Tetrahedron: Asymmetry Vol. 2, No. 8, pp. 785-788, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

New Chiral Solvating Agents: 1,5-Benzothiazepines

Claudio Giordano,* Angelo Restelli

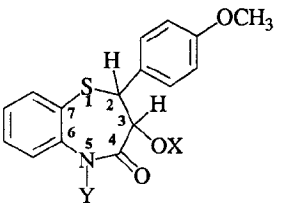
Istituto di Ricerca Chimica "G. Zambon"- Zambon Group S.p.A. - Via Cimabue, 26/28 - 20032 Cormano (Milano) - Italy

(*Received* 11 *June* 1991)

Abstract: *For the first time it is reported that 1,5-benzothiazepines (**1a-e**) (Figure I) behave as effective chiral solvating agents (CSA) for NMR enantiomeric excess (ee) determination of different classes of compounds such as α-arylalkanoic acids, α-hydroxy acids, alkanesulfonic acids, alcohols and 1,5-benzothiazepines. The molecular association between CSA and substrate is explained in terms of N-H and/or O-H hydrogen bonding.*

The enantiomeric purity determination is a problem to be faced in approaching asymmetric synthesis. A practical answer comes from the use of NMR spectroscopy in the presence of chiral substances which convert enantiomers into diastereomers. The substances come in three varieties: chiral lanthanide shift reagents (CLSR),[1] chiral "solvents" (CSA),[2] and chiral derivatizing reagents.[3] Rarely, anisochrony ($\Delta\delta$)[4] of mixtures of enantiomers in ^{1}H NMR spectra allows the ee determination in the absence of any auxiliary.[5]
Recently, we reported[5c] a new example of self-chiral discrimination by NMR which has been conveniently used for enantiomeric purity determination of 1,5-benzothiazepines **1** (Figure I).

Figure I

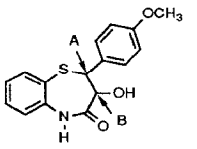
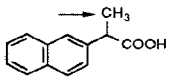
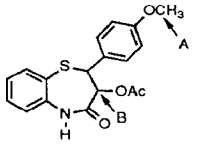
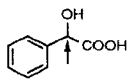
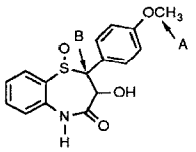
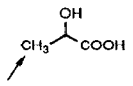
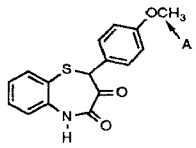
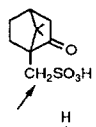
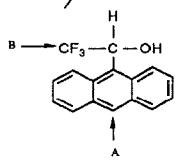


1

X = H	Y = H	Cis	2S,3S	(+)-**1a**;	2R,3R	(-)-**1a**
X = $OCCH_3$	Y = H	Cis	2S,3S	(+)-**1b**;	2R,3R	(-)-**1b**
X = H	Y = H	Trans	2S*,3R*	(+)-**1c**;	2S*,3R*	(-)-**1c**
X = H	Y = CH_3	Cis	2S,3S	(+)-**1d**;	2R,3R	(-)-**1d**
X = H	Y = $(CH_2)_2N(CH_3)_2$	Cis	2S,3S	(+)-**1e**;	2R,3R	(-)-**1e**

Now we report, for the first time,[6] that 1,5-benzothiazepines **1** are useful CSA for ^{1}H and ^{19}F NMR ee determination of different classes of compounds. A particular attention is devoted to compound **(+)-1a** since its enantiomerically enriched mixtures show the best degree of self-chiral aggregation in solution and because it is commerically available[7] and is inexpensive being an intermediate in the industrial manufacturing of Diltiazem[5c] (X = $OCCH_3$; Y = $(CH_2)_2N(CH_3)_2$ HCl; 2S,3S).

Table I:[8] ^{1}H and ^{19}F Chemical shifts differences ($\Delta\delta$) of NMR signals of racemic compounds induced by **(+)1a**.

Entries	Racemic Compounds	$\Delta\delta^{a}$ (ppm)	Entries	Racemic Compounds	$\Delta\delta^{a}$ (ppm)
1	**1c** 	A 0.007[b] B 0.01	5		A 0.007[c]
2	**1b** 	A 0.04[b] B 0.02	6		A 0.025[d]
3	**1f**[9] 	A 0.037[b] B 0.02	7		A 0.007
4	**1g**[10] 	A 0.021	8		A 0.004[d]
			9		A 0.01 B 0.02[c,e]

a) ($\delta\Delta$) were determined for $8.4x10^{-2}$ M CSA solution in $CDCl_3$, the molar ratio between racemic substrates and CSA being 1:9. Difference in chemical shift between the enantiotopic protons indicated by the arrows; b) For **1c**, **1b**, and **1f** the signals of **(+)1c**, **(+)1b**, and **(+)1f**, respectively, are at higher fields; c) The signal of compound with **(R)** configuration is at higher fields; d) The signal of compound with **(S)** configuration is at higher fields; e) Sensitive nucleus ^{19}F.

Table I summarizes the results of NMR shift experiments by **(+)-1a** of racemic compounds solutions in $CDCl_3$; among the several resonances that showed chemical shift nonequivalence between enantiomers, only those resonances suitable (signal separation) for accurate and thus quantization of composition are reported.

The analysis of the data reveals that the enantiomerically pure 1,5-benzothiazepine **(+)1a** behaves as effective CSA for differently substituted 1,5-benzothiazepines as well as towards α–arylalkanoic acids (2-(6-methoxy-2-naphthyl)-propanoic acid),[11] α–hydroxy acids (mandelic and lactic acids), alkanesulfonic acids (camphorsulfonic acid) and "activated" alcohols [2,2,2-trifluoro-1-(9-anthrylethanol)]. In the latter case the signals that best define the nonequivalence of the enantiomers spectra are due to the ^{19}F nucleus.

The phenomenon is strongly solvent dependent. Halogenated solvents ($CDCl_3$, CD_2Cl_2, CCl_4) and aromatic solvents (benzene-d_6, toluene-d_8) are useful for anisochrony ($\Delta\delta$) detection, $CDCl_3$ being the solvent of choice because the CSA has sufficient solubility in it. In contrast, the chemical shift differences ($\Delta\delta$) are not observed in N,N-dimethylformammide-d_7, dimethylsulfoxide-d_6, and methanol-d_4.

A 1: 9 molar ratio between racemic or enantiomerically enriched substrates and CSA for $8.4x10^{-2}$ M CSA solution in $CDCl_3$ is an useful condition for ee determination, $8.4x10^{-2}$ being M the solubility of **(+)-1a**.

Under the above conditions, the concentration ratio of enantiomers could be determined from 99:1 to 50:50 with an accuracy of ±1%.[12]

Compound **(+)-1b**,[5c] whose racemic as well as enantiomerically enriched mixtures showed self-chiral aggregation phenomenon,[5c] behaves similarly. Thus, when 1,5-benzothiazepine **(+)-1b** is added to a solution of racemic **1a** (under the experimental conditions given above) two sets of signals in 1:1 ratio having 0.04 ppm (Δδ) appear for the p-methoxy group protons.

To establish whether the CSA ability of 1,5-benzothiazepines was due to their self-aggregation properties, other representatives such as **(+)-1c**,[5c] **(+)-1d**,[5c] **(+)-1e**,[13] which do not show anisochrony in the NMR spectra, were tested. The addition of **(+)-1c** or **(+)-1d** or **(+)-1e** to a solution of racemic **1a** produces chemical shift nonequivalence. The (Δδ) values are 0.05 ppm for **(+)-1c**, 0.006 ppm for **(+)-1d** for the p-methoxy group protons and 0.08 ppm for **(+)-1e** for the N-H proton. It is worth noting that 1,5-benzothiazepines **1** protected both at nitrogen and oxygen, i.e. O-acetyl, N-methyl **(+)-1a**, are not chiral solvating agents.

From the spectroscopic behaviour it comes out that the CSA ability of 1,5-benzothiazepines **1** is mainly related to their interactions with the substrate through N-H or O-H hydrogen bond. The importance of the interaction through N-H or O-H hydrogen bonding is substantiated by the experiments in polar solvents whose ability in weakening intramolecular hydrogen bonding is well known.

Acknowledgements: The authors thank Mr. R. Casagrande for technical assistance.

References and Notes

1. (a) Sullivan, G. R. *"Topics in Stereochemistry"*, Eliel, E. L.; Allinger , N. L.; Wiley Interscience, New York, **1978**, *10*, 287; (b) *"Lanthanide Shift Reagent in Stereochemical Analysis - Methods in Stereochemical Analysis"*, edited by Marril, T. C.; VCH Publishers, Inc., New York, **1986**.
2. (a) Pirkle, W. H.; Sikkenge, D. L. *J.Org.Chem.* **1977**, *42*, 1370; (b) Pirkle, W. H.; Hoover, D. J. *"Topics in Stereochemistry"*, Eliel, E. L.; Allinger , N. L.; Wiley Interscience, New York, **1982**, *13*, 263; (c) Abraham, R. J.; Plant, J.; Bedford, G. R.; Wright, B. *Org.Magn.Reson.* **1984**, *22*, 57; (d) Toda, F.; Mori, K.; Okada, J.; Node, M.; Itoh, A.; Oomine, K. *Chem.Lett.* **1988**, 131.
   For recent references on new CSA see: (e) Rosini, C.; Salvadori, P. *J.Org.Chem.* **1988**, *53*, 4579; (f) Benson, S. C.; Cai, P.; Colon, M. ; Hiza, A.; Tokles, M.;Snyder, J. K. *J.Org.Chem.*. **1988**, *53*, 5335; (g) Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *J.Org.Chem.* **1989**, *54*, 5826; (h) Toda, F;. Tojotaka, R.; Fukuda, H. *Tetrahedron Asym.* **1990**, *1*, 303.
3. Shozo Yamaguchi *"Asymmetric Synthesis"*, J. D. Morrison (Ed.), *1*, Academic Press Inc., New York **1983**: chapter 7.
4. In this case the (Δδ) value is the chemical shift difference between the signals from a proton experiencing nonequivalence by self-discrimination phenomenon.
5. (a) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic', M. *J.Am.Chem.Soc.* **1969**, *91*, 1871; (b) Horeau, A.; Guetté, J. P. *Tetrahedron* **1974**, *30*, 1923; (c) Giordano, C.; Restelli, A.; Villa, M.; Annunziata, R. *J.Org.Chem.* **1991**, *56*, 2270; (d) Harger, M. J. P. *J.Chem.Soc. Chem.Commun.* **1976**, 555; (e) Harger, M. J. P. *J.Chem.Soc. Perkin Trans.II* **1977**, 1882; (f) Harger, M. J. P. *J.Chem.Soc Perkin Trans.II* **1978**, 326; (g) Kabachnik, M. I.; Mastryukova, T. A.; Fedin, E. I.; Vaisberg, M. S.; Morozov, L. L.; Petrovsky, P. V.; Shipov, A. E. *Tetrahedron* **1976**, *32*, 1719; (h) Kabachnik, M. I.; Mastryukova, T. A.; Fedin, E. I.; Vaisberg, M. S.; Morozov, L. L.; Petrovsky, P. V.; Shipov, A. E. *Russ.Chem.Rev.* **1978**, *47*, 821; (i) Tong, C. M.; Marraud, M.; Neel, J. *C.R.Acad.Sc.Paris* **1975**, *281 C*, 691; (j) Dobashi, A.; Saito, N.; Motoyama, Y.; Hara, S. *J.Am.Chem.Soc.* **1986**, *108*, 307.

6. Chiral phosphinic acid derivatives[5e,f] behave similarly: they represent an example of self induced anisochrony in ^{1}H NMR spectra, and have also shown to be useful CSA for ee determination of structurally related compounds.
7. (+)**1a** and (-)**1d** are commercially available from Zambon Group S.p.A., Via Lillo del Duca, 10 - 20091 Bresso (Milan) Italy (telefax no. ++39 2 66501492).
8. The experiments were carried out at 22 °C in $CDCl_3$. A 1:9 molar ratio between enantiomerically enriched substrates and CSA for a $8.4x10^{-2}$ M CSA solution was used. NMR spectra were recorded with Varian XL 300 spectrometer at 300 MHz for ^{1}H, at 75.4 MHz for ^{13}C and at 283.2 for ^{19}F. The temperature was controlled to ±1 ° C. The chemical shifts are reported in ppm (d) relative to internal tetramethylsilane. Racemic**1b**, **1c**, **1f** were prepared by mixing the pure enantiomers.
9. The configuration at the sulfur is unknown, the configuration at C_3 is (S) while the configuration at C_2 is assumed to be (S)

Preparation of compounds (+)1f and (-)1f. Metachloroperbenzoic acid (15.3 g, assay 90%, 80 mmol) was added at room temperature to a stirred solution of (+)**1a** or (-)**1a** (20 g, 66.5 mmol) in methylene chloride (200 mL). The reaction mixture was stirred for 12 h at room temperature. The precipitate that formed was collected by filtration, and suspended in 1M sodium hydroxide solution (80 mL). The suspension was stirred for 1 h; the precipitate was filtered, washed with water and dried under reduced pressure to afford (+)**1f** or (-)**1f** (9.5 g, 29.9 mmol, 45% yield).

(+)**1f** mp 215 -220 °C; $[\alpha]_D^{20}$ +442 (c 0.5; DMSO). ^{1}H NMR ($CDCl_3$) 3.81 (s, 3H), 4.55 (d, 1 H, B part AB system, J = 8.54 Hz), 4.6 (d, 1H, A part AB system, J = 8.54 Hz), 6.9 - 7.9 (8H, aromatic H), 9.25 (broad signal, 1H); ^{13}C NMR (DMSO-d_6) 55 19 (q), 64.54 (d), 78.62 (d), 113.88 (d), 122.95 (d), 124.3 (d), 125.0 (s), 126.78 (d), 131.56 (d), 131.71 (d), 133.83 (s), 135.03 (s),159.45 (s), 171.36 s; CI MS m/e 318 $(M+1)^+$. Isobutane chemical ionization mass spectra were recorded at 110 eV with a Finnigan MAT 8220 instrument equipped with a Data General Nova 4X data system.

10. **Preparation of racemic 1g.** Potassium *tert*-butoxide (1.95 g, 16 mmol) was added under stirring at room temperature to a mixture of benzophenone (4.7 g, 26 mmol) and (+)**1a** (1.5 g, 5 mmol) in tetrahydrofurane (30 mL). The reaction mixture was heated to 70 °C and stirred at 70 °C for 20 h. After cooling to room temperature the mixture was poured into a 0.1M potassium phosphate buffered solution (pH 7) (50 mL) and extracted with ethyl acetate (2x30 mL). The combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a crude product which was purified by flash chromatography to give pure **1g** (1.1 g, 3.6 mmol, 70% yield).

1g mp 164 -166 °C. Compound **1g** in $CDCl_3$ is present in keto-enol equilibrium.

Ketone: ^{1}H NMR ($CDCl_3$) 3.75 (s, 3H), 5.4 (s, 1 H), 6.8 - 7.7 (8 H, aromatic H); 8.7 (1 H, broad signal); ^{13}C NMR (DMSO-d_6) 55.09 (q), 64.24 (d), 114.02 (d), 123.33 (d), 124.9 (s), 126.22 (d), 127.6 (s), 129.64 (d), 131.68 (d), 136.42 (d), 141.22 (s) 159.35 (s) 169.41 (s), 195.95 (s).

Enol: ^{1}H NMR ($CDCl_3$) 3.8 (s, 3H), 6.85 - 7.65 (8 H, aromatic H), 8.6 (broad signal,1H); ^{13}C NMR (DMSO- d_6) 55.09 (q). 113.33 (d), 113.84 (s), 122.3 (d), 125.05 (d), 129.23 (s), 129.64 (d), 130.06 (d), 130.7 (s), 132.08 (d), 140.56 (s) 146.00 (s). 158.26 (s), 167.13 (s).

CI MS[11] m/e 300 $(M+1)^+$. Isobutane chemical ionization mass spectra were recorded at 110 eV with a Finnigan MAT 8220 instrument equipped with a Data General Nova 4X data system.

11. The S(+) enantiomer is known as Naproxen, a non steroidal antiinflammatory drug. (a) Castaldi, G.; Belli, A.; Uggeri, F.; Giordano, C. *J.Org.Chem.* **1983**, *48*, 4658; (b) Giordano, C.; Castaldi, G.; Cavicchioli, S.; Villa, M. *Tetrahedron* **1989**, *45*, 4243.
12. Accuracy comes from e.e. determination of mixtures of different e.e., prepared by mixing the pure enantiomers.
13. Kojic'-Prodic', B.; Ruzic'-Toros, Z.; Sunjic', V. *Helv.Chim.Acta* **1984**, *67*, 916.