

Cocrystallizing Agents for Amino Acids I. The Crystal Structure of L-Glutamic Acid·2-Methylimidazole

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The L-glutamic acid (2-aminopentanedioic acid, L-Glu) 2-methylimidazole (2MI) 1:1 complex crystallizes in the monoclinic space group $C2$ with two L-Glu anions and two 2MI cations in the asymmetric unit, together with a solvent water molecule located on the twofold axis. The structure was solved by direct methods and refined to a final $wR(F_o^2)=0.124$ for 5506 unique reflections and $R(F_o)=0.046$ for 4578 observed reflections ($I > 2.0 \sigma I$) collected at 120 K. Cell parameters: $a=19.487(6)$, $b=7.935(3)$, $c=20.351(5)$ Å, $\beta=131.39(2)^\circ$. The crystals were prepared as part of a program aimed at finding suitable cocrystallization agents for amino acids and peptides. The two L-Glu molecules have different side-chain conformations, but have very similar hydrogen bond arrangements, except that only one molecule has an interaction with the water molecule. The 2MI molecules act as cross-links between head-to-tail L-Glu-chains. One 2MI is disordered over two equally populated positions close to the twofold rotation axis.

The growth of amino acid or peptide crystals is often met with mixed success leading to either amorphous or microcrystalline precipitations, or the crystals formed display habits which make them unsuitable for X-ray crystallographic work, either exceedingly thin needles or two-dimensional flakes. Generally, these compounds are crystallized in the zwitterionic form, but an alternative approach is to take advantage of their acidic and basic properties and crystallize them as salts, usually as cations in, e.g., hydrochlorides. We have previously¹ pointed out that when investigations are performed with regard to the biological activities exhibited by these molecules, potentially the most interesting ionization state is the one observed in aqueous solution at physiological pH. In this connection, the number of acidic residues in the peptide, n_A , and the number of basic residues, n_B , are of importance. When $n_A=n_B=0$, or more generally when $n_A=n_B$, peptide cations always possess protonated C-terminal carboxylate groups. Since associated pK_a values normally range from 1.7 to 2.6, this corresponds to non-physiological, low pH-values. If, however, the peptide in question has $n_A > n_B$ (acidic peptides) or $n_B > n_A$ (basic peptides) it can be crystallized as an anion or a cation in a salt while retaining its physiological protonation state. One then needs to find suitable counterions able to facilitate crystal growth.

A special option, which has been thoroughly investi-

gated and is summarized in Ref. 2, is cocrystallization with another amino acid or peptide. We have undertaken a systematic program to find organic bases and acids, other than amino acids, that will form salts and have a positive effect on crystal quality. The organic bases we have tested belong to four different groups: (A) pyridine derivatives, (B) guanidine and derivatives, (C) aliphatic amines and (D) imidazole and derivatives. Our search is

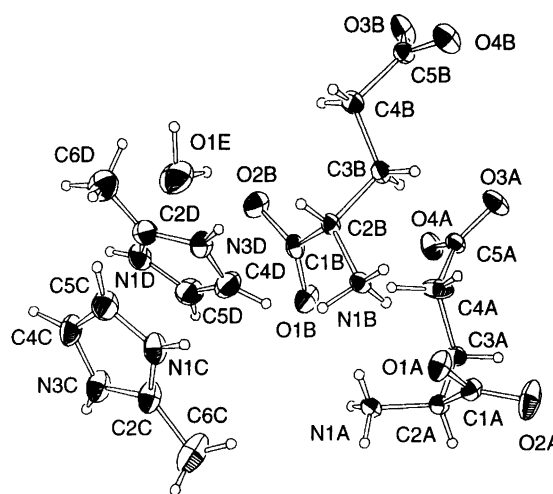


Fig. 1. The asymmetric unit with atomic numbering. Thermal ellipsoids for heavy atoms are shown at 50% probability level. H-atoms are shown as spheres of arbitrary size. The disordered 2-methylimidazole ring D is shown in Position 2.

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not exhaustive, but the results seem to indicate that the imidazole group is the most promising for cocrystallization with L-aspartic acid and L-glutamic acid. We have obtained crystals for salts with 4-nitroimidazole and 2-methylimidazole, while compounds belonging to groups (A)–(C) generally failed to give highly crystalline salts. Prior to our investigation, however, the crystal structures of several complexes between diamines and L-aspartic acid³ or L-glutamic acid^{4–7} have been presented, as well as the L-glutamate NH_4^+ ⁸ and L-aspartate guanidinium⁹ salts. In this paper we present the structure of the L-glutamic acid (L-Glu)–2-methylimidazole (2MI) complex.

Nomenclature. The symbol $d(\text{X–Y})$ is used to denote the X–Y bond length, while $d(\text{X}\cdots\text{Y})$ is a non-bonded X \cdots Y distance.

Table 1. Crystal data, intensity collection and structure refinement.

Formula	$\text{C}_5\text{H}_8\text{NO}_4^- \cdot \text{C}_4\text{H}_7\text{N}_2^+ \cdot 1/4\text{H}_2\text{O}$
Formula weight/g mol ⁻¹	233.74
Crystal size/mm	1.00 × 0.40 × 0.40
Color, habit	Colorless block
Crystal system	Monoclinic
Space group	C2 (No. 5)
Cell dimensions/Å, °	$a = 19.487(6)$ $b = 7.935(3)$ $c = 20.351(5)$ $\beta = 131.39(2)$
Volume/Å ³	2361(1)
Z	8
$D_{\text{calc}}/\text{g cm}^{-3}$	1.315
Diffractometer	Nicolet P3
Radiation	Mo K α ($\lambda = 0.71069 \text{ \AA}$)
Monochromator	Graphite crystal
T/K	120
Scan mode	2θ
Scan speed/° min ⁻¹	4.0
Scan range/°	$2\theta_{\alpha 1} - 0.8$ to $2\theta_{\alpha 2} + 0.8$
2θ range/°	5.0–70.0
Standard reflections	3 measured every 96 refl.
Variation in standard intensities (%)	< 2.0
Index ranges	$0 \leq h \leq 31$ $0 \leq k \leq 12$ $-32 \leq l \leq 24$
No. of reflections measured	5644
No. of unique reflections	5506
No. of observed reflections	4578
$[I > 2.0\sigma(I)] = n$	
Absorption correction	None
Refinement	on F^2
No. of parameters = p	391
$R(F_o)$ (observed) ^a	0.046
$wR(F_o^2)$ (all) ^b	0.124
$S = \{\sum [w(F_o^2 - F_c^2)^2] / (n - p)\}^{1/2}$	1.045
Residual electron density/e Å ⁻³	+0.31, -0.22

^a $R(F_o) = \sum |F_o| - |F_c| / \sum |F_o|$. ^b $wR(F_o^2) = \{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]\}^{1/2}$ with $w = 1/[\sigma^2(F_o^2) + (0.0710P)^2 + 0.05049P]$ where $P = (F_o^2 + 2F_c^2)/3$.

Experimental

Preparation. The crystals were grown by slow evaporation of an aqueous solution containing equimolar amounts of L-Glu and 2MI.

Data collection. Experimental conditions are given in Table 1. Cell parameters were determined from 25 general reflections with $25^\circ < 2\theta < 35^\circ$.

Refinement. The structure was solved by the direct methods program SIR92.¹⁰ Only reflections with $2\theta < 50^\circ$ were used. As was inferred from the cell dimensions, there are two L-Glu anions and two 2MI cations in the asymmetric unit. These are denoted Glu(A), Glu(B), 2MI(C) and 2MI(D), respectively. Additionally, there is one solvent water molecule, W(E), located on the twofold rotation axis. The structure was refined with SHELXL93.¹¹ For 2MI(D) several atoms showed

Table 2. Fractional atomic coordinates with standard deviations and equivalent isotropic temperature factors (Å²).

Atom	x	y	z	U^a
O1A	0.57043(8)	0.5872(2)	0.21318(8)	0.029(1)
O2A	0.58172(9)	0.6513(3)	0.11433(9)	0.044(1)
O3A	0.44091(9)	1.1987(2)	0.10817(11)	0.033(1)
O4A	0.29770(8)	1.1102(2)	0.02104(9)	0.031(1)
O1B	0.43160(8)	0.6369(2)	0.25130(8)	0.031(1)
O2B	0.42440(8)	0.7760(2)	0.34195(9)	0.032(1)
O3B	0.56366(8)	1.3182(2)	0.40347(10)	0.030(1)
O4B	0.70620(8)	1.2265(2)	0.48618(9)	0.032(1)
O1E	0.50000	0.6337(4)	0.50000	0.055(1)
N1A	0.39009(9)	0.5254(2)	0.09327(10)	0.020(1)
N1B	0.61661(8)	0.6041(2)	0.37549(9)	0.019(1)
N1C	0.39305(10)	0.2976(3)	0.34429(10)	0.030(1)
N3C	0.25011(10)	0.2263(3)	0.25510(11)	0.033(1)
N1D ₁	0.1112(3)	0.6564(6)	0.1713(3)	0.033(1)
N1D ₂	0.2503(5)	0.6995(15)	0.2287(5)	0.029(2)
N3D ₁	0.1032(3)	0.7207(7)	0.1502(3)	0.031(1)
N3D ₂	0.2478(5)	0.7375(16)	0.2206(5)	0.032(2)
C1A	0.53719(10)	0.6150(2)	0.13710(10)	0.022(1)
C2A	0.43224(9)	0.6143(2)	0.06275(9)	0.018(1)
C3A	0.39521(10)	0.7933(2)	0.03321(10)	0.021(1)
C4A	0.4168(2)	0.9044(2)	0.10607(12)	0.034(1)
C5A	0.38152(11)	1.0834(2)	0.07552(11)	0.021(1)
C1B	0.46737(9)	0.7083(2)	0.32143(10)	0.021(1)
C2B	0.57167(9)	0.7277(2)	0.39111(10)	0.018(1)
C3B	0.60021(11)	0.9085(2)	0.39182(11)	0.020(1)
C4B	0.59150(13)	1.0282(2)	0.44478(13)	0.026(1)
C5B	0.62345(10)	1.2034(2)	0.44594(10)	0.020(1)
C2C	0.32610(11)	0.2284(3)	0.26669(11)	0.030(1)
C4C	0.26979(13)	0.2968(4)	0.32762(14)	0.036(1)
C5C	0.35942(14)	0.3407(3)	0.38403(14)	0.035(1)
C6C	0.3354(2)	0.1606(5)	0.2049(2)	0.056(1)
C2D ₁	0.1914(4)	0.7245(23)	0.2407(5)	0.026(2)
C4D ₁	0.2052(3)	0.6341(11)	0.1470(3)	0.049(2)
C5D ₁	0.1186(3)	0.6043(11)	0.1116(3)	0.056(2)
C6D ₁	0.2168(8)	0.7738(22)	0.3233(6)	0.046(3)
C2D ₂	0.1871(6)	0.7200(27)	0.2308(6)	0.036(2)
C4D ₂	0.2024(4)	0.7271(9)	0.1325(4)	0.042(1)
C5D ₂	0.1134(3)	0.7157(9)	0.0898(3)	0.041(1)
C6D ₂	0.2047(9)	0.7482(20)	0.3117(6)	0.049(2)

^a $U_{\text{eq}} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$.

unreasonably elongated thermal ellipsoids in ORTEP-drawings¹² obtained after the initial cycles of anisotropic refinement. A difference Fourier synthesis revealed two peaks in the electron density map for these atoms. Accordingly, 2MI(D) is disordered in the crystal, and two alternative positions were refined for the six heavy atoms in the molecule. These are referred to as Position 1 and Position 2, and are denoted 2MI(D)₁

Table 3. Bond lengths (Å), bond angles (°) and selected torsion angles (°).

	Glu(A)	Glu(B)		
O1–C1	1.241(2)	1.236(2)		
O2–C1	1.258(2)	1.275(2)		
O3–C5	1.266(2)	1.266(2)		
O4–C5	1.244(2)	1.248(2)		
N1–C2	1.494(2)	1.483(2)		
C1–C2	1.543(2)	1.535(2)		
C2–C3	1.525(2)	1.536(2)		
C3–C4	1.526(2)	1.528(2)		
C4–C5	1.520(3)	1.518(3)		
	2MI(C)	2MI(D) ₁	2MI(D) ₂	
N1–C2	1.332(3)	1.345(9)	1.348(9)	
N1–C5	1.379(3)	1.376(6)	1.370(6)	
N3–C2	1.337(2)	1.335(9)	1.336(9)	
N3–C4	1.375(3)	1.370(8)	1.381(8)	
C2–C6	1.486(3)	1.458(8)	1.460(9)	
C4–C5	1.356(3)	1.348(7)	1.334(6)	
	Glu(A)	Glu(B)		
O1–C1–O2	125.6(2)	125.5(1)		
O1–C1–C2	118.9(1)	120.3(1)		
O2–C1–C2	115.4(1)	114.2(1)		
N1–C2–C1	109.3(1)	110.2(1)		
N1–C2–C3	110.9(1)	111.1(1)		
C1–C2–C3	111.0(1)	110.7(1)		
C2–C3–C4	113.6(1)	112.2(1)		
C3–C4–C5	112.5(1)	110.2(1)		
O3–C5–O4	123.4(2)	123.3(2)		
O3–C5–C4	116.9(2)	117.8(2)		
O4–C5–C4	119.8(2)	118.9(1)		
	2MI(C)	2MI(D) ₁	2MI(D) ₂	
C2–N1–C5	109.0(2)	108.7(4)	108.2(5)	
C2–N3–C4	108.4(2)	109.8(6)	108.9(6)	
N1–C2–N3	108.5(2)	106.9(6)	107.2(7)	
N1–C2–C6	125.5(2)	126.3(8)	124.3(8)	
N3–C2–C6	126.0(2)	124.9(7)	126.0(9)	
N3–C4–C5	107.6(2)	106.7(5)	106.9(4)	
N1–C5–C4	106.6(2)	107.4(4)	108.2(4)	
	W(E)			
H1–O1–H1 ^a	95(5)			
	Glu(A)	Glu(B)		
N1–C2–C1–O1	–18.1(2)	–19.9(2)		
N1–C2–C1–O2	164.7(2)	162.5(2)		
N1–C2–C3–C4 (χ^1)	62.1(2)	–155.1(1)		
C2–C3–C4–C5 (χ^2)	178.3(2)	178.1(1)		
C3–C4–C5–O3 ($\chi^{3,2}$)	–113.1(2)	110.2(2)		
C3–C4–C5–O3 ($\chi^{3,1}$)	66.7(2)	–67.8(2)		

^a Symmetry code: 1–x, y, 1–z.

and 2MI(D)₂. For reasons to be described later, the population of each form is constrained to 0.500. The distances between the two alternative atomic positions range from 0.16 Å for C2D₁/C2D₂ to 0.96 Å for C5D₁/C5D₂.

All heavy atoms were refined anisotropically, using SHELXL93 DELU 0.01 0.01 and SIMU 0.02 0.02 0.6 restraints¹¹ for 2MI(D)₁ and 2MI(D)₂. The H-atoms of the Glu(A) and Glu(B) amino groups were refined isotropically, other H-atoms on Glu(A), Glu(B) and 2MI(C) were placed geometrically. Refinement then allowed the H-atoms to move along the C–H bond direction with the C–H distance being kept constant for all H atoms on the same C atom. The U_{iso} values were fixed at $1.2 \times U_{\text{eq}}$ of the bonded atom. Positional parameters were refined for the water H-atom H1E, with $U_{\text{iso}} = 1.5 \times U_{\text{eq}}$ of O1E. The 2MI(D)₁ and 2MI(D)₂ H-atoms were placed geometrically and treated as riding atoms with $d(\text{N–H}) = 0.86$ Å and $d(\text{C–H}) = 0.93$ Å for ring atoms and 0.96 Å for methyl groups. Isotropic temperature factors were assigned as described above, except that a free variable for U_{iso} was refined for the two methyl groups. Details on the refinement are given in Table 1. Atomic scattering factors were from Ref. 13.

Cambridge Structural Database (CSD). Peptide structures were retrieved from the CSD (April 1995 release)¹⁴ by means of the program QUEST. A maximum *R*-factor of 0.10 was used. The main-chain and side-chain conformations were studied with the GSTAT program.

Table 4. Side-chain torsion angles (°) for L-Glu anions in various crystal structures.^a

Compound	χ^1	χ^2	χ^3	Ref.
L-Arg L-Glu·H ₂ O	–57	–172	–3	20
L-Arg D-Glu·3H ₂ O	–179	–178	–40	21
L-Arg D-Glu·H ₂ O	–54	175	19	22
D-L-Arg D-L-Glu·H ₂ O	175	75	3	2
L-Lys D-Glu	–52	167	20	23
	–57	174	16	
Ammonium	–172	175	–26	8
L-Glu·H ₂ O				
1,3-Diaminopropane	66	172	–4	4
bis(L-Glu)	61	–175	–5	
1,3-Diaminopropane	56	158	40	4
bis(DL-Glu)	54	171	84	
Putrescine bis(L-Glu)	65	–179	7	5
	65	174	–52	
Putrescine bis(DL-Glu)	66	169	17	6
1,6-Diaminohexane	177	71	14	7
bis(L-Glu)	73	–76	10	
2-Methylimidazole	62	178	67	This work
L-Glu	–155	178	–68	

^a Values for D-Glu have been reversed to correspond to the L-isomer.

Results and discussion

An ORTEP¹² drawing of the asymmetric unit with atomic numbering is shown in Fig. 1. Final atomic coordinates for heavy atoms are listed in Table 2, molecular geometry is given in Table 3.

Bond lengths and bond angles. For Glu(A), Glu(B) and 2MI(C) there are no deviations from normal values. For 2MI(D) the disorder produced some bond lengths that

appear either too short or too long compared with 2MI(C), but the deviations are not serious.

L-Glu conformation. Other crystal structures with L-Glu anions were retrieved from the Cambridge Structural Database.¹⁴ The side-chain conformations are listed in Table 4. All three rotamers were observed at χ^1 , but χ^2 is generally *trans*. It can be seen from Table 3 that six of the 11 structures have two L-Glu molecules in the asymmetric unit, and that usually, their conformations are very similar. The exceptions are the structures of L-Glu

Table 5. Hydrogen bond distances (Å) and angles (°).

D-H...O	D-H	H...O ^a	H...O ^b	D...O	D-H...O
N1A-H1A...O3A ^{ic}	0.88(3)	1.85(3)	1.69	2.720(2)	175(2)
N1A-H2A...O4A ⁱⁱ	0.91(3)	1.92(3)	1.80	2.828(2)	174(3)
N1A-H3A...O1B	0.88(3)	2.05(3)	1.90	2.888(2)	160(2)
N1B-H1B...O3B ⁱ	0.97(3)	1.74(3)	1.68	2.704(2)	176(2)
N1B-H2B...O4B ⁱⁱⁱ	0.89(3)	1.98(2)	1.85	2.817(2)	156(2)
N1B-H3B...O1A	0.87(3)	1.95(3)	1.79	2.794(2)	164(3)
N1C-H1C...O3B ⁱ	0.81(3)	1.88(2)	1.67	2.690(2)	172 ^d
N3C-H3C...O2A ^{iv}	0.81(3)	1.83(2)	1.61	2.626(2)	168
N1D ₁ -H1D ₁ ...O3A ^{iv}	0.86 ^d	1.88	1.73	2.673(4)	152
N3D ₁ -H3D ₁ ...O2B	0.86	1.76	1.59	2.618(7)	177
N1D ₂ -H1D ₂ ...O3A ^{iv}	0.86	1.83	1.66	2.680(4)	172
N3D ₂ -H3D ₂ ...O2B	0.86	1.75	1.58	2.607(7)	176
O1E-H1E...O2B	1.02(5)	1.81(3)	1.87	2.743(2)	151(4)
C3B-H5B...O4B ⁱⁱⁱ	0.96(2)	2.41(2)	2.32	3.178(2)	136
C5C-H5C...O1E	0.93(3)	2.50(2)	2.40	3.151(4)	127
C4D ₂ -H4D ₂ ...O4A ⁱⁱ	0.93	2.49	2.36	3.257(5)	140

^a Refined H-atom positions, except for H-atoms on 2MI(D₁) and 2MI(D₂). ^b Normalized¹⁵ H-atom positions: $d(\text{O-H}) = 0.95 \text{ \AA}$, $d(\text{N-H}) = 1.03 \text{ \AA}$, $d(\text{C-H}) = 1.10 \text{ \AA}$.¹⁶ ^c Symmetry codes: ⁱ $x, y-1, z$; ⁱⁱ $-x+1/2, y-1/2, -z$; ⁱⁱⁱ $-x+3/2, y-1/2, -z+1$; ^{iv} $x-1/2, y-1/2, z$. ^d Esd meaningless due to constrained refinement.

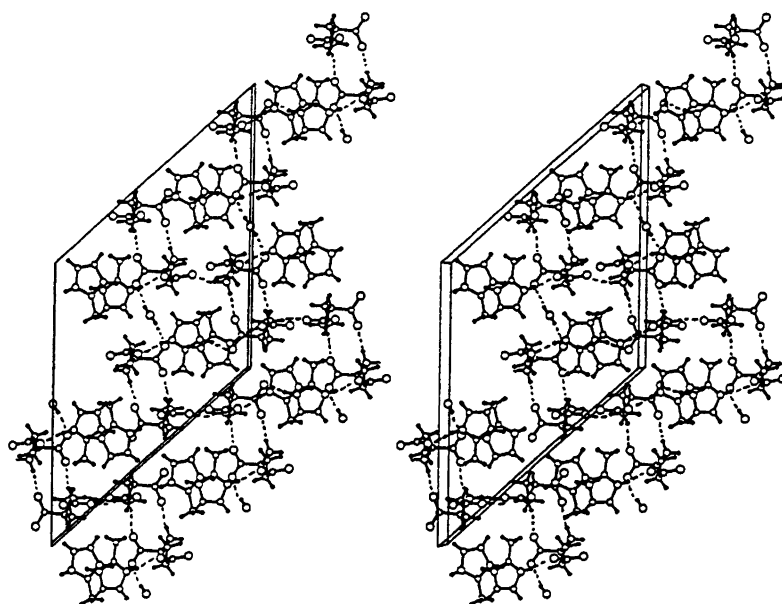


Fig. 2. Stereoview of the packing arrangement and the unit cell along the *b*-axis with the disordered 2-methylimidazole ring D shown in Position 2. The short 2.01 Å intermolecular H...H contact across the twofold axis is readily recognized.

2MI and L-Glu diaminoethane⁷ in which the conformations are significantly different.

Hydrogen bonds and molecular packing. The three-dimensional hydrogen-bond network contains 11 different interactions [or 13 counting the two alternatives for 2MI(D)] which are listed and normalized^{15,16} in Table 5. The crystal packing is shown in Fig. 2. Glu(A) and Glu(B) molecules form separate head-to-tail chains parallel to the *b*-axis through one of the amino H-atoms and the side chain γ -carboxylate group, Fig. 3(a). The second amino H-atom is donated to the α -carboxylate group in an identical molecule related by a twofold screw axis, while the third is part of an ten-membered H-bonded ring involving both Glu(A) and Glu(B). The Glu molecules form a zig-zag pattern with the two 2MI molecules acting as cross-links, Fig. 3(b), as well as the solvent water molecule, Fig. 2. 2MI(C) forms H-bonds to the α -carboxylate of Glu(A) and the side-chain γ -carboxylate of Glu(B), while for 2MI(D) the Glu labels A and B are opposite. In either case the H-bond

to the α -carboxylate is the shorter, which is a bit surprising since the less acidic γ -carboxylate groups would normally be considered to be somewhat better acceptors. W(E) donates H-atoms to two Glu(B) α -carboxylate groups. H-bond patterns rather similar to the one observed for L-Glu 2MI occur for the DL-Glu diaminopropane⁴ and L-Glu putrescine⁵ complexes, in which the two 2MI cations are replaced by the diamine link antiparallel L-Glu chains, while in the present structure the chains are parallel. Other related patterns have been observed in a number of complexes between imidazole and various dicarboxylic acids.¹⁷

Overall, the H-bonds listed in Table 5 are quite short, and seven out of 13 interactions with N-H or O-H donors have H-bond angles $>170^\circ$. The short H-bonds may be the result of the undersaturation of the H-bond accepting capacity of the carboxylate groups. Three of the four carboxylate groups participate in three classical H-bonds each, and the last one only two. In a survey of the crystal structures of short, linear peptides,¹⁸ the

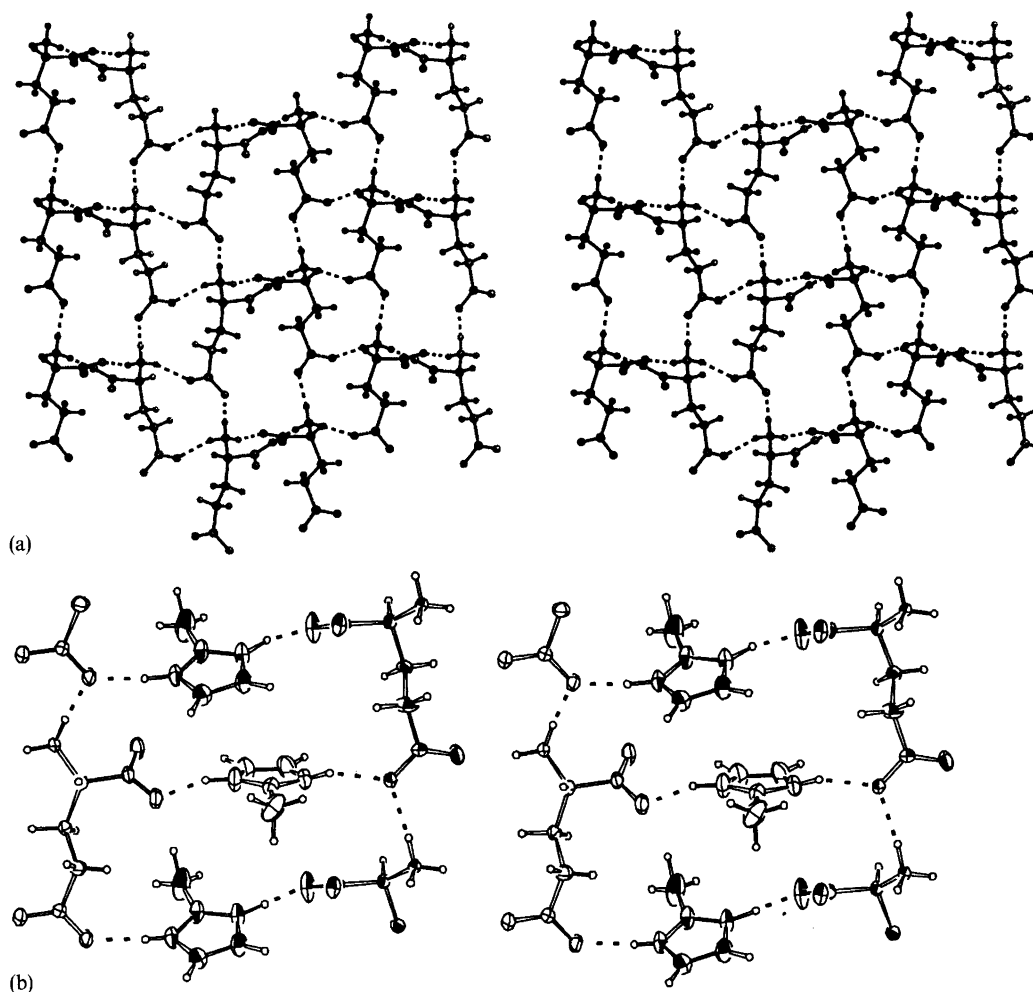


Fig. 3. Details of the molecular packing pattern and hydrogen bonding: (a) hydrogen bonds between the L-Glu molecules; Glu(B) is shown in grey; (b) 2-methylimidazole (2MI) cross-links between L-Glu chains; L-Glu(A) and 2MI(C) are represented by shaded ellipsoids, L-Glu(B) and 2MI(D)₂ with unshaded ellipsoids.

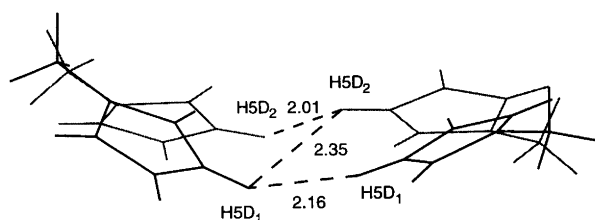


Fig. 4. Disorder for 2-methylimidazole molecule D at the twofold axis. Position 2 is indicated in grey. Intermolecular H...H contacts are indicated, with distances given in Å.

average number H-atoms accepted by C-terminal main-chain carboxylate groups in hydrates was 4.05, and no occurrences of groups accepting only two H-atoms were found. Theoretical studies have indicated that H-bonds between two specific functional groups tend to decrease in length when the acceptor (or donor) is engaged in a smaller number of other H-bonds to other donors (or acceptors).¹⁹

Imidazole and its derivatives often crystallize in planar sheets in which short contacts with ring C-H donors are common.¹⁷ In the present structure there is only one short contact involving a ring C-H, with W(E) as acceptor. Due to the twofold symmetry W(E) is then an acceptor in two weak H-bonds.

The disorder observed for 2MI(D) can be readily explained by the crystal packing. When a 2MI(D)₁ or 2MI(D)₂ molecule (or even an average structure) is rotated around the twofold axis to generate the symmetry-related molecule, an intermolecular H...H contact that is too short results. Thus, $d(\text{H5D}_1 \cdots \text{H5D}_1)$ is 2.16 Å and $d(\text{H5D}_2 \cdots \text{H5D}_2)$ is 2.01 Å, Fig. 4. This means that, locally, the crystallographic twofold symmetry must be broken, and one molecule of each form is present on opposite sides of the rotation axis. The H...H contact is still rather short, with $d(\text{H5D}_1 \cdots \text{H5D}_2) = 2.35$ Å. Other short intermolecular H...H contacts include $d(\text{H6A} \cdots \text{H5D}_1) = 2.24$ Å and $d(\text{H5A} \cdots \text{H6C}) = 2.26$ Å.

Supplementary material. Tables giving fractional coordinates for H atoms and anisotropic temperature parameters for heavy atoms are available from the authors on request, also by e-mail: c.h.gorbitz@kjemi.uio.no

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