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Analysis of Chiral Carboxylic Acids by NMR Using New Optically Active Amines

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Abstract: The two amines (+)-9-(1-aminoethyl)phenanthrene 3 and (-)-9-(1-amino-ethyl)anthracene 4 have been prepared by resolution of the corresponding racemic amines and tested as auxiliaries for the NMR analysis of racemic carboxylic acids including highly polar acids such as 6. (-)-4 turns out to be the most effective auxiliary among the arylmethylamines of type 1.

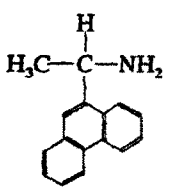
Optically active amines are well known auxiliaries for the NMR determination of the enantiomeric ratio of chiral carboxylic acids. In most cases amines of type 1 have been used[1a].(For recent use of 1,2-diphenyldiaminoethane see[1b].)

$$Ar - CH(CH_3) - NH_2 + R^* - CO_2H \rightleftarrows Ar - CH(CH_3) - NH_3^{\oplus}\ R^* - CO_2^{\ominus}$$

1 a Ar = phenyl
b Ar = 1-naphthyl
c Ar = 2-naphthyl

2

Unfortunately, the separation of the NMR signals obtained from diastereomeric salts of type 2 is quite often small. Therefore, we have reinvestigated amines of type 1, possessing however larger aryl groups which promise larger anisotropic effects[2] and thus larger NMR signal separations. The enantiomers (+)-3 and (-)-4, hitherto unknown, were prepared from the racemic amines and (*R*)-mandelic acid. *rac*-3 was



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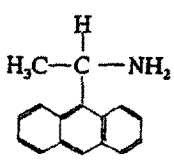

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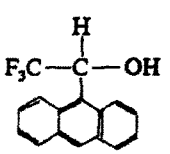

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prepared for the first time by hydrogenating the corresponding oxime[3,4], and *rac*-4 according to lit.[5,6]. The enantiomeric purity was determined by NMR using (+)-2,2,2-trifluoro-1(9-anthryl)ethanol (5) to

≥ 98% ee for both compounds. (+)-3 and (-)-4 were added to different carboxylic acids (equimolar in $CDCl_3$; c = 0.1 mol/L) and the ^{1}H-NMR signal separation was compared with that from 1b, the most effective auxiliary among the known amines of type 1. (-)-4 gives the largest separation of the NMR-signals (table 1) and is thus the most suitable auxiliary among the amines of type 1. Compound 3 gives salts of type 2 which are only sparingly soluble in $CDCl_3$, thus prohibiting its wide application.

Table 1. $\Delta\Delta\delta$-values (in ppm) of the diastereomeric salts 2 formed from *rac*-carboxylic acids and the optically active amines 1b, 3 and 4 in $CDCl_3$ at room temp. ; c = 0.1 mol/L.

carboxylic acid \ amine		1b	3	4
H_3C-CHBr-CO_2H	2-H	0.035	0.042	0.08
	3-H	0.119	0.060	0.102
H_3C-CH(C_6H_5)-CO_2H	2-H	0.084	a)	0.109
	3-H	0.019	a)	0.039
H_5C_6-CH(OH)-CO_2H	2-H	0.118	a)	0.366
H_3C-CH(NH-$COCF_3$)-CO_2H	2-H	0.017	a)	0.07
	3-H	0.010	a)	0.099

a) Salts are only sparingly soluble in $CDCl_3$.

Besides simple carboxylic acids, also the highly polar carboxylic acid 3-hydroxypentanediacid-monomethylester 6 was investigated. This compound[7], a precursor for the synthesis of biologically interesting compounds, was chosen because its enantiomeric ratio could be determined only after two-fold derivatization (3 steps) followed by HPLC-investigation of the diastereomers[8]. 6 was added to several amines of type 1 and the mixture investigated by ^{1}H- and ^{13}C-NMR spectroscopy. Again, 4 gave the largest separations. The ^{1}H-NMR-spectrum is complex due to the presence of a five spin system. Therefore, quantification of the ratio was performed via ^{13}C-NMR (figure 1). The separation ($\Delta\Delta\delta$) of the CH_2 signal at 42.2 ppm is 0.07 ppm at 25 °C and reaches 0.15 ppm at -15 °C.

$$H_3C-O_2C-CH_2-CH(OH)-CH_2-CO_2H$$

6

In summary, the analysis of *rac*-carboxylic acids including polar species is best performed with (+)-4 as auxiliary. Larger aromatic substituents than that in 4 probably would further enlarge the separation of the NMR-signals. However, the solubility of the salts of type 2 with large groups in chloroform and

other suitable NMR-solvents is expected to decrease preventing NMR measurements (see 3). It should also be mentioned that 4 has a structure similar that of 5. Obviously, the 9-anthryl substituent favourably contributes to the ability of a compound to act as an auxiliary for NMR analysis.

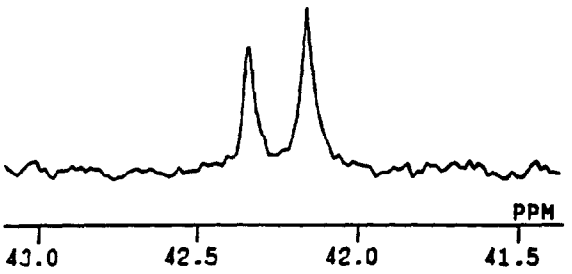

Fig. 1. 100 MHz ^{13}C-NMR spectrum (part only) in $CDCl_3$ of the salt between(-)- 4 and 6 at -15 °C. Only the split signal of one of the two CH_2 groups is shown. Ratio of the enantiomers 55:45.

Experimental

(+)-9-(1-Aminoethyl)-phenanthrene (3). 3.0 g (13 mmol) 9-acetylphenanthrenoxime[3,4] is dissolved in 130 mL methanol. After addition of 0.3 g Raney-nickel the mixture is hydrogenated at 3 bar over 48 hours. The catalyst is filtered off and the solvent evaporated leaving 3.1 g oil. The oil is purified by dissolving in dry diethylether, through which gaseous hydrogen chloride is bubbled. The precipitate is washed with diethylether yielding the hydrochloride, m.p. 261-262 °C. The salt is added to a 1:1 mixture of 25% ammonia and diethylether and the mixture is stirred for 30 min. The ether layer is dried ($MgSO_4$) and the ether evaporated yielding 2.0 g, 9.0 mmol, 71 % of an oil. The oil and 1.3 g (9.0 mmol) (*R*)-mandelic acid are dissolved in chloroform and the solvent is evaporated. The residue is recrystallized 5 times from ethanol yielding 0.38 g (1.0 mmol, 11 %) of the corresponding salt, m.p. 194-195 °C. The crystals are added to 50 mL 25 % ammonia and 20 ml diethylether, and the mixture is stirred for 30 min. The ether phase is separated and the water phase extracted twice with each 20 mL aliquots of diethylether. The combined ether phase is extracted with 20 ml of saturated NaCl solution and dried over $MgSO_4$. Evaporation yields 0.20g (0.83 mmol, 10%) (+)-(3), m.p. 81-81.5 °C; $[\alpha]_D^{20}$ = +35 (chloroform, 0.57); ee ≥ 98 %.

^{1}H-NMR ($CDCl_3$): δ = 1.6 (d, J = 6.7 Hz, 3H, CH_3), 1.7 (s broad, 2H, NH_2), 4.9 (q, J = 6.7 Hz, 1H), 7.2 - 8.7 (m, 9H).

^{13}C-NMR ($CDCl_3$): δ = 24.6 (q), 46.5 (d), 122.0 (d), 122.4 (d), 123.4 (d), 123.5 (d), 126.1 (d), 126.3 (d),

126.6 (d), 126.7 (d), 128.5 (d), 129.7 (s), 130.1 (s), 130.7 (s), 131.7 (s), 141.3 (s).

$C_{16}H_{15}N$ (221.30)	Calculated:	C	86.84	H	6.83	N	6.33
	Found:	C	86.50	H	6.80	N	6.20

(-)-9-(1-Aminoethyl)anthracene (4). (±)-(4) is prepared by reducing 9-acetyl-anthracen-imin[5] with $NaCNBH_3$/acetic acid[6]; yield 96 %. Resolution was performed with (*R*)-mandelic acid as described above; m.p. of the ammonium salt 190-192 °C. (-)-4 is obtained from the salt in 8 % yield, m.p. 108-109 °C (from cyclohexane/ethylacetate). $[\alpha]_D^{20}$ = -17 (chloroform, 0.59). ee ≥ 98 %.

^{1}H-NMR ($CDCl_3$): δ = 1.8 (d, J = 7.0 Hz, 3H, CH_3), 2.0 (broad s, 2H, NH_2), 5.7 (q, J = 7.0 Hz, 1H), 7.3 - 8.3 (m, 9H).

^{13}C-NMR: δ = 23.8 (q), 46.1 (d), 124.4 (d), 124.9 (d), 127.0 (s), 128.8 (d), 129.2 (d), 129.2 (d), 131.6 (s), 137.5 (s).

References

[1a] Review: G.R. Weisman in Asymmetric Synthesis (Ed. J.D. Morrison), 1983, 1, 153.

[1b] R. Fulwood, D. Parker, Tetrahedron: Asymmetry 1992, 3, 25.

[2] For anisotropy effects in ^{13}C-NMR spectroscopy see: R.H. Levin, J.D. Roberts, Tetrahedron Lett. 1973, 135; H.O. Kalinowski, W. Lubosch, D. Seebach, Chem. Ber.1977, 110, 3733.

[3] W.E. Bachmann, C.H. Boatner, J. Am. Chem. Soc. 1936, 58, 2097.

[4] E. Mosettig, J. van de Kamp, J. Amer. Chem. Soc. 1930, 52, 3704.

[5] M. Martynoff, M. Chanvin, M. Crumez, N. Lefèvre, Bull. Soc. Chim. Fr. 1958, 164.

[6] E. Ciganek (E.I. Du Pont de Nemours Comp.), US-Patent 4.076.830; 28.2.1978, Int. Cl^2 C 07 D 209/70 (Chem. Abstr. *89*, 24136 n).

[7] Enzymatically prepared and kindly delivered by Prof. M. Schneider, Wuppertal

[8] J. Monteiro, J.Braun, F. Le Goffic, Syntheric. Comm. 1990, 20, 315.

[9] Review on auxiliaries for the NMR-analysis of enantiomers: D.Parker, Chem. Rev. 1991, 91, 1441.