which would predict relative k_{H_2O} values in the opposite order than is seen. Instead, the relative k_{H_2O} values follow the trend given by the dipole moments[43] for ICl (1.24) > IBr (0.72) > I_2 (0.00). This shows the importance of aquation.

The reactions of IBr_2^- with I^-, with OH^-, and with water parallel the behavior of ICl_2^-. The reactive species with I^- is IBr, while both H_2OIBr and IBr can react with OH^-. The degree of specific H_2O coordination of IBr(aq) (to form H_2OIBr) is less than for ICl(aq). Our best estimate gives 50% H_2OIBr and 50% IBr. The uncertainty is large, but the I^- and base rate constants indicate a lower degree of specific water coordination for IBr. This is consistent with a smaller dipole moment for IBr compared to ICl. Nevertheless, the hydrolysis rate constant for IBr(aq) is 3×10^4 to 6×10^2 larger than previous estimates.[4,5]

This work also shows that the PAF technique can be used to measure very rapid reversible as well as irreversible kinetics.

Acknowledgment. This work was supported by National Science Foundation Grants CHE-8720318 and CHE-9024291.

Registry No. IBr, 7789-33-5; I^-, 20461-54-5.

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Non-Metal Redox Kinetics: A Reexamination of the Mechanism of the Reaction between Hypochlorite and Nitrite Ions

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Hypochlorite oxidation of NO_2^- does not take place by oxygen atom transfer, but proceeds by Cl^+ transfer from HOCl to NO_2^- to give NO_2Cl as a reaction intermediate. The kinetics indicate that the subsequent decomposition of NO_2Cl proceeds by two pathways: loss of Cl^- to give NO_2^+ and reaction of NO_2Cl with NO_2^- to form N_2O_4 and Cl^-. At high Cl^- and low OH^- and NO_2^- concentrations the overall rate of NO_3^- formation is suppressed by Cl^-. The relative reactivities for the reaction with NO_2^+ are $OH^- \gg Cl^- \gg H_2O$. Although oxygen isotope experiments are consistent with a Cl^+ transfer mechanism, the rate of exchange of oxygen between OCl^- and H_2O is relatively rapid (even at high pH in the absence of Cl^-). We predict that the OCl^-/H_2O exchange rate in base will be independent of OH^- concentration.

Introduction

The reaction between hypochlorite ion and nitrite ion (eq 1) has long been one of the classic examples of an oxygen atom

$$OCl^- + NO_2^- \rightarrow Cl^- + NO_3^- \qquad (1)$$

transfer process,[1] and it is still a frequently used textbook example.[2] This is based on the work of Anbar and Taube,[1] who reported that ^{18}O was completely transferred from $^{18}OCl^-$ to give labeled nitrate.

In recent years Margerum and co-workers[3-7] have studied a series of much more rapid redox reactions of hypochlorite, where the overall stoichiometry gives the appearance of oxygen atom transfer (eqs 2-5). All four of these reactions are acid-catalyzed,

$$OCl^- + I^- \rightarrow OI^- + Cl^- \qquad (2)$$

$$OCl^- + Br^- \rightarrow OBr^- + Cl^- \qquad (3)$$

$$OCl^- + SO_3^{2-} \rightarrow SO_4^{2-} + Cl^- \qquad (4)$$

$$OCl^- + CN^- \rightarrow OCN^- + Cl^- \qquad (5)$$

and in each case HOCl is many orders of magnitude more reactive than OCl^-. Direct evidence is found for Cl^+ transfer rather than O atom transfer in the reactions with sulfite[8] and with cyanide.[7] The kinetics and mechanisms in each case indicate nucleophilic attack at chlorine rather than at oxygen to give the initial products in eqs 6-9. Subsequent hydrolysis reactions occur (eqs 10-13)

$$HOCl + I^- \rightarrow ICl + OH^- \qquad (6)$$

$$HOCl + Br^- \rightarrow BrCl + OH^- \qquad (7)$$

$$HOCl + SO_3^{2-} \rightarrow ClSO_3^- + OH^- \qquad (8)$$

$$HOCl + CN^- \rightarrow ClCN + OH^- \qquad (9)$$

$$ICl + 2OH^- \rightarrow OI^- + Cl^- + H_2O \qquad (10)$$

$$BrCl + 2OH^- \rightarrow OBr^- + Cl^- + H_2O \qquad (11)$$

$$ClSO_3^- + H_2O \rightarrow SO_4^{2-} + Cl^- + 2H^+ \qquad (12)$$

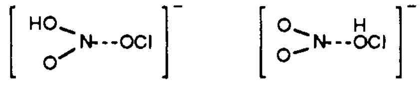
$$ClCN + 2OH^- \rightarrow OCN^- + Cl^- + H_2O \qquad (13)$$

to give the product stoichiometry in eqs 2-5. The kinetics of hydrolysis have been determined for ICl,[9] $ClSO_3^-$,[8] and ClCN.[10]

The question as to why NO_2^- should behave so differently than other nucleophiles prompted us to reexamine the OCl^-/NO_2^- reaction. A simple rate expression (eq 14) is expected from the

$$\frac{-d[OCl^-]}{dt} = k[NO_2^-][OCl^-] \qquad (14)$$

Anbar and Taube[1] mechanism. They did not determine the actual rate expression, but they discussed the possibility that the activated complexes might also include the following two structures:



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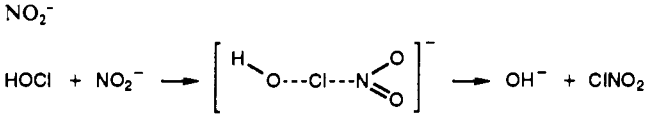
Scheme I. Cl^+ Transfer Mechanism via the HOCl Reaction with NO_2^-



A kinetic study a few years later by Lister and Rosenblum[11] (which ignored the Anbar and Taube paper) reported the rate expression in eq 15 at 50–70 °C in 0.117–0.397 M NaOH.

$$\frac{-d[OCl^-]}{dt} = k[HOCl][NO_2^-] \qquad (15)$$

In 1973, Pendlebury and Smith[12] studied the kinetics of oxidation of nitrite by aqueous chlorine in acid and reported a complex rate expression (eq 16).

$$\frac{-d[Cl_2]}{dt} = \frac{[Cl_2][NO_2^-]}{K'_a[Cl^-]^2}(f + g[HNO_2]) \qquad (16)$$

In this expression, K'_a is the ionization constant for HNO_2 and f and g are combinations of rate constants for a multistep mechanism, where NO_2Cl, $HN_2O_4^+$, and NO_2^+ are reaction intermediates.

In 1976, Cachaza and co-workers[13] studied the kinetics of oxidation of nitrite by hypochlorite in basic solution and also found two paths, one with a first-order dependence in $[NO_2^-]$ and another with a second-order dependence in $[NO_2^-]$ as given in eq 17. They

$$\frac{-d[OCl^-]}{dt} = \frac{[OCl^-][NO_2^-]}{[OH^-]^2}(d + e[NO_2^-]) \qquad (17)$$

adopted a mechanism very similar to that proposed by Pendlebury and Smith with NO_2Cl, N_2O_4, and NO_2^+ as reaction intermediates. Cachaza et al. studied the reaction over a narrow pH range (11.0–11.8) and found a $1/[OH^-]^2$ dependence as shown by eq 17. They also suggested that NO_2^- attacks the chlorine of HOCl to give NO_2Cl, but no mention was made of the significance of their mechanism relative to the proposed oxygen atom transfer mechanism.[1]

In this work, we determine the rate expression of the OCl^-/NO_2^- reaction over a wide pH range (from 7.9 to 13.0) in order to overlap the pH conditions used by Anbar[1] and by Lister.[11] We test the effect of NO_2^-, as well as OH^-, over a much larger range of concentrations than used by Cachaza,[13] and we show that high concentrations of Cl^- can suppress the rate as expected from the Pendlebury and Smith mechanism. Our work verifies this general mechanism and gives new information about the rate constants. As indicated in Scheme I, NO_2Cl is a reaction intermediate (formed by Cl^+ transfer from HOCl to NO_2^-) under the conditions where Anbar believed that oxygen atom transfer occurred. We use ^{15}N NMR methods to distinguish ^{18}O from ^{16}O in the nitrate ion that is the final reaction product. These results contradict Anbar's results[1] and show no evidence for direct O atom transfer. This means that NO_2^- cannot be used in a quench reaction to determine the extent of oxygen atom exchange between water and OCl^-. Therefore, we also use ^{17}O NMR to measure the extent of this exchange and show that the exchange rate is many orders of magnitude faster than previously proposed.[1]

Experimental Section

Reagents. Sodium hypochlorite solutions for most studies were freshly prepared by bubbling $Cl_2(g)$ into aqueous NaOH solutions. In some instances an AR grade 12% NaOCl solution (Mallinckrodt) was used. (The solution was stored in a freezer to minimize the disproportionation of hypochlorite.) All these solutions have equal Cl^- and OCl^- concentrations. "Chloride-free" hypochlorite solutions were prepared by a method similar to that of Cady.[14] In a modified procedure, $Cl_2(g)$ (Matheson ultrahigh purity 99.9%) was bubbled into a slurry of HgO (yellow form) in CCl_4, which was stirred and cooled in an ice bath for 2 h to generate Cl_2O. The slurry was flushed with Ar(g) to remove any dissolved Cl_2 and filtered. The Cl_2O solution in CCl_4 was extracted with a NaOH solution to give aqueous OCl^-. Tests of these solutions showed the $[Cl^-]/[OCl^-]$ ratios to be less than 10^{-4}. The solutions were standardized by iodometric methods[15] and used within 24 h of their preparation. A molar absorptivity value of 350 M^{-1} cm^{-1} for OCl^- at 292 nm was confirmed and used for secondary standardizations.

Nitrite solutions were prepared from reagent grade $NaNO_2$ (J. T. Baker, 97%) and were standardized with OCl^- solutions. (Excess OCl^- at pH 8 was added. After 30 min the solution was adjusted to pH 2 with acetic acid, excess KI was added, and the resulting I_3^- solution was titrated immediately with thiosulfate.)

Sodium hydroxide solutions were standardized by titration with potassium hydrogen phthalate. Buffer solutions were prepared from reagent grade $B(OH)_3$, $NaHCO_3$, and Na_2HPO_4 with appropriate amounts of NaOH. Solutions of NaCl were used for studies of the chloride ion effect. Ionic strength was maintained at 0.50 M with a solution of recrystallized $NaClO_4$ (standardized gravimetrically).

NMR experiments used $Na^{15}NO_2$ (97.2% chemical purity) and $Na^{15}NO_3$ (both 99 atom % ^{15}N) and $H_2{}^{18}O$ (97 atom % ^{18}O), all from MSD Isotopes. $H_2{}^{16}O$ (99.99%) and $H_2{}^{17}O$ (20% enriched) were obtained from Cambridge Isotope Laboratories.

Methods. An Orion Model 601A Research pH meter equipped with a combination electrode was used for pH measurements. Because the observed rate constants change by more than 10 orders of magnitude as the OH^- concentration is varied, it is very important to know the OH^- concentration accurately. Calculated values from standard base were used for reactions studied in 0.10 and 0.17 M NaOH. In lower base, all pH measurements were corrected to $-\log [H^+]$ values by calibration titrations[16] with $HClO_4$ and NaOH solutions in 0.50 M $NaClO_4$. The OH^- concentration was calculated from these $p[H^+]$ values and the pK_w value of 13.72 at 25.0 °C with an ionic strength of 0.50 M.[17]

Kinetic Measurements of the OCl^- and NO_2^- Reaction. The reactions were observed at 25.0 °C by following the loss of OCl^- absorbance at 292 nm, where the ϵ values (M^{-1} cm^{-1}) are 350 (OCl^-), 8.8 (NO_2^-), and 6.4 (NO_3^-). The reactions were studied under pseudo-first-order conditions with constant OH^- concentration for each run and with NO_2^- concentrations in at least 10-fold excess over OCl^- concentrations. Plots of ln $(A - A_\infty)$ vs time gave excellent fits for the first-order decay of OCl^- (eq 18, where $[OCl^-]_T = [OCl^-] + [HOCl]$). The pK_a value for HOCl is

$$\frac{-d[OCl^-]_T}{dt} = k_{obsd}[OCl^-]_T \qquad (18)$$

7.50 at 25.0 °C and an ionic strength of 0.50 M.[6] In order to express the rate constant in terms of OCl^- at the lower pH values, the rate constant is given as $k_{obsd}[(K_a + [H^+])/K_a]$.

Reactions with k_{obsd} values larger than 0.005 s^{-1} were followed with a Dionex-Durrum Model D-110 stopped-flow spectrophotometer (1.88-cm cell path) interfaced to a Zenith 151 CPU with a Metrabyte DASH-16 A/D card. Slower reactions were followed by use of a Perkin-Elmer Model 320 UV-vis spectrophotometer (1.00 cm cell path) with a P-E Model 3600 data station. A hypochlorite reference solution in 0.1 M NaOH was monitored to correct for OCl^- self-decomposition that takes place over the 40-day observation period. The even slower reactions in 0.17 M NaOH used initial rate methods with data taken from a Perkin-Elmer Lambda-9 UV-vis-near-IR spectrophotometer interfaced to a Zenith 386/20 PC. Data were acquired by use of PECSS software with 901 points taken in 90 min. A path length of 0.10 cm was used to permit high concentrations of NO_2^- and OCl^- so that an observable absorbance change could be monitored in a reasonable period of time.

NMR Measurements. A Varian XL-200A spectrometer with a 5-mm broad-band switchable probe was used to obtain ^{15}N spectra at 20.28 MHz. Aqueous solutions of $Na^{15}N^{16}O_3$ were used as an ^{15}N reference (0 ppm). D_2O was added for signal lock after the reaction between NO_2^- and OCl^-. Typical parameters were as follows: 300-Hz sweep width; 10-s acquisition time; 10-s delay; 60–90° pulse width; 0.50-s preacquisition delay; 0.050 line broadening factor.

Varian VXR-500 and VXR-600S spectrometers were used to obtain ^{17}O spectra at 67.7 and 81.3 MHz, respectively. The $^{17}OCl^-$ signal is almost buried under the $H_2{}^{17}O$ signal (reference for 0 ppm). The ^{17}O signal for OCl^- can be resolved from the water peak, because the T_1 of water is longer than the T_1 of hypochlorite. The pulse sequence used to

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Table I. Effect of Hydroxide Ion Concentration on the Kinetics of the OCl^- and NO_2^- Reaction[a,b]

$10^5[OH^-]$, M	$k_{obsd}(K_a + [H^+])/K_a$, s^{-1}	$10^5[OH^-]$, M	$k_{obsd}(K_a + [H^+])/K_a$, s^{-1}
A. $[NO_2^-] = 1.93 \times 10^{-3}$ M, $[OCl^-]_i = 0.15 \times 10^{-3}$ M, $[Cl^-]_i = 0.15 \times 10^{-3}$ M, $[Cl^-]_f = 0.30 \times 10^{-3}$ M, $[B(OH)_3]_T = 0.050$ M			
0.158	12.5 (3)	1.05	0.335 (6)
0.251	5.71 (9)	2.09	0.0790 (8)
0.468	1.87 (6)	3.98	0.0210 (1)
B. $[NO_2^-] = 24.0 \times 10^{-3}$ M, $[OCl^-]_i = 0.36 \times 10^{-3}$ M, $[Cl^-]_i = 0.36 \times 10^{-3}$ M, $[Cl^-]_f = 0.72 \times 10^{-3}$ M, $[CO_3^{2-}]_T = 0.10$ M			
8.71	0.278 (4)	12.0	0.152 (3)
9.33	0.250 (3)	14.1	0.112 (4)
10.0	0.217 (1)	20.4	0.0421 (7)
10.5	0.192 (4)		

[a] Conditions: $\mu = 0.50$ M, 25.0 °C. [b] Numbers in parentheses denote 1 standard deviation (for six trials) in the last decimal place given.

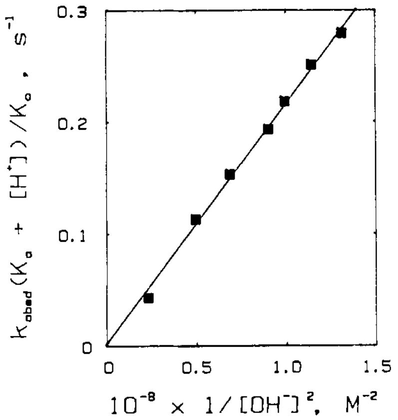

Figure 1. Dependence of k_{obsd} on the inverse square of the hydroxide ion concentration for 0.024 M nitrite reaction with hypochlorite.

null the $H_2{}^{17}O$ signal is (π–T_1(ln 2)–π/2–acquire).[18,19] An Oxford Instruments Model VTC4 instrument was used to control the temperature (±0.5 °C) of the VXR-500 NMR spectrometer. The ^1H methanol signal on the decoupler coil was used for temperature calibration.[20]

Results and Discussion

OH^- Dependence of k_{obsd}. Table I summarizes the effect of variation of the OH^- concentration on the pseudo-first-order rate constant for 1.93 and 24.0 mM NO_2^- concentrations. These data have a $1/[OH^-]^2$ dependence as shown in Figure 1 for the 24.0 mM NO_2^- data.

NO_2^- Dependence of k_{obsd}. Table II summarizes the effect of variation of the NO_2^- concentration for a 2.1×10^4 range of OH^- concentrations. The k_{obsd} values, which are proportional to $1/[OH^-]^2$ over the entire pH range, change by more than 9 orders of magnitude for these data. Figure 2 shows the $[NO_2^-]$ effect at p[H^+] 9.63, where the intercept corresponds to a first-order NO_2^- dependence and the slope corresponds to a second-order NO_2^- dependence. The relative contributions from the first-order and second-order NO_2^- paths are the same at all OH^- concentrations. Figure 3 shows the combined data for variation in both $[NO_2^-]$ and $[OH^-]$ concentrations where eq 19 defines k_{obsd} and

$$k_{obsd} = \frac{K_a[NO_2^-](d + e[NO_2^-])}{([H^+] + K_a)[OH^-]^2} \qquad (19)$$

eq 20 defines the adjusted rate constant, k_{adj}. Some scatter is seen

$$k_{adj} = \frac{k_{obsd}[OH^-]^2}{[NO_2^-]}\left(\frac{[H^+] + K_a}{K_a}\right) = d + e[NO_2^-] \qquad (20)$$

Table II. Effect of Nitrite Ion Concentration at Different $[OH^-]$ on the Kinetics of the OCl^- and NO_2^- Reaction[a,b]

$10^3[NO_2^-]$, M	$k_{obsd}(K_a + [H^+])/K_a$, s^{-1}	$10^3[NO_2^-]$, M	$k_{obsd}(K_a + [H^+])/K_a$, s^{-1}
A. $[OH^-] = 7.94 \times 10^{-6}$ M, $[B(OH)_3]_T = 0.050$ M, $[OCl^-]_i = 9.7 \times 10^{-5}$ M, $[OCl^-]_f = 1.94 \times 10^{-4}$ M			
1.45	0.43 (3)	2.32	0.86 (3)
1.54	0.44 (3)	4.83	2.26 (8)
1.64	0.46 (2)	9.65	5.7 (3)
1.83	0.59 (2)	19.3	22 (3)
2.03	0.75 (1)	29.0	34.4 (9)
2.12	0.74 (2)	38.6	69 (2)
2.22	0.79 (3)		
B. $[OH^-] = 8.12 \times 10^{-5}$ M, $[CO_3^{2-}]_T = 0.050$ M, $[OCl^-]_i = 0.5 \times 10^{-3}$ M, $[OCl^-]_f = 1.0 \times 10^{-3}$ M			
4.84	0.0219 (2)	24.2	0.320 (3)
9.68	0.0640 (2)	29.0	0.445 (3)
14.5	0.129 (2)	33.0	0.595 (3)
19.4	0.213 (1)		
$[NO_2^-]$, M	10^6k_{obsd},[c] s^{-1}	$[NO_2^-]$, M	10^6k_{obsd},[c] s^{-1}
C. $[OH^-] = 0.100$ M, $[OCl^-]_i = 3.0 \times 10^{-3}$ M, $[OCl^-]_f = 6.0 \times 10^{-3}$ M			
0.0869	2.6	0.0965	2.9
0.0917	2.6	0.106	3.4
D. $[OH^-] = 0.170$ M, $[OCl^-]_i = 0.032$ M			
0.080	0.029	0.200	0.15
0.120	0.054	0.240	0.19
0.120	0.059	0.280	0.25

[a] Conditions: $\mu = 0.50$ M, 25 °C, $[Cl^-]_i = [OCl^-]_i$. [b] Numbers in parentheses denote 1 standard deviation (for six trials) in the last decimal place given. [c] The k_{obsd} values in 0.1 M OH^- are adjusted for the self-decomposition of OCl^- that occurs over the 40-day period of observation. Initial rate methods are used for k_{obsd} values in 0.17 M OH^-. The data are for single runs.

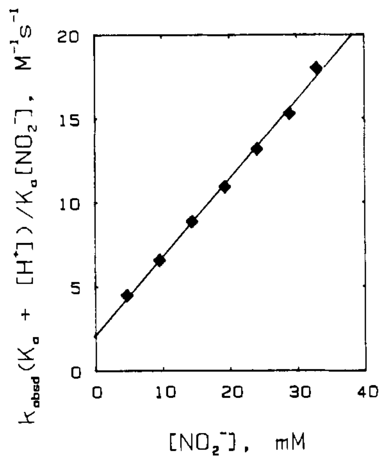

Figure 2. Effect of NO_2^- concentration on the observed rate constant at p[H^+] 9.63. The intercept gives the first-order dependence in NO_2^-, and the slope gives the second-order dependence in NO_2^-.

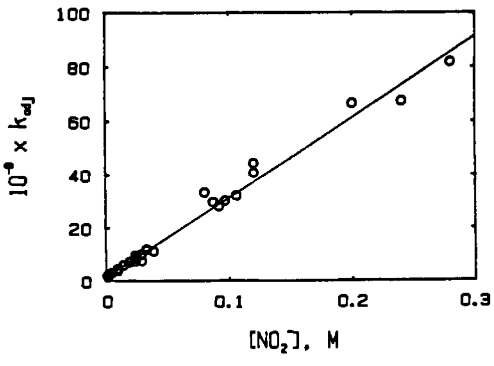

Figure 3. Dependence of the adjusted rate constant (eq 20) on nitrite concentration for all the data with variable OH^- and NO_2^-.

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in k_{adj} values because of the great sensitivity of the rate constants to the hydroxide ion concentration. Nevertheless, all the data fit the dependence in eqs 19 and 20 where $d = (1.4 \pm 0.2) \times 10^{-8}$ M s^{-1} and $e = (3.0 \pm 0.1) \times 10^{-6}$ s^{-1}. This is the same general dependence found by Cachaza et al.[13] Our values are more accurate, because we used a much wider range of concentrations and we collected data where the d term makes a larger percent contribution to the rate. Cachaza's d term was evaluated to be $(3.4 \pm 0.2) \times 10^{-8}$ M s^{-1}, which is a factor of 2.4 too large. His e term was $(2.8 \pm 0.2) \times 10^{-6}$ s^{-1}, which is within experimental error of our value.

Proposed Mechanism. We agree with the mechanism given by Cachaza et al.[13] in eqs 21–26, where HOCl reacts with NO_2^-

$$OCl^- + H_2O \rightleftarrows HOCl + OH^- \quad K_h \qquad (21)$$

$$HOCl + NO_2^- \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} NO_2Cl + OH^- \qquad (22)$$

$$NO_2Cl + NO_2^- \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} N_2O_4 + Cl^- \qquad (23)$$

$$N_2O_4 + OH^- \xrightarrow{k_3} NO_3^- + NO_2^- + H^+ \qquad (24)$$

$$NO_2Cl \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} NO_2^+ + Cl^- \qquad (25)$$

$$NO_2^+ + OH^- \xrightarrow{k_5} NO_3^- + H^+ \qquad (26)$$

by Cl^+ transfer to give nitryl chloride. The NO_2Cl decomposes by two paths: attack by NO_2^- to form N_2O_4 (eq 23) and dissociation to give NO_2^+ and Cl^- (eq 25). If $k_{-1}[OH^-] \gg (k_4 + k_2[NO_2^-])$, then HOCl and NO_2Cl are preequilibrium species. At low pH the concentration of HOCl may be appreciable. However, the concentration of NO_2Cl is negligible under all conditions, and the rate-determining steps are eqs 23 and 25. This leads to the rate expression in eq 27. Thus, $d = K_h k_1 k_4 / k_{-1}$ and

$$\frac{-d[OCl^-]}{dt} = \frac{K_h k_1 [NO_2^-]}{k_{-1}[OH^-]^2}(k_4 + k_2[NO_2^-])[OCl^-] \qquad (27)$$

$e = K_h k_1 k_2 / k_{-1}$. Since the value of K_h is $K_w/K_a = 10^{-13.72}/10^{-7.50} = 10^{-6.22}$ M, $k_1 k_4 / k_{-1} = 2.3 \times 10^{-2}$ s^{-1} and $k_1 k_2 / k_{-1} = 5.0$ M^{-1} s^{-1}, and the ratio k_2/k_4 is 217 M^{-1}.

The N_2O_4 path is preferred over the NO_2^+ path when the nitrite concentration exceeds 4.6×10^{-3} M. Lister and Rosenblum[11] used NO_2^- concentrations from 0.10 to 0.33 M in from 0.12 to 0.40 M NaOH at 50–70 °C and did not report a $[NO_2^-]^2$ rate term. They reported that the rate was proportional to $[NO_2^-]/[OH^-]$. At 25 °C, $OH^- = 0.17$ M, and $[NO_2^-] = 0.28$ M, we find that the $[NO_2^-]^2$ path accounts for more than 98% of the rate and that the rate is proportional to $[NO_2^-]^2/[OH^-]^2$. We have not tested the temperature dependence, but must conclude that either the mechanism changes drastically with increased temperature or an incorrect rate expression was reported.

Chloride Ion Effect. The Pendlebury and Smith[12] mechanism at $[H^+] = 0.17$–0.88 M and $[Cl^-] = 0.50$–1.88 M is given in eqs 28–32 and leads to the rate expression in eq 16, where the rate

$$NO_2^- + Cl_2 \underset{k'_{-1}}{\overset{k'_1}{\rightleftarrows}} NO_2Cl + Cl^- \qquad (28)$$

$$NO_2Cl + HNO_2 \underset{k'_{-2}}{\overset{k'_2}{\rightleftarrows}} HN_2O_4^+ + Cl^- \qquad (29)$$

$$HN_2O_4^+ + H_2O \xrightarrow{k'_3} NO_3^- + HNO_2 + 2H^+ \qquad (30)$$

$$NO_2Cl \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} NO_2^+ + Cl^- \qquad (31)$$

$$NO_2^+ + H_2O \xrightarrow{k'_5} NO_3^- + 2H^+ \qquad (32)$$

depends on $1/[Cl^-]^2$. At high $[Cl^-]$ and high $[H^+]$ values, the rate-determining steps shift to the k'_3 and k'_5 steps (eqs 30 and 32) as opposed to the reactions in base, where the k_2 and k_4 steps (eqs 23 and 25) are rate determining.

Table III. Effect of Chloride Ion Concentration on the Kinetics of the OCl^- and NO_2^- Reaction[a,b]

$[Cl^-]$, M	k_{obsd}, s^{-1}	$k_{obsd}(K_a + [H^+])/K_a$, s^{-1}
A. $[NO_2^-] = 1.93$ mM, $[OH^-] = 2.06 \times 10^{-6}$		
8×10^{-5}	7.0 (2)	9.1
0.031	5.7 (3)	7.4
0.062	5.2 (2)	6.7
0.093	4.4 (2)	5.8
0.124	4.3 (2)	5.6
0.155	3.9 (2)	5.1
0.186	3.7 (2)	4.8
B. $[NO_2^-] = 3.86$ mM, $[OH^-] = 2.13 \times 10^{-6}$		
8×10^{-5}	17 (3)	22
0.031	14.3 (3)	18.5
0.062	12.9 (3)	16.7
0.093	12.1 (1)	15.7
0.124	11.6 (1)	15.0
0.155	11.1 (5)	14.4
0.186	10.7 (2)	13.8

[a] Conditions: $\mu = 0.50$ M, 25.0 °C, 0.05 M $[B(OH)_3]_T$, $[OCl^-]_i = 0.08$ mM. [b] Numbers in parentheses denote 1 standard deviation in the last decimal place given.

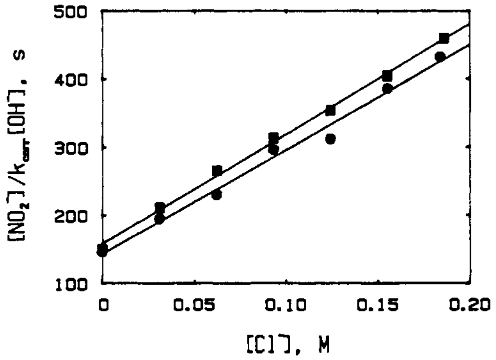


Figure 4. Chloride ion effect on the reciprocal of the corrected rate constant (eq 36): (■) 1.93 mM NO_3^-, 2.06×10^{-6} M OH^-; (●) 3.86 mM NO_3^-, 2.13×10^{-6} M OH^-.

Cachaza[13] showed that 0.3 M Cl^- had no kinetic effect on the reaction rates in 3×10^{-3} M OH^-. In our experiments where $[Cl^-] = [OCl^-]$, we saw no evidence of a Cl^- effect for different levels of initial OCl^- concentration (Tables I and II). This means that under these conditions the following inequalities are valid: $k_3[OH^-] \gg k_{-2}[Cl^-]$ and $k_5[OH^-] \gg k_{-4}[Cl^-]$. Low OH^- concentrations and high Cl^- concentrations are needed to test for a chloride effect. We find that high concentrations of Cl^- decrease the k_{obsd} values at p[H$^+$] 8. The effect is much greater at low NO_2^- than at high NO_2^- concentrations. This indicates that the reversibility of eq 25 contributes to the rate expression (i.e. $k_5[OH^-] \cong k_{-4}[Cl^-]$), while the inequality of $k_3[OH^-] \gg k_{-2}[Cl^-]$ is still valid for these conditions. With these assumptions, the expression for k_{obsd} is given by eq 33, on the basis of a steady-state

$$\frac{k_{obsd}(K_a + [H^+])}{K_a} = \frac{K_h k_1}{k_{-1}[OH^-]}\left(\frac{k_4 k_5 [NO_2^-]}{k_{-4}[Cl^-] + k_5[OH^-]}\right) + \frac{K_h k_1 k_2 [NO_2^-]^2}{k_{-1}[OH^-]^2} \qquad (33)$$

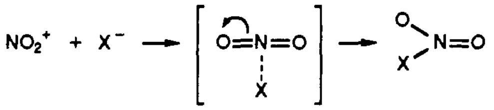
treatment for the NO_2^+ ion. A corrected rate constant (k_{cor}) is given in eq 34, where the $[NO_2^-]^2$ path is subtracted from the

$$k_{cor} = \frac{k_{obsd}(K_a + [H^+])}{K_a} - \frac{K_h k_1 k_2 [NO_2^-]^2}{k_{-1}[OH^-]^2} \qquad (34)$$

observed rate constant. The k_{cor} dependence on NO_2^-, OH^-, and Cl^- concentrations is given by eq 35. This equation can be

$$k_{cor} = \frac{K_h k_1 [NO_2^-]}{k_{-1}[OH]}\left(\frac{k_4 k_5}{k_{-4}[Cl^-] + k_5[OH^-]}\right) \qquad (35)$$

Scheme II. Proposed Mechanism for the Reaction of Nucleophiles (X^-) with NO_2^+



rearranged to give a linear dependence on chloride ion concentration (eq 36). Table III summarizes data for the Cl^- effect

$$\frac{[NO_2^-]}{k_{cor}[OH^-]} = \frac{k_{-1}(k_{-4}[Cl^-] + k_5[OH^-])}{K_h k_1 k_4 k_5} \qquad (36)$$

at two NO_2^- concentrations with slightly different OH^- concentrations. Figure 4 plots the left-hand side of eq 36 against $[Cl^-]$ for each set of data. The ratio of the intercept/slope values in Figure 4 equals $k_5[OH^-]/k_{-4}$. This gives k_5/k_{-4} values of $(4.6 \pm 0.3) \times 10^4$ for both sets of conditions. The linearity of the plots and the agreement of the k_5/k_{-4} ratios at different NO_2^- concentrations validates the assumptions. Tests at higher NO_2^- concentrations gave no evidence of contributions from the reversibility of eq 23. Therefore, the k_3/k_{-2} ratio must be considerably larger than 10^6.

Comparison of Rate Constants in Acid and in Base. The Pendlebury and Smith study in acid gave the ratio of rate constants (25.2 °C, μ = 2.75 M) in eq 37, while our study in base evaluated

$$\frac{k'_1 k_4 k'_5}{k'_{-1} k_{-4}} = \frac{60.8}{K'_a} \qquad (37)$$

the $K_h k_1 k_4 / k_{-1}$ ratio as 1.4×10^{-8}. By using $K'_a = 5.1 \times 10^{-4}$ and $K_h = 6.03 \times 10^{-7}$ and by neglecting the difference in ionic strength, we can combine these relationships to give eq 38. It

$$\left(\frac{k'_1 k_{-1}}{k'_{-1} k_1}\right)\frac{k'_5}{k_{-4}} = 5.1 \times 10^6 \qquad (38)$$

can be shown from the equilibrium hydrolysis constant of Cl_2 (0.5 μ, 25.0 °C)[21] that the ratio $(k'_1 k_{-1}/k'_{-1} k_1)$ equals $10^{10.72}$ and this leads to eq 39. With 10^{-3} M or greater Cl^- concentrations in acid

$$\frac{k'_5}{k_{-4}} = 9.8 \times 10^{-5}\ \mathrm{M} \qquad (39)$$

solutons, $k'_5 \ll k_{-4}[Cl^-]$, and the rate-determining step (k'_5) is the hydrolysis of NO_2^+.

Our results in base give the ratio in eq 40, so that $k_5[OH^-] > k_{-4}[Cl^-]$, unless low $[OH^-]$ and high $[Cl^-]$ values are used. At

$$\frac{k_5}{k_{-4}} = 4.6 \times 10^4 \qquad (40)$$

low Cl^- concentration in basic solutions, the rate-determining step (k_4) is the dissociation of NO_2Cl to give NO_2^+, which then reacts rapidly with OH^-. This comparison also permits the relative reactivity of NO_2^+ with OH^- and with H_2O to be estimated (eq 41). If we use the molarity of water (55.5 M) to give the same

$$\frac{k_5}{k'_5} = 4.7 \times 10^8\ \mathrm{M}^{-1} \qquad (41)$$

units (k''_5 (M^{-1} s^{-1}) = $k'_5/55.5$), then the ratio k_5/k''_5 is 2.6×10^{10}. Hydroxide ion is 10 orders of magnitude more reactive with NO_2^+ than is H_2O, and OH^- is 4.6×10^4 times more reactive than Cl^-. Scheme II shows the proposed nucleophilic attack of X^- on NO_2^+.

^{15}N NMR Studies of the $^{18}O/^{16}O$ Composition of Nitrate Ion. The ^{15}N chemical shift in nitrate ion depends on the isotopic composition of the oxygens.[22] A 0.056 ppm shift of the ^{15}N signal occurs per ^{18}O in NO_3^-. The isotopic exchange of NO_2^- and of NO_3^- with water is slow.[23,24] Therefore, NMR studies of nitrate ion after the reaction between $^{15}N(^{16}O)_2^-$ in $H_2{}^{18}O$ with $^{16}OCl^-$ provide a much more direct method to measure the isotopic composition of the products than the previously used procedures.[1] If O atom transfer from $^{16}OCl^-$ to $^{15}N(^{16}O)_2^-$ takes place, the product should be $^{15}N(^{16}O)_3^-$. Figure 5 shows the observed spectrum of the products, where the $^{15}N(^{16}O)_2{}^{18}O^-$ composition of the products is the same as the percent ^{18}O in the solvent. This is the expected result for the Cl^+ transfer mechanism where the third oxygen in NO_3^- comes from the solvent (eqs 22, 24, 26). In these experiments (Table IV), the $^{15}NO_2^-$ solutions were prepared by the addition of $Na^{15}NO_2$ solid to the previously buffered $H_2{}^{18}O$ solutions and used within an hour to prevent $^{18}O/^{16}O$ exchange of the nitrite ion before reaction. Chloride-free OCl^- solutions were prepared in H_2O (1% ^{18}O) with carbonate buffer at p[H^+] 9.68. These solutions were mixed to give the initial concentrations (Table IV), and the $^{18}O/^{16}O$ composition of the NO_3^- was determined within 24 h. Under these conditions neither the NO_2^- nor NO_3^- will exchange with $H_2{}^{18}O$.

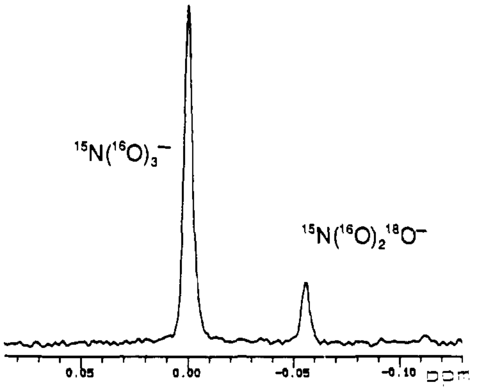


Figure 5. ^{15}N NMR (20.28 MHz, 25 °C) spectrum showing that the isotopic composition of nitrate (formed from hypochlorite and nitrite) depends on the $H_2{}^{18}O$ content of the solvent.

Table IV. ^{15}N NMR Determination of $^{18}O/^{16}O$ Composition of NO_2^-[a]

$[NO_2^-]$,[b] M	$[OCl^-]$,[b] M	% ^{18}O in H_2O	% ^{18}O in NO_3^-[c]
0.28	0.29	23	21
0.19	0.38	15	15

[a] p[H^+] 9.68, $[CO_2^{2-}]_T$ = 0.05 M, 25.0 °C, Varian XL-200A. [b] Natural abundance ^{18}O = 1%. [c] Direct O atom transfer would give 1% ^{18}O.

Anbar's values[1] for the rate of OCl^-/H_2O exchange under these conditions (high pH, no Cl^-) would predict negligible exchange of $^{16}OCl^-$ with $H_2{}^{18}O$ compared to the rate of reaction of OCl^- with NO_2^-. We can conclude from our isotope experiments and from our mechanistic studies that Anbar should not have observed evidence for oxygen atom transfer from OCl^- to NO_2^- under the conditions used. However, this also means that NO_2^- cannot be used as a quenching reagent to measure the extent of oxygen exchange between OCl^- and H_2O. Therefore, the reported exchange rate[1] was not actually measured and this exchange rate is unknown. If oxygen exchange for OCl^-/H_2O is slow, our isotope labeling experiments prove that direct oxygen atom transfer does not occur. On the other hand, if the O atom exchange of OCl^-/H_2O is very fast, the ^{18}O content of OCl^- and H_2O will be the same regardless of whether a Cl^+ transfer or an O atom transfer mechanism is correct.

Oxygen Exchange of OCl^- with H_2O. We elected to use ^{17}O NMR methods to measure the rate of exchange in eq 42. The

$$OCl^- + H_2{}^*O \rightleftarrows {}^*OCl^- + H_2O \qquad (42)$$

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Table V. Chemical Shifts for ^{17}O Species

species	δ values, ppm	
	measd[a]	lit.
H_2O	0^b	0^b
ClO^-	12 ± 3	
ClO_2^-	141 ± 3	
ClO_3^-	284 ± 3	290^c
NO_2^-	655 ± 5	
NO_3^-	406 ± 5	410^d
CO_3^{2-}	181 ± 3	192^e

[a] Varian VXR-600S NMR, $\mu = 1.0$ M, 20–23 °C. [b] Referenced to the $H_2{}^{17}O$ signal at 0 ppm. [c] Alei, M. *J. Chem. Phys.* **1965**, *43*, 2904–2906. [d] Andersson, L. O.; Mason, J. *J. Chem. Soc. Dalton Trans.* **1974**, 202–205. [e] Figgis, B. N.; Kidd, R. S.; Nyholm, R. S. *Proc. R. Soc. London, A* **1962**, *269*, 469–480.

Table VI. Water–Hypochlorite ^{17}O Exchange[a]

$[OH^-]$, M	$[OCl^-]$, M	temp, °C	exptl $t_{1/2}$,[b,c] s
0.68	0.23	15	<130
0.80	0.10	15	<130
0.62	0.29	15	<130
0.68	0.23	25	<130

[a] Varian VXR-500 NMR, $\mu = 1.0$ M. [b] $[Cl^-] < 1 \times 10^{-5}$ M; exchange is complete within the mixing and observation time interval. [c] The calculated $t_{1/2}$ values from ref 1 are $(7.4–9.5) \times 10^6$ s.

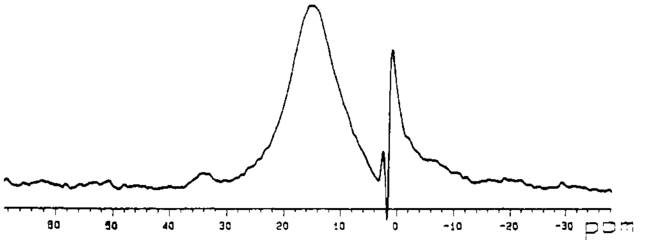

Figure 6. ^{17}O NMR signal for $^{17}OCl^-$ in $H_2{}^{17}O$ (0 ppm) with a pulse sequence to suppress the $H_2{}^{17}O$ signal at 67.7 MHz (Varian VXR-500 instrument) and 25.0 °C.

$^{17}OCl^-$ signal had not been previously reported, nor could we find values for ClO_2^-. Table V summarizes the ^{17}O chemical shifts for OCl^-, for ClO_2^-, and for other species of interest in this study. It is difficult to find the $^{17}OCl^-$ signal because it is so close to the $H_2{}^{17}O$ signal. Nevertheless, the use of high-field NMR instruments (500 or 600 MHz ^1H) and techniques to null the $H_2{}^{17}O$ signal makes it possible to see a distinct $^{17}OCl^-$ peak with reasonable signal-to-noise values (Figure 6). The identity of the signal was verified by its disappearance after the addition of NO_2^-.

We attempted to measure the exchange rate in eq 42 by mixing Cl^--free $^{16}OCl^-$ in high concentrations of OH^- (^{17}O natural abundance, 0.037%) with $H_2{}^{17}O$ (20% ^{17}O) at 15 or 25 °C (Table VI). The final ^{17}O content of the solution is 2–4%. It was about 520 s from the time of mixing until reliable data could be acquired. The exchange reaction was at least 94% complete after this time interval. The exchange half-life must be less than 130 s ($k_{ex} > 5.3 \times 10^{-3}$ s^{-1}) under these conditions, because we observed no change of signal with time. This exchange rate is at least a factor of 7×10^4 faster than calculated from Anbar's results for these conditions.[1]

The ^{17}O NMR data show resolvable peaks for OCl^- and H_2O and no evidence of exchange broadening from 5 to 35 °C. Therefore, the k_{ex} value must be at least a factor of 4 less than $\pi/\sqrt{2}(12 \text{ ppm} \times 67.7 \text{ MHz})$,[25] that is, it is less than 5×10^2 s^{-1}. In summary, our results indicate that the k_{ex} value for eq 42 must be between 5×10^{-3} and 5×10^2 s^{-1}, which is a difficult range to measure even by NMR methods.

Proposed Exchange Mechanism for OCl^- and H_2O. Our studies of HOCl reactions with CN^-, SO_3^{2-}, I^-, Br^-, and NO_2^- show that these nucleophiles react at the chlorine atom in HOCl. We expect OH^- to behave similarly (Scheme III). This leads to the mechanism in eqs 43–46 for isotopic exchange by $*OCl^-$ and H_2O.

Scheme III. Proposed Mechanism for Oxygen Exchange via OH^- Attack on HOCl

$$H{*}OCl + OH^- \rightleftharpoons (H{*}O{-}Cl{-}OH) \rightleftharpoons {*}OH^- + HOCl$$

$$*OCl^- + H_2O \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} H*OCl + OH^- \qquad (43)$$

$$H*OCl + OH^- \underset{k_b}{\overset{k_b}{\rightleftharpoons}} *OH^- + HOCl \qquad (44)$$

$$HOCl + OH^- \underset{k_a}{\overset{k_{-a}}{\rightleftharpoons}} OCl^- + H_2O \qquad (45)$$

$$*OH^- + H_2O \underset{k_c}{\overset{k_c}{\rightleftharpoons}} H_2*O + OH^- \qquad (46)$$

The proton transfer reaction in eq 46 is known to be very fast.[26] Equations 43 and 45 are also rapid proton-transfer reactions; a k_{-a} value of 1.9×10^{10} M^{-1} s^{-1} was determined recently.[7] The Cl^+ transfer reaction in eq 44 is expected to be rapid, but not as fast as the H^+ transfer reactions. Therefore, $k_b[OH^-] \ll k_{-a}[OH^-]$ and the exchange rate constant (k_{ex}) is given by eq 47, where there

$$k_{ex} = \frac{k_a}{k_{-a}} k_b = K_h k_b = 10^{-6.22} k_b \qquad (47)$$

is no OH^- concentration dependence. Our ^{17}O NMR data indicate that k_{ex} (s^{-1}) falls between 5×10^{-3} and 5×10^2, so that k_b (M^{-1} s^{-1}) must be between 9×10^3 and 8×10^8.

Rate constants for the reactions of nucleophiles with HOCl have been shown[7] to follow the Swain–Scott relationship[27] (eq 48),

$$\log\left(\frac{k}{k_0}\right) = sn \qquad (48)$$

where n is the nucleophilicity and the sensitivity factor, s, is 4.7. With an n value of 4.20 for OH^-, the correlation predicts a k_b value (for OH^- attack at the chlorine of HOCl) of 4.5×10^4 M^{-1} s^{-1} at 25 °C. This value is only a factor of 5 larger than the lower limit obtained from the ^{17}O data. The predicted k_{ex} value from eq 47 is 2.7×10^{-2} s^{-1}. This corresponds to a half-life of 25 s for the exchange process, which is outside the experimental range possible with the present design of our 500- and 600-MHz NMR instruments, because it takes much longer than this to mechanically insert the samples and obtain the first spectrum.

In summary, we predict that the exchange rate for $*OCl^-$ with H_2O will be independent of $[OH^-]$ (above pH 8.5) and will have a half-life of about 25 s. If the prediction is correct, the time required for the OCl^-/NO_2^- reaction (>90% complete under the conditions given in Table IV) will be at least 2 orders of magnitude less than the half-life of the OCl^-/H_2O exchange. A consequence of this prediction is that the $^{16}O/^{18}O$ ratio found in $^{15}NO_3^-$ would be valid supporting evidence of the Cl^+ transfer mechanism. Our ^{15}N–$^{16}O/^{18}O$ results are important in any case, because they show that the isotope labeling evidence for O atom transfer that was given 33 years ago[1] cannot be correct.

Conclusions. Mechanistic data show that the reaction between OCl^- and NO_2^- is not an oxygen atom transfer process. Instead, the reaction occurs by a Cl^+ transfer process via HOCl and forms NO_2Cl as an intermediate species.

Our evidence of the Cl^- dependence in base together with earlier studies[12] in acid show that the relative values of the rate constants of NO_2^+ reactions for OH^-:Cl^-:H_2O are 4.6×10^4:1:1.8×10^{-6}. The rate constants are highly dependent on the nucleophilic strength of these three species. A sensitivity factor (eq 48) of 4.0 is needed when NO_2^+ is the electrophile, to account for the relative

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nucleophilic reactivity of OH^- versus Cl^-.

The previously reported[1] rate of oxygen atom exchange between OCl^- and H_2O is not correct. We show that the rate is relatively rapid even in Cl^--free solutions with high OH^- concentrations. Our ^{17}O studies indicate that the exchange rate constant is greater than 5×10^{-3} s^{-1} and is less than 5×10^{2} s^{-1}. On the basis of a previous correlation[7] for rate constants of nucleophiles with HOCl, we predict a rate constant equal to approximately 4.5×10^4 M^{-1} s^{-1} for the transfer of Cl^+ from HOCl to OH^-. This would correspond to an exchange rate constant of 2.7×10^{-2} s^{-1} for OCl^- and H_2O (a $t_{1/2}$ value of 25 s) that is independent of OH^- and Cl^- concentrations.

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Registry No. HOCl, 14380-61-1; NO_2, 14797-65-0; Cl, 16887-00-6.

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Kinetic and Equilibrium Studies of the Complexation of Aqueous Iron(III) by Daunomycin, Quinizarin, and Quinizarin-2-sulfonate

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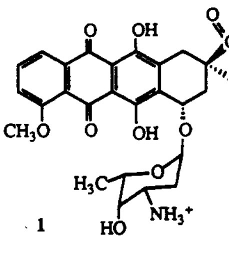
The equilibria and kinetics for the reaction of solvated iron(III) with daunomycin, quinizarin, and quinizarin-2-sulfonate have been studied in 0.01 and 0.06 M H^+, at 25 °C in 0.50 M $NaClO_4/HClO_4$ in water and 42.8% by volume methanol for quinizarin. The ligands (QzH_2) all have the 1,4-dihydroxyanthraquinone function, which is used to complex iron(III) to give $(H_2O)_4Fe^{III}(QzH)$ and $((H_2O)_4Fe^{III})_2(Qz)$ complexes from the analysis of the spectrophotometric equilibrium data with [Fe(III)] $\gg$ [QzH_2]. Stopped-flow kinetic studies indicate that the reaction is biphasic and this is attributed to successive formation of $(H_2O)_4Fe^{III}(QzH)$ and $((H_2O)_4Fe^{III})_2(Qz)$. The major reaction pathway for the two stages involves hydrolyzed iron(III) ($(H_2O)_5FeOH^{2+}$) and QzH_2 or $(H_2O)_4Fe^{III}(QzH)$, but the reaction of the bis(μ-hydroxo)iron(III) dimer with QzH_2 and $(H_2O)_4Fe^{III}(QzH)$ makes a significant contribution. Daunomycin is generally about 20 times slower to react than the other ligands. The rate constants for the various stages and paths are compared and discussed.

Introduction

This study was undertaken to investigate the kinetics of complexation of aqueous iron(III) by daunomycin (daunorubicine) (**1**). Daunomycin and the structurally similar adriamycin (doxorubicin) (**2**) show outstanding anticancer potency although they have quite different ranges of application[1] and adriamycin has about twice the cardiotoxicity of daunomycin.[2,3] Zweier and co-workers[4-6] have observed that adriamycin is complexed and oxidized by aqueous iron(III) while daunomycin forms a complex with iron(III) but is not oxidized. Zweier suggested that the oxidation involves the ketol sidechain of adriamycin and that the toxicity is realted to radical products of the oxidation, while Gianni et al.[7] isolated the major oxidation products.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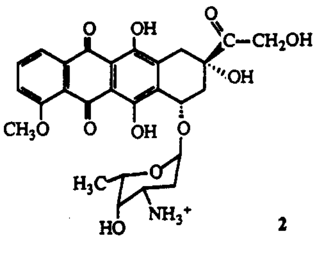
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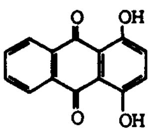
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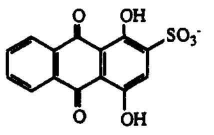
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In order to provide kinetic background information, the functionally related quinizarin (1,4-dihydroxy-anthraquinone) (**3**) and quinizarin-2-sulfonate (**4**) also have been studied. Daunomycin has several potential sites for coordination of iron, but the hydroxyquinone function would be the expected site, and the behavior of daunomycin should parallel that of the simpler hydroxyquinones if this is true. Previous experience[8,9] has shown that a knowledge of the equilibrium constants for complex formation is very useful for the kinetic interpretation of such systems. Kiraly and Martin[10] reported the pK_a's and equilibrium constants for the 1:1 iron(III) complexes of quinizarin (in 50% ethanol) and daunomycin. The quinizarin-2-sulfonate ($QzSH_2^-$) system was studied spectrophotometrically by Thomson and Atkinson,[11] who concluded that there are $FeQzSH^+$ and $Fe_4(QzSH)_3^{6+}$ complexes, but the conclusions were critized by Budesinsky[12] because only one acidity was used. Preliminary spectrophotometric and kinetic studies indicated that these systems may not have been fully characterized, and new multiwavelength spectrophotometric equilibrium measurements are reported here.

Biochemical studies have concentrated on the tris(daunomycin) and tris(adriamycin) complexes of iron(III). The main question is whether the iron(III) complexes are strong enough to persist in the biological system at adventitious iron(III) concentrations (~2 μM) and in competition with transferrin ($K = 10^{31}$), but this work has largely ignored the oxidation of adriamycin. May et al.[13] studied adriamycin complexation potentiometrically and spectrophotometrically and reported $\beta_3 = 10^{33.4}$ M^{-3}. Beraldo et al.[14] critically discussed some of the work of Kiraly and Martin and May et al. and differences in the ligand pK_a values. Martin[15]

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