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N-[3-(Cytosin-1-yl)propionyl]-L-isoleucine, a heavily hydrated structure with four cytosine–isoleucine hybrids in the asymmetric unit

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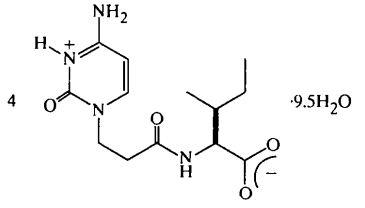
Abstract

A hybrid molecule, *N*-[3-(4-amino-1,2-dihydro-2-oxopyrimidin-1-yl)propionyl]-L-isoleucine (C-Ile), was crystallized with four cytosine–isoleucine hybrid molecules and 9.5 waters of hydration in the asymmetric unit, *i.e.* $4C_{13}H_{20}N_4O_4{\cdot}9.5H_2O$. The conformations of the four independent C-Ile molecules are similar, but not identical. They are interconnected by hydrogen bonds, many of which involve bridging solvent molecules.

Comment

A hybrid molecule, *N*-[3-(cytosin-1-yl)propionyl]-L-isoleucine (C-Ile), was synthesized as part of a series of studies designed to investigate interactions between nucleic acids and peptides (Kamiichi *et al.*, 1987). We have reported the structure of *N*-[3-(cytosin-1-yl)propionyl]-L-tryptophan (Ishida *et al.*, 1993; Doi *et al.*, 1998), and the importance (Hamilton & Little, 1990) of the aromatic ring in nucleic base and peptide interactions was evaluated. The present investigation enables comparison of the contributions of alkyl and aromatic groups in such interactions.



C-Ile

Since Ile has no polar atom in its side chain, an anhydrous crystal form was expected for C-Ile by analogy with the structures of related hybrid molecules. However, the crystals are highly solvated and have four crystallographically independent hybrid molecules in the asymmetric unit. The structure was solved using *LODEM* (Matsugaki & Shiono, 1998), which is a density modification program designed to produce an *ab initio* solution by refining random phase sets. The C-Ile molecules (Fig. 1) are related by pseudo-2_1 symmetry along the x axis in the crystal packing. They form hydrogen bonds between the imino and amino groups (N3 and N4) of the bases and the carboxyl groups (O10 and O10*T*) of the isoleucine residues (Table 1); the modes of interaction are comparable in all four molecules. The C-termini of the molecules

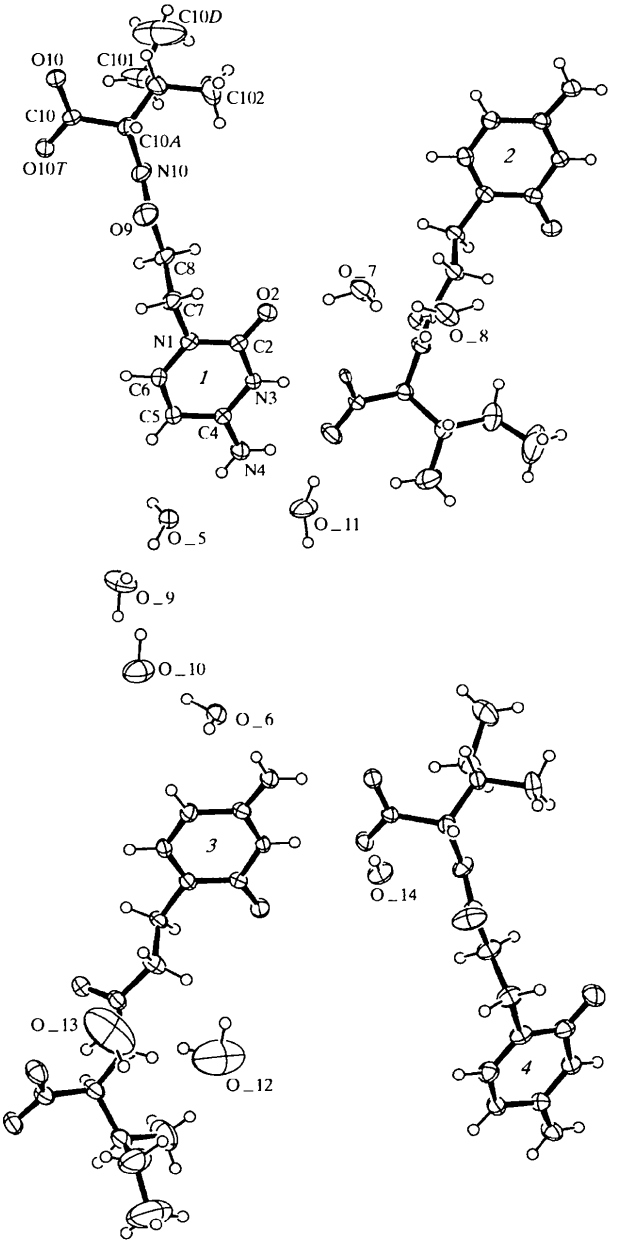


Fig. 1. An *ORTEP*III view (Burnett & Johnson, 1996) of the title compound. Displacement ellipsoids are drawn at the 50% probability level. The four independent molecules are represented by italic numbers.

seem to be in the anionic form since the C10—O10 and C10—O10*T* bond distances range from 1.229 (4) to 1.262 (4) Å. In addition, donor–acceptor hydrogen-bonding relationships suggest that the cytosine bases are protonated at the N3 position and that the C-Ile molecules are zwitterionic.

Stacking interactions involving the cytosine bases only are observed between molecules 1 and 2, and between molecules 3 and 4; no specific interactions are observed between neighboring cytosine bases and Ile side chains. Molecular-fitting calculations show small but significant differences among the conformations of the four molecules. These calculations (Pflugrath *et al.*, 1984) were performed by superimposing the cytosine moieties (N1 → O9 including H atoms); r.m.s. deviations of 0.151, 0.296 and 0.131 Å are obtained for molecules 2, 3 and 4, respectively, by fitting them against molecule 1. Fig. 2 shows the superimposition of the molecules and the relative conformational differences in the side chains of Ile. The related torsion angles φ (C9—N10—C10*A*—C10) are −98.5 (4), −122.1 (4), −75.3 (5) and −102.0 (4)°, and χ (N10—C10*A*—C10*B*—C10*1*) are 65.6 (6), −55.7 (5), 67.5 (6) and 64.6 (4)° for molecules 1, 2, 3 and 4, respectively. These conformational differences appear to be mediated by differences in hydrogen bonding to solvent (Table 1).

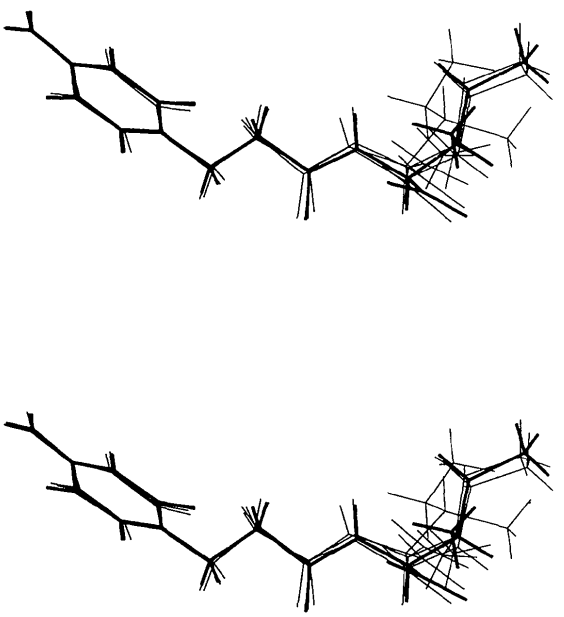


Fig. 2. A stereoview of the superimposition of the four independent molecules. Thick lines show molecule 1.

Experimental

C-Ile was synthesized by coupling 1-ethylcarboxycytosine and isoleucine methyl ester according to a previous report (Kamiichi *et al.*, 1987). Crystals were obtained from aqueous solution, though most of them were twinned or were unsuitable for X-ray diffraction studies. The sample was purified by high-performance liquid chromatography, because very slight contamination seems to affect the crystallization. A crystal suitable for X-ray diffraction was then obtained.

Crystal data

$4C_{13}H_{20}N_4O_4 \cdot 9.5H_2O$
M_r = 1356.47
Orthorhombic
$C222_1$
a = 14.190 (3) Å
b = 57.435 (10) Å
c = 17.4063 (18) Å
V = 14186 (4) Å^3
Z = 8
D_x = 1.270 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54180 Å
Cell parameters from 25 reflections
θ = 20.58–22.06°
μ = 0.861 mm^{-1}
T = 293 (2) K
Plate
0.60 × 0.11 × 0.08 mm
Colorless

Data collection

Rigaku AFC-5*R* diffractometer
2θ–ω scans
Absorption correction: none
12 671 measured reflections
6626 independent reflections (plus 5495 Friedel-related reflections)
11 006 reflections with $I > 2\sigma(I)$
R_{int} = 0.102
θ_{max} = 65.14°
h = −16 → 16
k = 0 → 67
l = 0 → 20
3 standard reflections
every 150 reflections
intensity decay: 7.78%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.076
$wR(F^2)$ = 0.222
S = 1.003
12 121 reflections
845 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.1656P)^2 + 14.4219P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.683 e Å^{-3}
$\Delta\rho_{min}$ = −0.523 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.0 (2)

Table 1. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
Molecule 1				
N3_1—H3_1···O10*T*_2^{i}	0.86	1.78	2.635 (4)	172
N4_1—H4*A*_1···O10_2^{i}	0.87	1.93	2.784 (4)	165
N4_1—H4*B*_1···O_5	0.85	2.10	2.942 (4)	171
N10_1—H10_1···O_7	0.86	2.01	2.849 (4)	165
Molecule 2				
N3_2—H3_2···O10*T*_1^{i}	0.86	1.80	2.657 (4)	171
N4_2—H4*A*_2···O10_1^{i}	0.86	1.94	2.788 (4)	173
N4_2—H4*B*_2···O_6	0.87	2.03	2.890 (4)	172
N10_2—H10_2···O_8	0.86	2.02	2.872 (4)	172
Molecule 3				
N3_3—H3_3···O10*T*_4	0.86	1.89	2.745 (4)	173
N4_3—H4*A*_3···O10_4	0.87	1.90	2.763 (4)	173
N4_3—H4*B*_3···O_6	0.86	2.01	2.852 (4)	170
N10_3—H10_3···O_12	0.86	2.33	3.167 (11)	164
Molecule 4				
N3_4—H3_4···O10*T*_3^{ii}	0.86	1.90	2.756 (4)	173
N4_4—H4*A*_4···O10_3^{ii}	0.86	1.89	2.739 (4)	169
N4_4—H4*B*_4···O_5^{iii}	0.86	1.97	2.829 (4)	173
N10_4—H10_4···O2_3^{iv}	0.86	2.45	3.211 (4)	149

Water related				
O_5—HA_5···O_11	0.93	1.78	2.695 (5)	167
O_5—HB_5···O_9	1.02	1.71	2.725 (5)	172
O_6—HA_6···O10_3	1.00	1.90	2.775 (4)	145
O_6—HB_6···O_10	0.99	1.67	2.664 (5)	178
O_7—HA_7···O9_2	0.97	1.73	2.707 (4)	178
O_7—HB_7···O2_1	0.98	1.77	2.746 (4)	176
O_8—HA_8···O_7	0.95	1.80	2.757 (5)	179
O_8—HB_8···O2_2	0.98	2.16	3.138 (4)	173
O_9—HA_9···O10_1	0.98	1.90	2.874 (5)	173
O_9—HB_9···O10_4	0.97	1.83	2.803 (4)	175
O_10—HA_10···O10_1	1.01	1.72	2.724 (4)	174
O_10—HB_10···O10_4	1.01	1.92	2.928 (5)	175
O_11—HA_11···O10_3	0.99	1.82	2.814 (5)	176
O_11—HB_11···O10_2	0.97	1.72	2.688 (5)	179
O_12—HA_12···O_13	1.03	2.11	3.140 (18)	176
O_12—HB_12···O2_4	0.96	2.17	3.128 (8)	178
O_12—HA_12···N10_3	1.03	2.86	3.167 (11)	98
O_13—HA_13···O10T_3	0.96	1.89	2.831 (10)	169
O_13—HB_13···O9_4	1.07	1.93	2.983 (9)	170
O_14—H_14···O10T_4	1.00	1.86	2.850 (3)	177

Symmetry codes: (i) $\frac{1}{2}-x, \frac{1}{2}-y, z-\frac{1}{2}$; (ii) $x, y, 1+z$; (iii) $1-x, -y, z-\frac{1}{2}$; (iv) $x, -y, 1-z$.

The title structure was solved using *LODEM* (Matsugaki & Shiono, 1998), which is a density modification program designed to produce an *ab initio* solution by refining random phase sets. The program transforms the density (ρ) by $\rho' = \rho[1-\exp\{-0.5(\rho/0.2\rho_c)^2\}]$, if $\rho > 0$, or $\rho' = 0$, if $\rho < 0$, where ρ_c is the expected average peak height of light atoms in the structure. The results of structure determinations are given in terms of phases or peak positions in an asymmetric unit. The basic idea of the procedure is to remove negative density and also to sharpen peaks. Ten peaks remained in the final difference Fourier map. One of them (O_14) was located on a special position. These peaks were assigned as water molecules since no atom was found within covalent bond distance. The Flack (1983) parameter is consistent with the known absolute stereochemistry of the starting materials.

Data collection: *MSC/AFC Diffractmeter Control Software* (Molecular Structure Corporation, 1991). Cell refinement: *MSC/AFC Diffractmeter Control Software*. Data reduction: *MSC/AFC Diffractmeter Control Software*. Program(s) used to solve structure: *LODEM* (Matsugaki & Shiono, 1998). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *ORTEP*III (Burnett & Johnson, 1996). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1078). Services for accessing these data are described at the back of the journal.

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Hexamethylenetetramine is a fourfold acceptor of O—H···N hydrogen bonds in its 1:2 adduct with 2,2′-biphenol

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Abstract

In hexamethylenetetramine–2,2′-biphenol (1/2), $C_6H_{12}N_4{\cdot}2C_{12}H_{10}O_2$, the biphenol acts as a double donor of O—H···N hydrogen bonds and the hexamethylenetetramine acts as a fourfold acceptor. The molecules are assembled into deeply puckered pseudo-tetragonal nets built from $R_8^8(44)$ rings.

Comment

In hydrogen-bonded systems, hexamethylenetetramine (HMTA, $C_6H_{12}N_4$) generally acts as a double acceptor of hydrogen bonds (Dahl & Hassel, 1971; Mak *et al.*, 1978; Mahmoud & Wallwork, 1979; Ferguson *et al.*, 1995; Coupar, Glidewell & Ferguson, 1997; Meehan *et al.*, 1997). Rather less frequently, HMTA behaves as an acceptor of just one hydrogen bond (Mak *et al.*, 1986; Coupar, Glidewell & Ferguson, 1997) or of three

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