Mechanism of the Reaction of Carbon and Nitrogen Nucleophiles with the Model Carcinogens *O*-Pivaloyl-*N*-arylhydroxylamines: Competing S_N2 Substitution and S_N1 Solvolysis

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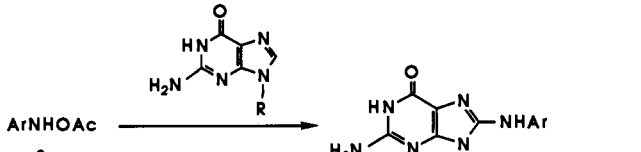
Abstract: The reaction of *N,N*-dimethylaniline (**4**) and aniline (**5**) with the *O*-pivaloyl-*N*-arylhydroxylamines (**1a–f**) in MeOH exhibits second-order kinetics and generates products of nucleophilic attack on the nitrogen of the hydroxylamine derivative. The characteristics of this reaction are not consistent with a nitrene or SET mechanism, an S_N1 reaction with rate-limiting attack of the nucleophile, or nucleophile-assisted ionization. The only mechanism consistent with the available data, including substituent effects ($\rho^+ \approx -3.0$), cyclic voltammetry results, and product identifications, is an S_N2 process. This reaction occurs in competition with an S_N1 solvolysis that shows significant substituent dependence ($\rho^+ = -8.5$). The reaction of **1** with **5** generates products of nucleophilic attack by both carbon (**8**, **9**) and nitrogen (**10**). Competitive attack by carbon apparently occurs because of transition-state stabilization caused by the incipient C–N bond. The successful competition of the S_N2 reactions with S_N1 solvolysis for the esters **1a** and **1b**, which are similar in reactivity to the putative carcinogens **2a–c**, indicates that certain adducts isolated from in vivo experiments, including **3**, may be formed via S_N2 mechanisms.

The *O*-pivaloyl-*N*-arylhydroxylamines (**1**) have been the subject of a number of investigations in our laboratory.[1] These compounds serve as models for the O-acetyl-*N*-arylhydroxylamines (**2**), which are putative carcinogenic metabolites of polycyclic aromatic amines.[2] These materials have recently been shown to react with deoxyguanosine in mixed-solvent systems to generate the "C-8 adducts", **3**, in low yields (eq 1).[3] These adducts have also been isolated from in vitro and in vivo studies and are thought to play an important role in the induction of cancer by **2**.[4]



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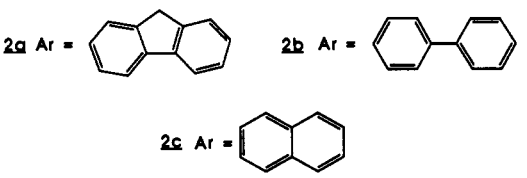
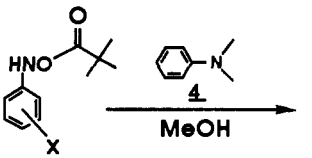
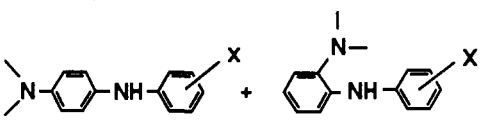


It has generally been assumed that these adducts are formed via nitrenium ion processes,[2,4] but as we recently pointed out,[1c] arylnitrenium ions undergo nucleophilic attack at aromatic carbons ortho and para to the carbon bearing the nitrogen, not directly at the nitrogen itself. Nucleophilic substitution via an S_N2 mechanism appeared to be a viable means for the formation of such adducts.

In a preliminary study, we found that **1d–f** react in high yield with *N,N*-dimethylaniline (**4**) in MeOH to yield the adducts **6** and **7** by an S_N2 mechanism (eq 2).[1c] This was the first documented example of nucleophilic substitution with bimolecular kinetics in ester derivatives of *N*-arylhydroxylamines. Subsequently, Boche and co-workers also demonstrated bimolecular kinetics for the reaction of *N*-methylaniline with *N*-(4-cyanophenyl)-*O*-(diphenylphosphinoyl)hydroxylamine.[5] They reported a greater than 90% yield of the hydrazine product (eq 3).[5]





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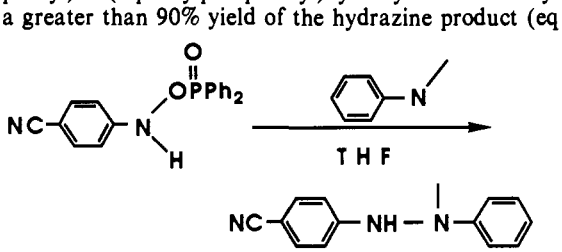

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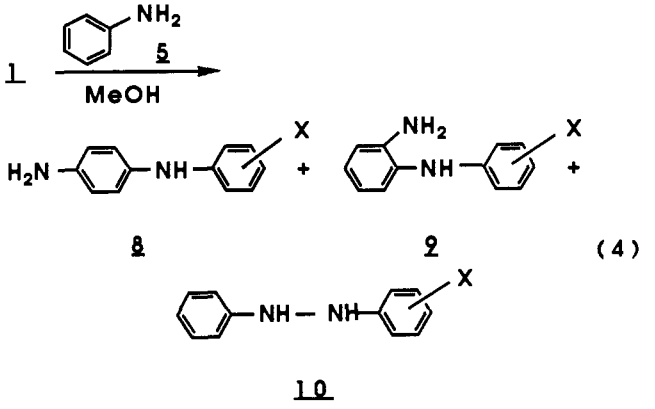
In this paper, we demonstrate that the reaction of eq 2 also occurs for the more reactive esters **1a–c** with no observable change in mechanism. We also have examined the reaction of **1a–e** with aniline (**5**) in MeOH and have found that this material behaves as both a carbon and nitrogen nucleophile toward **1** via an S_N2 process (eq 4). The implication of these results with respect to chemical carcinogenesis by **2** is discussed herein.



Experimental Section

Synthesis of 1. The synthesis and characterization of **1d–f** have been described.[1a,6] The esters **1a–c** were synthesized from the corresponding hydroxylamines by the method published for **1d**.[1a] The hydroxylamines were in turn obtained by reduction of the corresponding nitroaromatics by standard procedures.[7] The esters **1a–c** must be stored at −75 °C to avoid rapid decomposition after isolation from the reaction mixture. They were all obtained as oils that solidified upon storage at low temperature. Spectral data for **1a–c** follow.

1a: IR (neat) 3247, 3025, 2974, 1731, 1513, 1119 cm^{-1}; ^1H NMR (90 MHz, C_6D_6) δ 9.13 (1 H, s), 6.94 (4 H, s), 2.12 (3 H, s), 1.16 (9 H, s); high-resolution MS *m/e* 207.1274, $C_{12}H_{17}NO_2$ requires 207.1260.

1b: IR (neat) 3245, 3033, 2975, 1738, 1607, 1519, 1489, 1274, 1118 cm^{-1}; ^1H NMR (90 MHz, CD_2Cl_2) δ 8.85 (1 H, s), 7.61–7.35 (7 H, m), 7.09 (2 H, d, *J* = 8.4 Hz), 1.31 (9 H, s); high-resolution MS *m/e* 269.1419, $C_{17}H_{19}NO_2$ requires 269.1415.

1c: IR (neat) 3250, 2974, 1740, 1602, 1491, 1120 cm^{-1}; ^1H NMR (90 MHz, C_6D_6) δ 9.09 (1 H, s), 7.12–6.90 (5 H, m), 1.15 (9 H, s).

Kinetics. Decomposition of **1a–e** was monitored at 25 ± 1 °C in MeOD-d_4 (99.5% deuterated) by ^1H NMR spectroscopy. Reactions were initiated by addition of appropriate amounts of **1** to 0.5 mL of the MeOD-d_4 solution, previously incubated in an NMR tube at 25 °C for at least 0.5 h, to obtain initial concentrations of **1** of ca. 2–3 mM. After the solution was mixed, the NMR tube was placed in the thermostated probe of a 90-MHz NMR and spectral data were obtained at appropriate intervals. Concentrations of **4** and **5** in the range 0.05–1.0 M were obtained by appropriate mixture of these amines with MeOD-d_4. *N,N*-Dimethylaniline (**4**) was purified by vacuum distillation after drying overnight over CaH_2. Anilline (**5**) was purified by a standard method.[8] The resonances for the *tert*-butyl groups of the starting esters and reaction products were well-separated from all other resonances of the NMR spectra of these reaction mixtures (ca. δ 1.5–1.1) and were also well-separated from each other within this chemical shift range. Normalized peak area vs time data were used to obtain pseudo-first-order rate constants (k_{obs}), either by fitting the peak area data to the standard first-order or consecutive first-order rate equation[9] or by a linear least-squares fit of ln [peak area] vs time for the esters **1a–e**. Data were routinely taken for at least 3 half-lives except for the slowest reactions ($k_{obs} \leq 1.0 \times 10^{-6}$ s^{-1}) for which data were obtained for ca. 2 half-lives.

Product Studies. Reaction products for the solvolysis of **1** in MeOH or for the reactions of **1** with **4** and **5** in MeOH were isolated from 10- or 25-mL reaction mixtures containing 1–2 mM **1** and appropriate concentrations of **4** and **5**. The amines were purified as described previously for the kinetics. Reagent-grade MeOH (1.5 L) was purified by initial distillation from ca. 5 g of $NaBH_4$ followed by fractional distillation from ca. 10 g of $Mg(OCH_3)_2$ at a 20/1 reflux ratio. The first and last 10% of the distillate was discarded in both distillations.

Reactions were initiated by addition of ca. 0.1 M benzene solutions of **1** to the appropriate MeOH solution stirred under a N_2 atmosphere. Reaction products were isolated by rotary evaporation of the reaction mixtures after a minimum of 6 half-lives as calculated from the kinetic data. Removal of **4** or **5** required a vacuum of 0.1 Torr. The residue that remained was subjected to preparative layer chromatography on silica gel (CH_2Cl_2 or CH_2Cl_2/EtOAc used as eluents). After initial separation, reaction products were further purified by recrystallization or preparative layer chromatography on silica gel. Reaction products were characterized by ^1H NMR, IR, GC/MS, and HPLC. Materials were identified by comparison to commercially available samples (**8c**, **9c**, **9d**, **10c**), samples synthesized by known procedures (**6c**,[10] **7c**,[11] **8a**,[12] **8d**,[13] **9a**,[14] **10a**,[15] **10d**,[16] **11a**,[17] **11c**,[17] **11d**,[18] **13a**,[19] **13d**,[20] **14**,[21] **16**[22]), samples obtained from an independent synthesis (**15**), or samples previously characterized in this laboratory (**6d–f**,[1c] **7d–f**,[1c] **12d**[1a]). Other materials (**6a**, **6b**, **7a**, **7b**, **12a**) were identified from their spectral data. Details of the identification of **6a**, **6b**, **7a**, **7b**, **12a**, **14**, and **15** follow.

4-Methyl-4′-(*N,N*-dimethylamino)diphenylamine (6a): mp 89–90 °C; IR (KBr) 3377, 3017, 2909, 1612, 1513, 1312, 1177, 806 cm^{-1}; ^1H NMR (90 MHz, CD_2Cl_2) δ 7.47 (2 H, d, *J* = 9.2 Hz), 7.08 (4 H, AA′BB′ q, *J* = 8.8 Hz), 7.03 (2 H, d, *J* = 9.2 Hz), 6.05 (1 H, s, broad), 3.18 (6 H, s), 2.31 (3 H, s); high-resolution MS *m/e* 226.1455, $C_{15}H_{18}N_2$ requires 226.1470.

4-Phenyl-4′-(*N,N*-dimethylamino)diphenylamine (6b): mp 124–126 °C; IR (KBr) 3417, 3020, 2910, 1613, 1529, 1490, 1317, 812, 760 cm^{-1}; ^1H NMR (90 MHz, CD_2Cl_2) δ 7.59 (2 H, d, *J* = 8.8 Hz), 7.56 (2 H, d, *J* = 9.2 Hz), 7.55–7.30 (5 H, m), 7.21 (2 H, d, *J* = 8.8 Hz), 7.16 (2 H, d, *J* = 9.2 Hz), 6.00 (1 H, s, broad), 3.37 (6 H, s); high-resolution MS *m/e* 288.1618, $C_{20}H_{20}N_2$ requires 288.1628.

4-Methyl-2′-(*N,N*-dimethylamino)diphenylamine (7a): brown oil; IR (neat) 3359, 2939, 1594, 1518, 1452, 1299, 743 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.19 (1 H, d, *J* = 7.3 Hz), 7.11–7.08 (3 H, m), 7.05 (2 H, AA′BB′ pattern, upfield portion, *J* = 8.5 Hz), 6.94 (1 H, t, *J* = 7.3 Hz), 6.79 (1 H, t, *J* = 7.3 Hz), 6.45 (1 H, s, broad), 2.66 (6 H, s), 2.30 (3 H, s); high-resolution MS *m/e* 226.1465, $C_{15}H_{18}N_2$ requires 226.1470.

4-Phenyl-2′-(*N,N*-dimethylamino)diphenylamine (7b): yellow oil; IR (neat) 3359, 3030, 2940, 1595, 1523, 1488, 1455, 1326, 749 cm^{-1}; ^1H NMR (90 MHz, CD_2Cl_2) δ 7.6–6.8 (13 H, m), 6.71 (1 H, s, broad), 2.68 (6 H, s); high-resolution MS *m/e* 288.1633, $C_{20}H_{20}N_2$ requires 288.1628.

2-Hydroxy-4-methylpivalanilide (12a): mp 134–136 °C; IR (KBR) 3428, 3092 (br), 1640, 1600, 1537, 1415, 1289 cm^{-1}; ^1H NMR (90 MHz, CD_2Cl_2) δ 8.90 (1 H, s), 7.59 (1 H, s, broad), 6.92–6.70 (3 H, m), 2.28 (3 H, s), 1.33 (9 H, s); high-resolution MS *m/e* 207.1259, $C_{12}H_{17}NO_2$ requires 207.1260.

4-Methoxy-4-methylcyclohexa-2,5-dienone Imine (14). The material was easily detected in methanolysis reaction mixtures of **1a** by GC/MS and ^1H NMR of solvolysis products of **1a** in MeOD-d_4. It always decomposed into a polymeric material upon attempted isolation and purification. An authentic sample of the imine was prepared by a published procedure[21] from *p*-toluidine by treatment with NaN_3 to yield *p*-tolyl azide and by acid-catalyzed methanolysis of the azide. This yielded a sample of **14** contaminated with some polymeric material. Attempts at further purification always lead to decomposition. Spectral characteristics of **14** produced by this method were equivalent to those of the sample generated by solvolysis of **1a**: ^1H NMR (90 MHz, $CDCl_3$) δ 6.24 (4 H, AA′BB′ q, *J* = 10.3 Hz), 3.06 (3 H, s), 2.26 (1 H, s), 1.30 (3 H, s); GC/MS *m/e* 137 (M^+), 122, 106. The compounds generated from the solvolysis reaction and from methanolysis of *p*-tolyl azide both yielded 4-methoxy-4-methylcyclohexa-2,5-dienone[23] upon hydrolysis in 1 mM HCl.

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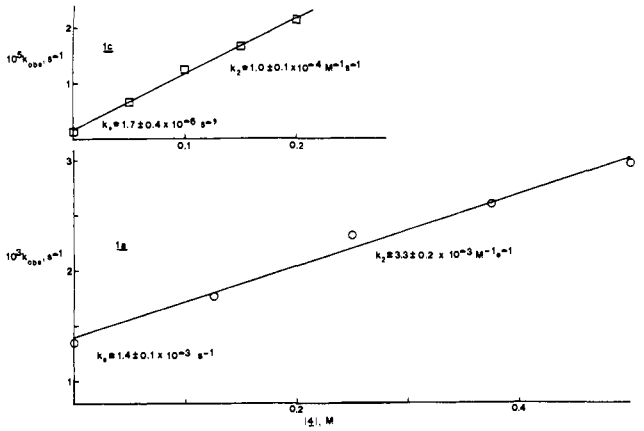


Figure 1. Plots of the pseudo-first-order rate constant (k_{obs}) vs [**4**] for **1a** and **1c** at 25 °C in MeOD-d_4.

4-Methoxy-4-methylcyclohexa-2,5-dienone *N*-Phenylimine (15). 4-Methoxy-4-methylcyclohexa-2,5-dienone[23] (50 mg, 0.36 mmol) and aniline (100 mg, 108 mmol) were combined in 5 mL of dry MeOH. The mixture was stirred under N_2, and 20 μL of BF_3·Et_2O was added. After the mixture was stirred overnight, the MeOH was removed by rotary evaporation and the residue was taken up into 10 mL of CH_2Cl_2. This solution was washed once with 10 mL of H_2O and dried over Na_2SO_4. After concentration of the sample to ca. 1 mL, it was applied to a short (4-cm) column of silica gel. The column was first washed with CH_2Cl_2 and then with EtOAc. The desired product was obtained as a yellow oil (36 mg, 47%) after evaporation of the EtOAc solution: IR (neat) 3050, 2978, 2930, 1602, 1586, 1483, 1088 cm^{-1}; ^{1}H NMR (90 MHz, CD_2Cl_2) δ 7.33–6.26 (9 H, m), 3.13 (3 H, s), 1.36 (3 H, s); GC/MS *m/e* 213 (M^+), 198, 183, 182, 167; high-resolution MS *m/e* 213.1145, $C_{14}H_{15}NO$ requires 213.1155.

Quantification of reaction products was performed by HPLC on a μBondapak C-18 column; MeOH/H_2O (60/40, 70/30, 80/20), containing 0.05 M 1/1 HOAc/KOAc at a flow rate of 1.0 or 1.4 mL/min, was used as the eluent. Peaks were monitored by UV spectroscopy at 250 nm, and extinction coefficients were determined from peak areas of authentic compounds. Analysis was performed by triplicate 5- or 10-μL injections of the reaction mixture, which was initially 1 mM in **1**. Since **4** or **5** often obscured the peaks of interest, these materials were usually removed under vacuum after rotary evaporation of the MeOH. The residue was brought back to volume by addition of MeOH before the analysis was performed. Quantification of reaction products was also performed from ^{1}H NMR peak areas of the kinetic reaction mixtures after 10 half-lives. Further quantification and identification were obtained by GC/MS performed with a Hewlett-Packard 5890 gas chromatograph and 5971A mass-selective detector. The column used in this study was a 25 m × 0.1 mm fused silica column with a 0.1-μm bonded methyl silicone stationary phase.

Cyclic Voltammetry. Cyclic voltammetry was performed with a BAS-100 electrochemical analyzer. The cell was equipped with a Pt or carbon disk working electrode, a Pt wire counter electrode, and a saturated NaCl–SCE reference electrode. The reference compartment was isolated from the working compartment by a cracked-tip glass junction to minimize the introduction of H_2O into the working solution. Measurements were made on **4** and the esters of **1e** and **1f** (ca. 1 mM) in dry DMF containing 0.2 M tetra-*n*-butylammonium perchlorate. The solutions were maintained under a nitrogen atmosphere and were actively out-gassed prior to measurement. Scan rates ranged from 50 to 200 mV/s. Ferrocene was used as an internal standard to calibrate the voltage axis. This eliminated errors arising from variable junction potentials.

Results

The decomposition of **1a–e** in MeOD-d_4 at 25 ± 1 °C in the presence or absence of *N,N*-dimethylaniline (**4**) or aniline (**5**) proceeds in a clean pseudo-first-order fashion for at least 3 half-lives. Initial studies showed that the presence of O_2 had no effect on reaction rates, so no attempt to remove O_2 was made in the kinetic study. The first-order rate constant (k_{obs}) is dependent on the concentration of **4** or **5** as shown in Figure 1 for **1a** and **1c**. The rate data were fit to eq 5 to obtain the solvolysis

$$k_{obs} = k_s + k_2[\text{amine}] \quad (5)$$

rate constant (k_s) and the second-order rate constant for the reaction of **1** with **4** or **5** (k_2). We previously demonstrated similar kinetics for the reaction of **1d–f** with **4**.[1c] These rate constants are gathered in Table I.

Table I. Solvolysis Rate Constants and Second-Order Rate Constants for the Reactions of **1** with **4** and **5** in MeOD-d_4 at 25 °C

		k_2, M^{-1} s^{-1}	
ester	k_s, s^{-1}	**4**	**5**
1a	$(1.4 \pm 0.1) \times 10^{-3}$	$(3.3 \pm 0.2) \times 10^{-3}$	$(1.7 \pm 0.1) \times 10^{-3}$
1b	$(1.1 \pm 0.1) \times 10^{-3}$	$(3.7 \pm 0.2) \times 10^{-3}$	$(1.1 \pm 0.2) \times 10^{-3}$
1c	$(1.7 \pm 0.4) \times 10^{-6}$	$(1.0 \pm 0.1) \times 10^{-4}$	$(3.1 \pm 0.3) \times 10^{-5}$
1d	$(1.0 \pm 0.2) \times 10^{-6}$ [a]	$(1.1 \pm 0.1) \times 10^{-4}$ [a]	$(2.2 \pm 0.1) \times 10^{-5}$
1e	$<1.0 \times 10^{-7}$ [b]	$(3.4 \pm 0.2) \times 10^{-5}$ [a]	$(1.0 \pm 0.1) \times 10^{-5}$
1f		$(1.8 \pm 0.3) \times 10^{-6}$ [a]	

[a] From ref 1c. [b] No reaction was observed over a period of 50 h at 25 °C.

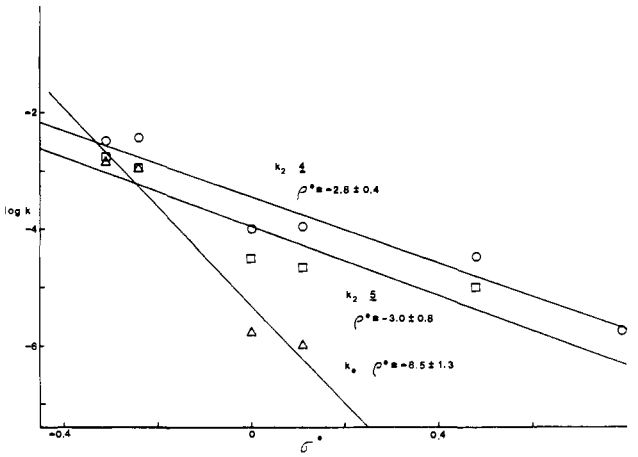


Figure 2. log k_s and log k_2 vs σ^+ for **1a–f** at 25 °C in MeOD-d_4. Circles for k_2 for reaction with **4**, squares are k_2 for reaction with **5**, and triangles are k_s.

A plot of log k_s or log k_2 vs the σ^+ parameter for the ring substituents of **1a–f** is shown in Figure 2. The correlations, particularly for k_2, are modest, but it is clear that the second-order processes are much less sensitive to ring substituents than the solvolysis reactions. The value of ρ^+ for k_s of −8.5 ± 1.3 is in the range expected for nitrenium ion processes in H_2O and alcohols.[1,7,24]

Although the disappearance of **1**, monitored by the change in area of the *tert*-butyl peak of the ester, is always first-order in nature, the appearance of some solvolysis products does not show simple first-order kinetics for all the compounds studied. Figure 3 shows a portion of the NMR spectrum of the solvolysis reaction mixture for **1a** in MeOD-d_4, which contains the *tert*-butyl resonances of **1a** and its solvolysis products. The disappearance of **1a** (δ 1.29) and the appearance of pivalic acid (δ 1.19) exhibit simple first-order behavior as shown in Figure 4, which displays normalized ^{1}H NMR peak areas for **1a** and its solvolysis products as a function of time at 15 °C. The rate constants obtained from a nonlinear least-squares fit of the two data sets to the first-order rate equation are equivalent within experimental error (Figure 4). The methyl resonance of 4-methoxy-4-methylcyclohexa-2,5-dienone imine (**14**) appears in this region at δ 1.35, and its appearance is also characterized by a simple first-order pattern (not shown in Figure 4) and a rate constant of $(5.8 \pm 0.2) \times 10^{-4}$ s^{-1} at 15 °C. This is experimentally equivalent to those observed for **1a** and pivalic acid.

The appearance of 2-hydroxy-4-methylpivalanilide (**12a**; δ 1.31 in Figure 3) does not follow a first-order pattern but is adequately fit by the equation for two consecutive first-order processes. One

(24) (a) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 2567–2569. (b) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1972**, *94*, 3891–3896. (c) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498, 1499. (d) Panda, M.; Novak, M.; Magonski, J. *J. Am. Chem. Soc.* **1989**, *111*, 4524, 4525.

Table II. Yields of Solvolysis and Substitution Products for **1a** at 25 °C

conditions	% yield[a]									
	12a	**13a**	**14**	**6a + 7a (calc)**[b]	**6a + 7a (obs)**	**6a/7a**	**8a**	**9a**	**10a**[c]	**15**
MeOH	25 ± 2	7 ± 1	63 ± 4							
0.125 M **4**	*d*	*d*	*d*	23 ± 2	20 ± 1	2.05				
0.250 M **4**	16 ± 1	4 ± 1	35 ± 2	37 ± 3	35 ± 1	2.02				
0.375 M **4**	*d*	*d*	*d*	47 ± 4	47 ± 1	2.15				
0.500 M **4**	10 ± 1	3 ± 1	25 ± 2	54 ± 4	53 ± 1	2.19				
1.0 M **5**	14 ± 1	*d*	*d*				15 ± 1[e]	2.7 ± 0.6[e]	33 ± 1[e]	12 ± 2

[a] Concentration of **1a** ca. 1.0 mM. Yields determined by triplicate injections on μ Bondapak C-18 HPLC column or from NMR peak areas (**12a**, **13a**, and **14**) after completion of the reaction. [b] Calculated from the kinetic data of Table I. [c] Combined yield of **10a** and its oxidation product **11a**. [d] Not determined. [e] Calculated combined percent yield of **8a**, **9a**, and **10a** from the kinetic data of Table I is 55 ± 4% at 1.0 M **5**.

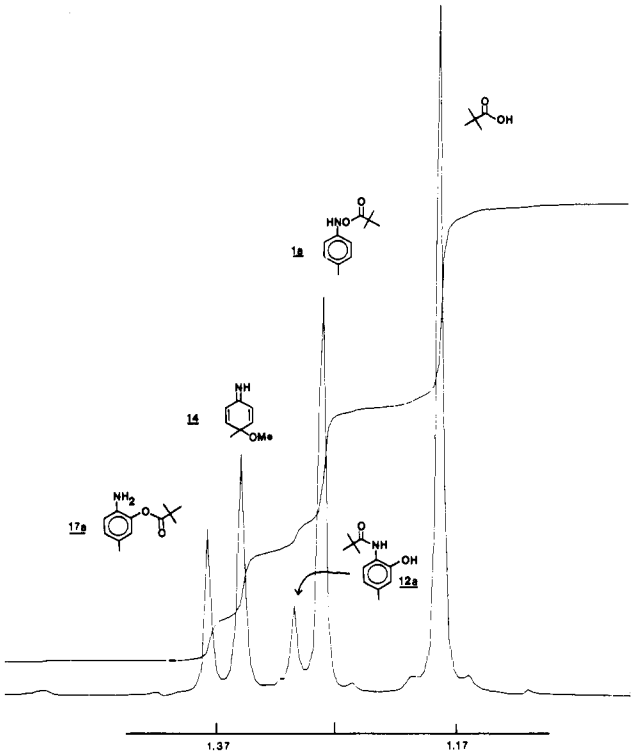


Figure 3. Portion of the ^{1}H NMR spectrum obtained during the solvolysis of **1a** in MeOD-d_4.

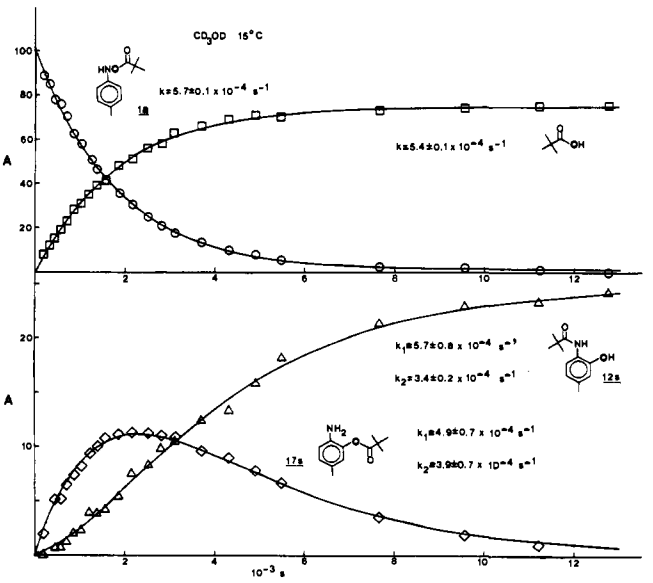
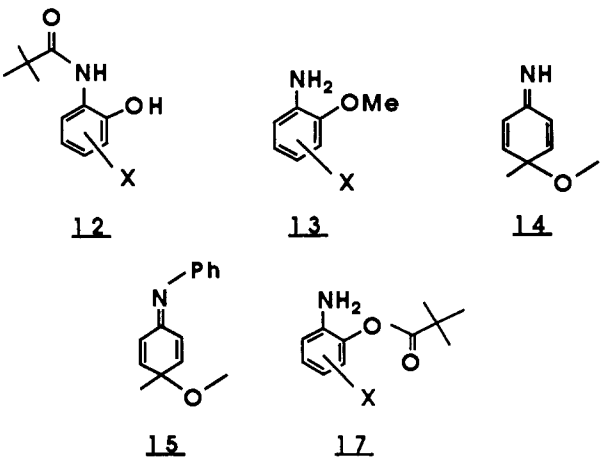


Figure 4. Normalized peak areas vs time for **1a** and several of its solvolysis products taken during the decomposition of **1a** in MeOD-d_4 at 15 °C. Rate constants were obtained by nonlinear least-squares fits to appropriate rate equations.

of the two rate constants obtained from this fit, $(5.7 \pm 0.8) \times 10^{-4}$ s^{-1}, is equivalent to the first-order rate constant obtained from **1a**, pivalic acid, and **14**. The other, $(3.4 \pm 0.2) \times 10^{-4}$ s^{-1}, is unique. A transient species gives rise to the peak at δ 1.39 (Figure 3). Data in Figure 4 show that this material initially builds up to ~12% of the total normalized *tert*-butyl peak area and then slowly decays away. A fit of these data to the equation for consecutive first-order processes generates two rate constants that are in good agreement with those obtained for **12a** (Figure 4). A transient species isomeric with **1a** and **12a** can also be observed by GC/MS at early reaction times. In addition to the molecular ion (*m/e* 207), prominent ions at *m/e* 57 ($(CH_3)_3C^+$) and 123 ($CH_3C_6H_3(NH_2)OH^{\bullet+}$) are also observed for this species. The transient species has been identified as the ester **17a**. This identification is based, in part, on our previous observation and characterization of a similar intermediate, **17d**, that is generated during the hydrolysis of **1d**.[1a] This intermediate rearranges in H_2O into the corresponding amide, **12d**.[1a]

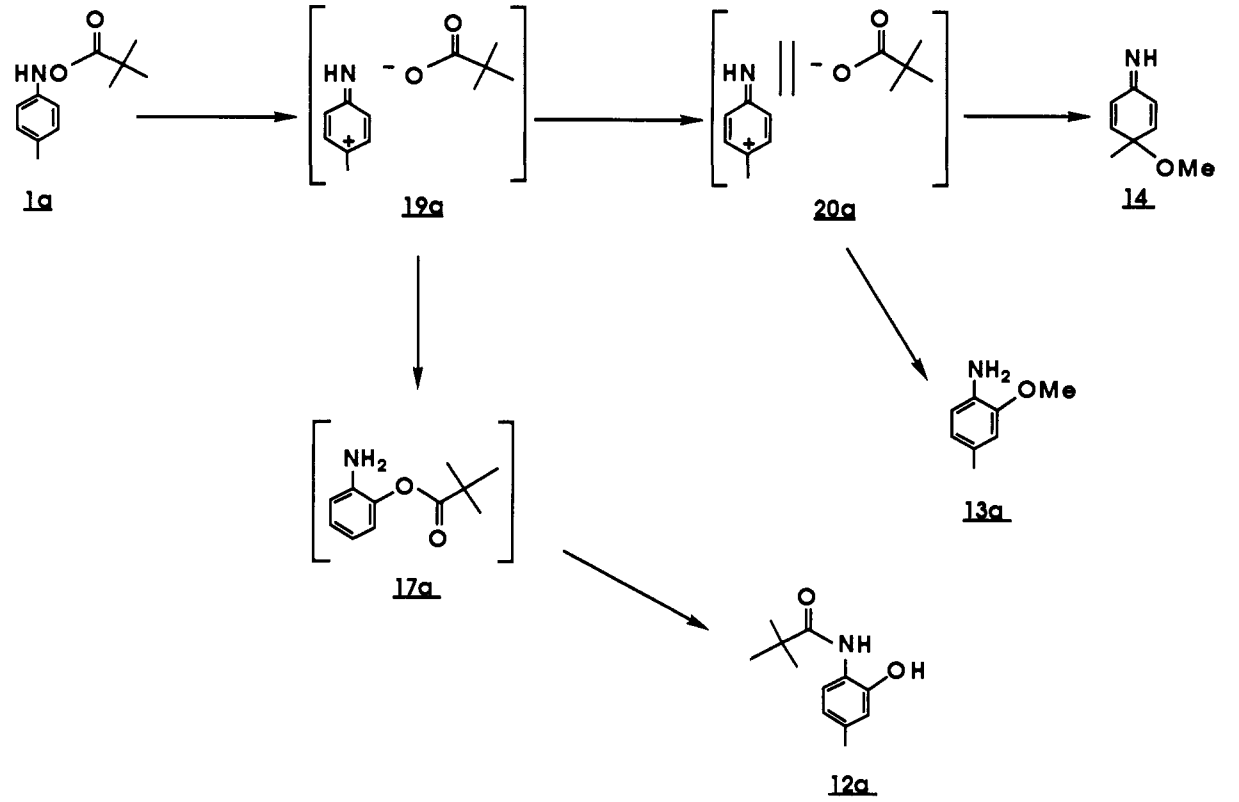


Similar results were obtained for the biphenyl ester **1b**, but no transient species were observed during the methanolysis reactions of **1c** and **1d** that proceed much more slowly than the methanolysis of **1a** or **1b** (Table I).

Results of detailed product studies carried out with **1a** are presented in Table II. In the absence of **4** or **5**, the major solvolysis products are **12a** and **14**. ^{1}H NMR of solvolysis reaction mixtures of **1a** in MeOD-d_4 show that the yields of **12a** and **14** are constant within the concentration range of **1a** of 10^{-4}–10^{-2} M. The minor product **13a** is also detected. Similar products were observed by Gassman and co-workers from the silver ion promoted methanolysis of *N-tert*-butyl-*N*-chloro-*p*-toluidine.[25] The yields of these materials decrease as the concentration of **4** increases, and two new products, the diphenylamines **6a** and **7a**, are generated. The data of Table II show that the combined yields of **6a** and **7a** are in excellent agreement with those predicted from the kinetic data if it is assumed that these materials are generated by the second-order process involving **1a** and **4**. There is very good

(25) Gassman, P. G.; Campbell, G. A.; Frederick, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 7377, 7378; **1972**, *94*, 3884–3891.

Scheme I

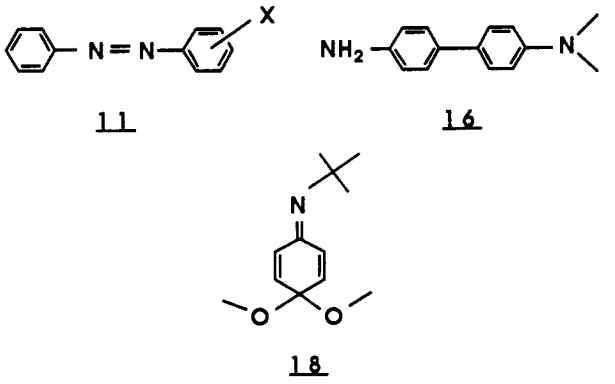


agreement between calculated and predicted yields in the concentration range of **4** of 0.125–0.500 M. The ratio of **6a**/**7a** is independent of the concentration of **4** at 2.1 ± 0.1. When **4** is replaced by **5**, the analogous products **8a** and **9a** are generated, as well as the hydrazine **10a**. Small amounts of the azo compound **11a** were also detected, but control experiments with authentic **10a** show that this material undergoes some oxidation during the workup leading to analysis. The yield reported in Table II for **10a** is the combined yield of **10a** and **11a**. All other solvolysis and substitution products were shown to be stable to the reaction conditions by appropriate control experiments except **14**, which is converted into the *N*-phenylimine **15** in the presence of **5**. At 1.0 M in **5**, it appears that essentially all of **14** is converted into **15**, but at lower concentrations of **5** significant amounts of both **14** and **15** can be detected by ^{1}H NMR of reaction mixtures.

The yield of **15** reported in Table II is about half that expected from the data for the ratio **14**/**12a** under other conditions. This is probably due to the loss of some of **15** during the removal of **5** under vacuum before analysis. The GC/MS results show that **15** is a relatively volatile compound compared to the other reaction products. The combined yield of **8a**, **9a**, and **10** of 51 ± 2% is in good agreement with the 55 ± 4% yield expected for the substitution products from the kinetic results.

Analyses of the yields of substitution products generated from **1b–d** in the presence of **4** and **5** are presented in Table III. We previously showed that the decomposition of **1d–f** in the presence of **4** led to formation of the corresponding diphenylamines **6** and **7**.[1c] In all cases, high combined yields of the substitution products are observed. In addition, decomposition of **1c** in the presence of **4** leads to the detection of a low yield of *N,N*-dimethylbenzidine (**16**). No other significant (>1% yield) substitution products were detected by either HPLC or GC/MS of the reaction mixtures of **1b**, **1c**, or **1d** after removal of **4** or **5** under vacuum.

The solvolysis products of **1d** were also investigated. The two major products were **12d**, detected in 56 ± 2% yield, and **13d**, detected in 32 ± 2% yield. In the silver ion promoted methanolysis of *N*-*tert*-butyl-*N*,*p*-dichloroaniline, Gassman and co-workers found evidence for a low yield (~10%) of the 4,4-dimethoxycyclohexa-2,5-dienone imine (**18**).[25] No similar product was detected in this study, but low yields of such a material may have escaped detection.



Cyclic voltammetry in DMF containing 0.2 M tetra-*n*-butylammonium perchlorate provided peak potentials for the oxidation of **4** and reduction of **1e** and **1f**. All of these processes were irreversible under the conditions of the experiment, but peak potentials were essentially invariant to scan rates in the range of 50–200 mV/s. Ferrocene was used as an internal standard to calibrate these potentials since the potential of the ferrocene/ferrocenium couple under these conditions is known to be +0.31 V vs SCE.[26] At 100 mV/s scan rate, the calibrated peak potentials were +0.67 V for the oxidation of **4**, −2.00 V for the reduction of **1e**, and −1.95 V for the reduction of **1f**.

Discussion

The methanolysis of **1** exhibits all the characteristics of a nitrenium ion process. The large sensitivity of k_s to ring substituents ($\rho^+ = -8.5$), the products derived from nucleophilic attack of solvent on the aromatic ring (**13**, **14**), and the rearrangement products (**17** → **12**) have all been taken as evidence in other cases for the involvement of nitrenium ion intermediates.[1,7,9,24,25] The

(26) Gassman, P. G.; Macomber, P. W.; Hershberger, J. W. *Organometallics* **1983**, *2*, 1470–1472.

Table III. Yields of Substitution Products of **1b**, **1c**, and **1d** in the Presence of **4** or **5**[a]

ester	conditions	% yield[b] 6	7	8	9	10[c]	16	predicted % yield of combined substitn prod[d]
1b	1.0 M **4**	62 ± 2	19 ± 1					79 ± 2
1c	1.0 M **4**	45 ± 2	50 ± 1				3.0 ± 0.3	98 ± 1
1c	1.0 M **5**			29 ± 2	2.7 ± 0.3	41 ± 1		95 ± 1
1d	3.7 M **4**[e]	72	10					>99
1d	1.0 M **5**			46 ± 1	3.4 ± 0.1	38 ± 2		96 ± 1

[a] Ca. 1.00 mM in **1**. T = 25 °C. [b] Determined by HPLC except where indicated. [c] This is the combined yield of **10** and **11**, its oxidation product, which is always present in small amounts. [d] Calculated from the data of Table I. [e] These yields are from ref 1c and are isolated yields of the two diphenylamines.

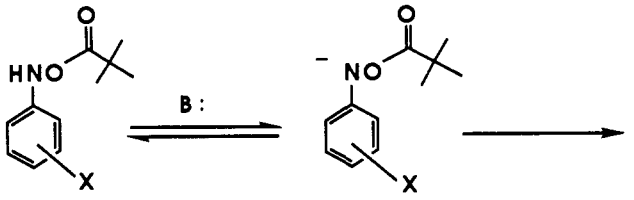
products obtained in this study are, in particular, very similar to those observed by Gassman and co-workers for the alcoholysis of ring-substituted *N-tert*-butyl-*N*-chloroanilines.[24a,b,25] A mechanism for the methanolysis of **1a** that is consistent with all available data is presented in Scheme I. The tight ion pair, **19a**, generated by heterolysis of the N–O bond of **1a** can undergo internal return to **17a**, which subsequently rearranges to **12a**. The kinetic data shown in Figure 4 clearly show that **12a** is generated in a two-step process from a detectable intermediate that we have identified as **17a**. The observation that the yield of **12a** is independent of the initial concentration of **1a** in the concentration range 10^{-4}–10^{-2} M indicates that **12a** is generated by essentially intramolecular processes. The tight ion pair can also collapse to a solvent-separated ion pair, **20a**, that can be attacked by solvent to generate **13a** and **14**. A similar mechanism can explain the methanolysis products of **1d**. McClelland has shown that the 2,6-(dimethylphenyl)nitrenium ion has a significant lifetime in H_2O ($t_{1/2} \approx 10^{-9}$ s),[27] so it is likely that **1a–d** generate discreet ionic species in MeOH. The solvolysis of **1e** and **1f** in MeOH was not investigated for this study due to the slowness of these reactions, but it is possible that the solvolysis of these species occurs without the intermediacy of nitrenium ions, which would be expected in these two cases to have vanishingly short lifetimes.[28]

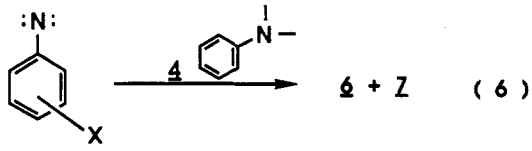
One difference between our results and those of Gassman is that we do not detect the aniline derivatives **21** that were always significant products of the alcoholysis of *N-tert*-butyl-*N*-chloroanilines.[24a,b,25] These compounds were initially thought to be derived from H• abstraction by triplet ions formed by spin inversion in the initially formed singlet ions,[24,25] but calculations now suggest that for arylnitrenium ions the triplet ions are at much higher energy than the singlet species.[29] We have shown that the esters **1** are susceptible to direct reduction to the corresponding anilines by a number of species, including Fe^{2+} and Cu^{1+},[1a,b] and nitrenium ions themselves are also easily reduced by a variety of reagents, including I^-.[30] It appears likely that the reduction products observed in the earlier studies are due to direct reduction of the *N*-chloroanilines, or of the singlet nitrenium ions derived from them, by minor impurities present in the solvent.

The data in Table II indicate that **4** or **5** does not significantly compete with MeOH for the ion-pair intermediate **20a** under our reaction conditions. The products **6a–10a** are generated in biomolecular processes not involving a nitrenium ion (see the following text), and GC/MS results indicate that no other products isomeric with these are generated in yields greater than 1% under any of our reaction conditions. On the basis of these observations and an approximate concentration of 25 M for MeOH in the dilute solutions used here, we can estimate that the upper limit for the ratio of the bimolecular rate constants for trapping of **20a** by **4** or **5** and MeOH is ca. 2.

We have now documented that the esters **1a–f** react with *N*,*N*-dimethylaniline (**4**) and aniline (**5**) in MeOH to generate products of apparent nucleophilic substitution at the nitrogen of the ester (**6–10**). The correlation of the product study and kinetic data (Table II) shows that these materials are generated in the kinetically second-order process observed by ^{1}H NMR. The kinetic data are not consistent with nucleophilic attack of **4** or **5** on a nitrenium ion formed by rate-limiting N–O bond heterolysis. A number of other mechanistic possibilities may be considered.

Base-induced α-elimination to generate the nitrene **21**,[1d] followed by trapping with **4** is a possible source of **6** and **7** (eq 6). This is a known reaction of *p*-(nitrophenyl)nitrene and a number of other electron-deficient arylnitrenes.[31] The reaction apparently





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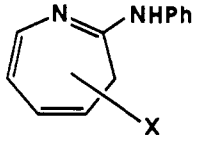
does not occur with less electron-deficient species such as phenylnitrene or p-tolylnitrene, and always leads to greater yields of the ortho product **7**.[31] In this study, **6** and **7** are generated in high yield throughout the series **1a–f** and the para isomer, **6**, is generally the major isomer. In the presence of primary aromatic amines such as **5**, arylnitrenes are known to form aminoazepines (**22**),[32,33] but no such products were detected in this study. The available evidence does not support a nitrene mechanism.



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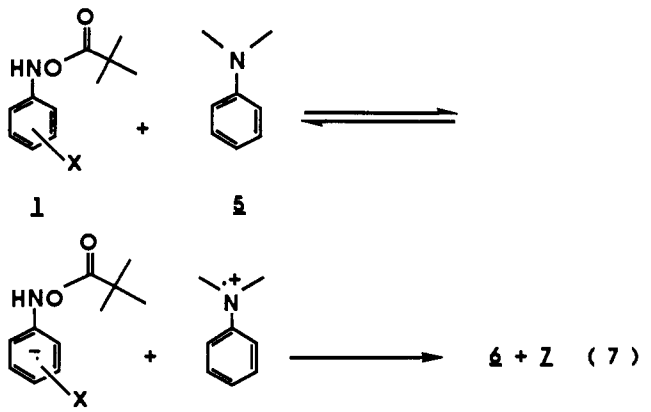
A single-electron transfer (SET) mechanism (eq 7) might also account for the reaction products; however, results from the cyclic voltammetry studies indicate that electron transfer from **4** to **1** is very unfavorable in DMF. For example, the potential for electron transfer from **4** to **1e** is ca. −2.7 V according to the voltammetric results. This corresponds to an equilibrium constant of 2×10^{-46} at 25 °C. If we assume a rate constant for electron transfer in the thermodynamically favorable direction of 10^{11} M^{-1}

(27) Fishbein, J. C.; McClelland, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 2824, 2825.
(28) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689–4691. Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361–1372.
(29) Ford, G. P.; Scribner, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 4281–4291.
(30) Pelecanou, M.; Novak, M. *J. Am. Chem. Soc.* **1985**, *107*, 4499–4503.
(31) Abramovitch, R. A.; Scriven, E. F. V. *J. Chem. Soc., Chem. Commun.* **1970**, 787, 788. Abramovich, R. A.; Challand, S. R.; Scriven, E. F. V. *J. Org. Chem.* **1972**, *37*, 2705–2710.
(32) Huisgen, R.; Vossius, D.; Appl, M. *Chem. Ber.* **1958**, *91*, 1–12. Huisgen, R.; Appl, M. *Chem. Ber.* **1958**, *91*, 12–21.
(33) Boche and co-workers have demonstrated aminoazepine formation from the reaction of certain *N*-arylhydroxylamine derivatives and aliphatic amines: Bosold, F.; Boche, G.; Kleemiss, W. *Tetrahedron Lett.* **1988**, *29*, 1781–1784.



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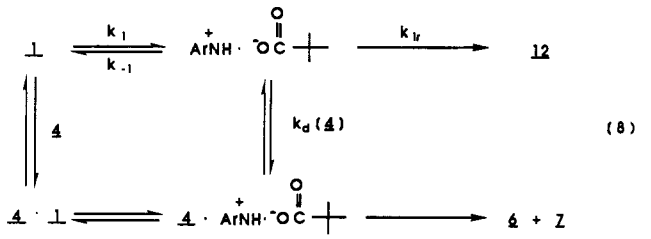
6 + Z (7)

s^{-1},[34] then the rate constant for electron transfer from **4** to **1e** in DMF is 2×10^{-35} M^{-1} s^{-1}. Since the voltammetry of **4** and **1** was irreversible, the peak potentials observed may include significant overvoltages so that −2.7 V represents an upper limit to the true potential. Solvation differences in transferring from DMF to MeOH may also affect the thermodynamics of electron transfer, but the observed rate constant for the reaction of **4** and **1e** in MeOH of 3.4×10^{-5} M^{-1} s^{-1} would require a potential for electron transfer of −0.9 V. It is unlikely that overvoltages or the solvent changes could account for that big a difference in potential. The SET mechanism appears to be unlikely on the basis of this evidence and the observed substituent effect for the bimolecular reactions. The *p*-nitro ester, **1f**, should be the most efficient one-electron acceptor in the series and should react with **4** via a SET mechanism at the largest rate. The data of Table I show that, in fact, it has the smallest rate constant for bimolecular reaction with **4** of the series **1a–f**.

An S_N1 mechanism could exhibit bimolecular kinetics if there is rate-limiting trapping of an ion-pair intermediate or preassociation of the substrate and nucleophile (nucleophile-assisted ionization) (eq 8).[35] Rate-limiting trapping of the ion-pair intermediate would require that k_d[**4**] (or k_d[**5**]) be competitive with or greater than k_{ir} throughout the series **1a–f** since k_2/k_s (Table I) provides a lower limit for k_d/k_{ir}. We have previously shown that nucleophiles and other trapping species do not effectively compete with internal return of a tight ion pair for nitrenium ion sulfate or pivalate ion pairs in aqueous solution.[1,7,9,36] It would also be unlikely that the conditions for rate-limiting trapping of the ion pair, k_d[**4**] (or k_d[**5**]) $\ll k_{-1}$, hold throughout the series **1a–f** at concentrations of **4** or **5** in the range 0.05–1.0 M. The preassociation mechanism would only be expected in cases in which the nitrenium ion is relatively unstable,[35] but bimolecular kinetics are observed throughout the series **1a–f**. In addition, this mechanism would require that **4** or **5** be between 30 and 3.0×10^3 fold more effective at assisting ionization than MeOH in the series **1a–d** in which the methanolysis rate constant was accurately determined. The observed sensitivity to ring substituents for these reactions ($\rho^+ = -2.8$ for **4** and −3.0 for **5**) is significantly smaller than that observed for nitrenium ion processes under a variety of similar conditions ($\rho^+ \approx -5$ to −8)[1,7,24] and is much smaller than that observed for the methanolysis of **1** under the same conditions ($\rho^+ = -8.5$).



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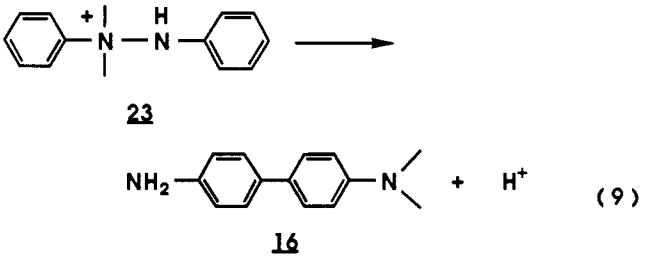
The low sensitivity of k_2 to ring substituents indicates significant bond formation between **4** or **5** and **1** in the rate-limiting step. The kinetic results and other observations are most consistent with an S_N2 mechanism. Such a mechanism has been invoked previously by ourselves for the reaction of **1d–f** with **4**,[1c] by Okamoto for the reaction of activated aromatics with arylhydroxylamines in trifluoroacetic acid[37] and by Boche and co-workers to explain the bimolecular kinetics of eq 3,[5] but this is the first study to provide evidence for an S_N2 reaction at nitrogen competing with S_N1 solvolysis of *N*-arylhydroxylamine derivatives over a range of reactivity spanned by the esters **1a–f**.

The lack of any apparent S_N2 reaction of **1a–d** with MeOH may be a function of the relative weakness of the N–O bond and the kinetic stability of the nitrenium ion.[27] We expect that there will be a change in mechanism for the solvolysis of these esters as the nitrenium ion lifetime approaches that of a molecular vibration.[28] A study of the solvolysis of **1e**, **1f**, and other members of this series containing electron-deficient substituents will commence shortly.

The data of Tables II and III clearly show that **5** can act as both a carbon and nitrogen nucleophile toward **1**. The ratio of products of attack of nitrogen vs attack of carbon varies from 1.9 ± 0.1 for **1a** to 0.8 ± 0.1 for **1d**. Nucleophilic attack of the nitrogen of **4** could not lead to a stable neutral product directly, but the cationic hydrazine derivative generated in such a process might lead to a stable product via a benzidine rearrangement. In particular, the hydrazine derivative generated from attack of the nitrogen of **4** on **1c**, **23**, would be expected to rearrange predominately into *N*,*N*-dimethylbenzidine (**16**; eq 9).[38] In fact, **16** is



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16 (9)

detected in low yield (3.0 ± 0.3%) among the reaction products of **4** and **1c**. Products similar to the diphenylamines **6** and **7** are often formed during the acid-catalyzed rearrangements of *N*,*N*′-diarylhydrazines, but the ortho product always predominates in these cases and the para product is always a minor constituent of the product mixture.[38] It may be that some of the ortho product **7** is formed by rearrangement of **23** or a similar intermediate derived from the other esters, but it does not appear that this could be a source of the high yields of **6** observed in all cases. The ratio **6**/**7** is always somewhat lower than the corresponding ratio **8**/**9** for the analogous products obtained from the reaction of **5** with **1**. For example, **6**/**7** is 2.1 ± 0.1, while **8**/**9** is 5.6 ± 1.3 for **1a**. The lower ratio of **6**/**7** may indicate that some of **7** is derived from rearrangement of an initially formed hydrazine derivative. Control experiments do confirm that **10** does not rearrange into **8** or **9** under our reaction conditions. It is perhaps surprising that the ortho and para carbons compete with the $-NH_2$ in the reactions of **5** with **1** since direct attack of $-NH_2$ on **1** yields a stable hydrazine **10** after deprotonation. The greater thermodynamic stability of the C–N bond compared to the N–N bond[39] may play a role in stabilizing the transition state leading to the products **8** and **9**.

Boche and co-workers have reported that *O*-pivaloyl- and *O*-acetyl-*N*-arylhydroxylamines similar to **1a–f** react with *N*-methylaniline to generated hydrazines **24** and materials with structures **25** and **26**.[3,5,40] They do not report diphenylamine

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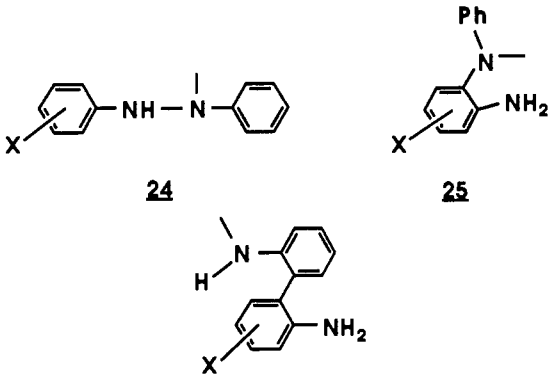
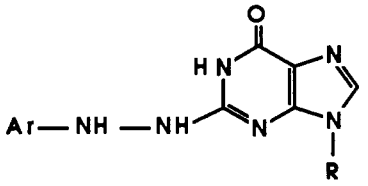


24 25

26

derivatives similar to **6**–**9**. Their reaction conditions, neat *N*-methylaniline or *N*-methylaniline with small amounts of polar solvents, are quite different from our dilute solutions of **4** or **5** in MeOH. Although compounds similar to **25** or **26** are not major constituents of our reaction mixtures, GC/MS results do show low yields (<1%) in some cases of unidentified materials that are isomers of the major products. These may be compounds analogous to **25** or **26**. Since both **25** and **26** are among the products expected from a benzidine-type rearrangement of the *N*-methylhydrazine (**24**),[38] they may not be initial reaction products and their detection must not be over interpreted until it has been demonstrated that they are not derived from **24**.

This study has demonstrated that S_N2 nucleophilic substitution by neutral carbon and nitrogen nucleophiles can occur in competition with S_N1 solvolysis in a polar solvent even on the highly reactive esters **1a** and **1b**. This is particularly important because these esters have overall reactivity very similar to the putative carcinogens **2a**–**c**.[3] These materials are known to generate the "C-8 adducts" **3** and other adducts such as the hydrazine **27** in



27

low yield when incubated with deoxyguanosine in mixed-solvent systems.[3] The same adducts have been isolated from in vivo and in vitro studies employing the corresponding amines or hydroxylamines.[4] Since nucleophilic substitution on nitrenium ions in aqueous or alcoholic solvents has been shown invariably to occur on the aromatic ring and not the nitrogen.[1,7,9,24,25] these adducts are not likely to be generated from nitrenium ion intermediates, This study indicates that S_N2 substitution on the nitrogen of **2** can account for such products. We are currently examining the reactions of **1a**–**c** with other nucleophiles to further delineate the characteristics of the S_N2 reaction.

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Registry No. 1a, 132540-70-6; **1b**, 119273-48-2; **1c**, 114838-64-1; **1d**, 116278-63-8; **1e**, 116278-64-9; **1f**, 88867-70-3; **4**, 121-69-7; **5**, 62-53-3; **6a**, 132540-71-7; **6b**, 132540-72-8; **7a**, 132540-73-9; **7b**, 132540-74-0; **12a**, 98922-98-6; **14**, 132540-75-1; **15**, 132540-76-2.

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