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Reduction Reactions of Gold(III) Bromocomplexes in Dimethyl Sulfoxide

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Abstract

The reactions of $AuBr_4^-$ with uracil and uridine in dimethyl sulfoxide (Me_2SO) lead to the reduction of gold(III) to gold(I) and to the formation of the corresponding 5-bromopyrimidine. In Me_2SO containing water the 5-bromo-6-hydroxy-5,6-dihydropyrimidine is also formed. The observed redox kinetics are consistent with a mechanism involving reductive elimination of bromine from the gold(III) complex followed by halogenation of the pyrimidine. The specific rates for the reduction of $AuBr_4^-$ with both pyrimidines in Me_2SO and in the partially aqueous solvent are greater than those for the corresponding reactions in water, uracil being more reactive than uridine. The tetrabromoaurate(III) ion is also reduced by Me_2SO. The triphenylphosphine complex $Au(PPh_3)Br_3$ reacts with uridine in Me_2SO to give 5-bromouridine. Reduction of gold(III) to gold(I) also occurs through a reaction involving the formation of triphenylphosphine oxide.

Introduction

Redox reactions may play a role when gold(III) complexes interact with nucleic acids. The complexes $AuBr_4^-$ and $Au(CN)_2Br_2^-$ have been shown previously to be reduced by uracil or uridine in water through reductive elimination of molecular bromine followed by halogenation of the pyrimidine [1, 2]. In this paper studies of the reduction of $AuBr_4^-$ by uracil and uridine in Me_2SO are reported in order to provide information on solvent effects upon the reactivity of auric compounds. Reactions of the triphenylphosphine complex $Au(PPh_3)Br_3$ in Me_2SO are also described.

Experimental

$K[AuBr_4]$, $Au(PPh_3)Br_3$, $Au(PPh_3)Br$, triphenylphosphine oxide and 5-bromouracil were prepared according to literature methods. All other chemicals were reagent grade. ^1H and ^{31}P NMR spectra were recorded on Bruker WP60 and JEOL FX-90Q spectrometers. Chemical shifts were measured relative to external $SiMe_4$ (^1H) and 85% H_3PO_4 (^{31}P). UV–Vis spectra were recorded on Perkin-Elmer 576ST and Lambda 5 spectrophotometers equipped with thermostatted cell compartments using an appropriate reference blank in each case. Kinetic runs were started by fast mixing of prethermostatted solutions of the reactants.

Results

^1H NMR spectra of uracil (4×10^{-2} and 0.14 M) in $Me_2SO\text{-}d_6$ show signals at $\delta = 10.96$ (H3), 10.83 (H1), 7.38 (H6), 5.44 (H5), $|J_{5,6}| = 7.5$ Hz. Splitting of the H1 and H6 resonances is observed upon addition of acid, $|J_{1,6}| = 5.5$ Hz. The spectrum of 0.1 M 5-bromouracil shows signals at $\delta = 11.37$ (H1 and H3) and 7.89 (H6). Splitting of the NH resonance into two signals at 11.49 (H3) and 11.22 (H1) and coupling between H1 and H6 ($|J_{1,6}| = 6.0$ Hz) is observed upon addition of acid. When molecular bromine is added to a solution of uracil in $Me_2SO\text{-}d_6$ appearance of 5-bromouracil is shown by the NMR spectrum of the solution together with a downfield shift of the proton resonance of HDO contained in the solvent due to the formation of HBr. If the bromination is carried out in the presence of added water the proton spectra of the mixtures show formation of signals from 5-bromouracil together with doublet resonances at $\delta = 4.80$ and 4.24 assigned to 5-bromo-6-hydroxy-5,6-dihydrouracil, $|J_{5,6}| = 2.5$ Hz. ^1H NMR spectra show that the reaction of $AuBr_4^-$ with uracil in $Me_2SO\text{-}d_6$ produces 5-bromouracil. When the reaction is carried out in the presence of added water 5-bromo-6-hydroxy-5,6-dihydrouracil is also formed. In the reaction of 0.028 M $AuBr_4^-$ and 0.11 M uracil in the presence of 5.5 M D_2O the observed amount of bromohydrin was less than 10% of 5-bromouracil after 80 min, when

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c. 80% bromination of uracil had occurred. Chemical shifts of uracil and of the bromination products in the reacting mixtures are not affected by the presence of gold complexes.

^1H NMR spectra of uridine 3.1×10^{-2} and 5.3×10^{-2} M in Me_2SO-d_6 show signals at $\delta = 11.28$ (H3), 7.89 (H6), 5.64 (H5), 5.78 (H1′), 5.3 (OH, 1H), 5.4 (OH, 2H), c. 3.3–4.2 (H2′–5′), $|J_{5,6}| = 8.0$ Hz. When uridine (4.6×10^{-2} M) in Me_2SO-d_6 is treated with an equimolar amount of bromine the formation of 5-bromouridine is observed. Resonances of this species occur at $\delta = 11.78$ (H3), 8.47 (H6), 5.73 (H1′), c. 3.4–4.2 (H2′–5′). Ribose oxydryl proton resonances are not apparent due to exchange with water and the acid formed upon bromination. Proton spectra show that the reaction of $AuBr_4^-$ and uridine in Me_2SO-d_6 produces 5-bromouridine. If the reaction is carried out in the presence of added water (e.g. 10%) the spectra of the mixtures show the formation of signals from 5-bromouridine together with resonances assigned to 5-bromo-6-hydroxy-5,6-dihydrouridine. H6 and H5 signals of this species appear as a set of doublets at $\delta = 5.26$–5.20 and 4.34–4.26, $|J_{5,6}| = 2.5$ Hz.

The tetrabromoaurate(III) ion is not stable in Me_2SO. It is observed that the absorbance of the solutions in the range 350–500 nm slowly decreases, while the ratios of optical densities at the different wavelengths remain constant. For example, the absorbance of a solution of 10^{-2} M $AuBr_4^-$ is decreased to 90% after 5 h and to 85% after 30 h; the absorbance of a solution of 5×10^{-4} M $AuBr_4^-$ in the presence of 10% H_2O is decreased to 50% after 2 h and to 3% after 22 h. ^1H NMR spectra of solutions of $AuBr_4^-$ in Me_2-SO-d_6 display a slow downfield shift of the signal of HDO contained in the solvent, indicating the formation of acidic species. Half times of the reaction of $AuBr_4^-$ with the solvent appear to increase as the initial concentration of gold is increased. The rates of this reaction are not significantly affected by changes of the concentration of added NaBr in the range 0–5×10^{-2} M. In the study of the reactions of $AuBr_4^-$ with the pyrimidines experimental conditions were chosen for which the relative rate of the reaction with the solvent was negligible. Freshly prepared solutions of the reactants were used for each kinetic run, although no significant changes of specific rates were observed upon ageing when allowance was made for the partial reduction of $AuBr_4^-$. It was also found that the bromination reaction of the pyrimidines by the system Me_2SO–Br^-–H^+ is much slower than the bromination reaction with $AuBr_4^-$. For example, the formation of 5-bromouracil in a solution of 5×10^{-2} M uracil containing 0.12 M NaBr, 2.7 M D_2O and 0.18 M D_2SO_4 was shown by NMR measurements to be less than 40% after 36 days.

Kinetic experiments were carried out at 25 °C in Me_2SO and in Me_2SO containing added water (2–10%). Although in the partially aqueous solution bromohydrin is formed from uracil and uridine in addition to 5-bromopyrimidine, found as the only product in Me_2SO, it is observed that the rate of reduction of $AuBr_4^-$ by uracil is not significantly affected by the addition of water up to 10%. The reactions were carried out in the presence of added $(Et_4N)Br$ and H_2SO_4 in order to maintain the concentrations of bromide and hydrogen ions constant. The ionic strength was maintained at the required value by addition of $NaNO_3$. The reactions of $AuBr_4^-$ with uracil and uridine are accompanied by a decrease of absorbance in the range 350–500 nm, the ratios of optical densities at the different wavelengths remaining constant. The absorption is zero at completion of the reactions, in agreement with the formation of gold(I). The spectrum of $AuBr_2^-$ does not display absorption bands in the range 350–500 nm [3].

The kinetics of the reactions, carried out in the presence of excess of pyrimidine, were found to fit the rate law (1), where $[Au]_T$ is the total gold concentration, allowing for the presence of gold(I) in the starting solutions of $AuBr_4^-$, and $[Au^{III}]_0$ is the initial concentration of $AuBr_4^-$.

$$[Au]_T \ln[Au^{III}] - [Au^{III}] = [Au]_T \ln[Au^{III}]_0 - [Au^{III}]_0 - k_{obs}t \qquad (1)$$

The concentrations of $AuBr_4^-$ were estimated from the absorbance at 470 nm. Due to the instability of $AuBr_4^-$ in Me_2SO the specific absorption of this species has been estimated by extrapolation. Values of k_{obs} obtained for different concentrations are reported in Table 1. In addition to the experiments quoted, two experiments were carried out by reacting 0.03 M $AuBr_4^-$ with 0.03 M uridine in Me_2SO-d_6 and in Me_2SO-d_6 containing 10% D_2O. Changes of uridine concentrations were measured by integral intensities of ^1H NMR resonances. From these measurements the ratio $[Au^{III}]/[Au]_T$ as a function of time was calculated (see Fig. 1). In the partially aqueous solvent 5-bromouridine and 5-bromo-6-hydroxy-5,6-dihydrouridine are formed in comparable amounts.

^1H NMR spectra show that the reaction of $Au(PPh_3)Br_3$ with uridine in Me_2SO-d_6 produces 5-bromouridine. In the reaction of 5×10^{-2} M $Au(PPh_3)Br_3$ and 5×10^{-2} M uridine, carried out at 25 °C by rapid dissolution of the complex into a solution of the pyrimidine, the extent of bromination is c. 15% after 30 min and 24 h. When 5×10^{-2} M $Au(PPh_3)Br_3$ and 5×10^{-2} M uridine are mixed in the presence of 5×10^{-2} M $Au(PPh_3)Br$ no bromination of uridine can be observed after 24 h. Decrease of absorption and ^{31}P NMR spectra of these mixtures and of solutions of $Au(PPh_3)Br_3$ show that gold(III)

TABLE 1. Rate constants for the reduction of $AuBr_4^-$ by pyrimidines in Me_2SO at 25 °C (5% water; ionic strength $I = 0.045$ M)

	$10^4 \times [AuBr_4^-]$ (M)	$10^2 \times [H^+]$ (M)	$10^3 \times [Br^-]$ (M)	$10^3 \times$ [Pyrimidine] (M)	$10^6 \times k_{obs}$ (M s^{-1})	$10^4 \times k_{obs}$/[Pyrimidine] (s^{-1})
Uracil	4.7	2.3	10	5.0	1.1	2.2
	8.9	2.3	10	9.7	2.4	2.5
	4.0	2.3	9.9	5.0	1.3	2.6
	5.0	2.3	10	50	8.7	1.7
	5.0	2.3	10	30	6.3	2.1
	5.0	2.3	10	20	4.6	2.3
	5.0	2.3	10	10	2.2	2.2
	5.3	2.3	5.2	10	2.5	2.5
	5.0	2.3	10	7.5	1.7	2.3
	4.9	0.46	1.0	10	2.7	2.7
	5.2	2.3	1.1	10	2.6	2.6
	4.9[a]	2.3	10	10	2.5	2.5
	5.2[b]	2.0	9.8	9.8	2.5	2.6
	5.1[b]	2.3	9.9	10	2.3	2.3
	5.3	0.23	10	10	2.6	2.6
	5.1	11	10	19	4.6	2.4
	5.2[c]	2.0	10	10	2.1	2.1
Uridine	5.1	2.3	10	10	0.16	0.16
	5.3	0.23	10	10	0.17	0.17
	5.2	2.3	10	50	0.75	0.15
	5.2	2.3	10	25	0.39	0.16
	5.1	2.3	10	7.6	0.16	0.21
	5.1	2.3	10	4.6	0.097	0.21

[a] 2% Water. [b] 10% Water. [c] No added water.

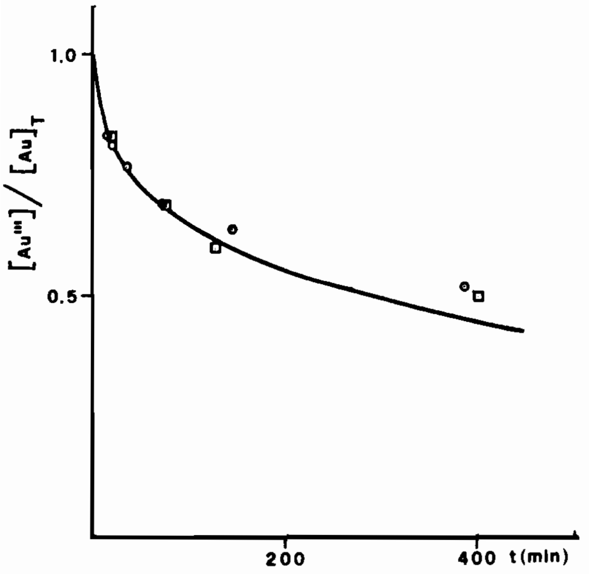

Fig. 1. Ratio of gold(III) over total gold as a function of time for the reaction of 0.03 M $AuBr_4^-$ with 0.03 M uridine in $Me_2SO\text{-}d_6$ (○) and in $Me_2SO\text{-}d_6$ containing 10% D_2O (□).

is reduced to gold(I) also through a reaction involving formation of triphenylphosphine oxide (Ph_3PO). Formation of Ph_3PO also occurs in solutions of $Au(PPh_3)Br$ containing the ions H^+ and Br^- through oxidation by Me_2SO.

The ^{31}P resonances of PPh_3 and Ph_3PO in $Me_2SO\text{-}d_6$ occur at $\delta = -6.9$ and 25.5, respectively. The ^{31}P spectra of the mixtures of $Au(PPh_3)Br_3$ and uridine measured after 5 days display a signal at $\delta = 25.5$ assigned to Ph_3PO. The spectrum of 4×10^{-2} M $Au(PPh_3)Br$ shows the ^{31}P resonance at $\delta = 34.5$, no changes occurring after 24 h. An identical spectrum unchanged over 24 h is displayed by a mixture of 4×10^{-2} M $Au(PPh_3)Br$ and 4×10^{-2} M $(Bu_4N)Br$. When D_2SO_4 is added to this mixture a decrease of the signal at $\delta = 34.5$ and an increase of the signal at $\delta = 25.5$ are observed, the relative intensities being *c.* 1:20 after 24 h. The spectrum of 5×10^{-2} M $Au(PPh_3)Br_3$ measured 20 min after dissolution of the compound displays a signal at $\delta = 25.5$, indicating complete oxidation of PPh_3 to Ph_3PO. The reacting mixture also shows a downfield shift of the proton resonance of HDO contained in the solvent. When 5×10^{-2} M $Au(PPh_3)Br$ is added to this mixture signals at $\delta = 34.5$ and 25.5 are observed with relative intensities in the approximate ratio of 1:3 after 1.5 h and 1:25 after 3 days.

Discussion

The reactions of $AuBr_4^-$ with uracil and uridine in Me_2SO lead to reduction of gold(III) to gold(I) and to formation of the corresponding 5-bromopyrimidine. In the partially aqueous solvent the 5-bromo-6-hydroxy-5,6-dihydropyrimidine is also produced. The rates of reduction of $AuBr_4^-$, however, are not appreciably dependent on the water concentration up to 10%. The tetrabromoaurate(III) ion is also observed to partake to a slower reaction with the solvent. Spectroscopic results for this reaction are consistent with reduction of gold(III) to gold(I).

The experimental rate expression (1) for the reduction of $AuBr_4^-$ by uracil and uridine in Me_2SO is identical with the rate law observed for the reactions in water [1, 2], suggesting a mechanism of the type (2) and (3).

$$AuBr_4^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AuBr_2^- + Br_2 \qquad (2)$$

$$Br_2 + \text{pyrimidine} \xrightarrow{k_2} \text{products} \qquad (3)$$

The rate law (4), where $[Au]_T$ is the total gold concentration, is derived for the mechanism (2) and (3) assuming (i) first-order kinetics for reductive elimination from $AuBr_4^-$ (k_1), (ii) second-order kinetics for both oxidative addition to $AuBr_2^-$ (k_{-1}) and bromination of the pyrimidine (k_2) and (iii) $k_{-1}[AuBr_2^-] \gg k_2[\text{pyrimidine}]$.

$$-\frac{d[Au^{III}]}{dt} = \frac{k_1 k_2 [Au^{III}][\text{pyrimidine}]}{k_{-1}([Au]_T - [Au^{III}])} \qquad (4)$$

The integrated form of (4) for pseudo-first-order conditions with respect to the pyrimidine is identical with the experimental rate expression (1), where $k_{obs} = (k_1 k_2/k_{-1})[\text{pyrimidine}]$. Values of $k_{obs}/[\text{pyrimidine}]$ reported in Table 1 are reasonably consistent for each reactant and give mean values of $k_1 k_2/k_{-1} = (2.4 \pm 0.1) \times 10^{-4}$ s^{-1} (uracil) and $(1.8 \pm 0.1) \times 10^{-5}$ s^{-1} (uridine). The specific rates are independent of the concentration of the bromide and hydrogen ions. The Br^- ion, however, is likely involved in both the direct and reverse reaction (2) [1, 4]. Also, reductive elimination and oxidative addition reactions of solvolysis products of the complexes cannot be ruled out. The rate expression (4) also gives good fits to kinetic results for the reaction of 3×10^{-2} M $AuBr_4^-$ and 3×10^{-2} M uridine in Me_2SO-d_6 and in Me_2SO-d_6 containing 10% D_2O. The integrated form of eqn. (4) for equal initial concentrations of the reactants is given by eqn. (5) by means of which the curve plotted in Fig. 1 is obtained using the calculated value of $k_1 k_2/k_{-1}$.

$$[Au]_T/[Au^{III}] + \ln([Au^{III}]/[Au]_T) = (k_1 k_2/k_{-1})t + 1 \qquad (5)$$

The agreement with observed rates is relevant as a much higher gold(III) concentration was used with respect to kinetic runs quoted in Table 1. Molecular bromine is known to react with Me_2SO [5]. However, the presence of Br_2 in the proposed mechanism of (2) and (3) is reasonable as the reaction of the halogen with Me_2SO is slower than the bromination of the pyrimidines.

Comparison of $k_1 k_2/k_{-1}$ values shows that uracil is more reactive than uridine toward bromination, consistent with the electron-withdrawing effect of the ribose substituent. The specific rates for reduction of $AuBr_4^-$ in Me_2SO with both pyrimidines are greater than those for the corresponding reactions in water $(k_1 k_2/k_{-1}) = (7.8 \pm 0.1) \times 10^{-6}$ s^{-1} (uracil) and $(2.2 \pm 0.1) \times 10^{-6}$ s^{-1} (uridine) [1, 2]. According to the mechanism of (2) and (3) this difference can be ascribed to increased tendency of $AuBr_4^-$ to reductive elimination in Me_2SO relative to water and/or to enhancement of rates of the Br_2–pyrimidine reactions. It should be noted that the interaction of molecular bromine with Me_2SO involves formation of an adduct of the type $[Me_2SO(Br)]^+Br_3^-$ [5], possibly providing a more active species for the bromination of the pyrimidines.

Concentration effects on rates suggest that the reduction of $AuBr_4^-$ by Me_2SO also occurs through reductive elimination of Br_2 by the gold(III) complex, followed by reaction of molecular bromine with the solvent. Formation of acidic species is observed in this reaction as in the reaction of Br_2 with Me_2SO. It can be noted that while the tetrabromoaurate(III) ion is reduced by Me_2SO the complexes $Au(Me_2S)Br$ and $Au(Me_2S)Br_3$ are produced by oxidation of metallic gold by Me_2SO in the presence of hydrogen bromide [6].

The complex $Au(PPh_3)Br_3$ is found to react with uridine in Me_2SO to give 5-bromouridine. Reduction of gold(III) to gold(I) in Me_2SO solutions of $Au(PPh_3)Br_3$ also takes place through a reaction involving the formation of triphenylphosphine oxide. The overall eqn. (6) can be proposed in agreement with the observed protonation of water contained in the solutions.

$$\begin{aligned} &Au(PPh_3)Br_3 + Me_2SO + H_2O \\ &\quad = Au(Me_2SO)Br + Ph_3PO + 2HBr \qquad (6) \end{aligned}$$

The reaction mechanism likely involves displacement of PPh_3 by Me_2SO from $Au(PPh_3)Br_3$ followed by reduction of gold(III) to gold(I) by free triphenylphosphine. Accordingly, the complex $Au(PPh_3)Br_3$ is found to be more unstable in Me_2SO than in non-coordinating solvents. The formation of Ph_3PO in Me_2SO solutions of $Au(PPh_3)Br$ containing HBr is also observed as a slower reaction. The fact that bromination of uridine by $Au(PPh_3)Br_3$ is not observed in the presence of added $Au(PPh_3)Br$ can be accounted for by the predominant reduction by PPh_3 or by inhibition effects in a mechanism similar to that proposed for $AuBr_4^-$.

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