicholson, that the progression of product formation under their conditions is from **21** to **15** and **22** and then to **16–18**. We also have confirmed the preference for cleavage of the ethyl group, as noted above. The % deEt for the nitrosation of each substrate (**21**, **15** and **22**) was also comparable in 75% HOAc–1 M HCl using a 10 fold excess of $NaNO_2$ (**8**, 63%; **10**, 64%; **15**, 67%).

In our prior work where we showed that aromatic *o*-nitro compounds arise in reactions of 4-substituted aromatic amines by radical cation–NO_2 recombination,[10] ^{15}N-NMR CIDNP experiments were critical in reaching these conclusions. The presence of radical cations in the media, as detected by these nitration reactions, was a strong indicator of their role in nitrosamine formation by Mechanism B. Accordingly, we examined the reaction of **21** with acidic $Na^{15}NO_2$ by time-based ^{15}N NMR. Enhanced emission signals (CIDNP) were observed for **15** and **23** during the first 3 min of the reaction (Fig. 1), which is indicative of their formation by a process involving radical recombination of the amine radical cation **11** and NO_2. A detailed explanation of the emission using the Kaptein equation,[26] which is essentially the same as that published by us and others,[27–31] previously, is given in the Supporting Information.† Numerous investigations have shown that the nitrite catalyzed or nitrite mediated nitration of phenols and aromatic amines does not involve the nitronium ion NO_2^+, but proceeds by radical recombination.[32,33] Thus, the *p*-nitroamine **15**, and the *o*-nitroamine **23** are arising by radical recombination, yet we did not see any signals for the formation of the dinitroaniline **18**, which would arise from the radical cations derived from either **15** or **23**. This was true also when **15** alone was used as a substrate. This may be a consequence of the very short life time of the 4-nitrodialkylaniline radical cation due to the electron

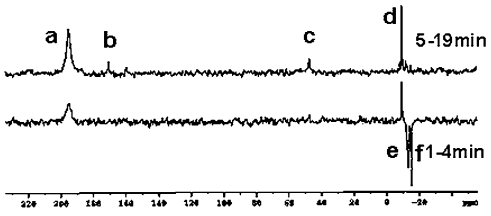
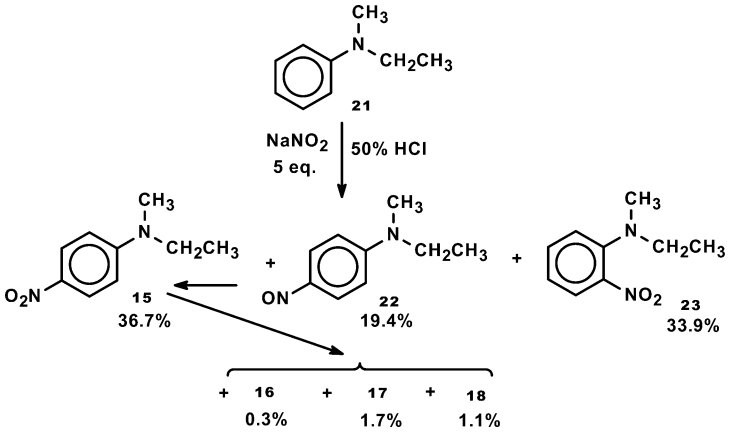


Fig. 1 ^{15}N NMR CIDNP spectra for the reaction of **21** with $Na^{15}NO_2$ in 83% HOAc–0.6 M HCl. Line assignments: a, $H^{15}NO_2$; b, **17**; c, **22**; d, $Ph^{15}NO_2$ standard; e, **23**; f, **15**.



Scheme 6 Reinvestigation of Hodgson–Nicholson nitrosation.

withdrawing destabilizing effect of the nitro group, and its very rapid recombination with NO_2 to give **18**. Yet, given what we know about the mechanisms of nitro compound formation under these reactions conditions it is highly probable that **18** is formed from the radical cation of **15** by reaction with NO_2.[10,21–25]

We did not observe ^{15}N CIDNP spectra for the formation of the 4-nitrosoaniline **22**, which is likely formed by a classical electrophilic aromatic nitrosation mechanism. Surprisingly, no evidence exists for *ortho* C-nitrosation of aromatic amines.[10] This may be due to reversibility coupled to rate limiting deprotonation of the Wheland intermediate.[34–36] *o*-Nitrosodialkylanilines are unknown and we have been unable to make them. It is possible, but unlikely that they are involved in the chemistry we are observing.[37]

Kinetics and deuterium isotope effects

To further explore the role of possible intermediates in the preferential deethylation of **15** we turned to kinetics and kinetic deuterium isotope effect (KDIE) experiments. The nitrosation of **15** in 75% HOAc–3.3 M H_2SO_4, where the nitrosation proceeds with a preference for deethylation (83% deEt), is first order in both the amine and in $NaNO_2$ (rate $= k_{obs}$[Amine][$NaNO_2$]^n, where $n = 1.15 \pm 0.14$). Kinetics were determined at variable but known excess [NO_2^-]. To further investigate the nitrosation mechanism giving preferential cleavage of the larger alkyl group, KDIEs were determined for the nitrosation of **15** and **15-D$_2$**. The deuterated compound was prepared by mild reduction of *N*-methyl-4-nitroacetanilide with lithium aluminium deuteride. The relevant kinetic data are given in Table 4. Isotope effects were determined both under conditions where demethylation dominated (92% HOAc), Table 4 entries 2a–c, and where deethylation dominated (82% HOAc–3.3 M H_2SO_4), Table 4; entries 1a–c. We give the rates and isotope effects observed for loss of **15** and the formation of nitrosamines **16** (demethylation) and **17** (deethylation). The other major product in these reactions is the dinitro compound **18**, for which we have not given the rate data.

Evaluation of the data in Table 4, as well as comparison of it with those we[8,10] have previously obtained for similar substrates reveal several important features. Most tertiary amine nitrosation reactions investigated so far exhibit kinetics where the reaction is first order in amine and second order in [NO_2^-].[9,10,38] The second order [NO_2^-] term arises because N_2O_3 is the effective nitrosation agent. The nitrosation of **15** in 75% HOAc–3.3 M H_2SO_4 is first order in [NO_2^-]. We noted above that the extent of the reaction increased with increasing acidity (Table 1). Here we see quantitatively by comparing the rate constants for loss of the amine, entries 1a and 2a of Table 4, that the nitrosation in the stronger acid is 27 times more rapid. This is a highly unusual phenomenon. Normally amine nitrosation rates decrease with decreasing pH below pH 3.4 due to the protonation of the amine which "protects" it against nitrosation. Thus increasing the acidity increases the rate and changes the regioselectivity to preferred deethylation. The fact that the reaction is first order in NO_2^- indicates that N_2O_3 is not the nitrosating agent, but the rate of nitrosating agent formation is not rate determining (first order in amine). We propose that NO^+ is the active "nitrosating agent", as we discuss further below. While acetyl nitrite could be the nitrosating agent, the careful kinetic work of Casado and his colleagues using amines of comparable basicity to ours, suggest that this is not likely.[39] Acetyl nitrite has only been shown to be important in acetic acid nitrosations when the amine concentration is very high compared to the initial [NO_2^-].

The KDIE experiments were conducted in two ways. Rates were determined by following the change in UV absorbance as a function of time, and by using HPLC to follow the time course of the loss of amine and the appearance of each product. The rate constants determined for amine loss by either method are comparable and yield KDIE data which are essentially the same. Neither reaction in 82% HOAc–3.3 M H_2SO_4, preferred deethylation, ($k_H/k_D = 1.3 \pm 0.23$,), nor reaction in 92% HOAc, preferred demethylation, ($k_H/k_D = 1.03 \pm 0.23$) results in a significant primary deuterium isotope effect for the loss of the amine. These are the mechanistically significant KDIE observations and show that the α-CH bond of the ethyl group (the only one tested here) is not broken in the rate determining step. Entries 1c and 2c of Table 4 reveal a significant isotope effect for deethylation as measured by the formation of the nitrosamines, but these are "product deuterium isotope effects" that result from product partitioning after the rate determining step. α-Deuteration of the ethyl group results in increased demethylation (the % deEt changes from 88% to 59% with deuteration), and increased nitro compound formation while maintaining the same approximate rate of amine loss, showing a linkage between dealkylation and nitro compound formation such as we have observed before.[10] The KDIE data presented here contrast with those determined for the nitrosation of 4-chloro-*N*,*N*-dimethylaniline ($k_H/k_D = 4.38$, 21 °C, 60% HOAc, pH 3.4) and 4-carboethoxy-*N*,*N*-dimethylaniline ($k_H/k_D = 3.69$, 21 °C, 60% HOAc, pH 3.4) where the transformation was occurring by a combination of mechanisms A and B.[10] These new data strongly suggest that preferential deethylation is occurring by a different mechanism.

The possible role of NO^+

Many nitrosation reactions at high acidity are known to involve NO^+ as the active nitrosating agent.[38,40] It is formed from nitrous acid by protonation of the OH oxygen to generate the nitrous acidium ion which then dissociates to NO^+ and H_2O [see eqn. (1) to (4)]. The reaction kinetics (first order in [NO_2^-]) for the nitrosation of **15** are consistent with the hypothesis that NO^+ is the nitrosating agent. Using literature data[41] for various equilibrium constants we calculated the [NO^+] as a function of the acidity of the mixtures reported in Table 1 where the % deEt is demonstrated to increase with increasing acidity. The relevant plots are shown in Fig. 2 and clearly demonstrate that the extent of deethylation increases with the [NO^+], which increases with increasing acidity.

To further explore the possible role of NO^+ in the changing regiochemistry of the reaction we examined the reaction of

Table 4 Rate and KDIE data for the nitrosation of **15**

Entry	Compound[a]	Solvent	$k_H/10^{-5}$ s^{-1}[b]	$k_D/10^{-5}$ s^{-1}[b]	k_H/k_D
1a	**15**[c]	82% HOAc, 3.3 M H_2SO_4	263 ± 42	202 ± 16	1.30 ± 0.23
1b	**16**	82% HOAc, 3.3 M H_2SO_4	4.36 ± 0.44	4.70 ± 0.91	0.93 ± 0.20
1c	**17**	82% HOAc, 3.3 M H_2SO_4	21.7 ± 1.3	4.47 ± 0.51	4.83 ± 0.63
2a	**15**[c]	92% HOAc	9.60 ± 0.61	9.35 ± 0.33	1.03 ± 0.07
2b	**16**	92% HOAc	5.59 ± 0.80	5.92 ± 1.08	0.95 ± 0.22
2c	**17**	92% HOAc	0.73 ± 0.05	0.19 ± 0.02	5.99 ± 1.04

[a] The unlisted product is **18**. [b] Rate of loss of **15**, rates of formation of **16** and **17**. [c] [**15**]$_i$ = 5.9 mM, [$NaNO_2$] = 59 mM.

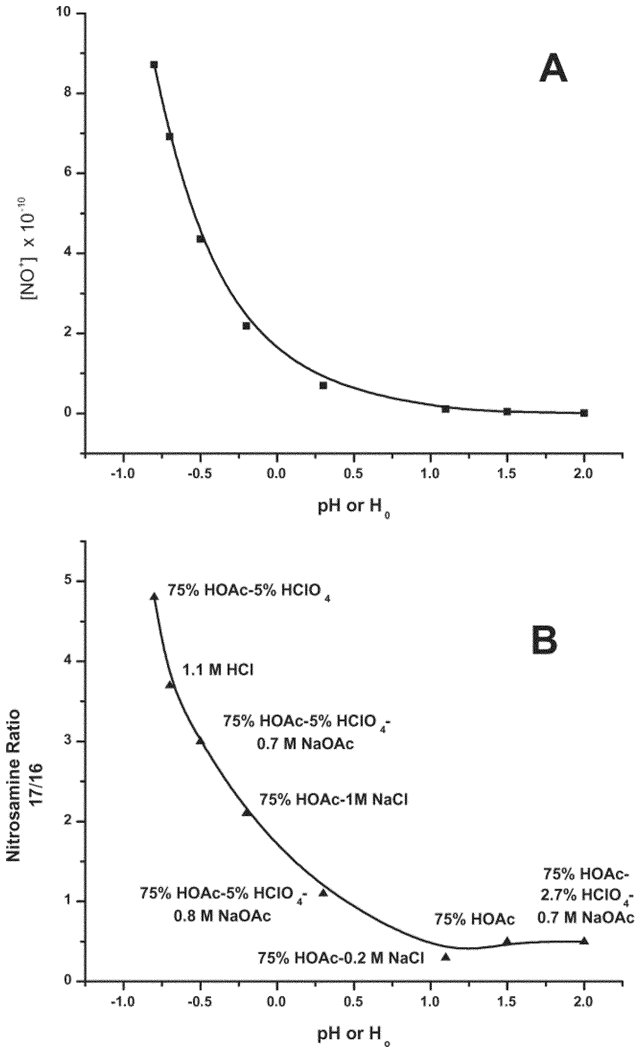


Fig. 2 Panel A: The calculated variation in $[NO^+]$ with acidity is shown. Panel B: The experimental variation in the nitrosamine ratio (**17/16**) (deethylation/demethylation) with acidity is shown. The acid mixture at each point is given.

$NOBF_4$ with **15** in CH_3CN under several sets of conditions. The data are given in Table 5. In runs 1 and 2 the goal was to determine the extent of deethylation. In all cases the % deEt is 85–87% as it is when the transformation is conducted at the highest acid concentrations. We were somewhat surprised to find that the reaction proceeds with predominant deethylation because we anticipated that Mechanism A, which involves NOH elimination, would play a larger role. To test this, we measured the % N_2O formed and compared its yields to those of the nitrosamines as we had done in the acidic nitrosations. The data for runs 3 and 4 show that only 3–4% of nitrosamine formation is occurring by Mechanism A. It is noteworthy that the dinitro compound **18** is formed in all reactions despite the fact that we took precautions to exclude O_2, which would oxidize any NO formed to NO_2. Its yield was increased significantly by the addition of a small amount of H_2O (compare runs 3 and 4), and by the use of less $NOBF_4$ compared to amine (runs 3 and 4 compared to runs 1 and 2).

Several pieces of evidence presented above now converge to strongly support a role for NO^+ in the changing regiochemistry of *N*,*N*-alkyl aromatic amine nitrosative dealkylation. Unlike most amine nitrosation reactions the rate of the transformation increases at higher acidity where the NO^+ concentration is greatest. The reaction kinetics show that the reaction is 1st order in "NO_2^-" as is well established for transformations involving NO^+, but not N_2O_3, the main nitrosating agent at modest acidities, which requires second order kinetics in "NO_2^-". Both the nitrosation reactions at high acidity and thence high relative $[NO^+]$ and the reactions with $NOBF_4$ result in highly regioselective deethylation of **15**.

$$Am + NO^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AmNO^+ \quad (5)$$

$$AmNO^+ \xrightarrow{k_2} Am^{\bullet+} + NO^{\bullet} \quad (6)$$

$$-\frac{d[Am]}{dt} = \frac{k_1 k_2 K_a K_4 [H^+][Am_T][NO_2^-]}{(k_{-1} + k_2) K_N [H_2O]} \quad (7)$$

At this point it is helpful to reconcile our rate data with a derived rate equation. For the purposes of clarity, we only consider the process which is giving predominant deethylation, which occurs at high acidity. We propose the operation of the simple scheme illustrated by eqns. (5) and (6), which gives rise to the rate eqn. (7), where Am is the amine, $AmNO^+$ is some complex of NO^+ and the amine, K_a is the dissociation constant of the protonated amine (AmH^+), Am_T is the analyzable concentration of the amine = [Am] + [AmH^+], and K_N and K_4 are defined by eqns. (1) and (4) respectively. We have assumed that $K_a \ll [H^+]$ and that $[AmNO^+]$ is at steady state. This rate equation is in complete agreement with our experimental observations, those being that the reaction is first order in amine and NO_2^-. The Equation also predicts that the transformation will become more rapid as the acidity increases. Depending upon the relative magnitudes of k_{-1} and k_2, either the nitrosation step or the decomposition of $AmNO^+$ could be rate limiting. As we discuss below, we believe it is that latter process.

We propose that NO^+ is acting as a one electron acceptor and is oxidizing the aromatic amine to a radical cation similar to the process depicted in Mechanism B. However, we do not propose that NO^+ itself is involved in the product determining step which is giving rise to the altered regiochemistry where preferential deethylation is observed. We have come to this conclusion through several lines of evidence and reasoning. The oxidation potential of **15** can be estimated from its dimethyl analog, for which two values have been reported, $E^0_{ox} = 1.57$ V *vs.* NHE[21] and $E^0_{ox} = 1.43$ V *vs.* NHE,[15] and its oxidation by NO^+ ($E^0_{red} = 1.51$ V *vs.* NHE[42]) is certainly plausible. The reaction of $NOBF_4$ with *N*-cyclopropyl-*N*-methyl-4-chloroaniline **24** gives exclusive cleavage of the cyclopropyl group to give 4-chloro-*N*-methyl-*N*-nitrosoaniline **25** as the sole product in 27% yield, with 56% recovery of the starting material. This

Table 5 Products from the reaction of **15** with $NOBF_4$

Run	Conditions	% deEt[a]	% Mechanism A[b]	%**17**	%**16**	%**18**	%**15**	%**20**	% N_2O[c]
1	Dry CH_3CN[d]	85.5	—	38.5	9.8	26.7	0.6	—	—
2	Dry CH_3CN[d]	85.1[e]	—	34.3	10.4	20.2	20.4	7.2	—
3	Dry CH_3CN[f]	85.8	4.4 ± 0.9	9.7	2.4	47.9	28	—	0.3
4	Wet CH_3CN[f,g]	86.7	3.5 ± 1.3	5.2	1.2	61.0	5.7	—	0.1

[a] Corrected for the number of α-H atoms. [b] Percent of nitrosamine formed by path A = 200[N_2O]/([**16**] + [**17**])%. [c] Determined by headspace analysis. [d] 0.012 M **15** with 5.3 equivalents of $NOBF_4$, under N_2. [e] The isolated secondary amine was incorporated into the calculation of the % deEt. [f] 0.0088 M **15** with 2.5 equivalents of $NOBF_4$, under N_2. [g] 1 μL H_2O added to simulate conditions of N_2O headspace calibration (see Experimental section).

suggests formation of a radical center on the amine nitrogen; followed by a rapid ring opening and ultimately cleavage of the cyclopropyl substituent.[10,11] We have observed this for the aqueous nitrosation reactions of other *N*-cyclopropyl-*N*-alkyl aromatic amines, previously.[10,11] It is important to note that the ring opening of the *N*-cyclopropyl substituent in the radical cation is so fast as to preclude recombination of the radical cation with NO_2 to generate aromatic nitro compounds. However, in both the acidic nitrosation reactions and in the $NOBF_4$ reactions in CH_3CN we do observe nitro compound formation in competition with nitrosative dealkylation. These observations, as well as the ^{15}N-CIDNP data, strongly imply a role for an amine radical cation in these transformations and NO^+ is a logical oxidant.

Using Marcus theory (see Supporting Information†) we have performed calculations which indicate that electron transfer from the aromatic amine system to NO^+ will occur by an inner sphere rather than by an outer sphere process. *A priori*, there would appear to be only three types of molecular sites in the aromatic amine for transient covalent bond formation between that moiety and NO^+, the nitrogen unshared pair, one of the *ortho* ring carbons (σ-complex), or π-coordination with the aromatic ring face. By examining the reaction of NO with aromatic amine radical cations and related transformations, we previously produced evidence for the reversible homolytic dissociation of the nitrosammonium ion.[10] However, we always observed competitive nitrosative dealkylation by NOH elimination in these processes (competition between mechanistic paths A and B). Here we observe little reaction by NOH elimination in either very strong acid or with $NOBF_4$. This suggests that if the nitrosammonium ion **10** forms by NO^+ coordination of the N unshared pair, and that it dissociates to the radical cation and NO nearly exclusively, which seems rather implausible. While we certainly cannot rule out this reaction channel, it seems likely that the electron exchange in more probably occurring by through homolytic dissociation of either the π- or σ-complexed intermediates mentioned above to the amine radical cation and NO.

Another role for NO^+ could possibly involve direct hydride abstraction of the α-H of the *N*-alkyl group to form the iminium ion **13**. This process would almost certainly give rise to a large KDIE for amine loss by deethylation, which is not observed, and the formation of NOH, which does not accompany preferred deethylation. (α-Deuteration of the ethyl group does result in a small increase in N_2O production (Table 2, entry 5) and a small KDIE (1.3, Table 4, entry 1c) because of an increased contribution of Mechanism A). Thus we can exclude hydride abstraction as the principal pathway giving rise to preferred deethylation. These arguments support a role for NO^+ in the production of the radical cation, but do not lead us to conclude that it is directly responsible for the altered regiochemistry. In our prior work we invoked the formation of a radical cation from the homolysis of nitrosammonium which was produced from a NO^+ donor (likely N_2O_3), not NO^+ itself. Dealkylation was then proposed to occur by deprotonation of the alkyl group in the product determining step (Mechanism B).[10] We have demonstrated that this does not lead to preferential deethylation. What is different about the current system which seems to preclude the operation of this pathway at higher acidity or with $NOBF_4$? The most obvious answer, is that the "effective base" concentration is very low at high acidity and in the $NOBF_4$ chemistry. A weak base such as a weakly basic anion, or H_2O must be present in sufficient concentration to accept the proton in the acid–base reaction at the α-position of the *N*-alkyl group. These hydrogens are known to be acidic,[18,19] but this reaction must be increasingly precluded as the acidity increases. As a result of these arguments, we have been required to consider other reactants and pathways of *N*-dealkylation. The presence of nitro products suggests a possible role for NO_2 in the *N*-dealkylation chemistry.

Nitrogen dioxide

We examined the reaction of **15** with NO_2 in three different solvents, CH_3CN, glacial HOAc, and CH_3CN containing a small amount of H_2O. The product data are given in Table 6. As can be seen, in CH_3CN the first formed product is the dinitroaniline **18** which then reacts further to give *N*-methyl-2,4-dinitroaniline **26** by deethylation and *N*-ethyl-2,4-dinitroaniline **27** through demethylation (entries 1–3). The data show, as we found with the nitrosation at high acidity, and with $NOBF_4$, that the regioselectivity is high and that the transformation proceeds with predominant deethylation. The % deEt does not change with time (compare entries 2 and 3, and 5 and 6). A high degree of deethylation is even seen in glacial acetic acid (entry 4). On the other hand a dramatic difference is seen for the reactions in CH_3CN–2% H_2O (entries 5 and 6). Here the predominant reaction is demethylation! We propose that this shift in reaction regiochemistry results from the presence of the base, H_2O, which is able to deprotonate the amine radical cation by Mechanism B or produce the nitrosamine by Mechanism A. The formation of **18** is indicative of a radical cation intermediate. The radical cation could form by one of the routes described above for the acidic nitrosation reactions. There is evidence for the formation of NO^+ from NO_2 *via* N_2O_4 as shown in eqn. (8). Evidence for the dissociation of N_2O_4 as shown comes in the form of bands observed for NO_2, NO^+ and NO_3^- in Raman[43] and IR[44,45] spectra. Nitrogen dioxide bubbled into a solution of 18-crown-6 in CH_2Cl_2 has been isolated and characterized as the $[NO^+ \cdot 18\text{-crown-6}\ (NO_3)_2^-]$ salt.[46] Formation of nitrosamines from the reaction of NO_2 with secondary amines has been well documented.[47–50] Nitrosation of tertiary amines by NO_2, has also been mentioned,[51] but there is little discussion in the literature of the mechanism by which this transformation occurs. Because we observe the formation of nitro compounds in all transformations where the regioselectivity is highly biased toward deethylation, and because nitration in our systems involves NO_2, we believe it is logical to consider that NO_2 may play an important role in altering the regiochemistry of the *N*-dealkylation toward preferred deethylation.

$$2NO_2 \rightleftharpoons N_2O_4 \rightleftharpoons NO^+ + NO_3^+ \quad (8)$$

From a physical organic chemical perspective, a transformation that removes a hydrogen from the α-carbon of the *N*-alkyl substituent of a radical cation must be endothermic, and must involve the development of electron deficiency at that carbon.

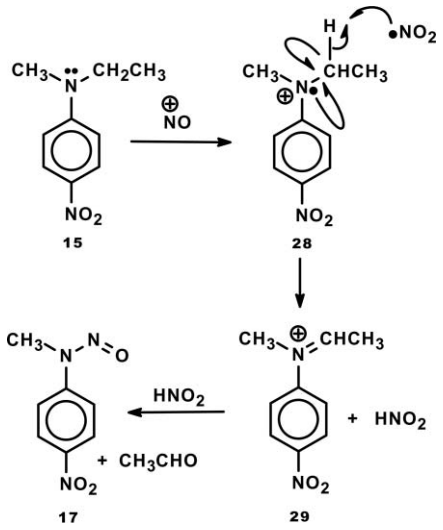
Table 6 The reaction of NO_2 with **15** in various solvents

Entry	Solvent	Rxn. time/min	**18**	**17**	**16**	**26**	**27**	% deEt
1	CH_3CN	1	95.9	—	—	—	—	—
2	CH_3CN	3	76.5	—	—	3.5	0.6	89.2
3	CH_3CN	20	—	—	—	70.8	13	90.0
4	HOAc	20	78.5	6.8	2.7	—	—	78.9
5	CH_3CN–2% H_2O	1	1.3	2.2	7.1	—	—	31.0
6	CH_3CN–2% H_2O	20	15.7	4.7	17.5	—	—	31.0

In the hydrogen yielding ethyl group, the developing electron deficiency at its α-carbon is inductively stabilized by the adjacent CH_3, compared to the same process at the *N*-CH_3. Endothermic H atom abstractions by radicals are well known to proceed with a high degree of regioselectivity. Consider, for example, the Br-atom abstraction of a hydrogen from an alkane. The hydrogen abstraction step is endothermic. The transition state structure resembles the product electron deficient radical, and a high degree of regioselectivity is observed where the H-atom is removed from the carbon most able to stabilize the developing electron deficiency, normally the most highly substituted one. In our system H atom abstraction from the α-carbon of the radical cation results in the formation of a carbocation or more precisely an iminium ion, a carbocation stabilized by resonance donation of the unshared pair on N.

Nitrogen dioxide arises from nitrous acid through the formation and homolysis of N_2O_3 and by the air oxidation of NO. It is known to abstract hydrogen atoms from a variety of substrates,[52,53] and it is plausible that it does so in this reaction. The low homolytic O–H bond dissociation energy of HNO_2 (78 kcal mol^{-1})[54,55] suggests the H atom abstraction by NO_2 will be endothermic, and thus occur *via* a more product-like transition state, and as we have explained above lead to preferential deethylation.

Hydrogen atom abstraction from the α-position of amine radical cations by poor H atom abstractors has been reported under conditions where the effective base concentration is very low.[56,57] Some studies have shown that this reaction proceeds with a preference for reaction of the more substituted alkyl group.[58] As a result of these considerations, our evidence and relevant literature data, we propose that the mechanism of aromatic amine *N*-dealkylation that gives rise to highly preferential *N*-deethylation, and which occurs in strong acid, with $NOBF_4$, and with NO_2 in the absence of significant H_2O, proceeds as depicted in Scheme 7. This represents a new mechanism of nitrosative *N*-dealkylation. The key steps involve generation of the radical cation **28** in a rate determining step, and NO_2 mediated α-H atom abstraction from the more substituted N alkyl group of this species to give the iminium ion **29** and nitrous acid. The conversion of **29** to **17** by nitrous acid has literature precedent.[59] The incursion of this mechanism is undoubtedly driven by the absence of a base concentration significant enough to provide for competitive deprotonation of this acidic radical cation, as well as the presence of a free radical, NO_2, able to abstract an H-atom from the alkyl group. When **15** was reacted with nitrous acid in open vessel, the % deEt (62%) was lower than when the identical reaction was carried out in a sealed flask (82% deEt) using 75% HOAc–5% $HClO_4$–0.7 M NaOAc. Sealing the vessel minimizes the NO and NO_2 loss to the atmosphere, and the increase in % deEt under sealed conditions illustrates the importance of a volatile reagent in the mechanism giving preferential deethylation. Control experiments in both dry CH_3CN and in strong acid showed that there was no significant reaction when NO and **15** were mixed, as expected.



Scheme 7 Mechanism C: H atom abstraction from radical cation.

While the radical **12** (see Scheme 3) could occur *via* a direct α-CH abstraction by NO_2, in order for this path to predominate, **12** would have to be oxidized to the iminium ion **13** more rapidly than it recombines with any radical species, since the latter processes would give different products, none of which are observed. We did not measure kinetics or KDIE for the reaction of **15** with NO_2, which is very fast, but the arguments presented and the similarities with the nitrosations in strongly acidic media suggest that this pathway is unlikely here. The NO_2 reaction probably takes a slightly different course when more electron rich amines are employed as substrates because these compounds have a lower oxidation potential and electron transfer to NO_2 to form a radical cation is more likely than it is with **15**.

Variation of regiochemistry within a run

As noted above, we had observed changes in the regiochemistry of nitrosative *N*-dealkylation of ethyl 4-*N*-ethyl-*N*-methylaminobenzoate during the course of a run. In the course of our investigation we also observed this phenomenon for the nitrosation of **15** under some conditions. A more thorough investigation yielded the data given in Fig. 3. The nitrosation of **15** in 75% HOAc–5% $HClO_4$–0.8 M NaOAc was examined in two ways. In the first case a concentrated solution of sodium nitrite was added to **15** in the acid solution. In the other case the nitrous acid solution was prepared in the same acid mixture and **15** added to it. In both cases the regiochemistry of dealkylation changes from predominant demethylation to deethylation with increasing run time. The data presented in Fig. 3 show that the change in the mode of addition results in three effects. When the amine is added to the preformed nitrous acid, 1) higher initial

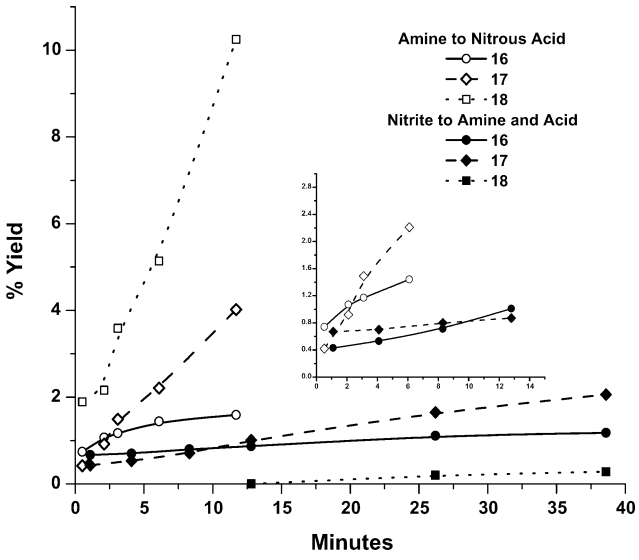


Fig. 3 Product yields arising from the nitrosation of *N*-ethyl-*N*-methyl-4-nitroanaline **15** in 75% HOAc–5% $HClO_4$–0.8 M NaOAc are given as function of time. The transformation was conducted in two ways. The lines with the closed symbol show product yields when a 10 eq. of sodium nitrite was added to a solution of the substrate amine in acid. The lines with the open symbols show product yields when the substrate amine was added to a freshly prepared solution of nitrous acid. The inset is an expansion of the first 15 minutes of the transformation and clearly shows that the yield of the initial major product **16** is overtaken by the production (deethylation) of **17** in each case. The yield cross over point is reached more rapidly, 2 min, in the freshly made solution of nitrous acid, than it is (10 min) when nitrite is added to the acidic solution.

product yields result; 2) the change over time from demethylation to deethylation is shorter; and 3) the percent yield of the nitro compound, **18**, is much greater. Since both transformations are conducted at the same acidity, the changes must result from changes in NO_2 concentrations. When $NaNO_2$ is added to the acidic amine solution, more time is required for equilibration and the generation of NO_2 both by the decomposition of N_2O_3 and the oxidation of NO. Evidence in support of this is seen in the yields of **18**, which forms from NO_2. As the concentration of NO_2 increases, dealkylation through H-atom abstraction becomes more competitive, and this results in predominant deethylation. The yields given in Fig 3 are, of course, cumulative. To determine how the change in regiochemistry changes with time (data not shown) we made plots of the change in product yield per unit time as a function of time. To do this we simply subtracted the cumulative yield of **17** from the prior yield and divided it by the time interval between points in Fig. 3. This type of data analysis showed that the extent of deethylation peaks at 8 min for amine addition to HNO_2 and at about 13 min for the other case. Thus, as the reaction goes on and NO_2 is either lost to reaction or the atmosphere the % deEt decreases after an initial increase.

Because we had examined the *N*,*N*-dialkyl-4-chloroaniline system extensively,[10] we also chose to examine the nitrosative dealkylation of 4-chloro-*N*-ethyl-*N*-methylaniline **30** at higher acidities than employed previously. Comparison of the compounds with the nitro and chloro substituents, **15** and **30**, is complicated by their immense difference in nitrosation reaction rates. Under identical conditions, with a 10-fold excess of $NaNO_2$ in acetic acid, **30** is consumed entirely in less than 5 minutes, whereas the majority of **15** remains after 2 hours. This is likely due to either differences in the nitrosation rates and/or the ease of oxidation of the substrates, since **30** is more basic, more nucleophilic and has an oxidation potential which is ~0.7 V less than that of **15**, by comparison to the dimethyl analogues.[19]

The regiochemistry of the nitrosative dealkylation of **30** is also dependent on the reaction acidity and initial [$NaNO_2$]. Nitrosation of **30** with a 2 fold excess of $NaNO_2$ in 75% acetic acid, gave 4-chloro-*N*-ethyl-*N*-nitrosoaniline **31** as the major nitrosamine after 6 min (2.4% **31**, 2.1% **32**, 57% deEt). When a 10-fold excess of $NaNO_2$ is used, the % deEt increases to 71% at a reaction time of 2 min. In each case, the other products were 4-chloro-*N*-methyl-*N*-nitrosoaniline **32**, and 4-chloro-2-nitro-*N*-ethyl-*N*-methylaniline **33**, the major product in all cases. However, on the addition of 5% $HClO_4$, the % deEt changed with the run time. Early in the reaction demethylation dominated (giving **31**, 49% deEt), but as the reaction progressed, the proportion of **32** (deethylation) increased, so that at the end of the run **32** was the major nitrosamine product (63% deEt). These observations support the conclusions made for the nitrosation of **15**; that at higher acidity an alternative mechanism participates resulting in preferential cleavage of the larger alkyl group, and that several different mechanisms, which are subject to subtle changes in reaction conditions, are operative in nitrosamine formation. Increased deethylation with greater concentrations of initial NO_2^- can be explained by the larger amounts of NO_2 produced by these conditions.

Comparison of the data above for the nitrosation of **30** in 75% HOAc with that for **15** (run 2, Table 1) in the same acid mixture (10 × $NaNO_2$) shows that the ring substituent influences the % deEt. For *p*-Cl deethylation is predominant, whereas the major nitrosamine is formed by demethylation when the ring substituent is *p*-NO_2. The large excess of $NaNO_2$ ensures large concentrations of NO_2. For the *p*-Cl amine, which has the lower oxidation potential, the role of the radical cation is evident by the large relative yields of nitro compound (76–83% at reaction completion). Thus as evidenced by rate and relative product yields, more radical cation forms from the *p*-Cl amine than does from the *p*-NO_2 amine under the same conditions. The α-H atoms of the amine radical cations also have different pK_a's, the *p*-NO_2 being more acidic (3 *vs.* 9 for *p*-Cl).[18,19] Competition between deprotonation (Mechanism B) and H-atom abstraction from the radical cation at the same acidity will lead to a greater degree of deprotonation for the *p*-NO_2 amine radical cation because of its greater acidity. From another perspective, higher acidities are required to suppress the deprotonation process for the *p*-NO_2 compound compared to its *p*-Cl analog. This is why we observe more deethylation for the *p*-Cl compound at the same acidity. The comparison of the nitrous acid chemistry of these two substrates supports our hypothesis regarding the mechanistic origin of the regiochemical change in the nitrosative *N*-dealkylation of aromatic amines.

$NOBF_4$ Reactions

As discussed above, the incursion of the H-atom abstraction mechanism in aqueous acid, Mechanism C, results principally from three factors, generation of the amine radical cation, suppression of its α-H deprotonation at high acidity by a decrease in the available base concentration, and H-atom abstraction of the α-H by NO_2, which competes with recombination of the radical cation with NO_2 to generate the nitro compound. As noted above in our discussion of the data presented in Table 5, $NOBF_4$ also reacts in CH_3CN with **15** to give mainly **17** by highly preferred deethylation. Application of our new mechanism to this process requires the presence of NO_2, the source of which is not immediately obvious. Yet these transformations also result in the formation of the *o*-NO_2 product **18**. The generation of the radical cation **28** by electron transfer from **15** to NO^+ is supported by their respective oxidation potentials. The NO produced in this reaction could react with O_2 to give NO_2, a rapid process,[60] yet we took strong measures to prevent oxygen contamination. Hydrolysis of $NOBF_4$ by traces of H_2O resulting from either trace contamination or production in the reaction mixture provides a more likely explanation for the formation of NO_2 under these conditions, and is well supported by our data. We believe that significant amounts of NO_2 form in this media by homolysis of N_2O_3, which is generated from the reaction of $NOBF_4$ with the HNO_2 produced in the hydrolysis of $NOBF_4$ [see eqns. (9), (10) and (3)]. Water is produced from NOH decomposition (Scheme 2). If NOH elimination occurs under these conditions, then H_2O equivalent to the amount of N_2O formed will be produced. For determination of the amount of N_2O evolved in the reaction of **15** with $NOBF_4$, it was necessary to add 1 μL of water to the reaction since aqueous NaN_3 was required for accurate preparation of a calibration curve. This resulted in a higher yield of **18** (61.0%) than under anhydrous conditions, but a similar nitrosamine ratio (86% deEt), as shown in Table 5. Thus, the small amounts of H_2O in this reaction are only changing the percentage of the path that takes the nitrosamine course, and favor nitro compound formation through the hydrolytic, then homolytic production of NO_2 from N_2O_3. Analysis of the N_2O yield (0.1%) showed that under these conditions, which favor deethylation, only 3.5 ± 1.3% of the total nitrosamine formed by Mechanism A (Table 5).

$$NOBF_4 + H_2O \rightarrow HNO_2 + HBF_4 \quad (9)$$

$$NOBF_4 + HNO_2 \rightarrow N_2O_3 + HBF_4 \quad (10)$$

Summary and conclusions

By using the *p*-NO_2 amine **15**, as our principal substrate, but by also employing the *p*-Cl analog **30**, we have demonstrated that the regiochemistry of *N*-dealkylation leading to nitrosamine formation changes with the acidity of the media and propose that the *N*-deethylation observed at high acidity arises from the NO_2 mediated H-atom abstraction from an intermediate radical cation produced from the effective one electron oxidation of the amine by NO^+. The fact that preferred deethylation of these substrates does not occur with significant N_2O production as

required by Mechanism A, that it does not involve observation of a primary KDIE for the loss of the amine, and the that the regiochemistry is different from that of electrochemically or chemically generated radical cations which are undergoing *N*-dealkylation by amine radical cation deprotonation (preferred demethylation) requires the incursion of a new mechanism of *N*-dealkylation. Evidence supporting the involvement of NO^+ in this process is provided by the kinetics [see eqn. (7)] which are first order in amine, nitrite, and [H^+], by the fact that the % deEt increases with the calculated [NO^+], which increases with increasing acidity as does the rate, and by the fact that reactions of the amine with $NOBF_4$ in acetonitrile give a high % deEt, as occurs in strong acid. The proposal that NO^+ is acting as an effecting one electron oxidant through an inner sphere process to produce an amine radical cation is supported by respective reactant oxidation potentials, application of Marcus theory, extensive chemical precedent, particularly mechanism studies of nitrite mediated aromatic nitration reactions, the lack of a primary kinetic deuterium isotope effect for the loss of the amine, and our observation of ^{15}N-CIDNP for the formation of the nitro compounds **15** and **23**, which arise from the recombination of NO_2 with a radical cation in the "nitrosation" of **21**. Evidence that the dealkylation at high acidity occurs through NO_2 mediated H-atom abstraction from the more substituted *N*-alkyl substituent (here ethyl *vs.* methyl) is provided by the observations that: 1) the % deEt of **15** is increased when the reaction is sealed confining volatile reactant; 2) reaction of **15** with NO_2 in CH_3CN and glacial HOAc results in preferred deethylation (79–90%) but changes to 31% upon addition of 2% H_2O to CH_3CN because the transformation changes to deprotonation of the radical cation by H_2O; 3) the % deEt of **30** is greater at higher initial [NO_2^-] where the [NO_2] is greater; 4) the change in the regiochemistry of dealkylation from demethylation to deethylation occurs more rapidly in the nitrosation of **15** when NO_2^- and acid are pre-mixed allowing for higher concentrations of NO_2 to develop prior to the addition of the amine; 5) physical organic chemical precedent which predict that the NO_2 mediated H-atom abstraction is endothermic and will result in a product-like transition state structure where the H-atom abstraction will occur so as to generate the incipient positive charge at the C-atom most able to electronically stabilize it; and 6) that significant competitive ring nitration involving NO_2 always occurs when preferential deethylation is observed showing that NO_2 is present.

In our prior work we presented evidence for the formation of the amine radical cation **11** by reversible homolysis of the nitrosammonium ion **10**.[10] Here we are purposefully less specific about the exact nature of the oxidation process because Mechanism A, loss of NOH from the nitrosammonium ion, does not compete effectively in strong acid. The stronger acid, resulting in higher concentrations of NO^+ and the much less basic (*p*-NO_2 *vs.* *p*-Cl) amine substrate may combine to provide a more competitive oxidation channel to the radical cation. The radical cation produced enters into three competitive transformations, recombination with NO_2 to generate a nitro compound, *N*-alkyl α-CH deprotonation, and *N*-alkyl α-CH H-atom abstraction, which ultimately lead to iminium ions and then nitrosamines. No prior studies reveal the detailed factors underlying how the first of these processes competes with the other two. We observe much more ring nitration as the aromatic ring substituents become less electron withdrawing. In the case of **21**, the unsubstituted amine, recombination with NO_2 to generate **15** and **23** appeared to be the only reaction of the radical cation. When the ring is substituted with Cl or NO_2, then the other processes compete. The more electron rich unsubstituted radical cation has a longer life time and radical–radical recombination becomes more probable leading to more nitro product. We have previously shown for the *p*-Cl and *p*-EtO_2C substituted amines that an increase of the basicity of the medium, *e.g.* addition of sodium acetate, results in increased rates of radical cation α-CH deprotonation (Mechanism B). Here we have demonstrated that this process is effectively shut down as the acidity of the medium increases. This leads to the incursion of the H-atom abstraction process which gives the iminium ion directly. Very high acidities are required for the relatively acidic radical cation derived from **15** compared to the less acidic radical cation with *p*-Cl derived from **30**. Thus we may anticipate a greater role for the H-atom abstraction mechanism as the aromatic amines become more electron rich and their derived radical cations become less acidic and less amenable to facile C–H deprotonation. On the other hand, pathway A also appears to become more competitive with these substrates at lower acidity.[10]

We believe that the data and interpretation presented here significantly clarify the mechanism and factors which result in the regiochemistry and the change thereof with changing reaction conditions involved in the nitrosative dealkylation of aromatic dialkyl amines. While no one piece of evidence actually defines the H-atom abstraction mechanism, the body of work and literature precedent strongly support the rationality of our proposal for the occurrence of this new mechanism of nitrosative amine dealkylation. This mechanism is only anticipated to occur when radical cations can be formed and structural or media factors prevail to reduce the rate of the apparently more favorable α-CH deprotonation pathway.

Experimental

Caution

Nitrosamines, and nitrosation reaction mixtures which produce them, should be considered carcinogenic and appropriate care taken in their handling. We performed all operations in well ventilated hoods. Nitrosamines are effectively destroyed by treatment with 30% HBr–glacial acetic and we routinely treat all of our glassware with this solution prior to further cleansing. Dilute aqueous solutions of nitrosamines can be destroyed by bringing the solution to pH 12–13 and reaction with aluminium foil or Raney-nickel.

Synthesis

Synthesis of amines and nitrosamines. In most cases, known compounds were prepared by literature procedures, or modifications thereof. Any significant changes to syntheses are described in the Supporting Information.† The nitrosamines were prepared as described by Hodgson and Nicholson.[14] Slight modifications of the procedures used by Lamm were used for the secondary amines.[61] The hydrazones were also prepared by a literature method.[62] Other compounds: *N*-ethyl-*N*-methyl-4-nitrosoaniline **22**,[63] *N*-ethyl-*N*-methyl-2-nitroaniline **23**,[64] *N*-ethyl-*N*-methyl-2,4-dinitroaniline **18**,[65] *N*-ethyl-*N*-methyl-4-chloro-2-nitroaniline **33**.[66]

Synthesis of *N*-ethyl-*N*-methyl-4-nitroaniline (15). This is a known compound,[67] however, no efficient methods for its synthesis have been described previously. In this synthesis, 4-bromonitroaniline (3.0 g, 0.015 mol) and *N*-methylethylamine (2.8 g, 47 mmol) were dissolved in 10 mL pyridine, in a 15 mL pressure tube. The cap was screwed on tightly and the vessel heated to 115 °C for 48 hours in an oil bath. The solution was cooled, added to 50 mL water, the precipitate filtered and recrystallized from ethanol yielding **15** (2.35 g, 87%), melting at 85–86 °C. δ_H (250 MHz, $CDCl_3$, Me_4Si) 8.11 (d, 2H), 6.60 (d, 2H), 3.49 (q, 2H), 3.06 (s, 3H), 1.21 (t, 3H). δ_C (250 MHz, $CDCl_3$, Me_4Si) 153.14, 136.55, 126.23, 110.01, 46.89, 37.74, 11.49.

Synthesis of *N*-(1,1-D_2)ethyl-*N*-methyl-4-nitroaniline (15-D_2). *N*-Methyl-4-nitroacetanilide was prepared by a standard literature procedure,[68] and reduced with lithium aluminium deuteride by a known mild reduction method.[67] The product was purified by silica column (10% ethyl acetate in hexanes), giving **15-D_2**

(0.30 g, 16%); mp 82–84 °C. δ_H (250 MHz, $CDCl_3$, Me_4Si) 8.11 (d, 2H), 6.60 (d, 2H), 3.06 (s, 3H), 1.20 (s, 3H), isotopic purity >95%.

Synthesis of 4-chloro-*N*-ethyl-*N*-methylaniline (30). This is a known compound and was prepared from 4-bromochlorobenzene and *N*-methylethylamine by a published Pd coupling method,[69] in 92% yield. The spectral data are consistent with those in the literature.

Nitrosation reactions

Nitrosation of 21. The nitrosation was repeated as described by Hodgson and Nicholson, [14] with a modified procedure for product analysis. The reaction mixture was made basic with KOH, the products extracted into 3 × 15 mL ethyl acetate, washed with NaCl, then with water, dried over Na_2SO_4 and the solvent removed. The product mixture was separated by silica column (10% ethyl acetate in hexanes), and the fractions identified by ^{1}H NMR and GC–MS. To quantify the products, **21** (26 mg, 0.20 mmol) in 100 mL of 0.12 M HCl was reacted with 20 mL of $NaNO_2$ (0.05 M) which was added rapidly at 0 °C. Samples (5 mL) were worked up as described above and the organic extract made to 3 mL with benzonitrile (2.81 mM) in acetonitrile, as an external standard, and analyzed by HPLC.

General Procedure for the nitrosation of 15. In a typical experiment, a 0.0138 M solution of **15** was prepared in an acidic solvent. Methyl 3-nitrobenzoate was added as an internal standard. Of this solution, 9 mL was transferred to a round bottom flask with stir bar, and subsequently sodium nitrite (1 mL, 0.115 M) added rapidly by syringe.

Standard workup and analysis procedure. At a designated time, a 0.6 mL aliquot of the reaction mixture was quenched with 5 mL saturated sodium bicarbonate, extracted into 3 × 5 mL ether, washed with 5 mL water and dried over Na_2SO_4. The solvent was removed, and the sample dissolved in 0.5 mL acetonitrile for HPLC analysis.

Nitrosation of 15 with prior equilibration of acid and nitrite. A 50 mL round bottom flask with a stir bar was charged with 8.9 mL of a mixture of 75% HOAc–5% $HClO_4$–0.8 M NaOAc and stoppered. Sodium nitrite (1 mL, 0.115 M) was added by syringe through the septum. After 15 minutes, **15** (2.83 M) and methyl 3-nitrobenzoate (0.75 M), were added by syringe, in 0.2 mL of 75% HOAc–5% $HClO_4$–0.8 M NaOAc. Samples (0.6 mL) were removed throughout the course of the reaction, worked up and analyzed by the standard procedure.

General procedure for nitrosation of 30. A procedure identical to that used for the nitrosation of **15** was employed, using 1,3-dinitrobenzene as the internal standard. The products were identified by LC-MS and by spiking the HPLC run.

Quantification of aldehyde byproducts. An adaptation of a method used previously was utilized.[62] The general procedure was used to nitrosate **15** (3.6 M H_2SO_4 in 90% acetic acid). After 5 min, a 1 mL aliquot was added to 8 mL of NaOH (1 M) followed by, 1 mL sulfamic acid (0.17 M). After 1 min, 2 mL of 2,4-dinitrophenylhydrazine (DNP, 2 mM 18% phosphoric acid in ethanol) was added and stirred for 10 min. The organic products were extracted into 3 × 10 mL diethyl ether, washed with 5 mL distilled water, dried over K_2CO_3, and analyzed by HPLC. To determine the extraction efficiency of the aldehyde trapping procedure, control recovery experiments were conducted using formaldehyde and acetaldehyde. In a typical experiment, the aldehyde (2.3 mM) and internal standard in 3.6 M H_2SO_4–90% HOAc was stirred for 5 min following the addition of 1 mL $NaNO_2$. Work up and analysis was identical to that used for the nitrosation. Recoveries although low (CH_2O 9.8 ± 0.9%, CH_3CHO 35.2 ± 2.9%), are reproducible and are probably a result of either incomplete derivatization or extraction.

Measurement of N_2O evolved during the nitrosation reaction. The method and calibration was the same as used previously,[10] except the headspace was analyzed by GC-ECD following sampling through an acid trap containing NaOH and anhydrous $CaSO_4$.

Reaction of 15 with NO_2. A 100 mL round bottom flask was charged with 6 mL of **15** (11.2 mM) in of acetic acid. Methyl 3-nitrobenzoate was added as an internal standard. The headspace above the reaction was replaced with nitrogen dioxide at atmospheric pressure. Samples (0.2 mL) were subjected to standard work up and analysis. This reaction was also carried out in dry acetonitrile and in 98% acetonitrile. These samples were analyzed directly by HPLC, after blowing nitrogen through the solution.

Nitrosation of *N*,*N*-dialkylanilines with $NOBF_4$. An oven dried, stoppered, round bottom flask was charged with a 3 mL solution of **15** (3.7 mM) and methyl 3-nitrobenzoate (5.0 mM) in dry, degassed acetonitrile. The headspace was replaced with nitrogen, and 3 mL nitrosonium tetrafluoroborate (0.13 M) in dry, degassed acetonitrile was added by syringe. After 40 min, a 0.6 mL was sample was subjected to work up and analysis by the standard procedure. This procedure was repeated using *N*-cyclopropyl-*N*-methyl-4-chloroaniline **24** (0.12 M), which had been prepared previously in this laboratory, with 1,3-dinitrobenzene (0.04 M) as an internal standard. The sole product, 4-chloro-*N*-methyl-*N*-nitrosoaniline **25**, was identified by GC-MS, and by spiking the HPLC run.

To quantify the amount of N_2O evolved in the reaction of **15** with $NOBF_4$, the method used for N_2O determination under acidic conditions was modified slightly. The calibration curve was prepared by addition of various concentrations of aqueous NaN_3 (1 μL) to $NOBF_4$ in acetonitrile. For consistency, the nitrosation of **15** was repeated with the addition of 1 μL distilled water.

Oxidation of 15 with Ce(IV). To 5 mL of **15** (2.2 mM) and methyl 3-nitrobenzoate (0.5 mM) in 75% acetic acid was added 1 mL of aqueous $Ce(NH_4)_2(NO_2)_6$ (1.7 mM), with stirring. After consumption of the oxidant, as determined by starch/KI paper (<20 s), 0.6 ml of the reaction was subjected to standard work up and analysis. The products were identified by LC-MS. The reaction was also conducted in 75% acetic acid–5% $HClO_4$.

Electrochemical Oxidation of 15. Electrochemical oxidations were carried out in a split cell using a platinum anode and cathode, and a standard calomel reference electrode. In a typical experiment, the cathode and buffer region were filled with 75% acetic acid. The anode region was filled with 12 mL of **15** (11.7 mM) and methyl 3-nitrobenzoate (5.0 mM) in 75% acetic acid. A constant voltage of 1.91 V was applied to the system for 24 h, after which a 0.6 mL sample of the solution in the anode region was subjected to standard work up and analysis.

Kinetic experiments

Determination of KDIE for 15-D_2. In a typical experiment, a 100 mL flask was charged with 9.2 mL of 90% acetic acid containing **15** (6.9 mM) and internal standard (1.7 mM) at 28 °C. While stirring, 1 mL of aqueous $NaNO_2$ (57 mM) was added rapidly. Samples (0.2 mL) were taken at frequent intervals and subjected to standard work up and analysis. At least eight samples were taken during each run, and the concentrations of the organic components determined from their peak areas, relative to the standard. The runs were repeated 3 times, and the rate of loss of **15** and the rate of product formation determined from plots of ln ($[\mathbf{15}]_0 - [P]$) *vs.* time, where [P] = [product]. The errors were estimated from the standard deviation of the slope, determined by linear regression. Similar procedures were used

for other kinetic runs, including **15-D$_2$**, and k_H/k_D determined. Rates of substrate consumption were also determined by UV, and were comparable.

Determination of the reaction order in nitrite. In a typical experiment, **15** (13.7 mM) and internal standard (4.2 mM) in 75% HOAc–3.6 M H_2SO_4 was stirred at 23 °C, and reacted with the following concentrations of $NaNO_2$: 0.69 M, 0.35 M, 0.38 M, 0.45 M, 0.48 M, 0.55 M. A plot of ln (k) against ln [$NaNO_2$] gave straight lines for **15** and for both nitrosamines. The results were corroborated by UV.

Supporting Information

Explanations of CIDNP, and additional experimental details for kinetics experiments, syntheses of several known compounds, and N_2O determinations are given.

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