2,2′-Dimethylbiphenyl-6,6′-dicarboxylic acid enforces two attached valine molecules to form up a chiral host lattice

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Crystals of (*R*)-valyl 2,2′-dimethylbiphenyl-6,6′-dicarboxylate 3 and (*S*)-valyl 2,2′-dimethylbiphenyl-6,6′-dicarboxylate 4 are stabilised by a network of inter- and intramolecular hydrogen bonds; together with the space requirement of the biphenyl core, structures result which contain cavities filled by THF (3) or EtOH molecules engaged in hydrogen bridging (4).

The regular structural motifs of proteins, β-strands and α-helices have been imitated using artificial amino acids. β-Sheets, β-turns or unusual helices have been targets of recent research.[1] Other examples are cyclic peptides of alternating chirality which aggregate to dimers in the form of antiparallel or parallel β-sheets.[2] We used an organic dicarboxylic acid as spacer to provide the optimal geometry for a parallel β-sheet.[3] However, the active centers of natural peptide oligomers as the enzymes or catalytic antibodies[4] are often located in regions of irregular peptide conformations. While it may be very difficult to design such active centers from scratch it is promising to study organic spacer units which hold attached peptide chains in divergent directions so that regular sheets or helices cannot be formed by self-association. Here, we report the synthesis and the solid state structure of two small peptides where biphenyldicarboxylic acid **2** is used as nucleation point of an irregular peptide structure.

Methyl 2-iodo-3-methylbenzoate **1** was prepared from *m*-toluic acid.[5] The biaryl coupling forming the dimethyl ester of **2** was achieved in high yields using a specially activated copper catalyst (Scheme 1). (*S*)-**2** was isolated from the brucine salt of the carboxylic acid. The peptide coupling of (*S*)-**2** with 2 equiv. of (*R*) or (*S*)-valine methyl ester yields **3** and **4** (after hydrolysis of the valine ester groups) in almost quantitative yield. Diethyl cyanophosphonate was used for the sterically demanding peptide coupling.[6]

Crystals of **3** and **4** were grown from THF–EtOH and from EtOH. They contain THF and EtOH guest molecules. The X-ray determined solid state structures‡ of **3** and **4** shows that the attachment of four substituents in the *o*,*o*′-positions of the biphenyl core results in a divergence of the two peptide chains by almost 90° (Fig. 1).

The unit cell of **4** contains two different molecules with slightly different orientation of the valine side-chains. The dihedral angles ϕ in the peptide chains A and B of **3** and **4** [A(**3**): ϕ = 112.2°, B(**3**): ϕ = 121.7°, A(**4**)/A′(**4**): ϕ = −67.3/−93.4°, B(**4**)/B′(**4**): ϕ = −116.8/−137.4°] belong to regions of the Ramachandran diagram were extended and helical peptide structures have been located[6] (note the change in sign with the chirality of the amino acid). The biphenyl core obviously does not enforce energetically disfavoured geometries in attached peptides.

In both structures, an intramolecular hydrogen bond is formed between the Val-NH proton of one peptide chain (A) and the biphenylic-carbonyl oxygen of the other chain B. The chains A and B are however identical in the NMR spectra of **3** and **4** in DMSO at 30 °C. Even low temperature spectra of the corresponding dimethyl esters in $CDCl_3$ (−40 °C) contain only one set of signals for both peptide chains. So it can be assumed

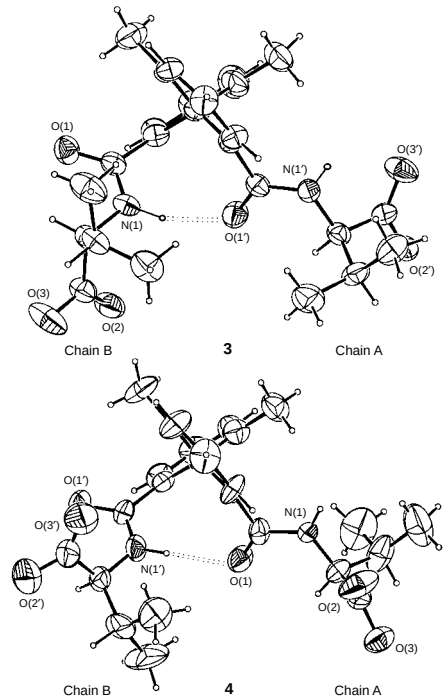
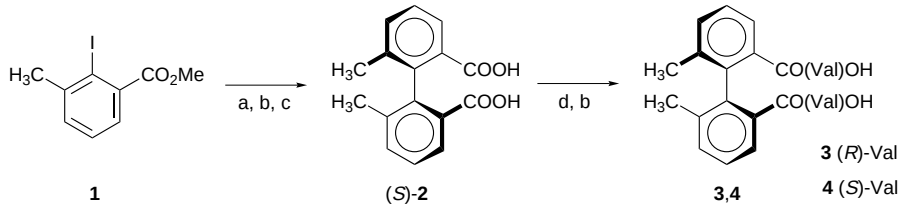


Fig. 1 ORTEP plot of the molecules **3** and **4** in the solid state. Both compounds develop the same intramolecular hydrogen bond, but the orientation of the valine side-chains is different.



Scheme 1 *Reagents and conditions*: (*a*) **1** (10 g), dendritic copper (Aldrich, 3 μ, 6 g), DMF (20 ml), 150 °C; distill. 92%: (*b*) KOH, EtOH, H_2O (60 °C) then HCl, quant.: (*c*) acetone, MeOH, brucine, 40% (*S*)-**2**, see ref. 5: (*d*) D (or L)-valine methyl ester, diethyl cyanophosphonate, triethylamine, DMF, 90–92%

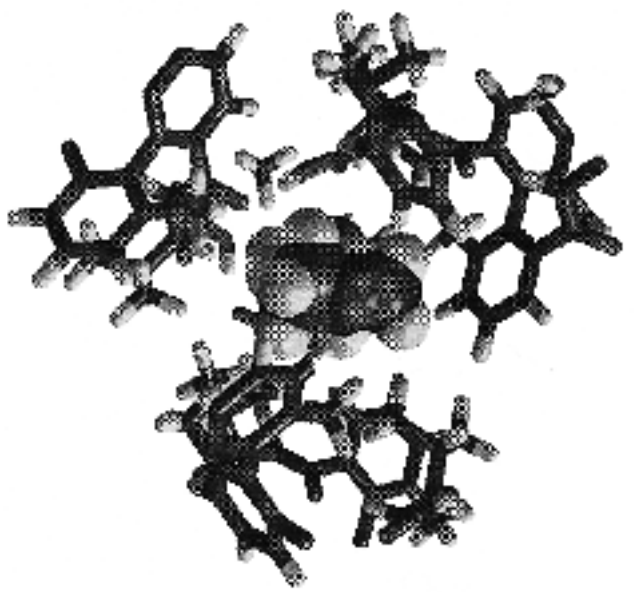


Fig. 2 Coordination of THF (drawn as CPK model) in the solid state structure of **3** (drawn as tubes). A second disordered THF molecule can be seen behind the THF in front.

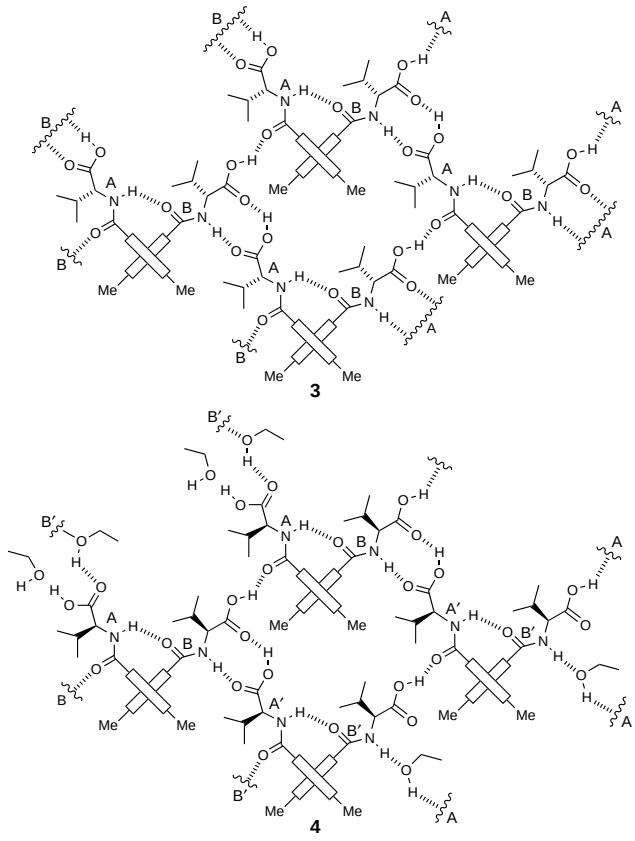


Fig. 3 Schematic two dimensional drawing of the hydrogen bond network in the solid state structure of **3** and **4**. The structure of **4** contains an EtOH molecule disordered over two sites.

that the chains A and B interconvert rapidly on the NMR timescale if the solid state conformation persists in solution.

The crystal lattice of **3** encapsulates THF molecules at two different positions. The THF guests are surrounded by a lipophilic environment of aromatic CH groups and CH_3 groups of valine and of the biphenyl unit (Fig. 2) One of the THF molecules is disordered (site occupation factor = 0.5) and fills only every second position available.

Whereas the conformations of the peptide chains differ in **3** and **4** (see above and Fig. 1), both molecules have an almost identical network of intermolecular hydrogen bonds (see Fig. 3). The carboxylic groups do not form carboxylic acid dimers but are engaged in hydrogen bonding to the amide groups. The carboxylic OH group of chain B is in contact with the CO group at the biphenyl core of chain A building an infinite structure of hydrogen bonded molecules (in **3** and **4**). The carboxylic group of chain A uses the HN–Cα–CO unit of chain B to build up another strand of hydrogen bonds almost orthogonal to the first one. Compound **4** uses EtOH molecules to complete this second strand of hydrogen bonds.

The biphenyl core **2** serves as a molecular cross for attached peptides. The intra- and inter-molecular hydrogen bonds found in the solid state structure of **3** and **4** do not resemble the common β-sheets or helical structures of peptides. Biaryl diacids are known to form inclusion complexes with several organic guests.[8] The peptides in **3** and **4** obviously do not reduce this tendency and may be ideal tools to alter the properties of these cavities. We are looking forward to synthesising host–guest lattices of biphenyl peptides containing longer peptide chains.

Notes and References

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‡ *Crystal data* for $C_{26}H_{32}N_2O_6{\cdot}2C_4H_8O$ (**3**): Siemens P4 diffractometer, Mo-Kα radiation, M = 612.74, 0.68 × 0.52 × 0.48 mm, orthorhombic, space group $P2_12_12_1$, a = 11.107(5), b = 15.013(6), c = 20.813(7) Å, U = 3471(2) Å^3, F(000) = 1320, Z = 4, D_c = 1.173 g cm^{-3}, R = 0.086 [for data with $I > 2\sigma(I)$], wR_2 = 0.269 for 5958 reflections (Θ_{max} = 25.14°). The asymmetric unit contains an THF molecule disordered over two sites (site occupation factors = 0.5). The structure was resolved with SHELXS and refined with SHELXL.

Crystal data for $C_{26}H_{32}N_2O_6{\cdot}0.5\ C_2H_5OH$ (**4**): Siemens P4 diffractometer, Mo-Kα radiation, M = 983.14, 0.68 × 0.36 × 0.10 mm, monoclinic, space group $P2_1$, a = 11.480(8), b = 10.186(4), c = 25.274(9) Å, β = 100.18(5)°, U = 2909 Å^3, F(000) = 1052, Z = 4, D_c = 1.122 g cm^{-3}, R = 0.083 [for data with $I > 2\sigma(I)$], wR_2 = 0.272 for 4012 unique reflections (Θ_{max} = 25.51°).The asymmetric unit contains an EtOH molecule disordered over two sites (site occupation factors = 0.5). The structure was resolved with SHELXS and refined with SHELXL. CCDC 182/748.

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