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Preparation of enantiomers of 1-(1-naphthyl)-2,2-dimethylpropylamine and their behaviour as chiral solvating agents: study of diastereochemic association by Job's plots and intermolecular NOE measurements

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Abstract

Enantiomers of 1-(1-naphthyl)-2,2-dimethylpropylamine have been obtained and considered as chiral solvating agents against several compounds. The formed complexes have been studied with the aid of the nuclear Overhauser effect and its stoichiometry by the method of continuous variations. Two diastereoisomeric complexes present similar geometry of association by π–π-stacking of the aromatic rings and by hydrogen bonding of the functional groups. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The rotational barrier of a bond is one of the essential factors in the chiral discriminatory ability in complex formation. In demonstrating this, the preparation[1,2] of 9-anthryl-*tert*-butylcarbinol as a chiral solvating agent and its behaviour were recently reported showing the importance of the *t*-butyl group to study the complex structure. The intermolecular nuclear Overhauser effect (NOE) was used to analyze[2,3] in a qualitative way the proximity of various parts of the chiral molecules for which enantiodifferentiation occurred.

Optically active amines have been used extensively as chiral solvating agents (CSA) in the NMR determination of the enantiomeric excess of chiral carboxylic acids.[4] Anisotropic groups in chiral amines have given rise to chemical non-equivalence in the diastereomeric complexes formed between amine and acid compounds. The preparation of enantiomers of 9-(1-amino-2,2-dimethylpropyl)-9,10-dihydroanthracene and their behaviour as chiral solvating agent have been described.[5]

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1-(1-Naphthyl)ethylamine was reported, firstly, by Pirkle et al. to assign the absolute configuration of alkylarylcarbinols and acids.[6] In order to study the effect of a higher rotational barrier, and to increase the possibility of obtaining intermolecular NOEs, a *t*-butyl group was introduced and the 1-(1-naphthyl)-2,2-dimethylpropylamine **1** was synthesised. The enantiomers were separated by chiral HPLC and tested against several chiral molecules as acids and alcohols.

2. Results and discussion

Racemic 1-(1-naphthyl)-2,2-dimethylpropylamine **1** was obtained by reducing 1-(1-naphthyl)-2,2-dimethylpropylimine **2**, which was prepared by reaction of the lithium derivative of 1-bromonaphthalene with pivalonitrile (Fig. 1).

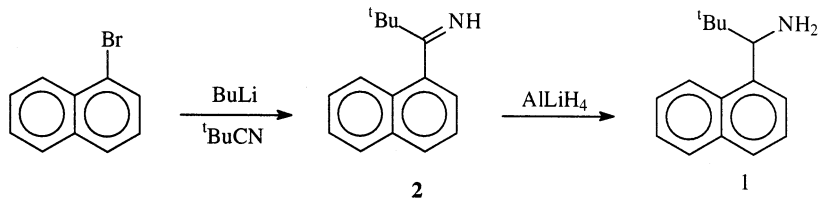


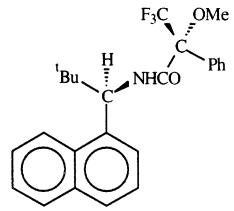
Figure 1. Scheme of synthesis of **1**

Separation of the enantiomers of **1** was achieved by direct chromatography using a Whelk-O1 semi-preparative chiral column. Hexane/*i*-PrOH (9:1) was used as elution solvent with a 3.5 ml min^{-1} flow rate. $K_{(S)}=3.2$; $K_{(R)}=5.9$; $\alpha=1.85$. The first enantiomer eluted was (+)-**1** and the second (−)-**1**. Their absolute configuration was assigned ((*S*)-(+)-**1** and (*R*)-(−)-**1**) by X-ray diffraction of the amide derivative of (−)-**1**: 1*N*-[1-(1-naphthyl)-2,2-dimethyl-(1*R*)-propyl]-3,3,3-trifluoro-2-methoxy-2-phenyl-(2*R*)-propylamide, **3**, (Fig. 2) obtained by reaction of (*R*)-**1** with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride.

2.1. Conformational studies

Restricted rotation about the sp^2–sp^3 bond in carbinols of the type ArRR′COH has been studied extensively in recent years.[7] Lunazzi et al. employed dynamic nuclear magnetic resonance to study atropisomers generated by this rotation. Although imines,[8] sulfoxides,[9] sulfones,[10] ketones[11] and phosphines[12] bearing naphthyl as an aromatic group were also examined, no references exist when an amine is present on the sp^3 carbon. Dynamic HPLC was also useful in detecting these isomers.[13]

Here, a complete study was performed on 1-(1-naphthyl)-2,2-dimethylpropylamine **1**, where a pair of conformational atropisomers exists owing to the simultaneous presence of a stereogenic center (the carbon atom) and a stereogenic axis (sp^2–sp^3) (Figs. 3 and 4).



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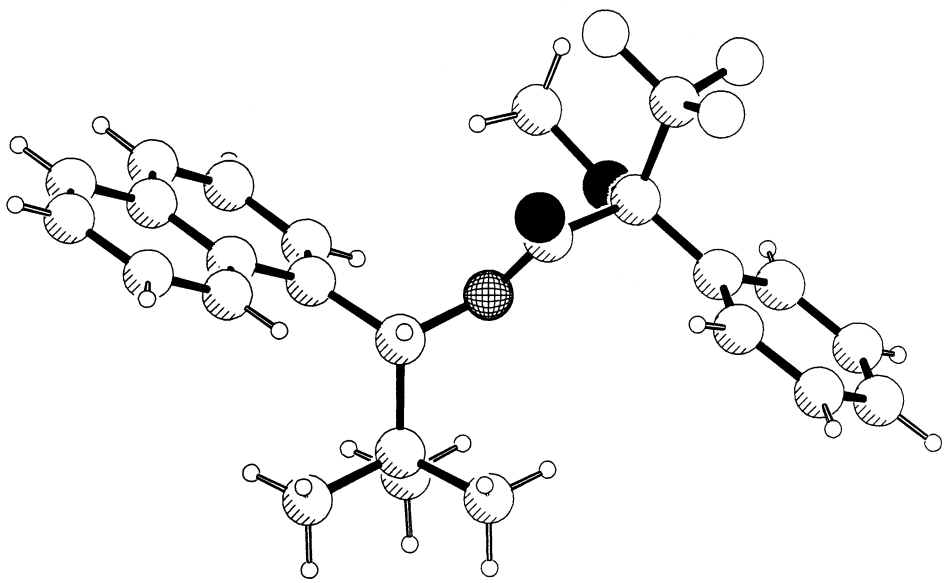
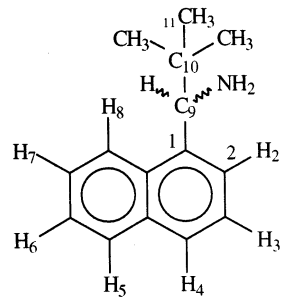


Figure 2. Representation of X-ray diffraction of amide **3**



1

Figure 3. Numbering of compound **1**

MM3 calculations[14] (Fig. 5) were used to estimate the barriers of rotation about the sp^2–sp^3 axis. Two atropisomers, *ac* and *sc*, are of differing stability, with the *ac* atropisomer being more stable with a 3.45 kcal mol^{-1} energy difference, which means that *ac* atropisomer is predominant in a 99.3 to 0.7 population. Interconversion of the more abundant (*ac*) into the less abundant atropisomer (*sc*) can be achieved following two different pathways: *tert*-butyl group rotation

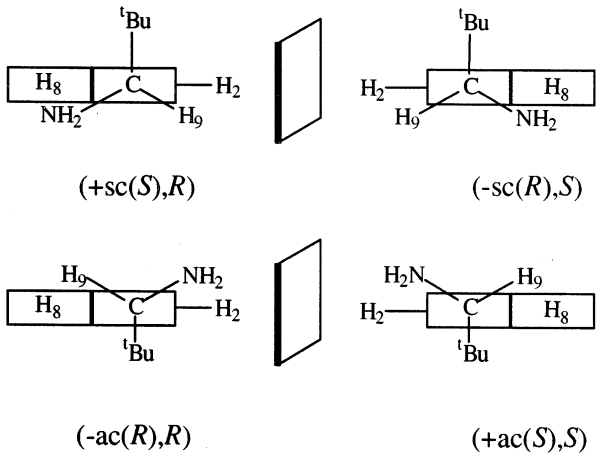


Figure 4. *R* or *S* nomenclature used for chiral centre and nomenclature for atropisomers sp^2–sp^3 used for the chiral axis

over proton H_8 or over H_2, where the latter has the lowest energy pathway. Hence the corresponding calculated free energy of activation can be derived ($\Delta G^* = 15$ kcal mol^{-1}). The variable temperature NMR experiment did not afford changes in the signal shape nor any chemical shift of any proton in the amine. The X-ray structure confirms that only the *ac* atropisomer is present in the solid state (Fig. 6).

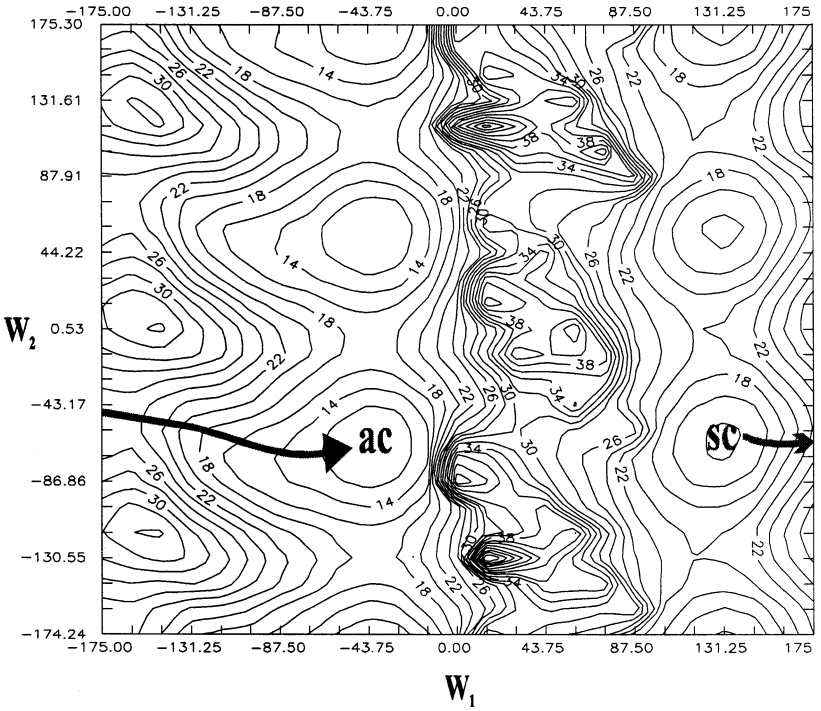


Figure 5. Steric energy plot for atropisomer conversion of **1**. Diedric angles used for the study were $W_1 = N–C_9–C_1–C_2$ and $W_2 = CH_3–C_{10}–C_9–C_1$. Lowest energy conversion pathway between atropisomers is shown.

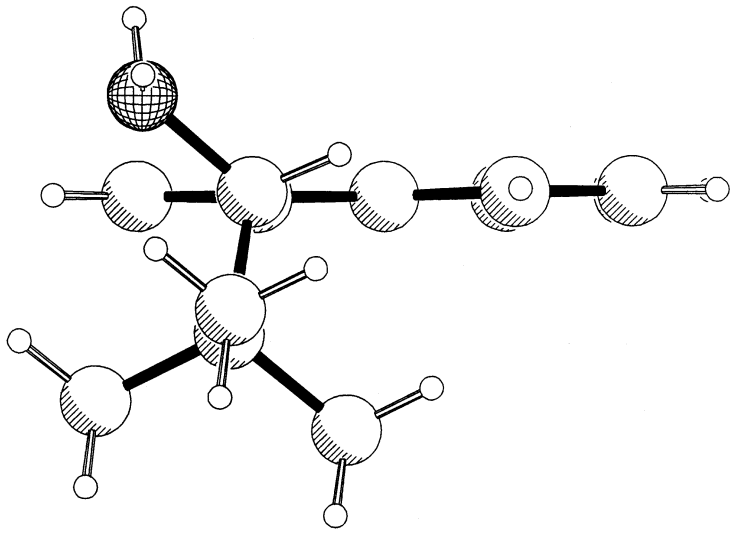


Figure 6. Molecular structure obtained by X-ray diffraction for (*S*)-**1**

2.2. Chiral induction activity

A mixture of a racemic and non-racemic chiral compound (Fig. 7) (methoxy mandelic acid **4**, 1-phenyl-1,2-ethanediol **5**, 3-phenylbutyric acid **6**, ibuprofen **7**, 2-bromopropionic acid **8**, 2,2,2-trifluoro-1-(9-anthryl)-ethanol **9** and *trans*-1,2-diphenylethylene oxide **10**) with between one and two equivalents of one enantiomer (*R* or *S*) of **1** gave diastereomeric complexes in which ^{1}H NMR chemical shift non-equivalence was observed. Integration of the separate anisochronous resonances allowed measurement of enantiomeric purity. All experiments were carried out in a 400 MHz spectrometer at 298 K and using $CDCl_3$ as a solvent. Results are shown in Table 1.

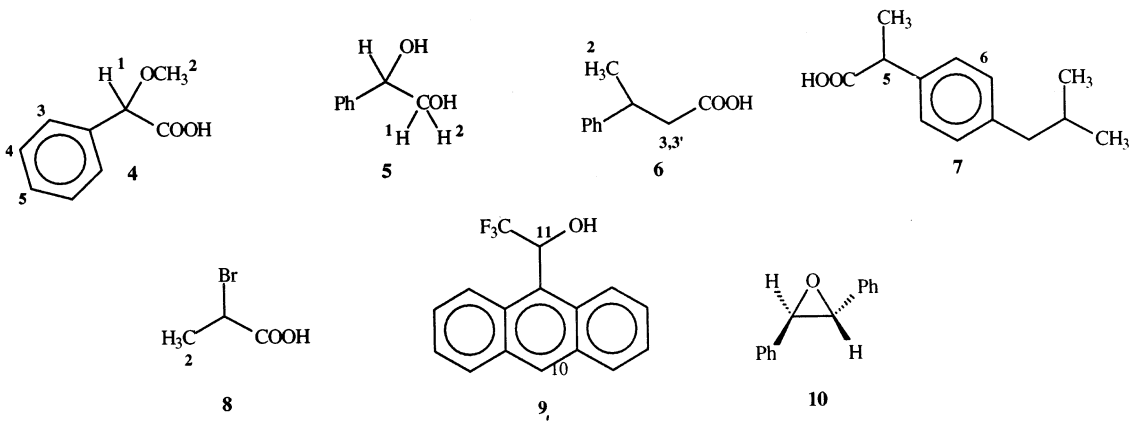


Figure 7. Compounds **4**–**10**

Table 1
Measurement of the maximum induced chemical shift on racemic compounds **4**–**9** using (*R*)-**1** or (*S*)-**1** as CSA

Substrate	Observed resonance	Stoichiometry **1**:chiral solut	$\Delta\delta_H$ (ppm)
4	H_1	1.5	0.10
	H_2	1.5	0.09
	$H_3/H_4/H_5$	1.5	0.09
5	H_2	1.5	0.01
	H_3	1.5	0.01
6	H_2	1[a]	0.02
	H_3	1[a]	0.02
	$H_{3'}$	1[a]	0.01
7	H_5	1.5	0.02
	H_6	1.5	0.03
8	H_2	1[a]	0.09
9	H_{11}	1.5	0.07
	H_{10}	1.5	0.01

[a] Salt formation.

Fig. 8 shows a part of the NMR spectrum corresponding to the addition of 1.5 equivalents of (*S*)-**1** to the racemic compound and to the one enriched enantiomer of compound **4**. The observed non-equivalence of the methyne (H_1) and methyl (H_2) signals increased at higher concentrations of the amine (*S*)-**1**, with a maximum being recorded at 1.5 equivalents of amine.

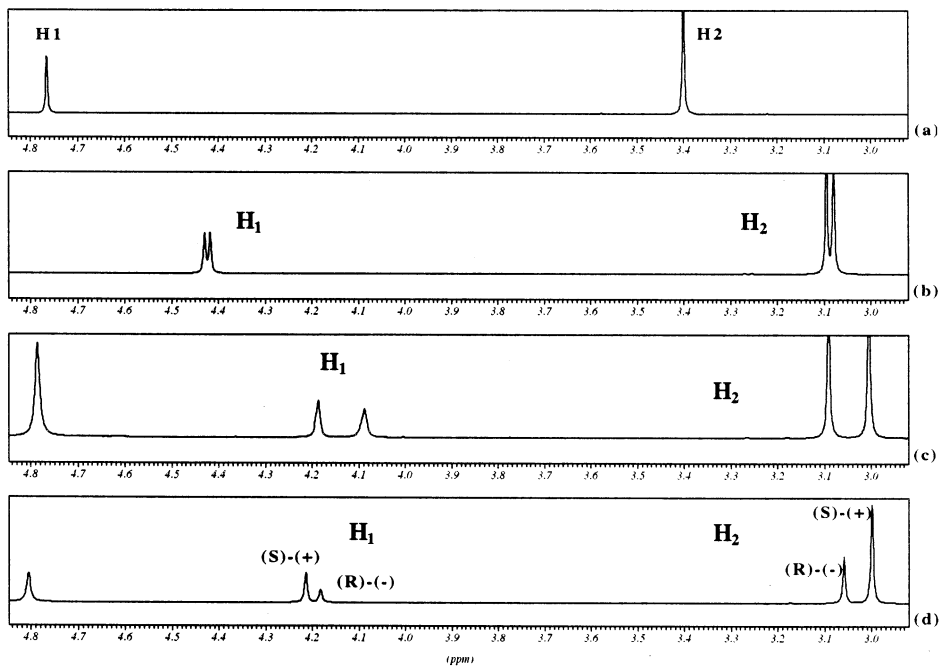


Figure 8. Evolution of aliphatic $\Delta\delta_H$ for acid **4**; (a) pure **4**; (b) 400 MHz ^1H NMR spectrum of **4** with 0.5 equivalents of (*S*)-**1**; (c) with 1.5 equivalents of (*S*)-**1**; (d) addition of 1 equivalent of (*S*)-**1** to a one enantiomer enriched ($1R/1S = 1/3$) of **4**

Compound **4** shows the greatest shift in non-equivalence between enantiomers. Different hydrogen bonds between the acidity sites in the acid and between the basic sites in the amine together with π–π-stacking interactions between aromatic rings provides the force for chiral recognition.[15]

Two complexes were examined in order to study the interactions between the solvating agent and the chiral solute in greater detail: the two enantiomers of the methoxy mandelic acid **4** with (*S*)-**1** (called **S1S4** and **S1R4**). First we examined the chemical shifts between complexes in 1:1 mixtures of (*S*)-**1** with each enantiomer of **4**. Table 2 shows the results of the NMR experiments. The differences in chemical shift for each enantiomer with respect to the free compound in the presence of the amine **1** were measured. The influence of the chiral compound was markedly different; while the behaviour of the protons of **1** are similar for two complexes, the H_1, H_3 and H_4 of the (*R*)-**4** enantiomer was shifted to higher fields than was the (*S*)-**4** enantiomer. These results explained that energetically and/or geometrically the two complexes, **S1R4** and **S1S4**, must be different.

Table 2
Chemical shift changes (ppm) for 1:1 mixtures of (*S*)-**1** with each enantiomer of **4**

Proton	**1** or **4**	**S1S4**		**S1R4**		
		δ	$\Delta\delta$	δ	$\Delta\delta$	$\Delta\Delta\delta$
H_2-**1**	7.68	7.61	−0.07	7.67	−0.01	−0.06
H_3-**1**	7.45	7.36	−0.09	7.40	−0.05	−0.04
H_4-**1**	7.74	7.72	−0.02	7.76	+0.02	−0.04
H_5-**1**	7.84	7.79	−0.05	7.82	−0.02	−0.03
H_6-**1**	7.45	7.41	−0.04	7.43	−0.02	−0.02
H_7-**1**	7.45	7.41	−0.04	7.43	−0.02	−0.02
H_8-**1**	8.19	7.89	−0.30	7.93	−0.26	−0.04
H_9-**1**	4.78	4.83	+0.05	4.83	+0.05	0.00
H_{11}-**1**	0.97	0.85	−0.12	0.79	−0.18	+0.06
H_1-**4**	4.77	4.28	−0.49	4.03	−0.74	+0.25
H_2-**4**	3.40	3.01	−0.39	3.07	−0.33	−0.06
H_3-**4**	7.42	7.24	−0.18	6.95	−0.47	+0.29
H_4-**4**	7.35	7.15	−0.20	7.05	−0.30	+0.10
H_5-**4**	7.35	7.15	−0.20	7.10	−0.25	+0.05

2.3. NOE measurements

Intermolecular NOE values were obtained for the two complexes **S1S4** and **S1R4**. High quality NOE spectra were obtained using gradients techniques as DPFGNOE.[16] Diverse intermolecular NOE was observed between protons of **1** and **4** indicating the short distance between the two components. Fig. 9 shows several intermolecular 1D spectra observed in the **S1R4** complex. Similar results were found when analogous 2D sequences were applied. When H_9 of **1S** was saturated an important NOE effect on the methoxy protons of **4** appears. When the last methoxy group was irradiated, several proton signals of the naphthyl ring were present in the spectra, those nearest to the chiral centre, indicating the proximity of the substituted ring of the naphthyl group to the methoxy group of **4**.

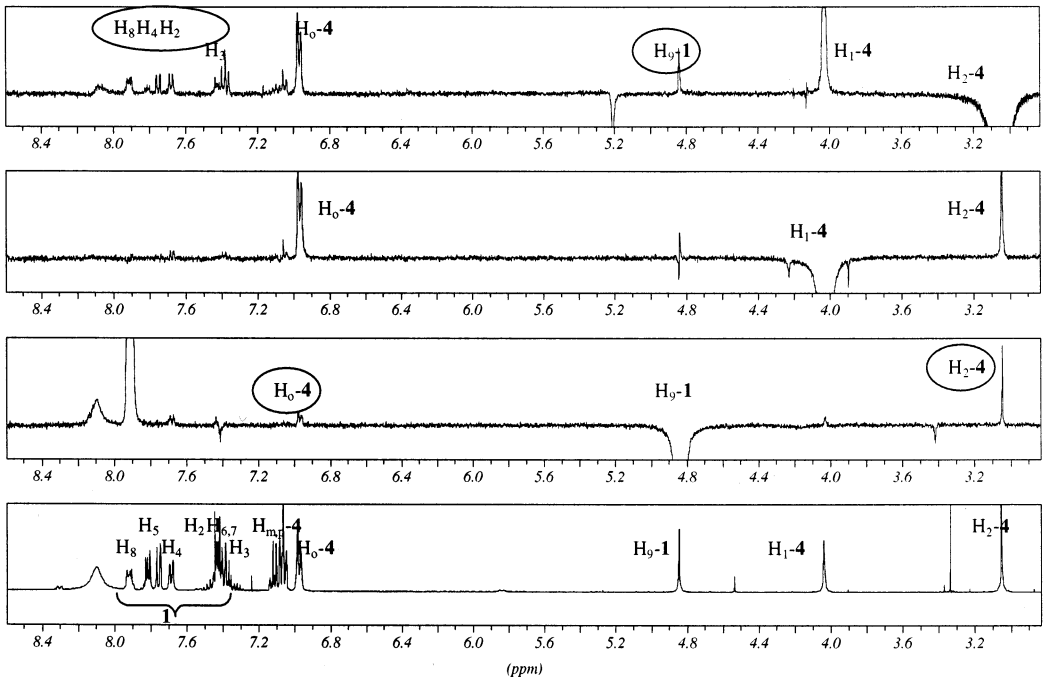


Figure 9. 400 MHz NOE spectra of a 1:1 mixture **S1R4**. DPFGNOE method was used with a mixing time of 400 ms. Intermolecular signals are encircled

No intermolecular cross relaxation is present when H_1 of **4** is inverted demonstrating that this proton is outside of the complex. Similar results were obtained for the **S1S4** complex, indicating a similar geometry of the association: the involvement of the substituted ring of the naphthyl group and the stereogenic center of **1** in front of the benzene ring, the acidic function and methoxyl group of the **4**.

A knowledge of the stoichiometry of the associate is basic data in determining the structure of the complexes. As the chemical shift of a nucleus is a mean value of the several species presents in the solution, when its solubility is complete, Job's method[17] (method of continuous variations[18]) can be applied to calculate the stoichiometry of the complexes in solution. The two complexes, **S1S4** and **S1R4**, were analysed: seventeen samples of a constant total concentration were prepared containing variable ratios of the two components. Only complex **S1S4** is described here.

The ^1H NMR spectra of seventeen samples were recorded at 300 K and chemical shift variations were observed for protons of amine **1** and the acid **4**. The plot of the variation of the chemical shift of the H_2 and H_3 of **4** and amine protons H_2, H_8, and H_9 versus the ratio between the concentration of each compound (**1** or **4**) and the total concentration (0.04 M) are reflected in Figs. 10 and 11.

The X coordinate of the parabolic curve maximum represents stoichiometry. In the case being examined here, a completely different behaviour is observed when the signal from the one or other components are considered. For acid protons H_2 and H_3 and amine proton H_9 the maximum corresponds to a **4**/**1** ratio of 2/1, that is, each amine **1** has two acids **4** surrounding it. Moreover when amine protons H_8 and H_2 are studied, the stoichiometry of the complex is 1/1, indicating that these protons are only influenced by one acid molecule, (*S*)-**4**. This

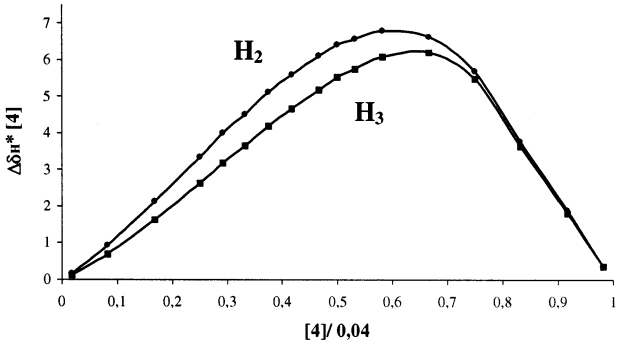


Figure 10. Job's plots of variation of chemical shift for acid protons H_2 and H_3 in **S1S4** complex

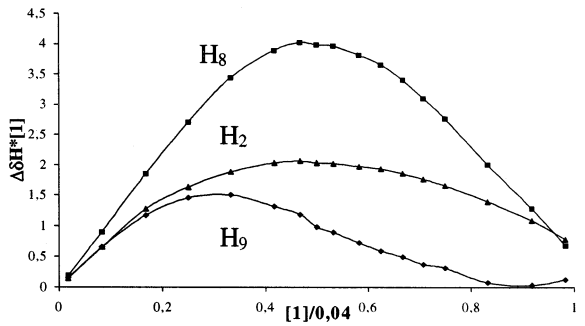


Figure 11. Job's plots of variation of chemical shift for amine protons H_9, H_8 and H_2 in the **S1S4** complex

anomalous behaviour might be induced by the presence of other processes. It has been described[19] that when other (or more than one, dimerization, etc.) interactions are present the Job's plots obtained might be strongly affected giving incorrect stoichiometries. Only NMR (involving the observation of each of the components separately) can provide this type of differential information.

If we consider that logical processes such as the dimerization of the acid compounds might be responsible for the abnormal behaviour and that conditions such as the low concentrations used here where trimer species is statistically unlikely, a 1/1 association can be assumed. The same results were obtained for complex **S1R4**.

3. Experimental

3.1. Synthesis: 1-(1-naphthyl)-2,2-dimethylpropylimine ***2***

A solution (1.6 M) of butyllithium (15.7 ml, 25.11 mmol) was slowly added to a diethyl oxide (60 ml) solution of 1-bromonaphthalene (4 g, 19.32 mmol) kept under N_2 at 0°C with continuous stirring. The reaction was completed after two hours and pivalonitrile (2.78 ml, 25.11 mmol) was added dropwise, keeping temperature at 0°C. After 90 minutes at room temperature, the reaction was quenched and the organic layer was separated, dried and concentrated. The residue was filtered and a white solid (85% yield) was obtained. Mp: 50–52°C. IR (KBr) cm^{-1}:

3240, 3051, 2966, 2868, 1609, 1476, 1391, 1216, 1159, 906, 780. ^{1}H NMR ($CDCl_3$) (ppm): 1.29 (s), 7.22 (d), 7.41 (t), 7.46 (m), 7.72 (m), 7.79 (d), 7.83 (m), 9.2 (broad). ^{13}C NMR ($CDCl_3$) (ppm): 28.5, 40.7, 123.1, 124.4, 125.9, 126.2, 127.9, 128.2, 130.4, 133.6, 139.5, 189.4. EM m/z (%): 211 (21), 196 (23), 155 (13), 154 (100), 127 (27).

3.2. 1-(1-Naphthyl)-2,2-dimethylpropylamine **1**

A diethyl oxide solution (10 ml) of 1-(1-naphthyl)-2,2-dimethylpropylimine (1 g, 4.77 mmol) was slowly added to a diethyl oxide (20 ml) solution of $AlLiH_4$ (543 mg, 14.32 mmol) kept under N_2 with continuos stirring and refluxed for 22 hours. The reaction was quenched and the organic layer separated, dried and concentrated. A white solid was obtained with an 80% yield, mp: 44–46°C. (*S*)-**1**: $[\alpha]_D^{20}=+54.2$; $c=1.01$; CH_2Cl_2. (*R*)-**1**: $[\alpha]_D^{20}=-58.5$; $c=1.06$; CH_2Cl_2. IR (KBr) cm^{-1}: 3388, 3051, 2945, 2868, 1595, 1511, 1476, 1398, 1363, 801, 780. ^{1}H NMR ($CDCl_3$) (ppm): 0.97 (s, ^{t}Bu), 1.61 (s, H_{NH}), 4.78 (s, H_9), 7.45 (m, H_6/H_7), 7.48 (t, H_3, $J_{AB}=6.72$ Hz), 7.68 (d, H_2), 7.74 (d, H_4, $J_{AB}=7.92$ Hz), 7.84 (dd, H_5, $J_{AB}=7.92$ Hz), 8.19 (d, H_8, $J_{AB}=8.52$ Hz). ^{13}C NMR ($CDCl_3$) (ppm): 26.9, 36.4, 57.2, 123.8, 125.0, 125.1, 125.4, 127.2, 128.8, 132.4, 133.4, 140.6. EM m/z (%): 213 (2), 157 (13), 156 (100), 129 (29), 128 (11). $C_{15}H_{19}N$, calcd: C, 84.46%; H, 8.98%; N, 6.57%; found: 84.29%; H, 9.04%; N, 6.57%.

3.3. 1N-[1-(1-Naphthyl)-2,2-dimethyl-(1R)-propyl]-3,3,3-trifluoro-2-methoxy-2-phenyl-(2R)-propylamide **3**

(*R*)-(−)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (100 mg, 0.4 mmol) was slowly added to a methylene chloride (2 ml) solution of 1(*R*)-(1-naphthyl)-2,2-dimethylpropylamine (*R*)-**1** (64 mg, 0.3 mmol) and triethylamine (0.06 ml, 0.4 mmol) kept under N_2 with continuous stirring. After 2 hours, the reaction was quenched and the organic phase dried and concentrated. A white powder was obtained (115 mg) in 89% yield. Mp: 108–109°C. $[\alpha]_D^{20}=-30.8$; $c=0.585$; CH_2Cl_2. IR (KBr) cm^{-1}: 3437, 2966, 1687, 1511, 1265, 1166, 1096, 1005, 780, 702. ^{1}H NMR ($CDCl_3$) (ppm): 0.90 (s, 9H), 3.40 (s, 3H), 5.86 (d, H_9, $J_{AB}=9.1$ Hz), 7.31 (d, H_2, $J_{AB}=7.0$ Hz), 7.36 (d, NH), 7.40 (m, H_{11}, $J_{AB}=7.3$ Hz), 7.44 (t, H_3, $J_{AB}=8.2$ Hz), 7.45 (m, H_6, $J_{AB}=7.9$ Hz), 7.50 (m, H_7, $J_{AB}=8.5$ Hz), 7.60 (m, H_{10}, $J_{AB}=2.0$ Hz), 7.76 (d, H_4), 7.83 (d, H_5), 8.31 (d, H_8). ^{13}C NMR ($CDCl_3$) (ppm): 26.9, 36.1, 54.8, 55.3, 84, 124, 124.3, 124.5, 125.5, 126.1, 127.5, 127.9, 128.5, 128.7, 129.4, 132.3, 132.9, 133.6, 136.6, 165.5. EM m/z (%): 429 (1), 373 (18), 372 (44), 189 (100), 155 (19), 154 (18), 141 (25), 127 (15), 119 (12), 105 (15), 69 (12), 41 (13). $C_{25}H_{26}F_3NO_2$, calcd: C, 69.92%; H, 6.10%; N, 3.26%; found: 69.92%; H, 6.01%; N, 3.14%.

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