Facile C−S Bond Activation of Levamisole Hydrochloride on a Triruthenium Cluster Core

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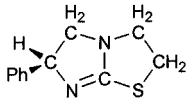
The reaction of $[Ru_3(CO)_{12}]$ with levamisole hydrochloride ([Hlvms]Cl) leads to $[Ru_3(\mu\text{-}Cl)(\mu\text{-}\eta^2\text{-}C_{11}H_{13}N_2S\text{-}C,S)(CO)_9]$ (**1**). This complex contains a new ligand that arises from an unprecedented oxidative addition of an S–C bond of protonated levamisole to a metal atom, and is the first example of a non-mononuclear complex derivative of levamisole. The mechanism of this reaction has been partially elucidated by studying the reaction of $[Ru_3(MeCN)_2(CO)_{10}]$ with [Hlvms]Cl and $[Ru_3(\mu\text{-}Cl)(CO)_{10}]^-$ with [Hlvms][BF_4]. It is concluded that upon treatment with levamisole hydrochloride, $[Ru_3(CO)_{12}]$ is attacked by the chloride anion to give $[Ru_3(\mu\text{-}Cl)(CO)_{10}]^-$; a subsequent coupling of this cluster anion with the $[Hlvms]^+$ cation leads to an uncharacterized neutral derivative which has an intact [Hlvms] group attached to a ruthenium atom through the sulfur atom. This neutral derivative readily undergoes an S–C bond activation process to give compound **1**.

Introduction

Levamisole (lvms), (−)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole, and levamisole hydrochloride ([Hlvms]Cl) are well-known anthelmintic drugs with immunomodulatory[1] and anticancer[2] activities.



levamisole

From the point of view of coordination chemistry, levamisole is an attractive ligand because (a) it possesses three heteroatoms liable to attach metal atoms, (b) it has several C-heteroatom bonds that can be activated or modified by reaction with metal complexes, and (c) due to the presence of a stereogenic carbon atom, it may lead to optically active metal-containing products.

Very few inorganic derivatives of levamisole have been reported so far, the only examples being the complexes $[MCl_2(lvms)_2]$ (M = Co,[3] Ni,[3] Pd,[4] Cu,[3] Zn[3]), [Pd(η^2-amino acidato)$(lvms)_2$]Cl[4] and [PtCl(en)(lvms)]Cl.[5] Interestingly, the zinc complex $[ZnCl_2(lvms)_2]$ is less toxic and has a higher immunomodulating activity than uncomplexed levamisole.[3] In all these coordination compounds, levamisole behaves as a monodentate ligand which binds the metal through the N^7 atom. It is noteworthy that no complexes derived from levamisole hydrochloride and no complexes of nuclearity higher than one derived from any form of levamisole have been reported previously.

The molecular activation of C−S bonds by metal cluster complexes is currently receiving a great deal of attention in relation to hydrodesulfurization processes.[6] In particular, the use of transition metal carbonyl clusters as models for catalyst surfaces is based on the cluster-surface analogy proposed by Muetterties,[7] in which the cluster is viewed as a small fragment of the surface. Although it is realized that the metal atoms of molecular clusters are chemically very different from those of bulk metals, it is believed that the coordination of molecules to clusters and surfaces is similar because they are essentially localized phenomena.[6]

We now report the reactions of some triruthenium carbonyl cluster complexes with levamisole and levamisole hydrochloride, in which a facile C−S bond activation process has been recognized as a key reaction step.

Results and Discussion

The reactions of $[Ru_3(CO)_{12}]$ and $[Ru_3(MeCN)_2(CO)_{10}]$ with levamisole at different temperatures (10−80 °C) led to mixtures of many compounds which could not be satisfact-

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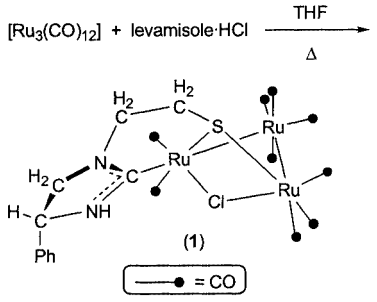
orily separated and identified. However, levamisole hydrochloride reacted smoothly with $[Ru_3(CO)_{12}]$ in THF at reflux temperature to give $[Ru_3(\mu\text{-}Cl)(\mu\text{-}\eta^2\text{-}C_{11}H_{13}N_2S\text{-}C,S)(CO)_9]$ (**1**) in high yield (Scheme 1).



Scheme 1. Synthesis of compound **1**

An X-ray diffraction study on $\mathbf{1}\cdot C_6H_6$ (Figure 1, Table 1) revealed that this compound is a 50-electron cluster with an open edge which is doubly bridged by the chloride ligand and by the sulfur atom of a 1-ethylenethiolate-3,4,5-trihydro-4-phenylimidazol-2-yl ligand. The C^2 atom of the imidazole ring is also attached to one of the ruthenium atoms of the open edge. The original N-*H* proton and the original chirality of levamisole hydrochloride are maintained in compound **1**.

Interestingly, the new organic ligand of complex **1** arises from an unprecedented oxidative addition of an S−C bond of protonated levamisole to a metal atom. Complex **1** is also the first example of a non-mononuclear derivative of levamisole.

In an attempt to shed light on the reaction pathway that leads to compound **1** from $[Ru_3(CO)_{12}]$, we treated the activated complex $[Ru_3(MeCN)_2(CO)_{10}]$[8] with levamisole hydrochloride in dichloromethane, expecting the observation of intermediates that are stable at room temperature. The anionic complex $[Ru_3(\mu\text{-}Cl)(CO)_{10}]^-$ was observed immediately by IR spectroscopy.[9] A spot TLC analysis of the solution also indicated the presence of small amounts of **1**, $[Ru_3(CO)_{12}]$ and a yellow compound that decomposed on the TLC plate after a couple of minutes. Heating this solution to reflux temperature led to compound **1** as the major product. In a subsequent experiment, we treated $[Ru_3(\mu\text{-}Cl)(CO)_{10}]^-$ (formed in situ from $[Ru_3(CO)_{12}]$ and [PPN]Cl)[9] with $[Hlvms][BF_4]$ (made from levamisole and $[HOEt_2][BF_4]$). Again, a mixture of $[Ru_3(CO)_{12}]$, the unknown yellow product and compound **1** was observed *at room temperature*. Unfortunately, all attempts to isolate the yellow compound were unsuccessful, since chromatographic supports promoted its transformation into complex **1**.

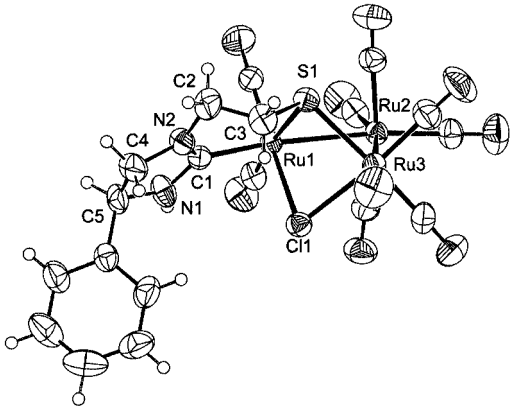


Figure 1. Molecular structure of compound **1**; thermal ellipsoids are drawn at the 50% probability level

Table 1. Selected interatomic distances and angles in $\mathbf{1}\cdot C_6H_6$

Distances (Å)		Angles (°)	
Ru(1)−Ru(2)	2.8788(9)	Ru(1)−Ru(2)−Ru(3)	68.87(3)
Ru(1)−Ru(3)	3.2431(8)	Ru(1)−S(1)−Ru(3)	84.58(6)
Ru(2)−Ru(3)	2.8568(8)	Ru(1)−Cl(1)−Ru(3)	80.91(5)
Ru(1)−S(1)	2.408(1)	Ru(1)−S(1)−C(3)	104.4(2)
Ru(1)−Cl(1)	2.506(1)	Ru(3)−S(1)−C(3)	107.9(2)
Ru(1)−C(1)	2.084(6)	Ru(1)−C(1)−N(1)	121.8(5)
Ru(3)−S(1)	2.411(1)	Ru(1)−C(1)−N(2)	130.3(5)
Ru(3)−Cl(1)	2.493(1)	S(1)−C(3)−C(2)	111.1(5)
S(1)−C(3)	1.826(6)	N(2)−C(2)−C(3)	112.1(6)
N(1)−C(1)	1.351(8)	C(1)−N(2)−C(2)	126.8(5)
N(1)−C(5)	1.460(7)	N(1)−C(1)−N(2)	107.8(5)
N(2)−C(1)	1.304(8)	C(1)−N(1)−C(5)	113.5(5)
N(2)−C(2)	1.464(9)	N(1)−C(5)−C(4)	101.6(5)
N(2)−C(4)	1.463(7)	C(1)−N(2)−C(4)	114.2(5)
C(2)−C(3)	1.49(1)	N(2)−C(2)−C(3)	112.1(6)
C(4)−C(5)	1.53(1)	N(2)−C(4)−C(5)	102.3(5)

The above data suggest that upon treatment with levamisole hydrochloride, $[Ru_3(CO)_{12}]$ is attacked by the chloride anion to give $[Ru_3(\mu\text{-}Cl)(CO)_{10}]^-$. A subsequent coupling of this anion with the $[Hlvms]^+$ cation would lead to a neutral derivative which probably has an intact [Hlvms] group attached to a ruthenium atom through the sulfur atom, but which readily undergoes an S−C bond activation process to give compound **1**. The low solubility of levamisole hydrochloride in THF at room temperature made it necessary to carry out the reaction at reflux temperature and this prevented the observation of intermediates.

Metal cluster-mediated S−C bond activation processes have often been achieved when working with organic sulfur-containing compounds at elevated temperatures.[6] However, such processes have never been observed at room temperature in ruthenium cluster chemistry.[10−14] For comparison purposes, it should be noted that the reaction of $[Ru_3(CO)_{12}]$ with thiophene proceeds via C−S bond cleavage to yield the sulfur-free ferrole-type complex $[Ru_2(\mu\text{-}C_4H_4)(CO)_6]$ and the tetranuclear cluster $[Ru_4(\mu_3\text{-}S)(\mu\text{-}C_4H_4)(CO)_{11}]$.[10] Analogous products were obtained from the reactions with 2-methylthiophene.[10] In the reaction of $[Ru_3(CO)_{12}]$ with benzothiophene, the insertion of a metal atom into the less hindered C−S bond occurs to give the ruthenium analogs of benzoferrole and benzothiaferrole, in addition to the desulfurized ruthenaindenyl complex $[Ru_3(\mu_3\text{-}C_8H_6)(CO)_6]$.[11] Similarly, regiospecific insertion into the less hindered C−S bond occurs in the reaction of $[Ru_3(CO)_{12}]$ with 2,2′-bithiophene, which leads to $[Ru_2(\mu\text{-}C_8H_6S)(CO)_6]$.[12] The sulfide derivatives $[Ru_3(\mu_3\text{-}S)(CO)_{10}]$, $[Ru_3(\mu_3\text{-}S)(\mu\text{-}H)_2(CO)_9]$ and $[Ru_4(\mu_4\text{-}S)(CO)_{11}]$ have been

prepared from $[Ru_3(CO)_{12}]$ and thiophenol.[13] The reaction of $[Ru_3(CO)_{12}]$ with 2-(diphenylphosphanyl)thiophenol gives the phenyl derivative $[Ru_3(\mu_3\text{-}S)(\mu\text{-}C_6H_5)(\mu\text{-}PPh_2)(PPh_3)(CO)_6]$, in which both C−S and C−P bonds have been activated.[14]

Further studies on the synthesis of levamisole-derived metal complexes are underway.

Concluding Remarks

From the above results, the following conclusions can be drawn:

(a) The synthesis of the first non-mononuclear metal complex derivative of levamisole is described (compound **1**). Only a few inorganic derivatives of levamisole have been reported previously,[3−5] some of which have important biological activity as immunomodulatory drugs.[3]

(b) Compound **1** is the first metal complex derivative of levamisole hydrochloride. The chirality of the free ligand is maintained in the metal complex.

(c) Compound **1** arises from a facile S−C bond activation process which opens the thiazolic ring. Such a process is unprecedented for levamisole and its derivatives.

(d) Chemical evidence has been presented that sheds light on the mechanism of the formation of compound **1** from $[Ru_3(CO)_{12}]$ and levamisole hydrochloride. It reveals that the S−C bond activation process also takes place at room temperature. The activation of S−C bonds by ruthenium clusters has never been observed previously at room temperature.

Experimental Section

General Remarks: Solvents were dried over sodium diphenyl ketyl (THF, hydrocarbons) and distilled under nitrogen prior to use. The reactions were carried out under nitrogen, using Schlenk-vacuum line techniques, and were routinely monitored by solution IR spectroscopy (carbonyl stretching region). IR: Perkin−Elmer Paragon 1000 FT. NMR: Bruker DPX-300, room temperature, $SiMe_4$ as internal standard. Microanalyses were obtained from the University of Oviedo Analytical Service. FAB-MS were obtained from the University of Santiago de Compostela Mass Spectroscopic Service; data given refer to the most abundant molecular ion isotopomer.

Compound 1: A mixture of $[Ru_3(CO)_{12}]$ (100 mg, 0.158 mmol) and levamisole hydrochloride (42 mg, 0.173 mmol) in THF (25 mL) was stirred at reflux temperature for 40 min. After cooling down to room temperature, the insoluble excess of levamisole hydrochloride was filtered off. Concentration to ca. 5 mL and addition of hexane (15 mL) led to precipitation of compound **1** as an orange solid (105 mg, 93%). $C_{20}H_{13}ClN_2O_9Ru_3S$ (796.09): calcd. C 30.18, H 1.65, N 3.52; found C 30.26, H 1.71, N 3.42. FAB-MS: *m/z* = 797 [M^+]. IR (CH_2Cl_2): ν(CO) = 2085 (m), 2048 (s), 2003 (vs), 1993 (sh), 1948 (w) cm^{-1}. ^1H NMR (CD_2Cl_2): δ = 7.6−7.2 (m, 5 H), 6.44 (br. s, 1 H), 5.05 (m, 1 H), 4.4−2.9 (m, 6 H) ppm.

X-ray Crystallographic Study: A single crystal of **1**·C_6H_6 was measured on a Nonius CAD4 diffractometer, equipped with a graphite crystal monochromator, using the ω-2θ scan technique with a variable scan rate and a maximum scan time of 60 s per reflection (Table 2). 2648 Friedel pairs were measured. An empirical absorption correction was applied using XABS2,[15] maximum and minimum transmission factors 0.683 and 0.571. Lorentz and polarization corrections were applied and data reduced to F_0^2 values. The structure was solved by Patterson interpretation using DIRDIF-96.[16] Isotropic and full-matrix anisotropic least-squares refinements were carried out using SHELXL-97.[17] All non H-atoms were refined anisotropically. Hydrogen atom positions were geometrically calculated and refined riding on their parent atoms, except for the N-*H* proton, which was observed and freely refined. The molecular plot was made with the EUCLID program package.[18] The WINGX program system[19] was used throughout the structure determination.

Table 2. Crystallographic and refinement data for **1**·C_6H_6

Formula	$C_{20}H_{13}ClN_2O_9Ru_3S{\cdot}C_6H_6$
Molecular weight	874.15
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a [Å]	12.752(6)
b [Å]	13.174(4)
c [Å]	18.334(9)
V [Å^3]	3080.1(19)
Z	4
F(000)	1704
$D_{calcd.}$ [g cm^{-3}]	1.659
λ (radiation) [Å]	0.71073 (Mo-K_α)
Crystal size [mm^3]	0.33 × 0.26 × 0.23
T [K]	293(2)
μ [mm^{-1}]	1.659
Min./max. *h, k, l*	−15/15, −16/16, −22/22
Measured reflns	6776
Unique reflns	6035
Reflns with [$I > 2\sigma(I)$]	5109
Parameters	367
GoF on F^2	1.081
R_1 (on *F*, $I > 2\sigma(I)$]	0.0336
wR_2 (on F^2, all data)	0.0871
Min., max Δρ, [e Å^{-3}]	−0.631, 0.486
Flack parameter	−0.04(5)

CCDC-178931 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

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