Rhodium(II) Carboxylato Complexes

PROPERTIES AND POTENTIAL APPLICATIONS

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Interest in rhodium(II) carboxylato complexes, initially stimulated by their unusual structure and oxidation state, has been maintained in recent years by controversy concerning their electronic structure and by their recently discovered anti-tumour activity.

Il'ya Il'ich Chernyaev, late director of the N.S. Kurnakov Institute of General and Inorganic Chemistry of the Academy of Sciences of the U.S.S.R., and co-workers uncovered a new and fruitful area of rhodium chemistry in 1960 when they reported an air-stable green crystalline complex obtained by heating rhodium(III) chloride under reflux in neat formic acid (1). This product was initially formulated by them as a rhodium(I) species $H[Rh(O_2CH)_2.0.5\ H_2O]$ but was quickly found to lack acid character, and was subsequently identified by X-ray diffraction methods as dirhodium(II)tetraformate monohydrate $[Rh_2(O_2CH)_4(H_2O)]$—the first example of a new class of binuclear rhodium(II) carboxylato complexes possessing the now familiar "lantern" structure illustrated in Figure 1 (2). The diamagnetic character of the rhodium(II) (d^7) complex—μ_{eff} about 0.5BM, temperature independent—was attributed to an axial metal-metal interaction. Rhodium(II) carboxylates were the first and remain the most numerous examples of complexes containing rhodium in the relatively uncommon 2+ oxidation state. Derivatives of approximately twenty-five different carboxylic acids have been made, either by minor variations of the original method or by use of simple carboxylate anion exchange reactions. These complexes usually crystallise as solvates $[Rh_2(O_2CR)_4(sol^v)_n]$ and react readily with neutral (L) and anionic (X) donor ligands to form a wide variety of adducts $[Rh_2(O_2CR)_4L_n]$ and salts $M_n^I[Rh_2(O_2CR)_4X_n]$ (n = 1, 2; M = alkali metal or protonated N-base), respectively. Products of this type, several hundred of which are now known, are noted for their varied and often brilliant colours, which reflect the nature of the axial donor atoms—blue or green for oxygen, pink or red for nitrogen, burgundy or orange for sulphur and orange or red-brown for phosphorus.

Interest in these complexes, initially stimulated by their unusual structure and rhodium oxidation state, has been maintained in recent years by controversy concerning the nature of their axial ligand-rhodium and rhodium-rhodium interactions (3,4), and by their recently discovered anti-tumour activity (5,6). In addition rhodium(II) carboxylates have shown promise as stationary phases for gas chromatography (7) and as catalysts for the selective hydrogenation (8) and oxidation (9) of olefins.

Structural and Electronic Properties

X-ray diffraction studies, prompted by interest in the axial bonding interactions, have been reported for about thirty rhodium(II) carboxylato adducts $[Rh_2(O_2CR)_4L_2]$ containing a variety of carboxylate bridges and axial donor groups. All possess the "lantern" structure and

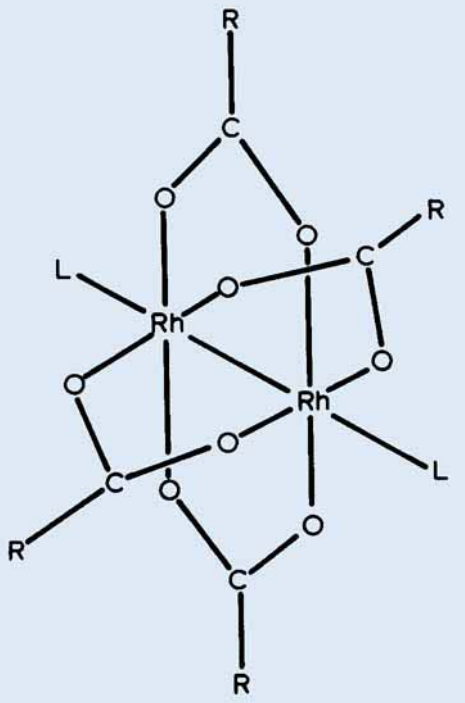

Fig. 1 The "lantern structure" found in rhodium(II) carboxylato complexes

have intramolecular rhodium-rhodium distances (2.3165 to 2.486 Å) which are dependent upon the nature of the axial donor ligands but are all considerably shorter than expected for a rhodium-rhodium single bond (about 2.7 Å). Since comparisons with related structures indicate that the short rhodium-rhodium distances are not imposed by the steric requirements of the bridging carboxylate ligands, they were originally taken by some authors to imply the presence of a rhodium-rhodium triple bond (10,11). Formation of relatively stable adducts with several traditional π-acids [notably CO, $P(OMe)_3$, $P(OPh)_3$ and PPh_3] has led to speculation that the Rh_2^{II} centre has good π-donor as well as strong σ-acceptor capacity (12). However, these views are not in accord with conclusions drawn from more recent spectroscopic studies and theoretical calculations (3,4,13). Thus Norman and co-workers have concluded from molecular orbital calculations and supporting electronic spectra data that the complex $[Rh_2(O_2CH)_4(H_2O)_2]$ has a rhodium-rhodium single bond interaction arising from a $\sigma^2, \pi^4, \delta^2, \pi^{*4}, \delta^{*2}$ electronic configuration (3).

Electron spin resonance (E.S.R.) data indicate a different ordering of the energy levels in the cationic radicals $[Rh_2(O_2CR)_4L_2]^+$ [where $L = PPh_3$, $P(OPh)_3$ and $P(OCH_2)_3CEt$] (14) but are nevertheless consistent with a rhodium-rhodium bond order of unity, and are in agreement with theoretical calculations on $[Rh_2(O_2CH)_4(PH_3)_2]$ (15). Raman active bands at about 350 to 280 cm^{-1} originally attributed to $\nu(Rh \equiv Rh)$ (16) are now considered to be consistent with the presence of a rhodium-rhodium single bond (15). However, an alternative assignment, more in keeping with the latter arrangement, attributes Raman active bands in the region about 160 to 150 cm^{-1} to ν(Rh-Rh) (17). The main body of opinion now inclines to the view that the rhodium-rhodium interaction in the binuclear "lantern" structures has a formal bond order of unity but is remarkably strong and resistant to attack. This conclusion is supported by chemical evidence, see below.

In an attempt to resolve the controversy concerning the nature of the axial metal-ligand bonds, X-ray diffraction studies have been performed on the phosphorus donor adducts $[Rh_2(O_2CR)_4L_2]$ [where $R = CH_3$, CF_3; $L = PPh_3$, $P(OPh)_3$] (18,19). These reveal unusually long rhodium-phosphorus bonds (about 2.41 to 2.48 Å) which display a relatively small decrease in length on replacing PPh_3 by $P(OPh)_3$. The length of the rhodium-phosphorus bonds has been attributed to the large *trans* influence of the rhodium-rhodium bond, and the lack of significant variation has been taken to indicate a dominant rhodium-phosphorus σ-bonding interaction with little or no π-orbital overlap (18). This situation contrasts sharply with that found for substituted chromium(0) complexes $[Cr(CO)_5L']$ [$L' = PPh_3$, $P(OPh)_3$] where the change from

PPh_3 to $P(OPh)_3$ is accompanied by a pronounced shortening of the chromium-phosphorus bond length. E.S.R. spectra for the cation radicals $[Rh_2(O_2CR)_4L_2]^+$ [$L = PPh_3$, $P(OPh)_3$, $P(OCH_2)_3CEt$] are also consistent with an essentially σ-interaction between the axial phosphorus donors and the Rh_2^{II} centre (14).

Much effort has been expended in the collection of X-ray photoelectronic spectra (ESCA) data but few positive conclusions have been reached; the Rh $3d_{5/2}$ binding energy (approximately 309 eV) is consistent with rhodium in the oxidation state 2+ but is insensitive to changes in the nature of the axial ligands (20). Many infrared studies including several full normal co-ordinate analyses have been reported (21,22). Intense absorptions at about 450 to 320 cm^{-1} have been attributed to ν(Rh-O); vibrations associated with the "lantern" structure reflect the nature of the carboxylate group but are relatively insensitive to changes in the identity of the axial donor ligands. Although many of the complexes $[Rh_2(O_2CR)_4L_2]$ offer considerable scope for useful nuclear magnetic resonance (NMR) work remarkably few studies have been described to date. However, brief reports on magnetic moment measurements (Evans' method), carboxylate exchange reactions, adenine co-ordination sites [N(1) and N(7)], and formation of mono- and bis-(trialkylphosphite) adducts illustrate the range of problems in this field amenable to NMR investigation. Direct observation of the ^{103}Rh signal from $[Rh_2(O_2CMe)_4\{P(OMe)_3\}_2]$ has also been achieved (23).

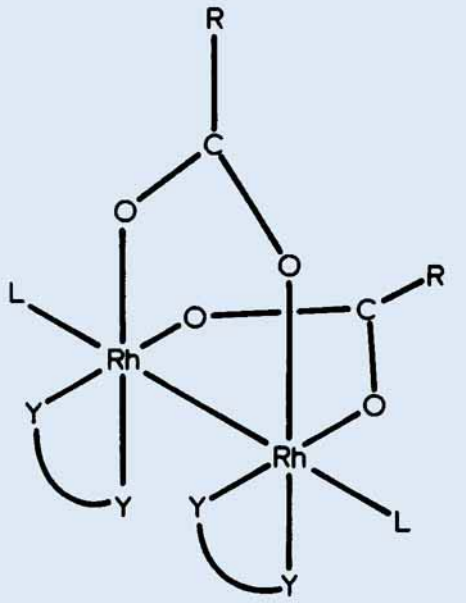

Fig. 2 The structure adopted by rhodium(II) carboxylato complexes containing chelating agents

Chemical Reactivity

The chemistry of the binuclear "lantern" cluster is attracting increasing attention. In sharp contrast to closely related ruthenium (II/III) carboxylates $[Ru_2(O_2CR)_4Cl]$, which possess a multiple metal-metal bond but react readily to form mono-nuclear products, the rhodium(II) carboxylates show considerable resistance to disruption of the "lantern" structure. Monodentate neutral and anionic ligands merely occupy the axial sites and are susceptible to facile exchange or thermal dissociation. The preference of the rhodium(II) centre towards different types of axial ligand can be profoundly altered by changes in the nature of the carboxylate bridges (O_2CR). Thus dimethyl sulphoxide (Me_2SO) co-ordinates through sulphur when R = Me or Et but through oxygen when $R = CF_3$ (24). Under more vigorous conditions the carboxylate anions can be replaced by other bridging anionic ligands with retention of the metal-metal bonds to afford new binuclear rhodium(II) species including $[Rh_2(CO_3)_4]^{4-}$ (25), $[Rh_2(SO_4)_4]^{4-}$(25) and $[Rh_2(H_2PO_4)_4]$ (26). With chelating anionic ligands partial or complete disruption of the carboxylate cage structure occurs to give products of the form $[Rh_2(O_2CR)_2(Y\text{-}Y)_2L_2]$, see Figure 2 or $[Rh_2(Y\text{-}Y)_4L_2]$, Figure 3 [Y-Y = acetylacetonate (27) or dimethylglyoximate (28)]; cationic complexes of

similar structure $[Rh_2(O_2CR)_2(Y\text{-}Y)_2L_2]^{2+}$ (where Y-Y = *o*-phenanthroline or 2,2′-dipyridyl) can be prepared by indirect methods (29). Protonation of $[Rh_2(O_2CMe)_4]$ by strong acids (HBF_4) in methanol solution affords $[Rh_2(O_2CMe)_3\ aq]^+$ and $[Rh_2(O_2CMe)_2\ aq]^{2+}$ as the major products (30), not as originally claimed Rh_2^{4+} aquo ions. Carbonylation of these solutions, at one atmosphere and 75°C, provides a convenient route to $[Rh_6(CO)_{16}]$ in good yield (31).

Diffusion controlled, reversible, one-electron oxidation of rhodium(II) carboxylates produces binuclear cationic species $[Rh_2(O_2CR)_4L_2]^+$ which are violet or orange in solution depending upon the solvent, and slowly disproportionate to rhodium(II) carboxylates and rhodium(III) species (32). The electronic structures of these binuclear cations, which do not involve discrete rhodium(II) and rhodium(III) centres, have been discussed at length (4). The electrochemical reduction of rhodium(II) carboxylates appears to be an irreversible multi-electron process giving ill-characterised products.

Anti-Tumour Activity

In the early 1970s interest in rhodium(II) carboxylates gained a new impetus when their potential as anti-cancer agents was discovered by Bear and co-workers (5,6) at the University of Houston.

Rhodium(II) carboxylates are among the most promising noble metal anti-tumour agents studied since the discovery of the chemotherapeutic properties of *cis*-$[PtCl_2(NH_3)_2]$ (cisplatin) and related species.

In vivo studies have shown rhodium(II) carboxylates to produce partial or complete regression of Ehrlich, sarcoma 180, leukaemia P 388 and L 1210 ascites tumours in mice (6). These results have prompted much work on the biochemical and biological activity of rhodium(II) carboxylates. Studies on biological ligands have shown that species containing unprotonated amino groups including adenine nucleotides and polynucleotides, single stranded DNA, RN ase A, bovine serum albumin and certain amino acids, notably histidine and methionine bind tightly but reversibly to rhodium(II) carboxylates (6,33).

In contrast sulphydryl containing entities, particularly cysteine and glutathione, bind irreversibly with breakdown of the "lantern" structure and liberation of free carboxylic acid (33). Recent work on the irreversible inhibition of sulphydryl containing enzymes by rhodium(II) carboxylates strongly implies that the latter reaction is responsible for the biological activity of these compounds (33). One possible explanation for the toxic and anti-tumour activity of rhodium(II) carboxylates stems from their ability to inhibit DNA (but not RNA) replication (6). Rhodium(II) carboxylates do not bind to double stranded DNA therefore it seems possible that they achieve their effect by inhibiting one or more of the enzymes essential for DNA synthesis, rather than by interacting directly with DNA itself. Since DNA polymerase α, which is particularly active in copying "activated" double-stranded DNA, is known to be strongly inhibited by sulphydryl group blocking reagents it is conceivable that rhodium(II) carboxylates achieve their inhibitory effect on DNA synthesis by deactivating this particular enzyme. The minimal inhibition of RNA synthesis observed suggests that the catalytic activity of RNA

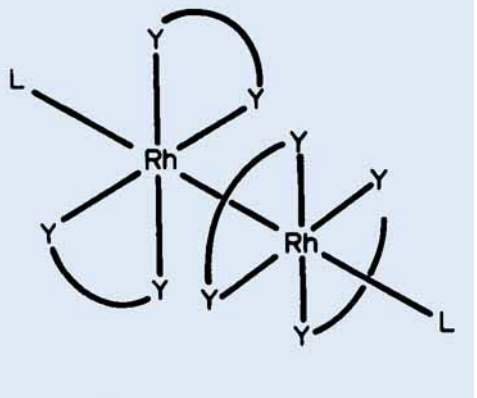

Fig. 3 The structure of binuclear complexes derived from rhodium(II) carboxylates

polymerase does not depend on sulphydryl groups (6).

Differences in the anti-tumour activity of some rhodium(II) carboxylates (butyrate > propionate > acetate > methoxyacetate) are too large to be explained in terms of stability, and are probably attributable to changes in lipophilicity (34). Simple extension of the carboxylate chain beyond C_4 impairs the therapeutic effects of the complex (34). The oxidised species $[Rh_2(O_2CR)_4]^+$, which are more water soluble than the uncharged parent compounds to which they slowly revert in solution; are also more active against tumours. However, the origins of this enhanced activity are not yet clear (35).

Finally chemotherapeutic studies on rhodium(II) carboxylates are encouraged by the observation that, unlike *cis*-$[PtCl_2(NH_3)_2]$ and many other anti-tumour agents, they produce only slight chromosome damage in cells which have been treated (6).

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