Modes of Xanthine Complexation to Dirhodium Tetrakis[(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetate] in Solution and in the Solid State

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Rhodium Complexes, Xanthines

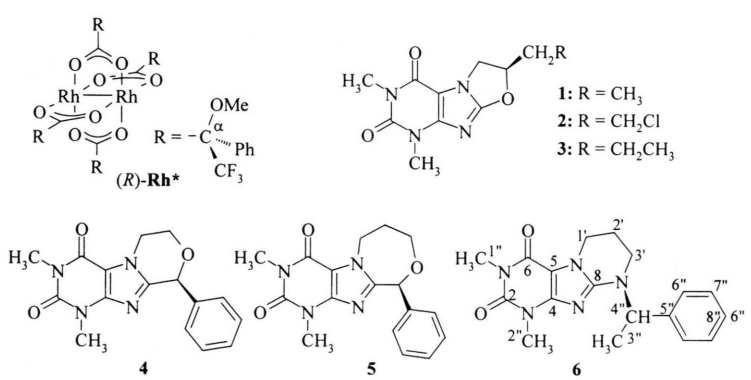
It is shown by IR and NMR studies that the xanthines **1–5** prefer a side-on complexation to the chiral dirhodium tetrakis[(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate] (**Rh***) in solution whereas carbonyl groups are involved in the solid state. For **6**, at least the carbonyl group C-6 contributes to complexation in solution as well. Alternating strands of **6** and **Rh*** exist in the solid state as revealed by X-ray diffraction analysis described in detail. The determination of enantiomeric excess of the chiral xanthine **6** can easily be accomplished by the "dirhodium method" (^{1}H and ^{13}C NMR in the presence of **Rh***).

Introduction

For a couple of years we have been interested in the potential of the chiral dirhodium complex **Rh*** (dirhodium tetrakis[(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate]; $Rh_2(MTPA)_4$, MTPA ≡ Mosher acid) as an NMR auxiliary for the determination of enantiomeric purity [1], especially in cases where the investigated substrate molecules contain only functional groups which do not respond properly to chiral lanthanide shift reagents. Very recently, we reported on the extension of this method to polyfunctional xanthines **1–5** [2] (Scheme 1) where we noticed an intriguing difference in the binding modes in solution and in the solid state. In order to shed more light on this seemingly contradictory results we extended our NMR investigation to compound **6** (Scheme 1; it is compound **7** in ref. [2]) and investigated the IR spectra of all xanthines **1–6** in the absence and presence of **Rh*** and in the two aggregation states ($CDCl_3$ solution and solid state).

Results and Discussion

Investigating the xanthines **1–5** (as racemates or non-racemic mixtures) by NMR in the absence and presence of enantiomerically pure (*R*)-**Rh*** we came to the conclusion that side-on complexation of the imidazole unit (Scheme 2) should prevail



Scheme 1. Structures of **Rh*** and of xanthine derivatives **1–6**.

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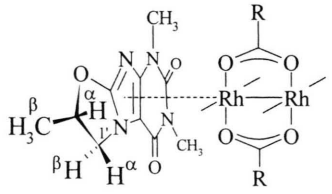
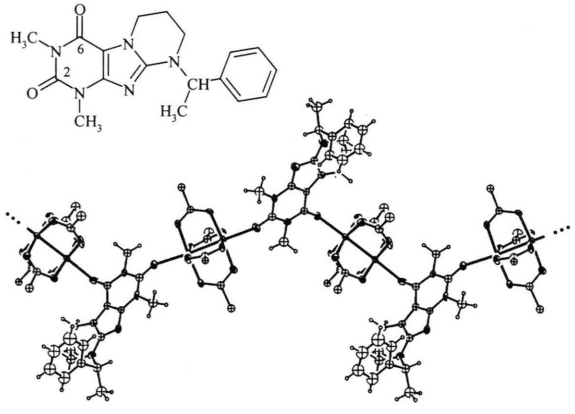


Scheme 2. Side-on complexation of **1** to **Rh*** (only two acylate residues depicted) [2].

because a clear side differentiation of diastereotopic methylene protons (seen from dispersion effects $\Delta\nu$) is apparent [2]. Moreover, no ^1H and ^{13}C signal reveals a clear complexation (seen from paramagnetic complexation shifts $\Delta\delta$) for any particular atom.

In contrast, an X-ray investigation showed alternating strands of **Rh*** and of **6** molecules in the crystal where each **Rh*** molecule complexes carbonyl oxygens of the same position in two different xanthine ligands; *i.e.*, one binds to the C-2 carbonyls on both rhodium atoms whereas the next binds to two C-6 carbonyl groups (see Scheme 3). Further details of the X-ray study are given in the Experimental Part.



Scheme 3. Section of a strand of **Rh*** and **6** as determined by X-ray diffraction; for better visibility all Mosher acid residues are represented by the C-α atom only. The structure of **6** is inserted for better comparability.

In order to find out whether this is indeed a contradiction we decided to extend the NMR spectral investigation to **6** using a non-racemic mixture (*S*/*R* = 2:1, prepared by mixing appropriate amounts of the pure enantiomers) and to compare the data with those of **1–5**. The ^1H and ^{13}C chemical shifts of **6** are collected in Table I. The assignment methods (using 1D- and 2D-correlation experiments) have been described before [2] as well as the definition of the complexation shifts $\Delta\delta$ (in ppm) as the signal displacements due to the addition of an equimolar amount of **Rh*** and of the dispersion effects $\Delta\nu$ (in Hz) as signal splittings due to the existence of diastereomeric **Rh*** ··· xanthine complexes.

An inspection of the NMR data showed that the complexation mode of **6** indeed differs from that of **1–5** to some extent. Whereas the latter showed no significant C=O complexation in solution ($\Delta\delta$-values of <1 ppm for C-2 and 0–2 ppm for C-6 [2]) there is a moderate deshielding of C-6 in **6** ($\Delta\delta$ = 2.41). On the other hand, clear side differentiation can be identified as well; very different dispersions appear within the pairs of diastereomeric protons at C-1′ and at C-3′ (Table I). These experimental evidences suggest the following interpretation: in contrast to **1–5**, a solution equilibrium exists for **6** in which the C-6 carbonyl group competes with side-on complexation to some extent. A C-2 carbonyl complexation cannot be identified safely.

It should be noted that the enantiomeric excess of **6** can easily be monitored from the dispersion of the ^1H NMR signals of H-2″, H-3″ and H-4″ (2.9, 2.2 and 6.3 Hz, respectively) caused by the existence of diastereomeric complexes in the presence of **Rh***, *i.e.*, our "dirhodium method" for chiral recognition is again successful.

In order to get a closer insight into the various complexation modes in solution and in the solid state we decided to inspect the IR bands of all xanthines **1–6** in the absence and presence of (*R*)-**Rh*** and in both aggregation states (Table II).

The assignment of the pertinent IR bands has been performed on the basis of IR data reported in the literature for a series of structurally very similar xanthines [3]. Thus, the carbonyl band with the larger wavenumbers ($\tilde{\nu}$ = 1693–1706 cm^{-1}) corresponds to C-2 whereas the other one ($\tilde{\nu}$ = 1649–1658 cm^{-1}) can be assigned to C-6. It should be noted that a further band appears in close vicinity at $\tilde{\nu}$ = 1600–1610 cm^{-1} which originates from C=C and/or C=N vibrations [3].

As can been seen from Table II, both carbonyl bands in the pure substrates are hardly affected in their wavenumbers by the transition from the liquid to the solid phase (compare Fig. 1 and Ta-

Table I. ^{1}H and ^{13}C chemical shifts δ (in ppm), complexation shifts $\Delta\delta$ (in ppm), and dispersions (in Hz) of **6**. For experimental details and the methods of signal assignments see ref. [2].

	δ [ppm] pure sample	δ [ppm] in presence of **Rh***		$\Delta\delta$ [ppm] in the presence of **Rh***		$\Delta\nu$ [Hz]
		S	*R*	*S*	*R*	
H-1′qe	4.238 ddd	4.294	4.273	+0.06	+0.03	10.6
H-1′qa	4.136 ddd	4.167	4.167	+0.03	+0.03	0–1
H-2′	ca 2.04 m ca 1.98 m	ca 1.80[a]		ca −0.2[a]		n.d.[b]
H-3′qe	2.961 ddd	2.849	2.813	−0.11	−0.15	17.7
H-3′qa	3.214 ddd	3.067	overlap	−0.15	n.d.[b]	0–1 or 8–9[c]
H-1″	3.374 s	3.551	3.544	+0.18	+0.17	3.7
H-2″	3.537 s	3.582	3.587	+0.04	+0.05	2.9
H-3″	1.614 d	1.589	1.584	−0.03	−0.03	2.2
H-4″	5.869 q	5.859	5.873	+0.02	0	6.9
H-6″	7.355 dm	ca 7.34		−0.02		n.d.[b]
H-7″	7.355 dm	ca 7.34		−0.02		n.d.[b]
H-8″	7.295 m	n.d.[b]		n.d.[b]		n.d.[b]
C-2	151.99	152.26	152.23	+0.27	+0.24	3.4
C-4	149.06	150.42	150.45	+1.36	+1.39	3.1
C-5	102.99	104.63		+1.64		0
C-6	153.88	156.29 br[d]		+2.41		n.d.[b]
C-8	151.79	152.50	152.52	+0.71	+0.73	1.9
C-1′	41.77	41.83	41.82	+0.06	+0.05	1.7
C-2′	21.36	20.94	20.90	−0.42	−0.46	4.6
C-3′	38.34	38.29	38.22	−0.05	−0.12	8.9
C-1″	27.58	28.53		+0.95		0
C-2″	29.72	30.05	30.06	+0.33	+0.34	0–1
C-3″	15.69	15.78	15.65	+0.09	−0.04	17.0
C-4″	54.04	54.15	54.10	+0.11	+0.06	5.5
C-5″	140.03	139.97	139.94	−0.06	−0.09	4.1
C-6″	127.18	127.14	127.16	−0.04	−0.02	2.2
C-7″	128.59	128.58	128.60	−0.01	+0.01	1.7
C-8″	127.66	127.64		−0.02		0–1

[a] Not resolvable; [b] n.d.: not detectable due to signal complexity; [c] due to signal overlap it cannot be decided safely whether $\Delta\nu$ is either 0–1 or 8–9 Hz; [d] broadened signal.

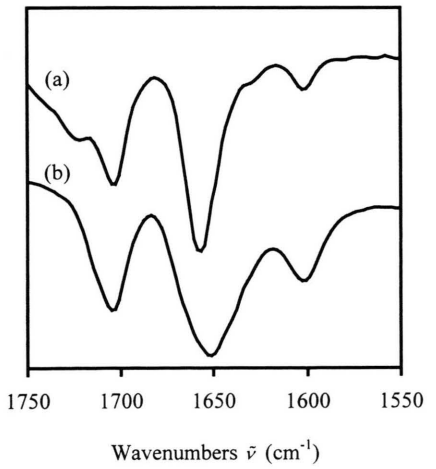


Fig. 1. Sections of the IR spectra of **1**, (a) in $CDCl_3$ solution, (b) in the solid state.

ble II, column III) so that any significant effect in the presence of **Rh*** has to be attributed to complexation. However, the corresponding data of the xanthine-**Rh*** complexes (Table II, column III) are significantly higher, particularly for the C-6 carbonyl indicating a difference of the binding modes in the two aggregation states. Conversely, if band shifts originated by complexation are calculated (Table II, columns IV and V) it turns out that, in the case of the substrates **1–5**, the complexation shifts in solution (Table II, column IV) are close to zero so that we have to assume that no significant complexation at any of the two C=O occurs here. This is different for **6** (Fig. 2, top) where the band shifts are significantly larger (−4 for C-2 and −11 cm^{-1} for C-6). Here, some C=O complexation – particularly at C-6 – exists, a fact which has already been noticed from the NMR spectral eval-

Table II. IR wavenumbers $\tilde{\nu}$ (section between 1550 and 1750 cm^{-1}) of **1–6** in the absence and presence of **Rh***, each in $CDCl_3$ solution and in the solid state.

			$\tilde{\nu}$			$\Delta\tilde{\nu}$:	
			Solution (Column I)	Solid state (Column II)	Solution → solid state (Column III)	Soluation (Column IV)	Solid state (Column V)
1	C-2	pure	1704 (m)	1704 (m)	0		
	C-2	+**Rh***	1704 (m)	1697 (m)	−7	0	−7
	C-6	pure	1657 (s)	1652 (s)	−5		
	C-6	+**Rh***	1659 (s)	1638 (w)	−21	+2	−14
2	C-2	pure	1706 (m)	1703 (m)	−3		
	C-2	+**Rh***	1706 (m)	1698 (m)	−8	0	−5
	C-6	pure	1658 (s)	1650 (s)	−8		
	C-6	+**Rh***	1660 (s)	1638 (w)	−22	+2	−12
3	C-2	pure	1704 (m)	1704 (m)	0		
	C-2	+**Rh***	1704 (m)	1701 (m)	−3	0	−3
	C-6	pure	1656 (s)	1651 (s)	−5		
	C-6	+**Rh***	1658 (s)	1640 (s)	−18	+2	−11
4	C-2	pure	1703 (m)	1699 (s)	−4		
	C-2	+**Rh***	1703 (m)	1702 (m)	−1	0	+3
	C-6	pure	1658 (s)	1650 (s)	−8		
	C-6	+**Rh***	1657 (m)	1633 (w)	−24	−1	−17
5	C-2	pure	1701 (m)	1707 (m)	+6		
	C-2	+**Rh***	1700 (m)	1698 (m)	−2	−1	−9
	C-6	pure	1656 (s)	1650 (s)	−6		
	C-6	+**Rh***	1655 (m)	1647 (w)	−8	−1	−3
6	C-2	pure	1693 (m)	1695 (m)	+2		
	C-2	+**Rh***	1689 (m)	1671 (w)	−18	−4	−24
	C-6	pure	1649 (s)	1644 (s)	−5		
	C-6	+**Rh***	1638 (m)	1635 (w)	−3	−11	−11

uation (see above). Finally, an inspection of the complexation shifts in the solid state (Table II, column V) shows large and significant values for all compounds (compare Fig. 2, bottom) which is in agreement with the crystal structure result of **6**. We expect that the same or a very similar complexation mode exists for the other xanthines as well; however, it was not possible to obtain crystals of sufficient quality for X-ray diffraction. Probably, this is due to the fact that these compounds were not available in enantiomerically pure form.

In conclusion, the xanthines **1–5** strongly prefer the side-on binding to the dirhodium complex **Rh*** in the liquid state ($CDCl_3$ solution) whereas C-6 carbonyl complexation competes in the case of **6** to a certain extent. The IR data in the solid state indicate that here C=O complexation is predominant as shown by crystal structure determination of **Rh*-6**.

Experimental

The NMR spectra of compounds **1** to **5** were published before [2], those of **6** were recorded on a Bruker DRX-500 spectrometer at 500.1 MHz (^1H) and 125.8 MHz ($\{^1H\}$-BB decoupled ^{13}C) at ambient temperature. In a typical experiment 40 mg **Rh*** ($3.5 \cdot 10^{-2}$ mmol) were dissolved in 0.5 ml $CDCl_3$ containing 17.2 mg of acetone-d_6 for better solubility (7.7 molar relative to **Rh***). All chemical shifts are referenced to internal tetramethylsilane ($\delta = 0$). Standard Bruker software was used for all one- and two-dimensional experiments. EI mass spectra were obtained on a Finnigan MAT 312 (70 eV) with direct inlet. IR spectra were taken on a Bruker Vector 22 (attenuated total reflection mode, ATR) in the solid state and in $CDCl_3$ solutions identical to those prepared for the NMR studies [2].

Crystal structure analysis of **Rh*-6**

$C_{117}H_{107}Cl_3F_{24}N_{10}O_{28}Rh_4$, M = 3075.12 g/mol, green crystal of irregular shape, size $0.26 \times 0.17 \times 0.07$ mm, monoclinic, space group $P2_1$, (No. 4), a = 19.517(2), b = 14.080(1), c = 23.918(2) Å, $\alpha = 90.00°$, $\beta = 106.04(1)°$, $\gamma = 90.00°$, V = 6316.8(9) Å^3, Z = 2, D_x = 1.617 g/cm^3, T = 300(2) K, Stoe IPDS diffractometer, λ(Mo–K_α) =

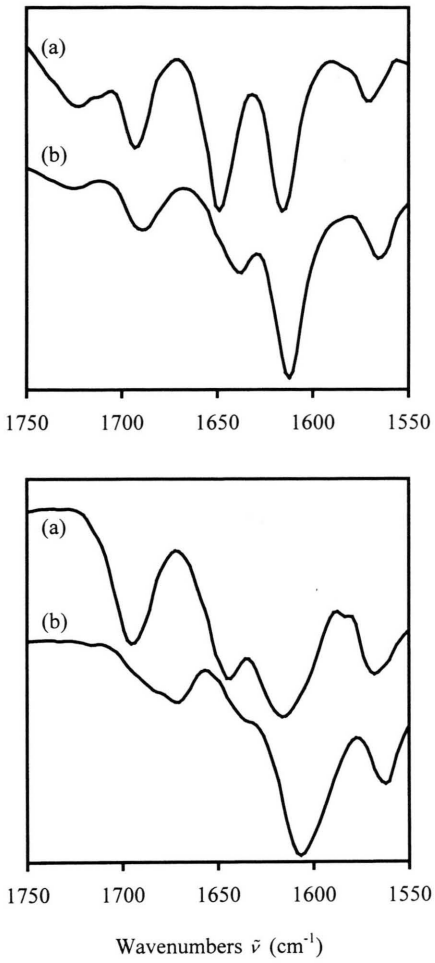
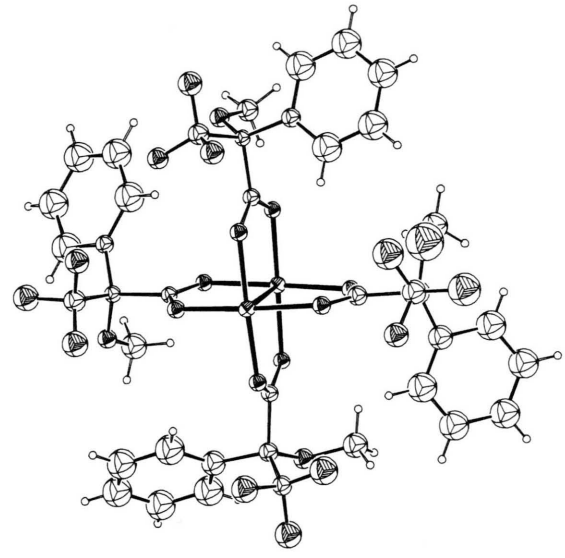


Fig. 2. Sections of the IR spectra of **6**; top: in $CDCl_3$ solution, (a) pure **6** and (b) in the presence of **Rh***; bottom: in the solid state, (a) pure **6** and (b) in the presence of **Rh***.

0.71073 Å, Θ_{max} = 24.15°, 34069 measured, 19523 unique (R_{int} = 0.0636) and 7851 observed ($I > 2\sigma_I$) reflections, 604 refined parameters, $R_{gt}(F)$ = 0.068, $wR(F^2)$ = 0.121. Full crystallographic details without structure factors have been deposited at CCDC, no. 154420.

There are two **Rh*** complexes, two molecules of compound **6**, and one disordered solvent moleule ($CHCl_3$) in the asymmetric unit. **Rh*** and **6** are bonded in an alternating sequence forming an infinite chain in the [100] direction (see Scheme 3). A second chain in the same direction is related to the first one by the crystallographic twofold screw axis. The first **Rh*** complex (center of gravity approximately in position 0.25, 0.34, 0.25) is shown



Scheme 4. One Rh* complex (see Scheme 3 and text) without ligands as determined by X-ray diffraction.

in Scheme 4 without its axial ligands. It is easily seen that the conformation of the ligands is such that the complex has nearly the symmetry of point group 4 (C_4). The second **Rh*** complex (center of gravity approximately in position 0.75, 0.18, 0.25) is similar, but the torsion angle of one phenyl group is quite different. The two symmetrically independent molecules of compound **6** are almost identical in their conformation. Axial Rh-O bond lengths are 2.235(10) to 2.307(12) Å. These distances are significantly larger than Rh-O bond lengths for acylate residues: 1.990(9) to 2.093(11) Å. Rh-Rh bond lengths are 2.3804(14) and 2.3772(15) Å. It is interesting to note that the dirhodium tetraacylate skeletons adopt chiral conformations (Scheme 4); O-Rh-Rh-O torsion angles for the acylates are 0 to 2.6° for one and 3.1 to 4.6° for the other **Rh*** entity.

Syntheses

1,3-Dimethyl-2,4-dioxo-9-(1-phenylethyl)-1,3,6,7,8,9-hexahydropyrimido[2,1-f]purine (**6**)

Compound **6** has been described previously [4] but its structure was confirmed only by elemental analysis and UV spectra. Different starting materials, modified reaction conditions and isolation methods provided **6** in purer form. The starting material, 7-(3-chloropropyl)-8-bromotheophylline [5], was obtained by a modified two-phase chloroalkylation in acetone in the presence of anhydrous

K_2CO_3 and benzyltriethylammonium chloride (TEBA) as catalyst: a mixture of 8-bromotheophylline (5.16 g, 0.02 mol) [6], anhydr. K_2CO_3 (2.8 g, 0.02 mol) TEBA (0.30 g), 1-bromo-3-chloropropane (4 ml, 0.04 mol) in of acetone (40 ml) was heated at reflux for 10 h with stirring. The precipitate was filtered off from the hot mixture, mixed with 40 ml of 15% NaOH (to remove unreacted 8-bromotheophylline), washed with water (to remove inorganic salts) and recrystallized from ethanol. The acetone filtrate was cooled and the main crop of 7-(3-chloropropyl)-8-bromotheophylline was separated and recrystallized from ethanol. Total yield 86%; m.p. 132–133 °C (lit. [5]: 131 °C). The substance was used to synthesize compound **6**.

A mixture of 7-(3-chloropropyl)-8-bromotheophylline (3.3 g, 0.01 mol), racemic 1-phenylethylamine (4 ml, 0.03 mol) and butanol (6 ml) was heated at reflux for 10 h. Then, butanol was removed by distillation under reduced pressure and the excess of amine by steam distillation. Compound **6** was precipitated in water solution, separated after cooling and recrystallized from 70% ethanol. Yield 95%; mp. 142–3 °C (lit. [4]: 137 °C); TLC: Kieselgel $60F_{254}$, R_f = 0.56 (benzene – acetone, 7:3). – IR (solid state): $\tilde{\nu}$ = 3541, 3476, 2945, 1695, 1644, 1616, 1568, 1535, 1478, 1453, 1431, 1400, 1372, 1225, 1204, 1177, 1070, 1037, 977, 914, 884, 765. – MS (EI, 70 eV): *m/z* (%) = 340 (15) $[M+H]^+$, 339 (36) $[M^+]$, 236 (15) $[M^+-C_8H_7]$, 235 (100) $[M^+-C_8H_8]$, 234 (12) $[M^+-C_8H_9]$, 207 (8) $[235-CO]^+$, 191 (13), 178 (7), 159 (14), 149 (8), 133 (9) $[C_9H_{11}N^+]$, 105 (48) $[C_8H_9+]$. – $C_{18}H_{21}N_5O_2$ (339.40): calcd. C 63.70, H 6.24, N 20.64; found C 63.84, H 6.57, N 21.08.

The preparation of **Rh*** has been reported before [1a]; for the xanthines **1–5** see ref. [2].

Acknowledgements

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