Lithium coordination to amino acids and peptides. Synthesis, spectroscopic characterization and structure determination of lithium complexes of neutral and anionic glycine and diglycine

Gerhard Müller*, Gerd-Michael Maier and Martin Lutz
Fakultat fur Chemie, Universitat Konstanz, Universitatstrasse 10, D-78464 Constance (Germany)

(Received October 14, 1993; revised December 9, 1993)

Abstract

Lithium complexes of neutral and anionic glycine (GlyH) and glycylglycine (diglycine; GlyGlyH) have been prepared. They were crystallized from water or water/alcohol mixtures in the form of $[Li(GlyH)(H_2O)]^+Cl^-$ (**1**), Li^+Gly^- (**2**), $[Li(GlyGlyH)]^+Cl^-$ (**3**) and $Li^+GlyGly^- \cdot 1H_2O$ (**5**). The complexation of Li^+ by the amino acids and dipeptides is accompanied by characteristic low field shifts of their ^{13}C NMR resonances but details about the coordination modes are only available from solid-state structure determinations (**1**: $C_2H_7ClLiNO_3$, monoclinic, space group $P2_1/c$ (No. 14), $a=10.103(2)$, $b=5.064(1)$, $c=11.930(2)$ Å, $\beta=107.39(1)°$, $V=582.46$ Å^3, $Z=4$, $R_w=0.059$; **2**: **2**: $C_2H_4LiNO_2$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a=4.998(1)$, $b=7.864(1)$, $c=9.261(1)$ Å, $V=364.0$ Å^3, $Z=4$, $R_w=0.054$; **3**: $C_4H_8ClLiN_2O_3$, triclinic, $P\bar{1}$ (No. 2), $a=5.033(1)$, $b=7.533(1)$, $c=10.132(2)$ Å, $\alpha=76.54(1)$, $\beta=88.42(1)$, $\gamma=84.56(1)°$, $V=371.9$ Å^3, $Z=2$, $R_w=0.030$; **5**: $C_4H_9LiN_2O_4$, monoclinic, space group $P2_1$ (No. 4), $a=7.290(1)$, $b=4.923(1)$, $c=10.431(1)$ Å, $\beta=101.73(1)°$, $V=366.5$ Å^3, $Z=2$, $R_w=0.034$). The structure of **3** is isotypic with the previously described Br^- salt $[Li(GlyGlyH)]^+Br^-$ (R. Meulemans, P. Piret and M van Meersche, *Bull. Soc Chim. Belg., 80* (1971) 73). In all four complexes the Li^+ cation is tetrahedrally four-coordinate. Three of the coordination sites are occupied by carboxylate oxygen atoms from three different but crystallographically equivalent glycine or diglycine molecules, respectively. The fourth coordination site at Li^+ is different in each complex. In **1** the lithium coordination sphere is completed by a water molecule, in **2** the (deprotonated) amino group of the amino acid acts as additional donor, while in **3** and **5** the keto oxygen atom of the peptide bond is Li^+-coordinated. Quite remarkably, in **5** neither the deprotonated $-NH_2$ group nor the cocrystallized water molecule effectively compete for Li^+ coordination but are only engaged in an intricate net of hydrogen bonding interactions. On the basis of these results the following sequence of donor atom strength towards Li^+ may be established for these ligands. $-COO^- \approx C(O) > -NH_2 > H_2O$. Further weight is given to this conclusion by the fact that the Li^+ coordination to the carboxylate groups is identical in all four complexes: one of their oxygen atoms bridges two Li^+ cations while the second one is coordinated to a single third Li^+. The lithium coordination has drastic effects on the conformation of the peptide backbone in the dipeptides in **3** and **5**. They are different from each other as well as from that of uncomplexed diglycine in the solid state.

Key words: Crystal structures; Lithium complexes; Amino acid complexes; Peptide complexes

Introduction

Metal ions often play a crucial role in the function of proteins [1]. In a variety of important biochemical substrate transformations they are known to be the reaction centers. Intricately connected with this role is the question of the binding sites of the metal ion in the protein and the effect the metal ion has on the protein conformation. In some cases metal ions in proteins are presumed to have only a structural function, i.e. they are instrumental in determining the tertiary or quaternary protein structure. Important cases include some zinc metalloenzymes and proteins [2], most notably the zinc fingers [3]. It appears that the conformation determining role metal ions can play in proteins must be paralleled with that of hydrogen bonds and disulfide bridges.

For a variety of reasons first row transition metals and Zn^{2+} seem to be particularly well suited for the above mentioned purposes. Main-group metals are less often encountered as important constituents in proteins, the most prominent example being probably Ca^{2+} [4]. In contrast to many transition metals, the mode of binding of main-group metals to proteins is often more

*Author to whom correspondence should be addressed.

SSDI 0020-1693(93)03786-A

difficult to probe due to their generally weaker complexation and often also unfavorable spectroscopic properties. This applies particularly to solution studies but reliable information with regard to the solid state often also lacks rigorous experimental scrutiny. Nevertheless, Mg^{2+} and Ca^{2+} are generally believed to bind predominantly to the side chain carboxylate groups of aspartate and glutamate residues in proteins [5]. With phosphate containing biomolecules Mg^{2+} and, to a lesser extent, Ca^{2+} have a predominant tendency to be phosphate coordinated. An arbitrary, but important, example is the role of Mg^{2+} as cofactor in transfer and hydrolysis of phosphates [6, 7]. Biomineralization [8] of $CaCO_3$ and calcium phosphates is known to be mediated by proteins, segments of which are rich in aspartate and glutamate or O-phosphoserine whose anionic side chain carboxylates and phosphates, respectively, are responsible for Ca^{2+} binding.

As part of a larger project aimed at the elucidation of the mode of coordination of main-group metal ions to amino acids and peptides, as well as of their conformation determining role in peptides, we are currently studying a series of Li^+ complexes of neutral and anionic amino acids and di- and tripeptides. Particular attention is given to the metal binding sites of the ligands in the solid state as well as to the peptide conformation. Lithium was chosen because it fairly strictly adheres to tetrahedral four-fold coordination in its complexes with many (non-cyclic) biomolecules [9], thereby allowing for an easier generalization of the results. To our knowledge only a few Li^+ complexes of amino acids and small peptides have been characterized structurally as yet, and in these the ligands were almost exclusively neutral. In particular, the ligands used were di- and triglycine [10], L-alanylglycine [11], mono-anionic L-aspartate [12], cyclodisarcosyl [13] and antamanide [14]

Lithium is generally regarded as non-essential for the human metabolism but may have important effects on it [15, 16]. Thus Li_2CO_3, when administered in high doses, has long been known as an established pharmaceutical against certain forms of manic-depressive psychoses [17]. Li^+ administered in trace quantities is also believed to be beneficial for humans [16a].

Addition of simple alkaline metal salts, as, for example, LiCl, to proteins has long been known to have dramatic effects on solubility and conformation [18]. Seebach discusses important aspects of the interaction between lithium and peptides with respect to solubilization and enantioselective alkylation but gives no structural details [19].

In this paper we report on synthesis, spectroscopic characterization and structure determination of Li^+ complexes of neutral and anionic glycine and diglycine, specifically on $[Li(GlyH)(H_2O)]^+Cl^-$ (**1**), Li^+Gly^- (**2**), $[Li(GlyGlyH)^+Cl^-$ (**3**), $Li^+GlyGly^-$ (**4**), and $Li^+GlyGly^- \cdot 1H_2O$ (**5**). The syntheses of **1** and **3** [20] were first described by Pfeiffer (and co-workers) in his pioneering work on alkaline and alkaline earth cation complexes of amino acids and small neutral peptides [20c, 21]. Complex **2** was first prepared from glycine and $LiNO_3$ in liquid ammonia [22].

Experimental

All preparations were done in standard glassware without exclusion of atmospheric oxygen. Solvents other than water were repeatedly distilled before use, the water was deionized. Reagents were used as received from the manufacturer: Glycine (Roth), diglycine (Sigma), 98% LiOH (Merck), LiCl (Riedel-de Haen). IR spectra were recorded as nujol mulls between KBr windows on a Perkin-Elmer 1760X FTIR spectrometer. 250 MHz ^1H NMR and 100.6 MHz ^{13}C NMR spectra were recorded on Bruker WM250 and Jeol JNM GX400 instruments, respectively. Chemical shifts are in ppm with negative signs referring to high field. Standards were either H_2O in D_2O (4.63 ppm, ^1H NMR) or the sodium salt of 3-(trimethylsilyl)-1-propanesulfonic acid (0 ppm, ^1H NMR, ^{13}C NMR; Janssen Chimica). Elemental analyses were performed by the microanalytical laboratory of the Universität Konstanz on a Heraeus CHN-O-RAPID. Melting points were determined in open capillaries in a Büchi 530 apparatus and are uncorrected. The yields refer to analytically pure substances and are not optimized.

Syntheses

Preparation of $[Li(GlyH)(H_2O)]^+Cl^-$ (1)

According to the original synthesis of Pfeiffer [20] a filtrated solution of 1.50 g (20 mmol) of glycine and 1.67 g (40 mmol) of LiCl in 10 ml of water was heated on a water bath until the volume was sufficiently reduced and crystals started to grow. After cooling to room temperature the colorless crystals were filtered off, washed with abs. EtOH and dried *in vacuo*. Yield 1.49 g (11.0 mmol, 55.1% with respect to glycine), m.p. 125 °C. In a second fraction another 0.38 g (2.78 mmol) of **1** was isolated. Ir (cm^{-1}): 3360(s), 3223(s), 3099(s), 2791(m), 2676(m), 2598(m), 2498(w), 2387(w), 2293(w), 2175(m), 1861(w), 1634(s,sh), 1580(s), 1468(s), 1451(s), 1423(s), 1378(s), 1335(s), 1305(s), 1170(w), 1118(s), 1101(s), 1024(s), 897(s), 698(s), 601(s), 540(s). ^1H NMR (D_2O, 23 °C): $\delta = 3.6$ (s, CH_2). $^{13}C\{^1H\}$ NMR (D_2O, 23 °C): $\delta = 44.1$ (s, CH_2), 175.0 (s, COO). *Anal.* Calc. for $C_2H_7ClLiNO_3$ (135.475): C, 17.73; H, 5.21; N, 10.34. Found: C, 17.52; H, 5.16; N, 10.27%.

Preparation of Li^+Gly^- (2)

To 15.01 g (200 mmol) of glycine suspended in 25 ml of H_2O, 4.89 g (200 mmol) of LiOH were added in portions. The resulting (not entirely clear) solution was refluxed for 30 min, filtered hot and the water was removed *in vacuo* almost entirely. The residue was dissolved in as little hot H_2O as possible. Upon cooling to 4 °C colorless crystals formed which were filtered off, washed with cold EtOH/H_2O (4:1) and dried *in vacuo*. From the highly viscous mother liquor further substance may be isolated after prolonged standing. Yield (2 fractions) 5.59 g (69.01 mmol, 34.51%), m.p. >198 °C color change; 236 °C melting with decomposition. IR (cm^{-1}): 3406(m), 3352(s), 3298(s), 2089(w), 1623(s), 1583(s), 1457(s), 1416(s), 1378(s), 1334(s), 1313(s), 1170(m), 1107(m), 996(s), 951(s), 904(s), 822(w), 687(s), 648(m), 584(s), 554(s), 415(s). ^1H NMR (D_2O, 23 °C): $\delta = 3.2$ (s, CH_2). $^{13}C\{^1H\}$ NMR (D_2O, 23 °C): $\delta = 47.3$ (s, CH_2), 184.1 (s, COO). *Anal.* Calc. for $C_2H_4LiNO_2$ (80.999): C, 29.66; H, 4.98; N, 17.29. Found: C, 29.31; H, 5.05; N, 16.86%.

Preparation of $[Li(GlyGlyH)]^+Cl^-$ (3)

As for **1** from 1.32 g (10 mmol) of diglycine and 0.85 g (10 mmol) of LiCl in 10 ml of H_2O. Yield (several fractions) 1.36 g (7.82 mmol, 78.16%), m.p. >255 °C color change; >280 °C melting with decomposition. IR (cm^{-1}): 3289(m), 3211(s), 3130(s), 3068(s), 2688(m), 2582(w), 2006(w), 1673(s), 1600(s,sh), 1485(s), 1447(s), 1435(s), 1419(s), 1394(m), 1314(m), 1273(m), 1237(w), 1158(w), 1120(m), 1085(m), 1048(w), 1010(w), 959(w), 910(m), 723(m), 665(w), 599(w), 571(m), 532(w), 467(m), 411(m). ^1H NMR (D_2O, 23 °C): $\delta = 3.81$ (s, CH_2), 3.87 (s, CH_2). $^{13}C\{^1H\}$ NMR (D_2O, 23 °C): $\delta = 43.2$ (s, CH_2, N terminus), 45.9 (s, CH_2, C terminus), 169.6 (s, C(O)N), 179.0 (s, COO). *Anal.* Calc. for $C_4H_8ClLiN_2O_3$ (174.512): C, 27.53; H, 4.62; N, 16.05. Found: C, 26.90; H, 4.71; N, 15.89%.

Preparation of $Li^+GlyGly^-$ (4)

To 1.32 g (10 mmol) of diglycine in 25 ml of hot abs. MeOH, 0.24 g (10 mmol) of LiOH were added and the solution refluxed for 30 min. Upon cooling a white microcrystalline precipitate formed which was filtered off and dried *in vacuo*. A second fraction was obtained after removal of the MeOH. Yield 1.30 g (9.46 mmol, 94.6%), m.p. >230 °C color change; 256 °C melting with decomposition. IR (cm^{-1}): 3394(s), 3359(w), 3310(s), 3094(m), 1683(s), 1652(s), 1539(s), 1447(s), 1409(s), 1378(s), 1342(m), 1312(s), 1277(m), 1007(w), 987(m), 928(m), 851(m), 752(m), 722(m), 699(m), 606(m), 569(m), 534(s), 518(m), 408(s). ^1H NMR (D_2O, 23 °C): $\delta = 3.2$ (s, CH_2), 3.6 (s, CH_2). $^{13}C\{^1H\}$ NMR (D_2O, 23 °C): $\delta = 45.8$ (s, CH_2, N terminus), 46.5 (s, CH_2, C terminus), 178.1 (s, C(O)N), 179.4 (s, COO). *Anal.* Calc. for $C_4H_7LiN_2O_3$ (138.051): C, 34.80; H, 5.11; N, 20.29. Found: C, 34.62; H, 5.13; N, 20.26%.

Preparation of $Li^+GlyGly^- \cdot 1H_2O$ (5)

Recrystallization of 6.35 g (46.00 mmol) of **4** from EtOH/H_2O (6:1) yielded (several fractions) 5.22 g (33.48 mmol, 72.78%) of colorless crystalline **5** which was dried over $CaCl_2$ in an exsiccator. M.p. >210 °C color change; 249 °C melting with decomposition. IR (cm^{-1}): 3359(s), 3277(m), 3095(m), 1686(s), 1605(s), 1570(s), 1462(s), 1429(s), 1397(s), 1378(s), 1319(m), 1277(s), 1166(w), 1128(w), 1072(w), 1035(m), 974(m), 928(w), 889(w), 722(m), 614(w), 567(w), 548(w), 426(m). ^1H NMR and $^{13}C\{^1H\}$ NMR in D_2O as for **4**. *Anal.* Calc. for $C_4H_9LiN_2O_4$ (156.066): C, 30.78; H, 5.81; N, 17.94. Found: C, 30.50; H, 5.79; N, 17.60%.

X-ray structure determinations

Suitable single crystals of **1–3** and **5** were obtained as described above. They were mounted on glass fibers and examined directly on a diffractometer (Enraf-Nonius CAD4, Mo Kα radiation, $\lambda = 0.71069$ Å, graphite monochromator). The crystal systems indicated by preliminary search and indexing procedures were checked for higher metrical symmetry by Reduced-Cell-Calculations (DELOS [23], LePage [24]). The space group of **3** was assumed to be $P\bar{1}$, that of **5**, $P2_1$, which was confirmed by the successful refinement of the structures. The space groups of **1** and **2** were fully determined by the systematic absences. Exact cell constants were determined by refinement on the Bragg angles of 25 high-angle reflexions from various parts of reciprocal space carefully centered on the diffractometer. The structure of $[Li(GlyGlyH)]^+Cl^-$ (**3**), was found to be isotypic with the analogous Br^- salt, the structure of which has been reported previously [10a]. Because this early structure determination was done with photographic methods, and consequently with reduced precision, we found it desirable to redetermine the structure with state of the art methods. $[Li(GlyGlyH)]^+Br^-$ [10a] is reported in a non-reduced unit cell which thus differs from the one used by us for **3***. Table 1 collects the crystal data and numbers pertinent to data collection, structure solution and refinement.

The integrated intensities measured were corrected for Lorentz–polarization effects. Crystal decay was checked by the measurement of three monitor reflexions repeated every 3600 s of X-ray exposure time. For **1** these measurements indicated a linear intensity decay of −5.2% which was corrected for. Only random intensity fluctuations were observed for the other com-

*Furthermore, in the original publication of the Br^- salt [10a], the *y* coordinate of the Li atom position apparently is in error.

TABLE 1 Crystal structure data for **1**, **2**, **3** and **5**

	1	**2**	**3**	**5**
Formula	$C_2H_7ClLiNO_3$	$C_2H_4LiNO_2$	$C_4H_8ClLiN_2O_3$	$C_4H_9LiN_2O_4$
M_r	135.475	80.999	174.512	156 066
Crystal system	monoclinic	orthorhombic	triclinic	monoclinic
Space group	$P2_1/c$ (No. 14)	$P2_12_12_1$ (No. 19)	$P\bar{1}$ (No. 2)	$P2_1$ (No. 4)
a (Å)	10.103(2)	4.998(1)	5.033(1)	7 290(1)
b (Å)	5.064(1)	7.864(1)	7.533(1)	4 923(1)
c (Å)	11.930(2)	9.261(1)	10 132(2)	10 431(1)
α (°)	90	90	76 54(1)	90
β (°)	107.39(1)	90	88 42(1)	101.73(1)
γ (°)	90	90	84 56(1)	90
V (Å^3)	582.5	364.0	371.9	366.5
Z	4	4	2	2
D_{calc} (g/cm^3)	1.545	1.478	1.558	1.414
μ(Mo Kα) (cm^{-1})	5 7	1 2	4 7	1.1
F(000) (e)	280	168	180	164
T (°C)	−55	−40	−50	−40
Scan	$\vartheta/2\vartheta$	$\vartheta/2\vartheta$	$\vartheta/2\vartheta$	$\vartheta/2\vartheta$
Scan width (in ω)	0.75 + 0.35 tan ϑ	0.9 + 0.35 tan ϑ	0 8 + 0.35 tan ϑ	0.8 + 0.35 tan ϑ
$(\sin\vartheta/\lambda)_{max}$ (Å^{-1})	0 865	0.648	0 647	0 646
hkl Range	+17, ±8, ±20	+6, +10, ±12	+6, ±9, ±13	+9, +6, ±13
Reflections: measured/unique	7152/3163	991/828	1879/1686	1000/926
R_{int}	0.01	0.02	0.01	0 01
Absorption correction	empirical	no	no	no
Relative transmission	0.86–1.00			
Parameters refined	101	55	132	110
$R^{(a)}$	0 038	0.049	0 028	0.030
$R_w{}^b$	0.059	0.054	0 030	0.034
$\Delta\rho_{fin}$: max./min. (e/Å^3)	0 56/−0.94	±0.46	0 39/−0.30	0.15/−0.19

[a] $R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$ [b] $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{1/2}$; $w = 1/\sigma^2(F_o)$. Function minimized: $\Sigma w(|F_o| - |F_c|)^2$.

plexes (**2**: −2.0%; **3**: +0.8%; **5**: −0.9%) and were not corrected. An empirical absorption correction was applied for **1**. This was based on ψ scans around the diffraction vectors of nine selected reflexions near $\chi = 90°$ which served to evaluate the transmission curves. For **2**, **3** and **5** absorption corrections were not deemed necessary. The structure factors of reflexions with negative intensities (i.e. those with accidental background fluctuations larger than them) were assigned a positive value small with respect to their standard deviations so that they could be included in all calculations. The resulting structure factors were merged to give unique data sets. An 'unobserved' threshold was not used throughout the calculations. The structures were solved by direct methods and completed by Fourier syntheses. After anisotropic refinement of all non-H atoms, all H atoms could be located in difference syntheses. In **1** and **3** they were freely refined with isotropic displacement parameters, in **5** only the hydrogen atoms at nitrogen were refined. All other H atoms were included as constant into structure factor calculations ($U_{iso} = 0.05$ Å^2). All non-H atoms were refined with anisotropic displacement parameters. For **2** and **5** which crystallize in non-centrosymmetric space groups refinement of the inverse structures did not yield significant differences. The final atomic coordinates are collected in Tables 2–5. Scattering factors for neutral spherical atoms were those given by Cromer and Waber [25],

TABLE 2. Fractional atomic coordinates and equivalent isotropic displacement parameters (H atoms: isotropic displacement parameters) for **1**

Atom	*x/a*	*y/b*	*z/c*	$U_{eq/iso}$[a]
Li	0.5873(3)	0.2054(5)	0 2463(2)	0.018
Cl	0.04839(4)	0 18355(6)	0 14313(3)	0.020
N(1)	0.8269(1)	−0 3244(2)	0.0738(1)	0.018
C(1A)	0.7078(2)	−0 1551(3)	0 0740(1)	0.019
C(1)	0.6161(1)	−0 2950(2)	0.1363(1)	0.014
O(11)	0.6175(1)	−0.5408(2)	0.13677(9)	0.020
O(12)	0.5446(1)	−0.1492(2)	0.1816(1)	0 020
O(1W)	0 7706(1)	0 1772(2)	0.3640(1)	0 024
H(1N1)	0.880(3)	−0.366(5)	0.151(2)	0 053(7)
H(1N2)	0 802(3)	−0.474(5)	0 035(2)	0 047(7)
H(1N3)	0.885(3)	−0.252(5)	0 033(2)	0 053(7)
H(1A1)	0.653(2)	−0.131(4)	−0.006(2)	0 019(5)
H(1A2)	0.755(3)	0 021(6)	0.121(2)	0.055(8)
H(1W1)	0 806(3)	0 041(7)	0.342(3)	0.08(1)
H(1W2)	0.810(3)	0.308(7)	0.360(3)	0.08(1)

[a] $U_{eq} = \frac{1}{3}\Sigma_i\Sigma_j U_{ij} a^*_i a^*_j \mathbf{a}_i \mathbf{a}_j$

TABLE 3. Fractional atomic coordinates and equivalent isotropic displacement parameters (H atoms: isotropic displacement parameters) for **2**

Atom	*x/a*	*y/b*	*z/c*	$U_{eq/iso}$
Li	0.246(1)	0.1751(6)	−0.0774(5)	0.019
N(1)	0.3037(5)	0.7721(3)	0.2079(2)	0.021
C(1A)	0.1350(6)	0.6283(4)	0.1660(3)	0.022
C(1)	0.2616(6)	0.4967(3)	0.0680(2)	0.015
O(11)	0.5051(4)	0.5134(2)	0.0358(2)	0.019
O(12)	0.1152(4)	0.3761(2)	0.0273(2)	0.022
H(1N1)[a]	0.4624	0.7467	0.1979	0.050
H(1N2)[a]	0.2821	0.8599	0.1416	0.050
H(1A1)[a]	−0.0069	0.6623	0.1314	0.050
H(1A2)[a]	0.0658	0.5787	0.2478	0.050

[a]Atom not refined.

TABLE 4. Fractional atomic coordinates and equivalent isotropic displacement parameters (H atoms: isotropic displacement parameters) for **3**

Atom	*x/a*	*y/b*	*z/c*	$U_{eq/iso}$
Li	0.2995(5)	−0.6176(3)	0.5133(2)	0.020
Cl	0.33137(7)	0.27741(5)	1.04348(3)	0.026
N(1)	−0.1579(3)	0.3592(2)	0.8516(1)	0.022
C(1A)	−0.1955(3)	0.1808(2)	0.8209(1)	0.021
C(1)	0.0355(3)	0.1227(2)	0.7371(1)	0.016
O(1)	0.1943(2)	0.2325(1)	0.68074(9)	0 022
N(2)	0.0457(3)	−0 0496(2)	0.7266(1)	0.023
C(2A)	0.2494(3)	−0 1276(2)	0.6472(2)	0.024
C(2)	0.1559(3)	−0.2864(2)	0.5976(1)	0.016
O(21)	−0.0785(2)	−0.3275(1)	0.62226(9)	0.020
O(22)	0.3257(2)	−0.3664(1)	0.53244(9)	0.021
H(1N1)	−0.142(4)	0.449(2)	0.776(2)	0.044(5)
H(1N2)	−0.300(4)	0.397(3)	0.900(2)	0.055(6)
H(1N3)	0.002(4)	0.352(2)	0.914(2)	0.047(5)
H(1A1)	−0.357(4)	0.193(2)	0.767(2)	0.037(5)
H(1A2)	−0.205(3)	0.094(2)	0.903(2)	0.029(4)
H(2N)	−0.064(4)	−0.118(2)	0.776(2)	0.033(5)
H(2A1)	0.410(4)	−0.175(2)	0.700(2)	0.035(5)
H(2A2)	0.295(4)	−0.033(2)	0.566(2)	0.036(5)

for the H atoms a bonded spherical atom model was used [26]. Corrections for $\Delta f'$ and $\Delta f''$ were applied for all atoms except hydrogen [27]. Programs used included SHELXS-86 [28] (structure solution), SHELX-76 [29] (refinement), ORTEP [30], SCHAKAL 92 [31] (structure drawings) as well as locally written routines. See also 'Supplementary material'.

Results and discussion

Synthesis and spectroscopic characterization

The LiCl complexes of neutral GlyH and GlyGlyH (**1**, **3**) were prepared following the established procedures of Pfeiffer [20, 21]. Thus single crystals of **1** result from simply mixing of GlyH and LiCl in aqueous

TABLE 5. Fractional atomic coordinates and equivalent isotropic displacement parameters (H atoms: isotropic displacement parameters) for **5**

Atom	*x/a*	*y/b*	*z/c*	$U_{eq/iso}$
Li	0.3707(5)	0 4943(9)	0.4963(3)	0 024
N(1)	−0.2872(3)	0.4789(7)	0.7875(2)	0.035
C(1A)	−0.1270(3)	0.3142(7)	0 8424(2)	0.034
C(1)	−0.0642(3)	0.1094(6)	0.7508(2)	0.025
O(1)	−0.1723(2)	0.02379[a]	0.6530(1)	0.041
N(2)	0.1107(2)	0.0206(6)	0.7877(2)	0.026
C(2A)	0.1977(3)	−0.1559(6)	0.7053(2)	0.028
C(2)	0.3196(3)	−0.0031(6)	0.6273(2)	0.022
O(21)	0 3207(2)	0.2488(5)	0.6296(1)	0.033
O(22)	0.4137(2)	−0.1479(5)	0.5651(1)	0.029
O(1W)	0.3982(2)	0.2075(6)	0.0004(1)	0.040
H(1N1)	−0.264(3)	0.583(7)	0.721(3)	0.049(8)
H(1N2)	−0.391(3)	0.388(7)	0.749(2)	0.049(8)
H(2N)	0.197(3)	0.107(7)	0.863(2)	0.053(8)
H(1A1)[b]	−0.15410	0.23350	0.91350	0.050
H(1A2)[b]	−0.01730	0.40360	0.89390	0.050
H(2A1)[b]	0.10710	−0.26250	0.65410	0.050
H(2A2)[b]	0.27070	−0.29100	0.76250	0.050
H(1W1)[b]	0.37790	0.16120	0.08140	0.050
H(1W2)[b]	0.44560	0.35400	0.02070	0 050

[a]Coordinate not refined. [b]Atom not refined.

solution and subsequent evaporation of the solvent. The lithium complexes of the deprotonated ligands Gly^- and $GlyGly^-$ (**2**, **4**) form by treatment of the ligands with LiOH in water (**2**)* or absolute MeOH (**4**). This method is conceivably more convenient than the original synthesis in liquid ammonia. Single crystals of **2** and **5** ($=\mathbf{4}\cdot 1H_2O$) may be obtained with difficulty from $EtOH/H_2O$ mixtures. All complexes are colorless, high-melting salts. Before melting sets in a color change of the complexes is usually observed, indicative of beginning decomposition.

The IR spectra of **1**–**5** (see 'Experimental') show noticeable changes with respect to the free (neutral) ligands but an assignment of the coordination mode was not possible on this basis. In particular, even the usually characteristic carboxylate bands do not allow a clear-cut assignment of the metal coordination due to the large number and partial overlap of absorptions. Also the largely ionic nature of the metal ligand interaction is not expected to have very pronounced effects on the carboxylate bands.

In the ^{13}C NMR spectra (see 'Experimental') the complexation is clearly accompanied by a slight shift of all the ^{13}C resonances to lower field with respect to those of the uncomplexed ligands [33, 34]. This shift is particularly pronounced if the atom adjacent to the C atom is deprotonated before complexation. This is in accord with the previously observed low-field shift

*Li^+Gly^- has also been prepared in ethanol by essentially the same method [32].

of the ^{13}C NMR resonances upon gradually increased deprotonation of GlyGlyH [33] and GlyH [34]. The Li^+ complexation clearly enhances this effect further.

In contrast to the ^{13}C NMR spectra, the ^1H NMR resonances of glycine and glycinepeptides are known to be shifted to higher field upon deprotonation [35]. The Li^+ complexation in **1–3** and **5** does not lead to significant changes of the respective resonances (see 'Experimental').

Details about the lithium coordination can only be obtained from solid-state structure determinations. Key features of the crystal and molecular structures of **1–3** and **5** are shown in Figs. 1–10. Tables 6–9 summarize important bond lengths and angles. Table 10 contains the hydrogen bond interactions. As is clearly evident from Fig. 1, in the solid state the lithium cation in **1** is four-coordinate, the coordination geometry being close to an ideal tetrahedron. The coordinating atoms are three oxygen atoms from the carboxylate groups of three different but crystallographically equivalent glycine ligands, the fourth coordination site is occupied by the oxygen atom of the water molecule. Taken the 1:1 stoichiometry of **1** into account, this implies that each carboxylate group binds to three different lithium cations, one oxygen atom bridging two of them, the second being coordinated to just one Li^+ (Fig. 2). Quite remarkably, this coordination pattern of the carboxylate group towards Li^+ is identical in all four complexes, as is the tetrahedral four-coordination of Li^+ (Figs. 3, 5, 6, 8 and 10). Similar features have been observed frequently in other amino acid, and generally carboxylic acid, complexes of Li^+ [12], but other coordination modes also occur. However, the coordination polymer resulting from the bridging of the lithium cations by the amino acid carboxylate groups is different in **3** (Fig. 8) from that in **1**, **2** and **5** (Figs.

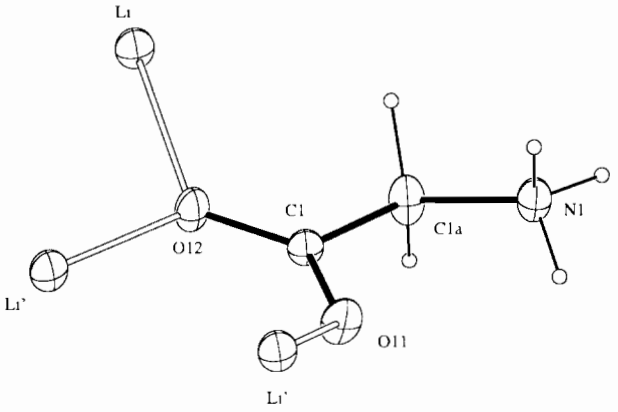

Fig. 2. Structure of the glycine coordination in **1** (ORTEP, symmetry operations Li': $1-x$, $y-0.5$, $0.5-z$, Li'': x, $y-1$, z).

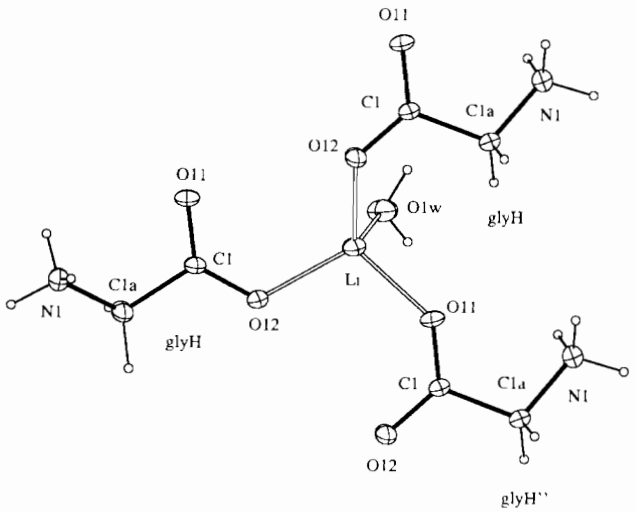

Fig. 1. Structure of the lithium coordination in the crystal of **1** and crystallographic numbering scheme adopted (ORTEP; displacement ellipsoids at the 50% level; H atoms with arbitrary radii; symmetry operations: GlyH' $1-x$, $0.5+y$, $0.5-z$; GlyH'' x, $1+y$, z).

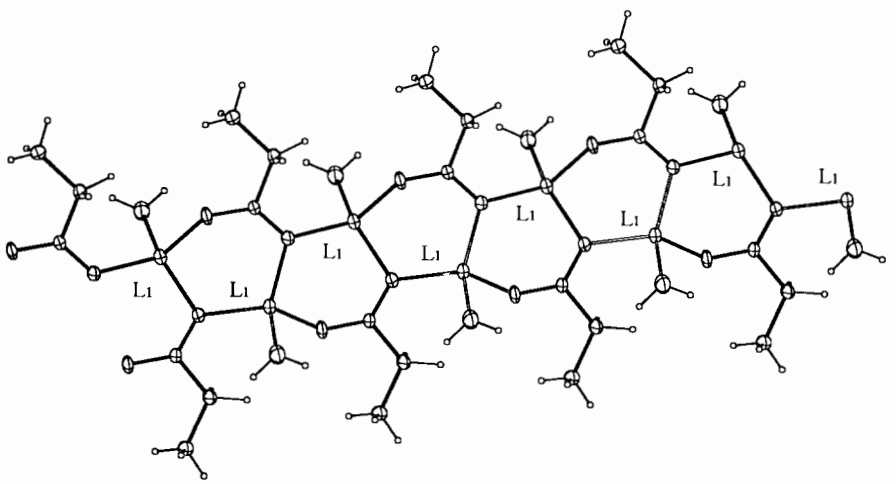

Fig. 3 Coordination polymer in the crystal of **1** (ORTEP; without hydrogen bonds).

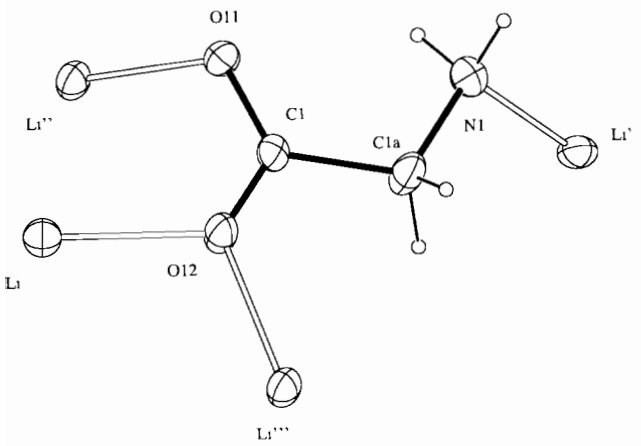

Fig. 4. Structure of the glycinate coordination in **2** (ORTEP; symmetry operations. Li′: $0.5-x$, $1-y$, $0.5+z$; Li″: $0.5+x$, $0.5-y$, $-z$; Li‴: $x-0.5$; $0.5-y$, $-z$)

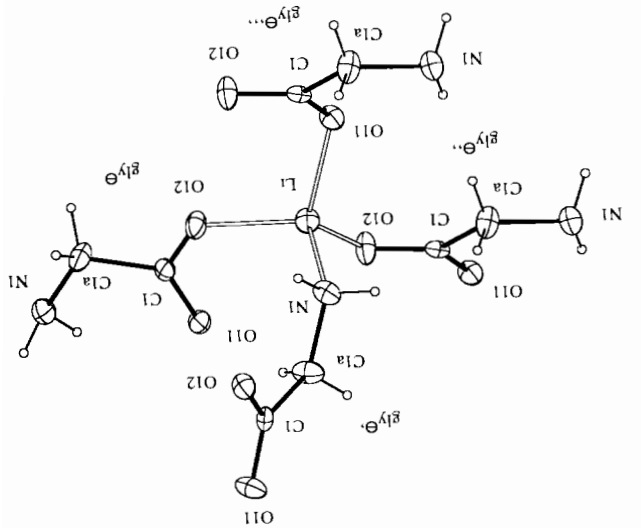

Fig 5. Structure of the lithium coordination in **2** (ORTEP, symmetry operations: $Gly^{-\prime}$. $0.5-x$, $1-y$, $z-0.5$; $Gly^{-\prime\prime}$: $0.5+x$, $0.5-y$, $-z$; $Gly^{-\prime\prime\prime}$: $x-0.5$, $0.5-y$, $-z$)

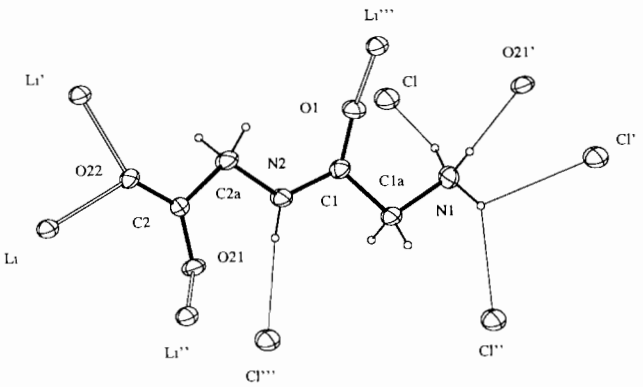

Fig. 7. Structure of the diglycine coordination in **3** (ORTEP; symmetry operations Li′: $1-x$, $-y-1$, $1-z$; Li″ $-x$, $-y-1$, $1-z$; Li‴: x, $1+y$, z; Cl′: $-x$, $1-y$, $2-z$; Cl″: $x-1$, y, z; Cl‴: $-x$, $-y$, $2-z$; O(21)′· x, $1+y$, z).

3, 6 and 10). Whereas in **1**, **2** and **5** strands of fused puckered six-membered rings [Li–O–Li–O–C–O] result, in **3** there are alternating fused eight- and four-membered rings as repeating motif ([Li–O–C–O–Li–O–C–O] and [Li–O–Li–O], respectively).

Besides the carboxylate groups, the keto oxygen atom of the peptide linkages in diglycine (in **3** and **5**) and the deprotonated amino nitrogen atoms (in **2** and **5**) are potential donor sites to Li^+, as are the water molecules ubiquitously present during crystallization. As can be seen in Figs. 7 and 9, the keto oxygen atom is always lithium coordinated, thereby completing the respective lithium coordination spheres to four. Interestingly, in **2**, where no such keto oxygen atom is available, it is the amino function which is coordinated (Figs. 4, 5 and 6). Even more surprising is the fact that in **4** the (deprotonated) amino terminus of $GlyGly^-$ remains uncoordinated as does the additional water molecule which is incorporated into the crystal only interstitially and held in place with strong hydrogen bonds to neighboring amino groups and water molecules (Fig. 9 and Table 10). Likewise, all H atoms of the

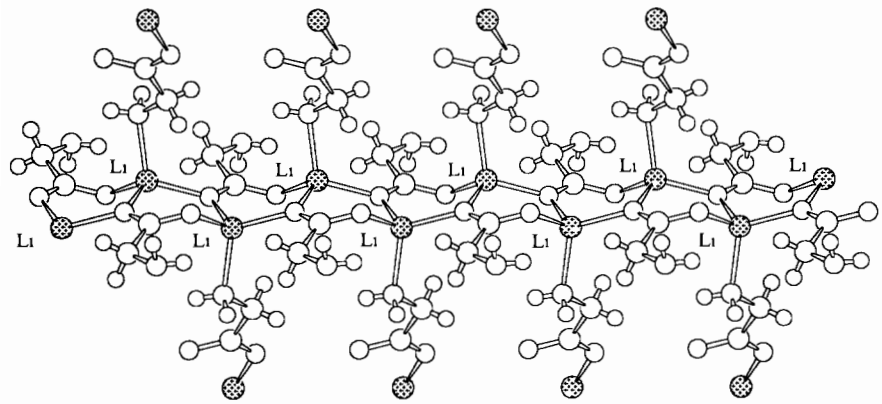

Fig. 6. Part of the coordination polymer in the crystal of **2** (SCHAKAL; without hydrogen bonds)

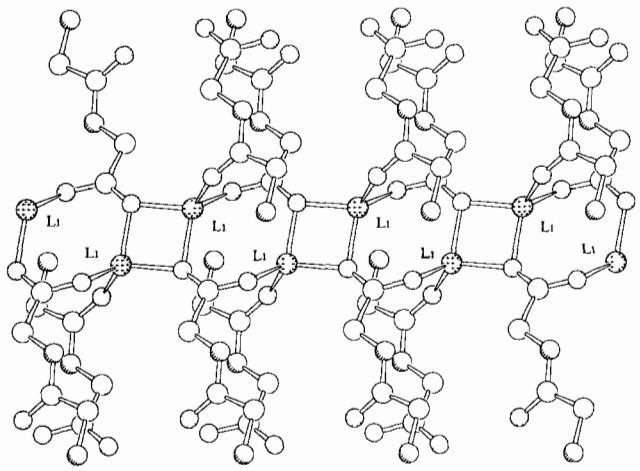

Fig. 8. Part of the coordination polymer in the crystal of **3** (SCHAKAL; without hydrogen bonds)

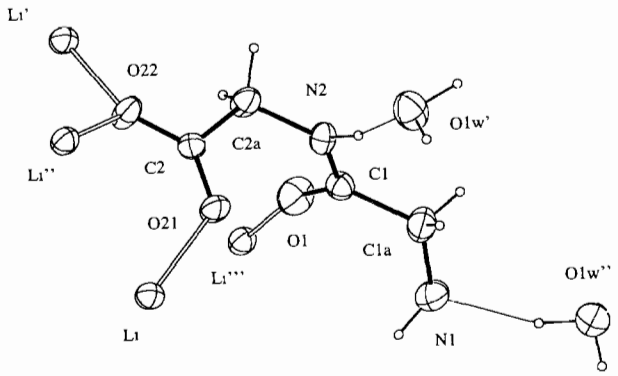

Fig. 9. Structure of the glycylglycinate coordination in **5** (ORTEP; symmetry operations: Li': $x, y-1, z$; Li'': $1-x, y-0.5, 1-z$; Li''': $-x, y-0.5, 1-z$; O(1W)': $x, y, 1+z$; O(1W)'': $-x, 0.5+y, 1-z$).

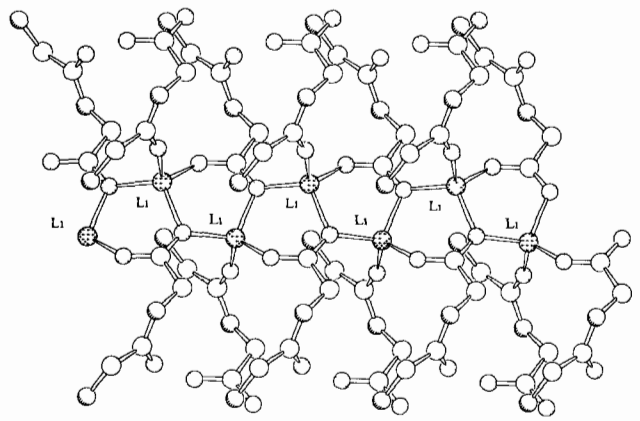

Fig. 10. Part of the coordination polymer in the crystal of **5** (SCHAKAL; without hydrogen bonds).

protonated amino groups in **1** and **3** are engaged in an intricate network of hydrogen bonds, as are all the water protons in **1** and **5**, and finally also the amido hydrogens in **3** and **5** (Table 10). In addition to the bridging role of Li^+ already mentioned above, the

TABLE 6. Selected interatomic distances (Å) and angles (°) in the structure of **1** with e s.d.s in units of the last significant figure in parentheses (for symmetry operations used see captions to Figs. 1 and 2)

Bond lengths			
Li–O(12)	1.951(3)	Li'–O(12)	1.935(3)
Li''–O(11)	1.922(3)	Li–O(1W)	1.966(3)
N(1)–C(1A)	1.478(2)	C(1A)–C(1)	1 524(2)
C(1)–O(11)	1.245(2)	C(1)–O(12)	1.262(2)
Bond angles			
O(11)''–Li–O(12)	114.1(1)	O(11)''–Li–O(1W)	103.1(1)
O(12)–Li–O(1W)	105.4(1)	O(1W)–Li–O(12)'	109.7(1)
O(11)''–Li–O(12)'	108.5(1)	O(12)–Li–O(12)'	115.2(1)
C(1)–C(1A)–C(1)	110.2(1)	C(1A)–C(1)–O(11)	117.4(1)
C(1A)–C(1)–O(12)	116.5(1)	O(11)–C(1)–O(12)	126.2(1)
Li''–O(11)–C(1)	131.9(1)	Li–O(12)–C(1)	128.4(1)
Li'–O(12)–C(1)	121.7(1)	Li–O(12)–Li'	105.9(1)

TABLE 7. Selected interatomic distances (Å) and angles (°) in the structure of **2** (for symmetry operations used see captions to Figs. 4 and 5)

Bond lengths			
Li''–O(11)	1.950(5)	Li–O(12)	1.967(4)
Li'''–O(12)	1.943(5)	Li'–N(1)	2.046(5)
N(1)–C(1A)	1.463(3)	C(1A)–C(1)	1.515(4)
C(1)–O(11)	1 260(3)	C(1)–O(12)	1.256(3)
Bond angles			
O(12)–Li–N(1)'	106.0(2)	O(12)–Li–O(12)''	111.4(2)
O(12)–Li–O(11)'''	107.9(2)	N(1)'–Li–O(12)''	113.0(2)
N(1)'–Li–O(11)'''	105.7(2)	O(12)''–Li–O(11)'''	112.5(2)
Li'–N(1)–C(1A)	110.2(2)	N(1)–C(1A)–C(1)	116.5(2)
C(1A)–C(1)–O(11)	118.3(3)	C(1A)–C(1)–O(12)	116.9(2)
O(11)–C(1)–O(12)	124.8(2)	Li''–O(11)–C(1)	118.1(2)
Li–O(12)–C(1)	124.1(2)	Li'''–O(12)–C(1)	129.6(2)
Li–O(12)–Li'''	105.5(2)		

TABLE 8 Selected interatomic distances (Å) and angles (°) in the structure of **3** (for symmetry operations used see caption to Fig. 7; O(1)'''. $x, y-1, z$; O(21)'': $-x, -y-1, 1-z$, O(22)': $1-x, -y-1, 1-z$)

Bond lengths			
Li'''–O(1)	1.898(2)	Li–O(22)	1.963(2)
Li'–O(22)	1 930(2)	Li''–O(21)	1.932(2)
N(1)–C(1A)	1.478(2)	C(1A)–C(1)	1.512(2)
C(1)–O(1)	1.236(2)	C(1)–N(2)	1.323(2)
N(2)–C(2A)	1.451(2)	C(2A)–C(2)	1.519(2)
C(2)–O(21)	1.251(2)	C(2)–O(22)	1.259(1)
Bond angles			
O(1)'''–Li–O(22)	110 2(1)	O(21)''–Li–O(22)	122.4(1)
O(22)'–Li–O(22)	89.0(1)	O(1)'''–Li–O(21)''	105.3(1)
O(1)'''–Li–O(22)'	117.2(1)	O(22)'–Li–O(21)''	112.8(1)
N(1)–C(1A)–C(1)	110.5(1)	C(1A)–C(1)–O(1)	121.2(1)
C(1A)–C(1)–N(2)	114.7(1)	O(1)–C(1)–N(2)	124.1(1)
Li–O(1)–C(1)	145.3(1)	C(1)–N(2)–C(2A)	122.3(1)
N(2)–C(2A)–C(2)	112.0(1)	C(2A)–C(2)–O(21)	119.2(1)
C(2A)–C(2)–O(22)	115.8(1)	O(21)–C(2)–O(22)	125 0(1)
Li''–O(21)–C(2)	122.2(1)	Li–O(22)–C(2)	122.4(1)
Li'–O(22)–C(2)	141.9(1)	Li–O(22)–Li'	91.0(1)

TABLE 9. Selected interatomic distances (Å) and angles (°) in the structure of **5** (for symmetry operations used see caption to Fig. 9; O(1)‴: $-x$, $0.5+y$, $1-z$; O(22)′: x, $1+y$, z; O(22)″· $1-x$, $0.5+y$, $1-z$)

Bond lengths			
Li–O(21)	1.932(4)	Li′–O(22)	1.903(4)
Li″–O(22)	1.945(4)	Li‴–O(1)	1.904(3)
N(1)–C(1A)	1.441(3)	C(1A)–C(1)	1.522(3)
C(1)–O(1)	1.230(2)	C(1)–N(2)	1.329(2)
N(2)–C(2A)	1.455(3)	C(2A)–C(2)	1.520(3)
C(2)–O(21)	1.240(3)	C(2)–O(22)	1.258(2)
Bond angles			
O(21)–Li–O(22)′	110.4(2)	O(21)–Li–O(22)″	107.2(2)
O(21)–Li–O(1)‴	114.4(2)	O(22)′–Li–O(22)″	112.0(2)
O(22)′–Li–O(1)‴	106.1(2)	O(22)″–Li–O(1)‴	106.8(2)
N(1)–C(1A)–C(1)	116.5(2)	C(1A)–C(1)–O(1)	121.6(2)
C(1A)–C(1)–N(2)	115.5(2)	O(1)–C(1)–N(2)	122.9(2)
Li‴–O(1)–C(1)	163.2(2)	C(1)–N(2)–C(2A)	122.2(2)
N(2)–C(2A)–C(2)	113.1(2)	C(2A)–C(2)–O(21)	119.1(2)
C(2A)–C(2)–O(22)	115.8(2)	O(21)–C(2)–O(22)	125.1(2)
Li–O(21)–C(2)	127.8(2)	Li′–O(22)–C(2)	130.8(2)
Li″–O(22)–C(2)	121.9(2)	Li′–O(22)–Li″	107.0(2)

network of hydrogen bonds provides another linkage between the ligands, water molecules and Cl^- ions in the crystals of **1–3** and **5**.

On the basis of these results the following sequence of donor atom capability towards Li^+ may be established for the glycine and diglycine complexes presented in this paper: $-COO^- \approx C(O) > -NH_2 > H_2O$. In other words, Li^+ is preferentially coordinated by carboxylate and keto oxygen atoms. If additional vacant coordination sites are available the amino nitrogen atom seems to be preferred over water molecules. It should be stressed that these conclusions are not biased by grossly different coordination modes of the carboxylate groups nor by any kind of chelate formation.

A further important feature in the crystal structures of **3** and **5** is the conformation of the peptide backbones as characterized by the torsion angles summarized in Table 11. As can also be seen in Figs. 7 and 9, the backbone conformations in **3** and **5** are different, that in **3** giving rise to an almost perfectly extended peptide. The conformation in **5** is more folded as a result of an entirely different torsion angle φ_2*. It should be noted that the peptide linkages are in an almost perfect *trans* conformation in both structures (ω_1 close to 180°). An extended peptide conformation as in **3** is also observed in the crystal structure of diglycine itself (Table 11) where intermolecular hydrogen bonding is clearly

*It should be noted at this point that due to the missing substituents at C(1A) ($=C_\alpha$) glycine containing peptides are particularly flexible and may give rise to a broad range of sterically possible peptide conformations.

TABLE 10. Hydrogen bonds in the crystal structures of **1**, **2**, **3** and **5**

A–H···B	A–H (Å)	H· ·B (Å)	A···B (Å)	A–H ·B (°)
[Li(GlyH)(H₂O)]⁺Cl⁻ (**1**)				
N(1)–H(1N1)···Cl[a]	0.94(3)	2.36(3)	3.233(1)	155(2)
N(1)–H(1N2)···O(1W)[b]	0.88(3)	2.23(3)	2.989(2)	145(2)
N(1)–H(1N3)···Cl[c]	0.95(3)	2.41(3)	3.278(1)	152(2)
O(1W)–H(1W1)···Cl[d]	0.86(4)	2.30(4)	3.114(1)	158(3)
O(1W)–H(1W2)···Cl[e]	0.78(3)	2.39(3)	3.166(1)	175(3)
Symmetry operations: [a]$1-x$, $y-0.5$, $0.5-z$; [b]x, $-y-0.5$, $z-0.5$; [c]$1-x$, $-y$, $-z$; [d]$1-x$, $y-0.5$, $0.5-z$; [e]$1-x$, $0.5+y$, $0.5-z$.				
Li⁺Gly⁻ (**2**)				
N(1)–H(1N1) ··O(11)	0.82	2.38	2.774(3)	110.1
N(1)–H(1N2)·· O(11)[a]	0.93	2.37	3.189(3)	146.9
Symmetry operations: [a]$x-0.5$, $1.5-y$, $-z$.				
[Li(GlyGlyH)]⁺Cl⁻ (**3**)				
N(1)–H(1N1)···O(21)[a]	0.90(2)	2.06(2)	2.951(2)	172(2)
N(1)–H(1N2)···Cl[b]	0.92(2)	2.44(2)	3.200(1)	141(2)
N(1)–H(1N2)···Cl[c]	0.92(2)	2.63(2)	3.200(1)	121(2)
N(1)–H(1N3)···Cl	1.02(2)	2.10(2)	3.106(1)	168(2)
N(2)–H(2N)···Cl[d]	0.86(2)	2.40(2)	3.239(1)	166(2)
Symmetry operations: [a]x, $1+y$, z; [b]$x-1$, y, z, [c]$-x$, $1-y$, $2-z$; [d]$-x$, $-y$, $2-z$.				
Li⁺GlyGly⁻·1H₂O (**5**)				
N(1)–H(1N1)···O(1)[a]	0.90(3)	2.42(3)	3.216(2)	147(2)
N(1)–H(1N2)···O(21)[b]	0.90(3)	2.32(3)	3.202(2)	167(3)
N(2)–H(2N)···O(1W)[c]	1.00(3)	1.90(2)	2.877(2)	167(2)
O(1W)–H(1W1)· ·N(1)[d]	0.92	1.87	2.747(3)	161
O(1W)–H(1W2)···O(1W)[e]	0.81	2.12	2.876(3)	156
Symmetry operations: [a]x, $1+y$, z; [b]$x-1$, y, z; [c]x, y, $1+z$; [d]$-x$, $y-0.5$, $1-z$; [e]$1-x$, $0.5+y$, $-z$.				

TABLE 11. Important torsion angles (°) in the structures of **3** and **5**

	3	**5**	α-GlyGlyH[a]	β-GlyGlyH[b]
N(1)–C(1A)–C(1)–N(2) (ψ_1)	167.7	160 3	150 98(3)	156.2
C(1A)–C(1)–N(2)–C(2A) (ω_1)	178.3	−174 2	176.09(3)	178.7
C(1)–N(2)–C(2A)–C(2) (φ_2)	−154 0	97 7	157.12(3)	177 7

[a]Ref. 36a. [b]Ref. 36c.

the cause [36]. Although this hydrogen bonding pattern is grossly altered by the coordination of Li^+ in **3** (as well as in **5**) no simple explanation with regard to the conformation determining influence of Li^+ and Cl^- can be given at this moment. A more detailed analysis of the diglycine conformation including an extension of the conformational study to the solution, as based on the ^{13}C NMR spectra, is in progress and will be reported elsewhere.

Supplementary material

Further crystal structure data may be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen (Germany), by quoting the depository number CSD-57885, the names of the authors and the literature citation.

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft, Bonn–Bad Godesberg, and Fonds der Chemischen Industrie, Frankfurt/Main for continuous generous support.

References

1 (a) M.J. Kendrick, M.T. May, M.J. Plishka and K.D. Robinson, *Metals in Biological Systems,* Ellis Horwood, New York, 1992, (b) W. Kaim and B. Schwederski, *Bioanorganische Chemie,* Teubner, Stuttgart, 1991; (c) J.J.R Fraústo da Silva and R.J.P. Williams, *The Biological Chemistry of the Elements,* Clarendon, Oxford, 1991; (d) K. Burger (ed.), *Biocoordination Chemistry. Coordination Equilibria in Biologically Active Systems,* Ellis Horwood, New York, 1990; (e) R.W. Hay, *Bio-inorganic Chemistry,* Ellis Horwood, Chichester, UK, 1984; (f) H. Sigel (ed), *Metal Ions in Biological Systems,* Marcel Dekker, New York, 1974–1993.

2 (a) B L. Vallee and D.S. Auld, *Biochemistry, 29* (1990) 5647, (b) I. Bertini, C Luchinat, W. Maret and M Zeppezauer (eds), *Zinc Enzymes,* Birkhäuser, Boston, MA, 1986; (c) I. Bertini, C. Luchinat and R. Monnanni, *J Chem Educ , 62* (1985) 924, (d) H .Sigel (ed), *Metal Ions in Biological Systems,* Vol. 15, Marcel Dekker, New York, 1983

3 R. Kaptein, *Curr Opinion Struct Biol , 1* (1991) 63

4 (a) E I. Ochiai, *J Chem Educ , 68* (1991) 10, (b) C Gerday, L. Bolis and R. Gilles (eds.), *Calcium and Calcium Binding Proteins,* Springer, Berlin, 1988; (c) H. Sigel (ed), *Metal Ions in Biological Systems,* Vol 17, Marcel Dekker, New York, 1984; (d) F.L. Siegel, *Struct. Bonding (Berlin), 17* (1973) 221.

5 H Schmidbaur, H.G. Classen and J. Helbig, *Angew. Chem., 102* (1990) 1122; *Angew Chem , Int Ed Engl , 29* (1990) 1090.

6 H. Sigel (ed.), *Metal Ions in Biological Systems,* Vol 26, Marcel Dekker, New York, 1990.

7 (a) R. Cini, M.C. Burla, A Nunzi, G P. Polidori and P.F. Zanazzi, *J Chem Soc , Dalton Trans ,* (1984) 2467; (b) R Cini, M. Sabat, M. Sundaralingam, M.C. Burla, A Nunzi, G Polidori and P.F. Zanazzi, *J Biomol. Struct Dyn , 1* (1983) 633.

8 (a) S. Mann, J. Webb and R.J.P Williams (eds), *Biomineralization,* VCH, Weinheim, Germany, 1990, (b) H.A. Lowenstam and S. Weiner, *On Biomineralization,* Oxford University Press, Oxford, UK, 1989; (c) S. Weiner, *CRC Rev. Biochem., 20* (1986) 365, (d) S Mann, *Struct Bonding (Berlin), 54* (1983) 125.

9 U. Olsher, R M. Izatt, J.S. Bradshaw and N K. Dalley, *Chem Rev., 91* (1991) 137

10 (a) R Meulemans, P Piret and M van Meersche, *Bull. Soc Chim Belg , 80* (1971) 73; (b) R Meulemans, P. Piret and M. van Meersche, *Acta Crystallogr , Sect B, 27* (1971) 1187.

11 J P. Declercq, R Meulemans, P Piret and M van Meersche, *Acta Crystallogr , Sect B, 27* (1971) 539

12 H Schmidbaur, I. Bach, D.L. Wilkinson and G. Müller, *Chem Ber , 122* (1989) 1427.

13 N Takahashi, I Tanaka, T. Yamane, T. Ashida, T. Sugihara, Y. Imanishi and T Higashimura, *Acta Crystallogr , Sect B, 33* (1977) 2132

14 (a) I L Karle, *J Am Chem Soc , 96* (1974) 4000; (b) I.L. Karle, J Karle, T. Wieland, W Burgermeister, H. Faulstich and B Witkop, *Proc. Nat Acad Sci U S A , 70* (1973) 1836.

15 H Sigel (ed.), *Metal Ions in Biological Systems,* Vol. 14, Marcel Dekker, New York, 1982.

16 (a) G N. Schrauzer and K.-F Klippel (eds.), *Lithium in Biology and Medicine,* VCH, Weinheim, Germany, 1991, (b) R.O Bach (ed), *Lithium – Current Applications in Science, Medicine and Technology,* Wiley, New York, 1985.

17 (a) N.J Birch, *Lithium Inorganic Pharmacology,* IRL Press, Oxford, UK, 1988; (b) F N. Johnson, *The History of Lithium Therapy and The Psychopharmacology of Lithium,* Macmillan, London, 1984.

18 P Douzou and C. Balny, *Adv Protein Chem , 32* (1978) 77.

19 D Seebach, *Angew Chem , 100* (1988) 1685, *Angew Chem , Int Ed Engl , 27* (1988) 1624

20 (a) P Pfeiffer and J von Modelski, *Hoppe-Seyler's Z Physiol Chem , 85* (1913) 1; (b) *81* (1912) 331, (c) P. Pfeiffer, *Hoppe-Seyler's Z Physiol Chem , 133* (1924) 22

21 P Pfeiffer and F. Wittka, *Chem Ber., 48* (1915) 1289

22 M.A. Bernard, A. Busnot and N. Decker, *Bull Soc. Chim. Fr*, (1970) 2475.
23 H. Zimmermann and H. Burzlaff, *Z Kristallogr*, *170* (1985) 241.
24 Y. Le Page, *J. Appl. Crystallogr.*, *15* (1982) 255.
25 D.T. Cromer and J.T. Waber, *Acta Crystallogr.*, *18* (1965) 104.
26 R.F .Stewart, E.R. Davidson and W.T. Simpson, *J Chem Phys.*, *42* (1965) 3175.
27 *International Tables for X-ray Crystallography,* Vol. IV, Kynoch, Birmingham, UK, 1974 (present distributor: Kluwer, Dordrecht, Netherlands).
28 G.M. Sheldrick, in G.M. Sheldrick, C. Kruger and R. Goddard (eds.), *Crystallographic Computing 3,* Oxford University Press, Oxford, UK, 1985, p. 175.
29 G.M. Sheldrick, *SHELX-76*, program for crystal structure determination, University of Cambridge, Cambridge, UK, 1976.
30 C.K Johnson, ORTEP-II, *Rep ORNL-5138*, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.
31 E. Keller, *SCHAKAL 92*, a computer program for the graphic representation of molecular and crystallographic models, Universitat Freiburg, Freiburg, Germany, 1993.
32 M.A. Ansari and J C. Craig, *Synth. Commun*, *21* (1991) 1971.
33 M. Christl and J.D Roberts, *J. Am Chem. Soc.*, *94* (1972) 4565.
34 W. Voelter, G. Jung, E. Breitmaier, E. Bayer, *Z Naturforsch., Teil B, 26* (1971) 213
35 K. Niwa, S. Toda, K. Fuwa and H. Haraguchi, *Agric Biol Chem*, *41* (1977) 1287.
36 (a). Å. Kvick, A R. Al-Karaghouli and T.F. Koetzle, *Acta Crystallogr*, *Sect B, 33* (1977) 3796 (α-GlyGlyH, neutron diffraction); (b) A.B. Biswas, E.W. Hughes, B.D. Sharma and J.N. Wilson, *Acta Crystallogr*, *Sect B, 24* (1968) 40 (α-GlyGlyH, X-ray diffraction); (c) E.W. Hughes and W.J. Moore, *J Am. Chem. Soc., 71* (1949) 2618 (β-GlyGlyH, X-ray diffraction).