Inorg. Chem. **2007**, *46*, 818–824

Coordination of Biologically Important α-Amino Acids to Calcium(II) at High pH: Insights from Crystal Structures of Calcium α-Aminocarboxylates

Stefan Fox,[†] Insa BUsching,[‡] Walter Barklage,[‡] and Henry Strasdeit*,[†]

Department of Bioinorganic Chemistry, Institute of Chemistry, University of Hohenheim, Garbenstrasse 30, D-70599 Stuttgart, Germany, and Institute of Pure and Applied Chemistry, University of Oldenburg, Carl-von-Ossietzky-Strasse 9-11, D-26129 Oldenburg, Germany

Received September 26, 2006

A series of calcium α-aminocarboxylates was prepared by refluxing aqueous solutions/suspensions of calcium hydroxide and the respective α-amino acid. The colorless, crystalline hydrates $Ca(gly)_2 \cdot H_2O$ (**1**), $Ca(ala)_2 \cdot 3H_2O$ (**2**), $Ca(val)_2 \cdot H_2O$ (**3**), $Ca(leu)_2 \cdot 3H_2O$ (**4**), $Ca(met)_2 \cdot nH_2O$ (**5**, $n \approx 2$), and $Ca(pro)_2 \cdot H_2O$ (**6**) have been isolated in yields between 29 and 67% ($gly^- =$ glycinate, $ala^- =$ *rac*-alaninate, $val^- =$ *rac*-valinate, $leu^- =$ *rac*-leucinate, $met^- =$ *rac*-methioninate, $pro^- =$ *rac*-prolinate). The compounds **1**–**6** are readily soluble in water. The 0.10 M solutions have ca. pH 10–11 which is consistent with a noticeable degree of dissociation. The ^{13}C NMR spectra of **1**–**6** in D_2O were measured, and their comparison with those of the corresponding tetramethylammonium α-aminocarboxylates point to carboxylate coordination in solution, but no indication of nitrogen coordination was found. Infrared spectra of **1**–**6** gave similar results for the solid state. Complete single-crystal X-ray structure analyses of **1**–**4** and preliminary ones of **5** and **6**, however, revealed that all aminocarboxylate ligands are N,O-chelating. Crystals of **2** consist of mononuclear complexes, while the other five compounds form three different types of one-dimensional coordination polymers. Structural diversity is also observed with the binding modes of the aminocarboxylate ligands and the calcium environment. Besides terminal aminocarboxylate coordination, there are three different types of aminocarboxylate bridges. The calcium ions are seven- or eight-coordinate in N2O5 and N2O6 coordination environments, respectively; one or three water molecules are part of the first ligand sphere of each metal ion. The crystal structures support conjectures about the existence of the yet undetected solution species $[Ca_x(aa)_{2x}(H_2O)_n]$ ($aa^- =$ α-aminocarboxylate). For example, $x = 1$ is realized in crystalline $[Ca(ala)_2(H_2O)_3]$ (**2**), and in **4** $[Ca_2(leu)_4(H_2O)_4]$ complexes ($x = 2$) are linked to infinite chains by bridging aqua ligands.

Introduction

Calcium performs numerous biological functions in all life forms, especially in higher organisms.[1] Most of these functions depend on spezialized calcium-binding proteins in which Ca^{2+} is nearly exclusively bonded to oxygen donors. A recent survey of the coordination of Ca^{2+} in proteins reveals that among 190 coordination groups with two or more protein donors there are 175 which have at least one coordinated carboxylate group from aspartic acid or glutamic acid side chains.[2] According to the principle of hard and soft acids and bases (HSAB), the "hard" Ca^{2+} ion prefers to bind to "hard" Lewis bases.[3,4] The marked preference of Ca^{2+} for carboxylate ligands is therefore not unexpected. Among the low-molecular-weight carboxylates are the α-amino acids $^+NH_3CHRCO_2^-$. They occur, for example, in blood plasma where they are thought to form a "metal−buffer" system,[5,6]

* To whom correspondence should be addressed. E-mail: h-strasd@uni-hohenheim.de.
[†] University of Hohenheim.
[‡] University of Oldenburg.

(1) Fraústo da Silva, J. J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements*, 2nd ed.; Oxford University Press: Oxford, U.K., 2001; Chapter 10.
(2) Harding, M. M. *Acta Crystallogr.* **2004**, *D60*, 849−859.
(3) Pearson, R. G. *Inorg. Chem.* **1988**, *27*, 734−740.
(4) Pearson, R. G. *Chemical Hardness*; Wiley-VCH: Weinheim, Germany, 1997; Chapter 1.
(5) Laurie, S. H. In *Handbook of Metal−Ligand Interactions in Biological Fluids: Bioinorganic Chemistry*; Berthon, G., Ed.; Dekker: New York, 1995; Vol. 1, pp 603−619.
(6) Faure, H.; Favier, A. In *Handbook of Metal−Ligand Interactions in Biological Fluids: Bioinorganic Chemistry*; Berthon, G., Ed.; Dekker: New York, 1995; Vol. 2, pp 1163−1169.

10.1021/ic061838b CCC: $37.00
Published on Web 01/12/2007

in lymph, tissue fluids, and milk.[6] α-Amino acids are also found in sediments[7] and even in carbon-rich meteorites, the so-called carbonaceous chondrites.[8,9] Calcium is as widespread as amino acids. It constitutes, for example, 1.4% of the human body and 4.15% of Earth's continental crust.[10] Thus, there are many systems, living and nonliving, in which Ca^{2+}−amino acid interactions are to be expected.

An α-amino acid with no functional side chain, such as glycine (Hgly, R = H) or alanine (Hala, R = CH_3), forms two potential ligands, namely $^+NH_3CHRCO_2^-$ (Haa) and at higher pH values $NH_2CHRCO_2^-$ (aa^-). In aqueous solution, the neutral amino acids interact with Ca^{2+}, however, so weakly that in some potentiometric studies only the aa^- complexes $[Ca(aa)]^+$ were found.[11,12] But even these complexes have low stability constants. Their log *K* values, which refer to the equilibrium $Ca^{2+} + aa^- \rightleftharpoons [Ca(aa)]^+$, fall in the ranges 1.03−1.51 and 1.19−1.36 for $[Ca(gly)]^+$ and $[Ca(ala)]^+$, respectively (at 25 or 37 °C and various ionic strengths).[11−17] $[Ca(Haa)]^{2+}$, the only other species detected in aqueous solution, is far less stable. The log *K* value of the equilibrium $Ca^{2+} + Haa \rightleftharpoons [Ca(Haa)]^{2+}$ is 0.24−0.41 (25 °C, I = 0−0.5 M) for the glycine complex[15,17] and 0.35 (25 °C, I = 0 M) for the alanine complex.[16] On the basis of the stability and protonation constants given in ref 16, we calculated a typical species distribution diagram by assuming total concentrations of Ca^{2+} and alanine of 10 mM each.[18] It showed that the complex $[Ca(Hala)]^{2+}$ represents a maximum of only 2% of the total calcium between pH 3.4 and 8.6 and less than 1% below pH 2.2 and above pH 9.8. $[Ca(Hala)]^{2+}$ is thus marginally significant. When the solution becomes increasingly basic, the alaninato complex $[Ca(ala)]^+$ emerges at pH 8.5 and at pH 11.8 reaches a constant concentration corresponding to 16% of the total calcium.

On the basis of known stability data it is well conceivable that in strongly basic solutions (above ca. pH 10) the yet undetected 1:2 complexes $[Ca(aa)_2]$ exist as minor species. Analogous complexes of several other divalent cations (e.g. Mn^{2+}, Zn^{2+}, and Cd^{2+}) with glycinate and aliphatic aminocarboxylates such as alaninate, valinate, and leucinate are well-known in solution.[5,19] As high concentrations can be achieved in Ca^{2+}−aminocarboxylate solutions (see Results and Discussion), even multinuclear complexes, for example of the type $[Ca_x(aa)_{2x}]$ ($x \geq 2$), may exist. The coordination mode of aminocarboxylate ligands in calcium complexes is unclear, though N,O-chelation has been inferred from line broadening of the ^{14}N and ^{17}O NMR signals in alkaline Ca^{2+}−Hgly and Ca^{2+}−Hala solutions.[12,20] However, the broadening of the ^{14}N signals is weak, and further evidence for coordination of the NH_2 group, e.g., from ^{14}N and ^{15}N NMR chemical shifts or vibrational spectra, is lacking.[20]

Probing in solution the coordination modes of aa^- ligands and the existence of Ca^{2+}−aa^- complexes other than $[Ca(aa)]^+$ remains difficult. Information from the solid state can therefore be useful in deducing compositional and structural possibilities of dissolved species. To this end, we have prepared new compounds of the general formula $Ca(aa)_2 \cdot nH_2O$ from concentrated, strongly basic solutions of Ca^{2+} and six different α-amino acids. Synthetic details, crystal structures, and spectroscopic properties of these compounds are discussed below.

Experimental Section

Materials and Methods. Racemic amino acids (purity 99+%), glycine (98%), calcium hydroxide (95+%, ACS reagent), tetramethylammonium hydroxide pentahydrate (99%), and methanol (reagent grade) were purchased commercially and used without further purification. Deionized water was used throughout the syntheses of the calcium aminocarboxylates **1**−**6**. The preparation and spectroscopic characterization of calcium valinate monohydrate (**3**) were described by us earlier.[21] IR spectra (KBr pellets, 4000−400 cm^{-1}, 2 cm^{-1} resolution) were recorded on a Thermo Nicolet 5700 FT-IR spectrometer. $^{13}C\{^1H\}$ NMR spectra (75.4 MHz) were measured in D_2O using Bruker AM 300 and Varian INOVA 300 instruments. 1,4-Dioxane served as the internal standard (δ = 67.19 ppm).[22] Elemental analyses of the compounds **1**, **2**, and **4** were performed by Analytische Laboratorien Malissa and Reuter, Lindlar, Germany. Analyses of the compounds **5** and **6** were obtained on a Carlo Erba analyzer MOD 1104 (C/H/N) and by standard complexometric titration (Ca) in our laboratories. The water contents of **4** and **5** were determined thermogravimetrically on a Linseis L81-II thermal balance; 10−15 mg samples were heated in a slow stream of pure nitrogen gas at a heating rate of 10 K min^{-1}. For both compounds the dehydration process resulted in well-defined steps in the TG curves (two steps between 75 and 175 °C for **4**, one step between 85 and 140 °C for **5**).

Preparation of $Ca(gly)_2 \cdot H_2O$ (1). $Ca(OH)_2$ (1.48 g, 20.0 mmol) was added to a solution of glycine (1.50 g, 20.0 mmol) in water (20 mL). The reaction mixture was heated under reflux for 6 h and then filtered hot to remove unreacted $Ca(OH)_2$. Most of the water was removed from the filtrate by rotary evaporation. On standing at room temperature for 4 weeks, a white crystalline precipitate of **1** formed, which was collected on a glass filter, washed with a small amount of ice-cold water, and dried under vacuum. Yield: 0.71 g (34%). Anal. Calcd for $C_4H_8CaN_2O_4 \cdot H_2O$: C, 23.30; H, 4.89; Ca, 19.44; N, 13.58. Found: C, 23.37; H, 4.78; Ca, 19.15; N, 13.67. IR: 3362 (m), 3287 (m), 1629 (m), 1567 (vs), 1406 (s),

(7) Kvenvolden, K. A. *Annu. Rev. Earth Planet. Sci.* **1975**, *3*, 183−212.
(8) Shock, E. L.; Schulte, M. D. *Geochim. Cosmochim. Acta* **1990**, *54*, 3159−3173.
(9) Botta, O.; Bada, J. L. *Surv. Geophys.* **2002**, *23*, 411−467.
(10) *CRC Handbook of Chemistry and Physics*, 84th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 2003; pp 7-17 and 14-17.
(11) Hardel, M. *Z. Physiol. Chem.* **1966**, *346*, 224−228.
(12) Maeda, M.; Okada, K.; Tsukamoto, Y.; Wakabayashi, K.; Ito, K. *J. Chem. Soc., Dalton Trans.* **1990**, 2337−2339.
(13) Davies, C. W.; Waind, G. M. *J. Chem. Soc.* **1950**, 301−303.
(14) Colman-Porter, C. A.; Monk, C. B. *J. Chem. Soc.* **1952**, 4363−4368.
(15) Daniele, P. G.; De Robertis, A.; De Stefano, C.; Sammartano, S.; Rigano, C. *J. Chem. Soc., Dalton Trans.* **1985**, 2353−2361.
(16) Casale, A.; De Robertis, A.; De Stefano, C.; Gianguzza, A. *Thermochim. Acta* **1989**, *140*, 59−66.
(17) Casale, A.; De Robertis, A.; De Stefano, C.; Gianguzza, A.; Patanè, G.; Rigano, C.; Sammartano, S. *Thermochim. Acta* **1995**, *255*, 109−141.
(18) Pettit, L. D.; Powell, K. J. *IUPAC Stability Constants Database (SC-Database)*, release 5, version 5.18; Academic Software: Otley, U.K., 2001.
(19) Sóvágó, I.; Kiss, T.; Gergely, A. *Pure Appl. Chem.* **1993**, *65*, 1029−1080.
(20) Maeda, M.; Okada, K.; Ito, K. *J. Inorg. Biochem.* **1991**, *41*, 143−147.
(21) Strasdeit, H.; Büsching, I.; Behrends, S.; Saak, W.; Barklage, W. *Chem.—Eur. J.* **2001**, 1133−1142.
(22) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512−7515.

1329 (m), 1027 (m), 711 (m), 674 cm^{-1} (m). ^{13}C NMR (0.10 M solution): δ 45.2, 182.4.

Preparation of $Ca(ala)_2 \cdot 3H_2O$ (2). $Ca(OH)_2$ (1.48 g, 20.0 mmol) was added to a solution of *rac*-alanine (1.78 g, 20.0 mmol) in water (20 mL). The reaction mixture was heated under reflux for 6 h and then filtered hot to remove unreacted $Ca(OH)_2$. Water was removed from the filtrate by rotary evaporation until a viscous solution remained which solidified at room temperature. The white crystalline product was transferred onto a glass filter by use of three 3-mL portions of ice-cold water and dried under vacuum for a few minutes. Yield: 1.76 g (65%). Anal. Calcd for $C_6H_{12}CaN_2O_4 \cdot 3H_2O$: C, 26.66; H, 6.71; Ca, 14.83; N, 10.36. Found: C, 26.58; H, 6.67; Ca, 14.70; N, 10.24. IR: 3331 (m), 1564 (vs), 1460 (m), 1420 (s), 1319 (s), 1130 (m), 1080 (m), 1003 (m), 857 (m), 780 (m), 702 cm^{-1} (m, br). ^{13}C NMR (0.10 M solution): δ 20.9, 52.0, 185.2.

Preparation of $Ca(leu)_2 \cdot 3H_2O$ (4). $Ca(OH)_2$ (1.48 g, 20.0 mmol) was added to a solution of *rac*-leucine (2.62 g, 20.0 mmol) in water (60 mL). The reaction mixture was heated under reflux for 6 h and then filtered to remove unreacted $Ca(OH)_2$. Water was removed from the filtrate by rotary evaporation until precipitation occurred. After 2 d the white crystalline product was collected on a glass filter, washed with a small amount of ice-cold water, and dried under vacuum. Yield: 2.29 g (67%, based on the formation of $Ca(leu)_2 \cdot 2.3H_2O$). Anal. Calcd for $C_{12}H_{24}CaN_2O_4 \cdot 2.3H_2O$: C, 42.16; H, 8.43; Ca, 11.72; N, 8.19; H_2O, 12.1. Found: C, 42.25; H, 8.16; Ca, 11.67; N, 8.21; H_2O, 11.9. IR: 3365 (s, br), 2956 (s), 2935 (m), 2871 (m), 1569 (vs), 1468 (m), 1416 (s), 1345 (m), 961 (m), 941 (m), 744 (m), 685 cm^{-1} (m). ^{13}C NMR (0.10 M solution): δ 21.8, 23.1, 25.0, 44.7, 55.1, 185.1.

Preparation of $Ca(met)_2 \cdot nH_2O$ (5). $Ca(OH)_2$ (1.48 g, 20.0 mmol) was added to a solution of *rac*-methionine (2.98 g, 20.0 mmol) in water (20 mL). The reaction mixture was heated under reflux for 6 h and then filtered to remove unreacted $Ca(OH)_2$. The filtrate was concentrated by rotary evaporation to a volume of ca. 10 mL. A white crystalline precipitate of **5** formed overnight. It was collected on a glass filter, washed with a small amount of ice-cold water, and dried under vacuum. Yield: 2.16 g (57% for n = 2.2). Anal. Calcd for $C_{10}H_{20}CaN_2O_4S_2 \cdot 2.2H_2O$: C, 31.93; H, 6.54; Ca, 10.66; N, 7.45; H_2O, 10.5. Found: C, 31.73; H, 6.11; Ca, 10.76; N, 7.12; H_2O, 10.6. IR: 3349 (s, br), 2914 (m), 1564 (vs), 1419 (s), 1356 (m), 1341 (m), 1266 (w), 1089 (w), 1022 (w), 771 cm^{-1} (m). ^{13}C NMR (0.10 M solution): δ 14.7, 30.3, 34.6, 55.8, 183.4.

Preparation of $Ca(pro)_2 \cdot H_2O$ (6). $Ca(OH)_2$ (1.48 g, 20.0 mmol) was added to a solution of *rac*-proline (2.30 g, 20.0 mmol) in water (40 mL). The reaction mixture was heated under reflux for 6 h and then filtered to remove unreacted $Ca(OH)_2$. A white crystalline precipitate of **6** was obtained by slow gas-phase diffusion of methanol into the filtrate. The product was collected on a glass filter, washed with a small amount of a 1:1 (v/v) water/methanol mixture, and dried under vacuum. Concentration of the filtrate yielded a second crop of **6**. Yield: 1.37 g (48%). Anal. Calcd for $C_{10}H_{16}CaN_2O_4 \cdot H_2O$: C, 41.95; H, 6.34; Ca, 14.00; N, 9.78. Found: C, 42.45; H, 6.49; Ca, 13.41; N, 9.65. IR: 3304 (m), 3287 (m), 3193 (m, br), 2962 (m), 2864 (m), 1745 (m), 1630 (m), 1574 (vs), 1440 (s), 1298 (m), 1087 (m), 927 (m), 820 (m), 706 cm^{-1} (m). ^{13}C NMR (0.10 M solution): δ 25.9, 31.3, 46.7, 62.2, 183.4.

^{13}C NMR Data for Tetramethylammonium Aminocarboxylates. The 0.20 M aqueous solutions of NMe_4^+ aminocarboxylates were prepared in situ by dissolving equimolar amounts of $NMe_4OH \cdot 5H_2O$ and the respective amino acid in D_2O. The ^{13}C resonance of the NMe_4^+ cation was observed as a barely resolved 1:1:1 triplet (due to $^{14}N-^{13}C$ coupling) at 55.9 ppm and is omitted in the following lists. In the case of $NMe_4^+met^-$, superposition with one of the anion signals occurred. $NMe_4^+gly^-$: δ 45.3, 182.1. $NMe_4^+ala^-$: δ 20.9, 52.0, 185.0. $NMe_4^+val^-$: δ 17.3, 19.7, 32.3, 62.5, 183.6. $NMe_4^+leu^-$: δ 22.0, 23.1, 25.0, 44.8, 55.2, 184.7. $NMe_4^+met^-$: δ 14.7, 30.3, 34.7, 55.9, 183.1. $NMe_4^+pro^-$: δ 25.7, 31.4, 46.6, 62.2, 182.9.

X-ray Crystallography. Suitable single crystals were obtained from syntheses identical with or very similar to those described above. Diffraction data were collected on Siemens/STOE AED2 (compounds **1**, **3**, and **4**) and STOE IPDS (compound **2**) diffractometers with use of Mo Kα radiation (λ = 0.710 73 Å). The measuring temperature was 23 °C (**1**, **3**, **4**) and −60 °C (**2**), respectively. Absorption corrections were applied to the data for **2** and **4**, and a "long-needle" correction was applied in the case of **3**. All structures were solved by direct methods and refined on F^2 values. The programs SHELXTL PLUS[23] and SHELXL-97[24] were used. All non-hydrogen atoms were refined anisotropically except a threefold disordered water oxygen atom in **4**. Hydrogen atoms attached to carbon atoms were assigned to calculated positions. Hydrogen atom positions at oxygen or nitrogen atoms were either refined or calculated. Pertinent crystallographic data and structure refinement parameters are summarized in Table 1. The program DIAMOND[25] was used to prepare the graphical representations of the structures.

Preliminary diffraction data for **5** and **6** were collected at 23 °C. **5** crystallizes in the triclinic crystal system with a = 7.497(1), b = 8.509(1), c = 14.864(2) Å, α = 96.43(1), β = 92.67(1), and γ = 105.20(1)°. **6** crystallizes in the monoclinic crystal system with a = 11.060(2), b = 6.345(1), c = 9.764(2) Å, and β = 103.80(3)°.

Results and Discussion

Syntheses. The calcium α-aminocarboxylates described here form when aqueous suspensions/solutions of calcium hydroxide and the respective α-amino acid (Haa) are refluxed. After removal of excess calcium hydroxide, the products can be crystallized as colorless hydrates of the general formula $Ca(aa)_2 \cdot nH_2O$:

$$Ca(OH)_2 + 2Haa + (n-2)H_2O \rightarrow Ca(aa)_2 \cdot nH_2O \quad (1)$$

By this method the compounds $Ca(gly)_2 \cdot H_2O$ (**1**), $Ca(ala)_2 \cdot 3H_2O$ (**2**), $Ca(val)_2 \cdot H_2O$ (**3**),[26] $Ca(leu)_2 \cdot 3H_2O$ (**4**), $Ca(met)_2 \cdot nH_2O$ (**5**, $n \approx 2$), and $Ca(pro)_2 \cdot H_2O$ (**6**) are accessible in yields between 29 and 67% (see Chart 1 for the aminocarboxylate structures). Chiral amino acids were used as racemates. The compounds **1**−**6** were obtained in analytically pure form. They usually crystallized readily. Only in the case of the glycinate **1**, strongly delayed crystallization was sometimes observed. In the synthesis of the methionate **5**, an unpleasant smell of the reaction mixture indicated some decomposition of the amino acid. This, however, did not affect the purity of the isolated product. To our knowledge, compounds **1**−**6** have not yet been described by others in

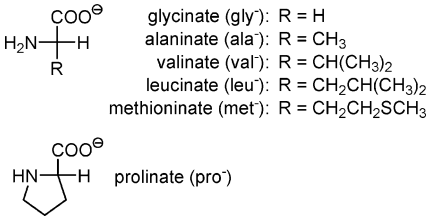
(23) Sheldrick, G. M. *SHELXTL PLUS*; Siemens Analytical X-ray Instruments Inc.: Madison, WI, 1990.
(24) Sheldrick, G. M. SHELXL-97; Universität Göttingen: Göttingen, Germany, 1997.
(25) *DIAMOND, Crystal and Molecular Structure Visualization*, version 3.1; Crystal Impact: Bonn, Germany, 2005.
(26) We have already described the syntheses of **3** and the related compound $Ca(iva)_2 \cdot nH_2O$ in ref 21; iva^- is the anion of the nonprotein α-amino acid isovaline (2-amino-2-methylbutanoic acid).

Table 1. Crystallographic Data and Refinement Details for Compounds **1**−**4**

param	**1**	**2**	**3**	**4**
empirical formula	$C_4H_{10}CaN_2O_5$	$C_6H_{18}CaN_2O_7$	$C_{10}H_{22}CaN_2O_5$	$C_{12}H_{30}CaN_2O_7$
fw	206.21	270.29	290.37	354.45
cryst system	triclinic	monoclinic	monoclinic	triclinic
space group	$P\bar{1}$ (No. 2)	$C2/c$ (No. 15)	$C2/c$ (No. 15)	$P\bar{1}$ (No. 2)
a (Å)	6.436(1)	14.143(1)	24.210(2)	7.595(1)
b (Å)	7.900(1)	6.433(1)	6.290(1)	8.433(1)
c (Å)	8.210(2)	13.814(1)	9.841(1)	15.127(3)
α (deg)	80.21(2)	90	90	83.89(1)
β (deg)	81.80(3)	109.15(1)	98.97(1)	80.81(2)
γ (deg)	73.57(2)	90	90	77.48(1)
V (Å^3)	392.6(1)	1187.3(2)	1480.3(3)	931.1(2)
Z	2	4	4	2
ρ_{calcd} (g cm^{-3})	1.745	1.512	1.303	1.264
$\mu_{MoK\alpha}$ (mm^{-1})	0.787	0.551	0.438	0.368
cryst size (mm)	0.76 × 0.34 × 0.11	0.90 × 0.51 × 0.40	3.80 × 0.20 × 0.19	0.75 × 0.49 × 0.08
data/restraints/params	1703/0/115	1080/0/89	1460/0/89	2936/0/226
GOF on F^2	1.140	1.096	1.079	1.048
R1 [$I > 2\sigma(I)$][a]	0.0326	0.0289	0.0371	0.0469
wR2 (all data)[b]	0.0868	0.0756	0.1035	0.1110
largest diff peak and hole (e•Å^{-3})	0.514 and −0.314	0.516 and −0.225	0.571 and −0.170	0.390 and −0.282

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$.

Chart 1. Structures of Aminocarboxylate Ligands Discussed in This Paper



the scientific literature. Only the preparation of "bis(glycinato)calcium" by a solid-phase reaction has been reported.[27] There are also a few patents dealing with the preparation of calcium aminocarboxylates, mainly the glycinate. In one of these patents, calcium glycinate is correctly formulated as the monohydrate **1**.[28] We found that calcium oxide or granular calcium metal may be used instead of calcium hydroxide. For example, in the reaction with valine all three starting materials gave comparable yields. In contrast, calcium carbonate is not suited.

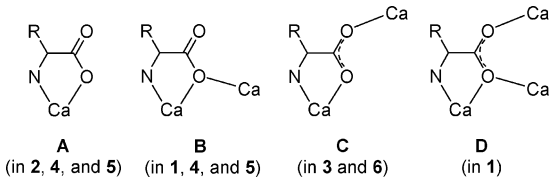
After 6 h reaction time, the reaction mixtures that contained calcium hydroxide and the amino acid in an initial molar ratio of 1:1 had pH values near 12.4, which is equal to the pH of a saturated calcium hydroxide solution. After filtration from excess hydroxide and total evaporation of the filtrate, the products obtained were nevertheless contaminated with unreacted amino acid. No improvements were achieved by prolonging the reaction time or by varying the ratio of the reactants. As the calcium aminocarboxylates and the amino acids have similar solubilities, it is therefore crucial for the purity of the products that not too much water is evaporated from the filtrate. This problem is the main reason why the yields remained moderate. The addition of another solvent was only advantageous in the preparation of **6** where methanol was allowed to diffuse into the filtrate via the gas phase. Fortunately, amino acid contaminations are easily detectable by infrared spectroscopy, for example by the appearance of NH_3^+ absorptions (NH_2^+ in the case of Hpro) in the 2500−2750 cm^{-1} region.

Properties in Solution. The calcium aminocarboxylate hydrates exhibit excellent solubilities in water. For example, an aqueous solution of **2** saturated at room temperature has a concentration of 1.2 M or 23% $Ca(ala)_2$ by mass. Solutions of the compounds **1**−**6** are moderately basic, having ca. pH 10−11 at 0.10 M concentration. This observation is consistent with a noticeable portion of noncoordinated aminocarboxylate. The ^{13}C NMR solution spectra show common sharp signals of the free and the (possibly differently) coordinated aminocarboxylate anions. They thus reflect a time-averaged situation and indicate a ligand exchange that is fast, at least on the NMR time scale.[29] We have compared the ^{13}C NMR chemical shifts of **1**−**6** with those of the respective tetramethylammonium aminocarboxylates $NMe_4^+aa^-$. All samples measured had the same total aminocarboxylate concentration of 0.20 M (see Experimental Section). It showed that on going from a NMe_4^+ to the corresponding Ca^{2+} aminocarboxylate, the chemical shift of the carboxylate C atom changed by up to +0.5 ppm. The other signals, including that of the α-C atom, were shifted by no more than ±0.2 ppm, which cannot be considered significant.

The $NMe_4^+aa^-$ salts were chosen for comparison because the stability constants of the $[NMe_4(aa)]$ "complexes" are expected to be approximately 1 order of magnitude lower than those of the analogous calcium complexes. Data for NEt_4^+ complexes are available: log K values of −0.4 ± 0.05 and 0.15 ± 0.2 at 25 °C have been reported for $[NEt_4(gly)]$ and $[NEt_4(ala)]$, respectively.[16,17] We used these data to calculate pH-dependent species distributions in 0.20 M solutions.[18] At pH 11.0, only 7% and 18%, respectively, of the amino acid were found to be coordinated as aa^-. It is reasonable to assume that these percentages are similar for the NMe_4^+ complexes. However, much higher percentages are calculated for the systems Ca^{2+}−Hgly[17] and Ca^{2+}−Hala[16]

(27) Zhong, G. *Hecheng Huaxue* **2004**, *12*, 591−594.
(28) Zhang, W. Chinese Patent No. 1436770, 2003.
(29) Ca^{2+} is a typical labile metal ion; see for example: Richens, D. T. *Chem. Rev.* **2005**, *105*, 1961−2002.

Chart 2. Schematic Representation of the Coordination Modes of the Aminocarboxylate Ligands in Compounds **1**−**6**



where 30% and 37%, respectively, of the amino acid are bonded in the $[Ca(aa)]^+$ complexes (at pH 11.0, 0.10 M total concentration of calcium, 0.20 M total concentration of amino acid). Even more aa^- molecules would be metal-coordinated if $[Ca(aa)_2]$ complexes exist in these systems (see Introduction). Nevertheless, effects of the coordination to Ca^{2+} are nearly absent in the ^{13}C NMR spectra of **1**−**6**. Only the carboxylate C atoms, in most cases, experience very small downfield shifts probably caused by calcium−oxygen interactions. But there is no indication from the NMR spectra that the nitrogen atoms are coordinated.

Solid-State Infrared Spectra. The IR spectra of the compounds **1**−**6** immediately show that the amino acids are present in the deprotonated state. For example, the NH_2^+ (Hpro) and NH_3^+ absorptions between 2500 and 2750 cm^{-1} are missing. Furthermore, a weak but highly characteristic NH_3^+ band which occurs between 2090 and 2160 cm^{-1} in the spectra of the amino acids (except for Hpro) has also disappeared. In the spectra of all the complexes a very strong absorption is observed in the narrow range of 1564−1574 cm^{-1}. It is attributed to the antisymmetric stretching vibration of the COO^- groups. This absorption has been shifted by 17−30 cm^{-1} to lower frequencies compared to its position in the spectra of the free amino acids. The degree of shift seems to correlate roughly with the binding mode of the aminocarboxylate ligands. For example, the compounds **4** and **5** which belong to a common type of coordination polymer, as demonstrated by X-ray crystal structure analysis (see below), show shifts of −18 and −17 cm^{-1}, respectively. The same is true for the compounds **3** and **6** which show IR band shifts of −30 and −24 cm^{-1}, respectively. On the other hand, the shift is not characteristic of a specific type of carboxylate binding. For example, the terminal coordination of alaninate in **2** strongly differs from the bridging one of valinate in **3** (A and C, respectively, in Chart 2), but nevertheless the two compounds show virtually identical shifts of −29 and −30 cm^{-1}, respectively.

Crystal Structures. The solid-state structures of **1**−**6** have been determined by single-crystal X-ray diffraction. For **5** and **6** refinement was hampered by disorder and/or twinning problems. Therefore, no metrical data will be given here for these structures. However, the refinements proceeded far enough to reveal that **5** is built from the same type of coordination polymer as **4** and **6** is analogously related to **3**. The structures of **1**−**4** are shown in Figures 1−4. Ellipsoid plots are provided as Supporting Information. Bond lengths and bond angles at the calcium atoms are compiled in Table 2.

Common structural features of **1**−**6** include the following: (i) There is N,O-chelation; i.e., each aminocarboxylate

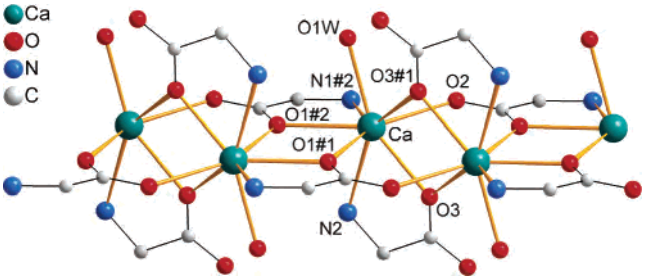


Figure 1. Portion of the infinite one-dimensional coordination polymer in $Ca(gly)_2 \cdot H_2O$ (**1**). Hydrogen atoms have been omitted for clarity. For symmetry transformations, see the footnote to Table 2.

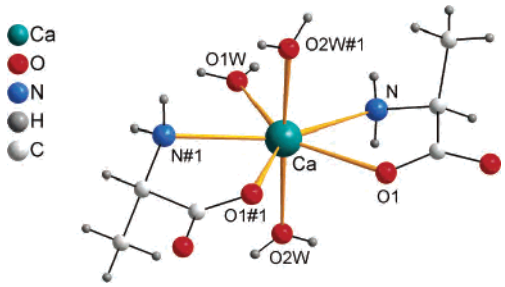


Figure 2. Molecular structure of $Ca(ala)_2 \cdot 3H_2O$ (**2**). For symmetry transformation, see the footnote to Table 2.

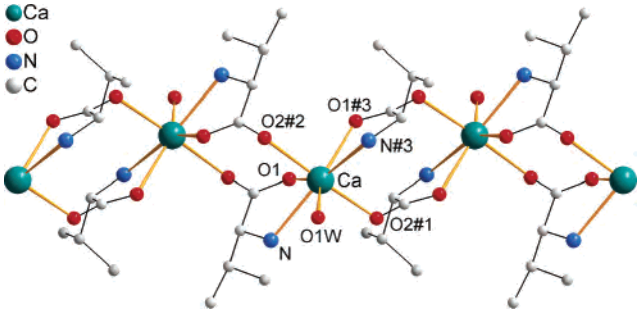


Figure 3. Portion of the infinite one-dimensional coordination polymer in $Ca(val)_2 \cdot H_2O$ (**3**). Hydrogen atoms have been omitted for clarity. For symmetry transformations, see the footnote to Table 2.

coordinates via both the carboxylate group and the amino group. (ii) No O,O-chelation occurs. (iii) Aqua ligands complete the coordination spheres of the calcium ions. The coordination numbers are 7 (N2O5 donor sets in **2**, **3**, and **6**) and 8 (N2O6 donor sets in **1**, **4**, and **5**), respectively. The Ca−O(carboxylate) bond lengths in **1**−**4** fall in the ranges of 2.367(1)−2.500(1) and 2.419(1)−2.521(1) Å for terminal and bridging oxygen atoms, respectively. A study based on data extracted from the Cambridge Structural Database (CSD) found a range of 2.27−2.49 Å for Ca−O bonds involving monodentate carboxylates.[30] The values observed for our calcium aminocarboxylates are thus unexceptional. This is also true for the $Ca-OH_2$(terminal) bond lengths which lie between 2.306(2) and 2.434(2) Å. The CSD study mentioned gives 2.31−2.49 and 2.33−2.60 Å for $Ca-OH_2$ bond lengths in seven- and eight-coordinate complexes, respectively.[30] The $Ca-OH_2$ bond lengths of the bridging aqua ligands (2.515(2) and 2.530(2) Å, in **4**) are distinctly longer than those of the terminal ones. The lengths of the Ca−N bonds fall in the narrow range 2.556(2)−2.614(2) Å.

(30) Harding, M. M. *Acta Crystallogr.* **1999**, *D55*, 1432−1443.

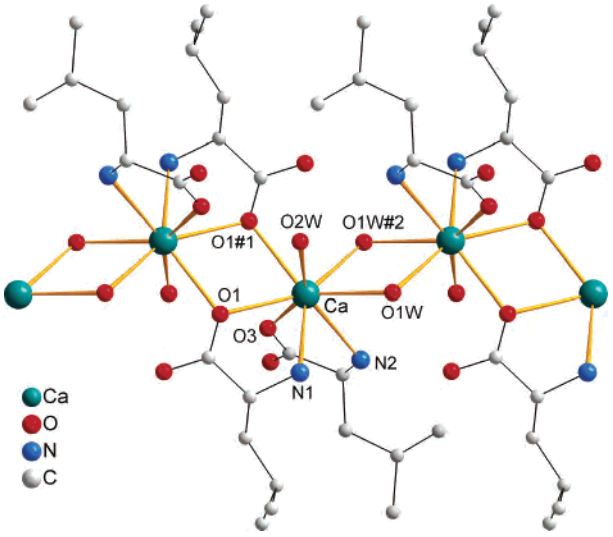


Figure 4. Portion of the infinite one-dimensional coordination polymer in $Ca(leu)_2 \cdot 3H_2O$ (**4**). Hydrogen atoms have been omitted for clarity. For symmetry transformations, see the footnote to Table 2.

Chart 2 shows the different coordination modes of the aminocarboxylate ligands in **1**−**6**. The basic motif is the terminal N,O-chelating form **A**. When **A** is bonded to a second Ca^{2+} ion, two different types of bridging are possible, both of which have been found (**B** and **C**). The μ_3-bridging form **D** which exists in the glycinate **1** results in a rather compact metal−ligand arrangement. A CSD search shows that structurally authenticated examples of this aminocarboxylate bridging mode are mainly restricted to glycinate and prolinate in mixed transition-metal lanthanoid complexes.[31] In order to have a short and unequivocal description of the individual binding modes of coordinatively flexible ligands, the Harris notation has been developed.[32] Application of this notation to Chart 2 gives the designations [1.011] (**A**), [2.021] (**B**), $[2.1_1 1_2 1_2]$ (**C**), and $[3.1_1 2_{23} 1_3]$ (**D**).

Crystals of **1**, **3**, and **4** consist of one-dimensional coordination polymers. Their calcium ions form zigzag chains with Ca···Ca···Ca angles of 112.7° (**1**), 122.0° (**3**), and 139.4° (**4**), respectively. In **1** and **3**, bridging is solely by carboxylate groups (Figures 1 and 3). Nevertheless, the two structures are clearly different from each other because the bridging modes are different (see Chart 2). The Ca−O−Ca bridges in **1** cause much shorter Ca···Ca distances (3.749 and 3.981 Å) than the Ca−O−C−O−Ca bridges in **3** (5.627 Å). In contrast to **1** and **3**, the leucinate **4** contains calcium ions that are alternatingly connected by aminocarboxylate and aqua ligands: ···Ca(μ-OH_2)$_2$Ca(μ-leu)$_2$Ca(μ-OH_2)$_2$Ca··· (Figure 4). It is tempting to hypothesize that the polymeric chains of **4** form by condensation of dissolved dinuclear [$(H_2O)_n$(leu)Ca(μ-leu)$_2$Ca(leu)$(H_2O)_n$] complexes.

Table 2. Bond Lengths (Å) and Angles (deg) at the Calcium Atoms in **1**−**4**

$Ca(gly)_2 \cdot H_2O$ (**1**)[a]			
Ca−O1$^{\#1}$	2.419(1)	Ca−O3$^{\#1}$	2.487(2)
Ca−O1$^{\#2}$	2.521(1)	Ca−O1W	2.422(2)
Ca−O2	2.500(1)	Ca−N1$^{\#2}$	2.556(2)
Ca−O3	2.425(1)	Ca−N2	2.614(2)
O1$^{\#1}$−Ca−O1W	101.08(6)	O2−Ca−O1$^{\#2}$	143.05(4)
O1$^{\#1}$−Ca−O3	82.50(5)	O1$^{\#1}$−Ca−N1$^{\#2}$	138.60(5)
O1W−Ca−O3	151.85(5)	O1W−Ca−N1$^{\#2}$	74.84(6)
O1$^{\#1}$−Ca−O3$^{\#1}$	75.56(5)	O3−Ca−N1$^{\#2}$	120.54(5)
O1W−Ca−O3$^{\#1}$	73.56(5)	O3$^{\#1}$−Ca−N1$^{\#2}$	137.49(5)
O3−Ca−O3$^{\#1}$	80.51(5)	O2−Ca−N1$^{\#2}$	77.25(5)
O1$^{\#1}$−Ca−O2	144.09(4)	O1$^{\#2}$−Ca−N1$^{\#2}$	66.50(5)
O1W−Ca−O2	89.37(6)	O1$^{\#1}$−Ca−N2	85.27(6)
O3−Ca−O2	73.15(5)	O1W−Ca−N2	142.61(6)
O3$^{\#1}$−Ca−O2	74.72(5)	O3−Ca−N2	65.17(6)
O1$^{\#1}$−Ca−O1$^{\#2}$	72.63(5)	O3$^{\#1}$−Ca−N2	142.60(6)
O1W−Ca−O1$^{\#2}$	74.89(6)	O2−Ca−N2	106.99(6)
O3−Ca−O1#2	131.75(5)	O1$^{\#2}$−Ca−N2	72.01(6)
O3$^{\#1}$−Ca−O1$^{\#2}$	129.14(5)	N1$^{\#2}$−Ca−N2	76.39(7)
$Ca(ala)_2 \cdot 3H_2O$ (**2**)[b]			
Ca−O1	2.414(1)	Ca−O2W	2.364(1)
Ca−O1W	2.353(2)	Ca−N	2.584(2)
O1W−Ca−O2W	92.43(3)	O2W−Ca−N$^{\#1}$	97.06(5)
O2W−Ca−O2W$^{\#1}$	175.14(7)	O1−Ca−N$^{\#1}$	145.41(4)
O1W−Ca−O1	139.37(3)	O1W−Ca−N	75.17(3)
O2W−Ca−O1	85.23(4)	O2W−Ca−N	84.19(5)
O2W−Ca−O1$^{\#1}$	91.08(5)	O1−Ca−N	64.22(4)
O1−Ca−O1$^{\#1}$	81.27(6)	N$^{\#1}$−Ca−N	150.35(7)
$Ca(val)_2 \cdot H_2O$ (**3**)[c]			
Ca−O1	2.407(2)	Ca−O1W	2.306(2)
Ca−O2$^{\#1}$	2.367(1)	Ca−N	2.597(2)
O1W−Ca−O2$^{\#1}$	92.72(4)	O1−Ca−N$^{\#3}$	144.67(6)
O2$^{\#1}$−Ca−O2$^{\#2}$	174.57(7)	O1W−Ca−N	75.77(5)
O1W−Ca−O1	139.35(3)	O2$^{\#1}$−Ca−N	90.19(7)
O2$^{\#1}$−Ca−O1	90.60(5)	O2$^{\#2}$−Ca−N	91.14(7)
O2$^{\#2}$−Ca−O1	85.27(5)	O1−Ca−N	63.71(6)
O1−Ca−O1$^{\#3}$	81.29(7)	N$^{\#3}$−Ca−N	151.54(9)
$Ca(leu)_2 \cdot 3H_2O$ (**4**)[d]			
Ca−O1	2.480(2)	Ca−O1W$^{\#2}$	2.515(2)
Ca−O1$^{\#1}$	2.489(2)	Ca−O2W	2.434(2)
Ca−O3	2.370(2)	Ca−N1	2.583(3)
Ca−O1W	2.530(2)	Ca−N2	2.582(3)
O3−Ca−O2W	150.01(8)	O1W$^{\#2}$−Ca−O1W	72.14(8)
O3−Ca−O1	80.43(7)	O3−Ca−N2	65.00(8)
O2W−Ca−O1	76.62(8)	O2W−Ca−N2	144.73(9)
O3−Ca−O1$^{\#1}$	82.70(7)	O1−Ca−N2	122.96(9)
O2W−Ca−O1$^{\#1}$	72.05(8)	O1$^{\#1}$−Ca−N2	138.79(8)
O1−Ca−O1$^{\#1}$	71.98(8)	O1W$^{\#2}$−Ca−N2	74.92(10)
O3−Ca−O1W$^{\#2}$	89.28(8)	O1W−Ca−N2	73.69(8)
O2W−Ca−O1W$^{\#2}$	101.68(9)	O3−Ca−N1	99.37(9)
O1−Ca−O1W$^{\#2}$	151.14(7)	O2W−Ca−N1	87.69(10)
O1$^{\#1}$−Ca−O1W$^{\#2}$	80.04(7)	O1−Ca−N1	63.99(8)
O3−Ca−O1W	137.92(7)	O1$^{\#1}$−Ca−N1	134.73(8)
O2W−Ca−O1W	71.97(8)	O1W$^{\#2}$−Ca−N1	144.77(8)
O1−Ca−O1W	131.78(7)	O1W−Ca−N1	78.93(8)
O1$^{\#1}$−Ca−O1W	128.13(8)	N2−Ca−N1	78.04(11)

[a] Symmetry transformations used to generate equivalent atoms for **1**: (#1) $-x, -y, -z$; (#2) $x + 1, y, z$. [b] Symmetry transformations used to generate equivalent atoms for **2**: (#1) $-x + 1, y, -z + 3/2$. [c] Symmetry transformations used to generate equivalent atoms for **3**: (#1) $x, -y, z + 1/2$; (#2) $-x + 1, -y, -z$; (#3) $-x + 1, y, -z + 1/2$. [d] Symmetry transformations used to generate equivalent atoms for **4**: (#1) $-x + 1, -y, -z + 1$; (#2) $-x, -y, -z + 1$.

(31) *Cambridge Structural Database*, version 5.27, Aug 2006 update; Cambridge Crystallographic Data Centre: Cambridge, U.K., 2006.

(32) The Harris notation describes the binding mode as $[X.Y_1Y_2Y_3...Y_n]$, where X is the overall number of metal atoms bound by the whole ligand and each Y value refers to the number of metal atoms attached to an individual donor atom. As a simple α-aminocarboxylate has three donor atoms, there are three values for Y. The ordering of Y follows the Cahn−Ingold−Prelog priority rules, hence, O before N. If necessary, the metal atoms are numbered, and the numbers are given as subscripts to Y. See: Coxall, R. A.; Harris, S. G.; Henderson, D. K.; Parsons, S.; Tasker, P. A.; Winpenny, R. E. P. *J. Chem. Soc., Dalton Trans.* **2000**, 2349−2356.

The alaninate **2** has a nonpolymeric crystal structure built from mononuclear $[Ca(ala)_2(H_2O)_3]$ complexes and thus strongly differs from the other compounds described here. The reason for this is unclear. The steric requirement of the aminocarboxylate side chain seems not to be the determining factor because the smaller glycinate as well as the larger valinate, leucinate, methioninate, and prolinate all form polymers. The coordination polyhedron in **2**, as in **3**, is best described as a distorted pentagonal bipyramid with two oxygen atoms forming the apexes (**2**, O2W, $O2W^{\#1}$; **3**, $O2^{\#1}$, $O2^{\#2}$). Owing to the centrosymmetry of their space groups, crystals of **1**−**4** are racemic. An individual $[Ca(ala)_2(H_2O)_3]$ complex in **2**, however, contains alaninato ligands of identical configuration. Figure 2 shows the L,L-form. This stereoselectivity probably does not reflect the situation in solution. Studies on related complexes of other metal ions indicate that the mutual interaction of two small aminocarboxylates, such as alaninate, at the same metal center is usually to weak to cause stereochemical preferences.[33] The presence of chiral complexes in crystals of **2** must therefore be attributed to packing effects.

As far as we know, no other crystal structures exist of homometallic calcium complexes of simple α-aminocarboxylates, i.e., with nonfunctionalized side chains.[31] $[Ca(L\text{-hyp})_2(H_2O)_3]$ ($hyp^- = 4$-hydroxyprolinate) seems to be the only reported calcium complex that is structurally closely related to one of the complexes described here, namely $[Ca(ala)_2(H_2O)_3]$ (**2**).[34] Both show basically the same coordination, but the alaninato complex is much less distorted from ideal pentagonal bipyramidal geometry. It is interesting to note that while the 4-hydroxyprolinate has a mononuclear structure, the prolinate **6** is polymeric. This difference might be attributed to a structure-determining influence of the extended hydrogen-bonding network in the former, which includes the OH groups of the aminocarboxylates. The crystal structures of Ca(L-asp)·nH_2O ($n = 2$ and 4, asp^{2-} = aspartate)[35] and Ca(L-glu)·$3H_2O$ (glu^{2-} = glutamate)[36] should also be mentioned here. The asp^{2-} and glu^{2-} ligands are N,O-(α)-chelating, but additionally the carboxylate group of the side chain coordinates. Therefore, there is only a more distant relationship to the structures of **1**−**6**.

Conclusions

The following are the principle results and conclusions of this study:

(i) Calcium α-aminocarboxylates are accessible from the reaction of calcium hydroxide with the respective α-amino acid in boiling aqueous solution/suspension. This method has been successfully tested with glycine and the racemic forms of alanine, valine, leucine, methionine, proline, and isovaline. It should be generally applicable as long as the amino acid side chain is sufficiently stable toward hot, strongly alkaline solutions.

(ii) The calcium α-aminocarboxylates crystallize as hydrates, which are readily soluble in water. The alkaline character of their solutions is consistent with a noticeable degree of dissociation. Calcium coordination by carboxylate groups is suggested by ^{13}C NMR spectra in D_2O and is more clearly visible in the solid-state infrared spectra. The spectra give no indication of coordinated amino groups. Crystal structure analyses, however, reveal that all amino groups are metal-bound.

(iii) In the solid state, the calcium α-aminocarboxylate hydrates show a large structural diversity. Besides a mononuclear complex (**2**), three different types of one-dimensional coordination polymers (**1**; **3**, **6**; **4**, **5**) have been found. The structures of **4** and **5** are built from dinuclear aminocarboxylate complexes which are linked by aqua bridges. Though the aminocarboxylate ligands adopt four different binding modes, the basic motif of a five-membered chelate ring involving the carboxylate and the amino group is common to all of them.

(iv) The structures of calcium α-aminocarboxylates in solution, especially at higher concentrations, remain elusive. But our findings that complexes of the type $[Ca(aa)_2(H_2O)_n]$ (in **2**) and $[Ca_2(aa)_4(H_2O)_n]$ (linked to infinite chains in **4** and **5**) occur in the solid state support the idea that these mono- and dinuclear complexes might also be significant species in concentrated solutions. Furthermore it is reasonable to assume that the strong preference for N,O-chelation observed in the solid state should exist in solution, too.

Acknowledgment. We thank W. Saak and D. Haase for help with the crystal structure determinations and S. Schmid for assistance with the preparative work. Financial support from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

Supporting Information Available: X-ray crystallographic files in CIF format and ellipsoid plots with complete labeling schemes of the non-hydrogen atoms for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

IC061838B

(33) Pettit, L. D.; Hefford, R. J. W. Stereoselectivity in the Metal Complexes of Amino Acids and Dipeptides. In *Metal Ions in Biological Systems*; Sigel, H., Ed; Marcel Dekker: New York, 1979; Vol. 9, pp 173−212.

(34) Kim, E. E.; Sicignano, A.; Eriks, K. *J. Am. Chem. Soc.* **1985**, *107*, 6042−6046.

(35) Schmidbaur, H.; Bach, I.; Wilkinson, D. L.; Müller, G. *Chem. Ber.* **1989**, *122*, 1439−1444.

(36) Einspahr, H.; Bugg, C. E. *Acta Crystallogr.* **1974**, *B30*, 1037−1043.