Organotin(IV) compounds of 2-thiopyridine. Crystal and molecular structure of dicyclohexyltin(IV) bis(2-pyridylthiolate)

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Abstract

Dicyclohexyltin(IV) bis(2-pyridylthiolate), compound **1**, crystallizes in the orthorhombic system, $a = 16.448(3)$, $b = 40.315(8)$ and $c = 7.113(3)$. Its molecular structure is best described as a tetrahedron, based on the two carbon–tin and the two sulfur–tin bonds, which is however strongly distorted as a consequence of two weak additional nitrogen–tin bonds. Compound **1** and four other diorganotin(IV) bis(2-pyridylthiolates) are characterized by Mössbauer, ^1H, ^{13}C and ^{119}Sn NMR spectroscopy, and by FAB mass spectrometry. Their *in vitro* antitumour activity against two human tumour cell lines, MCF-7 and WiDr is reported. The ID_{50} values found are comparable to those found for *cis*-platin, but deceptively higher than for many other diorganotin compounds.

Introduction

Many diorganotin(IV) compounds have already been prepared, characterized and tested *in vitro* against human tumour cell lines [1]. They exhibit prescreening activities which are sometimes much better than those of *cis*-platin [2]. Most of them possess one or more tin–oxygen bonds that can be easily hydrolyzed. This gives rise to intermediates that are believed to link as R_2Sn^{2+} moieties to biocellular macromolecules like DNA [3]. This work aims to provide some indirect support to this hypothesis. We prepared five compounds which do not contain any Sn–O bonds but rather Sn–S bonds. As previously [2], the compounds synthesized contain nitrogen atoms that can give rise to additional intramolecular coordination towards tin, a feature common to several compounds shown previously to be active [1]. The ligand chosen for this purpose is L = 2-pyridylthiolate and the compounds described are all of the type $RR'SnL_2$.

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Results and discussion

Crystal structure of (cyclo-$C_6H_{11})_2Sn(S\text{-}C_5NH_4)_2$ (1)

Compound **1** crystallizes in the orthorhombic space group *Fdd*2, $a = 16.448(3)$, $b = 40.315(8)$ and $c = 7.113(3)$. The molecular structure and the numbering used are shown in Fig. 1. Selected interatomic distances and bond angles are given in Table 1. The structure consists of discrete monomeric molecules with crystallographic $C2$ symmetry, the tin atom lying on the two-fold axis. The tin atom is bonded to the two cyclohexyl groups and to the two sulfur atoms of the two ligands in a distorted tetrahedral geometry. There are two additional weak coordinative Sn–N bonds which are significantly shorter than the sum of the van der Waals radii of these atoms. The Sn–N bond (2.72 Å) is slightly shorter than that reported [4] for n-$Bu_2Sn(2\text{-}S\text{-}C_5H_3N\text{-}5\text{-}NO_2)_2$, and the Sn–S bond (2.50 Å), slightly longer. The length of the Sn–S bond is however quite comparable to those found in organotin derivatives of dithiocarbamates [5]. Bond lengths and angles around the tin atom in compound **1** and in similar derivatives are compared in Table 2.

Compound **1** is best described as a tetrahedron, based on the two carbon and the two sulfur atoms strongly bound to tin, which is distorted because of the additional

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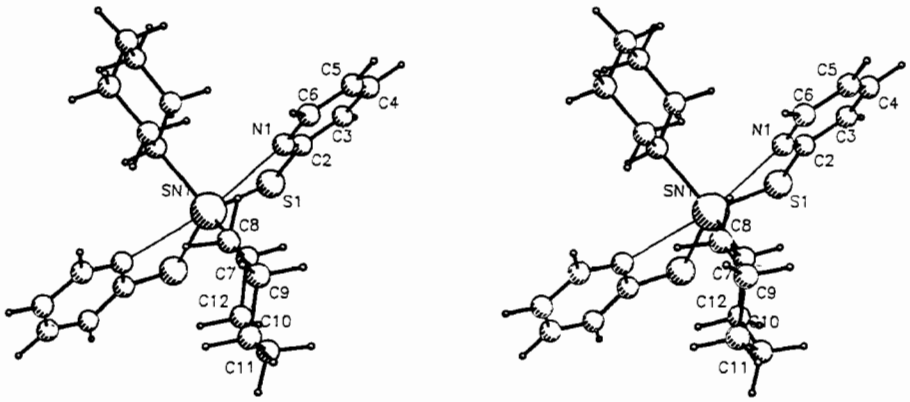


Fig. 1. Molecular structure and numbering scheme of (*cyclo*-$C_6H_{11})_2Sn(S\text{-}C_5NH_4)_2$ (**1**).

TABLE 1. Selected bond lengths (Å) and angles (°) in (*cyclo*-$C_6H_{11})_2Sn(S\text{-}C_5NH_4)_2$, (**1**)*

Around tin			
Sn–S	2.503(2)	S–Sn–S	91.4(2)
Sn–N	2.721(6)	S–Sn–C(7)	109.5(2)
Sn–C(7)	2.200(6)		
N–Sn–S	60.7(2)	N–Sn–S*	151.5(2)
N–Sn–C(7)	79.5(3)	N–Sn–C(7)*	86.2(3)
C(2)–S–Sn	90.7(2)	C(8)–C(7)–Sn	109.9(5)
C(12)–C(7)–Sn	112.6(4)	C(7)*–Sn–S	106.9(2)
C(7)*–Sn–C(7)	126.9(3)	N–Sn–N*	147.6(3)
2-Pyridinethiolate ligand			
C(2)–S	1.769(6)	C(6)–N–C(2)	118.6(5)
C(2)–N	1.339(7)	N–C(2)–S	116.1(4)
C(6)–N	1.339(9)	C(3)–C(2)–S	122.0(5)
C(2)–C(3)	1.394(7)	C(3)–C(2)–N	121.8(5)
C(4)–C(3)	1.376(11)	C(4)–C(3)–C(2)	118.7(6)
C(4)–C(5)	1.382(11)	C(5)–C(4)–C(3)	119.6(6)
C(6)–C(5)	1.374(9)	C(6)–C(5)–C(4)	118.4(7)
		C(5)–C(6)–N	122.9(7)
Cyclohexyl group			
C(8)–C(7)	1.517(7)	C(12)–C(7)–C(8)	112.9(6)
C(12)–C(7)	1.520(8)	C(9)–C(8)–C(7)	110.1(6)
C(8)–C(9)	1.532(8)	C(10)–C(9)–C(8)	111.5(6)
C(10)–C(9)	1.495(12)	C(11)–C(10)–C(9)	111.0(7)
C(10)–C(11)	1.525(12)	C(12)–C(11)–C(10)	111.9(8)
C(12)–C(11)	1.517(10)	C(11)–C(12)–C(7)	111.3(6)

*An asterisk denotes an atom related by the crystallographic two-fold axis.

presence of the two weak tin–nitrogen coordination bonds. Alternatively the structure might be viewed as a very distorted octahedron with the largest deviation from the ideal values for the C–Sn–C and N–Sn–N angles, or even better as a skew trapezoidal bipyramid in which the equatorial plane is formed by the succession of S, S, N and N atoms. The long vertex of the trapeze is constituted by the two nitrogen atoms, the short one by the two sulfur atoms (see Fig. 2). The apical positions are therefore occupied by the two carbon atoms.

Syntheses of compounds 1–5

Besides compound **1**, (*cyclo*-$C_6H_{11})_2Sn(H_4NC_5\text{-}2\text{-}S)_2$, a series of four other related diorganotin derivatives $RR'Sn(H_4NC_5\text{-}2\text{-}S)_2$, **2–5**, were synthesized by reacting the suitable diorganotin oxide with 2-thiopyridine in toluene/ethanol 4/1 [9].

The yields obtained, the melting points of these compounds and the recrystallization solvents used are given in Table 3.

Mössbauer parameters of compounds 1–5

The Mössbauer parameters of compounds **1–5** are given in Table 4. The *QS* values of compounds **1–3** confirm the solid state geometry evidenced by X-ray diffraction, since they are intermediate between the typical values of tetrahedral geometries (1.7–2.2 mm/s) and those of octahedral ones (3.5–4.2 mm/s).

^1H NMR spectra of compounds 1–5

The proton NMR spectra of compounds **1–5** are described in Table 5. The complexity of the cyclohexyl resonances only allowed a partial assignment. In contrast, the resonances of the aromatic protons exhibit patterns allowing an easy assignment based on the *ortho*-J_{23} coupling constant of 5 Hz characteristic for pyridine rings [2i].

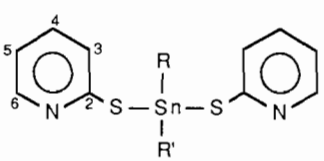


TABLE 2. Structural data of some diorganotin bis-chelates

$R_2Sn(chelate)_2$[a]	R–Sn–R angle (°)	Angle in chelate cycle	Sn–C (Å)	Sn–X (Å)	Reference
$Me_2Sn(acac)_2$	180	86	2.14	2.18; 2.20	6
$Me_2Sn(oxin)_2$	110.7	73.4	2.15	2.10; 2.11 (X=O)	7
		73.7	2.17	2.31; 2.38 (X=N)	
$Me_2Sn(2\text{-}S\text{-}C_5H_4N\text{-}1\text{-}O)_2$	138.9	72.0	2.11	2.54; 2.57 (X=S)	8
		73.5	2.13	2.36; 2.41 (X=O)	
$n\text{-}Bu_2Sn(2\text{-}S\text{-}C_5H_3N\text{-}5\text{-}NO_2)_2$	129.2	59.5	2.16	2.48 (X=S)	4
				2.77 (X=N)	
$(cyhex)_2Sn(2\text{-}S\text{-}C_5H_4N)_2$	126.9	60.7	2.20	2.50 (X=S)	this work
				2.72 (X=N)	

[a]acac: acetylacetonate; oxin: oxinate.

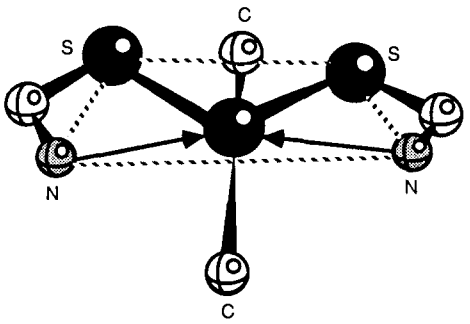


Fig. 2. Coordination sphere around tin in $(cyclo\text{-}C_6H_{11})_2Sn(S\text{-}C_5NH_4)_2$ (**1**).

TABLE 3. Recrystallization solvents, yields and melting points of compounds **1–5**

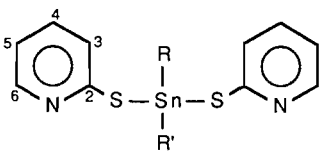
Compound	RR'	Recrystallization solvent	Yield (%)	Melting point (°C)
1	cy-Hex_2	hexane	70	156–157
2	n-Bu_2	toluene	74	37–38
3	Et_2	$CHCl_3$ + hexane	90	119–120
4	EtPh	$CHCl_3$ + hexane	75	126–127
5	Ph_2	$CHCl_3$ + hexane	77	171–172

TABLE 4. Mössbauer parameters (isomer shift (*IS*), quadrupole splitting (*QS*) and band widths (Γ_1 and Γ_2) of a series of diorganotin compounds of 2-thiopyridine, $RR'Sn(2\text{-}S\text{-}C_5NH_4)_2$, compounds **1–5**

Compound	RR'	*IS*	*QS*	Γ_1	Γ_2
1	cy-Hex_2	1.64	2.84	0.90	0.94
2	n-Bu_2	1.53	2.89	0.86	0.90
3	Et_2	1.52	2.87	1.11	1.15
4	EtPh	1.42	2.59	1.01	1.06
5	Ph_2	1.32	2.30	0.78	0.92

^{13}C NMR spectra of compounds 1–5

The ^{13}C NMR spectra (solvent $CDCl_3$) of the compounds are described in Table 6. The assignment has been done on the basis of the DEPT spectra and of the chemical shift increments of substituents on aromatic rings [11]. From the ^1J(C–Sn) coupling constant observed for compound **2**, an angle of $130 \pm 10°$ can be calculated from the relationship established for di-n-butyltin compounds [12]. This value is close to the angle observed in the solid state for compound **1** (126.9°) and to those observed (129.2°) and calculated (127°) for the 5-nitro analog [4].



^{119}Sn NMR spectra of compounds 1–5

The ^{119}Sn chemical shifts of compounds **1–5** are given in Table 7. They are comparable to those of diorganotin dicarboxylates [2] and characteristic for geometries intermediate between distorted tetrahedral and octahedral ones. Hence, the solution structure of compounds **1–5** is likely to be the same as in the solid state of **1**, basically a distorted tetrahedron based on the Sn–C and Sn–S bonds, with two additional weaker Sn–N bonds.

FAB mass spectra of compounds 1–5

The FAB mass spectra of compounds **1–5** are described in Table 8. The molecular ion is visible for three of the five compounds. A fragmentation pattern compatible with literature data [13] is proposed in Fig. 3.

TABLE 5. ^1H chemical shifts in ppm with respect to TMS as internal reference characterizing compounds **1–5**, with multiplicities and coupling constants in Hz between parentheses (solvent $CDCl_3$)

H	**1**, cyclo-Hex_2Sn	**2**, Bu_2Sn	**3**, Et_2Sn	**4**, EtPhSn	**5**, Ph_2Sn
CH_3		0.81 (t, 7)	1.35 (t, 8) ^3J(Sn–H) = 138/132	1.38 (t, 8) ^3J(Sn–H) = 152/145	
CH_2	1.07–1.65(m)[a]	1.27–1.40(m)			
CH_2	1.07–1.65(m)[a]	1.57–1.70(m)			
CH_2Sn		1.57–1.70(m) ^2J(Sn–H) ≈ 70	1.66 (q, 8) ^2J(Sn–H) = 68/65	1.81 (q, 8) ^2J(Sn–H) = 75/72	
CHSn	2.01 (tt, 13,3)				
o-C_6H_5				7.59–7.93(m) ^3J(Sn–H) ≈ 86	7.62–7.95(m) ^3J(Sn–H) ≈ 84
m and *p*-C_6H_5				7.30–7.36(m)	7.26–7.33(m)
3-H	7.33 (bd, 7)	7.31 (dd, 7,1)	7.36 (dd, 8,1)	7.35 (d, 8)	7.35–7.40(m)
4-H	7.46 (ddd, 7,7,2)	7.44 (ddd, 7,7,2)	7.49 (ddd, 8,8,1)	7.41 (ddd, 8,8,1)	7.35–7.40(m)
5-H	6.96 (ddd, 7,5,1)	6.92 (ddd, 7,5,1)	6.97 (ddd, 8,5,1)	6.84 (ddd, 8,5,1)	6.79 (ddd, 8,5,1)
6-H	8.22 (bd, 5)	8.11 (d, 5)	8.18 (dd, 5,1)	7.98 (b)	8.10 (d, 5)

b: broad; d: doublet; m: complex pattern; q: quartet; t: triplet. [a]The signal of the β-axial protons is seen as a doublet (13) at 2.18 ppm [10].

TABLE 6. ^{13}C chemical shifts in ppm with respect to TMS as external reference and coupling constants in Hz of compounds **1–5**. Calculated values based on the aromatic increment of the SH group are given between parentheses

C	**1**, cyclo-Hex_2Sn	**2**, Bu_2Sn	**3**, Et_2Sn	**4**, EtPhSn	**5**, Ph_2Sn
CH_3 or CH_2	26.7	13.6	10.8 ^2J(C–Sn) = 41	10.5 ^2J(C–Sn) = 40	
CH_2	28.9 ^3J(C–Sn) = 103	26.4 ^3J(C–Sn) = 102			
CH_2	30.9 ^2J(C–Sn) = 27	28.3 ^2J(C–Sn) = 34			
CH_2Sn or CHSn	44.6 ^1J(C–Sn) = 543/516	26.6 ^1J(C–Sn) = 558/534	19.5 ^1J(C–Sn) = 580/555	20.0 ^1J(C–Sn) = 652/624	
i-C_6H_5				145.9	148.6
o-C_6H_5				134.7 ^2J(C–Sn) = 53	134.8 ^2J(C–Sn) = 60
m-C_6H_5				128.2 ^3J(C–Sn) = 73	128.7 ^3J(C–Sn) = 79
p-C_6H_5				128.6	129.3 ^4J(C–Sn) = 20
C-2 (151.8)	164.6	164.0	164.5	165.2	164.9
C-3 (124.9)	124.8	124.7	125.0	125.7	124.4
C-4 (136.5)	136.6	136.7	137.2	137.1	138.3
C-5 (121.0)	117.7	117.8	118.3	117.4	118.4
C-6 (149.9)	146.6	146.6	147.0	144.9	144.9

^1J(C–Sn): resolved $^1J(^{13}C–^{119}Sn)$ and $^1J(^{13}C–^{117}Sn)$ couplings; ^2J(C–Sn) and ^3J(C–Sn): unresolved $^2J(^{13}C–^{119/117}Sn)$ and $^3J(^{13}C–^{119/117}Sn)$ couplings.

TABLE 7. ^{119}Sn chemical shifts in ppm with respect to tetramethyltin as external reference characterizing compounds **1** to **5** (solvent $CDCl_3$)

	1, cyclo-Hex_2Sn	**2**, Bu_2Sn	**3**, Et_2Sn	**4**, EtPhSn	**5**, Ph_2Sn
δ	−160.5	−121.2	−116.0	−186.1	−296.6

In vitro antitumour activities of compounds 2–5

The *in vitro* activities of compounds **2–5**, expressed as ID_{50} values against two human tumour cell lines, MCF-7, a mammary tumour, and WiDr, a colon carcinoma, are given in Table 9. They are compared to the ID_{50} values obtained for some reference compounds [14]. All the activities are rather poor. They are in general significantly lower than those of compounds with ligands giving rise to Sn–O bonds, from carboxylates for instance. We attribute this lower activity to the more covalent character of the Sn–S bond with respect to the Sn–O bond. This should result in a lower sensitivity of the present diorganotin bis(2-pyridylthiolates) to easy hydrolysis, a well-known prerequisite to any reasonable

TABLE 8. Fragment-ions observed in the FAB mass spectra of compounds 1–5

Fragment-ion	Compound, R, R'				
	1, cy-Hex$_2$	2, Bu$_2$	3, Et$_2$	4, EtPh[a]	5, Ph$_2$
RR'Sn(2-S-C_5NH_4)$_2$H$^+$		1	9	2	
RSn(2-S-C_5NH_4)$_2^+$	82	13	11	10	9
R'Sn(2-S-C_5NH_4)$_2^+$	82	13	11	9	9
RR'Sn(2-S-C_5NH_4)$^+$	21	100	100	100	62
(2-S-C_5NH_4)Sn$^+$	100	52	55	100	100
RSn$^+$					27
HSn$^+$		2			
Sn$^{\cdot+}$	28	1			11

[a]A fragment-ion corresponding to Et$_2$Sn(2-S-C_5NH_4)$^+$ was also observed (6%).

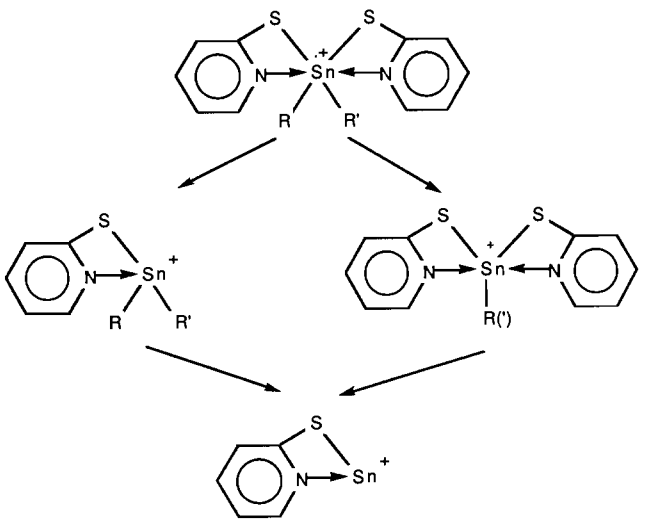


Fig. 3. Fragmentation scheme proposed for compounds 1–5.

TABLE 9. ID_{50} values in ng/ml against two human tumour cell lines, MCF-7 and WiDr, of compounds 2–5 and of some reference compounds

Compound	MCF-7	WiDr
2	334	1290
3	501	1143
4	299	928
5	292	1182
Doxorubicin [14]	63	31
Cis-platin [14]	850	624
Etoposide [14]	187	624
Mitomycin C [14]	3	17

antitumour activity, as demonstrated for *cis*-platin [15] and recently suggested for tin compounds [3].

Experimental

X-ray diffraction analysis of compound 1

Data collection and structure refinement parameters are given in Table 10 and atomic coordinates in Table 11. See also 'Supplementary material'.

TABLE 10. Data collection at 21 °C and structure refinement parameters obtained for compound 1

Formula unit	$C_{22}H_{30}N_2S_2Sn$
Crystal shape: colourless prism	0.3×0.1×0.1 mm
No.; 2θ range of reflections for lattice parameters (°)	20; 3–28
Orthorhombic space group	*Fdd*2
Unit cell	
a (Å)	16.448(3)
b (Å)	40.315(8)
c (Å)	7.113(3)
V (Å^3)	4716.6(21)
Z	8
D_{calc} (g cm^{-3})	1.423
μ(Mo Kα) (cm^{-1})	11.61
λ(Mo Kα) (Å)	0.71069
Monochromator	graphite
$2\theta_{max}$ (Å)	49
ω–2θ (scan width, deg)	1.2
Index range (h, k, l)	$0 \leqslant h \leqslant 19$, $0 \leqslant k \leqslant 45$, $0 \leqslant l \leqslant 8$
Independent reflections	
measured	1097
observed ($I > 2.5\sigma$)	990
No absorption correction	
Method used to solve structure	direct methods (SHELX86) [16]
Refinement using *F*	Anisotropic least-squares (SHELX76) [17]
Some hydrogen atoms were revealed in the difference map. However all H atoms were placed in fixed idealized positions riding on carbon for the final cycles of refinement	
Weighting scheme	$w = (\sigma^2 + gF^2)^{-1}$, $g = 0.00172$
Value of R, R_w, S	0.023, 0.025, 0.697
Max height in final ΔF-map (e Å^{-3})	0.37
Final (Δ/σ) max.	0.04
No intermolecular interactions exceeding van der Waals forces	

Equipment

The Mössbauer spectra were recorded as described previously [2]. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 270 instrument at 270.13

TABLE 11. Atomic coordinates ($\times 10^5$ for Sn, 10^4 for the other atoms) of (*cyclo*-$C_6H_{11})_2Sn(S\text{-}C_5NH_4)_2$ (**1**) with e.s.d.s in parentheses

	x/a	*y/b*	*z/c*
SN1	0(0)	0(0)	5000(0)
S1	311(1)	426(0)	2543(3)
N1	605(3)	599(1)	6068(7)
C2	626(4)	710(1)	4294(8)
C3	907(4)	1027(1)	3850(10)
C4	1188(5)	1226(1)	5278(15)
C5	1174(5)	1111(2)	7108(11)
C6	870(4)	799(1)	7441(12)
C7	1134(3)	−155(2)	6383(9)
C8	1017(4)	−162(2)	8497(9)
C9	1808(4)	−266(2)	9468(10)
C10	2105(5)	−594(2)	8762(14)
C11	2228(5)	−586(2)	6637(14)
C12	1462(4)	−480(2)	5610(10)
H3	904(4)	1114(1)	2414(10)
H4	1418(5)	1471(1)	4971(15)
H5	1397(5)	1263(2)	8249(11)
H6	844(4)	711(1)	8874(12)
H7	1481(3)	25(2)	6057(9)
H8	843(4)	82(2)	8977(9)
H8′	543(4)	−337(2)	8845(9)
H9	1703(4)	−283(2)	10963(10)
H9′	2267(4)	−80(2)	9198(10)
H10	2676(5)	−652(2)	9433(14)
H10′	1662(5)	−782(2)	9105(14)
H11	2397(5)	−831(2)	6168(14)
H11′	2709(5)	−414(2)	6310(14)
H12	1600(4)	−449(2)	4136(10)
H12′	1005(4)	−671(2)	5775(10)

and 67.93 MHz, respectively. The ^{119}Sn NMR spectra were obtained from a Bruker WM 500 instrument at 186.5 MHz. The mass spectra were recorded on a V.G. Micromass 7070 F instrument (source temperature 200 °C). The structure determination was done with a Huber automated four-circle diffractometer, data collection at 21 °C.

Supplementary material

Lists of thermal parameters, structure factors, and complete tables of bond lengths and angles are available from author J.M.-P.

Acknowledgements

We thank Mr A. Verwee for recording the ^1H and ^{13}C NMR spectra, Dr B. Mahieu, for the Mössbauer spectra, and Mr M. Desmet for the mass spectra. We are grateful to Dr D. de Vos and Dr P. Lelieveld who performed the *in vitro* tests. Financial support from the Belgian Nationaal Fonds voor Wetenschappelijk Onderzoek, N.F.W.O. (grant number FKFO 20127.90) (M.G.; R.W.) and from the Ministère de l'Education Nationale du Maroc (M. Bouâlam) is gratefully acknowledged.

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