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Chiral Recognition of Aminoalcohols by ^1H and ^{13}C NMR Spectroscopy using Binaphthyl Derivatives as Chiral Solvating Agents

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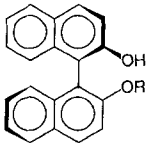
There is a considerable interest in methods to determine the enantiomeric purity of chiral compounds, the most important of which are several chromatographic and NMR methods based on the formation of diastereomeric complexes or derivatives. As NMR auxiliaries chiral lanthanide shift reagents (CLSR) [1–4] or other transition metal complexes [5], chiral solvating agents (CSA) [1, 4, 6–12], and chemical derivatizing agents (CDA) [1, 4, 13–17] can be used to convert the enantiomers into diastereomers.

In a preliminary ^1H NMR study [18] we found that mono- and dihydroxy-substituted binaphthols of the type **1** are useful agents in chiral recognition of aminoalcohols.



	1a	1b	1c	1d	1e
R	H	CH_3	$CH(CH_3)_2$	$PO(OCH_3)_2$	$SO_2N(CH_2)_4$

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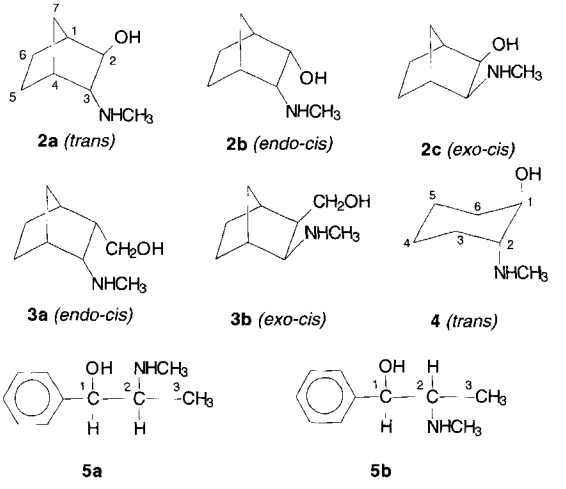
In the present paper we want to report the ^1H and ^{13}C NMR results obtained with the cyclic *N*-methyl-aminoalcohols **2**–**4** and the non-cyclic compounds **5** (**5a** = ephedrine; **5b** = pseudo-ephedrine) using the optically active binaphthyl derivatives **1a**–**e** as CSAs.

The substrate/agent mixtures were measured in $CDCl_3$ solution with different concentrations and molar ratios of substrate/agent. The ^1H and ^{13}C chemical shifts and separations $\Delta\delta$ found for the appropriate signals in the spectra are given in Tables 1–3. It can be seen that different signals in the ^1H and ^{13}C NMR spectra are doubled in dependence on the substrate as well as the agent. Furthermore, the shift differences $\Delta\delta$ of any host-guest pairs depend essentially on the molar ratio and the absolute concentration of the components in solution.

In the ^1H NMR spectra mainly the CH_3N signal showed to be a very useful indicator in observing the effect of chiral discrimination. Only in case of **2a** remarkable splittings for H-1 and H-2 could also be observed (Table 1). The largest shift differences were found for the host-guest pair (±)-**2a**/(+)-**1a**.



In case of the *endo-cis*-compound **2b** and *exo-cis*-compound **2c** the splittings found are essentially smaller. Nevertheless, the following order can be stated with respect to the magnitude of splitting:

2a (*trans*) >> **2b** (*endo-cis*) > **2c** (*exo-cis*).

The same order in splitting magnitude seems to be valid also for the hydroxymethyl compounds **3**, i.e. **3a** (*endo-cis*) > **3b** (*exo-cis*), although only small splittings of the CH_3N signals could be observed compared with **2**. Furthermore, for the host-guest pair (±)-**4**/(+)-**1a** (*trans*-hydroxy-methylamino-cyclohexane/binaphthol) a significantly higher value of the CH_3N signal separation was found. Finally, only low $\Delta\delta$ values were found for the non-cyclic compounds **5a** and **5b**.

The chemical shift non-equivalences could also be observed in the ^{13}C NMR spectra, in which partly considerable signal splittings were obtained (Tables 2 and 3). Number and magnitude of the signal separations are surprising taking into consideration that the anisotropy effects responsible for the transfer of chiral information in the ^{13}C NMR spectra, in general, are assumed to be not so significant as in the ^1H NMR spectra .

Tab. 1 ^1H Chemical shifts δ (ppm) and shift differences $\Delta\delta$ (ppm and Hz) of compounds **2**–**5** in absence and presence of **1a**–**e** (in $CDCl_3$; 0.02 M; T = 303 K)

Substrate/ Agent	Molar ratio (s/a)	δ (ppm)	$NHCH_3$ $\Delta\delta$ (ppm)	(Hz)
(±)-**2a**	– [a]	2.402	–	–
(±)-**2a**/(+)-**1a**	1:1 [b]	2.14; 2.02	0.120	36.0
	1:2 [c]	2.090; 1.901	0.189	54.9
	1:3 [d]	2.016; 1.783	0.233	69.8
(±)-**2a**/(–)-**1b**	1:1	2.345; 2.338	0.007	2.1
	1:2	2.302; 2.286	0.016	4.5
(±)-**2a**/(–)-**1c**	1:1 [e]	2.386	–	–
	1:2 [e]	2.341	–	–
(±)-**2a**/(–)-**1d**	1:1	2.342; 2.295	0.047	13.9
	1:2	2.291; 2.207	0.084	25.3
(±)-**2a**/(–)-**1e**	1:1	2.355; 2.313	0.042	12.7
(±)-**2b**	–	2.435	–	–
(±)-**2b**/(+)-**1a**	1:1	2.360; 2.342	0.018	5.6
	1:2	2.310; 2.276	0.034	10.5
(±)-**2b**/(–)-**1b**	1:1	2.392; 2.383	0.009	2.6
	1:2	2.383; 2.364	0.019	5.6
(±)-**2c**	–	2.408	–	–
(±)-**2c**/(+)-**1a**	1:1	2.388; 2.382	0.006	1.9
	1:2	2.369; 2.357	0.012	3.6
(±)-**2c**/(–)-**1b**	1:1	2.404; 2.402	0.002	0.6
	1:2	2.402; 2.398	0.004	1.4
(±)-**2c**/(–)-**1d**	1:1	2.399; 2.394	0.005	1.5
	1:2	2.393; 2.384	0.009	2.8
(±)-**3a**	–	2.290	–	–
(±)-**3a**/(+)-**1a**	1:1	2.312; 2.307	0.005	1.5
	1:2	2.297; 2.288	0.009	2.6
	1:3	2.288; 2.276	0.012	3.4
(±)-**3b**	–	2.415	–	–
(±)-**3b**/(+)-**1a**	1:10	2.263; 2.253	0.010	3.0
(±)-**4**	–	2.39	–	–
(±)-**4**/(+)-**1a**	1:1	2.346; 2.317	0.029	8.8
	1:2	2.276; 2.225	0.051	15.3
	1:1 [f]	2.104; 1.985	0.119	35.6
(±)-**5a**	–	2.484	–	–
(±)-**5a**/(+)-**1a** [g]	1:1	2.444; 2.424	0.020	5.7
(±)-**5b**	–	2.437	–	–
(±)-**5b**/(+)-**1a** [h]	1:1	2.411; 2.398	0.013	3.9

[a]) H-1 δ = 2.08; H-2 δ = 3.22 [b]) H-1 δ = 1.99, 1.93; $\Delta\delta$ = 0.06 ppm (15.8 Hz); H-2 δ = 3.04, 2.81; $\Delta\delta$ = 0.23 ppm (68.5 Hz) [c]) H-1 δ = 2.02, 1.93; $\Delta\delta$ = 0.09 ppm (26.2 Hz); H-2 δ = 3.03, 2.68; $\Delta\delta$ = 0.35 ppm (104.5 Hz) [d]) H-1 δ = 2.18, 1.91; $\Delta\delta$ = 0.27 ppm (79.8 Hz); H-2 δ = 2.98, 2.55; $\Delta\delta$ = 0.43 ppm (130.5 Hz) [e]) 0.01 molar [f]) 0.2 molar [g]) H-3 (two doublets, $\Delta\delta$ = 0.014 ppm (4.3 Hz) [h]) H-3 (two doublets, $\Delta\delta$ = 0.002 ppm (0.7 Hz)

Tab. 2 ^{13}C Chemical shifts δ (ppm) of compounds **2, 4** and **5** (in $CDCl_3$; 0.05 M; T = 303 K)

Cpd.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	$NHCH_3$
2a	44.57	81.21	72.95	38.39	19.81	25.38	34.65	34.99
2b	42.27	67.80	60.51	39.88	20.64	19.72	33.94	35.64
2c	42.09	73.00	66.84	43.26	23.84	27.53	32.07	36.75
4	73.53	65.07	29.66	24.96	24.45	33.68	–	33.21
5a	72.96	60.40	14.31	–	–	–	–	34.03
5b	77.66	61.38	15.72	–	–	–	–	33.50

To obtain a quantitative measure for the stability of the association complexes we estimated the association constants by measuring a dilution series using the so-called "equimolar method" [19]. The values of association constants K and Free Enthalpies $\Delta G°$ for some complexes obtained on the basis of the CH_3N signal splittings are given in Table 4. The determination of the induced chemical shifts (difference of the signal positions in presence and absence of the CSA), which are required for the graphical determination of the association constants, was carried out using the substrate as racemates or, if available, as enantiomers. In the use of racemates posssible interactions between the diastereomeric complexes in solution have to be considered. However, as can be seen for the pair (+)-**2a**/(+)-**1a** and the pair (+)-**4a**/(+)-**1a** the K values obtained in this or the other way are in fairly good agreement.

The experimental findings show that the ^1H-chemical shift non-equivalences $\Delta\delta$ (Table 1) correspond generally to the association constants K of the formed diastereomeric complexes (Table 4) confirming that the stability of these complexes is an important prerequisite for observing the chemical shift non-equivalences. Both parameters depend on the sterical arrangement of the substituents as well as the rigidity of backbone of the substrate. The particularly high $\Delta\delta$ and K values found for the pair (±)-**2a**/(+)-**1a** point out that there is an optimal interaction between substrate and agent in this case. The considerable difference to the values found for the other complexes led us to the conclusion that the reason for this should be the formation of a cyclic substrate–agent complex, similarly to the findings of Reeder *et al.* [11] on the alkaloids quinine and quinidine, by simultaneous interaction between the both OH groups of **1a** and the CH_3NH as well as the OH groups of **2a**. The possibility of formation of such cyclic complexes was also confirmed by means of molecular modelling which demonstrated the preference of the *trans*-compound **2a** in this respect.

In case of **2b** and **2c** the interaction of both OH groups of the agent **1a** with both the CH_3NH and the OH group of the substrate, is hindered for sterical reasons. Therefore, only one of the both OH groups of **1a** should be needed for complexation with the NH group in **2b** and **2c**, respectively. This assumption is supported by the results using agents **1b**–**e** in which only one of the both OH functions is available for complexation. Whereas in case of **2b** and **2c** a change of agent **1a** by **1b** or **1d** did not change essentially the signal separations, with **2a**, in fact, a drastic decrease of the $\Delta\delta$ values was found (Table 1).

With agent **1c**, contrary to **1b**, not any signal separations were observed, possibly for sterical reasons due to the bulky isopropyl moiety. In the case of complex **2a** with the phosphorous ester derivative **1d** and the sulfate derivative **1e** we found again evident splittings of the CH_3NH signal. Surprisingly, the non-equivalences were found to be considerably larger than using the methoxy-substituted agent **1b**.

For the *trans*-disubstituted cyclohexane **4** an essentially lower $\Delta\delta$ value for the CH_3N signals and also lower association constants were found compared to the *trans*-disubstituted compound **2a**, which should to be explained with the flexibility of the cyclohexane ring system.

The comparably low signal separations observed for the non-cyclic compounds **5a** and **5b** as well as the lower K values

Tab. 3 ^{13}C Chemical shift differences $\Delta\delta$ (ppm) and Hz (in parentheses) of compounds **2**, **4** and **5** in presence of **1a–d** (in $CDCl_3$; 1:1; 0.05 M; T = 303 K)

Substrate	Agent	C-1	C-2	C-3	C-4	C-5	C-6	C-7	$NHCH_3$
(±)-**2a**	(+)-**1a**	0.058 (17.4)	0.031 (9.4)	–	0.017 (5.1)	0.021 (6.3)	0.006 (1.9)	0.057 (17.2)	0.012 (3.7)
	(+)-**1a** [a]	0.077 (23.1)	0.052 (15.7)	0.006 (1.8)	0.031 (9.2)	0.031 (9.2)	0.012 (3.7)	0.071 (21.3)	0.015 (4.6)
	(–)-**1b**	0.029 (8.8)	0.022 (6.7)	0.006 (1.8)	0.022 (6.5)	0.014 (4.1)	0.006 (1.7)	–	–
	(–)-**1c**	–	–	–	–	–	–	–	–
	(–)-**1d**	–	0.034 (10.2)	0.015 (4.4)	0.028 (8.5)	–	0.006 (1.9)	0.031 (9.2)	0.035 (10.6)
(±)-**2b**	(+)-**1a**	–	–	–	0.013 (3.9)	–	–	–	0.024 (7.3)
	(+)-**1a** [a]	0.009 (2.7)	–	0.009 (2.7)	0.028 (8.3)	0.009 (2.8)	–	–	0.052 (15.6)
	(–)-**1b**	–	–	–	0.006 (1.8)	–	–	–	0.011 (3.2)
	(–)-**1d**	0.010 (2.9)	–	–	0.020 (6.1)	–	–	–	0.038 (11.3)
(±)-**2c**	(+)-**1a** [b]	0.030 (8.9)	–	–	–	–	–	–	0.029 (8.7)
(±)-**4**	(+)-**1a**	0.031 (9.4)	–	0.034 (10.2)	0.007 (2.2)	–	0.006 (1.8)	–	0.032 (9.5)
(±)-**5a**	(+)-**1a**	0.014 (1.1)	–	–	–	–	–	–	0.043 (3.3)
(±)-**5b**	(+)-**1a**	0.010 (1.1)	–	–	–	–	–	–	0.036 (2.7)

[a] Molar ratio (s/a) 1:2 [b] Molar ratio (s/a) 1:3

Tab. 4 Association constants K (L mol^{-1}) and Free Enthalpies $-\Delta G°$ (kJ mol^{-1}) of selected complexes ($CDCl_3$; T = 303 K)

Substrate	Agent	Complex	K	$-\Delta G°$
(+)-**2a**	(+)-**1a**	(+)-**2a**/(+)-**1a**	37.6 ± 0.3	9.1
(±)-**2a**	(+)-**1a**	(+)-**2a**/(+)-**1a**	36.8 ± 1.6	9.1
(±)-**2a**	(+)-**1a**	(–)-**2a**/(+)-**1a**	37.4 ± 1.9	9.1
(±)-**2a**	(–)-**1b**	(+)-**2a**/(–)-**1b** [a]	5.4 ± 0.1	4.2
(±)-**2a**	(–)-**1b**	(–)-**2a**/(–)-**1b** [a]	4.5 ± 0.1	3.8
(–)-**2a**	(–)-**1d**	(–)-**2a**/(–)-**1d**	12.9 ± 0.2	6.4
(±)-**2c**	(+)-**1a**	(+)-**2c**/(+)-**1a**	5.0 ± 0.1	4.1
(±)-**2c**	(+)-**1a**	(–)-**2c**/(+)-**1a**	1.8 ± 0.01	1.4
(+)-**2c**	(–)-**1b**	(+)-**2c**/(–)-**1b**	2.1 ± 0.3	1.9
(+)-**4**	(+)-**1a**	(+)-**4**/(+)-**1a**	4.1 ± 0.1	3.5
(±)-**4**	(+)-**1a**	(+)-**4**/(+)-**1a**	5.7 ± 0.1	4.4
(±)-**4**	(+)-**1a**	(–)-**4**/(+)-**1a**	7.2 ± 0.1	5.0
(+)-**5a**	(+)-**1a**	(+)-**5a**/(+)-**1a**	4.4 ± 0.1	3.7
(–)-**5a**	(+)-**1a**	(–)-**5a**/(+)-**1a**	6.5 ± 0.2	4.7
(+)-**5b**	(+)-**1a**	(+)-**5b**/(+)-**1a**	5.2 ± 0.2	4.1
(–)-**5b**	(+)-**1a**	(–)-**5b**/(+)-**1a**	4.9 ± 0.2	4.0

[a] Assignment can be reversed

should also be referred to the conformative flexibility of these substrates causing a decreased stability of the formed diastereomeric complexes.

The ^{13}C NMR results given in Table 3 are not so representative with respect to a correlation with structural factors, though the high $\Delta\delta$ values, found especially for C-1 and C-7, also point at the exceptional position of the pair (±)-**2a**/(+)-**1a** compared to the others.

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Experimental

The ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer BRUKER ARX 300 (^1H: 300.13 MHz, ^{13}C: 75.47 MHz). The calibration of spectra was carried out using solvent peaks ($CDCl_3$: δ ^1H = 7.25 ppm, δ ^{13}C = 77.0 ppm). The assignments of the ^1H and ^{13}C NMR signals of the substrates were established recording DEPT, $^1H/^1H$ COSY, and $^{13}C/^1H$ COSY spectra [20].

Compounds (+)-**1a** and (–)-**1b** were prepared as given in [21] and [22]. The preparation of compounds (–)-**1d** and **2a-2c** is described in [18], that of **3a** and **3b** in [23]. The optically active compounds **3a** and **3b** for comparison purposes see [24]. Compounds **4**, (+)-**4** and (–)-**4**, respectively, were prepared as given in [25]. Ephedrine (**5a**) and pseudoephedrine (**5b**) were purchased from Aldrich.

Preparation of Pyrrolidine-1-sulfonic acid 2'-hydroxy-[1,1']binaphthalenyl-2-yl ester (**1e**)

0.5 g (1.43 mmole) (–)-1,1'-Binaphthyl-2,2'-diyl-sulfate ($[\alpha]_D^{25}$ = –648.8, c = 1, THF) [26] are dissolved in 25 g (0.35 mole) pyrrolidine under stirring. The mixture is refluxed for 8.5 h. After evaporating the remaining pyrrolidine the residue is dissolved in heated ethanol, cooled to 0 °C, and kept standing over night. The precipitation formed is filtered off and washed with ethanol. Yield 77%; F = 91 °C; $[\alpha]_D^{25}$ = –28.9 (c = 1, MeOH).

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