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### Self-assembly of enantiopure and racemic 2,2',6,6'-tetrasubstituted biaryl tectons into hydrogen bonded chiral squares and infinite chiral square layers

Petr Holý, a Jiří Závada, a,\* Ivana Císařová<sup>b</sup> and Jaroslav Podlaha<sup>b</sup>

<sup>a</sup>Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

<sup>b</sup>Department of Inorganic Chemistry, Faculty of Natural Sciences, Charles University, Hlavova 2030, 128 40 Prague 2, Czech Republic

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Abstract—Both chiral and achiral hydrogen bonding o-,o-,o'-,o'-tetrasubstituted biaryls often exhibit unique self-assembling properties giving rise to chiral square cyclotetramers. The individual chiral squares self-assemble further with the formation of infinite layers which are either achiral or are chiral (homochiral). A priori analysis reveals various hydrogen bonding modes which may take part in the self-assembly, differing each from the other by structure and symmetry of the resulting squares and layers. Results of the theoretical analysis are compared with the experimental findings obtained from X-ray crystallographic analysis of three novel and two already known isosteric biaryl tectons, (S)-2a, (RS)-2a, 3a, (S)-5 and (RS)-5, respectively. © 2002 Elsevier Science Ltd. All rights reserved.

#### 1. Introduction

Supramolecular chemistry inspires the design of microporous layers employing self-assembly of molecular subunits (tectons) driven by non-covalent interactions as the synthetic tool.<sup>1–3</sup> Our recent discovery that biphenyl-2,2',6,6'-tetracarboxylic acid  $1a^4$  as well as the corresponding tetraamide 1b,<sup>5</sup> and also the 1:1 adduct  $1a \cdot 1b^6$  self-assemble with the formation of infinite 2D layers set up from cyclotetrameric hydrogen-bonded square compartments (Fig. 1) opens interesting vistas in this direction.

In contrast to the individual molecules 1a and 1b that possess  $D_{2d}$  symmetry and are thus achiral, the self-assembled cyclotetrameric squares possess  $D_4$  symmetry and are chiral. Squares of opposite chirality (*R* or *S*) alternate, however, in the resulting infinite network which is accordingly again achiral.

In order to attain chirality of the overall network, the individual self-assembling tectons must be made chiral. The requisite chiralization of the parent achiral biaryl tectons 1a and 1b can be accomplished by a pairwise

differentiation of the ortho substituents giving rise to chiral molecules  $2 (X \neq Y, C_2 \text{ symmetry})$ . If only one pair of the distinct substituents (X or Y) is capable of hydrogen bonding, discrete homochiral squares of  $D_4$  symmetry<sup>7</sup> or homochiral helices<sup>8</sup> result. However, *if both pairs of substituents (X as well as Y) are endowed with hydrogenbonding ability, infinite homochiral square layers should be produced.* 

Herein, we explore the formation of infinite homochiral square layers organized by intermolecular carboxyl and amide double hydrogen bonds. Towards this end, we have designed 6,6'-dicarbamoylbiphenyl-2,2'-dicarboxylic acid **2a** as a convenient chiral tecton and employed at the same time its positional isomer **3a** as the achiral counterpart.



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<sup>\*</sup> Corresponding author. Fax: (+4202)-3333 1733; e-mail: zavada@ uochb.cas.cz



Figure 1. Schematic representation of square layers in the crystal of tetraacid 1a (A), tetraamide 1b (B) and in the co-crystal 1a·1b (C). Projection in direction of the biaryl axis indicates the orientation of substituents (wedges) directing downward from the upper phenyl and upward from the lower phenyl. The complementary hydrogen bonded substituents always connect alternate (upper versus lower) phenyl rings and, therefore, are visualized by two concordant wedges.

#### 2. Results and discussion

#### 2.1. Synthesis

Dianhydride 4, easily available<sup>9</sup> from the parent tetraacid 1a, was chosen as the starting compound for preparation of the target 2,2',6,6'-tetrasubstituted biphenyl compounds 2a and 3a. Reaction of 4 with benzyl alcohol (Scheme 1) afforded two positionally isomeric diester diacids as the sole products, which could be easily separated by column chromatography, converted into the corresponding dicarbamoyl diesters and the ester groups smoothly cleaved by hydrogenolysis. On comparison with the partial hydrolysis of the corresponding tetraesters 1c (X=COOMe)<sup>10</sup> or with the partial alcoholysis of the corresponding tetrachloride 1d (X=COCl),<sup>11</sup> both yielding complex product mixtures, this novel approach greatly simplifies the isolation/separation procedures.

Employment of the optically active benzylic alcohol, (S)-1-phenylethanol, in the dianhydride **4** alcoholysis (Scheme 1) provides additional advantages resulting from diastereoselective course of the ring-opening reaction. Absolute configuration of the resulting enantiomer (S)-**2a** has been ascribed, unambiguously, by correlation with the configuration of the diastereoisomeric

diester (S)-2d established on the basis of X-ray diffraction analysis.

## 2.2. X-Ray crystallographic analysis of the novel biaryl tectons (S)-2a, (RS)-2a and 3a

**2.2.1.** Molecular structures. The molecular structures of (S)-2a, (RS)-2a and 3a are depicted in Section 4. For all the novel structures, the intramolecular bond angles and distances are unexceptional. However, there are large differences in the mutual dihedral angles of phenyl planes (64.1–80.7°) and, especially, in the dihedral angles of carboxyl and carbamoyl groups relatively to the parent phenyl plane (9.8–60.7°). The geometry of the hydrogen bonds is remarkably similar in all structures and the average values of their geometry (with standard deviations of the mean in parentheses) are as follows: O–H 0.96(6), H…O 1.66(5), O…O 2.595(7) Å, O–H…O 168(4)°; N–H 0.91(4), H…O 2.06(5), N…O 2.948(6) Å, N–H…O 165(5)°.

**2.2.2. Self-assembly of the enantiopure tecton (S)-2a.** In contrast to the achiral tectons **1a**, **1b** and **1a**•**1b**, each allowing only one mode of intermolecular double hydrogen bonding (Fig. 1, A–C, respectively), a priori analysis suggests four possible modes of self-assembly



Scheme 1. Reagents and conditions: (i) py, DMAP; (ii) (COCl)<sub>2</sub>,  $CH_2Cl_2$ , DMAP; (iii) aq.  $NH_4OH$ , dioxane; (iv)  $H_2$ , Pd/C,  $CH_3OH/H_2O$ .

(Fig. 2, **D**–**G**) for the homochiral tecton (S)-2a. The first mode (**D**) rests on the combination of two homofunctional double hydrogen bonds, carboxyl–carboxyl and amide–amide, analogous to those found, individually, in **1a** and **1b** (Fig. 1, **A** and **B**, respectively). The second mode (**E**) is based exclusively on the heterofunctional (carboxyl–amide) double hydrogen bond established earlier<sup>6</sup> in the molecular complex **1a**•1b (Fig. 1, **C**). The remaining two modes (**F** and **G**) consist of a blend of the homo- and heterofunctional double hydrogen bonds. Notably, the alternative modes may also differ by symmetry (see the symmetry symbols inside the individual squares in Fig. 2). Irrespective of the individual differences in hydrogen bonding and symmetry, each of the four alternative modes **D**–**G** is set up from homochiral squares and can accordingly afford infinite homochiral layers.

In order to determine which (if any) of the four alternative hydrogen bonding modes actually operates in the self-assembled crystal, the tecton (S)-2a was subjected to X-ray diffraction analysis. It was found that forma-

Figure 2. Four theoretical modes of hydrogen bonding of the homochiral tecton (S)-2a visualized as described in Fig. 1.

tion of infinite homochiral square layers occurs in the crystal (Fig. 3) via the hydrogen bonding mode **F**, employing both homo- and heterofunctional double hydrogen bonds. The individual homochiral 2D layers are arranged in a staggered manner (similarly as the achiral tectons **1ab**, **1b** and **1a**•**1b**) and are interconnected by intermolecular amide–amide single hydrogen bonds (one direct and one solvent-mediated bond per each square). The resulting 3D framework is rigidified by complementary intramolecular amide–amide single hydrogen bonds (one additional pair of bonds per square).

**2.2.3.** Self-assembly of the racemic tecton (RS)-2a. Conceptually, self-assembly of the racemate (RS)-2a may offer a greater number of hydrogen bonding modes than the corresponding enantiopure tecton (S)-2a, as a consequence of the variable distribution of opposite enantiomers in the resulting supramolecular network.

At the simplest level of the a priori analysis, there are two possible patterns of the enantiomeric distribution differing each from the other by a horizontal/vertical or diagonal alternation of the opposite enantiomers in the square network. Each of the two distribution patterns allows operation of four distinct hydrogen bonding modes (Fig. 4; H–K and L–O, respectively) which are analogous with those considered above for the enantiopure tecton (S)-2a. They invariantly allow formation of chiral squares, with the stipulation that squares of opposite chirality in the racemic compound alternate vertically and/or horizontally and the resulting layers are accordingly achiral.

In a more complex analysis of the racemate, alternation of higher homochiral aggregates of the hydrogen bonded tectons in place of the individual chiral molecules also has to be taken into account as another viable pattern of the enantiomeric distribution. Alternation of opposite homochiral 2D layers resulting in a single racemic crystal and stacking of homochiral layers leading to a racemic mixture (a conglomerate<sup>12,13</sup>) of homochiral crystals represent in this respect two possible scenarios.<sup>12–15</sup> Accordingly, formation of infinite homochiral square layers from racemic tectons cannot be ruled out.



Figure 3. Segment of an infinite chiral layer in the crystal of (S)-2a formed by intermolecular double hydrogen bonds. Disordered water molecules and all hydrogens are omitted for clarity. Carbon atoms are not distinguished, oxygens and nitrogen atoms are drawn as red and blue circles, respectively.

$$(RS)-2a \equiv \swarrow^R + \checkmark^S$$

 $COOH = \bigcirc$ ,  $CONH_2 = \checkmark$ 



Figure 4. Eight theoretical modes of hydrogen bonding of the racemic tecton (RS)-2a corresponding either to the horizontal/vertical (H-K) or to the diagonal alteration of enantiomers (L-O) visualized as described in Fig. 1.

Of the aforementioned alternatives, X-ray diffraction analysis established (Fig. 5) that a simple horizontal/ vertical alternation of the molecular tectons (S)- and (*R*)-2a, linked by the homofunctional carboxyl-carboxyl and amide-amide double hydrogen bonds (mode H) accounts for the single-crystal selfassembly of the racemate (RS)-2a into achiral layers. A closer examination of the crystal structure of (RS)-2a shows that the individual 2D layers are stacked in a staggered manner and are interconnected by intermolecular amide-amide single hydrogen bonds. The resulting 3D framework is rigidified by intramolecular amide-amide single hydrogen bonds, similarly as noted above for the enantiopure tecton (S)-2a.

**2.2.4.** Self-assembly of the achiral isomer 3a. 2,2'-Dicarbamoylbiphenyl-6,6'-dicarboxylic acid 3a is the achiral counterpart of the chiral tecton 2a. A priori stereochemical analysis suggests that the achiral tecton 3a allows formation of the chiral squares by two alternative hydrogen bonding modes, exploiting either the homofunctional (carboxyl-carboxyl and amide-amide) or the heterofunctional (carboxyl-amide) double hydrogen bonds (Fig. 6; P and Q, respectively). The latter of the two alternative modes (Q) actually operates in the crystal 3a (Fig. 7).

#### 2.3. Comparison with earlier crystallographic results

The present study has been stimulated by our earlier investigation<sup>16</sup> of a related biaryl tecton, 2,2'-bipyridine-3,3'-dicarboxylic acid-1,1'-dioxide **5**, which together with the novel tecton **2a** have in common two

important properties, (a) chirality of the biaryl axis, and (b) two pairs of distinct *ortho-*, *ortho'*-substituents capable of participation in the formation of intermolecular hydrogen bonds.



**2.3.1. Comparison of the enantiopure tectons (S)-2a versus (S)-5.** As has already been pointed out, the enantiopure biphenyl tecton (S)-**2a** employs a blend of the homo- and heterofunctional double hydrogen bonds in the self-assembly via the hydrogen bonding mode **F**. Whereas, the corresponding bipyridyl tecton (S)-**5** exploits<sup>16</sup> the heterofunctional  $-N-O\cdots$ HOOC- single hydrogen bond, which is analogous with the hydrogen bonding mode **E**. Reasons for this difference can be explained as follows.

In the self-assembly of the biphenyl tecton (S)-2a both the participating (carboxyl and amide) functional groups serve simultaneously<sup>17,18</sup> as an acceptor as well as a donor in the hydrogen bond, thus allowing 'a free choice' among the four alternative hydrogen bonding modes **D–G** (Fig. 2). As a contrast, only one of the functional groups (carboxyl) in the bipyridyl tecton **5** can serve the dual acceptor–donor role, the other (amine oxide) group being solely hydrogen bond accep-



Figure 5. Segment of an infinite achiral layer in the crystal of (RS)-2a formed by intermolecular double hydrogen bonds. Disordered water molecules and all hydrogens are omitted for clarity. Carbon atoms are not distinguished, oxygens in carboxyls are drawn as red circles, disordered oxygen/nitrogen atoms in carbamoyl groups are shown as red/blue-halved circles.



Figure 6. Two theoretical modes of hydrogen bonding of the achiral tecton 3a visualized as described in Fig. 1.

tor. Thus, the bipyridyl tecton 5 is relegated to the formation of square layers via the heterofunctional hydrogen bonds.

**2.3.2. The racemic tectons (**RS**)-2a versus (**RS**)-5.** The corresponding racemates (RS**)-2a** and (RS**)-5** exploit different hydrogen bonding modes in the single-crystal self-assembly. The homofunctional (carboxyl-carboxyl and amide-amide) double hydrogen bonds operate in the self-assembly of the former whereas the heterofunctional (carboxyl-amine oxide) single hydrogen bonds are engaged<sup>16</sup> in the self-assembly of the latter racemate.

Notably, the distribution pattern of the opposite enantiomers found in the single crystals of the two racemates is also different. As has already been noted, a regular horizontal/vertical alternation of enantiomerically opposite molecular tectons occurs in the crystal of the biphenyl racemate (RS)-2a and the resulting individual infinite square layers are accordingly achiral. In a striking contrast, in the corresponding crystal of (RS)-5 the individual infinite square layers are homochiral, being set up from tectons that are enantiomerically uniform. Within a single racemic crystal of



Figure 7. Segment of an infinite achiral layer in the crystal of 3a formed by intermolecular double hydrogen bonds, details as in Fig. 3.

the tecton (RS)-5, enantiomeric separation accordingly occurs on the level of the alternating homochiral 2D layers. Only a few similar cases have been reported in literature to date.<sup>12–15</sup>

#### 3. Conclusion

Hydrogen bonding o-,o-,o'-,o'-tetrasubstituted chiral as well as achiral biaryls exhibit unique self-assembling properties, giving rise to chiral square cyclotetramers. The individual chiral squares self-assemble further to form of infinite open square layers which are either achiral or are chiral (homochiral). Biaryls which are achiral yield achiral layers. Biaryls which are chiral and enantiomerically uniform give homochiral layers. Racemic biaryls exhibit intermediate behaviour, affording either achiral or chiral (homochiral) square layers, depending on the nature of the biaryl substituents.

A priori analysis shows that several hydrogen bonding modes can compete in the self-assembly, giving rise to alternative supramolecular chiral squares and infinite layers. In the case of racemic tectons variability of the enantiomeric distribution must be also taken into account.

Results of the theoretical analysis were compared with the experimental findings obtained from X-ray crystallographic analysis of five isosteric biaryl tectons, (S)-2a, (RS)-2a, 3a, (S)-5, and (RS)-5, distinguished by chirality, by enantiomeric homogeneity, or by hydrogen bonding ability of the individual substituents.

#### 4. Experimental

#### 4.1. General

Melting points were determined on a Kofler apparatus and are uncorrected. <sup>1</sup>H NMR spectra were measured on a Varian Unity XL-200 spectrometer (200 MHz, FT mode). Mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument. Thioglycerol/ glycerol and 2-hydroxyethyl disulfide matrices were used for FAB techniques. Silica gel 60 (0.063–0.200 mm, Fluka) was used for column chromatography. TLC analyses were done on aluminium sheets silica gel 60  $F_{254}$  (Merck) with UV detection.

# 4.2. Preparation of dibenzyl esters and their transformations

4.2.1. Reaction of dianhydride 4 with benzyl alcohol. A mixture of dianhydride 4 (1.00 g, 3.4 mmol), benzyl alcohol (1.00 g, 9.25 mmol), dry pyridine (8 mL) and 4-dimethylaminopyridine (100 mg, 0.82 mmol) was heated to 110°C under stirring for 6 h. After cooling, the mixture was treated with aq. HCl (2 M, 100 mL) and extracted with ethyl acetate (4×30 mL). The combined extracts were washed with 10% aq. sodium carbonate (3×30 mL). The washing was acidified with conc. HCl to pH 1, the pasty precipitate was taken up in ethyl acetate ( $4 \times 20$  mL), dried with MgSO<sub>4</sub> and evaporated in vacuo. The semi-solid residue (1.52 g) was separated into the individual products by column chromatography (silica gel, eluent toluene:ethyl acetate:acetic acid 80:19:1) followed by crystallization from a toluene-heptane mixture.

**Biphenyl-2,2',6,6'-tetracarboxylic** acid 2',6'-dibenzyl ester 3b: yield 759 mg (44%), mp 218–220°C. Anal. calcd for  $C_{30}H_{22}O_{8:}$  C, 70.58; H, 4.34. Found C, 70.38; H, 4.44%. <sup>1</sup>H NMR spectrum was in accord with the reported data.<sup>11</sup>

(*RS*)-Biphenyl-2,2',6,6'-tetracarboxylic acid 6,6'-dibenzyl ester (*RS*)-2b: yield 523 mg (30%), mp 231–232°C. Anal. calcd for  $C_{30}H_{22}O_8$ : C, 70.58; H, 4.34. Found C, 70.61; H, 4.29%. <sup>1</sup>H NMR spectrum was in accord with the reported data.<sup>11</sup>

4.2.2. 2',6'-Dicarbamoylbiphenyl-2,6-dicarboxylic acid dibenzyl ester 3c. Oxalyl chloride (1.455 g, 11.46 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol) were added to a solution of dibenzyl ester 3b (400 mg, 0.783 mmol) in dry dichloromethane (10 mL) and the mixture was stirred at rt for 12 h. After evaporation of the volatiles, the residue was dissolved in dioxane (20 mL) and added dropwise into a stirred solution of conc. aq. NH<sub>4</sub>OH (5 mL) in dioxane (5 mL). After 1 h stirring, the mixture was taken to dryness and the crude product was crystallized from aq. ethanol. Yield 370 mg (92%), mp 215–217°C. <sup>1</sup>H NMR spectrum (DMSO- $d_6$ )  $\delta$  7.97 (d, J=7.9 Hz, 2H), 7.42-7.56 (m, 3H), 7.20-7.38 (m, 11H), 7.03 (br s, 2H), 6.97 (br s, 2H), 4.99 (s, 4H). MS FAB spectrum (m/z, % rel.): 509 (MH<sup>+</sup>, 9), 309 (8), 278 (21), 250 (9), 231 (30), 184 (9), 154 (76), 137 (100), 109 (34), 91 (23). Anal. calcd for  $C_{30}H_{24}N_2O_6$ : C, 70.86; H, 4.76; N, 5.51. Found C, 70.68; H, 4.85; N, 5.38%.

**4.2.3. 6,6'-Dicarbamoyl-(***RS***)-biphenyl-2,2'-dicarboxylic acid dibenzyl ester (***RS***)-2c. Prepared analogously from the racemic dibenzyl ester <b>2b** (420 mg, 0.823 mmol). Yield 395 mg (94%), mp 187–189°C. <sup>1</sup>H NMR spectrum (DMSO- $d_6$ )  $\delta$  7.76 (br s, 2H), 7.84 (dd, *J*=7.6 Hz, *J*=1.5 Hz, 2H), 7.56 (dd, *J*=7.6 Hz, *J*=1.5 Hz, 2H), 7.43 (t, *J*=7.6 Hz, 2H), 7.24–7.36 (m, 8H), 7.10–7.21 (m, 4H), 5.03 (d, *J*=12.5 Hz, 2H), 4.88 (d, *J*=12.5 Hz, 2H). MS FAB spectrum (*m*/*z*, % rel.): 509 (MH<sup>+</sup>, 22), 419 (2), 251 (4), 181 (14), 91 (100). Anal. calcd for  $C_{30}H_{24}N_2O_6$ ; C, 70.86; H, 4.76; N, 5.51. Found C, 70.60; H, 4.90; N, 5.41%.

4.2.4. 2',6'-Dicarbamoylbiphenyl-2,6-dicarboxylic acid 3a. Palladium on carbon (10% Pd/C, 50 mg) was added to a solution of dicarbamoyldiester 3c (250 mg, 0.492 mmol) in 60% aq. methanol (150 mL) and the suspension was stirred under H<sub>2</sub> atmosphere at rt overnight. The catalyst was filtered off and washed with 50% aq. methanol (2×50 mL). The combined filtrate and washings were evaporated to dryness and the residue was crystallized from hot water. Yield 150 mg (93%), mp 346-348°C. <sup>1</sup>H NMR spectrum  $(DMSO-d_6)$   $\delta$  13.35 (br s, 2H), 7.79 (d, J=7.6 Hz, 2H), 7.42–7.66 (m, 8H). MS FAB spectrum (m/z, % rel.): 329 (MH+, 2), 235 (13), 201 (23), 187 (25), 181 (12), 171 (95), 159 (34), 149 (15), 110 (36), 91 (100). Anal. calcd for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub>. C, 58.54; H, 3.68; N, 8.53. Found C, 58.39; H, 3.74; N, 8.38%.

**4.2.5. 6,6'-Dicarbamoyl-(***RS***)-biphenyl-2,2'-dicarboxylic acid (***RS***)-2a. Prepared analogously from the dicarbamoyldiester (***RS***)-2c (220 mg, 0.433 mmol). Yield 128 mg (90%), mp 307–309°C (dec.). <sup>1</sup>H NMR spectrum (DMSO-d\_6) \delta 12.48 (br s, 2H), 7.89 (dd,** *J***=7.6 Hz,** *J***=1.5 Hz, 2H), 7.80 (br s, 2H), 7.54 (dd,** *J***=7.6 Hz,** *J***=1.5 Hz, 2H), 7.45 (t,** *J***=7.6 Hz, 2H), 7.27 (br s, 2H). MS FAB spectrum (***m***/***z***, % rel.): 329 (MH<sup>+</sup>, 2), 274 (4), 257 (5), 232 (3), 202 (13), 181 (12), 149 (6), 126 (9), 110 (100), 91 (38), 75 (54), 57 (61). Anal. calcd for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub>: C, 58.54; H, 3.68; N, 8.53. Found C, 58.54; H, 3.85; N, 8.28%.** 

# 4.3. Preparation of (S)-1-phenylethyl esters and their transformations

**4.3.1. Reaction of dianhydride 4 with** (S)-(-)-1-**phenylethanol**. Performed analogously as the reaction with benzyl alcohol (Section 4.2.1) starting from dianhydride **4** (1.18 g, 4 mmol) and (S)-(-)-1-phenylethanol (1.22 g, 10 mmol).

Biphenyl-2,2',6,6'-tetracarboxylic acid 2',6'-bis-[(S)-1phenylethyl] ester 3d: yield 905 mg (42%), mp 188– 190°C. <sup>1</sup>H NMR spectrum (DMSO- $d_6$ )  $\delta$  8.05 (d, J=7.9 Hz, 2H), 8.01 (d, J=7.9 Hz, 2H), 7.52 (t, J=7.9 Hz, 2H), 7.05–7.35 (m, 10H), 5.66 (q, J=6.4Hz, 2H), 1.06 (d, J=6.4 Hz, 6H). MS FAB spectrum (m/z, % rel.): 561 (MNa<sup>+</sup>, 10), 539 (MH<sup>+</sup>, 8), 435 (8), 331 (50), 313 (100), 269 (10), 251 (22). Anal. calcd for  $C_{32}H_{26}O_8$ ; C, 71.37; H, 4.87. Found C, 71.21; H, 4.82.

(S)-Biphenyl-2,2',6,6'-tetracarboxylic acid 6,6'-bis-[(S)-1-phenylethyl] ester (S)-2d: yield 603 mg (28%), mp 184–186°C. <sup>1</sup>H NMR spectrum (DMSO- $d_6$ )  $\delta$  8.05 (dd, J=7.8 Hz, J=1.4. Hz, 2H), 8.01 (dd, J=7.8 Hz, J=1.4 Hz, 2H), 7.52 (t, J=7.8 Hz, 2H), 7.05–7.30 (m, 10H), 5.65 (q, J=6.4 Hz, 2H), 1.04 (d, J=6.4 Hz, 6H). MS FAB spectrum (m/z, % rel.): 561 (MNa<sup>+</sup>, 15), 539 (MH<sup>+</sup>, 12), 435 (9), 331 (60), 313 (100), 269 (15), 251 (15). Anal. calcd for C<sub>32</sub>H<sub>26</sub>O<sub>8</sub>. C, 71.37; H, 4.87. Found C, 71.36; H, 4.86%. (*R*)-Biphenyl-2,2',6,6'-tetracarboxylic acid 6,6'-bis-[(*S*)-1-phenylethyl] ester (*R*)-2d: yield 43 mg (2%), mp 168– 170°C. <sup>1</sup>H NMR spectrum (DMSO- $d_6$ )  $\delta$  8.03 (d, J=7.8 Hz, 4H), 7.53 (t, J=7.8 Hz, 2H), 7.00–7.28 (m, 10H), 5.64 (q, J=6.4 Hz, 2H), 1.07 (d, J=6.4 Hz, 6H). MS FAB spectrum (m/z, % rel.): 539 (MH<sup>+</sup>, 12), 435 (8), 417 (7), 352 (40), 331 (50), 313 (100). Anal. calcd for C<sub>32</sub>H<sub>26</sub>O<sub>8</sub>: C, 71.37; H, 4.87. Found C, 71.28; H, 4.89%.

**4.3.2. 6,6'-Dicarbamoyl-(S)-biphenyl-2,2'-dicarboxylic** acid bis[(S)-1-phenylethyl] ester (S)-2e. Prepared from diester (S)-2d (300 mg, 0.557 mmol) analogously as described above for dibenzyl derivative 3c. Yield 275 mg (92%), mp 167–169°C. <sup>1</sup>H NMR spectrum (DMSO $d_6$ )  $\delta$  7.89 (dd, J=7.6 Hz, J=1.5 Hz, 2H), 7.75 (br s, 2H), 7.57 (dd, J=7.56 Hz, J=1.5 Hz, 2H), 7.46 (t, J=7.6 Hz, 2H), 7.32 (br s, 2H), 7.20–7.30 (m, 10H), 5.66 (q, J=6.8 Hz, 2H), 1.28 (d, J=6.8 Hz, 6H). spectrum (m/z, % rel.): 537 (MH<sup>+</sup>, 27), 433 (14), 329 (100), 312 (40), 269 (13), 251 (53). Anal. calcd for  $C_{32}H_{28}N_2O_6$ . C, 71.63; H, 5.26; N, 5.22. Found C, 71.46; H, 5.36; N, 5.18%.

**4.3.3. 6,6'-Dicarbamoyl-(S)-biphenyl-2,2'-dicarboxylic acid (S)-2a.** Prepared from (S)-**2e** (250 mg, 0.466 mmol) analogously as described above for the positional isomer **3a.** Yield 139 mg (91%), mp 320°C (dec.),  $[\alpha]_D^{20}$ -32.8 (c 0.25, 50% aq. methanol). <sup>1</sup>H NMR and MS FAB spectra are in accord with those of (*RS*)-**2a.** Anal. calcd for  $C_{16}H_{12}N_2O_6$ : C, 58.54; H, 3.68; N, 8.53. Found C, 58.39; H, 3.91; N, 8.38%.

#### 4.4. X-Ray diffraction analysis

Single crystals of compounds (S)-2a, (RS)-2a and 3a were grown from their aqueous solutions by slow cooling. Single crystals of the diester (S)-2d were obtained by a slow diffusion of hexane into the toluene solution. Crystal data, measurement and refinement details for compounds listed above are summarized in Table 1.

(S)-2a monohydrate contains two crystallographically independent molecules which differ significantly in their relative conformation, see inset of Fig. 8. The water molecule is held in a void of the structure by secondary hydrogen bonds and is disordered over two positions with the fixed relative occupancy of 75:25; since the two positions are mutually closely spaced, the hydrogen bonding scheme is essentially unaffected by the disorder. The carbon-bonded hydrogen atoms were fixed in theoretical positions and assigned temperature parameters 1.2 of their parent carbons, the other hydrogen atoms were refined isotropically (except of those of the minor position of the disordered water which were not found).

In the crystal of (RS)-2a hemihydrate both carbamoyl groups exhibit rotational disorder about their bonds to the aromatic carbons which makes impossible to distin-

Table 1	1.	Crystal	data,	measurement	and	refinement	details <sup>a</sup>

Compound	(S)- <b>2a</b>	( <i>RS</i> )-2a	3a	(S)-2d
Empirical formula	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>6.5</sub>	C <sub>16</sub> H <sub>13</sub> N <sub>2</sub> O <sub>6.5</sub>	C <sub>16</sub> H <sub>12</sub> N <sub>2</sub> O <sub>6</sub>	C <sub>32</sub> H <sub>26</sub> O <sub>8</sub>
Crystal system	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_122_1$ (no. 18)	$P2_1/c$ (no. 14)	<i>Pna</i> 2 <sub>1</sub> (no. 33)	<i>P</i> 2 <sub>1</sub> (no. 4)
a (Å)	11.4170(1)	10.1500(4)	10.643(1)	8.8730(1)
b (Å)	13.0690(2)	11.5400(4)	13.512(2)	31.8750(3)
<i>c</i> (Å)	20.4990(3)	13.0890(4)	10.337(1)	9.7690(1)
β (°)		103.340(2)		94.0010(6)
Ζ	8	4	4	4
V (Å <sup>3</sup> )	3058.63(7)	1491.76(9)	1486.5(3)	2756.20(5)
$D_{\rm calcd} \ ({\rm g \ cm^{-3}})$	1.469	1.502	1.467	1.298
Temperature (K)	150(2)	150(2)	150(2)	150(2)
Crystal size (mm)	$0.3 \times 0.5 \times 0.55$	$0.25 \times 0.25 \times 0.45$	$0.25 \times 0.3 \times 0.3$	$0.25 \times 0.3 \times 0.35$
$\mu ({\rm mm^{-1}})$	0.116	0.119	0.115	0.093
h Range	-13, 13	-12, 12	0, 12	-11, 11
k Range	-16, 16	-13, 13	-16, 16	-40, 40
l Range	-26, 26	-15, 15	0, 12	-12, 12
Reflections measured	36664	19515	2704	41995
Independent reflections $(R_{int})$	6534(0.027)	2627(0.027)	1388(0.037)	11952(0.037)
Observed reflections $[I > 2\sigma(I)]$	5879	2521	1225	9952
No. of parameters	545	234	265	735
GOF	1.060	1.231	1.034	1.022
R, wR (observed data)	0.040, 0.091	0.064, 0.145	0.026, 0.064	0.055, 0.135

<sup>a</sup> Data in common: Nonius KappaCCD and CAD4-MACHIII diffractometers for (S)-2a, (RS)-2a, (S)-2d and 3a, respectively, Mo K $\alpha$ ,  $\lambda = 0.71073$ , direct methods (SIR-92<sup>19</sup>), full-matrix least-squares refinement on  $F^2$  (SHELXL-97<sup>20</sup>); see text for further details of individual structures.



**Figure 8.** Perspective view of one of the two independent molecules of (S)-2a with atom labelling (40% probability ellipsoids, hydrogen atoms as spheres of arbitrary size). An overlay of the two molecules with one phenyl ring as reference is given in the inset.

guish their oxygen and nitrogen atoms. The disorder was modelled in 50:50 fixed occupancy with two hydrogen atoms of half occupancy assigned to each disordered N/O atom (Fig. 9). Fortunately, the disorder does not affect the overall hydrogen bonding scheme since the two disordered groups are hydrogen-bonded

mutually and, therefore, the net result is the 180° rotational disorder of the whole double carbamoyl hydrogen bridge. The water molecule is again hold in a void by secondary hydrogen bonds. Hydrogen atoms were treated as above except of the disordered ones which were fixed in calculated positions.

In the crystal of 3a all hydrogen atoms were refined isotropically; the molecular structure is shown in Fig. 10.

In the crystal of (S)-2d there are again two crystallographically independent molecules of remarkably different conformation (see inset of Fig. 11). One phenyl group of one molecule is heavily disordered over two positions modelled with the fixed 80:20 occupancy. Hydrogen atoms were treated as for (S)-2a.

Crystallographic data (excluding structure factors) for the structures (S)-2a, (RS)-2a, 3a and (S)-2d have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 173042, CCDC 173043, CCDC 173044 and CCDC 173045, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Figure 9. Perspective view of one molecule of (RS)-2a with atom labelling (40% probability ellipsoids, hydrogen atoms as spheres of arbitrary size). Hydrogen atoms of disordered carbamoyl groups are omitted.



Figure 10. Perspective view of one of the two independent molecules of 3a with atom labelling (50% probability ellipsoids, hydrogen atoms as spheres of arbitrary size).



Figure 11. Perspective view of one molecule of (S)-2d (unaffected by disorder) with atom labelling (40% probability ellipsoids, hydrogen atoms as spheres of arbitrary size). Overlay of the two molecules is given in inset.

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