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Enantiodifferentiation of Aliphatic Ethers by the Dirhodium Method

Edison Díaz Gómez,[a] Dieter Albert,[a] Helmut Duddeck,*[a] Sergei I. Kozhushkov,[b] and Armin de Meijere[b]

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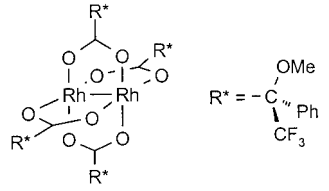
The enantiomers of chiral aliphatic ethers can easily be differentiated by the dirhodium method, i.e. by ^{1}H and ^{13}C NMR spectroscopy in the presence of the chiral auxiliary Rh_2[(+)-MTPA]$_4$. This is the first direct chiral recognition by spectroscopic methods in this class of ligand compounds.

Introduction

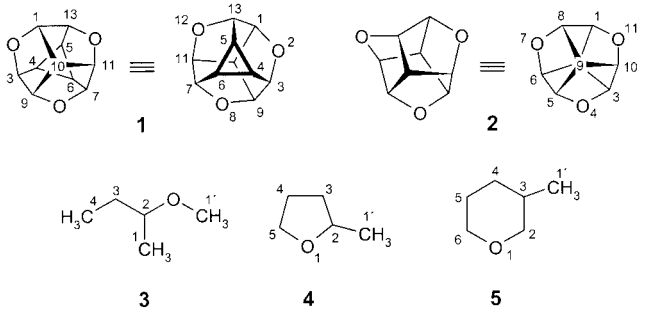
About a decade ago, we discovered the potential of the chiral enantiomerically pure dirhodium complex $Rh^{(+II)}_2$-[(+)-MTPA]$_4$ [**Rh***, MTPA-H = methoxytrifluoromethylphenylacetic acid ≡ Mosher's acid; Scheme 1] to act as an auxiliary for chiral recognition of alkenes by NMR spectroscopy.[1] In the following years, we explored this method and found that it complements the application of the classical chiral lanthanide shift reagents (CLSRs) and other chiral solvating agents[2] since it works perfectly well for a variety of chiral soft Lewis-base ligands for which CLSRs usually fail.[3] In all those cases, NMR signals (^{1}H, ^{13}C, ^{15}N, ^{31}P and ^{77}Se) are duplicated due to the formation of diastereomeric adducts (dispersion, $\Delta\nu$) so that the enantiomeric composition of the chiral ligands can be determined by signal integration. Moreover, it is convenient that positive (paramagnetic) complexation shifts ($\Delta\delta$; signal shifts due to the addition of **Rh***) are generally small and reach noticeable values only for atoms close to the binding site. Thus, the $\Delta\delta$ parameter indicates reliably the atom coordinated to the rhodium site in **Rh***. It should be added that the adduct-formation equilibria are generally fast, and only averaged NMR signals can be observed at room temperature.[3]

Very recently, we extended our studies to hard Lewis-base ligands (esters and amides)[4] and observed that, apparently, the auxiliary **Rh*** binds quite selectively if several such binding sites are available. This encouraged us to subject another hard functionality to the dirhodium complex experiment, namely chiral aliphatic ethers (Scheme 2), a class of compounds which occurs quite frequently among



Scheme 1. Structure of the dirhodium complex **Rh***.

natural products and is, therefore, an object of intensive synthetic effort.[5] There is no doubt that a safe and easy-to-apply analytical method to determine enantiomeric ratios is urgently required. To the best of our knowledge, however, such a method for direct observation does apparently not exist. Therefore, we want to communicate here our recent results of dirhodium-method experiments involving the aliphatic ethers **1**,[6] **2**[7–9] and **3**–**5**, the data of which are compiled in Table 1.



Scheme 2. Structures of ethers **1**–**5** investigated.

Results and Discussion

Racemic 2,8,12-trioxahexacyclo[8.3.0.0^{3,9}.0^{4,6}.0^{5,13}.0^{7,11}]-tridecane (**1**)[6] and 4,7,11-trioxapentacyclo-[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**2**)[9b] have been separated into their pure enantiomers by chiral HPLC, but there was no

[a] Institut für Organische Chemie der Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany
Fax: +511-762-4616
E-mail: helmut.duddeck@mbox.oci.uni-hannover.de
[b] Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen, Tammannstr. 2, 37077 Göttingen, Germany

Table 1. Chemical shifts (δ, in ppm), complexation shifts ($\Delta\delta$, in ppm) and dispersion effects ($\Delta\nu$, in Hz) of the ethers **1**–**5**; all NMR spectra recorded at 9.4 T (400.1 MHz ^{1}H and 100.6 MHz ^{13}C).

	Atom number		$\delta(^1H)$	$\Delta\delta(^1H)$[a]	$\Delta\nu(^1H)$	$\delta(^{13}C)$	$\Delta\delta(^{13}C)$[a]	$\Delta\nu(^{13}C)$
1	4, 5, 6		1.70	0.15	2	13.1	0.8	2
	3, 7, 13		4.47	0.55	–[b]	77.4	1.0	3
	1, 9, 11		4.52	0.52	–[b]	67.3	2.3	0
	10		3.08	0.33	6	47.5	0.4	1
2	2,9		2.44	0.36	16	43.5	0.8	0
	1,3,5,6,8,10		4.73	0.56	0–1[c]	86.7	1.5	0
3	1		1.12	0.39	6	18.4	–0.7	0
	2		3.23	1.06	7	78.0	5.4	12
	3		1.43	0.26	13 ± 1[c]	28.7	–1.2	10
			1.55	0.56	12 ± 2[c]			
	4		0.90	0.11	8	9.5	1.0	1
	1′		3.32	0.61	0	55.8	–0.1	23
4	2		3.88	1.07	16	75.0	5.0	12
	3[d]	*cis*	1.36	0.57	–[b]	32.9	0.4	1
		trans	1.95	0.43	–[b]			
	4[d]	*cis*	1.83	ca. 0.4[c]	–[b]	25.7	0.1	6
		trans	1.81	ca. 0.4[c]	–[b]			
	5[d]	*cis*	3.83	ca. 0.9[c]	–[b]	67.5	4.0	6
		trans	3.65	ca. 0.9[c]	–[b]			
	1′		1.18	0.35	15	20.8	0.3	4
5	2[e]	ax	2.98	0.74	12	74.7	3.3	1
		eq	3.81	0.88	17			
	3		1.69	0.57	–[b]	31.0	–0.5	8
	4[e]	ax	1.61	ca. 0.6[c]	–[b]	25.9	–0.4	2
		eq	1.58	ca. –0.2[c]	–[b]			
	5[e]	ax	1.13	0.24	0	31.9	–0.1	2
		eq	1.81	0.14	0–1[c]			
	6[e]	ax	3.32	0.75	8	68.1	3.9	1
		eq	3.88	0.91	15			
	1′		0.81	0.01	7	17.4	–0.3	2

[a] Complexation shifts $\Delta\delta$ are averaged values. [b] Some dispersion effects $\Delta\nu(^1H)$ were not safely detectable due to signal complexity (high-order effects) and/or overlap. [c] Value estimated from complex high-order signals. [d] Stereochemical assignments of CH_2 protons by NOE experiments, *cis* and *trans* relative to the methyl group. [e] Stereochemical assignment by inspection of signal multiplicities as well as homo- and heteronuclear 2D NMR correlations.

direct way of spectroscopic enantiodifferentiation. In its ^{1}H NMR spectrum, **1** shows high-order spin systems consisting of four signals (4/5/6-H, 10-H, 3/7/13-H and 1/9/11-H), the latter two being close together in the spectrum (Table 1). In spite of complex signal multiplicities, ^{1}H dispersion effects can easily be detected by using selective ^{1}H decoupling techniques. For example, if the transitions of 1/9/11-H are saturated, the 10-H signal appears as a sharp singlet which is duplicated in the presence of an equimolar amount of **Rh*** (Figure 1). ^{13}C signal splittings can be observed as well (Table 1).

Similarly, the NMR signal of 2/9-H of racemic **2**[7–9] splits into two when that of 1/3/5/6/8/10-H is saturated (Figure 2). Here, the two ^{13}C signals showed no significant diastereomeric dispersion (Table 1).

These surprisingly positive results prompted us to explore whether or not these signal dispersions are unique properties related to the special tetrahydrofuran ring conformations in **1** and **2**. So, we selected three chiral ethers (as racemates) representing a wide range of typical ether structures, acyclic dialkyl ethers (**3**), tetrahydrofurans (**4**) and tetrahydropyrans (**5**). The NMR spectroscopic data obtained for those ligands are collected in Table 1 as well. In each case we found diastereomeric dispersions suitable for the determination of enantiomeric excesses. Of course, ^{13}C signal intensities should be taken with caution for this purpose, but all our previous results showed that they reflect more or less the same composition in the mixtures of enantiomers as ^{1}H signals, probably as a consequence of the fact that all nuclei experience very similar spin-lattice relaxation and NOE interactions in both enantiomers.

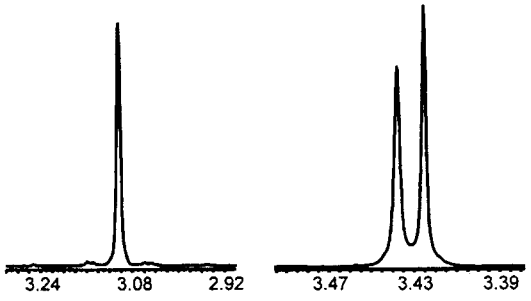


Figure 1. ^{1}H NMR signal of 10-H of **1** under 1/9/11-H decoupling; left: free ligand, right: in the presence of an equimolar amount of **Rh*** ($\Delta\nu$ = 6 Hz).

As a representative example, the NMR spectral sections in Figure 3 display typical signal splittings for H-1 and C-1′ of 2-butyl methyl ether (**3**).

These results prove that the dirhodium method is capable of recognizing chirality in aliphatic ethers whatever their

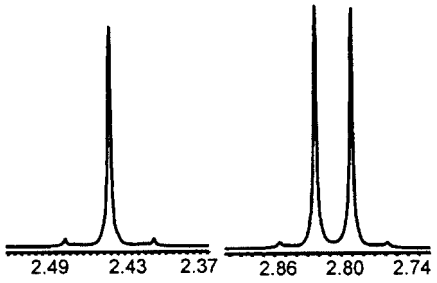


Figure 2. ^{1}H NMR signal of 2/9-H of **2** under 1/3/5/6/8/10-H decoupling; left: free ligand, right: in the presence of an equimolar amount of **Rh*** ($\Delta\nu$ = 16 Hz).

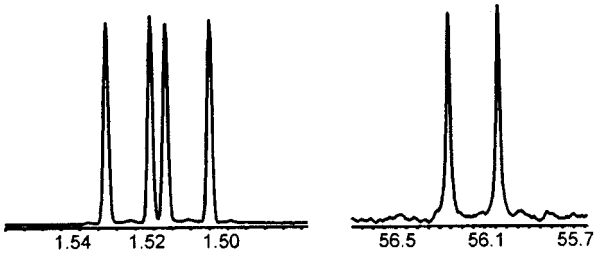


Figure 3. NMR signals of **3** in the presence of an equimolar amount of **Rh***; left: 1-H, $\Delta\nu$ = 6 Hz, ^3J(1-H,2-H) = 6.4 Hz; right: C-1′ ($\Delta\nu$ = 23 Hz).

molecular structure may be. Apparently, there is always a good chance to find at least one ^{1}H or ^{13}C signal reflecting this by signal splitting due to diastereomeric dispersion.

Currently, we are exploring the nature of the **Rh***–ether adducts and how to extend this method to aromatic ethers and acetals. At this stage, it is not yet clear whether a correlation rule for the determination of absolute configuration may emerge, a rule analogous to those described by us previously for some spirochalcogenuranes[11] and phospholene chalcogenides.[12]

Experimental Section

^{1}H (400.1 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded with a Bruker Avance DPX-400 spectrometer (9.4 T), some ^{1}H NMR spectra also at 500.1 MHz (^{1}H) with a Bruker Avance DRX-500 spectrometer. Chemical shift standard was internal tetramethylsilane (δ = 0 ppm for ^{1}H and ^{13}C). Signal assignments were assisted by DEPT, COSY, HMQC, HMBC and NOE experiments (standard Bruker software). The ether ligands **1**–**5** (Scheme 2) and **Rh*** were dissolved in $CDCl_3$ (0.7 mL) in equimolar amounts. Typically, **Rh*** (48.6 mg, 0.043 mM) was employed. No [D_6]acetone was added for assisting **Rh*** solubility[3,4,10] in order to avoid competition of acetone molecules with the ether ligands in the adduct formation. Instead, the dissolution process was accelerated by exposing the NMR sample tubes to an ultrasonic bath for 15–20 min. The syntheses of **Rh***,[1] **1**[6] and **2**[7–9] have been described before. The ethers **3** to **5** are commercially available.

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