1,2-Diphenylethane-1,2-diamine: An Effective NMR Chiral Solvating Agent for Chiral Carboxylic Acids

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(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, **1**, acts as an effective chiral solvating agent (CSA) in the ^{1}H NMR analysis of the enantiomeric purity of chiral carboxylic acids. In the 2:1 salt complexes with a range of acids including α-arylpropanoic, α-halo carboxylic acid and primary carboxylic acids, RCH_2CO_2H, the diastereotopic resonances in ^{1}H NMR were typically more than 0.05 ppm shift non-equivalent. The effect of temperature, stoichiometry, acid enantiomeric purity, concentration and solvent on the observed shift non-equivalence was studied. The structure of the CSA was varied systematically and the observed non-equivalence with **1**, may be attributed to the anisotropy of the second aryl ring which is proximate to the substituents α to the carboxylic acid group.

The majority of non-chiroptical methods that are used for the determination of the enantiomeric purity of chiral carboxylic acids are indirect and involve the formation of diastereoisomeric esters or amides prior to NMR[1] or HPLC analysis.[2] Methods that rely upon the formation of short-lived diastereoisomeric complexes include the NMR analyses with chiral lanthanide shift reagents and with chiral solvating agents. In the former case, direct application of the traditional chiral β-diketonate complexes to acids is rare owing to line broadening and the poor σ-binding ability of a carboxylic acid carbonyl group to the lanthanide. Simple methyl esters or better still *N*,*N*-dimethylamides are preferred.[1,3] In the latter case, there have been several reports describing the use of α-arylethylamines as chiral solvating agents for carboxylic acids although the observed chemical shift non-equivalence is usually quite small.[4,5] Certainly the ease of use and direct applicability of an enantiomerically pure amine as a chiral solvating agent for acids makes it an attractive reagent in chiral analysis. The reciprocal experiment—whereby an enantiopure chiral acid is used as a chiral solvating agent in amine analysis—has been much more intensively studied.[1,6,7]

In seeking a suitable chiral solvating agent there are several obvious criteria which should be met. The compound should be readily soluble in common non-polar solvents (*e.g.*, $CDCl_3$, C_6D_6) in both the free and complexed form. It should possess a relatively simple ^{1}H NMR spectrum so as not to obscure the observation of anisochronous resonances. Both enantiomers should be readily available so that if problems of solubility are encountered with one set of diastereoisomeric salts, the other set can be screened in parallel. Finally the amine should possess anisotropic groups (*e.g.*, phenyl rings, carbonyl groups or localised lone-pairs) that will give rise to chemical shift non-equivalence. With these criteria in mind, and having investigated the properties of a large number of potential enantiopure mono-amines as chiral solvating agents,[8] the C_2-symmetric chiral diamine, **1** was studied. It is readily available in both enantiomeric forms[9] and has been used recently as a chiral reagent in a variety of stereoselective aldol, Diels–Alder,[10] allylation,[11] osmylation,[12] epoxidation[13] and Michael addition[14] reactions.

The use of **1** as a chiral solvating agent is reported,[15] screening a wide range of chiral carboxylic acids (1°, 2° and 3°), and optimising the experimental conditions (solvent, temperature, concentration and stoichiometry) in order to maximise the observed ^{1}H NMR chemical shift non-equivalence in the diastereoisomeric salts.

Results and Discussion

The preparation of the sample for the ^{1}H NMR experiments is very straightforward. Typically 50 μmol of the diamine **1** was mixed with 100 μmol of the chiral acid (for 1:2 stoichiometry), the mixture dissolved in $CDCl_3$ or C_6D_6 and the ^{1}H NMR spectrum recorded at once. A series of racemic mono- and dicarboxylic acids was examined and the chemical-shift non-equivalence ($\Delta\delta_H$) of certain substrate resonances in the diastereoisomeric complexes was measured. Values of $\Delta\delta_H$ using (*R*)-**1** at both 1:1 and 2:1 stoichiometries are given (Table 1). Higher values of $\Delta\delta_H$ were most often found at 2:1 stoichiometry, although this was not found with the *endo*-norbornene derivative **12** where steric inhibition of 2:1 complexation may be a contributory factor. The low—but useful—shift non-equivalence for the testing substrate 2-methylbutyric acid, **9** (entry 8) reflects the similarity in steric demand of methyl *versus* ethyl in the two diastereoisomeric complexes. The observed shift non-equivalence of the methyl doublets and triplets in **9** (Fig. 1) is sufficient not only to allow

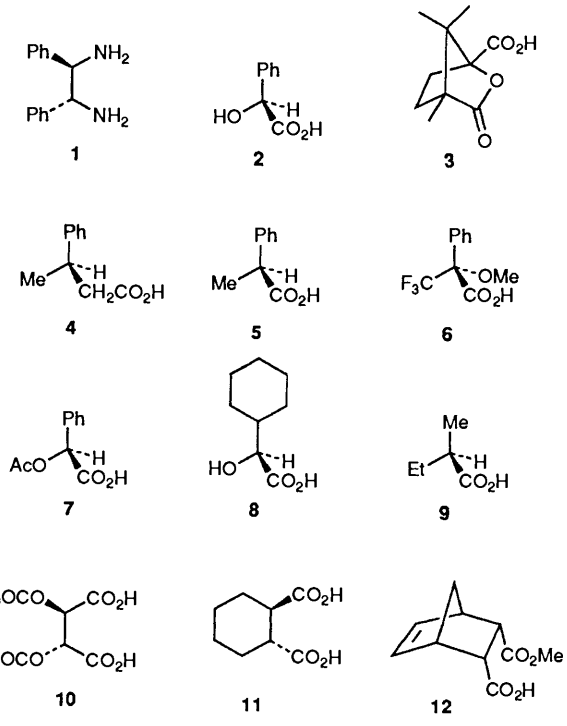


Table 1 ^{1}H NMR shift non-equivalence observed (293 K) for mono- and di-carboxylic acids[a]

Entry	Substrate	Observed resonance	Solvent	$\Delta\delta_H$ (ppm) Stoichiometry 1:1	2:1
1	**2**	2-H	$CDCl_3$	—	0.193
			C_6D_6–C_5D_5N (10:1)	0.049	0.059
2	**3**	—	$CDCl_3$	—	—
		CH_3	C_6D_6	—	0.013
3	**4**	2-CH_2	$CDCl_3$	0.007	—
			C_6D_6	0.009	—
		2-H	$CDCl_3$	—	0.028
		2-CH_3	C_6D_6	0.009	0.019
4	**5**	2-H	$CDCl_3$	—	0.076
			C_6D_6	0.011	0.089
		2-CH_3	$CDCl_3$	—	0.027
			C_6D_6	—	0.012
5	**6**	2-OCH_3	$CDCl_3$	—	0.057
			C_6D_6	0.064	0.065
6	**7**	2-H	$CDCl_3$	0.152	0.171
			C_6D_6	0.163	0.178
		2-OAc	$CDCl_3$	0.054	0.076
			C_6D_6	0.050	0.016
7	**8**	2-H	$CDCl_3$	0.076	0.098
8	**9**	2-CH_3	$CDCl_3$	—	0.006
		—	C_6D_6	—	—
9	**10**	2-H	$CDCl_3$–C_5D_5N (5:1)	0.039	<0.005
10	**11**	2-H	$CDCl_3$	0.027	<0.005
			C_6D_6	0.053	<0.005
11	**12**	OCH_3	$CDCl_3$	0.027	0.006
			C_6D_6	0.015	0.017

[a] Spectra were recorded at 400 or 500 MHz.

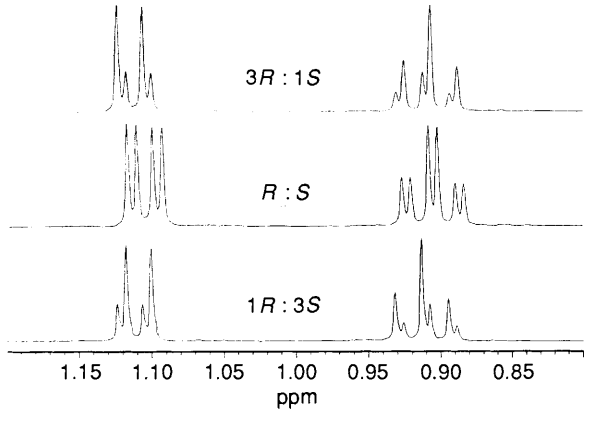


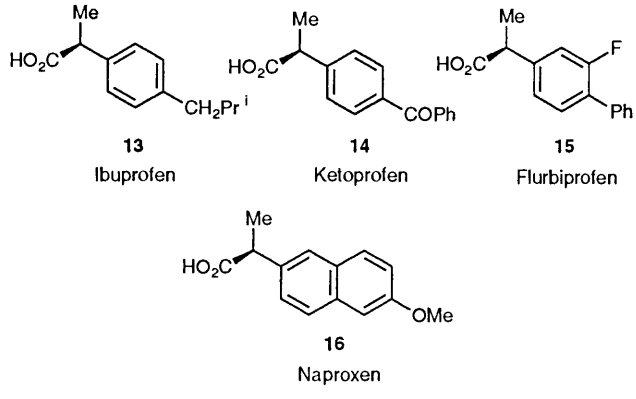
Fig. 1 Shift non-equivalence in methyl resonances of 2-methylbutyric acid, **9**, of varying enantiomeric composition in the presence of (*R*)-**1** ($CDCl_3$, 293 K)

the assignment of absolute configuration of the sample but also—with the aid of selective decoupling of the proximate proton resonances—to permit the determination of enantiomeric purity of enantiomerically enriched samples. The largest shift non-equivalence observed in this series was with (*R*)-**1** and *O*-acetylmandelic acid at 2:1 stoichiometry (0.18 ppm for the mandelate methine resonance in C_6D_6). With the diacids **10** and **11** shift non-equivalence was noted only at 1:1 stoichiometry.

Table 2 ^{1}H NMR shift non-equivalence (293 K) for selected 2-arylpropanoic acids

Entry	Substrate	Observed resonance	Solvent	$\Delta\delta_H$ (ppm) Stoichiometry 1:1	2:1
1	**13**	2-H	$CDCl_3$	0.049	0.099
			C_6D_6	0.014	0.168
		2-CH_3	$CDCl_3$	0.016	0.031
			C_6D_6	—	0.027
2	**14**	2-H	$CDCl_3$	0.014	0.032
			C_6D_6	0.019	0.056
		2-CH_3	$CDCl_3$	0.012	0.025
			C_6D_6	0.014	0.025
3	**15**	2-H	$CDCl_3$	0.036	0.075
			C_6D_6	0.017	0.090
		2-CH_3	$CDCl_3$	0.020	0.039
			C_6D_6	—	0.021
4	**16**	2-H	$CDCl_3$	0.034	0.068
			C_6D_6	0.012	0.091
		2-CH_3	$CDCl_3$	0.018	0.034
			C_6D_6	—	0.025
5	**5**	2-H	C_6D_6	0.011	0.089
		2-CH_3	$CDCl_3$	—	0.027

A series of anti-inflammatory agents in the α-arylpropanoic acid class was studied (Table 2). High ^{1}H NMR shift non-equivalences were observed for both the methyl and methine resonances. With Ibuprofen, **13**, for example, the methine



quartet was 0.168 ppm non-equivalent in a 2:1 complex with **1** in C_6D_6 (293 K). There was a strong solvent dependence for the shift non-equivalence in both the 1:1 and 2:1 complexes. This effect was particularly marked for the methine non-equivalence in the α-aryl propanoic acids (Table 2). With Flurbiprofen, **15**, for example, the highest $\Delta\delta_H$ was observed in [$^2H_6$]benzene at 2:1 stoichiometry: at 1:1 stoichiometry, maximal $\Delta\delta_H$ was found in deuteriochloroform reflecting the sensitivity of the effect of solvation in stabilising a given conformer in the diastereoisomeric salt complexes (Fig. 2). The enantiomeric purity of samples of **5**, **13**, **15**, **16** and **19** was measured accurately by integrating the separate resonances of the diastereoisomeric salt complexes. Care was taken to ensure that accurate and reliable integrals were obtained (*i.e.*, that the observed signals were fully 'relaxed'). This is par-

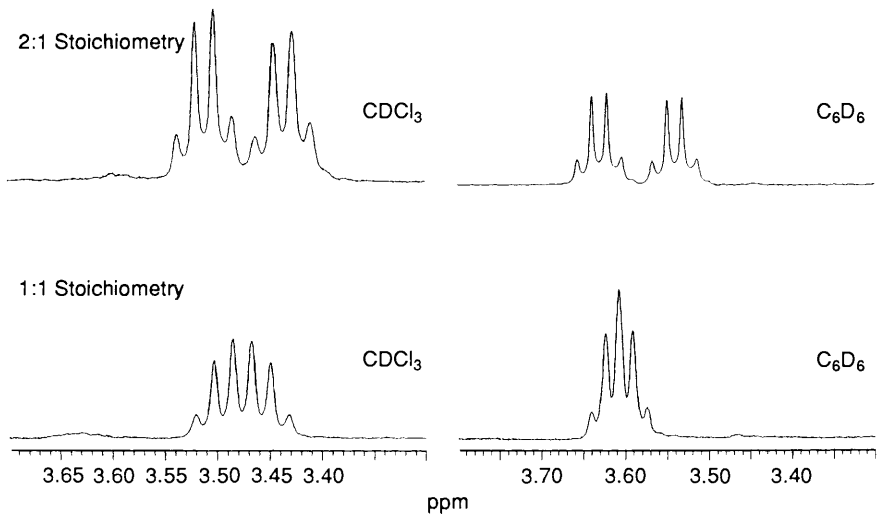


Fig. 2 Solvent dependence of the shift non equivalence for the methine resonances of Flurbiprofen, **15**, in the presence of (*R*)-**1** (293 K, 400 MHz)

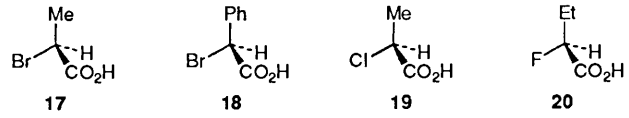
Table 3 Analysis of enantiomeric purity of chiral carboxylic acids using DPDAE, **1**

Entry	Substrate	Solvent	Observed resonance[a]	Enantiomeric composition % *R*	% *S*	Enantiomeric excess (%)[c]
1	**13**	C_6D_6	2-H[b]	99.6	0.4	99.2
				1.0	99.0	98.0
2	**15**	C_6D_6	2-H[b]	99.4	0.6	98.8
				3.7	96.2	92.5
3	**16**	$CDCl_3$	2-CH_3	0.6	99.4	98.8
4	**5**	$CDCl_3$	2-CH_3	99.0	1.0	98.0
				0.1	99.9	99.8
5	**19**	$CDCl_3$	2-CH_3	99.8	0.2	99.6
				0.2	99.8	99.6

[a] Enantiomeric compositions derived by comparing the carbon-13 satellites of the major diastereoisomer with the resonance of the minor. [b] Enantiomeric composition derived by comparing the integrals of the resonances due to the major and minor diastereoisomers. [c] Errors estimated to be ± 0.15.

ticularly necessary when measuring methyl resonances where the ^{13}C satellite peaks (1.08% of the major resonance) are very useful in calibrating enantiomeric purity determinations. In each case using (*R*)-**1**, the methyl doublet of the (*S*)-α-arylpropanoic acid resonanted to lower frequency of the *R* in their respective diastereoisomeric salt complexes. Of course using (*S*)-**1**, the reverse is true and the '*S*-methyl doublet' resonates to higher frequency of the '*R*'-derived resonance. Values reported (Table 3) indicate that some samples were essentially enantiomerically pure [*e.g.*, (*S*)-**5** and (*R*)- and (*S*)-**19**, see below).

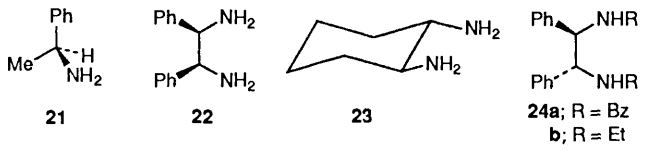
The series of α-halo acids (Table 4) displayed the highest chemical shift non-equivalence of all chiral mono-acids examined (for both methyl and methine resonances). For example in the 2:1 complex of α-bromophenylacetic acid, **18**,



with (*R*)-**1** in C_6D_6, the methine singlets were separated by 0.34 ppm in the two diastereoisomeric salt complexes. Very large non-equivalence was also found with α-chloropropanoic acid, **19** (0.27 ppm for the methyl doublets in the 2:1 complex in $CDCl_3$) (Table 4). This method is therefore readily applicable to the chiral assay of α-fluoro, α-chloro and α-bromo carboxylic acids all of which are sensitive to racemisation under certain

Table 4 ^1H NMR shift non-equivalence ($\Delta\delta_H$, 293 K) for α-halopropanoic acids and **1**

Entry	Substrate	Observed resonance	Solvent	$\Delta\delta_H$ (ppm) Stoichiometry 1:1	2:1
1	**17**	2-CH_3	$CDCl_3$	0.080	0.023
			C_6D_6	0.118	—
		2-H	$CDCl_3$	0.086	0.037
			C_6D_6	0.046	—
2	**18**	2-H	$CDCl_3$	0.176	0.287
			C_6D_6	0.206	0.339
3	**19**	2-CH_3	$CDCl_3$	0.105	0.269
			C_6D_6	0.062	0.151
		2-H	$CDCl_3$	0.129	0.240
			C_6D_6	—	0.150
4	**20**	2-CH_3	$CDCl_3$	0.054	0.086
			C_6D_6	0.081	0.089
		2-F	$CDCl_3$	—	0.125
			C_6D_6	—	0.172



21 **22** **23** **24a**; R = Bz **b**; R = Et

derivatisation conditions because of the relatively high acidity of the methine hydrogen.

A limited comparison of the efficacy of (*R*)-**1** with (*R*)-α-methylbenzylamine, **21**, as chiral solvating agents for acids was made. In each case (Table 5), the 1 : 1 complexes with **21** resulted in lower shift non-equivalence than with the corresponding complexes of (*R*)-**1**, except with the diacid **11**. Although further studies were not made at this point, 2 : 1 complexes of **21** with chiral diacids may be more useful than 1 : 1 complexes with **1** in chiral assays of this type.

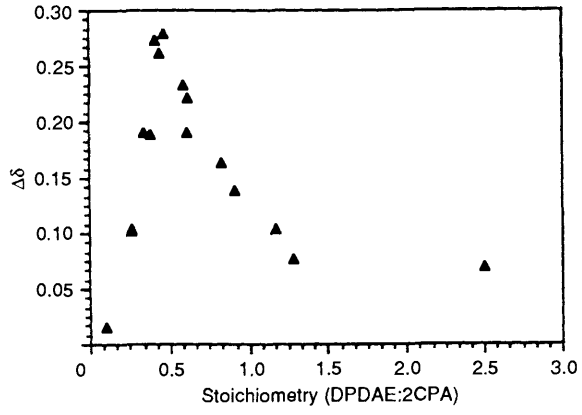


Fig. 3 Variation of chemical shift non-equivalence with acid : amine ratio ($\Delta\delta_H$) for the methyl resonances of racemic α-chloropropanoic acid, **19**, in the presence of **1** ($CDCl_3$, 293 K, 0.1 mol dm^{-3})

Parameters Determining Chemical-shift Non-equivalence.— In order better to understand the origins of the observed anisochronicity and to optimise the value of the chemical shift non-equivalence, the variation of $\Delta\delta$ with amine : acid stoichiometry, concentration, substrate enantiomeric purity and temperature was studied. In addition the structure of the chiral solvating agent, **1**, was modified in a systematic manner in order further to probe the structural requirements of an effective chiral solvating agent.

(*a*) *Effect of stoichiometry.* Standard solutions of both the acid and the diamine **1** (0.1 mol dm^{-3}) were prepared and mixed to give the desired stoichiometry ratio. With 2-chloropropanoic acid, **19**, for example, the observed shift non-equivalence for the methyl and methine resonances was recorded in the range 10 : 1 to 2 : 5 acid to diamine (Fig. 3). Maximum shift non-equivalence was observed at a 2 : 1 ratio of acid : amine and a limiting value of $\Delta\delta_H$ was found at higher amine concentrations. The rapid increase in non-equivalence as the acid : amine ratio changes from 10 : 1 to 2 : 1 is probably related to more than one factor. The concentration of 'free' acid (*i.e.*, uncomplexed acid) although enhancing the equilibrium towards formation of a 2 : 1 complex does not contribute to the observed non-equivalence.[1] Indeed salt formation will compete with acid dimerisation in these non-polar solvents, and the concentration of dimers will

Table 5 ^1H NMR shift non-equivalence (293 K, $\Delta\delta_H$) with 2-methylbenzylamine for selected chiral carboxylic acids[a]

Entry	Substrate	Observed resonance	Solvent	$\Delta\delta_H$ (ppm)
1	**3**	CH_3	C_6D_6	0.045
2	**7**	2-H	C_6D_6	0.157
		2-OAc		0.016
3	**11**	2-H	C_6D_6	0.086
4	**13**	2-CH_3	C_6D_6	0.041
5	**19**	2-CH_3	C_6D_6	0.01

[a] Chemical shift non-equivalence was measured at one molar equivalent of acid to amine.

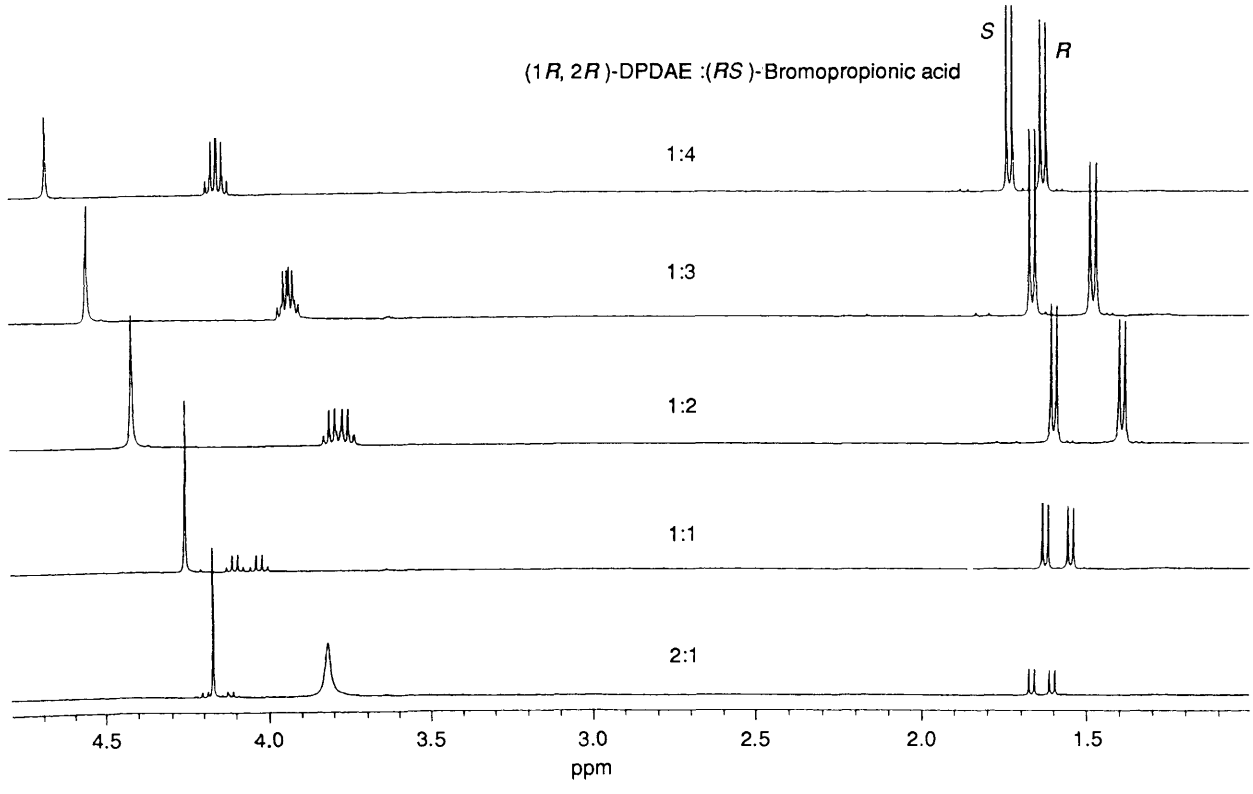


Fig. 4 Variation of $\Delta\delta_H$ for racemic α-bromopropanoic acid, **17**, in the presence of (*R*)-**1** ($CDCl_3$, 293 K, 0.1 mol dm^{-3})

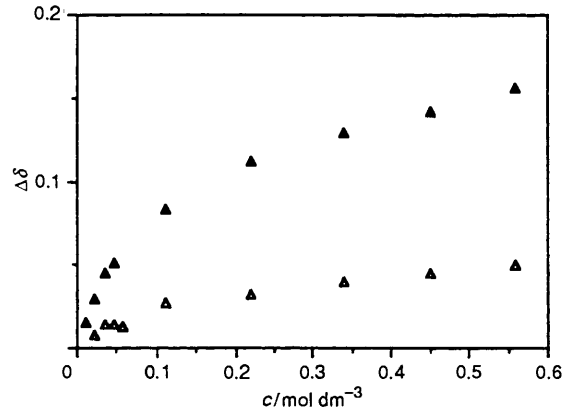


Fig. 5 Variation of $\Delta\delta_H$ with concentration for the diastereoisomeric complexes of racemic **5** (2-phenylpropanoic acid) and (*R*)-**1** ($CDCl_3$, 293 K): ▲, methine; △, methyl

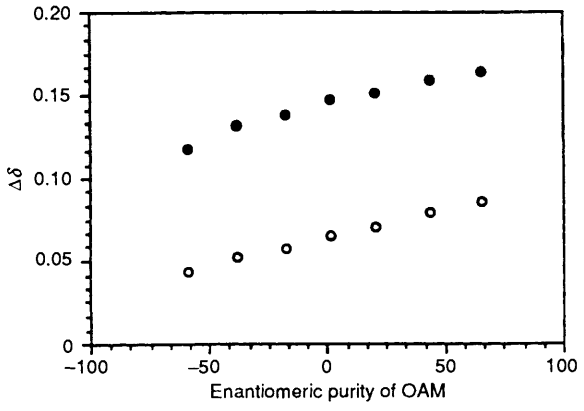


Fig. 6 Variation of $\Delta\delta_H$ with enantiomeric composition in the complexes of (*S*)-**1** and *O*-acetylmandelic acid, **7** (293 K, $CDCl_3$, 0.1 mol dm^{-3}). An ee of −100% refers to enantiomerically pure (*S*)-**7**: ○, OAc; ●, methine.

Table 6 Measurement of $\Delta\delta_H$ ([$^2H_8$]toluene) against temperature for Ibuprofen **13** in the presence of (*R*)-**1** (2:1)

	$\delta_{\alpha\text{-methine}}$(obs)			$\delta_{\alpha\text{-methyl}}$(obs)		
T/K	Hf[a]	Lf[a]	$\Delta\delta_H$ (ppm)	Hf[a]	Lf[a]	$\Delta\delta_H$ (ppm)
313	3.671	3.651	0.020	—	—	—
303	3.674	3.622	0.052	1.495	1.490	0.005
293	3.659	3.574	0.085	1.476	1.463	0.013
283	3.654	3.492	0.162	1.482	1.456	0.026
273	3.647	3.390	0.257	1.494	1.447	0.047
263	3.642	3.283	0.359	1.515	1.441	0.074
253	—	—	—	1.538	1.428	0.110
243	—	—	—	1.573	1.428	0.145

[a] Hf and Lf are the high and low frequency resonances, respectively.

of course increase with 'free' acid concentration. At ratios of acid:amine of less than 2:1, the observed $\Delta\delta_H$ diminished presumably due to competitive formation of 1:1 acid:amine complexes with a lower intrinsic chemical shift non-equivalence for the observed resonances. The limiting value observed (*e.g.*, 0.07 ppm for the methyl doublet of **19** in $CDCl_3$) probably represents a good measure of the instrinsic value of $\Delta\delta_H$ for the 1:1 complex.

With α-bromopropanoic, similar effects were noted although in this case, the diastereotopic α-methyl doublets were shifted to lower frequency as the optimal 2:1 stoichiometry value was approached (Fig. 4). Indeed in the (*R*,*R*) salt (the lower frequency doublet), a larger variation in chemical shift with changes in acid:amino ratio was noted. This implies that the diastereotopic methyl groups in the (*R*,*R*) complex are closer,

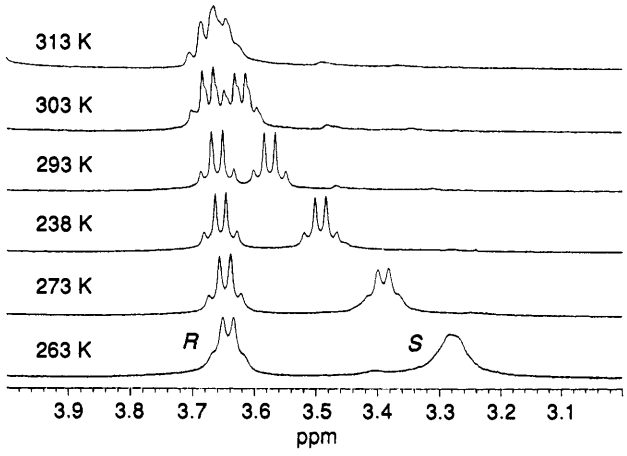


Fig. 7 Variation of $\Delta\delta_H$ with temperature for the methine quartets of Ibuprofen, **17**, in its 2:1 complex with (*R*)-**1** ([$^2H_8$]toluene, 0.1 mol dm^{-3}, 400 MHz)

on average, to the neighbouring anisotropic phenyl group in the preferred conformation. A different type of behaviour may be discerned, in this case, for the diastereotopic methine quartets (Fig. 4). In this case the highest $\Delta\delta_H$ is observed at 1:1 stoichiometry implying that the 1:1 and 2:1 complexes probably have different relative conformations with different relative distances in the two diastereoisomeric complexes between the C–H or C–Me group and the anisotropic phenyl group.

(*b*) *Effect of concentration.* Proton NMR spectra for the complex of (*R*)-**1** with racemic 2-phenylpropanoic acid, **5**, were recorded in $CDCl_3$ and C_6D_6 in the concentration range 0.5 mol dm^{-3} down to 0.005 mol dm^{-3}. For both the methine and methyl resonances, $\Delta\delta_H$ increased quite steeply up to about 0.1 mol dm^{-3} (Fig. 5). No reduction in $\Delta\delta_H$ due to ion-pair aggregation was noted in this concentration range, although in C_6D_6 this effect was observed for concentrations greater than 0.5 mol dm^{-3}. Clearly increasing the concentration of both acid and amine favours the formation of the salt complexes. It was noted that the diastereoisomeric complex of (*S*)-**5** and (*R*)-**1**, which appeared as the lower frequency doublet, exhibited a greater sensitivity in chemical shift to changes in concentration. This differential sensitivity [*i.e.*, compared with that observed for the (*R*)-**5**:(*R*)-**1** salt] may relate to the fact that the association constants for salt formation are different for the two diastereoisomeric complexes.

(*c*) *Effect of enantiomeric composition.* In the complexes of *O*-acetylmandelic acid and (*S*)-**1** in deuteriochloroform, at constant concentration and temperature, the variation of $\Delta\delta_H$ for the mandelate methine and acetyl singlets was studied as a function of the pre-determined enantiomeric purity of the chiral acid. A linear relationship was found over the enantiomeric excess range 66% *R* to 60% S, as has been observed previously in related systems.[4,7] This is again simply a consequence of the non-equivalence of the association constants for diastereoisomeric salt formation (Fig. 6). For the methine resonance of **7**, as the enantiomeric purity of the (*R*)-**7** sample increases, its chemical shift in the (*R*)-**7**:(*S*)-**1** complex shifts to lower frequency. At the same time, the acetyl singlet due to the (*R*)-**7**:(*S*)-**1** complex shifts to higher frequency while the acetyl resonance in the (*S*)-**7**:(*S*)-**1** complex is more or less unchanged as enantiomeric purity is varied. This differential effect must reflect the fact that the acetyl methyl group in the (*R*)-**7**:(*S*)-**1** salt complex is closer to the anisotropic phenyl group of **1** than it is in the corresponding (*S*)-**7**:(*S*)-**1** complex.

Table 7 Measurement of $\Delta\delta_H$ using (1*R*,2*R*)-cyclohexane-1,2-diamine, **23**, with selected chiral carboxylic acids (1:2 stoichiometry, 293 K)

Entry	Substrate[a]	Observed resonance	Solvent	$\Delta\delta_H$ (ppm)
1	**13**	2-H	$CDCl_3$	0.018
			C_6D_6	0.024
		2-CH_3	$CDCl_3$	0.014
2	**15**	2-CH_3	$CDCl_3$	0.019
			C_6D_6	0.007
		2-H	$CDCl_3$	0.018
			C_6D_6	0.019
3	**16**	2-CH_3	$CDCl_3$	0.099
4	**14**	2-CH_3	$CDCl_3$	0.002
			C_6D_6	0.002
		2-H	C_6D_6	0.009
5	**7**	2-OAc	$CDCl_3$	0.010
			C_6D_6	0.014

[a] 2-Chloropropanoic acid, **19**, and 2-bromopropanoic acid, **17**, were tested but gave no observed chemical-shift non-equivalence.

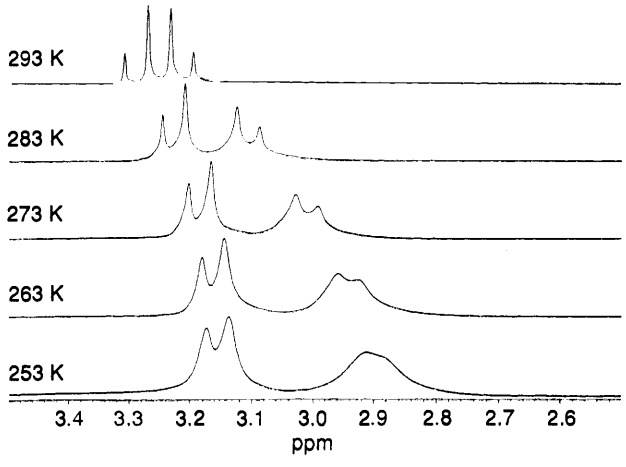


Fig. 8 Variation of $\Delta\delta_H$ for the diastereotopic methylene hydrogens of phenylacetic acid, **25**, in its 2:1 complex with (*R*)-**1** (0.1 mol dm^{-3})

(*d*) *Effect of temperature.* The temperature dependence of $\Delta\delta_H$ for the diastereoisomeric complexes derived from racemic ibuprofen **13** and (*R*)-**1** in [$^2H_8$]toluene was measured in the range 323–223 K (Table 6). A plot of the logarithm of $\Delta\delta_H$ *versus* $1/T$ for the methyl and methine resonances does not conform to the linear dependence expected for a Boltzmann distribution of conformers. However, it is apparent that as the temperature is lowered, $\Delta\delta_H$ increases significantly and this can be correlated primarily to an increasingly preferred population of a particular low-energy conformation for *one* of the diastereoisomeric complexes in which the methyl group (for example) spends more time on average in the vicinity of the anisotropic phenyl groups of **1**. The variation of $\Delta\delta_H$ with temperature for the methine quartets follows a similar pattern (Fig. 7). With decreasing temperature, the resonance due to the (*S*)-**13**:(*R*)-**1** complex shifts to lower frequency while that due to the (*R*)-**13**:(*R*)-**1** complex is relatively static. Clearly in the (*S*)-**13**:(*R*)-**1** complex differential shielding is occurring. In addition, the low temperature spectra reveal a different degree of line-broadening for the two multiplets (Fig. 7). This could be considered to arise from different free energies of activation of exchange between free and bound acids in the two diastereoisomeric salt complexes, with a slower rate of exchange for the (*S*)-**13**:(*R*)-**1** complex. Alternatively, selective broadening may arise due to the differing frequency difference ($\Delta\nu$ in Hz) between the limiting resonance frequencies for free and bound acid for the two complexes. The extent of broadening will be dependent on $\Delta\nu$ and for an equally populated two-site exchange system is given by eqn. (1) where $1/T_2$ is the natural

$$\frac{1}{T_2'} = \frac{1}{T_2} + \left[\frac{\Delta\nu}{2}\right]^2 \tau \qquad (1)$$

linewidth (rad s^{-1}), and $1/T_2'$ is the observed linewidth. Larger frequency differences ($\Delta\nu$) may therefore give increased broadening compared with the expected natural linewidth. In the case of ibuprofen, the frequency difference $\Delta\nu$ between the shifts of the free and bound acid is indeed larger for the (*S*)-**17**:(*R*)-**1** complex than for the (*R*)-**17**:(*R*)-**1** complex. This is perhaps a more likely explanation of the observed phenomenon.

(*e*) *Variation of solvating agent structure.* The corresponding achiral diamine **22** (1*R*,2*S*)-1,2-diphenylethane-1,2-diamine was examined as a solvating agent in order to ascertain whether any 'self-recognition' in the 2:1 acid:amine complexes may have been occurring. In principle two sets of diastereoisomeric 2:1 complexes may form which may be chemical shift non-equivalent: the isochronous *R*,*R* and *S*,*S* complexes of a given chiral acid with **22**, and the diastereoisomeric *meso* complex. In both $CDCl_3$ and C_6D_6 however, no chemical-shift non-equivalence was observed with **13**, **15**, **16** and **17**.

Replacement of the anisotropic phenyl groups in **1** was examined by studying the role of the C_2-symmetric diamine (1*R*,2*R*)-*trans*-cyclohexane-1,2-diamine, **23**, as a chiral solvating agent. Various chiral acids were examined in 2:1 complexes with **23** (Table 7). Only substrates that possessed aryl groups appeared to give measurable $\Delta\delta_H$ values in the 2:1 complexes. In each case the measured value of $\Delta\delta_H$ was considerably less than that found for **1**, although with Naproxen, **16**, in $CDCl_3$ the shift non-equivalence for the methyl doublets was 0.099 ppm (*cf.*, 0.034 ppm with **1**) although no measurable $\Delta\delta_H$ was found in C_6D_6.

It had been noted in related work[8] that secondary amine chiral solvating agents *tended* to give higher chemical shift non-equivalence with a given chiral acid than their primary or tertiary amine analogues [*e.g.* (−)-ephedrine *versus* norephedrine and *N*-methylephedrine]. Therefore both the *N*,*N*′-dibenzyl and *N*,*N*′-diethyl amines **24a** and **24b** were examined comparatively as chiral solvating agents. Although only a very limited range of chiral acids was examined (Table 8), it was evident that *N*-monoalkylation tended substantially to reduce the measured $\Delta\delta_H$, suggesting that the degree of hydrogen-bonding may be significant in maximising $\Delta\delta_H$.

(*f*) *Analysis of primary carboxylic acids.* In primary carboxylic acids, RCH_2CO_2H, the internally enantiotopic methylene hydrogens may be rendered internally diastereotopic by complexation with a chiral substrate. Chemical shift non-equivalence between H_R and H_S will ensue if, in the preferred conformation in solution, one of these hydrogens spends more time, on average, in a different local magnetic environment compared with the other.[16]

It was found that **1**, in its 1:1 and 2:1 complexes with a variety of alkyl and aryl primary carboxylic acids does function as a useful chiral solvating agent (Table 9). This may constitute the first example of internal diastereotopicity being induced by an external non-covalently bound chiral reagent for the methylene hydrogens of primary carboxylic acids. As before, at higher concentrations (0.4 *vs.* 0.1 mol dm^{-3}) the observed non-equivalence, $\Delta\delta_{H_S,H_R}$ was larger. The highest non-equivalence was found with the α-aryl carboxylic acids, as has been noted in other systems.[1,16] Although the unbranched alkyl acids gave only modest values of $\Delta\delta_{H_S,H_R}$, none failed to given non-equivalence. Certainly this method gives sufficient $\Delta\delta_H$ to allow

Table 8 The measurement of $\Delta\delta_H$ for chiral solvating agents **24a**, **24b** with selected chiral carboxylic acids (2:1 complexes)

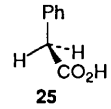
		24a			**24b**		
Entry	Substrate	Observed resonance	Solvent	$\Delta\delta_H$ (ppm)	Observed resonance	Solvent	$\Delta\delta_H$ (ppm)
1[a]	**13**	2-CH_3	$CDCl_3$	0.010	2-CH_3	$CDCl_3$	0.019
			C_6D_6	0.008		C_6D_6	—
2	**19**	2-CH_3	$CDCl_3$	0.032	2-H	$CDCl_3$	0.027
			C_6D_6	0.037		C_6D_6	0.027

[a] 0.025 mmol amine.

Table 9 Measurement of $\Delta\delta_H(H_S/H_R)$ for the achiral primary carboxylic acids **25–30** using the chiral solvating agent 1,2-DPDAE, **1**

			$\Delta\delta_H$[a] (ppm)			
			1:1 stoichiometry		2:1 stoichiometry	
Entry	Substrate	Solvent	0.4 mol dm^{-3}	0.1 mol dm^{-3}	0.4 mol dm^{-3}	0.1 mol dm^{-3}
1	**25**	$CDCl_3$	0.051	0.048	0.136	0.056
		C_6D_6	—	—	0.031	0.016
		$C_6D_5CD_3$	—	0.012	—	0.017
2	**26**	$CDCl_3$	0.035	—	0.042	—
		C_6D_6	—	—	—	—
3	**27**	$CDCl_3$	0.060	0.063	0.130	0.082
		C_6D_6	—	—	—	—
4	**28**	$CDCl_3$	—	—	0.015	—
		C_6D_6	—	—	—	—
5	**29**	$CDCl_3$	—	—	0.035	—
		C_6D_6	—	—	—	—
6	**30**	$CDCl_3$	—	—	—	0.024
		C_6D_6	—	—	0.033	0.030

[a] Spectra were recorded at 2:1 or 1:1 acid to amine stoichiometry at 0.4 or 0.1 mmol/cm^{-3} acid concentration at 298 K.



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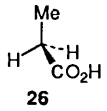

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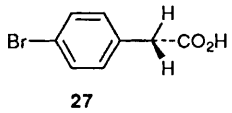

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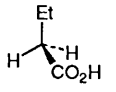

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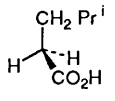

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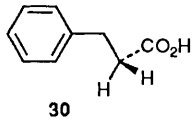

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the determination of the enantiomeric purity of α-deuterio (or α-tritio *via* ^3H NMR) primary carboxylic acids by ^1H NMR. It has the advantage over the best existing method,[17] that a separate derivatisation step is not needed, although the measured value of $\Delta\delta_{H_S,H_R}$ is slightly less than that found with methyl mandelate derivatives.[17] Moreover, by lowering the temperature, the observed non-equivalence increases. With phenylacetic acid, **25**, for example, $\Delta\delta_H$ increases from 0.06 ppm at 293 K to 0.25 ppm at 253 K (Fig. 8). The observed temperature dependence of H_S and H_R also indicates that one of these hydrogens is closer than the other to a phenyl ring in a conformer which becomes preferentially populated as the temperature falls.

Conclusions

The chiral diamine **1** is a versatile chiral solvating agent inducing high ^1H NMR chemical shift non-equivalence in its 2:1 diastereoisomeric salt complexes with a broad spectrum of chiral carboxylic acids. This permits the direct analysis of the enantiomeric purity of these acids in a quick method where the sample may readily be recovered by an acid/base wash.

Attempts were made to probe the conformation of the 2:1 complexes by seeking intermolecular NOE effects between the amine resonances (*e.g.*, the methine and *ortho* C–H protons of **1**) and those of the acid (*e.g.*, with **7**, **17** and **13**). The failure to observe any consistent intermolecular NOE (either using a NOESY or ROESY pulse sequence) effects precluded any firm conclusions being drawn, although it could be interpreted in terms of a complex structure wherein the acid and amine groups are not close in space.

Although no direct evidence exists, the following considerations need to be borne in mind in devising a working model for the observed enantiomer differentiation. Firstly in the 2:1 salt complex, it is likely that the two 'partially protonated' amines will adopt an *anti*-conformation, both to minimise electrostatic repulsion and to reduce the net dipole moment of the complex in the non-polar NMR solvent. Given that the 2:1 complexes exhibit higher shift non-equivalence than the corresponding 1:1 complexes, it is likely that the relative position of both aryl rings with respect to the carboxylic acid substituents is important. Moreover the fact that α-methylbenzylamine—which is effectively a subunit of **1**—engenders only small values of $\Delta\delta_H$ in its complexes, highlights the importance of the second aryl group in inducing non-equivalence.

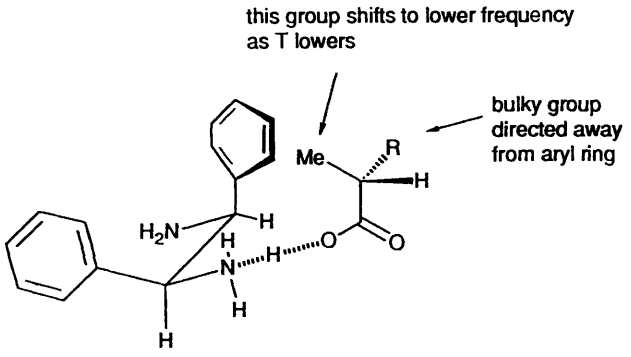

Fig. 9 A model of the 2:1 diastereoisomeric complexes of (*S*)-**1** with a chiral acid (shown as *S* for R of higher priority than Me). Only one interaction is shown for clarity.

The differential shifts of diastereotopic resonances that were obtained by varying several experimental parameters (*e.g.*, temperature, CSA structure) suggested that one of the observed groups α to the carboxylic acid (CH_3 or H usually) was close in space to an aryl ring of the CSA, **1**. This was highlighted by the temperature dependence of the chemical shift of the pro-*R* and pro-*S* hydrogens of primary carboxylic acids and by the selective shift of the α-methyl group (*e.g.*, with 2-bromopropanoic acid) to low frequency in one of the diastereoisomeric salt complexes. A *tentative* model may be proposed (Fig. 9), which embraces these points. In the postulated shift-determining conformer the methine groups of **1** are directed away from the chiral acid moiety. The overall complex retains C_2 symmetry (in the figure only one interaction is shown for clarity) and the most bulky substituent of the acid group is directed away from the phenyl rings of **1**. The anisotropy of the second phenyl ring leads to a larger shift in the position of the closest acid 2-substituent (shown as the Me group in Fig. 9) while the other substituent is less perturbed by this more distant phenyl ring. It should be noted that the fact that $\Delta\delta_H$ is a sensitive function of solvent ($CDCl_3$ *vs.* C_6D_6, particularly for the α-aryl propanoic acids) implies that the difference in free energy between the postulated conformer and other low-energy conformers is small.

Experimental

Proton NMR spectra were recorded on a Bruker AC250, a Varian VR 400S or a Bruker AMX500 spectrometer. Diastereoisomeric salt complexes were prepared by adding 0.05 mmol of (*R*)- or (*S*)-**1** (prepared by the method of Saigo[18] adapted by Corey[9]) to a solution of the chiral acid (0.10 mmol) in a suitable deuteriated solvent ($CDCl_3$, C_6D_6 or C_7D_8). Samples for NMR analysis were filtered and degassed prior to analysis. Temperatures were maintained at the stated level (± 1 °C) using the Bruker temperature control unit, previously calibrated with *100%* methanol. The *meso*-diamine, **22**, was prepared as described in the literature,[19] m.p. 119 °C (lit.,[19] 120 °C).

Samples of the Flurbiprofen, Ibuprofen and Ketoprofen were gratefully received from Mr. J. V. Wilkinson (Boots Pharmaceuticals, Analytic Development, Nottingham) and all other samples were purchased from Aldrich. A sample of racemic Naproxen **16** was obtained by boiling (*S*)-Naproxen (5.5 g, 24 mmol) (Aldrich) in ethanolic base (72 h, 50 cm^3 of 2.5 mmol dm^{-3} NaOH solution in 95:5 ethanol–water) followed by acidification, extraction into chloroform (3 × 20 cm^3), evaporation of the solvent and recrystallisation from chloroform–hexane (1:4) to yield a colourless solid (4.8 g, 87%), $[\alpha]_D^{20} = 0$ (*c* 1, $CHCl_3$). A sample of 2-fluorobutanoic acid was received from Dr. David O'Hagan (Department of Chemistry, University of Durham).

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