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The effect of pressure on the porous peptide L-alanyl-L-valine**†

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Supporting information:
CCDC 761398 and 761399 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif. See http://dx.doi.org/10.1039/C000942C
Abstract

The first ever study on the effects of pressure on a porous dipeptide are presented to 0.2 GPa. On increasing pressure, closing up of the large porous holes, shortening of hydrogen bonds, and a pressure induced ordering of the thermal parameters on the L-valine residue can be observed.

Introduction

The synthesis of peptide based porous structures has become a subject of increasing interest due to their possible applications in gas storage and selective absorption properties. These very stable organic framework materials contain large porous channels (3-10 Å) capable of freely taking up and loosing solvent without loss of crystallinity.1, 2 Furthermore, gas molecules can be trapped and released in a parallel manner, offering a sponge-like alternative to ‘chemically bound’ hydrogen storage materials (e.g. borohydrides).3, 4 The selectivity of these materials sorption properties is related directly to the size of their pores. Traditionally, pore size modification is achieved via chemical manipulation, with a variety of peptides readily available with pore sizes that can be adjusted by modifying the amino acid residues used. Recently, in a study on a porous metal organic framework (MOF) material, it was shown that a similar effect can also be achieved by applying external hydrostatic pressure,5 while similar high-pressure studies on zeolites often results in pore content modification. Here we present the first ever reported high-pressure study on a porous dipeptide, L-alanyl-L-valine (AV) to 0.2 GPa.

Solvent free crystals of AV crystallise in the hexagonal space group P61 (a = 14.462(2) Å, c = 10.027 (1) Vol. = 1816.2(4) Å³).6 The dipeptide assembles through H-bonds to form spiral hexagonal channels that extend along the c-axis. These channels have been previously reported by Moudrakovski et al., 20047 to encapsulate Xe gas, and have been noted for their exceptional stability, retaining their porous framework even after guest solvent is removed.8 This is quite different behaviour to many other porous materials which often transform into a denser phase after the guest is removed.8 AV has also been investigated crystallographically with acetonitrile, methanol and a mixture of 2-propoanol and water in the pores, though sorption of larger guests induces a doubling of the unit cell dimensions (P61, a = 28.7247(16) Å, c = 9.009(8) Å, Vol. = 7074.83 Å³)6 All of the above phases of AV have been shown to be accessible via an initial acetonitrile solvate phase.

Prior to our high-pressure experiment, an ambient pressure and temperature data set was collected on a crystal of AV (0.1 x 0.2 x 0.2 mm) in order to provide data for comparison with the high pressure study which was also performed at ambient temperature. The same crystal was then loaded into a modified Merrill-Bassett diamond anvil cell (DAC) equipped with 600μm culet diamonds and a
tungsten gasket. The sample and a chip of ruby (as a pressure calibrant) were loaded into the DAC with a 4:1 (v/v) mixture of methanol and ethanol as a hydrostatic medium. The ruby fluorescence method was utilised to measure the pressure. High pressure diffraction data were then collected at 0.2 GPa. On increasing pressure further to 0.5 GPa the sample became polycrystalline. Extracting thermal parameters from high-pressure data can often be troublesome due to the low completeness of the data caused by shading of the high-pressure cell. With data being seriously reduced in one direction refinement of thermal parameters is difficult at best. Here, high-pressure data were collected using short wavelength (λ = 0.4872 Å) synchrotron radiation at the SRS on Station 9.8. Compressing the diffraction pattern in this way resulted in a completeness of 84.6% to 0.8 Å resolution allowing us to refine thermal parameters freely. The pore volume was calculated using the SQUEEZE algorithm within PLATON. Void analysis was carried out using the program MERCURY with a probe radius and grid spacing of 1.2 and 1.0 Å respectively.

Under ambient conditions, AV has been previously reported to display positional disorder for the L-Val side chain methyl groups. In this study we have not modelled any positional disorder in our ambient pressure structure, though the principal axes of the thermal ellipsoids of the two methyl carbon atoms, C6 and C7, have values which could indicate that this is also present here (maximum values of 0.1969 and 0.2911 respectively). On increasing pressure to 0.2 GPa, these reduce to 0.1287 and 0.0885 for C6 and C7 respectively, effectively ordering on increasing pressure (Fig. 1). Reduction of thermal parameters on increasing pressure is not unexpected and is analogous to the reduction in thermal motion on decreasing temperature, though the driving force here is to smaller volume.

![Fig. 1. Thermal ellipsoid plots of L-alanyl-L-valine at (a) ambient pressure and (b) 0.2 GPa as viewed along the c-axis. Thermal ellipsoids are drawn at the 50% probability level. Colour scheme is red: oxygen, blue: nitrogen, grey: carbon and dark grey: hydrogen. Note the ordering of the methyl groups on the L-valine residue at the centre of the pore as well as the main chain carboxylate groups.](image-url)
A second, very obvious effect of increasing pressure is the closure of the channels within the structure, which occurs via a cork-screw like motion (Fig. 2). Reduction in the size of the void can be quantified by comparing the calculated void volume using the SQUEEZE algorithm in PLATON,\textsuperscript{11} which reduces from 326 to 265 Å\textsuperscript{3} per unit cell on increasing pressure from ambient to 0.2 GPa. Mapping the void space within porous materials is now possible within the program MERCURY.\textsuperscript{12} By comparing the void space in AV at ambient pressure and 0.2 GPa, the closure of this void and its change in shape on increasing pressure can be clearly seen (Fig. 3). The compression of AV occurs mostly through this reduction in void volume (reducing by 61 Å\textsuperscript{3}) with shortening of the unit cell parameters mainly within the $ab$-face rather than the $c$-axis (3.07 and 0.90% reduction for $a$-axis and $c$-axis respectively). The reduction in unit cell volume is 6.9% (ca. 125 Å\textsuperscript{3}), which is quite an extraordinary compression. In high-pressure studies of amino acids, values of this magnitude are not observed until much higher pressures, including L-serine (7.3% to 2.9 GPa),\textsuperscript{13} L-cystine (6.8% to 2.3 GPa)\textsuperscript{14} and L-cysteine (11% to 1.8 GPa).\textsuperscript{15} Due to the magnitude of the compression observed for AV, it is unsurprising that the sample became polycrystalline between 0.2 and 0.5 GPa.

**Fig. 2.** Space-filling plots of L-alanyl-L-valine at (a) ambient pressure and (b) 0.2 GPa as viewed along the c-axis. Colour scheme as in Figure 1. Note the closure of the central void on increasing pressure.

**←Fig. 3.** Void analysis as carried out in the program MERCURY\textsuperscript{12} of the central void in L-alanyl-L-valine at (a) ambient pressure and (b) 0.2 GPa. Van der Waals radii for (c) Carbon and (d) Hydrogen are included for comparison at the same scale. Note the decrease in size and shape of the central pore channel on increasing pressure.
In previous high-pressure experiments on amino acids, closure of small voids in the structure were observed, while H-bonding contacts were driven to their lower limits as observed under ambient pressure conditions before the structures underwent a phase transition.\(^{16}\) In the structure of AV there are four main hydrogen bonding interactions, two of these interact across 2\(_1\)-screw axes (N1H14...O2 and N2H24...O3), while the other two (N1H12...O3 and N1H13...O1) interact along 3\(_1\)-axes (Table 1). On increasing pressure to 0.2 GPa, only N1H12...O3 and N1H13...O1 distributed about the 3\(_1\)-axis actually contract, while N1H14...O2 and N2H24...O3 actually increase in length on increasing pressure, though the changes observed here are not statistically significant. This is counterintuitive, especially considering it is the shortest interactions observed under ambient pressure conditions that contract. Both N1H14...O2 and N2H24...O3 interact across the \(ab\)-face. Compression here is driven by the closure of the voids which takes place via the cork-screw action mentioned previously, a motion that actually increases the length of these H bonds. Compression along the \(c\)-axis, however, directly affects and shortens the N1H12...O3 and N1H13...O1 interactions.

<table>
<thead>
<tr>
<th>Pressure</th>
<th>ambient</th>
<th>0.2 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1H12..O3†</td>
<td>1.90</td>
<td>1.86</td>
</tr>
<tr>
<td>H12..O3</td>
<td>2.700(7)</td>
<td>2.663(8)</td>
</tr>
<tr>
<td>N1..O3</td>
<td>149</td>
<td>149</td>
</tr>
<tr>
<td>&lt;N1H12O3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1H13..O1⊥</td>
<td>1.92</td>
<td>1.85</td>
</tr>
<tr>
<td>H13..O1</td>
<td>2.710(6)</td>
<td>2.651(9)</td>
</tr>
<tr>
<td>N1..O1</td>
<td>147</td>
<td>148</td>
</tr>
<tr>
<td>&lt;N1H5O1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1H14..O2⊥</td>
<td>1.86</td>
<td>1.90</td>
</tr>
<tr>
<td>H14..O2</td>
<td>2.717(8)</td>
<td>2.729(8)</td>
</tr>
<tr>
<td>N1..O2</td>
<td>161</td>
<td>154</td>
</tr>
<tr>
<td>&lt;N1H14O2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2H24..O3⊥</td>
<td>2.09</td>
<td>2.12</td>
</tr>
<tr>
<td>H24..O3</td>
<td>2.935(6)</td>
<td>2.950(7)</td>
</tr>
<tr>
<td>N2..O3</td>
<td>166</td>
<td>161</td>
</tr>
<tr>
<td>&lt;N2H24O3</td>
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</table>

Table 1. Table of H-bonding parameters for L-alanyl-L-valine at ambient pressure and 0.2 GPa. Distances are in Å, angles in °. Symmetry operators are (i) 1-x+y,1-x,2/3+z, (ii) 1-y,x-y,1/3+z, (iii) x-y,x,1/6+z and (iv) 1-x,-y,1/2+z. (i) and (i) interact along the 3\(_1\)-axes, while (iii) and (iv) interact across the 2\(_1\)-axes (see text).

In summary, we have presented the first detailed example showing what happens to the structure of a porous dipeptide on increasing pressure. At 0.2 GPa, AV shows a large reduction in the thermal...
motion of the valine side chain, causing a central large conical void to close-up. The closure of this void is mediated through a cork-screw like action of the molecules which actually cause the lengths of H-bonds interacting across the $ab$-face of the cell to increase on increasing pressure. The reduction in cell volume from ambient to 0.2 GPa pressure (modest for these types of experiments) is highly significant and comparable to the compression observed previously in other amino acid structures at pressures one magnitude higher. Considering the sorption properties of these materials are currently studied at $ca.$ 0.01 GPa pressures, large changes in pore size and volume must take place within the regime used to study their gas sorption behaviour, making the measurements here very topical in understanding porous peptide sorption behaviour. Modification of the pore volume, size, shape and therefore selectivity has therefore been achieved on application of pressure; Fig. 3 clearly demonstrates the change in available pore space for capture of gas molecules. In previous experiments, the hydrostatic media that are used to apply pressure evenly to the sample have been observed to enter the pores of MOFs. This has not been observed here, though unusual sorption behaviour has been observed in AV under ambient pressure conditions when exposed to larger solvent guest molecules.
Endnotes and references

AV was purchased from Sigma and used as received. Crystals were prepared by vapour diffusion of acetonitrile into a concentrated aqueous solution. Solvent free crystals were obtained by allowing the crystals to dry naturally for ca. 30 days. X-ray diffraction data of the ambient pressure and temperature crystal structure were collected with Mo-Kα radiation (λ = 0.71073 Å) at room temperature and pressure on a Bruker Smart Apex diffractometer. Refinement was carried out against |F|2 in CRYSTALS17 starting from the ambient temperature coordinates of Moudrakovski et al., 2004.18 Hydrogen atoms attached to carbon and nitrogen were placed geometrically. Crystal data for ambient pressure: C8H16N2O3, M = 188.23, hexagonal, a = 14.4270(17) Å, c = 10.0102(15) Å, V = 1804.4(4) Å3, T = 293 K, space group P61, Z = 6, 55579 reflections measured, 1945 independent reflections (Rint = 0.110). The final R1 values were 0.0648 (I > 2σ(I)). The final wR(F2) values were 0.1665 (I > 2σ(I)). The final R1 values were 0.1111 (all data). The final wR(F2) values were 0.2188 (all data). High pressure diffraction data were collected on the same sample on a Bruker APEX II diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). High pressure diffraction data were collected with synchrotron radiation on the same sample (0.1 × 0.2 × 0.2 mm3) on a Bruker APEX II diffractometer at the SRS on Station 9.8 (λ = 0.4872 Å). Data collection and processing procedures followed ref.19 The data were integrated using the program SAINT20 using 'dynamic masks' to avoid integration of regions of the detector shaded by the body of the pressure cell.19 Absorption corrections for the DAC and sample were carried out with the programs SHADE21 and SADABS22 respectively. The high pressure refinement of AV at 0.2 GPa was carried out against |F|2 using all data CRYSTALS.17 All 1,2 and 1,3 distances were restrained to the values observed from our ambient pressure structure. Torsion angles were refined freely. Hydrogen atoms attached to carbon and nitrogen were placed geometrically. Crystal data for 0.2 GPa: C8H16N2O3, M = 188.23, hexagonal, a = 13.9836(19) Å, c = 9.9229(15) Å, V = 1680.4(4) Å3, T = 293 K, space group P61, Z = 6, 13027 reflections measured, 987 independent reflections (Rint = 0.1607). The final R1 values were 0.0615 (I > 2σ(I)). The final wR(F2) values were 0.1376 (I > 2σ(I)). The final R1 values were 0.1276 (all data). The final wR(F2) values were 0.1712 (all data).


