Pyrazolylborate−Zinc Complexes of RNA Precursors and Analogues Thereof

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The Tp* ligand tris(3-cumenyl-5-methylpyrazolyl)borate was found to stabilize zinc complexes of nucleobases, of their natural precursors, and of nucleoside and nucleotide derivatives. Dihydroorotic acid and orotic acid are bound as monodentate carboxylate ligands. Uracil is coordinated via its deprotonated N1; 6-methylthiouracil acts as a bidentate ligand via N1 and S. Analogously, xanthine is a monodentate ligand bound by its deprotonated N7, while 6-mercaptopurine seems to bind in a bidentate fashion via N7 and S. Spectroscopic evidence indicates coordination of uridine and 2′,3′-*O*-isopropylideneuridine via their deprotonated N3, as well as of xanthosine via N7. The hydrolytic cleavage of 2′,3′-*O*-isopropylideneuridine 5′-(bis(*p*-nitrophenyl) phosphate) by Tp*Zn−OH is preceded by an attachment of one Tp*Zn unit to the deprotonated uracil base, presumably via N3.

Introduction

Metal coordination of nucleobases, their precursors, and their derivatives and of nucleosides and nucleotides is a very active area of research, motivated by the importance of platinum anticancer drugs as well as by the involvement of many metal-containing enzymes in gene-related processes.[1−6] Activities of inorganic chemists in the field span the whole range from solution equilibrium studies of purine base−metal complexes to the chemical modification of specific genes.

Among the metal ions probed for such purposes, zinc plays a less important role,[1,2,7] despite its presence in various enzymes along the biosynthetic pathways of the nucleobases or for phosphate transfers during nucleotide interconversions.[5,8,9] Significant contributions to the zinc complex chemistry of nucleobases, nucleosides, sugar-derived phosphates, and nucleotides have been made by the research groups of Marzilli,[10] Sigel,[5,11] Dubler,[12] and more recently Lippert[13] and Kimura,[14] among others.[15]

We became attracted to the nucleobases and their derivatives through our studies of zinc complexes of drug substances, some of which are derivatives of the nucleobases.[16−20] During these studies it became obvious that the deprotonation of mildly acidic ($pK_a > 9$) NH functions is facilitated in the presence of zinc ions and that encapsulation of zinc by sterically demanding tripodal ligands facilitates complexation of the corresponding anionic species. Specifically the cumenyl-substituted pyrazolylborate ligand $Tp^{Cum,Me}$ [21] (hereafter abbreviated as Tp*; $Tp^{Cum,Me}$ = tris(3-cumenyl-5-methylpyrazolyl)borate, cumenyl = 4-isopropylphenyl; see figures below) was found to stabilize a wide range of monoanionic species X by protecting them in the hydrophobic pocket of the neutral complexes Tp*Zn−X.[19,21,22]

This paper describes the results of a survey aimed at testing the coordinative properties of nucleobase precursors, nucleobases, and nucleoside and nucleotide analogues toward zinc in the Tp*Zn environment. The chemical species employed were those which relate to the base constituents of the RNAs. The goal of the study was to gain basic knowledge by isolating complexes and gathering structural information. It is hoped that this knowledge will allow further studies related to molecular recognition, drug targeting, and metal complex−DNA or −RNA interactions.

Experimental Section

All experimental techniques and the standard IR and NMR equipment were as described previously.[23] Starting materials were obtained commercially. The complex $Tp^{Cum,Me}$Zn−OH (Tp*Zn−OH) was prepared according to the published procedure.[21]

Tp*Zn−Dihydroorotate. A solution of Tp*Zn−OH (200 mg, 0.29 mmol) in 30 mL of dichloromethane was treated with a solution of L-dihydroorotic acid (DHOroH, 46 mg, 0.29 mmol) in 20 mL of methanol. After 2 h of stirring, the volume of the solution was reduced

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to 25 mL in vacuo. The resulting colorless precipitate was filtered off and dried in vacuo. Recrystallization from benzene yielded 196 mg (82%) of Tp*Zn−DHOro, colorless crystals, mp 230 °C dec. IR (KBr, cm^{-1}): 3409m (NH), 2547m (BH), 1700s, 1663s, 1372s (CO). ^{1}H-NMR ($CDCl_3$, δ): 1.24 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 2.05 [dd, ^3J = 13.4 Hz, ^2J = 17.1 Hz, 1H, CH_2 (DHOro)], 2.53 [s, 9H, Me (pz)], 2.57 [dd, ^3J = 4.5 Hz, ^2J = 17.1 Hz, 1H, CH_2 (DHOro)], 2.89 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 3.41 [dd, ^3J = 4.5 Hz, ^2J = 13.1 Hz, 1H, O_2CC*H* (DHOro)], 5.48 [s, 1H, N*H* (DHOro)], 6.18 [s, 3H, H (pz)], 7.21 [d, ^3J = 8.2 Hz, 6H, Ph(3,5)], 7.45 [d, ^3J = 8.2 Hz, 6H, Ph(2,6)]. Anal. Calc for $C_{44}H_{51}BN_8O_4Zn$ (M_r = 832.1): C, 63.51; H, 6.18; N, 13.47. Found: C, 64.34; H, 6.50; N, 12.73.

Tp*Zn−Orotate. Orotic acid (50 mg, 0.29 mmol) dissolved in 50 mL of hot methanol was added to a solution of Tp*Zn−OH (OroH, 200 mg, 0.29 mmol) in 30 mL of dichloromethane. After 15 h of stirring, a colorless precipitate formed, which was filtered off and washed with a few milliliters of hot methanol. A 188 mg amount (78%) of Tp*Zn−Oro remained as a colorless powder, mp >250 °C dec. Attempts at crystallizing the compound failed due to its low solubility in most solvents. IR (KBr, cm^{-1}): 3382m (NH), 2550m (BH), 1688s, 1640s, 1380s (CO). ^{1}H-NMR (DMSO-d_6, δ): 1.21 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 2,24 [s, 9H, Me (pz)], 2.89 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 5.88 [s, 1H, N*H* (Oro)], 6.37 [s, 3H, H (pz)], 6.49 [s, 1H, C*H* (Oro)], 7.24 [d, ^3J = 8.2 Hz, 6H, Ph(3,5)], 7.64 [d, ^3J = 8.2 Hz, 6H, Ph(2,6)], 10.39 [s, 1H, N*H* (Oro)]. Anal. Calc for $C_{44}H_{49}BN_8O_4Zn$ (M_r = 830.1): C, 63.66; H, 5.95; N, 13.50. Found: C, 63.02; H, 5.83; N, 14.20.

Tp*Zn−Uracilate. A suspension of uracil (UraH, 32 mg, 0.29 mmol) in 20 mL of methanol was added to a solution of Tp*Zn−OH (200 mg, 0.29 mmol) in 30 mL of dichloromethane. After 3 h of stirring, a clear solution formed. Slow evaporation of the solvent produced a microcrystalline precipitate, which was filtered off, washed with 10 mL of methanol, and dried in an oil pump vacuum. Yield: 223 mg (91%) of colorless Tp*Zn−Ura·2CH_3OH, mp 234 °C. IR (KBr, cm^{-1}): 3129m (NH), 2550m (BH), 1713s, 1683s (CO). ^{1}H-NMR ($CDCl_3$; δ): 1.23 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 2.55 [s, 9H, Me (pz)], 2.89 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 5.01 [d, ^3J = 7.2 Hz, 1H, C*H* (Ura)], 5.49 [d, ^3J = 7.2 Hz, 1H, C*H* (Ura)], 6.17 [s, 3H, H (pz)], 6.48 [s, 1H, N*H* (Ura)], 7.17 [d, ^3J = 8.2 Hz, 6H, Ph(3,5)], 7.35 [d, ^3J = 8.2 Hz, 6H, Ph(2,6)]. Anal. Calc for $C_{43}H_{49}BN_8O_2Zn$ (M_r = 786.1): C, 65.70; H, 6.28; N, 14.25. Found: C, 65.31; H, 6.30; N, 13.10.

Tp*Zn−6-Methyl-2-thiouracilate. A suspension of 6-methyl-2-thiouracil (TuraH, 41 mg, 0.29 mmol) in 20 mL of methanol was added to a solution of Tp*Zn−OH (200 mg, 0.29 mmol) in 30 mL of dichloromethane. After 5 h of stirring, a clear solution formed. The volume of the solution was reduced to 25 mL in vacuo. Within 4 h, colorless crystals of Tp*Zn−Tura, mp 183 °C, formed, which were filtered off and dried in vacuo. Yield: 210 mg (89%). IR (KBr, cm^{-1}): 3415m (NH), 2524m (BH), 1651s (CO). ^{1}H-NMR ($CDCl_3$, δ): 0.76 [s, 3H, Me (Tura)], 1.20 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 2.56 [s, 9H, Me (pz)], 2.84 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 4.78 [s, 1H, C*H* (Tura)], 6.14 [s, 3H, H (pz)], 7.12 [d, ^3J = 8.2 Hz, 6H, Ph(3,5)], 7.50 [d, ^3J = 8.2 Hz, 6H, Ph(2,6)], 8.46 [s, 1H, N*H* (Tura)]. Anal. Calc for $C_{44}H_{51}BN_8OSZn$ (M_r = 816.2): C, 64.75; H, 6.30; N, 13.73. Found: C, 63.82; H, 6.29; N 13.47.

Tp*Zn−Xanthinate. A solution of xanthine (XanH, 44 mg, 0.29 mmol) in 20 mL of methanol was added to a solution of Tp*Zn−OH (200 mg, 0.29 mmol) in 30 mL of dichloromethane. After 2 h of stirring, the volume of the solution was reduced to 25 mL in vacuo. After the mixture was cooled to 4 °C for 1 day, colorless crystals of Tp*Zn−Xan·2.5CH_3OH formed, which were filtered off and dried in an oil pump vacuum, upon which they lost all solvent. Yield: 197 mg (77%) of colorless powder, mp 211 °C. IR (KBr, cm^{-1}): 3427m (NH), 2546m (BH), 1693s (CO). ^{1}H-NMR ($CDCl_3$, δ): 1.18 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 2.56 [s, 9H, Me (pz)], 2.83 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 6.06 [s, 1H, C*H* (Xan)], 6.15 [s, 3H, H (pz)], 6.56 [s, 1H, N*H* (Xan)], 6.99 [d, ^3J = 8.2 Hz, 6H, Ph(3,5)], 7.22 [d, ^3J = 8.2 Hz, 6H, Ph(2,6)], 8.38 [s, 1H, N*H* (Xan)]. Anal. Calc for $C_{44}H_{49}BN_{10}O_2Zn$ (M_r = 826.1): C, 63.96; H, 5.98; N, 16.95. Found: C, 63.55; H, 5.96; N, 15.71.

Tp*Zn−Mercaptopurinate. A solution of 6-mercaptopurine (MerH, 49 mg, 0.29 mmol) in 20 mL of methanol was added to a solution of Tp*Zn−OH (200 mg, 0.29 mmol) in 30 mL of dichloromethane. After 2 h of stirring, the volume was reduced to 25 mL in vacuo. Within a few minutes, a microcrystalline precipitate of Tp*Zn−Mer·CH_3OH appeared, which was filtered off, washed with 10 mL of methanol, and dried in vacuo. Yield: 190 mg (80%). Mp: 215 °C. IR (KBr, cm^{-1}): 3418m (NH), 2537m (BH). ^{1}H-NMR ($CDCl_3$, δ): 0.96 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 2.59 [s, 9H, Me (pz)], 2.59 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 6.14 [s, 3H, H (pz)], 6.90 [d, ^3J = 8.2 Hz, 7H, Ph(3,5) and C*H* (Mer)], 7.45 [d, ^3J = 8.2 Hz, 7H, Ph(2,6) and C*H* (Mer)]. Anal. Calc for $C_{44}H_{49}BN_{10}SZn$·CH_3OH (M_r = 826.2 + 32.0): C, 62.98; H, 6.22; N, 16.32. Found: C, 62.51; H, 5.86; N, 16.16.

Tp*Zn−Uridinate. A solution of Tp*Zn−OH (200 mg, 0.29 mmol) in 30 mL of dichloromethane was treated with a solution of uridine (UrdH, 71 mg, 0.29 mmol) in 20 mL of methanol. After 2 h of stirring, all solvent was removed in vacuo. The residue was redissolved in a minimum amount of boiling cyclohexane. Upon cooling, 220 mg (83%) of Tp*Zn−Urd was precipitated as colorless, asbestos-like crystals, mp 183 °C, which where filtered off and dried in vacuo. IR (KBr, cm^{-1}): 3413s (OH), 2543m (BH), 1638s, 1582s (CO). ^{1}H-NMR ($CDCl_3$, δ): 1.21 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 1.60 [s, 3H, O*H* (Rib)], 2.52 [s, 9H, Me (pz)], 2.85 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 3.50−3.80 [m, 2H, C5′H_2 (Rib)], 3.95 [m, 2H, C2′*H* and C3′*H* (Rib)], 4.31 [m, 1H, C4′*H* (Rib)], 4.58 [d, ^3J = 3.5 Hz, 1H, C1′*H* (Rib)], 5.18 [d, ^3J = 7.8 Hz, 1H, C*H* (Urd)], 6.15 [s, 3H, H (pz)], 7.03 [d, ^3J = 7.8 Hz, 1H, C*H* (Urd)], 7.11 [d, ^3J = 8.2 Hz, 6H, Ph(3,5)], 7.46 [d, ^3J = 8.2 Hz, 6H, Ph(2,6)]. Anal. Calc for $C_{48}H_{57}BN_8O_6Zn$ (M_r = 918.2): C, 62.79; H, 6.26; N, 12.20. Found: C, 62.89; H, 6.51; N, 11.18.

Tp*Zn−2′,3′-*O*-Isopropylideneuridinate. A solution of Tp*Zn−OH (200 mg, 0.29 mmol) in 30 mL of dichloromethane was treated with a solution of 2′,3′-*O*-isopropylideneuridine[24] (iUrdH, 82 mg, 0.29 mmol) in 20 mL of methanol. Workup as before yielded 156 mg (56%) of Tp*Zn−iUrd as colorless, asbestos-like crystals, mp 182 °C. IR (KBr, cm^{-1}): 2542m (BH), 1671s, 1646s, 1595s (CO). ^{1}H-NMR ($CDCl_3$, δ): 1.21 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 1.32 [s, 3H, Me (Rib)], 2.52 [s, 9H, Me (pz)], 2.86 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 3.36−3.57 [m, 2H, C5′H_2 (Rib)], 4.01 [m, 1H, C3′*H* (Rib)], 4.25 [m, 1H, C2′*H* (Rib)], 4.63−4.68 [m, 1H, C4′*H* (Rib)], 4.70 [m, 1H, C1′*H* (Rib)], 5.15 [d, ^3J = 7.9 Hz, 1H, C*H* (Urd)], 6.13 [s, 3H, H (pz)], 6.65 [d, ^3J = 7.9 Hz, 1H, C*H* (Urd)], 7.11 [d, ^3J = 8.2 Hz, 6H, Ph(3,5)], 7.44 [d, ^3J = 8.2 Hz, 6H, Ph(2,6)]. Anal. Calc for $C_{51}H_{61}BN_8O_6Zn$ (M_r = 958.3): C, 63.92; H, 6.42; N, 11.69. Found: C, 62.90; H, 6.51; N, 11.35.

Tp*Zn−Xanthosinate. A solution of Tp*Zn−OH (200 mg, 0.29 mmol) in 30 mL of dichloromethane was treated with a solution of xanthosine (XaoH, 93 mg, 0.29 mmol) in 20 mL of methanol. Workup as before yielded from the cyclohexane solution after 3 d 168 mg (61%) of Tp*Zn−Xao as a colorless powder, mp 192 °C. IR (KBr, cm^{-1}): 3420s (OH), 2545m (BH), 1681s, 1621s (CO). ^{1}H-NMR (DMSO-d_6, δ): 1.23 [d, ^3J = 6.9 Hz, 18H, Me (*i*-Pr)], 2.53 [s, 9H, Me (pz)], 2.81 [spt, ^3J = 6.9 Hz, 3H, H (*i*-Pr)], 3.41−3.63 [m, 2H, C5′H_2 (Rib)], 3.70 [m, 1H, C4′*H* (Rib)], 3.95 [m, 2H, C2′*H* and C3′*H* (Rib)], 4.99 [d, ^3J = 4.3 Hz, 1H, C1′*H* (Rib)], 6.40 [s, 4H, H (pz) and C*H* (Xan)], 7.19 [d, ^3J = 8.2 Hz, 6H, Ph(3,5)], 7.51 [d, ^3J = 8.2 Hz, 6H, Ph(2,6)], 10.27 [s, 1H, N*H* (Xan)]. Anal. Calc for $C_{49}H_{57}BN_{10}O_6Zn$ (M_r = 958.2): C, 61.42; H, 6.00; N, 14.62. Found: C, 61.60; H, 5.85; N, 13.88.

Tp*Zn−2′,3′-*O*-Isopropylideneuridinate 5′-(Bis(*p*-nitrophenyl) phosphate). A solution of Tp*Zn−OH (500 mg, 0.77 mmol) and 2′,3′-*O*-isopropylideneuridine 5′-(bis(*p*-nitrophenyl) phosphate) (iUmpH; prepared according to the procedures of Pfleiderer and Ukita;[25] 438 mg, 0.77 mmol) in 40 mL of dichloromethane was stirred for 30 min. After filtration, all volatiles were removed in an oil pump vacuum. An 890 mg amount (96%) of Tp*Zn−iUmp remained as a colorless powder, mp 97 °C. IR (KBr, cm^{-1}): 2546m (BH), 1673m, 1649s, 1616s (CO). ^{1}H-NMR ($CDCl_3$, δ): 1.21 [d, ^3J = 6.8 Hz, 18H, Me (*i*-Pr)], 1.28 [s, 3H, Me (Rib)], 1.39 [s, 3H, Me (Rib)], 2.51 [s, 9H, Me (pz)], 2.86 [spt, ^3J = 6.8 Hz, 3H, H (*i*-Pr)], 3.84 [m, ^3J = 7.6 Hz, 2H, C5′H_2 (Rib)], 3.99 [m, ^3J = 3 Hz, 1H, C4′*H* (Rib)], 3.99 [m, ^3J = 3 Hz, 1H, C2′*H* (Rib)], 4.34 [dd, ^3J = 3.0 Hz, ^3J = 3.0 Hz, 1H, C3′*H* (Rib)], 4.86 [s, 1H, C1′*H* (Rib)], 5.16 [d, ^3J = 7.6 Hz, 1H, C*H* (Urd)],

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Table 1. Crystallographic Details[a]

	Tp*Zn−DHoro	Tp*Zn−Ura	Tp*Zn−Tura	Tp*Zn−Xan
formula	$C_{44}H_{51}BN_8O_4Zn\cdot C_6H_6$	$C_{43}H_{49}BN_8O_2Zn$	$C_{44}H_{51}BN_8OSZn$	$C_{44}H_{49}BN_{10}O_2Zn\cdot 2.5MeOH$
M_r	910.22	786.11	816.19	906.23
color	colorless	colorless	colorless	colorless
crystal size (mm)	0.6 × 0.3 × 0.3	0.5 × 0.5 × 0.4	0.6 × 0.6 × 0.6	0.5 × 0.5 × 0.5
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
Z	2	2	2	2
a (Å)	10.709(2)	13.059(1)	12.418(1)	11.434(2)
b (Å)	15.043(1)	13.658(1)	13.985(1)	14.179(3)
c (Å)	17.205(2)	13.970(1)	14.962(2)	15.399(3)
α (deg)	69.34(1)	93.62(1)	111.43(1)	84.40(3)
β (deg)	87.56(1)	110.38(1)	111.19(1)	71.16(3)
γ (deg)	71.02(1)	114.76(1)	97.30(1)	80.96(3)
V (Å^3)	2444.2(6)	2056.1(3)	2152.3(4)	2330.5(8)
d_{calc} (g/cm^3)	1.24	1.27	1.26	1.29
d_{obs} (g/cm^3)	1.20	1.23	1.22	1.25
μ (mm^{-1})	0.55	0.64	0.66	0.58
2θ range	5−52	5−43	5−52	6−46
hkl ranges	*h*: −13 to +13	*h*: −13 to +11	*h*: −15 to +14	*h*: −12 to +13
	k: −17 to +18	*k*: 0 to +13	*k*: −17 to +16	*k*: −16 to 0
	l: 0 to +21	*l*: −12 to +14	*l*: 0 to +18	*l*: −18 to +17
no. of reflns measd	9900	4186	8801	6787
no. of indep reflns	9563	3987	8459	6478
no. of obsd reflns (I≥2σ(I))	5445	3461	4454	2591
no. of parameters	583	496	505	574
R_1(obs reflns)	0.062	0.029	0.047	0.084
wR_2(all reflns)	0.221	0.082	0.130	0.388
res el density (e/Å^3)	+0.4, −0.4	+0.3, −0.1	+0.3, −0.4	+0.6, −0.8

[a] $R_1 = \sum|F_o - F_c|/\sum F_o$, w$R_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

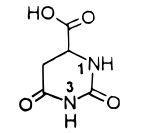
6.13 [s, 3H, H (pz)], 6.65 [d, ^3J = 7.6 Hz, 1H, C*H* (Urd)], 7.11 [d, ^3J = 8.1 Hz, 6H, Cum(3,5)], 7.21 [d, ^3J = 10.6 Hz, 2H, C*H* (Nit(3,5))], 7.23 [d, ^3J = 10.6 Hz, 2H, C*H* (Nit(3,5))], 7.45 [d, ^3J = 8.1 Hz, 6H, Cum(2,6)], 8.06 [d, ^3J = 10.6 Hz, 4H, C*H* (Nit(2,6))]. ^{31}P-NMR ($CDCl_3$, δ): −14.36 [t, ^3J = 7.6 Hz]. Anal. Calc for $C_{63}H_{68}BN_{10}O_{13}PZn$ (M_r = 1280.5): C, 59.10; H, 5.35; N, 10.94; Zn, 5.11. Found: C, 58.70; H, 5.33; N, 11.01; Zn, 5.01.

Structure Determinations. Crystals of Tp*Zn−DHOro and Tp*Zn−Ura were obtained from benzene; those of Tp*Zn−Tura and Tp*Zn−Xan resulted from the reaction mixtures. The crystals of Tp*Zn−DHOro contain one formula unit of benzene; those of Tp*Zn−Xan contain 2.5 formula units of methanol. In both cases, the cocrystallized solvent was easily lost upon exposure to air, causing the crystals to crumble. For this reason, the data set of Tp*Zn−Xan was obtained on a sample sealed in a capillary in the presence of methanol. Diffraction data were recorded at room temperature with the $\omega/2\theta$ technique on a Nonius CAD4 diffractometer fitted with a molybdenum tube (Kα, λ = 0.7107 Å) and a graphite monochromator. The structures were solved with direct methods and refined anisotropically with the SHELX program suite.[26] Hydrogen atoms were included with fixed distances and isotropic temperature factors 1.2 times those of their attached atoms (1.5 times in methyl groups). Parameters were refined against F^2. The R values are defined as $R_1 = \sum|F_o - F_c|/\sum F_o$ and w$R_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$. Drawings were produced with SCHAKAL.[27] Table 1 lists the crystallographic data.

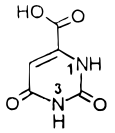
Results and Discussion

When generated by *de novo* biosynthesis, the pyrimidine nucleotides originate from amino acids via heterocyclic carboxylic acids. Attachment of the ribose and phosphate units and decarboxylation lead to uridine monophosphate, which is the precursor of the other pyrimidine nucleotides.[28] Zinc enzymes are involved in several steps of this sequence,[8,9,29−31] including the formation of oligonucleotides and polymerase activity.[5,8,32,33] Furthermore, metal complexes of many of the species along this line, including zinc complexes, have been found to act as drugs.[3,12,34] It therefore seems justified to gather information on the complexes involved in terms of metal−ligand interactions.

Dihydroorotic Acid and Orotic Acid. Biochemically, dihydroorotate is formed from *N*-carbamyl-L-aspartate by the zinc enzyme dihydroorotase.[35,36] It is converted by another metal enzyme (iron-containing dihydroorotate dehydrogenase) to orotate.[37] It has long been known that orotic acid has drug properties.[38] Accordingly, zinc complexes of dihydroorotate[39] and orotate[18,40−42] have been studied by others and ourselves, and several crystal structures have been reported.



dihydroorotic acid
DHOroH



orotic acid
OroH

We found both the dihydroorotate and the orotate complexes of the Tp*Zn unit (Tp* = Tp^{Cum,Me} = tris(3-cumenyl-5-methyl-

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(39) Hambley, T. W.; Christopherson, R. I.; Zvargulis, E. S. *Inorg. Chem.* **1995**, *34*, 6550−6552.

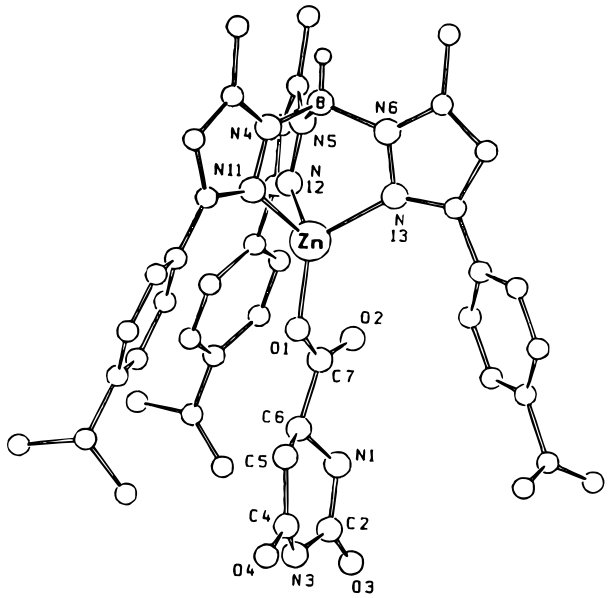
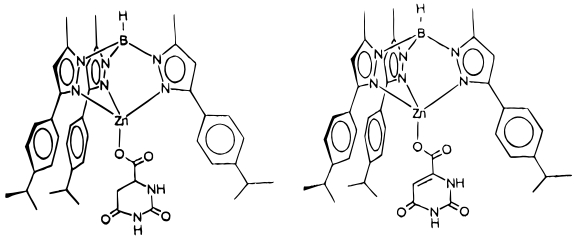


Figure 1. Molecular structure of Tp*Zn−DHOro. Selected bond distances (Å) and angles (deg): Zn−O1 1.894(4), Zn−N11 2.028(4), Zn−N12 2.019(4), Zn−N13 2.036(5), O1−C7 1.296(7), C7−O2 1.202(7), Zn···O2 2.897(5); O1−Zn−N11 115.5(2), O1−Zn−N12 127.1(2), O1−Zn−N13 124.2(2), Zn−O1−C7 115.7(4).

pyrazolyl)borate, cumenyl = 4-isopropylphenyl; see figures below) easy to prepare by reactions of Tp*Zn−OH with the acids. The constitution of the complexes is evident from the NMR data (see Experimental Section), which exhibit the typical high-field shifts of the signals of the coligands due to their embedding between the aromatic cumenyl groups.[21] The IR spectra for both complexes are quite similar. Specifically, the position and spread of the bands due to the carboxylate groups[43,44] (1700 and 1372 cm^{-1} for Tp*Zn−DHOro, 1688 and 1380 cm^{-1} for Tp*Zn−Oro) identify dihydroorotate and orotate as monodentate carboxylate ligands.

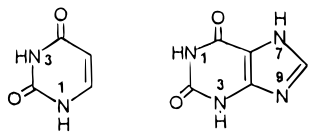


For Tp*Zn−DHOro, the coordination derived from the spectra was confirmed by a structure determination; see Figure 1. Suitable crystals of Tp*Zn−Oro could not be obtained, but it is to be assumed that the bonding pattern is the same in both compounds. Specifically, a bidentate coordination of orotate involving a five-membered chelate ring with participation of the ureido N atom, as observed in the simple complexes $(Oro)Zn(NH_3)_3$[41] and $(Oro)Zn(H_2O)_4$,[42] seems impossible, as this would require further deprotonation of the orotate, necessitating the presence of an additional counterion in the isolated Tp*Zn−Oro compound. The structure determination of Tp*Zn−DHOro was cumbersome because the molecule is asymmetric, but the crystal data (*E* statistics, intensities of Friedel pairs) are centrosymmetric. In order to solve the structure, pseudocentrosymmetry was assumed, resulting from disorder caused by a 180° rotation around the C6−C7 bond. This disorder makes C5 and N1 indistinguishable and all atoms of the six-membered ring ill-defined, requiring split positions for C4 and O4, while the rest of the molecule is not affected.

The bond distances and angles around zinc are typical for TpZn−carboxylate complexes, including the characteristic distortion of the tetrahedral symmetry due to the orientation of the carboxylate ligand.[45] The encapsulation of the dihydroorotate inside the Tp* ligands forces the second carboxylate O atom into the vicinity of zinc, yet at a nonbonding distance of ca. 2.9 Å. Thus Tp*Zn−DHOro shares the monodentate carboxylate coordination with the only other structurally investigated zinc dihydroorotate complex, $Zn(DHOro)_2(H_2O)_2$, which, however, has carboxylate bridges between zinc ions.[39] The orientations and shapes of the nonplanar heterocycle attached to the carboxylate carbon are similar in both complexes.

The attachment of dihydroorotate and orotate to zinc in these and the other reported complexes is as expected; i.e., zinc is closest to the location of the negative charge of the heterocyclic carboxylate. The ligating carboxylate group is the one that is left after the other one of *N*-carbamyl-L-aspartate has undergone zinc-catalyzed amide formation during formation of dihydroorotate.[30] Thus the structures of zinc dihydroorotate and zinc orotate complexes cannot yield mechanistic information related to the enzyme dihydroorotase. However, they complement the accumulating body of evidence[45] that zinc enzyme catalyzed interconversions of carboxylates start with monodentate rather than the often depicted[39] bidentate carboxylate coordination.

Uracil and Xanthine. The nucleobase uracil follows orotic acid in its *de novo* biosynthesis. It is not known whether a zinc enzyme participates in this process. However, xanthine is formed from guanine by the enzyme guanine deaminase,[46] which probably contains an active center comprosed of a tetrahedral $(His,Cys)_3Zn−OH$ unit, just like the related hydrolases adenosine deaminase[47] and cytidine deaminase.[31] It was therefore of interest to discover how zinc coordinates to the nucleobases themselves.



While we could not produce zinc complexes by reacting adenine and guanine with Tp*Zn−OH, the reactions with uracil and xanthine were successful. By deprotonation of the heteroaromatic NH functions the Zn−N coordinated complexes, Tp*Zn−Ura and Tp*Zn−Xan were formed. The compositions of the complexes could be derived from their spectra (see Experimental Section). The coordination modes were found by the structure determinations (see below). Uracil is bound to zinc via N1; xanthine, via N7. In both cases, this cannot be directly related to the acid−base properties of the corresponding NH functions: while the monoanion of uracil exists as a 1:1

(40) Karipides, A.; Thomas, B. *Acta Crystallogr., Sect. C* **1986**, *42*, 1705−1707.
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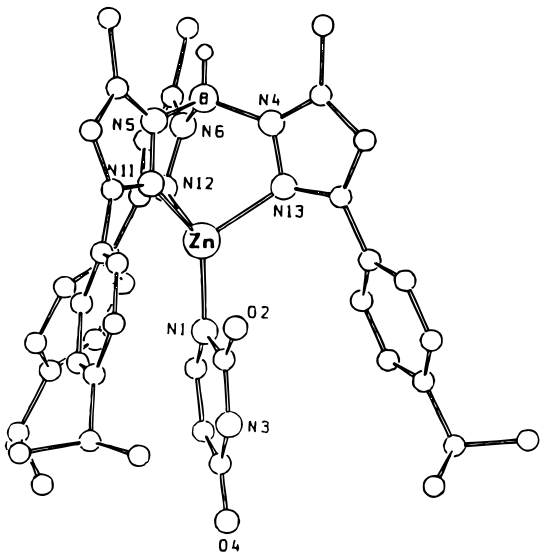
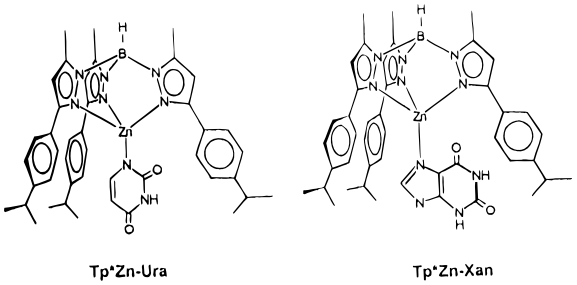


Figure 2. Molecular structure of Tp*Zn−Ura. Selected bond distances (Å): Zn−N1 1.940(2), Zn−N11 2.031(3), Zn−N12 2.096(2), Zn−N13 2.035(2).

tautomeric mixture of the N1- and N3-deprotonated species, the most acidic NH function of xanthine is located at N1.[48] Thus a more favorable steric disposition around the zinc ion or the involvent of the "acidic" hydrogen atoms in hydrogen bonding (see below) may be invoked to explain the observed coordination. Similar observations have been made for uracil and xanthine complexes of other metals,[5,48,49] and a slight preference of metal ion binding to N7 rather than to N1 of purine nucleobases has also been observed for the corresponding nucleosides.[5,50]



The molecular structure of Tp*Zn−Ura (Figure 2) displays a reasonably symmetrical ZnN_4 coordination. The Zn−N7 distance is typically shorter than the other three Zn−N distances, as in all TpZn−X complexes. The closest known analogue of Tp*Zn−Ura is the cationic complex [Tp*Zn−2-methylimidazole]$^+$,[51] resembling it in all geometrical details. The uracilate ligand is planar (average deviation from the common plane ±0.01 Å). We are not aware of a structure determination of any other reported zinc−uracil complex. However, the Zn−N3 distances in zinc complexes of 1-methylcytosine[13,52] and cytidine 5′-phosphate[10c] (2.00−2.07 Å) are considerably longer than Zn−N1 in Tp*Zn−Ura. Metal-(uracilate-N1) coordination is observed in a square planar platinum complex[53] and an octahedral nickel complex,[54] while both N1 and N3 of uracilate were found to coordinate to platinum in a Pt−uracilate tetramer.[55]

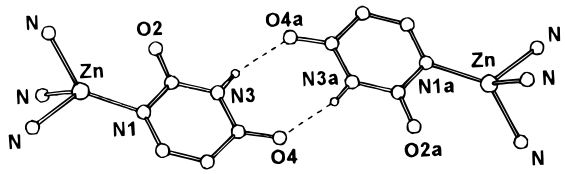


Figure 3. Base pairing of Tp*Zn−Ura.

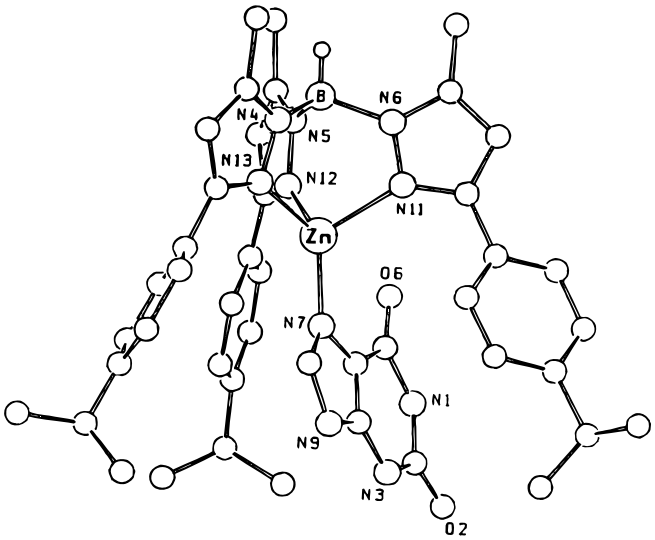


Figure 4. Molecular structure of Tp*Zn−Xan excluding the hydrogen-bonded methanol molecules. Selected bond distances (Å): Zn−N7 1.946(9), Zn−N11 2.042(10), Zn−N12 2.012(9), Zn−N13 2.064(10).

The most noticeable feature of the structure of Tp*Zn−Ura is the association of two molecules each across a center of symmetry by means of two hydrogen bridges. Figure 3 shows the arrangement which is a variation of the classical base-pairing mechanism. The two symmetry-equivalent O4−N3 linkages are 2.88 Å long.

The molecular structure of Tp*Zn−Xan (Figure 4) displays a ligand arrangement around zinc whose geometrical details closely resemble those in Tp*Zn−Ura and hence deserve no further comment. The xanthinate moiety is close to ideally planar again. The formation of a five-membered chelate ring involving the atoms N7 and O6 has not occurred although this seems possible due to the position of O6. This is in agreement with the rarity of this kind of chelation in complexes of oxopurines.[12] Coordination of the N7 atom of xanthine to zinc has also been observed in $Zn(H_2O)_4$(xanthosinate)$_2$,[56] while neutral xanthine in $ZnCl_2$(xanthine)$_2$ uses N9 for metal coordination.[57] Inosine and guanosine 5′-phosphates also use N7 for coordination to zinc,[10b] while ATP in (bipy)Zn(ATP)$_2$ is only phosphate-coordinated.[58]

The open end of the xanthinate ligand in Tp*Zn−Xan is again involved in hydrogen bonding. This time, however, it is not linked directly to another nucleobase but to several molecules of cocrystallized methanol which establish a connection to a symmetry-related molecule of Tp*Zn−Xan. Figure 5 displays

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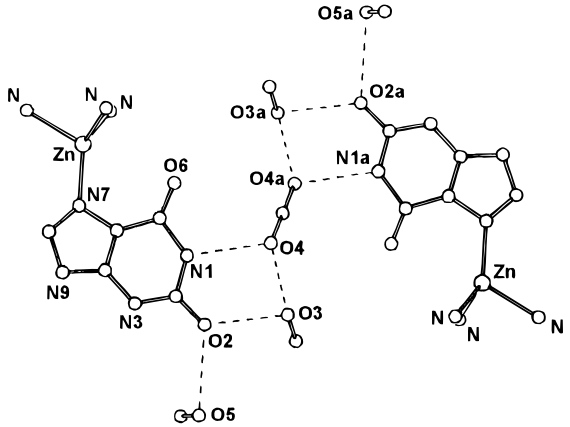
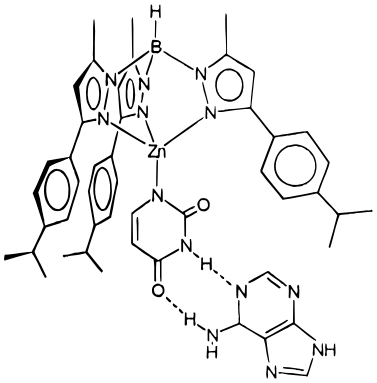


Figure 5. Hydrogen-bonding network of methanol molecules between two molecules of Tp*Zn−Xan.

this. In the center of the drawing is a methanol molecule disordered across a center of symmetry. This molecule is not well-defined crystallographically, and its omission does not disturb the other hydrogen bonds. Crystals of Tp*Zn−Xan·2.5CH_3OH had a strong tendency to lose methanol and crumble even when stored in the presence of their mother liquor, which was the reason for the unsatisfactory quality of the data set.

The hydrogen-bonding interactions present in these nucleobase complexes pointed to the possibility of binding free nucleobases or nucleosides to the zinc complexes of uracil and xanthine. This could be verified for Tp*Zn−Ura. The presence of this complex in solution makes uracil and adenine soluble in dichloromethane, where they normally have a very low solubility. The solubilization may be explained by base pairing as suggested below for the combination Tp*Zn−Ura·adenine. So far, attempts to obtain such adducts as crystalline materials have failed. After crystallization, only the individual components could be identified. It is, however, obvious that this type of molecular recognition is important for the specific attachment of metal-containing reagents to nucleic acids or polynucleotides.



6-Methylthiouracil and 6-Mercaptopurine. These two non-natural nucleobases were chosen because they are close relatives of uracil and xanthine, having one CO function replaced by a CS function. They probably owe their action as drugs[12,59] to this close relationship. We included them in this study because it could be expected that the thiophilicity of zinc might give rise to different coordination patterns in comparison to those of uracil and xanthine. The coordination chemistry of sulfur-containing purine derivatives has been extensively studied by

(59) Skellern, G. G. In *Sulphur-Containing Drugs and Related Organic Compounds*; Damani, L. A., Ed.; Ellis Horwood: Chichester, U.K., 1989; Vol. 1, Part B.

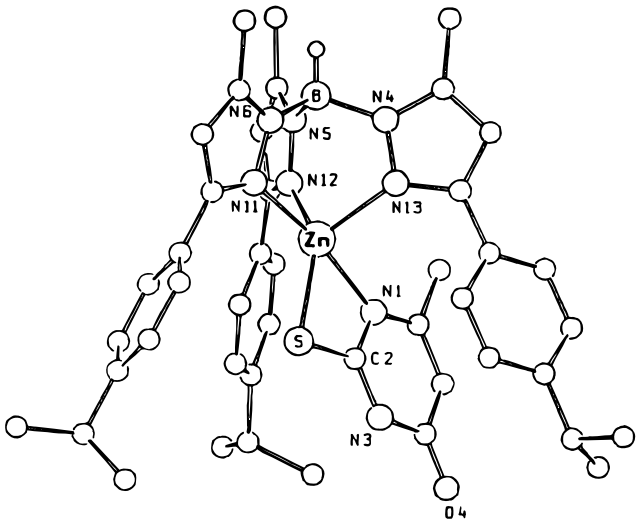
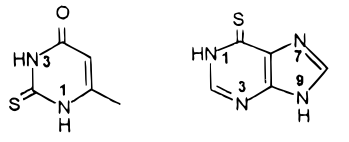


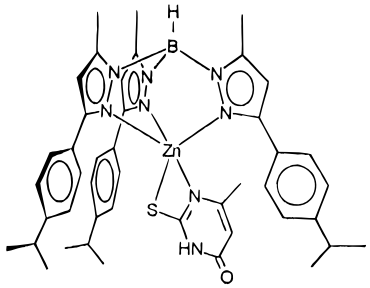
Figure 6. Molecular structure of Tp*Zn−Tura. Selected bond distances (Å) and angles (deg): Zn−N1 2.263(3), Zn−N12 2.065(3), Zn−N13 2.065(3), Zn−N11 2.115(3), Zn−S 2.355(1), N1−C2 1.325(5), S−C2 1.708(4), N1−Zn−N11 171.2(1), Zn−N1−C2 92.9(2), Zn−S−C2 80.8(1), S−Zn−N1 68.5(1), S−C2−N1 117.5(3).

Dubler,[12] and zinc−mercaptopurine complexes have already been described by him[12] and us.[20]



6-methyl-2-thiouracil TuraH | 6-mercaptopurine MerH

The reactions of Tp*Zn−OH with both sulfur-containing nucleobases went straightforward and yielded the complexes Tp*Zn−Tura and Tp*Zn−Mer. Their composition could again be derived from the spectra (see Experimental Section), but only Tp*Zn−Tura yielded X-ray-quality crystals which allowed the determination of its constitution.



Tp*Zn-Tura

The molecular structure of Tp*Zn−Tura (Figure 6) shows that the sulfur atom, as expected, participates in the coordination. The coordination pattern of a four-membered chelate ring is, however, unprecedented in zinc−pyrazolylborate chemistry. Nevertheless it does not seem to be unusual for zinc, as it occurs with very similar bond lengths and angles in Zn(6-amino-2-thiouracilato)$_2$(OH_2)[60] and Zn(pyrimidine-2-thiolato)$_2$(py).[61] Both the Zn−S and Zn−N distances are quite long when compared with other such distances in zinc−pyrazolylborate complexes.[21] The bond distances within the chelate ring, specifically the short

(60) Romero, M. A.; Sanchez, M. P.; Quiros, M.; Sanchez, F.; Salas, J. M.; Moreno, M. N.; Faure, R. *Can. J. Chem.* **1993**, *71*, 29−33.
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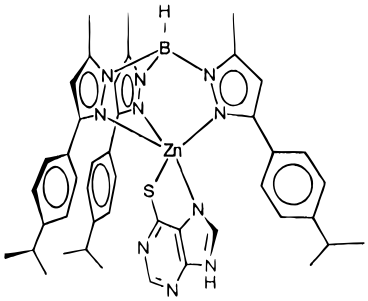
N1−C40 bond length, indicate that the thiouracil ligand is bound in the thioenolate form. The coordination geometry about zinc is severely distorted trigonal bipyramidal with the pyrazole nitrogen N8 and the thiouracil nitrogen N1 on the axial positions.

The thiouracil ligand is planar within ±0.01 Å. Its NH function in the 3-position and its carbonyl group are again pointing toward the "outside" of the pyrazolylborate ligand pocket. As a consequence, just as in Tp*Zn−Ura, two complex molecules are associated via a pair of hydrogen bridges across a crystallographic center of symmetry. A similar type of hydrogen bridging is observed in the structure of Zn(6-amino-2-thiouracilato)$_2$(OH_2).[60] Accompanying with this tendency for self-association is, again just as for Tp*Zn−Ura, the ability of Tp*Zn−Tura to solubilize adenine and uracil in dichloromethane.

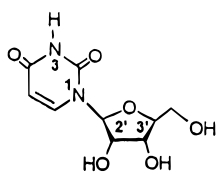
For the complex Tp*Zn−Mer, there is only weak spectroscopic evidence for a possible structure. There is no characteristic ν(CO) band in the IR, and the two CH ^{1}H-NMR resonances of the mercaptopurine ligand are hidden under the aromatic resonances of the Tp* ligand. The only strong piece of evidence is the significant upfield shift of the Tp* ^{1}H-NMR signals in comparison to those of Tp*Zn−OH.[21] As in other cases,[21,22,51] this indicates the embedding of an aromatic system between the substituents on the pyrazolylborate ligand. The size of this effect (e.g., it strongly affects the pyrazole methyne signal) points to a close association of mercaptopurine and zinc. In our opinion, the best interpretation for this is N,S chelation as depicted below. It is in agreement with the structures of cadmium and platinum complexes of monoanionic mercaptopurine.[12] Similar five-membered chelate rings in TpZn−L complexes have been observed as a N,N chelate for L = acetazolamide[19] and as a N,S chelate for L = cysteine ethyl ester.[51] However, neutral mercaptopurine has been found to coordinate to zinc in a monodentate fashion in the structure of Zn(Mer)$_2$$Cl_2$·$CH_3OH$,[12] and dianionic mercaptopurine forms a polymeric Zn(NH_3)$_2$ complex in which it links two zinc ions by coordination via N1 and N7.[20]



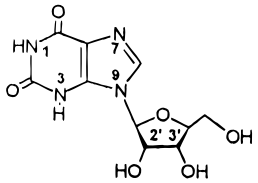
Tp*Zn-Mer

Assuming the depicted structure for Tp*Zn−Mer and hence N,S-chelation by both sulfur-containing nucleobases, it can be stated that their structures can be related to the physiological activity of their nucleobases. As long as they are administered as metal compounds or their action affects metal-containing enzymes, it is evident that the difference in metal coordination between them and the related sulfur-free nucleobases must have physiological consequences related to the functions of these nucleobases. On the other hand, their similarity to the sulfur-free nucleobases in terms of association via hydrogen bonds, as shown above for uracil and 6-methylthiouracil, demonstrates that they can become attached to, and affect, the same targets as these nucleobases. This, in turn, may be of value for the design of metal-containing drugs.

Uridine and Xanthosine. Uridine and xanthosine are the ribose-containing nucleosides of the two natural nucleobases uracil and xanthine. It was of interest to discover whether the presence of the sugar changes their mode of attachment to zinc. Their reaction with Tp*Zn−OH was again straightforward, involving the expected deprotonation and coordination, but X-ray-quality crystals of the products could not be obtained.



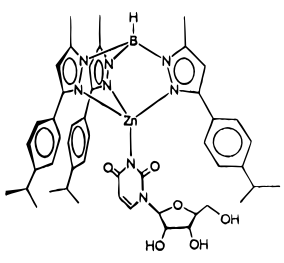
uridine
UrdH



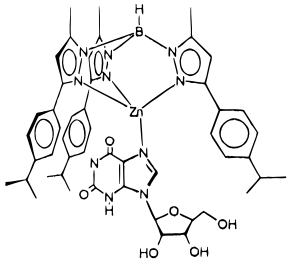
xanthosine
XaoH

The only plausible point of attachment of uridine is the imide nitrogen in the 3-position. The general similarity of the ^{1}H-NMR spectrum of Tp*Zn−Urd to that of Tp*Zn−Ura and the lack of any changes of the ^{1}H-NMR data due to the ribose unit in comparison to the case of free uridine are in agreement with this. The strongest indicator of N3 coordination is the significant shift of the ν(CO) IR bands in comparison to those of the free base. The same has been observed for the only reported case of a structurally characterized zinc complex of a uridine derivative, 3′-azido-3′-deoxythymidine.[62]

The spectroscopic evidence for the mode of coordination of xanthosine is less conclusive. The general similarity of the ^{1}H-NMR spectra of Tp*Zn−Xan and Tp*Zn−Xao indicates similar coordinations, i.e. binding via N7. This conflicts with the deprotonation at N1 and the shifts of the ν(CO) IR bands (i.e., those of the two CO groups attached to N1) in the same order of magnitude as observed for Tp*Zn−Urd. The fact that not only Tp*Zn−Xan but also Zn(xanthosinate)$_2$(H_2O)$_4$[56] crystallize with zinc coordinated to N7 leads us to prefer this bonding mode. Consequently, the suggested structures for the two complexes are as follows:



Tp*Zn-Urd

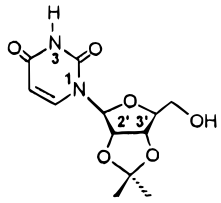


Tp*Zn-Xao

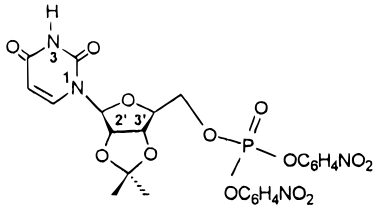
2′,3′-*O*-Isopropylideneuridine and 2′,3′-*O*-Isopropylideneuridine 5′-(Bis(*p*-nitrophenyl) phosphate). As the final step in the approach toward zinc coordination by the nucleobases of RNAs, the interaction between the Tp*Zn unit and a mononucleotide derivative was investigated. At this point, however, interference by the main property of Tp*Zn−OH, i.e. its strong hydrolytic activity, was to be expected. In fact, Tp*Zn−OH effects stoichiometric cleavage of phosphate esters, including sugar phosphates and the UMP derivative chosen here, under very mild conditions.[63,64] Careful reaction control did, however, allow the isolation of the base adduct as the initial reaction product. In line with the use of uracil derivatives

(62) Shionoya, M.; Kimura, E.; Shiro, M. *J. Am. Chem. Soc.* **1993**, *115*, 6730−6737.
(63) Ruf, M.; Weis, K.; Vahrenkamp, H. *J. Chem. Soc., Chem. Commun.* **1994**, 135−136.
(64) Weis, K.; Vahrenkamp, H. Unpublished work.

throughout this paper and with the purpose of having control over the point of phosphate attachment to the sugar, 2′,3′-*O*-isopropylidene uridine 5′-(bis(*p*-nitrophenyl) phosphate) was chosen as a UMP analogue. For reference purposes its synthetic precursor 2′,3′-*O*-isopropylideneuridine was included in the study.

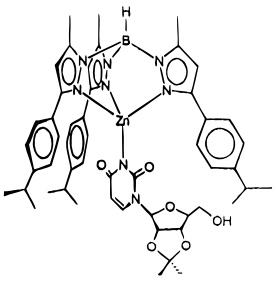


2′-3′-isopropylidene-
uridine
iUrdH

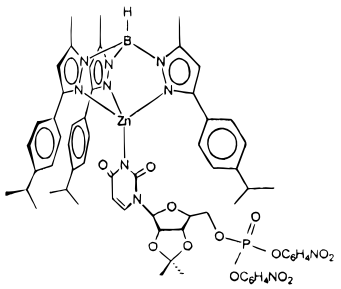


2′-3′-isopropylidene-
uridine-bis(p-nitrophenyl)-phosphate
iUmpH

The reactions between Tp*Zn−OH and these two uridine derivatives proceeded as smoothly as the ones reported above. Of the resulting complexes, Tp*Zn−iUmp was so labile that attempts to crystallize it induced decomposition leading to product mixtures containing Tp*Zn−*p*-nitrophenolate. Tp*Zn−iUmp could, however, be isolated analytically pure from the reaction solution. The IR data in the ν(CO) region (see Experimental Section) group the uridine-derived complexes Tp*Zn−Urd, Tp*Zn−iUrd, and Tp*Zn−iUmp together and distinguish them from Tp*Zn−Ura, for which uracil attachment via the N1 nitrogen is established. The ^{1}H-NMR spectra of Tp*Zn−iUrd and Tp*Zn−iUmp are similar, assisted by the fact that the isopropylidene group is a good NMR handle, but for the nucleoside part of the molecules they offer little in terms of a relation to Tp*Zn−Urd. On the basis of this information and on common sense, the same coordination of iUrd and iUmp to



Tp*Zn-iUrd



Tp*Zn-iUmp

zinc is proposed as above for the uridinate complex, i.e. via the N3 nitrogen (see the formulas). Thus the whole series of nucleobase-derived complexes described here is assumed to have a structure in which a heterocyclic nitrogen atom of an anionic nucleobase is the point of attachment to zinc.

Conclusions

The complexes described here have highlighted two favorable properties of the Tp* ligand: it provides its complexes of divalent metals with an encapsulating pocket which protects unusual coligands, and it favors the formation of neutral complexes, hiding the polar interactions in its interior and being mostly hydrophobic on its outside. In the present case, this means that NH functions of nucleobases are easily deprotonated and the attachment of zinc to their heterocycles is easily achieved.

While the carboxylate coordination in the orotate and dihydroorotate complexes is the one that one would expect, this is not the case for the Zn−N(heterocycle) coordination. ZnN_4 coordination in TpZn complexes is rare and requires the presence of nitrogen coligands derived from very acidic NH functions, in line with the observation that there are hardly any cationic TpZnL complexes of neutral ligands L.[65] This fact may also cause limitations in the scope of Tp*Zn complexes of nucleobase derivatives. Of the four bases tested here, adenine and guanine did not produce stable complexes. Only uracil and xanthine, which share the property of having the rather acidic CO−NH−CO unit, could be incorporated.

As observed by others before, the point of attachment of the anionic nucleobases to zinc in the complexes described here is not necessarily the deprotonated nitrogen atom. While it is too early to make systematic statements regarding the preferred bonding combinations, it is obvious that this is important for biochemical or medical effects related to zinc−nucleobase interactions. In the same context, we would also hesitate to draw conclusions from the observed bonding patterns about the possible roles of zinc in the *de novo* biosynthesis of the nucleobases or their interconversions. On the other hand, the typical differences between the normal and the sulfur-containing nucleobases in terms of zinc coordination relate not only to the drug action of the latter but also to the involvement of the metals (e.g., zinc) in the affected biological process.

The present study has confirmed that zinc-ligating properties are present in all species along the chemical pathway from the amino acids to the nucleotides. In the beginning (amino acids, dihydroorotate) and in the end (sugar phosphates) oxygen coordination by carboxylate or phosphate groups is possible and preferred. Between these stages, when good anionic oxygen donors are not available, the coordination of heterocyclic nitrogen works equally well. The oxygen coordination can be directly related to the dominating biological function of zinc, i.e. hydrolytic interconversions. The biological implications of the nitrogen coordination in this context are less clear.

However, the findings of this paper point to a biomimetic use of the zinc−nucleobase complexes. In the free nucleobases, zinc is attached to the nitrogen atom which bears the ribose unit in the nucleosides and nucleotides. This leaves those parts of the bases exposed to the "outside" of the Tp*Zn−base complexes which are responsible for the base pairing. As the crystal structures and the solubilization of adenine and uracil show, the base-pairing properties can be utilized. Further studies will have to show whether some new coordination chemistry or some practical use thereof can be developed.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Supporting Information Available: Fully labeled ORTEP plots and listings of crystal data, bond distances and angles, anisotropic thermal parameters, and all atomic coordinates and isotropic thermal parameters for all four structures (31 pages). Ordering information is given on any current masthead page.

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(65) Brandsch, T.; Schell, F. A.; Weis, K.; Ruf, M.; Müller, B.; Vahrenkamp, H. *Chem. Ber.* **1997**, *130*, 283−289.