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Solvent Site Preferences in the Crystal Structures of L-Leucyl-L-leucine Alcohol (1:1) Complexes

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The dipeptide L-Leu-L-Leu forms isomorphous 1:1 solvates with ethanol, 1-propanol and 2-propanol, space group $P2_1$ with $Z=4$. The two peptide molecules in the asymmetric unit have different hydrogen bonding interactions as well as side chain and main chain conformations. This leaves two solvent pockets with slightly different environments. When mixtures of ethanol and either of the two propanols are used as precipitating agents, the propanol is selectively incorporated at both solvent sites. When a mixture of 1-propanol and 2-propanol is used, however, one site shows a preference for 1-propanol, while the other site shows a similar preference for 2-propanol. The structures of the L-Leu-L-Leu 1-propanol 2-propanol solvate is a rare example of a mixed solvate. The potential for using mixed solvents in crystallization experiments is discussed.

In the Cambridge Structural Database[1] more than 10% of the crystal structures include cocrystallized organic solvent molecules. The propensity to include solvent is correlated with the size of the solute molecule, and the percentage of solvates is steadily increasing.[2] Usually the solvent molecule attracts little attention, or is even regarded as a nuisance which may cause crystals to be unstable, introduce disorder into an otherwise ordered structure, or render mass spectroscopy investigations more complicated. For many compounds, however, it should be kept in mind that the presence of solvent molecules is of vital importance for a successful crystallization outcome. Structures with large empty channels or cavities are generally not stable,[3] and for certain compounds crystals may not be obtained if the intrinsically unstable scaffolding of solute molecules is not supported by carefully selected solvent molecules.

Depending on their size (and chemical environment) channels and cavities in crystals are occupied by water molecules or other solvent molecules, but there seems to be a complete lack of research dealing with the structural flexibility of such solvent pockets in small molecule structures. It is thus not known if, e.g., cocrystallized ethanol molecules can usually be replaced by methanol or propanol molecules without major modifications to the rest of the structure. Such knowledge would be very useful for concerted crystallization experiments aimed at scanning effectively a large number of solvent inclusion options. A number of factors need to be considered, such as the size, shape, hydrogen bonding capacity and hydrophobicity of both the solvent and the solute molecule.

Dipeptides with two hydrophobic residues can occasionally be crystallized without solvent (or as hydrates) in hexagonal space groups,[4–6] but more often form monoclinic or orthorhombic crystals which are divided into hydrophilic and hydrophobic layers.[7–11] The latter group in general requires cocrystallization of a suitable organic solvent molecule, that is a molecule which can accept one of the three amino N–H atoms and play a crucial role in the hydrogen bond network. Furthermore, the solvent molecules have a function as space fillers in the hydrophobic layers, and thus form bridges between polar and non-polar regions in the crystal.

Together with L-Leu-L-Val,[7] L-Leu-L-Leu is unique in forming reasonably large crystals from certain solvents, as distinct from the frequently encountered thin needles and the less common thin flakes observed for hydrophobic dipeptides in general. While the alcohol solvates of L-Leu-L-Val grow crystals in different space groups, a series of isomorphous alcohol solvates exists for L-Leu-L-Leu, and this property has been used to carry out a systematic investigation of solvent inclusion. The potential benefits and problems associated with the use of solvent mixtures rather than pure solvents in crystallization experiments are discussed at the end of this paper.

Experimental

Preparation. L-Leu-L-Leu was obtained from Sigma. In initial experiments crystals were prepared by placing 30 μl of an 11 mg ml^{-1} aqueous solution in small test tubes, with subsequent equilibration by gas phase diffusion of methanol, ethanol, 1-propanol, 2-propanol,

1-butanol, 2-butanol, 2-methyl-1-propanol (isobutanol) or 2-methyl-2-propanol (*tert*-butanol). When methanol and the four butanols were used only extremely thin needles unsuitable for diffraction experiments were formed, with the exception of one isobutanol batch which also yielded a few plate-shaped crystals. The structure of the latter solvate is completely different from those of the simpler alcohols, and will be discussed elsewhere.[9] Further experiments employed mixtures of two or three alcohols with varied compositions as precipitating agents.

Data collection. Crystallographic data were collected on a Siemens SMART CCD diffractometer. The data collections with SMART[12] nominally covered over a hemisphere of reciprocal space, by a combination of four or five sets of exposures; two with the detector set at $2\theta = 29°$ and either two with $2\theta = 49°$ or three with $2\theta = 55°$. Each set had a different φ angle for the crystal and each exposure covered 0.3–0.6° in ω with exposure times between 30 and 45 s. The crystal-to-detector distance was 5.0 cm. Data reduction was carried out with SAINT[13] and absorption correction with SADABS.[14] Experimental conditions are summarized in Table 1.

Structure determination and refinement. The isomorphous structures of the ethanol solvate (LLE), the 1-propanol solvate (LL1P), the 2-propanol solvate (LL2P) and the mixed 1-propanol 2-propanol solvate (LL1P2P) were solved routinely with SHELXS[15] in the space group $P2_1$. There are two peptide molecules, **A** and **B**, in the asymmetric unit, while two solvent molecules reside in solvent pockets **C** and **D**. The structures were refined with SHELXTL.[16] H-atoms bonded to O or N were refined isotropically, other H-atoms were placed geometrically and refined with a riding model (including free

Table 1. Experimental details.

	LLE	LL1P	LL2P	LL1P2P
Formula	$C_{12}H_{24}N_2O_3 \cdot C_2H_6O$	$C_{12}H_{24}N_2O_3 \cdot C_3H_8O$	$C_{12}H_{24}N_2O_3 \cdot C_3H_8O$	$C_{12}H_{24}N_2O_3 \cdot C_3H_8O$
Formula weight/g mol^{-1}	290.40	304.43	304.43	304.43
Cell setting	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
a/Å	8.6634(2)	8.6404(2)	8.7343(2)	8.6799(1)
b/Å	24.0971(6)	24.6286(5)	23.9980(5)	24.2657(1)
c/Å	9.3265(2)	9.3670(2)	9.4480(2)	9.3949(1)
β/°	115.3793(4)	115.1749(9)	115.2674(3)	115.1488(5)
V/Å^3	1759.12(7)	1803.97(7)	1790.89(7)	1791.21(3)
Z	4	4	4	4
D_{calc}/g cm^{-3}	1.097	1.121	1.129	1.129
Radiation	Mo Kα	Mo Kα	Mo Kα	Mo Kα
λ/Å	0.71073	0.71073	0.71073	0.71073
No. of reflections for cell parameters	6009	8192	8192	8192
μ/mm^{-1}	0.079	0.080	0.081	0.081
T/K	150(2)	150(2)	150(2)	150(2)
Color, habit	Colorless block	Colorless plate	Colorless plate	Colorless block
Crystal size/mm	0.25 × 0.25 × 0.10	0.80 × 0.55 × 0.08	0.30 × 0.20 × 0.05	0.60 × 0.35 × 0.35
Diffractometer	Siemens SMART CCD	Siemens SMART CCD	Siemens SMART CCD	Siemens SMART CCD
Absorption correction	Multiscan[a]	Multiscan[a]	Multiscan[a]	Multiscan[a]
No. of reflections measured	17835	28827	18080	18094
No. of independent reflections	10995	18683	9903	8382
No. with $[I > 2\sigma(I)]$	6081	16289	5728	7601
R_{int}	0.0742	0.0357	0.0541	0.0271
θ_{max}/°	36.69	40.42	36.71	35.01
Index ranges	$-10 \leqslant h \leqslant 14$ $-39 \leqslant k \leqslant 34$ $-11 \leqslant l \leqslant 15$	$-15 \leqslant h \leqslant 15$ $-44 \leqslant k \leqslant 42$ $-15 \leqslant l \leqslant 16$	$-10 \leqslant h \leqslant 14$ $-39 \leqslant k \leqslant 25$ $-15 \leqslant l \leqslant 12$	$-13 \leqslant h \leqslant 11$ $-37 \leqslant k \leqslant 22$ $-14 \leqslant l \leqslant 13$
Refinement	on F^2	on F^2	on F^2	on F^2
$R(F)$ $[I > 2\sigma(I)]$	0.0783	0.0712	0.0626	0.0447
$wR(F^2)$	0.1447	0.1583	0.1667	0.1066
S	1.062	1.182	0.997	1.118
No. of parameters	437	456	447	510
Weights a and b^b	0.0184, 0.125	0.0367, 0.567	0.0822, 0.000	0.0380, 0.352
$(\Delta/\sigma)_{max}$	0.022	0.011	0.066	0.003
Residual electron density (e Å^{-3})	+0.345, −0.244	+0.433, −0.308	+0.284, −0.419	+0.305, −0.195
Extinction correction	SHELXTL	None	None	None
Extinction coefficient	0.0177(14)	—	—	—

[a]SADABS.[16] [b]$w = 1/[\sigma^2(F_o^2) + (a^*P)^2 + b^*P]$ where $P = (F_o^2 + 2F_c^2)/3$.

rotation about C–C bonds for fully occupied methyl groups), but with the C–H distances free to refine. All H-atoms connected to the same C-atom were given the same shifts. U_{iso} values were constrained to be $1.2U_{eq}$ of the carrier atom, or $1.5U_{eq}$ for methyl, hydroxy and amino groups. For LL1P2P a free variable for U_{iso} was refined for each of the two amino groups.

In the LLE and LL1P structures solvent molecules in the **C**-pocket are disordered over a major and a minor position, with occupancies 0.632(11):0.368(11) and 0.825(5):0.175(5), respectively. Heavy atoms in the least populated positions were refined isotropically, while atoms in the most populated positions were subjected to normal anisotropic refinement.

The solvent pockets in the LL1P2P are both occupied partly by 1-propanol molecules and partly by 2-propanol molecules. In position **C** 2-propanol predominates with an occupancy of 0.681(7) vs. 0.319(7) for 1-propanol, while in position **D** 1-propanol is favored over 2-propanol with occupancies 0.588(6) and 0.412(6), respectively. All heavy atoms were refined anisotropically.

In cases of solvent disorder, equivalent solvent molecules were constrained to have similar bond lengths and bond angles by a mild SHELXTL SAME 0.01 0.01 command. Details on the refinements are given in Table 1.

Cambridge Structural Database studies. Solvates of organic compounds were retrieved from the Cambridge Structural Database (CSD, October 1997 release)[1] by means of the program QUEST. Solvates were identified by the keyword 'solvate' in the compound name, various combinations of solvents were found by combined tests after building the specific solvent molecules.

Results and discussion

Refinement results are given in Table 1. Atomic coordinates for all structures are available from the author on request. The molecular structures of LLE, LL1P and LL1P2P are shown in Fig. 1. The structure of LL2P is virtually identical with the LL1P2P structure once the two 1-propanol molecules in Fig. 1(c) have been removed, and has not been shown. The unit cell and crystal packing pattern of LL2P is depicted in Fig. 2. Molecular geometry parameters are listed in Table 2, while normalized[17] hydrogen bond geometries are given in Table 3.

Molecular geometry. Bond lengths and bond angles for the L-Leu-L-Leu dipeptide are normal for all four complexes, with no important differences between them. The peptide main chains of the **A**-molecules are slightly less extended than those of the **B**-molecules. Side chain conformations are different in **A** and **B** at χ^1 as well as $\chi^{2,1}$ and $\chi^{2,2}$ for both residues.

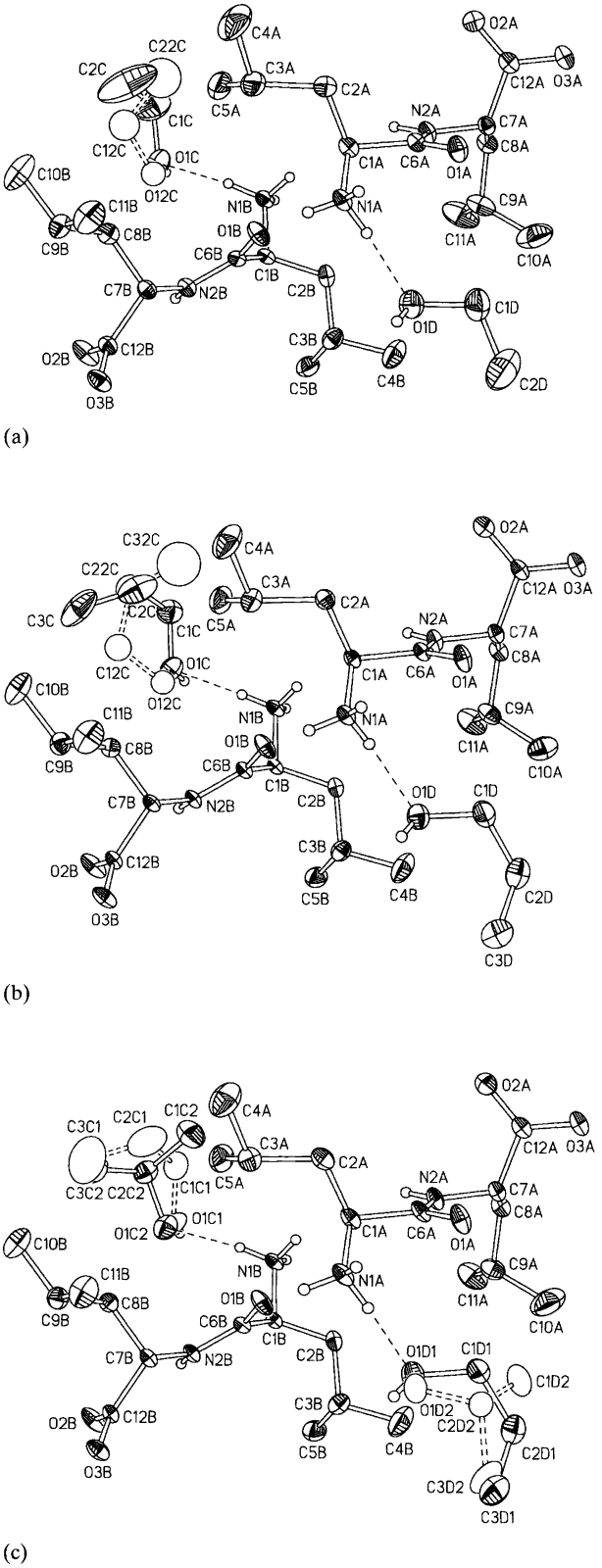

Fig. 1. The asymmetric unit of (a) LLE, (b) LL1P and (c) LL1P2P with atomic numbering. Thermal ellipsoids for heavy atoms are shown at the 50% probability level. The minor components of disordered molecules are shown with boundary ellipsoids only (isotropic for LLE and LL1P). Selected H-atoms are shown as spheres of arbitrary size.

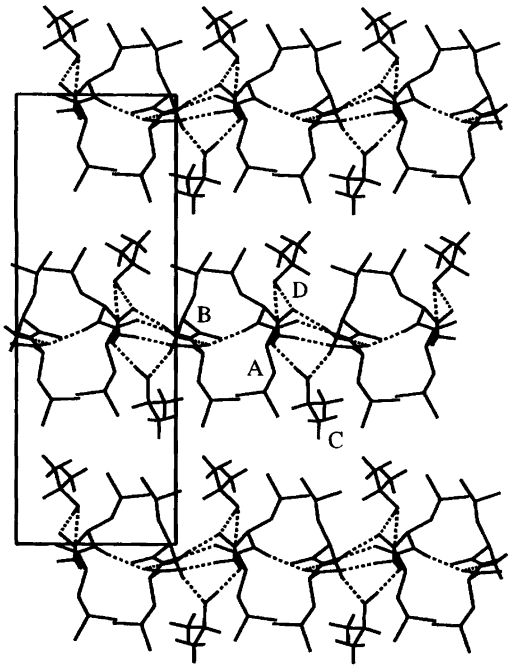

Fig. 2. The packing arrangement and the unit cell of LL2P viewed along the *a*-axis with a horizontal *c*-axis. Hydrogen bonds are indicated by dotted lines.

Crystal packing pattern. The crystal packing, which is different from that of the L-Leu-L-Leu · DMSO solvate,[11] is illustrated in Fig. 2. It is immediately apparent that the structure is divided into hydrophobic layers encompassing peptide side chains and alcohol alkyl groups, and hydrophilic layers with peptide main chains, but also the hydroxy groups of the solvent alcohol molecules which participate in hydrogen bonding.

Hydrogen bonds. The two-dimensional hydrogen bond pattern, which has not been observed previously in dipeptide structures, is shown in Fig. 3. Two head-to-tail chains,[18] one consisting of **A**-molecules and one consisting of **B**-molecules, run in opposite directions and are linked by three N–H···O hydrogen bonds creating a β-sheet-like **A**–**B** ribbon. The hydroxy group of the **C**-alcohol molecules serves as a fourth link between the two chains. The **D**-molecules, on the other hand, bind exclusively to **A**-molecules, but serve the same function as acceptor for one of the three amino N–H atoms. A weak C–H···O H-bond constitutes the fifth link between the **A** and **B**-chains. The independent **A**–**B** ribbons are much more loosely tied together, with only one N–H···O and one C–H···O hydrogen bond.

Table 2. Selected bond lengths (Å), bond angles (°) and torsion angles (°) for L-Leu-L-Leu alcohol solvates.

	LLE		LL1P		LL2P		LL1P2P	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
N1–C1	1.492(3)	1.496(3)	1.496(2)	1.495(2)	1.501(3)	1.502(3)	1.494(2)	1.495(2)
N2–C6	1.331(3)	1.342(3)	1.330(2)	1.345(2)	1.332(3)	1.341(3)	1.331(2)	1.342(2)
O1–C6	1.243(3)	1.233(3)	1.241(2)	1.233(2)	1.247(3)	1.245(3)	1.238(2)	1.234(2)
O2–C12	1.247(3)	1.246(3)	1.248(2)	1.251(2)	1.239(3)	1.253(3)	1.247(2)	1.249(2)
O3–C12	1.276(3)	1.263(3)	1.268(2)	1.267(2)	1.269(3)	1.263(3)	1.266(2)	1.264(2)
C7–C12	1.542(3)	1.547(3)	1.536(2)	1.543(2)	1.547(3)	1.540(3)	1.540(2)	1.539(2)
C9–C10	1.517(5)	1.524(4)	1.528(3)	1.533(3)	1.526(4)	1.528(4)	1.519(4)	1.530(3)
N1–C1–C6	106.3(2)	107.7(2)	105.71(10)	107.65(10)	106.0(2)	107.9(2)	105.75(12)	107.77(12)
C1–C6–N2	115.9(2)	115.2(2)	116.28(10)	115.10(10)	116.5(2)	115.8(2)	116.13(12)	115.50(11)
C6–N2–C7	120.3(2)	121.5(2)	120.38(10)	121.93(10)	121.4(2)	122.0(2)	120.42(11)	122.14(11)
N2–C7–C12	111.9(2)	108.2(2)	112.64(11)	107.86(10)	112.2(2)	108.5(2)	112.69(13)	108.25(11)
O2–C12–O3	125.4(2)	125.2(2)	125.59(13)	125.10(11)	125.8(2)	125.0(2)	125.43(14)	125.00(12)
C1–C2–C3	114.9(2)	113.5(2)	114.48(11)	113.43(11)	114.8(2)	113.6(2)	114.53(13)	113.44(12)
C7–C8–C9	112.9(2)	116.2(2)	113.00(12)	115.43(11)	112.7(2)	116.0(2)	112.77(13)	115.60(12)
N1–C1–C6–N2 (ψ_1)	138.8(2)	113.1(2)	137.07(11)	113.98(12)	141.1(2)	113.0(2)	138.40(13)	113.38(13)
C1–C6–N2–C7 (ω_1)	178.0(2)	−173.3(2)	−179.91(11)	−174.55(11)	178.8(2)	−173.0(2)	179.85(13)	−173.84(12)
C6–N2–C7–C12 (φ_2)	−82.8(3)	−156.7(2)	−83.64(15)	−155.14(11)	−81.3(2)	−155.6(2)	−82.6(2)	−155.48(13)
N2–C7–C12–O2 (ψ_T)	−25.3(3)	−48.8(3)	−25.9(2)	−48.8(2)	−30.6(2)	−45.3(2)	−27.7(2)	−46.3(2)
N1–C1–C2–C3 (χ_1^1)	−67.4(3)	−167.2(2)	−67.39(15)	−167.94(11)	−68.8(2)	−170.5(2)	−67.7(2)	−169.39(12)
C1–C2–C3–C4 ($\chi_1^{2,1}$)	169.3(3)	−172.7(2)	168.5(2)	−173.53(15)	168.7(2)	−173.9(2)	169.3(2)	−173.4(2)
C1–C2–C3–C5 ($\chi_1^{2,2}$)	−67.7(3)	63.8(3)	−68.3(2)	63.6(2)	−69.5(2)	62.7(2)	−68.4(2)	63.5(2)
N2–C7–C8–C9 (χ_2^1)	−71.0(3)	−179.1(2)	−68.5(2)	−179.23(11)	−71.5(2)	−178.3(2)	−69.8(2)	−178.73(11)
C7–C8–C9–C10 ($\chi_2^{2,1}$)	−77.6(3)	−172.4(3)	−77.3(2)	−173.46(15)	−84.5(3)	−172.6(2)	−81.0(2)	−173.33(14)
C7–C8–C9–C11 ($\chi_2^{2,2}$)	158.1(3)	65.1(3)	159.0(2)	64.6(2)	150.3(2)	64.8(3)	155.3(2)	64.8(2)
	C	**D**	**C**	**D**	**C**	**D**	**C**	**D**
O1–C1[a]	1.425(7)	1.428(4)	1.425(4)	1.430(2)			*1.460(14)*	1.435(10)
O1–C2					1.435(4)	1.444(3)	1.447(9)	*1.451(11)*
O1–C1–C2	110.3(6)	111.9(3)	107.7(2)	112.4(2)			*108.0(8)*	111.3(5)
O1–C2–C1					110.2(3)	106.9(2)	110.0(5)	*108.5(5)*
O1–C1–C2–C3			−61.0(3)	−61.6(3)			*−56.4(17)*	−64.5(7)

[a]For LLE and LL1P only values for the most populated position are given. For LL1P2P values for the minor components are given in *italic*.

Table 3. Hydrogen bond distances (Å) and angles (°) with normalized[17] H-atom positions.[a]

	H···O				*D*···O				*D*–H···O			
D–H···O	LLE	LL1P	LL2P	LL1P2P	LLE	LL1P	LL2P	LL1P2P	LLE	LL1P	LL2P	LL1P2P
N1A–H1A···O2A^{i,a}	2.11	2.04	2.17	2.05	2.998(3)	2.941(2)	3.057(3)	2.985(2)	143	145	142	149
N1A–H2A···O2B^{ii}	1.81	1.82	1.80	1.81	2.837(3)	2.842(2)	2.824(3)	2.837(2)	176	174	171	178
N1A–H3A···O1D	1.86	1.84	1.87	1.78	2.886(3)	2.865(2)	2.901(3)	2.808(11)	174	175	174	177
N2A–H4A···O3B^{iii}	1.79	1.79	1.84	1.80	2.823(3)	2.815(1)	2.862(3)	2.830(2)	178	172	171	178
C1A–H11A···O1B	2.33	2.34	2.33	2.33	3.095(3)	3.117(1)	3.137(3)	3.129(2)	125	126	129	128
N1B–H1B···O1C	1.84	1.81	1.86	1.87	2.848(7)	2.811(2)	2.858(3)	2.870(12)	164	163	162	163
N1B–H2B···O3A^{iv}	1.90	1.92	1.89	1.95	2.842(3)	2.862(2)	2.835(3)	2.849(2)	150	150	151	145
N1B–H3B···O3B^{iii}	1.78	1.75	1.76	1.76	2.751(3)	2.745(1)	2.762(2)	2.756(2)	157	162	164	162
N2B–H4B···O1A^{iv}	1.94	1.95	1.97	1.94	2.943(3)	2.924(1)	2.983(3)	2.948(1)	164	158	168	164
C1B–H11B···O1A^{iv}	2.25	2.23	2.26	2.24	3.250(3)	3.224(1)	3.269(3)	3.244(2)	150	149	151	150
O1C–H1C···O2A^{iv}	1.78	1.76	1.83	1.88	2.713(7)	2.707(2)	2.777(3)	2.820(9)	166	179	179	168
O1D–H1D···O3A^{i}	1.78	1.81	1.76	1.87	2.680(3)	2.689(2)	2.674(3)	2.749(9)	156	154	154	153

[a] d(O–H) = 0.95 Å, d(N–H) = 1.03 Å, d(C–H) = 1.10 Å. [b] Symmetry codes: $^{i}x-1, y, z$; $^{ii}x+1, y, z+1$; $^{iii}x+1, y, z$; $^{iv}x-1, y, z-1$. [c] For disordered solvent molecules in LLE, LL1P and LL1P2P only geometries involving the most occupied positions are given.

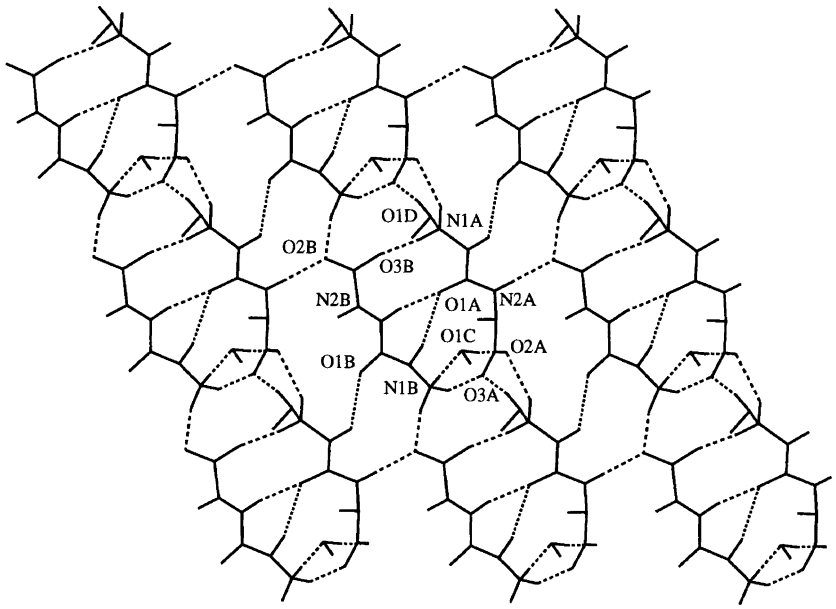

Fig. 3. A hydrogen bonded layer in the crystal structure of LL2P. H-bonds with C–H donors are shown as dotted rather than dashed lines.

Selectivity of the solvent pockets. After completing crystallization experiments with pure alcohols as precipitating agents, further experiments were carried out with a series of alcohol mixtures. The two first mixtures tested were 1 : 1 ethanol–1-propanol and 1 : 1 ethanol–2-propanol. In either case the crystals obtained were devoid of ethanol. It is thus immediately clear that the two propanol molecules fit better into the solvent pockets and impose less strain on the rest of the structure than ethanol. There is no methanol solvate, since methanol is too small a molecule to fill the pockets effectively, and also no butanol solvates, since these molecules are too large.

The next experiment involved using a 1 : 1 mixture of 1-propanol and 2-propanol as the solvent. It can be seen from Fig. 2 that **C** and **D** molecules sit in solvent pockets which are quite similar, but not identical. We therefore anticipated that the two solvent sites could have different specificities for the alcohols. The resulting structure of the LL1P2P complex, described above, shows that this is indeed true: In pocket **C** there is a rough 2 : 1 preference for 2-propanol, while for site **D** there is a 3 : 2 preference for 1-propanol. The difference between the two sites is not radical, but illustrates a very important concept in the crystallization of organic molecules:

(1) When there are two or more crystallographically independent solvent sites in a crystal structure, they will have different affinities for various solvent molecules.

For the LL1P2P complex the situation is simple in that both solvent sites, in the absence of several alternative solvent molecules, can incorporate the same solvent molecule (ethanol, 1-propanol or 2-propanol). It is not, however, difficult to envision the existence of crystal

structures with solvent sites of very different size and shape or with very different chemical environments, so that two different solvent molecules are required for formation of a crystal. We can thus further postulate that:

(2) Some organic molecules will form crystals only in the presence of two or more different solvents. This is equivalent to saying that some compounds will defy all crystallization attempts as long as only pure solvents are used. Further research is in progress.

Very few mixed solvates were found in the Cambridge Structural Database,[1] and it appears that they are usually the result of syntheses that involved different solvents in subsequent steps. A solvent mixture was thus not deliberately used for crystallization purposes. Seventeen crystal structures were found with two different cocrystallized alcohol molecules, all of them methanol ethanol solvates of large organic molecules. In just four cases[19–22] were solvent mixtures used in the final crystallization by slow evaporation, while one crystallization[23] involved diffusion of methanol into an ethanolic solution of the solute. It seems that the use of solvent mixtures by organic chemists in crystallizations is quite limited.

Benefits and problems associated with using solvent mixtures in crystallization experiments. Two benefits of using a solvent mixture are obvious: (1) Instead of setting of a large number of crystallization experiments in search for the 'right' solvent for high quality crystal formation, a smaller number of experiments with solvent mixtures can be used. (2) Mixed solvent crystals may be obtained, unavailable with pure solvents.

It has also been pointed out previously[24] that in slow evaporation experiments, solvent mixtures make it possible to control the crystallization rate and final solution composition accurately, and avoid drying of crystals and crust formation on the glass walls. Our approach, using solvent mixtures in vapor diffusion experiments appears to be completely new. An advantage is that not only can the composition of the vapor over the mixture be easily calculated from tabulated values, but the large excess of solvent volume over the volume of the initial solute solution means that the composition changes very little with time, which is not true for evaporation experiments employing mixtures.

For certain compounds or even families of compounds it can be stated with a high degree of certainty that the final crystal structure is unlikely to include solvent. This is especially true for many low molecular weight molecules. Even if the choice of solvent may still affect the crystal habit, the potential benefits of using solvent mixtures will then be small.

Working with mixtures, it must be kept in mind that if a specific solvent molecule is to be incorporated into a crystal structure, a certain concentration is required; below a certain level no crystal will be obtained. Future experiments will establish guidelines for composition of mixtures designed to optimize the crystallization outcome. At this stage we have experimented briefly with L-Leu-L-Leu and (A) 2-propanol–2-butanol mixtures and (B) methanol–ethanol mixtures. For (A) it was found that with an almost saturated solution of L-Leu-L-Leu (see Experimental) nice LL2P crystals were obtained when the proportion of 2-propanol in the starting mixture was higher than about 35%, while for (B) about 60% ethanol content was required to form crystals (and indeed precipitation at all). In additional experiments with the dipeptide L-Val-L-Leu,[9] which forms only ethanol solvates, it was found that crystals were obtained from ethanol–2-propanol mixtures when the precipitating solution contained more than 30% ethanol. From these early experiments it may appear that the desired solvent molecules must be present in fairly large quantities, and that mixtures containing two or three different solvents, rather than four or more, will be best suited to crystallization experiments.

Finally, it is noteworthy that while the LL2P structure is completely ordered, the use of a solvent mixture for obtaining the LL1P2P crystals has resulted in a disordered structure. This renders the crystal structure refinement more laborious and may represent a general disadvantage of mixed solvates, but the problem could be overcome if one avoids mixtures in which two or more components have almost the same molecular volume.

Supplementary material. CIFs and tables giving fractional coordinates for all atoms and anisotropic temperature parameters for heavy atoms are available from the author on request. E-mail: c.h.gorbitz@kjemi.uio.no

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