Reactions of Tetrabromoaurate(III) and Dicyanodibromoaurate(III) with Uracil
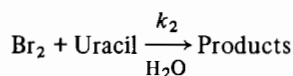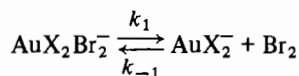
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Abstract

The reactions of $AuBr_4^-$ and $Au(CN)_2Br_2^-$ with uracil in water produce gold(I) and 5-bromouracil and/or 5-bromo-6-hydroxy-5,6-dihydrouracil. The observed kinetics of the reactions are consistent with a mechanism involving a fast redox pre-equilibrium followed by bromination of the pyrimidine ($X^- = Br^-$ or CN^-):

$$AuX_2Br_2^- \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} AuX_2^- + Br_2$$

$$Br_2 + Uracil \xrightarrow[H_2O]{k_2} Products$$

The calculated equilibrium constant $K = k_1/k_{-1}$ is 1.6×10^{-10} M for $AuBr_4^-$ and 1.7×10^{-11} M for $Au(CN)_2Br_2^-$. Specific rates for the reduction of $AuBr_4^-$ are correspondingly greater than those for the reduction of $Au(CN)_2Br_2^-$.

Introduction

Metal binding to nucleic acid constituents has been extensively studied. In contrast, information is lacking about redox reactions of metal complexes with nucleotides and their derivatives. In a previous work [1] it was shown that the reaction of $AuBr_4^-$ with uridine (1-β-ribofuranosyl-1H,3H-pyrimidine-2,4-dione) leads to reduction of gold(III) to gold(I) and to formation of 5-bromo-6-hydroxy-5,6-dihyrouridine. The suggested mechanism for the reaction involves reductive elimination of bromine from $AuBr_4^-$ followed by halogenation of the nucleoside. This report extends this study to the reactions of $AuBr_4^-$ and $Au(CN)_2Br_2^-$ with uracil (1H,3H-pyrimidine-2,4-dione) in water, the object being to provide information on ligand effects upon the reactivity of gold(III) complexes. Uracil has been used here as kinetic results for the reaction of this pyrimidine with molecular bromine as have been reported [2].

Experimental

The salts $K[AuBr_4]$ and $K[Au(CN)_2Br_2]$ and 5-bromouracil were prepared according to literature methods. Solutions of 5-bromo-6-hydroxy-5,6-dihydrouracil were prepared by adding bromine to a suspension of uracil under stirring and removing the slight excess of halogen used after complete dissolution of the pyrimidine. All other chemicals were reagent grade. The solutions for UV-Vis spectroscopic measurements were prepared from deionized and distilled water. Proton NMR spectra of solutions in D_2O were recorded on a Bruker WP60 spectrometer. UV-Vis spectra were recorded on Perkin-Elmer 576 ST and Lambda 5 spectrophotometers equipped with thermostatted cell compartments. Kinetic runs were followed spectrophotometrically using an appropriate reference blank in each case. The solutions were pre-thermostatted and the reactions started by fast mixing of the solutions of the complexes and of uracil.

Results

^{1}H NMR spectra of reaction mixtures of $K[AuBr_4]$ and uracil in D_2O compared with literature spectra [3] show formation of 5-bromo-6-hydroxy-5,6-dihydrouracil (bromohydrin) and 5-bromouracil. Chemical shifts of unreacted uracil and of bromination products do not change during the redox reaction indicating that metal coordination of these species does not occur. The reaction is accompanied by a decrease in absorbance in the range 300–500 nm, the ratios of optical densities at the different wavelengths remaining constant. These results are consistent with reduction of $AuBr_4^-$ to $AuBr_2^-$; the spectrum of the gold(I) complex does not display absorption bands in the range 300–500 nm [4]. Formation of metallic gold was observed in the concentrated mixtures (*ca.* 10^{-2} M) used for NMR measurements, due to disproportion of gold(I) formed from the bromination reaction [1]. UV spectra of reacting mixtures with concentrations used for kinetic experiments show that the nature

of the bromination products is related to the reaction rates. Uracil and 5-bromouracil display bands with maxima at 258 and 274 nm, respectively, whereas no absorption bands are displayed by the bromohydrin at $\lambda > 220$ nm. In the case of relatively fast reactions rates (e.g. for 10^{-4} M $AuBr_4^-$ and 10^{-2} M uracil) a decrease in absorbance is observed at $\lambda < 300$ nm to give, eventually, a negative band against equimolar uracil as reference. In the case of slower reactions (e.g. for 1.3×10^{-4} M $AuBr_4^-$ and 1.1×10^{-3} M uracil) the presence of an isosbestic point at $\lambda = 300$ nm and formation of an absorption band at $\lambda = 282$ nm were observed. It is found that the spectra of $AuBr_4^-$ and 5-bromouracil display an isosbestic point at 300 nm. Moreover, the spectrum of 5-bromouracil against equimolar uracil as reference shows a positive band at 282 nm and a negative band at 252 nm. Therefore, the UV and NMR results are consistent with the formation of 5-bromouracil as the bromination product, in the case of relatively slow reaction rates, and of 5-bromouracil and bromohydrin in the case of faster reaction rates.

All kinetic experiments were carried out at 25 °C in the presence of added H_2SO_4 and NaBr. The ionic strength was maintained at 1.0 M with $NaNO_3$ in some cases. Large excess of acid, bromine and uracil compared to gold was used in order to keep the concentration of these species constant during each kinetic run and to avoid any significant hydrolysis of $AuBr_4^-$ [5]. In the experimental conditions, uracil is in the neutral diketo form and its degree of autoassociation is assumed to be negligible by analogy with uridine [6]. The reduction of gold(III) is complete in the conditions of kinetic experiments. Kinetic data for the reduction reaction of $AuBr_4^-$ by uracil were found to comply with the rate law (1), where $[Au]_o$ is the starting concentration of gold(III):

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

The concentrations of $AuBr_4^-$ were estimated from the absorbance at 385 nm and the rate constants, k_{obs}, and were calculated from plots of ($[Au]_o \ln[Au^{III}] - [Au^{III}]$) vs. t by least-squares analysis. Linear plots from eqn. (1) were obtained for greater than 80% completion of reaction. Values of k_{obs} are reported in Table I.

^{1}H NMR spectra of reaction mixtures of $Au(CN)_2$-Br_2^- and uracil in D_2O show formation of 5-bromouracil. Bromohydrin could not be detected before solid AuCN begin to form (e.g. 5 h for a 10^{-2} M reaction mixture). Formation of AuCN is not observed in the condition used for kinetic experiments. Chemical shifts of unreacted uracil and of 5-bromouracil do not change during the reaction. The bromination reaction is accompanied by a decrease of the absorption band of $Au(CN)_2Br_2^-$ at 324 nm in agreement

with reduction to $Au(CN)_2^-$; the spectrum of the gold(I) complex does not display absorption bands at $\lambda > 250$ nm [7]. Formation of this product is consistent with the relative stability of $Au(CN)_2^-$ and $AuBr_2^-$ [8]. The UV-Vis spectra of freshly prepared solutions of $Au(CN)_2Br_2^-$ ($10^{-4} - 10^{-3}$ M) do not significantly change with acidity ($[H^+] < 0.4$ M), whereas dependence on bromide concentration is observed. Addition of bromide to solutions of the complex with and without added acid give rise to an increase of absorbance in the range 280–450 nm in the time required to make the solutions. This observation is accounted for by bromide for cyanide substitution at gold(III), according to eqn. (2) for acidic solutions:

$$Au(CN)_2Br_2^- + H^+ + Br^- = Au(CN)Br_3^- + HCN \qquad (2)$$
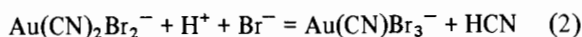
By comparing UV-Vis spectra of $Au(CN)_2Br_2^-$ 7×10^{-4} M in the presence of 10^{-2} M H^+ with no added bromide and with Br^- 10^{-2} M or 1.0 M, a degree of substitution $<6\%$ can be evaluated for the solution containing 10^{-2} Br^-. The formation of $Au(CN)Br_3^-$ is shown also in equimolar mixtures of $Au(CN)_2Br_2^-$ and $AuBr_4^-$. Difference spectra of equilibrated solutions of the complexes ($5 \times 10^{-5} - 5 \times 10^{-4}$ M) in the range 300–450 nm display a positive band at 340 nm, an intermediate wavelength between the absorption maxima of $Au(CN)_2$-Br_2^- (324 nm) and $AuBr_4^-$ (385 nm). Solutions of $Au(CN)_2Br_2^-$ under experimental conditions are relatively stable. However, explored reaction times were limited by a slow decay of the complex (e.g. a 3.5×10^{-5} M solution in the presence of 10^{-2} Br^- showed ca. 5% decrease in absorbance at 240 nm after 6 h). UV spectra of reaction mixtures of $Au(CN)_2Br_2^-$ and uracil are consistent with the formation of 5-bromouracil as the only bromination product. The spectra show an isosbestic point at ca. 300 nm, the wavelength slightly shifting with changes of bromide concentration, and the formation of an absorption band at 280–290 nm. The isosbestic point, well maintained during the reaction except in the case of solutions containing concentrated Br^- (1.0 M), is found to correspond to the isosbestic point of uracil and $Au(CN)_2Br_2^-$ at the appropriate bromide concentration. All kinetic experiments were carried out at 25 °C in the presence of added H_2SO_4. In most cases, NaBr was also added and the ionic strength maintained at 1.0 M; in one experiment $K[Au(CN)_2]$ was also added. Large excesses of acid and uracil compared to gold were used in each case. Kinetic data for the redox reactions carried out in the presence of 10^{-2} M Br^- or without added bromide were found to comply to the rate law (3), where $[Au]_T$ is the total gold concentration ($[Au^{III}] + [Au^I]$) and $[Au^{III}]_o$ is the starting concentration of dicyanodibromoaurate(III):

TABLE I. Rate Constants for the Reduction of Gold(III) by Uracil in Water at 25 °C.

	10^4 [Au^{III}] (M)	10^2 [H$^+$] (M)	[Br$^-$] (M)	10^3 [Uracil] (M)	$10^8 k_{obs}$ (M × s^{-1})	$10^6 k_{obs}$/[Uracil] (s^{-1})
AuBr$_4^-$	1.3	2.7	1.0	1.1	0.86	7.8
	1.3	2.7	1.0	9.6	7.5	7.8
	1.3	2.7	1.0	4.8	3.7	7.7
	1.3	2.7	1.0	13	11	8.5
	1.3	2.7	1.0	7.5	5.5	7.3
	1.3	2.7	1.0	3.8	2.9	7.6
	0.66	2.7	1.0	7.5	5.5	7.3
	5.1	2.7	1.0	7.5	5.3	7.1
	1.3	0.27	1.0	10	8.2	8.2
	1.3	0.5	1.0	10	8.1	8.1
	1.2	9.6	0.85	10	7.8	7.8
	1.2[a]	3.9	0.01	10	8.5	8.5
	1.2[a]	3.9	0.0019	9.9	8.1	8.2
	1.5	3.9	1.0	3.7	2.9	7.8
Au(CN)$_2$Br$_2^-$	3.6[a]	1.0	0.01	5.0	0.5	1.0
	3.6[a]	1.0	0.01	2.5	0.2	0.8
	4.0[a]	1.0	0.01	25	2.6	1.0
	3.5[a]	1.0	0.01	10	0.74	0.74
	2.1[a,b]	1.0	0.01	14	1.0	0.71
	2.3	1.0		14	1.1	0.79
	2.3	50		14	0.89	0.64
	2.3	40		14	1.0	0.71
	3.5	1.0	1.0	15	1.7	1.1
	3.5	1.0	1.0	10	0.99	0.99
	6.9	1.0	1.0	10	0.77	0.77
	6.2	1.0	1.0	20	1.8	0.9

[a]Ionic strength I = 1 M by addition of NaNO₃.   [b]KAu(CN)₂ 1.0 × 10⁻⁴ added.

$$[Au]_T \ln[Au^{III}] - [Au^{III}] =$$
$$[Au]_T \ln[Au^{III}]_o - [Au^{III}]_o - k_{obs}t \qquad (3)$$

The concentrations of [Au(CN)₂Br₂⁻] were estimated from the absorbance at 350 or 360 nm and the rate constants, k_{obs}, were calculated from plots of ([Au]$_T$ ln[Au^{III}] − [Au^{III}]) *vs.* t by least-squares analysis. Linear plots from eqn. (3) were obtained for the explored reaction degrees (50–80%). Values of k_{obs} are reported in Table I. For reactions carried out in the presence of 1.0 M bromide, non-linear plots were obtained from eqn. (3); k_{obs} values were calculated from initial slopes as reported in Table I.

Discussion

The kinetic results for the reduction of AuBr₄⁻ by uracil are consistent with the reaction mechanism (4, 5):
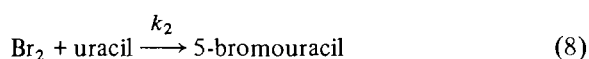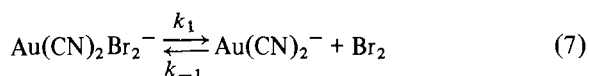
$$AuBr_4^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AuBr_2^- + Br_2 \qquad (4)$$

$$Br_2 + uracil \xrightarrow[H_2O]{k_2} \text{5-bromo-6-hydroxy-5,6-dihydro-}$$
$$\text{uracil (and/or 5- bromouracil)} \qquad (5)$$
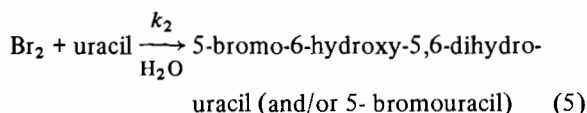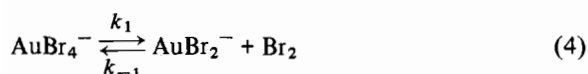
Reductive elimination from AuBr₄⁻ (k_1) and oxidative addition to AuBr₂⁻ (k_{-1}) are assumed to be first-order and second-order reactions, respectively, while the reaction of Br₂ with uracil is known to be second-order [2]. By assuming also $k_{-1}[AuBr_2^-] \gg k_2$·[uracil], the rate law (6) is obtained, where [Au]$_T$ is the total gold concentration ([Au^{III}] + [Au^I]):

$$-\frac{d[Au^{III}]}{dt} = \frac{k_1 k_2 [Au^{III}][uracil]}{k_{-1}([Au]_T - [Au^{III}])} \qquad (6)$$

The integrated form of (6) is identical with the experimental rate expression (1), where [Au]$_o$ = [Au]$_T$ and $k_{obs} = (k_1 k_2/k_{-1})$[uracil]. Specific rates are found to be independent of the concentration of added bromide. This result is consistent with a mechanism of the type (4, 5), as for the analogous reaction with uridine, even if Br⁻ is likely to be involved as a reactant in both the reductive elimination and the oxidative addition of bromine [1]. The reaction rates are also independent of the hydrogen ion concentra-

tion, in agreement with the observation that the reaction of Br_2 with deprotonated uracil is not important within the pH range used [2]. Values of $k_{obs}/$[uracil] reported in Table I are reasonably consistent and give a mean value of $k_1k_2/k_{-1} = (7.8 \pm 0.1) \times 10^{-6}$ s^{-1}. Dividing this value by the reported value of $k_2 = 5 \times 10^4$ M^{-1} s^{-1} [2] gives a value for the equilibrium constant of reaction (4), $K = 1.6 \times 10^{-10}$ M, close to K values obtained from standard electrode potentials ($K = 2.9 \times 10^{-10}$ [8], 3.4×10^{-10} [9], 1.1×10^{-9} [10]). For the analogous reaction of $AuBr_4^-$ with uridine a value of $k_1k_2/k_{-1} = (2.2 \pm 0.1) \times 10^{-6}$ s^{-1} has been obtained [1].

The kinetic results for the reduction of $Au(CN)_2$-Br_2^- by uracil are also consistent with a mechanism involving a fast redox pre-equilibrium followed by bromination of the pyrimidine (7, 8):

$$Au(CN)_2Br_2^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Au(CN)_2^- + Br_2 \qquad (7)$$

$$Br_2 + uracil \overset{k_2}{\longrightarrow} 5\text{-bromouracil} \qquad (8)$$

The fact that in this case 5-bromouracil is the only observed bromination product is not indicative of a different reaction mechanism as the same result has been found for the system $AuBr_4^-$–uracil in some conditions. The nature of the halogenation products in these reactions is possibly related to occurrence of different pathways for the reaction of Br_2 with the pyrimidine [3]. The reactions carried out with bromide concentrations, for which substitution of CN$^-$ by Br$^-$ is negligible (0–10^{-2} M), obey the experimental expression (3), consistent with rate law (6). Values of $k_{obs}/$[uracil] reported in Table I for 10^{-2} M bromide are reasonably consistent and give a mean value of $k_1k_2/k_{-1} = (8.5 \pm 0.4) \times 10^{-7}$ s^{-1}. Similar values are obtained for experiments carried out without added bromide. The reaction rates are also independent of the hydrogen ion concentration, showing no effect of the possible protonation of $Au(CN)_2Br_2^-$ or $Au(CN)_2^-$ [7]. Linear plots from eqn. (3) are not obtained for kinetic runs carried out in the presence of concentrated bromide (1.0 M), as in these conditions formation of $Au(CN)Br_3^-$ occurs to a significant extent and the concentration ratio [$Au(CN)Br_3^-$]/$Au(CN)_2Br_2^-$] is not constant. Approximate rate constants calculated from initial slopes give values of $k_{obs}/$[uracil] similar to those found for other bromide concentrations. Dividing the mean value of k_1k_2/k_{-1} for the reactions carried out in the presence of 10^{-2} M bromide by k_2 gives

a value for the equilibrium constant of reaction (7) $K = 1.7 \times 10^{-11}$ M. It can be noted that a value of $K = 1.9 \times 10^{-9}$ M from potentiometric titration of $Au(CN)_2^-$ with Br_2 has been reported [7]. However, experimental procedures and conditions for this measurement are not described. On this basis, higher K value reduction of $Au(CN)_2Br_2^-$ would be expected to be faster than the reduction of $AuBr_4^-$, according to the proposed reaction mechanism, unless both reductive elimination (k_1) and oxidative addition (k_{-1}) for the cyanide complexes were relatively slow reactions (i.e. condition k_{-1}[Au(CN)$_2^-$] $\gg k_2$[uracil] and rate law (6) are not consistent).

Comparison of rate constant of the reactions with uracil shows that the reactivity of $AuBr_4^-$ toward reduction is somewhat greater than that of $Au(CN)_2$-Br_2^-. This result is consistent with previous spectroscopic observations on tetrahaloaurate(III) and dicyanodihaloaurate(III) ions [11]. The intense bands displayed by these complexes in the UV-Vis region have been assigned to ligand-to-metal charge transfer (LMCT), from occupied halide-based orbitals to the lowest energy σ^* orbital, which is primarily $5d_{x^2-y^2}$ localized on gold. For corresponding LMCT bands an energy shift $Au(CN)_2X_2^- > AuX_4^-$ is observed. This is accounted for by the increase in stability of the σ^* orbital as the strong σ donor CN$^-$ is replaced by a weaker σ donor halide. It is noted that the LMCT transitions can be viewed as an incipient reduction of the metal with concomitant oxidation of the halide ligand and can be, therefore, related to the stability of the complexes toward reductive elimination.

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