Enantiomeric NMR analysis of organic acids with the Corey chiral controller

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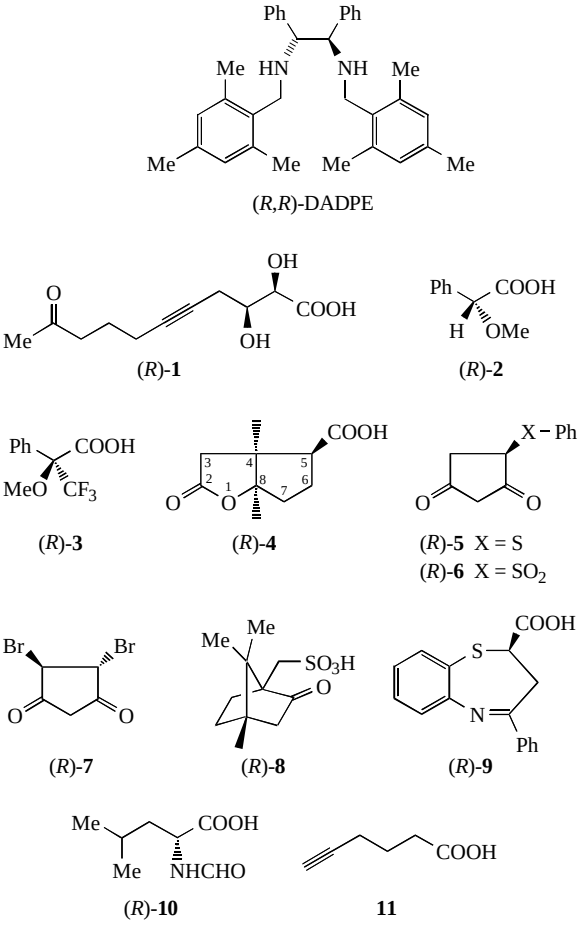
(*R*,*R*)-1,2-Di-(2,4,6-trimethylbenzylamino)-1,2-diphenylethane (the Corey chiral controller) was found to be an effective chiral NMR shift reagent for the determination of the enantiomer ratio in chiral carboxylic and sulfonic acids and cyclic β-diketones.

Determination of an enantiomer ratio (enantiomeric analysis) in the mixtures of enantiomers is a difficult but unavoidable procedure in any chiral total synthesis so widespread in the present days. There are several more or less general solutions of the problem. The most general solutions are NMR analysis with chiral lanthanide shift reagents and chromatography on chiral columns. The NMR analysis of diastereomeric mixtures of esters, amides and amine salts with chiral acids is by far the most popular substrate-specific method for enantiomeric analysis of alcohols and amines.[1]

The best method for the enantiomeric analysis of carboxylic acids is NMR analysis of diastereomeric salt mixtures formed *in situ* with (*R*,*R*)-1,2-diphenylethane-1,2-diamine (DPDAE).[2] However, this diamine was found to be inapplicable to the analysis of ketoacid **1** because of rapid formation of Schiff bases in $CDCl_3$ solution. As ketoacid **1** was important for us as a key intermediate in the total synthesis of eicosanoids[3] so we were looking for a substitute of DPDAE devoid of its reactivity.

Enantiomeric (*R*,*R*)- and (*S*,*S*)-1,2-di-(2,4,6-trimethylbenzylamino)-1,2-diphenylethanes (DADPE) are excellent chiral controllers in an enantioselective olefin dihydroxylation reaction.[4] The structure of DADPE has been tailored by E. J. Corey[5] specially for this purpose. A complex of DADPE with osmium tetroxide binds olefins in a stereospecific manner due to the existence of an asymmetric groove in the predominant conformation of DADPE. It is believed that other types of complex formation with DADPE can be highly stereo- or enantiospecific as well. On the other hand, being hindered bis-secondary diamine, DADPE is much less reactive in comparison with DPDAE. We report here the salt formation of chiral acidic compounds with DADPE and its application to enantiomeric NMR analysis.



Scheme 1 For chiral compounds, only enantiomers with the *R*-configuration of a chiral centre proximal to an acidic functional group are presented.

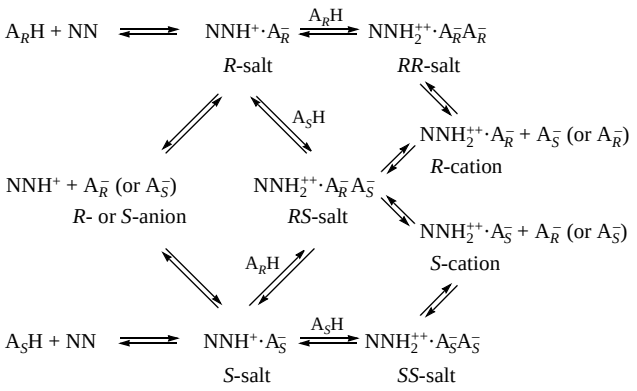
The acidic compounds studied are presented in Scheme 1. These are chiral carboxylic acids **1**–**4**, **9** and **10**, sulfonic acid **8**, and cyclic β-diketones **5**–**7**. Acids **1**–**4** and **8** were used each as a pair of enantiomers or as a racemic mixture and a single enantiomer. Achiral acid **11** was used for comparison purposes. ^{1}H NMR spectra were measured for mixtures of (*R*,*R*)-DADPE with the acids taken as racemic mixtures or, if available, as scalemic mixtures with known enantiomeric composition (approximately 4:6). The enantiomeric differences of signal shifts were taken from these spectra (Table 1).† The signal shifts induced by salt formation were calculated by comparison of the spectra of salts and corresponding individual compounds.

The interaction of the diamine (*R*,*R*)-DADPE with an acid in a solution gives rise to a set of equilibria presented in Scheme 2, where NN and AH are a diamine and an acid, respectively. This interaction can lead to the formation of basic (1:1, acid:diamine) and neutral (2:1) salts depending on the composition of the mixture, existing as ion pairs (or triades), free ions or mixtures of them. In the case of an enantimer mixture, each enantiomer forms its own basic and (homo-)neutral salts, and the formation of a hetero-neutral salt becomes also possible. As the equilibria are rapid in the NMR time scale, the observed chemical shifts, for erxample, of *R*-acid signals are a weighted average of the chemical shifts in all species containing this enantiomer. This is also true for the *S*-enantiomer of the acid. Chemical shifts of acid enantiomer residues in the corresponding basic, homo- and hetero-neutral salts, and cations thereof, all diastereomeric by pairs, should be different from each other; therefore, enantiomeric differences for acid signals in the spectrum are possible.‡

The other reason for enantiomeric differences can be the inequality of association constants for the formation or dissociation of diastereomeric salts. This reason is believed to be at least as significant for an enantiomer discrimination in salts of monobasic amines and DPDAE due to anisochronicity.[1,2] For DADPE we assume that the association constants for salt formation are sufficient to provide the nearly quantitative salt

† Spectra of salts were recorded on a Bruker DRX500 spectrometer (500 MHz) at 30 °C in $CDCl_3$ for the solutions 0.05 M in (*R*,*R*)-DADPE and 0.1 M in acidic compounds. Compounds with low solubility in $CDCl_3$ (**5**–**7**, **9**, **10**) are much more soluble in the presence of DADPE and were used as saturated solutions with the acid:diamine ratios shown in Table 1.

‡ The situation is quite different for the signals of the diamine (*R*,*R*)-DADPE. Although the positions of the signals in the mixtures with acids depend on the acid structure and an acid:diamine ratio, the salt formation with the mixtures of acid enantiomers never induced any enantiomeric splitting of enantiomerically pure diamine signals due to the rapid equilibria of a single diamine residue between all diamine-containing species.



Scheme 2 Salt formation equilibria with the participation of (*R*,*R*)-DADPE.

formation in deuterochloroform solution, and dissociation of the formed salts into ions is insignificant. This assumption is based on the following observations. The induced chemical shifts ($\Delta\delta = \delta_{salt} - \delta_{free\ acid}$) of acid (*S*)-**1** in mixtures with the diamine (*R*,*R*)-DADPE vary insignificantly with changing acid–base ratios from 0.6:1 to 2:1.§ An analogous result was obtained previously[6] with Mosher acid **3**. In addition, the substitution of deuterochloroform as a solvent for deuterobenzene does not increase significantly enantiomeric differences in the spectrum of acid **2** (*cf.* ref. 7).

An acid:diamine ratio of 2:1 is most convenient from the practical point of view, and it was used throughout if possible.† At this ratio, acid (*S*)-**1** with (*R*,*R*)-DADPE in $CDCl_3$ produces a salt solution stable during several days (NMR data). The NMR spectrum of the salt exhibits significant induced $\Delta\delta$ values for both acid and diamine signals.§ These $\Delta\delta$ values reach –0.234 ppm for one of the acid signals and +0.91 ppm for one of the diamine signals. The reason of these large $\Delta\delta$ values is not only ionization but, in a greater extent, complexation of the molecules due to an additional functionality in the acid residue. This is evident from the spectrum of the salt of model acid **11** where $\Delta\delta$ are no higher than +0.04 and +0.23 ppm for the acid and diamine signals, respectively.¶

The spectra of 2:1 salts of enantiomeric acids (*R*)-**1** and (*S*)-**1** have different $\Delta\delta$.†† The enantiomeric differences of $\Delta\delta$ ($\Delta\Delta\delta$ = = $\Delta\delta_{R\text{-enantiomer}} - \Delta\delta_{S\text{-enantiomer}}$) reach +0.056 ppm for one of the acid signal (Table 1, entry 2). However, the spectra of mixtures of acid enantiomers could differ from the superposition of the spectra of individual enantiomers due to formation of a hetero-neutral *RS*-salt mentioned above (Scheme 2). Indeed, we found that the mixing of two solutions of diastereomerically individual salts produces a new spectrum with single diamine signals, but with enantiomerically splitted signals of the acid with new $\Delta\Delta\delta$ values. Luckily enough these new $\Delta\Delta\delta$ values are even larger for some signals (Table 1, entry 1) thus providing an excellent measurement method for acid enantiomer ratios. In a particular case of acid **1**, the detection of 1% of minor enantiomer is easy by measurement of signal intensities of the proton H^3 in spite of a multiplet character ($W_{1/2}$ 19 Hz) of this signal reporter.

Analogously, with the 2:1 (if possible) salts of the enantiomer mixtures, $\Delta\Delta\delta$ were measured for all other chiral acids shown in Scheme 1 (entries 3–11 in Table 1). In all cases, with only two exceptions, the enantiomeric differences were observed with $\Delta\Delta\delta$ values sufficient to measure the ratio of enantiomers. One of the obvious exceptions is acid **9**. Amino acid **9** exists as an internal salt and is not transformed into a salt with the (less basic) external base (*R*,*R*)-DADPE thus lacking considerable $\Delta\delta$. The second exception, Mosher acid **3**, is most probably the result of an accident. The spectrum of the corresponding salt shows substantial $\Delta\delta$ for acid signals‡‡ and large $\Delta\delta$ values as well as $\Delta\Delta\delta$ for diamine signals. The latter were used for the analysis of the enantiomer composition of DADPE.[6]

A specific and sometimes unique property of DADPE as a chiral shift reagent is its long-range action in enantiomeric proton discrimination. Significant $\Delta\Delta\delta$ are generated for the signals of protons separated from the location of a charge in an anion of the acid by five and even larger number of bonds. In acid **8** (Table 1, entry 9) DADPE produces $\Delta\Delta\delta$ 0.059 ppm for the signal of one of the methyl groups remote from the charge by more than 5 Å. For comparison, with DPDAE $\Delta\Delta\delta$ 0.013 ppm was observed in a similar case (methyl group of camphanic acid).[2] Thus, acyclic (**1**, **2** and **10**), cyclic (**5**–**7**), and three-dimensional bicyclic acids (**4** and **8**) can be analysed with DADPE for the enantiomer ratio.

The shifting properties of DADPE are in some contrast with the observation that its close analogue, *N*,*N*′-dibenzyl-DPDAE, has greatly reduced enantiodifferentiating properties.[2] However, this distinction is in agreement with the remark[5] that, in contrast to DADPE, *N*,*N*′-dibenzyl-DPDAE was not an effective controller for enantioselective dihydroxylation reaction due to greater rotational flexibility.

Another possible application of (*R*,*R*)-DADPE (or its equally available enantiomer[6]) as a chiral shift reagent is the detection of compound chirality. An example is dibromide **7** with an unknown relative configuration of bromine atoms.§§ The observation of large $\Delta\Delta\delta$ values in the spectrum of its salt (entry 8,

Table 1 Enantiomeric differences of chemical shifts induced in the ^{1}H NMR spectra of racemic or scalemic mixtures of acid enantiomers by (*R*,*R*)-DADPE.

Entry	Acid	Acid:DADPE ratio[a]	Chemical shift differences of splitted signals ($\Delta\Delta\delta$/ppm[b])
1	**1**	2:1	–0.018 (H^2), +0.069 (H^3)
2	**1**[c]	2:1	–0.026 (H^2), +0.056 (H^3)
3	**2**	2:1	+0.008 (H^2), +0.010 (OMe), +0.032 (*o*-H^{Ph})
4	**3**	2:1	No differences[d]
5	**4**	2:1	–0.010 (H^4_A), –0.027 (H^4_B), –0.010 (H^5), –0.005 (H^6)
6	**5**[e]	2:1	0.093 (=CH), 0.000 (CH_AH_B), 0.008 (CH_AH_B), 0.084 (CHS), 0.040 (*o*-H^{Ph})
7	**6**[e]	0.6:1	0.106 (=CH), 0.000 (CH_AH_B), 0.042 (CH_AH_B), 0.360 ($CHSO_2$)
8	**7**[e]	1.5:1	0.129 (=CH), 0.064 (CHBr)
9	**8**	2:1	–0.059 (C^9H_3), –0.011 ($C^{10}H_3$)
10	**9**	2:1	No differences
11	**10**[e]		0.009 (CHN), 0.016 (CHO), 0.015 (C^AH_3), 0.000 (C^BH_3)

[a]Molar ratios. The sum of enantiomers is taken as an acid concentration. [b]$\Delta\Delta\delta = \delta$ (signal of *R*-acid) – δ (signal of *S*-acid). Therefore '+' sign means a more pronounced induced shift in low field or a less pronounced shift in high field. [c]Differences between two spectra of individual enantiomers. [d]Some broadening of the OMe signal is observed. [e]No sign for $\Delta\Delta\delta$ is available due to an arbitrary assignment of the enantiomers.

§ $\Delta\delta$/ppm for 0.6:1 and 2:1 salts, respectively. (*S*)-**1** residue: –0.23, –0.26 and –0.208 (d, 1H, H^2, *J* 3.6–4.0 Hz, shift from 4.37 ppm), –0.09, –0.14 and –0.138 (br. t, 1H, H^3, *J* 5.8–6.0 Hz, shift from 4.15 ppm), +0.02, 0.00 and +0.03 (q, 2H, C^8H_2, *J* 6.4–7.3 Hz, shift from 1.75 ppm), –0.02, –0.06 and –0.04 (s, 3H, $C^{11}H_3$, shift from 2.20 ppm); (*R*,*R*)-DADPE residue: +0.26, +0.36 and +0.38 (d, 1H, CH_AH_B, *J* 11–13 Hz, shift from 3.47 ppm), +0.27, +0.36 and +0.36 (d, 1H, CH_AH_B, *J* 11–13 Hz, shift from 3.53 ppm), +0.19, +0.38 and +0.75 (br. s, 1H, CHN, shift from 3.70 ppm), ≤ 0.06 (all other).

¶ $\Delta\delta$/ppm for 2:1 salt. Acid **11** residue: –0.02 (t, 2H, C^2H_2, *J* 7.5 Hz, shift from 2.50 ppm), +0.02 (quint., 2H, C^3H_2, *J* 7.5 Hz, shift from 1.84 ppm), +0.04 (td, 2H, C^4H_2, *J* 7.5 and 2.5 Hz, shift from 2.26 ppm), +0.03 (t, 1H, H^6, shift from 1.95 ppm); (*R*,*R*)-DADPE residue: +0.14 (d, 1H, CH_AH_B, *J* 12.9 Hz), +0.23 (d, 1H, CH_AH_B, *J* 12.9 Hz), +0.12 (br. s, 1H, CHN), ≤ 0.05 (all other).

†† $\Delta\delta$/ppm for 2:1 salt. (*R*)-**1** residue: –0.234 (m, 1H, H^2), –0.082 (br. t, 1H, H^3, *J* 6.0 Hz), +0.04 (q, 2H, C^8H_2, *J* 7.4 Hz), –0.05 (s, 3H, $C^{11}H_3$); (*R*,*R*)-DADPE residue: +0.36 (d, 1H, CH_AH_B, *J* 11.2 Hz), +0.38 (d, 1H, CH_AH_B, *J* 11.2 Hz), +0.91 (br. s, 1H, CHN), ≤ 0.10 (all other).

‡‡ $\Delta\delta$/ppm for 2:1 salts. (*R*)- or (*S*)-**3** residues: –0.09 (br. s, 3H, OMe, shift from 3.59 ppm), +0.07 (d, 2H, 2*o*-H^{Ph}, *J* 7.6 Hz, shift from 7.49 ppm); $\Delta\delta$ for (*R*,*R*)-DADPE residue see in ref. 6.

§§ Dibromide **7** was prepared by partial debromination of the corresponding 2,4,5-tribromide.[8]

Table 1) proves unambigously the chirality of the molecule and hence the *trans*-configuration of the bromine atoms.

In summary, DADPE enantiomers appear to be a useful addition to a set of chiral shift reagents for the NMR analysis of enantiomer ratio of various acidic substances.

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