The synthesis and X-ray structures of the geometric isomers of 1-amino-1,2-cyclopentanedicarboxylic acid

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The geometric isomers of 1-amino-1,2-cyclopentanedicarboxylic acid were isolated as the hydrolysis products of 2-cyclopentanecarboxylic acid-5,5′-hydantoin. The hydantoin ester was formed from ethyl -2-oxocyclopentanecarboxylate via a Bucherer–Bergs reaction. Hydrolysis of the hydantoin at elevated temperatures gave a mixture of *trans*- and *cis*-1-amino-1,2-cyclopentanedicarboxylic acids indicating epimerization during hydrolysis. The *trans* product has not been described previously and the *cis* not extensively characterized. X-ray crystallography reveals that both isomers are zwitterionic in the solid state and the *cis* isomer molecules are linked by unusually strong hydrogen bonding. Structures were confirmed by ^{13}C NMR, X-ray crystallography, and elemental analysis. Physical data are also presented.

KENNETH CURRY, HUGH MCLENNAN, STEVEN J. RETTIG et JAMES TROTTER. Can. J. Chem. **71**, 76 (1993).

Les isomères géométriques de l'acide 1-amino-cyclopentane-1,2-dicarboxylique ont été isolés comme produits d'hydrolyse de la 5,5′-hydantoïne de l'acide cyclopentane-2-carboxylique. On a obtenu l'ester hydantoïne par une réaction de Bucherer–Bergs sur le 2-oxocyclopentanecarboxylate d'éthyle. L'hydrolyse de l'hydantoïne à température élevée conduit à un mélange des acides 1-amino-cyclopentane-1,2-dicarboxyliques *trans* et *cis* indiquant qu'une épimérisation se produit au cours de l'hydrolyse. Le produit *trans* n'avait pas été décrit antérieurement alors que le composé *cis* n'avait pas été très bien caractérisé. La cristallographie des rayons X révèle que, dans la phase solide, les deux isomères sont zwitterioniques et que les molécules de l'isomère *cis* sont reliées par des liaisons hydrogènes inhabituellement fortes. On a confirmé les structures par RMN du ^{13}C, par diffraction des rayons X et par analyse élémentaire. On rapporte aussi les données physiques.

[Traduit par la rédaction]

Introduction

Considerable recent interest has been generated in the pharmacology of acidic amino acids related to glutamic and aspartic acids because of the perceived role of these compounds as synaptic transmitters in the mammalian central nervous system. One method of analyzing the receptors that mediate these neuronal events is to produce rigid analogs of glutamic and aspartic acids (1–3). The synthesis of the glutamic acid analogs, *trans*- and *cis*-1-amino-1,3-cyclopentanedicarboxylic acids, has already been described (4) and we report here on the synthesis of the corresponding aspartic acid analogs, *cis*-**4** and *trans*-**5** 1-amino-1,2-cyclopentanedicarboxylic acids (Fig. 1).[3]

Experimental

Melting points were determined on a Fisher–Johns apparatus; UV λ_{max} was determined on an L.K.B. Ultrospec II or a Pye–Unicam SP-8-100 dual beam spectrophotometer.

Ethyl 2-cyclopentanecarboxylate-1-spiro-5-hydantoin, 2

Compound **2** was prepared by a modification of the method of Connors and Ross (5), resulting in two products that were separated by fractional crystallization from chloroform and methanol. After cooling, **2** was isolated as a white solid, 51 g (56%), mp 141°C (lit. (5) mp 145°C), and confirmed by ^{13}C NMR. The second product was determined by ^{13}C NMR to be 2-cyclopentanecarboxylic acid-1-spiro-5-hydantoin **3**. Yield 10.4%. NMR data are presented in Table 1.

2-Cyclopentanecarboxylic acid-1-spiro-5-hydantoin, 3

Hydrolysis of **2** in 4 M hydrochloric acid (HCl) gave 43.5 g of a colorless crystalline material, mp 220°C (lit. (5) mp 225–226°C); UV λ_{max} 307 nm. ^{13}C NMR (Table 1) revealed this to be a single product consistent with the predicted structure of **3**. Anal. calcd. for $C_8H_{10}N_2O_4$: C 48.48, H 5.09, N 14.14; found: C 48.60, H 5.14, N 14.22.

cis- *and* trans-*1-Amino-1,2-cyclopentanedicarboxylic acids, 4 and 5*

Compound **3** (14.0 mmol, 2.8 g) was suspended in 100 mL of 6 M HCl and placed in a pressure reaction vessel. The vessel was sealed and maintained at 155–160°C for 6 h. The vessel was allowed to cool to room temperature and the resulting solution evaporated to dryness *in vacuo* at 60°C to leave a yellow solid. The solid was dissolved in isopropyl alcohol and treated with propylene oxide to remove residual hydrogen chloride. A white solid precipitated on standing and revealed two ninhydrin staining spots running on silica gel 60 TLC and eluting with 90:10 methanol–water, R_f 0.22 (*trans*), 0.48 (*cis*). The two amino acids were separated by fractional crystallization from water and methanol or by column chromatography on silica gel 60 with a gradient of 50:50 to 100:0, methanol–chloroform. In the case of fractional crystallization the first isomer to precipitate was *trans*, mp 220°C, UV λ_{max} 185.4 nm, structure confirmed by ^{13}C NMR and X-ray crystallography (Table 1 and Figs. 2 and 3). The amino acids were prepared for elemental analysis by precipitation from isopropyl alcohol with addition of propylene oxide to solutions of the chloride salts. The powders were then dried *in vacuo* at 70°C for 24 h. Anal. calcd. for $C_7H_{11}NO_4$: C 48.55, H 6.40, N 8.09; found (anhydrous mate-

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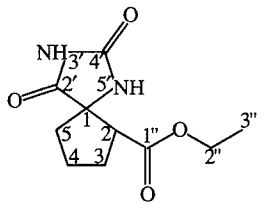
[3]In the *cis* isomer, the C(1)—NH_3^+ and C(2)—CO_2H groups are *cis* (higher priority groups); the carboxyl groups are *trans*. Vice versa for the *trans* isomer.

TABLE 1. ^{13}C NMR chemical shifts relative to TMS



Compound number	Chemical shift (ppm)									
	C1	C2	C3	C4	C5	C2′	C4′	C1″	C2″	C3″
2	70.5	52.3	26.5	22.5	37.3	178.1	180.1	170.6	60.8	13.5
3	72.7	56.1	28.8	23.1	37.3	179.1	191.3	169.3		
4	67.8	53.2	28.6	21.8	36.0	179.8		177.4		
5	68.0	56.2	28.6	22.2	36.2	180.5		179.5		

TABLE 2. Crystallographic data[a]

Compound	*cis*-**4**·H_2O	*trans*-**5**·H_2O
Formula	$C_7H_{11}NO_4 \cdot H_2O$	$C_7H_{11}NO_4 \cdot H_2O$
fw	191.18	191.18
Crystal system	Orthorhombic	Monoclinic
a(Å)	12.366(3)	10.8222(8)
b(Å)	6.516(2)	7.6853(8)
c(Å)	21.005(1)	11.4415(8)
β (deg)	90	109.448(5)
V (Å^3)	1692.5(7)	897.32(13)
Space group	$Pca2_1$	$P2_1/c$
Z	8	4
ρ_c (g/cm^3)	1.50	1.41
F(000)	816	408
μ(Cu-K$_\alpha$) (cm^{-1})	10.53	9.93
Crystal dimensions (mm)	0.08 × 0.25 × 0.30	0.07 × 0.30 × 0.35
Transmission factors	0.88–1.00	0.83–1.00
Scan type	ω–2θ	ω–2θ
Scan range (deg in ω)	1.31 + 0.30 tan θ	1.25 + 0.30 tan θ
Scan speed (deg/min)	32 (up to 8 rescans)	32 (up to 8 rescans)
Data collected	$\pm h, +k, +l$	$\pm h, +k, +l$
$2\theta_{max}$ (deg)	155	155
Crystal decay	Negligible	Negligible
Total reflections	3842	1851
Unique reflections	2077	1752
R_{merge}	0.020	0.016
Reflections with $I \geq 3\sigma(I)$	1509	1432
Number of variables	243	155
R	0.040	0.043
R_w	0.052	0.059
S	2.20	2.34
Max. Δ/σ (final cycle)	0.26	0.06
Max. residual density (e/Å^3)	0.16	0.14

[a]Temperature 294 K, Rigaku AFC6S diffractometer, Cu-K$_\alpha$ radiation (λ = 1.54178 Å), graphite monochromator, takeoff angle 6.0°, aperture 6.0 × 6.0 mm at a distance of 285 mm from the crystal, stationary background counts at each end of the scan (scan/background time ratio 2:1, up to 8 recans), $\sigma^2(F^2) = [S^2(C + 4B) + (0.035F^2)^2]/Lp^2$ (S = scan rate, C = scan count, B = normalized background count), function minimized $\Sigma w(|F_o| - |F_c|)^2$ where $w = 4F_c^2/\sigma^2(F_o^2)$, $R = \Sigma||F_o| - |F_c||/\Sigma|F_c|$, $R_w = (\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2)^{1/2}$, and $S = [\Sigma w(|F_o| - |F_c|)^2/(m\text{-}n)]^{1/2}$. Values given for R, R_w, and S are based on those reflections with $I \geq 3\sigma(I)$.

TABLE 3. Final atomic coordinates (fractional) and equivalent isotropic thermal parameters[a]

Atom	*x*	*y*	*z*	B_{eq}[b]
		cis isomer		
O(1)	0.0022(3)	0.1565(6)	0.3983	4.7
O(2)	−0.0159(2)	0.1453(4)	0.5033(2)	3.3
O(3)	0.2898(3)	0.1543(5)	0.4226(2)	4.3
O(4)	0.3403(2)	0.1117(4)	0.5232(2)	3.0
O(5)	0.2542(3)	0.3311(5)	0.2862(2)	4.7
O(6)	0.2675(2)	0.4537(4)	0.1809(2)	3.3
O(7)	−0.0358(3)	0.3424(5)	0.2649(2)	4.7
O(8)	−0.0866(2)	0.3960(4)	0.1650(2)	3.3
O(9)	0.4736(2)	0.2776(5)	0.3351(2)	3.7
O(10)	−0.2198(2)	0.2237(5)	0.3509(2)	3.7
N(1)	0.1402(3)	0.4617(6)	0.3974(3)	2.4
N(2)	0.1130(3)	0.0325(6)	0.2877(3)	2.6
C(1)	0.1030(2)	0.3946(5)	0.4617(2)	2.0
C(2)	0.1985(3)	0.3415(5)	0.5051(2)	2.0
C(3)	0.2468(3)	0.5511(8)	0.5225(3)	3.1
C(4)	0.1538(4)	0.7056(6)	0.5153(3)	3.1
C(5)	0.0553(3)	0.5807(5)	0.4955(3)	2.6
C(6)	0.0225(3)	0.2163(5)	0.4530(2)	2.3
C(7)	0.2801(3)	0.1924(5)	0.4798(2)	2.3
C(8)	0.1496(2)	0.1023(5)	0.2228(2)	2.1
C(9)	0.0532(3)	0.1601(5)	0.1805(2)	2.1
C(10)	0.0013(3)	−0.0503(8)	0.1645(3)	2.9
C(11)	0.0952(3)	−0.2005(6)	0.1641(3)	3.5
C(12)	0.1954(3)	−0.0814(6)	0.1860(3)	2.8
C(13)	0.2303(3)	0.2794(5)	0.2321(2)	2.4
C(14)	−0.0281(3)	0.3118(5)	0.2075(2)	2.3
		trans isomer		
O(1)	0.0165(1)	0.1141(2)	0.3911(1)	3.9
O(2)	0.2066(1)	0.1562(2)	0.3600(1)	3.9
O(3)	0.1027(1)	0.5130(2)	0.4364(2)	4.7
O(4)	0.3012(1)	0.6122(2)	0.4588(2)	4.8
O(5)	0.1874(2)	0.8112(2)	0.2716(2)	4.9
N	0.0975(1)	0.2205(2)	0.6205(1)	2.6
C(1)	0.2018(1)	0.2018(2)	0.5632(1)	2.3
C(2)	0.2847(2)	0.3686(2)	0.5793(2)	2.7
C(3)	0.4213(2)	0.3077(3)	0.5871(2)	4.0
C(4)[1]	0.4396(4)	0.1527(8)	0.6704(5)	4.9
C(4A)[2]	0.4229(7)	0.1013(11)	0.6078(7)	5.0
C(5)	0.3024(2)	0.0617(3)	0.6308(2)	3.5
C(6)	0.1349(2)	0.1540(2)	0.4261(1)	2.8
C(7)	0.2207(2)	0.5045(2)	0.4839(2)	2.9

[a]Superscripts 1 and 2 refer to site occupancy factors of 0.60 and 0.40, respectively.

[b]$B_{eq} = (8\pi^2/3)\Sigma\Sigma U_{ij} a_i^* a_j^* (\mathbf{a}_i \cdot \mathbf{a}_j)$.

rial): C 48.46, H 6.42, N 8.13. The second was the *cis* isomer, mp 230°C (lit. (5) mp 249°C for NH_4^+ salt), UV λ_{max} 186.8 nm. Found (anhydrous material): C 48.30, H 6.57, N 8.06. Column chromatography gave first **4**, at approximately 70:30, chloroform–methanol, and second, **5**.

*X-ray crystallographic analyses of compounds **4** and **5***

Crystallographic data for *cis*-**4** and *trans*-**5** (both compounds crystallize as monohydrates) are presented in Table 2. Unit-cell parameters were determined by least-squares refinement on diffractometer setting angles for 25 reflections (θ = 42–58° and 28–49° for the *cis* and *trans* isomers, respectively). The data were processed[4] and corrected for Lp and absorption (empirical, azimuthal scans for four reflections).

[4]TEXSAN structure analysis package. Molecular Structure Corp. 1985.

TABLE 4. Bond lengths (Å) and angles (deg)

	cis		
	Molecule A	Molecule B[a]	*trans*
Atoms		Distances	
O(1)—C(6)	1.239(5)	1.220(5)	1.247(2)
O(2)—C(6)	1.248(5)	1.266(5)	1.252(2)
O(3)—C(7)	1.233(5)	1.226(5)	1.212(2)
O(4)—C(7)	1.289(4)	1.273(4)	1.301(2)
N—C(1)	1.492(5)	1.507(6)	1.489(2)
C(1)—C(2)	1.532(4)	1.534(4)	1.540(2)
C(1)—C(5)	1.524(5)	1.533(5)	1.544(2)
C(1)—C(6)	1.540(4)	1.538(4)	1.537(2)
C(2)—C(3)	1.535(5)	1.551(5)	1.525(2)
C(2)—C(7)	1.498(5)	1.520(5)	1.503(3)
C(3)—C(4)	1.536(6)	1.519(6)	1.497(6)
C(3)—C(4A)	—	—	1.603(9)
C(4)—C(5)	1.522(5)	1.533(5)	1.566(5)
C(4A)—C(5)	—	—	1.446(7)
Atoms		Angles	
N—C(1)—C(2)	111.5(3)	111.4(3)	111.3(1)
N—C(1)—C(5)	107.9(3)	109.3(3)	111.0(1)
N—C(1)—C(6)	108.2(3)	107.8(3)	107.7(1)
C(2)—C(1)—C(5)	101.5(3)	100.8(3)	103.6(1)
C(2)—C(1)—C(6)	113.5(3)	113.2(3)	112.3(1)
C(5)—C(1)—C(6)	114.0(3)	114.2(3)	111.0(1)
C(1)—C(2)—C(3)	103.9(3)	103.3(3)	105.5(1)
C(1)—C(2)—C(7)	117.0(3)	117.2(3)	112.5(1)
C(3)—C(2)—C(7)	113.5(3)	112.5(3)	117.3(1)
C(2)—C(3)—C(4)	105.6(3)	104.7(3)	101.6(2)
C(2)—C(3)—C(4A)	—	—	106.0(3)
C(3)—C(4)—C(5)	106.0(3)	106.9(3)	105.0(3)
C(3)—C(4A)—C(5)	—	—	105.6(4)
C(1)—C(5)—C(4)	104.1(3)	104.4(3)	106.1(2)
C(1)—C(5)—C(4A)	—	—	106.9(3)
O(1)—C(6)—O(2)	126.3(3)	126.7(3)	126.0(2)
O(1)—C(6)—C(1)	118.6(3)	118.9(3)	118.1(1)
O(2)—C(6)—C(1)	115.2(3)	114.4(3)	115.9(1)
O(3)—C(6)—O(4)	123.4(3)	125.1(3)	123.3(2)
O(3)—C(6)—C(2)	122.8(3)	121.7(3)	121.7(2)
O(4)—C(6)—C(2)	113.8(3)	113.2(3)	115.0(2)

[a]The atoms O(5–8), N(2), and C(8–14) constituting this molecule correspond, respectively, to atoms O(1–4), N(1), and C(1–7) of molecule A.

Both structures were solved by direct methods. The non-hydrogen atoms of both compounds were refined with anisotropic thermal parameters. For the *cis* isomer the two hydrogen atoms associated with the carboxylic acid moieties (H(7) and H(8)) were refined with isotropic thermal parameters and the remaining hydrogen atoms were fixed in idealized positions (the orientations of the $-NH_3^+$ groups based on observed difference map peaks, O/N/C-H = 0.98 Å, $B_H = 1.2\ B_{bonded\ atom}$). Conformational disorder in the five-membered ring of the *trans* isomer was indicated by anomalous thermal parameters for the atom C(4). A split-atom model for C(4) was refined, the occupancy factors (0.6/0.4) being determined by refinement with fixed isotropic thermal parameters. In the final stages of refinement the occupancy factors were kept fixed and anisotropic thermal parameters were employed for C(4) and C(4A). All ordered hydrogen atoms in the *trans* isomer were refined with isotropic thermal parameters and the disordered hydrogen atom positions were calculated as described above for the *cis* isomer.

The solution of the structure of the *cis* isomer was initiated in the noncentrosymmetric (but racemic) space group $Pca2_1$ on the basis of the *E*-statistics. The two molecules in the asymmetric unit are

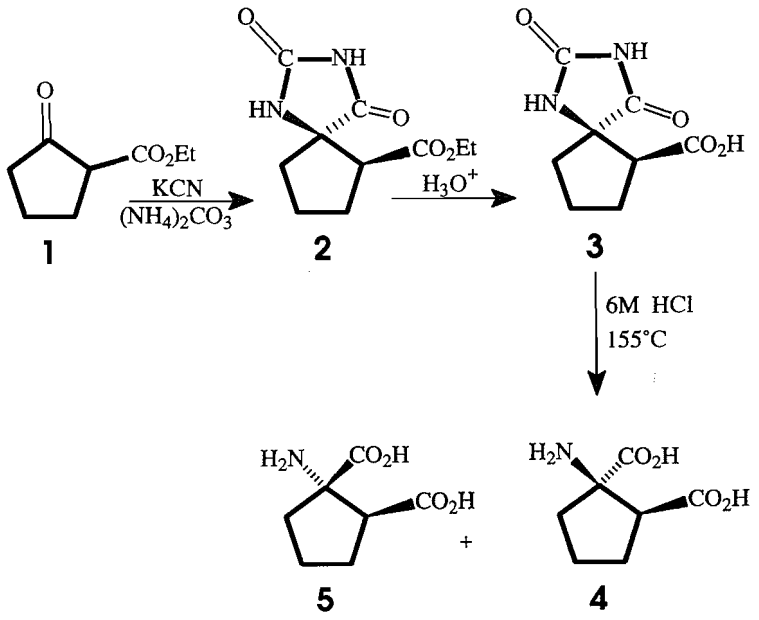


FIG. 1. Schematic for the synthesis of *cis* and *trans*-1-amino-1,2-cyclopentanedicarboxylic acids.

related to one another by a pseudo-inversion centre at approximately (1/8, 1/4, 0.34) (see Table 3). Attempts to refine the structure in the centrosymmetric space group *Pcam* (after appropriate coordinate translations) were unsuccessful. Parallel refinement of the opposite polarity (anomalous dispersion corrections for C, N, O) resulted in marginally higher residuals, the R and R_w ratios being 0.0402/0.0401 = 1.003 and 0.0524/0.0522 = 1.004, respectively. Neutral atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were taken from the *International tables for X-ray crystallography* (9).

Final atomic coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms are given in Table 3. Bond lengths and angles, selected torsion angles, and details of the hydrogen bonding are presented in Tables 4–6. Hydrogen coordinates, anisotropic thermal parameters, torsion angles, least-squares planes, intermolecular distances, and structure factors are included as supplementary material.[5]

Results and discussion

Since previous studies had indicated that Bucherer–Bergs hydantoin formation gave one geometric isomer exclusively (5) it was expected that the final product would consist of the *cis* amino acid only. Figure 1 shows the synthetic route and indicates that the most efficient method of hydrolysis with hydrochloric acid leads to epimerization of the final product into *trans* and *cis* amino acids. The *trans* isomer has not been described previously and is of particular interest because the rigidity of the ring and close proximity of the carboxyl groups result in a compound that resembles a folded conformation of glutamic and aspartic acids.

Using a version of the Simplex method (6), the optimum reaction conditions were determined and gave a total yield of approximately 65% for the formation of hydantoin **3** and its ester **2**. The yield of hydantoin was found to be dependent on time, temperature, and concentration of reactants. In particular, the presence of cyanide seemed to suppress the reaction, thus its concentration was kept low by gradual addition over a 24 h period. For unhindered systems, hydantoin formation takes place in 4–6 h; in the present study it was necessary to increase this period to 48 h. As the reaction proceeds, ethyl 2-cyclopentanecarboxylate-1-spiro-5-hydantoin **2** was formed and hydrolyzed *in situ* to give increasing amounts of **3**. The stereospecificity of the Bucherer–Bergs reaction has been discussed in detail with reference to restricted ring systems (7, 8) and, in the present synthesis, conditions are further restrained by the presence of an ester group at C(2) of the cyclic ketone **1**. Alkaline hydrolysis of **3** gave yields that were very low. Refluxing for 48 h in 2 M barium hydroxide gave no product at all while hydrolysis with 2 M sodium hydroxide at 140°C gave only very low yields of the *cis* amino acid (<5%). The best results were obtained with acid hydrolysis using 6 M HCl at 155°C for 6 h. The reaction mixture was found to contain both *cis*-**4** and *trans*-**5** amino acids with a total yield of 46%.

X-ray crystal structure of cis-**4** *and* trans-**5** *1-amino-1,2-cyclopentanedicarboxylic acid monohydrates*

Stereoviews of the asymmetric units (showing atom labeling schemes) of *cis*-**4** and *trans*-**5** (monohydrates) are shown in Fig. 2. The *cis* and *trans* isomers have (1*SR*,2*RS*) and (1*SR*,2*SR*) relative stereochemistries, respectively. Bond lengths and angles in the two isomers (Table 4) are generally as expected. The major structural differences between the two isomers, on the molecular level, can be seen by a comparison of the torsion angles in Table 5. The five-membered rings in both of the crystallographically independent

[5]Supplementary material mentioned in the text may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, Canada K1A 0R6.

Tables of hydrogen atom coordinates and bond lengths and angles involving hydrogen atoms have also been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemistry Laboratory, 12 Union Road, Cambridge CB2 1EZ, U.K.

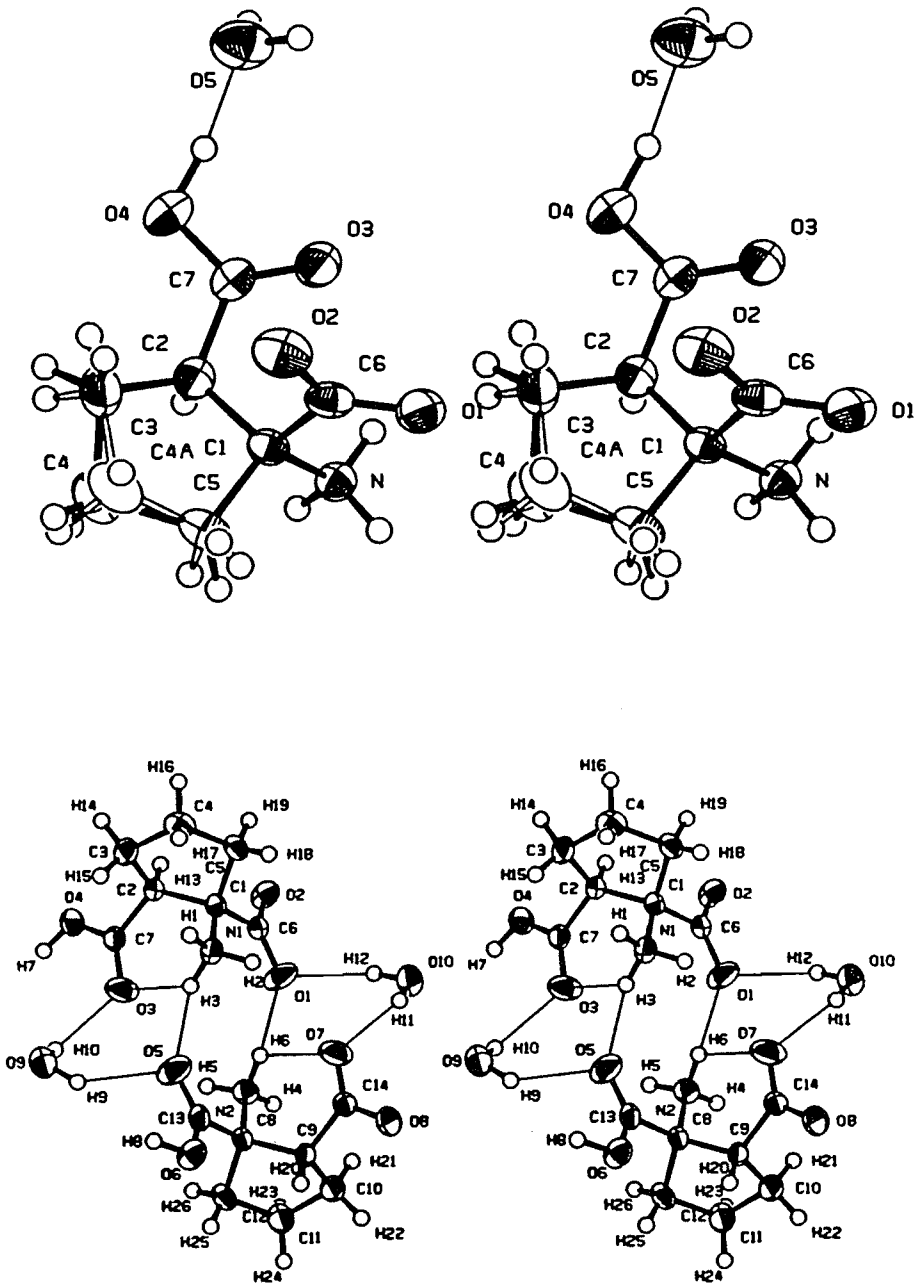


FIG. 2. Stereoviews of *trans*- and *cis*-1-amino-1,2-cyclopentanedicarboxylic acids.

molecules of the *cis* isomer and the minor component of the disordered cyclopentane ring in the *trans* isomer (that containing C(4A)) may be classified as C1-envelopes with varying degrees of irregularity. The conformation of the five-membered ring in the major component of the *trans* isomer is that of a C3-envelope.

Both molecules exist as zwitterions in the solid state. The deprotonated carboxylate group is that bonded to C1 in the *trans* isomer, while for the *cis* isomer the C1-carboxylate group is deprotonated in molecule A (containing N1) and the C1 and C2-carboxylate groups are nearly equivalent and share what is most likely a symmetrically O···H···O hydrogen-bonded proton in molecule B (containing N2) (see below).

Extensive hydrogen bonding dominates the packing arrangements in both crystal structures (see Table 6 and Fig. 3). Both crystal structures contain dimeric units with the individual molecules linked by N—H···O hydrogen bonds about crystallographic (*trans* isomer) or approximate (*cis* isomer) inversion centres. In the *trans* isomer these dimeric units are linked to one another along both the *b* and *c* axes by pairs of N—H···O hydrogen bonds and bridging OH···(H)O—H···O hydrogen-bonded water molecules, forming infinite sheets. In the *trans* isomer the protonated carboxylic acid group is strongly hydrogen-bonded to the water molecule (H···O = 1.57(3), O···O = 2.586(2) Å). The dimeric units in the *cis* isomer are also cross-linked by hydrogen bonds to form infinite sheets parallel to the *ab* plane, but the hydrogen bonding between dimers is different from that

TABLE 5. Torsion angles (deg)[a]

(*a*) Intra-annular

	cis-**4**		*trans*-**5**	
	Mol. A	Mol. B	Major	Minor
C(5)—C(1)—C(2)—C(3)	−41.3(3)	43.9(3)	29.6(2)	29.6(2)
C(1)—C(2)—C(3)—C(4)	24.8(4)	−30.9(4)	−42.9(3)	−13.3(4)
C(2)—C(3)—C(4)—C(5)	1.2(5)	5.6(5)	38.6(4)	−9.1(5)
C(3)—C(4)—C(5)—C(1)	−26.9(4)	21.8(5)	−20.8(4)	28.0(5)
C(4)—C(5)—C(1)—C(2)	41.9(4)	−40.4(4)	−5.5(3)	−36.7(4)

(*b*)

	cis-**4**		
	Mol. A	Mol. B	*trans*-**5**
N(1)—C(1)—C(2)—C(7)	−52.4(4)	52.2(4)	−82.0(2)
N(1)—C(1)—C(2)—C(3)	73.6(4)	−72.0(4)	148.9(1)
N(1)—C(1)—C(2)—H	−173.0	174.0	33.0(1)
C(6)—C(1)—C(2)—C(7)	70.1(4)	−69.5(4)	38.8(2)
C(6)—C(1)—C(2)—C(3)	−163.8(3)	166.3(3)	−90.2(2)
C(6)—C(1)—C(2)—H	−50.0	52.0	154.0(1)
C(5)—C(1)—C(2)—C(7)	−167.1(3)	168.1(3)	158.7(1)
C(5)—C(1)—C(2)—H	72.0	−70.0	−86.0(1)

[a]These angles refer to the 1*S*,2*R* and 1*R*,2*S* isomers, respectively, for the two independent molecules (A and B) of "*cis*-**4**" and to the 1*S*,2*S* isomer for "*trans*-**5**".

TABLE 6. Hydrogen bonding parameters (distance in Å, angles in degrees)

Interaction[a]	N/O—H	O···H	N/O···O	N/O—H···O
		cis Isomer		
N(1)—H(1)···O(10)^{7}	0.98	2.02	2.856(5)	142
N(1)—H(2)···O(9)^{8}	0.98	2.04	2.973(5)	143
N(1)—H(3)···O(3)^{1}	0.98	2.06	2.777(5)	129
N(1)—H(3)···O(5)^{1}	0.98	2.12	2.859(6)	131
N(2)—H(4)···O(9)^{9}	0.98	2.01	2.837(5)	141
N(2)—H(4)···O(10)^{10}	0.98	2.04	2.971(6)	158
N(2)—H(6)···O(1)^{1}	0.98	2.08	2.816(6)	130
N(2)—H(6)···O(7)^{1}	0.98	2.13	2.773(6)	121
O(4)—H(7)···O(2)^{10}	0.98(5)	1.51(5)	2.478(4)	170(5)
O(6)—H(8)···O(8)^{7}	1.08(8)	1.47(8)	2.455(4)	148(7)
O(9)—H(10)···O(5)^{1}	0.98	2.14	2.923(5)	136
O(9)—H(10)···O(3)^{1}	0.98	2.23	3.031(5)	138
O(10)—H(11)···O(7)^{1}	0.98	2.13	3.005(5)	148
O(10)—H(12)···O(1)^{1}	0.98	2.14	2.953(5)	140
O(10)—H(12)···O(3)^{9}	0.98	2.28	2.890(4)	119
		trans Isomer		
O(4)—H(1)···O(5)^{1}	1.04(3)	1.57(3)	2.586(2)	167(3)
N—H(2)···O(1)^{2}	0.98(3)	1.87(3)	2.836(2)	170(2)
N—H(3)···O(2)^{3}	1.04(2)	1.73(2)	2.765(2)	175(2)
N—H(4)···O(3)^{4}	0.96(3)	1.99(3)	2.893(2)	157(2)
O(5)—H(13)···O(1)^{5}	0.86(3)	1.99(4)	2.810(2)	161(3)
O(5)—H(13)···O(2)^{6}	0.90(4)	2.00(4)	2.821(2)	151(3)

[a]Superscripts refer to symmetry operations (1) x, y, z; (2) $-x$, $-y$, 1-z; (3) x, 1/2-y, 1/2+z; (4) $-x$, 1−y, 1-z; (5) $-x$, 1/2+y, 1/2-z; (6) x, 1+y, z; (7) 1/2+x, 1-y, z; (8) x-1/2, 1-y, z; (9) x-1/2, $-y$, z; (10) 1/2+x, $-y$, z.

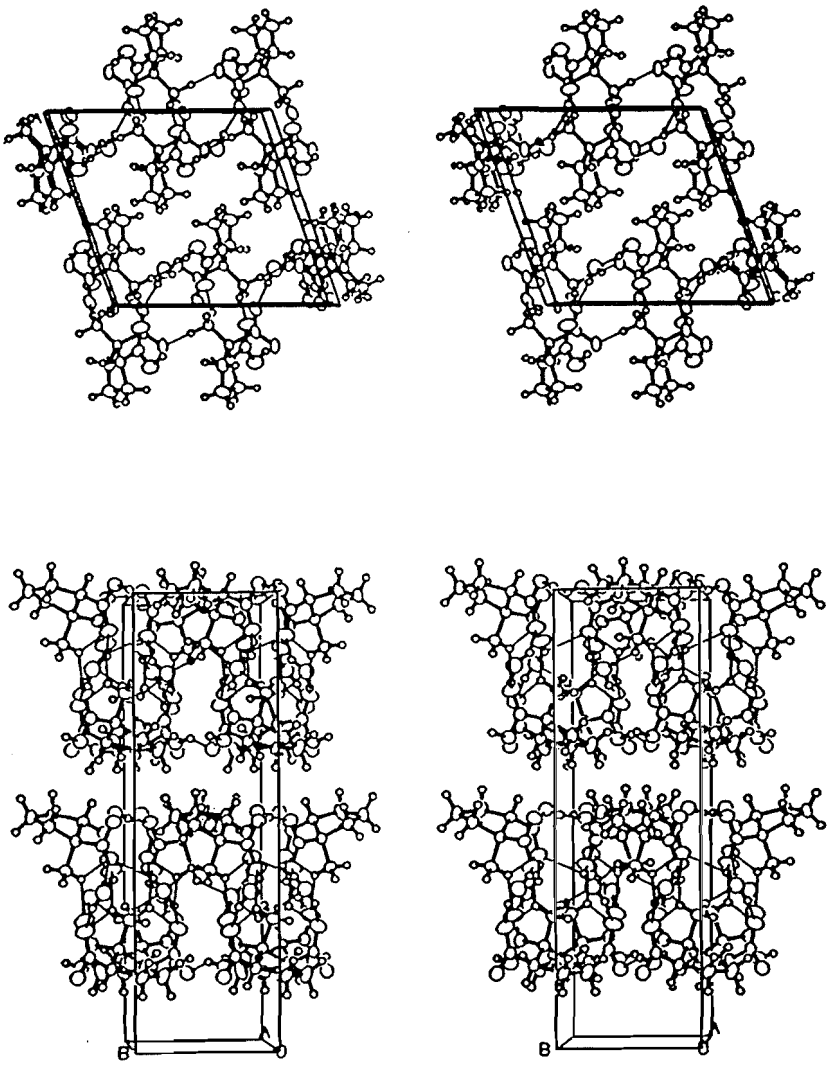


FIG. 3. Packing arrangements for *trans*- and *cis*-1-amino-1,2-cyclopentanedicarboxylic acids.

observed in the structure of the *trans* isomer. Molecules A are linked head-to-tail along *a* by very strong (O···H = 1.51(5), O···O = 2.478(3) Å) hydrogen bonds between protonated and deprotonated carboxylate groups. Molecules B are also linked to one another by the same type of hydrogen bond (O···H = 1.47(8), O···O = 2.455(3) Å), but to dimers translated along the *b* axis with respect to those linked through molecules A. In addition, the dimers in the *cis* isomer are bridged along both *a* and *b* by pairs of bridging $(O\cdots H_2O\cdots HN)_2$ hydrogen-bonded water molecules (O···N = 2.837(5)–2.973(5), O···O = 2.890(4)–3.031(5) Å). The existence of extra bifurcated hydrogen-bonding interactions (1.5 per molecule) in the structure of the *cis* isomer, along with other packing considerations (especially the orientation of the cyclopentane rings with respect to the hydrophobic channels between the hydrogen-bonded layers), is probably responsible for the higher density of the *cis* isomer in the solid state.

As a result of the very strong (O)CO···H···OC(O) hydrogen bonding in the *cis* isomer (see Table 6) the distinction between the COO^- and COOH groups becomes somewhat ambiguous. In molecule A, with the longer O···O distance, the C—O bond lengths (C(7)—O(4) = 1.289(4) and C(6)—O(2) = 1.248(5) Å) and the location of the refined hydrogen atom H(7) (bonded to O(4)) are consistent with protonation of the C(7) carboxylate group. In molecule B, the O···O distance in the strong hydrogen bond is 0.023(5) Å shorter than in molecule A and the two C—O distances involved are not significantly different (C(13)—O(6) = 1.266(5) and C(14)—O(8) = 1.273(4) Å). However, the hydrogen atom H(8) involved in this interaction refined to a position nearer to O(6), the oxygen atom having the shorter C—O bond. In view of the relatively large thermal parameter for H(8) and the near equivalence of the dimensions of the C(13) and C(14) carboxylate moieties, it is likely that the O(6)···H(8)···O(8) interaction is symmetric. The COO^- and COOH functions are clearly distinguished in the *trans* isomer with C—O bond lengths of 1.247(2) and 1.252(2) Å in the former and C—O(H) and C=O distances of 1.301(2) and 1.212(2) Å in the latter.

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