

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

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SUPPORTING INFORMATION

Justification of the Signal Enhancement Seen by ^{15}N NMR

The sign of the enhancement intensity can be rationalized by the Kaptien equation¹, modified for ^{15}N ,² which is expressed as $\Gamma = -\mu \cdot \epsilon \cdot \Delta g \cdot a$. A qualitative value for the enhancement factor Γ can be determined by analysis of the component parts of the equation. For a radical pair formed by diffusion of triplet precursors, μ is positive. A product that forms from radicals within a solvent cage has a positive ϵ . The value $\Delta g = g_{\text{NO}_2} - g_{\text{rad.cat}}$ for the reaction of NO_2 with an N,N-dialkylaniline radical cation has been estimated at approximately -0.0032 .³ Since the ^{15}N -electron coupling constant for NO_2 is also negative,⁴ this gives an overall negative value for Γ , indicating enhanced emission, which is what we observe for the formation of **15** and **23**. Thus, the nitration mechanism is in accord with the prior work.³

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Justification for Inner Sphere Oxidation (see Scheme 3 of article)

The change in the nitrosamine ratio parallels the change in $[\text{NO}^+]$ with acidity. Since NO^+ is a potent oxidant, whose reduction potential is likely greater than the oxidation potential of **15**, it is plausible that the initial transformation in the nitrosation reaction at higher acidity is a single electron transfer from **15** (or **9** of Scheme 3) to NO^+ . This is believed to occur via the homolysis nitrosammonium ion **10**, rather than by outer sphere electron transfer. This

assertion is supported by estimation of the activation energy ΔG^\ddagger of the electron transfer, using the Marcus equation, $\Delta G^\ddagger = (\lambda/4) (1 + \Delta G^\circ/\lambda)^2$. This technique has been used previously as a guideline for the nature of the electron transfer in aromatic nitrations.¹ The necessary data for estimation of ΔG^\ddagger for the oxidation of *N,N*-dialkylanilines, in acetonitrile, are available in the literature. The total reorganization energy λ can be estimated from the sum of the reorganization energies for the couples NO^+/NO (70 kcal mol^{-1})² and $\text{ArH}^{*\cdot}/\text{ArH}$. The reorganization energy for the one electron oxidation of *N,N*-dimethylaniline was determined to be 0.27 eV^3 (6 kcal mol^{-1}), and is not expected to be significantly affected by the para substituent.² The total standard free energy for the electron transfer ΔG° can be estimated from the standard oxidation potentials of the species involved in the couple.¹ Using the oxidation potentials determined for para substituted *N,N*-dimethylanilines by Seo et al,⁴ the activation energies of electron transfer from **15** and **30** to NO^+ were estimated at 18 kcal mol^{-1} and 14 kcal mol^{-1} respectively. These are significantly larger than the estimated minimum threshold for bonded electron transfers,⁵ indicating NO^+ forms a bond with the organic substrate prior to oxidation. This agrees with our previous work, which showed the oxidation of *N,N*-dialkylanilines to involve the reversible homolysis of the *N*-NO bond.⁶

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ADDITIONAL EXPERIMENTAL DETAILS

Instrumentation. Melting points were determined using Thomas Hoover capillary melting point apparatus, and are uncorrected. HPLC experiments were carried out using a Waters system interface module, a Waters 712 WISP autosampler, a Waters 490 programmable multiwavelength detector and two Waters pumps. Millennium software was used for data analysis. A Zorbax ODS C-18 4.6 mm x 25 cm column was used for these studies. UV spectra and kinetic data were obtained with a Hewlett Packard (HP) 8453 UV-vis spectrophotometer, connected to a Haake A80 temperature controller, and analyzed with HP software. Gas chromatography (GC) used an HP 5890 Series II GC, coupled with either a flame ignition detector (FID), using a 30 m x 0.25 mm DB-5 J & W Scientific capillary column, or an electron capture detector (ECD) using a 30 m x 0.53 mm Supel-Q Plot column by Supleco. For the mass spectroscopic analyses, an Agilent 6890 Series GC, with a 5973 Network mass selective detector and 5973N Data Analysis software, was used with a 30 m x 0.25 mm HP-5MS column from Agilent. NMR spectra were obtained with a Bruker AMX 300 MHz (^1H , ^{13}C) and a Bruker ARX 500 MHz (^{15}N). Electrochemical oxidations were done using an EG & G Princeton Applied Research Potentiostat/ Galvanostat Model 273. pH measurements were made using an Orion Research digital pH/millivolt meter 611, using an Orion combination pH electrode.

Materials. Organic solvents used for liquid chromatography were of HPLC grade by Fischer. The aqueous phase comprised of water distilled with Corning AG-3ADA distillation apparatus. All HPLC solvents were vacuum filtered with Millipore apparatus before use. Acetonitrile was dried by distillation over phosphorus pentoxide. Nitric oxide from Aldrich (98.5%) was purified by passing through 5 M KOH, followed by a CaSO₄ drying tube and finally a dry ice/ acetone bath. Nitrogen dioxide was supplied by Matheson. All other materials were acquired from Aldrich or Sigma and were purified by standard techniques.

Synthesis of *N*-(1,1-D₂)Ethyl-*N*-methyl-4-nitroaniline (15-D₂). *N*-Methyl-4-nitroacetanilide was prepared by a standard literature procedure,¹ and recrystallized from hot ethanol before use in the subsequent mild reduction step.² An oven dried 2-necked round bottom flask was charged with *N*-methyl-4-nitroanthranilide (1.94 g, 0.010 mol) and 9 mL dry ether. The flask was fitted with an oven dried condenser and a dry septum, and the air inside replaced by a steady stream of dry N₂. In a separate oven dried 25 mL round bottom flask with balloon, lithium aluminum deuteride (LAD) (9 mL, 1.0 M in dry ether) was added slowly to AlCl₃ (6 mL, 1.5 M in dry ether) and equilibrated under N₂ for 15 min. The AlCl₃-LAD mixture was added to the amide solution by syringe over 20 min. The reaction was stirred for a further 10 min, and then 6 mL of water was added followed by 2 mL of 75% H₂SO₄. The organic products were extracted into 3 x 10 mL ether, washed with water, dried over Na₂SO₄, filtered and the solvent evaporated. The desired product was collected by flash column (10% ethyl acetate in hexanes), in 16% yield (0.30 g); mp 82-84 °C. ¹H NMR (250 MHz, CDCl₃) δ 8.11 (d, 2H), 6.60 (d, 2H), 3.06 (s, 3H), 1.20 (s, 3H).

Synthesis of 4-Chloro-*N*-ethyl-*N*-methylaniline. This synthesis was based on a published coupling technique.³ 4-Bromochlorobenzene (1.06 g, 5.53 x 10⁻³ mol) was combined with *N*-ethylmethylamine (0.65 g, 1.00 x 10⁻² mol), potassium *t*-butoxide (0.99 g, 1.03 x 10⁻² mol), BINAP (3.0 mg, 4.8 x 10⁻⁵ mol), Pd₂(dba)₃ (13.9 mg, 1.5 x 10⁻⁵ mol) and 15 mL dry toluene in a 30 mL pressure tube, and heated at 80 °C for 23 h. The product mixture was filtered through celite, washed with ethyl acetate and extracted into 3 x 15 mL 1 M HCl. The combined fractions were made basic with NaOH, extracted into 3 x 15 mL ether, washed with 10 mL of distilled water and dried over Na₂SO₄. Removal of the solvent yielded 0.86 g (5.09 x 10⁻³ mol, 92%) of pure, colorless oil. ¹H NMR (250 MHz, CDCl₃) δ 7.15 (d, 2H), 6.61 (d, 2H), 3.36 (q, 2H), 2.88 (s, 3H), 1.10 (t, 3H). ¹³C NMR (250 MHz, CDCl₃) δ 147.67, 128.85, 120.73, 113.42, 46.88, 37.50, 10.99.

Determination of H_o. 4-Chloro-2-nitroaniline (7.3 mg, 0.053 mmol) was used as an indicator and made to 250 mL with water. The molar absorptivity coefficient, ε, was determined at 424 nm, by measuring the UV absorption (A = εcl). A second solution of 4-chloro-2-nitroaniline (7.5 mg, 0.054 mmol) was made to 25 mL with conc. HCl, and ε_{424nm} determined. The value of ε at λ_{max} for the sample was also determined with 2-nitro-4-chloroaniline (2.7 mg, 0.020 mmol) made to 25 mL with the acid solution to be tested. Each solution was tested a minimum of 4 times. H_o was calculated using the equation, H_o = pK_{BH+} - log{(ε_B - ε)/(ε - ε_{BH+})}, where pK_{BH+} applies to the indicator and ε_B, ε_{BH+} and ε are the molar absorptivities of the indicator in water, HCl and the sample respectively. Data are listed in Table 8.

Table 8. Molar Absorptivity of 4-Chloro-2-nitroaniline and Calculated H_o

Acid	$\epsilon_{(\lambda_{max})}$ ($M^{-1}cm^{-1}$)	H_o
12.1M HCl	0	
distilled H ₂ O	4564 \pm 112	
75% HOAc/ 1.0 M HCl	3933 \pm 432	-0.23 \pm 0.03
75% HOAc/ 5% HClO ₄ / 0.73 M NaOAc	3506 \pm 602	-0.51 \pm 0.09
1.0 M HCl	3030 \pm 840	-0.73 \pm 0.20
75% HOAc/ 5% HClO ₄	2874 \pm 512	-0.80 \pm 0.14

Measurement of N₂O Evolved During the Nitrosation Reaction. The general procedure for nitrosation was followed, with modifications. The acidic amine solution (5 mL) was transferred to a 3-necked round bottom flask, equipped with a stir bar, thermometer and leveling bulb. The flask was sealed with septa, and 1 mL NaNO₂ added by syringe. After 36 minutes, the headspace was adjusted to atmospheric pressure, sampled by gastight syringe, through an acid trap containing NaOH and anhydrous CaSO₄, and analyzed GC-ECD. A 0.6 mL aliquot of the reaction was subjected to work up and analysis by the standard procedure.

Calibration for N₂O. A calibration curve was prepared by measuring the amount of N₂O evolved in the reaction of various quantities of azide with nitrite, under relevant acidic conditions. To a 3-necked round bottom flask, equipped with a thermometer and a leveling bulb, was added 5 mL of acidic solvent, 0.5 mL NaNO₂, 0.4 mL water and 0.1 mL NaN₃. The reaction was stirred for 20 minutes, the headspace sampled, and analyzed by GC-ECD. The N₂O peak area was recorded. This procedure was repeated with a minimum of 4 different concentrations of NaN₃. A plot of [NaN₃] (= [N₂O]) vs. peak area gave a straight line, and was used to determine the amount of N₂O evolved during the amine nitrosation. This calibration was repeated each time a nitrosation reaction was monitored.

Determination of the KDIE for 1a by UV. A stock solution of **15** (63.8 μ M) in 10 mL glacial acetic acid was prepared and 3 mL transferred to a quartz cuvette and placed in the UV cell at 28 °C, with stirring. Sodium nitrite (0.33 mL, 5.71mM) was added rapidly, and data accumulation started after a delay of 30 s, with a spectrum obtained every 30 s for the first 300 s, after which the delay time was increased by 5%. The decrease in absorbance at 430 nm was recorded, and a plot of ln(abs) vs. time gave a straight line. The rate of consumption of **15** was determined from an average of 3 runs. These data were referenced to a blank made by combining 3 mL HOAc and 0.33 mL of 5.71 mM NaNO₂ in a cuvette. These experiments were repeated with **15-D₂**, and k_H/k_D was determined.

Determination of the Reaction Order in Nitrite by HPLC. A stock solution consisting of **15** (13.7 mM) and methyl 3-nitrobenzoate (4.2 mM) in 75% HOAc/ 3.6 M H₂SO₄ was prepared, and 5 mL of this solution was transferred to a 100 mL round bottom flask, with a stir bar, at 23 °C. After the addition of 1 mL of sodium nitrite (0.69 M), the reaction was followed by the removal of 0.2 mL samples which were worked up and analyzed by the standard procedure. A minimum of eight samples were taken during the course of each reaction. The reaction was repeated with the

following NaNO_2 concentrations: 0.35 M, 0.38 M, 0.45 M, 0.48 M, 0.55 M. The rate of nitrosamine formation was determined at each nitrite concentration. A plot of $\ln(k)$ against $\ln[\text{NaNO}_2]$ gave straight lines for both nitrosamines.

Determination of the Reaction Order in Nitrite by UV. A cuvette was filled with 3 mL of a stock solution consisting of **15** (0.19 mM) in 75% HOAc/ 3.6 M H_2SO_4 , and stirred at 23 °C. After the addition of 10 μL of sodium nitrite, the reaction was monitored by UV. The reaction was repeated at five different concentrations in the range 0.93 M- 2.76 M, and at least twice at each concentration. The pseudo-first order rate constant was determined at each nitrite concentration, and a plot of $\ln(k)$ vs. $\ln[\text{NaNO}_2]$ was linear.

^{15}N CIDNP NMR Experiments. Freshly distilled *N*-ethyl-*N*-methylaniline **21** (74 mM) and nitro- ^{15}N -benzene (0.17 M), as an internal standard, were made to 10 mL with 83% HOAc/ 0.6 M HCl. Of this solution, 0.9 mL was transferred to an NMR tube, and 0.1 mL $\text{Na}^{15}\text{NO}_2$ (3.68 M) added. The reaction was monitored by ^{15}N NMR, accumulating spectra in 3 min blocks. A pulse angle of 30° and a pulse delay of 2 seconds were used to facilitate rapid sampling. Negative CIDNP enhancements were seen at -13.8 ppm and -15.6 ppm. Chemical shifts of the products were obtained by separating the products of the H^{15}NO_2 nitrosation of **21** by flash chromatography and acquiring ^{15}N NMR spectra of the components. The identities of the compounds were confirmed by GC-MS and ^1H NMR. The peaks observed during the nitrosation reaction were identified as: δ 194.9 ppm, HONO; 170.3 ppm, **16**; 170.2 ppm, **17**; 47.6 ppm, **22**; -8.2 ppm, " NO^+ "; -10.0 ppm, nitrobenzene; -14.2 ppm, **15**; -15.4 ppm, **23**. All chemical shifts are relative to external standard CH_3NO_2 ($\delta = 0$). The procedure was repeated using **22** and **15**, for which no signal enhancements were seen.

References

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