Acta Chemica Scandinavica, 1998: 52: 218–226
Printed in UK – all rights reserved

Copyright © Acta Chemica Scandinavica 1998

ACTA
CHEMICA SCANDINAVICA
ISSN 0904-213X

Cocrystallizing Agents for Amino Acids. II. The Crystal Structures of L-Histidine · 4,5-Imidazoledicarboxylic Acid (1 : 1) and L-Lysine · 4,5-Imidazoledicarboxylic Acid (1 : 1)

Carl Henrik Görbitz* and Johanne Husdal

Department of Chemistry, University of Oslo, PO Box 1033 Blindern, N-0315 Oslo, Norway

Görbitz, C. H. and Husdal, J., 1998. Cocrystallizing Agents for Amino Acids. II. The Crystal Structures of L-Histidine · 4,5-Imidazoledicarboxylic Acid (1 : 1) and L-Lysine · 4,5-Imidazoledicarboxylic Acid (1 : 1). – Acta Chem. Scand. 52: 218–226. © Acta Chemica Scandinavica 1998.

The crystal structure of L-histidine (L-His) · 4,5-imidazoledicarboxylic acid (IDC) (1 : 1) has been refined to a final R (F_o) = 0.035 for 2857 observed reflections ($I > 2.5\sigma I$). A C–H···O hydrogen bond between the charged L-His side chain and an IDC carboxylate is among the shortest of this type ever observed. The dimensions are d(H···O) = 2.11(2) Å, d(C···O) = 2.912(2) Å and α(C-H···O) = 147(2)°. The crystal structure of L-lysine (L-Lys) IDC (2 : 2) (two L-Lys cations and two IDC anions in the asymmetric unit) has been refined to a final R (F_o) = 0.052 for 4153 observed reflections. One of the two L-Lys molecules has a unique eclipsed side chain conformation with a 128.9(5)° C^{β}–C^{γ}–C^{δ}–C^{ε} torsion angle.

The crystals were prepared as part of a program aimed at finding suitable cocrystallization agents for amino acids and peptides. For basic amino acids IDC is the best complementary organic acid found in this search. The crystal packing of the amino acids in the structures adapts to the need for stacking of the IDC molecules in layers with 3.3 Å spacing.

One of the lines of research pursued in our laboratory is the development of methods and techniques that will enhance our ability to grow high quality crystals of amino acids and peptides. As part of this investigation we have carried out cocrystallizations with a range of different compounds. Ref. 1 outlines the basic philosophy of these studies, and presents results for experiments involving acidic amino acids (Asp, Glu) and organic bases. We now present further results for basic amino acids (Arg, Lys, His) mixed with organic acids.

Extensive studies of 1 : 1 complexes between basic and acidic amino acids have been summarized in Ref. 2. Apart from the acetates (see below), other crystal structures of complexes between basic amino acids and organic acids presented in the past include L-Arg L-ascorbate,[3] DL-Arg hemisuccinate dihydrate,[4] L-Arg hemisuccinate hemisuccinic acid monohydrate,[4] L-Arg formate,[5] DL-Arg formate dihydrate,[5] L-His dihydrogentrimesate acetone solvate,[6] L-His α-ketoisocaproic acid ethanol solvate,[7] L-Lys D-pantothenate (no coordinates),[8] L-Lys hemisuccinate,[9] L-Lys succinate succinic acid,[9] DL-Lys hemisuccinate hemisuccinic acid,[9] L-Lys formate,[10] and DL-Lys formate.[10] The acids we have tested belong to six different groups: (A) aliphatic monocarboxylic acids, (B) aliphatic dicarboxylic acids, (C) picric acid, (D) sulfonic acids, (E) aromatic mono- and dicarboxylic acids and (F) 4,5-imidazoledicarboxylic acid (IDC). As before,[1] such a search cannot be exhaustive, but provides some insight into promising candidates for further experiments.

The three basic amino acids all form rather nice crystals with acetic acid, and several structures have been published: L-Arg acetate,[11] L-His acetate,[12] L-His acetate dihydrate (monoclinic),[12] L-His acetate dihydrate (triclinic),[13] and L-Lys acetate.[14] Small crystals could also be made with propionic acid (L-Arg, L-His) and formic acid (all three).[5,10] Other experiments, employing vapour diffusion of an organic solvent into an aqueous solution of the amino acid or slow evaporation from aqueous solution, were largely unsuccessful, although small needles or thin flakes were occasionally obtained. Only two crystallization batches produced large, high quality crystals: L-His IDC (1 : 1) (HISIDC) and L-Lys IDC (1 : 1) (LYSIDC), the two title compounds. L-Arg gave rather thin needles with IDC.

In most amino acid crystal structures the molecules are stacked on top of each other along a short crystallographic axis in the 5.1–5.7 Å range, which is more or less perpendicular to a least-squares plane calculated from all the heavy atoms in a molecule. The axis range

* To whom correspondence should be addressed.

is determined by the chiral C^{α}-atom (and other sp^3-hybridized C-atoms) which extends amino acids in three dimensions. In contrast, several common unsaturated molecules are more or less two-dimensional. When hydrogen bonding is abundant, these structures can form two-dimensional hydrogen-bonded sheets with a van der Waals' separation around 3.3 Å. It was of interest to see whether the amino acids would retain their usual packing arrangement in the crystal structures of the two title complexes with a two-dimensional molecule (IDC).

Nomenclature. The symbol $d(X–Y)$ is used to denote the X–Y bond length, while $d(X\cdots Y)$ is a non-bonded $X\cdots Y$ distance. The C^{α}-moiety of the amino acids, including the carboxylate and amino groups, is referred to as the 'head group', as opposed to the side chain.

Experimental

Preparation. The crystals were grown by slow diffusion of ethanol (LYSIDC) or 2-propanol (HISIDC) into 50 µl of an aqueous solution containing equimolar amounts of the basic amino acid and the complementary acid from group (A)–(F) (total mass ≈ 3 mg).

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

Refinement. Both structures were solved by the direct methods program SIR92,[15] revealing in the asymmetric unit of LYSIDC two L-Lys cations, hereafter called Lys(A) and Lys(B) and two IDC anions called IDC(C) and IDC(D). Refinement with GX[16] included anisotropic heavy atoms and for HISIDC isotropic H-atoms. For LYSIDC U_{iso} values for H-atoms were kept fixed at $1.2 \times U_{eq}$ of the bonded atom, or $1.5 \times U_{eq}$ for amino group and hydroxy group H-atoms. Further details are given in Table 1. Atomic scattering factors were taken from Ref. 17.

Cambridge Structural Database (CSD). Relevant structures were retrieved from the CSD (October 1996 release)[18] and their conformations analyzed by means of the accompanying programs QUEST3D and VISTA.

Results and discussion

ORTEP-II[19] drawings of the asymmetric units of HISIDC and LYSIDC are shown in Fig. 1 and Fig. 2,

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

	L-His·4,5-IDC	L-Lys·4,5-IDC
Formula	$C_6H_{10}N_3O_2^+ \cdot C_5H_3N_2O_4^-$	$C_6H_{15}N_2O_2^+ \cdot C_5H_3N_2O_4^-$
Formula weight/g mol^{-1}	311.29	302.19
Crystal size/mm	0.70 × 0.30 × 0.20	0.55 × 0.40 × 0.12
Color, habit	Colorless block	Colorless block
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$ (No. 4)	$P2_1$ (No. 4)
Cell dimensions/Å, °	a=8.921(2)	a=6.634(2)
	b=6.656(1)	b=28.629(7)
	c=12.040(2)	c=7.057(2)
	β=110.19(1)	β=97.53(2)
Volume/Å^3	670.9(2)	1331.8(5)
Z	2	4
D_{calc}/g cm^{-3}	1.541	1.548
Diffractometer	Nicolet P3	Nicolet P3
Radiation	Mo Kα (λ=0.710 69 Å)	Mo Kα (λ=0.710 69 Å)
Monochromator	Graphite crystal	Graphite crystal
T/K	120	120
Scan mode	2θ	2θ
Scan speed/° min^{-1}	4.0	4.0
2θ range/°	5.0–70.0	5.0–70.0
Standard reflections	3 measured every 96 refl.	3 measured every 96 refl.
Variation in standard intensities (%)	<2.0	<3.0
Index ranges	$-13 \leq h \leq 4$	$0 \leq h \leq 10$
	$0 \leq k \leq 10$	$0 \leq k \leq 46$
	$-18 \leq l \leq 18$	$-11 \leq l \leq 11$
No. of reflections measured	3066	6016
No. of observed reflections $[I > 2.5\sigma(I)] = n$	2857	4153
Absorption correction	None	None
Refinement	on F	on F
No. of parameters = p	250	486
$R = \Sigma\lvert\Delta F\rvert / \Sigma\lvert F_o\rvert$[a]	0.035	0.052
$R_w = [\Sigma w(\Delta F)^2 / \Sigma\, w(F_o)^2]^{1/2}$[b]	0.041	0.045
$S = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$	2.16	1.73
Residual electron density/e Å^{-3}	+0.37, −0.32	+0.37, −0.35

[a] $\Delta F = \lvert F_o\rvert - \lvert F_c\rvert$. [b] $w = 1/[\sigma^2(F_o) + 0.0004F_o^2]$.

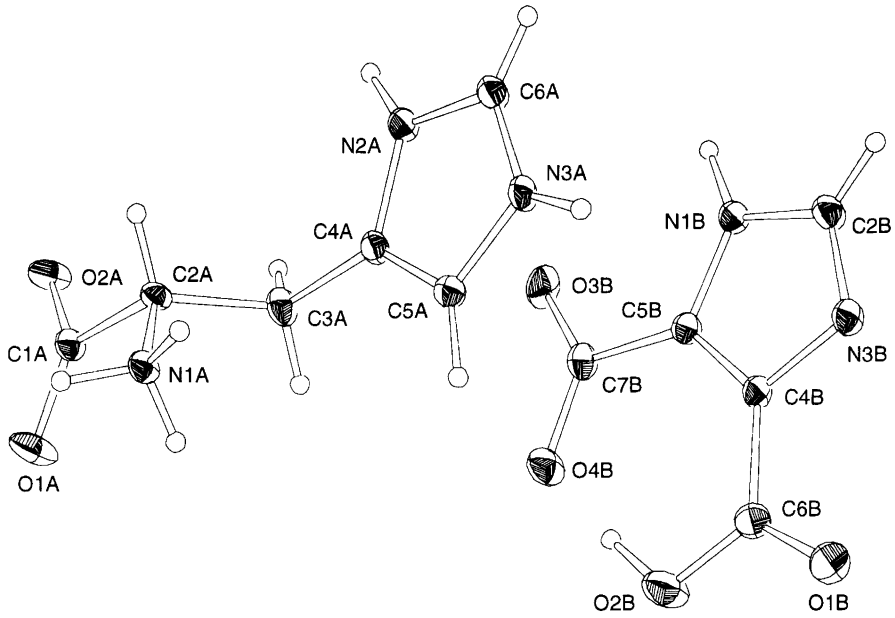


Fig. 1. The asymmetric unit of HISIDC with atomic numbering. In Fig. 1 and Fig. 2 the thermal ellipsoids for heavy atoms are shown at the 50% probability level. H-atoms are shown as spheres of arbitrary size.

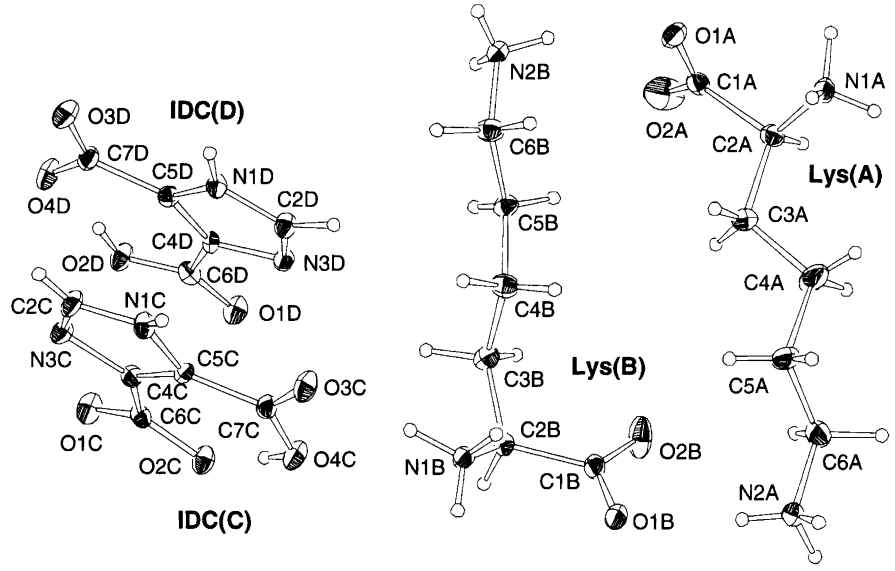


Fig. 2. The asymmetric unit of LYSIDC with atomic numbering.

respectively. Final atomic coordinates for heavy atoms are listed in Tables 2 and 3, while selected molecular geometry parameters are given in Table 4.

L-*His structure* (HISIDC). L-His is present in the crystal as a cation, with a protonated imidazole ring. There are no deviations from normal values for bond lengths and bond angles. The side chain is in a usual *gauche*$^-$ conformation at χ^1, with the ring plane almost at right angles to C^α–C^β–C^γ [$\chi^2 = -87.3(3)^\circ$, Table 4]. The positively charged ring system and the negatively charged α-carboxylate group are at maximum separation with no intramolecular hydrogen bonds.

L-*Lys structure* (LYSIDC). Bond lengths and bond angles are normal. The orientations of the side chains in molecules A and B are different at the C^α–C^β bond; χ^1 is *gauche*$^-$ for Lys(A), but *gauche*$^+$ for Lys(B). Other torsion angles in the two side chains are *trans*, except for the very unusual occurrence of a completely eclipsed conformation at $\chi^3 = 128.9(5)^\circ$ for Lys(A). Such conformations are very rare: among 4417 R–CH_2–CH_2–CH_2–CH_2–R (R = H, C, N, O) fragments located in 1038 crystal structures (error-free, *R*-factor <0.10, no disorder allowed) retrieved from the Cambridge Structural Database[18] only 20, or less than 0.5%, had C–C–C–C torsion angles within 10° of one of the eclipsed

Table 2. Fractional atomic coordinates with standard deviations and equivalent isotropic temperature factors (Å^2) for L-His · 4,5-imidazoledicarboxylic acid.

Atom	*x*	*y*	*z*	U_{eq}[a]
O1A	0.40595(12)	0.2171[b]	0.46048(9)	0.023
O2A	0.63312(12)	0.2494(3)	0.61323(8)	0.021
O1B	0.71630(13)	0.6934(3)	−0.14886(8)	0.025
O2B	0.60480(12)	0.7342(4)	−0.01194(9)	0.027
O3B	0.92676(14)	0.7703(3)	0.36130(9)	0.022
O4B	0.69679(13)	0.7706(3)	0.20736(9)	0.022
N1A	0.54983(16)	0.0257(3)	0.32656(11)	0.014
N2A	0.95975(14)	0.2533(3)	0.20688(10)	0.015
N3A	0.99609(14)	0.2149(3)	0.39237(10)	0.015
N1B	1.09844(14)	0.7041(3)	0.21110(10)	0.016
N3B	1.02139(15)	0.6755(3)	0.01598(10)	0.017
C1A	0.55251(16)	0.2039(4)	0.50709(11)	0.015
C2A	0.65141(16)	0.1400(3)	0.43148(12)	0.013
C3A	0.72004(19)	0.3294(4)	0.39381(13)	0.018
C4A	0.83451(17)	0.2837(4)	0.33196(12)	0.014
C5A	0.81308(16)	0.2597(4)	0.21537(11)	0.015
C6A	1.06889(17)	0.2125(4)	0.31479(11)	0.016
C2B	1.14432(17)	0.6781(4)	0.11639(12)	0.019
C4B	0.88907(16)	0.7025(4)	0.04873(11)	0.014
C5B	0.93640(16)	0.7204(4)	0.17095(11)	0.014
C6B	0.72960(17)	0.7095(4)	−0.04463(11)	0.018
C7B	0.84821(17)	0.7553(4)	0.25424(12)	0.016

[a] $U_{eq} = \frac{1}{3}\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \boldsymbol{a}_i \boldsymbol{a}_j$. [b] *b*-Axis anchor.

conformations at 0, 120 and 240°. This fraction remains unchanged if only structures with *R*-factor <0.075 are used (15 out of 3437). More than 90% of the fragments have torsion angles in the range 160–200°. As in L-His, the L-Lys side chain carries a positive charge, while the head group is zwitterionic. The molecule is thus a cation in the crystal, as it is in aqueous solution at physiological pH.[1]

4,5-Imidazoledicarboxylic acid structure. IDC is poorly solouble in water, but dissolves readily in acid or base. From its cationic form IDC can be deprotonated in three steps to the dianion (Scheme 1).

The last proton is very tightly bonded due to its participation in a very strong hydrogen bond between the two neighbouring carboxylate/carboxy groups. This H-bond requires that the hydroxy group is rotated to put the H-atom in the *anti* position, which for monocarboxylic acid is considerably less common than the normal *syn* configuration at the C^{α}–C^{β} bond. A CSD crystal structure search (error-free, *R*-factor <0.10) found 71 H-bonds of this type. The shortest interactions occur in hydrogen phthalates with $d(O\cdots O)$ averaging 2.392 Å for 18 observations from 2.351 to 2.421 Å. Hydrogen maleates constitute the largest group with 45 observations in the range 2.399–2.470 Å with average 2.426 Å. Among the eight remaining structures (range 2.421–2.478 Å, average 2.447 Å) there are two five-membered 3,4-furandicarboxylic acid ring systems, which have been crystallized as the potassium salt[20] (2.439 Å) or as a complex with 1,8-bis(dimethylamino)naphthalene[21] (2.468 Å). These figures mean that even though the corresponding

Table 3. Fractional atomic coordinates with standard deviations and equivalent isotropic temperature factors (Å^2) for L-Lys · 4,5-imidazoledicarboxylic acid.

Atom	*x*	*y*	*z*	U_{eq}[a]
O1A	0.0935(3)	0.5393[b]	1.0970(3)	0.021
O2A	0.4016(3)	0.5327(1)	1.2589(3)	0.038
O1B	0.8265(3)	0.4647(1)	0.3698(3)	0.023
O2B	0.8817(3)	0.4687(1)	0.6866(3)	0.029
O1C	1.3896(3)	0.7759(1)	0.5758(3)	0.022
O2C	1.3412(3)	0.7003(1)	0.5240(3)	0.019
O3C	0.7383(3)	0.6532(1)	0.2729(3)	0.021
O4C	1.0656(3)	0.6479(1)	0.3865(3)	0.020
O1D	1.3912(3)	0.7249(1)	1.0648(3)	0.021
O2D	1.3396(3)	0.8004(1)	1.0254(3)	0.020
O3D	0.7361(3)	0.8484(1)	0.7663(3)	0.023
O4D	1.0597(4)	0.8534(1)	0.8989(3)	0.022
N1A	0.0380(3)	0.4480(1)	1.0611(3)	0.016
N2A	0.6860(4)	0.3732(1)	0.4506(4)	0.021
N1B	0.8007(3)	0.5569(1)	0.3257(3)	0.015
N2B	0.3020(4)	0.6293(1)	1.0497(4)	0.020
N1C	0.7600(4)	0.7505(1)	0.2708(4)	0.015
N3C	1.0060(3)	0.7987(1)	0.3919(3)	0.015
N1D	0.7571(4)	0.7513(1)	0.7685(4)	0.014
N3D	1.0028(3)	0.7029(1)	0.8873(4)	0.015
C1A	0.2491(4)	0.5164(1)	1.1602(4)	0.018
C2A	0.2521(4)	0.4651(1)	1.0996(4)	0.016
C3A	0.3563(5)	0.4614(1)	0.9181(4)	0.020
C4A	0.3680(9)	0.4125(1)	0.8406(7)	0.055
C5A	0.4429(6)	0.4105(1)	0.6434(6)	0.031
C6A	0.6147(5)	0.3763(1)	0.6427(5)	0.021
C1B	0.8655(4)	0.4865(1)	0.5261(4)	0.016
C2B	0.9003(4)	0.5395(1)	0.5138(4)	0.014
C3B	0.8355(4)	0.5679(1)	0.6782(4)	0.018
C4B	0.6063(4)	0.5735(1)	0.6782(4)	0.018
C5B	0.5603(5)	0.5912(1)	0.8723(5)	0.015
C6B	0.3557(5)	0.6150(1)	0.8595(5)	0.020
C2C	0.8194(5)	0.7949(1)	0.3036(5)	0.017
C4C	1.0725(4)	0.7530(1)	0.4165(4)	0.013
C5C	0.9207(4)	0.7226(1)	0.3430(4)	0.012
C6C	1.2790(4)	0.7435(1)	0.5125(4)	0.014
C7C	0.9040(5)	0.6714(1)	0.3321(4)	0.016
C2D	0.8146(4)	0.7065(1)	0.7984(4)	0.017
C4D	1.0696(4)	0.7481(1)	0.9140(4)	0.012
C5D	0.9163(4)	0.7787(1)	0.8399(4)	0.013
C6D	1.2793(5)	0.7572(1)	1.0058(4)	0.015
C7D	0.8992(5)	0.8304(1)	0.8326(4)	0.017

[a] $U_{eq} = \frac{1}{3}\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \boldsymbol{a}_i \boldsymbol{a}_j$. [b] *b*-Axis anchor.

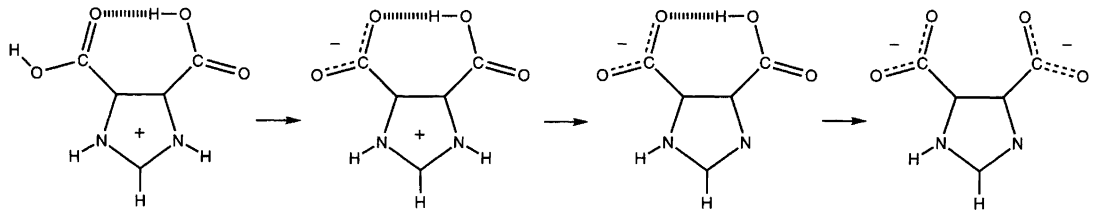
hydrogen bonds in HISIDC and IDC(C) and IDC(D) in LYSIDC, with $d(O\cdots O)$=2.492(2), 2.465(3) and 2.473(3) Å, respectively, are very short by usual standards, they are in fact long for this particular type of intramolecular interaction. The H-bond in HISIDC even represents a new upper limit for the observed $d(O\cdots O)$ range.

The reason for this is not obvious, although it might be pointed out that five-membered rings give smaller ring angles at the two points of carboxyl(ate) attachment than six-membered aromatic rings, which in turn increases the angle between the two C(ring)–C(OO) bonds. The ring C4–C5 bond lengths in the IDC structures average 1.387 Å, and have been stretched considerably compared with the same bond in imidazole measuring 1.357(2) Å.[22]

Table 4. Bond lengths (Å), bond angles ( ) and selected torsion angles ( ) for L-His · 4,5-imidazoledicarboxylic acid (His, IDC) and L-Lys · 4,5-imidazoledicarboxylic acid [Lys(A), Lys(B), IDC(C), IDC(D)].

	His	Lys(A)	Lys(B)
O1A–C1A[a]	1.235(2)	1.255(4)	1.264(4)
O2A–C1A	1.268(2)	1.241(4)	1.233(4)
N1A–C2A	1.485(3)	1.494(4)	1.488(4)
N2A–C4A	1.387(2)		
N2A–C6A	1.337(2)	1.495(5)	1.491(5)
N3A–C5A	1.380(2)		
N3A–C6A	1.328(2)		
C1A–C2A	1.531(3)	1.533(5)	1.544(4)
C2A–C3A	1.537(3)	1.536(5)	1.525(4)
C3A–C4A	1.488(3)	1.512(6)	1.529(5)
C4A–C5A	1.359(2)	1.538(7)	1.529(5)
C5A–C6A		1.505(6)	1.511(5)
	IDC	IDC(C)	IDC(D)
O1B–C6B[b]	1.224(2)	1.230(4)	1.225(4)
O2B–C6B	1.313(2)	1.306(4)	1.305(4)
O3B–C7B	1.240(2)	1.239(4)	1.234(4)
O4B–C7B	1.276(2)	1.281(4)	1.287(4)
N1B–C2B	1.349(2)	1.345(5)	1.348(5)
N1B–C5B	1.361(2)	1.375(4)	1.359(4)
N3B–C2B	1.323(2)	1.315(4)	1.325(4)
N3B–C4B	1.379(2)	1.388(5)	1.376(5)
C4B–C5B	1.389(2)	1.380(5)	1.392(5)
C4B–C6B	1.478(2)	1.471(5)	1.478(5)
C5B–C7B	1.491(2)	1.476(5)	1.488(5)
	His	Lys(A)	Lys(B)
C4A–N2A–C6A[a]	109.3(2)		
C5A–N3A–C6A	108.9(2)		
O1A–C1A–O2A	125.8(2)	125.0(3)	125.4(3)
O1A–C1A–C2A	119.1(2)	116.4(3)	116.9(3)
O2A–C1A–C2A	115.0(2)	118.6(3)	117.7(3)
N1A–C2A–C1A	109.9(2)	108.6(3)	109.2(3)
N1A–C2A–C3A	110.9(2)	110.4(3)	111.1(3)
C1A–C2A–C3A	108.5(2)	108.7(3)	115.1(3)
C2A–C3A–C4A	113.1(2)	114.5(3)	115.8(3)
N2A–C4A–C3A	122.4(2)		
N2A–C4A–C5A	105.9(2)		
C3A–C4A–C5A	131.6(2)	113.5(4)	110.5(3)
N3A–C5A–C4A	107.6(2)		
N2A–C6A–N3A	108.2(2)		
C4A–C5A–N2A		111.9(3)	113.0(3)
	IDC	IDC(C)	IDC(D)
C2B–N1B–C5B[b]	107.8(2)	106.9(3)	107.7(3)
C2B–N3B–C4B	105.0(2)	104.1(3)	104.9(3)
N1B–C2B–N3B	112.1(2)	113.4(3)	112.2(3)
N3B–C4B–C5B	109.7(2)	110.2(3)	109.7(3)
N3B–C4B–C6B	118.7(2)	119.5(3)	119.6(3)
C5B–C4B–C6B	131.6(2)	130.2(3)	130.7(3)
N1B–C5B–C4B	105.5(2)	105.3(3)	105.6(3)
N1B–C5B–C7B	121.1(2)	120.7(3)	120.8(3)
C4B–C5B–C7B	133.5(2)	134.0(3)	133.6(3)
O1B–C6B–O2B	121.7(2)	121.7(3)	121.3(3)
O1B–C6B–C4B	120.3(2)	120.2(3)	120.5(3)
O2B–C6B–C4B	118.0(2)	118.1(3)	118.2(3)
O3B–C7B–O4B	125.8(2)	123.4(3)	124.4(3)
O3B–C7B–C5B	118.1(2)	119.6(3)	119.3(3)
O4B–C7B–C5B	116.0(2)	117.0(3)	116.3(3)
	His	Lys(A)	Lys(B)
N1A–C2A–C1A–O1A[a]	−23.1(2)	−27.7(3)	22.7(3)
N1A–C2A–C3A–C4A (χ^1)	−66.1(2)	−60.4(4)	51.9(3)
C2A–C3A–C4A–N2A (χ^2)	−87.3(3)		
C2A–C3A–C4A–C5A (χ^2)		171.2(5)	165.4(4)
C3A–C4A–C5A–C6A (χ^3)		128.9(5)	157.3(3)
C4A–C5A–C6A–N2A (χ^4)		178.7(5)	175.8(4)
	IDC	IDC(C)	IDC(D)
N3B–C4B–C6B–O2B	179.6(3)	−176.2(5)	178.5(5)
N1B–C5B–C7B–O4B	179.2(3)	173.8(5)	−178.1(5)

[a]Atom names *xn***B** for Lys(B). [b]Atom names *xn***C** for IDC(C), *xn***D** for IDC(D).



Scheme 1.

The bond is, however, still shorter than the corresponding bond in hydrogen phthalates, which is always stretched in a similar manner. As usual, there is also some opening of the C–C–C′ angles, which are larger than the N–C–C′ angles (averages 132.2° and 120.1°, respectively), to alleviate uncomfortably short O···O distances. d(O···O) is also sensitive to rotation around the C–C′ bonds (Scheme 1), but the torsion angles listed in Table 4 show that deviations from planarity are small for all three IDC molecules, and indeed insignificant for HISIDC which has the largest d(O···O).

It can be seen from Fig. 2 that the location of the carboxylic H-atom is different in IDC(C) and IDC(D). The positioning of this proton was straightforward for IDC(D), but difference Fourier maps revealed electron density close to both O2C and O4C for IDC(C). Independent of the starting position of the H-atom, however, an unconstrained refinement always resulted in an H-atom position close to O4C. On the other hand, as judged by the covalent C–O bond lengths in the molecule, which are almost identical with those observed in IDC(D) (Table 4), a covalent bond to O2C seems more likely. We cannot draw definite conclusions on this matter from the present data.

Crystal packing and hydrogen bonds. The crystal packing of HISIDC is illustrated in Fig. 3. One of the L-His amino group H-atoms is accepted by the carboxylate group of the neighbouring L-His related by a twofold screw axis, generating a left-handed hydrogen-bonded spiral parallel to the b-axis. The two other amino H-atoms are accepted by IDC molecules in two adjacent two-dimensional layers formed by the side chain imidazole group of L-His and IDC. One such layer is illustrated in Fig. 4, which also shows all the hydrogen bonds in

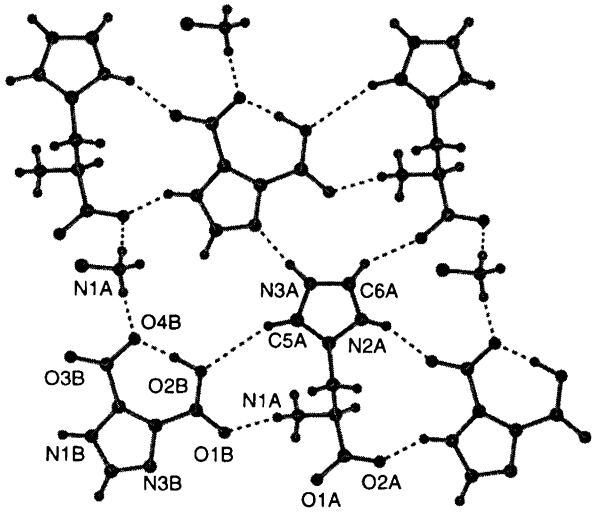


Fig. 4. A hydrogen bonded layer in the crystal structure of HISIDC. There are seven different interactions in the layer, including one intramolecular for IDC, and two interactions with bridging L-His α-amino groups from molecules located in a layer above the one shown. See also Fig. 3.

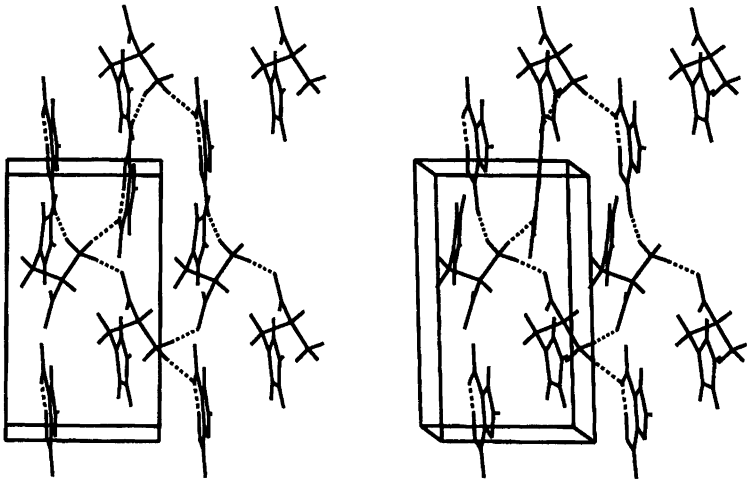


Fig. 3. Stereoview of the packing arrangement and the unit cell of HISIDC, viewed along the a-axis with horizontal b-axis. Hydrogen bonds are indicated as dotted lines.

Table 5. Hydrogen bond distances (Å) and angles (·) for L-His · 4,5-imidazoledicarboxylic acid.

D–H···A	*D*–H	H···A	*D*···A	*D*–H···A
N1A–H11A···O4B$^{i a}$	0.88(3)	1.96(2)	2.821(2)	169(2)
N1A–H12A···O1B^{ii}	0.88(3)	1.98(2)	2.820(2)	158(2)
N1A–H13A···O2A^{iii}	0.96(3)	1.76(3)	2.718(2)	175(2)
N2A–H2A···O3B^{iv}	0.89(2)	1.96(2)	2.806(2)	158(2)
N3A–H3A···N3B^{v}	0.97(3)	1.80(3)	2.758(2)	169(3)
C5A–H51A···O2B^{ii}	1.00(2)	2.75(2)	3.691(2)	157(2)
C6A–H61A···O1A^{vi}	0.91(3)	2.11(2)	2.912(2)	147(2)
N1B–H1B···O2A^{vii}	0.96(3)	1.74(2)	2.608(2)	149(2)
O2B–H2B···O4B	1.00(3)	1.49(3)	2.492(2)	172(4)

[a]Symmetry codes: $^{i}x, y-1, z$; $^{ii}1-x, y-1/2, -z$; $^{iii}1-x, y-1/2, 1-z$; $^{iv}2-x, y-1/2, 1-z$; $^{v}2-x, y-1/2, -z$; $^{vi}x+1, y, z$; $^{vii}2-x, y+1/2, 1-z$.

the structure, listed in Table 5. One of two C–H···O interactions is very long, but the second is among the shortest ever recorded in a crystal structure, with $d(\mathrm{H}\cdots\mathrm{O})=2.11(2)$ Å and $d(\mathrm{C}\cdots\mathrm{O})=2.912(2)$ Å (Table 5). When the C–H bond length [0.91(2) Å] is normalized[23] to 1.100 Å, the value for $d(\mathrm{H}\cdots\mathrm{O})=$ 1.947 Å. The crystal structure of 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide hydrochloride monohydrate [24] is the only example found in the CSD of a similar contact with $d(\mathrm{H}\cdots\mathrm{O})<2.20$ Å [$d(\mathrm{H}\cdots\mathrm{O})=$ 2.14 Å experimentally, 1.974 Å normalized]. Additionally, very short contacts exist in imidazolium hydrogen succinate[25] with $d(\mathrm{H}\cdots\mathrm{O})=2.13$ Å and imidazolium succinamate succinamic acid[25] with $d(\mathrm{H}\cdots\mathrm{O})=2.11$ Å.

Table 6. Hydrogen bond distances (Å) and angles (°) for L-Lys · 4,5-imidazoledicarboxylic acid.

D–H···A	*D*–H	H···A	*D*···A	*D*–H···A
N1A–H11A···O1B$^{i a}$	0.95(4)	1.84(3)	2.783(3)	169(3)
N1A–H12A···O4D^{ii}	0.87(4)	1.98(4)	2.812(3)	159(3)
N1A–H13A···O2B^{iii}	0.85(4)	1.93(4)	2.772(3)	171(4)
N2A–H21A···O1C^{iv}	0.93(5)	2.45(4)	2.838(4)	105(3)
N2A–H21A···O3D^{v}	0.93(5)	2.25(4)	3.091(4)	151(3)
N2A–H22A···O1C^{iv}	0.87(5)	2.45(4)	2.838(4)	108(3)
N2A–H22A···N3C^{iv}	0.87(5)	2.27(4)	3.062(4)	151(4)
N2A–H23A···O1B	0.83(5)	2.04(4)	2.868(4)	173(4)
N1B–H11B···O1A^{vi}	0.86(4)	1.92(3)	2.731(3)	155(3)
N1B–H12B···O3C	0.96(4)	1.85(4)	2.718(3)	172(3)
N1B–H13B···O2A^{vii}	1.00(4)	1.73(3)	2.811(3)	168(3)
N2B–H21B···O1A	0.88(5)	2.22(4)	2.970(3)	144(3)
N2B–H21B···O2A	0.88(5)	2.46(4)	3.170(4)	138(3)
N2B–H22B···O1D^{iii}	0.87(5)	2.55(4)	2.804(4)	98(3)
N2B–H22B···N3D^{iii}	0.87(5)	2.20(4)	3.017(4)	156(4)
N2B–H23B···O3C^{viii}	0.93(4)	2.27(4)	3.182(4)	169(4)
N2B–H23B···O1D^{iii}	0.93(4)	2.47(4)	2.804(4)	101(3)
N1C–H1C···O1D^{ix}	0.90(4)	1.89(3)	2.774(3)	169(3)
O4C–H4C···O2C	0.80(4)	1.66(4)	2.465(3)	179(4)
N1D–H1D···O1C^{iii}	0.89(4)	1.85(3)	2.723(3)	167(3)
O2D–H2D···O4C	0.79(4)	1.68(4)	2.473(3)	174(4)

[a]Symmetry codes: $^{i}x-1, y, z+1$; $^{ii}1-x, y-1\,2, 2-z$; $^{iii}x-1, y, z$; $^{iv}2-x, y-1\,2, 1-z$; $^{v}1-x, y-1\,2, 1-z$; $^{vi}x+1, y, z-1$; $^{vii}x, y, z-1$; $^{viii}x, y, z+1$; $^{ix}x-1, y, z-1$.

The normalized $d(\mathrm{H}\cdots\mathrm{O})$ values are 1.993 and 1.956 Å, respectively. The unprecedented shortness of the interaction in the HISIDC structure is a result of the inherent imbalance between the number of donors and acceptors

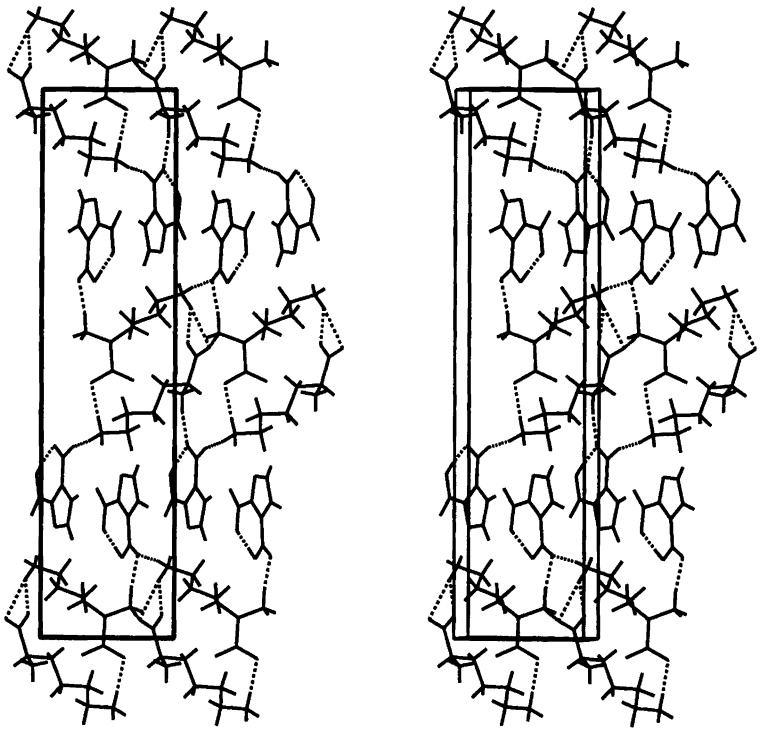


Fig. 5. The packing arrangement and the unit cell of LYSIDC, viewed along the *a*-axis with horizontal *c*-axis. Lys(A) and Lys(B) in the L-Lys dimers are distinguishable, with Lys(B) being the donor in the three-centre hydrogen bond.

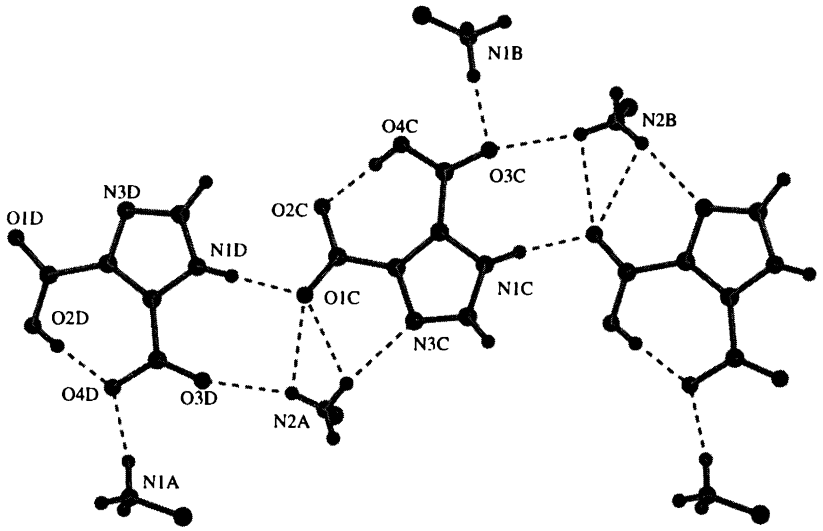


Fig. 6. A hydrogen bonded ribbon in the crystal structure of LYSIDC. Side chain ε-amino groups are integral parts of the ribbon through formation of four unusual three-center interactions.

in the crystal. There are only seven classical N–H and O–H donors, but about 12 acceptor sites (counting four on each carboxylate group, three on –COOH and one on the ring >N:). The L-His α-carboxylate group accepts only two (N–)H and (O–)H atoms, an extremely rare event.[26] O1A is unique in accepting no such H-atoms whatsoever, and is thus a very strong acceptor for a C–H from a charged imidazole group, which is known to be a good donor.

The crystal packing of LYSIDC is illustrated in Fig. 5, while hydrogen bond parameters are listed in Table 6. A dimer is formed by the two Lys molecules in the asymmetric unit, which are connected by two hydrogen bonds with side chain donors and carboxylate acceptors. The dimers are in turn interconnected by two perpendicular $(H–N1A–H\cdots O1B–C1B–O2B)_n$ and $(H–N1B–H\cdots O1A–C1A–O2A)_n$ chains (not readily discernible in Fig. 4) utilizing the Lys(A) and Lys(B) α-carboxylate and α-amino groups.

There are no distinct layers in the LYSIDC structure, but IDC(C) and IDC(D) take part in hydrogen-bonded ribbons, Fig. 6. The ribbons also include the two side chain $–NH_3^+$ groups, which form four three-centre interactions, and the last H-atom of each of the two α-NH_3^+ groups. The latter H-atom is accepted by O3C in IDC(C) and O4D in IDC(D), the only significant difference between their hydrogen bonding arrangements.

The ribbons in LYSIDC are stacked with a separation of about 3.3 Å, as are the layers in HISIDC. The shortest axis in the two structures is 6.656 Å for HISIDC and 6.634 Å for LYSIDC, i.e., outside the normal range for crystal structures of isolated animo acids. It is obviously necessary to stack IDC, and in the case of HISIDC also the L-His side-chain imidazole group, in a favourable manner. This in turn leads to profoundly modified molecular packing of the amino acid molecules in the complexes relative to what is observed for the free acids.

Supplementary material. Tables giving fractional coordinates for all 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

References

1. Görbitz, C. H. and Husdal, J. *Acta Chem. Scand.* 50 (1996) 796.
2. Soman, J., Vijayan, M., Ramakrishnan, B. and Row, T. N. G. *Biopolymers 29* (1990) 533.
3. Sudhakar, V. and Vijayan, M. *Acta Crystallogr., Sect. B 36* (1980) 120.
4. Prasad, G. S. and Vijayan, M. *Int. J. Peptide Protein Res. 35* (1990) 357.
5. Suresh, S., Padmanabhan, S. and Vijayan, M. *J. Biomol. Struct. Dyn.* 11 (1994) 1425.
6. Herbstein, F. H. and Kapon, M. *Acta Crystallogr., Sect. B 35* (1979) 1614.
7. Nagashima, N., Kishimoto, S., Tanabe, T. and Iitaka, Y. *Anal. Sci. 9* (1993) 743.
8. Salunke, D. M. and Vijayan, M. *Biochim. Biophys. Acta 789* (1984) 175.
9. Prasad, G. S. and Vijayan, M. *Acta Crystallogr., Sect. B 47* (1991) 927.
10. Suresh, S. and Vijayan, M. *Acta Crystallogr., Sect. B 51* (1995) 353.
11. Suresh, S. and Vijayan, M. *Int. J. Peptide Protein Res. 21* (1983) 223.
12. Suresh, S., Prasad, G. S. and Vijayan, M. *Int. J. Peptide Protein Res. 43* (1994) 139.
13. Rømming, C., Mostad, A. and Nystøl, K. A. *Z. Kristallogr. 210* (1995) 352.
14. Suresh, S. and Vijayan, M. *Int. J. Peptide Protein Res. 22.* (1983) 617.
15. Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. and Camalli, M. *J. Appl. Crystallogr. 27* (1994) 435.
16. Mallinson, P. R. and Muir, K. W. *J. Appl. Crystallogr. 18* (1985) 51.
17. *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham 1974, Vol. 4.

18. Allen, F. H. and Kennard, O. *Chem. Design Automation News 8* (1993) 31.
19. Johnson, C. K. ORTEP II. Report ORNL-5138, Oak Ridge National Laboratory, Tennesee, USA 1976.
20. Jaulmes, S. *Acta Crystallogr., Sect. B 34* (1978) 116.
21. Głowiak, T., Grech, E., Malarski, Z. and Sobczyk, L. *J. Mol. Struct. 295* (1993) 105.
22. Craven, B. M., McMullan, R. K., Bell, J. D. and Freeman, H. C. *Acta Crystallogr., Sect. B 33* (1977) 2585.
23. Taylor, R. and Kennard, O. *Acta Crystallogr., Sect. B 39* (1983) 133.
24. Edwards, S. L., Sherfinski, J. S. and Marsh, R. E. *J. Am. Chem. Soc. 96* (1974) 2593
25. MacDonald, J. C. Ph.D.-thesis, University of Minnesota, USA, 1993.
26. Görbitz, C. H. and Etter, M. C. *Int. J. Peptide Protein Res. 39* (1992) 93.

Received April 7, 1997.