Chiral Discrimination of Some Annelated Xanthine Derivatives by the Dirhodium Method

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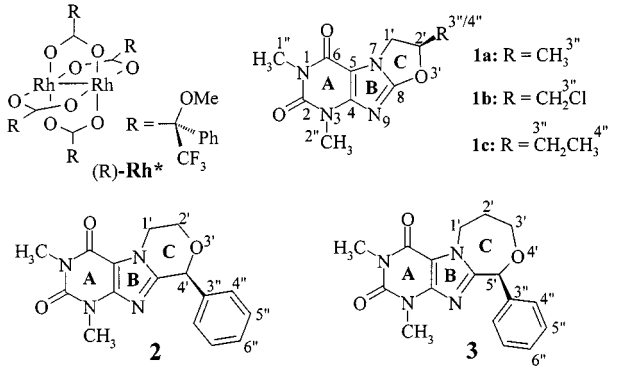
Keywords: Xanthines / NMR spectroscopy / Chirality / Rhodium / Chiral resolution

Complete ^1H and ^{13}C signal assignments and conformation analyses of the title compounds (racemic mixtures) were performed. Most ^1H and ^{13}C NMR signals were resolved in the presence of the enantiomerically pure dirhodium complex $Rh_2(MTPA)_4$ (**Rh***) allowing for clear and simple chiral recognition. A detailed interpretation of the signal shifts ($\Delta\delta$) and dispersions ($\Delta\nu$) in the diastereomeric complexes suggested that the π-system around the C-4/C-5 bond of the central imidazole ring (**B**) is a binding site of the xanthine derivatives. This assumption was based on HOMO–LUMO considerations including back-donation and on the fact that diastereotopic dispersions for protons within methylene groups are very different. Signal shifts are in the range of 0.5 to 1 ppm for carbon atoms close to the binding site and fade away at the periphery of the molecule. Dispersions are spread all over the molecule.

Introduction

Methylxanthines exhibit a variety of pharmacological effects including CNS stimulatory activity.[1] Annelation of five-, six- or seven-membered rings at the 7,8-positions of theophylline changes their pharmacological properties, making them sedative, neuroleptic, hypothermic and contraceptive agents.[2,3] In the course of our investigations into the methylxanthine group, annelated oxazole-, oxazine-, and oxazepine derivatives of theophylline (**1**, **2**, and **3**, respectively; Scheme 1) were obtained and pharmacologically tested. They have shown in vivo antiepileptic activity and in vitro affinity to adenosine but not to $GABA_A$ receptors.[4] The compounds possess stereogenic centers in their structures. To evaluate the enantiomeric activity, an efficient method for chiral recognition was needed.

During the past few years it has been proven that the dirhodium method, i.e. the use of dirhodium tetrakis-[(*R*)-α-methoxy-α-(trifluoromethyl)-α-phenylacetate] (**Rh***), [$Rh_2(MTPA)_4$; MTPA ≡ Mosher acid] as a chiral auxiliary, is an excellent tool for the chiral recognition of a variety of monofunctional compounds which cannot be investigated by chiral lanthanide shift reagents (CLSR).[5,6] To further these studies, we investigated the xanthine derivatives **1**–**3** which serve as models for testing multifunctional compounds.



Scheme 1. Structures of dirhodium tetrakis[(*R*)-α-methoxy-α-(trifluoromethyl)-α-phenylacetate]

Results and Discussion

Syntheses

Two types of theophylline derivatives with annelated chiral systems of hydrogenated 1,3-oxazole (type **1**), 1,3-oxazine and 1,4-oxazepine (type **2**, **3**) were investigated. Compounds of type **1** were prepared as outlined in Scheme 2a by the reaction of 8-bromotheophylline with oxiranes (propylene oxide, epichlorohydrine, 1,2-butylene oxide).

Compounds **1a** and **1b** (Scheme 2a) were reported previously[7] but their structures were confirmed only by means of elemental analyses. The starting material for the syntheses of compounds **2** and **3** was 8-(hydroxybenzyl)theophylline (**5**) obtained by the melting of 5,6-diamino-1,3-dimethyluracil with racemic mandelic acid and the dehydration of the resulting 6-amino-5-(hydroxyphenylacetamido)-1,3-dimethyluracil (**4**) in an alkaline medium (Scheme 2b). 8-Hydroxybenzyltheophylline cyclized to form compound **2** in a catalytic two-phase reaction with dibromoethane in the presence of K_2CO_3 and benzyltriethylammonium chloride (TEBA) as phase-transfer catalyst in acetone. Cyclization

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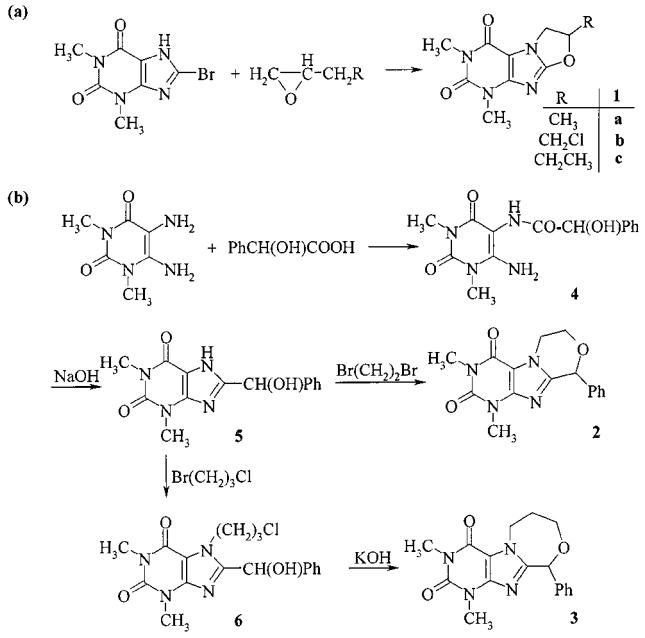


Scheme 2. Synthesis of the xanthine derivatives **1**−**3**

to the oxazepine ring containing derivative **3** required a two-step reaction (Scheme 2b). At first, 7-(3-chloropropyl)-8-(α-hydroxybenzyl)theophylline (**6**) was obtained by reacting **5** with 1-bromo-3-chloropropane under the same conditions as above. Cyclization was then carried out in an alcoholic solution of KOH.

NMR Results

All compounds **1a**−**1c**, **2** and **3** were dissolved in $CDCl_3$, and [D_6]acetone was added until a molar ratio of **Rh***/[D_6]acetone = 1:7.7 was achieved, in order to increase the solubility of (*R*)-**Rh*** (see also exp. Section).[8] The results of the NMR measurements are collected in Table 1 and 2; for the assignments of the signals see below. Nearly all substrate signals were split into two when the chiral dirhodium tetracarboxylate **Rh*** was added to the solution. This is due to the diastereomerism of the new complexes formed. In Table 1 and 2, the top number for each entry indicates the chemical shift of the pure compound (without **Rh***) whereas the second line contains (left) the complexation shifts due to the presence of an equimolar amount of **Rh*** (Δδ, in ppm) and (right) the corresponding signal dispersion (Δν, in Hz). It should be noted that it was not possible to determine the respective Δδ-values of the individual diastereomers, since all substrates were racemates. The larger absolute values of Δδ (if detectable) were thus taken first in each entry.

In most instances, series of spectra were recorded varying the concentration ratios of the samples (**1a**−**1c**, **2** and **3**) to **Rh*** ranging from 1:0.25 to 1:2. It was found that the max-

Table 1. ^{1}H chemical shifts δ (in ppm), complexation shifts Δδ (in ppm), and dispersions Δν (in Hz) of **1**−**3**

	1a δ (ppm)[a] Δδ (ppm) | Δν (Hz)	**1b** δ (ppm) Δδ (ppm) | Δν (Hz)	**1c** δ (ppm) Δδ (ppm) | Δν (Hz)	**2** δ (ppm) Δδ (ppm) | Δν (Hz)	**3** δ (ppm) Δδ (ppm) | Δν (Hz)
1′	α: 4.523 dd 0.08/0.05 | 16.1 β: 3.970 dd 0.04/0.03 | 5.1	α: 4.563 dd −0.02/0.02 | 19.1 β: 3.392 dd 0.05/0.01 | 22.0	α: 4.502 dd 0.04/0.00 | 18.1 β: 4.040 dd 0.04/0.02 | 12.9	α: 4.44−4.53 m ≈ 0.05 | n.d. β: 4.44−4.53 m ≈ 0.05 | n.d.	α: 4.909 ddd 0.09/0.05 | ≈ 15 β: 4.690 ddd −0.06/−0.04 | ≈ 12
2′	5.527 m −0.28/−0.26 | 7.3	5.630 m −0.4/−0.4 | 2.9	5.368 m −0.27/−0.27 | 4.0	α: 4.078 ddd 0.06/0.00 | 30.2 β: 4.243 ddd 0−0.1 | 10±5	α: 2.12−2.09 m ≈ 0.2 | n.d β: 2.12−2.09 m ≈ −0.6 | n.d.
3′					α: 3.931 ddd ≈ 0.2 | n.d. β: 4.174 ddd ≈ 0.05 | n.d.
4′				5.917 br s 0.21/0.16 | 24.0	
5′					5.918 br s 0.40/0.35 | 26.8
1"	3.379 s 0.15/0.13 | 9.7	3.380 s 0.13/0.13 | 2.2	3.370 s 0.15/0.13 | 10.2	3.412 s 0.09/0.09 | 2.6	3.412 s 0.09/0.08 | 3.4
2"	3.509 s 0.04/0.03 | 4.3	3.511 s 0.07/0.03 | 20.2	3.502 s 0.05/0.03 | 10.6	3.526 s 0.03/0.03 | 1.2	3.493 s −0.02/−0.01 | 2.1
3"	1.697 d −0.27/−0.25 | 10.7	a: 3.945 d −0.26 | <1 b: 3.896 d −0.30 | n.d.	a: ≈ 2.04 m ≈ −0.2 | n.d. b: ≈ 1.96 m ≈ −0.2 | n.d.	7.36−7.42 m ≈ 0 | n.d.	
4"			1.115 t −0.24/−0.20 | 21.3	7.36−7.42 m ≈ 0 | n.d.	7.297 ≈ −0.1 | n.d.
5"				7.36−7.42 m ≈ 0 | n.d.	≈ 7.39 ≈ −0.3 | n.d.
6"				7.36−7.42 m ≈ 0 | n.d.	≈ 7.36 ≈ −0.1 | n.d.

[a] In $CDCl_3$ with a small amount of [D_6]acetone (for concentrations see Exp. Section); chemical shifts in ppm relative to tetramethylsilane (δ = 0); signal shifts Δδ in ppm due to complexation with (+)-**Rh*** (1:1 molar); dispersion effects Δν in diastereomeric complexes with (+)-**Rh***; n.d.: not detectable due to signal complexity and/or overlap.

Table 2. ^{13}C chemical shifts δ (in ppm), complexation shifts Δδ (in ppm), and dispersions Δν (in Hz) of **1−3** (See caption to Table 1; asterisked values may be interchanged)

	1a δ (ppm) Δδ (ppm) | Δν (Hz)	**1b** δ (ppm) Δδ (ppm) | Δν (Hz)	**1c** δ (ppm) Δδ (ppm) | Δν (Hz)	**2** δ (ppm) Δδ (ppm) | Δν (Hz)	**3** δ (ppm) Δδ (ppm) | Δν (Hz)
2	151.61 −0.3 | <1	151.55 −0.5/−0.1 | 4.8	151.62 0.6 | <1	151.74 0.5 | 2.6	152.01 0.3 | 5.0
4	151.48 0.0 | ≈ 1	151.22 0.8/0.7 | 5.0	151.44 0.2 | 2.8	148.35* ≈0.6/≈ 0.4 | 16.4	147.79 −0.1 | 0.5
5	102.20 1.1 | 1.7	102.23 0.9 | <1	102.17 −0.1 | 1.9	106.79 0.6 | 4.6	107.83 0.1/0.0 | 10.1
6	154.04 ≈ 2.0 | 8−10	153.98 1.7/1.6 | 7.5	154.04 1.8/1.7 | ≈ 15	155.22 1.0 | 5.8	155.99 0.3/0.1 | 18.0
8	162.18 2.2/2.1 | 12.2	161.49 2.1/2.0 | 12.2	162.22 2.0/1.8 | 18.0	148.30* ≈ 0.5/≈ 0.4 | 8.2	154.50 −0.4 | 7.0
1′	50.46 0.2/0.1 | 15.4	46.67 0.4/0.3 | 12.0	48.59 0.1/−0.1 | 18.7	44.44 0 | <1	44.54 0.1/−0.0 | 8.4
2′	85.65 1.2/1.1 | 8.4	86.00 0.7/0.6 | 9.4	90.34 1.0/0.8 | 19.2	61.07 −0.3/−0.2 | 7.0	29.82 −0.4/−0.4 | 1.2
3′					68.77 −0.4/−0.2 | 20.4
4′				76.02 −0.1/0.0 | 7.7	
5′					79.22 −0.1 | 2.6
1"	27.93 0.7 | ≈ 1	27.98 1.6 | 3.8	27.92 0.6 | <1	27.90 0.5 | 3.1	28.36 0.0 | 3.8
2"	30.13 0.2 | 1.4	30.17 1.1 | 5.5	30.11 1.2/1.1 | 6.2	29.98 0.4/0.3 | 6.2	30.22 −0.2 | 4.3
3"	20.33 −0.9 | 5.3	43.81 −0.7/−0.6 | 7.2	27.68 −0.8/−0.7 | 11.5	136.87 −0.1 | <1	137.04 −0.8 | <1
4"			8.76 −0.7/−0.6 | 9.1	127.98 0.1 | 2.6	128.02 −0.2 | n.d.
5"				128.68 −0.1 | 2.6	128.04 −0.2 | n.d.
6"				129.03 0.0 | 4.8	129.02 0.3 | 1.2

imum signal shifts and dispersions were reached at a 1:1 molar ratio and further addition of **Rh*** no longer increased those parameters significantly. This is in agreement with the assumption that the equilibrium is kinetically unstable (fast exchange on the NMR time-scale).[6,8]

$$S + Rh^* \rightleftarrows S\cdots Rh^* \ (S = \mathbf{1a-1c}, \mathbf{2}, \mathbf{3})$$

Signal Assignments

The ^1H and ^{13}C signal in both the free and the complexed substrates were assigned based on 1D- and 2D NMR spectroscopy comprising DEPT, gradient-selected $^1H,^1H$-COSY, HMQC, HMBC and NOESY experiments. Thereby, a complete and unequivocal assignment of most protons and carbons was possible. The identification of the two methyl H-1" and H-2" (singlets between δ = 3.37 and 3.53) as well as the C-2, C-4 and C-6 signals (singlets between δ = 151.5 and 162.2) deserve attention. Each of the methyl proton signals showed two HMBC peaks for couplings to the carbons mentioned. For each molecule, one carbon is coupled to both protons so that this can be assigned safely to C-2. However, the differentiation of C-4 and C-6 could not be achieved by correlation methods because both couple to the protons of only one methyl group and to no other proton. Here, a ^{13}C NMR experiment with **2** (as a representative example) in the presence of an increasing amount of $Yb(fod)_3$ (Figure 1) was performed, and it was shown that the two carbonyl groups are the binding sites and experience the strongest deshielding on the addition of $Yb(fod)_3$. In contrast, C-4 (like other more remote carbons) shows much less pronounced Yb effects. This experiment allowed for the differentiation not only of the C-6 and C-4 atoms but, consequently, of the H-1" and H-2" atoms as well. In the free **2**, the signals of C-4 and C-8 are very close together and could not be differentiated by HMBC. However, owing to their different Δδ-values, the corresponding carbon signals in the complex could be resolved and assigned safely because of HMBC cross-peaks identifying the C-8, H-1′ coupling.

Stereochemical assignments were based on NOESY correlations; the β-position was arbitrarily chosen for the substituents (CH_3 in **1a**, CH_2Cl in **1b**, C_2H_5 in **1c** and C_6H_5 in **2** and **3**; see Scheme 1).

Conformational Analysis of the Free Xanthines 1−3

It can be expected that conformational equilibria may be different for the free and the complexed substrate molecules. Nevertheless, it seemed interesting to study the behaviour of the free xanthine derivatives, particularly compounds **2** and **3**, where the anellated six- and seven-membered rings, respectively, may adopt various conformations.

In all three compounds **1a−1c**, the five-membered oxazoline **C**-ring is practically coplanar as shown by AM1 and

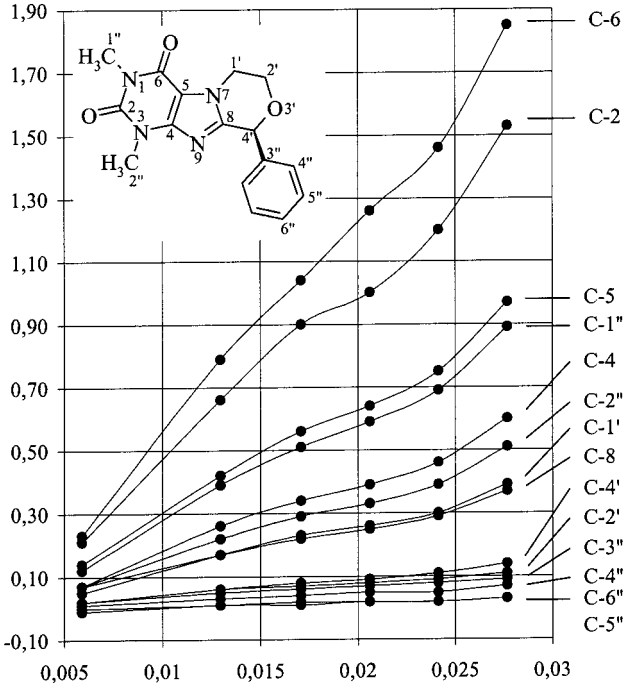


Figure 1. ^{13}C NMR signal shifts of **2** (in ppm) induced by increasing amounts (molar ratios) of $Yb(fod)_3$

ab initio calculations. This was confirmed by the relevant *vicinal* ^{1} H,^{1}H coupling constants between H-1α/H-2α and H-1β/H-2α: the H-1α/H-2α values are 8.0 Hz for **1a**, 8.6 Hz for **1b** and 8.2 Hz for **1c** indicative of a torsion angle of about 0° in the H-1α−C-1−C-2−H-2α fragment. On the other hand, the H-1β/H-2α values are 7.6 Hz, 6.3 Hz and 7.5 Hz, respectively, corresponding to torsion angles of 120−130° for the H-1β−C-1−C-2−H-2α fragment.

For **2** and **3**, the **C**-ring protons showed complex multiplets owing to overlap and high-order effects, so that clear-cut conclusions from ^{1}H,^{1}H coupling constants could not drawn. AM1 calculations of **2** indicated that the phenyl group at C-4′ prefers the pseudo-axial position of the half-chair ring, resulting in a stabilization of that form by approximately 3 kJ/mol relative to the conformation with the pseudo-equatorial phenyl group. The annelated seven-membered ring of **3** can adopt chair and boat conformations; clearly, the chair is much more stable. The preference of the pseudo-axial phenyl position is somewhat more pronounced than in **2** (ca 6 kJ/mol).

Complexation Shifts (Δδ)

Our earlier studies[5,6] on the chiral discrimination of monofunctional compounds with the dirhodium method have shown that protons are deshielded moderately (Δδ up to +0.5 ppm) by complexation with **Rh*** only if they are close to the binding site. On the other hand, a small shielding (Δδ less than −0.2 ppm) may occur for protons at the periphery of the substrate molecule. The deshielding is apparently inductive in nature, whereas the shielding can be ascribed to anisotropy effects exerted by the substituents of the Mosher acid.[5,6]

Inspecting the Δδ(^{1}H) values of the compounds **1**−**3** (Table 1), it is remarkable that only a few significant deshielding and shielding effects can be observed. There are significant positive Δδ-values only for H-1" in all three compounds **1**, as well as for H-4′ in **2** and H-5′ in **3** in the C*H*Ph-groups next to the central **B**-ring. The most significant deshielding ^{13}C complexation shifts (>1 ppm) are found at **B**-ring carbons and C-6. On the other hand, noticeable negative Δδ-values (^{1}H and ^{13}C) are found in more peripheral segments of the molecules (**C**-ring and attached substituents).

All these values do not point clearly to a binding site close to any particular proton or carbon.

Dispersion Effects (Δν)

The Δν-values were mostly read directly from the doubled signals in the NMR spectra (see for example Figure 2). In some cases with very complex multiplets, they were taken from the multiplet broadening (in Hz) when going from the signal of the free substrate to that of the complex. However, this technique could not applied to some cases with second-order signals. The dispersion effects were then estimated within an error limit of ±1 Hz or, alternatively, they were marked as "n.d." (not detectable) in Table 1 and 2.

All ^{1}H signals (when not obscured) display significant dispersion effects Δν (Table 1), and this observation holds for most ^{13}C signals as well (Table 2). Some typical spectral features are shown in Figure 2.

Similar to the complexation shifts, no preferred molecular region can be identified. However, it is obvious that clear differences exist between the dispersions Δν of diastereotopic protons for some substrate atoms in the diastereomeric complexes, indicating a face differentiation of the xanthine, i.e., there seems to be a face-on complexation as exemplified for **1a** in Scheme 3. It is reasonable to assume that hydrogen atoms directed inwards (H-α in Scheme 3) come into closer contact with the chiral Mosher acid residues and thereby experience a stronger anisotropic influence than those directed outwards (H-β), since the latter are further away. Keeping this rationalization in mind, one has to conclude that the methyl group in **1a** is directed outwards in the favoured substrate-to-**Rh*** orientation (Scheme 3), since the H-1′α-proton shows a much larger dispersion (16.1 Hz) than H-1′β (5.1 Hz).

This sequence is less pronounced in the ethyl derivative **1c** (H-1′α: 18.1 Hz; H-1′β: 12.9 Hz), a fact which may be interpreted in terms of a decreased difference in the steric demand of the two faces of molecule **1c** owing to a preferred position of the flexible terminal methyl group 4" (see conformational analysis discussed above).

Apparently, the binding mode of **1b** with the chloromethyl side-chain is different from that of **1a** and **1c**. The dispersion effects of both H-1′ atoms are very strong and similar, but the sequence is reversed (H-1′α: 19.1 Hz; H-1′-β: 22.0 Hz). In addition, the Δν-value of H-1" is only 2.2 Hz whereas it is 9.7 Hz for **1a** and 10.2 Hz for **1c**. The tendency at the other *N*-methyl protons H-2" is opposite: **1a**: 4.3 Hz,

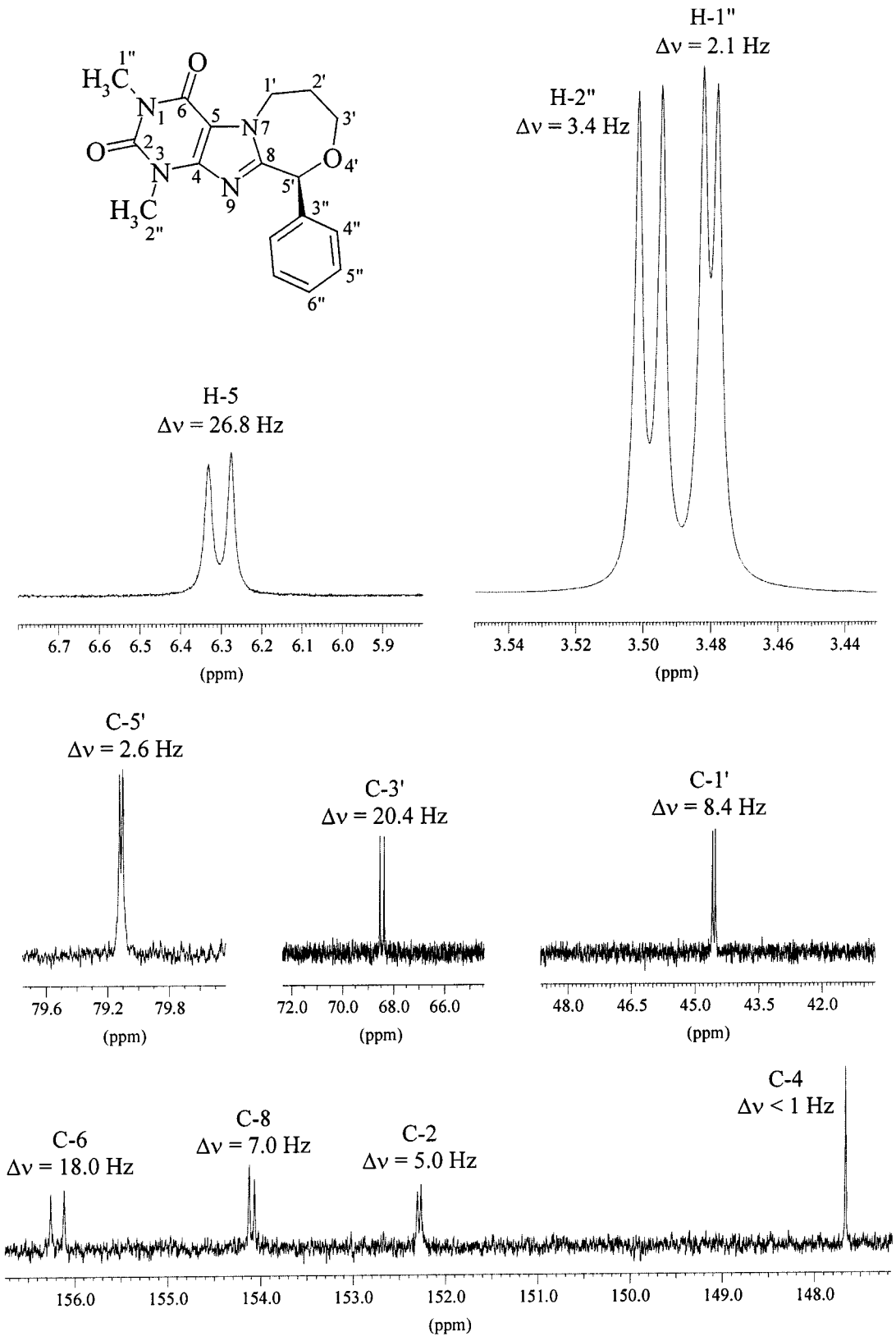
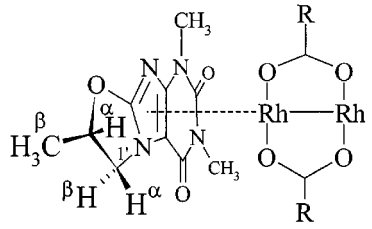


Figure 2. Sections of the ^{1}H (top) and ^{13}C NMR (bottom) spectra of **3** in the presence of an equimolar amount of **Rh***

1c: 10.6 Hz, **1b**: 20.2 Hz, and a striking difference can also be observed for the H-3" atoms in **1a** (10.7 Hz) and the **1b** (diastereotopic protons; a: <1 Hz, b: not detectable). H-3" Δν values of **1c** are not detectable. Furthermore, divergences in the Δν-tendencies within the series of compounds **1** can also be observed for some carbon signals (Table 2), e.g. at C-2 (**1a**: <1 Hz; **1b**: 4.8 Hz; **1c**: <1 Hz) or C-4 (**1a**: ca 1 Hz; **1b**: 5.0 Hz; **1c**: 2.8 Hz), and analogous tendencies



Scheme 3. Approach of **1a** to **Rh*** (only two acyl residues are depicted)

are observed not only for peripheral carbons (e.g. C-1", C-2" and C-3") but also for those close to the binding site, especially C-4 (**1a**: ca 1 Hz; **1b**: 5.0 Hz; **1c**: 2.8 Hz) and C-6 (**1a**: 8−10 Hz; **1b**: 7.5 Hz; **1c**: ca 15 Hz). Here, a variation in the binding modes seems to be the reason (see below).

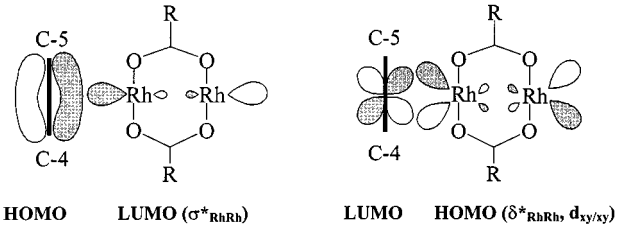
Unfortunately, the dispersions of most **C**-ring protons in **2** and **3** could not be determined safely. However, the H-2′ data of **2** and the H-1′ data of **3** seem to indicate that these molecules again show a face preference similar to that of **1a**. However, the divergences in the H-1" and H-2" values as well as in the C-1" and C-2" values in **2** and **3** compared to those of series-**1** molecules suggest different orientations within the complex.

Binding Sites and Binding Mode

It appears that the central imidazole ring (ring **B**) is involved in the binding to the rhodium atom. It has been shown that ligation of substrates to dirhodium tetracarboxylate complexes may occur through a double HOMO−LUMO contact including back-donation; the HOMO and LUMO orbitals of **Rh*** being δ* and σ*, respectively.[9,10] Therefore, we calculated (by ab initio Hartree−Fock 3−21G* and *semi-empirical AM1* methods) the HOMO and LUMO of the xanthine derivatives and found that, indeed, the orbital lobes with greatest spatial extension meet the geometry requirements for ligating the rhodium−rhodium bond orbitals. These π-orbitals (Scheme 4) are centred close to the C-4−C-5 bond with the LUMO extended towards C-6. It should be noted that the HOMO and LUMO calculated by the AM1 semi-empirical method are very similar to those calculated by Hartree−Fock ab initio methods. They do not vary significantly in the whole series of substrate molecules and the oxygen atoms of ring **C** are hardly involved (series **1**) or not at all (**2** and **3**).

Scheme 4. HOMO (left) and LUMO (right) of **1a**; semi-empirical calculation (AM-1)

Scheme 5 gives a schematic view of the binding between the orbitals of the substrate and the rhodium atoms involved. These calculations support the face-on orientation of the ligated substrate molecules as suggested by the NMR spectroscopic data (see above).



HOMO **LUMO (σ^*_{RhRh})** **LUMO** **HOMO (δ^*_{RhRh}, $d_{xy/xy}$)**

Scheme 5. Schematic representation of the face-on bonding (left) and back-donation (right) in **1a**; only two carboxylate residues are depicted

This interpretation, however, does not account for all observed Δδ and Δν values, and especially not for the divergences within the series of compounds **1**. To our surprise, a recent X-ray study of a similar xanthine derivative **7**[11] showed linear strands with consecutive xanthine and **Rh*** molecules where one **Rh*** entity complexes to a C-2 carbonyl group on each side, whereas the next **Rh*** complexes to two C-6 carbonyls (Scheme 6).[12]

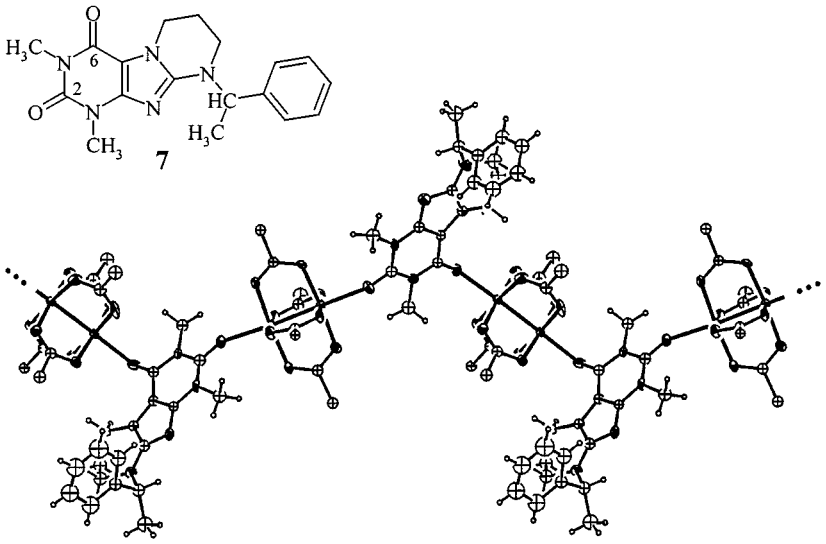
It thus follows that there is an equilibrium between kinetically unstable complexes with different binding sites in solution. This equilibrium is strongly dependent on the structure of the substrate. This can explain the differences in the complexation effects on the observed NMR parameters. Apparently, the π-system (face-on complexation) competes with an edge-on complexation at the C-6 and eventually at the C-2 carbonyl group. Further exploration of this presumed binding-mode equilibrium is a topic of current investigation in our laboratory. Preliminary IR studies support the above interpretation.

Conclusion

It was shown that the dirhodium method is well suited for chiral recognition by observing signal dispersions Δν, even for multifunctional compounds such as xanthine derivatives. As expected, complexation shifts Δδ are very moderate or even negligible so that 1:1 mixtures of the substrates and **Rh*** can be prepared without an extensive change of signal sequences in the spectrum.

The advantage of the method is demonstrated by its surprising sensitivity; for example, by the fact that the *para*-carbon in **2** (C-6") experiences a 4.8 Hz signal dispersion, although it is expected to be far away from the Mosher acid residues.

The binding mode can, at least partly, be rationalized by a simple HOMO/LUMO model pointing to a face-on complexation. The dispersion values (Δν) indicate face differentiation and allow for some conclusions to be drawn with regard to the conformational arrangement inside the substrate−**Rh*** complex. However, a binding to the carbonyl oxygens may contribute.



Scheme 6. Structure of derivative **7** and its orientation with respect to **Rh*** molecules in the solid state, as determined by X-ray investigation.[12] For sake of clarity, the Mosher acid R residues in the **Rh*** molecules have been replaced by one C only.

Experimental Section

Melting points were determined with a Büchi 530 apparatus and are uncorrected. − The ^{1}H NMR spectra of compounds **4** and **5** were obtained on a Bruker DPX-250 (250 MHz) and that of **6** on a Bruker AC-200F spectrometer (200 MHz). For the other compounds (**1**−**3**) the NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500.1 MHz (^{1} H) and 125.8 MHz ({^{1}H}-BB decoupled ^{13}C) at ambient temperature. In a typical experiment, **Rh*** (40 mg, 3.5×10^{-2} mmol) were dissolved in $CDCl_3$ (0.5 mL) containing [D_6]acetone (17.2 mg, 7.7 molar relative to **Rh***). All chemical shifts are referenced to internal tetramethylsilane (δ = 0). Standard Bruker software was used for all one- and two-dimensional experiments. − EI mass spectra were obtained on a Finnigan MAT CH7A (70 eV) with direct inlet. − IR spectra of **1c** and **2** were recorded with a Perkin−Elmer 297 and for remaining compounds with a Jasco FT IR 410 in KBr discs. − TLC was performed on Merck plates (Kieselgel 60 F_{254}), solvent system: chloroform/acetone/propanol 6:3:1. − The PC-based program package SPARTAN Pro® was employed for all calculations (AM1 and ab initio Hartree−Fock 3−21G*).

The synthesis of the dirhodium complex (*R*)-**Rh*** has been described before.[5]

Note that the atom-numbering in the following section is done according to IUPAC nomenclature, whereas the numbering in Scheme 1 has been changed for reasons of convenience in the NMR discussion.

7-Ethyl-1,3,6,7-tetrahydro-1,3-dimethyl-2,4-dioxo-1,3-oxazolo[3,2-*f*]-purine (1c): A solution of of 8-bromotheophylline[13] (2.58 g, 0.01 mol) and of 1,2-epoxybutane (2.5 mL, 0.03 mol) was heated at reflux in propanol (12 mL) with a catalytic amount of pyridine (0.3 mL) for 3 h. After cooling, the precipitated product was filtered off and recrystallized. R_f = 0.84. − Yield 92%; m.p. 186−188 °C (from EtOH). − EI-MS; *m*/*z* (%): 250 (100) $[M]^+$, 235 (25), 196 (92), 208 (19), 181 (24), 83 (49), 55 (19). − IR: (ṽ = 2949, 2885, 1660 (C=O), 1053 (C−O) cm^{-1}. − $C_{11}H_{14}N_4O_3$ (250.26): calcd. C 52.84, H 5.64, N 22.39; found C 53.13, H 5.46, N 21.99.

6-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-(hydroxyphenylacetamido)pyrimidine (4): A mixture of racemic mandelic acid (5.6 g, 0.036 mol) and 5,6-diamino-1,3-dimethyluracil (5.6 g, 0.032 mol) was melted and then heated on a steam bath for 2 h. The crude product was recrystallized. R_f = 0.42. − Yield 61%. − M.p. 138−140 °C (from H_2O). − ^{1}H NMR ([D_6]DMSO): δ = 3.10 (s, 3 H, N^3CH_3), 3.29 (s, 3 H, N^1CH_3), 5.06−5.08 (d, *J* = 3.5 Hz, 1 H, OH), 6.07−6.09 (d, *J* = 4.0 Hz, 1 H, CH), 6.49 (s, 2 H, NH_2), 7.24−7.55 (m, 5 H, C_6H_5), 8.58 (s, 1 H, NH). − IR: (ṽ = 3436 (OH), 3318, 3230 (NH), 1664 (C=O), 1617, 1498, 1056 (C−O) cm^{-1}. − $C_{14}H_{16}N_4O_4$ (304.31)·H_2O: calcd. C 52.18, H 5.63, N 17.37; found C 52.54, H 5.57, N 17.00.

8-(Hydroxyphenylmethyl)theophylline (5): Compound **4** (6 g, 0.018 mol) was added to a solution of NaOH (0.8 g, 0.02 mol) in water (30 mL) and the mixture was heated at reflux for 1.5 hours. After cooling glacial acetic acid was added to until a pH of 6.5 was obtained. The crude compound **5** was precipitated, separated and recrystallized. R_f = 0.76. − Yield 95%. − M.p. 98−99 °C (from 30% EtOH). − ^{1}H NMR ($CDCl_3$): δ = 3.34 (s, 3 H, H-2"), 3.50 (s, 3 H, H-1"), 4.96 (br s, 1 H, OH), 5.99 (s, 1 H, C*H*OH), 7.26−7.33 (m, 3 H, H-5"/6",7"), 7.37−7.42 (m, 2 H, H-4"/8"). − ^{13}C NMR ([D_6]DMSO): δ = 28.37 (N^3-CH_3), 30.02 (N^1-CH_3), 33.70 (N^7-CH_2), 42.94 (CH_2CH_2Cl), 44.02 (CH_2Cl), 68.65 CHOH), 107.39 (C-5), 126.64 (C-3′, C-5′)), 128.20 (C-4′), 128.92 (C-2′, C-6′), 141.20 (C-1′), 147.92 (C-8), 151.53 (C-4), 154.36, 154.88 (C-2, C-6). − IR: (ṽ = 3423 (OH), 3178, 1702, 1644 (C=O), 1058 (C−O) cm^{-1}. − $C_{14}H_{14}N_4O_3$ (286.29): calcd. C 58.76, H 4.83, N 19.58; found C 58.66, H 4.65, N 19.28.

1,3,6,7-Tetrahydro-1,3-dimethyl-2,4-dioxo-9-phenyl-9*H*-1,4-oxazino-[4,3-*f*]purine (2): A mixture of compound **5** (1.14 g, 4 mmol), anhydrous K_2CO_3 (0.56 g, 4 mmol), TEBA (0.04 g) and dibromoethane (0.75 mL, 8 mmol) in acetone (50 mL) was heated at reflux with stirring for 10 h. After removal of inorganic salts by filtration of the hot mixture, the filtrate was frozen at −20 °C for 12 hours, the precipitate was then collected by filtration and recrystallized. R_f = 0.88. − Yield 70%. − M.p. 169−170 °C (from EtOH). − For NMR spectroscopic data see Table 1 and 2. − EI-MS; *m*/*z* (%): 312 (100) $[M]^+$, 284 (18), 235 (18), 199 (12), 105 (100), 77 (51), 67 (22), 55 (27). − IR: (ṽ = 3063, 2945, 1660 (C=O), 1073 (C−O) cm^{-1}. − $C_{16}H_{16}N_4O_3$ (312.34): calcd. C 61.54, H 5.17, N 17.94; found C 62.00, H 5.32, N 18.02.

7-(3-Chloropropyl)-8-(hydroxyphenylmethyl)theophylline (6): A mixture of compound **5** (1.14 g, 4 mmol), anhydrous K_2CO_3 (0.55 g, 4 mmol), TEBA (0.04 g) and 1-bromo-3-chloropropane (0.8 mL, 8 mmol) in acetone (30 mL) was heated at reflux with stirring for 12 h. After removal of inorganic salts the filtrate was evaporated to dryness. To the oily residue a small amount of water was added, and the precipitated product was collected and recrystallized. R_f = 0.77. − Yield 79%. − M.p. 136−138 °C (from EtOH). − ^{1}H NMR ($CDCl_3$): δ = 1.93−1.96 (m, 2 H, $CH_2-CH_2-CH_2$), 3.37 (s, 3 H, N^3CH_3), 3.58 (s, 3 H, N^1-CH_3), 3.39−3.40 (m, 2 H, CH_2Cl), 4.22−4.29 (m, 2 H, N^7CH_2), 5.79−6.01 (d, J = 6 Hz, OH), 7.26−7.39 (m, 5 H, C_6H_5). − EI-MS; *m/z* (%): 362 (100) $[M]^+$, 327 (69), 296 (34), 285 (36), 269 (26), 209 (52), 105 (54), 77 (52). − IR: (ṽ = 3409 (OH), 3062, 2956, 1664 (C=O) cm^{-1}. − $C_{17}H_{19}N_4O_3Cl$ (362.82): calcd. C 56.28, H 5.29, N 15.44; found C 56.00, H 5.31, N 15.15.

1,3,6,7,8,10-Hexahydro-1,3-dimethyl-2,4-dioxo-10-phenyl-1,4-oxazepino[4,3-*f*]purine (3): To a solution of KOH (0.28 g, 5 mmol) in absolute ethanol (20 mL), compound **6** (1.81 g, 5 mmol) was added, and the mixture was heated at reflux for 3 h. Material precipitated during reaction (KCl) was removed by filtration. After cooling, crude **3** was separated and recrystallized. R_f = 0.87. Yield 61%. − M.p. 182−183 °C (from EtOH). − for NMR spectroscopic data see Table 1 and 2. − EI-MS; *m/z* (%): 326 (61) $[M]^+$, 296 (15), 268 (10), 210 (31), 105 (68), 77 (51), 55 (57). − IR: (ṽ = 3068, 2950, 1654 (C=O), 1051 (C−O) cm^{-1}. − $C_{17}H_{18}N_4O_3$ (326.36): calcd. C 62.56, H 5.27, N 17.19: found C 62.65, H 5.24, N 16.98.

Acknowledgments

This work is part of the project "Biologically Active Natural Products: Chemical Diversity" of the Institute of Organic Chemistry, Hanover University. It was supported by the Deutsche Forschungsgemeinschaft (Du 98/14), the Fonds der Chemischen Industrie and by the Polish State Committee for Scientific Research (KBN) grant No 4 P05F 007 13. The authors are grateful to Dr. R. Wartchow, Hannover, for supplying the X-ray structure.

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Received May 3, 2000
[O00222]