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Synthesis and Characterization of N(8)-Coordinated Metal Complexes of the Anti-Hyperuricemia Drug Allopurinol: Bis(allopurinol)triaqua(sulfato)metal(II) Hydrates (Metal = Co, Ni, Zn, Cd)

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Four metal complexes of allopurinol have been synthesized in the form of single crystals from aqueous solutions: bis(allopurinol)triaqua(sulfato)metal(II) hydrates with the general formula $M^{II}(allopurinol)_2SO_4{\cdot}4H_2O$ (M = Co, Ni, Zn, Cd). They crystallize in the triclinic space group $P\bar{1}$ with $Z = 2$ formula units per cell. Cell dimensions are $a = 8.527$ (1) Å, $b = 9.927$ (3) Å, $c = 10.550$ (1) Å, $\alpha = 96.00$ (2)°, $\beta = 92.75$ (1)°, $\gamma = 95.95$ (2)°, and $V = 881.8$ (5) Å^3 for the cobalt complex, $a = 8.479$ (2) Å, $b = 9.849$ (3) Å, $c = 10.558$ (3) Å, $\alpha = 95.74$ (2)°, $\beta = 92.60$ (2)°, $\gamma = 95.06$ (2)°, and $V = 872.6$ (8) Å^3 for the nickel complex, $a = 8.548$ (3) Å, $b = 9.892$ (2) Å, $c = 10.565$ (3) Å, $\alpha = 95.95$ (2)°, $\beta = 92.83$ (3)°, $\gamma = 95.34$ (2)°, and $V = 883.2$ (8) Å^3 for the zinc complex, and $a = 8.678$ (3) Å, $b = 10.102$ (3) Å, $c = 10.594$ (4) Å, $\alpha = 96.02$ (3)°, $\beta = 92.62$ (3)°, $\gamma = 95.43$ (3)°, and $V = 918.0$ (10) Å^3 for the cadmium complex. The structures of the cobalt and cadmium complexes were solved by Patterson syntheses on the basis of 7474 and 9962 observed reflections and refined to R values of 0.033 and 0.029, respectively. On the basis of single-crystal and powder X-ray diffraction data, thermoanalytical measurements, and IR spectra, the nickel and zinc complexes are shown to be isostructural with their cobalt and cadmium analogues. The structure of these complexes may be represented by the formula $[M^{II}SO_4(C_5H_4N_4O)_2(H_2O)_3]{\cdot}H_2O$. The metal ions are situated in the center of a slightly distorted octahedron with two N(8)-coordinating allopurinol ligands in trans positions. N(8) and not N(9) is the preferred coordination site of neutral, unsubstituted allopurinol in the complexes described here. Allopurinol is protonated at N(1) and N(9); the corresponding H atoms as well as the H atoms of the water molecules are involved in an extended hydrogen-bonding system. Stacking of the purine bases with essentially superimposed six-membered rings and mean stacking distances of about 3.24 Å are observed. Hydrogen-bonding distances resulting from the structure analysis and coordination of the metal to a ring nitrogen atom are consistent with the interpretation of the IR data. The thermal decomposition of the complexes is a two-step reaction, including a dehydration followed by a decomposition to the corresponding metal oxides.

Introduction

The interaction of metal ions with nucleic acid bases, nucleosides, or nucleotides has been the subject of numerous chemical and crystallographic studies.[1,2] One interesting aspect of such investigations is the antitumor activity established for different metal complexes, as e.g. *cis*-$Pt(NH_3)_2Cl_2$,[3] which is believed to be based on the interaction of the metal atom with cellular DNA. Whereas the formation of metal complexes of adenine and guanine, the major purine bases occuring in DNA and RNA, has been studied intensively in solution as well as in the solid state,[4,5] only a small amount of crystallographic data of metal complexes of oxopurines (Figure 1) such as hypoxanthine (I) and its 7-deaza-8-aza isomer allopurinol (IV), xanthine (II), and uric acid (III) have been reported. These complexes have been proven much more difficult to crystallize.[4]

Xanthine oxidase is a molybdenum- and iron-containing enzyme, which is capable of catalyzing the oxidation of a wide variety of aromatic heterocycles and aldehydes to their hydroxy derivatives.[6] A biologically important reaction catalyzed by this enzyme is the oxidation of hypoxanthine, formed by degradation of nucleic acids, via xanthine to uric acid, which subsequently is released from the active site of the enzyme. In the case of metabolic errors, the uric acid level may be increased and sodium hydrogenurate hydrate crystals are deposited in joints. This disease, known as gout, is clinically treated by the drug allopurinol (pyrazolo[3,4-*d*]pyrimidin-6-one). Allopurinol is currently the drug of choice, worldwide, for the treatment of hyperuricemia and gouty arthritis.[7] It is also a substrate for xanthine oxidase. The enzymatic oxidation product of allopurinol is alloxanthine (V; pyrazolo[3,4-*d*]pyrimidin-2,6-dione), which is believed to bind extremely tightly to the reduced form of the molybdenum center to inhibit the enzyme and thus to inhibit the production of uric acid.[6] Patients receiving the drug allopurinol therefore excrete much of their purine as hypoxanthine and xanthine.

For the coordination of the molybdenum center by alloxanthine different structural models have been developed. A coordination of the nitrogen atom N(8) to Mo(IV) has been proposed on the basis of EPR experiments by Hawkes et al.[8] whereas a Mo(IV) alloxanthine complex coordinating through N(9) and stabilized by a N(8)···H–N(enzyme) hydrogen bond is assumed by Stiefel.[9] According to Stiefel, N(9) coordination to molybdenum by xanthine is also believed to occur in the biological mechanism of oxidation of this molecule (where N(7), but not C(8), would represent an alternative coordination site) to uric acid. Alternative models including Mo(IV) binding of xanthine followed by disulfide attack at C(8), as well as a model where a nucleophile X^- attached to molybdenum first attacks C(8), followed by Mo(IV) attachment to N(9), have also been presented.[7]

In addition, allopurinol is used in the treatment of leukemia in conjunction with the antitumor drug 6-mercaptopurine. The inhibition of xanthine oxidase by allopurinol reduces the elimination of 6-mercaptopurine, whose oxidation is also catalyzed by this enzyme.[10]

Crystallographic investigations of metal complexes of allopurinol and of 8-azahypoxanthine (VI) elucidate the potential coordinating capacity of the nitrogen atom N(8) and allow a comparison with the metal binding sites N(7) and N(9) of the naturally occurring purines hypoxanthine and xanthine. Coordination sites of unsubstituted oxopurines established by X-ray crystallography so far are as follows: (a) *N(7)* of monodentate hypoxanthine in $M^{II}(hyxan)SO_4{\cdot}5H_2O$ with M = Co, Ni,[11,12] in $Ru^{III}(hyxan)(NH_3)_5Cl_3{\cdot}3H_2O$,[13] and in $Cd^{II}(8\text{-azahyxan}^-)_2{\cdot}4H_2O$[14] (hyxan =

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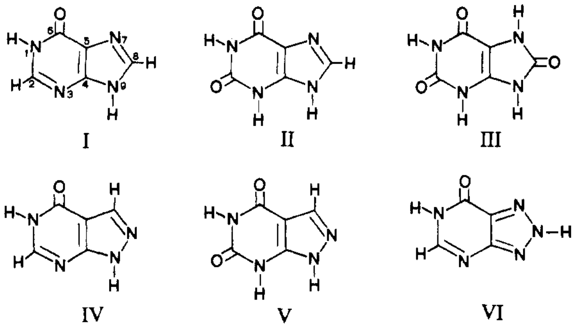

Figure 1. Formula and numbering scheme of oxypurines: (I) hypoxanthine; (II) xanthine; (III) uric acid; (IV) allopurinol (pyrazolo[3,4-*d*]pyrimidin-6-one); (V) alloxanthine (pyrazolo[3,4-*d*]pyrimidin-2,6-dione); (VI) 8-azahypoxanthine.

hypoxanthine; 8-azahyxan = 8-azahypoxanthine); (b) *N(9)* of monodentate purines in $Cu^{II}(xan)_2Cl_2·2H_2O$ and $Cu^{II}(Hur^-)_2·6H_2O$,[15] in $Cu^{II}(allo^+)Cl_3$,[16] in the isostructural complexes $Zn^{II}(8\text{-azahyxan}^-)_2·4H_2O$[17] and $Hg^{II}(8\text{-azahyxan}^-)_2·4H_2O$,[18] and in $Co^{III}(xan^-)(dmg^-)_2(Bu_3P)·H_2O·CH_3OH$[19] (xan = xanthine; Hur = hydrogenurate; allo = allopurinol; dmg = dimethylglyoxime); (c) *N(3) and N(9)* of bridging hypoxanthine in the dimeric complexes $Cu^{II}(hyxan)_2Cl_2·3H_2O$[20] and $M^{II}(hyxan)SO_4·2H_2O$, M = Cu, Zn, Cd;[21] (d) *N(3) and N(7)* of hypoxanthine in $Cu^{II}(hyxan)SO_4·H_2O$[11] forming infinite copper–hypoxanthine chains; (e) *N(1) and N(9)* in $(CH_3Hg)_2(8\text{-azahyxan}^{2-})$[17] and $(CH_3Hg)_2(allo^{2-})·2H_2O$;[22] (f) *N(9), N(7)/O(6), and N(1)/O(2)* chelating xanthine in a trinuclear 3:1 titanocene–xanthine complex of composition $[(\eta^5\text{-}C_5H_5)_2Ti]_3Cl(xan^{2-})$.[23]

Whereas all (with one exception) hypoxanthine–metal complexes structurally characterized by X-ray crystallography involve the neutral ligand, the two structures of unsubstituted allopurinol–metal complexes published up to now deal with either deprotonated or protonated ionic ligands. In this paper, the synthesis and X-ray crystallographic, thermogravimetric, and infrared spectroscopic characterization of the first metal complexes of neutral, unsubstituted allopurinol are presented.

Experimental Section

Synthesis. Allopurinol was purchased from Sigma Chemical Co., Bâle, Switzerland, and the metal sulfates were obtained from Fluka, Buchs, Switzerland. All chemicals were used without further purification.

$Co^{II}(allo)_2SO_4·4H_2O$. To a solution of 100 mg (0.73 mmol) of allopurinol in 10 mL of H_2O was added 3.0 g (10.7 mmol) of $CoSO_4·7H_2O$ dissolved in 10 mL of H_2O. The resulting mixture was heated to boiling and then kept for crystallization at 75 °C. After 2 weeks rose-colored crystals were formed.

$Ni^{II}(allo)_2SO_4·4H_2O$. This compound was prepared by heating a solution of 100 mg (0.73 mmol) of allopurinol and 5.0 g (19.0 mmol) of $NiSO_4·6H_2O$ in 20 mL of H_2O to boiling and keeping it for crystallization at 75 °C. One week later green crystals could be isolated from the solution.

Table I. Analytical Data (%) of Metal–Allopurinol Complexes of the Type $M(allo)_2SO_4·4H_2O$[a]

compd	C[b]	H	N	S	H_2O
M = Co, $CoC_{10}H_{16}N_8O_{10}S$,	24.06	3.23	22.44	6.42	14.4
M_r = 499.28	24.05	3.10	22.48	6.47	14.5
M = Ni, $NiC_{10}H_{16}N_8O_{10}S$,	24.07	3.23	22.45	6.42	14.4
M_r = 499.04	23.95	3.24	22.70	6.51	14.8
M = Zn, $ZnC_{10}H_{16}N_8O_{10}S$,	23.75	3.19	22.16	6.34	14.2
M_r = 505.72	23.68	3.14	22.44	6.19	14.2
M = Cd, $CdC_{10}H_{16}N_8O_{10}S$,	21.73	2.92	20.27	5.80	13.0
M_r = 552.75	21.69	2.94	20.40	5.82	12.8

[a] The water content was derived from thermogravimetric analysis. [b] The first value given is the calculated value, and the second value, the observed value.

Table II. Structure Determination Parameters of $M(allo)_2SO_4·4H_2O$

	M = Co	M = Cd
calcd density, $g·cm^{-3}$	1.88	2.00
obsd density, $g·cm^{-3}$	1.88	2.01
cryst size, mm	0.40 × 0.38 × 0.13	0.31 × 0.44 × 0.57
abs coeff, μ, cm^{-1}	10.9	13.3
max transmission coeff	0.890	0.686
min transmission coeff	0.730	0.606
data collecn range 2θ, deg	2–80	2–80
range of h,k,l measd	−15,15/−17,17/0,19	−15,15/−18,18/0,19
no. of rflcns measd (including stds)	11 569	12 017
no. of unique rflcns	10 887	11 328
no. of rflcns with $I \geq 3\sigma(I)$	7474	9962
no. of variables	335	335
R	0.033	0.029
R_w	0.037	0.035

$Zn^{II}(allo)_2SO_4·4H_2O$. This complex was synthesized by adding 3.0 g (10.4 mmol) of $ZnSO_4·7H_2O$ in 2.5 mL of H_2O to a solution of 50 mg (0.37 mmol) of allopurinol in 2.5 mL of H_2O. The resulting solution was kept for crystallization at 75 °C. After 5 days colorless crystals were formed.

$Cd^{II}(allo)_2SO_4·4H_2O$. To 100 mg (0.73 mmol) of allopurinol dissolved in 5 mL of H_2O was added a solution of 5.2 g (20.3 mmol) of $CdSO_4·{}^8/_3H_2O$ in 5 mL of H_2O. The reaction mixture was heated and then filtered and kept at 75 °C. After 8 days colorless crystals could be isolated from the solution.

The pH values of the reaction solutions described above, measured with a glass pH electrode (Metrohm), were 4.7 (Co), 3.6 (Ni), 4.2 (Zn), and 3.3 (Cd). Depending on the duration of the crystallization process, all syntheses could be performed with high yields of 40–80%.

Analytical data of the compounds are summarized in Table I.

Crystallographic Studies. Cell parameters of all complexes were derived from precession and Weissenberg photographs and refined by the least-squares method with 25 reflections (11° < θ < 20°) carefully centered on the diffractometer. Intensity data of the cobalt and cadmium complexes were collected at room temperature on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromatized Mo Kα radiation (λ = 0.710 73 Å). The ω–2θ scan technique with variable scan speeds of 2.86–10° min^{-1} (Co) and 2.86–20° min^{-1} (Cd) was used. Six standard reflections were checked at an interval of every 3 h. For the cobalt complex 5% loss of intensities during data collection was observed and corrected for in data reduction, whereas for the cadmium complex no significant decrease was noted. Five (Co) or four (Cd) reflections were collected every 300 reflections to control orientation. The data were corrected for Lorentz and polarization effects. A numerical absorption correction based on 14 (Co) or 16 (Cd) carefully indexed crystal faces was applied. Both structures could be solved by Patterson syntheses with SHELXS86[24] and were refined with SHELX76.[25] Least-squares refinements were carried out by minimizing $\sum w(|F_o| - |F_c|)^2$, with $w = 1/\sigma^2(F_o)$ and anisotropic thermal parameters for all non-hydrogen atoms. Additional structure determination parameters are given in Table II.

In both metal complexes all hydrogen atoms could be localized in difference Fourier maps and were refined with variable positional and

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Table III. Positional Parameters of $Co(allo)_2SO_4\cdot 4H_2O^a$

atom	x	y	z	U_{eq}/U_{iso}, Å^2
Co	0.21026 (3)	0.02965 (2)	0.27436 (2)	0.01600 (4)
S(1)	−0.16976 (5)	−0.00765 (4)	0.24629 (4)	0.01680 (4)
O(11)	−0.0243 (1)	−0.0344 (1)	0.3203 (1)	0.0238 (2)
O(12)	−0.1560 (1)	0.1371 (1)	0.2244 (1)	0.0263 (2)
O(13)	−0.3058 (1)	−0.0373 (1)	0.3251 (1)	0.0239 (2)
O(14)	−0.1903 (1)	−0.0958 (1)	0.1264 (1)	0.0317 (3)
N(1A)	0.3379 (1)	−0.5222 (1)	−0.0923 (1)	0.0225 (3)
C(2A)	0.2372 (2)	−0.5776 (1)	−0.0108 (1)	0.0265 (4)
N(3A)	0.1680 (1)	−0.5103 (1)	0.0788 (1)	0.0279 (3)
C(4A)	0.2100 (1)	−0.3729 (1)	0.0844 (1)	0.0201 (3)
C(5A)	0.3112 (1)	−0.3050 (1)	0.0065 (1)	0.0188 (3)
C(6A)	0.3839 (1)	−0.3838 (1)	−0.0908 (1)	0.0194 (3)
O(6A)	0.4761 (1)	−0.3430 (1)	−0.1687 (1)	0.0309 (3)
C(7A)	0.3166 (2)	−0.1666 (1)	0.0523 (1)	0.0225 (3)
N(8A)	0.2256 (1)	−0.1507 (1)	0.1497 (1)	0.0220 (3)
N(9A)	0.1596 (1)	−0.2781 (1)	0.1683 (1)	0.0231 (3)
N(1B)	0.1749 (1)	0.6155 (1)	0.6307 (1)	0.0213 (3)
C(2B)	0.0855 (2)	0.5288 (1)	0.6960 (1)	0.0214 (3)
N(3B)	0.0585 (1)	0.3970 (1)	0.6665 (1)	0.0208 (3)
C(4B)	0.1302 (1)	0.3534 (1)	0.5594 (1)	0.0169 (3)
C(5B)	0.2243 (1)	0.4328 (1)	0.4852 (1)	0.0182 (3)
C(6B)	0.2516 (1)	0.5771 (1)	0.5213 (1)	0.0213 (3)
O(6B)	0.3291 (1)	0.6630 (1)	0.4668 (1)	0.0366 (3)
C(7B)	0.2655 (2)	0.3409 (1)	0.3848 (1)	0.0229 (3)
N(8B)	0.2021 (1)	0.2154 (1)	0.3974 (1)	0.0209 (3)
N(9B)	0.1179 (1)	0.2242 (1)	0.5045 (1)	0.0193 (3)
O(1)	0.4395 (1)	0.0905 (1)	0.2309 (1)	0.0308 (3)
O(2)	0.1355 (1)	0.1359 (1)	0.1242 (1)	0.0269 (3)
O(3)	0.2864 (2)	−0.0680 (1)	0.4278 (1)	0.0353 (4)
O(4)	0.5484 (2)	0.6923 (1)	0.2778 (1)	0.0417 (4)
H(1A)	0.379 (3)	−0.580 (2)	−0.151 (2)	0.037 (6)
H(2A)	0.219 (2)	−0.675 (2)	−0.023 (2)	0.031 (6)
H(7A)	0.373 (2)	−0.088 (2)	0.019 (2)	0.032 (6)
H(9A)	0.086 (3)	−0.292 (2)	0.222 (2)	0.039 (7)
H(11)	0.514 (3)	0.056 (2)	0.266 (2)	0.044 (8)
H(12)	0.471 (3)	0.169 (3)	0.211 (3)	0.074 (10)
H(21)	0.142 (3)	0.111 (2)	0.056 (2)	0.043 (8)
H(22)	0.027 (4)	0.141 (3)	0.130 (3)	0.086 (11)
H(31)	0.301 (3)	−0.034 (3)	0.502 (3)	0.054 (8)
H(32)	0.299 (3)	−0.148 (3)	0.433 (3)	0.061 (9)
H(41)	0.583 (3)	0.772 (3)	0.293 (3)	0.067 (10)
H(42)	0.499 (4)	0.667 (3)	0.323 (3)	0.073 (11)
H(1B)	0.184 (3)	0.705 (2)	0.662 (2)	0.052 (8)
H(2B)	0.036 (2)	0.566 (2)	0.766 (2)	0.028 (6)
H(7B)	0.328 (2)	0.360 (2)	0.311 (2)	0.029 (6)
H(9B)	0.079 (2)	0.152 (2)	0.536 (2)	0.033 (6)

[a] $U_{eq} = {}^1/_3\sum_i\sum_j U_{ij}a^*_i\cdot a^*_j\cdot a_i\cdot a_j$.

Table IV. Positional Parameters of $Cd(allo)_2SO_4\cdot 4H_2O^a$

atom	x	y	z	U_{eq}/U_{iso}, Å^2
Cd	0.20696 (1)	0.03008 (1)	0.27226 (1)	0.01890 (2)
S(1)	−0.17682 (4)	−0.01134 (3)	0.24992 (3)	0.01910 (4)
O(11)	−0.0386 (1)	−0.0353 (1)	0.3309 (1)	0.0333 (2)
O(12)	−0.1633 (1)	0.1299 (1)	0.2261 (1)	0.0301 (2)
O(13)	−0.3167 (1)	−0.0405 (1)	0.3213 (1)	0.0275 (2)
O(14)	−0.1862 (1)	−0.0986 (1)	0.1316 (1)	0.0401 (3)
N(1A)	0.3444 (1)	−0.5272 (1)	−0.0990 (1)	0.0246 (2)
C(2A)	0.2438 (2)	−0.5818 (1)	−0.0188 (1)	0.0294 (3)
N(3A)	0.1730 (1)	−0.5155 (1)	0.0692 (1)	0.0313 (3)
C(4A)	0.2118 (1)	−0.3813 (1)	0.0749 (1)	0.0223 (2)
C(5A)	0.3127 (1)	−0.3147 (1)	−0.0017 (1)	0.0205 (2)
C(6A)	0.3867 (1)	−0.3915 (1)	−0.0974 (1)	0.0214 (2)
O(6A)	0.4783 (1)	−0.3509 (1)	−0.1741 (1)	0.0332 (2)
C(7A)	0.3146 (1)	−0.1787 (1)	0.0437 (1)	0.0254 (3)
N(8A)	0.2217 (1)	−0.1638 (1)	0.1384 (1)	0.0260 (2)
N(9A)	0.1586 (1)	−0.2890 (1)	0.1568 (1)	0.0272 (2)
N(1B)	0.1668 (1)	0.6202 (1)	0.6366 (1)	0.0235 (2)
C(2B)	0.0789 (1)	0.5352 (1)	0.7021 (1)	0.0235 (2)
N(3B)	0.0553 (1)	0.4056 (1)	0.6738 (1)	0.0230 (2)
C(4B)	0.1287 (1)	0.3620 (1)	0.5685 (1)	0.0184 (2)
C(5B)	0.2206 (1)	0.4399 (1)	0.4943 (1)	0.0211 (2)
C(6B)	0.2448 (1)	0.5808 (1)	0.5293 (1)	0.0245 (2)
O(6B)	0.3219 (1)	0.6641 (1)	0.4750 (1)	0.0435 (3)
C(7B)	0.2659 (1)	0.3493 (1)	0.3961 (1)	0.0269 (3)
N(8B)	0.2059 (1)	0.2263 (1)	0.4097 (1)	0.0251 (2)
N(9B)	0.1209 (1)	0.2352 (1)	0.5153 (1)	0.0220 (2)
O(1)	0.4480 (1)	0.0925 (1)	0.2113 (1)	0.0362 (3)
O(2)	0.1157 (1)	0.1438 (1)	0.1122 (1)	0.0345 (3)
O(3)	0.3042 (2)	−0.0709 (1)	0.4355 (1)	0.0472 (4)
O(4)	0.5401 (1)	0.6955 (1)	0.2827 (1)	0.0454 (3)
H(1A)	0.386 (2)	−0.583 (2)	−0.157 (2)	0.033 (6)
H(2A)	0.228 (3)	−0.685 (2)	−0.037 (2)	0.055 (8)
H(7A)	0.371 (2)	−0.103 (2)	0.012 (2)	0.036 (6)
H(9A)	0.091 (3)	−0.303 (3)	0.203 (3)	0.060 (8)
H(11)	0.511 (3)	0.055 (3)	0.254 (3)	0.067 (9)
H(12)	0.475 (3)	0.168 (3)	0.198 (3)	0.053 (8)
H(21)	0.132 (3)	0.119 (2)	0.034 (2)	0.046 (7)
H(22)	0.018 (3)	0.151 (2)	0.114 (2)	0.040 (7)
H(31)	0.311 (3)	−0.019 (2)	0.510 (2)	0.051 (8)
H(32)	0.298 (3)	−0.147 (3)	0.443 (3)	0.055 (8)
H(41)	0.586 (3)	0.781 (3)	0.301 (2)	0.050 (8)
H(42)	0.480 (3)	0.677 (3)	0.343 (3)	0.057 (8)
H(1B)	0.185 (3)	0.703 (3)	0.671 (3)	0.057 (8)
H(2B)	0.026 (2)	0.576 (2)	0.768 (2)	0.025 (5)
H(7B)	0.326 (2)	0.367 (2)	0.325 (2)	0.024 (5)
H(9B)	0.089 (3)	0.159 (2)	0.542 (2)	0.037 (6)

[a] See footnote *a* of Table III.

isotropic thermal parameters. The final refinement of the cobalt compound, using 7474 reflections with $I \geq 3\sigma(I)$ and 335 variable parameters, converged to $R = 0.033$ and $R_w = 0.037$ with a maximum shift to error ratio of 0.02. The maximum and minimum heights of the final difference Fourier map were 0.41 and −0.79 e·Å^{-3} (located 0.67 Å from the cobalt atom), respectively. The structure of the cadmium complex was refined in the same way, except that 16 reflections with $F_o \ll F_c$ were excluded from the final refinement, because secondary extinction was suspected. Values of $R = 0.029$ and $R_w = 0.035$ were obtained from the refinement including 9962 reflections with $I \geq 3\sigma(I)$ and 335 variable parameters. The largest shift to error ratio was 0.02, and maximum and minimum heights of the final difference Fourier map of 0.68 and −1.50 e·Å^{-3} (located 0.65 Å from the cadmium atom) were observed. Atomic positional and isotropic thermal parameters are listed in Tables III and IV.

Powder diffraction diagrams were recorded on a Nonius-Guinier-IV camera (Johansson monochromator, Cu Kα_1 radiation).

Thermogravimetric Analysis. Thermogravimetric data were collected on a Perkin-Elmer TGS-2 thermobalance under a flowing oxygen atmosphere with a heating rate of 10° min^{-1}. The weight of the samples used ranged from 15.90 to 18.64 mg.

Infrared Spectra. Solid-state IR spectra were carried out in CsI pellets on a Perkin-Elmer Type 983 spectrophotometer and in KBr pellets or in Nujol on a Perkin-Elmer Type 781 spectrophotometer.

Results and Discussion

Table V. Crystal Data of $M(allo)_2SO_4\cdot 4H_2O$

	M = Co	M = Ni	M = Zn	M = Cd
cryst syst	triclinic	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a, Å	8.527 (1)	8.479 (2)	8.548 (3)	8.678 (3)
b, Å	9.927 (3)	9.849 (3)	9.892 (2)	10.102 (3)
c, Å	10.550 (1)	10.558 (3)	10.565 (3)	10.594 (4)
α, deg	96.00 (2)	95.74 (2)	95.95 (2)	96.02 (3)
β, deg	92.75 (1)	92.60 (2)	92.83 (3)	92.62 (3)
γ, deg	95.95 (2)	95.06 (2)	95.34 (2)	95.43 (3)
V, Å^3	881.8 (5)	872.6 (8)	883.2 (8)	918.0 (10)
Z	2	2	2	2

Description of the Structures. Crystal data of the four allopurinol complexes are listed in Table V. They all crystallize in the triclinic space group $P\bar{1}$ with very similar cell parameters, indicating an isostructural relationship. The small differences in the cell dimensions and mainly in the cell volumes are paralleled by the corresponding ionic radii of the metals involved. The isostructural relationship of the cobalt and cadmium complexes has been proven by the results of the structure determination described below. An analysis of the corresponding powder diffraction diagrams, IR spectra, and thermoanalytical data of the complexes supports the assumption of identical structures also for the nickel and zinc complexes.

The monomeric structures exhibit slightly distorted octahedral coordination of the metal atoms by two N(8) atoms of allopurinol

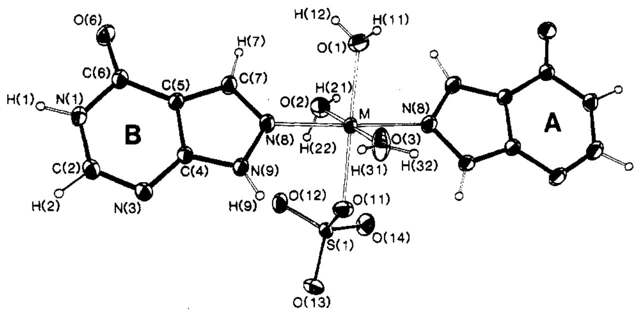

Figure 2. Coordination polyhedron of the metal atom in M(allo)$_2$SO$_4$·4H$_2$O. The thermal ellipsoids shown refer to the cobalt complex and are drawn at the 50% probability level.

Table VI. Interatomic Bond Distances (Å) of M(allo)$_2$SO$_4$·4H$_2$O

Metal Coordination Polyhedra

	M = Co	M = Cd		M = Co	M = Cd
M–N(8A)	2.128 (1)	2.312 (1)	M–O(2)	2.102 (1)	2.298 (1)
M–N(8B)	2.151 (1)	2.335 (1)	M–O(3)	2.083 (1)	2.267 (1)
M–O(1)	2.073 (1)	2.269 (1)	M–O(11)	2.129 (1)	2.303 (1)

Allopurinol

	M = Co		M = Cd	
	molecule A	molecule B	molecule A	molecule B
N(1)–C(2)	1.360 (2)	1.355 (2)	1.365 (2)	1.360 (2)
C(2)–N(3)	1.301 (2)	1.306 (2)	1.302 (2)	1.306 (2)
N(3)–C(4)	1.369 (2)	1.363 (2)	1.360 (2)	1.363 (2)
C(4)–C(5)	1.392 (2)	1.392 (2)	1.395 (2)	1.394 (2)
C(5)–C(6)	1.429 (2)	1.435 (2)	1.425 (2)	1.426 (2)
C(6)–N(1)	1.387 (2)	1.392 (2)	1.383 (2)	1.391 (2)
C(5)–C(7)	1.403 (2)	1.406 (2)	1.405 (2)	1.407 (2)
C(7)–N(8)	1.324 (2)	1.328 (2)	1.321 (2)	1.326 (2)
N(8)–N(9)	1.367 (2)	1.367 (2)	1.366 (2)	1.367 (2)
N(9)–C(4)	1.341 (2)	1.343 (2)	1.337 (2)	1.338 (2)
C(6)–O(6)	1.234 (2)	1.232 (2)	1.237 (2)	1.232 (2)
N(1)–H(1)	0.91 (2)	0.91 (2)	0.90 (2)	0.88 (3)
C(2)–H(2)	0.96 (2)	0.93 (2)	1.03 (2)	0.93 (2)
C(7)–H(7)	0.98 (2)	0.99 (2)	0.97 (2)	0.96 (2)
N(9)–H(9)	0.88 (2)	0.86 (2)	0.79 (3)	0.87 (2)

Sulfate

	M = Co	M = Cd		M = Co	M = Cd
S(1)–O(11)	1.496 (1)	1.496 (1)	S(1)–O(13)	1.482 (1)	1.481 (1)
S(1)–O(12)	1.473 (1)	1.469 (1)	S(1)–O(14)	1.453 (1)	1.449 (1)

in trans positions and by four oxygen atoms of three water molecules and one sulfate group. The noncoordinating water molecule is hydrogen-bonded to O(6B) and to O(13) of the sulfate group. Figure 2 shows the molecular structure, which may be represented by the formula [M^{II}SO$_4$(C$_5$H$_4$N$_4$O)$_2$(H$_2$O)$_3$]·H$_2$O. Interatomic bond distances and angles are summarized in Tables VI and VII.

There are two crystallographically independent allopurinol molecules in the cell. Both are protonated at N(1) and N(9) but not at N(3) or N(8), in the cobalt as well as in the cadmium complex. Allopurinol acts as a monodentate ligand, coordinating through N(8). For purines, a general rule has repeatedly been formulated[18,22] that metal cations will coordinate first to the nitrogen atom of the five-membered ring, which is protonated in the free, neutral base, this being normally N(9). Apart from the fact that it is not clear whether or not this rule should hold independent of the protonation state of the ligand in the metal complex, the rule clearly is broken as shown by the data presented for allopurinol in this paper.

Table VII. Interatomic Bond Angles (deg) of M(allo)$_2$SO$_4$·4H$_2$O

Metal Coordination Polyhedra

	M = Co	M = Cd
N(8A)–M–O(1)	86.7 (1)	85.3 (1)
N(8A)–M–O(2)	92.6 (1)	93.5 (1)
N(8A)–M–N(8B)	177.9 (1)	177.0 (1)
N(8A)–M–O(3)	89.7 (1)	89.2 (1)
N(8A)–M–O(11)	93.2 (1)	93.9 (1)
O(1)–M–O(2)	87.0 (1)	86.6 (1)
O(1)–M–N(8B)	91.3 (1)	92.2 (1)
O(1)–M–O(3)	92.5 (1)	91.9 (1)
O(1)–M–O(11)	179.3 (1)	179.0 (1)
O(2)–M–N(8B)	86.7 (1)	87.9 (1)
O(2)–M–O(3)	177.6 (1)	176.7 (1)
O(2)–M–O(11)	93.6 (1)	93.0 (1)
N(8B)–M–O(3)	91.0 (1)	89.2 (1)
N(8B)–M–O(11)	88.8 (1)	88.6 (1)
O(3)–M–O(11)	86.9 (1)	88.6 (1)

Allopurinol

	M = Co		M = Cd	
	molecule A	molecule B	molecule A	molecule B
C(6)–N(1)–C(2)	124.6 (1)	124.8 (1)	124.4 (1)	124.5 (1)
N(1)–C(2)–N(3)	125.8 (2)	125.4 (1)	125.7 (1)	125.3 (1)
C(2)–N(3)–C(4)	111.8 (1)	112.4 (1)	112.1 (1)	112.5 (1)
N(3)–C(4)–C(5)	127.4 (1)	127.1 (1)	127.2 (1)	127.0 (1)
C(4)–C(5)–C(6)	118.5 (1)	118.7 (1)	118.7 (1)	118.7 (1)
C(5)–C(6)–N(1)	111.8 (1)	111.5 (1)	112.0 (1)	112.0 (1)
C(4)–C(5)–C(7)	105.1 (1)	105.0 (1)	104.7 (1)	105.1 (1)
C(5)–C(7)–N(8)	110.4 (1)	110.2 (1)	110.3 (1)	109.9 (1)
C(7)–N(8)–N(9)	106.5 (1)	106.7 (1)	106.8 (1)	106.9 (1)
N(8)–N(9)–C(4)	110.8 (1)	110.5 (1)	110.6 (1)	110.7 (1)
N(9)–C(4)–C(5)	107.2 (1)	107.6 (1)	107.5 (1)	107.4 (1)
N(3)–C(4)–N(9)	125.3 (1)	125.3 (1)	125.3 (1)	125.6 (1)
C(6)–C(5)–C(7)	136.4 (1)	136.3 (1)	136.5 (1)	136.1 (1)
N(1)–C(6)–O(6)	120.0 (1)	120.6 (1)	119.9 (1)	120.6 (1)
C(5)–C(6)–O(6)	128.2 (1)	127.8 (2)	128.1 (1)	127.3 (1)
C(2)–N(1)–H(1)	117 (1)	116 (2)	118 (1)	117 (2)
C(6)–N(1)–H(1)	118 (1)	119 (2)	118 (1)	118 (2)
N(1)–C(2)–H(2)	114 (1)	118 (1)	112 (1)	115 (1)
N(3)–C(2)–H(2)	120 (1)	117 (1)	123 (1)	119 (1)
C(5)–C(7)–H(7)	129 (1)	129 (1)	128 (1)	129 (1)
N(8)–C(7)–H(7)	121 (1)	121 (1)	122 (1)	121 (1)
C(4)–N(9)–H(9)	126 (1)	128 (1)	125 (2)	133 (2)
N(8)–N(9)–H(9)	123 (1)	121 (1)	124 (2)	116 (2)

Metal–Allopurinol

	M = Co	M = Cd
M–N(8A)–C(7A)	127.7 (1)	126.1 (1)
M–N(8A)–N(9A)	125.1 (1)	126.0 (1)
M–N(8B)–C(7B)	129.4 (1)	129.2 (1)
M–N(8B)–N(9B)	123.8 (1)	123.4 (1)
M–O(11)–S(1)	124.3 (1)	119.8 (1)

Sulfate

	M = Co	M = Cd
O(11)–S(1)–O(12)	108.9 (1)	108.7 (1)
O(11)–S(1)–O(13)	107.4 (1)	107.9 (1)
O(11)–S(1)–O(14)	110.1 (1)	110.0 (1)
O(12)–S(1)–O(13)	109.4 (1)	109.5 (1)
O(12)–S(1)–O(14)	111.3 (1)	110.9 (1)
O(13)–S(1)–O(14)	109.8 (1)	109.9 (1)

Neutral allopurinol is protonated at N(1) and N(9) in the solid state,[26] but metal coordination of the neutral ligand occurs at N(8), the nitrogen atom that is not protonated in the free base. The same holds for hypoxanthine. Neutral hypoxanthine is protonated at N(1) and N(9),[27] but it coordinates exclusively through N(7) in its monomeric complexes.[11,12] In a recent paper of Sheldrick and Bell[22] it has been suggested that, as for the neutral purines and the 8-azapurines, N(9) is the preferred binding site in allopurinol. Our data, in contrast, show that N(8) of neutral allopurinol can act as a binding site without N(9) being blocked by, e.g., methylation. Crystallographic studies of further allo-

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[26] Prusiner, P.; Sundaralingam, M. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1972**, *B28*, 2148.

[27] Schmalle, H.; Hänggi, G.; Dubler, E. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1988**, *C44*, 732.

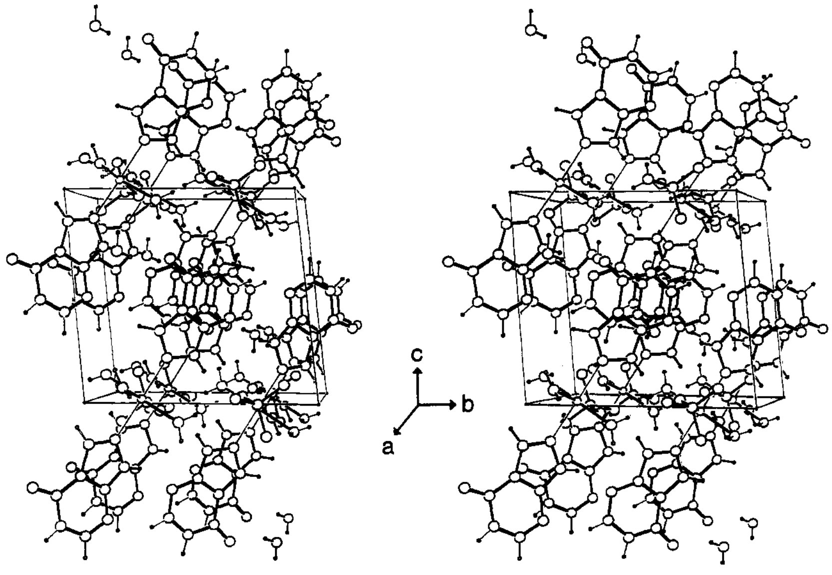

Figure 3. Stereoview of the unit cell of $M(allo)_2SO_4 \cdot 4H_2O$. The parameters drawn refer to the cadmium complex.

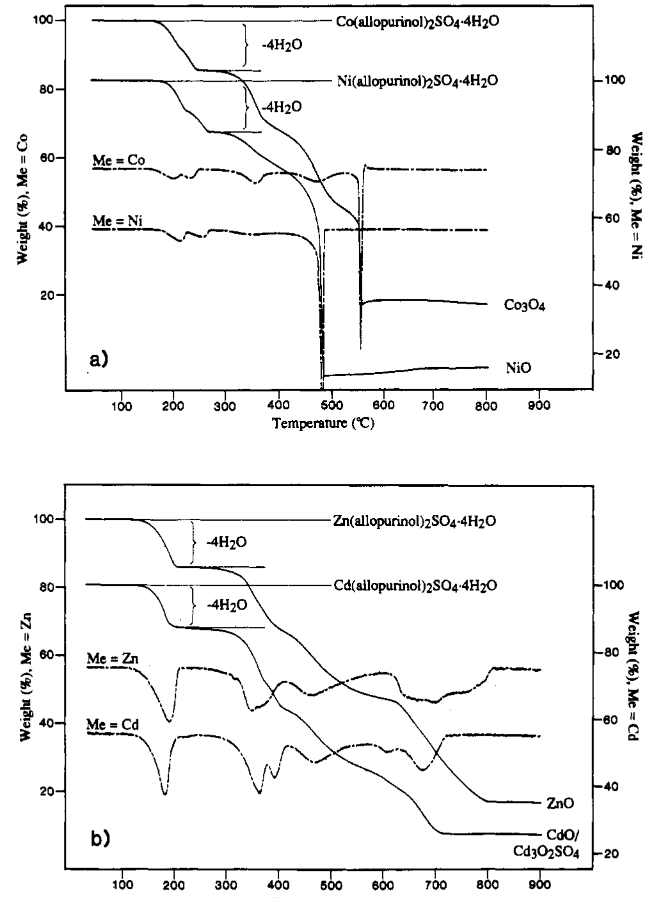

Figure 4. Thermogravimetric data of $M(allo)_2SO_4 \cdot 4H_2O$: (a) M = Co and Ni; (b) M = Zn and Cd. Dotted lines represent derivative thermogravimetric curves.

purinol–metal complexes of the type $M^{II}(allo)_2Cl_2 \cdot 2H_2O$[28] also point to the fact that N(8) is a preferred binding site of neutral, unsubstituted allopurinol. These data may support those structural models for the mechanism of action of allopurinol inhibiting the molybdenum enzyme xanthine oxidase, which suggest coordination of allopurinol to the metal via N(8) and not via N(9).

A comparison of bonding distances and angles within the allopurinol base between the four molecules A and B in the cobalt and cadmium complexes shows there is excellent agreement of the data. The maximum deviation of a single bond length from the mean value of all four corresponding bond lengths is 0.006 Å for C(5)–C(6) and C(6)–N(1); the respective deviation of a single bonding angle is 0.55° for C(5)–C(6)–O(6). Taylor and Kennard[29] have reviewed the effect of protonation of N atoms on the geometry of purine base derivatives. The major influence observed is an increase of the corresponding C–N–C angle of about 4° upon protonation of the N atom. In addition, it has been shown that metal coordination to hypoxanthine[12] or its thio analogue 6-mercaptopurine[30] instead of protonation can induce similar, though much smaller (up to a maximum of about 30%) but still significant, changes in the geometry of the purine base. A similar analysis of bonding angles and lengths of the metal complexes presented here is difficult, because in $M(allo)_2SO_4 \cdot 4H_2O$ allopurinol is protonated at N(1) and N(9) and coordinates through N(8). The corresponding protonated molecule in allo·HCl, in contrast, is protonated at N(1), N(3), and N(8),[22] but not at N(9). Therefore, an exact comparison of corresponding bonding angles can hardly be conclusive. Nevertheless, the minor increase of the C(7)–N(8)–N(9) angle from 106.4 (3)° in neutral allopurinol, where N(8) is not protonated[26] to 106.5 (1)–106.9 (1)° in the N(8)-coordinated structures described here may be indicative of a very small effect of metal coordination on the geometry of the purine ligand.

In both complexes the purine rings are approximately planar. Maximum deviations of a single atom from the best plane through the nine ring atoms are 0.016 Å (C(5A)) and 0.021 Å (C(5B)) in $Co(allo)_2SO_4 \cdot 4H_2O$ and 0.012 Å (C(5A)) and 0.018 Å (C(4B)) in the corresponding cadmium complex. The respective deviations of the oxgyen atoms are 0.006 Å (O(6A)), 0.017 Å (O(6B)), 0.015 Å (O(6A)) and 0.000 Å (O(6B)).

The solid-state stacking pattern found in most purine structures is also retained in these metal complexes. According to Bugg's classification,[31] a stacking of type II occurs, where the bases are stacked rotated approximately 180° with respect to each other. The stacked bases are nearly parallel with a dihedral angle between the purine planes of 6.3° for the Co complex and of 6.2° for the Cd complex. As may be seen in the stereo drawing of the structure (Figure 3), the stacked bases are related by inversion and show an intimate contact of the essentially superimposed six-membered

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(28) Hänggi, G.; Schmalle, H.; Dubler, E. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* in press.

(29) Taylor, R.; Kennard, O. *J. Mol. Struct.* **1982**, *78*, 1.

(30) Dubler, E.; Gyr, E. *Inorg. Chem.* **1988**, *27*, 1466.

(31) Bugg, C. E. *The Jerusalem Symposia on Quantum Chemistry and Biochemistry*; Jerusalem Academy of Sciences and Humanities: Jerusalem, 1972; Vol. 4, p 178.

Table VIII. Hydrogen-Bonding Contacts in $M(allo)_2SO_4{\cdot}4H_2O$

	M = Co			M = Cd		
X–H···Y	X–H, Å	X–Y, Å	X–H···Y, deg	X–H, Å	X–Y, Å	X–H···Y, deg
N(1A)–H(1A)···O(4)	0.91 (2)	2.730 (2)	176 (2)	0.90 (2)	2.737 (2)	176 (2)
N(9A)–H(9A)···N(3B)	0.88 (2)	2.860 (2)	158 (2)	0.79 (3)	2.896 (2)	160 (3)
N(1B)–H(1B)···O(12)	0.91 (2)	2.777 (2)	158 (2)	0.88 (3)	2.782 (2)	161 (2)
N(9B)–H(9B)···O(11)	0.86 (2)	2.857 (2)	155 (2)	0.87 (2)	2.788 (2)	156 (2)
O(1)–H(11)···O(13)	0.84 (2)	2.818 (2)	172 (2)	0.84 (3)	2.822 (2)	168 (3)
O(1)–H(12)···O(6A)	0.85 (3)	2.692 (2)	176 (3)	0.81 (3)	2.702 (2)	174 (3)
O(2)–H(21)···O(14)	0.75 (3)	2.703 (2)	164 (2)	0.87 (3)	2.684 (2)	169 (2)
O(3)–H(31)···O(13)	0.82 (3)	2.696 (2)	173 (3)	0.90 (3)	2.694 (2)	164 (2)
O(3)–H(32)···O(6B)	0.82 (3)	2.802 (2)	174 (3)	0.78 (3)	2.770 (2)	170 (3)
O(4)–H(41)···O(13)	0.82 (3)	2.823 (2)	173 (3)	0.91 (3)	2.815 (2)	174 (2)
O(4)–H(42)···O(6B)	0.70 (3)	2.815 (2)	160 (3)	0.87 (3)	2.866 (2)	169 (3)

rings. The shortest stacking distance between allopurinol bases, calculated as the mean distance of all atoms of one molecule from the least-squares plane through the stacking molecule, is 3.24 Å in the Co complex and 3.23 Å in the Cd complex.

Thermogravimetric Data. Thermogravimetric degradation curves and their derivatives of the allopurinol complexes are presented in Figure 4. The four compounds exhibit a strikingly similar decomposition behavior, supporting the suggestion of isostructural relationships. All thermal decompositions occur in two steps: a dehydration reaction followed by a decomposition to the corresponding metal oxide.

The dehydration reaction $M(allo)_2SO_4{\cdot}4H_2O \rightarrow M(allo)_2SO_4$ is observed in the temperature range 170–265 °C for the Co and Ni complexes and 130–210 °C for the Cd and Zn complexes. Under the experimental conditions used, there was no evidence for the formation of stable compounds with intermediate degrees of hydration. The anhydrous complexes are decomposed to the corresponding metal oxides in the temperature ranges 290–480/560 °C (Ni, Co) and 280–710/800 °C (Cd, Zn), except for the cadmium compound, where in addition to CdO, $Cd_3O_2SO_4$ was observed as final product. Calculated and observed weight losses for dehydrations as well as for the complete decompositions are in good agreement. The final products were characterized by X-ray powder diffractometry, and the data corresponded with the values given for Co_3O_4, NiO, ZnO, CdO, and $Cd_3O_2SO_4$, respectively.[32]

Infrared Spectra. The solid-state IR spectra of the free ligand and of the cobalt complex, recorded in the range 4000–200 cm^{-1}, are shown in Figure 5. The spectra of the three other metal complexes with Ni, Zn, and Cd are nearly identical with that of the cobalt complex, supporting their isostructural relationship. In CsI or KBr, significant differences of the spectrum of the Cd complex compared to the spectra of the other metal complexes are observed. Since in Nujol, in contrast, the spectrum of the cadmium complex coincides with that of the cobalt compound shown in Figure 5, the changes observed in the spectrum recorded in CsI or KBr possibly are due to a partial decomposition of the original Cd complex. Uncomplexed neutral allopurinol exhibits a spectrum with distinct differences of frequencies and intensities of the absorptions compared to those of the metal complexes. Tentative band assignments for oxopurine bases and their metal complexes given in the literature are $\nu_{NH} \hat{=} 3200–2550$ cm^{-1}, $\nu_{CH} \hat{=} 3100–3000$ cm^{-1}, $\nu_{C=O} \hat{=} 1740–1650$ cm^{-1}, $\nu_{C=C}$ and $\nu_{C=N} \hat{=} 1650–1520$ cm^{-1}, $\delta_{NH} \hat{=} 1570–1510$ cm^{-1}, ν_{CN} and ring vibrations $\hat{=} 1510–1110$ cm^{-1}, several ligand and ring vibrations $\hat{=} 1050–200$ cm^{-1}, and finally ν_{MN} and $\nu_{MO} \hat{=} 500–200$ cm^{-1}.[33-35]

For allopurinol, the intense carbonyl absorption appears at about 1695 cm^{-1} in the free ligand as well as in its metal complexes. Coordination of the O(6) atom is ruled out in all these cases, since such a coordination should slightly decrease the double-bond character of the C=O bond and therefore lead to lower frequencies. Participation of ring nitrogen atoms in coordination is evident by the C=C and C=N stretching frequencies, which are shifting and splitting upon complex formation.[36,37] The strong absorption at 1589 cm^{-1} in allopurinol appears in the form of a doublet at 1601/1575 cm^{-1} (Co), 1600/1574 cm^{-1} (Ni), 1600/1575 cm^{-1} (Zn) and 1600/1572 cm^{-1} (Cd). Significant splitting upon complex formation is also observed for the 1241-cm^{-1} absorption of allopurinol, which has been tentatively ascribed to a ν_{NN} stretching mode of the triazolo group in 8-azahypoxanthine.[38] The 1241-cm^{-1} absorption shifts to 1257/1235 cm^{-1} (Co), 1258/1236 cm^{-1} (Ni), 1255/1235 cm^{-1} (Zn), and 1252/1232 cm^{-1} (Cd).

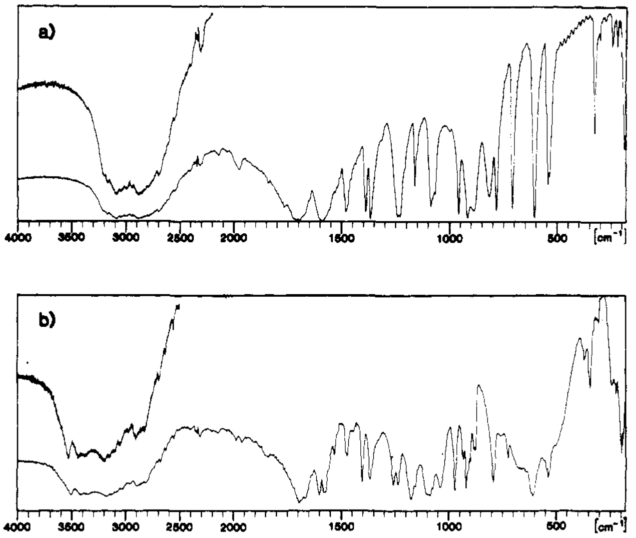

Figure 5. Solid-state infrared absorption spectra in the region 4000–200 cm^{-1} in CsI pellets: (a) allopurinol; (b) $Co(allo)_2SO_4{\cdot}4H_2O$.

Finally the broad bands in the region 4000–2500 cm^{-1} are ascribed to N–H and O–H stretching modes, possibly involved in hydrogen bonding of the type N–H···O, N–H···N, or O–H···O. Lautié et al.[39] and Novak[40] have given graphic presentations for the correlations between N–H and O–H stretching frequencies and the corresponding N···O and O···O interatomic distances of hydrogen-bonded groups. A tentative assignment of the most pronounced bands in the spectrum of the cobalt complex (2810, 2885, 3025, and 3120 cm^{-1}) to ν_{NH} of hydrogen-bonded groups corresponds to N···O distances in the range from 2.73 to 2.88 Å. These distances are in remarkably good agreement with the data derived from the crystallographic analysis. The bands observed at 3165 and 3420 cm^{-1} correspond to O–H···O hydrogen bonds with O···O distances of 2.68 and 2.82 Å, again coinciding with the crystallographic results.

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A summary of hydrogen-bonded contacts observed in M(allo)$_2$SO$_4$·4H$_2$O complexes is given in Table VIII.

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Registry No. Co^{II}(allo)$_2$SO$_4$·4H$_2$O, 115512-16-8; Ni^{II}(allo)$_2$SO$_4$·4H$_2$O, 115512-17-9; Zn^{II}(allo)$_2$SO$_4$·4H$_2$O, 115512-18-0; Cd^{II}(allo)$_2$SO$_4$·4H$_2$O, 115512-19-1.

Supplementary Material Available: Tables of anisotropic thermal parameters and of bonding distances and angles involving H atoms (3 pages); listings of observed and calculated structure factors (74 pages). Ordering information is given on any current masthead page.

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Technetium Metallothioneins

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Transchelation of ^{99m}Tc from TcO(GH)$_2$ (GH = glucoheptonate) for Zn^{2+} in metallothionein (MT) was evaluated as a function of MT concentration, pH, buffer, and reaction time. Incorporation of >90% of the ^{99m}Tc presented was achieved in <1 h at [MT] = 7 × 10^{-6} M in 0.01 M sodium phosphate, pH 6.5. To further understand the chemical nature of the ^{99m}TcMT binding, the long-lived ^{99}Tc radionuclide was utilized to prepare macroscopic quantities of TcMT for conventional chemical and spectroscopic analysis. Various ^{99}Tc$_x$,ZnMT species were prepared by exchange labeling with ^{99}TcO(GH)$_2$ in 0.01 M sodium phosphate, pH 7.0. The incorporation of Tc into Zn$_7$MT is almost quantitative at low ^{99}Tc/MT ratios. As many as seven Tc atoms could be incorporated into MT. The UV-visible spectra of ^{99}Tc$_x$,ZnMT species showed an absorbance at 405 nm with an extinction coefficient of 2500 per Tc atom, which is characteristic with a Tc-thiolate charge-transfer transition. The Raman spectra show a band in the 940-960-cm^{-1} region, indicating that the TcO^{3+} core is bound in square-base-pyramidal geometry. Consumption of MT sulfhydryl groups indicates that initially ^{99}Tc atoms bind with the stoichiometry ^{99}TcO(Cys)$_4$. As more ^{99}Tc atoms (three to five) are bound, ligation of additional sulfhydryl groups is not observed, suggesting that Cys residues are bridging TcO^{3+} cores as in [(^{99}TcO)$_2$(SCH$_2$CH$_2$S)$_3$]. Further consumption of Cys residues occurs abruptly with incorporation of the final ^{99}Tc atoms and suggests that the tertiary structure of the MT cluster system has been disrupted.

Introduction

Metallothioneins (MT's) are a class of small, sulfur-rich metal-binding proteins that play an important role in sequestering metal ions in heavy-metal poisoning[1] and probably function in the homeostatis of essential metals like zinc and copper.[2,3] The twenty cysteine (Cys) residues in mammalian thioneins (mol wt 6100) are found at invariant positions in the primary sequences and are responsible for metal binding.[4,5] Zinc, cadmium, and copper are tightly bound in metal thiolate clusters by MT in vivo. Many other metal ions are bound by MT with seven atoms of divalent and up to twenty atoms of monovalent metal ions bound per molecule.[6,7] NMR spectroscopy[8] and X-ray crystallography[9] have determined that two cluster systems are formed as 7-mol quantities of divalent cations are bound in mammalian metallothioneins. The α cluster containing four metal cations bound by eleven Cys thiolates in a bicyclo[3.1.3] structure results from the tetrahedral coordination of thiolates around the metal cations; the β cluster consists of nine Cys thiolates bound by three metal cations in a six-membered ring. The positively charged lysine residues have been postulated to stabilize the tertiary structure of the negatively charged clusters of MT.[10,11] Because of the thermodynamic stability of heavy-metal sulfhydryl bonds,[12,13] MT's offer promise as carriers of diagnostic and therapeutic radionuclides in the radiolabeling of biologically important molecules.[14]

Technetium-99m, a 140-keV γ emitter with a half-life of 6 h, is widely used in diagnostic nuclear medicine and is the radionuclide of choice in the radiodiagnosis of diseases. Monoclonal antibodies have been radiolabeled with technetium either by direct means[15,16] or through the use of bifunctional chelating agents including DTPA (diethylenetriaminepentaacetic acid)[17,18] and DADS [*N,N'*-bis(mercaptoacetamido)ethylenediamine].[19] Since Tc is known to form inert coordination complexes with aliphatic thiols, we have investigated the use of MT as a bifunctional chelator for the labeling of monoclonal antibodies with technetium. In this paper, we describe the synthesis and characterization of ^{99m}Tc and ^{99}Tc,ZnMT's. With the use of ^{99}Tc, a 85-keV (average) β-emitting isotope with a half-life of 2.12 × 10^5 years, macroscopic amounts of ^{99}Tc,ZnMT's were prepared and characterized by chemical and spectroscopic methods. The formation of TcO(Cys)$_4$

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