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CHALCOGEN ATOM COMPETITION IN THE COORDINATION OF BICYCLIC β -LACTAM DERIVATIVES TO A DIRHODIUM TETRACARBOXYLATE COMPLEX

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This paper is dedicated to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

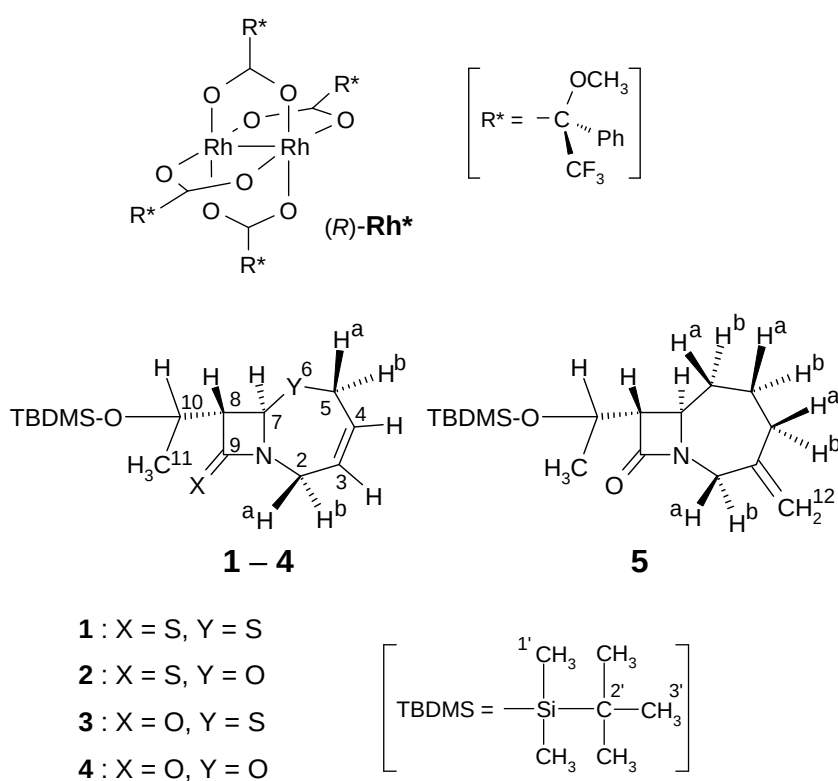
Abstract – NMR spectra of five enantiopure β -lactam derivatives with varying oxygen and sulfur atoms (**1** to **5**) have been recorded in the presence of an equimolar amount of a 2:1-mixture of (*R*)-**Rh*** and (*S*)-**Rh*** [(*R/S*)-**Rh***]. No carboxylate ligand exchange between the two enantiomeric dirhodium complexes was observed. In general, sulfur is a much better donor than oxygen in axial coordination to rhodium. If both chalcogen atoms are equal (S in **1** and O in **4**) the doubly bonded atom is the preferred binding site ($C^9=X$). In the compounds with mixed chalcogen atoms, sulfur prevails as donor regardless of its bond order. This behaviour can be rationalized by comparing calculated molecular orbital energies and electronic charges. Olefinic groups do not contribute to binding significantly. All β -lactam derivatives were enantiopure so that it was possible to monitor significant chemical shift differences of the 1H , ^{13}C and ^{19}F NMR resonances for the two **Rh*** enantiomers. An experiment with racemic 4-vinyloxyazetidin-2-one (**6**) and (*R*)-**Rh*** suggests that the dirhodium method is effective for enantiodifferentiation of β -lactams.

INTRODUCTION

β -Lactams belong to one of the largest, versatile and commercially beneficial classes of antibiotic families. However, the extensive use of penicillins and cephalosporins has created an increasing number

of resistant strains of bacteria. This fact has prompted the search for new structural variants of β -lactam antibiotics with enhanced and/or novel biological profiles.¹ A variety of β -lactam analogues have been synthesized to overcome the defense mechanisms of the bacteria.² It is well known that the significant biological activity of β -lactam derivatives is closely related to their stereostructure.

Clavams and oxacephams, representing oxaanalogues of penicillins and cephalosporins, respectively, have demonstrated that the high biological activity of β -lactam antibiotics is not dependent on the presence of the sulfur atom. Some oxa- and carbaanalogues are more active than natural congeners and exhibit high activities in both enantiomeric forms.³



Scheme 1. Structures of the dirhodium complex (*R*)-**Rh*** and the (7*R*),(8*R*),(10*R*)- β -lactame derivatives **1** to **5** investigated.

For all these reasons, a reliable configuration determination of such bioactive compounds is of significant importance. So, we decided to test the application of the dirhodium method for enantiodifferentiation in this important class of compounds (Scheme 1). During the last decade, we have shown that the dirhodium method, i.e. observation of NMR signal dispersions of chiral substrates in the presence of the enantiopure auxiliary $\text{Rh}^{\text{III}}_2[(R)\text{-}(+)\text{-MTPA}]_4$ (**Rh***, MTPA-H = methoxytrifluoromethylphenylacetic acid $\equiv$ Mosher's acid; see Scheme 1, top) is well suited for soft-base ligands⁴ which mostly fail when chiral lanthanide shift reagents⁵ are used. Very recently, we were able to show that the application of the dirhodium method can be extended beneficially to hard-base ligands, too. For example, it is very successful in the chiral

recognition of ethers.⁶ Moreover, we found a remarkable selectivity if the substrate molecule contains several carbonyl groups (amides and esters) as potential binding sites.⁷

Table 1. ¹H and ¹³C chemical shifts (δ) of the β-lactam derivatives **1** to **5**; in ppm relative to TMS; solvent: CDCl₃.

	1		2		3		4		5	
	¹ H	¹³ C	¹ H	¹³ C	¹ H	¹³ C	¹ H	¹³ C	¹ H	¹³ C
2a	3.85	44.1	3.85	44.7	3.67	41.1	3.71	41.8	3.71	49.2
2b	4.80		4.72		4.39		4.41		4.10	
3	5.56	126.2	5.62	124.2	5.53	127.5	5.61	125.9	-	144.6
4	5.93	129.7	5.67	128.6	5.94	130.2	5.68	128.5	4a: 2.57 4b: 1.92	36.5
5a	3.42	24.3	4.44	66.6	3.49	24.3	4.45	67.7	2.03	35.7
5b	2.99		4.25		2.99		4.23		1.41	
6a	-	-	-	-	-	-	-	-	2.00	29.9
6b									1.38	
7	5.38	64.9	5.57	90.4	4.92	57.9	5.25	84.7	3.56	55.3
8	3.07	67.3	2.99	65.4	3.16	66.7	3.07	64.3	2.63	63.2
9	-	200.8	-	200.5	-	166.3	-	166.0	-	167.5
10	4.32	65.3	4.27	64.8	4.25	64.6	4.23	64.1	4.16	65.5
11	1.27	22.0	1.28	22.2	1.23	22.4	1.29	22.5	1.19	22.6
12	-	-	-	-	-	-	-	-	4.94	116.2
1' ^a	0.09	-4.0	0.08	-4.0	0.07	-4.2	0.09	-4.3	0.06	-4.2
	0.08	-4.7	0.07	-4.7	0.06	-5.2	0.01	-5.2	0.06	-5.0
2'	-	17.9	-	17.9	-	17.9	-	17.9	-	17.8
3'	0.86	25.8	0.85	25.8	0.86	25.6	0.89	25.7	0.87	0.87

^a Diastereotopic methyl groups; no stereochemical assignments.

RESULTS AND DISCUSSION

In continuation of our study on the selectivity of ligand atoms, we were interested in oxygen- and sulfur-containing molecules which allow a direct comparison of their binding properties. The β-lactams with their annelated seven-membered rings (**1** to **5**, Scheme 1) proved to be excellent candidates. However, these compounds were available only in (7*R*),(8*R*),(10*R*)-configuration, i.e. as pure enantiomers. In order to produce diastereomeric interactions in the **Rh*** ... ligand adducts, we had to prepare a non-racemic mixture of (*R*)-**Rh*** and (*S*)-**Rh*** (2:1) (“inverted” dirhodium experiment conditions); for further details see Experimental. Thereby, we monitored complexation shifts (Δδ) for all substrate atoms providing information for evaluating and comparing the chalcogen donor properties. However, no dispersion effects Δν appear at the substrate signals due to the “inversion” of the dirhodium method conditions⁸ but,

conversely, such effects can be observed for the **Rh*** signals affording intriguing information on the ligand $\cdots$ **Rh*** interaction within the adduct. All NMR data are collected in Tables 1 to 4.

Table 2. ^1H and ^{13}C complexations shifts ($\Delta\delta$, in ppm) of β -lactam derivatives **1** to **5** in the presence of an equimolar amount of **Rh***; in ppm relative to TMS; solvent: CDCl_3 .

	1		2		3		4		5	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
2a	+0.32	+2.0	+0.24	+1.6	+0.18	+0.6	+0.10	+0.4	+0.26	+1.1
2b	+0.06		+0.21		+0.08		+0.20		+0.23	
3	-0.42	-0.6	+0.06	-0.7	-0.23	+0.2	+0.21	+0.1	-	+0.4
4	-0.45	-3.3	+0.10	-0.4	-0.15	-4.0	+0.22	-0.6	4a: +0.02 4b: +0.04	+0.1
5a	+0.28	+1.9	+0.08	-0.3	+0.42	+2.7	+0.15	-2.8	-0.52	-1.0
5b	+0.06		+0.11		+0.44		+0.16		+0.05	
6a	-	-	-	-	-	-	-	-	-0.06	-0.8
6b									+0.12	
7	+0.61	+1.0	+0.29	+1.4	+0.57	+0.6	+0.31	+0.9	+0.29	+0.6
8	+0.84	-2.0	+0.60	-2.2	+0.63	+0.4	+0.30	-0.6	+0.31	-1.0
9	-	+3.3	-	+3.1	-	+1.8	-	+4.1	-	+5.2
10	+0.22	+0.3	+0.17	0.0	+0.09	-0.5	+0.15	0.0	+0.22	-0.4
11	-0.31	-1.3	-0.21	-0.8	-0.19	-0.9	-0.07	-0.4	-0.08	-0.3
12	-	-	-	-	-	-	-	-	+0.54	-1.8
1'	-0.01	-0.6	-0.06	-0.2	-0.07	-0.3	-0.03	-0.2	-0.05	-0.3
	-0.09	+0.4	0.00	0.0	-0.02	-0.1	+0.07	0.0	0.00	-0.1
2'	-	-0.1	-	-0.1	-	0.0	-	0.0	-	-0.1
3'	-0.04	0.0	0.00	0.0	-0.05	0.0	-0.01	0.0	0.00	0.0

CHALCOGEN LIGANDS AND ADDUCT FORMATION MODES

As mentioned before, the atomic site within a substrate molecule binding to **Rh*** can be estimated from complexation shifts⁴ ($\Delta\delta$, Table 2). This parameter adopts positive values of moderate magnitudes (deshielding) if the nucleus under inspection is close to the ligating atom whereas $\Delta\delta$ -values are close to zero, maybe even negative, if they are further away. The reason for deshielding is a slight increase of the inductive effect of the ligating atom compared to the free species.⁹ Both ^1H and ^{13}C are useful but ^{13}C mostly provides more lucid information due to its higher chemical shift sensitivity and due to the fact that it is often closer to the ligating atom than the next-nearest hydrogen.

As reported before,^{4,10} sulfur and oxygen belong to different categories as far as their binding properties to **Rh*** are concerned. Sulfur – as a third-row element – is a soft Lewis base and binds strongly; using both mechanisms, electrostatic and orbital (HOMO-LUMO) interaction.¹¹ In contrast, oxygen – as a

second-row element – is a hard Lewis base. Here, HOMO-LUMO interactions are weak, and essentially it is electrostatic interaction which is involved in adduct formation.^{6,7} For a more detailed analysis we calculated molecular orbital energies by density functional methods (B3LYP 6-31G*).¹² In order to reduce calculation times and to avoid a conformational analysis of the side chain attached to C-8, we replaced the TBDMS-O-CH(CH₃) group by CH₃ (**1'** – **5'**); we expect no significant contributions of that molecular moiety to the molecular orbitals discussed.

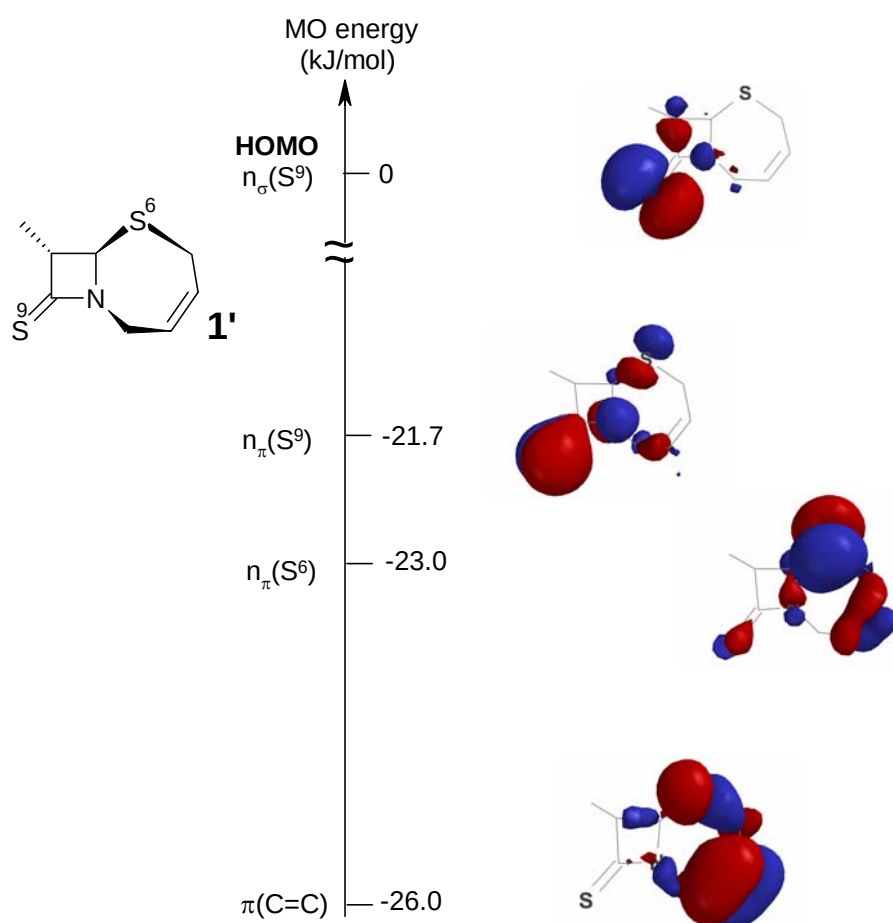


Figure 1. Energies of the highest occupied molecular orbitals of **1'**, the 8-methyl analogue of **1**, relative to the HOMO energy; density functional calculations B3LYP 6-31G*.¹²

As expected, a S > O preference is observed for the β -lactams **1** to **5**. In the 9-thia-thiazepam **1**, both atoms X and Y are sulfur so that, principally, both are available as binding sites. An inspection of the $\Delta\delta$ -values, however, reveals that it is basically the doubly bonded sulfur S-9 which binds to **Rh***: $\Delta\delta(C-9) = +3.3$ ppm (Table 2). The endocyclic sulfur S-6 may contribute [$\Delta\delta(C-5) = +1.9$ and $\Delta\delta(C-7) = +1.0$ ppm] but distinctly to a lesser extent. This selectivity can be rationalized by inspecting the highest occupied molecular orbitals of this molecule (Figure 1).

The two highest occupied orbitals of **1'** involve the free electron pairs of S-9, and it is particularly the HOMO which stabilizes the binding by orbital interaction. Only the third orbital, ca 23 kJ/mol lower than the HOMO, is essentially a free electron pair of the endocyclic S-6 oriented perpendicularly with respect to the C-5 – S-6 – C-7 plane. Any further occupied orbitals, e.g. the π -orbital of the carbon-carbon double bond is even lower in its energy and plays no significant role. Indeed, all complexation shifts of olefinic hydrogens and carbons are negative (Table 2) indicating that they are far away from the complexation site and exposed to shielding influences of the Mosher acid phenyl groups. The predominance of the S-9 interaction ($\text{HOMO}(\mathbf{1}') \rightarrow \text{LUMO}(\text{Rh}^*)$), is further supported by the possibility of back-donation: $\text{HOMO}(\text{Rh}^*) \rightarrow \text{LUMO}(\mathbf{1}')$ (see Figure 2).

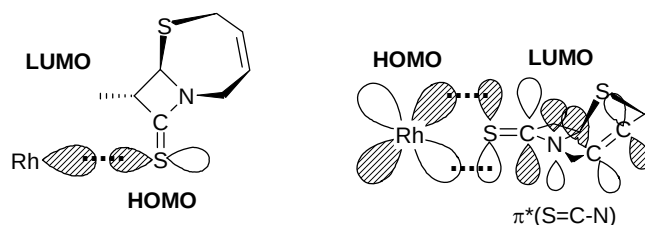


Figure 2. Schematic representations of the HOMO-LUMO interaction (left) and back-donation (right) in the $\text{Rh}^* \cdots \mathbf{1}'$ - adduct.

Coordination of the 9-thia-oxazepam **2** is analogous to that of **1** because there is a C=S group in **2** as well [$\Delta\delta(\text{C-9}) = +3.1$ ppm, Table 2]. On the other hand, it is the sulfur atom of the thiazepam **3** which binds to Rh^* [$\Delta\delta(\text{C-9}) = +1.8$ ppm, only]. S-6 is positioned inside the seven-membered ring so that the HOMO-LUMO interaction is expected to be weaker than in **1'** and **2'**. Back-donation involves only the π^* -orbital of **3'** (Figure 3), another argument for a weaker $\text{Rh}^* \cdots \text{S}$ binding.

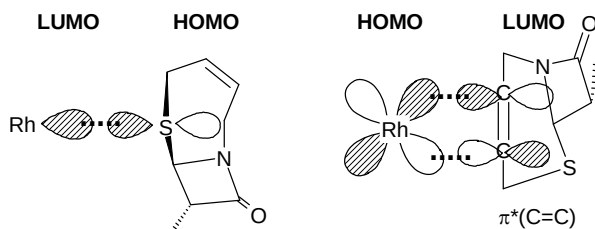


Figure 3. Schematic representations of the HOMO-LUMO interaction (left) and back-donation (right) in the $\text{Rh}^* \cdots \mathbf{3}'$ - adduct.

In the oxazepam **4** where no sulfur is available, the carbonyl oxygen atom O-9 is by far the dominating binding site: $\Delta\delta(\text{C-9}) = +4.1$, $\Delta\delta(\text{C-5}) = -2.8$ and $\Delta\delta(\text{C-7}) = +0.9$ ppm (Table 2). Electrostatic charges at oxygen atoms may play a role in this preference: O-9, -0.472 and O-6, -0.425 e.u. A HOMO-LUMO

contribution, although weaker than in the thio-analogues, may contribute as well. The HOMO of **4'** is an orbital consisting of the in-plane n-orbital of O-9, the p-orbital of the nitrogen and the π -orbital of the C=C double bond. The MO which is essentially the C=C π -orbital is ca 25.5 kJ/mol lower in energy, and the highest orbital involving free electron pairs of the endocyclic O-6 is even lower, namely 27.5 kJ/mol. The carbonyl oxygen atom of the carbazepam **5** is the binding site as well: $\Delta\delta(\text{C-9}) = +5.2$ ppm whereas the exocyclic double bond, although in principle a donor as well,¹³ is not involved as can be read from the insignificant $\Delta\delta$ -values of the olefinic hydrogens and carbons (Table 2). This is in accordance with the MO energies which are analogous to those of **4**.

In summary, a sequence in **Rh*** coordination selectivities can be deduced from these considerations:

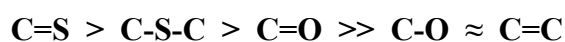


Table 3. ^1H , ^{13}C and ^{19}F shifts and complexations shifts ($\Delta\delta$, in ppm) of **Rh*** as pure complex and in the presence of an equimolar amount of the β -lactam derivatives **1** to **5**; in ppm relative to TMS; solvent: CDCl_3

	Rh* δ (ppm)	$\Delta\delta$ (ppm)				
		1	2	3	4	5
OCH_3	3.17	0.00	-0.03	-0.03	-0.04	-0.02
OCH_3	54.7	0.0	-0.1	0.0	0.0	0.0
<i>ipso-C</i>	131.7	-0.1	-0.1	0.0	+0.2	-0.1
<i>ortho-CH</i>	7.27	+0.03	-0.02	-0.01	-0.01	0.00
<i>ortho-CH</i>	127.6	0.0	0.0	0.0	+0.1	0.0
<i>meta-CH</i>	7.20	+0.04	+0.02	-0.01	+0.01	+0.02
<i>meta-CH</i>	129.2	+0.1	+0.1	0.0	-0.1	+0.1
<i>para-CH</i>	7.10	+0.05	+0.04	0.00	+0.02	+0.03
<i>para-CH</i>	128.0	+0.1	+0.1	+0.1	+0.1	+0.1
<i>quart.-C</i>	84.3	+0.1	+0.2	+0.1	0.0	+0.2
COO	185.9	+0.4	+0.7	+0.4	+0.9	+0.5
CF_3	122.7	0.0	+0.1	0.0	+0.1	0.0
CF_3	-72.5	+0.1	+0.2	+0.1	+0.4	0.0

There is another NMR spectral parameter which reacts on adduct formation; namely the complexation shifts $\Delta\delta$ of the carboxyl carbons in the Mosher acid residues (COO , Table 3) which are the only significant ones among all **Rh*** hydrogen and carbon atoms. Recently, Deubel has shown that the Rh–Rh distance is increased on coordination of an axial ligand.¹¹ Such bond elongation can influence the O–C–O bond angle in the carboxylates and, thereby, affect the ^{13}C chemical shifts; i.e. complexation shifts larger than experimental error limits (± 0.1 ppm) should be observable. And this is, indeed, the case: **1**, +0.4; **2**, +0.7; **3**, +0.4; **4**, +0.9; **5**, +0.5 ppm (Table 3).

DIASTEREOMERIC DISPERSIONS

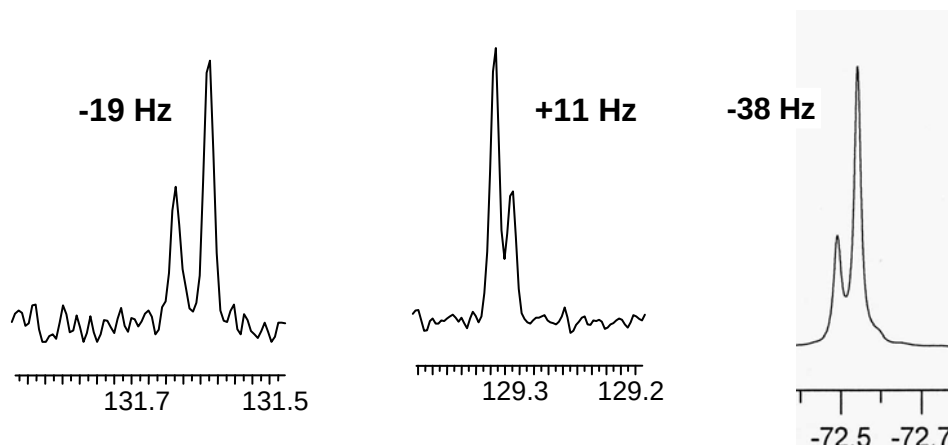


Figure 4. Signal dispersions $\Delta\nu$ of the *ipso*- (left), the *meta*-carbon (central) and of **Rh*** and the ^{19}F NMR signal (right) in presence of an equimolar amount of **5**.

Table 4. ^1H , ^{13}C and ^{19}F dispersion effects of **Rh*** ($\Delta\nu$, in Hz; recorded at 11.7 Tesla, if not otherwise noted) in the presence of an equimolar amount of the β -lactam derivatives **1** to **5**; solvent: CDCl_3 .

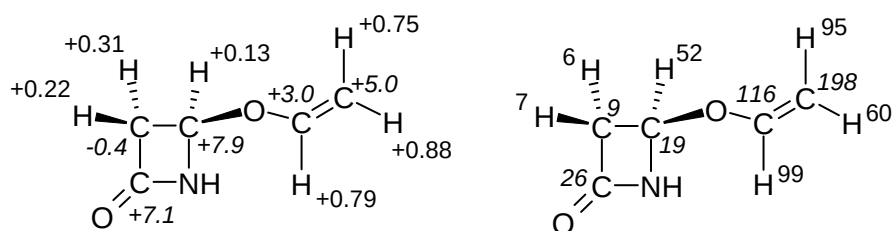
	1	2	3	4	5
OCH_3	-2	+6	-4	+4	0
OCH_3	0	+7	0	+8	0
<i>ipso</i> -C	0	0	0	0	-19
<i>ortho</i> -CH	0	0	0	0	0
<i>ortho</i> -CH	0	-9	0	-13	0
<i>meta</i> -CH	0	0	0	0	0
<i>meta</i> -CH	0	0	0	0	+11
<i>para</i> -CH	0	-8	0	0	0
<i>para</i> -CH	0	0	0	0	0
<i>quart.</i> -C	0	0	0	0	0
COO	0	0	0	0	0
CF_3	0	0	0	0	0
CF_3^a	-6	+47	-19	+40	-38

For the first time in our research project on the potential of the dirhodium method, “inverted” dirhodium experiment conditions (“non-racemic **Rh***” and enantiopure ligands) have been employed. They allowed to monitor diastereomeric dispersion effects ($\Delta\nu$, in Hz; Figure 4 and Table 4) at the ^1H , ^{13}C and ^{19}F signals of the dirhodium complex.⁸

Although all β -lactams **1** to **5** belong to the same enantiomeric series, there is no pattern in the signs of the observed dispersion effects (Table 4) which would raise one’s hopes that a correlation rule for

determining absolute configurations may emerge from those data, as we have reported for chalcogenuranes¹⁴ and some phosphine chalcogenides.¹⁵

Since, however, it is not allowed to conclude from dispersion data of **Rh*** in the “inverse” dirhodium method to dispersions of the ligand molecules in the “regular” dirhodium method, we performed an exploratory “regular” experiment with racemic 4-vinyloxyazetidin-2-one (**6**), a structurally related β -lactam.¹⁶ Scheme 2 shows the complexation shifts (left) and dispersion effects (right) when this sample was recorded with an equimolar amount of enantiopure (*R*)-**Rh*** (recorded at 11.7 Tesla).



Scheme 2. Averaged complexation shifts ($\Delta\delta$, left) and dispersion effects ($\Delta\nu$, right) of 4-vinyloxyazetidin-2-one (**6**); for discussion see text; values in italics refer to ^{13}C , the others to ^1H .

The large complexation shifts ($\Delta\delta$) observed for any ^1H and ^{13}C atoms of **6** (Scheme 2, left) prove that an efficient coordination exists between **Rh*** and **6**, and that apparently both, the carbonyl oxygen and the $\text{C}=\text{C}$ group are involved. In addition, dispersion effects ($\Delta\nu$, in Hz) adopt exceptionally large values. Even if one considers that **6** is much smaller than in the β -lactams **1** to **5** and, thereby, inner-adduct steric repulsion is less pronounced, there is no doubt that the dirhodium method is an efficient tool for enantiodifferentiation of β -lactams in general.

EXPERIMENTAL

COMPOUNDS

(*R*)-**Rh*** and (*S*)-**Rh*** have been prepared separately according to a known synthetic pathway.¹³ Subsequently, the two samples were mixed in a ratio of 2 : 1 and dissolved in CDCl_3 . During the time required for all NMR experiments (a few days), there was no scrambling of the chiral Mosher acid residues. Such process would be easily detected by ^1H NMR spectroscopy because it would form a variety of diastereomeric dirhodium complexes with a large number of different methoxy signals. Instead, always one methoxy signals was observed only.

The β -lactam derivatives **1** to **5** were enantiopure possessing the (7*R*),(8*R*),(10*R*)-configuration; their syntheses will be published elsewhere.¹

NMR SPECTROSCOPY

^1H and ^{13}C NMR measurements were performed at 303 K under routine conditions on a Bruker DRX-500 spectrometer (resonance frequencies: ^1H , 500.1 MHz and ^{13}C , 125.8 MHz) using the XWIN NMR acquisition and processing software. A 5 mm triple broadband inverse probe equipped with z-gradient coil was used for ^1H and ^{13}C measurements. ^1H NMR, ^{13}C NMR, COSY, ^{13}C , ^1H -HSQC and ^{13}C , ^1H -HMBC experiments were performed by the use of standard Bruker software. Chloroform- d was used for all studies.

^{19}F NMR spectra were performed on a Varian Mercury 400 spectrometer (^{19}F resonance frequency 376.3 MHz), equipped with a 5 mm $^1\text{H}/^{19}\text{F}/^{13}\text{C}/^{31}\text{P}$ PFG auto-switchable probe. Each measurement was performed twice: at first, with the parameters spectral width ca 220 ppm, acquisition time 0.78 s, relaxation delay 4 s, 32K (64K) data matrix and ca. 80 transients, and then with the spectral width 16 ppm and acquisition time 5.3 s. The spectra were referred to ^{19}F signal of external CFCl_3 (0.0 ppm).

The dirhodium experiments were carried out as “inverted” standard experiments.⁴ (*R/S*)-**Rh*** (2 : 1) and an equimolar amount of the ligands **1** to **5**, respectively, were dissolved in 0.7 ml CDCl_3 . Quantities of 24.3 mg of **Rh*** (0.025 mmolar concentration) were employed. The dissolution process was accelerated by exposing the NMR sample tubes to an ultrasonic bath for a couple of minutes. No Mosher carboxylate ligand exchange between (*R*)-**Rh*** and (*S*)-**Rh*** took place under those conditions.

Note that $\Delta\nu$ -values are B_0 -dependent; in this work all dispersion values are given in Hz, as determined at $B_0 = 11.7$ Tesla corresponding to 500 MHz for ^1H , 125.7 MHz for ^{13}C , and at $B_0 = 9.4$ Tesla corresponding to 376.3 MHz for ^{19}F .

ACKNOWLEDGEMENTS

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