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Interactions of Tetra-μ-acetato Dirhodium(II) with Sulfur-containing Aminoacids

G. PNEUMATIKAKIS* and P. PSAROULIS

University of Athens, Inorganic Chemistry Laboratory, Navarinou 13A, Athens 144, Greece

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The reactions of aminoacids containing both free or acylated sulfydryl groups with the antitumour complex $[Rh_2(O_2CMe)_4]$ have been studied. The reactions of this complex with the first class of ligands lead to monomeric square planar rhodium(II) (S,N) bonded chelate complexes, which have been characterized by elemental analyses, ir, electronic and esr spectra, and by room temperature magnetic susceptibility measurements. The reactions with the second class of ligands lead to the formation of 1:2 adducts without breaking of the acetato cage and the adducts were characterized by the same techniques.

Introduction

Tetrakis-μ-acetato dirhodium(II), $[Rh_2(O_2CMe)_4]$, exhibits anticancer activity against many types of tumours as has been demonstrated by Bear and his co-workers [1–3]. The interaction of this complex with several molecules of biological importance has also been studied by the same workers [3, 4]. They found that the complex inhibited DNA synthesis and that it reacted mainly with poly-A but not with poly-C and poly-G [3]. They also reported the formation constants of the complex with ado-5′-P, ado-5′-PP, ado-5′-PPP, imidazole, *etc.* [5–7]. Recently we studied the interactions of $[Rh_2(O_2CMe)_4]$ with nucleosides and nucleotides and reported on the nature of the products formed and the binding sites of the ligands [8, 9]. Bear and his co-workers also found that cysteine causes the breakdown of the cage structure of the rhodium(II) complexes and reported on the behaviour of free SH groups containing enzymes after exposure to rhodium(II) carboxylates [4].

In this paper we report on the reactions of $[Rh_2(O_2CMe)_4]$ with cysteine and cysteine derivatives containing both free and acylated SH groups in aqueous solutions and the nature of the isolated products.

*Author for correspondence.

Results and Discussion

The acetate derivatives of certain bivalent metal ions, such as Cu, Cr, Mo, *etc.*, of the formula $[M_2(O_2CMe)_4]$ are dimeric and contain a metal–metal bond [10, 11]. Chernyaev *et al.* [12] reported the analogous rhodium(II) dimer. $[Rh_2(O_2CMe)_4]$ may form 1:1 or 1:2 adducts with ligands occupying the two axial positions. The complexes formed are green or blue-green with oxygen donor ligands, rose-red, violet, or pink with nitrogen donors, and violet or orange with sulfur donors [3, 5, 8, 9, 13, 14]. It has been observed by Bear and co-workers [4, 15] that reaction of cysteine with rhodium(II) complexes is dramatically different from the reaction involving any of the other aminoacids. Instead of reversible axial binding, characteristic of other ligands, cysteine causes the breakdown of the carboxylate cage liberating acetate ions. However no products have been isolated and no changes in the oxidation state of rhodium have been reported. With these two objectives we decided to investigate further the reaction of $[Rh_2(O_2CMe)_4]$ with a series of cysteine derivatives.

Reactions with Free SH Group Containing Aminoacids

The aminoacids used are l-cysteine, l-cysteine methylester, and l-penicillamine. All these aminoacids contain free SH groups and they essentially behave in the same way towards the rhodium(II) dimer. Mixing the rhodium(II) dimer and aqueous solutions of the ligands at molar ratio 1:4 and stirring for about 2 hr resulted in dark-red solutions from which the complexes were isolated with excess acetone. The analytical results for these complexes fit well to the general formula RhL_2 (Table I).

The binding sites of the aminoacids to the rhodium in the complexes are deduced from their ir spectra (Table II). The absence of the weak absorption of the -SH group at *ca.* 2500 cm^{-1} present in the free ligands, indicates the formation of S–M bonds in all the complexes and the possibility of *trans* geometries due to the strong *trans* influence of the sulfur [16–19]. The bands at 3100 cm^{-1}, at 3230

TABLE I. Analytical and Magnetic Moment Data of the Complexes.

Compound	C%	H%	N%	Rh%	μ_{eff} (μB)
$Rh(Cys^-)_2$	21.20 (20.99)	3.62 (3.50)	8.38 (8.16)	29.60 (30.03)	1.85
$Rh(O\text{-}MeCys^-)_2$	25.50 (25.88)	4.20 (4.31)	7.30 (7.55)	27.32 (27.76)	1.91
$Ph(Penicillamine^-)_2$	33.48 (33.72)	5.42 (5.62)	6.32 (6.56)	23.80 (24.12)	1.87
$[Rh_2(O_2CMe)_4(S\text{-}MeCys)_2]$	26.68 (26.97)	4.02 (4.21)	3.62 (3.93)	28.50 (28.93)	diamagnetic
$[Rh_2(O_2CMe)_4(S\text{-}EtCys)_2]$	29.40 (29.19)	4.70 (4.59)	3.99 (3.78)	27.42 (27.84)	diamagnetic
$[Rh_2(O_2CMe)_4(Met)_2]$	28.88 (29.19)	4.35 (4.59)	3.56 (3.78)	28.35 (27.84)	diamagnetic

[a]The numbers in parentheses correspond to the calculated figures.

TABLE II. Ir Spectral Assignments of the Complexes.

Compound	νNH_2	δNH_2	$\nu_{asym}COO$
$Rh(Cys^-)_2$	3100	1560	1710
$Rh(O\text{-}MeCys^-)_2$	3230 3215	1569	1730
$Rh(penicillamine^-)_2$	3200	1572	1705
$[Rh_2(O_2CMe)_4(S\text{-}MeCys)_2]$	3420	1595	1710
$[Rh_2(O_2CMe)_4(S\text{-}EtCys)_2]$	3400	1585	1700
$[Rh_2(O_2CMe)_4(Met)_2]$	3410	1590	1965

and 3215 cm^{-1}, and at 3200 cm^{-1} for the cysteine, cysteine methylester, and penicillamine complexes respectively are assigned to the coordinated $\nu(NH_2)$ motions [16, 17, 20–22]. On the other hand the strong bands at 1560, 1569, and 1572 cm^{-1} of the above complexes are due to the coordinated $\delta(NH_2)$ motions [16, 19, 22]. The cysteine and penicillamine complexes show a strong band at 1710 and 1705 cm^{-1} respectively, assigned to $\nu_{asym}(COOH)$ indicating non-involvement of the carboxyl group in coordination [17–19, 23], while the strong band at 1720 cm^{-1} in the spectrum of the l-cysteine methylester complex is assigned to the ester carbonyl group. It is suggested from the above evidence that all three aminoacids used act as bidentate ligands through their sulfydryl and amino groups.

The room temperature magnetic moments of the complexes are in the range 1.8 to 1.9 μB. The complexes therefore may be formulated as mononuclear, low spin (S = 1/2), square-planar complexes of rhodium(II), and may be considered as further examples of such complexes obtained by the action of disodium maleonitriledithiolate on rhodium(II) acetate [24].

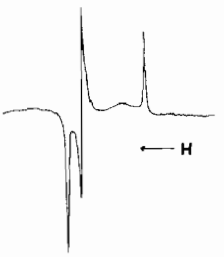

Fig. 1. Electron spin resonance spectrum of $Rh(O\text{-}MeCys^-)_2$.

The esr spectrum of the complex $Rh(O\text{-}MeCys^-)_2$ is shown in Fig. 1. The three g values obtained are: g_1 = 1.955, g_2 = 2.020, g_3 = 2.035 and were determined by using polycrystalline diphenyldipicrylhydrazyl (g = 2.0036) as a reference. The three line spectrum is similar to the spectrum of the polycrystalline complex $[(n\text{-}C_4H_9)_4N]_2Rh(MNT)_2$ [24], which contains rhodium(II), and also resembles the frozen solution spectra obtained for the electronically similar $Ni(TDT)_2^-$, $Ni(MNT)_2^-$, $Pd(MNT)_2^-$, and $Pt(MNT)_2^-$ complexes, which have S = 1/2 [25, 26]. From the esr and static susceptibility results, we conclude that the square planar $Rh(O\text{-}MeCys^-)_2$, $Rh(Cys^-)_2$, and $Rh(Penicillamine^-)_2$ complexes have a spin doublet ground state and that these complexes are among the very few mononuclear rhodium(II) complexes.

All these Rh(II) monomeric complexes show a weak band around 575 nm which may be assigned to a d–d transition [27].

Reactions with Thioether Aminoacids

The aminoacids used are S-methylcysteine (S-MeCys), S-ethylcysteine (S-EtCys), and methionine (Met). Mixing $[Rh_2(O_2CMe)_4]$ with the ligands in

water at molar ratio 1:2 and stirring for about 2 hr produced orange-violet solutions from which the complexes were isolated with excess acetone. The chemical analyses correspond to 1:2 adducts (Table I). The orange-violet colour of the adducts is an indication of sulfur bonded to the axial positions of the rhodium(II) dimer. The sulfur involvement in bonding with the metal is also deduced from the fact that neither the amino group nor the carboxylic group are participating in bonding as is evident from the ir spectra of the adducts. The strong broad band at around 3400 cm^{-1} in all three adducts may be assigned to a non-coordinated $\nu(NH_2)$ vibration, while the strong band at around 1590 cm^{-1} may also be assigned to a non-coordinated $\delta(NH_2)$ vibration. Upon deuteration the first of these bands is shifted to about 2400 cm^{-1}, while the second disappears and this further supports the above assignments. All three complexes show a strong band around 1700 cm^{-1} assigned to $\nu_{asym}(COOH)$ indicating a non-involvement of the carboxyl group in coordination.

Anhydrous $[Rh_2(O_2CMe)_4]$ gives two bands at 617 and 442 nm [14]. The first of these bands is shifted to lower wavelengths upon adduct formation, while the second remains essentially constant [14], or may become a shoulder but at the same region [28]. Thus the S-methylcysteine adduct of $[Rh_2(O_2CMe)_4]$ has a band at 558 nm, that of S-ethylcysteine at 560 nm, and that of methionine at 562 nm in aqueous solutions compared with 584 nm for $[Rh_2(O_2CMe)_4(OH_2)_2]$ [14]. In all three adducts the band at 442 nm becomes a shoulder and appears at 530 nm.

Experimental

Materials

The aminoacids and $RhCl_3 \cdot aq$ were purchased from Fluka A.G. and were used without further purification. The complex $[Rh_2(O_2CMe)_4(HOMe)_2]$ was prepared according to the literature [29].

Methods

Infrared spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer in KBr pellets and in Nujol mulls, the positions of the bands are given within ±2 cm^{-1}. Visible spectra were obtained with a Cary Model 17D spectrophotometer. Magnetic moments were determined by the Gouy method with diamagnetic corrections. Electron spin resonance spectra were recorded by using a Varian Y 4502 spectrometer with 100 Kc field modulation, operating at 9500 Kc. Microanalyses were performed in the Laboratories of the National Hellenic Research Foundation (N.H.R.F.), Athens.

Preparation of the Complexes

General procedure for bis-(cysteinato)rhodium(II), $Rh(Cys^-)_2$, bis(cysteinatomethylester)rhodium(II), $Rh(O\text{-}MeCys^-)_2$, and bis-(penicillaminato)rhodium (II), $Rh(penicillamine^-)_2$

Nitrogen degassed suspension of $[Rh_2(O_2CMe)_4(HOMe)_2]$ (0.506 g, 1 mmol) in water (50 ml) was stirred, under nitrogen, with a four-fold molar excess of each of the above aminoacids for 2 hr. The rhodium(II) dimer was dissolved and the solution turned to dark-red. The solution was rotoevaporated to about 10 ml and the complexes precipitated with excess acetone.

General procedure for bis-(S-methylcysteine)-tetra-μ-acetato dirhodium(II), $[Rh_2(O_2CMe)_4(S\text{-}MeCys)_2]$, bis-(S-ethylcysteine)tetra-μ-acetato-dirhodium(II), $[Rh_2(O_2CMe)_4(S\text{-}EtCys)_2]$, and bis-(1-methionine)-tetra-μ-acetato-dirhodium(II), $[Rh_2(O_2CMe)_4(Met)_2]$

$[Rh_2(O_2CMe)_4(HOMe)_2]$ (0.506 g, 1 mmol) was suspended in 50 ml water and to that were added 2 mmol from each of the above aminoacids. The mixtures were stirred overnight at room temperature under nitrogen. The resulted orange-violet solutions were rotoevaporated at 50 °C to about 10 ml and the complexes were precipitated with excess acetone.

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