A spectroscopic and electrochemical investigation of the oxidation pathway of glycyl-D,L-methionine and its N-acetyl derivative induced by gold(III)

Biljana Đ. Glišić · Snežana Rajković · Zorka D. Stanić · Miloš I. Djuran

Abstract The $^1$H nuclear magnetic resonance spectroscopy was applied to study the reaction of the dipeptide glycyl-D,L-methionine (H-Gly-D,L-Met-OH) and its N-acetylated derivative (Ac-Gly-D,L-Met-OH) with hydrogen tetrachloridoaurate(III) (H[AuCl$_4$]). The corresponding peptide and [AuCl$_4$]$^-$ were reacted in 1:1, 2:1, and 3:1 molar ratios, and all reactions were performed at pH 2.45 in 0.01 M DCI as solvent and at 25°C. It was found that the first step of these reactions is coordination of Au(III) to the thioether sulfur atom with formation of the gold(III)-peptide complex [AuCl$_3$(R-Gly-Met-OH-S)] (R=H or Ac). This intermediate gold(III) complex further reacts with an additional methionine residue to generate the R-Gly-Met-OH chlorosulfonium cation as the second intermediate product, which readily undergoes hydrolysis to give the corresponding sulfoxide. The oxidation of the methionine residue in the reaction between H-Gly-D,L-Met-OH and [AuCl$_4$]$^-$ was five times faster ($k_2=0.363\pm0.074$ M$^{-1}$s$^{-1}$) in comparison to the same process with N-acetylated derivative of this peptide ($k_2=0.074\pm0.007$ M$^{-1}$s$^{-1}$). The difference in the oxidation rates between these two peptides can be attributed to the free terminal amino group of H-Gly-D,L-Met-OH dipeptide. This study contributes to a better understanding of the mechanism of the Au(III)-induced oxidation of methionine and methionine-containing peptides in relation to the severe toxicity of anti-arthritis and anticancer gold-based drugs.

Keywords Glycyl-D,L-methionine · Gold(III)-induced oxidation · $^1$H NMR · UV-Vis · Cyclic voltammetry · Gold-based drugs

Introduction

The clinical use of gold compounds, chrysotherapy, is an accepted part of modern medicine [1–4]. Injectable gold(I) thiolates, such as sodium aurothiomalate, aurothioglucose, and aurothiopropanol sulfonate, and the oral drug auranofin are used clinically against rheumatoid arthritis [1–4]. A large number of gold(I) compounds have also been tested for antitumor activity against various cancerous cell lines [5–9]. A wide variety of phosphinegold(I) thiolates display significant cytotoxicity in vitro [10, 11]. Gold(III) complexes, isostructural and isoelectronic with platinum(II), have also been evaluated as potential candidates for cancer treatment. In comparison to Pt(II) complexes, Au(III) analogs are relatively unstable, light-sensitive [12], and easily reducible, which makes them less effective [13], and probably more toxic as metal-based drugs. However, in recent years, new gold(III) compounds were synthesized, characterized, and shown to have appreciable stability under physiological conditions [14]. In order to enhance the stability of the gold(III) center, polydentate ligands, such as polyamines, cyclam, terpyridine, phenanthroline, and dithiocarbamates, were used [13–16]. Some of these gold(III) complexes displayed in vitro cytotoxicity comparable or even higher than cisplatin toward several human tumor cell lines resistant to cisplatin [11, 16–22].
The clinical application of gold complexes is limited because of severe toxicity such as blood disorders and kidney damage [23]. It was suggested that Au(III) produced from Au(I) drugs might be responsible for the toxic side effects encountered in chrysotherapy [20, 23–25]. Strong oxidants, which can oxidize Au(I) to Au(III), are potentially available in vivo in inflammatory situations [26, 27]. Antiarthritic gold(I) drugs can be oxidized to Au(III) by the hypochlorite ion generated from H₂O₂ and Cl⁻ in the presence of the enzyme myeloperoxidase, which is produced and released by phagocytic cells [27]. Au(III) is very short-lived in the presence of different biomolecules because it can rapidly oxidize them, thereby being reduced to Au(I). It has been known for some time that Au(III) can oxidize thiol to disulfide [28, 29], cleave the disulfide bond of cystine to give the sulfonic acid [28–31], oxidize dialkyl sulfides to sulfoxide [32], the sulfur atom of the amino acid methionine stereospecifically to methionine-sulfoxide [33–37], and can desulfonate thioamides [38]. The structural consequences of these reactions can play an important role in the toxic side effects of gold-based drugs.

Previous kinetics studies of the reaction between [AuCl₄]⁻ and amino acid L-methionine provide evidence that this reaction occurred in two stages [34, 35]. Very fast substitution of one chloride ion in [AuCl₄]⁻ complex by a methionine molecule was followed by slow reduction of this intermediate Au(III)–methionine complex with formation of the methionine-sulfoxide and Au(I) species as the final products of this reaction. Although the oxidation of amino acid methionine by Au(III) ion has been extensively investigated, the mechanism of the redox process is not yet completely understood. In order to gain more information on the mechanism of methionine oxidation with gold(III) ion in the present study, special attention was paid to the identification of intermediate and final products for the reactions of glycyl-D,L-methionine dipeptide and its N-acetylated derivative with hydrogen tetrachloroaurate(III).

**Experimental**

**Materials**

Tetrachloroaurate(III) acid (H[AuCl₄].3H₂O), the dipeptide glycyl-D,L-methionine (H-Gly-D,L-Met-OH), and deuterium oxide (99.8 %) were obtained from the Sigma-Aldrich Chemical Co. Hydrochloric acid and potassium chloride were obtained from Zorka Pharma, Šabac. All the employed chemicals were of analytical reagent grade, and doubly distilled water was used throughout. The terminal amino group in the H-Gly-D,L-Met-OH dipeptide was acetylated by a standard method [39].

1H NMR spectroscopy

All the 1H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 2000 spectrometer (200 MHz) using 5-mm NMR tubes. Sodium trimethylsilylpropane-3-sulfonate (TSP) was used as an internal reference. The 1H NMR spectra were acquired using the WATERGATE sequence for water suppression. Typical acquisition conditions were as follows, 90° pulses, 24,000 data points, 4 s acquisition time, 1 s relaxation delay, collection of 16–128 transients, and final digital resolution of 0.18 Hz per point. All the NMR spectra were processed using the Varian VNMR software (version 6.1, revision C). The chemical shifts are reported in parts per million (ppm).

The NMR samples were prepared in 0.01 M DCl in D₂O as solvent, and the total volume was 600 μl. Fresh solutions of dipeptide and H[AuCl₄]·3H₂O were prepared separately and then mixed in different molar ratios (1:1, 2:1, and 3:1) at room temperature. The initial concentration of H[AuCl₄] was 20 mM. All rate constants were obtained from 1H NMR measurements. The values of the rate constants for the reactions between equimolar amounts of [AuCl₄]⁻ and R-Gly-D,L-Met-OH dipeptide (R=H or Ac) were determined when the data from the reactions were fitted to a second-order process [40] by plotting x/a_0(a_o–x) against t (where a_o is the initial concentration of the R-Gly-D,L-Met-OH dipeptide and x is the concentration of the corresponding sulfoxide at time t).

**UV-Vis spectrophotometry**

The ultraviolet-visible (UV-Vis) spectra were recorded on a Perkin Elmer Lambda 35 double-beam spectrophotometer equipped with thermostated 1.00-cm quartz Suprasil cells. Stock solutions of H[AuCl₄]·3H₂O and dipeptide were prepared directly before use in 0.01 M HCl (pH 2.00). H-Gly-D,L-Met-OH and H[AuCl₄] were mixed in 1:1, 2:1, and 3:1 molar ratios, respectively, at room temperature, with the concentration of H[AuCl₄] in the final solution being 5×10⁻⁵ M. The kinetic measurements were made by repetitively scanning the spectra at set time intervals over the wavelength range 200–500 nm. Data were collected and analyzed using Origin 6.1 and Microsoft Office Excel 2003 programs.

**Voltammetric measurements by cyclic voltammetry**

Cyclic voltammetric (CV) measurements were performed with an Autolab potentiostat (PGSTAT 302 N). The working electrode for the cyclic voltammetric measurements was glassy carbon (GC) with 3 mm inner and 9 mm outer diameter of the PTFE sleeve. Prior to use, the GC electrode was wet-polished on an Alpha A
polishing cloth (Mark V Lab) with successively smaller particles (0.3- and 0.05-μm diameter) of alumina. The electrode was washed twice with doubly distilled water and then with the background electrolyte solution. The washed electrode was then placed into a voltammetric cell with supporting electrolyte solution. The reference electrode was a saturated calomel electrode type 401 (Radiometer, Copenhagen), and the counter electrode was a platinum wire.

Stock solutions of H[AuCl₄]·3H₂O and the dipeptide were prepared just before use by dissolving H[AuCl₄]·3H₂O and H-Gly-D,L-Met-OH in 0.01 M HCl, which were then diluted with 0.01 M HCl to give the working solutions. The required amount of the dipeptide and H[AuCl₄] were mixed in different molar ratios (1:1, 2:1, and 3:1, respectively) with the final concentration of H[AuCl₄] being 1.05 mM. The supporting electrolyte used to perform the cyclic voltammetric experiments was 0.04 M NaCl at pH 2.00. The time interval between two consecutive voltammograms was 30 s.

The measurements were realized in the background electrolyte (pH 2.00) at a scan rate of 0.070 V s⁻¹. The conditions were the following, E_begin=0.0 V, E_end=1.5 V, and E_step=0.003 V. All experiments were performed at room temperature and repeated at least three times. The data were collected and analyzed using the Origin 6.1 program.

pH measurements

All pH measurements were made at room temperature. The pH meter (Iskra MA 5704) was calibrated with a Fischer-certified buffer solution of pH 4.00. Reported pH values were corrected for the deuterium isotopic effect by adding 0.45 units to the pH meter reading [41].

Results and discussion

The reactions between H-Gly-D,L-Met-OH or Ac-Gly- D,L-Met-OH, and [AuCl₄]⁻ were studied by ¹H NMR spectroscopy, and in addition of this study, the reaction of H-Gly-D,L-Met-OH with [AuCl₄]⁻ was investigated by UV-Vis and CV techniques. All reactions were performed at pH 2.45 in 0.01 M HCl (or pH 2.00 in 0.01 M HCl) as solvent and at 25°C. Differences in the reactivity between these two dipeptides were compared in order to investigate the influence of the terminal amino group of glycine on the rate of oxidation of the methionine residue. All reactions were carried out in different molar ratios (peptide, gold(III)=1:1, 2:1, and 3:1, respectively), and for each case, the reaction mixture was kept at pH 2.00 in order to suppress, or minimize, hydrolysis of [AuCl₄]⁻ anion that was reported to be completed at pH 3.80 [42]. However, in our case, hydrolytic products of [AuCl₄]⁻ followed by very fast reduction of gold (III) to Au(0) appeared at pH≥3.00.

The reaction of [AuCl₄]⁻ with an equimolar amounts of H-Gly-D,L-Met-OH and Ac-Gly-D,L-Met-OH dipeptides

When an equimolar amount of H[AuCl₄]·3H₂O was incubated with the corresponding R-Gly-D,L-Met-OH dipeptide (R=H or Ac) under the above-mentioned conditions, three NMR detectable products were observed in solution in the first 3 min of the reaction (Fig. 1). The time dependence of the formation of the products in this reaction is shown in Fig. 2. The major product obtained in a yield of 52% was H-Gly-Met-OH sulfoxide and 47% for Ac-Gly-Met-OH sulfoxide (product 3; Fig. 1), formed by the oxidation of the corresponding dipeptides with [AuCl₄]⁻. The resonance at 2.71 ppm was assigned to the methyl protons of product 3, which is in agreement with those previously reported for [H-Gly-Met-OH sulfoxide][AuCl₄]⁺ characterized by ¹H NMR spectroscopy and X-ray crystallography [37].

The other two products 1 and 2 in Fig. 1, observed in the first 3 min of the reaction, were intermediate species. Product 1 resulted from the coordination of Au(III) to the thioether sulfur with formation of the gold(III)-peptide complex [AuCl₃(R-Gly-Met-OH-S)]. This intermediate gold(III) complex further reacts with an additional methionine residue to generate Au(I) complex and intermediate species 2 which readily undergoes hydrolysis yielding to the corresponding sulfoxide 3 as the final product in this investigated reaction. The reaction pathway for the present investigation reaction (see Fig. 1) is thus similar to that
operative in the oxidation of organic sulfides with bromine, resulting in the corresponding sulfoxides [43, 44]. Furthermore, the same reaction mechanism was suggested by Natile et al. in the kinetic study of the reduction gold(III) to gold(I) by dialkyl sulfides in aqueous methanol solution [32]. The formations of products 1 and 2 are evident in the $^1$H NMR spectrum from the chemical shifts of the resonances at 2.89 and 2.79 ppm, due to the methyl protons of the methionine residue (Fig. 2a, b). The signal at 2.89 ppm belongs to the product 1 while the upfield shifted signal at 2.79 ppm was assigned to the $-\text{S-CH}_3$ protons of product 2. The concentration of each intermediate product was calculated from the integral values of these two signals and during the first 3 min of the reaction these products were obtained in a yield of 28% (or 30%) for 1 and 20% (or 23%) for product 2 for H-Gly-D,L-Met-OH and Ac-Gly-D,L-Met-OH, respectively. The total amount of products 1 and 2 and the final product 3 was always equal to the initial concentration of the dipeptide. The intensities of the signals at 2.79 and 2.89 ppm decreased during time with their complete disappearance after the subsequent 9 min for H-Gly-D,L-Met-OH and 57 min for Ac-Gly-D,L-Met-OH (Fig. 2a, b). During this time, the intensity of the signal at 2.71 ppm for the methyl protons of product 3 was enhanced, and finally, its concentration was equal to the initial concentration of the corresponding dipeptide.

From above proton NMR results, it can be concluded that at the stoichiometric amounts of the reactants, the oxidation of the methionine residue in H-Gly-D,L-Met-OH to its sulfoxide was five times faster ($k_2=0.363\pm0.074 \text{ M}^{-1}\text{s}^{-1}$) in comparison to the same process between the $\text{N-}$acetylated derivative of this peptide and $[\text{AuCl}_4]^-$ ($k_2=0.074\pm0.007 \text{ M}^{-1}\text{s}^{-1}$). The difference in the oxidation rates between these two peptides can be attributed to the free terminal amino group of H-Gly-D,L-Met-OH dipeptide. These results are in accordance with those previously reported for the reaction of L-methionine with $[\text{AuCl}_4]^-$, where it was stated that the NH$_2$ group was involved in the oxidation of this amino acid to its sulfoxide [34, 35].

The reaction of H-Gly-D,L-Met-OH with H[AuCl$_4$]$_3$H$_2$O was studied by UV-Vis spectrophotometric measurements in 0.01 M HCl as solvent (pH 2.00) at 25°C; see Fig. 3. As it can be seen from this figure, when an equimolar amount of the peptide was added to a solution of [AuCl$_4$]$^-$, the
absorbance of two maxima at $\lambda=226$ and $\lambda=313$ nm decreased during 12 min of the reaction, which indicates a decreasing $\text{[AuCl}_4^-\text{]}$ concentration. After this time, no change in the absorbance was observed, indicating that this redox process was finished. The total amount of $\text{[AuCl}_4^-\text{]}$ consumed during this redox reaction was calculated from differences in absorbance of the maximum at $\lambda=226$ nm before addition of the peptide and after 12 min of the reaction. It was found that approximately 33% of $\text{[AuCl}_4^-\text{]}$ remained in solution after completion of this redox reaction. Due to the fact that the oxidation of methionine residue in the presence of gold(III) was undoubtedly confirmed as a stoichiometric reaction [34, 35], obviously, the excess of $\text{[AuCl}_4^-\text{]}$ resulted from the disproportionation of $\text{[AuCl}_2^-\text{]}$ to Au(0) and $\text{[AuCl}_4^-\text{]}$. The disproportionation of the aqueous Au(I) complex was extensively investigated in literature, and the following reaction for decomposition of this complex was proposed: $3\text{[AuCl}_2^-\text{]}\leftrightarrow 2\text{Au}(0) + \text{[AuCl}_4^-\text{]} + 2\text{Cl}^-\text{[45, 46]}$. It was found that the rate of this reaction at room temperature was very slow in the early stage of the reaction and then rapidly increased to values that remained approximately constant with further reaction progress ($\log K=7.4$ at 25°C) [46, 47]. Furthermore, recent crystallographic results for $\text{[H-Gly-Met-OH sulfoxide][AuCl}_4^-\text{]}$ obtained by oxidation of the corresponding peptide in the presence of an equimolar amount of $\text{[AuCl}_4^-\text{]}$ additionally confirmed that disproportionation of $\text{[AuCl}_2^-\text{]}$ occurred under these circumstances [37].

The above $^1$H NMR and UV-Vis results for the reaction of H-Gly-D,L-Met-OH with $\text{[AuCl}_4^-\text{]}$ revealed good agreement with those obtained for CV measurements. The survey cyclic voltammogram (Fig. 4a) of a 1.05 mM solution of H[AuCl$_4$] in 0.01 M HCl in the presence of 0.04 M NaCl as background electrolyte recorded at a GC electrode displayed a distinct cathodic peak I at 0.32 V: AuCl$_4^-$ + 3e$^- \rightarrow \text{Au}(0) + 4\text{Cl}^-\text{[48]}. The Au(III)–Au(0) reduction was also evident from the presence of metallic gold on the electrode surface. In the cyclic voltammogram, no $\text{[AuCl}_2^-\text{]}$ complex could be detected due to the fact that the chlorido ligand is not a $\pi$-acceptor which could stabilize this complex [48]. On the reverse sweep, a definite oxidation wave I’ at 1.02 V was observed (Fig. 4a): $\text{Au}(0) + 4\text{Cl}^- \rightarrow \text{AuCl}_4^- + 3\text{e}^-\text{.}$

As a result of the formation of product 1 (see Fig. 1) in the reaction between equimolar amounts of H-Gly-D,L-Met-OH and H[AuCl$_4$], the characteristic peak I’ was shifted from 1.02 to 0.85 V (peak II’, Fig. 4a). Furthermore, as a consequence of the progress of this reaction, the current response decreased with time in relation to characteristic
anodic peak II, while the characteristic cathodic peak II increased (at 0.35 V; Fig. 4b). The current enhancement of the cathodic peak is purely dependent on the degree of reduction of Au(III) to Au(0). As can be also seen from Fig. 4b, the reaction was finished after 12 min. This is coupled with the fact that, after 12 min, there was no change of the current response of the characteristic anodic peak as well as the characteristic cathodic peak.

The reaction of [AuCl₄]⁻ with an excess of H-Gly-D,L-Met-OH and Ac-Gly-D,L-Met-OH dipeptides

The oxidation of the methionine residue in the presence of [AuCl₄]⁻ was studied in an excess of the H-Gly-D,L-Met-OH or the Ac-Gly-D,L-Met-OH dipeptide. The [AuCl₄]⁻ and the corresponding peptide were mixed in 1:2 or 1:3 molar ratio, respectively, and all reactions were performed under the above-mentioned experimental conditions. The first ¹H NMR spectrum ran in the first 3 min of reaction indicated that the oxidation of the methionine residue was almost over. The absence of resonances in the ¹H NMR spectrum at 2.89 and 2.79 ppm due to the methyl protons of the intermediate products 1 and 2, respectively, (see Fig. 1) indicates that the redox process with an excess of the H-Gly-D,L-Met-OH or Ac-Gly-D,L-Met-OH dipeptide was much faster than with equimolar amounts of [AuCl₄]⁻ and dipeptide. The amount of product 3 was calculated from the intensity of the signal at 2.71 ppm in respect to the initial concentration of the dipeptide, and the total amount of this product was approximately 50% for the 1:2 and 33% for the 1:3 molar ratio for each sulfoxide. The singlets at 2.50 ppm for H-Gly-D,L-Met-OH and at 2.56 ppm for Ac-Gly-D,L-Met-OH were assigned to the methyl protons of these two dipeptides both coordinated to Au(I) through the methionine sulfur atom. These chemical shifts are consistent with those previously reported for polynuclear Au(I)–sulfur-type complexes [49]. When the reaction of [AuCl₄]⁻ with H-Gly-D,L-Met-OH was followed during time, the signal at 2.50 ppm shifted to a higher field, from 2.50 to 2.11 ppm. It can be assumed that this shifting was caused by the replacement of H-Gly-D,L-Met-OH in the polynuclear [[Au(H-Gly-Met-OH-S)]₂]ₙ complex with chloride ion, resulting after 6 h in the formation of free dipeptide (signal at 2.11 ppm). These results are in accordance with those previously reported of the relatively strong affinity of Au(I) for sulfur-containing ligands, such as thiols, thiolates, and sulfides, and also of the lability of Au(I)–sulfur bound species in solution [50]. However, in the reaction between Ac-Gly-D,L-Met-OH and [AuCl₄]⁻ under the above-mentioned conditions, the chemical shifts of the resonance at 2.56 ppm due to the methyl protons of the polynuclear [[Au(Ac-Gly-Met-OH-S)]₂]ₙ complex did not change during 6 days of reaction. The consistent value for the chemical shifts of these protons can be explained by the higher stability of the polynuclear [[Au(Ac-Gly-Met-OH-S)]₂]ₙ complex with respect to that obtained in the reaction of the non-acetylated dipeptide with a free terminal amino group. These results are in accordance with those previously reported by Sadler et al. [36] that the stability of Au(I)-methionine species is dependent on the availability of free NH₂ groups, which catalyze their disproportionation.

Fig. 5 Cyclic voltammograms of product 1 recorded in the first 30 s of the reaction between H[AuCl₄] and H-Gly-D,L-Met-OH in 1:1 (solid line), 1:2 (dotted line), and 1:3 (dashed line) molar ratios, respectively. The inserted figure shows the dependence of the peak current of the characteristic anodic peak of product 1 in relation to increasing concentrations of peptide.
The reaction of $[\text{AuCl}_4]^{-}$ with excess of H-Gly-D,L-Met-OH was also investigated under the above-mentioned experimental conditions by UV-Vis and CV measurements. Very fast change in absorbance of $[\text{AuCl}_4]^{-}$ with no presence of this anion in the UV-Vis spectrum was observed at the end of these reactions. These findings are in accordance to the fact that the color of the solution had finally changed from yellow to colorless. Also, the current response of the anodic peak also decreased rapidly under these circumstances (see Fig. 5).

Concluding remarks

From the present investigation of the reactions of H$[\text{AuCl}_4]$ with H-Gly-D,L-Met-OH and its N-acetyl derivative Ac-Gly-D,L-Met-OH, at pH 2.45 in 0.01 M DCI (or pH 2.00 in 0.01 M HCl) and at 25°C, the following conclusions can be drawn. The gold(III)-induced oxidation of the methionine residue in these peptides to the corresponding sulfoxides proceeded in two steps. The first step of this reaction is very fast coordination of Au(III) to the thioether sulfur with formation of the gold(III)–peptide complex $[\text{AuCl}_3(\text{R-Gly-Met-OH-S})]$ (R=H or Ac). This gold(III) complex further reacts with an additional methionine residue to generate the R-Gly-Met-OH chlorosulfonium cation as the second intermediate product, which readily undergoes hydrolysis to give the corresponding sulfoxide. The $[\text{AuCl}_2]$ complex formed in the reaction with equimolar amounts of reactants showed a strong tendency to disproportionate to $[\text{AuCl}_4]$ and metallic gold as the final products of this redox process. However, in the presence of excess of the dipeptide, the resulting polynuclear H-Gly-D,L-Met-S-Au(I) and Ac-Gly-D,L-Met-S-Au(I) complexes showed themselves to be quite stable products. The finding that the oxidation of the methionine residue in Ac-Gly-D,L-Met-OH to its sulfoxide was five times slower than that in the non-protected H-Gly-D,L-Met-OH dipeptide undoubtedly confirmed that the terminal amino group of the methionine-containing peptide had an evident influence on the acceleration of this redox process.

The results from this study together with those obtained in previous studies [33–37] show that gold(III)-induced oxidation of methionine, methionine-containing peptides, and proteins may be important in relation to the severe toxicity of gold-based drugs. Based on the above-mentioned hypotheses, studies aimed at investigating the interactions of gold(III) complexes with sulfur-containing peptides can be of great importance for the medical application of gold-based drugs.

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References

1. Reynolds JEF, Prasad AB (1982) Martindale: The Extra Pharmacopoeia, 28th edn. The Pharmaceutical Press, London
2. Miranda S, Vergara E, Mohr F, De Vos D, Cerrada E, Mendia A, Laguna M (2008) Inorg Chem 47:5641–5648
3. Zou J, Taylor P, Dornan J, Robinson SP, Walkinshaw MD, Sadler PJ (2000) Angew Chem Int Ed 39:2931–2934
4. Fricker SP (1996) Gold Bull 29:53–60
5. Berners-Price SJ, Mirabelli CK, Johnson RK, Mattern MR, McCabe FL, Faucette LF, Sung CM, Mong SM, Sadler PJ, Crooke ST (1986) Cancer Res 46:5486–5493
6. McKeage MJ, Berners-Price SJ, Galetts P, Bowen RJ, Brouwer W, Ding L, Zhuang L, Baguley BC (2000) Cancer Chemother Pharmacol 46:343–350
7. Caruso F, Rossi M, Tanski J, Pettinari C, Marchetti F (2003) J Med Chem 46:1737–1742
8. Pillarsetty N, Katti KK, Hoffman TJ, Volkert WA, Katti KV, Kamei H, Koide T (2003) J Med Chem 46:1130–1132
9. Suresh D, Balakrishna MS, Rathinasamy K, Panda D, Mobin SM (2008) Dalton Trans 21:2812–2814
10. Tiekink ERT (2002) Crit Rev Oncol Hematol 42:225–248
11. Ott I (2009) Coord Chem Rev 253:1–1681
12. Carotti S, Guerri A, Mazzei T, Messori L, Mini E, Orioli P (1998) Inorg Chim Acta 281:90–94
13. Ronconi L, Marzano C, Zanello P, Corsini M, Miolo G, Macè C, Trevisan A, Fregona D (2006) J Med Chem 49:1648–1657
14. Messori L, Marcon G, Orioli P (2003) Bioinorg Chem Appl 1:177–187
15. Cinellu MA (2009) Chemistry of Gold(III) Complexes with Nitrogen and Oxigen Ligands. In: Mohr F (ed) Gold Chemistry, Applications and Future Directions in the Life Sciences. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, pp 47–92
16. Ronconi L, Fregona D (2009) Dalton Trans 48:10670–10680
17. Casini A, Kelter G, Gabbiani C, Cinella MA, Minghetti G, Fregona D, Fiebig HH, Messori L (2009) J Biol Inorg Chem 14:1139–1149
18. Bindoli A, Rigobello MP, Scutari G, Gabbiani C, Minghetti G, Corsini M, Miolo G, Macè C, Trevisan A, Fregona D (2009) Coord Chem Rev 253:1692–1707
19. Nobili S, Mini E, Landini I, Gabbiani C, Cinella MA, Fregona D (2010) Med Res Rev 30:550–580
20. Gabbiani C, Cinella MA, Messori L (2007) Gold Bull 40:73–81
21. Che CM, Sun RWY, Yu WY et al. (2003) Chem Commun 1:177–187
22. Gabbiani C, Cinella MA, Messori L, Guerri A, Cinella MA, Minghetti G, Corsini M, Rosani C, Zanello P, Arca M (2008) Inorg Chem 47:2368–2379
23. Best SL, Sadler PJ (1996) Gold Bull 29:87–93
24. Shaw CF III (1979) Inorg Perspect Biol Med 2:287–355
25. Shaw CF III (1999) Chem Rev 99:2589–2600
26. Schuhmann D, Kubicka-Muranyi M, Mirtschewa J, Gunther J, Kind P, Gleichmann E (1990) J Immunol 145:2132–2139
27. Beverly B, Couri D (1987) Fed Proc 46:854
28. Brown DH, Smith WE (1983) Am Chem Soc Symp Ser 209:401–418
29. Smith WE, Reglinski J (1991) Perspect Bioinorg Chem 1:183–208
30. Shaw CF III, Cancro MP, Witkiewicz PL, Eldridge JE (1980) Inorg Chem 19:3198–3201
31. Witkiewicz PL, Shaw CF III (1981) J Chem Soc Chem Commun 1111–1114
32. Annibale G, Canovese L, Cattalini L, Natile G (1980) J Chem Soc Dalton Trans 7:1017–1021
33. Bordignon E, Cattalini L, Natile G et al. (1973) J Chem Soc Chem Commun 878–879.
34. Natile G, Bordignon E, Cattalini L (1976) Inorg Chem 15:246–248
35. Vujačić AV, Savić JZ, Sovilj SP, Mészáros Szécsényi K, Todorović N, Petković MŽ, Vasić VM (2009) Polyhedron 28:593–599
36. Isab AA, Sadler PJ (1977) Biochim Biophys Acta 492:322–330
37. Rychlewskas U, Warżajtis B, Gliśić BD et al. (2010) Acta Crystallogr Sect C: m51–m54
38. Kowalski P, Mitka K, Ossowska K, Kolarska Z (2005) Tetrahedron 61:1933–1953
39. Zhu L, Kostić NM (1992) Inorg Chem 31:3994–4001
40. Laidler KJ (1987) Chemical Kinetics, 3rd edn. Harper & Row, New York
41. Krežel A, Bal W (2004) J Inorg Biochem 98:161–166
42. Robb W (1967) Inorg Chem 6:382–386
43. Kowalski P, Mitka K, Ossowska K, Kolarsa Z (2005) Tetrahedron 61:1933–1953
44. Patai S, Rappoport Z (1994) Syntheses of Sulphones. Sulfoxides and Cyclic Sulphides, Wiley, Chichester
45. Harrison JA, Thompson J (1975) J Electroanal Chem Interfac 59:273–280
46. Gammons CH, Yu Y, Williams-Jones AE (1997) Geochim Cosmochim Acta 61:1971–1983
47. Nikolaeva NM, Erenburg AM, Antipina VA (1972) Izvest Sib Otd Akad Nauk SSSR Ser Khim 4:126–129
48. Zhu S, Gorski W, Powell DR, Walmsley JA (2006) Inorg Chem 45:2688–2694
49. Bell JD, Norman RE, Sadler PJ (1987) J Inorg Biochem 31:241–246
50. Abdou HE, Mohamed AA, Fackler JP Jr, Burini A, Galassi R, López-de-Luzuriaga JM, Olmos ME (2009) Coord Chem Rev 253:1661–1669