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DETERMINATION OF THE CHIRAL PURITY OF AMINOALCOHOLS BY ^{1}H NMR SPECTROSCOPY

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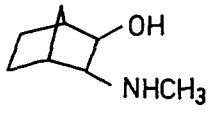
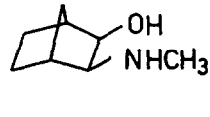
Abstract: 2,2'-Dihydroxy-1,1'-binaphthyl derivatives were used as chiral shift reagents in the chiral recognition of carbocyclic aminoalcohols. The induced chemical shift differences are dependent on the ability of one or both of the OH groups of the shift reagent to coordinate with the substrate molecule for reasons of structure and stereochemistry.

Introduction

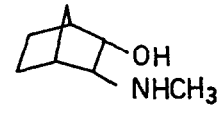
The NMR spectroscopy is one of the most important methods to determine the enantiomeric purity of chiral compounds. In order to use NMR as a tool for such determinations the presence of a chiral auxiliary is required converting the enantiomers into diastereomers. These auxiliaries can be divided into three types: chiral lanthanide shift reagents (CLSR),[1-3] chiral solvatation agents (CSA),[4-6] and chemical derivatizing reagents.[7-9]
In the course of our investigations of norbornyl compounds we were faced with the question of optical purity of the cyclic aminoalcohols 1 - 3.



1 (trans)

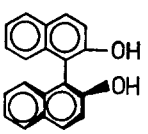


2 (exo-cis)



3 (endo-cis)

The use of chiral lanthanide shift reagents did not give acceptable separations of the signals in ^{1}H NMR spectra. Recently, Toda et al.[10,11] have found that 2,2'-dihydroxy-1,1'-binaphthyl (4) is useful as a chiral shift reagent in ^{1}H NMR spectroscopy to determine enantiomeric purity of a wide variety of organic compounds. Another compound on the basis of binaphthyl described by Shapiro et al.[12] to be useful in the chiral recognition of amines, is 1,1'-binaphthyl-2,2'-diylphosphoric acid (5). On the other hand, the optical purity of binaphthyl derivatives can be determined by using quinine as CSA.[5]



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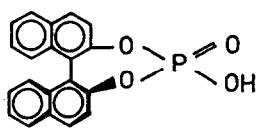

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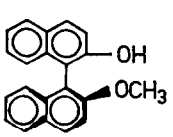
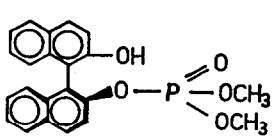
Stimulated by these results we have applied the optically active compounds 4 and 5 to the aminoalcohols 1 - 3. In case of 5, we did not observe any splitting of the methyl signals under the measuring conditions (80 MHz), however, a splitting occured by addition of 4 to the racemates of 1 - 3.

It has been of particular interest to study the relationship between chemical shift values and the steric position of substituents in the substrate and the structure of reagent. In addition to compound 4, the monosubstituted derivatives 6 and 7 should be tested whether they are useful in chiral recognition.



6



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Results and Discussion

The ^1H NMR measurements were performed on $CDCl_3$ solutions of the optically active compounds 4, 6 or 7 with the aminoalcohols 1 - 3, and the splitting of the NCH_3 signal was observed. In Table 1 the chemical shift values obtained for different host-guest molar ratios are given.

It can be seen that the largest $\Delta\delta$ values were obtained for the trans compound 1 using the binaphthol 4. In case of compounds 2 and 3 the signal separations are essentially lower.

From these differences it follows that the position of the substituents in the substrate is essential for an optimal host-guest complexation.

It can be shown by the model that only in case of trans compound 1 there is a good interaction between the CH_3NH and OH group of the substrate, and the two OH groups of 4. For this reason, a stable complex with an unflexible conformation is formed. This is the cause for the significantly high signal splitting. In case of compounds 2 and 3, for steric reasons, the interaction is only possible with the CH_3NH group. Therefore, only one of the two OH groups of the reagent is neccesary for complex formation.

This interpretation is supported by the results obtained using the reagents 6 and 7, in which one of the two OH functions is blocked. In case of 1 a drastic decrease of the $\Delta\delta$ values is observed, whereas with the compounds 2 and 3 a change of the reagent 4 by 6 or 7, in fact, remains without consequences.

The results obtained show that the splittings of the indicator signals in the ^1H NMR spectra of compounds 1 - 3 in the presence of the binaphthyl derivatives used are large enough for a quantitative determination of the enantiomeric purity. In practice it is important to find the optimal molar ratio between substrate and reagent not only to achieve a sufficient separation of signals, but also to avoid an overlapping with other signals in the spectra.

Table 1

Chemical shift values of the CH_3N protons of compounds 1 - 3 in the absence and presence of (+)-4, (-)-6, and (-)-7 (in $CDCl_3$, 0.1 molar)

Substrate	Reagent	Molar ratio (s/r)	δ_{CH_3} (ppm)		Δδ (Hz)
(±)-1 (trans)	-	-	2.37		-
	(+)-4	1 : 1	1.75	2.00	19.6
	(+)-4	1 : 2	1.52	1.82	23.7
	(+)-4	1 : 3	1.42	1.74	25.9
	(-)-6	1 : 1	2.16	2.19	3.0
	(-)-6	1 : 2	2.00	2.08	5.8
	(-)-7	1 : 1	2.11	2.24	9.5
	(-)-7	1 : 2	1.96	2.15	14.9
(+)-1	(+)-4	1 : 1	1.73		-
(-)-1	(+)-4	1 : 1	1.99		-
(±)-2 (exo-cis)	-	-	2.69		-
	(+)-4	1 : 1	2.61	2.63	1.8
	(+)-4	1 : 2	2.11	2.14	2.8
	(+)-4	1 : 3	1.95	1.99	3.4
	(-)-6	1 : 1	2.37	2.38	0.8
	(-)-6	1 : 2	2.33	2.35	1.7
(±)-3 (endo-cis)	-	-	2.33		-
	(+)-4	1 : 1	2.16	2.22	5.0
	(+)-4	1 : 2	1.95	2.04	7.8
	(-)-6	1 : 1	2.28	2.32	3.7
	(-)-6	1 : 2	2.20	2.28	6.6
	(-)-7	1 : 2	2.16	2.25	7.8
(-)-3	(+)-4	1 : 2	1.96		-

EXPERIMENTAL

The NMR spectra were recorded with an 80 MHz spectrometer BS 487 C from TESLA. Compounds (+)-4, (+)-5, and (-)-6 were prepared as given in the literature.[13-16] The newly synthesized compound (-)-7 was prepared by partial methylation of (+)-2-hydroxy-1,1'-binaphthyl phosphoric acid[16] with diazomethane: m. p. = 164 - 166 °C (crystallized from EtOH); $[\alpha]_D^{24.5}$ = -6.3° (c = 1.25, MeOH); (racemate: m. p. = 177 - 181 °C); ^{1}H NMR methyl: 2 doublets, δ = 3.51 ($^3J_{^1H-^{31}P}$ = 11.5 Hz); δ = 3.13 ($^3J_{^1H-^{31}P}$ = 11.5 Hz); anal. calcd. for $C_{22}H_{19}O_5P$: C, 67.00; H, 4.86; P, 7.85; found: C, 66.75; H, 4.95; P, 7.10.

2-exo-Hydroxy,3-endo-methylamino-norbornane (1): (±)-1, m. p. 72 - 75 °C, was synthesized by reaction of exo-norbornane epoxide with methylamine in a bomb tube.[17] (+)- and (-)-1 were prepared by optical resolution of (±)-1 using (+)-tartaric acid.[17] (+)-1, m. p. 91 - 93 °C, $[\alpha]_D^{25}$ = +30.5° (c = 1, EtOH); (-)-1, m. p. 91 - 92 °C, $[\alpha]_D^{25}$ = -29.7° (c = 1, EtOH), anal. calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92; found: C, 67.92; H, 10.87; N, 10.04.

2-exo-Hydroxy,3-exo-methylamino-norbornane (2): Norbornane reacts with chloramine-T in the presence of a catalytic amount of osmium tetroxide to 2-exo-hydroxy,3-exo-(N-tosyl-amino)-norbornane.[18] Methylation in alkaline ethanol gives 2-exo-hydroxy,3-exo-(N-tosyl-methylamino)-norbornane. The following treatment with conc. hydrochloric acid in a bomb tube (72 h, 100 °C) afforded the hydrochloride of 2, m. p. 237 - 239 °C, which was converted into the free base (±)-2, m. p. 78 - 80 °C, using a calculated amount of ethanolic sodium hydroxide at 0 °C, and recrystallized from hexane. Anal. calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92; found: C, 68.12; H, 10.98; N, 10.10.

2-endo-Hydroxy,3-endo-methylamino-norbornane (3): These endo-cis-isomers were prepared by conversion of the appropriate trans-methylamino-norbornanols 2 via the N-benzoyl derivatives.[19] (±)-3, m. p. 53 - 55 °C; (-)-3, m. p. 64 - 66 °C, $[\alpha]_D^{25}$ = -25° (c = 1, EtOH), anal. calcd. for $C_8H_{15}NO$: C, 48.04; H, 10.71; N, 9.92; found: C, 67.89; H, 10.81; N, 9.98.

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