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2,4,6-Tri[(*S*)-1′-methylbenzylamino]-1,3,5-triazine: a new NMR chiral solvating agent for 3,5-dinitrophenyl derivatives; an attempt at a chiral discrimination rationale

Gloria Uccello-Barretta, Simona Samaritani, Rita Menicagli and Piero Salvadori*

Dipartimento di Chimica e Chimica Industriale and Centro di Studi del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Via Risorgimento 35, 56126 Pisa, Italy

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Abstract

The use of 2,4,6-tri[(*S*)-1′-methylbenzylamino]-1,3,5-triazine as a chiral solvating agent for the NMR evaluation of the enantiomeric excess of 3,5-dinitrophenyl derivatives is reported along with an investigation into the origin of the enantiodiscrimination process.

1. Introduction

The continuous search for direct and reliable methods for determining the enantiomeric composition of chiral compounds has led to an extensive development of chiral auxiliaries for NMR spectroscopy.[1] Among them, chiral solvating agents (CSAs)[2] are very attractive, as their use only involves the preparation of a usually equimolar mixture of CSA with the chiral analyte in a suitable deuterated solvent and the recording of a routine NMR spectrum.

In view of the practical advantages of their use, several classes of CSA have been studied over the last 10–20 years. Multiselector chiral auxiliaries, showing enhanced versatilities with respect to traditional ones, may represent an interesting development in this field.

Triazine based CSAs,[3] which can be easily prepared starting from 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride),[4] have shown great potential for the determination of the enantiomeric purity of chiral functionalized substrates in solution. However, no clear evidence has been obtained until now about the stereochemical basis of their enantiodiscriminating capabilities.

In the present work the enantiodiscriminating ability of 2,4,6-tri[(*S*)-1′-methylbenzylamino]-1,3,5-triazine **1** (Fig. 1) towards 3,5-dinitrophenyl derivatives **2**–**6** (Fig. 2) of chiral compounds is reported along with an NMR investigation of the enantiodiscrimination process.

* Corresponding author. Tel: +0039 50 918273; fax: +0039 50 918260; e-mail: psalva@dcci.unipi.it

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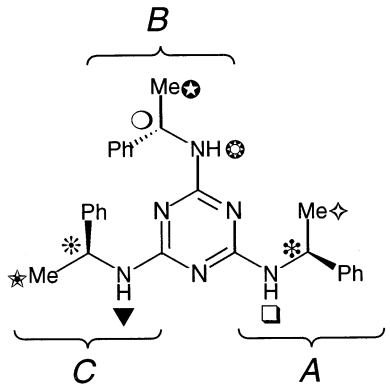

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Figure 1.

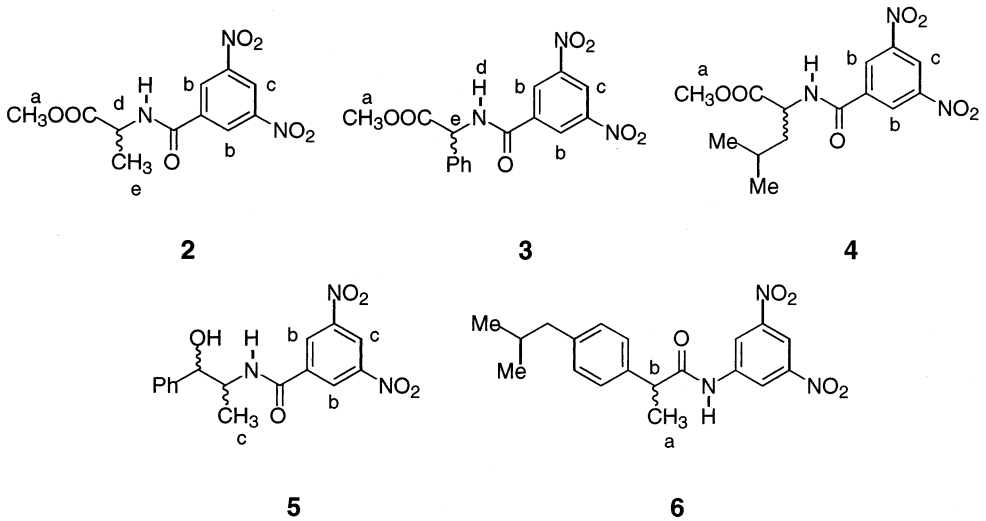

Figure 2.

2. Results and discussion

2,4,6-Tri[(*S*)-1′-methylbenzylamino]-1,3,5-triazine **1** (Fig. 1) was prepared by reacting 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) with three molar equivalents of (*S*)-1-methylbenzylamine in the presence of K_2CO_3 and a catalytic amount of 18-crown-6, according to reported procedures.[3a, 4]

The enantiodiscriminating ability of **1** in solution was tested by analyzing the ^1H NMR spectra in $CDCl_3$ of mixtures containing equimolar amounts of **1** and the racemic compounds **2**–**6** (Fig. 2).

In all cases 3,5-dinitrophenyl protons showed appreciable doubling and the corresponding values of non-equivalences, measured at 25°C, are shown in Table 1.

The expected increase of the non-equivalences can be achieved by lowering the temperature (–20°C) as shown in Table 1 for the equimolar mixture **1**/**2**. In this last case in particular, the *b* and *a* protons of **2** produced two completely resolved sharp doublets at 8.82 and 8.78 ppm and

Table 1
Values of non-equivalences [$\Delta\Delta\delta$[a] (Hz)] measured for proton[b] resonances of compounds **2**–**6** in the presence of **1** [**1**/**2**–**6** = 1/1, 20–30 mM][c]

Compound	Protons	$\Delta\Delta\delta$
2	a	1.8 (3.6)[d]
	b	3.6 (12.4)[d]
	c	1.3 (4.7)[d]
	d	nd (1.2)[d]
	e	nd (6.5)[d]
3	a	4.1
	b	6.9
	c	2.4
	d	7.3
	e	1.6
4	a	2.8
	b	4.1
	c	3.2
5	a	2.0
	b	2.8
	c	4.5
6	a	2.8
	b	4.1

[a] $\Delta\Delta\delta$ = difference in *chemical shifts* between the two enantiomers in the presence of the chiral solvating agent.
[b] ^{1}H NMR, 300 MHz, 25°C, $CDCl_3$.
[c] Cf. Fig. 2.
[d] Non-equivalences at −20°C.

two singlets at 3.72 and 3.71 ppm, respectively, while the c protons gave rise to two partially superimposed triplets at 9.02 and 9.01 ppm (Fig. 3 **B**).

In order to gain a deeper insight into the mechanism of interaction between **1** and the discriminated substrates, the derivative **3** (Fig. 2), for which the greatest non-equivalences had been measured (Table 1), was closely investigated.

At first the stereochemistry of **1** in solution had to be established: owing to its *C*3 symmetry, suitable experimental conditions had to be found to distinguish the otherwise equivalent signals of each of the three 1-methylbenzylamino moieties **A**, **B** and **C** (Fig. 1).

^{1}H NMR spectra of **1** were recorded in CD_2Cl_2 solution at different temperatures (Fig. 4). As expected, the lowering of the temperature led to the progressive decoalescence of signals of the three units (Fig. 4 **A**–**D**) and, at −20°C, the methyl, methine and amino groups of each 1-methylbenzylamino substituent produced sharp signals which could be attributed by suitable decoupling experiments.

In particular (Table 2), three doublets were observed at 1.23, 1.29 and 1.34 ppm (CH_{3A}, CH_{3B} and CH_{3C}, respectively); CH_A gave rise to a sharp quintet at 5.07 ppm, while CH_B and CH_C produced two partially superimposed quintets at 4.86 and 4.91 ppm; three well-resolved doublets were observed at 5.27, 5.56 and 5.77 ppm (NH_C, NH_B and NH_A, respectively).

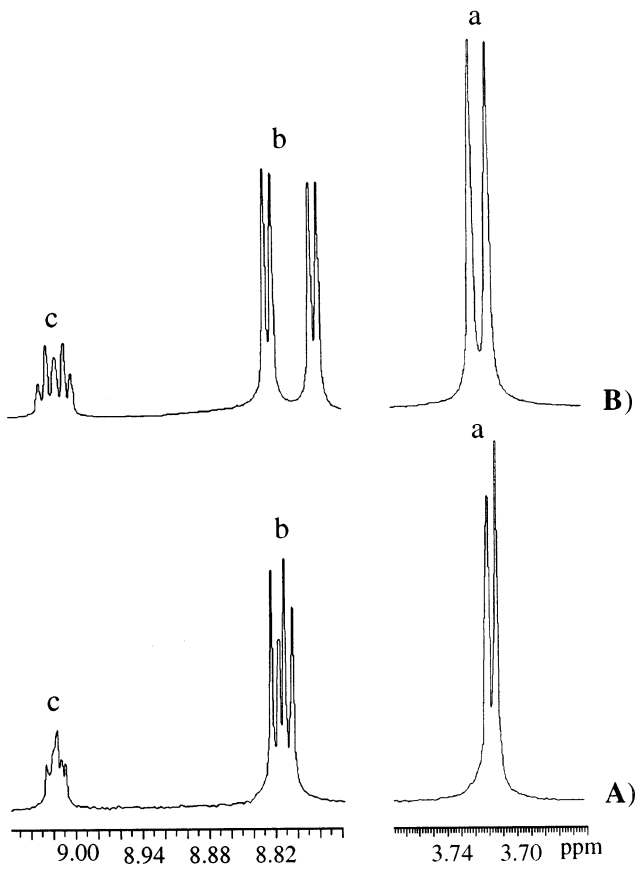

Figure 3. ^{1}H NMR spectra (300 MHz) of the mixture **1**/(*RS*)-**2** ([**1**]/[**2**] = 1/1, 20 mM, $CDCl_3$) at **A**: 25°C; **B**: −20°C

Under the same experimental conditions a 2D ROESY map of **1** was acquired: although it was not possible to distinguish the aromatic protons signals of each moiety, in the trace corresponding to the superimposition of the phenyl resonances of **1** a strong NOE was observed on both NH_B and NH_A protons, while the NOE on the NH_C proton was much less intense (Fig. 5 **A**).

Since it can be reasonably assumed that, inside each 1-methylbenzylamino substituent, an equivalent NOE is produced by the aromatic protons on the NH group, the more intense NOE observed on NH_A and NH_B had to be ascribed by their nearness to the phenylic protons of adjacent units. The analysis of the 2D ROESY map also allowed interesting information about the relative positions of the methyl and amino groups of each 1-methylbenzylamino substituent to be obtained. As a matter of fact, while NH_A produces a strong NOE only on CH_{3A} protons, as NH_B does on CH_{3B}, a strong NOE is caused on both CH_{3B} and CH_{3C} by NH_C (Fig. 6), showing the proximity of NH_C and CH_{3B} groups.

Moreover, the three dihedral angles θ_A, θ_B and θ_C (Table 3), identified by the H–N–C–H fragment of each 1-methylbenzylamino substituent, were evaluated using a modified Karplus equation[5] where the experimentally determined J_{NH-CH} values were used.

It is noteworthy that, for each 1-methylbenzylamino substituent, between the two possible solutions of the Karplus equation, the value of θ corresponding to a relative *pseudo-transoid*

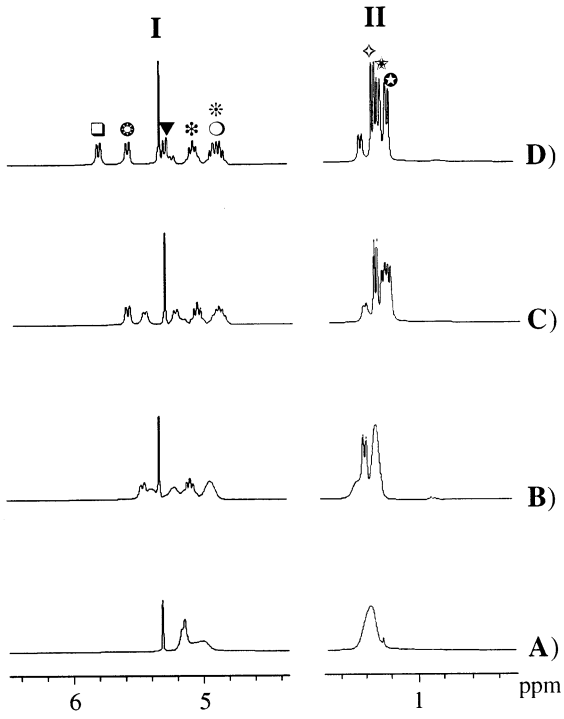

Figure 4. ^{1}H NMR spectra (300 MHz, CD_2Cl_2) spectral regions corresponding to NH and CH (**I**) and methyl (**II**) resonances of **1** (50 mM) at **A**: 25°C; **B**: 0°C; **C**: –10°C; **D**: –20°C; NH_A (□), NH_B (✪), NH_C (▼); CH_A (✻), CH_B (○), CH_C (✳), CH_{3A} (✧), CH_{3B} (✪), CH_{3C} (★)

Table 2
^{1}H NMR (300 MHz, CD_2Cl_2, −20°C) chemical shifts (δ ppm) of NH, CH and CH_3 groups of **A**, **B** and **C** moieties of **1** in the pure compound and in the presence of equimolar amounts of (*R*)- and (*S*)-**3** (50 mM)

	δ (ppm)								
	NH			CH			CH_3		
	A	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
1	5.77	5.56	5.27	5.07	4.91	4.86	1.34	1.23	1.29
1/(*R*)-**3**	5.90	5.53	5.42	4.85	4.89	4.87	1.23	1.23	1.31
1/(*S*)-**3**	5.76	5.57	5.30	4.97	4.81	4.85	1.32	1.16	1.32

disposition of the C–H and N–H bonds was chosen: actually no appreciable NH/CH dipolar interactions were outlined by NOE measurements.

Since the relevant NOEs between the aromatic and NH protons suggest that these could be located out of the plane of the triazine ring, the conformational model shown in Fig. 7 can be proposed for **1** in solution: taking the 1,3,5-triazine ring as a reference plane, the NH_A proton is situated over the plane and oriented towards the phenylic ring of the *C* unit, the NH_B proton is located under the plane and oriented towards the phenylic ring of the *A* moiety; eventually, the NH_C proton is localized under the plane and is directed towards the methyl group of the *B*

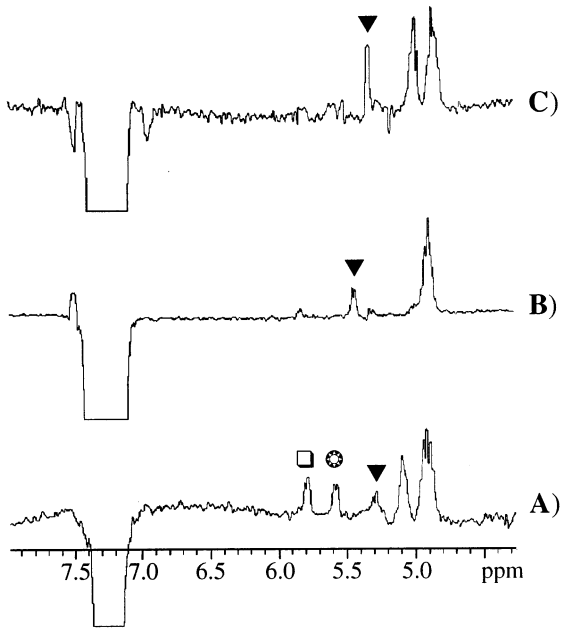

Figure 5. 2D ROESY traces (300 MHz, CD_2Cl_2, −20°C) of aromatic protons of **A**: **1** (50 mM); **B**: **1**/(*R*)-**3** [**1**/(*R*)-**3** = 1/1, 50 mM]; **C**: **1**/(*S*)-**3** [**1**/(*S*)-**3** = 1/1, 50 mM]; NH_A (□), NH_B (✪), NH_C (▼)

1-methylbenzylamino substituent. In this way the relevant dipolar interaction between both NH_A and NH_B and phenyl protons, as well as the one between NH_C and both CH_{3C} and CH_{3B} can be justified. Our model is different from the one reported for 2,4,6-tri(*N*,*N*-dialkylamino)-1,3,5-triazine derivatives by Katritzky[6] and supporting hyperconjugation between the triazine ring and esocyclic nitrogens; similar hyperconjugation in **1** should give rise to coplanarity between the NH groups and the heteroaromatic ring.

The complexation shifts in the equimolar mixtures **1**/(*R*)-**3** and **1**/(*S*)-**3** were evaluated under the experimental conditions previously employed for the determination of the stereochemistry of **1** in solution (300 MHz, CD_2Cl_2, −20°C) to obtain some information about the stereochemistry of the interaction.

The signals of methyl, methine and amino groups of each 1-methylbenzylamino substituent (**A**, **B** and **C**) of **1** were again attributed by suitable decoupling experiments: the corresponding resonances are summarized in Table 4.

In particular, in the equimolar mixture **1**/(*R*)-**3**, CH_{3A} and CH_{3B} protons produced two superimposed doublets at 1.23 ppm, while CH_{3C} protons gave rise to a resolved doublet at 1.31 ppm; two partially superimposed quintets and a resolved one (Fig. 8 **B**) were observed at 4.87, 4.89 and 4.85 ppm (CH_C, CH_B and CH_A, respectively); the three amino groups produced separate resonances at 5.42, 5.43 and 5.90 ppm (NH_C, NH_B and NH_A, respectively).

The comparison between the spectra of **1** (Fig. 8 **A**) and those of the two mixtures **1**/(*R*)-**3** (Fig. 8 **B**) and **1**/(*S*)-**3** (Fig. 8 **C**) clearly shows that the presence of any of the enantiomers produces an appreciable broadening of the NH_A and NH_B signals, while it does not influence the pattern of the NH_C signal. Moreover, the complexation shifts calculated for the NH signals of **1** in the (*R*)-**3**/**1** mixture were appreciably higher than those calculated for the (*S*)-**3**/**1** mixture (Table 4).

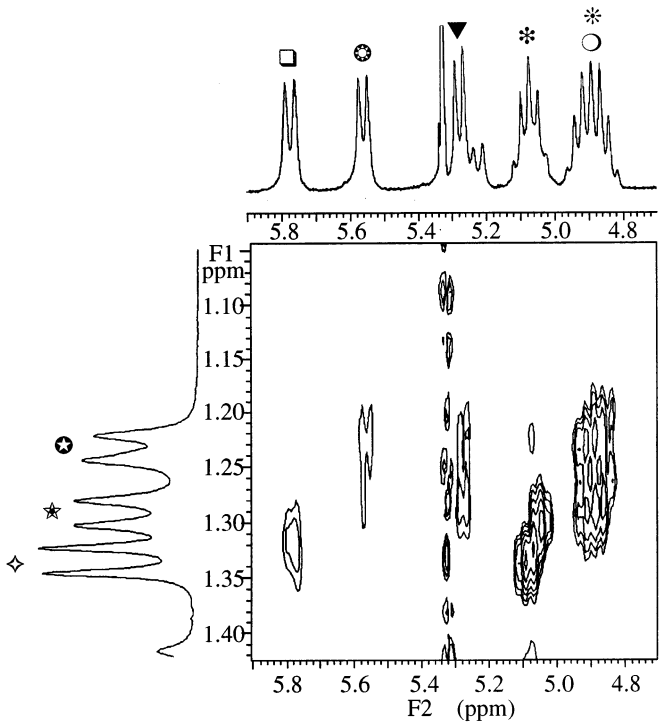

Figure 6. 2D ROESY map (300 MHz, CD_2Cl_2, −20°C) of **1** (50 mM); NH_A (□), NH_B (◎), NH_C (▼); CH_A (❊), CH_B (○), CH_C (✳), CH_{3A} (✧), CH_{3B} (✪), CH_{3C} (★)

Table 3
NH–CH (Hz) coupling constants and dihedral angles H–N–C/N–C–H (θ°) calculated for **A**, **B** and **C** moieties of **1** by a Karplus equation[5]

	A	B	C
J NH/CH (Hz)	8.5	7.5	7.5
θ H–N–C–H (°)	151	144	144

The inspection of the 2D ROESY maps of the two mixtures allowed further information about the conformation of the chiral solvating agent in the presence of the enantiomers of **3** to be obtained.

In particular, the trace of the aromatic protons of **1** revealed a strong NOE with NH_C, while the corresponding effects on NH_A and NH_B were definitely negligible (Fig. 5 **B**, **C**). Moreover, the traces of the methyl groups showed that, in both cases, NH_C produces a strong NOE only on CH_{3C}, while no NOEs involving NH_A and NH_B are observed, thus showing that both (*R*)- and (*S*)-**3** produce significant conformational changes in the chiral auxiliary.

The comparison between the ^{13}C NMR spectra (300 MHz, −20°C) of (*RS*)-**3** (Fig. 9 **A**) and of an equimolar mixture **1**/(*RS*)-**3** (Fig. 9 **B**) demonstrates that the signals of both carbonilic groups of **3** are doubled in the presence of **1**, thus suggesting that both the amide and the ester

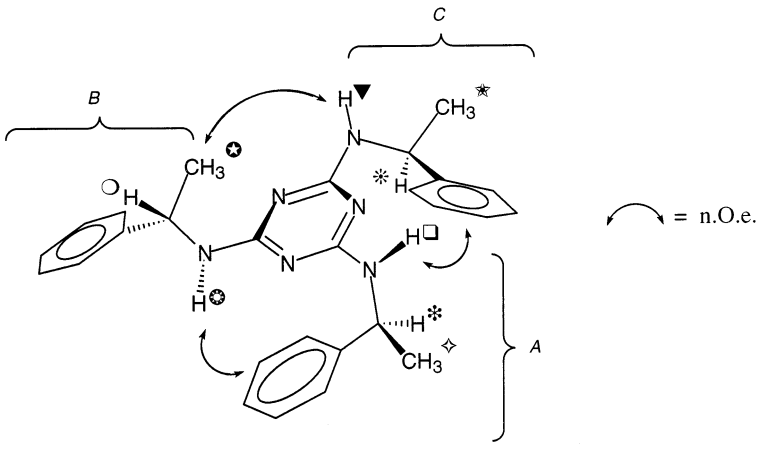

Figure 7. Conformation model of **1** in CD_2Cl_2 solution

Table 4
Complexation shifts ($\Delta\delta$, Hz) for selected protons of **1** in the presence of (*R*)- and (*S*)-**3**

	$\Delta\delta$ (Hz)[a] NH		
	A	**B**	**C**
1/(*R*)-**3**	39	−9	45
1/(*S*)-**3**	−3	3	9

[a] $\Delta\delta$ = difference between chemical *shifts* (Hz) of **1** as a pure compound (300 MHz, CD_2Cl_2, 50 mM) and in the presence of the substrate [300 MHz, CD_2Cl_2, 50 mM, **1**/(*R*)-**3** = 1/1 and **1**/(*S*)-**3** = 1/1].

functionalities of the substrate are involved in interaction with the chiral solvating agent, probably by means of its NH groups lying out of the triazine plane and therefore being available for interaction with the analyte.

The NMR data described above point out the conformational changes occurring when **1** interacts with both enantiomers of **3**. The line broadening observed for NH_A and NH_B in **1**/(*R*)-**3** and **1**/(*S*)-**3** mixtures is remarkably diagnostic of the kind of interaction occurring with both enantiomers. This effect can be ascribed to a significant immobilization of NH_A and NH_B, consequent to their simultaneous interaction with the amide and the ester carbonyl groups of the substrate. As a matter of fact these two groups are also significantly doubled in the mixture **1**/(*RS*)-**3**.

The third unit of **1**, named **C**, probably acts independently by means of its NH_C group interacting with another substrate molecule.

A similar situation might hold for (*R*)- and (*S*)-**3**, since the line broadening of NH_A and NH_B is similar for the two mixtures: the lower complexation shifts observed for (*S*)-**3** with respect to (*R*)-**3** can be ascribed to a higher steric hindrance in the former enantiomer, which inhibits its efficiency as a bidentate ligand, thus lowering the association degree.

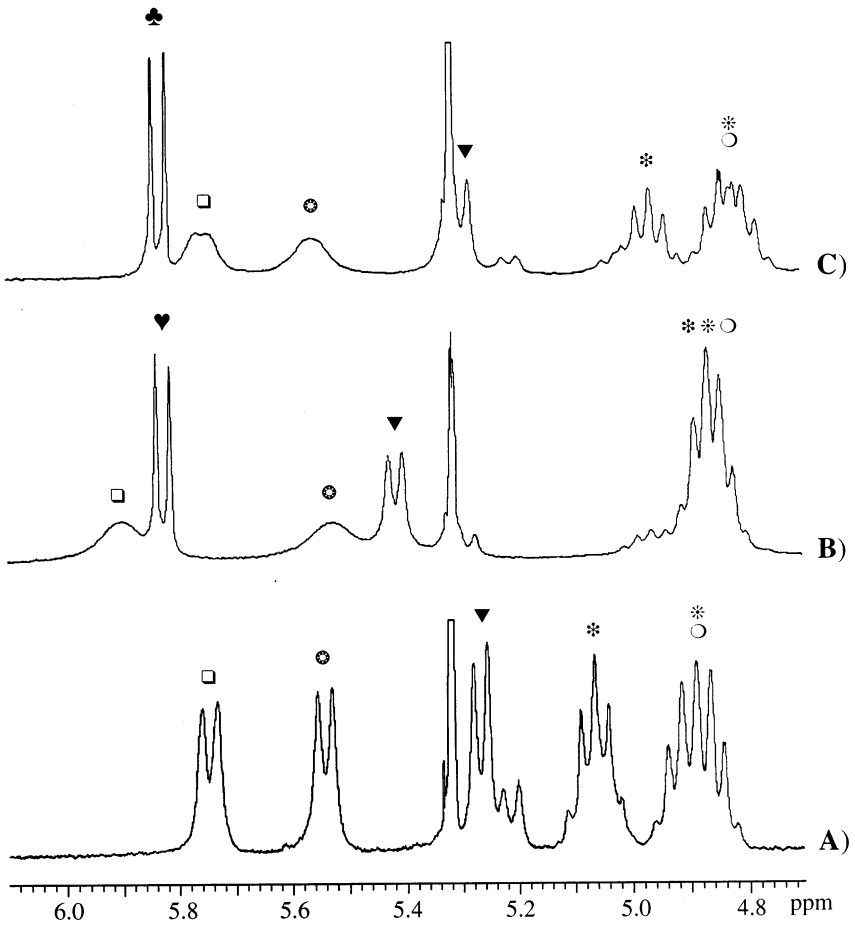

Figure 8. ^{1}H NMR spectra (300 MHz, CD_2Cl_2, −20°C) spectral regions corresponding to the CH and NH protons of **A**: **1** 50 mM; **B**: **1**/(*R*)-**3** [**1**/(*R*)-**3** = 1/1, 50 mM]; **C**: **1**/(*S*)-**3** [**1**/(*S*)-**3** = 1/1, 50 mM]; NH_A (□), NH_B (❂), NH_C (▼), CH_A (❇), CH_B (○), CH_C (✳), CH of (*R*)-**3** (♥), CH of (*S*)-**3** (♣)

3. Conclusions

The overall reported data, besides proving the enantiodiscriminating ability of **1** towards chiral 3,5-dinitrophenyl derivatives, afford clear evidence of the conformational changes undergone by the triazine chiral auxiliary due to its interaction with the chiral analyte, and of the ability of each methylbenzylamino unit of **1** to interact independently with substrate molecules; hence this work represents an improvement in the comprehension of the interaction mechanism of these chiral solvating agents with chiral substrates.

4. Experimental

Solvents were purified and/or dried according to reported procedures.[7] (*S*)-1-Methylbenzylamine $\{[\alpha]_D^{25} = -37.8$ (neat), e.e. 99%$\}$[8] was distilled before use and stored under nitrogen; 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) was recrystallized from carbon tetrachloride[7]

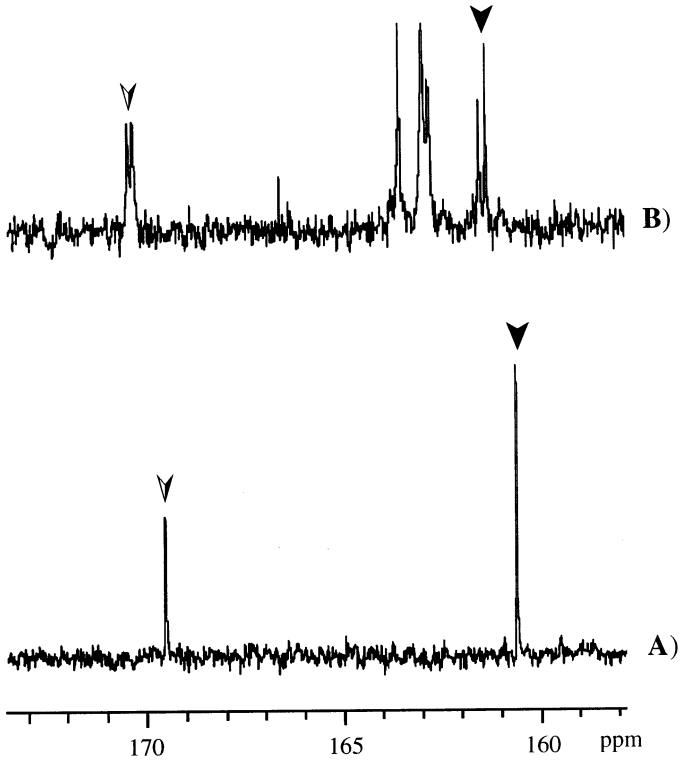

Figure 9. ^{13}C NMR spectra (300 MHz, CD_2Cl_2, −20°C) of **A**: (*RS*)-**3** (75 mM); **B**: **1**/(*RS*)-**3** [**1**/(*RS*)-**3** = 1/1, 75 mM]

and stored under nitrogen. Thin layer chromatography (TLC) was carried out on silica gel plates 60 (Fluka) and compounds were visualized with iodine or by examination under UV light. Flash chromatography was carried out on silica gel 60 (Fluka, 220–440 mesh ASTM). Mass spectra were performed by a Perkin–Elmer Q-Mass 910 spectrometer interfaced with a Perkin–Elmer 8500 gas-chromatograph. NMR measurements were carried out by a Varian VXR-300 spectrometer equipped with a temperature control unit (±0.1°C). 2D ROESY spectra were acquired with the minimum spectral width in both dimensions, in 2K data points using four scans for each of the 512 t_1 increments and using mixing times between 1 and 0.1 s. The data were zero-filled to 2×1K and a Gaussian function was applied for processing in both dimensions. Optical rotatory power was measured on a Perkin–Elmer 142 polarimeter, equipped with a temperature control unit (±0.1°C).

4.1. 2,4,6-Tri[(S)-1'-methylbenzylamino]-1,3,5-triazine **1**

A mixture of 2,4,6-trichloro-1,3,5-triazine K_2CO_3, 18-crown-6 ([cyanuric chloride]/K_2CO_3]/[18-crown-6] = 1/3/0.03 molar ratio) in dry toluene was treated, under nitrogen, with a toluenic solution of (*S*)-1-methylbenzylamine ([cyanuric chloride]/[(*S*)-1-methylbenzylamine] = 1/3 molar ratio). The mixture was refluxed for 48 h and then filtered using a short package of celite. The solvent was removed and the crude product was purified by flash chromatography (*n*-hexane/ethyl acetate = 70/30 v/v). The recovered (82% yield) chemically pure glassy solid showed:

$[\alpha]_D^{25} = -146.1$ ($c = 0.883$, $CHCl_3$); *m/e* (1%): 438 (M^+, 40.8), 423 (11.2), 318 (6.4), 214 (35.8), 120 (69.1), 105 (100); ^1H NMR ($CDCl_3$, 25°C): 7.30 (m, 5H, Ph); 5.15–4.90 (m, 2H, N*H*, PhC*H*CH_3); 1.35 (m, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 25°C): 165.4, 144.7, 126.8, 126.4, 126.0, 49.9, 22.6.

4.2. (RS)-N-(3,5-Dinitrobenzoyl)-alanine methyl ester **2**

Compound **2**, prepared according to a reported procedure,[9] showed: ^1H NMR ($CDCl_3$, 25°C): 9.18 (1H); 8.95 (2H); 7.15 (1H); 4.75 (1H); 3.71 (3H); 1.45 (3H).

4.3. (RS)-N-(3,5-Dinitrobenzoyl)-phenylglycine methyl ester **3**

Compound **3**, prepared according to a reported procedure,[9] showed: ^1H NMR ($CDCl_3$, 25°C): 9.15 (1H); 8.95 (2H); 7.65 (1H); 5.78 (1H); 3.81 (3H).

4.4. (RS)-N-(3,5-Dinitrobenzoyl)-valine methyl ester **4**

Compound **4**, prepared according to a reported procedure,[9] showed: ^1H NMR ($CDCl_3$, 25°C): 9.18 (1H); 8.95 (2H); 7.18 (1H); 4.83 (1H); 3.84 (3H); 2.35 (1H); 1.04 (6H).

4.5. 2-(3′,5′-Dinitrobenzamido)-1-phenyl-1-propanol **5**

Racemic **5**, prepared according to a reported procedure,[10] showed: ^1H NMR ($CDCl_3$, 25°C): 9.14 (1H); 8.91 (2H); 7.26–7.50 (5H); 6.57 (1H); 5.02 (1H); 4.53 (1H); 2.55 (1H); 1.14 (3H).

4.6. (RS)-N-(3′,5′-Dinitrophenyl)-2-(p-isobutylphenyl)-propionamide **6**

Compound **6**, prepared according to a reported procedure,[10] showed: ^1H NMR ($CDCl_3$, 25°C): 8.72 (3H); 7.71 (1H); 7.23 (4H); 3.80 (1H); 2.49 (2H); 1.85 (1H); 1.63 (3H); 0.95 (6H).

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