Reactivity and Selectivity of Nitrenium Ions Derived from Ester Derivatives of Carcinogenic *N*-(4-Biphenylyl)hydroxylamine and the Corresponding Hydroxamic Acid

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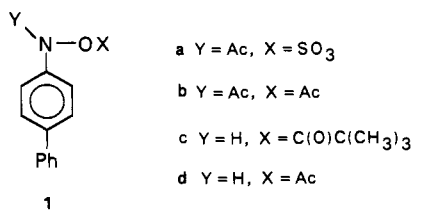
Received May 14, 1993®

Abstract: *N*-Acetyl-*N*-(sulfonatooxy)-4-aminobiphenyl (**1a**) and *N*-(4-biphenylyl)-*O*-pivaloylhydroxylamine (**1c**) decompose in 5% CH_3CN/H_2O, μ = 0.5 M, at 20 °C via rate-limiting N–O bond heterolysis to generate the nitrenium ion intermediates **2a** and **2b**, respectively. Addition of Cl^- (≤0.5 M) or N_3^- (≤0.05 M) causes a marked decrease in the yields of all hydrolysis products derived from **1a** and **1c**, except the rearrangement products **10a** and **11**, without any change in the hydrolysis rate constants. At 0.5 M Cl^- more than 75% of the trappable hydrolysis products of **1a** are replaced by the chloro adduct **7a** without any observable change in the hydrolysis rate constant, and at 0.025 M N_3^- 96% of the trappable hydrolysis products of **1a** are replaced by the azide adduct **8a**, again, without an observable change in the hydrolysis rate constant. Similar results are obtained for **1c**. The nucleophile/solvent selectivity ratios, k_{Cl}/k_s and k_{az}/k_s, are 7.4 ± 0.3 M^{-1} and (1.02 ± 0.04) × 10^3 M^{-1}, respectively, for **2a**. For **2b** k_{Cl}/k_s is 15.7 ± 0.8 M^{-1} and k_{az}/k_s is (2.9 ± 0.2) × 10^3 M^{-1}. If k_{az} is at the diffusion controlled limit of 5 × 10^9 M^{-1} s^{-1}, k_s for **2a** is 4.9 × 10^6 s^{-1}, and k_s for **2b** is 1.7 × 10^6 s^{-1}. Both of these ions are considerably less labile to solvent attack than 1-phenylethyl or cumyl carbocations with a 4-phenyl substituent. Surprisingly, **2a** and **2b** differ in their reactivity to solvent by only a factor of 3, while the estimated rate constants for their generation from starting materials with identical leaving groups differ by a factor of 10^6. This phenomenon is similar to the situation previously observed by Richard for 1-aryl-2,2,2-trifluoroethyl and 1-arylethyl carbocations and may be due to similar factors. A detailed mechanism for the hydrolysis of **1a** and **1c**, which is consistent with all available experimental data, is presented. The implications of these results for the mechanisms of chemical carcinogenesis by *N*-arylhydroxylamine derivatives are discussed.

It has been recognized for quite some time that ester derivatives of *N*-arylhydroxamic acids and *N*-arylhydroxylamines such as **1a–d** are ultimate carcinogens in mammals, including humans.[1,2]



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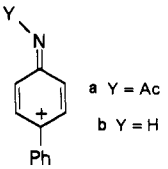

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These species are active *in vivo* without further metabolism.[1] It has been widely assumed that these materials cause genetic damage by reaction of the nitrenium ion derived from N–O bond heterolysis with nucleophilic sites on the DNA bases.[1] Structures of adducts derived from the reactions of the carcinogens with DNA are not inconsistent with this hypothesis,[1,3] but other mechanisms could also account for the formation of these adducts. Indeed, similar adducts are derived from the S_N2 reaction of simple aromatic amines with *N*-aryl-*O*-pivaloylhydroxylamines in MeOH or with *N*-(4-cyanophenyl)-*O*-(diphenylphosphinoyl)-hydroxylamine in THF.[4]

Nitrenium ions can serve as the intermediates for efficient reaction with DNA or other cellular nucleophiles only if they are trapped by solvent at a slow enough rate that these nucleophiles can effectively compete with the solvent. Lifetimes of reactive cations in aqueous solution can be determined by application of the "azide clock" method, which provides k_{az}/k_s, the ratio of the second-order rate constant for trapping of the cation by N_3^- and the pseudo-first-order rate constant for trapping by solvent.[5] McClelland has recently shown that, for a series of diarylmethyl and triarylmethyl carbocations generated by laser flash photolysis at 20 °C in CH_3CN/H_2O, k_{az} reaches a diffusion limited value of ca. 5 × 10^9 M^{-1} s^{-1}, as long as $k_s \geq 10^5$ s^{-1}.[6] The lifetime, $1/k_s$, of reactive cations can then be estimated from k_{az}/k_s data and

* Abstract published in *Advance ACS Abstracts*, September 1, 1993.

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0002-7863/93/1515-9453$04.00/0

the approximate diffusion-limited value of k_{az} of 5×10^9 M^{-1} s^{-1}. The few applications of this procedure to simple *N*-arylnitrenium ions suggest that these species may be very short-lived, nonselective electrophiles which are unlikely to be responsible for the *in vivo* effects of the carcinogenic esters.[7] The estimated values of k_s for the phenylnitrenium ion and (2,6-dimethylphenyl)nitrenium ions are 5×10^9 and 7×10^8 s^{-1}, respectively.[7] The former value indicates that a nucleophile reacting with phenylnitrenium ion in aqueous solution at a diffusion-limited rate could trap only about 50% of the ion at a nucleophile concentration of 1 M.

Measurements of k_{az}/k_s have not yet been reported for nitrenium ions derived from carcinogenic esters of *N*-arylhydroxamic acids and *N*-arylhydroxylamines. In this paper we show that the ultimate carcinogen **1a**[2] and the model carcinogen **1c** undergo hydrolysis in aqueous solution to produce the long-lived and highly selective nitrenium ions **2a** and **2b**, with k_{az}/k_s of 1.0×10^3 and 2.9×10^3 M^{-1}, respectively. The model compound **1c** was used in place of the ultimate carcinogenic metabolite **1d**[2] because of the known tendency of acetic acid esters of this type to undergo acyl transfer reactions which complicate the interpretation of kinetic and product data. Indeed, Underwood and co-workers have previously shown that **1b** undergoes exclusive C–O bond cleavage in 40% aqueous acetone to yield the corresponding hydroxamic acid.[8] The data presented here show that **2a** and **2b** are capable of reacting selectively with low concentrations of nucleophiles in an aqueous medium and could be responsible for the *in vivo* reactions of the ultimate carcinogens **1a** and **1d**.

Experimental Section

The syntheses of **1a** and **1c** have been described previously.[4b,9] All salts used in preparation of buffers were reagent grade and were used without further purification. The purification of CH_3CN, DMF, and H_2O used in the kinetic studies has been described elsewhere.[9,10] All other reagents and solvents were reagent grade and were used as is.

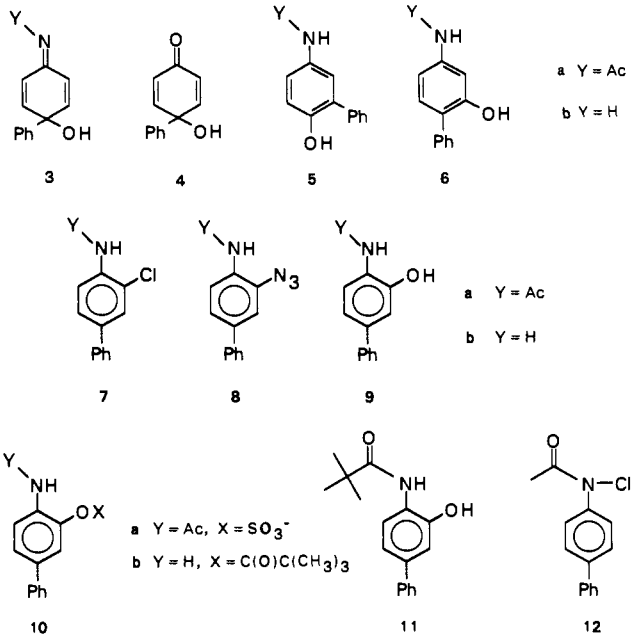
Kinetics. Kinetics of the decomposition of **1a** and **1c** were monitored by UV methods in 5% CH_3CN/H_2O at an ionic strength of 0.5 M, maintained with $NaClO_4$ or KCl. Experiments in which Cl^- or N_3^- concentrations were varied were performed with NaCl or NaN_3 and $NaClO_4$ at an ionic strength of 0.5 M. A 1/1 NaOAc/HOAc buffer (0.02 M total buffer), pH 4.6, was used to maintain the pH of the Cl^- solutions. The N_3^- served as its own buffer at N_3^-/HN_3 buffer ratios of 1/1, pH 4.5, or 19/1, pH 5.7. Reactions in which pH was varied were done in HCl solutions or in $ClCH_2CO_2H$, HOAc, NaH_2PO_4, or tris buffers all at 0.02 M in total buffer. All pH measurements were made at 20 °C with an Orion Model 701A pH meter equipped with a Radiometer GK-2402C electrode. The pH of all solutions was monitored before and after reaction and found to be constant within ±0.1 pH unit.

Concentrations of **1a** or **1c** of ca. 2.0×10^{-5} or 4.0×10^{-5} M were obtained by injection of 15 or 30 μL of 4 mM stock solutions of these compounds in DMF (**1a**) or CH_3CN (**1c**) into 3.0 mL of the buffer solution which had been incubating in the thermostated sample compartment of a Varian 2290 UV–vis spectrophotometer at either 20 or 0 °C. In the latter case dry N_2 was actively pumped through the cell compartment to prevent condensation on optical surfaces. Absorbance vs time data were collected at 248, 266, or 300 nm for **1a** and 242, 248, or 280 nm for **1c**. The longer wavelengths had to be used for reactions in N_3^- solutions.

The absorbance vs time data were fit either to the standard first-order rate equation or to an equation for two consecutive first-order processes as described elsewhere.[10] In all cases at least 3 half-lives of data were used in the fits and the standard deviations of the fits were within the error limits of the data. The experiments for **1c** at 0 °C were performed in duplicate because of its very rapid decomposition. Duplicate runs were in good agreement (±10%).

Product Analysis. Product yields were determined from the same solutions used for the kinetics studies. After reactions had reached completion, 20 μL samples were withdrawn for analysis by reverse-phase HPLC. Compounds were detected by UV absorbance at 250 nm. For **1a**, column and solvent conditions were C-18 μBondapak column, 6/4 $MeOH/H_2O$ buffered with 1/1 OAc^-/HOAc, 0.05 M total buffer, 1 mL/min. For **1c** the HPLC conditions were C-8 Beckman column, 5.5/4.5 or 6/4 $MeOH/H_2O$ buffered with 1/1 OAc^-/HOAc, 0.05 M total buffer, 1 mL/min. Components were identified by HPLC comparison to authentic samples and by isolation from larger scale reaction mixtures. Quantification was performed by determination of peak areas from triplicate injections. Extinction coefficients for each compound were determined from triplicate injections of appropriate concentrations of authentic materials.

The characterization of the hydrolysis products **4**, **5a**, and **6a** and the chloro adduct **7a**, derived from **1a**, has been described.[9] Characterization of **8a**, **9a**, and **10a** is described below.



3-Azido-4-(acetylamino)biphenyl (8a). A 500-mL solution of 0.5 M 1/1 NaN_3/HN_3 was stirred at 20 °C while 46 mg of **1a** dissolved in 2.5 mL of dry DMF was added to it. After 10 half-lives (5 h) the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). After drying over Na_2SO_4, the combined extracts were rotary evaporated to dryness. The residue was subjected to column chromatography on silica gel (1/4 $EtOAc/CH_2Cl_2$) to yield 30 mg (89%) of **8a**: mp 160–161 °C; IR (KBr) 3311, 2123, 1666, 1532, 1260, 759 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 8.38 (1H, d, J = 9 Hz), 7.61–7.57 (2H, m), 7.54 (1H, s, broad), 7.48–7.42 (2H, m) 7.39–7.33 (3H, m), 2.18 (3H, s); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 168.5 (C), 140.0 (C), 137.6 (C), 129.4 (C), 129.2 (CH), 128.5 (C), 127.9 (CH), 127.1 (CH), 124.4 (CH), 121.3 (CH), 116.6 (CH), 25.0 (CH_3); high-resolution MS *m/e* 252.1009, $C_{14}H_{12}N_4O$ requires 252.1011. The substitution pattern was confirmed by reduction of **8a** and authentic 3-nitro-4-(acetylamino)biphenyl to 3-amino-4-(acetylamino)biphenyl.

3-Nitro-4-(acetylamino)biphenyl. A stirred solution of 0.25 g of 4-(acetylamino)biphenyl in 2.4 mL of glacial acetic acid was warmed to 70 °C, and 0.16 mL of concentrated HNO_3 in 2.4 mL of glacial acetic acid was added to it in a dropwise fashion. After cooling to room temperature, H_2O was added and the precipitated product was collected by vacuum filtration, washed with distilled H_2O, and dried under vacuum. The material was recrystallized from EtOH to yield 0.20 g (66%) of yellow crystals: mp 130.5 °C (lit.[11] mp 132 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 10.32 (1H, s, broad), 8.82 (1H, d, J = 8.8 Hz), 8.42 (1H, d,

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J = 2.3 Hz), 7.87 (1H, dd, J = 8.8, 2.3 Hz) 7.60–7.57 (2H, m) 7.49–7.36 (3H, m), 2.30 (3H, s).

3-Amino-4-(acetylamino)biphenyl. A solution of 51 mg of 3-nitro-4-(acetylamino)biphenyl in 20 mL of dry THF and 14 mg of 10% Pd/C was added to a hydrogenation flask, and the mixture was hydrogenated at 50 psi for 5 h. The mixture was filtered through Celite, and the solvent was removed by rotary evaporation to yield 40 mg of product: mp 150–152 °C (lit.[12] mp 155 °C); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.57–7.54 (2H, m), 7.44–7.32 (4H, m), 7.23 (1H, d, J = 8.0 Hz), 7.01–6.98 (2H, m), 3.97 (2H, s, broad), 2.17 (3H, s); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 169.3, 141.8, 140.9, 140.4, 129.0, 127.6, 127.2, 126.2, 123.9, 118.0, 116.3, 23.8; high-resolution MS m/e 226.1106, $C_{14}H_{14}N_2O$ requires 226.1106. Identical material was formed by reduction of 5 mg of **8a** in 10 mL of dry THF with 3 mg of 10% Pd/C at 50 psi of H_2 for 4 h.

3-Hydroxy-4-(acetylamino)biphenyl (9a). Hydrogenation of 150 mg (0.7 mmol) of 3-hydroxy-4-nitrobiphenyl[13] in 20 mL of dry THF containing 12 mg of 10% Pd/C was accomplished by agitating the mixture under 55 psi of H_2 for 3 h at room temperature. The mixture was filtered through Celite, and the Celite was washed with 50 mL of THF, which was added to the reaction mixture. Et_3N (0.1 mL) was added to this mixture. The resulting solution was stirred as 0.054 mL (0.75 mmol) of acetyl chloride in 3 mL of THF was slowly added to it. The reaction mixture was heated on a steam bath for 15 min. After cooling, 50 mL of H_2O was added and the THF was removed by rotary evaporation. The precipitated product was collected by vacuum filtration, dried, and recrystallized from EtOH: mp 195–196 °C; IR (KBr) 3400, 1653, 1600, 1529, 1410 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.02 (1H, s), 7.61–7.56 (3H, m), 7.45–7.39 (2H, m), 7.36–7.31 (1H, m), 7.23 (1H, d, J = 1.9 Hz), 7.12 (1H, dd, J = 8.2, 1.9 Hz), 7.05 (1H, d, J = 8.2 Hz), 2.27 (3H, s); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 171.2 (C), 149.4 (C), 140.5 (C), 140.3 (C), 129.1 (CH), 127.8 (CH), 127.1 (CH), 125.3 (C), 122.8 (CH), 119.2 (CH), 118.4 (CH), 23.9 (CH_3).

3-(Sulfonatooxy)-4-(acetylamino)biphenyl (10a). This material was synthesized as its potassium salt from **9a** by the procedure previously described for **1a**:[9] mp 192–194 °C; IR (KBr) 3300, 1650, 1595, 1528, 1258 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (1H, s), 8.08 (1H, d, J = 8.5 Hz) 7.60–7.55 (2H, m) 7.48–7.30 (5H, m), 2.07 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 167.9, 143.1, 139.4, 135.5, 130.8, 128.9, 127.2, 126.3, 122.2, 121.8, 121.0, 24.2; high-resolution MS (FAB) m/e 383.9705, $C_{14}H_{12}NO_5SK_2$ requires 383.9705.

The product **10a** cannot be detected in hydrolysis reaction mixtures of **1a** by HPLC because its retention time is similar to that of DMF, which is present in the mixtures in much higher concentrations. It was detected and quantified by ^{1}H NMR of hydrolysis reaction mixtures of **1a** in 5% CD_3CN/D_2O that were initially about 0.5 mM in **1a**.

An authentic sample of the chloro adduct of **1c**, **7b**, was prepared as described in the literature.[14] The major hydrolysis product, **4**, was characterized as previously described.[9] The azide adduct, **8b**, and the rearranged material, **11**, were characterized as described below.

4-Amino-3-azidobiphenyl (8b). Although this material could be isolated from reaction mixtures by extraction with CH_2Cl_2, it always suffered significant decomposition, and attempts at purification led to further decomposition. In aqueous solution at or below room temperature it remained reasonably stable for several days as long as it was not exposed to strong light. The compound was characterized in solution by generation from **1c** in high-concentration azide buffers. Under these conditions the only significant contaminant was a small amount of **11**. For ^{1}H NMR, 0.125 mL of a 15.0 mM solution of **1c** in DMSO-d_6 was added to 0.375 mL of a 19/1 (N_3^-/HN_3) 0.4 M NaN_3 buffer in D_2O. After the reaction was completed (ca. 10 min), a ^{1}H NMR was obtained: ^{1}H NMR (300 MHz, 25/75 DMSO-d_6/D_2O) δ 7.52 (2H, m), 7.33 (2H, t, J = 7.6 Hz), 7.25 (1H, d, J = 2.0 Hz) 7.23 (1H, m, obscured), 7.19 (1H, dd, J = 8.2, 2.0 Hz) 6.78 (1H, d, J = 8.2 Hz). A ^{13}C NMR was obtained in a similar manner by mixing 0.25 mL of a 13.7 mM solution of **1c** in DMSO-d_6 with the NaN_3 buffer in D_2O: ^{13}C NMR (75.5 MHz, 50/50 DMSO-d_6/D_2O) δ 140.8 (C), 139.5 (C) 132.1 (C), 130.4 (CH), 128.2 (CH), 127.2 (CH), 126.7 (C), 125.4 (CH), 117.9 (CH), 117.1 (CH). The extinction coefficient for **8b** for HPLC quantification was determined from peak area measurements of HPLC chromatograms obtained from reaction mixtures of **1c** at high N_3^- concentration (>0.1 M). Under these conditions the only detectable reaction products are **8b** and **11**. It was assumed that **1c** was quantitatively converted into these two materials. Since the yield of **11** could be determined from HPLC peak areas, the yield of **8b** was obtained by difference, and the extinction coefficient was estimated from this yield and HPLC peak areas for **8b**.

3-Hydroxy-4-(pivaloylamino)biphenyl (11). This material was synthesized from 3-hydroxy-4-nitrobiphenyl as described above for **9a** except that pivaloyl chloride was used in place of acetyl chloride. The crude product was purified by column chromatography on silica gel (3/1 CH_2Cl_2/hexanes): mp 189–190 °C; IR (KBr) 3420, 1638, 1528, 1400 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.97 (1H, s), 7.62 (1H, s, broad), 7.57–7.52 (2H, m), 7.44–7.30 (3H, m), 7.26 (1H, d, J = 1.8 Hz), 7.10 (1H, dd, J = 8.2, 1.8 Hz), 7.04 (1H, d, J = 8.2 Hz), 1.35 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.0, 149.0, 140.2, 140.0, 128.7, 127.3, 126.8, 124.7, 122.4, 119.0, 118.3, 39.5, 27.7; high-resolution MS m/e 269.1413, $C_{17}H_{19}NO_2$ requires 269.1416.

***N*-Chloro-4-(acetylamino)biphenyl (12).** This material was synthesized as described in the literature by treatment of *N*-acetyl-4-aminobiphenyl with NaOCl.[14] The crude product was recrystallized from CCl_4: mp 128.0–128.5 °C (lit.[14] mp 127–128 °C) ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.68 (2H, d, J = 8.6 Hz), 7.48 (2H, d, J = 8.6 Hz), 7.64–7.32 (5H, m), 2.10 (3H, s); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 168.6 (C), 142.9 (C), 142.7 (C), 140.0 (C), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128,4 (CH), 127.5 (CH), 22.5 (CH_3).

The decomposition of **12** was monitored at 20 °C in a pH 3.0 $ClCH_2CO_2H$ buffer (μ = 0.5 M (KCl)) under the conditions described above for **1a**. HPLC was used to monitor the rate of decomposition of **12** and the products produced from its hydrolysis.

Table I. Hydrolysis Rate Constant for **1a**[a]

buffer	pH[b]	10^4k_0 at 20 °C (s^{-1})[c]
HCl	1.10	3.95 ± 0.04
HCl	1.50	3.66 ± 0.03
HCl	2.05	3.53 ± 0.03
HCl	2.41	3.73 ± 0.02
$ClCH_2CO_2H$	2.90	3.64 ± 0.02
HOAc	3.50	3.96 ± 0.04
HOAc	4.00	3.94 ± 0.05
HOAc	4.50	4.28 ± 0.03
HOAc	5.10	4.41 ± 0.03
HOAc	5.60	4.45 ± 0.03
KH_2PO_4	5.93	4.88 ± 0.05
KH_2PO_4	6.30	3.69 ± 0.02
KH_2PO_4	6.81	3.22 ± 0.02
KH_2PO_4	7.27	3.86 ± 0.12
KH_2PO_4	7.89	3.65 ± 0.01
tris	7.95	4.77 ± 0.17
tris	8.38	4.37 ± 0.18
tris	8.85	4.45 ± 0.20
tris	9.19	3.28 ± 0.20

[a] Conditions: HCl or 0.02 M buffers, μ = 0.5 M (KCl). Initial concentration of **1a** was ca. 2.0 × 10^{-5} M. [b] Measured after reaction at 20 °C. [c] Measured at 266 nm at pH < 5.9, and at 248 nm at pH > 5.9.

Results

Hydrolysis rate constants, k_0, were determined for **1a** by measurement of UV absorbance at 248 or 266 nm in 5% CH_3CN/H_2O (μ = 0.50 M (KCl)) at 20 °C in the pH range 1–9. The pH was maintained with HCl or buffers of $ClCH_2CO_2H$, CH_3CO_2H, KH_2PO_4, or tris (0.02 M). The hydrolysis rate constants, k_0, which are presented in Table I, are pH independent with an average value of (4.0 ± 0.5) × 10^{-4} s^{-1}. Another process with a first-order rate constant, k_1, could be observed at pH ≥ 5.9 when reactions were monitored at 248 nm. These rate constants and their pH dependence have been reported previously.[9] NMR data indicate that k_1 is associated with the disappearance of *N*-acetyl-4-hydroxy-4-phenyl-2,5-cyclohexadienone imine, **3a**, which is the major initial product of hydrolysis of **1a** in the absence of added nucleophiles.[9]

The hydrolysis of **1c** was monitored at 242 and 280 nm over a smaller pH range (3.7–5.6) in 0.02 M acetate buffers in 5% CH_3CN/H_2O (μ = 0.5 M ($NaClO_4$)) at 0 °C. The rate constants, k_0, for the disappearance of **1c** (Table II) were pH independent under these conditions with an average value of 0.13 ± 0.01 s^{-1}.

(12) Miller, E. C.; Sandin, R. B.; Miller, J. A.; Rusch, H. P. *Cancer Res.* **1956**, *16*, 525–534.
(13) Colbert, J. C.; Meigs, W.; Jenkins, R. L. *J. Am. Chem. Soc.* **1937**, *59*, 1122–1124.
(14) Scarborough, J.; Waters, L. *J. Chem. Soc.* **1926**, 557–560.

Table II. Hydrolysis Rate Constants for **1c**[a]

pH[b]	k_0 at 0 °C (s^{-1})[c]	$10^5 k_1$ at 20 °C (s^{-1})[d]
3.7	0.12 ± 0.01	2.84 ± 0.02
4.1	0.14 ± 0.02	3.44 ± 0.02
4.6	0.14 ± 0.02	3.91 ± 0.04
5.1	0.12 ± 0.02	4.01 ± 0.03
5.6	0.13 ± 0.04	4.36 ± 0.04

[a] Conditions: 0.02 M acetate buffers, μ = 0.5 M ($NaClO_4$). Initial concentration of **1c** was ca. 4×10^{-5} M. [b] Measured before and after reaction at 20 °C. [c] Average of two measurements taken at 242 and 280 nm. [d] Measured at 248 nm.

A second slower process, governed by k_1 (Table II), was observed at 248 nm. The latter rate constants were determined at 20 °C and show some pH dependence in the region in which the measurements were made. HPLC results (below) showed that the major stable hydrolysis product of **1c** in the absence of added nucleophiles, 4-hydroxy-4-phenyl-2,5-cyclohexadienone, **4**, was formed as a result of the process governed by k_1. From this information, and by analogy to the case of **1a**, it appears that the major initial product of hydrolysis of **1c** in the absence of added nucleophiles is 4-hydroxy-4-phenyl-2,5-cyclohexadienone imine, **3b**.

The major hydrolysis products for **1a** in the presence of KCl (μ = 0.5 M) in the pH range 1–8 have been reported.[9] The yields of **4**, **5a**, and **6a**, all of which are derived from decomposition of **3a**, vary with pH, but the sum of their yields is constant at constant [Cl^-], as is the yield of the product of Cl^- trapping, **7a**.[9] At [Cl^-] = 0.5 M, the yield of **7a** is 70 ± 3% throughout the pH range, while the combined yield of products derived from **3a** is 17 ± 3%. If N_3^- is used in place of Cl^-, a new product **8a** is formed, but N_3^- is much more competitive with the solvent than Cl^-. For example, at 0.01 M N_3^-, pH 4.5 (μ = 0.5 M ($NaClO_4$)), **8a** accounts for 85 ± 3% of the reaction products of **1a**.

Careful analyses of reaction rates and products were performed at 20 °C as a function of [Cl^-] (0–0.5 M) at pH 4.6 and [N_3^-] (0–0.05 M) at pH 4.5. A low-concentration acetate buffer (0.02 M) maintained pH in the former case, and N_3^-/HN_3 served as the buffer in the latter case. Ionic strength was maintained at 0.5 M by addition of $NaClO_4$. Kinetics were monitored at 266 nm (Cl^- solutions) or 300 nm (N_3^- solutions). Product yields were determined by HPLC or NMR methods after 10 half-lives (ca. 5 h) of the process governed by k_0. In the absence of either Cl^- or N_3^- the products of hydrolysis of **1a** found in this pH range are **4** (15 ± 1%), **5a** (75 ± 5%), **6a** (2.0 ± 0.2%), **9a** (1.0 ± 0.2%), and **10a** (1.4 ± 0.2%). Addition of Cl^- or N_3^- caused a decrease in the yield of all these products, except **10a**. In their place **7a** or **8a** is formed. If the nucleophile and solvent compete for the same species, such as **2a**, the fractions of product due to trapping by the nucleophile (f_{Nu}) or solvent (f_s) are related to the second-order rate constant for trapping by the nucleophile (k_{Nu}), the pseudo-first-order rate constant for trapping by solvent (k_s), and the concentration of the nucleophile, by eqs 1 and 2.[5]

$$\frac{1}{f_{Nu}} = 1 + \frac{k_s}{k_{Nu}[Nu]} \quad (1)$$

$$\frac{1}{f_s} = 1 + \frac{k_{Nu}[Nu]}{k_s} \quad (2)$$

Figure 1 shows that the product data for **1a** follow these relationships for both Cl^- and N_3^- in the concentration ranges examined. The product **10a** is not included in these results, but would have a minimal effect in any case because of its low yield. Figures 2 and 3 show that in the same concentration range k_0 is independent of the concentration of the added nucleophile and is equivalent, within experimental error, to the average value of k_0 determined over the pH range 1–9. The second rate constant, k_1, cannot be observed at pH < 5.9, but in separate experiments performed in phosphate buffers at pH 6.6, it was shown that k_1 is also independent of [Cl^-] or [N_3^-] (Figures 2 and 3). It was not possible to accurately measure k_1 at [N_3^-] > 2.5 mM because at these concentrations very little **3a**, the intermediate responsible for the process defined by k_1, is formed.

The rate constant ratios k_{Cl}/k_s of 7.4 ± 0.3 M^{-1} and k_{az}/k_s of (1.02 ± 0.04) × 10^3 M^{-1} indicate that both nucleophiles compete effectively with solvent for the cation **2a**. At [Cl^-] = 0.14 M, Cl^- traps 50% of **2a**, while at [N_3^-] = 0.98 mM, N_3^- traps 50% of **2a**. Thus, the relative reactivity of these nucleophilcs toward **2a** is N_3^-(54 000) > Cl^- (390) > H_2O (1).

In the absence of Cl^- or N_3^-, **1c** decomposes in acetate buffers under our reaction conditions into **4** (91 ± 6%) and **11** (6 ± 1%). The latter compound is most likely derived from intramolecular rearrangement of **10b**, which was not detected in this study. Products analogous to **10b** have been detected previously in the hydrolysis reaction of *N*-(4-chlorophenyl)-*O*-pivaloylhydroxylamine and the methanolysis of *N*-(4-tolyl)-*O*-pivaloylhydroxylamine.[4b,15] In both of these cases the transient ester rearranged into an amide analogous to **11**.[4b,15] The HPLC data of Figure 4 show that **4** is not an initial hydrolysis product of **1c**, which has a half-life of less than 3 s at 20 °C. This material is generated slowly, apparently by hydrolysis of **3b**, in a process governed by the rate constant k_1 described above.

The compounds **5b**, **6b**, and **9b**, which are analogous to **5a**, **6a**, and **9a**, were not detected among the hydrolysis products of **1c**. An upper limit for the yields of **5b** and **6b** is about 2% based on detection limits established with authentic compounds. The detection limit for **9b** is less than 1%.

Addition of Cl^- or N_3^- leads to a decrease in the yield of **4** and formation of **7b** or **8b**. The data shown in Figure 1 indicate that **1c** exhibits the same type of behavior as **1a**. These product studies were performed at 20 °C, at pH 4.6 for Cl^- and pH 5.7 for N_3^- with total ionic strength maintained at 0.5 M with $NaClO_4$. Product yields were determined after 5 half-lives of the k_1 process (ca. 24 h). Addition of Cl^- or N_3^- does not change the yield of **11**, so this product was not included in the results shown in Figure 1. The HPLC data (Figure 4) show that both **7b** and **8b** reach their final yields in the reaction mixtures shortly after mixing. These products are not generated during the period in which **3b** undergoes hydrolysis to **4**.

Figure 5 shows that the hydrolysis rate constant, k_0, for **1c**, measured at 0 °C, is insensitive to the addition of Cl^- or N_3^-. The highest concentrations of Cl^- and N_3^- at which k_0 was measured (0.20 M in Cl^-, 0.016 M in N_3^-) correspond to trapping of ca. 76% and 98%, respectively, of the trappable hydrolysis products of **1c**.

The selectivity ratios k_{Cl}/k_s of 15.7 ± 0.8 M^{-1} and k_{az}/k_s of (2.9 ± 0.2) × 10^3 M^{-1} indicate that the cation **2b** is 2–3 times as selective in its reactions with nucleophiles than is **2a**. Still, the two cations are remarkably similar in their reactivity considering that the rate constants for their formation from **1a** and **1c** at 0 °C are 4.8 × 10^{-5} and 0.13 s^{-1}, respectively.

Products such as **7a**, **7b**, **8a**, or **8b** could be derived by intramolecular rearrangement of an initial adduct formed by attack of the nucleophile on the nitrogen of **2a** or **2b**. To test this hypothesis, the authentic *N*-chloro adduct **12** was subjected to hydrolysis at pH 3.0 in $ClCH_2CO_2H$ buffer (μ = 0.5 M (KCl)) under conditions identical to those used to investigate the hydrolysis of **1a**. The product distribution obtained by HPLC analysis was similar to that obtained from **1a**, but the rate constant for decomposition of **12** is (3.6 ± 0.2) × 10^{-5} s^{-1}, which is 11-fold smaller than the rate constant for decomposition of **1a**. If **12** had been formed during the hydrolysis of **1a**, it would have easily been detected by UV and by its effect on the rate of production

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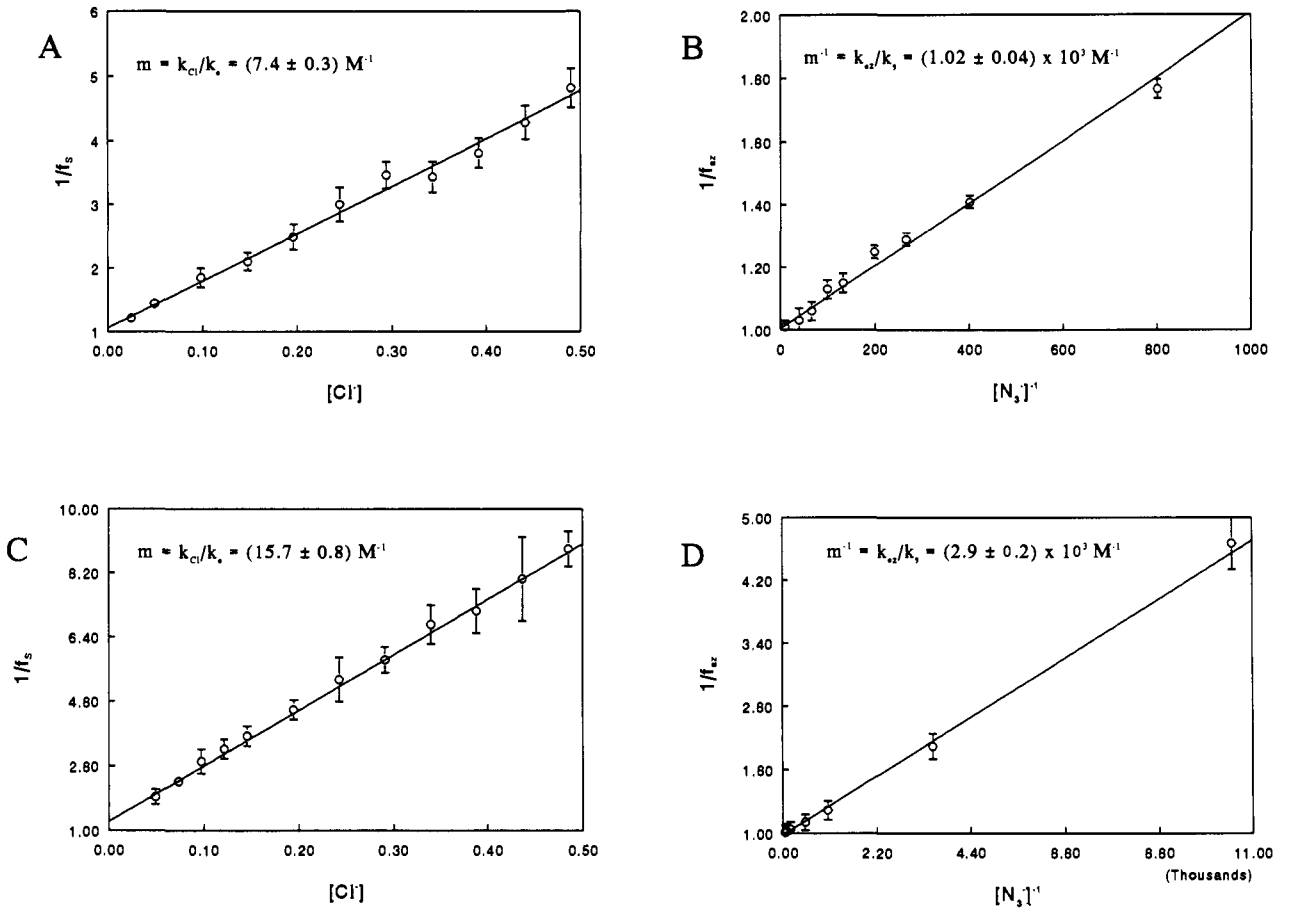


Figure 1. The dependence of reaction product yields on nucleophile concentration for **1a** and **1c** in 5% CH_3CN/H_2O at 20 °C (μ = 0.5 M ($NaClO_4$)): (A) $1/f_s$ vs $[Cl^-]$ for **1a** at pH 4.6; (B) $1/f_{az}$ vs $1/[N_3^-]$ for **1a** at pH 4.5; (C) $1/f_s$ vs $[Cl^-]$ for **1c** at pH 4.6; (D) $1/f_{az}$ vs $1/[N_3^-]$ for **1c** at pH 5.7. Regression lines were obtained from a weighted least squares fit. The value of k_{Nu}/k_s is shown for all cases.

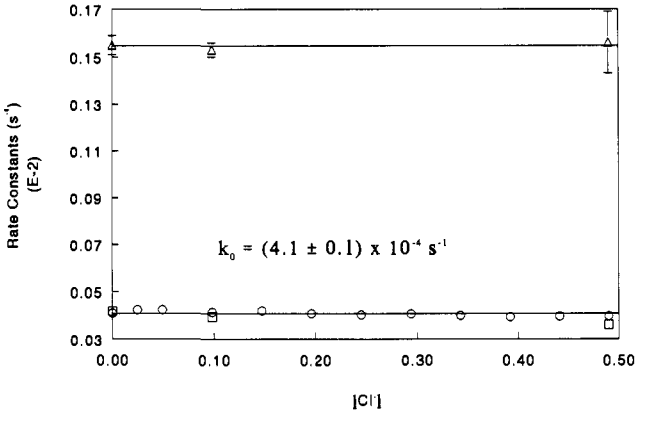


Figure 2. The rate constants k_0 and k_1 at 20 °C for **1a** as a function of $[Cl^-]$ at pH 4.6 and 6.6: (○) k_0 at pH 4.6; (□) k_0 at pH 6.6; (△) k_1 at pH 6.6. Error bars are included for all data with error limits ≥3.0 × 10^{-5} s^{-1}. The average value for k_0 is shown.

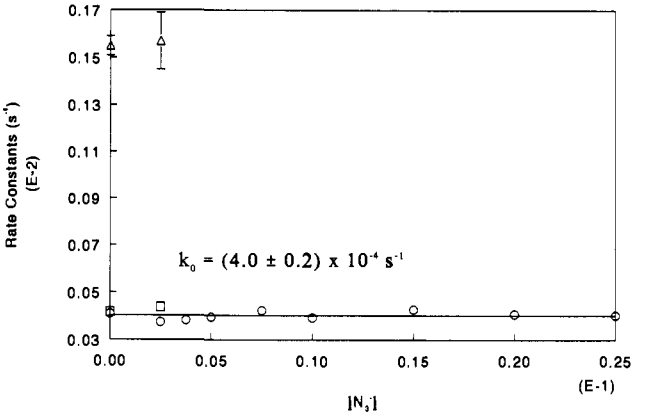


Figure 3. The rate constants k_0 and k_1 at 20 °C for **1a** as a function of $[N_3^-]$ at pH 4.5 and 6.6: (○) k_0 at pH 4.5; (□) k_0 at pH 6.6; (△) k_1 at pH 6.6. Error bars are included for all data with error limits ≥3.0 × 10^{-5} s^{-1}. The average value for k_0 is shown.

of hydrolysis products of **1a** monitored by HPLC. There is no evidence that **12** is produced in any of the hydrolysis reactions of **1a**.

Discussion

Mechanism of Hydrolysis. There is ample evidence that both **1a** and **1c** undergo hydrolysis in 5% CH_3CN/H_2O (μ = 0.5 M) by a mechanism involving rate limiting formation of a diffusionally equilibrated nitrenium ion. The rate constant k_0, which describes the disappearance of **1a** at 20 °C or **1c** at 0 °C, is independent of the concentration of Cl^- or N_3^- at constant ionic strength (Figures 2, 3, 5). In the same concentration ranges (0–0.5 M for $[Cl^-]$, 0–0.05 M for $[N_3^-]$) the chloro or azide adducts **7a** and **7b** or **8a** and **8b** make up a significant part of the product yield (Figure 1). For example, in acetate buffer at pH 4.6, k_0 is (3.96 ± 0.03) × 10^{-4} s^{-1} for **1a** at 0.49 M Cl^- and the yield of **7a** is 77 ± 3%. At the same pH in the absence of Cl^-, k_0 is (4.09 ± 0.03) × 10^{-4} s^{-1}. If **7a** were formed by an S_N2 process, k_0 would be ca. 17.8 × 10^{-4} s^{-1} at 0.49 M Cl^- to account for the observed yield of **7a**.

The data in Figure 1 show that the dependence of the yields of reaction products on nucleophile concentrations is consistent with competitive trapping of the intermediates **2a** and **2b** by solvent and the nucleophiles Cl^- or N_3^-.[5] The magnitudes of k_{Cl}/k_s and k_{az}/k_s for **2a** and **2b** indicate that both nitrenium ions are fairly

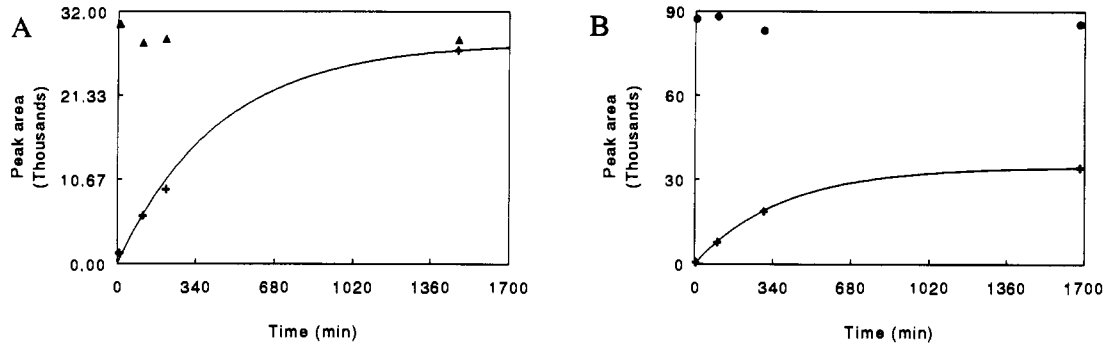


Figure 4. HPLC peak areas vs time for **4** (+), **7b** (▲), and **8b** (●) during the hydrolysis of **1c** at 20 °C. The time scale covers the slow process governed by k_1: (A) data taken from a 0.05 M Cl^- solution at pH 4.6; (B) data taken from a 0.285 mM N_3^- solution at pH 5.7. Initial concentration of **1c** is ca. 4.0×10^{-5} M. Theoretical lines for **4** were calculated from the first-order rate equation, the rate constants k_1 for **1c** in Table I, and the peak area for **4** at the completion of the reactions.

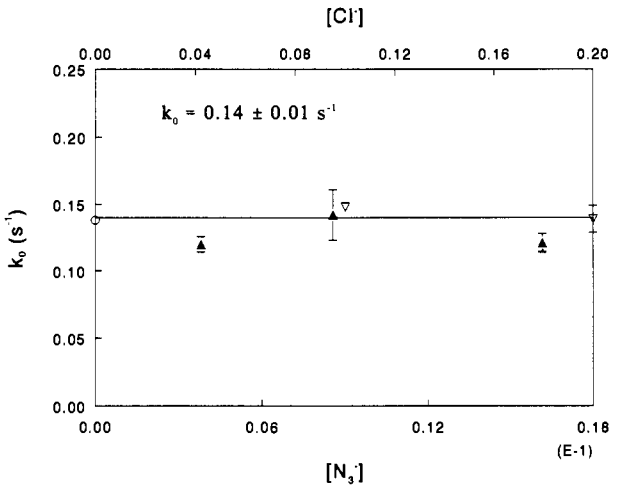


Figure 5. The dependence of k_0 for **1c** at 0 °C on [Cl^-] or [N_3^-]: (○) no added nucleophile (average value at pH 4.6 and 5.7); (▲) in N_3^- solutions at pH 5.7; (▽) in Cl^- solutions at pH 4.6. Error bars are included for all data with error limits ≥0.006 s^{-1}. The average value of k_0 is shown.

selective electrophiles with significant lifetimes. The only materials which are not produced by trapping of **2a** or **2b** are the rearrangement products **10a** and **11**. The yields of these products are insensitive to the concentration of either Cl^- or N_3^-, so they cannot be formed from the same intermediate or any species in equilibrium with that intermediate. As discussed above, **11** is likely formed by intramolecular rearrangement of the initially formed **10b**, although this material was not detected in this study.[4b,15]

Several of the hydrolysis products of **1a**, specifically **4**, **5a**, and **6a**, are formed from subsequent hydrolysis or rearrangement of the initially formed imine **3a**.[9] The HPLC data of Figure 4 demonstrate that, during the hydrolysis of **1c**, **4** is also generated in a much slower process that is governed by the rate constant k_1 presented in Table I. The most reasonable precursor to **4** is **3b**. In principle, the trapping of the ions **2a** and **2b** by solvent to generate **3a** and **3b** could be reversible. There is some evidence that a similar *N*-acetylquinol imine is generated reversibly during the hydrolysis of *N*-(sulfonatooxy)-2-(acetylamino)fluorene.[16] Several pieces of evidence indicate that this is not the case for either **3a** or **3b**. The yield of the chloro adduct **7a** is constant throughout the pH range 1–8 at constant [Cl^-].[9] It would be expected that the rate of reversion of **3a** to **2a** is pH dependent.[16] If so, it would be unlikely that the yield of **7a** remains constant throughout this pH range. The imine **3a** can only be directly detected at pH ≥ 5.9, but the data of Figures 2 and 3 show that at pH 6.6 the rate constant for decomposition of **3a**, k_1, is independent of [Cl^-] or [N_3^-]. This would not be the case if **3a** was in reversible equilibrium with **2a**. The HPLC data of Figure **4** also show that the concentrations of **7b** and **8b** do not change during the decomposition of **3b** into **4**. This precludes any reversible equilibrium between **2b** and **3b** under the conditions of these experiments. The data described here for **3a** and **3b** are also not consistent with any direct reaction of these quinol imines with Cl^- or N_3^-.

Finally, the kinetic data indicate that both **1a** and **1c** undergo hydrolysis without acid or base catalysis of the N–O bond cleavage process. Less reactive compounds of related structure do exhibit catalysis of N–O bond cleavage,[17] but more reactive compounds of this type do not require catalysis of the ionization process.[10,16,18]

The mechanism of Scheme I is consistent with all the data presented in this and the earlier report[9] for the hydrolysis of **1a** and **1c**. Its salient features include rate-limiting ionization of **1** to generate the contact ion pair **13**. This ion pair can undergo diffusional separation to generate the free ion **2**, or internal return with rearrangement to yield **10**. The low yields of the rearrangement products **10a** and **11**, 1.4% and 6%, respectively, are consistent with a relatively stable nitrenium ion that has a significant activation barrier for reaction with most nucleophiles. These yields are also in agreement with the expected relative nucleophilicity of SO_4^{2-} and pivalate ion. All other products are derived from nucleophilic attack of solvent or other species on **2**. Products such as **7** or **8** could be derived from rearrangement of an initially formed adduct at nitrogen, but our results with the authentic *N*-chloro compound **12** indicate that this is not the case for **7a**. Solvent attack on **2** leads to **3** and **9**. The latter compound is formed in much lower yield, and was unambiguously identified only in the case of **1a**. Of course, **3** is not stable in an aqueous environment and can undergo hydrolysis of the C=N bond or other reactions which have been discussed in detail elsewhere.[9] It appears that **3b** may undergo hydrolysis exclusively to **4** since **5b** and **6b** could not be detected in the hydrolysis mixtures of **1c** in the pH region 3.5–5.7. In that same pH region **3a** and related *N*-acylquinol imines and *N*-acylquinol ether imines always yield significant amounts of the dienone phenol rearrangement products such as **5a**.[9,16]

Reactivity and Selectivity of the Nitrenium Ions. The azide ion has a long history of use in carbocation chemistry as a mechanistic probe.[5,6,19,20] Since it reacts at a diffusion-controlled rate with

(16) Panda, M.; Novak, M.; Magonski, J. *J. Am. Chem. Soc.* **1989**, *111*, 4524–4525.

(17) Novak, M.; Rovin, L. H.; Pelecanou, M.; Mulero, J. J.; Lagerman, R. K. *J. Org. Chem.* **1987**, *52*, 2002–2010. Campbell, J. J.; Glover, S. A.; Hammond, G. P.; Rowbottom, C. A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 2067–2079.

(18) Novak, M.; Pelecanou, M.; Pollack, L. *J. Am. Chem. Soc.* **1986**, *108*, 112–120.

(19) Sneen, R. J.; Carter, V. J.; Kay, P. S. *J. Am. Chem. Soc.* **1966**, *88*, 2594–2595. Raber, D. A.; Harris, J. M.; Hall, R. E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1971**, *93*, 4821–4828. Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348–354. Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 6082–6095.

Scheme I

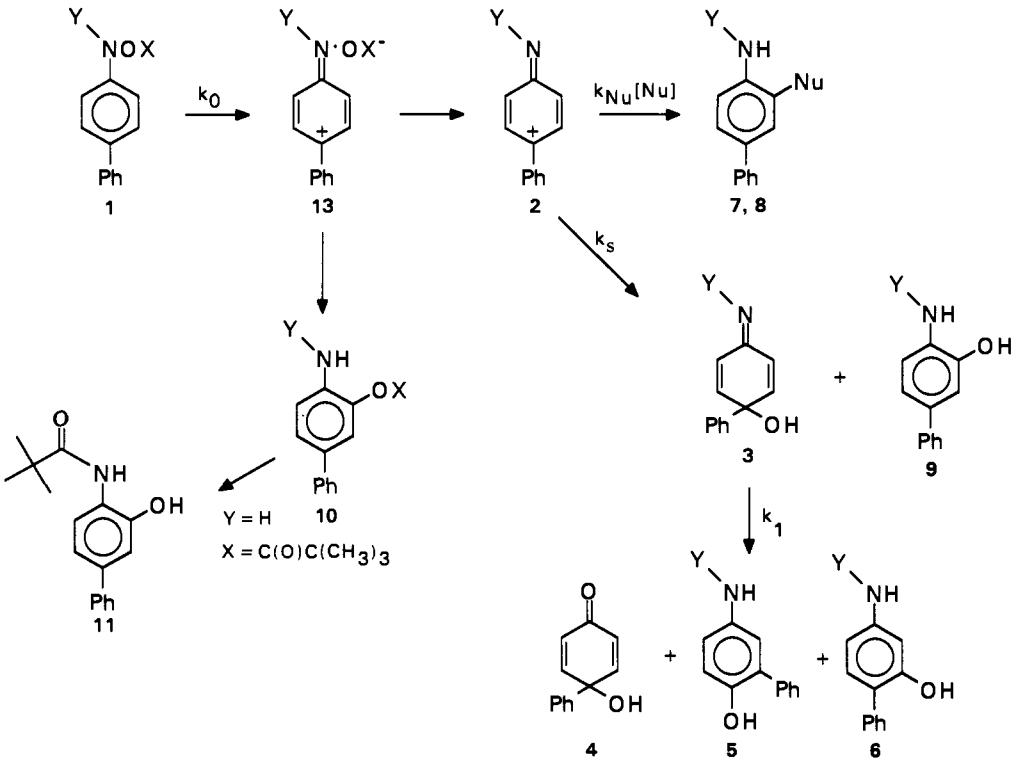


Table III. Estimated Values of k_{Cl}, k_s, and Nitrenium Ion Lifetimes for **2a**, **2b**, and Other *N*-Arylnitrenium Ions

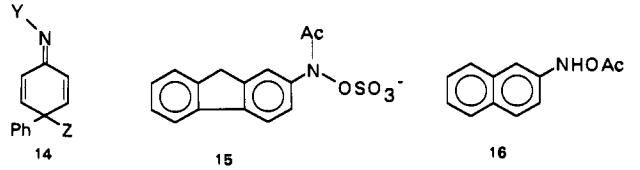
ion	k_{Cl} (M^{-1} s^{-1})	k_s (s^{-1})	lifetime (s)[a]
2a[b]	3.6×10^7	4.9×10^6	2.0×10^{-7}
2b[b]	2.7×10^7	1.7×10^6	5.9×10^{-7}
phenylnitrenium[c]		5×10^9	2.0×10^{-10}
(2,6-dimethylphenyl)nitrenium[d]		7×10^8	1.4×10^{-9}

[a] This is $1/k_s$. [b] Estimated for 5% CH_3CN/H_2O, $\mu = 0.5$ M, at 20 °C. [c] Reference 7b. Conditions not stated. [d] Reference 7a. Conditions: H_2O, $\mu = 1.0$ M, 40 °C.

moderately to highly reactive carbocations ($k_s \geq 10^5$ s^{-1}), it can be used as a clock to measure the rate constants for the reactions of other nucleophiles, including the solvent, with the cation.[5,6] It has been used less frequently in nitrenium ion chemistry, but there is evidence that it can be used in a similar sense with reactive nitrenium ions.[7]

If k_{az} for **2a** and **2b** (Scheme I) is assumed to be diffusion limited at 5×10^9 M^{-1} s^{-1}, k_{Cl}, the second-order rate constant for trapping of the cation by Cl^-, and k_s, the pseudo-first-order rate constant for trapping by solvent, can be estimated from the selectivity data presented earlier. The lifetime of the cation, $1/k_s$, indicates how selective the species will be in a particular solvent. The estimates for the rate constants and lifetimes in aqueous solution for **2a**, **2b**, and a few other *N*-arylnitrenium ions previously studied in another laboratory are reported in Table III. The results indicate that **2a** and **2b** are relatively long-lived species with lifetimes roughly comparable to that of the 4-methoxycumyl cation measured in 1/1 TFE/H_2O at 25 °C and the 4-chloro-4′-methoxydiphenylmethyl cation measured in 1/2 CH_3CN/H_2O at 20 °C.[6,20] Previously published correlations of log(k_{az}/k_s) vs σ^+ have allowed us to estimate the lifetime of the 4-phenylcumyl and 1-(4-biphenylyl)ethyl cations as 5×10^{-10} and 1×10^{-10} s, respectively, in 1/1 TFE/H_2O at 20–25 °C.[5a,b,20] The nitrenium ions **2a** and **2b** are 3–4 orders of magnitude less labile to attack of H_2O than these carbocations. McClelland has previously noted that nitrenium ion lifetimes are considerably longer than those of analogous carbocations.[7b] This was attributed to the activation barrier associated with formation of the initial nonaromatic products by attack of nucleophiles on the ring carbons. A similar activation barrier does not occur for carbocations because they undergo attack at a carbon external to the ring and do not lose aromatic stabilization in the product.[7b]

Attack of H_2O on **2a** occurs preferentially at the ring carbon para to the *N*-acyl substituent, rather than at the ortho carbons. The statistically corrected para/ortho reactivity ratio for attack of H_2O on **2a** is ca. 180/1. This ratio must be larger for **2b** because the ortho substitution product **9b** was not detected. It is unlikely that the para/ortho reactivity ratios for Cl^- and N_3^- are as large as those for the weakly nucleophilic solvent, but they will not be near 1.0 unless reaction at both sites occurs without an activation barrier. This is definitely not the case for Cl^- (see Table III) and may not be the case for N_3^-. The products of para attack, **14**, were not detected and would not be likely to be stable



Z = Cl or N_3

materials. Their most likely fate would be decomposition to regenerate **2a** or **2b**. If the para/ortho reactivity ratio for N_3^- is larger than 1.0, k_{az}, the rate constant for trapping of the ions by N_3^- to generate the ortho substitution products, **8a** or **8b**, must be less than the diffusion-limited value. If k_{az} is smaller than ca. 5×10^9 M^{-1} s^{-1}, k_{Cl} and k_s reported for **2a** and **2b** in Table III are upper limits for the true values and the reported lifetimes are lower limits for the true values.

It is clear from the selectivity data and the estimated rate constants of Table III that **2a** and **2b** exhibit similar reactivity toward H_2O, Cl^-, and N_3^-. This is quite remarkable considering that **1c** undergoes hydrolysis 2700-fold faster than **1a** at 0 °C.

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A correction for the effect of the two different leaving groups, SO_4^{2-} and pivalate, on the rate of reaction indicates that **2b** would be generated from **1d** about 10^6-fold faster than **2a** from **1b** under identical reaction conditions.[21] To account for this rate difference at 0 °C, $\Delta(\Delta G^{\ddagger})$ for N–O bond heterolysis of **1b** and **1d** must be ca. 7.5 kcal/mol. *Ab initio* MO calculations suggest that replacement of the N–H group with *N*-acetyl in an *N*-arylnitrenium ion may destabilize the ion by as much as 15 kcal/mol.[22]

Although the rate constants for formation of **2a** and **2b** from their precursors are obviously governed by their relative thermodynamic stabilities, their subsequent reactions with nucleophiles are almost independent of their stability. The rate constants for reaction of **2a** and **2b** with H_2O, k_s, differ only by a factor of 3. A similar phenomenon has been observed in the thermodynamic stability and lability of 1-aryl-2,2,2-trifluoroethyl carbocations and the corresponding 1-arylethyl cations.[23] This was attributed to an imbalance in the loss of inductive (destabilizing) and resonance (stabilizing) interactions in the transition state for carbocation capture by nucleophiles such that the fractional loss of resonance interactions exceeded that of the inductive interactions.[23] The same factor may be responsible in this case also. Because there are fewer data available for nitrenium ion reactions than for carbocation reactions, it is not currently possible to experimentally separate the effects of inductive and resonance interactions on the stability and lability of nitrenium ions. Nevertheless, we expect that the inductively withdrawing acetyl group will lower the energy of the empty p orbital on the nitrogen of the nitrenium ion. This will make resonance interactions between the aromatic ring and nitrogen in **2a** more important than in **2b** in determining the stability of the ion. If these resonance interactions are disrupted to a similar extent in the transition state for capture by a nucleophile, there will be a greater loss of resonance energy for **2a**. This will partially or completely offset the inductive effect, which would provide a greater driving force for the capture of **2a** by nucleophiles. We are currently gathering reactivity data on a number of other *N*-arylnitrenium ions with and without the *N*-acyl substituent in an effort to shed more light on this and other issues regarding nitrenium ion reactivity. One such issue is the effect of aryl substituents on nitrenium ion reactivity. It is obvious from the data of Table III that aryl substituents have a marked effect on k_s, but we do not yet have sufficient data for a detailed understanding of these effects. Preliminary results suggest that, unlike the case for carbocations, log k_s will not correlate well with σ^+.[24]

The rate data for Cl^- trapping of **2a** and **2b** show that there is a significant activation barrier for trapping of these cations by this nucleophile. Therefore, the ion pairs **2a**·Cl and **2b**·Cl do exist in aqueous solution. This indicates that other ion pairs composed of **2a** or **2b** and weakly or moderately reactive anions, such as **13** in Scheme I, can be expected to have a fleeting but finite lifetime in aqueous solution. This supports our contention than the rearrangement products **10a** and **11** are generated by internal return from an ion pair. As nitrenium ions become less stable, reactions with all nucleophiles will eventually become diffusion controlled and ion pairs such as **13** will decompose without an activation barrier. Consequently, they will not have a finite lifetime.

Nitrenium Ions and Carcinogenicity. This is the first report which demonstrates that nitrenium ions derived from a strongly carcinogenic *N*-arylhydroxylamine derivative have the requisite properties to react in a selective manner with biological nucleophiles, such as the bases of DNA, in an aqueous environment. Although the lifetimes of nitrenium ions derived from carcinogenic esters of other *N*-arylhydroxylamines such as **15** and **16** have not yet been determined, it appears from the structures of these species that they will also be relatively long-lived ions. This does not prove that these compounds undergo only nitrenium ion reactions *in vivo*. For example, **1c** itself has been shown to undergo S_N2 reactions with aromatic amines in MeOH.[4b] Admittedly, this solvent does suppress the ionization reaction to form the nitrenium ion, but under the same conditions **1a** reacts with the same amines by an S_N1 mechanism.[25] Apparently, we still have much to learn about the chemistry of these materials and the relationship of that chemistry to their carcinogenicity.

Acknowledgment. This work was supported by a grant from the American Cancer Society (CN-23J). Electron ionization high-resolution mass spectra were obtained at the Ohio State University Chemical Instrumentation Center, and high-resolution FAB spectra were obtained by Dr. Carolyn Cassady at Miami on a Bruker CMS-47X FT-ICR spectrometer funded by the Ohio Board of Regents Academic and Research Challenge Programs.

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