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$Ru_2(CO)_4(OOCR)_2(PPh_3)_2$ sawhorse-type complexes containing μ_2-η^2-carboxylato ligands derived from biologically active acids

Mathieu Auzias, Bruno Therrien, Georg Süss-Fink *

Institut de Chimie, Université de Neuchâtel, Case postale 158, CH-2009 Neuchâtel, Switzerland

Abstract

The thermal reaction of $Ru_3(CO)_{12}$ with the biologically active acids acetyl salicylic acid (Aspirin), α-methyl-4-(isobutyl)phenylacetic acid (Ibuprofen) and 3α,7α,12α-trihydroxy-5β-cholanic acid (cholic acid) in refluxing tetrahydrofuran, followed by addition of triphenylphosphine, gives the dinuclear complexes $Ru_2(CO)_4(OOCR)_2(PPh_3)_2$ (**1**: R = C_6H_4-2-OCOMe, **2**: R = CHMe-C_6H_4-4-Bu^t, **3**: $C_{23}H_{39}O_3$). The single-crystal structural analysis of **1** and **2** reveals a dinuclear $Ru_2(CO)_4$ sawhorse structure, the diruthenium backbone being bridged by the carboxylato ligands, while the two phosphine ligands occupy the axial positions at the ruthenium atoms. However, chiral carbon atoms in the carboxylic acid undergo racemisation during the thermal reaction.

Keywords: Carbonyl ligands; Carboxylato bridges; Biologically active acids; Dinuclear complexes; Ruthenium

1. Introduction

Sawhorse-type ruthenium complexes are well-known since 1969, when J. Lewis and co-workers reported their formation by refluxing $Ru_3(CO)_{12}$ in the corresponding carboxylic acid and the depolymerisation of these materials in coordinating solvents to give dinuclear complexes of the type $Ru_2(CO)_4(OOCR)_2L_2$, L being a two-electron donor [1]. These dinuclear complexes have been shown later, by a single-crystal X-ray structure analysis of $Ru_2(CO)_4(OOCBu^n)_2(PBu^t_3)_2$ to have a $Ru_2(CO)_4$ backbone in a sawhorse-type arrangement with two μ_2-η^2-carboxylato bridges and two axial (phosphine) ligands [2]. Since their discovery, a considerable number of such sawhorse-type diruthenium complexes with carboxylato bridges have been synthesized and studied [3], used in catalysis [4–6] or for the assembly of mesomorphic materials [7].

Herein, we present the synthesis and molecular structure of three new $Ru_2(CO)_4$ sawhorse-type complexes containing carboxylato ligands derived from biologically active molecules, such as anti-inflammatory drugs or steroid hormones. Acetyl salicylic acid (Aspirin) and α-methyl-4-(isobutyl)phenylacetic acid (Ibuprofen) are used as anti-inflammatory pain-killers, the biological function of which is to reduce the synthesis of prostaglandins by insertion into the enzymatic cavity of cyclo-oxygenase [8]. Cholic acid, a steroid hormone, is the most abundant bile acid in the human body, it plays an important role in fat emulsification during the digestion process [8].

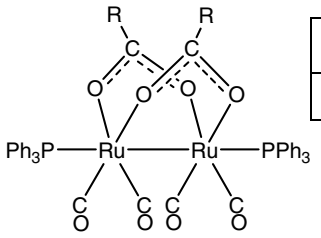
* Corresponding author.
E-mail address: georg.suess-fink@unine.ch (G. Süss-Fink).

2. Results and discussion

Dodecacarbonyltriruthenium reacts with the appropriate carboxylic acid in refluxing tetrahydrofuran to give, in the presence of triphenylphosphine, the dinuclear complexes $Ru_2(CO)_4(OOCR)_2(PPh_3)_2$ in good yields (see Scheme 1).

Compounds **1**, **2** and **3** are air-stable yellow crystalline powders which have been characterised by their IR, NMR and MS as well as by the micro-analytical data. All compounds **1**, **2** and **3** exhibit in the $\nu_{(CO)}$ region of the infrared spectrum, the characteristic pattern of the $Ru_2(CO)_4$ sawhorse unit.

$$2/3\ Ru_3(CO)_{12} + 2\ RCOOH + 2\ PPh_3 \longrightarrow Ru_2(CO)_4(OOCR)_2(PPh_3)_2 + 4\ CO + 2\ H_2$$



R	1	2	3
	C_6H_4-2-OCOMe	CHMe-C_6H_4-4-Bu^i	$C_{23}H_{39}O_3$

Scheme 1.

The single-crystal structure analyses of **1** and **2** show the $Ru_2(CO)_4$ sawhorse backbone with the two phosphine ligands in the axial positions and the carboxylato bridges in the equatorial positions. The Ru–Ru distances [**1**: 2.7362(4) Å, **2**: 2.7251(5) Å] are in the range of a ruthenium–ruthenium single bond, as it was also observed in analogous complexes [2,3b,3d]. The OCO bond angles of the carboxylato bridges [**1**: 125.0(2)° and 125.4(2)°, **2**: 125.0(4)° and 125.1(3)°] differ only slightly from those observed in other $Ru_2(CO)_4(OOCR)_2L_2$ complexes [2,3b,3d] (see Fig. 1).

While the aspirin derivative **1** is an achiral molecule, the ibuprofen derivative **2** containing an asymmetric carbon atom in both carboxylato ligands is chiral. Surprisingly, a dichloromethane solution of **2** shows no CD signal, although **2** had been synthesised with the *S* enantiomer of α-methyl-4-(isobutyl)phenylacetic acid (Ibuprofen). This suggests that racemisation must have occurred during the synthesis (thermal reaction at 120 °C), although the ^1H NMR signals of **2** in $CDCl_3$ do not split into two sets of signals upon addition of europium(III) tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorate] (chiral shift reagent), as expected for a racemic mixture. However, the racemised carboxylato ligands are clearly seen in the molecular structure of **2**. Comparative CD spectra of enantiopure commercial ibuprofen and of ibuprofen heated to 120 °C in thf during 12 h give no further information, because these compounds have an UV maximum of absorption around 260 nm which is outside the CD limit detection.

Compound **3**, being a steroid hormone derivative, was synthesised by reacting cholic acid with $Ru_3(CO)_{12}$. The molecular constitution can be deduced unambiguously from the spectroscopic data. The CD spectrum of **3** shows that it is not optically active, although it had been formed from enantiopure cholic acid. Obviously, cholic acid underwent racemisation during the synthesis of **3**. The racemisation is a consequence of the thermal treatment during the reaction. Indeed, comparative CD spectra of the enantiopure commercial cholic acid and of cholic acid heated in thf over 12 h, confirm the racemisation, since the CD signal disappears completely (see Fig. 3).

In conclusion, we have shown that biologically active molecules such as anti-inflammatory drugs and steroid hormones can be derivatised by their carboxylic acid function with $Ru_2(CO)_4$ sawhorse unit. However, chiral carbon atoms in the carboxylic acid undergo racemisation during the thermal process.

3. Experimental

3.1. General

All manipulations were carried out by routine methods under nitrogen atmosphere. Organic solvents were degassed and saturated with nitrogen prior to use. All reagents were

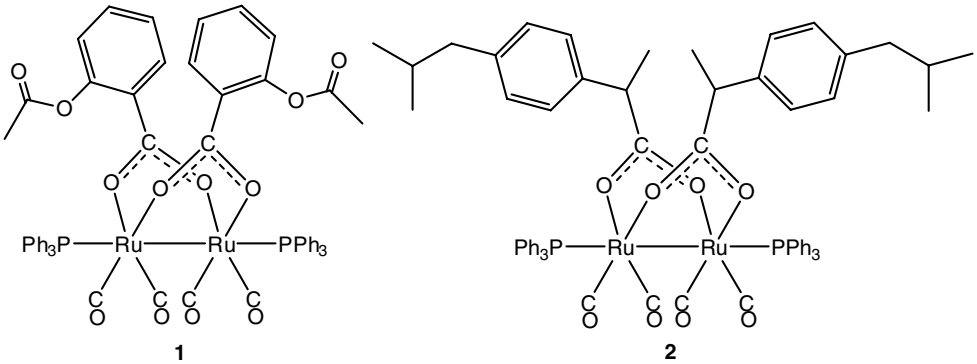


Fig. 1. Lewis representations of the aspirin and ibuprofen derivatives $Ru_2(CO)_4(OOCC_6H_4$-2-$OCOMe)_2(PPh_3)_2$ (**1**) and $Ru_2(CO)_4(OOCCHMe$-C_6H_4-4-$Bu^i)_2(PPh_3)_2$ (**2**).

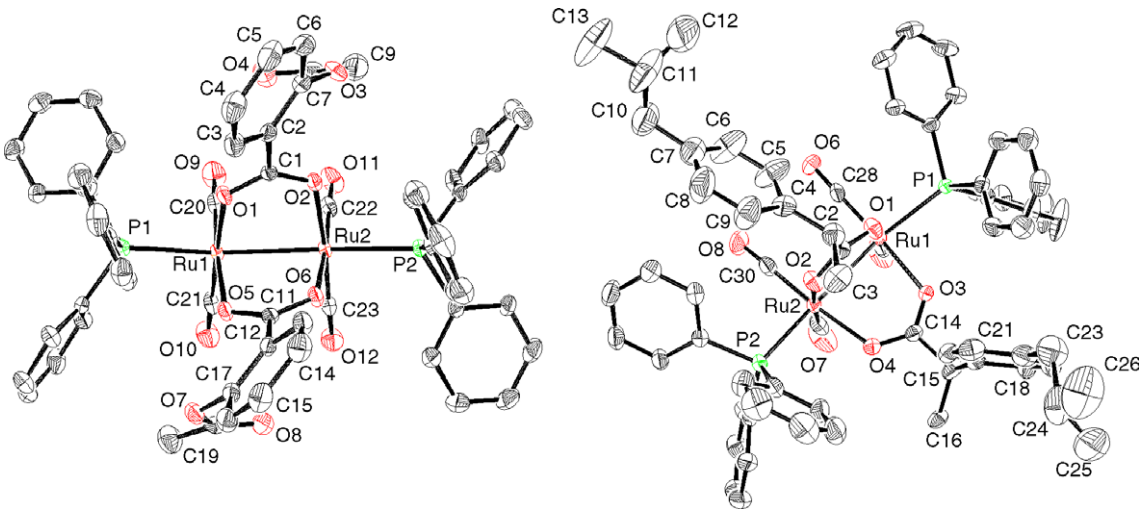


Fig. 2. Molecular structures of $Ru_2(CO)_4(OOCC_6H_4\text{-}2\text{-}OCOMe)_2(PPh_3)_2$ (**1**) and $Ru_2(CO)_4(OOCCHMe\text{-}C_6H_4\text{-}4\text{-}Bu^i)_2(PPh_3)_2$ (**2**), hydrogen atoms being omitted for clarity.

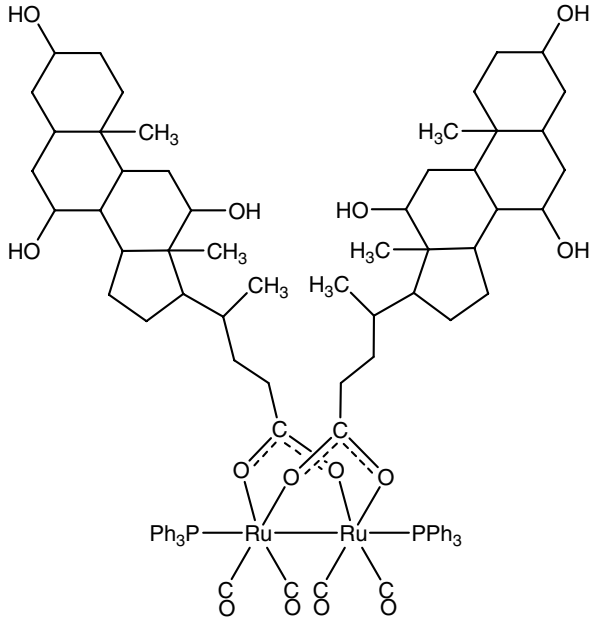


Fig. 3. Lewis representation of the cholic acid derivative $Ru_2(CO)_4(OOC\text{-}C_{23}H_{39}O_3)_2(PPh_3)_2$ (**3**).

purchased either from Aldrich or Fluka, and used as received. NMR spectra were recorded on a Bruker 400 MHz spectrometer. IR spectra were recorded on a Perkin–Elmer 1720X FT-IR spectrometer (4000–400 cm^{-1}). Microanalyses were performed by the Laboratory of Pharmaceutical Chemistry, University of Geneva, Switzerland. Electro-spray mass spectra were obtained in positive-ion mode with an LCQ Finnigan mass spectrometer. Dodecacarbonyltriruthenium [9] was prepared according to published methods.

3.2. General method for the preparation of complexes

A solution of $Ru_3(CO)_{12}$ (200 mg, 0.32 mmol) and the appropriate carboxylic acid (0.94 mmol) in dry tetrahydrofuran (40 ml) was heated at 120 °C in a pressure Schlenk tube for 12 h. Then the solvent was evaporated to give a yellow–brown residue, which was dissolved in tetrahydrofuran, and the triphenylphosphine (0.94 mmol) was added. The solution was stirred at room temperature for 2–3 h, evaporated and the product isolated from the residue by crystallization from a tetrahydrofuran/hexane mixture. In order to improve the purity, the raw product was subjected to a thin-layer chromatography on silica gel using dichloromethane as eluent and obtained as yellow powder.

$Ru_2(CO)_4(OOCC_6H_4\text{-}2\text{-}OCOMe)_2(PPh_3)_2$ (**1**): Yield: 77% (290 mg, 0.24 mmol). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$–7.53 ppm (m, 12H, H_{ar}), 7.46–7.33 (m, 18H, H_{ar}), 7.42 (m, 2H, H_{ar}), 7.03 (dd, 2H, H_{ar}, $J = 1.2$, 8 Hz), 6.91 (td, 2H, H_{ar}, $J = 1.2$, 8 Hz), 6.65 (dd, 2H, H_{ar}, $J = 1.7$, 8 Hz), 1.60 (s, 6H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 205.68$ ppm (4C, CO), 180.74 (2C, COO), 169.50 (2C, $COOCH_3$), 148.74 (2C, C_{ar}), 134.26 (6C, C_{ar}), 134.20 (12C, C_{ar}), 131.77 (2C, C_{ar}), 131.02 (2C, C_{ar}), 129.37 (6C, C_{ar}), 128.71 (12C, C_{ar}), 125.40 (2C, C_{ar}), 122.24 (2C, C_{ar}), 20.43 (2C, CH_3); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): $\delta = 13.03$ ppm; IR (CaF_2, THF): $\nu_{(CO)}$ 2022 vs, 1978 m, 1920 vs, $\nu_{(OCO)}$ 1566 s cm^{-1}; ESI-MS: 1221 $[M+Na]^+$, 959 $[M-PPh_3]^+$. *Anal.* Calc. for $C_{58}H_{44}O_{12}P_2Ru_2$ (1197.05): C, 58.19; H, 3.70. Found: C, 58.27; H, 3.83%.

$Ru_2(CO)_4(OOCCHMe\text{-}C_6H_4\text{-}4\text{-}Bu^i)_2(PPh_3)_2$ (**2**): Yield: 51% (198 mg, 0.16 mmol). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$–7.34 ppm (m, 30H, H_{ar}), 6.89 (d, 4H, H_{ar}, $J = 8$ Hz), 6.75 (d, 4H, H_{ar}, $J = 8$ Hz), 3.27 (q, 2H, CH, $J = 7$ Hz), 2.44 (d, 4H, CH_2, $J = 7$ Hz), 1.85 (m, 2H, CH), 1.02 (d, 6H, CH_3, $J = 7$ Hz), 0.92 (dd, 12H, CH_3, $J = 1.9$, 7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 205.70$ ppm (4C, CO), 189.84 (2C, COO), 140.03 (6C, C_{ar}), 134.24 (12C, C_{ar}), 129.97 (6C, C_{ar}), 129.16 (4C, C_{ar}), 128.59 (12C, C_{ar}), 127.58 (4C, C_{ar}), 47.93 (2C, CH), 45.53 (2C, CH_2), 30.67 (2C, CH), 22.90 (4C, CH_3), 19.38

(2C, CH_3); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): $\delta = 14.56$ ppm; IR (CaF_2, THF): $\nu_{(CO)}$ 2023 vs, 1980 m, 1953 vs, $\nu_{(OCO)}$ 1568 s cm^{-1}; ESI-MS: 1273 $[M+Na]^+$, 1250 $[M+H]^+$, 1223 $[M-4(CO)+2H]^+$. *Anal.* Calc. for $C_{66}H_{64}O_8P_2Ru_2 \cdot H_2O$ (1267.31): C, 62.55; H, 5.25. Found: C, 62.22; H, 5.20%.

$Ru_2(CO)_4(OOCC_{23}H_{39}O_3)_2(PPh_3)_2$ (**3**): Yield 83% (430 mg, 0.26 mmol). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$ ppm (m, 12H), 7.43–7.38 (m, 18H), 3.96 (s, 2H), 3.85 (s, 2H), 3.45 (br, 2H), 2.20 (m, 4H), 2.06–0.92 (m, 50H), 0.90 (s, 6H), 0.85 (d, 6H, $J = 6.4$ Hz), 0.63 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 205.90$ ppm (4C, CO), 189.38 (2C, COO), 134.27 (12C, C_{ar}), 133.76 (6C, C_{ar}), 130.04 (6C, C_{ar}), 128.54 (12C, C_{ar}), 73.55 (2C, CH), 72.42 (2C, CH), 68.98 (2C, CH), 47.73, 46.77, 41.89, 40.15, 40.08, 36.19, 35.76, 35.48, 35.30, 35.05, 32.90, 30.86, 28.55, 28.11, 26.63, 26.03, 23.60 (34 C, CH and C), 23.00 (2C, CH_3), 17.80 (2C, CH_3), 12.95 (2C, CH_3); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): $\delta = 15.30$ ppm; IR (CaF_2, THF): $\nu_{(CO)}$ 2022 vs, 1978 m, 1920 vs, $\nu_{(OCO)}$ 1566 s cm^{-1}; ESI-MS: 1677 $[M+Na]^+$, 1655 $[M+H]^+$; *Anal.* Calc. for $C_{88}H_{108}O_{14}P_2Ru_2$ (1653.88): C, 63.91; H, 6.58. Found: C, 63.51; H, 6.65%.

3.3. X-ray crystallography

The single-crystals of **1** and **2** are obtained by slow diffusion of hexane into a chloroform solution of **1** or by slow diffusion of methanol into a dichloromethane solution of **2**.

X-ray data for **1**; $C_{58}H_{44}O_{12}P_2Ru_2$, $M = 1197.01$ g mol^{-1}, monoclinic, $P2_1/n$ (no. 14), $a = 11.604(1)$, $b = 27.949(1)$, $c = 15.777(1)$ Å, $\beta = 91.62(1)°$, $U = 5114.6(7)$ $Å^3$, $T = 173$ K, $Z = 4$, μ (Mo Kα) = 0.718 mm^{-1}, 9931 reflections measured, 6525 unique ($R_{int} = 0.0485$) which were used in all calculations. The final wR (F^2) was 0.0607 (all data): X-ray data for **2**; $C_{66}H_{64}O_8P_2Ru_2$, $M = 1249.25$ g mol^{-1}, triclinic, $P\bar{1}$ (no. 2), $a = 13.339(2)$, $b = 13.462(2)$, $c = 18.442(2)$ Å, $\alpha = 76.97(1)$, $\beta = 75.04(1)$, $\gamma = 71.67(1)°$, $U = 2999.3(6)$ $Å^3$, $T = 173$ K, $Z = 2$, μ (Mo Kα) = 0.611 mm^{-1}, 10 927 reflections measured, 8809 unique ($R_{int} = 0.0497$) which were used in all calculations. The final wR (F^2) was 0.1032 (all data). In both, the data were measured using a Stoe Image Plate Diffraction system equipped with a ϕ circle goniometer, using Mo Kα graphite monochromated radiation ($\lambda = 0.71073$ Å) with ϕ range 0–200°, increment of 1.2°, $D_{max} - D_{min} = 12.45$–0.81 Å. The structure was solved by direct methods using the program SHELXS-97 [10]. The refinement and all further calculations were carried out using SHELXL-97 [11]. In **2**, the methyl groups of the asymmetric carbons were treated as disordered with partial occupancy factors of 50:50. In all cases, the hydrogen atoms were included in calculated positions and treated as riding atoms using the SHELXL default parameters. All non-H atoms were refined anisotropically, using weighted full-matrix least-square on F^2. Fig. 2 was drawn with ORTEP [12].

Acknowledgements

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Appendix A. Supplementary data

Full tables of atomic parameters, bond lengths and angles are deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, Deposition number: **1** – 293473 and **2** – 293474. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2006.04.015.

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