

Hydrogen Bond Architecture in Crystal Structures of *N*-Alkylated Hydrophobic Amino Acids

Carl Henrik Görbitz*, Alexander Bakos Leirvåg and Øyvind Jacobsen

Department of Chemistry, University of Oslo, P. O. Box 1033 Blindern, 0315 Oslo, Norway

E-mail: c.h.gorbitz@kjemi.uio.no

SUPPLEMENTARY MATERIAL

Figure 1S. To be compared with Figure 5.	page 2
Figure 2S. To be compared with Figure 8.	page 2
Synthesis	page 3
References	page 4

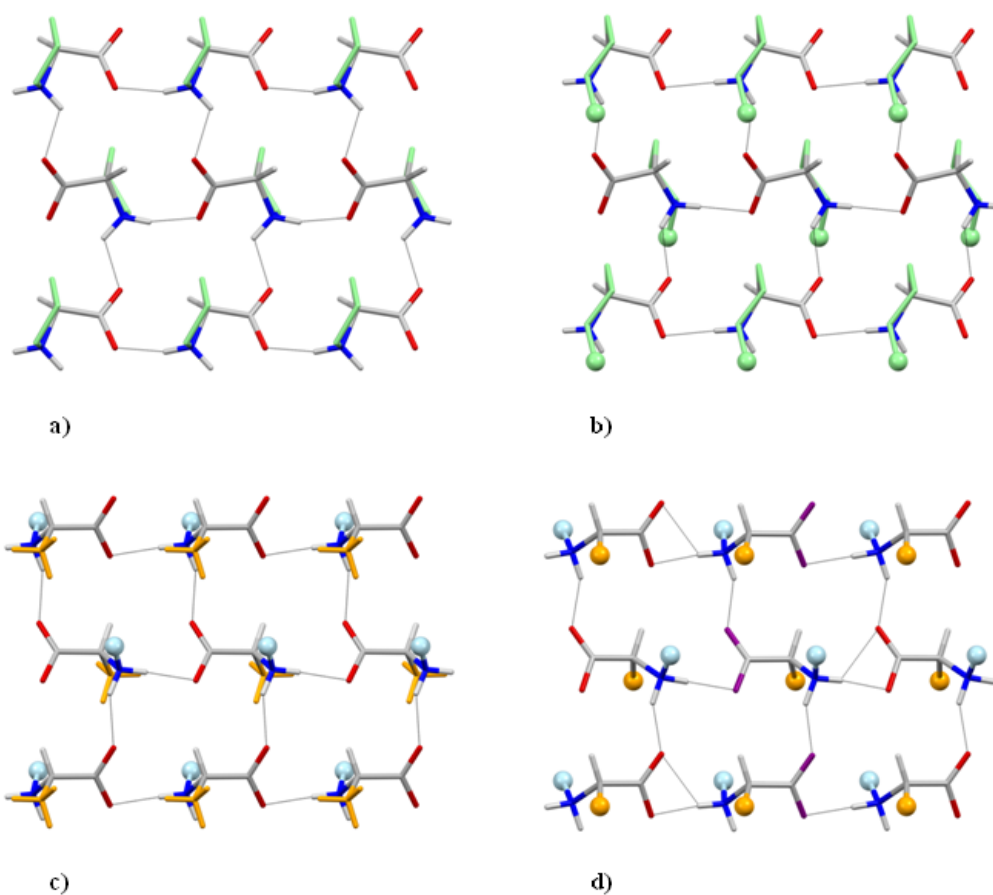


Figure 1S. Hydrogen-bonded sheets in (a) L-proline (CSD refcode PROLIN)¹, (b) (5R)-*cis*-5-(3-Methylbutyl)pyrrolidinium-2-carboxylate (GULCUM)², (c) *N*-(2-pyrimidylmethyl)-L-alanine (QURSIG)³ and *N*^α,*N*^ε,*N*^ζ-tri(cyanoethyl)-L-lysine (VEQZIB).⁴ Large hydrophobic groups are shown as small spheres.

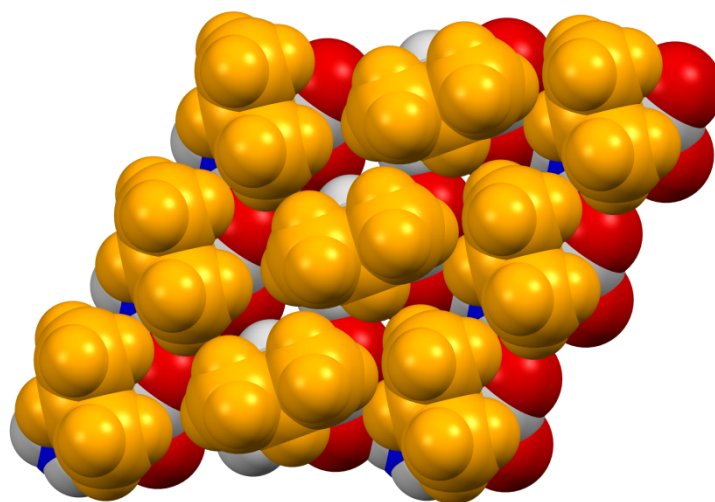


Figure 2S. Hydrophobic surface in the structure of L-Val.⁵

Synthesis

All *N*-alkylated amino acids were synthesized using the general method reported by Bastide and co-workers and Ohfuné and co-workers, *i.e.* by reductive amination of acetone or benzaldehyde (in the case of NBnV) with the corresponding proteinogenic amino acids.⁶⁻¹⁰ Sodium cyanoborohydride (NaBH₃CN) was used as reducing agent and MeOH as solvent.

***N*-Isopropyl-L-valine, NiPrV.** L-valine (2.586 g, 100.0% purity, 22.07 mmol, 1.000 eq.) was suspended in MeOH (28 mL) and sodium cyanoborohydride (0.831 g, 99.3% purity, 0.825 g NaBH₃CN, 13.1 mmol, 0.595 eq.) added at room temperature. Remains of sodium cyanoborohydride were dissolved in MeOH (5 mL) and the solution added to the suspension of L-valine. Next, acetone (1.412 g, 99.9% purity, 1.411 g CH₃COCH₃, 24.29 mmol, 1.100 eq.) was added over 1 min at room temperature. The reaction bottle was then equipped with a rubber septum and an empty balloon and the reaction mixture stirred for 19 h 30 min at room temperature. The reaction mixture was subsequently filtered under suction. The filtrate was used twice to wash out remaining solid material in the reaction bottle. The collected solid was washed with MeOH (4 × 7 mL), dried under suction for 20 min, transferred to a round bottomed flask and dried under reduced pressure on a rotary evaporator for another 45 min (bath temperature: 60°C, $p_{\min} \leq 4$ mmHg), affording the title compound as a white powder (1.201 g, 34%).

***N*-Isopropyl-D-valine.** The title compound was prepared completely analogously to NiPrV, with which it was mixed for crystallization of the racemate NiPrVR.

***N*-Isopropyl-L-phenylalanine, NiPrF.** L-phenylalanine (3.000 g, 100.0% purity, 18.16 mmol, 1.000 eq.) was suspended in MeOH (10 mL) and sodium cyanoborohydride (0.684 g, 99.3% purity, 0.679 g NaBH₃CN, 10.81 mmol, 0.595 eq.) added at room temperature. Remains of sodium cyanoborohydride were dissolved in MeOH (5 mL) and the solution added to the suspension of L-phenylalanine, followed by the addition of more MeOH (12 mL). Next, acetone (1.162 g, 99.9% purity, 1.161 g CH₃COCH₃, 19.99 mmol, 1.101 eq.) was added over 1 min at room temperature. The reaction bottle was then equipped with a septum and an empty balloon and the reaction mixture stirred for 24 h at room temperature. Because the reaction mixture formed a thick mass the bottle was manually swirled several times. The reaction mixture was subsequently filtered under suction. The filtrate was used twice to wash out remaining solid material in the reaction bottle. The collected solid was then washed with MeOH (4 × 5 mL), dried under suction for 20 min, transferred to a round bottomed flask and dried under reduced pressure on a rotary evaporator for another 45 min (bath temperature: 60°C, $p_{\min} \leq 6$ mmHg), affording the title compound as a white powder (3.349 g, 89%).

***N*-Isopropyl-L-leucine, NiPrL.** L-leucine (2.383 g, 99.8% purity, 2.378 g L-leucine, 18.13 mmol, 1.000 eq) was suspended in MeOH (10 mL) and sodium cyanoborohydride (0.685 g, 99.3% purity, 0.680 g NaBH₃CN, 10.8 mmol, 0.597 eq.) added at room temperature. Remains of sodium cyanoborohydride were dissolved in MeOH (5 mL) and the solution added to the suspension of L-leucine, followed by the addition of more MeOH (12 mL). Next, acetone (1.160 g, 99.9% purity, 1.159 g CH₃COCH₃, 19.95 mmol, 1.100 eq.) was added over 2 min at

room temperature. The reaction bottle was then equipped with a septum and an empty balloon and the reaction mixture stirred for 23 h 30 min at room temperature. Because the reaction mixture formed a thick mass the bottle was manually swirled several times. The reaction mixture was subsequently filtered under suction. The filtrate was used four times to wash out remaining solid material in the reaction bottle. The collected solid was dried under suction for 45 min, transferred to a round bottomed flask and dried under reduced pressure on a rotary evaporator for another 4 h 30 min (bath temperature: 60°C, $p_{\min} \leq 3$ mmHg), affording the title compound as a white powder (2.676 g, 85%)

N-Benzyl-L-valine, NBnV. L-Valine (2.344 g, 100.0% purity, 20.01 mmol, 1.000 eq.) was suspended in MeOH (20 mL) and sodium cyanoborohydride (0.887 g, 99.3% purity, 0.881 g NaBH₃CN, 14.0 mmol, 0.701 eq.) added at room temperature. Remains of sodium cyanoborohydride were dissolved in MeOH (5 mL) and the solution added to the suspension of L-valine. Next, benzaldehyde (2.352 g, 99.4% purity, 2.338 g C₆H₅CHO, 22.03 mmol, 1.101 eq.) was added over a period of 2 min at room temperature. Remains of benzaldehyde were dissolved in MeOH (5 mL). Starting 5 min after the bulk of benzaldehyde had been added, the solution was then added to the reaction mixture over 1 min. The reaction bottle was then equipped with a rubber septum and an empty balloon and the reaction mixture stirred for 22 h 45 min at room temperature. Because the reaction mixture formed a thick mass the bottle was manually swirled several times. The reaction mixture was subsequently filtered under suction. The filtrate was used three times to wash out remaining solid material in the reaction bottle. The collected solid was then dried under suction for 60 min, transferred to a round bottomed flask and dried under reduced pressure on a rotary evaporator for another 45 min (bath temperature: 60°C, $p_{\min} \leq 3$ mmHg), affording the title compound as a white powder (2.826 g, 68%).

References and Notes

- (1) Kayushina, R. L.; Vainshtein, B. K. *Kristallografiya* **1965**, *10*, 833.
- (2) Cini, E.; Giorgi, G.; Rodriquez, M.; Taddei, M. *Synlett* **2009**, 1562.
- (3) Li, X.; Liu, T.; Hu, B.; Li, G.; Zhang, H.; Cao, R. *Cryst. Growth Des.* **2010**, *10*, 3051.
- (4) Janiszewska, J.; Urbańczyk-Lipkowska, Z. *J. Mol. Struct.* **2006**, *789*, 112.
- (5) Dalhus, B.; Görbitz, C. H. *Acta Chem. Scand.* **1996**, *50*, 544.
- (6) Bastide, J.; Coste, C.; Marty, J. L. *C. R. Acad. Sci., Ser. IIc: Chim.* **1978**, *287*, 471.
- (7) Ohfuné, Y.; Kurokawa, N.; Higuchi, N.; Saito, M.; Hashimoto, M.; Tanaka, T. *Chem. Lett.* **1984**, 441.
- (8) Ohfuné, Y.; Higuchi, N.; Saito, M.; Hashimoto, M.; Tanaka, T. *Pept. Chem.* **1984**, Volume Date 1983, *21*, 89.
- (9) Jensen and co-workers appear to have been the first to synthesize *N*-alkylated amino acids (the natural product nopaline and its diastereomer isonopaline), by reductive amination of a ketone (α -ketoglutaric acid) with a proteinogenic amino acid (arginine) using NaBH₃CN as reducing agent, but did not explore the scope of the method for the synthesis of other *N*-alkylated amino acids. See Jensen, R. E.; Zdybak, W. T.; Yasuda, K.; Chilton, W. S. *Biochem. Biophys. Res. Commun.* **1977**, *75*, 1066.
- (10) Note that the precise reaction conditions employed in this study in some cases differ slightly from those reported earlier.