MAGNETIC RESONANCE IN CHEMISTRY, VOL. 35, 79–85 (1997)

Conformation of (*RS*)- and (*SS*)-*O*,*O*-(2,2′-Binaphthyl)-*N*-(α-benzylethyl) Phosphamidate

Jun Liu,[1]* Min Wang,[1] Mingan Wang,[1] Wanyi Chen,[1] Qifeng Shen[1] and Libin Ma[2]
[1] Department of Applied Chemistry, Beijing Agricultural University, Beijing 100094, China
[2] Beijing Institute of Microchemistry, Beijing 100094, China

The conformations of (*RS*)- and (*SS*)-*O*,*O*-(2,2′-binaphthyl)-*N*-(α-benzylethyl) phosphamidate (binaphthol phosphamidate) were examined by means of NMR, single-crystal x-ray diffraction and molecular mechanics calculations. There are physical and chemical differences between the two diastereoisomers such as different abilities to form clathrates with ethanol. These differences provide the theoretical basis for the resolution of racemic binaphthol with optically active α-phenylethylamine. © 1997 by John Wiley & Sons, Ltd.

Magn. Reson. Chem. 35, 79–85 (1997) No. of Figures: 7 No. of Tables: 2 No. of References: 18

Keywords: *O*,*O*-(2,2′-Binaphthyl)-*N*-(α-benzylethyl) phosphamidate; NMR; Single-crystal x-ray diffraction; molecular mechanics calculation

Received 19 December 1995; revised 16 August 1996; accepted 19 August 1996

INTRODUCTION

Optically active binaphthol is widely used in organic chemistry[1–4] and there are many methods for its resolution.[5–9] Chemical separation produces two kinds of optically active binaphthol and in recent years this method has been used in several studies.[10,11] Gong *et al.*[12] and Fabbri *et al.*[13] adopted two different procedures for separation, taking advantage of the different solubilities of the two binaphthol phosphamidates in ethanol and using the different abilities of phosphamidates to form clathrates with ethanol.[12,13] In both cases the separation was followed by degradation of the phosphamidates to the two binaphthol stereoisomers. The physical and chemical properties of phosphamidates, including solubility and ability to form clathrates, differ primarily because of conformational differences of the stereoisomers. This paper presents an analysis of the conformation of a pair of diastereoisomers of binaphthol phosphamidate (Fig. 1) as a basis for interpretation of their different abilities to form clathrates with ethanol. A number of NMR methods were used (^{1}H, ^{13}C, ^{31}P NMR, DEPT, H–H COSY, C–H COSY, ^{1}H{^{1}H}, HMBC) in addition to single-crystal x-ray diffraction and molecular mechanics calculations.

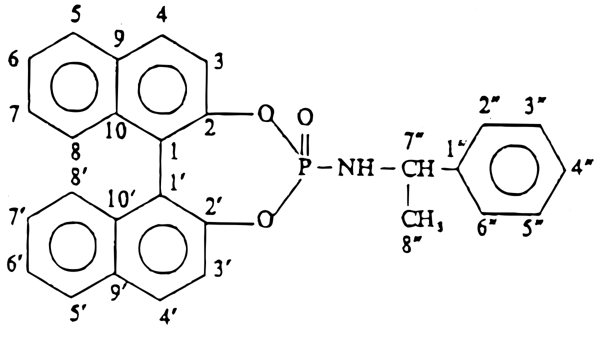

Figure 1. (*RS, SS*)-Binaphthol phosphamidate.

RESULTS AND DISCUSSION

Binaphthol has a C_2 chiral axis. When optically active (*S*)-α-phenylethylamine is used as a separation reagent, the resulting binaphthol phosphamidate has *RS* and *SS* diastereoisomers.

Binaphthol phosphoryl chloride, the intermediate product of the reaction, contains two naphthyl groups. The ^{1}H NMR spectrum indicates that the two naphthalenes are equivalent, displaying only one AB pattern and one ABCD pattern, whereas the ^{1}H NMR spectrum of the naphthalenes in binaphthol phosphamidate displays twice as many AB and ABCD patterns. Furthermore, differences in the ^{1}H NMR spectra of the *RS* and *SS* isomers (see Fig. 2) imply conformational differences. The complete assignments of the ^{1}H and ^{13}C NMR reported here permit a detailed study of these conformations.

We differentiated the types of carbon by means of ^{13}C NMR and DEPT experiments and distinguished the carbons which were coupled to the P atom. We assigned the two AB patterns and two ABCD patterns with an H–H COSY spectrum and found the correlations between C and H with C–H COSY experiments.

In the C–H COSY spectrum of the *SS* isomer, there is a cross peak between the doublet at 7.59 ppm and the carbon peak at 121.06 ppm (see Fig. 3). The carbon giving this peak is coupled to the P atom ($^3J_{\mathrm{POCC}} = 2.2$ Hz). The HMBC spectrum (Fig. 4) shows that the proton peak at 7.59 ppm arises from the carbon ($^2J_{\mathrm{POC}} = 9.7$ Hz) giving the peak at 146.12 ppm and the

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* *Correspondence to*: J. Liu.

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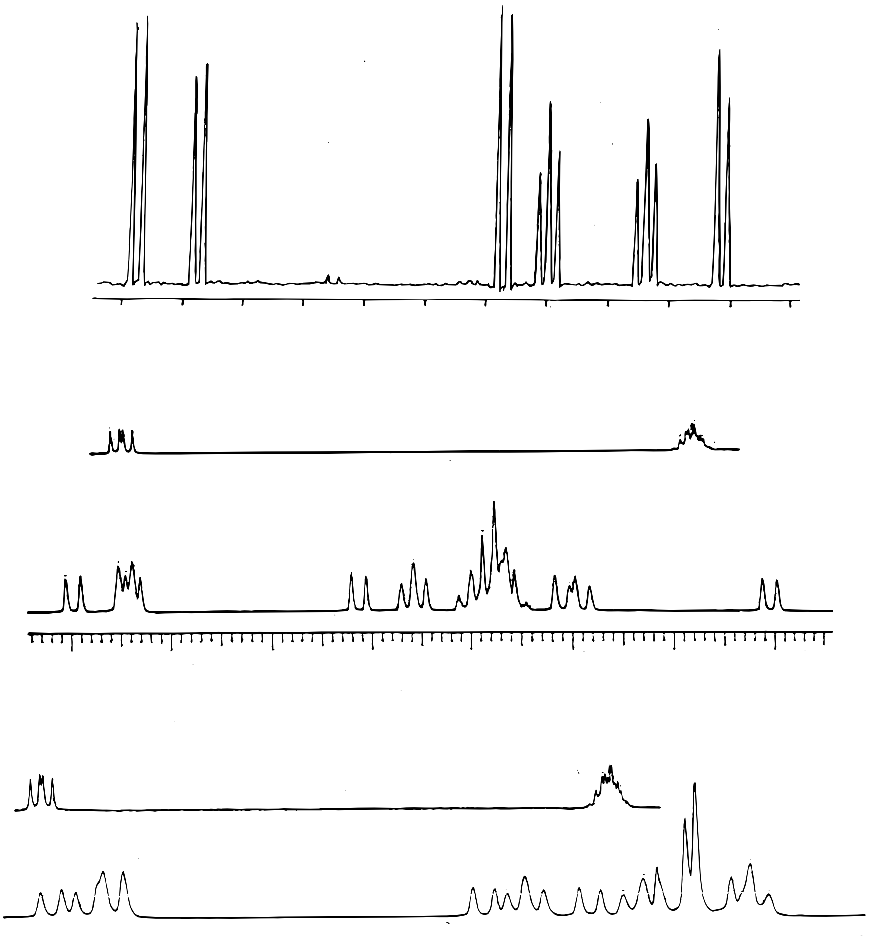

Figure 2. ^1H NMR spectra of binaphthol phosphoryl chloride and binaphthol phosphamidate. (A) Binaphthol phosphoryl chloride; (B) (*RS*)-binaphthol phosphamidate; (C) (*SS*)-binaphthol phosphamidate.

carbon ($^3J_{POCC} = 2.2$ Hz) at 120.69 ppm. Obviously, the carbon resonance at 146.12 ppm corresponds to C-2, the carbon resonance at 120.69 ppm is due to C-1 and the proton peak at 7.59 ppm is the proton H-3. The proton H-4 can be assigned to 8.19 ppm due to the cross peak between two protons at 7.59 and 8.19 ppm in the H–H COSY spectrum. The carbons C-3 and C-4 can then be assigned by the cross peaks of proton H-3 and the peak at 121.06 ppm, proton H-4 and the peak at 130.98 ppm in the C–H COSY spectrum. We can see from the HMBC spectrum that H-4 is coupled to the tertiary C giving the peak at 128.53 ppm. Thus, the latter carbon must be C-5. Then H-5 (δ 8.10 ppm) can be determined from the C–H COSY spectrum, and one of the ABCD patterns can be assigned from the H–H COSY spectrum, and to H-6 (δ 7.53 ppm), H-7 (δ 7.37 ppm) and H-8 (δ 7.18 ppm). The C–H COSY spectrum is again used to assign C-6 (δ 125.43 ppm), C-7 (δ 126.69 ppm) and C-8 (δ 126.06 ppm). In addition, the HMBC spectrum showed that H-8 is coupled to C-1 (δ 120.69 ppm). This observation provided further verification of the assignments. In the HMBC spectrum, the quaternary carbon with a peak at 130.97 ppm is correlated with H-6 (δ 7.53 ppm) and H-3 (δ 7.59 ppm). This carbon can be identified as C-9, while the quaternary carbon at 131.48 ppm has correlations with H-7 (δ 7.37 ppm) and H-4 (δ 8.19 ppm), so that carbon can be confirmed as C-10. In the H–H COSY spectrum, we can see another AB pattern composed of a doublet at 7.44 ppm and a doublet at 8.13 ppm, and another ABCD pattern. Apparently, they are assigned to H-3′–H-8′ by the cross peaks in the H–H COSY spectrum. The C-1′–C-10′ resonances are identified by the corresponding cross peaks in the C–H COSY and HMBC spectra.

In the HMBC spectrum, we observed that the methine H at 4.42 ppm has correlations with the quaternary carbon at 145.26 ppm and the tertiary carbon at 125.75 ppm. The methyl resonance at 1.43 ppm also has a correlation with the carbon at 145.26 ppm. It is clear that the carbon at 145.26 ppm is C-1″ and the carbon at 125.75 ppm is C-2″. With the help of the Sadtler atlas,[14] we can easily assign the C-3″–C-6″ resonances.

The ^1H and ^{13}C resonance assignments for the *RS* isomer can be obtained in a similar way (see Table 1).

From the above results we can see the following.

1. As indicated by the ^1H NMR spectra, the two naphthalene groups in the binaphthol phosphamidate molecule are obviously different, but the two naphthalene groups in the binaphthol phosphoryl chloride are equivalent. The strong anisotropic shielding associated with the benzene rings is probably responsible for the different naphthalene shifts in the binaphthol phosphamidates.
2. In (*RS*)-binaphthol phosphamidate, the chemical shifts of the H-3 and H-3′ protons are 6.82 and 7.63 ppm respectively. The difference may be due to the

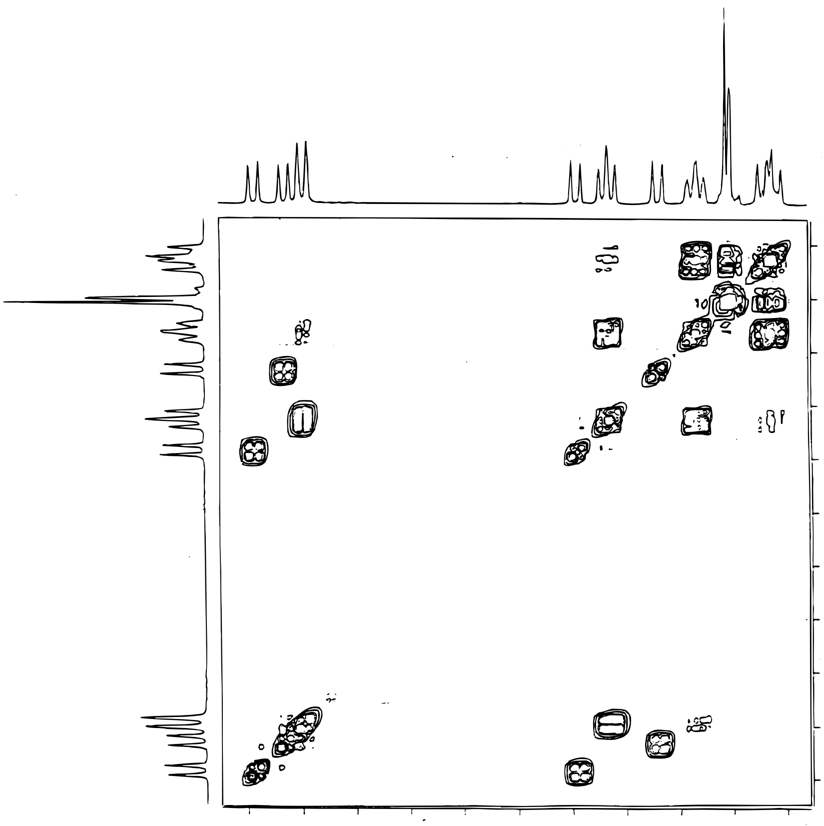

Figure 3. H–H COSY spectrum of the *SS* isomer.

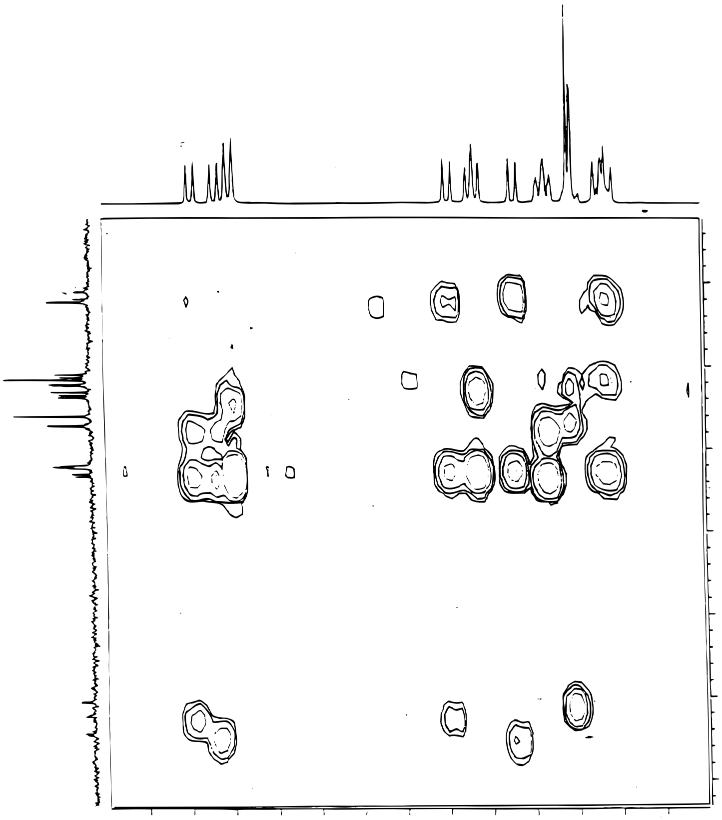

Figure 4. HMBC spectrum of the *SS* isomer.

Table 1. Chemical shifts and coupling constants of (*RS*)- and (*SS*)-binaphthol phosphamidate in DMSO-d_6 on a Bruker AM 500 spectrometer

	RS (δ_p = 12.65 ppm)			*SS* (δ_p = 12.17 ppm)		
Position	δH (ppm)	$^3J_{HH}$ (Hz)	δC (ppm)	δH (ppm)	$^3J_{HH}$ (Hz)	δC (ppm)
1			120.47 (d) $^3J_{POCC}$ = 2.2 Hz			120.69 (d) $^3J_{POCC}$ = 2.2 Hz
2			145.93 (d) $^2J_{POC}$ = 9.7 Hz			146.12 (d) $^2J_{POC}$ = 9.7 Hz
3	6.82 (d)	8.7	120.87 (d) $^3J_{POCC}$ = 2.2 Hz	7.59 (d)	8.8	121.06 (d) $^3J_{POCC}$ = 2.2 Hz
4	8.08 (d)	8.7	130.80	8.19 (d)	8.8	130.98
5	8.09 (d)	8.4	128.47	8.10 (d)	8.4	128.53
6	7.52 (dd)	7.5	125.42	7.53 (dd)	7.5	125.53
7	7.38 (dd)	7.5	126.83	7.37 (dd)	7.5	126.69
8	7.18 (d)	8.4	125.97	7.18 (d)	8.4	126.06
9			131.02			130.97
10			131.34			131.48
1′			146.91 (d) $^3J_{POCC}$ = 2.2 Hz			120.46 (d) $^3J_{POCC}$ = 2.2 Hz
2′			120.78 (d) $^2J_{POC}$ = 9.7 Hz			147.25 (d) $^2J_{POC}$ = 9.7 Hz
3′	7.63 (d)	8.7	121.06 (d) $^3J_{POCC}$ = 2.2 Hz	7.44 (d)	8.8	121.06 (d) $^3J_{POCC}$ = 2.2 Hz
4′	8.19 (d)	8.7	130.98	8.13 (d)	8.8	131.06
5′	8.09 (d)	8.4	128.54	8.10 (dd)	8.4	128.56
6′	7.52 (dd)	7.5	125.99	7.53 (dd)	7.5	125.60
7′	7.38 (dd)	7.5	126.87	7.37 (dd)	7.5	126.82
8′	7.21 (d)	8.4	125.97	7.21 (d)	8.4	126.08
9′			131.03			131.05
10′			131.47			131.62
1″			145.32 (d) $^3J_{PNCC}$ = 5.3 Hz			145.26 (d) $^3J_{PNCC}$ = 5.3 Hz
2″	7.35 (m)		125.97	7.30 (m)		125.97
3″	7.35 (m)		128.16	7.30 (m)		127.96
4″	7.35 (m)		126.70	7.21 (m)		126.50
5″	7.35 (m)		128.10	7.30 (m)		127.96
6″	7.35 (m)		125.97	7.30 (m)		125.75
7″	4.38 (m)	10.1, 6.9 $^3J_{PNCH}$ = 10.1 Hz	51.26 (d) $^2J_{PNC}$ = 7.1 Hz	4.42 (m)	10.1, 6.9 $^3J_{PNCH}$ = 10.1 Hz	50.83 (d) $^2J_{PNC}$ = 7.1 Hz
8″	1.38 (d)	6.9	24.79 (d) $^3J_{PNCC}$ = 5.3 Hz	1.43 (d)	6.9	25.59 (d) $^3J_{PNCC}$ = 5.3 Hz
NH	6.15 (q)	10.1 $^2J_{PNH}$ = 13.5 Hz		6.47 (q)	10.1 $^2J_{PNH}$ = 13.5 Hz	

movement of the H-3 resonance upfield as a result of shielding by the benzene ring, while H-3′ is in the deshielding region. In the *SS* isomer, the similar H-3 and H-3′ chemical shifts are apparently unaffected by the benzene ring.

3. In the *SS* isomer the chemical shift of H-4″ is different from those of the other protons in the benzene ring. The H-4″ resonance is at δ 7.21 ppm, whereas the other protons resonances are at 7.30 ppm. There is no difference for the five benzene protons in the *RS* isomer, which is identical with the Sadtler atlas.[15] The conformations of the *RS* and *SS* isomers can be inferred from the three features of the NMR spectrum.

From the above arguments, the conformation of the molecule is defined by the location of the benzene ring. From the molecular structure of binaphthol phosphamidate, it appears that the seven-membered ring consisting of four carbons, two oxygens and one phosphorus shows rigidity. Because the P—N bond in the phosphamidate fragment has partial double bond character, rotation is restricted. Rotation about the N—C-7″ bond determines the molecular conformation. Similarly, the rotation about the N—C-7″ bond determines the location of the benzene ring. From the chemical shifts of the H-3 and H-3′ atoms, both the position of the benzene ring and the molecular conformation can be inferred. With the above analysis of the chemical shifts of H-3 and H-3′, and the molecular model, it is easy to infer the conformations of the *RS* and *SS* isomers, respectively. This is because in the *RS* isomer, one naphthalene ring is in the shielding region of the benzene ring and H-3 is near the benzene ring plane. In the *SS* isomer the benzene ring lies between the two naphthalene rings. From the molecular model we see that the H—N—C-7″—H dihedral angles are about 160° in both isomers.

The $^1H\{^1H\}$ spectra, obtained by selective irradiation of the methyl protons, show that the coupling constants $^3J_{HNCH}$ are 10.1 Hz in the two isomers. From the Karplus equation, $^3J_{HNCH} = 9.4 \cos^2 \varphi - 1, 1 \cos \varphi + 0.4$, we obtained 160° for the N—H—C-7″—H dihedral angle. This angle is consistent with the proposed conformation.

The x-ray diffraction results for a single crystal of the *RS* isomer and molecular mechanics calculations for the *SS* isomer further confirm the molecular conformations (see Figs 5 and 6 and Table 2). The x-ray diffraction data show that the angle between the two naphthalene rings is 56.9° and the H—N—C-7″—H dihedral angle is 172.7°. The distances of H-3 from the carbons in the benzene ring are 3.211–4.028 Å, which implies that the H-3 proton is really in the shielding region of the benzene ring and close to the benzene ring plane.

Molecular mechanics results for the *SS* isomer show that the angle between the two naphthalene rings is 62.9°, the H—N—C-7″—H dihedral angle is 173.5° and the distances between the H-3 and the carbons of the

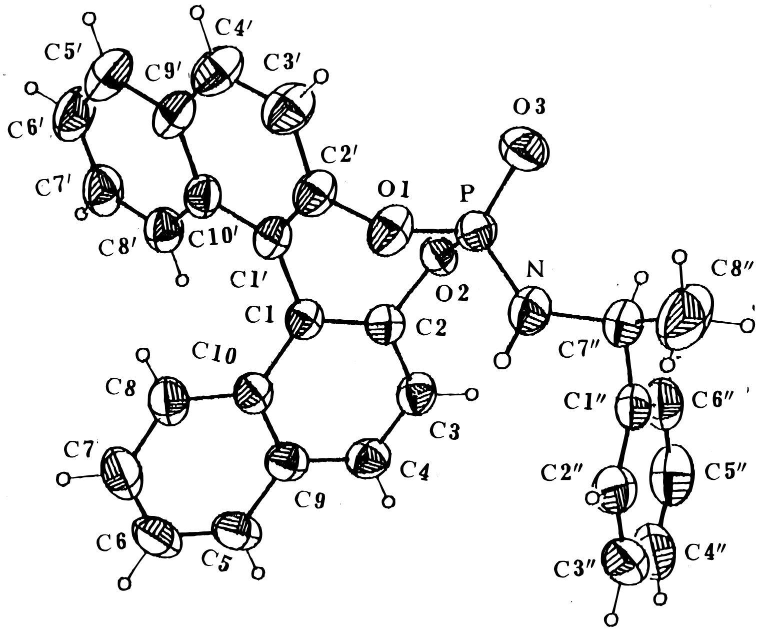

Figure 5. X-ray diffraction structure of the *RS* isomer.

benzene ring are 4.336–7.003 Å. Hence the benzene ring lies in the middle of the two naphthalene rings.

The conformational information on (*RS*)- and (*SS*)-binaphthol phosphamidates is based on four different types of data: (1) the chemical shifts of H-3 and H-3′, (2) the H–N and C-7″–H coupling constants, (3) single-crystal x-ray diffraction data and (4) the molecular mechanics results for the *SS* isomer.

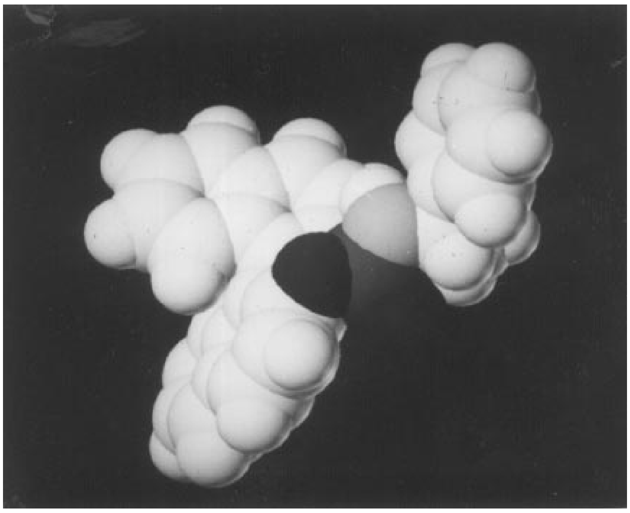

Figure 6. Molecular mechanics model of the *SS* isomer.

(*RS*)-Binaphthyl phosphamidate can form a clathrate with ethanol. The ^{1}H NMR spectrum shows that the ratio between the binaphthol phosphamidate and ethanol in the clathrate is 1:1. After analysing the single-crystal x-ray diffraction data for the clathrate for the *RS* isomer and ethanol, we find that the distance between the double-bonded O on the phosphorus atom in the *RS* isomer and the O in ethanol is 2.72 Å. The O···H—O bond angle is 145.4°. Hence, a hydrogen bond is formed. The distance between the O atom in ethanol and the N atom is 2.91 Å and the O···H—N bond angle is 175.3°. This shows that another hydrogen bond is formed. The ratio between (*RS*)-binaphthol phosphamidate and ethanol molecules is 1:1 (see Fig. 7). The *SS* isomer cannot form a clathrate with ethanol. The *SS* and *RS* isomers mainly differ in their conformations. In the clathrate of the *RS* isomer there is a small space between the binaphthol phosphamidate molecule and the ethanol molecule and it is easy to form two kinds of hydrogen bonds. In the *SS* isomer, however,

Table 2. Dihedral angles and the distances in binaphthol phosphamidate

	RS		*SS*	
Atoms	Dihedral angle (°)	Distance (Å)	Dihedral angle (°)	Distance (Å)
H-2—N—C-7″—H	172.7		173.5	
H-3—C-1″		3.293		4.729
H-3—C-2″		3.719		4.336
H-3—C-3″		4.028		5.501
H-3—C-4″		3.981		6.740
H-3—C-5″		3.581		7.003
H-3—C-6″		3.211		6.127
O-4—O-3		2.720		
O-4—N		2.913		

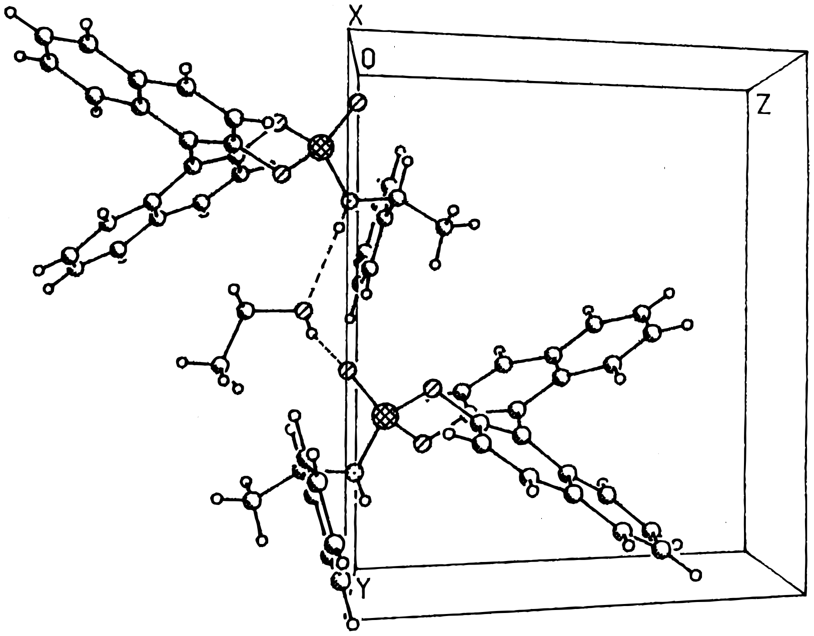

Figure 7. Packing diagram in the crystal of the *RS* isomer with ethanol.

there is a relatively larger space and, it would be difficult to form two kinds of hydrogen bonds.

CONCLUSIONS

The ^1H and ^{13}C NMR chemical shifts of the *RS* and *SS* isomers have been completely assigned on the basis of ^1H NMR, ^{13}C NMR, DEPT, H–H COSY, C–H COSY and HMBC spectra. Based on the above results, the conformations of (*RS*)- and (*SS*)-*O*,*O*-(*2*,*2*′-binaphthyl)-*N*-(α-benzylethyl) phosphamidates were analysed by NMR methods, single-crystal x-ray diffraction and molecular mechanics calculation. The conformational differences between the *RS* and *SS* isomers lead to their different solubilities and different abilities to form clathrates with ethanol. Hence we have provided a theoretical basis for using optically active α-phenylethylamine to separate the racemates of binaphthol.

EXPERIMENTAL

The *RS* or *SS* isomer (35 mg) was dissolved in DMSO-d_6 (0.5 ml, 99.8% D) in 5 mm tubes and spectra were referenced to the solvent peaks at $\delta_c = 39.7$ ppm, $\delta_H = 2.49$ ppm (TMS = 0.0 ppm). All NMR spectra were acquired at room temperature on a Bruker AM 500 spectrometer (^1H at 500.13 MHz, ^{13}C at 125.75 MHz). The ^1H NMR spectra were recorded at 500.13 MHz with a spectral width of 5 kHz collected into 8 K data points. Processing was carried out by zero filling to 16 K data points. The ^{13}C NMR spectra were recorded at 125.75 MHz using a spectral width of 17 kHz collected into 8 K data points. Processing was carried out by zero filling to 32 K data points. The H–H COSY spectra were acquired using a standard version of H–H COSY.[16] A 2.0 s pulse delay between acquisitions was used and a 512 × 256 matrix was collected over a 632 Hz spectral width. Data were zero filled before 2D Fourier transformation. The C–H COSY spectra were obtained with the standard version of C–H COSY.[17] A 256 × 1 K matrix was collected over 17 857 Hz in the ^{13}C dimension (F_2) and 1908 Hz in the ^1H dimension (F_1). For the HMBC[18] experiment, a 256 × 1 K matrix was collected over 3906 Hz in the ^1H dimension (F_2) and 8928 Hz in the ^{13}C dimension (F_1). A 2.0 s pulse delay was applied between acquisitions and a delay time of 70 ms was used to obtain the long-range correlations. Data were zero filled before 2D Fourier transformation.

The single-crystal structure of the *RS* isomer was determined at 293 K on a Syntex P3/R3 x-ray four-circle diffractometer. The space group was found to be $P2_1$ with $a = 9.359(2)$ Å, $b = 12.806(3)$ Å, $c = 11.641(2)$ Å, $\beta = 111.62(3)°$, $Z = 2$, $V = 1294.0(5)$ Å^3 and $D_c = 1.277$ g cm^{-3}. The structure was solved by direct methods and refined to a final $R = 0.0352$, $R_w = 0.0415$ for 3871 observed points using Mo Kα radiation ($\lambda = 0.7107$ Å).

SYBYL software and Tripos force fields were used for molecular mechanics calculations on the *SS* isomer.

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