A water wire in L-prolyl-L-serine hydrate

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List of supplementary material

References

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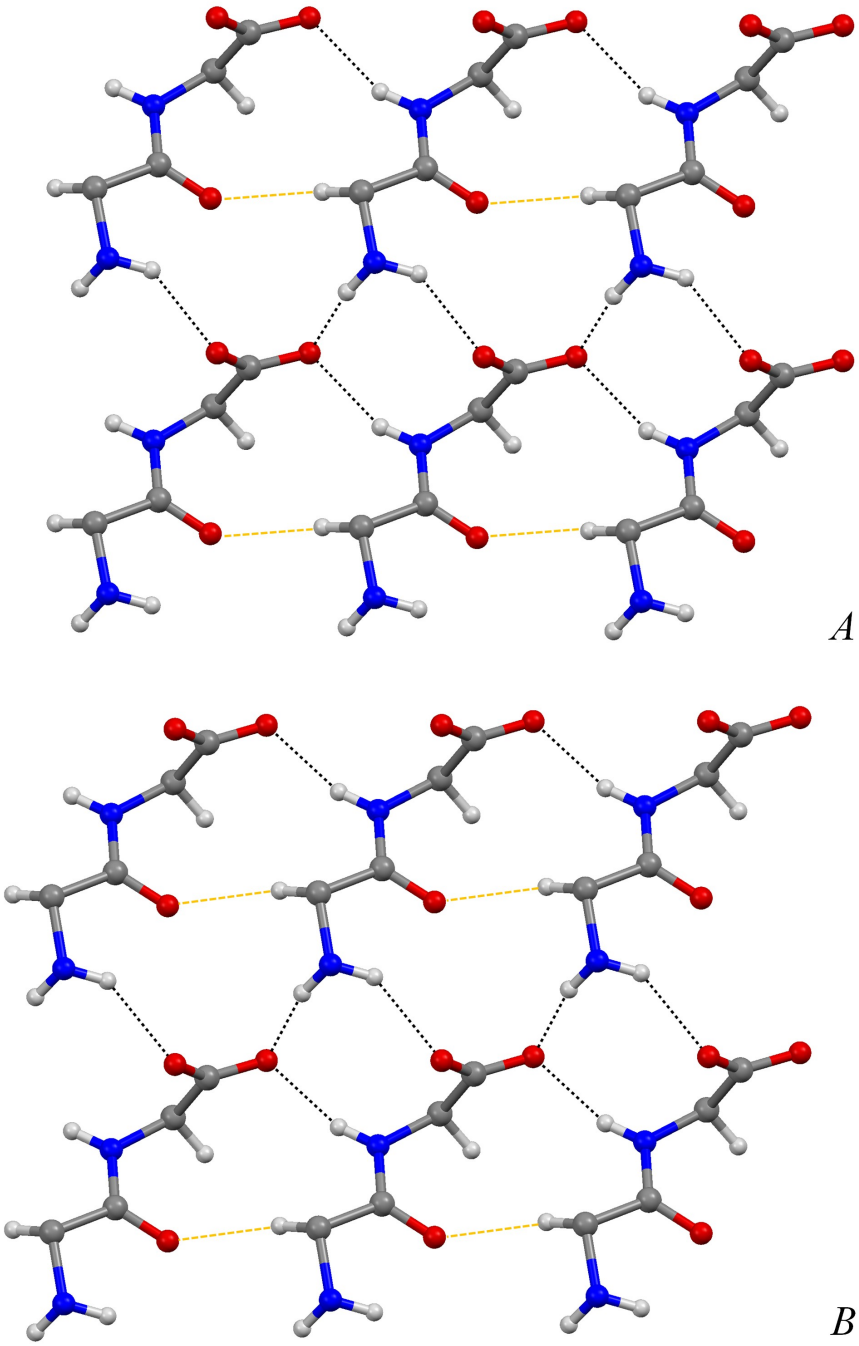


Figure 1S

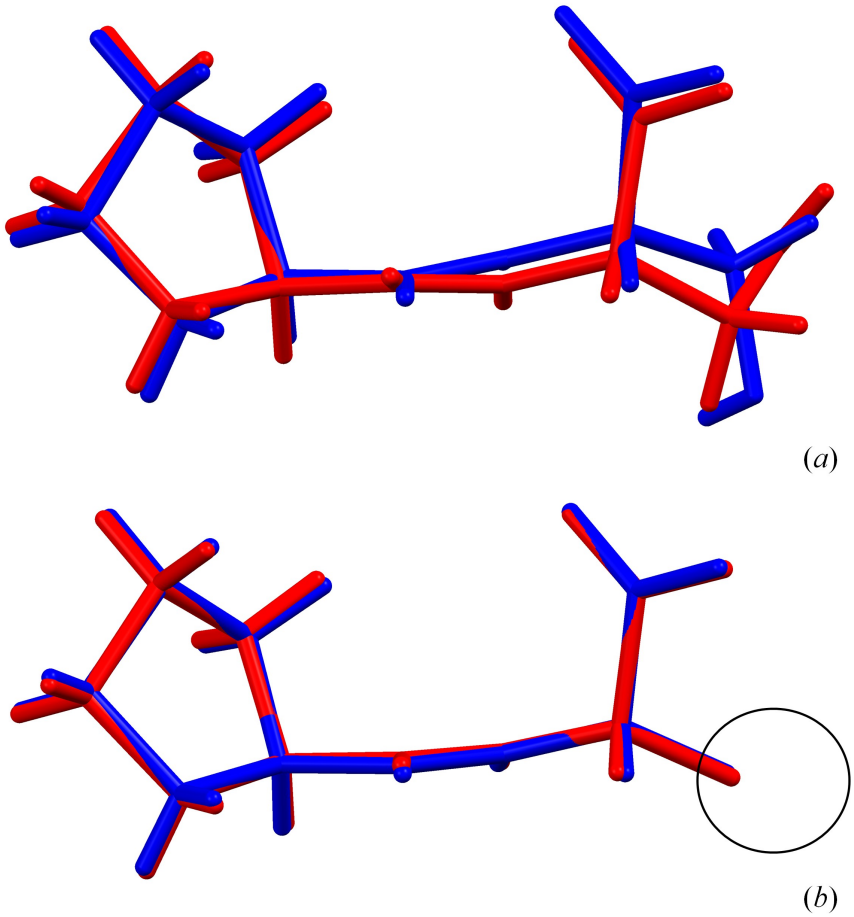


Figure 2S

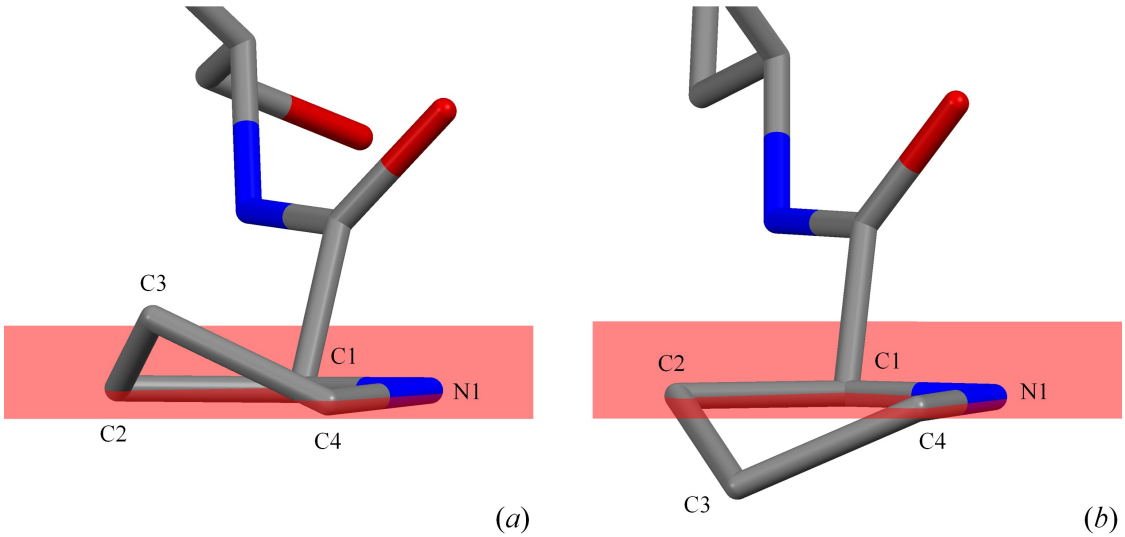
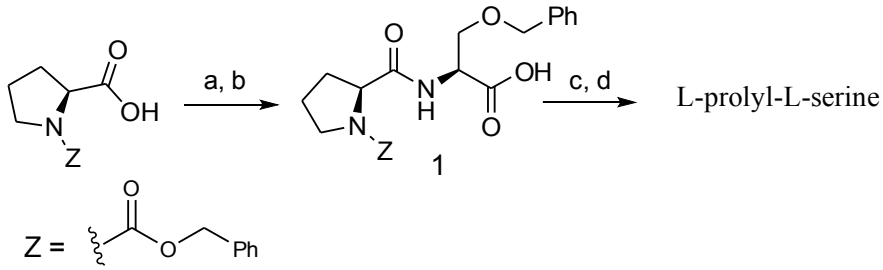


Figure 3S

Synthetic procedures

L-Prolyl-L-serine (I) was prepared by a short simplified and robust solution phase reaction process, as shown in Scheme 1.



a) N-hydroxysuccinimide, DCC, CH_2Cl_2, 2h, RT. **b**) L-BnO-Ser, $NaHCO_3$, Water, Acetone, 2h RT. **c**) THF, HCl, Pd/C, H_2, RT, 48h. **d**) 2N aq. NaOH, pH = 7-8

Scheme 1: Synthesis of (I)

1) Synthesis of (*S*)-3-(benzyloxy)-2-((*S*)-1-(benzyloxycarbonyl)pyrrolidine-2-carboxamido) propanoic acid (1)

(*S*)-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid (1.000 g, 4 mmol), *N*-hydroxysuccinimide (0.465 g, 4 mmol) and DCC (0.828 g, 4 mmol) were mixed in a clean, oven-dried round bottom flask (RBF). Dry dichloromethane (DCM) (50 mL) was charged in the above reactant mixture under dry nitrogen flow. The reaction mixture was stirred for 2h at room temperature. Subsequent filtration was carried out through a celite pad to remove the residual byproduct (dicyclohexyl urea). The DCM filtrate was evaporated under reduced pressure at 30 °C to obtain the residue of the succinate ester of Z-proline (1 g). Without further purification the succinate ester of *Z*-proline (0.70 g) was dissolved in acetone (10 mL) at room temperature. In another RBF (*S*)-2-amino-3-(benzyloxy)propanoic acid was added to 10 mL of water containing $NaHCO_3$ (0.338 g, 4 mmol) at room temperature. To this the solution of succinate ester of *Z*-proline was slowly added with continued stirring for 2 h. Acetone was evaporated from the reaction mixture under vacuum and residual water extracted by 20 mL of ethyl acetate to remove unwanted nonpolar impurities. The water residue was then diluted with 20 mL of fresh water, the solution cooled to between 5 - 0 °C and then acidified by 1M HCl till pH = 2-3. The aqueous solution was extracted by ethyl acetate (30 mLx 3) and the combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and filtered through whatman filter paper and evaporated under vacuum to obtain **1** (0.740 g).

MS ES^+ [M-H] 425, NMR data DMSO-d_6, DPX 300MHz, ^{1}H-NMR δ 12.78 (bs, 1 H, O*H*), 8.30-8.22 (m, 1 H, N*H*), 7.38-7.26 (m, 10 H, Ar-*H*), 5.12-4.94 (m, 2 H), 4.52-4.35 (m, 4 H),

3.81-3.32 (m, 4 H), 2.22-2.02 (m, 1H), 1.90-1.76 (m, 3H); ^{13}C-NMR δ 172.33 (2 *C*O), 154.64 (Z-*C*O), 138.82 (Ar*C*), 137.83 (Ar*C*), 129.04 (Ar*C*H), 128.31 (Ar*C*H), 127.79 (Ar*C*H), 73.06 (*C*H$_2$), 70.37 (*C*H$_2$), 66.67 (*C*H$_2$), 66.55 (*C*H), 59.80 (*C*H), 47.99 (*C*H$_2$), 31.95 (*C*H$_2$), 23.81 (*C*H$_2$).

2) Synthesis of (*S*)-3-hydroxy-2-((*S*)-pyrrolidine-2-carboxamido)propanoic acid (I)

1 (0.40 g) was dissolved in 20 mL of dry THF and the solution cooled to 5 - 0 °C. 10 % wet Pd/C (0.2 g) was charged in the solution followed by the addition of 0.5 mL of 4 M HCl solution in dioxane. The reaction mixture was stirred for 48 hrs at room temperature. Completion of the reaction was monitored by TLC (1:4, MeOH:DCM eluent system and ninhydrin spraying reagent for staining). The solvent THF was removed by decantation and sticky Pd/C cum product washed with extra THF (5 mL). The residual Pd/C was slurred in fresh water (5 mL) to dissolve the water soluble product. This slurry was filtered through the celite bed prepared in water. Evaporation of water filtrate was carried out under very high vacuum to obtain the syrupy product (I) (0.2 g). A small amount of syrupy residue was again dissolved in fresh water and neutralized with 1N NaOH solution till pH = 7-8. The neutralized solution was then used further for single crystal preparation.

NMR data : DPX 200MHz, ^{1}H-NMR DMSO-d_6, δ 10.33-10.15(m, 1H), 8.99-8.95 (d, 1H, J = 8 Hz), 8.49-8.475 (m, 1H), 4.31-4.20 (m, 2H), 3.73-3.57 (m, 2H), 3.17 (s, 2H), 2.39-2.20 (m, 1H), 1.95-1.70 (m, 3H); ^{13}C-NMR, δ 171.21 (*C*O), 168.33 (*C*OO), 60.94 (*C*H), 58.53 (*C*H$_2$), 55.17 (*C*H), 45.64 (*C*H$_2$), 29.72 (*C*H$_2$), 23.53 (*C*H$_2$).