Synthesis and Characterization of an Octanuclear Mixed-Ligand Copper(II) Complex of the Immunosuppressant Thiopurine Drug Azathioprine

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An octanuclear mixed-ligand copper(II) complex of the immunosuppressant drug azathioprine (AZA) and 2,2,6,6-tetramethylheptane-3,5-dione (THD), $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$, has been synthesized and characterized by X-ray crystallography and by mass spectrometric and magnetic measurements. Eight copper(II) ions, four monodeprotonated azathioprine$^-$ ligands, ten monodeprotonated THD$^-$ ligands, and two hydroxide anions are assembled to form a centrosymmetric, octanuclear molecule, where two tetranuclear moieties of the molecule are connected by four coordination bonds between copper atoms and the N(3) and N(9) atoms of two different AZA ligands. In each half of the molecule, all four copper atoms are five-coordinated with a square pyramidal geometry. Three copper atoms are bridged through a μ_3-OH$^-$ group to form a Cu_3OH cluster with Cu−Cu distances of 3.213(2), 3.585(2), and 3.672(2) Å, respectively, while the fourth one is separated from the cluster by a purine base. Antiferromagnetic coupling is observed within the two OH$^-$-bridged trinuclear copper clusters of the octanuclear molecule. The magnetic susceptibility data fit well with the theoretical model proposed ($J = -75$ cm^{-1}, $g = 2.235$). Three of the four purine nitrogen atoms (N(3), N(7), and N(9)) bind to copper atoms in both crystallographically independent AZA moieties. All of the 6-mercaptopurine (6-MP) fragments of AZA, a biologically active component of the drug, are buried inside the complex molecule. According to ESI-MS measurements, at least the main skeleton of the molecule is still present in solution despite partial decomposition of the complex via ligand exchange with the solvent. Crystal data: $P2_1/n$, $a = 21.754(4)$ Å, $b = 16.441(3)$ Å, $c = 25.209(5)$ Å, $\beta = 97.07(2)°$, $V = 8948(3)$ Å^3, $Z = 2$.

Introduction

Derivatives of purine nucleobases often exhibit pronounced pharmaceutical activities,[1] as, for example, allopurinol (treatment of gout), acyclovir (antiviral drug), and 6-mercaptopurine (6-MP, anticancer drug).[2] 6-MP suffers from extensive metabolic transformations in vivo. To protect its sulfur from oxidation and hydrolysis, attempts were made to introduce blocking groups that might be removed intracellularly to release 6-MP by, for example, some tumor-specific enzyme. The most successful compound was the 1-methyl-4-nitroimidazol-5-yl derivative, known as azathioprine (Imuran). Azathioprine (AZA, 6-[(1-methyl-4-nitroimidazol-5-yl)thio]purine) acts as a slow-release prodrug for 6-MP which, because of the proximity of the ortho-nitro group, is subject to attack by sulfhydryl groups and other nucleophiles in biological media.[2a] Chemical diagrams of the thiopurine drugs 6-MP and AZA as well as of the second ligand THD used in this work are given in Figure 1.

AZA was originally synthesized by Hitchings and Elion[2b] and is currently used as an adjuvant for the therapy of human leukemias, as an immunosuppressant, for example, in renal transplant patients and, in combination with other drugs, for the treatment of rheumatoid arthritis.

Synthesis and characterization of metal complexes of AZA and related purines attract growing attention by several reasons.

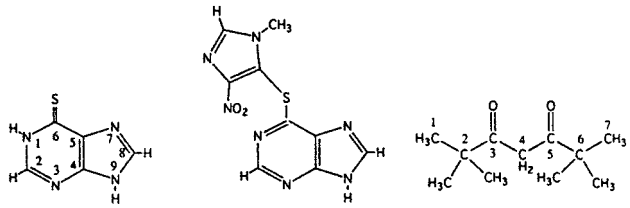

Figure 1. Structural formulas and numbering systems for 6-mercaptopurine (6-MP), azathioprine (AZA), and 2,2,6,6-tetramethylheptane-3,5-dione (THD).

On the basis of the well-known anticancer activity of *cis*-$PtCl_2(NH_3)_2$,[3] the activity and/or selectivity of the purine drugs might be enhanced by metal complexation. For example, it has been found that some metal complexes of purine derivatives such as 6-MP, especially those of platinum and palladium, show antitumor activity, which in some cases is enhanced with respect to the activity of the free ligand.[4] One possible mode of action of slow-acting antirheumatic drugs invokes the participation of their copper complexes as superoxide dismutase mimetics which destroy extracellular superoxide radicals.[5] The embedding of drug molecules such as AZA within the framework of a polynuclear mixed-ligand metal complex molecule as described in this paper could represent a new method to alter the biological

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properties of purine drugs such as, for example, activity, pharmacokinetics, or solubility and therefore also to alter their interaction with cell components such as nucleic acids or cell membranes. Last, but not least, AZA is a very interesting complexing ligand from the inorganic chemist's viewpoint, since it exhibits at least seven potential coordination sites: the four nitrogen atoms of the purine ring, the thioether bridge, and one nitrogen atom as well as the nitro group of the imidazole substituent.

The purine moiety of AZA has four nitrogen atoms [N(1), N(3), N(7), and N(9)]. In the crystal structures of neutral AZA[6] as well as of AZA·2H_2O,[7] AZA occurs as its N(9)−H tautomer. Deprotonation or tautomerization of this molecule renders all four positions to be potential coordination sites for metal ions. The complexation behavior of AZA with various metal ions was recently investigated by Singh[8] and by Chifotides.[9] In basic aqueous solutions, the formation of 2:1 complexes of Cu(II), Ni(II), and Co(II) with either $N(3)_{purine}/N(9)_{purine}$ or $N(7)_{purine}/S(6)$ bis-chelated, mononuclear structures has been suggested from potentiometric titration experiments.[8] From spectroscopic data, the preferred binding sites of AZA have been proposed to be N(9) in $Hg^{II}(AZA^-)_2$,[9b,c] $Pd^{II}(AZA^-)_2(H_2O)_2$,[9d] and $Ag^{I}(AZA)(AZA^-)$,[9d] whereas a N(3)/N(9) bridging coordination mode was suggested for $[(CH_3Hg^{II})_2(AZA^-)]NO_3$,[9b,c] $[Pt^{II}(NH_3)_2(AZA^-)]NO_3$, $Rh^{III}(AZA^-)Cl_2$, and $Ru^{III}(AZA^-)Cl_2$.[9d] Only one crystal structure of an AZA metal complex has been reported so far, demonstrating that monodentate binding of the neutral AZA ligand via N(3) occurs in the dimeric complex $[Rh^{II}_2(AZA)_2(\mu\text{-}Ac^-)_4]$·4DMAA.[9a] In contrast to most of the metal complexes of 6-MP,[10] no metal−sulfur interaction has been observed in the AZA complexes.

Here we report the synthesis, crystal structure, and characterization by mass spectrometric and magnetic measurements of an octanuclear copper(II) complex with AZA and 2,2,6,6-tetramethylheptane-3,5-dione (THD). THD has been chosen as the second ligand because it exhibits a hydrophobic surface to the solvent if coordinated to a metal ion and may therefore embed the predominantly hydrophilic AZA moieties. In the title complex, the 6-MP component of AZA points inwardly and is entirely surrounded by a coat assembled from the other parts of the complex molecule.

Experimental Section

All chemicals and solvents used for the synthesis were reagent grade. Azathioprine (AZA) was purchased from Sigma; 2,2,6,6-tetramethyl-3,5-heptanedione (THD) and other reagents were obtained from Fluka. All of them were used without further purification.

Preparation of [{$Cu_4(AZA^-)_2(THD^-)_5(OH^-)$}$_2$]·2$CH_3CN$. $Cu(THD)_2$ was prepared by the reaction of copper(II) acetate monohydrate (4.85 g, 24 mmol in 75 mL of H_2O) with THD (8.85 g, 48 mmol in 100 mL of 94% ethanol) at room temperature. The purple product, which immediately precipitated from the reaction mixture, was recrystallized twice from ethanol. Its purity was checked by X-ray powder diffractometry. The air-stable title compound was synthesized in acetonitrile solution. $Cu(THD)_2$ (3.44 g, 8 mmol) was dissolved in 20 mL of acetonitrile by heating at reflux, and this solution was mixed with a refluxed solution of 1.11 g (4 mmol) of AZA in 150 mL of acetonitrile. The reaction mixture was allowed to reflux for an additional 1 h and then, after filtration, was kept at 4 °C for 1 week. The blue-green crystalline product was isolated and recrystallized from acetonitrile solution at 4 °C by slow evaporation. OH^- anions obviously are introduced into the complex by using reagent grade AZA, which exhibits some nonstoichiometric water content. If the molar ratio of AZA/$Cu(THD)_2$ was increased from 1/2 to about 3/1, no mixed-ligand complexes could be isolated, probably because the AZA ligands completely displace the diketonate ligands. Anal. Calcd for $C_{150}H_{222}Cu_8N_{30}O_{30}S_4$: C, 50.58; H, 6.29; N, 11.85; S, 3.60. Found: C, 49.83; H, 5.93; N, 11.72; S, 3.36. IR (KBr, cm^{-1}): 3546 (w, ν_{O-H}), 3133 (w, $\nu_{C-H\ arom}$), 3116 (w, $\nu_{C-H\ arom}$).

Table 1. Crystal Data and Structure Determination Parameters for [{$Cu_4(AZA^-)_2(THD^-)_5(OH^-)$}$_2$]·2$CH_3CN$

empirical formula	$C_{150}H_{222}Cu_8N_{30}O_{30}S_4$
fw	3562.2
space group	$P2_1/n$
a	21.754(4) Å
b	16.441(3) Å
c	25.209(5) Å
α	90°
β	97.07(2)°
γ	90°
V	8948(3) Å^3
Z	2
d_{calc}	1.322 g/cm^3
θ range for data collection	1.2−26°
μ(Mo Kα)	1.05 mm^{-1}
no. of independent rflns	10945
no. of rflns with $I > 2\sigma(I)$	5952
no. of params refined	931
refinement method	full-matrix least-squares on F^2
R1 [$I > 2\sigma(I)$]	0.071
wR2 [$I > 2\sigma(I)$]	0.17[a]
R1 [all data]	0.21
wR2 [all data]	0.25[a]
final $(\Delta\rho)_{max}/(\Delta\rho)_{min}$	1.04/−0.67 e·Å^{-3}

[a] Weighting scheme: $w = 1/[\sigma^2(F_o^2) + (0.0901P)^2 + 40.50P]$, $P = [\max(F_o^2, 0) + 2F_c^2]/3$.

X-ray Crystallography. A crystal with the dimensions 0.27 × 0.40 × 0.10 mm^3 was selected for X-ray investigation on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromatized Mo Kα radiation at room temperature. Cell parameters were obtained by the least-squares refinement of 25 strong reflections in the range 5.5° < θ < 11.3°. Intensity data were collected on an Enraf-Nonius CAD4 diffractometer using the $\omega-2\theta$ scan technique with variable scan speeds. The MolEN program system[11] was used to correct the data for Lorentz−polarization and absorption effects. The structure was solved with the SHELXS-86 program system[12] and refined with SHELXL93.[13] The hydrogen atom of the bridging OH^- group was located from a difference Fourier synthesis and refined using an isotropic displacement parameter, whereas all other hydrogen atom positions were introduced at their calculated positions. The atoms of the solvent molecule and the methyl groups on the surface of the molecule exhibit slightly disordered positions. Crystal data and experimental structure determination parameters are given in Table 1; atomic coordinates and displacement parameters in Table 2.

Magnetic Measurements. Measurements of the magnetic susceptibility of a microcrystalline sample were performed with a SQUID magnetometer from Quantum Design in a field of 20 000 G. The diamagnetism was taken to be 9.04 × 10^{-4} cm^3 mol^{-1} on the basis of the magnetic measurements of AZA and the estimation from Pascal's constants. The temperature-independent paramagnetism (TIP) for every

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Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$[a]

atom	*x*	*y*	*z*	*U*(eq)	atom	*x*	*y*	*z*	*U*(eq)
Cu(1)	5068(1)	8775(1)	1005(1)	34(1)	C(47)	10211(9)	7373(11)	1618(7)	151(7)
Cu(2)	5308(1)	7820(1)	−231(1)	33(1)	C(51)	8265(7)	10873(9)	1202(6)	115(5)
Cu(3)	6494(1)	8554(1)	822(1)	35(1)	C(521)	8036(6)	9474(9)	1482(5)	108(5)
Cu(4)	9004(1)	8216(1)	166(1)	61(1)	C(522)	9137(7)	10020(10)	1612(6)	126(6)
O(1)	5511(3)	8134(3)	532(2)	31(2)	C(52)	8526(5)	9998(6)	1247(4)	60(3)
C(11)	4099(6)	10414(7)	2128(5)	81(4)	C(53)	8651(4)	9632(6)	713(4)	52(3)
C(12)	3740(5)	9666(6)	1943(4)	66(3)	C(54)	8637(5)	10103(7)	265(4)	66(3)
C(121)	3465(8)	9365(11)	2428(7)	138(6)	O(53)	8785(3)	8884(4)	738(3)	57(2)
C(122)	3249(6)	9895(8)	1501(5)	94(4)	C(55)	8824(4)	9833(6)	−224(4)	52(3)
C(13)	4172(4)	9057(5)	1730(4)	43(3)	O(55)	8955(3)	9107(4)	−323(3)	59(2)
C(14)	4238(4)	8272(6)	1930(4)	48(3)	C(56)	8892(6)	10441(7)	−684(5)	72(4)
O(13)	4453(3)	9321(4)	1352(2)	51(2)	C(561)	9553(8)	10727(11)	−576(7)	143(7)
C(15)	4642(4)	7680(5)	1768(3)	37(2)	C(562)	8831(9)	10025(11)	−1207(7)	151(7)
O(15)	4977(3)	7807(4)	1402(2)	49(2)	C(57)	8446(8)	11129(10)	−713(7)	135(6)
C(16)	4707(5)	6847(6)	2028(4)	55(3)	N(1A)	6736(4)	10871(4)	106(3)	47(2)
C(161)	4529(11)	6225(14)	1625(10)	216(11)	C(2A)	6762(4)	10110(6)	262(4)	50(3)
C(162)	5356(11)	6736(14)	2247(9)	203(10)	N(3A)	6326(3)	9670(4)	461(3)	36(2)
C(17)	4353(10)	6728(13)	2475(8)	177(8)	C(4A)	5803(4)	10091(5)	499(3)	26(2)
C(21)	4516(6)	7395(7)	−1950(5)	90(5)	C(5A)	5714(4)	10907(5)	330(3)	34(2)
C(22)	4793(5)	6601(7)	−1710(4)	60(3)	C(6A)	6207(4)	11276(6)	146(4)	45(3)
C(221)	5277(6)	6316(8)	−2054(5)	98(5)	S(6A)	6154(1)	12312(2)	−45(1)	68(1)
C(222)	4292(6)	5953(9)	−1708(6)	101(5)	N(7A)	5128(3)	11128(4)	416(3)	32(2)
C(23)	5083(4)	6735(6)	−1131(4)	44(3)	C(8A)	4890(4)	10471(5)	613(3)	32(2)
O(23)	4946(3)	7405(4)	−922(2)	43(2)	N(9A)	5258(3)	9822(4)	673(3)	30(2)
C(24)	5458(5)	6140(6)	−857(4)	50(3)	C(10A)	6923(4)	12586(6)	13(4)	49(3)
C(25)	5721(4)	6176(5)	−327(3)	41(3)	N(11A)	7233(4)	12705(5)	−424(4)	68(3)
O(25)	5645(3)	6782(4)	−19(2)	46(2)	C(12A)	7796(6)	13031(9)	−215(7)	119(6)
C(26)	6134(5)	5506(6)	−65(4)	57(3)	N(13A)	7849(7)	13054(9)	292(7)	149(6)
C(261)	6772(6)	5889(8)	53(6)	113(6)	C(14A)	7332(6)	12810(9)	435(6)	98(5)
C(262)	5932(7)	5282(8)	463(6)	114(5)	N(15A)	7267(9)	12810(15)	972(7)	220(10)
C(27)	6175(8)	4763(8)	−405(6)	150(7)	O(11A)	6808(8)	12416(14)	1085(5)	231(10)
C(31)	6026(7)	10252(7)	2098(5)	92(5)	O(12A)	7602(12)	13058(14)	1298(7)	353(14)
C(32)	6226(4)	9450(6)	2348(4)	46(3)	C(16A)	6997(8)	12530(12)	−983(5)	149(8)
C(321)	6764(6)	9593(8)	2795(5)	96(5)	N(1B)	6732(4)	7898(5)	−1349(3)	47(2)
C(322)	5684(6)	9074(8)	2616(6)	109(5)	C(2B)	6258(5)	8066(6)	−1075(4)	49(3)
C(33)	6411(4)	8850(5)	1933(3)	35(2)	N(3B)	6259(3)	8184(4)	−555(3)	36(2)
O(33)	6195(3)	9022(4)	1444(2)	43(2)	C(4B)	6821(4)	8122(5)	−287(3)	31(2)
C(34)	6770(5)	8191(6)	2085(4)	55(3)	C(5B)	7357(4)	7925(5)	−508(3)	38(2)
C(35)	6946(4)	7608(6)	1739(4)	47(3)	C(6B)	7290(4)	7831(6)	−1056(4)	47(3)
O(35)	6812(3)	7635(4)	1231(2)	52(2)	S(6B)	7939(1)	7604(2)	−1399(1)	78(1)
C(36)	7339(6)	6895(7)	1951(4)	71(4)	N(7B)	7856(3)	7881(5)	−106(3)	47(2)
C(361)	7309(11)	6716(15)	2500(9)	211(11)	C(8B)	7593(4)	8014(5)	329(4)	41(3)
C(362)	7003(13)	6122(17)	1771(11)	261(14)	N(9B)	6967(3)	8181(4)	253(3)	36(2)
C(37)	7903(11)	6830(15)	1726(10)	216(11)	C(10B)	7545(5)	7350(9)	−2014(4)	70(4)
C(41)	10423(7)	7528(9)	−942(6)	108(5)	N(11B)	7236(5)	6636(7)	−2112(4)	83(3)
C(42)	10085(5)	6804(7)	−763(4)	60(3)	C(12B)	6965(6)	6664(10)	−2630(5)	102(5)
C(422)	9571(6)	6563(10)	−1200(5)	113(6)	N(13B)	7094(5)	7323(9)	−2888(4)	100(4)
C(421)	10541(6)	6098(9)	−657(5)	97(5)	C(14B)	7433(6)	7751(8)	−2495(5)	75(4)
C(43)	9787(4)	7069(6)	−272(4)	52(3)	N(15B)	7614(5)	8582(8)	−2614(4)	98(4)
O(43)	9341(4)	7572(4)	−365(3)	68(2)	O(11B)	7876(5)	8985(7)	−2261(4)	126(4)
C(44)	10015(5)	6810(6)	240(4)	58(3)	O(12B)	7479(7)	8826(8)	−3072(5)	169(6)
C(45)	9761(6)	6998(7)	696(5)	68(4)	C(16B)	7196(7)	5975(9)	−1747(6)	112(5)
O(45)	9295(4)	7456(5)	716(3)	74(2)	N(3S)[b]	1877(12)	5093(15)	657(10)	221(12)
C(46)	10048(6)	6666(7)	1247(4)	70(4)	C(2S)[b]	1684(11)	4662(16)	343(10)	188(10)
C(461)	9575(8)	6156(10)	1474(7)	137(6)	C(1S)[b]	1513(10)	4188(15)	−120(9)	238(10)
C(462)	10603(8)	6159(12)	1233(7)	154(7)	H(1)	5554(30)	7698(39)	619(26)	8(19)

[a] $U(\text{eq}) = {}^1/_3\sum_i\sum_j U_{ij}a_i^*a_j^*a_ia_j$. [b] The atoms in the solvent molecule are slightly disordered.

cupric ion was taken to be 6.0×10^{-5} cm^3 mol^{-1}. $R = [\sum(\chi_{cal} - \chi_{exp})^2]/[\sum(\chi_{exp})^2] = 8.0 \times 10^{-5}$ for the least-squares-fitted parameters.

Mass Spectrometric Data. Electrospray ionization mass spectrometry (ESI-MS) measurements were done with a Finnigan MAT TSQ-700 instrument with an upper measuring limit of *m*/*z* 2000. No spectrum with a reasonable S/N ratio was obtained when the compound was dissolved in DMF or in toluene/acetone (v/v ≈ 1/2), while a poor S/N ratio was obtained when acetonitrile was used as the solvent. An optimized solvent of toluene/acetonitrile (v/v ≈ 1/2) was used for measuring the ESI-MS spectra. The strongest peaks appearing in the range *m*/*z* 1200−1900 are 1637, 1557, 1374, 1819, 1572, and 1505 (Figure 6).

Infrared Spectra. The solid-state infrared spectra (KBr) were recorded on a GALAXY Series FT-IR 6020 spectrophotometer from Mattson Instruments Inc.

Results and Discussion

Octanuclear Structure. The structure of $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$ contains eight copper(II) ions, four monodeprotonated azathioprine$^-$ ligands, ten monodeprotonated THD$^-$ ligands, and two hydroxide anions, assembled to form a centrosymmetric, octanuclear molecule (Figure 2). All THD$^-$ moieties act as chelating ligands, and one of them, in addition, behaves as a bridger between two metal ions.

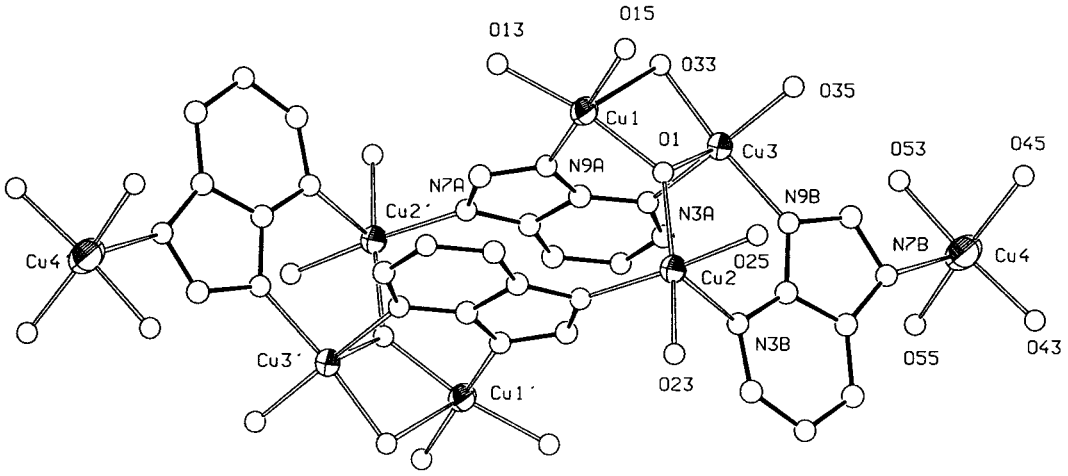

Figure 2. Structure scheme showing the arrangement of the Cu_3OH clusters, their connection to a fourth copper atom, and the centrosymmetric arrangement of the octanuclear molecule.

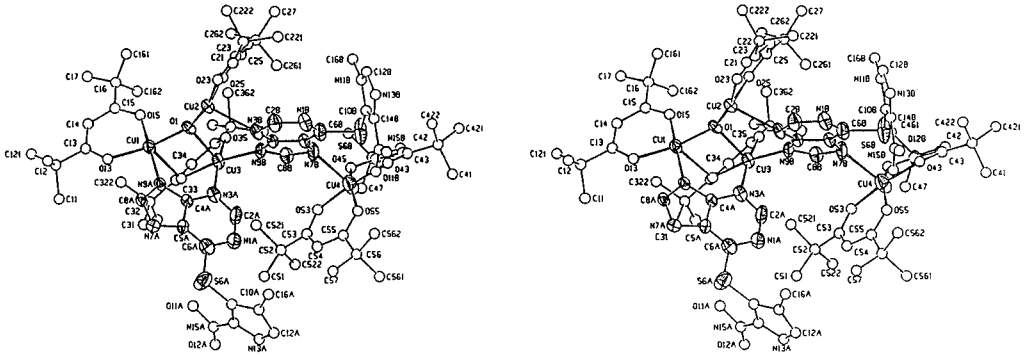

Figure 3. ORTEP stereoview of the tetranuclear subunit of $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$.

The hydrogen atom of the OH^- group within this complex was clearly detectable in a difference Fourier map during the refinement of the X-ray structure and was further confirmed by the finding of a sharp O−H vibration band at 3546 cm^{-1} in the IR spectrum. Two tetranuclear moieties of the molecule are connected by four coordination bonds between copper atoms and the N(3) and N(9) atoms of two different AZA ligands. In each half of the molecule, all four copper atoms are five-coordinated with a square pyramidal geometry. Among them, three are bridged through a μ_3-OH^- group to form a Cu_3OH cluster with Cu−Cu distances of 3.213(2), 3.585(2), and 3.672(2) Å, respectively, while the fourth one is separated from the cluster by a purine base. The Cu−O−Cu bonding angles within the Cu_3OH group range from 99.0(2) to 132.0(3)° and the corresponding angles Cu−O−H from 91(5) to 115(5)°. These values indicate an approximate sp^3 hybridization for the hydroxy oxygen atom. The shortest distance from the fourth copper atom to a copper atom of the Cu_3OH unit is 5.92 Å (Cu(4)−Cu(3), connected through a N(7)−C(8)−N(9) bridge of an AZA ligand) (Figure 3). The range of coordination bond lengths for the basal atoms of the pyramids is 1.904(6)−1.989(5) Å for Cu−O and 1.962(7)−2.061(7) Å for Cu−N, while the range of the bond lengths for the apical positions is 2.281(6)−2.595(6) Å for Cu−O and 2.392(7)−2.568(7) Å for Cu−N. A stereoview of the tetranuclear subunit is presented in Figure 3, and selected bond lengths and angles are given in Table 3.

The square pyramidal coordination polyhedron of all four copper atoms is significantly distorted, as indicated by the corresponding deviations of the interatomic angles X−Cu−Y from the ideal value of 90°: 78.9(2)−114.2(3)° (Cu(1)), 85.9(2)−99.6(2)° (Cu(2)), 86.8(3)−103.1(2)° (Cu(3)), and 85.4(3)−106.0(3)° (Cu(4)). In addition, all four copper atoms are displaced from the least-squares planes through the basal atoms in the direction of the apical coordinating atom by 0.052(3) Å (Cu(1)), 0.163(4) Å (Cu(2)), 0.213(3) Å (Cu(3)), and 0.207(4) Å (Cu(4)).

The structure of a related copper(II) complex using a polynucleating poly(aminophthalazine) ligand (O−P) with two tetranuclear complexes linked by a bidentate nitrate bridge to form an associated octanuclear species was recently reported.[14] In this complex, with the formula $\{[Cu_4(O-P)(\mu_2\text{-}OH)_2(\mu_2\text{-}NO_3)_2(H_2O)_7](\mu_2\text{-}NO_3)\}(NO_3)_7\cdot 6H_2O$, however, the tetranuclear subunits are separated into two dinuclear centers with very large inter-dinuclear copper−copper separations of about 8.8−13.3 Å, whereas in the complex reported here, the tetranuclear subunits exhibit a trinuclear Cu_3OH group separated from the fourth metal atom by about 5.9−9.1 Å. μ_3-OH-bridged Cu_3 clusters have also been established in $[(CuL)_3(OH)](ClO_4)_2$, HL representing the tridentate ligand 8-amino-5-aza-4-methyl-3-octen-2-one,[15] and in $[Cu_3(OH)(pz)_3(py)_3Cl_2]\cdot py$ (Hpz = pyrazole, py = pyridine).[16] In $[(CuL)_3(OH)](ClO_4)_2$, the three copper atoms are bound together by a single, triply bridging hydroxy group and by three different bridging carbonyl oxygen atoms. This arrangement exhibits approximate 3-fold symmetry with copper−copper distances of 3.25, 3.28, and 3.32 Å,

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Table 3. Selected Bond Lengths (Å) and Angles (deg) for $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$

Copper Coordination Polyhedra							
Cu(1)−O(15)	1.904(6)	Cu(2)−O(25)	1.907(6)	Cu(3)−O(35)	1.911(6)	Cu(4)−O(55)	1.910(7)
Cu(1)−O(13)	1.910(6)	Cu(2)−O(23)	1.943(6)	Cu(3)−O(33)	1.929(6)	Cu(4)−O(45)	1.916(7)
Cu(1)−O(1)	1.935(6)	Cu(2)−O(1)	1.989(5)	Cu(3)−N(9B)	1.962(7)	Cu(4)−O(43)	1.919(7)
Cu(1)−N(9A)	1.980(7)	Cu(2)−N(7A)[a]	2.000(7)	Cu(3)−N(3A)	2.061(7)	Cu(4)−O(53)	1.920(7)
Cu(1)−O(33)	2.595(6)	Cu(2)−N(3B)	2.392(7)	Cu(3)−O(1)	2.281(6)	Cu(4)−N(7B)	2.568(7)
Cu_3OH Group							
Cu(1)−O(1)	1.935(6)	Cu(2)−O(1)	1.989(5)	Cu(3)−O(1)	2.281(6)	O(1)−H(1)	0.75(6)
Cu(1)−Cu(2)	3.585(2)	Cu(1)−Cu(3)	3.213(2)	Cu(2)−Cu(3)	3.672(2)		
Cu(1)−O(1)−Cu(2)	132.0(3)	Cu(1)−O(1)−Cu(3)	99.0(2)	Cu(2)−O(1)−Cu(3)	118.5(3)		
Cu(1)−O(1)−H(1)	115(5)	Cu(2)−O(1)−H(1)	91(5)	Cu(3)−O(1)−H(1)	97(5)		
Additional Copper−Copper Distances							
Cu(1)−Cu(1′)	6.45	Cu(1)−Cu(2′)	5.95	Cu(1)−Cu(3′)	6.94	Cu(2)−Cu(2′)	7.41
Cu(2)−Cu(3′)	7.19	Cu(3)−Cu(3′)	8.68	Cu(4)−Cu(1)	9.12	Cu(4)−Cu(2)	8.01
Cu(4)−Cu(3)	5.92	Cu(4)−Cu(4′)	18.31				

	azathioprine ligand		
	molecule A	molecule B	azathioprine·$2H_2O$[7]
C(6)−S(6)	1.769(10)	1.784(10)	1.768(6)
S(6)−C(10)	1.723(10)	1.727(11)	1.737(6)
N(1)−C(2)	1.311(12)	1.340(12)	1.335(6)
C(2)−N(3)	1.338(11)	1.325(11)	1.334(6)
N(3)−C(4)	1.344(10)	1.326(10)	1.336(6)
C(4)−C(5)	1.414(11)	1.391(12)	1.394(6)
C(5)−N(7)	1.369(10)	1.392(11)	1.387(6)
N(7)−C(8)	1.319(10)	1.315(11)	1.312(6)
C(8)−N(9)	1.331(10)	1.381(11)	1.363(6)
N(9)−C(4)	1.387(10)	1.364(10)	1.368(6)
C(5)−C(6)	1.361(13)	1.380(12)	1.378(6)
N(1)−C(6)	1.345(11)	1.346(12)	1.323(6)
C(10)−N(11)	1.373(13)	1.36(2)	1.365(6)
N(11)−C(16)	1.47(2)	1.43(2)	1.475(6)
N(11)−C(12)	1.38(2)	1.37(2)	1.360(6)
C(12)−N(13)	1.27(2)	1.31(2)	1.305(6)
N(13)−C(14)	1.29(2)	1.36(2)	1.353(6)
C(14)−N(15)	1.38(2)	1.46(2)	1.435(6)
N(15)−O(11)	1.25(3)	1.196(14)	1.236(6)
N(15)−O(12)	1.11(2)	1.223(14)	1.217(6)
C(10)−C(14)	1.35(2)	1.38(2)	1.371(6)
C(2)−N(1)-C(6)	117.0(8)	115.6(8)	117.6(3)
C(2)−N(3)-C(4)	113.1(7)	112.5(8)	112.0(3)
C(5)−N(7)-C(8)	105.0(7)	102.7(7)	103.0(3)
C(4)−N(9)-C(8)	103.5(7)	103.2(7)	105.6(3)
C(6)−S(6)-C(10)	101.4(5)	98.7(5)	102.1(3)

[a] Symmetry transformation used to generate equivalent atoms: $-x + 1, -y + 2, -z$.

respectively. The situation in the azathioprine complex described here is less symmetric because, in addition to the triply bridging hydroxy group, the two Cu atoms Cu(1) and Cu(3) (internuclear distance 3.21 Å) are bridged by a common THD oxygen atom and an AZA ligand, whereas Cu(2) and Cu(3) (internuclear distance 3.67 Å) are bridged by an AZA ligand only and Cu(1) and Cu(2) (internuclear distance 3.59 Å) show no bridging additional to that by the μ_3-OH group.

Coordination Sites and Geometry of Azathioprine. Three of the four nitrogen atoms of the purine ring of azathioprine [N(3), N(7), and N(9)] in $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$ bind to copper ions in both crystallographically independent AZA^- anions. The N(1) positions are neither coordinating nor protonated. A partial-double-bond character has been assumed for the C(6)−S(6) bond in the neutral, free AZA ligand[6] and in its dihydrate[7] as well as in its rhodium complex.[9d] Compared with the corresponding distances of about 1.68 Å in 6-mercaptopurine structures[10] with a distinct double-bond character and with 1.81 Å in alkyl mercaptans[17] with a distinct single-bond character, the bond lengths of C(6)−S(6) (1.769(10)/1.784(6) Å) as well as of S(6)−C(10) (1.723(10)/1.727(11) Å) in the two crystallographically independent AZA molecules in $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$ support the assumption of a partial double bond for both C−S bonds.

Bugg and Thewalt[18] have analyzed the influence of substituents of N(6)-substituted adenines on the conformation of these purines. They have found that even relatively small aliphatic groups at the N(6) position tend to point away from the imidazole ring (the N(6)−C(10) bond is trans to the C(5)−C(6) bond). In analogy, S(6)-substituted thiopurines such as, for example, azathioprine are expected to adopt a conformation with a trans arrangement of the bonds C(5)−C(6) and S(6)−C(10) with respect to C(6)−S(6). In fact, such a conformation of azathioprine is found in all the crystal structures of relevant compounds determined up to now. The values listed in Table 4 show that the corresponding dihedral angles between the purine ring and the plane defined by C(6)−S(6)−C(10) lie within the range from 2.5 to 22.7° only. For steric reasons, the

(17) Landolt-Börnstein. *Numerical Data and Functional Relationships in Science and Technology*; Springer-Verlag: Berlin, 1976; New Series, Vol. 7, p 108.
(18) (a) Bugg, C. E.; Thewalt, U. *J. Am. Chem. Soc.* **1970**, *92*, 7441. (b) Bugg, C. E.; Thewalt, U. *Biochim. Biophys. Res. Commun.* **1972**, *46*, 779.

Table 4. Geometrical (Å, deg) and Conformational[a] Analysis of Azathioprine

	C(6)−S(6)	S(6)−C(10)	C(6)−S(6)−C(10)	pur/sulf	pur/imid	sulf/imid	imid/nit
$[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$ (A)	1.769(10)	1.723(10)	101.4(5)	22.7	82.9	76.7	11.6
$[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$ (B)	1.784(10)	1.727(11)	98.7(5)	12.3	77.4	75.2	6.4
$[Rh_2(AZA)_2(\mu\text{-}Ac^-)_4]\cdot 4DMAA$[9a]	1.74(1)	1.72(1)	98.6(6)	2.5	83.8	86.2	2.6
$AZA\cdot 2H_2O$[7]	1.768(6)	1.737(6)	102.1(3)	9.6	66.0	63.2	9.3
AZA[6]	1.77(2)	1.72(2)	100.5(8)	7.9	70.3	63.3	11.5

[a] Dihedral angles (deg) between the least-squares planes defined by the following atoms are given: purine ring (pur) N(1)−C(2)−N(3)−C(4)−C(5)−C(6)−N(7)−C(8)−N(9); sulfur plane (sulf) C(6)−S(6)−C(10); imidazole ring of the nitroimidazole substituent (imid) C(10)−N(11)−C(12)−N(13)−C(14); nitro group (nit) N(15)−O(11)−O(12).

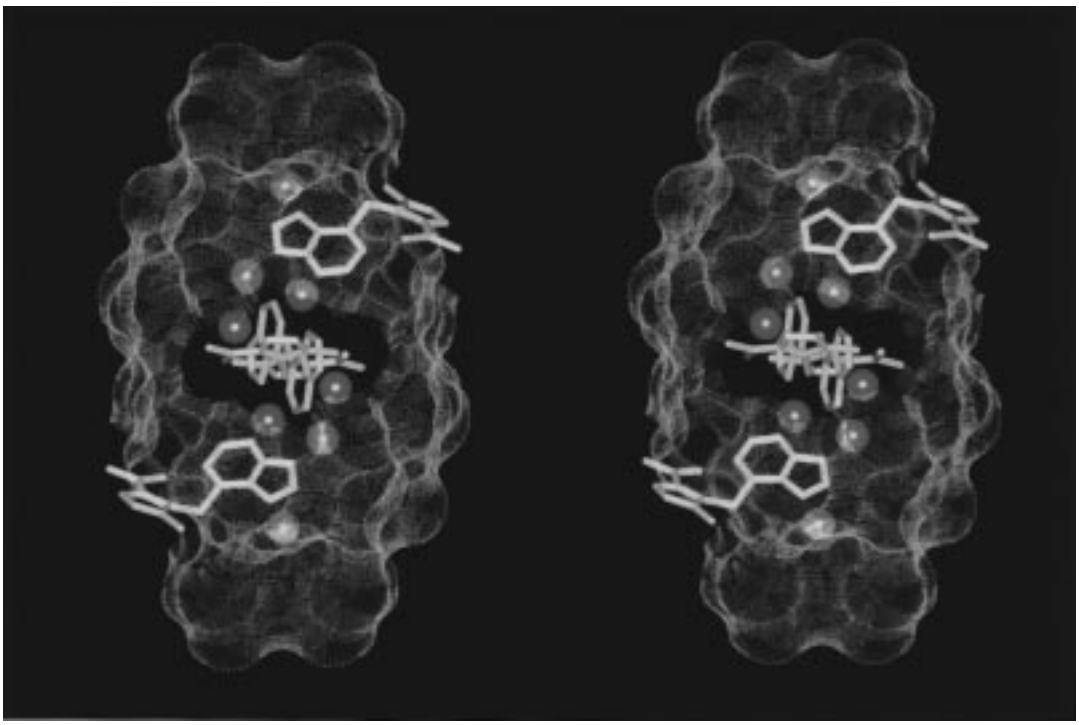

Figure 4. Stereoview of the octanuclear structure. The 6-thiopurine moieties of AZA are completely encapsulated within the octanuclear molecule. Key: red balls, copper; yellow-white sticks, AZA; blue dotted surface, parts of the solvent-accessible surface of the complex molecule originating from all of the components other than AZA (modeling programs CHEM-X[19] and INSIGHT[21]).

imidazole plane of the substituent tends to be approximately perpendicular to the purine plane as demonstrated by the corresponding dihedral angles within the range from 66.0 to 83.8°. The nitro group of azathioprine is almost coplanar with the imidazole ring, as evidenced by the small interplanar angles listed in Table 4.

Embedding of the Purine Moiety. An interesting feature of the octanuclear complex described here is the location of the 6-MP moieties of azathioprine within the molecule. All such moieties are buried inside the complex molecule. In terms of molecular modeling, the solvent-accessible surface of a molecule, that is, the surface which is actually in contact with the environment,[19,20] is formed by rolling a solvent molecule over the structure of interest. For our octanuclear complex molecule, this surface is formed exclusively by the methyl groups of the THD anions, the four nitroimidazoyl groups of the AZA anions, and the two above-mentioned isolated Cu(4) atoms. The solvent-accessible surface of the complex has been generated with the INSIGHT II[21] program and is given in a color stereo picture (Figure 4). In this representation, the contribution of the AZA moieties has been subtracted from such a surface of the whole molecule. It indicates that the 6-MP moieties of the molecule are totally buried inside the assembled cavities with the nitroimidazoyl rings of AZA moieties acting as caps for the cavities.

The surface of such a mixed-ligand polynuclear complex could be modified by changing its building blocks, for example, to make it more hydrophilic. This may be an interesting approach for an "inorganic" modification of a drug by assembling it together with other ligands to form a large metal complex molecule, acting as a prodrug. The drug could be subsequently released from the complex molecule within the biological environment via ligand exchange. A drug generally may be chemically modified to selectively alter properties such as biodistribution, pharmacokinetics, solubility, or antigenicity.[22] The design of molecular containers (hosts), into which small molecules (guests) are encapsulated or embedded mainly via intermolecular forces, is increasingly of interest to synthetic chemists.[23] The host can be a rigid hollow molecule,[24] a highly branched molecule,[25] a dimeric molecular assembly,[26] a mac-

(19) *CHEM-X reference guide*; Chemical Design Ltd.: Oxon, England, 1993.
(20) Conolly, M. J. *Science* **1983**, *221*, 709.
(21) *INSIGHT II user guide*; Biosym Technologies: San Diego, CA, 1993.
(22) Langer, R. *Science* **1990**, *249*, 1527.
(23) Cram, D. J. *Nature* **1992**, *356*, 29.
(24) Ghadiri, M. R. *Adv. Mater.* **1995**, *7*, 675.
(25) Jansen, J. F. G. A.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226.
(26) Meissner, R. S.; Rebek, J., Jr.; de Mendoza, J. *Science* **1995**, *270*, 1485.

rocyclic molecule,[27] or a cleftlike molecule.[28] The complex described here also may be regarded as a host (the polynuclear arrangement connected through the second ligands) with a guest (the purine drug). No other crystallographic result has been obtained so far which demonstrates a complete encapsulation of a purine ring by host molecules, although such types of complete burying phenomena abound in some complexes of proteins with purine derivatives.[29]

Magnetic Data. The arrangement of the paramagnetic copper(II) atoms ($S = {}^1/_2$) in the molecule indicates that different kinds of possible intramolecular magnetic coupling interactions have to be taken into consideration. First, there are magnetic interactions within the Cu_3 clusters mentioned above with Cu atoms bridged by a μ_3-OH^- group and Cu−Cu distances ranging from 3.21 to 3.67 Å. Second, interactions could occur between these two Cu_3 clusters, connected through two AZA molecules with Cu−Cu distances ranging from 5.95 to 8.68 Å. Finally, the magnetic interaction between the Cu_3 cluster and the fourth, isolated Cu atom of the tetranuclear subunit (Cu(4), interconnected with the Cu_3 cluster by a purine moiety with Cu−Cu distances ranging from 5.92 to 9.12 Å) has to be considered.

According to Kahn et al.,[30] the magnetic interaction of square-pyramidal copper(II) centers connected by an aromatic fragment is strongly dependent on the coplanarity of the basal planes around copper(II) with the bridging aromatic plane. To maximize the interaction, the two basal planes around the copper(II) ions must be as coplanar as possible and the apical bond length must be as large as possible. Since in the title complex N(7) and N(3) of the purine moiety connecting Cu(4) to the Cu_3 cluster are coordinating via apical bonds to the corresponding Cu(II) atoms, no such coplanarity can be achieved. The same holds for the three basal planes within the Cu_3 cluster, which are far from being coplanar with the plane of the purine moieties interconnecting the two Cu_3 units. Therefore, the interaction between the Cu_3 cluster and the fourth copper atom Cu(4) as well as that between the two Cu_3 clusters may be neglected compared to the moderately strong antiferromagnetic exchange interaction within the Cu_3 cluster. This assumption is supported by the excellent agreement between experimental and theoretical magnetic data based on this model as desribed below.

Hence, the molar magnetic susceptibility for the complex molecule was regarded as the sum of the independent tetranuclear halves of the molecule. The molar magnetic susceptibility for half of a molecule (χ_M) was further simplified by considering it to be the sum of the susceptibilities of an isolated copper(II) ion and a Cu_3 cluster. Magnetic coupling within a Cu_3 cluster has been reviewed by Gatteschi et al.[16] Assuming C_3 symmetry in the Cu_3 cluster, we have calculated χ_M for one Cu_4 unit from

$$\chi_M = \frac{N\beta^2 g^2}{4kT}\left(1 + \frac{1 + 5e^{3J/kT}}{1 + e^{3J/kT}}\right)$$

where the symbols have the usual meanings. Two optimized parameters ($J = -75$ cm^{-1}, $g = 2.235$) were obtained. The theoretical curves based on these optimized parameters are in perfect agreement with the experimental data points, as shown in Figure 5.

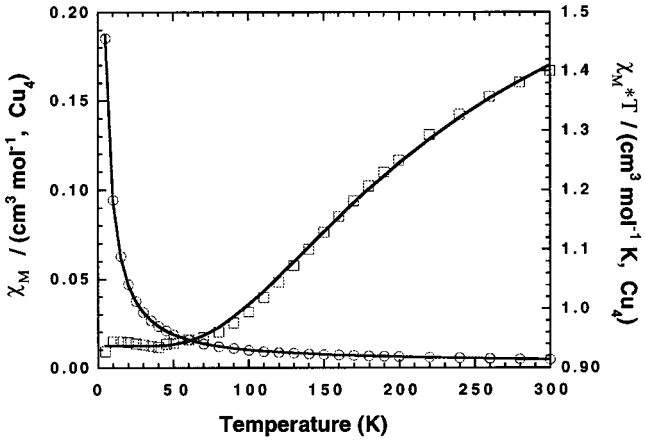

Figure 5. Temperature dependence of the molar magnetic susceptibility χ_M (○) and $\chi_M T$ (□) per Cu_4 unit in $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$. The solid lines are the theoretical fits with $J = -75$ cm^{-1} and $g = 2.235$.

According to Gatteschi et al.,[16] the magnetic coupling within Cu_3O moieties increases with the coplanarity of the square-planar basal coordination planes of the copper atoms, which are five-coordinated with a square-pyramidal geometry. The reported values for the coupling constant J vary from -1000 cm^{-1} in $[\{Cu_3(O)L_3(ClO_4)\}_2]$,[31] with a pronounced coplanarity of the least-squares planes defined by the CuL_4 square-planar coordination (interplanar angles of 27, 20, and 14°; sum of interplanar angles = 61°) down to -15 cm^{-1} in $[Cu_3(OH)L'_3]^{2+}$,[15] with minimal coplanarity (interplanar angles of 83, 86, and 82°; sum of interplanar angles = 251°). In the complex described here, J is -75 cm^{-1} and the corresponding interplanar angles are 60.7° for Cu(1)/Cu(2), 23.7° for Cu(1)/Cu(3), and 40.0° for Cu(2)/Cu(3); the sum of the interplanar angles is 124.4°. These values are in perfect line with the observed exponential decrease of the coupling constants J upon decrease of the coplanarity of the three basal planes of the interconnected square-pyramidal CuL_5 coordination polyhedra in complexes containing a Cu_3O group. The reported values of J from the literature have been modified according the definition used in this paper.

Mass Spectrometric Data. In view of the possible medical significance of the polynuclear metal complex described here or of similar, modified complexes, their solution behavior is of primary interest. Purine metal complexes often have very low solubilities in protic and/or aprotic solvents and in addition may show a tendency to decompose in solution. To check the nature of complexes existing in solutions of $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$, we have used ESI mass spectrometric measurements.

Having a dominating hydrophobic surface, the complex molecule is insoluble in protic solvents, although azathioprine alone is slightly soluble in water, ethanol, and some other solvents. For ESI-MS measurements, the complex was solved in a mixture of toluene and acetonitrile in the ratio 1:2. The absence of the multiply charged molecular ion peaks (m/z) M^{2+} (1740), M^{3+} (1160), and M^{4+} (870) in the spectrum indicates that the octanuclear complex is either unstable in toluene/acetonitrile solution or difficult to ionize. However, although the heaviest building block in the complex molecule is AZA (m/z 277), strong peaks with m/z values of up to 1820 are observed (Figure 6). Being on the surface of the octanuclear

(27) Kickham, J. E., Loeb, S. J.; Murphy, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7031.
(28) Tsao, B. L.; Pieters, R. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 2210.
(29) Noel, J. P.; Hamm, H. E.; Sigler, P. B. *Nature* **1993**, *366*, 654.
(30) Tinti, F.; Verdaguer, M.; Kahn, O.; Savariault, J.-M. *Inorg. Chem.* **1987**, *26*, 2380.
(31) Butcher, R. J.; O'Connor, C. J.; Sinn, E. *Inorg. Chem.* **1981**, *20*, 537.

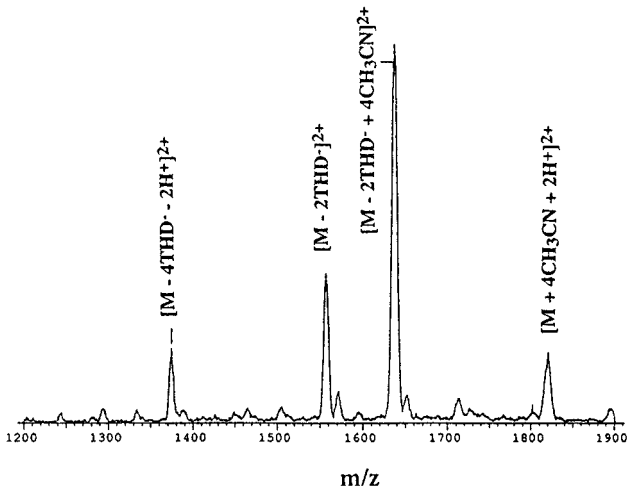

Figure 6. Positive-ion ESI-MS of $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$ in a mixture of toluene and acetonitrile (v/v = 1/2). M represents the octanuclear molecule.

molecule, the two isolated cupric ions Cu(4) and Cu(4′) are exposed to attacks by solvent molecules. As a consequence, ligand exchanges occur between THD^- and acetonitrile molecules, and positively charged particles are formed. One THD^- ligand may be substituted by two CH_3CN molecules, or if THD^- remains monodentately bonded to the metal ion, one additional CH_3CN molecule may be coordinated per THD^- molecule bonded to Cu(4) or Cu(4′). With these assumptions, the two strongest peaks, *m/z* 1637 $[[\{Cu_4(AZA^-)_2(THD^-)_4(CH_3CN)_2(OH^-)\}_2]^{2+}]$ and 1557 $[[\{Cu_4(AZA^-)_2(THD^-)_4(OH^-)\}_2]^{2+}]$, and a series of other strong peaks could be interpreted as the cations resulting from systematic ligand exchanges between THD^- and acetonitrile on the exposed copper ions as follows, *m/z*: 1819, $[M + 4CH_3CN + 2H^+]^{2+}$; 1637, $[M - 2THD^- + 4CH_3CN]^{2+}$; 1572, $[M - 2THD^- + CH_3CN]^{2+}$; 1557, $[M - 2THD^-]^{2+}$; 1505, $[M - 3THD^- + 2CH_3CN + H^+]^{2+}$; 1374, $[M - 4THD^- - 2H^+]^{2+}$.

Therefore, the octanuclear skeleton of the molecule is still present in these cations. Together with the fact that the compound can be recrystallized from acetonitrile, it can be concluded that at least the main skeleton of the octanuclear molecule is still present in solution despite its tendency to decompose.

Summary and Conclusions

In the mixed-ligand copper(II) complex of the immunosuppressant drug azathioprine and 2,2,6,6-tetramethylheptane-3,5-dione, $[\{Cu_4(AZA^-)_2(THD^-)_5(OH^-)\}_2]\cdot 2CH_3CN$, an octanuclear assembling of copper(II) ions, monodeprotonated azathioprine$^-$ ligands, monodeprotonated THD^- ligands, and hydroxide anions is observed. The azathioprine ligands coordinate to copper via three of the four purine nitrogen atoms (N(3), N(7), and N(9)).Three copper atoms are bridged through a μ_3-OH^- group to form a Cu_3OH cluster exhibiting antiferromagnetic coupling, whereas the fourth copper atom is separated from the cluster by a purine base. The magnetic data are in accordance with the observed exponential decrease of the coupling constants *J* upon decrease of the coplanarity of the three relevant basal planes of the interconnected square-pyramidal CuL_5 coordination polyhedra in different complexes containing a Cu_3O group.

ESI-MS measurements show that at least the main part of the octanuclear structure is preserved upon solution of the complex in a mixture of toluene and acetonitrile.

This is the first crystallographic evidence of a purine moiety being encapsulated within a chemically synthesized molecule or a guest−host complex. The embedding of purine moieties within the framework of a polynuclear mixed-ligand metal complex molecule could represent a new method to alter biological properties (pharmacokinetics, solubility) of purine drugs.

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Supporting Information Available: Listings of interatomic bond lengths and bond angles (6 pages). Ordering Information is given on any current masthead page.

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