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Reactions of 10-methyl-9,10-dihydroacridine with inorganic oxidants

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Reactions of 10-methyl-9,10-dihydroacridine with inorganic oxidants

by

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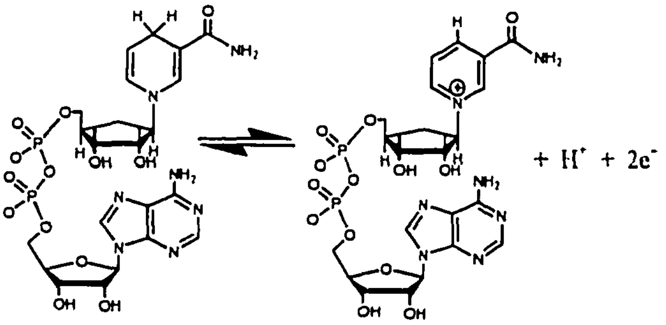
GENERAL INTRODUCTION

Introduction

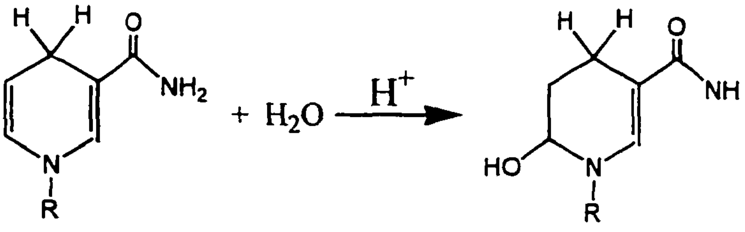
Dihydropyridines and their substituted analogs have attracted considerable attention due to their importance as dihydronicotinamide dinucleotide (NADH) models in biological redox reactions.[1-4]



NADH NAD+

References 1 through 4 correspond to the NADH studies, NADH modeling studies, free radicals and radical-cations of dihydropyridine analogs and their properties, and nonradical chemistry of dihydropyridines, respectively.

In particular, 10-methyl-9,10-dihydroacridine ($AcrH_2$) has been successfully employed in mechanistic studies of its reactions with various organic and inorganic oxidizing reagents.[5] The unique stability of dihydroacridines towards acid-catalyzed hydrolysis[6] (eq 1) has allowed extensive kinetic studies of their reactions with strong inorganic oxidants that often require acidic media.

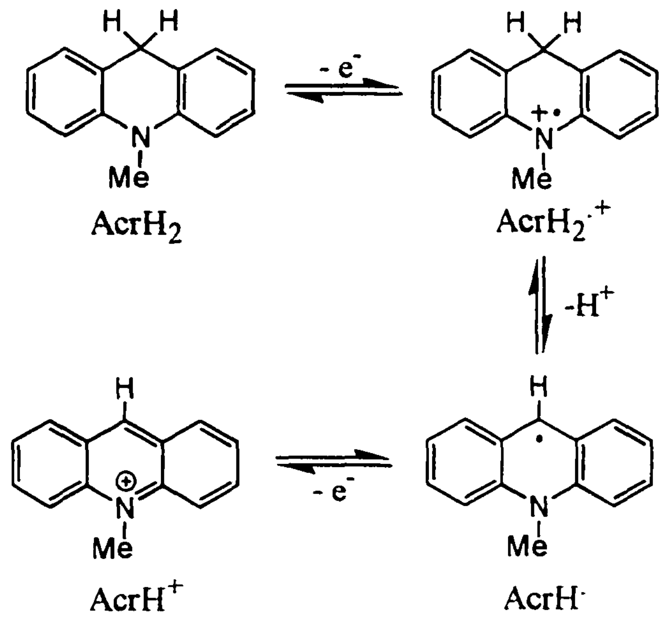


(1)

Hydride transfer, hydrogen atom abstraction, and electron transfer mechanisms have been proposed for oxidation of $AcrH_2$ by various organic and inorganic reagents. Hydride transfer was found in self-exchange reactions between dihydropyridine analogs and corresponding pyridinium cations. Similar mechanism was observed in oxidation of $AcrH_2$ by ketones and other carbonyl-containing compounds (Kreevoy, 1983). Hydrogen atom abstraction mechanism was reported for oxidation of $AcrH_2$ by oxygen and alkyl or aryl halides (Fukuzumi, 1983). Electron transfer oxidation of $AcrH_2$ was recently reported in the reactions with Cu^{2+}, $Fe(phen)_3^{3+}$, and Fe^{3+} in acetonitrile (Saveant, 1990; Fukuzumi, 1993).

Electrochemical properties of $AcrH_2$ are also well known from recent studies by Saveant and Fukuzumi. Scheme I shows electrochemical reactions of $AcrH_2$ in acetonitrile.

Scheme I



E^0 ($AcrH_2^{\bullet+}/AcrH_2$) = 1.02 V (vs. NHE)
E^0 ($AcrH^+/AcrH^\bullet$) = -0.19 V (vs. NHE)
pK_a ($AcrH_2^{\bullet+}$) = 7-8 (Fukuzumi), 0.6 (Saveant)

Bruice et al.[7] have reported a kinetic study of the oxidation of dihydropyridines by ferricyanide to the corresponding pyridinium cations in two consecutive one-electron steps, with the first step being rate controlling, eq 2.

$$PyH_2 \underset{Fe(CN)_6^{4-}}{\overset{Fe(CN)_6^{3-}}{\rightleftharpoons}} PyH_2^{\cdot +} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} PyH^{\cdot} \xrightarrow{Fe(CN)_6^{3-}} Py^+ \quad (2)$$

Recently, a similar mechanism for oxidation of $AcrH_2$ by tris-phenanthroline iron(III) complex in acetonitrile (AN) has been proposed by Fukuzumi et al.,[8] eq 3.

$$AcrH_2 \xrightarrow{Fe(phen)_3^{3+}} AcrH_2^{\cdot +} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} AcrH^{\cdot} \xrightarrow{Fe(phen)_3^{3+}} AcrH^+ \quad (3)$$

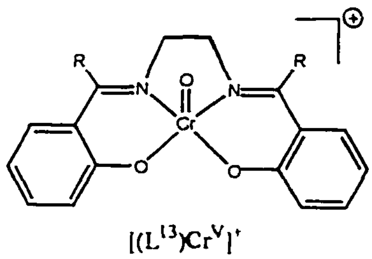
In this mechanism, the deprotonation of the radical cation is rate-controlling. The dihydropyridine radical cation was identified and characterized by UV-VIS and ESR spectroscopy. The pK_a of the radical cation was also determined.

Several factors, such as the oxidizing strength of the reagents used or the medium, can be responsible for the change in the rate-controlling step from the initial electron transfer to the deprotonation of the radical cation. It is still unknown which factors are most important. A further mechanistic study utilizing a systematic change in these factors should provide necessary information to answer this question.

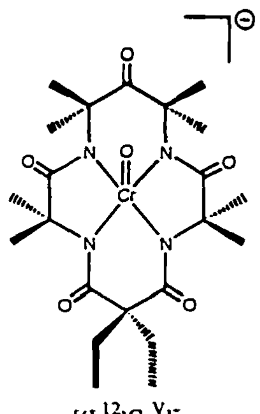
Although the mechanism of $AcrH_2$ oxidation in non-aqueous solvents now seems to be well understood, little is known about the kinetic behavior of dihydroacridines in semi-aqueous and aqueous media. More experimental data for these types of $AcrH_2$ reactions are necessary, especially considering the biological importance of aqueous chemistry. In this study we employed several inorganic oxidizing reagents to devise a unified mechanistic picture of $AcrH_2$ oxidation in AN/H_2O mixed solvent. The reduction potential of the inorganic oxidants was varied over a wide range to cover different modes of the oxidation mechanism. It can be shown that all the mechanisms fit into one scheme, where the strength of the oxidant determines which mode of oxidation the reaction adopts. The properties of $AcrH_2$ and its radical cation, such as the pK_a values and one-electron oxidation potentials, can also be determined in this medium, the most interesting being the H/D kinetic isotope effect for the acid ionization of the dihydroacridine radical cation.

Dihydroacridine has proven to be an excellent kinetic probe for monitoring Cr(IV) and Cr(V) species which are proposed to be important intermediates in various organic oxidations with chromate. Although aqua chromyl(IV) (CrO^{2+}) has been characterized in terms of its properties and reactivity,[9] the instability of the Cr(V) intermediates derived from chromate has precluded the direct determination of their properties. The transient complex trans-$(H_2O)LCrO^{3+}$ (L=[14]aneN_4) undergoes one-electron oxidation reactions with various organic and inorganic reducing reagents.[10] Several other stable Cr(V) complexes employing chelating and macrocyclic ligands to stabilize this unusual oxidation state have been reported.[11]

Some stable complexes of Cr^V



$[(L^{13})Cr^V]^+$



$[(L^{12})Cr^V]^-$

Since mechanistic or kinetic data are not available for the redox reactions of Cr(V) intermediates derived from simple chromate, it is desirable to obtain more data concerning the fundamental properties and reactivity of such species.

Here we propose a detailed mechanism for the reaction between 9-methyl-9,10-dihydroacridine and chromate ions in a mixed acetonitrile-water solvent. By applying conventional UV-VIS spectrophotometry and stopped-flow techniques, Cr(IV) and Cr(V) species could be identified as important intermediates in this system. From the implications of the chain-reaction mechanism found to operate in this system in the absence of oxygen, we have been able to determine the reactivities of Cr(IV) and Cr(V) intermediates in competitive electron transfer, hydrogen atom abstraction, and hydride transfer. Also to be noted is a specific inhibiting effect of oxygen which is different from the effect reported by Bruice et al.[7] in the oxidation of dihydropyridines with ferricyanide, which arises from the reaction between pyridinium radicals and O_2.

Dissertation Organization

The dissertation consists of two chapters. Chapter I corresponds to a paper published in *Inorganic Chemistry*. Chapter II is a manuscript to be submitted to the *Journal of the American Chemical Society*. Each chapter is self-contained with its own equations, figures, tables, schemes and references. Following the last manuscript is general conclusions. With the exception for the cyclic voltammetry measurements (Chapter I) which were performed by Dr. Victor Adamian, all the work in this dissertation was performed by the author of this thesis, Oleg E. Pestovsky.

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CHAPTER I

REACTIONS OF 10-METHYL-9,10-DIHYDROACRIDINE WITH INORGANIC OXIDIZING REAGENTS IN ACETONITRILE/WATER MIXED SOLVENT: A UNIFIED VIEW ON OXIDATION OF DIHYDROACRIDINE

Based on a paper published in *Inorganic Chemistry* *

Oleg Pestovsky, Andreja Bakac and James H. Espenson

Abstract

Reactions of 10-methyl-9,10-dihydroacridine with various inorganic oxidants in 20% acetonitrile/80% water solvent mixture fall into two categories depending on the strength of the oxidant used. Rapid electron transfer to the strong oxidizing reagents, Ce^{IV} and $IrCl_6^{2-}$, produces dihydroacridine radical cations, $AcrH_2^{\bullet+}$ (λ_{max} 650 nm). This is followed by the rate-determining loss of a proton and rapid oxidation of thus formed $AcrH^{\bullet}$ by the second equivalent of Ce^{IV} or $IrCl_6^{2-}$. The protonation of $AcrH^{\bullet}$ and deprotonation of $AcrH_2^{\bullet+}$ exhibit significant kinetic isotope effects. The use of d_2-acridine in H_2O/CH_3CN yields the secondary and solvent isotope effects separately. A large normal secondary isotope effect of 1.86 ± 0.17 for the protonation* of the acridinium radical suggests a possibility of nuclear tunneling. The reaction of

* Pestovsky, O.; Bakac, A.; Espenson, J. H. *Inorg. Chem.* **1998**, *37*, 1616

dihydroacridine with a mild oxidizing reagent, Fe^{3+}, is slow and shows no kinetic isotope effect. The initial electron transfer from $AcrH_2$ to Fe^{3+} is believed to be rate-determining.

Introduction

Dihydropyridines and their substituted analogs have attracted considerable attention due to their importance as dihydronicotinamide dinucleotide (NADH) models in biological redox reactions.[1-4] In particular, 10-methyl-9,10-dihydroacridine ($AcrH_2$) has been successfully employed in mechanistic studies of its reactions with various organic and inorganic oxidizing reagents.[5] The unique stability of dihydroacridines towards acid-catalyzed hydrolysis[6] has allowed extensive kinetic studies of their reactions with strong inorganic oxidants that often require acidic media. Bruice et al.[7] have reported a kinetic study of the oxidation of dihydropyridines by ferricyanide to the corresponding pyridinium cations in two consecutive one-electron steps, with the first step being rate controlling, eq 1.

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Recently, a similar mechanism for oxidation of $AcrH_2$ by tris-phenanthroline iron(III) complex in acetonitrile (AN) has been proposed by Fukuzumi et al.,[8] eq 2.

$$AcrH_2 \xrightarrow{Fe(phen)_3^{3+}} AcrH_2^{\cdot+} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} AcrH^{\cdot} \xrightarrow{Fe(phen)_3^{3+}} AcrH^+ \tag{2}$$

In this mechanism, the deprotonation of the radical cation is rate-controlling. The dihydropyridine radical cation was identified and characterized by UV-VIS and ESR spectroscopy. The pK_a of the radical cation was also determined. Several factors, such as the oxidizing strength of the reagents used or the medium, can be responsible for the change in the rate-controlling step from the initial electron transfer to the deprotonation of the radical cation. It is still unknown which factors are most important. A further mechanistic study utilizing a systematic change in these factors should provide necessary information to answer this question.

Although the mechanism of $AcrH_2$ oxidation in non-aqueous solvents now seems to be well understood, little is known about the kinetic behavior of dihydroacridines in semi-aqueous and aqueous media. More experimental data for these types of $AcrH_2$ reactions are necessary, especially considering the biological importance of aqueous chemistry. In this study we employed several inorganic oxidizing reagents to devise a unified mechanistic picture of $AcrH_2$ oxidation in AN/H_2O mixed solvent. The reduction potential of the inorganic oxidants was varied over a wide range to cover different modes of the oxidation mechanism. It can be shown that all the mechanisms fit into one scheme, where the strength of the oxidant determines which mode of oxidation the reaction adopts. The properties of $AcrH_2$ and its radical cation, such as the pK_a values and one-electron oxidation potentials, can also be determined in this medium, the most interesting being the H/D kinetic isotope effect for the acid ionization of the dihydroacridine radical cation.

Experimental Section

Materials. Perchloric acid (Fisher), acetonitrile (Fisher), deuterium oxide (Aldrich), methyl iodide (Aldrich), ceric(IV) ammonium nitrate (GFS), ammonium hexachloroiridate(IV) (Aldrich), lithium alumohydride (Aldrich), lithium alumodeuteride (Aldrich), 10-methylacridone (Aldrich), acridine (Aldrich) and iron(III) perchlorate (Aldrich) were used as received. High purity water was obtained by passing laboratory-distilled water through Millipore-Q purification system. Lithium perchlorate was obtained from Aldrich and was recrystallized from water 3 times. 10-methyl-9,10-dihydroacridine ($AcrH_2$) and its dideuterated analog $AcrD_2$ were prepared by reduction of 10-methylacridone with $LiAlH_4$ or $LiAlD_4$, respectively, according to the literature procedure.[9] 10-methylacridinium iodide was prepared by the reaction of acridine with methyl iodide according to a standard procedure.[10] The purity of the organic starting materials was checked by ^{1}H-NMR spectroscopy.

Kinetic studies. All the kinetic studies were carried out in 20% AN / 80% H_2O solvent mixture. All spectroscopic UV-VIS experiments were performed with use of a Shimadzu UV-3101 PC instrument at ambient temperature. Kinetic measurements for $AcrH_2$/Ce(IV) and $AcrH_2/IrCl_6^{2-}$ reactions were performed with an Applied Photophysics stopped-flow apparatus under anaerobic conditions. The temperature was controlled at 25.0±0.2 °C. Concentrations of $AcrH_2$ stock solutions were determined spectrophotometrically, ε_{285}=13,200 L mol^{-1} cm^{-1}. The ionic strength of the reaction solutions was maintained at 1 M by addition of lithium perchlorate. Reactions of $AcrH_2$ and $AcrD_2$ with Ce(IV) were monitored at 358 nm by observing the formation of acridinium ion (ε_{358} = 18,800 L mol^{-1} cm^{-1}), unless noted otherwise. Stock solutions of $IrCl_6^{2-}$ were standardized spectrophotometrically, ε_{487}=4075 L mol^{-1} cm^{-1}.[11] Aqueous solutions of iron(II) were prepared by reduction of iron(III) perchlorate with zinc amalgam under anaerobic conditions in aqueous 0.1 M $HClO_4$. The concentration of Fe^{3+} was determined spectrophotometrically, ε_{240}=4160 L mol^{-1} cm^{-1}.[12] Kinetics data were analyzed using Kaleidagraph v3.08 for PC software package. FitSim simulations were performed by converting the absorbance readings to concentration of the product $AcrH^+$ using the extinction coefficient difference of the slowest trace as a reference. The fitting was carried out on a Dell XPSPro computer using FitSim v4.0 for PC. For each mechanism, all the experimental traces were fitted simultaneously.

Cyclic voltammetry experiments were carried out with use of a BAS-100 electrochemical analyzer and a three-electrode system consisting of a glassy carbon or platinum disk working electrode, a platinum wire counter electrode and a saturated calomel electrode (SCE) as the reference. The SCE was separated from the bulk of the solution by a low porosity fritted-glass bridge, which contained the solvent/supporting electrolyte mixture. t-Bu_4NPF_6 and $NaClO_4$ were used as supporting electrolytes in AN and AN/H_2O solvents, respectively.

Results

Reaction with Ce(IV). At a low ceric ion concentration (0.2 mM), the reactions followed first order kinetics in both $AcrH_2$ and Ce^{IV} concentrations. Identical kinetics were obtained at the absorption maxima for $AcrH^+$ (λ_{max} 358 nm and 417 nm) and $AcrH_2^{\bullet+}$ (λ_{max} 650 nm). **Figure 1** shows representative traces at 358 nm and 640 nm. The second-order rate constants increase with increasing acid concentration in a nonlinear fashion, as shown in **Figure 2**. A tentative mechanism is shown in **Scheme I**.

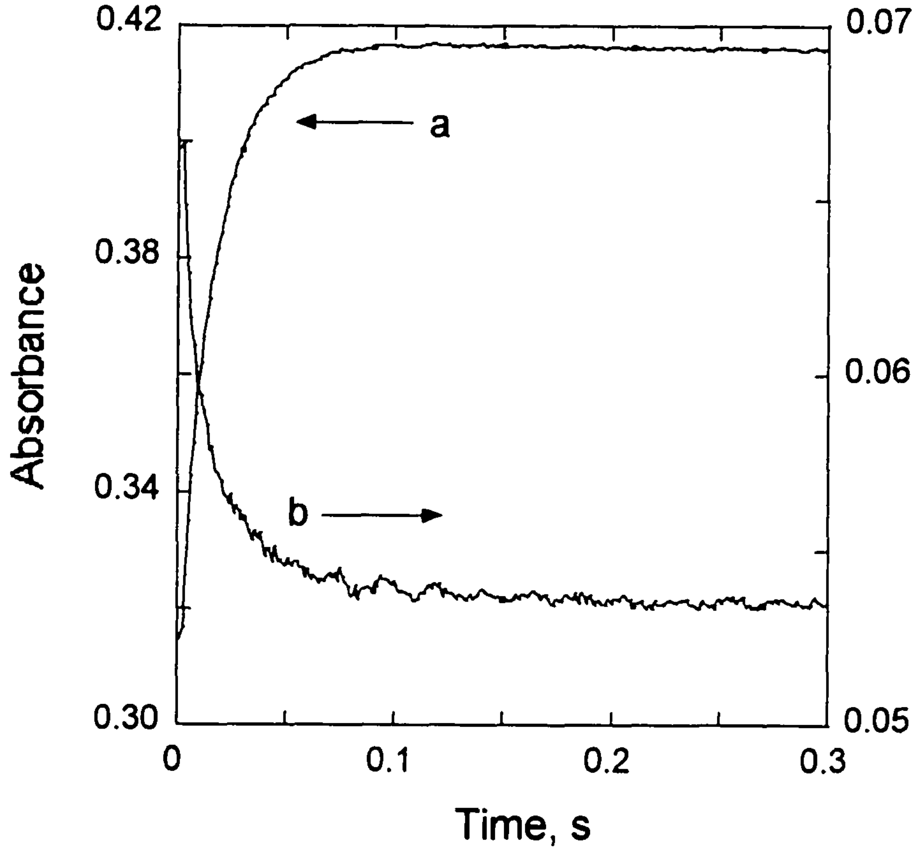


Figure 1. Reaction between 10^{-5} M $AcrH_2$ and 10^{-4} M Ce^{4+}. (a) Formation of $AcrH^+$ monitored at 358 nm. (b) Decay of $AcrH_2^{\bullet+}$ monitored at 640 nm. $[H^+] = 0.10$ M, ionic strength = 1.0 M.

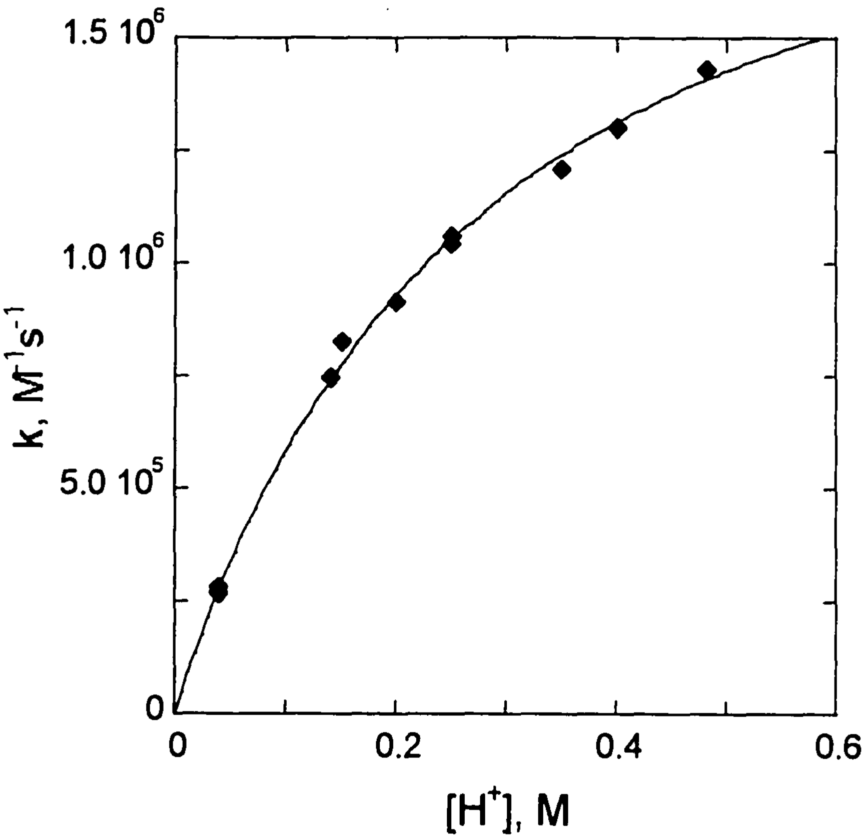


Figure 2. Plot of the second order rate constant against $[H^+]$ for the reaction between 1.5×10^{-5} M $AcrH_2$ and 2×10^{-4} M Ce^{4+}. Ionic strength = 1.0 M.

Scheme I

$$AcrH_2 + Ce^{4+} \xrightarrow{\text{fast}} AcrH_2^{\cdot +} + Ce^{3+}$$

$$AcrH_2^{\cdot +} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AcrH^{\cdot} + H^+$$

$$AcrH^{\cdot} + Ce^{4+} \xrightarrow{k_2} AcrH^+ + Ce^{3+}$$

$$Ce^{4+} \underset{H^+}{\overset{H_2O}{\rightleftharpoons}} Ce(OH)^{3+} \underset{H^+}{\overset{H_2O}{\rightleftharpoons}} Ce(OH)_2^{2+} \qquad K_1 = 13\ M \quad K_2 = 0.3\ M$$

$$K_1 \qquad\qquad K_2$$

The application of the steady state approximation to the concentration of AcrH• yields the following rate law:

$$v = \frac{k_1 k_2 [AcrH_2^{\cdot +}] [Ce^{IV}]_T}{k_{-1} ([H^+] + K_1 + K_1K_2/[H^+]) + k_2 [Ce^{IV}]_T} \tag{3}$$

$$k_{obs} = \frac{k_1 k_2 [Ce^{IV}{}_T]}{k_{-1} ([H^+] + K_1 + K_1K_2/[H^+]) + k_2 [Ce^{IV}]_T} \tag{3a}$$

Here $[Ce^{IV}]_T$ is the total concentration of the ceric ion, and K_1 and K_2 are the first and second acid ionization constants of cerium(IV) ions.[13]

Assuming that the $k_2[Ce^{IV}]_T$ term in the denominator is negligible at low ceric ion concentrations, eq 3 reduces to eq 4:

$$v = \frac{k_1 k_2 [AcrH_2^{\cdot +}] [Ce^{IV}]_T}{k_{-1} ([H^+] + K_1 + K_1K_2/[H^+])} \quad (4) \qquad k_{obs} = \frac{k_1 k_2 [Ce^{IV}]_T}{k_{-1} ([H^+] + K_1 + K_1K_2/[H^+])} \quad (4a)$$

The non-linear least-squares fit of the acid variation data to eq 4a yielded $k_1k_2/k_{-1} = (3.04 \pm 0.02) \times 10^7\ s^{-1}$. Assigning $7.4 \times 10^9\ L\ mol^{-1}\ s^{-1}$ as a value of k_2 (see Discussion) gives $pK_a(AcrH_2^{\cdot +}) = -\log (k_1/k_{-1}) = 2.39$.

Saturation kinetics were observed at higher concentrations of Ce^{IV}. **Figure 3** shows a reciprocal plot of the observed pseudo-first order rate constant of the $Ce^{IV}/AcrH_2$ reaction vs. the total ceric ion concentration. The $[Ce^{IV}]$ variation data were fitted to eq 5, which was derived by taking a reciprocal of eq 3a and separating the $1/[Ce^{IV}]_T$ term:

$$\frac{1}{k_{obs}} = \frac{1}{k_1} + \frac{k_{-1}\left([H^+] + K_1 + K_1K_2/[H^+]\right)}{k_1 k_2}\frac{1}{[Ce^{IV}]_T} \tag{5}$$

This treatment gave $k_1 = 721 \pm 29\ s^{-1}$ and $k_{-1} = (1.33 \pm 0.03) \times 10^5\ L\ mol^{-1}\ s^{-1}$.

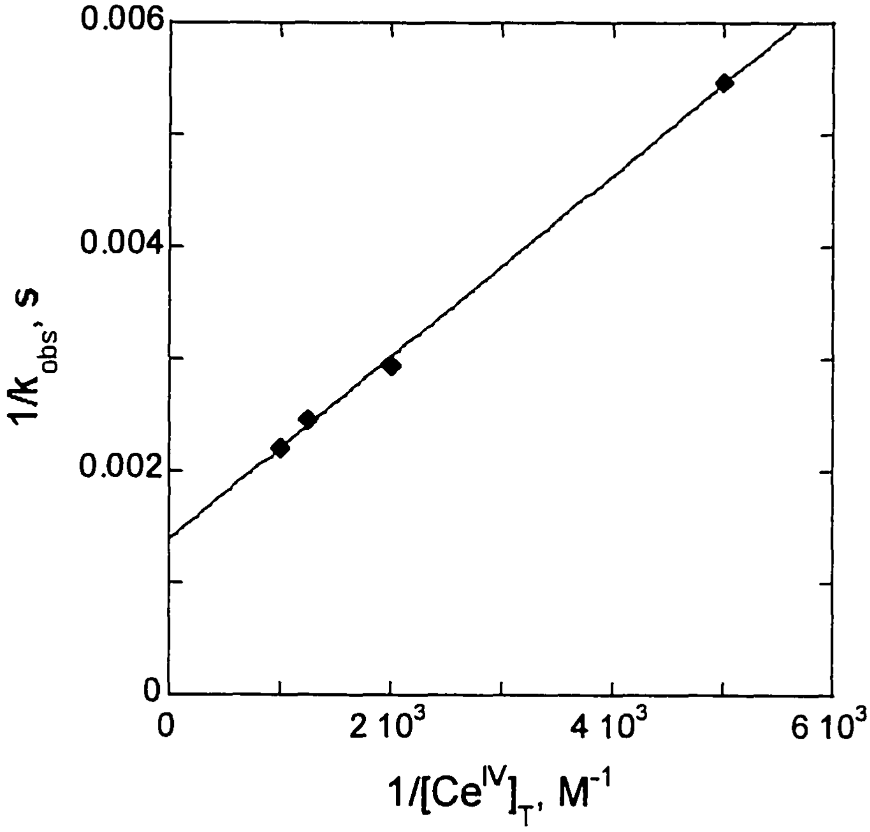


Figure 3. Plot of $1/k_{obs}$ against $1/[Ce]_T$ for the reaction between 1.5×10^{-5} M $AcrH_2$ and Ce^{4+}. $[H^+] = 0.2$ M, ionic strength = 1.0 M.Figure 3

A global fit of both acid variation and ceric ion variation data was performed. Equation 6 was derived by dividing the numerator and denominator of the right side of eq 3a by $k_2[Ce^{IV}]_T$:

$$k_{obs} = \frac{k_1}{\dfrac{k_{-1}\,([H^+] + K_1 + K_1K_2/[H^+])}{k_2\,[Ce^{IV}]_T} + 1} \tag{6}$$

Figure 4 shows a plot of k_{obs} vs. $([H^+] + K_1 + K_1K_2/[H^+])/[Ce^{IV}]_T$. The fitting of the data in **Figure 4** to eq 6 gave $k_1 = 691 \pm 36\ s^{-1}$ and $k_{-1} = (1.18 \pm 0.11) \times 10^5\ L\ mol^{-1}\ s^{-1}$. A more accurate value of pK_a for $AcrH_2^{\bullet+}$ was then calculated as $pK_a(AcrH_2^{\bullet+}) = -\log(k_1/k_{-1}) = 2.23 \pm 0.05$.

Kinetic isotope effects in Ce(IV) reactions. Reactions of Ce(IV) with $AcrD_2/AcrH_2$ were carried out in H_2O or D_2O mixtures with acetonitrile using the $[Ce^{IV}]$ variation method. The rate constants k_1 and k_{-1} were calculated from a non-linear least-squares fit of k_{obs} to eq 6. **Table 1** summarizes the k_1 and k_{-1} values for $AcrH_2/AcrD_2$ reactions with Ce(IV) in H_2O and D_2O.

Table 1. k_1 and k_{-1} rate constants for the reactions between Ce^{IV} and $AcrL_2$ in L_2O/AN [a]

Entry		k_1, s^{-1}	$k_{-1} \times 10^{-4}$, $L\ mol^{-1}\ s^{-1}$
1	$AcrH_2$ in H_2O	691 ± 36	11.8 ± 1.1
2	$AcrH_2$ in D_2O	688 ± 22	9.77 ± 0.67
3	$AcrD_2$ in H_2O	115 ± 3	2.23 ± 0.25
4	$AcrD_2$ in D_2O	106 ± 6	3.41 ± 0.58

[a] L = H or D

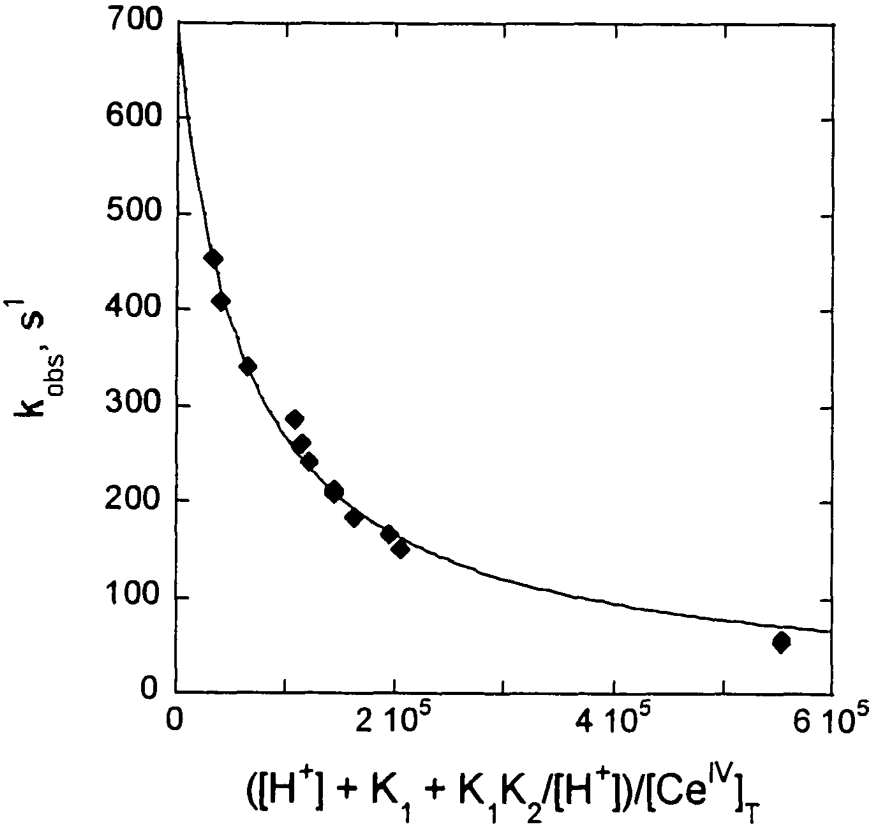


Figure 4. Global fit of acid and ceric ion variation data for the reaction between Ce^{4+} and $AcrH_2$. The experimental values of k_{obs} were fitted to equation 6.

A series of experiments with $AcrD_2$ (10^{-4} M) in D_2O were also carried out at a higher concentration of Ce^{IV} (4×10^{-3} M) and a constant acid concentration (0.4 M). The reaction was monitored in the spectral range from 560 to 720 nm. The resulting absorbance changes and pseudo-first order rate constants obtained from the exponential fitting of the kinetic traces were plotted against the wavelength, **Figure 5**.

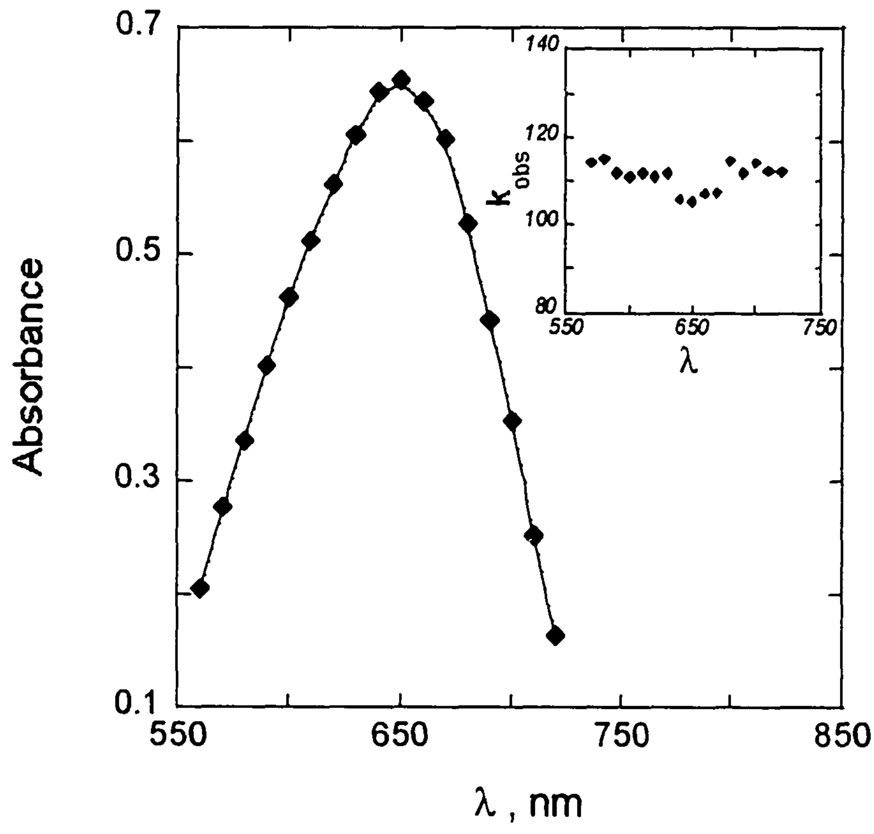


Figure 5. Absorbance changes in the reaction between 10^{-4} M $AcrD_2$ and 4×10^{-3} M Ce^{4+}. $[H^+]$ = 0.4 M, ionic strength = 1.0 M. Shown as an inset is the plot of the corresponding pseudo-first order rate constants against the wavelength.

Thus obtained spectrum of the acridinium radical cation exhibits a maximum at 650 nm with the extinction coefficient of 6530 L mol^{-1} cm^{-1}. The pseudo-first order rate constants vary slightly with the wavelength and approach 106 s^{-1} at the maximum absorbance change, in excellent agreement with the value obtained by the $[Ce^{IV}]$ variation method.

Reaction with hexachloroiridate(IV). The stoichiometry of hexachloroiridate(IV) reaction with $AcrD_2$ was determined spectrophotometrically under air-free conditions. A small excess of iridium complex was allowed to react with $AcrD_2$ and the spectra of the reaction mixture were recorded before and after the reaction. The excess of $IrCl_6^{2-}$ was calculated from the total absorbance reading at 487 nm. The spectrum of the product was obtained by subtracting the spectrum of the excess of $IrCl_6^{2-}$ from the final spectrum. The resulting spectrum matched that of an authentic sample of $AcrD^+$. The overall stoichiometry of the $IrCl_6^{2-}/AcrD_2$ reaction was 1.95:1 under air free conditions and ~1.5:1 in air saturated solutions. Under the latter conditions, the stoichiometry showed a minor dependence on the concentration of the iridium complex. The kinetics of hexachloroiridate(IV) reaction with $AcrD_2$ were studied in AN/H_2O mixture using the stopped-flow technique under air free conditions. Typical concentrations used were (0.50-1.0) × 10^{-3} M $IrCl_6^{2-}$, 5 × 10^{-5} M $AcrD_2$ and 0.10 M $HClO_4$ at 1.0 M ionic strength. The reaction was monitored at 358nm ($AcrD^+$) and 650nm ($AcrD_2^{\bullet+}$). The reaction followed first order kinetics at both wavelengths and yielded $k_\psi = 115 \pm 2$ s^{-1} independent of the concentrations of $IrCl_6^{2-}$ and H^+.

In a different set of experiments, $AcrH_2$ was used instead of $AcrD_2$. The concentrations of both $IrCl_6^{2-}$ and $AcrH_2$ were much lower (5 μM and 2 μM, respectively) to allow for the competition between reactions **-1** and **2** (**Scheme I**). The acid concentration was varied from 0.2 to 0.5 M at 1.0 M ionic strength. The reaction was monitored at 358 nm ($AcrH^+$) and followed pseudo-first order kinetics. Although we were unable to obtain reliable quantitative kinetics data under these conditions due to the limitation of our stopped-flow apparatus, a trend of decreasing rate constants, from ca. 500 to 200 s^{-1}, with increasing acid concentration was observed.

Reaction with aqueous iron(III). The reactions of $AcrH_2$ and $AcrD_2$ with Fe^{3+} were monitored in AN/H_2O mixture under air free conditions using conventional UV-VIS and stopped-flow techniques at 300 nm ($AcrH_2$), 358 nm ($AcrH^+$) and 640 nm ($AcrH_2^{\bullet+}$). In a typical kinetic run, Fe^{3+} (1 mM) was used in a large excess over $AcrH_2$ or $AcrD_2$ (5×10^{-5} M). In all of the experiments, the ionic strength was maintained at 1.0 or 0.1 M, and $[H^+]$ was varied from 0.1 to 0.5 M. No absorbance change was noted at 640 nm. At 300 nm and 358 nm the reaction followed first order kinetics and yielded the same pseudo-first order rate constants, indicating a clean substrate-to-product conversion. The pseudo-first order rate constants were proportional to the Fe^{3+} concentration and independent of the acidity.

The second order rate constants for the reactions of Fe^{3+} with $AcrH_2$ and $AcrD_2$ reactions were calculated from a linear plot of k_ψ vs. $[Fe^{3+}]$. At 0.1 and 1.0 M ionic strength, the second order rate constants of $Fe^{3+}/AcrH_2$ reaction were 37.9 ± 0.03 and 128 ± 1 L mol^{-1} s^{-1}, respectively. $AcrH_2$ and $AcrD_2$ yielded the same rate constants at a given ionic strength, indicating no kinetic isotope effect. No rate inhibition was observed when up to 1 mM Fe^{2+} was added.

Cyclic voltammetry of $AcrH_2$ in AN and AN/H_2O mixed solvents. Slow-scan cyclic voltammetry was performed on $AcrH_2$ solutions in pure acetonitrile and 20% AN / 80% H_2O solvent mixture under an argon atmosphere. In both solvents the cyclic voltammograms exhibited anodic waves with current maxima at 0.81 V and 0.46 V (vs. SCE in AN and AN/H_2O, respectively), but the complementary cathodic waves were not observed at scan rates of up to 3 V s^{-1}, **Figure 6.**

Discussion

The reaction of dihydroacridine with Ce(IV) in 20% AN/80% H_2O proceeds in two one-electron transfer steps, **Scheme I.** The first step is fast (not observable on a stopped-flow time scale) and produces a transient radical cation. The further oxidation of the radical cation was observed by monitoring either the product, $AcrH^+$, or the radical cation itself. Both species exhibit the same kinetic behavior suggesting that no by-products are formed in this reaction.

Since the reduction potential of $AcrH^+$/AcrH• couple is –0.43 V (vs. SCE in acetonitrile)[10] and the oxidation of dihydroacridine ($E(AcrH_2^{\bullet +}/AcrH_2)$ = +0.46 V vs. SCE) by Ce(IV) is too rapid to be monitored by the stopped-flow technique, it was reasonable to assume that the reaction between AcrH• and Ce^{4+} is diffusion controlled. Therefore we assign $k_2 = 7.4 \times 10^9$ L mol^{-1} s^{-1}.[14]

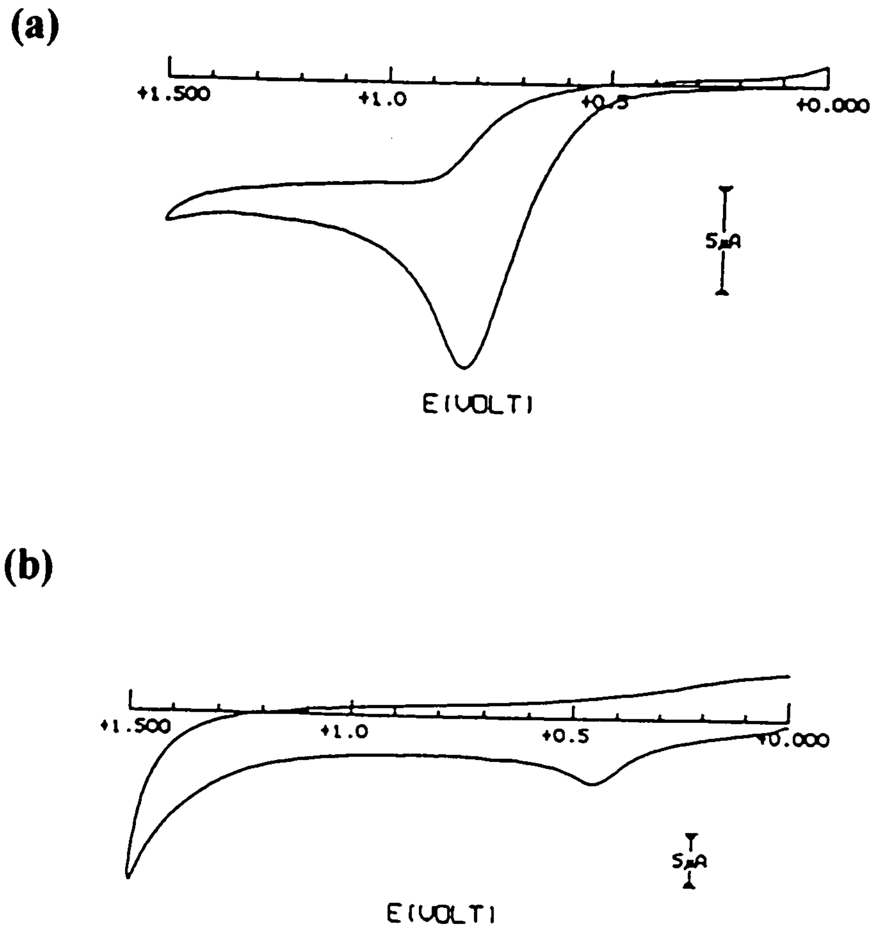


Figure 6. Cyclic voltammograms of $AcrH_2$ in a) AN, b) 20% AN/80% H_2O at 25 °C.

The fact that Ce(IV) exists mostly in the form of monohydroxy and dihydroxy species at $[H^+] = 0.1 - 0.5$ M[13b] has allowed us to study the competition between steps **2** and **–1** of **Scheme I** and thus determine the rate constants for the protonation and deprotonation equilibrium of the radical cation. A simple comparison of absolute rates for steps **–1** and **2** under conditions where the competition was observed ($[H^+] = 0.3$ M, $[Ce]_T = 2 \times 10^{-4}$ M, $[Ce^{4+}] \sim 2.3 \times 10^{-6}$ M, $[Ce(OH)^{3+}] \sim 10^{-4}$ M, $[Ce(OH_2)^{2+}] \sim 10^{-4}$ M) suggests that the reactive form of ceric ion is Ce^{4+}. This was also confirmed by the acid variation experiments in which the observed dependence of the reaction rates on the acid concentration matched the rate law derived from **Scheme I**.

Although the reaction mechanism depicted in **Scheme I** is very similar to that proposed earlier[8] in acetonitrile, we did not observe the disproportination of the radical cation, eq 7a. In fact, it is more reasonable to assume that the second order decay of the radical cation comes from the reaction of AcrH• with $AcrH_2^{\cdot+}$, eq 7b, a simple one-electron transfer reaction. KinSim simulations have shown that reaction 7b is unimportant under our experimental conditions and cannot contribute significantly to the decay of the radical cation.

$$2\ AcrH_2^{\cdot+} \xrightarrow{k_{disp}} AcrH_2 + AcrH^+ + H^+ \tag{7a}$$

$$AcrH^{\cdot} + AcrH_2^{\cdot+} \longrightarrow AcrH^+ + AcrH_2 \tag{7b}$$

The acid ionization constant $pK_a = 2.23$ for $AcrH_2^{\cdot+}$ is much lower than the values determined earlier at low concentrations of water in acetonitrile ($pK_a = 8.1$ at $[H_2O] = 0.029$ M and 6.8 at $[H_2O] = 0.29$ M).[8,10,15] A linear plot of pK_a vs. log $[H_2O]$ presented in ref. 8 allows us to estimate the corresponding pK_a value under our experimental conditions. Considering the degree of approximation used in such an analysis, the calculated value of 3.96 is in acceptable agreement with $pK_a = 2.23$ in 20% AN / 80% H_2O solvent mixture determined directly in this work. It has been noted[8,16] that water in acetonitrile has a large retardation effect on k_{-1} and a small acceleration effect on k_1 ($k_1 = 6.4\ s^{-1}$ and $k_{-1} = 8.06 \times 10^8\ L\ mol^{-1}\ s^{-1}$ at $[H_2O] = 0.029$ M; $k_1 = 11.5\ s^{-1}$ and $k_{-1} = 7.26 \times 10^7\ L\ mol^{-1}\ s^{-1}$ at $[H_2O] = 0.29$ M). Our data suggest that both k_1 and k_{-1} change significantly at higher concentrations of H_2O.

Kinetic isotope effects for k_1 and k_{-1} deserve special attention. A kinetic isotope effect of 9.0 for k_1 in acetonitrile has been reported.[8] From the experiments with $AcrD_2$ and $AcrH_2$ in D_2O and H_2O solvent mixtures with acetonitrile, we have been able to determine the kinetic isotope effects for both k_1 and k_{-1}. From entries 1 and 4 in **Table 1** we calculate $(k_H/k_D)_1 = 6.52 \pm 0.51$ and $(k_H/k_D)_{-1} = 3.45 \pm 0.68$. An apparently low value of k_{-1} in entry 3 of **Table 1** is probably a result of a complex reaction mechanism operating in $AcrD_2$/Ce(IV)/H_2O/AN system, as explained below.

Conditions in entry 3 of **Table 1** allow isotope scrambling in $AcrD_2^{\cdot+}$, **Scheme II**. KinSim simulations have shown that kinetic traces for formation of $AcrL^-$ retain the exponential form under such conditions, but the apparent k_{-1} depends on the values of k_1^{DH}, k_{-1}^{DH} and k_1^{HD}.

Scheme II

$$AcrD_2^{\cdot +} \underset{k_{-1}^{D}}{\overset{k_1^{D}}{\rightleftharpoons}} AcrD^{\cdot} + D^{+}$$

$$AcrH_2^{\cdot +} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AcrH^{\cdot} + H^{+}$$

$$AcrHD^{\cdot +} \underset{k_{-1}^{DH}}{\overset{k_1^{DH}}{\rightleftharpoons}} AcrD^{\cdot} + H^{+}$$

$$AcrHD^{\cdot +} \underset{k_{-1}^{HD}}{\overset{k_1^{HD}}{\rightleftharpoons}} AcrH^{\cdot} + D^{+}$$

$$AcrD^{\cdot} + Ce^{4+} \xrightarrow{k_2} AcrD^{+} + Ce^{3+}$$

$$AcrH^{\cdot} + Ce^{4+} \xrightarrow{k_2} AcrH^{+} + Ce^{3+}$$

Neglecting any secondary isotope effect on k_1 (see later) and taking the statistically corrected values of $k_1^{DH} = k_1/2 = 345\ s^{-1}$ and $k_1^{HD} = k_1^{D}/2 = 53\ s^{-1}$, the data in entry 3 yield $k_{-1}^{DH} = (6.34 \pm 0.04) \times 10^4\ L\ mol^{-1}\ s^{-1}$, **Figure** 7. In these calculations, the value of k_{-1}^{HD} was fixed at $5 \times 10^4\ L\ mol^{-1}\ s^{-1}$, but changing it in either direction by a factor of 10 did not affect the fitting due to a relatively small importance of this step. The value of k_{-1}^{DH} was then used to estimate the secondary and solvent isotope effects for k_{-1} separately. We define the secondary kinetic isotope effect for k_{-1} as $(k_H/k_D)_{-1}^{sec} = k_{-1}/k_{-1}^{DH} = 1.86 \pm 0.17$ and the solvent kinetic isotope effect for k_{-1} as $(k_H/k_D)_{-1}^{sol} = k_{-1}^{DH}/k_{-1}^{D} = 1.86 \pm 0.32$. Solvent isotope effects for a system $S + L_3O^{+} = SL^{+} + L_2O$ have been reported in the literature and usually range from 2.3 to 2.7.[17] The solvent isotope effect for k_1 determined in this study, 1.86 ± 0.32, is acceptably close, considering the uncertainty in the value. An attempt to fit the experimental data in entry 2 to the mechanism depicted in **Scheme II** was also made. Due to the short timescale of this reaction

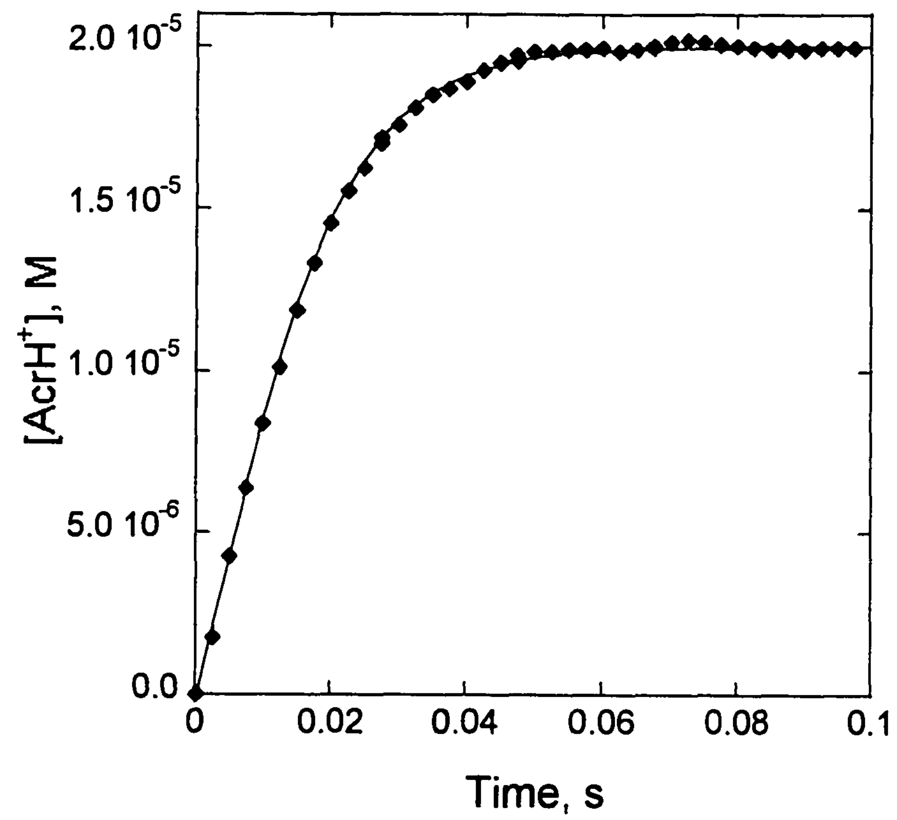


Figure 7. FitSim fit of the reaction between $2\text{x}10^{-5}$ M $AcrD_2$ with 1.25×10^{-4} M Ce(IV) in H_2O, $[H^+]$ = 0.3 M. An experimental kinetic trace was fitted to the reaction mechanism in Scheme II.

(ca. 50% completion during the mixing time of our stopped-flow apparatus) we were unable to obtain a satisfactory fit.

A series of FitSim simulations were performed to study the effect of the secondary isotope effect for k_1 on $(k_H/k_D)_{-1}^{sec}$. Arbitrary values of $(k_H/k_D)_1^{sec}$ were used to calculate k_1^{HD} and k_1^{DH}, and the corresponding values of $(k_H/k_D)_{-1}^{sec}$ were obtained from the fitting procedure described above. A trend of increasing $(k_H/k_D)_{-1}^{sec}$ with increasing $(k_H/k_D)_1^{sec}$ was observed, **Table 2**.

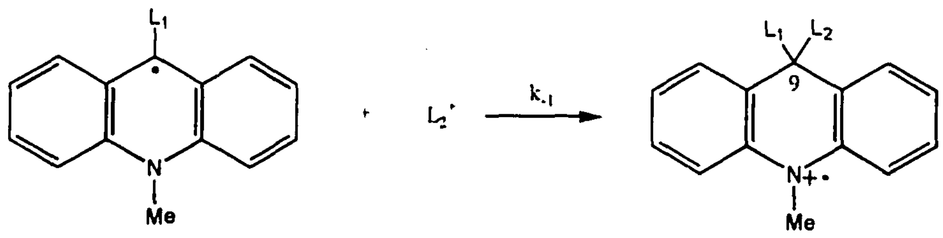
Table 2. Effect of the secondary kinetic isotope effect for k_1 on $(k_H/k_D)_{-1}^{sec}$

$(k_H/k_D)_1^{sec}$	k_1^{HD} [a], s^{-1}	k_1^{DH} [a], s^{-1}	$(k_H/k_D)_{-1}^{sec}$ [b]
1.0	53.0	345	1.86±0.17
1.1	58.3	314	1.93±0.18
1.2	63.6	288	1.99±0.19

[a] Calculated from k_1 and k_1^D based on $(k_H/k_D)_1^{sec}$. [b] Obtained from FitSim fitting

The quality of the fit was visibly worse at higher values (1.1 and 1.2) of $(k_H/k_D)_1^{sec}$. This result suggests that the secondary isotope effect for k_1 is either small or non-existent. This is somewhat surprising, since sizable α-D secondary isotope effects have been seen in similar reactions. A secondary isotope effect of 1.145 ± 0.009 was reported for a hydride abstraction from NADH by 4-cyano-2,6-dinitrobenzenesolfonate.[18] Unusually high α-D isotope effects of 1.38 and 1.50 (no error limits given) have been found for the reductions of acetone and cyclohexanone by various alcohol dehydrogenases.[19]

The secondary kinetic isotope effect is due to the presence of the non-transferred L_1 in position 9 of dihydroacridine molecule, eq 8.


(8)

Conventional transition state theory predicts a small inverse isotope effect for a conversion of an sp^2 hybridized C-L bond to an sp^3-like transition state in this reaction.[17a,20] A hydride transfer to the acridinium cation produces a small normal isotope effect whose magnitude depends on whether H^- or D^- is transferred.[2c,21] Nuclear tunneling along the reaction coordinate has been proposed to explain such an unusual kinetic behavior of the acridinium ion and some NADH systems.[21,22] The normal secondary isotope effect observed in this work suggests a possibility of tunneling in the protonation of AcrH•.

Reaction of dihydroacridine with $IrCl_6^{2-}$ proceeds by a mechanism similar to that for Ce(IV), **Scheme III**.

Scheme III

$$AcrL_2 + IrCl_6^{2-} \xrightarrow{\text{fast}} AcrL_2^{\cdot +} + IrCl_6^{3-}$$

$$AcrL_2^{\cdot +} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AcrL^{\cdot} + L^+$$

$$AcrL^{\cdot} + IrCl_6^{2-} \xrightarrow{k_2} AcrL^+ + IrCl_6^{3-} \qquad L = H \text{ or } D$$

An outer-sphere oxidation of $AcrL_2$ is proposed, based on the products and stoichiometry. Since hexachloroiridate does not form hydroxy species on the time scale of our stopped-flow experiments[11], we were able to obtain the limiting value of k_1 even at the concentrations of $IrCl_6^{2-}$ below 1 mM. The experimental value for k_1, 115 ± 2 s^{-1}, is in good agreement with the value of 106 s^{-1} obtained from the $AcrD_2$/Ce(IV) experiments. An attempt at using $AcrH_2$ with micromollar concentrations of $IrCl_6^{2-}$ to allow for the competition between steps **–1** and **2** in **Scheme III** was not completely successful, but a qualitative trend of increasing rates at lower acid concentrations was observed.

Reaction with Iron(III). **Scheme IV** shows a proposed mechanism of the reaction between Fe^{3+} and $AcrH_2$.

Scheme IV

$$AcrH_2 + Fe^{3+} \underset{k_{-0}}{\overset{k_0}{\rightleftharpoons}} AcrH_2^{\cdot +} + Fe^{2+}$$

$$AcrH_2^{\cdot +} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AcrH^{\cdot} + H^+$$

$$AcrH^{\cdot} + Fe^{3+} \xrightarrow{k_2} AcrH^+ + Fe^{2+}$$

By using the steady state approximation, one derives the rate law in eq 9.

$$v = \frac{k_0 k_2 [AcrH_2] [Fe^{3+}]^2}{k_2 [Fe^{3+}] + \frac{k_{-0} [Fe^{2+}]}{k_1} (k_{-1} [H^+] + k_2 [Fe^{3+}])} \qquad (9)$$

As shown below, this rate law reduces to eq 10 under our experimental conditions and the experimental second order rate constants are in fact k_0.

$$v = k_0 [AcrH_2] [Fe^{3+}] \qquad (10)$$

At $[H^+] = 0.1 - 0.5$ M and $[Fe^{3+}] = (5 - 20) \times 10^{-4}$ M, assuming that $k_2 [Fe^{3+}] >> k_{-1} [H^+]$ (this requires $k_2 >> 10^8$ L mol^{-1} s^{-1}), we can neglect the $k_{-1}[H^+]$ term in the denominator of eq 9. k_{-0} can be calculated from the equilibrium constant $K = k_0/k_{-0} = 15$ (estimated from the reduction potentials for Fe^{3+}/Fe^{2+} and $AcrH_2^{\bullet+}/AcrH_2$ couples).[23] From the value of K and the experimental value of k_0 at 1 M ionic strength we obtain $k_{-0} = k_0/K \approx 9$ L mol^{-1} s^{-1}. Even under the most unfavorable conditions in reaction of $AcrD_2$ with Fe^{3+} (5×10^{-4} M) with 1 mM of added Fe^{2+}, the term $k_{-0}[Fe^{2+}]/k_1 = 9 \times 10^{-3} / 106 = 8.5 \times 10^{-5} << 1$. The denominator of eq 9 reduces to k_2 [Fe^{3+}], resulting in the simplified rate law in eq 10. The absence of acid dependence and of the kinetic isotope effect on the rates of $AcrH_2/Fe^{3+}$ reaction also confirm the validity of **Scheme IV**.

General mechanism of one-electron oxidation of dihydroacridine. Scheme V represents a unified mechanism for the electron transfer oxidation of dihydroacridine.

Scheme V

$$AcrH_2 + Ox \underset{k_{-0}}{\overset{k_0}{\rightleftharpoons}} AcrH_2^{\cdot+} + Red$$

$$AcrH_2^{\cdot+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AcrH^{\cdot} + H^+$$

$$AcrH^{\cdot} + Ox \xrightarrow{k_2} AcrH^+ + Red$$

The first step in **Scheme V** is a reversible one-electron oxidation of dihydroacridine to the radical cation $AcrH_2^{\bullet+}$. The consecutive loss of H^+ and further oxidation of AcrH• complete the mechanism. Depending on the reduction potential of the oxidant, either of the first two reaction steps can be rate-determining. Strong oxidizing reagents with high self-exchange rate constants, such as Ce(IV) or $IrCl_6^{2-}$,[24,25] make step **0** practically irreversible and too rapid to be observed by the stopped-flow technique. Consequently, one can study the kinetics and chemical behavior of $AcrH_2^{\bullet+}$ as step **1** becomes rate-limiting. In the reaction with Fe^{3+}, which is a mild oxidant and has a small self-exchange rate constant[26], step **0** becomes rate-limiting. Another example of such kinetic behavior was observed in the reaction between $AcrH_2$ and chromate under similar conditions ($[H^+]$ = 0.1 M, 20% AN/80% H_2O mixed solvent).[27] Both hydrogen chromate and dichromate react with $AcrH_2$ in a complex chain reaction with the initiation step being one-electron oxidation of $AcrH_2$, eq 11.

$$HCrO_4^-/Cr_2O_7^{2-} + AcrH_2 + H^+ \longrightarrow AcrH_2^{\cdot+} + Cr^V \qquad (11)$$

Given the low standard reduction potential of Cr^{VI}/Cr^V couple[28], it is not surprising that the initial electron transfer from $AcrH_2$ to chromate is rate-limiting.

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CHAPTER II

REACTIONS OF 10-METHYL-9,10-DIHYDROACRIDINE WITH CHROMATE

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Abstract

The oxidation of $AcrH_2$ to $AcrH^+$ by hydrogen chromate ions is a chain reaction that is strongly inhibited by oxygen. The initiation reaction between $AcrH_2$ or $AcrD_2$ and H_2CrO_4 forms $AcrH_2^{\bullet+}$ and occurs by a 1e mechanism, $k^H = k^D = 4.6 \times 10^2$ L mol^{-1} s^{-1} (25 °C). The Cr^V produced along with $AcrH^\bullet$ (from the acid ionization of $AcrH_2^{\bullet+}$) are chain-carrying intermediates. The propagating reaction between $AcrH_2$ and Cr^V, $k = 1 \times 10^8$ L mol^{-1} s^{-1}, is of key importance since it is a branching reaction that yields two chain carriers, $AcrH^\bullet$ and CrO^{2+}, by hydrogen atom abstraction. The same partners react competitively by hydride ion abstraction, to yield Cr^{3+} and $AcrH^+$, $k = 1.2 \times 10^7$ L mol^{-1} s^{-1}, in the principal termination step. The reaction of CrO^{2+} and $AcrH_2$, $k^H = 1.0 \times 10^4$ and $k^D = 4.8 \times 10^3$ L mol^{-1} s^{-1}, proceeds by hydride ion transfer. The Cr^{2+} so produced could be trapped as $CrOO^{2+}$ when O_2 was present, thereupon terminating the chain. $AcrH_2$ itself reacts with $Cr_2O_7^{2-} + H^+$, $k = 5.6 \times 10^3$ L^2 mol^{-2} s^{-1}, but this step is not an

initiating reaction. From that, two successive electron transfer steps are believed to occur, yielding $Cr^{IV} + Cr^{VI} + AcrH^{+}$.

Introduction

Dihydronicotinamide adenine dinucleotide (NADH) and its analogs have attracted considerable interest due to their biological importance in electron-transfer reactions, in which these dihydropyridines serve as one- or two-electron reductants in various enzymatic processes.[1] One-electron, hydride and hydrogen atom transfer mechanisms have been proposed for biological and artificial redox reactions of dihydropyridines.[2] Due to the instability of dihydropyridines towards acid-catalyzed hydrolysis,[3] the majority of mechanistic studies have employed 10-methyl-9,10-dihydroacridine ($AcrH_2$) and its substituted analogs which have been shown to be stable in acidic aqueous and semi-aqueous media.[4] Recently Fukuzumi et al[5] have characterized 9-substituted dihydroacridine radical-cations ($AcrH_2^{\bullet+}$) in acetonitrile (AN) which were believed to be transient intermediates in biological reactions where a one-electron oxidation mechanism applies.[6] However, no information on the reactivity of such radical-cation intermediates in aqueous media has so far been reported.

Dihydroacridine has proven to be an excellent kinetic probe for monitoring Cr(IV) and Cr(V) species which are proposed to be important intermediates in various organic oxidations with chromate.[7,8] Although aqua chromyl(IV) (CrO^{2+}) has been characterized in terms of its properties and reactivity,[9] the instability of the Cr(V) intermediates derived from chromate has precluded the direct determination of their properties. The transient complex trans-$(H_2O)LCrO^{3+}$ (L=[14]aneN_4) undergoes one-electron oxidation reactions with various organic and inorganic reducing reagents.[10] Several other stable Cr(V) complexes employing chelating and macrocyclic ligands to stabilize this unusual oxidation state have been reported.[11] Since mechanistic or kinetic data are not available for the redox reactions of Cr(V) intermediates derived from simple chromate, it is desirable to obtain more data concerning the fundamental properties and reactivity of such species.

Here we propose a detailed mechanism for the reaction between 9-methyl-9,10-dihydroacridine and chromate ions in a mixed acetonitrile-water solvent. By applying conventional UV-VIS spectrophotometry and stopped-flow techniques, Cr(IV) and Cr(V) species could be identified as important intermediates in this system. From the implications of the chain-reaction mechanism found to operate in this system in the absence of oxygen, we have been able to determine the reactivities of Cr(IV) and Cr(V) intermediates in competitive electron transfer, hydrogen atom abstraction, and hydride transfer. Also to be noted is a specific inhibiting effect of oxygen which is different from the effect reported by Bruice et al.[12] in the oxidation of dihydropyridines with ferricyanide, which arrises from the reaction between pyridinium radicals and O_2.

Experimental Section

Materials. Perchloric acid, acetonitrile, d_3-acetonitrile, methanol, zinc metal, potassium dichromate, deuterium oxide, methyl iodide, lithium alumohydride, lithium alumodeuteride, 10-methylacridone and acridine were obtained from commercial sources and used as received. Aqueous solutions of Cr(II) were prepared by reduction of chromium(III) perchlorate with zinc amalgam under anaerobic conditions in aqueous 0.10 M $HClO_4$. High purity water was obtained by passing laboratory-distilled water through a Millipore-Q purification system. Lithium perchlorate was recrystallized from water three times. 10-Methyl-9,10-dihydroacridine ($AcrH_2$) and its 9,9'-dideuterated analog $AcrD_2$ were prepared by reduction of 10-methylacridone with $LiAlH_4$ or $LiAlD_4$, respectively, according to the literature procedure.[13] 10-Methylacridinium iodide was prepared by the reaction of acridine with MeI according to a standard procedure.[14] The purity of the organic starting materials was checked by ^1H-NMR spectroscopy.

Kinetic studies and instrumentation. All the kinetic studies were carried out in a 20% AN-80% H_2O solvent mixture. The ionic strength of the reaction solutions was maintained at 1.0 M by addition of lithium perchlorate. The temperature was controlled at 25.0±0.2 °C. The UV-vis experiments were performed with use of a Shimadzu UV-3101 PC instrument at ambient temperature. The stopped-flow experiments were performed with an Applied Photophysics stopped-flow apparatus under anaerobic conditions. Concentrations of $AcrH_2$ stock solutions were determined spectrophotometrically, ε_{285} = 13,200 L mol^{-1} cm^{-1}. Stock solutions of potassium dichromate were standardized by weight. Chromyl ion (CrO^{2+}) solutions were prepared in situ at pH = 1.0 by stopped-flow mixing of oxygen-free solutions of Cr^{2+} (0.20-0.40 mM) with air-saturated solutions of a substrate used in the experiment.[9a] The superoxochromium(III) ion (CrO_2^{2+}) was identified by its absorption maximum in UV at

290 nm, ε_{290} = 3000 L mol^{-1} cm^{-1}.[9] Kinetics data were analyzed by least-squares fitting; the KaleidaGraph v3.09 for PC software package was used. NMR and ESR spectroscopic data were obtained by use of a Bruker 400 and Bruker ER 200 D-SRC instruments, respectively. Kinetic simulations were performed with the use of a software package KinSim v.4.0 for PC on a Dell XPSPro computer.

Results

Stoichiometry of the reaction between $AcrH_2$ and chromate. Reactions of $AcrH_2$ with chromate were monitored by conventional UV-vis spectrophotometry. An excess of $AcrH_2$ (10:1 and 2:1, $[AcrH_2] = 2 \times 10^{-4}$ and 1×10^{-4} M, $[Cr^{VI}] = 2 \times 10^{-5}$ and 5×10^{-5} M) was used to determine the stoichiometry. Under air-free conditions, the reaction occurred during mixing and the amount of $AcrH^+$ produced was determined from its absorbance at either 358 or 417 nm. At the two wavelengths, the stoichiometry was $AcrH_2:Cr^{VI}$ = 2.88:2 and 2.94:2, respectively (approximately 3:2).

A series of experiments was performed to investigate the effect of methanol on the yield of $AcrH^+$ produced under air-free conditions ($[AcrH_2] = 2 \times 10^{-4}$ M, $[Cr^{VI}] = 2 \times 10^{-5}$ M, [MeOH] = 0.83 and 2.5 M). The yields of $AcrH^+$ decreased with increasing concentration of methanol, 68% and 57% at 0.83 and 2.5M MeOH, respectively, compared to the reaction without methanol.

When oxygen-saturated solutions were used under otherwise the same experimental conditions, the reaction was slower and could be monitored by following the buildup of $AcrH^+$. With the 10:1 starting $AcrH_2:Cr^{VI}$ ratio, the reaction exhibited biphasic behavior at 417 nm, **Figure 1**. When monitored at 320 nm, the isosbestic point of $AcrH_2$ and $AcrH^+$, $\varepsilon_{320}(AcrH_2) = \varepsilon_{320}(AcrH^+) = 2{,}750$ L mol^{-1} cm^{-1}, the consumption of chromate ($\varepsilon_{320} = 770$ L mol^{-1} cm^{-1}) was shown to be complete in ~ 500 s, **Figure 2**. The slow linear increase in absorbance at 417 nm at times > 500s can be attributed to the reaction of $AcrH_2$ with oxygen. This was confirmed in an independent experiment that had no chromate. The kinetic traces at 417 nm were fitted to the rate law of eq 1.

$$(Abs_t - Abs_0) = \Delta Abs\,[1 - \exp(-k_\psi\, t)] + m\, t \qquad (1)$$

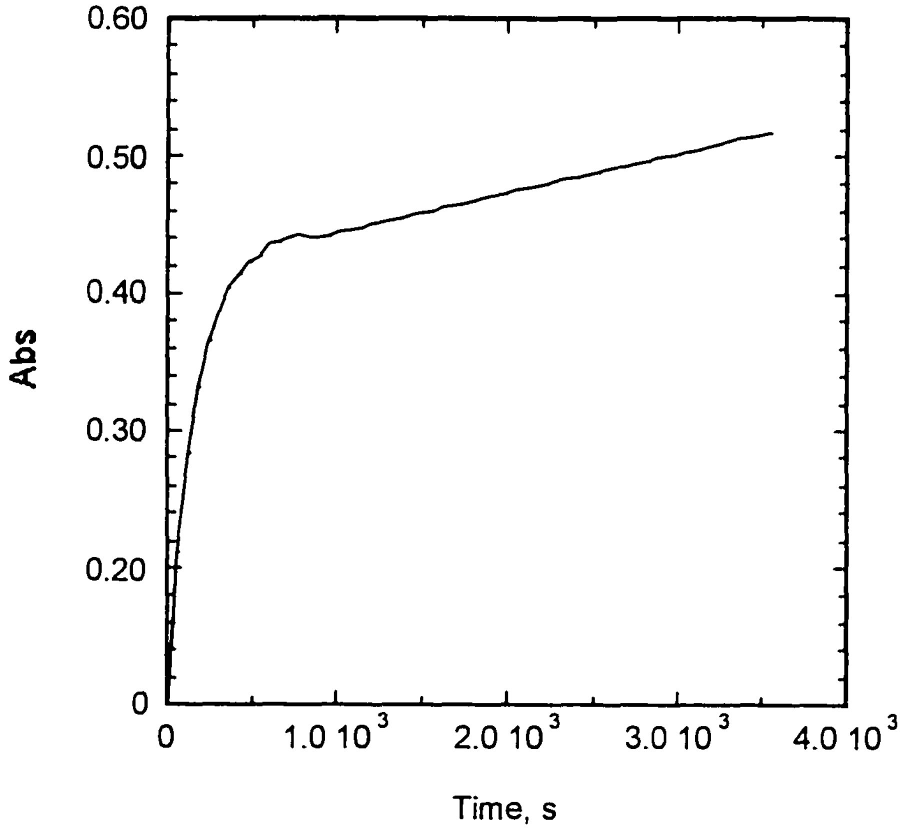


Figure 1. Reaction of $AcrH_2$ (2×10^{-4}M) with chromate (5×10^{-5} M) monitored at 417 nm. pH = 1, μ = 1 M, oxygen saturated solution. The slower linear part of the trace is due to the reaction between $AcrH_2$ and oxygen.

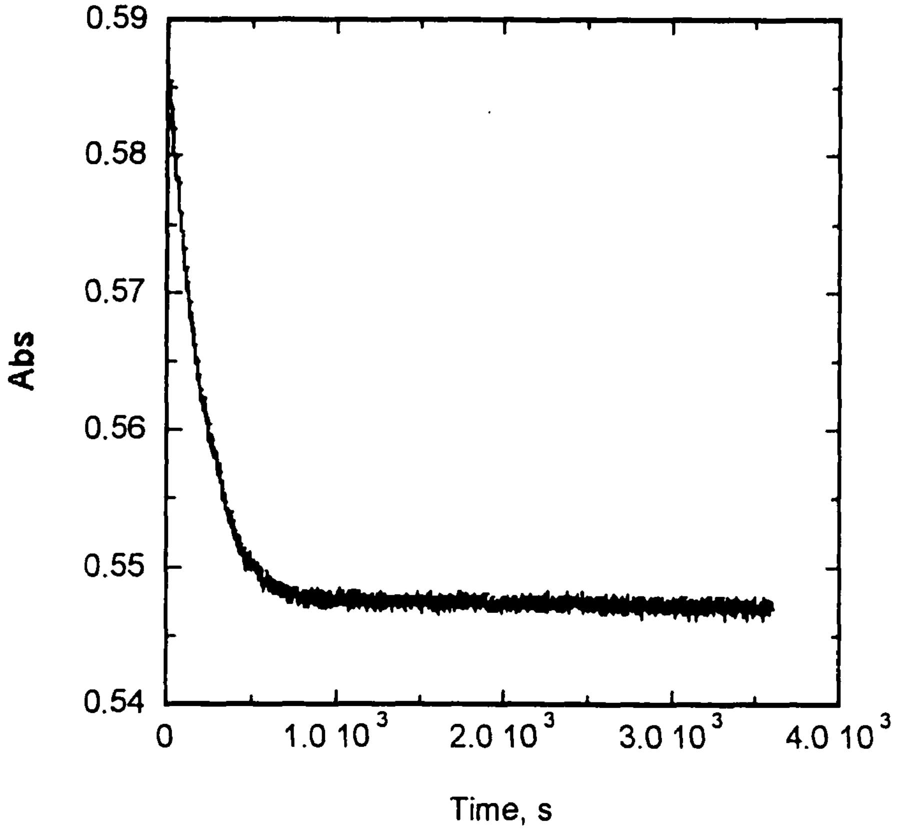


Figure 2. Reaction of $AcrH_2$ (2×10^{-4} M) and chromate (5×10^{-5} M), pH = 1, μ = 1 M, oxygen saturated solution. Consumption of chromate monitored at 320 nm, the isosbestic point for $AcrH_2/AcrH^{-}$ system.

The amplitude of the exponential term, ΔAbs, was then used to calculate the amount of $AcrH^+$ produced in the reaction with chromate. The stoichiometry in O_2 saturated solutions was found to be $AcrH_2:Cr^{VI}$ = 1.88:1 (approximately 2:1).

Kinetics of the reaction between $AcrH_2$ and chromate in oxygen- and air-saturated solutions. The data obeyed the pseudo-first-order rate law when a large excess of chromate was used ($[AcrH_2] = 2 \times 10^{-5}$ M, $[Cr^{VI}] = (2 - 17.5) \times 10^{-4}$ M). In order to investigate the $[H^+]$ effect on the rates of the reaction, a series of experiments was performed with varying acid concentration, **Figure 3**. Under all conditions, the reaction rates were proportional to $[H^+]$. Another series of experiments with varying chromate concentration showed a nonlinear dependence, **Figure 4**. The parabolic behavior of the rate constants with varying chromate concentration was attributed to participation of dichromate in the rate law. The data from Figure 4 were fitted to the rate law in eq 2.

$$k_\psi = 2\,[H^+]\,(k_{11}\,[HCrO_4^-] + k_{12}\,[Cr_2O_7^{2-}]) = [H^+]\,(k_{11}\,[Cr^{VI}]_T + K_d\,k_{12}\,[Cr^{VI}]_T^2) \quad (2)$$

where k_{11} and k_{12} are rate constants of the reactions of $AcrH_2$ with hydrogen chromate and dichromate, respectively, $K_d = 98\ M^{-1}$ is the equilibrium constant for dimerization of hydrogen chromate ion ($2\ HCrO_4^- \rightleftharpoons Cr_2O_7^{2-} + H_2O$),[15] and 2 is the stoichiometric factor. The fitting yielded $k_{11} = (1.12 \pm 0.04) \times 10^2\ L^2\ mol^{-2}\ s^{-1}$ and $k_{12} = (5.6 \pm 0.3) \times 10^3\ L^2\ mol^{-2}\ s^{-1}$.

When excess of $AcrH_2$ was used, the reaction followed mixed first-order and linear kinetics, eq 1. **Figure 5** shows a linear plot of the pseudo-first-order rate constants k_ψ obtained from the fitting of the kinetic traces to eq 1 against the acid concentration. A similar plot of k_ψ against $[AcrH_2]$ was not linear due to interference of the reaction

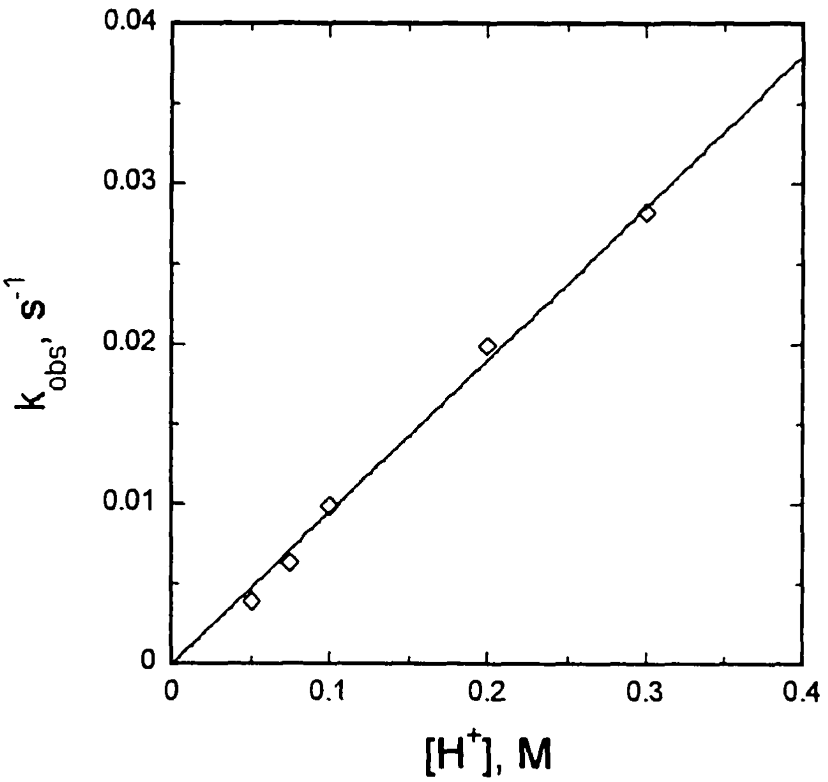


Figure 3. Acid effect in the reaction between $AcrH_2$ (2×10^{-5} M) and chromate (2×10^{-4} M), $[H^+] = 0.05 - 0.3$ M, $\mu = 1$ M, oxygen saturated solution.

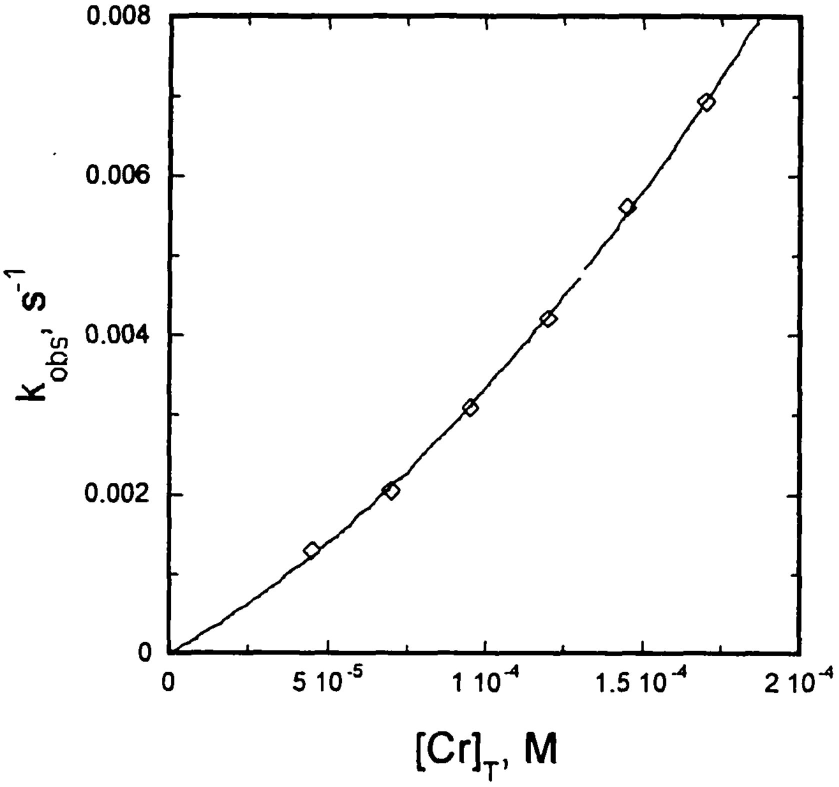


Figure 4. Chromate variation in the reaction between $AcrH_2$ (2×10^{-5} M) and (5 – 17.5) $\times 10^{-5}$ M chromate, pH = 1, μ = 1M, oxygen saturate solution.

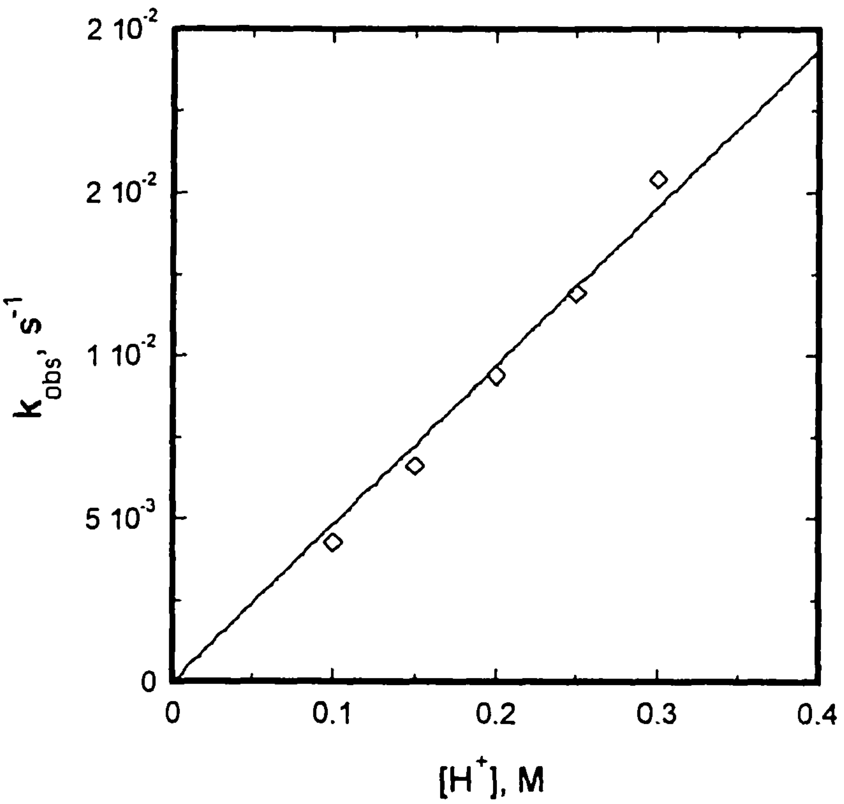


Figure 5. Acid effect on the reaction between $AcrH_2$ (2×10^{-4} M) and chromate (2×10^{-5} M), $[H^+] = 0.1 - 0.3$ M, $\mu = 1$, air saturated solution.

between $AcrH_2$ and oxygen. **Figure 6** shows a series of experiments performed with either excess of $AcrH_2$ or chromate, where after completion of the reaction a new aliquot of the limiting reagent was added to the reaction mixture. In the case where $AcrH_2$ was taken in a large excess, successive yields of $AcrH^+$ were lower with each new addition of chromate and the rates were diminished. Such behavior was not observed when chromate was in excess, where the interference of $AcrH_2/O_2$ reaction was minimal.

In another experiment, 4×10^{-5} M chromate was allowed to react with 8×10^{-5} M $AcrH_2$ in an oxygen-saturated solution. The reaction was monitored at 358 nm. After the reaction was finished, 2×10^{-4} M Fe^{2+} was added to scavenge CrO_2^{2+}, eq 3a,[9c] and UV spectra were recorded every 2 minutes. The spectra were corrected for the dilution factor and for the absorbance of $AcrH^+$ formed in reaction 3b.[16a,b] The corrected spectra were subtracted from the spectrum recorded before the addition of Fe^{2+}.

$$CrO_2^{2+} + Fe^{2+} + H^+ \longrightarrow CrO_2H^{2+} + Fe^{3+} \tag{3a}$$

$$2\,Fe^{3+} + AcrH_2 \longrightarrow 2\,Fe^{2+} + AcrH^+ + H^+ \tag{3b}$$

The resulting set of spectral changes that corresponds to the change in absorbance before and after the addition of Fe^{2+} is shown in **Figure 7**. The negative absorbance change around 290 nm suggests that a measurable amount of superoxochromium ion CrO_2^{2+} (approximately 50% of the starting amount of chromate ions) was present before addition of Fe^{2+}; it then was consumed in the reaction with Fe^{2+}.

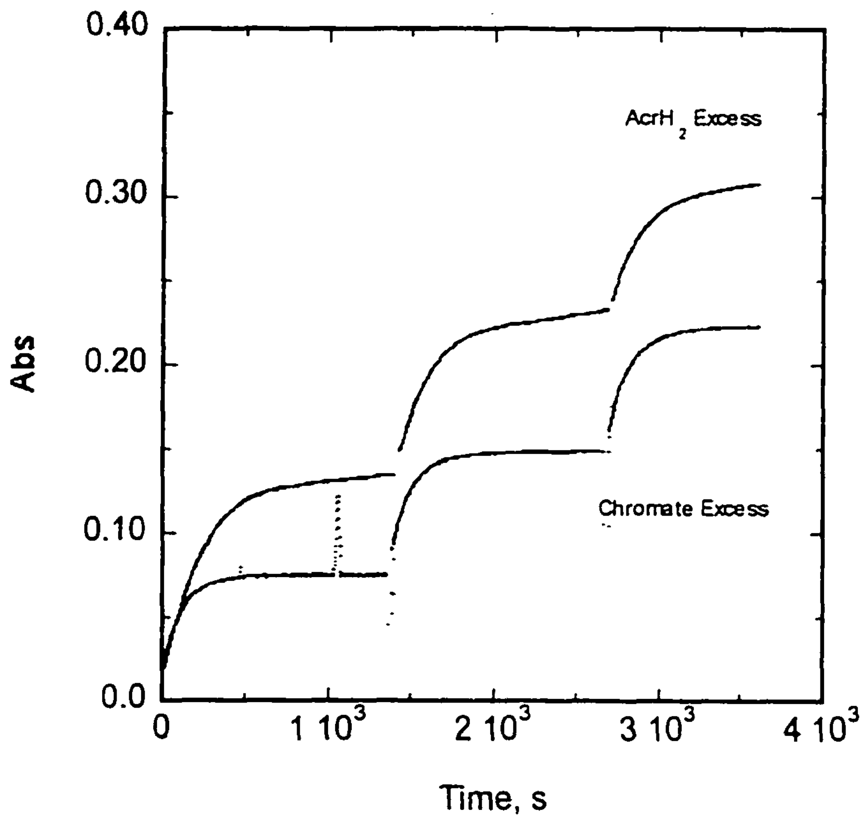


Figure 6. Reactions of a) $AcrH_2$ (2×10^{-5} M) with chromate (2×10^{-4} M) , bottom, b) $AcrH_2$ (2×10^{-4} M) with chromate (2×10^{-5} M) top, pH = 1, μ = 1 M. Each aliquot of the limiting reagent was added after 20 minutes in succession.

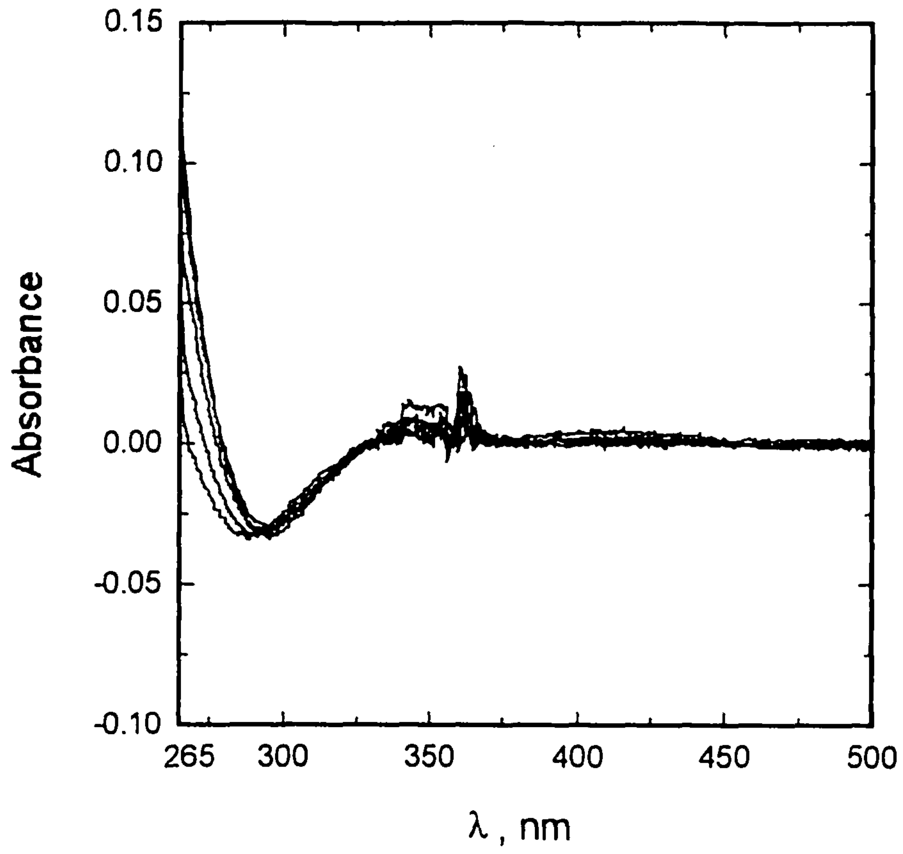


Figure 7. Reaction of $AcrH_2$ (8×10^{-5}M) with chromate (4×10^{-5} M) and Fe^{2+} (2×10^{-4} M), pH = 1, μ = 1 M, oxygen saturated solution. The Fe^{2+} solution was added after the reaction of chromate with $AcrH_2$ was complete. The spectral changes shown here represent the difference in absorbance before and immediately after the addition of Fe^{2+}.

Kinetics of the reaction between $AcrH_2$ and chromate under air-free conditions. This system was studied with the use of the stopped-flow technique. The reactions were monitored by following the buildup of $AcrH^+$ at 358 or 417 nm. Reaction rates were significantly higher compared to those obtained with oxygen- or air-saturated solutions, ranging from a 10- to 250-fold acceleration depending on whether excess of $AcrH_2$ or chromate was used, respectively. In both cases, the rates obeyed pseudo-first-order kinetics. **Figures 8 and 9** show the linear dependence of the pseudo-first-order rate

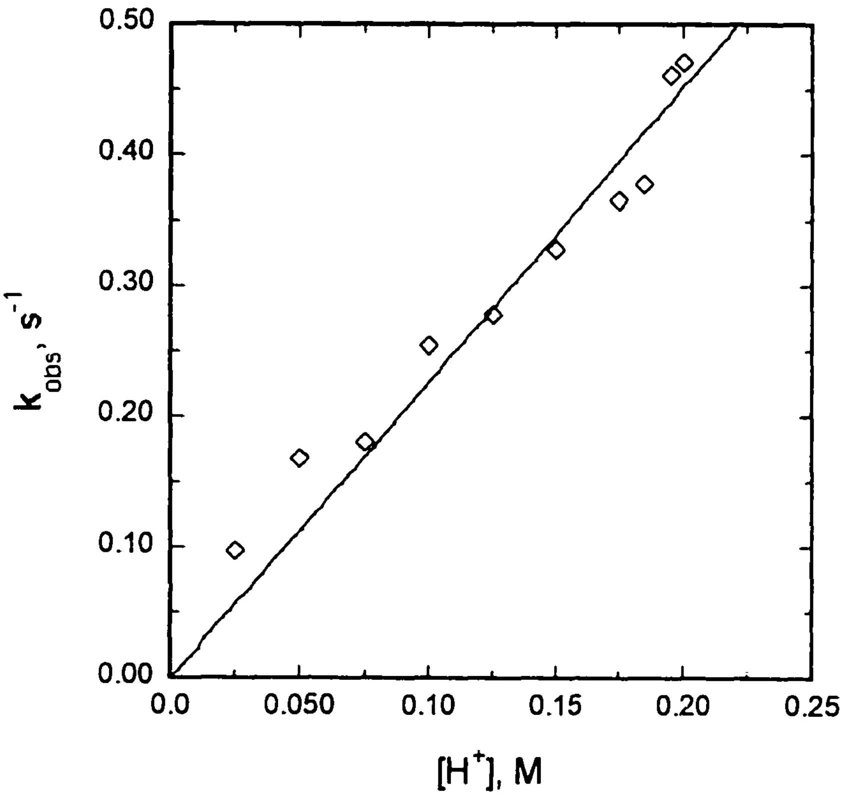


Figure 8. Acid effect on the reaction between $AcrH_2$ (7.5×10^{-5} M, 6.27×10^{-5} M average) and chromate (1.0×10^{-5} M), $[H^+] = 0.025 - 0.185$ M, $\mu = 1$ M, oxygen free solution.

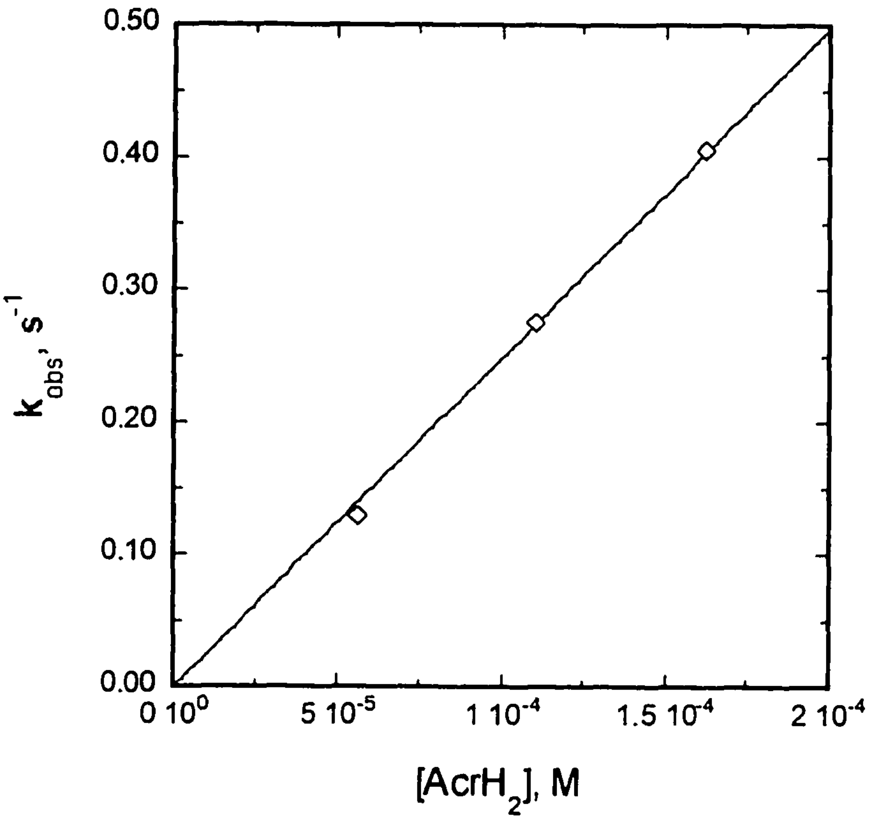


Figure 9. [$AcrH_2$] effect on the reaction between $AcrH_2$ ((5.6 – 16.2) × 10^{-5} M average) and chromate (3 × 10^{-5} M), pH = 1, μ = 1 M, oxygen free solution.

constants k_ψ on the acid and $AcrH_2$ concentrations. The fitting of data in Figures 8 and 9 to eq 4 yielded the third order rate constant $k_a = (2.49 \pm 0.04) \times 10^4$ L^2 mol^{-2} s^{-1}.

$$k_\psi = k_a [H^+] [AcrH_2] \tag{4}$$

In the case of excess chromate, the values of k_ψ showed a linear dependence on the chromate concentration, **Figure 10**. The k_ψ values in Figure 10 were fitted to equation $k_\psi = k_b [Cr^{VI}]_T$, from which the second order rate constant is $k_b = (9.53 \pm 0.02) \times 10^1$ L mol^{-1} s^{-1} (0.10 M H^+). Saturation kinetics was observed in the $[H^+]$ variation experiments, as shown in **Figure 11**. The data in Figures 10 and 11 are consistent with the rate law in eq 5.

$$v = k_c/(1 + k_d [H^+]) \times [H^+] [Cr^{VI}]_T [AcrH_2] \tag{5}$$

The fitting yielded $k_c = (1.10 \pm 0.03) \times 10^3$ L^2 mol^{-2} s^{-1} and $k_d = 1.90 \pm 0.10$ L mol^{-1}. No intermediates were observed upon mixing of the excess of chromate with $AcrH_2$ solution and taking a rapid spectral scan in the region between 300 and 700 nm.

A series of experiment with varying concentrations of sodium sulfate added to the reaction mixture with the excess of $AcrH_2$ was performed to study a possible formation of ion-pairs, as discussed later. No rate inhibition was observed when up to 0.05 M SO_4^{2-} was added.

Kinetic isotope effect studies. The 9,9'-dideuterated analog of $AcrH_2$, $AcrD_2$, was used (in D_2O/AN solvent mixture) to evaluate the kinetic isotope effect of the reaction between dihydroacridine and chromate. In oxygen saturated solutions, $[Cr^{VI}]_T$ variation experiments were performed, **Figure 12**. The fitting of the experimental data to eq 2 yielded $k_{11}^D = (9.4 \pm 1.7) \times 10^1$ L^2 mol^{-2} s^{-1} and $k_{12}^D = (6.5 \pm 1.2) \times 10^3$ L^2 mol^{-2} s^{-1}.

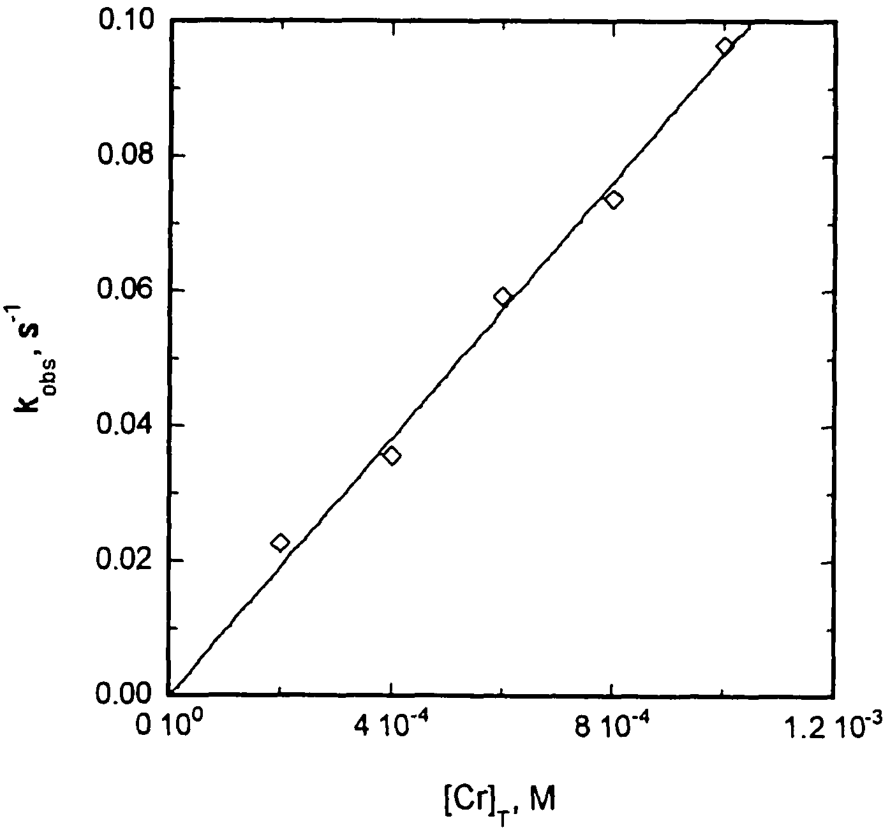


Figure 10. Chromate effect on the reaction between $AcrH_2$ (1.55×10^{-5} M) and chromate ($(2-10) \times 10^{-4}$ M), pH = 1, μ = 1, oxygen free solution.

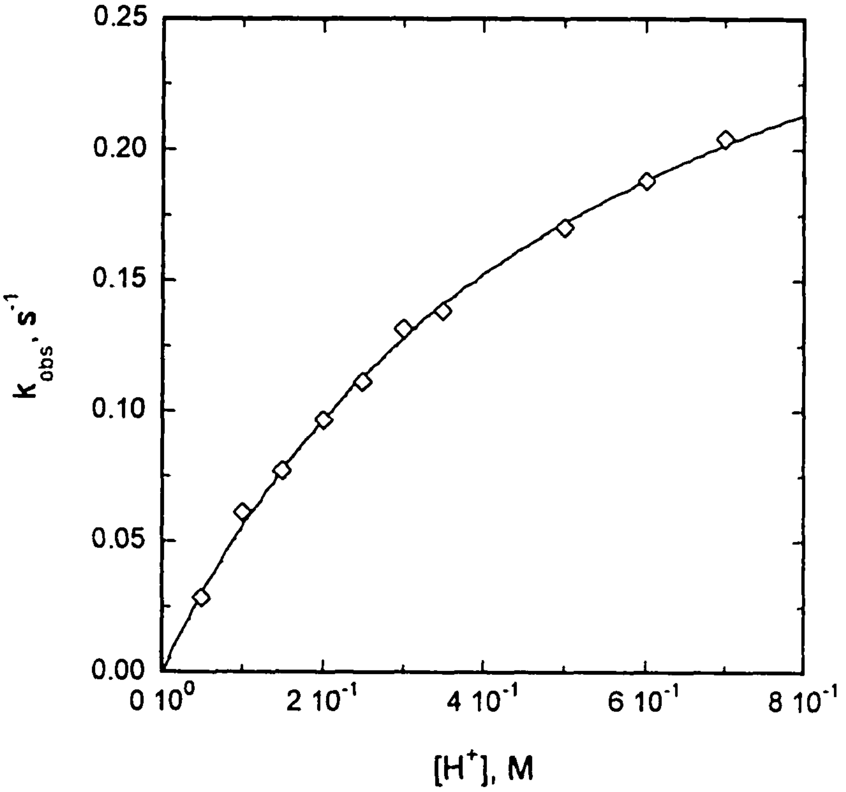


Figure 11. Acid effect on the reaction between $AcrH_2$ (1×10^{-5} M) and chromate (6×10^{-4} M), $[H^+] = 0.05 - 0.7$ M, $\mu = 1$ M, oxygen free solution.

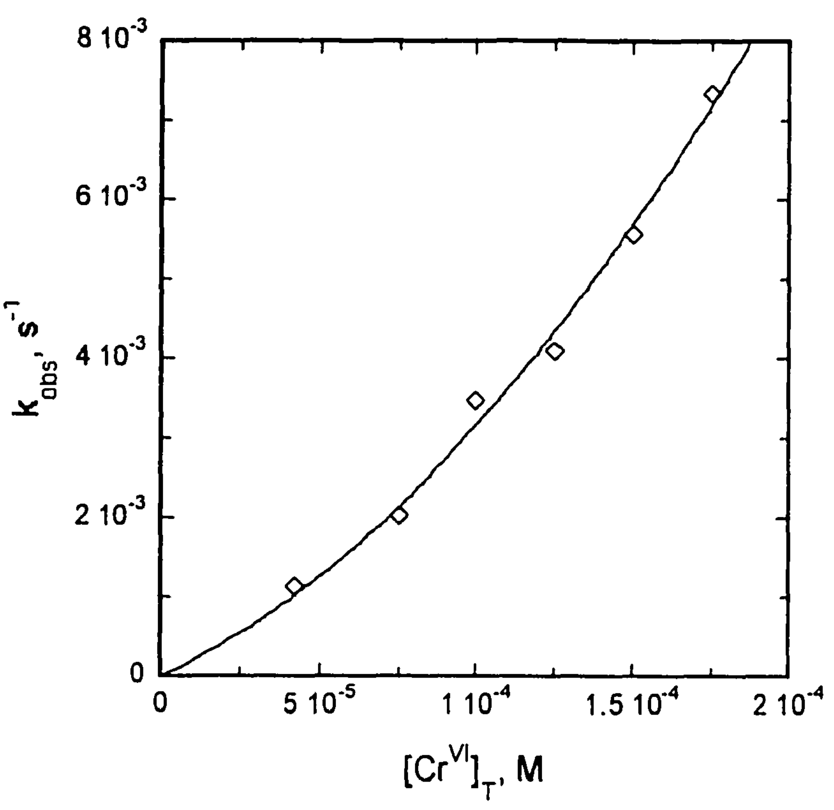


Figure 12. Chromate effect on the reaction between $AcrD_2$ (2×10^{-5} M) and chromate (($5 - 17.5) \times 10^{-4}$ M), pH = 1, $\mu = 1$ M, oxygen saturated solution.

The corresponding isotope effects are then $(k_H/k_D)_{11}$ = 1.2 ± 0.2 and $(k_H/k_D)_{12}$ = 0.86 ± 0.17.

The reaction under air-free conditions exhibited no kinetic isotope effect when an excess of chromate was used. Under the conditions with excess of $AcrD_2$ (μ = 0.10 M), the reaction showed a mild isotope effect of k_H/k_D = 1.71 ± 0.06, **Figure 13**.

In another series of experiments the kinetic isotope effect for the reaction between chromate and $AcrH_2$ under anaerobic conditions was determined with the use of product ratios calculated from ^{1}H-NMR data. In a typical kinetic run, an excess of $AcrD_2$ ((1 – 2) × 10^{-4} M) was mixed with $AcrH_2$ ((4 – 10) × 10^{-5} M) and the resulting mixture was allowed to react with chromate (2 × 10^{-5} M). The reaction was followed to completion by UV-vis spectroscopy and an ^{1}H-NMR spectrum was taken. The product ratios ($[AcrH^+]_\infty/[AcrD^+]_\infty$) and the absolute concentrations were determined by analyzing the relative peak areas for the proton in position 9 (I_a) and the eight protons in positions 1 – 8 (I_b). The following formulas were used in the calculations:

$$[AcrH^+]_\infty/[AcrD^+]_\infty = 8\, I_a / (I_b - 8\, I_a) = R \tag{6a}$$

$$[AcrH^+]_\infty = R\, \Delta Acr / (R + 1) \tag{6b}$$

$$[AcrD^+]_\infty = \Delta Acr / (R + 1) \tag{6c}$$

where ΔAcr = 3/2 $[Cr^6]_o$ (since chromate is the limiting reagent, 3/2 stoichiometric coefficient was used). The kinetic isotope effect for the chain reaction $(k_H/k_D)_{chain}$ was then calculated from eq 7.

$$(k_H/k_D)_{chain} = \frac{\ln \{ [AcrH_2]_0 / ([AcrH_2]_0 - [AcrH^+]_\infty) \}}{\ln \{ [AcrD_2]_0 / ([AcrD_2]_0 - [AcrD^+]_\infty) \}} \tag{7}$$

Due to the limited resolution of the NMR instrumentation and interference from HDO (traces of non-deuterated water were not excluded from $DClO_4$ stock solutions), the

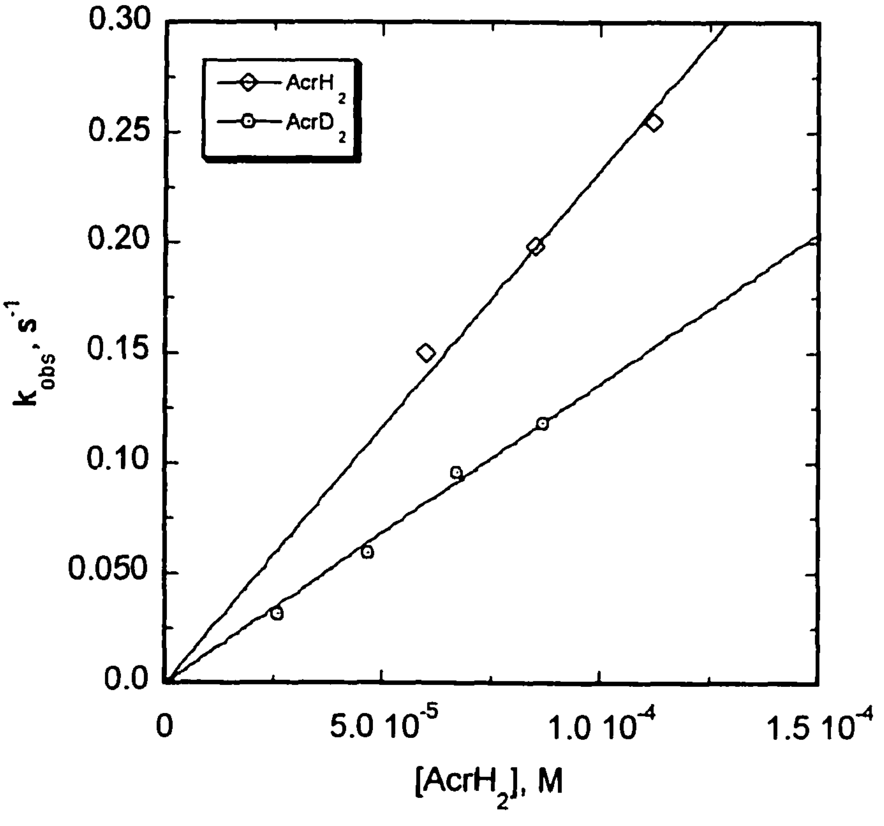


Figure 13. Reactions of $AcrH_2$ (in H_2O) and $AcrD_2$ (in D_2O) with chromate (1×10^{-5} M), pH = 1, $\mu = 0.1$ M, oxygen free solution.

$(k_H/k_D)_{chain}$ values have a sizable standard error, $(k_H/k_D)_{chain}$ = 3.0 ± 1.1. Isotope incorporation from the solvent into the products was not observed in the oxidation of $AcrH_2$ in D_2O or the oxidation of $AcrD_2$ in H_2O.

Reaction of chromyl ion (CrO^{2+}) with $AcrH_2$. Chromyl ions were generated in situ by reacting 3 × 10^{-4} M Cr^{2+} in an oxygen-free solution with an equal volume of an air-saturated solution of $AcrH_2$ (1 - 2 × 10^{-4} M) in a series of stopped-flow experiments.[9a] The concentration of chromyl ions was determined from the absorbance buildup of $AcrH^+$ at 358 nm; it varied from 5 to 7 × 10^{-5} M. Kinetics of the reaction obeyed a second-order rate law ($AcrH_2 + CrO^{2+} + H^+ \longrightarrow AcrH^+ + Cr^{2+} + H_2O$). The second-order rate constant k_2 for the reaction between CrO^{2+} and $AcrH_2$ was determined from a fit of the kinetic data to eq 8, $k_2 = (1.02 \pm 0.08) \times 10^4$ L mol^{-1} s^{-1}.

$$[AcrH^+]_t = [CrO^{2+}]_0 - \frac{\Delta_0 [CrO^{2+}]_0}{[AcrH_2]_0\, e^{k \Delta_0 t} - [CrO^{2+}]_0} \tag{8}$$

where $\Delta_0 = [AcrH_2]_0 - [CrO^{2+}]_0$.

A series of experiments was carried out with methanol as a competing reagent for CrO^{2+}. Methanol (0.10 M) was allowed to react with chromyl in the absence and presence of $AcrH_2$ (2 × 10^{-4} M), while keeping the experimental conditions identical. The kinetic traces from both experiments were fitted to a first-order rate law (the amount of $AcrH_2$ consumed under these conditions is relatively small since ~70% of chromyl ions should react with methanol). The pseudo-first-order rate constants thus obtained were 4.68 s^{-1} (0.10 M MeOH) and 6.43 s^{-1} (0.10 M MeOH, 2 × 10^{-4} M $AcrH_2$). The calculated rate constant, k_{MeOH} [MeOH] + k_2 [$AcrH_2$] = 4.68 + 2.04 = 6.72 s^{-1}, agrees with the measured value of 6.43 s^{-1}, and provides independent support for the value of k_2.

In another set of experiments, chromyl ions were preformed and then diluted to approximately 1.5×10^{-6} M. This solution of CrO^{2+} was allowed to react with $(5 - 12.5) \times 10^{-5}$ M $AcrH_2$ in a conventional UV-vis spectrophotometer. **Figure 14** shows a plot of k_ψ against the average $AcrH_2$ concentration. The second-order rate constant was calculated from the slope of the plot, $k_2 = (1.10 \pm 0.06) \times 10^4$ L mol^{-1} s^{-1}. This value is in excellent agreement with the value obtained in the stopped-flow experiments. The reaction with $AcrD_2$ under the same conditions yielded $k_2^D = (4.8 \pm 0.2) \times 10^3$ L mol^{-1} s^{-1}, **Figure 15**. The kinetic isotope effect was calculated as $(k_H/k_D)_2 = 2.29 \pm 0.16$.

Discussion

General observations and the reaction scheme. The experimental data described above suggest that a chain reaction operates under air-free conditions. The stoichiometry experiments provide the necessary information to deduce the final products under air-free and air-saturated conditions. Considering the fact that the only stable product formed from $AcrH_2$ is the acridinium ion $AcrH^+$, (simulation studies with the program KinSim showed that the dimerization of the radical $AcrH^•$ is not important under the conditions used in this study), the final chromium-containing product under air-free conditions must be Cr^{III}. Similarly, a formal "Cr^{II}" species must be formed when significant amounts of oxygen were present during the reaction and a stoichiometric ratio $AcrH_2$/Cr(VI) = 2:1 was observed. This species is probably the superoxochromium(III)

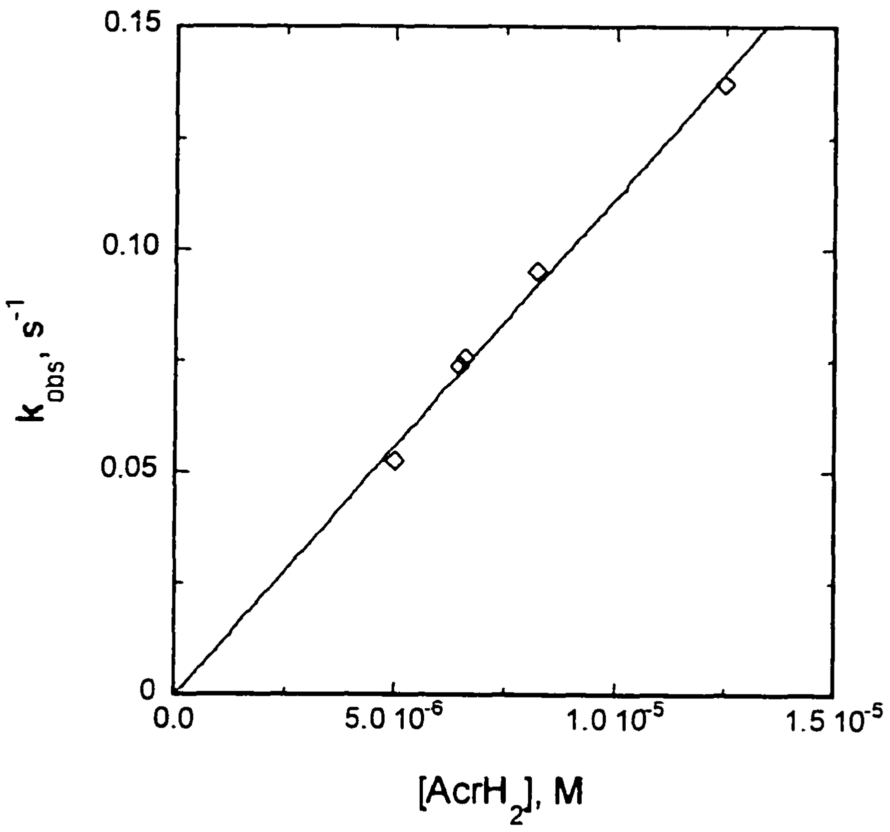


Figure 14. Reaction between CrO^{2+} ($\sim 1.5 \times 10^{-6}$ M) and $AcrH_2$ ($(5 - 12.5) \times 10^{-5}$ M), pH =1, m = 1 M, air saturated solution.

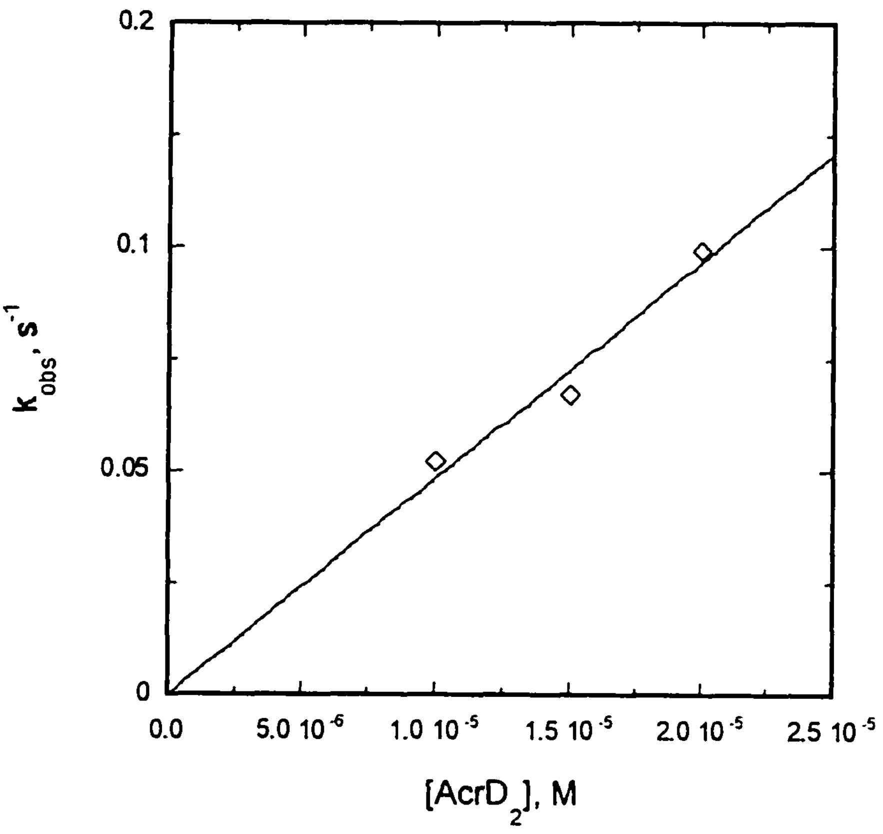
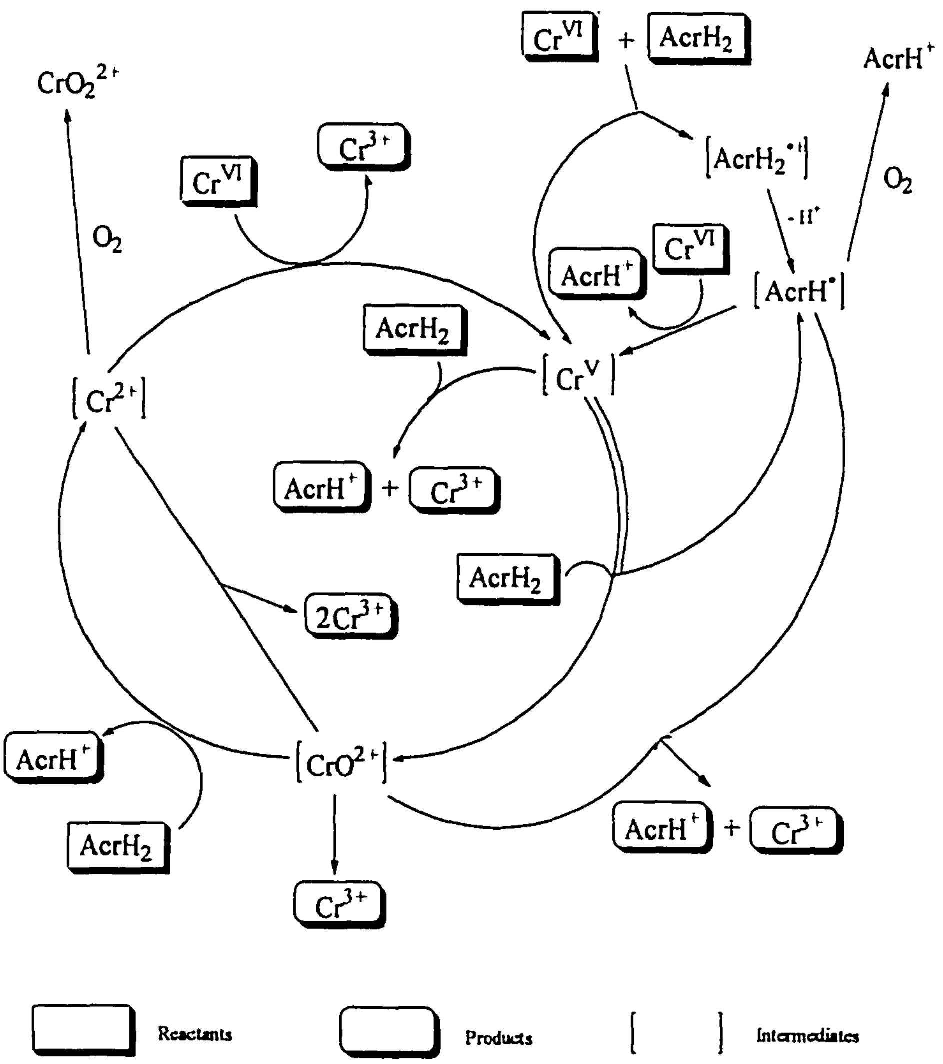


Figure 15. Reaction between $AcrD_2$ ($((1 - 2) \times 10^{-5}$ M) and chromyl ($\sim 1.5 \times 10^{-6}$ M), pH=1, $\mu = 1$, air saturated solution.

ion CrO_2^{2+}, formed in the reaction between Cr^{2+} and oxygen; its characteristic absorption at 290 nm was observed, as described in the Results section.

All the observations, including kinetics data and kinetic isotope effect experiments, are consistent with **Scheme I**. **Scheme II** shows a set of reactions with the corresponding rate constants, that were either obtained in this work or in previous studies. Also, the kinetics data are summarized in **Table I**. KinSim simulations confirmed, that under all conditions used in this study, Scheme I adequately describes the kinetic behavior of the chromate/$AcrH_2$ system.

Scheme I



Scheme II

$AcrH_2 + HCrO_4^- \xrightarrow{[H^+]} AcrH_2^{\bullet+} + Cr^V$	$k_I = 111\ M^{-2}s^{-1}$
$Cr^V + AcrH_2 \longrightarrow CrO^{2+} + AcrH^\bullet$	$k_5 = 10^5\text{-}10^7\ M^{-1}s^{-1}$
$CrO^{2+} + AcrH_2 \longrightarrow Cr^{2+} + AcrH^+$	$k_2 = 1 \times 10^4\ M^{-1}s^{-1}$
$Cr^{2+} + HCrO_4^- \longrightarrow Cr^{3+} + Cr^V$	$k_{Cr} = 2 \times 10^9\ M^{-1}s^{-1}$
$AcrH^\bullet + HCrO_4^- \longrightarrow AcrH^+ + Cr^V$	$k_A = 7.4 \times 10^9\ M^{-1}s^{-1}$
$AcrH_2^{\bullet+} \rightleftharpoons AcrH^\bullet + H^+$	$k_d = 690\ s^{-1}$, $k_p = 1.2 \times 10^5\ M^{-1}s^{-1}$
$Cr^{2+} + O_2 \longrightarrow CrO_2^{2+}$	$k_{O1} = 1.6 \times 10^8\ M^{-1}s^{-1}$
$AcrH^\bullet + O_2 \longrightarrow AcrH^+$	$k_{O2} = 4.3 \times 10^9\ M^{-1}s^{-1}$
$Cr^V + AcrH_2 \longrightarrow Cr^{3+} + AcrH^+$	$k_{T1} = 10^4\text{-}10^6\ M^{-1}s^{-1}$
$CrO^{2+} + Cr^{2+} \longrightarrow 2\ Cr^{3+}$	$k_{T2} = >10^7\ M^{-1}s^{-1}$
$AcrH^\bullet + CrO^{2+} \longrightarrow AcrH^+ + Cr^{3+}$	$k_{T3} = 7.4 \times 10^9\ M^{-1}s^{-1}$
$CrO^{2+} \longrightarrow Cr^{3+}$	$k_{dec} = \sim 0.1\ s^{-1}$
$Cr^{2+} + Cr^V \longrightarrow Cr^{3+} + CrO^{2+}$	k_{T4}
$Cr^V + AcrH^\bullet \longrightarrow CrO^{2+} + AcrH^+$	$k_{T5} = 7.4 \times 10^9\ M^{-1}s^{-1}$
$AcrH^\bullet + AcrH_2^{\bullet+} \longrightarrow AcrH^+ + AcrH_2$	$k_{T6} = 7.4 \times 10^9\ M^{-1}s^{-1}$
$2\ Cr^V \longrightarrow CrO^{2+} + HCrO_4^-$	k_{T7}

Table I. Summary of Kinetic Data for the Reactions of $AcrH_2$ with Chromate.

Reactants		Products	Rate constants	References
$H_2CrO_4 + AcrH_2$	$\rightarrow$	$Cr^V + AcrH_2^{\bullet +}$	436 ± 18	a
$Cr_2O_7^{2-} + AcrH_2 + H^+$	$\rightarrow$	$CrO^{2+} + HCrO_4^- + AcrH^+$	$(6.9 \pm 0.4) \times 10^3$	a
$Cr^V + AcrH_2$	$\rightarrow$	$CrO^{2+} + AcrH^\bullet$	$10^5 - 10^7$	b,c
$Cr^V + AcrH_2$	$\rightarrow$	$Cr^{3+} + AcrH^+$	$10^4 - 10^6$	b,c
$CrO^{2+} + AcrH_2$	$\rightarrow$	$Cr^{2+} + AcrH^+$	$(1.10 \pm 0.06) \times 10^4$	a
$Cr^{2+} + HCrO_4^-$	$\rightarrow$	$Cr^{3+} + Cr^V$	2×10^9	9a
$AcrH^\bullet + HCrO_4^-$	$\rightarrow$	$AcrH^+ + Cr^V$	7.4×10^9	d
$AcrH_2^{\bullet +}$	$\rightarrow$	$AcrH^\bullet + H^+$	690	16
	$\leftarrow$		1.2×10^5	16
$Cr^{2+} + O_2$	$\rightarrow$	CrO_2^{2+}	1.6×10^8	21
$AcrH^\bullet + O_2$	$\rightarrow$	$AcrH^+$	$\approx 4.3 \times 10^9$	a
$CrO^{2+} + Cr^{2+}$	$\rightarrow$	$2\ Cr^{3+}$	$> 10^7$	b
$AcrH^\bullet + CrO^{2+}$	$\rightarrow$	$AcrH^+ + Cr^{3+}$	7.4×10^9	d
CrO^{2+}	$\rightarrow$	Cr^{3+}	≈ 0.1	b

a) Obtained in this work

b) Estimated from KinSim simulations

c) See Discussion for acid effects

d) Diffusion-controlled rate constant (See ref. 5 and 20)

The initiation step in the chain reaction. The initiation step in Scheme I is the reaction between hydrogen chromate and dihydroacridine ions. The kinetics of the initiation step was studied under aerobic conditions, under which both chain cycles in Scheme I are effectively broken by the reactions of $AcrH^{\bullet}$ and Cr^{2+} with oxygen. The resulting scheme is reduced to the reactions occurring prior to the reactions with oxygen, and is kinetically controlled only by the initiation step.

The reaction between $AcrH^{\bullet}$ and oxygen was reported previously.[16a] In the reaction of $IrCl_6^{2-}$ with an excess of $AcrH_2$, the stoichiometry was reduced, when air-saturated solutions were used ($[IrCl_6^{2-}] = 2 \times 10^{-4}$ M, $[AcrH_2] = 5 \times 10^{-5}$ M, stoichiometry 1.4:1 in an air-saturated solution, 1.95:1 in an air-free solution). Assuming that the rate of the reaction between $AcrH^{\bullet}$ and $IrCl_6^{2-}$ is diffusion controlled, $k = 7.4 \times 10^9$ L mol^{-1} s^{-1}, one can estimate the rate constant for the reaction between $AcrH^{\bullet}$ and oxygen as ~ 4.3×10^9 L mol^{-1} s^{-1}. No other products besides $AcrH^+$ were observed.

Quantitative analysis of the kinetic data for the reaction between an excess of $AcrH_2$ with chromate in air-saturated and oxygen-saturated solutions was difficult because of the interference from the background reaction of excess $AcrH_2$ with oxygen. This limitation does not apply when excess of chromate is used, hence all of the quantitative studies of the $AcrH_2/Cr^{VI}$ reaction under aerobic conditions were carried out with the excess of chromate.

A series of nonlinear least-squares fittings of the $[H^+]$ and $[Cr^{VI}]_T$ variation data was performed to determine the elementary steps responsible for the observed kinetic behavior under aerobic conditions. The best fit occurred when both data sets were fitted simultaneously with H_2CrO_4 and $Cr_2O_7^{2-}$ as the actual reactive species participating in electron transfers from $AcrH_2$, eq 9.

$$k_{\psi} = 2\,(k^{e}_{11}\,[H_2CrO_4] + k^{e}_{12}\,[Cr_2O_7^{2-}]\,[H^+]) \tag{9}$$

where k^{e}_{11} is the bimolecular rate constant for the elementary electron transfer from $AcrH_2$ to H_2CrO_4, and k^{e}_{12} is the third-order rate constant for the electron transfer from $AcrH_2$ to $Cr_2O_7^{2-}$ with the assistance from H^+.[17] Overall, the latter reaction involves $HCr_2O_7^-$; since its K_a is not known, a third-order rate constant notation is adopted.

Equation 9 can be rearranged to eq 10 in terms of $[Cr^{VI}]_T$:

$$k_{obs} = 2\left[k^{e}_{11}\,[Cr^{VI}]_T \frac{[H^+]}{[H^+] + K_a} + k^{e}_{12}\,[H^+]\,[Cr^{VI}]_T^{\,2} \frac{K_d\,K_a^{\,2}}{([H^+] + K_a)^2} \right] \tag{10}$$

where K_d is the dimerization constant of $HCrO_4^-$, and K_a the acid ionization constant of H_2CrO_4. Using $K_d = 98\ M^{-1}$ and $K_a = 4.13$,[15] k^{e}_{11} and k^{e}_{12} were determined as 436 ± 18 L $mol^{-1}\ s^{-1}$ and $(6.9 \pm 0.4) \times 10^3\ L^2\ mol^{-2}\ s^{-1}$, respectively. **Figure 16** shows a plot of k_{obs}, determined in the $[H^+]$ and $[Cr^{VI}]_T$ variation experiments, against the values calculated from eq 10, using the rate constants obtained from the fitting. As can be seen in Figure 16, the agreement between the experimental and calculated k_{obs} is quite satisfactory.

The role of superoxochromim(III). As shown above, significant amounts of CrO_2^{2+} were found among products of the reaction between a small excess of $AcrH_2$ and chromate in air-saturated solutions. Two important conclusions can be made from these observations. First, CrO_2^{2+} does not react with $AcrH_2$ on the time scale of these

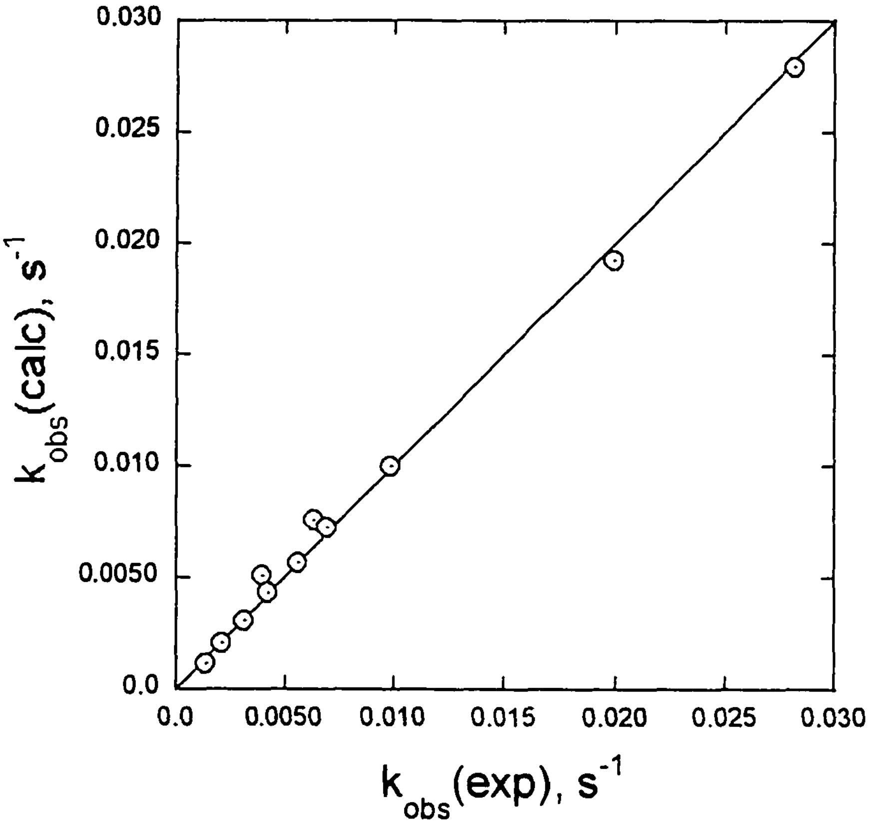


Figure 16. A comparison between the experimental and calculated values of the rate constant from the simultaneous fitting of the $[H^+]$ and $[Cr^{VI}]_T$ variation data for the reaction between excess chromate and $AcrH_2$ under aerobic conditions.

experiments (30 min to 1 hour). Second, the presence of CrO_2^{2+} indicates that Cr^{2+} is an important intermediate in the chain reaction. Since it is very unlikely that Cr^{3+} can be reduced to Cr^{2+} under these conditions, chromyl ions CrO^{2+} must also be present during the reaction.[9] Direct studies of the reaction between chromyl and $AcrH_2$ showed that, indeed, CrO^{2+} ions react with $AcrH_2$ and produce Cr^{2+} which in turn can give CrO_2^{2+} in the reaction with oxygen. This was also confirmed by the experiments in which the $AcrH^+$ yields were diminished upon addition of methanol, a good trapping reagent for CrO^{2+}.

Reactions of $AcrH_2$ with hydrogen chromate vs. dichromate in the chain reaction. From the lack of a significant kinetic isotope effect, the reactions of $AcrH_2$ with hydrogen chromate and dichromate are inferred to be electron transfer processes. Although both reactions involve an initial electron transfer with the formation of Cr^V and $AcrH_2^{\bullet+}$ intermediates, the absence of the second-order chromate term in the rate law of the reaction between chromate and $AcrH_2$ under air-free conditions shows that only the reaction with hydrogen chromate ions is important as a chain initiation process. It is not clear why the reaction of dichromate with $AcrH_2$ is not an effective chain initiator, although one might speculate that two consecutive one-electron transfers from $AcrH_2$ to $Cr_2O_7^{2-}$ will produce a dimeric mixed Cr^{IV}-Cr^{VI} species or a dimeric Cr^V intermediate, which will readily disproportionate to afford Cr^{VI} and Cr^{IV}. The second electron transfer and the required deprotonation of the acridine intermediate probably occur in a solvent cage containing an ion pair consisting of positively charged $AcrH_2^{\bullet+}$ and a double-negatively charged $HCr_2O_7^{2-}$ intermediates, eq 11.

$$HCr_2O_7^- + AcrH_2 \xrightarrow{et} [HCr_2O_7^{2-} \bullet AcrH_2^{\bullet+}] \xrightarrow[H^+]{et,\ H^+ \text{ transfer}} CrO^{2+} + HCrO_4^- + AcrH^+ \quad (11)$$

As shown later, the Cr^{IV} intermediate (chromyl ion, CrO^{2+}) is not an efficient chain carrier under the conditions of excess chromate.

Reactions of $AcrH_2$ with Cr^V intermediates. Reactions between $AcrH^{\bullet}$ and oxidizing reagents such as CrO^{2+} are presumed to be diffusion-controlled.[5,18] The reaction of $AcrH_2$ with Cr^V is necessary for an effective chain reaction mechanism. Reactions T_1, T_2 and T_3 of Scheme II are important termination steps that either control the overall propagation rate (T_1) or eliminate two chain carriers in one bimolecular process (T_2 and T_3). KinSim simulations showed that the other termination steps are unimportant under the experimental conditions used in this study. A kinetic isotope effect of 1.71 for the reaction of excess $AcrH_2$ with chromate under anaerobic conditions suggests that the reaction of $AcrH_2$ with Cr^V in step 5 should also have a significant isotope effect. Therefore, it is a hydrogen atom abstraction process, as opposed to an electron transfer.

A more accurate estimate of the kinetic isotope effect for the reaction between $AcrH_2$ and Cr^V can be obtained from the NMR data. The two product-forming reactions of $AcrH_2/AcrD_2$ with Cr-containing species that can distinguish between the two isotopic substrates are the reactions of Cr^V and CrO^{2+} (Scheme I).

$$Cr^V + AcrH_2 \xrightarrow[k_H/k_D = x]{k_5} CrO^{2+} + AcrH^{\bullet} \quad (12a)$$

$$CrO^{2+} + AcrH_2 \xrightarrow[k_H/k_D = y]{k_2} Cr^{2+} + AcrH \quad (12b)$$

Denoting the kinetic isotope effects for the two reactions in eq 12a and 12b as x and y, respectively, the overall kinetic isotope effect for the products $(k_H/k_D)_{chain}$ can be expressed in terms of x and y, eq 13a:

$$(k_H/k_D)_{chain} = \frac{2xy + x + y}{x + y + 2} \qquad (13a)$$

Equation 13a can be rearranged to solve for x, eq 13b:

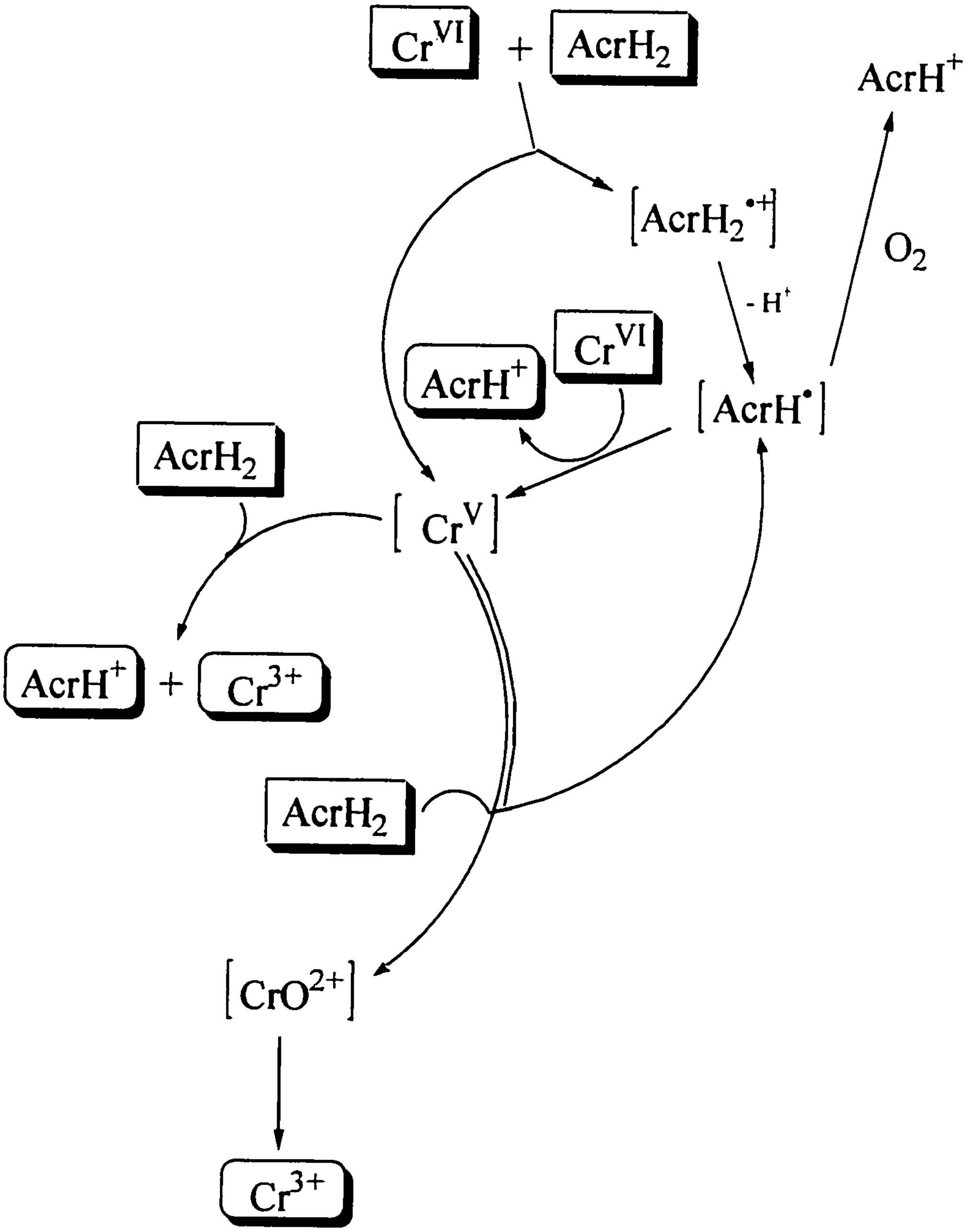
$$x = \frac{(k_H/k_D)_{chain}\, y + 2\,(k_H/k_D)_{chain} - y}{2y + 1 - (k_H/k_D)_{chain}} \qquad (13b)$$

Knowing the values of $(k_H/k_D)_{chain}$ and $(k_H/k_D)_2 = y$, the kinetic isotope effect for the reaction between $AcrH_2$ and Cr^V $(k_H/k_D)_5 = x$ can then be estimated. Due to instrumental limitations in the NMR experiments described in the Results section, the error in the value for $(k_H/k_D)_5 \approx 4.7 \pm 3.8$ is quite large. This calculation, despite the low precision, suggests, that the one-electron reaction between $AcrH_2$ and Cr^V is a hydrogen-atom abstraction process.

Reaction of $AcrH_2$ with excess chromate under anaerobic conditions. One possible explanation for the rate retardation with the change of the excess reagent involves a possibility of a chromate inhibition by forming an ion pair between hydrogen chromate and $AcrH_2^{\bullet +}$. This model is not valid, as the experiments with sodium sulfate added to the reaction mixture showed no change in the reaction rates.

Kinetic data for the reaction between $AcrH_2$ and excess chromate suggest that the second cycle involving a Cr^{2+} intermediate (Scheme I) is not operating under these conditions. **Schemes III** and **IV** show the important reactions in this system.

Scheme III


Cr^VI
+
AcrH2
AcrH^+
[AcrH2^•+]
O2
- H^+
Cr^VI
AcrH^+
[AcrH^•]
AcrH2
[Cr^V]
AcrH^+
+
Cr^3+
AcrH2
[CrO^2+]
Cr^3+

Scheme IV

$$AcrH_2 + HCrO_4^- \xrightarrow[{[H^+]}]{k_I} AcrH_2^{\bullet+} + Cr^V \qquad k_I = 111\ M^{-2}s^{-1}$$

$$Cr^V + AcrH_2 \xrightarrow{k_5} CrO^{2+} + AcrH^\bullet \qquad k_5 = 10^5\text{-}10^7\ M^{-1}s^{-1}$$

$$AcrH^\bullet + HCrO_4^- \xrightarrow{k_A} AcrH^+ + Cr^V \qquad k_A = 7.4 \times 10^9\ M^{-1}s^{-1}$$

$$AcrH_2^{\bullet+} \underset{k_p}{\overset{k_d}{\rightleftharpoons}} AcrH^\bullet + H^+ \qquad k_d = 690\ s^{-1},\ k_p = 1.2 \times 10^5\ M^{-1}s^{-1}$$

$$Cr^V + AcrH_2 \xrightarrow{k_{T1}} Cr^{3+} + AcrH^+ \qquad k_{T1} = 10^4\text{-}10^6\ M^{-1}s^{-1}$$

$$CrO^{2+} \xrightarrow{\text{decompos.}} Cr^{3+} \qquad k_{dec} = \sim 0.1\ s^{-1}$$

Under the conditions where an excess of chromate ion was used, the competing decomposition of the chromyl ions is much faster than the propagation step 2 (Scheme II). As a result, the cycle involving the reactions of $AcrH_2$ with chromyl ion, and of Cr^{2+} with Cr^{VI}, is not important. Further proof of the validity of this scheme was obtained when methanol (0.01 – 0.10 M) was introduced into the reaction mixture prior to the addition of chromate. The reaction that followed was much faster than without methanol, resembling the kinetics of the $AcrH_2$/chromate reaction with excess $AcrH_2$, except that the yields of $AcrH^+$ were diminished. In this experiment, methanol was added to promote the formation of Cr^{2+} from CrO^{2+} without the formation of $AcrH^+$.

Equation 14 shows the steady-state rate law that can be derived from Scheme IV.

$$v = 2\frac{k_I' k_5}{k_{T1}} [AcrH_2]\,[Cr^{VI}]_T \qquad (14)$$

Disregarding any acid effects for now and using $k_I' = k_I\,[H^+] = 11.1$ L mol^{-1} s^{-1} (0.10 M H^+), the chain length can be calculated as $k_5/k_{TI} = 4.3$. The low value of k_5/k_{TI} shows that the chain reaction under these conditions is not efficient, consistent with only ~ 10-fold rate acceleration compared to the reaction carried out under aerobic conditions.

Acid effect on the reaction between $AcrH_2$ and excess chromate under anaerobic conditions. As described in the Results section, saturation kinetics were observed for the acid effect on the reaction between $AcrH_2$ and an excess of chromate. The elementary reaction steps consistent with such kinetic behavior are shown in **Scheme V**.

Scheme V

$$AcrH_2 + H_3CrO_4 \xrightarrow{k_5} AcrH^+ + H_4CrO_4$$

$$AcrH_2 + H_3CrO_4 \xrightarrow{k_{TIa}} AcrH^{\bullet} + H_4CrO_4^{\bullet}$$

$$AcrH_2 + H_4CrO_4^+ \xrightarrow{k_{TIb}} AcrH^{\bullet} + H_5CrO_4$$

$$H_4CrO_4^+ \rightleftharpoons H_3CrO_4 + H^+ \qquad pK_{a0}$$

$$H_3CrO_4 \rightleftharpoons H_2CrO_4^- + H^+ \qquad pK_{a1} = 2.7$$

$$H_2CrO_4^- \rightleftharpoons HCrO_4^{2-} + H^+ \qquad pK_{a2} = 3.$$

$$HCrO_4^{2-} \rightleftharpoons CrO_4^{3-} + H^+ \qquad pK_{a3} = 7.$$

where k_5, k_{TIa} and k_{TIb} are the second-order rate constant for the elementary reactions between Cr^V and $AcrH_2$ in both 1e and 2e reactions; K_{a1}, K_{a2} and K_{a3} are the acid ionization constants for various Cr^V species known to be present in aqueous solution[19]; K_{a0} is the acid ionization constant for the uncharacterized tetraprotonated Cr^V species. The existence of $H_4CrO_4^+$ is a speculation, but is necessary to account for the experimentally observed rate law. Furthermore, it is reasonable to assume that $H_4CrO_4^+$

is a stronger 2-e oxidant than H_3CrO_4 for the process in which a formal hydride transfer occurs, because of the positive charge of the former.

The overall rate law of the chain reaction can then be expressed as in eq 15, accounting for the acid affect.

$$v = 2\, k_I\, k_5 \frac{K_{a0}}{k_{T1b}} \frac{[H^+]}{k_{T1a}\dfrac{K_{a0}}{k_{T1b}} + [H^+]} [AcrH_2]\,[Cr^{VI}] \qquad (15)$$

In the derivation above, the following assumptions were made: a) $[H_3CrO_4] \approx [Cr^V]_T$, total concentration of Cr^V intermediates, and b) $[H_4CrO_4^+] \approx [H^+]/K_{a0} \times [Cr^V]_T$. Both are justified considering the values of pK_a for different Cr^V intermediates and assuming that $K_{a0} >> [H^+]$ under the experimental conditions used (protonation of the triprotonated Cr^V species occurs only to a small degree, consistent with the fact that such a species has not been observed experimentally).[19] From the experimental data the ratios $k_5/k_{T1a} = 4.9$ and $k_{T1a}/k_{T1b} \times K_{a0} = 0.54$ were calculated, which allow to determine the partitioning of the different Cr^V species reacting with $AcrH_2$ at $[H^+] = 0.1$ M, eq 16.

$$AcrH_2 + \begin{cases} H_3CrO_4 \xrightarrow{4.9} AcrH^{\bullet} + H_4CrO_4 \\ H_3CrO_4 \xrightarrow{1} AcrH^+ + H_4CrO_4^- \\ H_4CrO_4^+ \xrightarrow{0.18} AcrH^+ + H_5CrO_4 \end{cases} \qquad (16)$$

Conclusions

The reaction between $AcrH_2$ and chromate was found to be a branching chain reaction, in which transient Cr^V, Cr^{IV}, Cr^{II} and $AcrH^{\bullet}/AcrH_2^{\bullet+}$ species are the chain carriers. Under aerobic conditions, both chain cycles are broken by the reactions of Cr^{2+}

and AcrH˙ with oxygen and the rate of the overall reaction is controlled solely by the initiation step. Kinetic evidence suggests that the initiation step are the reactions of $AcrH_2$ with the chromic acid H_2CrO_4 and hydrogen dichromate $HCr_2O_7^-$ which occur by an electron transfer pathway. Kinetic data and kinetic isotope effect studies provide useful information about the properties and reactivities of the transient chromium intermediates.

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(55) (a) Pestovsky, O.; Bakac, A.; Espenson, J. H. *Inorg. Chem.* **1998**, *37*, 1616 (b) A small excess of $AcrH_2$ (< 5 %) was present in the reaction mixture. The kinetics of the reaction between $AcrH_2$ and Fe^{3+} matched those reported previously (see ref. 16a). The correction for the reaction 3b was performed by assaying the excess $AcrH_2$ from the absorbance of the product $AcrH^+$ at 358 nm, generated during the reaction with Fe^{3+}. The spectral difference for the reaction 3b, $C_{AcrH2} \times [\varepsilon_{358}(AcrH^+) + 2\,\varepsilon_{358}(Fe^{2+}) - \varepsilon_{358}(AcrH_2) - 2\,\varepsilon_{358}(Fe^{3+})]$, was obtained from authentic samples of the corresponding reagents and was used to correct the spectral changes.

(56) The elementary reaction between dichromate and $AcrH_2$ probably occurs through an initial protonation of dichromate and the formation of $HCr_2O_7^-$. Since the value of the equilibrium constant for the acid ionization of $HCr_2O_7^-$ is unknown, the third-order rate constant is reported for the reaction between $AcrH_2$ and $Cr_2O_7^{2-}$.

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GENERAL CONCLUSIONS

Mechanisms of the reactions of 10-methyl-9,10-dihydroacridine with inorganic oxidizing reagent follow the same general scheme, Scheme V of Chapter I, in which an initial 1e oxidation of $AcrH_2$ produces the acridinium radical-cation $AcrH_2^{\bullet+}$. The following deprotonation of the radical-cation and the sequential oxidation of thus formed acridinium radical $AcrH^{\bullet}$ complete the 2e oxidation of $AcrH_2$, resulting in a formal hydride transfer from $AcrH_2$. Depending on the strength of the inorganic oxidant, the initial electron transfer or the following deprotonation of the radical-cation may be rate controlling. In the case of weak oxidizing reagents such as Fe_{aq}^{3+} or chromate(VI), the first electron transfer is rate-controlling and can be studied directly (the following reactions are much faster). The data from the kinetic isotope effect experiments suggest that the first 1e oxidation process is an electron transfer.

When strong oxidizing reagent with high standard oxidation potentials (Ce_{aq}^{4+}) or fast self-exchange electron transfer rates ($IrCl_6^{2-}$) are used, the initial electron transfer is fast and cannot be observed on the stopped-flow time scale. As a result, the properties of $AcrH_2^{\bullet+}$ can be studied directly, since it persists on the stopped-flow time scale. The pK_a of $AcrH_2^{\bullet+}$ was determined in 20% AN / 80% H_2O mixed solvent. Kinetic isotope experiments employing $AcrD_2$ instead of the proteo analog provide important information on intrinsic details of deprotonation of the radical-cation. Both ionization of $AcrH_2^{\bullet+}$ and protonation of $AcrH^{\bullet}$ have contribution of nuclear tunneling when H^+ is transferred.

The reaction of $AcrH_2$ with chromate(VI) was found to be a branching chain reaction that is strongly inhibited by O_2. An electron transfer from $AcrH_2$ to H_2CrO_4 is the initiation step of the chain reaction; it produces $AcrH^{\bullet}$ (through an initial formation and the sequential deprotonation of the radical-cation) and Cr^{V} intermediates that are the chain carriers. $Cr_2O_7^{2-}$ reacts with $AcrH_2$ but does not produce any chain-carrying intermediates when excess chromate is used. This finding is consistent with the formation of CrO^{2+} in 2e oxidation of $AcrH_2$ by dichromate: $AcrH_2 + Cr_2O_7^{2-} \rightarrow AcrH^{+} + Cr^{VI} + CrO^{2+}$.

A reaction between Cr^{V} and $AcrH_2$ can occur by either hydrogen atom abstraction of a formal hydride transfer. The former produces $AcrH^{\bullet}$ and CrO^{2+} , two chain-carrying intermediates, resulting in branching. Both chain branches, involving either $Cr^{V}/AcrH\bullet$ or $Cr^{V}/CrO^{2+}/Cr^{2+}$ intermediates are efficiently terminated in the presence of oxygen by the reactions of $AcrH^{\bullet}$ and Cr^{2+} with O_2, respectively.

A competitive hydride transfer from $AcrH_2$ to Cr^{V} produces $AcrH^{+}$ and Cr^{3+} thus resulting in an efficient chain termination. Acid effect studies suggest that a previously undetected intermediate $H_4CrO_4^{+}$ reacts with $AcrH_2$ by hydride transfer mechanism, competing with the reaction of H_3CrO_4 with $AcrH_2$ in the chain termination process. The kinetics data provide necessary information to determine the relative rates at which these competitive reactions occur at different pH.

The reaction between $AcrH_2$ and CrO^{2+} proceeds by a hydride transfer, which was proven by kinetic isotope effect experiments and competition with MeOH studies.

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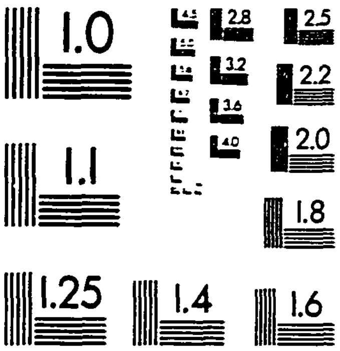
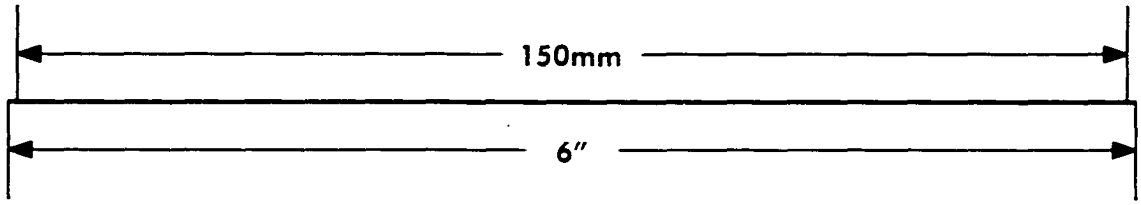
IMAGE EVALUATION TEST TARGET (QA-3)





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