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# Configurational and conformational NMR study of enantiopure 2,2-dimethyl-1-(1-naphthyl)propanol via its carbamate derivatives

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ABSTRACT: 2,2-Dimethyl-1-(1-naphthyl)propanol was synthesized and the corresponding enantiomers were isolated by chiral HPLC. These enantiomers gave diastereoisomeric carbamates by reaction with (*S*)-(−)-1-phenylethylisocyanate, which were studied by NMR. The comparison of NMR data and molecular mechanics calculations allowed us to determine the absolute configuration of corresponding alcohols. Finally, x-ray results were in agreement with the absolute configuration proposed from the NMR spectra. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: NMR; $^1$H NMR; chiral HPLC; carbamates; molecular mechanics (MM); x-ray

## INTRODUCTION

With the aim of discovering the behaviour of chiral compounds with certain conformational rigidity as chiral solvating agents and chiral inductors, we have prepared some *tert*-butyl derivatives of aromatic alcohols[1] and amines.[2] Some anthracene derivatives have been studied from a stereochemical point of view and we have also tried to determine[3] how chiral association is produced.

In the present paper we describe the preparation of 2,2-dimethyl-1-(1-naphthyl)propanol, **3**, the isolation of the two enantiomers by direct chromatographic separation on a chiral column and their structural study. Moreover, the reaction of an enantiopure isocyanate with racemic alcohol, **3**, gives diastereoisomeric carbamates, which are easily separated by HPLC chromatography,[4] and then easily hydrolysed to enantiopure alcohols. In our case, the use of isocyanate was indicated to obtain suitable solid compounds to study by means of x-ray diffraction techniques, so that their relative configuration could be determined. The structural study of the carbamates[5] was carried out by DNMR (dynamic NMR) and molecular mechanics (MM) calculations. The energies associated with the rotation around the carbonyl carbon–nitrogen bond were measured. The relative configuration of each diastereoisomer was determined by comparing chemical shifts in NMR spectra and the results of NOE experiments with the geometry proposed by MM calculations. Finally, the result of the absolute configuration given by the x-ray study confirmed the previous results.

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## EXPERIMENTAL

### Synthesis

**2,2-Dimethyl-1-(1-naphthyl)propanone (2).** A solution (1.6 M) of butyllithium in hexane (7.8 ml, 12.48 mmol) was slowly added to a diethyl ether (80 ml) solution of 1-bromonaphthalene (1.34 ml, 12.48 mmol) kept under $N_2$ with continuous stirring. The reaction was completed after 3 h, the mixture was cooled to 201 K and pivaloyl chloride (0.6 ml, 4.87 mmol) was added dropwise. After 10 h, the reaction was quenched and the organic layer was separated, dried and concentrated. The solid residue was purified by column chromatography on silica gel (hexane/dichloromethane 90/10 v/v) to give white needles (61% yield), m.p. 73–74 °C; IR (KBr) cm$^{-1}$: 3052, 2970, 2926, 1681 (C═O), 1477 and 720. $^1$H NMR ($CDCl_3$) (ppm): 1.30 (s, 9H), 7.33 (dd, 1H), 7.43 (t, 1H), 7.49 (m, 2H), 7.60 (m, 1H) and 7.83 (m, 2H). $^{13}$C NMR ($CDCl_3$) (ppm): 27.5, 45.8, 122.5, 124.5, 125.7, 126.4, 126.9, 128.6, 129.2, 130.2, 133.9, 139.2 and 214.7. EM *m*/*z* (%): 212 (16), 155 (100), 127 (33) and 57 (5).

**2,2-Dimethyl-1-(1-naphthyl)propanol (3).** A diethyl ether solution (15 ml) of 2,2-dimethyl-1-(1-naphthyl)propanone, **2** (313 mg, 1.48 mmol), was slowly added to a diethyl ether (70 ml) solution of $LiAlH_4$ (78.6 mg, 2.08 mmol) kept under $N_2$ with continuous stirring at room temperature. After 3 h, reduction was completed. The reaction was quenched and the organic layer was separated, dried and concentrated. The solid residue was purified by column chromatography on silica gel (hexane/dichloromethane 80/20 v/v) (97% yield). IR (film) cm$^{-1}$: 3450, 2952, 2871, 1364 and 785. $^1$H NMR ($CD_3COD_3$) (ppm): 0.88 (s, 9H), 4.65 (d, 1H), 5.41 (d, 1H), 7.46 (m, 2H), 7.49 (t, 1H), 7.70 (dd, 1H), 7.79 (d, 1H), 7.88 (dd, 1H) and 8.23 (d, 1H). $^{13}$C NMR ($CD_3COD_3$) (ppm): 26.5, 36.9, 73.0, 124.9, 125.3 (2C), 125.6, 126.4, 127.6, 129.1, 131.2, 132.5 and 139.4. EM *m*/*z* (%): 214 (6), 157 (100), 129 (90) and 57 (10).

Once the enantiomers of **3** were isolated, (+)-(*R*)-**3**: ($[\alpha]_D^{20} = +25.2$; $c = 1.42$, $CH_2Cl_2$); (−)-(*S*)-**3**: ($[\alpha]_D^{20} = -28.1$; $c = 1.35$, $CH_2Cl_2$).

***N*-(1-phenylethyl)carbamates (4a and 4b).** Enantiomer (*R*)-**3** (83.5 mg, 0.39 mmol) and (*S*)-(−)-1-phenylethylisocyanate 99% (165 µl, 1.17 mmol) were mixed and heated to 80 °C while protected by a drying tube for 72 h, according to the literature.[4] The mixture was then chromatographed with toluene/choromethane (2 : 1, v/v). Recrystalization from chloromethane gave white needles (71% yield), m.p. 116–117 °C; IR(KBr) cm$^{-1}$: 3290, 2971, 1690, 1520, 1240. EM *m*/*z* (%): 361 (2), 305 (5), 157 (100) and 77 (11). $C_{24}H_{27}NO_2$ calculated:

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C, 79.77%, H, 7.49%, N, 3.87%; found: C, 79.73%, H, 7.18%, N, 3.87%, (*R*,*S*)-**4** ($[\alpha]_D^{20} = +14.3$; $c = 1.02$, $CH_3Cl$).

The same reaction was used to obtain (*S*,*S*) diastereoisomer from (*S*)-**3**; m.p. 158–159 °C; (*S*,*S*)-**4**: ($[\alpha]_D^{20} = -26.5$; $c = 1.31$, $CH_3Cl$).

### NMR experiments

NMR experiments were conducted on Bruker ARX400 spectrometers with a 5 mm QNP probe using $CD_3COCD_3$ and $CDCI_3$ as solvents. The operating frequency was 400.16 MHz for $^1H$. All the steady-state NOE experiments were obtained on degassed samples with the DPFGENOE sequence[16] using a mixing time of 600 ms; two dummy scans were used.

NMR experiments at low temperature of **4a** and **4b** were recorded using $CD_3COCD_3$ and the temperatures was controlled to 0.1 °C using the Bruker variable temperature unit. All tubes were degassed and the rate constants were determined using a line shape simulation program.[17] The results were, for **4a** [$T$(K), $k(s^{-1})$, $\Delta\delta$(Hz)], (240, 3.33, 27.8), (270, 120.6, 16.54), (300, 200, 0) and (330, 1000, 0); for **4b** [$T$(K), $k(s^{-1})$, $\Delta\delta$(Hz)], (250, 2.0, 17.02), (270, 80.5, 8.06), (290, 166.6, 0) and (320, 333.3, 0). In all of the simulations a natural linewidth of 3.45 Hz was used.

### X-ray structure determination for compound 4a

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. Details of the crystals, collection and processing, and refinement are as follows.

**Crystal data.** Colourless crystals were grown by vapour diffusion of pentane in a $CH_2Cl_2$ solution. A prismatic crystal was mounted, 0.43 × 0.14 × 0.14 mm. $C_{24}H_{27}NO_2$, $M = 361.47$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 8.971$ (1) Å, $b = 14.676$ (3) Å, $c = 32.576$ (4) Å (from least-squares refinement on diffractometer angles for 25 automatically centred reflections, $9.9° < \theta < 12.1°$), $V = 4289$ (1) Å$^3$, $Z = 8$, $D_c = 1.120\,g\,cm^{-3}$, $\mu = 0.70\,cm^{-1}$ (Mo K$\alpha$).

**Data collection and processing.** Data were measured on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo K$\alpha$ radiation ($\lambda = 0.71069$ Å) and a $\omega$–$2\theta$ scan, $T = 293$ K, data collection range $2° < 2\theta < 50°$ ($0 \le h \le 10, 0 \le k \le 17, 0 \le l \le 38$), 3765 unique reflections. No significant variation in intensity of one standard reflection was observed.

**Structure solution and refinement.** The structure was solved by direct methods (SHELXS-86)[19] and refined by full-matrix least-squares procedures on $F^2$ for all reflections (SHELXL-97).[19] All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions with isotropic temperature factors 1.5 (methyl hydrogens) or 1.2 (the rest) times the $U_{eq}$ values of corresponding atoms. $R(F) = 0.066$ and $R_w(F^2) = 0.170$ for reflections with $I > 2\sigma(I)$.

## RESULTS AND DISCUSSION

### Synthesis and resolution

Racemic 2,2-dimethyl-1-(1-naphthyl)propanol, **3**, was obtained by reducing 2,2-dimethyl-1-(1-naphthyl)propanone, **2**. The reaction of the lithium derivative of 1-bromonaphthalene[7] with pivaloyl chloride, yielded the ketone **2**, 61% (Fig. 1). 2,2-Dimethyl-1-(1-naphthyl)propanone, **2**, was also studied by NMR in order to assign the $^1H$ and $^{13}C$ NMR signals.

Racemic 2,2-dimethyl-1-(1-naphthyl)propanol, **3**, was efficiently obtained by $LiAlH_4$ reduction of **2**. The enantiomers were isolated by direct chromatographic resolution using a Whelk-O1 (3*R*,4*R*)-4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene[8] as chiral column. Hexane/$^i$PrOH (98/2) was used as the elution solvent with a flow of 3 ml min$^{-1}$. The first enantiomer eluted was (+)-**3** and the second was (−)-**3**. Their absolute configuration is (*R*)-(+)-**3** and (*S*)-(−)-**3**, as shown at the end of the paper (Fig. 6). Once the enantiomers were isolated, they gave diastereoisomeric carbamates by reaction with (*S*)-(−)-1-phenylethylisocyanate:[9] (*R*,*S*)-**4a** and (*R*,*S*)-**4b**, derived from first and second alcohols, respectively (Fig. 2).

### Structural studies of carbamate derivatives

The complete assignment of the spectra signals was carried out using methods which include $^1H$–$^1H$-correlated two-dimensional techniques (COSY) and homonuclear $^1H\{^1H\}$NOE measurements (Table 1).

$^1H$ NMR spectra of the carbamate derivatives show, at room temperature, a slow rotation around the amide bond (Fig. 2). At 240 K, the NMR spectra of each carbamate show an equilibrium between two differently populated rotamers (*Z* and *E*), which indicates a difference in their relative stability (Fig. 3).

At higher temperature, all resonances are broad due to an increasing rate of conformational exchange,

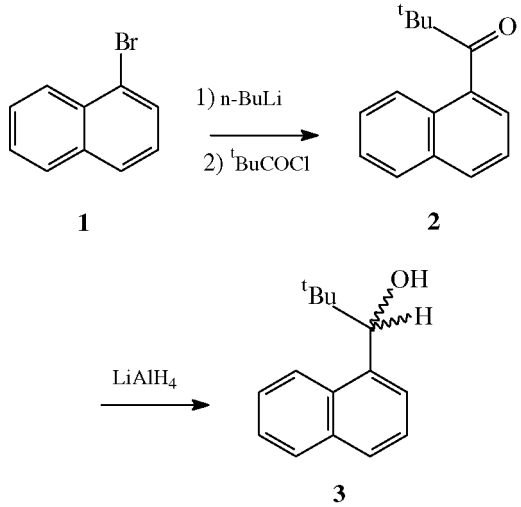


**Figure 1.** Synthesis of **3**.

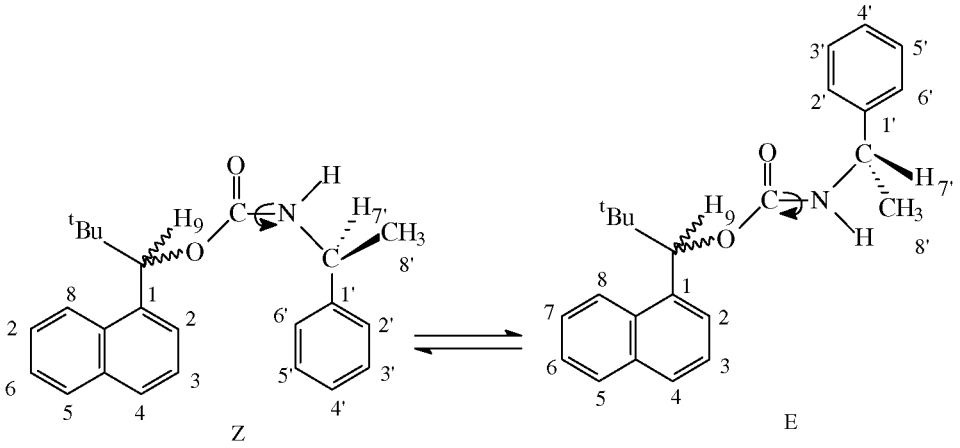


**Figure 2.** Diastereoisomeric carbamates, **4a**-(9*R*,7′*S*) and **4b**-(9*S*,7′*S*).

**Table 1.** $^1$H-NMR assignment of **4a** and **4b** at 240 K in $CD_3COCD_3$

| | [$\delta$($^1$H) (ppm)] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H-2 | H-3 | H-4 | H-5 | H-6 | H-7 | H-8 | H-9 | H-7′ | NH | $CH_3$ | $^t$Bu |
| **4a**-*Z* | 7.60 | 7.45 | 7.76 | 7.86 | — | — | 8.21 | 6.25 | 4.94 | 6.76 | 1.36 | 0.59 |
| **4a**-*E* | 7.52 | 7.35 | 7.76 | 7.82 | 7.40 | 7.45 | 8.25 | 6.23 | 4.64 | — | 1.36 | 0.92 |
| **4b**-*Z* | 6.07 | 6.88 | 7.62 | 7.77 | 7.44 | 7.39 | 8.18 | 6.23 | 4.86 | 6.76 | 1.36 | 0.85 |
| **4b**-*E* | 7.52 | 7.52 | 7.82 | 7.87 | 7.46 | 7.48 | 8.26 | 6.27 | 4.56 | 7.19 | 1.27 | 0.88 |

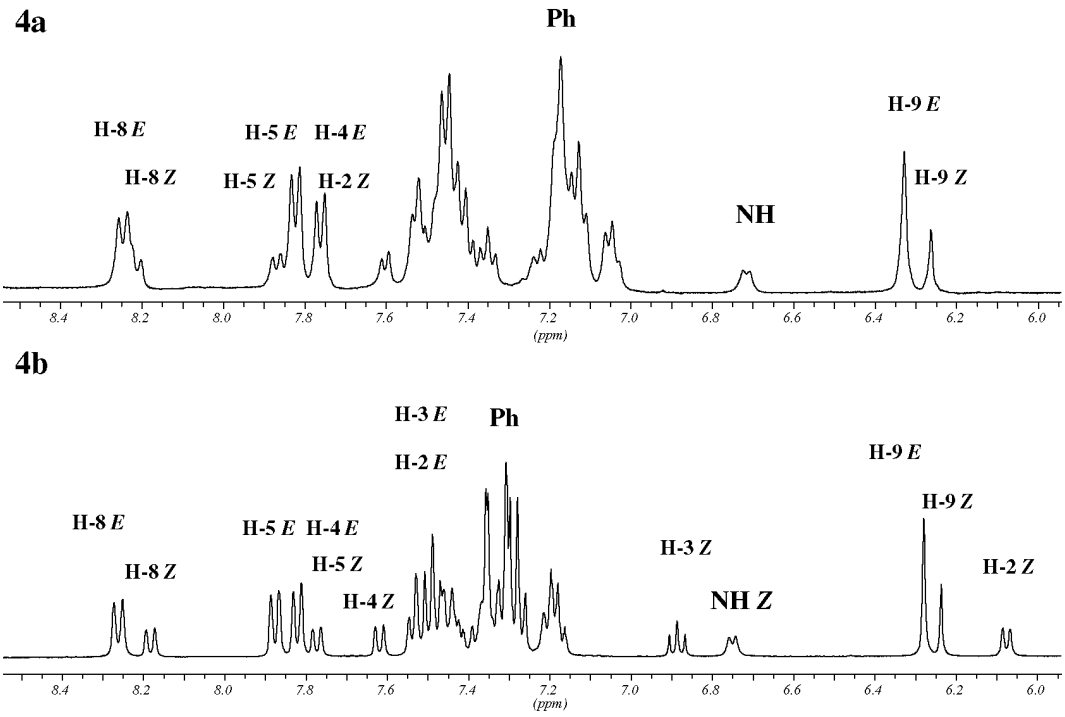


**Figure 3.** Part of NMR spectrum of **4a** and **4b** at 240 K in $CD_3COCD_3$.

finally achieving coalescence. Rate constants ($k$) were determined for each diastereoisomer by a complete $^1$H DNMR line shape analysis (CLSA)[10] performed on a resonance temperature dependence of the singlet H-g. $\Delta G^{\neq}$ values of the process were calculated using the Eyring equation (Table 2). These values are consistent with calculated barriers for carbamate rotation described in the literature.[1b,11]

## Determination of the absolute configuration: NMR experiments and MM calculations

Molecular mechanics calculations were performed on a Silicon Graphics INDY computer with R4600PC processor using Still's MacroModel v. 5.0 molecular modelling package.[12] MM3* was the selected force field[13] to carry out a full conformational analysis for

each carbamate. All rotatable bonds were driven in successive steps from +180° to −180° at 15° increments. Each structure was minimized in all variables except the one being driven. All obtained energy minima were fully optimized using the Polak–Ribiere conjugate gradient (PRCG)[14] minimization algorithm, allowing enough cycles to ensure the convergence. In these calculations $CHCl_3$ was used as solvent, as described in the GB/SA solvation model.[15] The calculations revealed for each carbamate that the rotamer of lower energy had *E* geometry for both diastereoisomers (Table 3). This result qualitatively agrees with the experimental energy differences ($\Delta G^\circ$) between the rotamers deduced from integrated NMR spectra (Table 2).

Assuming that the difference of chemical shifts (H-2 and H-3) of each rotamer of **4a** compared to **4b** arises from the proximity of the phenyl aromatic ring, we calculated (MM) the distances (Table 3) between $H_2$, $H_3$ and the centre of the phenyl ring.

The distance values between H-2 and H-3 towards the phenyl ring are very similar for both conformations (*Z* or *E*) in one of the diastereoisomers (*R*,*S*), while the same distances differ greatly between conformations (*Z* or *E*) for the (*S*,*S*) diastereoisomer. This is reflected in the similarity of the H-2 chemical shift of both rotamers in carbamate **4a** [H-2 (*Z*: 7.60; *E*: 7.52)] and the same for H-3 in **4a** [H-3 (*Z*: 7.45; *E*: 7.35)]. However, the distance values for H-2 and H-3 and the phenyl ring are markedly different in relation to the other diastereoisomer (*S*,*S*), which explains the large difference in chemical shift of these protons in each rotamer [H-2 (*Z*: 6.07; *E*: 7.52) and H-3 (*Z*: 6.88; *E*: 7.52)] of the carbamate **4b** derived from the (−)-**3** alcohol.

On the basis of these results, we can assume that the absolute configuration of carbamate **4a** derived from the first eluted alcohol-(+) is *R* and, by consequence, the absolute configuration of the second alcohol-(−) is *S*.

In addition, some NOE experiments were made at 240 K by the irradiation of H-9 and H-7 of both rotamers of each diastereoisomer (Figs 4 and 5). A NOE effect was observed (Table 4) on the $CH_3$ group and $^t$Bu

**Table 2.** Experimental energy values

| Compound | %*Z*−%*E* | $\Delta G^\circ$ (kcal/mol) | $T_c$ (K) | $k$ ($s^{-1}$) | $\Delta G^{\neq}$ (kcal/mol) |
|---|---|---|---|---|---|
| (*R*,*S*)-**4a** | 20−80 | 0.65 | 300 | 200 | 14.20 |
| (*S*,*S*)-**4b** | 25−75 | 0.56 | 290 | 170 | 14.09 |

**Table 3.** Energy values (kcal/mol) and distances (Å) between H-2 and H-3 to the phenyl ring for each diastereoisomer

| MM3* | Energy | d($H_2$-Ph) | d($H_3$-Ph) |
|---|---|---|---|
| (*R*,*S*)-*Z* (**4a**) | −22.46 | 6.9 | 8.8 |
| (*R*,*S*)-*E* (**4a**) | −24.56 | 6.2 | 8.0 |
| (*S*,*S*)-*Z* (**4b**) | −20.64 | 6.0 | 7.2 |
| (*S*,*S*)-*E* (**4b**) | −23.13 | 9.2 | 10.7 |

**Table 4.** NOE effect observed when H-7′ and H-9 of **4a** and **4b** were irradiated and the distances proposed by MM

| MM3* | d(H-7′-Bu) (Å) | NOE | d(H-9-$CH_3$) (Å) | NOE |
|---|---|---|---|---|
| (*R*,*S*)-*Z* (**4a**) | 3.0 | + | 5.5 | − |
| (*R*,*S*)-*E* (**4a**) | 6.2 | − | 4.4 | + |
| (*S*,*S*)-*Z* (**4b**) | 2.6 | + | 5.7 | − |
| (*S*,*S*)-*E* (**4b**) | 6.2 | − | 5.9 | − |

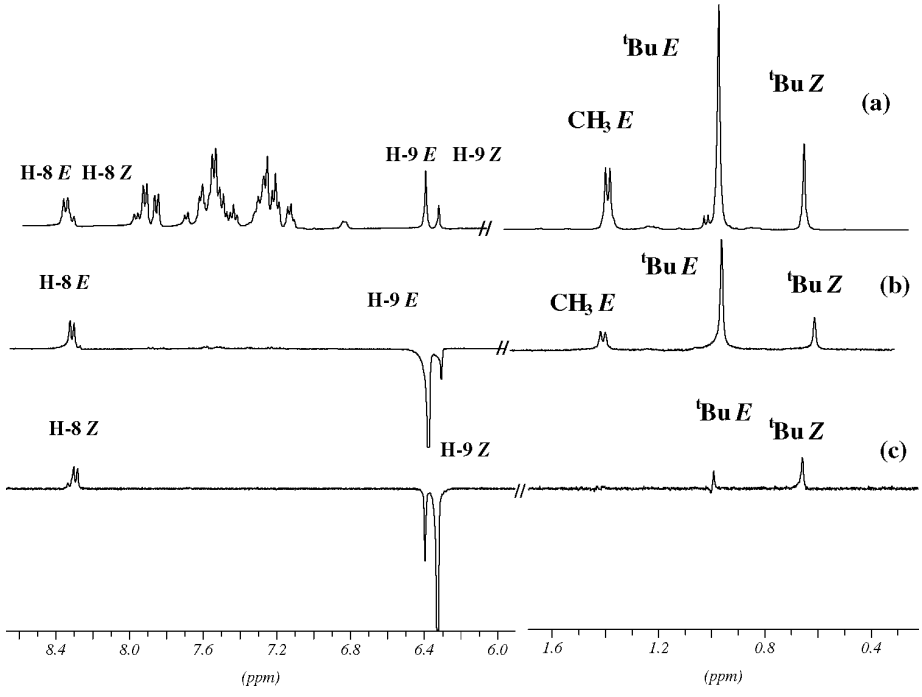


**Figure 4.** (a) $^1$H NMR spectra of **4a**. (b) Irradiation of H-9 *E*. (c) Irradiation of H-9 *Z*.

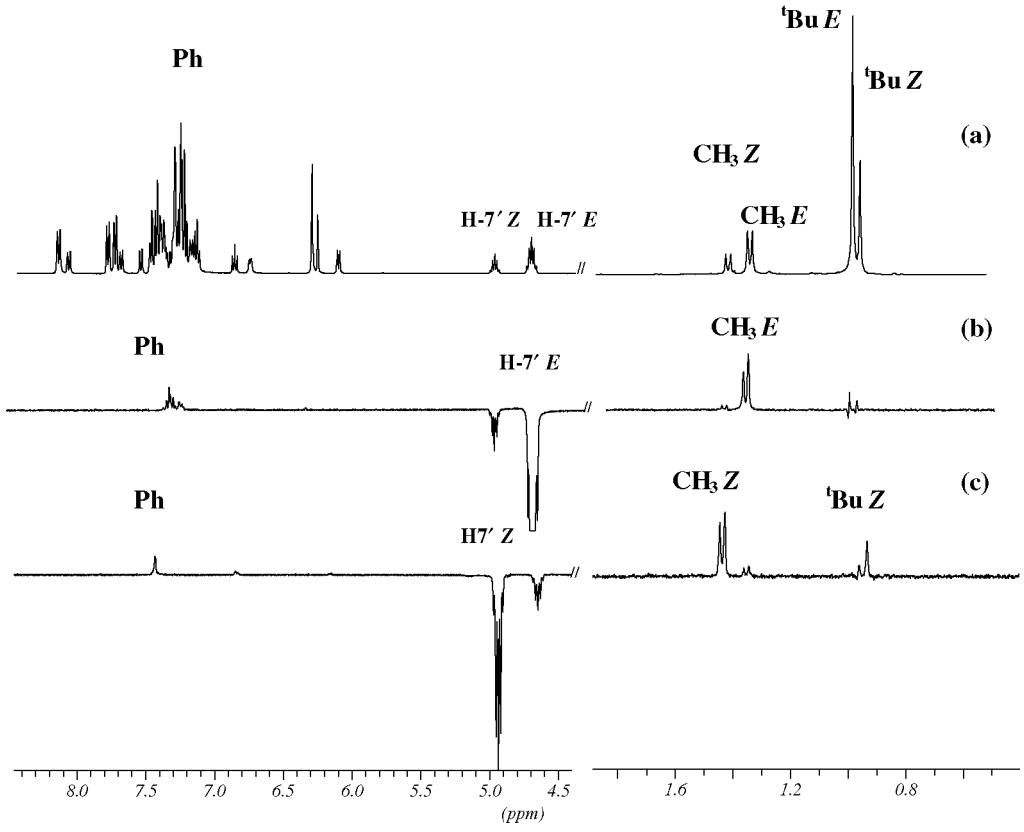


**Figure 5.** (a) $^1$H NMR spectra of **4b**. (b) Irradiation of H-7′ *E*. (c) Irradiation of H-7′ *Z*.

group, respectively, which is in agreement with calculated distances assuming **4a** in the (*R*,*S*) configuration and **4b** in the (*S*,*S*) configuration.

Suitable monocrystals of **4a** were obtained and subjected to x-ray analysis. Structures showed an (*R*,*S*) configuration, which agreed with the configuration proposed from the NMR spectra. In the solid state, only the **Z** conformation was observed (Fig. 6).

In the asymmetric unit there are two molecules which have similar geometries. These two molecules are associated into discrete dimers by means of two NH···O═C hydrogen bonds (Fig. 7). The distances in Å were: (NH···O, 2.206(4); N···O, 3.045(7); N–H, 0.860(5); N-H···O, 164.9(4); NH···O, 2.056(4); N···O, 2.915(7); N–H, 0.860(6); N–H···O, 176.9(3)).

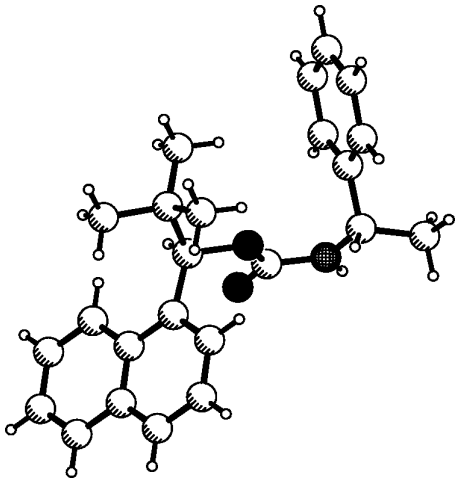

**Figure 6.** X-Ray structure of **4a** carbamate with (*R*,*S*) configuration.

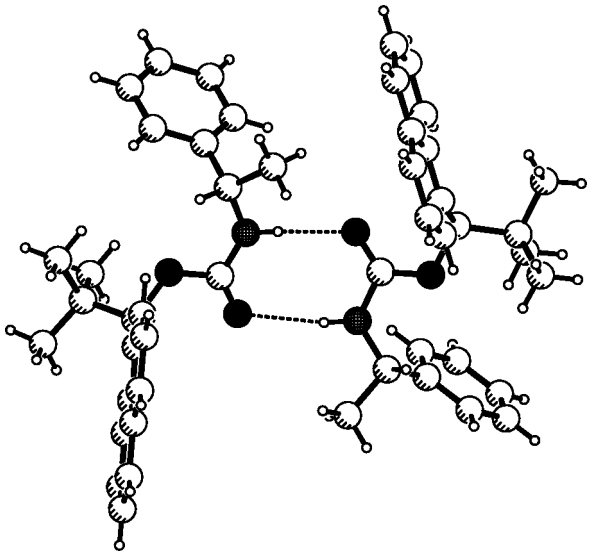

**Figure 7.** X-ray dimeric structure of **4a**.

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