Metal Bonding by Amino Acids: Preparation and Crystal Structures of Calcium Bis-L-pyroglutamate and Lithium L-Pyroglutamate

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Calcium bis-L-pyroglutamate and lithium L-pyroglutamate are prepared by reaction of the metal hydroxides with L-pyroglutamic acid in aqueous solution. In the solid state calcium bis-L-pyroglutamate adopts a layer structure, built up by sixteen-membered rings consisting of four L-pyroglutamate ligands bridging four calcium centers by their carboxylate groups. All three oxygen donors of the L-pyroglutamate ligands are attached to metal centers. The calcium atom lies at the center of a slightly distorted octahedron formed by four carboxylate oxygens and two amide oxygen atoms. Lithium L-pyroglutamate also features a layer structure. All three oxygen donors of the L-pyroglutamate ligand have contacts with metal atoms. The coordination sphere of the lithium atom is a slightly distorted tetrahedron consisting of three carboxylate oxygen atoms and one amide oxygen atom. The investigation of aqueous solutions of the compounds by multinuclear NMR (^{1}H, ^{13}C, ^{17}O) indicates extensive electrolytic dissociation in dilute solutions.

Metal L-pyroglutamates ("pidolates") are important drugs and components of e. g. cosmetics. This application is mainly oriented towards supplementation of alkali and alkaline earth metals, which play an essential role in biological systems[1,2]. Knowledge of the interaction of metal ions with ligand sites present in biological systems is still rudimentary. Even bonding of metal ions to one of the most prominent components, the amino acids, is not well understood. In an effort to get a deeper insight into the nature of the complexation of metals by amino acids we have recently directed our efforts to the elucidation of the interaction of metal ions with the L-pyroglutamate ligand.

L-Pyroglutamic acid, L-pGluH, has been found to function as an N-terminal component in proteins[3]. Free L-pyroglutamic acid is an intermediate in many biosyntheses and in the transport of amino acids through cell menbranes[4]. Recently, a new synthetic route to L-pyroglutamates has been described: By thermal dehydration of molten L-glutamate salts, L-pyroglutamate salts can be obtained in high yields and with very little racemization[5]. Only two of the products, sodium L-pyroglutamate trihydrate[6] and zinc bis-L-pyroglutamate dihydrate[7], have been obtained as crystalline samples for structure determination. $Zn(L\text{-}pGlu)_2(H_2O)_2$ features isolated complex molecules with a tetrahedral coordination at the zinc atom by two water molecules and two monodentate carboxylate contacts, but no interaction of the amide functions with the metal ion[7]. $Na(L\text{-}pGlu)(H_2O)_3$, however, adopts a chain structure with strings of symmetry-equivalent, hexacoordinate sodium atoms bridged by the carboxamide oxygen atoms and two water molecules. In this case the carboxylate groups have no metal contacts and are only engaged in hydrogen bonding[6].

We now report on the preparation, crystallization, and X-ray structure determination of calcium bis-L-pyroglutamate and lithium L-pyroglutamate. Both compounds are of great interest for medical applications, as illustrated by the use of the calcium salt in the therapy of calcium deficiency[8] and the potential of the lithium salt for treatment of psychical disorders.

Results

Calcium bis-L-pyroglutamate and lithium L-pyroglutamate are synthesized by neutralization of aqueous solutions of the metal hydroxides with stoichiometric amounts of L-pyroglutamic acid followed by precipitation with acetone. Crystalline samples of the two products are obtained by layering concentrated aqueous solutions of the metal L-pyroglutamates with acetone. No crystals are obtained from the aqueous solutions. $Ca(L\text{-}pGlu)_2$ crystallizes in the acentric space group $P2_12_12$ with four formula units in the unit cell and one calcium atom and two crystallographically independent L-pyroglutamate ligands in the asymmetric unit. $Ca(L\text{-}pGlu)_2$ adopts a layer structure with sixteen-membered rings not easily recognized as the main architectural feature. These rings contain four calcium centers which are connected via four bridging L-pyroglutamate ligands (Figure 1). The anions are connected via the carboxylate oxygen atoms (O1, O2 and O4, O5) to two different metal centers, and the oxygen donor of the amide function of the ligand is attached yet to another metal center (Figure 1). Distances and angles of the two crystallographically independent L-pyroglutamate ligands show neither significant deviations from the values determined for zinc bis-L-pyroglutamate dihydrate[7] and sodium L-pyroglutamate trihydrate[6] (Table 1), nor are there any noteworthy differences between the two anions in $Ca(L\text{-}pGlu)_2$. The calcium atom lies at the center of a slightly distorted octahedron (Figure 2; Table 1): Each calcium atom is connected with four other calcium centers by

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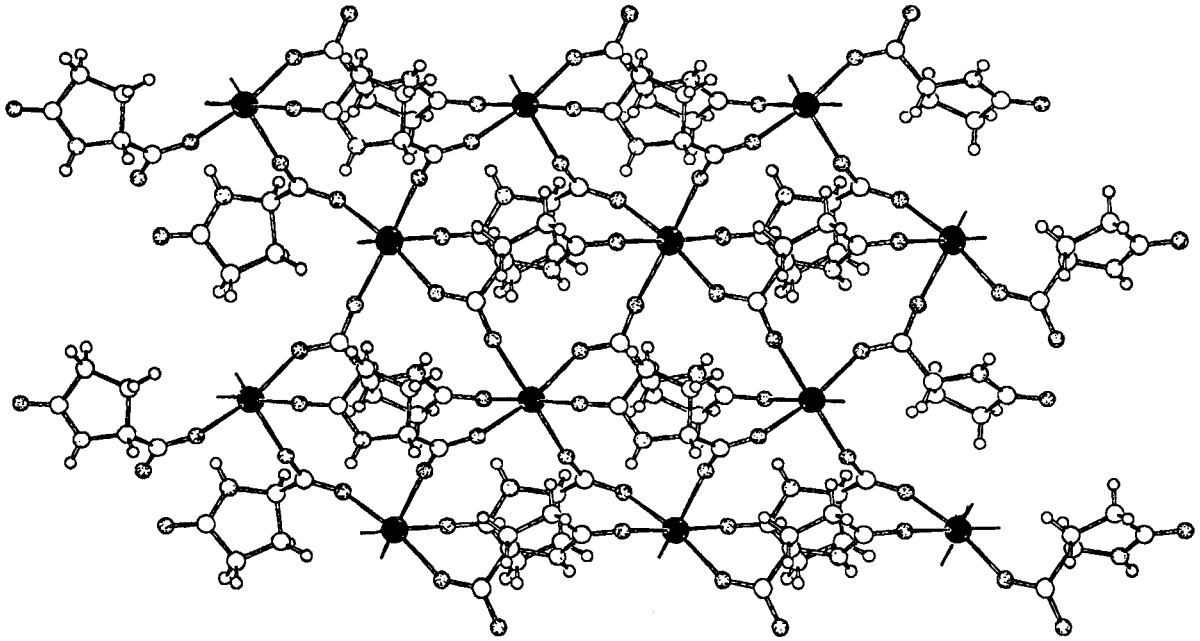

Figure 1. Crystal structure of calcium bis-L-pyroglutamate (Ca: black; O: heavy shading; N: light shading; C: large white; H: small white)

four carboxylate groups. The octahedral coordination sphere is completed by two amide oxygen donors. The Ca–O distances range from 2.296(1) to 2.334(1) Å with no systematic differences between $Ca-O_{carboxyl}$ and $Ca-O_{amide}$ bonds: The largest $Ca-O_{carboxyl}$ distance [Ca–O4 2.334(1) Å] is even slightly longer than the shortest $Ca-O_{amide}$ distance [Ca–O3 2.330(1) Å].

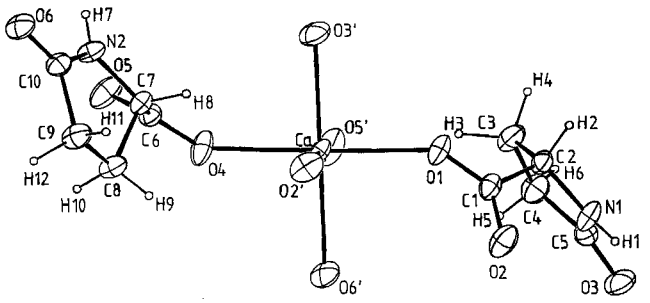

Figure 2. Inner coordination sphere of the calcium ion of Ca(L-pGlu)$_2$ with atomic numbering (ORTEP, displacement parameters at the 50% probability level; H atoms with arbitrary radii)

The crystals of Li(L-pGlu) are monoclinic, space group $P2_1$, with two formula units in the unit cell. The lattice features a layer structure: As in the case of the calcium compound all three oxygen donors of the L-pyroglutamate ligand are coordinated to metal centers (Figure 3). One of the carboxylate oxygen atoms is attached exclusively to one lithium atom whereas the other carboxylate oxygen bridges two lithium centers. The lithium atoms, which are arranged in double strings, feature a slightly distorted tetrahedral coordination sphere with three carboxylate oxygens and one amide oxygen as the constituents (Figure 4). The lithium–oxygen distances range from 1.940(3) to 2.019(3) Å with no clear distinction between the $Li-O_{carboxyl}$ and $Li-O_{amide}$ distances (Table 2).

Table 1. Interatomic distances [Å] and angles [°] in the crystal structure of calcium bis-L-pyroglutamate

O1	-- C1	1.248(2)	O1	-- CA	2.310(1)		
O2	-- C1	1.251(2)	O3	-- C5	1.240(2)		
O3	-- CA	2.329(1)	N1	-- C2	1.458(2)		
N1	-- C5	1.325(2)	C1	-- C2	1.537(2)		
C2	-- C3	1.541(3)	C3	-- C4	1.521(2)		
C4	-- C5	1.501(2)	O4	-- C6	1.251(2)		
O4	-- CA	2.333(1)	O5	-- C6	1.241(2)		
O6	-- C10	1.244(2)	O6	-- CA	2.398(1)		
N2	-- C7	1.464(2)	N2	-- C10	1.325(2)		
C6	-- C7	1.516(2)	C7	-- C8	1.532(2)		
C8	-- C9	1.528(2)	C9	-- C10	1.508(2)		
O2	-- CA	2.296(1)	O5	-- CA	2.281(1)		
C1	-O1 -CA	142.6(1)	C5	-O3 -CA	144.6(1)		
C2	-N1 -C5	115.1(1)	O1	-C1 -O2	125.9(2)		
O1	-C1 -C2	116.2(1)	O2	-C1 -C2	117.8(1)		
N1	-C2 -C1	112.1(1)	N1	-C2 -C3	103.5(1)		
C1	-C2 -C3	116.2(1)	C2	-C3 -C4	105.7(1)		
C3	-C4 -C5	105.5(1)	O3	-C5 -N1	124.7(2)		
O3	-C5 -C4	126.0(2)	N1	-C5 -C4	109.3(1)		
C6	-O4 -CA	140.0(1)	C10	-O6 -CA	134.1(1)		
C7	-N2 -C10	112.9(1)	O4	-C6 -O5	124.6(1)		
O4	-C6 -C7	116.3(1)	O5	-C6 -C7	119.1(1)		
N2	-C7 -C6	114.8(1)	N2	-C7 -C8	101.9(1)		
C6	-C7 -C8	112.4(1)	C7	-C8 -C9	102.8(1)		
C8	-C9 -C10	103.8(1)	O6	-C10 -N2	126.4(1)		
O6	-C10 -C9	124.8(1)	N2	-C10 -C9	108.8(1)		
O1	-CA -O3	92.9(1)	O1	-CA -O4	170.0(1)		
O3	-CA -O4	86.9(1)	O1	-CA -O6	87.4(1)		
O3	-CA -O6	177.0(1)	O4	-CA -O6	93.4(1)		
O1	-CA -O2	96.6(1)	O1	-CA -O5	84.9(1)		
O3	-CA -O5	97.3(1)	O2	-CA -O3	88.9(1)		
O4	-CA -O5	85.2(1)	O2	-CA -O4	93.4(1)		
O5	-CA -O6	85.7(1)	O2	-CA -O5	173.6(1)		
O2	-CA -O6	88.1(1)					

The NMR spectra (^1H, ^{13}C and ^{17}O) of aqueous solutions of Ca(L-pGlu)$_2$, Li(L-pGlu), and Na(L-pGlu)$(H_2O)_3$ show no significant differences in the chemical shift values and coupling constants for the pyroglutamate ligands.

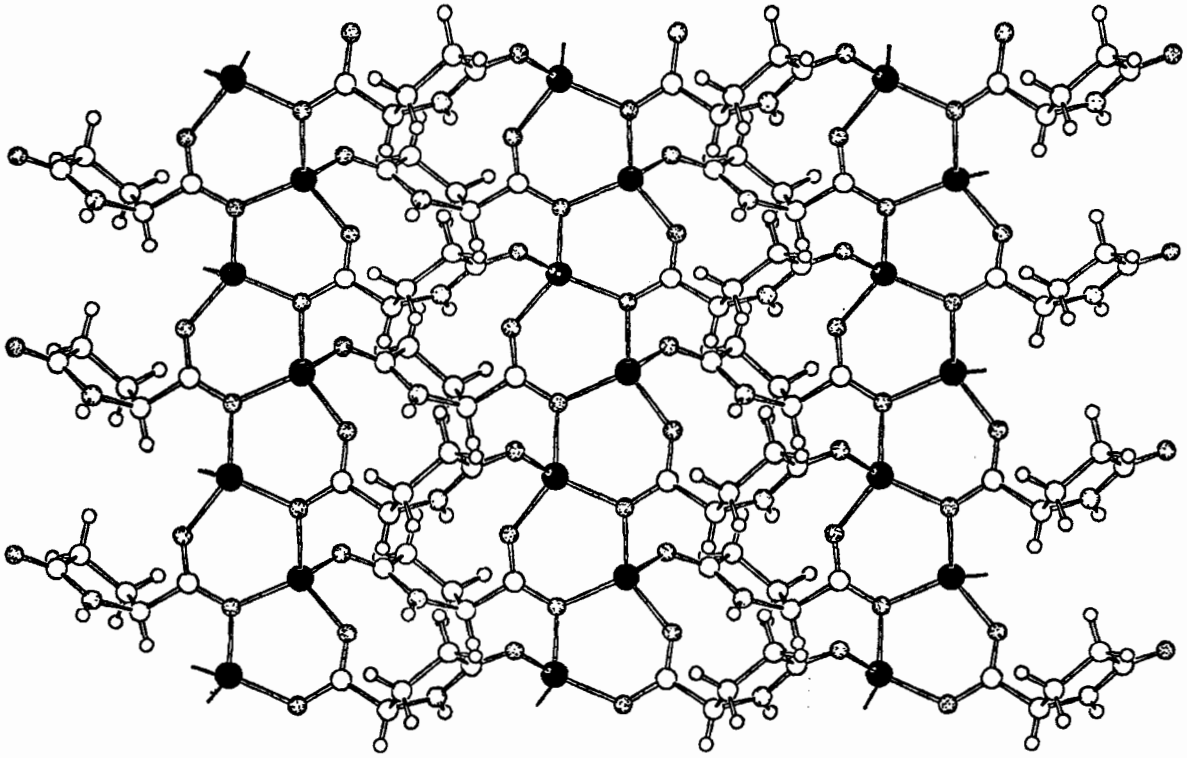

Figure 3. Crystal structure of lithium L-pyroglutamate (Li: black; O: heavy shading; N: light shading; C: large white; H: small white)

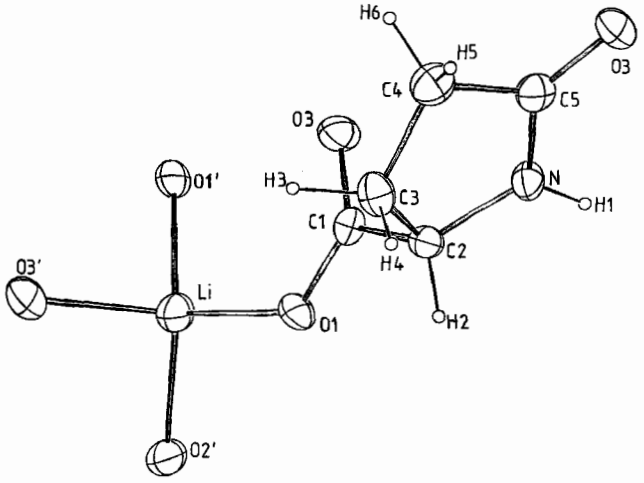

Figure 4. Inner coordination sphere of the lithium ion of Li(L-pGlu) with atomic numbering (ORTEP, displacement parameters at the 50% probability level; H atoms with arbitrary radii)

Table 2. Interatomic distances [Å] and angles [°] in the crystal structure of lithium L-pyroglutamate

O1	-- C1		1.262(2)	O1	-- LI		1.940(3)
O2	-- C1		1.248(2)	O3	-- C5		1.235(2)
O3	-- LI		1.983(3)	N	-- C2		1.453(2)
N	-- C5		1.341(2)	C1	-- C2		1.527(2)
C2	-- C3		1.552(3)	C3	-- C4		1.526(3)
C4	-- C5		1.507(3)	O1'	-- LI		2.019(3)
O2	-- LI		1.974(4)				
C1	-O1	-LI	125.6(1)	C5	-O3	-LI	130.8(1)
C2	-N	-C5	115.3(2)	O1	-C1	-O2	125.4(2)
O1	-C1	-C2	116.4(2)	O2	-C1	-C2	118.1(2)
N	-C2	-C1	113.3(2)	N	-C2	-C3	102.3(1)
C1	-C2	-C3	110.6(2)	C2	-C3	-C4	105.0(2)
C3	-C4	-C5	104.3(2)	O3	-C5	-N	124.6(2)
O3	-C5	-C4	126.9(2)	N	-C5	-C4	108.5(2)
O1	-LI	-O3	117.0(2)	O1	-LI	-O1'	113.4(2)
O2	-LI	-O1'	118.4(2)	O1	-LI	-O2	108.2(1)
O2	-LI	-O3	101.7(2)	O3	-LI	-O1'	97.7(1)

Discussion

The present results have shown further structural variations in L-pyroglutamate coordination: In Li(L-pGlu) and Ca(L-pGlu)$_2$, which both crystallize without hydrate water, all three oxygen donors of the ligand are coordinated to the metal centers. In the absence of hydrate water molecules in the crystals, only the amide hydrogen atoms are available for hydrogen bonding. Therefore, it is unlikely that they contribute significantly to the lattice stability. The crystal structures are governed largely by metal-oxygen contacts. On the other hand, in Na(L-pGlu)$(H_2O)_3$ the carboxylate group is exclusively involved in hydrogen bonding, and only the amide oxygen atoms are coordinated to the sodium atom. The solid-state structure of sodium L-pyroglutamate thus appears to be determined to a large extent by hydrogen bonds[6]. Finally, zinc bis-L-pyroglutamate seems to adopt an intermediate position between these two extremes. These microscopic characteristics have a strong influence on macroscopic properties such as melting points: Na(L-pGlu)-$(H_2O)_3$ already melts at 42°C, whereas the calcium and lithium salts decompose at very high temperatures [Li(L-pGlu)

289 °C, Ca(L-pGlu)$_2$ > 350 °C], while the zinc compound is in an intermediate position (m.p. 168 °C)[7].

The NMR investigations of aqueous solutions of the L-pyroglutamate salts have proved to be of little value for obtaining information on the coordination chemistry in solution. Neither in the ^{13}C- nor in the ^{1}H- or ^{17}O-NMR spectra significant differences between the ligand resonances of the sodium, lithium, and calcium compounds are observed. This result seems to exclude any strong metal complexation which should cause major differences, especially in ^{17}O NMR[9]. Previous investigations have shown, however, that even though diamagnetic calcium(II) cations do not induce strong shifts of the ligand carboxylate ^{17}O resonance, paramagnetic lanthanide ions comparable to calcium in ionic radius and complexing capabilities such as dysprosium do indeed cause major chemical shifts that can be related in a straightforward way to metal ligand contacts[10-12]. In the solutions of these dysprosium complexes the ligand exchange is normally fast on the ^{17}O-NMR time scale, such that averaged spectra of the free and complexed anions are observed with a considerable chemical shift caused by the metal ion[11]. Similar processes are assumed to be operative in the metal L-pyroglutamate solutions, perhaps with only rather short residence times of the ligand at a specific cation.

Previous investigations of the colligative properties (electrical conductivity, apparent molecular mass etc.) of pyroglutamates[6] indeed indicate extensive dissociation and solvation of the cation and the anion by water molecules.

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Experimental

All experiments were carried out in pure, bidistilled water. Reagents were commercial and of p.a. grade. – pH values: Knick apparatus, reference electrodes (AgCl/KCl) Ingold. – NMR: Bruker WP 100 SY (^{1}H, ^{13}C), Jeol CX 400 (^{17}O) spectrometers. Standards: ^{1}H NMR: internal standard *tert*-butyl alcohol (δ = 1.20), ^{13}C NMR: internal standard dioxane (δ = 66.7), ^{17}O NMR: external standard H_2O (δ = 0.0). – X-ray analyses: Enraf-Nonius CAD 4 diffractometer. Elemental analysis: Microanalytical laboratory of this institute according to standard procedures.

Calcium Bis-L-pyroglutamate: Calcium hydroxide (0.72 g, 9.72 mmol), dissolved in 25 ml of water, is treated with L-pyroglutamic acid (2.51 g, 19.44 mmol) under reflux for 2 h. The reaction mixture is then cooled to ambient temp. and filtered. The clear filtrate is concentrated in vacuo to 1/3 of the original volume, and 100 ml of acetone is slowly added to the remaining liquid. The white microcrystalline precipitate is filtered and dried in vacuo to give the product (2.45 g, 85% yield). Crystals suitable for X-ray structure investigation are grown by layering concentrated aqueous solutions of the product with acetone. – ^{1}H NMR (D_2O, 20 °C): δ = 3.94 (m, O_2CCH), 1.8–2.4 (m, CH_2, $COCH_2$). – ^{13}C{^{1}H}NMR (D_2O, 20 °C): δ = 181.7 (CO_2), 180.4 (CO), 58.3 ($HCCO_2$), 29.8 (CH_2CO), 25.3 (CH_2CHCO_2). – ^{17}O NMR (H_2O, 60 °C, 0.5 M solution): δ = 266.4 (CO_2); 256.3 (CO).

$C_{10}H_{12}CaN_2O_6$ (296.3) Calcd. C 40.54 H 4.08 N 9.45
Found C 39.57 H 4.17 N 9.33

Lithium L-Pyroglutamate: As described for the calcium analogue, 0.66 g of lithium hydroxide (27.55 mmol) and 3.56 g of L-pyroglutamic acid (27.55 mmol) afford 3.63 g of lithium L-pyroglutamate (97% yield). – ^{1}H NMR (D_2O, 20 °C): δ = 3.96 (m, CO_2CH); 1.8–2.4 (m, CH_2, $COCH_2$). – ^{13}C{^{1}H}NMR (D_2O, 20 °C): δ = 181.8 (CO_2), 180.0 (CO), 58.3 ($HCCO_2$), 29.8 (CH_2CO), 25.4 (CH_2CHCO_2). – ^{17}O NMR (H_2O, 60 °C, 1 M solution): δ = 264.5 (CO_2), 256.3 (CO).

$C_5H_6LiNO_3$ (135.0) Calcd. C 44.70 H 4.49 N 10.37
Found C 44.26 H 4.35 N 10.21

Sodium L-Pyroglutamate Trihydrate[5,6]: ^{1}H NMR (D_2O, 20 °C): δ = 4.01 (m, $CHCO_2$); 1.8–2.4 (m, CH_2, $COCH_2$). – ^{13}C{^{1}H}NMR (D_2O, 20 °C): δ = 181.7 (CO_2), 180.2 (CO), 58.4 ($CHCO_2$), 29.9 (CH_2CO), 25.5 (CH_2CHCO_2). – ^{17}O NMR (H_2O, 60 °C, 1 M solution): δ = 268.2 (CO_2), 258.9 (CO). – The crystal structure of sodium L-pyroglutamate has been published elsewhere[6].

Crystal Structure Determinations[13]

Ca(L-pGlu)$_2$: $C_{10}H_{12}CaN_2O_6$, M = 296.297, orthorhombic, a = 8.578(1), b = 15.493(1), c = 8.867(1) Å, V = 1178.42 Å^3, space group $P2_12_12$ (No. 18), Z = 4, D_{calc} = 1.670 g cm^{-3}, $F(000)$ = 616, μ(Mo-K_α) = 5.4 cm^{-1}. – Data collection: Mo-K_α radiation, λ = 0.71069 Å, graphite monochromator, Θ–2Θ scan, T = 23 °C. Lp correction was applied, but no absorption correction. 2552 intensity data were measured up to $(\sin\Theta/\lambda)_{max}$ = 0.615 Å^{-1}. After merging of equivalent data (R_{int} = 0.013) 2241 of the remaining 2296 independent structure factors were considered "observed" [$F_o \geq 1\sigma(F_o)$] and used for refinement. Three standard reflections were periodically measured. No significant change was observed during data collection. Reduced cell calculations did not indicate any higher symmetry (DELOS, LEPAGE). The structure was solved by direct methods (SHELXS-86) and completed by difference Fourier syntheses. All 12 hydrogen atoms in the asymmetric unit were located in difference Fourier syntheses. The non-hydrogen atoms were refined with anisotropic, the hydrogen atoms with isotropic displacement parameters (Number of refined parameters: 220). The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, $w = 1/\sigma^2(F_o)$. Final R and R_w values were 0.020 and 0.022, respectively. Refinement of the enantiomorphic coordinate set yielded higher R values (R = 0.026, R_w = 0.029). Residual electron density: +0.27/–0.25 e/Å^3. Final atomic coordinates of the non-hydrogen atoms are given in Table 3.

Table 3. Fractional atomic coordinates and thermal displacement parameters for calcium bis-L-pyroglutamate

ATOM	X/A	Y/B	Z/C	U(eq.)
O1	0.5550(1)	0.15384(8)	0.3910(1)	0.028
O2	0.3584(1)	0.20998(8)	0.5222(1)	0.034
O3	-0.0782(1)	0.12159(7)	0.2701(2)	0.041
N1	0.1466(2)	0.1006(1)	0.4008(2)	0.027
C1	0.4165(2)	0.1557(1)	0.4341(2)	0.024
C2	0.3116(2)	0.0818(1)	0.3789(2)	0.026
C3	0.3227(2)	0.0593(1)	0.2100(2)	0.032
C4	0.1648(2)	0.0825(1)	0.1432(2)	0.032
C5	0.0626(2)	0.1035(1)	0.2755(2)	0.026
O4	0.9120(1)	0.30475(8)	0.1023(1)	0.029
O5	1.1128(1)	0.30673(9)	-0.0530(1)	0.041
O6	1.5626(1)	0.35278(7)	0.2740(1)	0.032
N2	1.3263(2)	0.30882(9)	0.1805(2)	0.027
C6	1.0547(2)	0.3104(1)	0.0749(2)	0.021
C7	1.1607(2)	0.3240(1)	0.2097(2)	0.021
C8	1.1610(2)	0.4178(1)	0.2639(2)	0.029
C9	1.3202(2)	0.4263(1)	0.3400(2)	0.030
C10	1.4187(2)	0.35933(9)	0.2615(2)	0.024
CA	0.74179(3)	0.23409(2)	0.26627(3)	0.021

Table 4. Fractional atomic coordinates and thermal displacement parameters for lithium L-pyroglutamate

ATOM	X/A	Y/B	Z/C	U(eq.)
O1	0.8852(2)	0.63590	0.0452(1)	0.028
O2	0.9009(2)	1.0023(4)	0.2011(2)	0.025
O3	0.7606(2)	0.9085(4)	0.6458(2)	0.039
N	0.8308(2)	0.6759(4)	0.4452(2)	0.031
C1	0.8576(3)	0.7639(4)	0.1628(2)	0.022
C2	0.7515(3)	0.6160(5)	0.2569(2)	0.022
C3	0.5329(3)	0.7109(5)	0.1875(2)	0.027
C4	0.5321(3)	0.9033(5)	0.3285(2)	0.034
C5	0.7170(3)	0.8340(4)	0.4925(2)	0.024
LI	0.9711(5)	0.7862(6)	-0.1243(4)	0.030

Li(L-pGlu): $C_5H_6LiNO_3$, M = 135.048, monoclinic, a = 7.456(1), b = 5.035(1), c = 8.345(1) Å, β = 115.47(1)°, V = 282.832 Å^3, space group $P2_1$ (No. 4), Z = 2, D_{calc} = 1.586 g cm^{-3}, $F(000)$ = 140, μ(Mo-K_α) = 1.2 cm^{-1}. – Data collection: Mostly as for the Ca compound. 2200 reflections were measured up to $(\sin\Theta/\lambda)_{max}$ 0.615 Å^{-1}. After merging of equivalent data (R_{int} = 0.021) 1044 of the remaining 1098 independent structure factors were considered "observed" ($F_o \geq 1\,\sigma(F_o)$) and used for all calculations. The structure was solved by direct methods (SHELXS-86) and completed by difference Fourier syntheses. An empirical extinction correction was applied (SHELX-76). All 6 hydrogen atoms in the asymmetric unit were located in difference Fourier syntheses. The non-H atoms were refined with anisotropic, the H atoms with isotropic displacement parameters (Number of refined parameters: 115). The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, $w = 1/\sigma^2(F_o)$. Final R and R_w values were 0.031 and 0.022, respectively. Refinement of the inverse coordinate set yielded no differences in R values and geometrical parameters due to small anomalous dispersion. Residual electron density: +0.25/−0.27 e/Å^3. Final atomic coordinates of the non-hydrogen atoms are given in Table 4.

CAS Registry Numbers

Ca(L-pGlu)$_2$: 31377-05-6 / Li(L-pGlu): 38609-04-0 / Na(L-pGlu): 28874-51-3

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