

Metal Ion Binding by Amino Acids

The Crystal Structure of Racemic Magnesium Bis(hydrogen aspartate) Tetrahydrate $\text{Mg}(\text{L-AspH})(\text{D-AspH}) \cdot 4 \text{H}_2\text{O}$

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Magnesium hydrogen L-aspartate hydrogen D-aspartate tetrahydrate $\text{Mg}(\text{D-AspH})(\text{L-AspH}) \cdot 4 \text{H}_2\text{O}$ crystallizes on cooling from the reaction mixture obtained from equivalent quantities of racemic aspartic acid and magnesium hydroxide in water under reflux conditions. The same product is also formed by slow racemization in analogous experiments carried out with pure L-aspartic acid. — The compound crystallizes in the monoclinic space group $P2_1/c$ with centrosymmetric complex units, in which magnesium is in an octahedral environment of four water oxygen atoms in the equatorial plane and two β -carboxylate oxygen atoms in axial positions. The NH_3^+ and $\alpha\text{-CO}_2^-$ functions form a hydrogen-bonded system integrating the individual molecules into a three-dimensional network.

Magnesium complexes of the aminodicarboxylic acids are important pharmaceuticals with a wide spectrum of applications¹⁾. The two most important compositions are derived from L-aspartic acid L-AspH₂ with magnesium hydrogen L-aspartate chloride trihydrate²⁾ $\text{Mg}(\text{L-AspH})\text{Cl} \cdot 3 \text{H}_2\text{O}$ and magnesium bis(hydrogen L-aspartate) tetrahydrate³⁾ $\text{Mg}(\text{L-AspH})_2 \cdot 4 \text{H}_2\text{O}$ as the prominent representatives. The corresponding derivatives of L-glutamic acid L-GluH₂ are also widely used and show many similarities⁴⁾.

While the monoanionic hydrogen L-aspartate ligand L-AspH is typical for the system at $\text{pH} \leq 7$, the L-aspartate dianion L-Asp²⁻ is the predominant ligand in basic medium. Accordingly, a product of the composition $\text{Mg}(\text{L-Asp}) \cdot (\text{H}_2\text{O})_3$ is isolated from aqueous solution at $\text{pH} 9.85$.

In an attempt to contribute to the understanding of the biological activity of these complexes through a systematic study of their structure, we have demonstrated that the L-Asp²⁻ dianion functions as a tridentate ligand to magnesium with both carboxylate groups and the amino group as the donor centers³⁾, whereas the L-AspH⁻ monoanion (with its protonated amino function) is only bidentate²⁾. For related complexes of calcium⁵⁾, strontium, and barium⁴⁾, as well as of lithium and potassium⁶⁾, however, other structural features are emerging.

Bindung von Metall-Ionen durch Aminosäuren. — Die Kristallstruktur des racemischen Magnesium-bis(hydrogenaspartat)-Tetrahydrats $\text{Mg}(\text{L-AspH})(\text{D-AspH}) \cdot 4 \text{H}_2\text{O}$

Magnesium-L-Hydrogenaspartat-D-Hydrogenaspartat-Tetrahydrat $\text{Mg}(\text{L-AspH})(\text{D-AspH}) \cdot 4 \text{H}_2\text{O}$ fällt beim Abkühlen in kristalliner Form aus einer Reaktionsmischung aus, die in der Siedehitze aus äquivalenten Mengen von racemischer Asparaginsäure und Magnesiumhydroxid in Wasser bereitet wurde. Das gleiche Produkt entsteht in langsamer Racemisierung in analogen Experimenten, bei denen reine L-Asparaginsäure eingesetzt wurde. — Der Komplex kristallisiert in der monoklinen Raumgruppe $P2_1/c$ mit zentrosymmetrischen Komplexmolekülen, in denen das Magnesium oktaedrisch von vier äquatorial gebundenen Wassermolekülen und zwei axial koordinierten β -Carboxylat-Sauerstoffatomen umgeben ist. Die NH_3^+ - und $\alpha\text{-CO}_2^-$ -Funktionen bilden ein System von Wasserstoffbrückenbindungen, das die individuellen Komplexmoleküle zu einem dreidimensional verknüpften Netzwerk zusammenfügt.

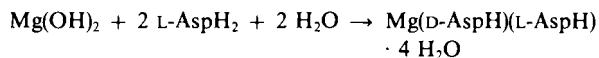
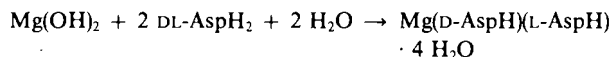
Obviously optical purity is another important aspect in the application of metal aminodicarboxylates, and, therefore, we became also interested in the racemization of the L-amino acid anions in the presence of magnesium ions in aqueous medium under certain conditions of pH and temperature. A literature survey shows that racemization of an aqueous solution of L-aspartic acid is slow even at temperatures above 100°C and in strong acid or base⁷⁻⁹⁾. In the presence of various metal ions or on the surface or in cavities of certain inorganic and organic polymers, the racemization rate is enhanced quite significantly^{10,11)}.

We describe here details of preparation³⁾ and the molecular structure of the racemic magnesium bis(hydrogen aspartate), which could be isolated as the crystalline tetrahydrate $\text{Mg}(\text{L-AspH})(\text{D-AspH}) \cdot 4 \text{H}_2\text{O}$. This product was obtained from racemic aspartic acid as well as by racemization of magnesium L-hydrogen aspartate.

Results

When a slurry of magnesium hydroxide and racemic aspartic acid in the molar ratio 1:2 in water is heated under reflux, a clear solution is obtained within two hours. Slow cooling of this reaction mixture to room temperature leads

to a crystalline precipitate of the racemic magnesium bis-(hydrogen aspartate) tetrahydrate in almost 90% yield.



The same product is also obtained in low yield from Mg(OH)_2 and L-aspartic acid through racemization under similar reaction conditions. It is the primary precipitate after concentration of the reaction mixture in vacuo to a smaller volume and crystallisation with methanol. Mg(L-AspH)_2 remains in solution under these conditions owing to its higher solubility. Aqueous solutions of $\text{Mg(D-AspH)(L-AspH)} \cdot 4 \text{H}_2\text{O}$ show a pH of 6.9.

Crystal Structure of $\text{Mg(D-AspH)(L-AspH)} \cdot 4 \text{H}_2\text{O}$

The compound crystallizes in the monoclinic space group $P2_1/c$ with two formula units in the unit cell. The crystals are built from discrete complex molecules having a crystallographic center of inversion. The magnesium ions are in an octahedral environment of six oxygen atoms. The four water molecules occupy the positions of the equatorial plane, while two β -carboxylate oxygen atoms (one from a hydrogen L- and one from a hydrogen D-aspartate anion) occupy the axial positions. The α -carboxylate groups are not coordinated to the magnesium, but are engaged in intermolecular hydrogen bonding. This is also true for the (protonated) amino function. Structural details are summarized in Tables 1 and 2, crystal data in Table 3.

The structure of the complex is shown in Figure 1. It is the most important feature of this structure, that in the crystal the DL-AspH anions are present only as monodentate ligands. It is tempting to suggest that *O,O*-chelation or -metal-bridging modes of coordination may also be absent in aqueous solutions, with pertinent consequences for complex stability. It should be pointed out, however, that the higher configurational flexibility in solution may well change the situation. There can be little doubt that there exists a delicate balance between energies of metal coordination by

water molecules or AspH anions on one hand and a large set of different hydrogen bonds on the other. It is therefore quite possible that the solid state structure is determined predominantly by the hydrogen bonding of the fixed network. The relatively low solubility of the complex with the DL-set of AspH anions as compared to the complex with the LL-set is also an indication for a favourable packing of the former, probably induced mainly by hydrogen bonds.

Unfortunately, the structures of any Mg(L-AspH)_2 or Mg(D-AspH)_2 hydrates have not yet been determined. It is possible that the stereochemically pure isomers show a different arrangement of the components, and the same uncertainty applies to the solution state.

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Experimental

General: All experiments were carried out in pure, bidistilled water. Reagents were commercial and of p.a. grade.

Magnesium(II) (Hydrogen D-Aspartate) (Hydrogen L-Aspartate) Tetrahydrate

a) L-Aspartic acid (6.66 g, 50 mmol) in 50 ml of water is treated with magnesium hydroxide (1.46 g, 25 mmol) for 30 min under reflux. The reaction mixture is then cooled to ambient temperature and concentrated to a volume of 20 ml in vacuo. The same volume of methanol is slowly added to the remaining viscous liquid. The white microcrystalline precipitate is filtered and again dissolved in 10 ml of water. Methanol vapour is allowed to slowly diffuse into this solution. Large crystals are formed at 2°C over 3 weeks. The solution of the product (0.8 g, 9% yield) in water has pH 6.90.

b) Treatment of racemic DL-aspartic acid (6.66 g, 50 mmol) in 50 ml of water with magnesium hydroxide (1.46 g, 25 mmol) for 2 h under reflux yields a reaction mixture, from which the product crystallizes upon standing for ca. 12 h with slow cooling to room temperature. 7.85 g of the product are obtained (87% yield).

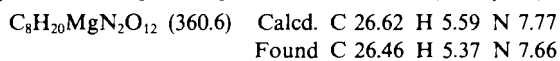


Table 1. Selected distances [\AA] and angles [$^\circ$] for $\text{Mg(L-AspH)(D-AspH)} \cdot 4 \text{H}_2\text{O}$ with standard deviations in units of the last significant figure in parentheses

Mg-O3	2.057 (2)	Mg-O5	2.070 (1)
Mg-O6	2.064 (1)	O1-C1	1.237 (3)
O2-C1	1.263 (3)	O3-C4	1.245 (3)
O4-C4	1.258 (3)	N-C2	1.493 (3)
C1-C2	1.529 (3)	C2-C3	1.522 (3)
C3-C4	1.518 (3)		
O3-Mg-O5	88.3 (1)	O3-Mg-O6	89.8 (1)
O5-Mg-O6	88.6 (1)	Mg-O3-C4	151.1 (2)
O1-C1-O2	126.3 (2)	O1-C1-C2	115.7 (2)
O2-C1-C2	118.0 (2)	N-C2-C1	111.3 (2)
N-C2-C3	109.6 (2)	C1-C2-C3	112.9 (2)
C2-C3-C4	115.0 (2)	O3-C4-O4	122.9 (2)
O3-C4-C3	118.1 (2)	O4-C4-C3	119.0 (2)

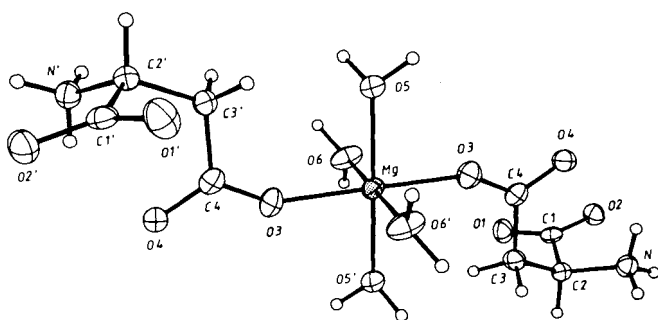


Figure 1. Structure of $\text{Mg(L-AspH)(D-AspH)} \cdot 4 \text{H}_2\text{O}$ in the crystal and atomic numbering scheme (ORTEP¹²), displacement parameters at the 50% probability level; H atoms with arbitrary radii)

Table 2. Hydrogen bond interactions (A—B...C, in Å) for Mg(L-AspH)(D-AspH) · 4 H₂O

A	B	C	A—B	B...C	A...C	Symm. op. ^{a)}
N	HN1	O2	0.898	2.003	2.872(2)	a
N	HN2	O1	0.911	2.366	2.941(2)	b
N	HN3	O4	0.939	1.944	2.857(2)	c
O5	HO51	O1	0.989	1.710	2.698(2)	d
O5	HO52	O2	0.937	1.910	2.817(2)	e
O6	HO61	O2	0.990	1.773	2.760(2)	d
O6	HO62	O4	0.992	1.949	2.918(2)	f

^{a)} Atoms C generated by the following symmetry operations: a: $-x, 1-y, -z$; b: $x-1, y, z$; c: $x, 0.5-y, 0.5+z$; d: $1-x, y-0.5, -z-0.5$; e: $-x, y-0.5, -z-0.5$; f: $1+x, y, z$.

Table 3. Atomic coordinates and equivalent isotropic displacement parameters for Mg(L-AspH)(D-AspH) · 4 H₂O. [$U_{eq} = (U_1U_2U_3)^{1/3}$, where U_i are the eigenvalues of the U_{ij} matrix]

Atom	X/A	Y/B	Z/C	U (eq.)
Mg	0.50000	0.00000	0.00000	0.033
O1	0.4976(3)	0.3794(1)	-0.0920(2)	0.056
O2	0.1451(3)	0.4526(1)	-0.1349(2)	0.043
O3	0.2511(3)	0.1048(1)	-0.0600(2)	0.066
O4	-0.0071(3)	0.2189(1)	-0.1293(2)	0.056
N	-0.0086(3)	0.3590(1)	0.0823(2)	0.039
C1	0.3008(4)	0.3971(2)	-0.0634(2)	0.029
C2	0.2482(4)	0.3483(2)	0.0751(2)	0.033
C3	0.3149(4)	0.2450(2)	0.0832(2)	0.039
C4	0.1776(4)	0.1856(2)	-0.0450(2)	0.033
O5	0.3041(3)	-0.0799(1)	-0.1732(2)	0.047
O6	0.6918(3)	0.0526(1)	-0.1487(2)	0.039

X-ray Structure Analysis of Mg(L-AspH)(D-AspH) · 4 H₂O: Enraf-Nonius CAD4 diffractometer, Mo-K α radiation, $\lambda = 0.71069$ Å, graphite monochromator, $T = 23^\circ\text{C}$. Crystal structure data: C₈H₂₀MgN₂O₁₂, $M_r = 360.560$, monoclinic, space group $P2_1/c$ (No. 14), $a = 5.725(2)$, $b = 14.283(3)$, $c = 9.125(2)$ Å, $\beta = 102.58(2)^\circ$, $V = 728.2$ Å³, $Z = 2$, $d_{\text{calc}} = 1.644$ g/cm³, $\mu(\text{Mo-K}\alpha) = 1.8$ cm⁻¹, $F(000) = 380$ e. The integrated intensities of 1466 reflections were measured up to $(\sin \Theta/\lambda)_{\text{max}} = 0.594$ Å⁻¹ using ω scan techniques ($\Delta\omega = 1.2 + 0.35 \tan \Theta$, hkl range: $+7, +16, \pm 12$). After Lp corrections and merging of equivalent data ($R_{\text{int}} = 0.01$) 1271 unique structure factors remained, 1048 of which with $F_o \geq 4.0 \sigma(F_o)$ were deemed "observed" and used for all further calculations. The structure was solved by Patterson methods and refined

to $R(R_w) = 0.033$ (0.029) for 109 refined parameters [non-H atoms anisotropic, NH₃ as rigid group, all other H atoms constant with $U_{\text{iso}} = 0.05$ Å²; all H atoms localized in difference maps; function minimized: $\Sigma w(|F_o| - |F_c|)^2$, $w = 1/\sigma^2(F_o)$, $(\text{shift/error})_{\text{max}} = 0.007$ in final cycle]. A final difference map was featureless, $\Delta\rho_{\text{fin}}$ (max/min) = $0.21/-0.26$ e/Å³. The programs used include DELOS¹³, LEPAGE¹⁴ (cell reduction), SHELXS-86¹⁵ (structure solution), SHELX-76¹⁶ (refinement), as well as locally written routines¹⁷. Table 1 lists selected distances and angles, Table 2 the hydrogen bond interactions, and Tab. 3 the atomic coordinates. Complete lists of atomic coordinates and observed and calculated structure factors have been deposited¹⁸.

CAS Registry Numbers

DL-AspH₂: 617-45-8 / L-AspH₂: 56-84-8 / Mg(DAspH)(L-AspH) · 4 H₂O: 116155-36-3

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- ¹⁸⁾ Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2 (FRG). Inquiries should be accompanied by the depository number CSD-53768, the names of the authors, and the literature citation.

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