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A CHIRAL SOLVATING AGENT FOR DIRECT NMR ASSAY OF THE ENANTIOMERIC PURITY OF CARBOXYLIC ACIDS

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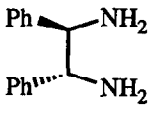
ABSTRACT: The formation of diastereoisomeric salt complexes of 1,2-diphenyl-1,2-diaminoethane and chiral carboxylic acids (including α-arylpropionic , α-deuterio and α-halo-carboxylic acids) allows the direct NMR determination of the enantiomeric purity of mono- and di-carboxylic acids.

Most non-chiroptical methods for the determination of the enantiomeric purity of chiral carboxylic acids are indirect, requiring formation of an ester or amide derivative prior to HPLC or NMR analysis.[1] NMR analysis of chiral acids with enantiopure lanthanide shift reagents is uncommon and is rendered difficult by line-broadening[3] so there is a need for alternative, direct methods of analysis. There have been isolated reports of the use of α-arylethylamines as chiral solvating agents for carboxylic acids although the observed chemical shift non-equivalence is usually very modest.[4] Herein the use of [R] or [S]-1,2-diphenyl-diaminoethane,[5] 1, is reported as a chiral solvating agent for carboxylic acids including several pharmacologically important anti-inflammatory agents, 2, and a number of α-halo acids 3 which are susceptible to racemisation in other methods of analysis.



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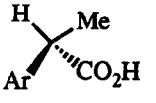

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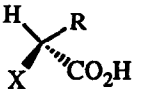
Ar = a] p-iBu-Ph [Ibuprofen]
b] 6-OMe-Np [Naproxen]
c] 2-F-biphenyl [Flurbiprofen]
d] p-{COPh}-Ph [Ketoprofen]
e] Ph



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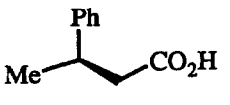
a] X = Cl , R = Me
b] X = Br , R = Me
c] X = F , R = Et



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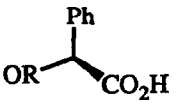
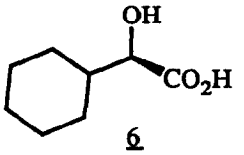


5 a] R = H
b] R = Ac



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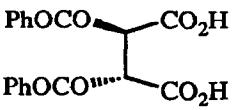

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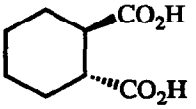

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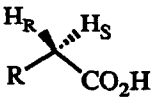


9 a] R = Ph
b] R = Me

Table 1. Measurement of the Enantiomeric Purity of Chiral Acids[a]

entry	substrate	observed resonance	$\Delta\delta_H$ (ppm) [+/- 0.005]	solvent
1	2a	2-H	0.17	C_6D_6
2	2b	2-H	0.09	C_6D_6
3	2c	2-Me	0.08	$CDCl_3$
4	2d	2-Me	0.03	$CDCl_3$
5	3a	2-Me	0.27	$CDCl_3$
6	3b	2-Me	0.23	$CDCl_3$
7	3c	4-Me	0.09[c]	$CDCl_3$
8	4	2-H	0.03	C_6D_6
9	5a	2-H	0.19	$CDCl_3$
10	5b	2-H	0.17	$CDCl_3$
11	6	2-H	0.10	$CDCl_3$
12	7	2-H	0.04[b]	$CDCl_3/C_5D_5N$(5:1)
13	8	2-H	0.05[b]	C_6D_6
14	9a	H_S/H_R	0.14	$CDCl_3$
15	9b	H_S/H_R	0.05	CDCl3

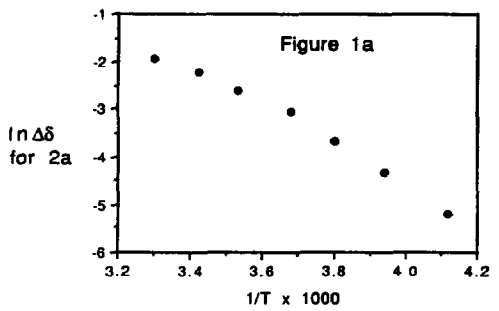
a 293K; 2:1 stoichiometry of {acid: 1 } ; usually 0.08M in substrate (see Fig1). Samples may be recovered by ether extraction from acid.Observed linewidths <1Hz.

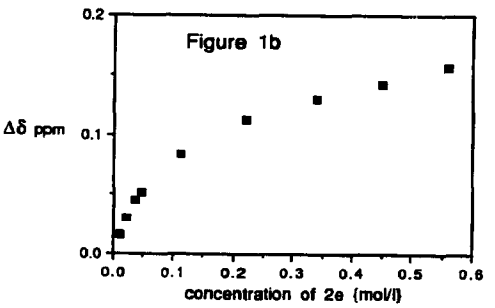
b 1:1 stoichiometry.

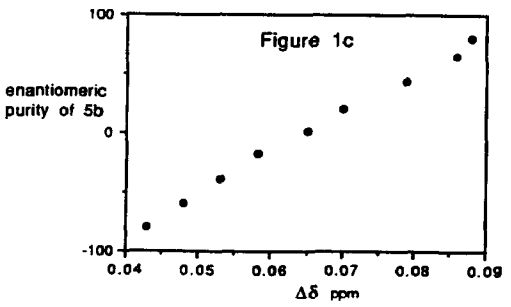
c $\Delta\delta_F$ = 0.125 ppm.

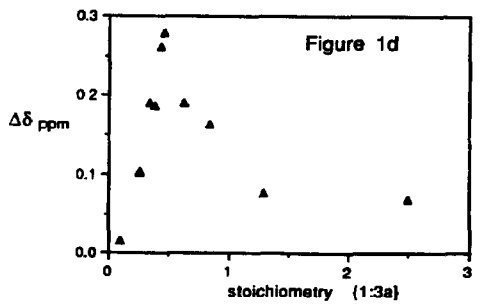
Admixture of (R)-1 with two equivalents of a chiral acid 2a-6 (Table 1) in $CDCl_3$ or C_6D_6 (according to the solubility of the salt) gives diastereoisomeric salt complexes in which large ^{1}H-NMR chemical shift non-equivalence was observed. Integration of the separate anisochronous resonances allows measurement of enantiomeric purity. Analysis of (2S)-(+)-6'-methoxy-α-methyl-2-naphthalene acetic acid , Naproxen , 2b[6] was carried out examining the methyl doublet (and taking advantage of the internal calibration provided by the ^{13}C-satellite peaks) giving a value of 96.2(2)% ee. Similarly commercial samples of (-) and (+) 2-fluoro-α-methyl-4-biphenylacetic acid , Flurbiprofen 2c ,were analysed and found to be 98.7(2) and 92.7(3) pure respectively.[7] With α-phenyl propionic acids, e.g. 2, the sense of the observed shift non-equivalence is consistent so that absolute configuration may be assigned with some confidence. In analyses with (R)-1, for example, the methyl doublet of the (S)- enantiomer in the complex resonates consistently to lower frequency of the doublet observed for the (R)-enantiomer.

The enantiotopic methylene protons of primary carboxylic acids e.g. 9 are rendered diastereotopic in the presence of 1 and are suficiently anisochronous to allow the determination of the enantiomeric purity of α-deuterio carboxylic acids either by ^{1}H or ^{2}H NMR .









The magnitude of the observed NMR shift non-equivalence is a sensitive function not only of substrate structure but also of solvent, temperature, concentration, substrate enantiomeric purity and stoichiometry (Figures 1a to 1d). The 'linear' variation of $\Delta\delta_{H_{R,S}}$ with enantiomeric composition has been observed previously[4] and is consistent with the non-equivalence of the association constants in diastereoisomeric salt formation. The dependence on concentration reveals an increase in the range 0.005 to 0.5 M with a maximum limit being approached close to 0.2M. The stoichiometry dependence suggests that formation of a significant amount of 2:1 complex is required to maximise $\Delta\delta_{H_{R,S}}$ [1:1 complexes usually give inferior values except for di-acids or bulky substrates] , and that ion-pair aggregation is not prevalent in this concentration range.[8] The increase in $\Delta\delta_{H_{R,S}}$ as the temperature is lowered may be correlated with an increasingly preferred population of a particular low energy conformation for one of the diastereoisomeric complexes in which the observed resonance spends more time, on average, proximate to the anisotropic phenyl group.

We thank SERC for support.

References and Notes

(1) Recent examples include (a) Parker, D., J. Chem. Soc. Perkin Trans. 2, 1983, 83; (b) 'Chromatographic Enantioseparation Methods and Applications', Lough, W.J., Ed., Blackie, Glasgow (1989).

(2) For a review: Parker, D., Chem. Rev., 1991, **91**, November issue.

(3) An alternative approach involves formation of dinuclear carboxylate complexes of an achiral lanthanide derivative: Alvarez, C., Barkaoui, L., Goasdoue, N., Daran, J.-C., Platzer, N., Rudler, H., and Vaissermann, J., J. Chem. Soc. Chem. Commun., (1990), 1507.

(4) (a) Guetté, J.P., Lacombe, L. and Horeau, A., Compt. Rend. Acad. Sci. Ser. C., 1968, **276**, 166; (b) Baxter, C.A.R., and Richards, H.C., Tetrahedron Lett., 1972, 1093; (c) Ejchart, A., and Jurczak, J., Bull. Acad. Pol. Sci., 1970, **18**, 445; (d) Aitken, R.A., and Gopal, J.A., Tetrahedron Asymm., 1990, **1**, 517.

(5) The enantiomeric purity of (S)-1 used in this work was ≥ 98% {$[\alpha]^{20} = +$ 104.1,{c.1, MeOH,} confirmed by ^{1}H-NMR analysis of the methine resonance in the presence of (R)-O-acetyl mandelic acid. The chiral solvating agent NMR method does not require the use of an enantiopure compound: reduction in enantiomeric purity leads to reduced values of $\Delta\delta_H$.[2,4]

(6) (S)-Naproxen obtained from Aldrich (28, 478-5); $[\alpha]_D^{20}$ + 66 (c.1, $CHCl_3$);

(7) Flurbiprofen obtained from Boots Pharmaceuticals (Nottingham). We thank Dr. K J Nicholl for a gift of these samples.

(8) Ion-pair aggregation usually results in reduced values of $\Delta\delta_{H_{S,R}}$: see for example - Villani, F.J., Costanzo, M.J., Inners, R.R., Mutter, M.S., and McLure, D.E., J. Org. Chem., 1986, **57**, 3715.