ture. The crude product **8** is purified by recrystallization from dichloromethane/diethyl ether or dichloromethane/ethyl acetate/diethyl ether via solvent diffusion (compare above).

Characteristic data of compounds **8a–c** are shown in Table II.

**Thermolysis of 1-Diazonio-2,3-bis(diisopropylamino)cyclopropenium Bis(hexachloroantimonate) (6d).** Solid **6d** (1.866 g, 2 mmol) (compare above) is continuously heated in a Schlenk tube to 130 °C under nitrogen atmosphere for 24 h in an oil bath. Beginning nitrogen extrusion is observed at about 75 °C and was complete after about 30 min. The volume of nitrogen was determined as 44.7 mL which is almost equal to 2 mmol. **6d** turned deeply black within 5 min, finally forming a black, oily foam. After cooling to room temperature, the residue was extracted with dichloromethane, followed by acetonitrile; evaporation of the solution and recrystallization of the brown crystalline residue from dichloromethane/diethyl ether yielded 0.151 g (25%) of bright yellow **1d**[10] which was identified by comparison with an independently synthesized sample.

The residue of the extraction does not show any indication of other cyclopropenium-derived products and seems to consist mainly of a totally insoluble dark polymer.

**Protonation of Diazonium Salts 6b and 6d, Giving Salts 16.** To a well-stirred suspension of 0.933 g (1 mmol) of bis(hexachloroantimonate) **6d** in 10 mL of dichloromethane under nitrogen is added rapidly 1.405 mL (0.878 g, 10 mmol) of 54% ethereal tetrafluoroboric acid at room temperature, and stirring is continued for 3 h. During this time, the reaction mixture turns dark brown. By addition of 30 mL of *n*-hexane, all saltlike products are precipitated, and the solvent is removed under nitrogen by decantation. The residue is treated with 5 mL of dichloromethane and 30 mL of hexane 3 times in succession. Finally, the remaining precipitate is dried in vacuo below 1 torr at room temperature overnight, yielding 0.468 g (89%) of **16** as a hygroscopic, yellowish-brown crystal powder: mp 79 °C dec; IR (KBr) 3100 (cyclo-$C_3$–H), 2975, 2700, 2135 ($N_2^+$), 1570 $cm^{-1}$ and very strong tetrafluoroborate absorptions. No NMR spectra could be obtained because of immediate decomposition in all common solvents under nitrogen extrusion, resulting in dark oily tars. Anal. Calcd for $C_{15}H_{29}N_4B_3F_{12}$: C, 34.26; H, 5.56; N, 10.65. Found: C, 35.03; H, 5.72; N, 11.08.

The same compound **16** could be obtained analytically pure from analogous treatment of the bis(tetrafluoroborate) **6b** with a 4 M excess of ethereal tetrafluoroboric acid in 94% yield.

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# Oxidation–Reduction Reactions of *N*-Sulfonoxyacetanilides: Mechanisms of the Halide-Induced Reduction of Models for the Carcinogenic Metabolites of Aromatic Amides

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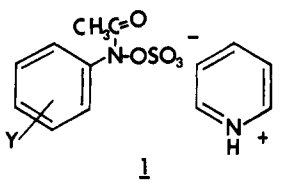
**Abstract:** The solvent-separated nitrenium ion–sulfate ion pairs generated during the hydrolysis of the *N*-sulfonoxyacetanilides undergo reduction in aqueous solutions of halide salts. Similar reactions have been explained previously by invoking the intermediacy of an *N*-halo intermediate which undergoes nucleophilic attack by the halide to generate the reduction product and molecular halogen. Several observations made on the reduction reactions of the *N*-sulfonoxyacetanilides are not entirely consistent with this mechanism. In KCl solution, *N*-sulfonoxy-*p*-bromoacetanilide (**1d**) undergoes reduction simultaneously with halogen exchange to yield *p*-chloroacetanilide (**7c**). This same ester is reduced to *p*-bromoacetanilide (**7d**) in KBr. Halogen exchange can be demonstrated in this case also through the use of $^{79}Br$-enriched KBr. These results can be explained by a reduction mechanism involving the intermediacy of an *N*-acetyl-4,4-dihalo-2,5-cyclohexadienimine (Scheme III). This mechanism accounts for 29 ± 8% of the reduction of **1d** in KBr according to the exchange data, so there must be a second mechanism of reduction. This may be the mechanism involving the *N*-halo intermediate, although there is no evidence which requires this conclusion. Radical-trapping studies indicate that neither path involves radical intermediates.

## Introduction

The sulfate esters of *N*-hydroxyacetanilides (**1**: Y = *p*-$CH_3$, H, *p*-Cl, *p*-Br, *m*-Br, 3,4-diCl) serve as models for the carcinogenic metabolites of aromatic amides.[1] In aqueous solution these




**1**

| | Y |
|---|---|
| 1a | p-$CH_3$ |
| b | H |
| c | p-Cl |
| d | p-Br |
| e | m-Br |
| f | 3,4-diCl |

compounds generate both intimate nitrenium ion–sulfate ion pairs which lead to rearranged products, and solvent-separated ion pairs which can be trapped by various reagents.[2,3] The closely related methanesulfonate esters of *N*-hydroxyacetanilides also decompose via nitrenium ion pathways.[4]

Reduction of **1** to the corresponding acetanilide occurs in aqueous solution in the presence of $I^-$, $Br^-$, and a number of other reagents. This reduction is also a characteristic reaction of *N*-acyloxypurines and *N*-acetoxy-*N*-arylamides such as *N*-acetoxy-*N*-acetyl-2-aminofluorene.[5,6] Although it is not known what role,

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if any, this reaction plays in the in vivo chemistry of these compounds, it has been demonstrated that there is a correlation between the mutagenic and carcinogenic activity of these esters and their tendency to undergo reduction.[6b,c] Similar reductions have been observed in studies involving hydroxylamine-*O*-sulfonate[7] and *N*-*tert*-butyl-*N*-chloroanilines.[8]

Although a number of mechanistic proposals have been made,[5,7,8] little direct evidence concerning the mechanism(s) of this reaction has been reported. As a result of kinetic and product study investigations, and the observation of halogen exchange during the reduction of **1d**, it can now be reported that the reduction of **1** in the presence of halide ions proceeds by two different pathways. One of these involves the intermediacy of a cyclohexadienimine intermediate (**14**, **15**). The other pathway has not been as well characterized, but it may proceed through an *N*-halo intermediate (**13**) that has been previously proposed to be involved in the reduction reactions of *N*-acyloxypurines.[5]

## Experimental Section

**Synthesis and Characterization of the *N*-Sulfonoxyacetanilides (1).** The synthesis, characterization and handling of **1** have been previously described.[2]

**Product Analyses.** Product studies of the solvolysis of **1** were performed at 40 °C in 0.5 M solutions of the salt of interest in 5% $CH_3C$-$N$-$H_2O$. The concentration of **1** employed was ca. 1.25 mM. The products were isolated from the reaction mixture and were identified, in most cases, either by direct comparison with commercially available samples or by comparison of physical and spectral properties with those in the literature. Details of the characterization of the solvolysis products of **1b** and **1c** have been reported previously.[2] The solvolysis of **1d** yields similar or identical products. As described previously,[2] 2-sulfonoxy-4-bromoacetanilide (**4d**), was converted to 2-hydroxy-4-bromoacetanilide (**3d**) during the isolation procedure. **3d** is also a direct solvolysis product of **1d**. This material has not been previously described: mp 194–195 °C; IR (KBr) 3388, 3078, 1656, 1586, 1536, 1408, 1270, 876 $cm^{-1}$; $^1H$ NMR (250 MHz, $CD_2Cl_2$) 2.24 (3 H, s), 6.87 (1 H, d, $J$ = 8.5 Hz), 6.99 (1 H, dd, $J$ = 2.2, 8.5 Hz), 7.13 (1 H, d, $J$ = 2.2 Hz) 7.56 (1 H, s, broad), 9.17 (1 H, s). Anal. Calcd for $C_8H_8NO_2Br$: C, 41.77; H, 3.50; N, 6.09. Found: C, 41.64; H, 3.56; N, 6.09.

The reduction and ring-halogenated products which are the main focus of this paper were characterized as follows. Acetanilide (**7b**), 4-chloroacetanilide (**7c**), 4-bromoacetanilide (**7d**), 2-chloroacetanilide (**5b**), and 2-bromo-4-chloroacetanilide (**9c**) were identified by comparison with commercially available materials (Aldrich, CPL, ICN Pharmaceuticals). The other materials, 2,4-dichloroacetanilide (**5c**), 2-chloro-4-bromoacetanilide (**5d**), and 2,4-dibromoacetanilide (**9d**), were identified from their IR and NMR spectral data, and by comparison of their melting points with literature values.[9] Authentic **9d** was also synthesized by acetylation of 2,4-dibromoaniline (Aldrich). Its properties were identical with those of the material isolated from the product studies.

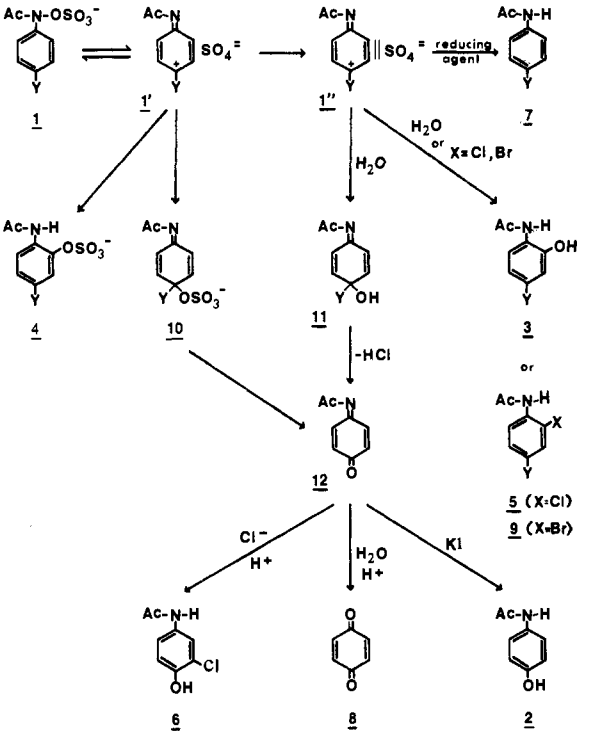
Yields were determined either from the weight of the isolated product or by calibration of HPLC peak areas with authentic samples. Details of these procedures have been previously described.[2]

The solvolysis of **1d** at 40 °C was also carried out in the presence of either 0.01 M *N*-*tert*-butyl-$\alpha$-phenylnitrone (PBN) or of 0.05 M 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy, free radical (4-hydroxy-TEMPO) in 5% $CH_3CN$–$H_2O$ solutions (10 mL) containing either 0.5 M KI or 0.5 M KBr. After the reaction reached completion, the yield of **7d** was determined by triplicate injections on the HPLC.

**Studies with *N*-Acetyl-*p*-benzoquinone Imine (12).** This compound was prepared according to published procedures[10] and was hydrolyzed in aqueous solutions similar to those used for the product studies of the esters **1b**, **1c**, and **1d**. Product analyses were performed on the HPLC as previously described.[2]

**Mass Spectral Analyses.** An HP 5995A GC–mass spectrometer was employed in this study (column: 3% SP-2250 on 80/100 Supelcoport, temperature 130–180 °C). $K^{79}Br$ was purchased from U.S. Services Inc., NJ. Its actual enrichment was determined to be 88.9 ± 0.2% by transforming it to lauryl bromide according to a published procedure[11] and subsequently analyzing the lauryl bromide by GC–MS.

**Scheme I**




**Kinetic Measurements.** Kinetics were performed in the same solutions employed for product studies. The concentration of the esters (**1**) was ca. $5 \times 10^{-5}$ M. The procedures for purification of solvents, preparation of solutions, and monitoring the progress of reactions by UV-visible absorption spectroscopy have been described previously.[2]

## Results and Discussion

Scheme I presents a general mechanistic interpretation of the results of previous investigations into the aqueous solution chemistry of the *N*-sulfonoxyacetanilides (**1**).[2,3] Linear free energy correlations of hydrolysis rate constants for **1a–f** and the nature of the isolated products indicate that **1** decomposes in aqueous solution via a nitrenium ion mechanism.[2,3] Similar studies on the decomposition of the related methanesulfonate esters of the *N*-

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**Table I.** Yields of Products of the Hydrolysis of **1c** and **1d** in 5% $CH_3CN-H_2O$ Containing 0.5 M Potassium Halides at 40 °C[a]

| ester | product | % yields in KCl[b] | % yields in KBr[b] | % yields in KI[c] |
|---|---|---|---|---|
| **1c** | 4-hydroxyacetanilide (**2**) | 3.7 ± 0.5 | trace[d] | 15 ± 3 |
| | 2-hydroxy-4-chloro-acetanilide (**3c**) | 4.9 ± 0.4 | 1.5 ± 0.2 | |
| | 2-sulfonoxy-4-chloro-acetanilide (**4c**) | 41 ± 2 | 39 ± 4 | 37 ± 2 |
| | 2,4-dichloroacetanilide (**5c**) | 20 ± 3 | | |
| | 3-chloro-4-hydroxy-acetanilide (**6**) | 8.0 ± 1.5 | | |
| | 4-chloroacetanilide (**7c**) | | 27 ± 1 | 47 ± 3 |
| | 1,4-benzoquinone (**8**) | 18 ± 4[e] | 18 ± 2[f] | |
| | 2-bromo-4-chloro-acetanilide (**9c**) | | 1.5 ± 0.8 | |
| **1d** | 4-hydroxyacetanilide (**2**) | 1.7 ± 0.1 | trace[d] | 7.9 ± 1.1 |
| | 2-hydroxy-4-bromo-acetanilide (**3d**) | 4.8 ± 0.1 | 1.3 ± 0.1 | |
| | 2-sulfonoxy-4-bromo-acetanilide (**4d**) | 40 ± 3 | 40 ± 3 | 28 ± 2 |
| | 2-chloro-4-bromo-acetanilide (**5d**) | 24 ± 1 | | |
| | 3-chloro-4-hydroxy-acetanilide (**6**) | 4.7 ± 0.2 | | |
| | 4-chloroacetanilide (**7c**) | 5.8 ± 0.1 | | |
| | 4-bromoacetanilide (**7d**) | | 32 ± 5 | 46 ± 2 |
| | 1,4-benzoquinone (**8**) | 10 ± 2[e] | 14 ± 2[f] | |
| | 2,4-dibromoacetanilide (**9d**) | | 2.2 ± 0.3 | |

[a] Initial concentrations of the esters were ca. 1.25 mM. Yields are reported with respect to the initial concentration of ester. [b] Yields were determined from HPLC peak areas. [c] Isolated yields. [d] Present, but in less than 0.5% yield. [e] This product is unstable under the reaction conditions. Yields are estimated from the yields of acetamide, a by-product of the formation of **8**. See ref 2. [f] Yields were determined from an extrapolation based on the initial rate of appearance of **8** since this product is unstable under the reaction conditions. See ref 2.

hydroxyacetanilides in various solvents also support such a mechanism.[4] In this scheme, **1** undergoes N–O bond cleavage to yield a tight nitrenium ion–sulfate ion pair, **1′**, which leads to rearrangement products (**4**, **10**), and a solvent-separated ion pair, **1″**, which can lead to a variety of products. The reasons for invoking two different ion-pair intermediates have been previously discussed.[2]

Although the mechanism of Scheme I is quite general, the various esters do exhibit some differences, particularly with regard to the fate of the intermediates **10** and **11**. If Y is a good leaving group (**1c**, **1d**), these species decompose to yield *N*-acetylbenzoquinone imine (**12**) which subsequently decomposes into **2**, **6**, and **8**.[13] If Y = H (**1b**), **10** and **11** decompose to yield 4-sulfonoxyacetanilide and 4-hydroxyacetanilide (**2**) directly (not shown in the scheme).[2] If Y = $CH_3$ (**1a**), a number of products resulting from Michael addition to **11**, 1,2-migration of $CH_3$, and hydrolysis of the C–N double bond result (also not shown in the scheme), but no evidence for the formation of **12** can be found.[3]

Table I lists the solvolysis products isolated from the decomposition of **1c** and **1d** in 5% $CH_3CN-H_2O$ containing one of the following salts: 0.5 M KI, 0.5 M KBr, or 0.5 M KCl. The reduction products, **7**, which are formed by the interaction of the halide ions with **1″** (see below), and the ring-halogenated materials, **5** and **9**, are of major interest with respect to the topic of this paper. Examination of Table I shows that the halides compete effectively with $H_2O$ to trap **1″** in these cases. The yields of reduction (**7b**) and ring-halogenated products (**7c**, **7d**) only are listed in Table II for **1b**. Since the para position is not blocked by a substituent in this case, ring-halogenation occurs predominantly at that position.

**Table II.** Reduction and Ring-Halogenated Products Obtained from the Hydrolysis of **1b** in 5% $CH_3CN-H_2O$ Containing 0.5 M Potassium Halides at 40 °C[a]

| products | % yields[b] in KCl | % yields[b] in KBr | % yields[b] in KI |
|---|---|---|---|
| acetanilide (**7b**) | | 2.9 ± 0.2 | 14 ± 1 |
| 4-chloroacetanilide (**7c**) | 2.5 ± 0.1[c] | | |
| 4-bromoacetanilide (**7d**) | | 2.5 ± 0.2 | |

[a] Initial concentration of **1b** was ca. 1.25 mM. Yields are reported with respect to **1b** initially present. [b] Yields determined from HPLC peak areas. [c] Traces (less than 0.5%) of 2-chloroacetanilide were also observed.

**Table III.** Values of $I_2{}^{\%}{}_{sat}$ and $K$ from Eq 1 for the Esters **1a–d** with Calculated Yields of $I_2$ at 0.5 M KI and Observed Yields of Reduction Products under the Same Conditions

| ester | $I_2{}^{\%}{}_{sat}$[a] | $K$ (M)[a] | calcd $I_2$ yield (%) in 0.5 M KI[b] | obsd yield (%) of reduction products in 0.5 M KI[c] |
|---|---|---|---|---|
| **1a** | 86 ± 6 | 0.78 ± 0.05 | 34 ± 3 | 37 ± 3 |
| **1b** | 38 ± 9 | 0.92 ± 0.23 | 13 ± 4 | 14 ± 1 |
| **1c** | 61 ± 1 | 0.018 ± 0.002 | 59 ± 1 | 62 ± 4 |
| **1d** | 50 ± 2 | 0.021 ± 0.003 | 57 ± 2 | 54 ± 3 |

[a] Values were determined by a weighted least-squares fit of the data to eq 1. All parameters are reported with their standard deviations. $I_2$ yields as a function of [KI] were determined as described in ref 2. All reactions were performed at 40 °C in 5% $CH_3CN-H_2O$ with initial ester concentration of ca. $5 \times 10^{-5}$ M. [b] Calculated from the parameters listed in this table. [c] Reduction products were: for **1a**, **7a**; for **1b**, **7b**; for **1c**, **7c**, and **2**; for **1d**, **7d**, and **2**. Data for **1b–d** taken from Tables I and II. Yield of **7a** was determined from HPLC peak areas.

According to Scheme I there are two intermediates which can undergo reduction, **1″** and **12**. The reduction of **12** to **2** under various conditions has been observed previously.[10a] KI is a very efficient reducing agent for **12**, although neither KBr nor KCl is effective in reducing authentic **12**. Examination of Table I shows, in fact, that moderate yields of **2** can be obtained when **1c** and **1d** undergo hydrolysis in 0.5 M KI solution. Very little of this product is observed when **1c** and **1d** undergo hydrolysis in KBr or KCl. The reduction of the intermediate **12** can be readily distinguished from the reduction of **1″** since the products of the two processes are different. Since **12** is not formed during the decomposition of **1a** or **1b**, this secondary reduction reaction does not occur in these cases.

In the presence of 0.5 M KI, the sulfate esters **1a–d** yield the corresponding reduction products, **7a–d**, with concomitant formation of $I_2$. The production of $I_2$ was monitored at 352 nm which is the absorption maximum for $I_2$ in this solvent system. In all cases the rate of $I_2$ production is comparable to the rate of sulfate ester decomposition in KCl solutions of the same concentration.[2,14] Plots of $I_2$ yield, as a percent of initial ester concentration, vs. KI concentration can be fit by a standard saturation curve (eq 1).[2]

$$I_2\% = \frac{[KI]\,(I_2\%_{sat})}{K + [KI]} \qquad (1)$$

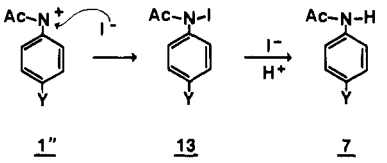
The calculated values of $K$ and the saturation yield of $I_2$, $I_2\%_{sat}$, for **1a–d** are listed in Table III. The calculated yields of $I_2$ at 0.5 M KI are also listed in Table III for the four esters, as are the observed yields of the corresponding reduction products.

Since the saturation yield of $I_2$, is, in all cases, less than 100%, it would appear that $I^-$ does not react directly with the sulfate esters. The presence of KI does not strongly affect the yield of the rearrangement product **4** (see Table I) so $I^-$ does not react with the tight ion pair **1′**. $I^-$ must react with the solvent-separated ion pair **1″**. Table I confirms that products such as **3**, which are

(13) This intermediate (**12**) cannot be directly detected during the hydrolysis reactions of **1c** and **1d** because it undergoes rapid decomposition. However, authentic **12** yields the same products, **2**, **6**, and **8**, in the same proportions as those found in the hydrolysis product mixtures of **1c** and **1d**, when it is subjected to the same hydrolysis conditions. Recent studies of the reactions of *N*-pivaloxy-4-methoxyacetanilide have shown that **12** can be detected by NMR and kinetic methods as an intermediate in the hydrolysis of this compound. Novak, M.; Pelecanou, M., unpublished results.

(14) The rate of decomposition of **1** in KI solution cannot be monitored directly because of strong UV absorbance by the salt.

**Scheme II**




derived from **1''**, cannot be detected in the presence of KI.

The data in Table III show that for **1c** and **1d** the yield of $I_2$ calculated in 0.5 M KI is in good agreement with the sum of the yields of the reduction products, **7c** and **2**, or **7d** and **2**, respectively. Since no hydroxylated products such as **3c** or **3d** can be detected in the presence of 0.5 M KI, it appears that $I^-$ completely scavenges **1c''** and **1d''** to generate the corresponding acetanilides at this concentration. This is reasonable since the yield of $I_2$ has essentially reached saturation in 0.5 M KI in both cases. Since **2** can be detected, **12** must be generated in KI solution. This must occur through the sequence **1'** → **10** → **12**.[2]

The yield of the acetanilide reduction product observed in 0.5 M KI is in good agreement with the calculated yield of $I_2$ for **1a** and **1b** also. Table III shows that KI is less efficient at trapping **1a''** and **1b''** since $K$, the concentration of KI at half-saturation, is much larger for **1a** and **1b** than for **1c** and **1d**. The yield of **7d** was normal when **1d** underwent hydrolysis in 0.5 M KI in the presence of the spin trap PBN[15] (0.01 M), or the radical trap 4-OH-TEMPO[16] (0.05 M).

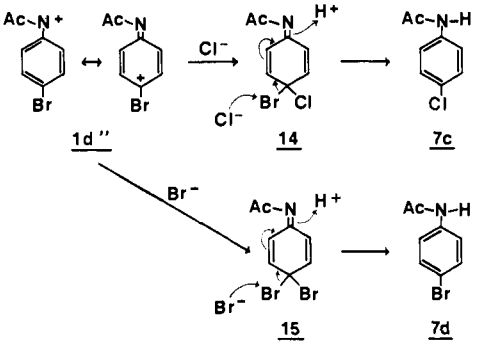
A mechanism analogous to that proposed for the oxidation of $I^-$ by hydroxylamine-*O*-sulfonate[7] and 3-acetoxyxanthine[5] (Scheme II) can explain the formation of **7a–d**, although it is not required by the data. In this mechanism, nucleophilic attack of $I^-$ on the nitrenium ion **1''** forms a reactive *N*-iodo intermediate (**13**). A second nucleophilic attack by $I^-$ at iodine generates $I_2$ and the reduction product. The nitrenium ion is considered[5] to be a "soft" acid according to the Pearson hard and soft acid and base (HSAB) classification.[17] Accordingly, it should exhibit a strong preference for reacting selectively with "soft" base nucleophiles, such as $I^-$. It is of interest to note that $I^-$ does not attack the "hard" acid carbenium ion sites of the delocalized cation **1''** to form ring-iodinated products.

Mechanisms involving triplet nitrenium ions[8,18] or other radical species would seem unlikely since the reduction is not inhibited by the presence of radical trapping species.

The reduction products **7b–d** are observed in the presence of 0.5 M KBr as well (Table I and II). $Br^-$ appears to be a less efficient reducing agent than $I^-$, since the yields of the reduction products are lower compared to their yields in the presence of $I^-$. The solvolysis reactions of **1b–d** were monitored in the visible region where $Br_2$ and $Br_3^-$ show absorption maxima at 405 and 470 nm, respectively.[5b] No $Br_2$ or $Br^{3-}$ were detected under these conditions. Control experiments carried out by injecting a 0.01 M $Br_2$ solution in $CH_3CN$ into a 5% $CH_3CN$–$H_2O$ solution containing 0.5 M KBr showed that $Br_2$ rapidly disappears under these conditions, so any $Br_2$ formed during the solvolysis experiments would escape detection.

The results are also apparently consistent with the reduction mechanism proposed for $I^-$. $Br^-$ is considered a "borderline" base according to HSAB and its reactivity toward the soft nitrogen center is expected to be reduced compared to $I^-$.[5,7] On the other hand, the reactivity of $Br^-$ toward the "hard" acid carbenium ion sites of the delocalized ion is expected to be greater than that of $I^-$. Accordingly, ring-brominated products are generated in low yield (Tables I and II). In KBr **1b** yields 4-bromoacetanilide (**7d**), **1c** gives 2-bromo-4-chloroacetanilide (**9c**), and **1d** yields 2,4-dibromoacetanilide (**9d**).

**Scheme III**




When the solvolysis is carried out in 0.5 M KCl, neither **1b** or **1c** yields any of the reduction products **7b** or **7c**. $Cl^-$, being an HSAB "hard" base,[5c,17] reacts at a carbenium ion site of the delocalized ions **1b''** and **1c''** to yield the ring-chlorinated products 4-chloroacetanilide (**7b**) and 2,4-dichloroacetanilide (**5c**), respectively. In KCl solution **1a** also yields a ring-chlorinated product, 2-chloro-4-methylacetanilide (**5a**), but no 4-methylacetanilide (**7a**).[3] Under the same conditions, **1d**, in addition to the ring-chlorinated product 2-chloro-4-bromoacetanilide (**5d**), yields a moderate amount of the reduction product 4-chloroacetanilide (**7c**) in which halogen exchange has occurred. The remarkable product **7c** alerted us to the existence of an alternative reduction pathway since the previously described mechanism cannot explain its formation. A reasonable mechanism for the formation of **7c** is shown in Scheme III. In this mechanism, $Cl^-$ attacks at the para position of the carbenium ion **1d''** to form the intermediate *N*-acetyl-4-chloro-4-bromo-2,5-cyclohexadienimine (**14**). In the next step, $Cl^-$ attacks at bromine to yield BrCl[19] and the reduction product **7c**.

Several examples in the literature support the proposed scheme.[20] It has been shown that 2,4,4,6-tetrabromocyclohexa-2,5-dienone brominated various types of polyenes under mild conditions; 4-bromo-2,4,6-trichlorocyclohexa-2,5-dienone gave the same products.[20a] The hexadienone was transformed to the corresponding anion which subsequently polymerized. No chlorinated polyenes were isolated. 4-Bromo-2,4,6-trichlorocyclohexa-2,5-dienone has been used as a brominating agent of phenols as well.[20b] These examples illustrate that in such species bromine, rather than chlorine, will undergo nucleophilic attack and serve as the electron source for the reduction of the dienone. Although no examples in the literature involve a 4,4-dihalocyclohexadienimine intermediate directly, the corresponding cyclohexadienones are completely analogous to the proposed intermediate.

In addition, there is evidence for the existence of other 4,4-disubstituted *N*-acetyl-2,5-cyclohexadienimine species. Gassman and Granrud isolated *N*-acetyl-4-methoxy-4-methyl-2,5-cyclohexadienimine from the methanolysis reactions of the methanesulfonate ester of *N*-hydroxy-*p*-acetotoluide,[4b] and we have obtained kinetic and spectral evidence for the intermediacy of *N*-acetyl-4-hydroxy-4-methyl-2,5-cyclohexadienimine during the hydrolysis reactions of **1a**.[3] Gassman and Campbell have also obtained 4-substituted *N-tert*-butyl-4-methoxy-2,5-cyclohexadienimine derivatives from the methanolysis of the corresponding 4-substituted *N-tert*-butyl-*N*-chloroanilines.[21] No attempts were made to isolate the dihalo intermediate because HPLC studies of these reactions always show that the reduction product is formed in a first-order manner with a rate constant equivalent to the rate of decomposition of the sulfate ester. Therefore, dihalo intermediates such as **14** do not build up to detectable levels during these reactions.

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**Table IV.** GC–MS Results for **7d**, **9d**, and **4d**[a] Isolated from the Hydrolysis of **1d** in 0.5 M KBr[b]

| | hydrolysis in normal KBr | hydrolysis in 88.9% enriched $K^{79}Br$ | control[e] |
|---|---|---|---|
| **7d**, $[(M + 2)/M](100)^{c,d}$ | 95.5 ± 0.9 | 78.3 ± 4.5 | 96.1 ± 3.5 |
| **9d**, $[(M + 2)/M](100)^{c,d}$ | 197.6 ± 2.8 | 106.6 ± 4.0 | |
| $[(M + 4)/M](100)^{c,d}$ | 93.3 ± 3.6 | 12.1 ± 0.1 | |
| **4d**,[a] $[(M + 2)/M](100)^{c,d}$ | 97.5 ± 3.9 | 97.5 ± 0.7 | |

[a] **4d** was analyzed as the corresponding methyl ether. See Experimental Section. [b] Experimental details can be found in the Experimental Section and in ref 2. [c] See Experimental Section for *m/e* of bromine containing ions which were used to calculate the (M + 2)/M and (M + 4)/M ratios for **7d**, **9d**, and **4d**. The reported values for each compound are averages of the observed ratios from several determinations with their standard deviations. [d] M + 2 and M + 4 peak intensities were corrected for the presence of other isotopes. [e] A 0.4 mM solution of **7d** was incubated in 0.5 M 88.9% enriched $K^{79}Br$ at 40 °C for the same length of time as in the hydrolysis experiments.

Reduction of **1d** in 0.5 M KBr is expected to involve, at least in part, the pathway of Scheme III. In order to verify this prediction, the hydrolysis of **1d** was carried out in the presence of 88.9 ± 0.2% enriched $K^{79}Br$. The products **7d**, **9d**, and **4d** as its corresponding methyl ether were analyzed for their isotopic bromine content by GC–MS. If the reduction mechanism in KBr involves the symmetric intermediate **15**, bromine exchange should occur and the reduction product **7d** should be enriched in $^{79}Br$. A control experiment was carried out to assure that no bromine exchange took place after the products were formed: authentic **7d** was incubated with enriched KBr under conditions identical with the solvolysis reaction and it was subsequently analyzed by GC–MS. Samples of **7d**, **9d**, and **4d** isolated from the solvolysis of **1d** in normal KBr were also subjected to GC–MS analysis for comparison purposes. Table IV summarizes the results.

The mass spectral data obtained for **4d** and **9d** are in agreement with the mechanism of Scheme I. The (M + 2)/M and (M + 4)/M ratios for **9d** are within 2% of those expected for nucleophilic attack of enriched $Br^-$ at the ortho position of the aromatic ring with no exchange at the para position. Within experimental error, no bromine exchange at the para position was observed during the formation of **4d** either.

However, the (M + 2)/M ratio for **7d**, obtained from the hydrolysis of **1d** in enriched KBr, was decreased by 18% compared to **7d** isolated from the control experiment which showed no exchange (Table IV). This decrease indicates that 29 ± 8% of the reduction proceeds via a pathway involving a symmetric intermediate such as **15**. The remaining **7d** must be produced by a pathway which does not permit halogen exchange to occur.

The solvolysis of **1d** was carried out in the presence of either the spin trap PBN (0.01 M) or the radical trap 4-OH-TEMPO (0.05 M) in 0.5 M KBr solution to test for the possibility of radical involvement in either reduction pathway. Within experimental error, the yield of **7d** is unaffected by the presence of the traps.

The other reduction pathway for **1d** in KBr solution may be similar to that proposed above for the KI reductions, but there is no evidence which requires this conclusion. In view of the results of the trapping experiments, it would appear that neither reduction pathway in KBr involves radical species.

In conclusion, these studies have demonstrated that the reduction of *N*-sulfonoxyacetanilides in aqueous solutions containing halide salts proceeds through two distinct pathways.[22] One of these paths may involve an *N*-halo intermediate, as in Scheme II. The formation of this intermediate is in competition with ring halogenation, and the final product of the reaction is determined by the relative reactivity of the halides toward the nitrenium and carbenium ion sites of **1″**. The "soft" base, $I^-$, reacts exclusively at the nitrenium ion site to generate reduction products. The "borderline" base, $Br^-$, attacks both carbenium and nitrenium ion sites to produce a mixture of ring-halogenated and reduced products. The "hard" base, $Cl^-$, attacks only the carbenium ion sites to generate ring-halogenated products. The data for the hydrolysis of **1b** in which the 4 position is not blocked (Table II) clearly indicate the sites of attack of the halides. It is of particular interest to note that the hydrolysis of **1b** in 0.5 M KI yields no 4-iodoacetanilide.

The second reduction pathway proceeds through attack of halide ion on the ring to form a 4-substituted-4-bromocyclohexadienimine intermediate as in Scheme III. Except for the fortuitous case of **1d**, in which bromine is already present as a ring substituent, this pathway can occur only in the presence of $Br^-$. $Br^-$ is unique among the halides in that it can attack at carbon to generate species similar to **15**, and can subsequently undergo nucleophilic attack itself.

The mechanism of Scheme III will not ordinarily operate in solutions of the other halides. As discussed above, $I^-$ will not attack the ring. $Cl^-$ presumably attacks the 4 position of **1″** in all cases to yield cyclohexadienimine intermediates similar to **14**. However, only in the case of **1d** is an intermediate produced which can lead to reduction products by the mechanism of Scheme III. Chlorine does not undergo nucleophilic attack to generate reduction products in our system or in the related 4,4-dihalocyclohexa-2,5-dienones,[20] although nucleophilic attack on chlorine has been reported in some other systems.[23] It appears that 4-chlorocyclohexa-2,5-dienimine intermediates (except the one derived from **1d**) can only lose $Cl^-$ to return to the cation, **1″**.

The ester **1b** (Y = H) represents a special case. Attack of $Cl^-$ or $Br^-$ at the 4 position of **1b″** yields *N*-acetyl-4-halo-2,5-cyclohexadienimine intermediates which can tautomerize to form the stable ring-halogenated products **7c** or **7d**, respectively.[24]

The *N*-sulfonoxyacetanilides also undergo reduction in aqueous solution in the presence of other reagents such as $SCN^-$ and $Fe^{2+}$.[2] The reaction in the presence of the pseudohalide, $SCN^-$, may very well go by one, or both, of the paths discussed above. However, the $Fe^{2+}$-mediated reduction cannot go by either of these paths. The mechanism of this reduction is currently under investigation.

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**Registry No.** **1a**, 91631-50-4; **1b**, 91631-52-6; **1c**, 91631-54-8; **1d**, 91631-56-0; **1e**, 91631-58-2; **1f**, 91631-60-6; **2**, 103-90-2; **3c**, 16323-09-4; **3d**, 16394-40-4; **4c**, 96648-97-4; **4d**, 96648-98-5; **5c**, 6975-29-7; **5d**, 3460-23-9; **6**, 3964-54-3; **7b**, 103-84-4; **7c**, 539-03-7; **7d**, 103-88-8; **8**, 106-51-4; **9c**, 57045-85-9; **9d**, 23373-04-8.

(22) There may, in fact, be more than two paths, but the most simple explanation of the available data requires only two paths.

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(24) The 2-halogenated products, **5** and **9**, which have been observed in most cases are most likely formed by a similar mechanism.