Pyrazolylboratozinc Complexes of Nucleosides and Nucleoside Analogues[‡]

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Attachment of deprotonated nucleosides or of alkylated nucleobases, as their analogues, to zinc was achieved by condensation reactions between TpZn-OH complexes and nucleobase derivatives. Pyrazolylboratozinc complexes with derivatives of uracil, thymine, guanine, xanthine and hypoxanthine were obtained and characterized by structure determination. In the uracil, thymine, guanine and hypoxanthine derivatives, zinc is bound to the nitrogen atom which bears the proton in the nucleoside. In the xanthine derivatives all three possible bonding modes are realized.

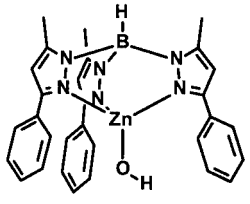
Introduction

The success of cisplatin as a drug has triggered a plethora of studies on the interactions of metal ions with nucleic acids, nucleotides and their constituents.[2−4] Among these, the number of those related to zinc is relatively small. Yet it is known that zinc affects the various structures of DNA,[5] of chromatin[6] and of ribosomes,[7] as well as impeding the melting of DNA[8,9] and facilitating the recombination of the double helix.[10] Furthermore zinc ions have structural and functional roles in nucleic acid-binding retroviruses,[11] in t-RNA, DNA, and RNA polymerases,[3,11] endonucleases,[13] cytidine and adenosine deaminases,[13] aspartate transcarbamoylase,[11] and dihydroorotase.[14]

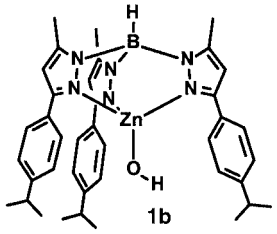
The small-molecule chemistry of zinc related to nucleotides, nucleobases and models thereof has evolved in recent years. Lippert[15] and Dubler[16] pioneered the studies of zinc-nucleobase interactions. Sigel[3,17] and Marzilli[18,19] made the leading contributions to zinc-nucleotide chemistry. Our own contributions to this field describe the interactions of nucleic acid constituents and analogues thereof with pyrazolylboratozinc units.[1,20,21]

The basis of the work reported here are our observations with nucleobases[1,21] and with drug substances, some of which are derivatives of the nucleobases.[22−26] All the substances investigated are nitrogen heterocycles with rather acidic NH functions. This was favourable as it facilitated the synthesis of pyrazolylboratozinc substrate (TpZn-X) complexes by a condensation reaction between TpZn-OH and the NH heterocycle HX. It was, however, unfavourable in terms of modelling zinc-nucleotide interactions, as the most acidic NH functions in the nucleobases are often those whose nitrogen is attached to the sugar moiety in the nucleotides. Due to this the nucleobases were attached to the TpZn unit by that nitrogen atom which is not available for attachment in DNA, RNA and their constituents.

To overcome this disadvantage we resorted to nucleobases which are alkylated at the nitrogen atom to which the sugar moiety would be attached. This paper describes the pyrazolylboratozinc complexes derived from such nucleoside analogues. The alkylated nucleobases represent uridine, thymidine, guanosine and xanthosine. A genuine nucleoside inosine (i.e. glycosylated hypoxanthine) was included in order to complement our previous studies with uridine and xanthosine.[21] The nucleobases were reacted with the pyrazolylborate-Zn-OH complexes **1a** and **1b**.



1a



1b

Results and Discussion

Uracil and Thymine

1-Methyluracil and 1-methylthymine were chosen as the simplest nucleoside analogues. Although their NH functions, flanked by two carbonyl groups, are quite acidic, their reactions with TpZn-OH were not straightforward. It turned out that the reaction products **2** and **3** are very moisture sensitive, easily reverting to the starting materials. Pure **2** and **3** were finally obtained after removing water

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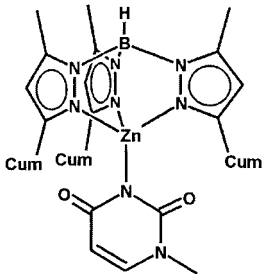
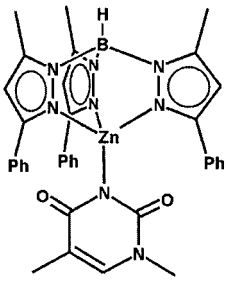
from the reaction mixture by running the reactions in a Soxhlet extractor filled with molecular sieves.

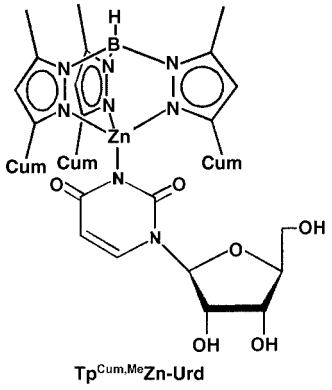


2



3

The structural assignment of **2** and **3** rests on the structure determination of **2** (see below). The spectroscopic data support the statement that all zinc complexes of 1-alkylated uracil and thymine derivatives have the nucleobase attached to zinc in the same way, i.e. via the N3 atom. The main feature is the position of the highest energy ν(CO) band in the IR spectrum. It is observed in the 1640−1670 cm^{-1} range here as well as in N_3O-tripod[27] and [12]ane-N_4 zinc complexes.[28] Its position is higher than that of the anionic 1-alkylated nucleobases, thereby excluding coordination via the oxygen atom, as this would lower the ν(CO) value. The structure determination of **2** and the similarity of all the spectroscopic data also confirm our previous structural assignment of the uridine $Tp^{Cum,Me}$Zn-Urd complex.[21]



$Tp^{Cum,Me}$Zn-Urd

Figure 1 shows the molecular structure of **2**. Notable features are the complete embedding of the nucleobase in the $Tp^{Cum,Me}$ ligand-pocket, the typically short[1,20,21] Zn−N3 bond, the non-existence of Zn−O interactions and the 10° angle between the Zn−N3 bond and the least-squares plane of the heterocycle. Unlike most other TpZn-nucleobase complexes[1,20,21] this one does not dimerize in the solid state via hydrogen bonding, as it does not contain NH or OH units.

Cytosine and Adenine

N1-alkylated cytosine and N9-alkylated adenine derivatives were found to be unsuitable for reactions with TpZn-OH. We had already observed that cytosine itself is not acidic enough for such a reaction while adenine is.[20] 9-Alkylated adenine has no additional heterocyclic (i.e. acidic) NH functions.

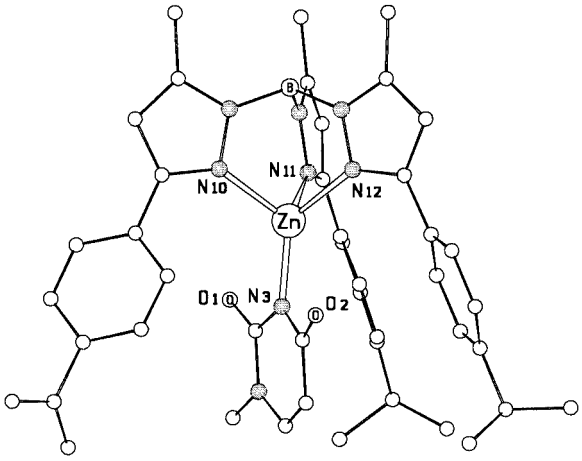
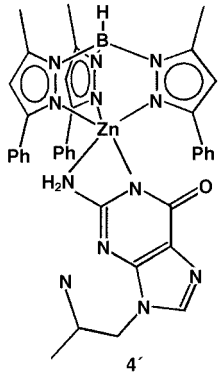


Figure 1. Molecular structure of **2**; relevant atomic distances (Å): Zn−N3 1.930(3), Zn−N10 2.034(3), Zn−N11 2.100(3), Zn−N12 2.049(3), Zn···O1 2.914(5), Zn···O2 3.086(5)

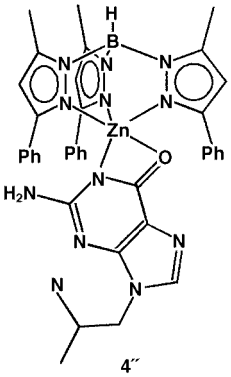
Guanine

The coordination chemistry of guanine is not well developed, and like others we have not been able to prepare zinc-guanine complexes.[20] Guanosine and 9-alkylated guanine derivatives, however, bind to zinc via N7 as uncharged molecules.[29−32] We tried to prepare a TpZn complex of anionic guanosine by reacting guanosine with **1a** and **1b** or the corresponding TpZn-H complexes. We failed, however, to separate the resulting product mixtures.

These problems did not exist when resorting to 9-isobutylguanine as a guanosine analogue. By reaction with $Tp^{Ph,Me}$Zn-H the expected complex **4** was obtained. Compound **4** seems to exist as two isomers **4′** and **4′′**. Precipitation from benzene by addition of heptane yielded **4′** as very thin needles which are not suitable for structure determination. Slow recrystallization of raw **4** or of **4′** from benzene/heptane yielded **4′′** as well-shaped crystals which were used for X-ray analysis. Based on this and on the spectroscopic evidence (see below) we assign the two isomers as follows:



4′



4′′

The molecular structure of **4′′** is shown in Figure 2. The nucleobase is attached to zinc as a bidentate ligand via N1 and the adjacent carbonyl oxygen, forming a four-membered chelate ring. Such a bonding mode is very rare for metal-nucleobase interactions. It has not been observed before with zinc, but it occurs in zinc complexes of α-pyridone,[33,34] and we have described related N,S chelate complexes of 6-methylthiouracil and 6-mercaptopurine.[21] The Zn−O and Zn−N1 bond lengths show that both interactions are strong, i.e. zinc is genuinely five-coordinate. However, the coordination geometry of zinc cannot be described as the transition from trigonal bipyramidal to square pyramidal.[35] It seems more appropriate to assume that N1 and O1 share the single coordination position of a ligand X in the TpZn-X complexes, like the two oxygen atoms of a symmetrically bidentate carboxylate ligand in TpM-carboxylate complexes.[35] Apart from this peculiar situation, the nitrogen atom which bonds to zinc (N1), is a typical, yet not the only possible, donor atom in other metal complexes of anionic guanosine derivatives.

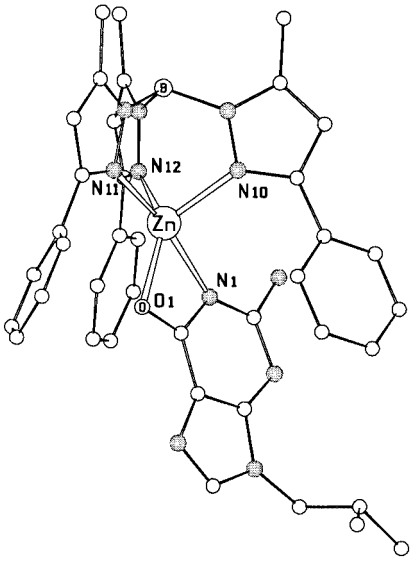


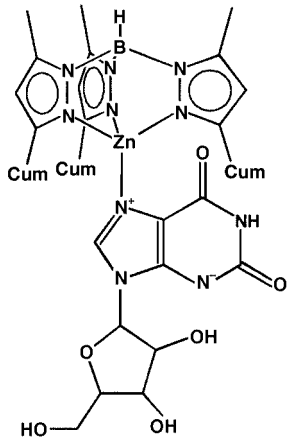
Figure 2. Molecular structure of **4′′**; relevant bond lengths (Å) and angles (°): Zn−O1 2.061(2), Zn−N1 2.182(3), Zn−N10 2.097(3), Zn−N11 2.103(3), Zn−N12 2.084(3), O1−Zn−N1 62.96(9)

In the solid state, complex **4′′** forms dimers across an inversion center by two symmetrically equivalent hydrogen bonds between the NH_2 group and N3. This is different from all other such dimer structures of TpZn-nucleobase complexes,[1,20,21] but it is the common type of self-association for guanosine and its derivatives.[40]

The solution NMR spectra of **4′** and **4′′** are identical, indicating a rapid equilibrium between their two structures or possibly a third structure, e.g. one with a monodentate attachment of the nucleobase via N1. The IR spectra of **4′** and **4′′** in KBr show small, yet significant, differences. These concern the vibrational modes of the C=O and NH_2 units. In free 9-isobutyguanine ν(CO) and δ(NH_2) appear as strong bands at 1688 and 1631 cm^{-1}, respectively. Zinc complexes of uncharged 9-alkylguanines show very little shifts for these two band positions. Complex **4′** has its ν(CO)band at 1692 cm^{-1} (i.e. unshifted) and its δ(NH_2) band at 1611 cm^{-1} (i.e. shifted to lower wavenumbers). Complex **4′′** shows no typical ν(CO) band and its δ(NH_2) band at 1638 cm^{-1} (i.e. unshifted). This indicates that in **4′′** the CO function is involved in the zinc bonding , as proved by the structure determination. Likewise in **4′** the NH_2 group seems to act as a donor. Taking into account that N1 is most probably the main donor for zinc in both isomers, this leads to the structural assignment given above for **4′**, again with a four-membered chelate ring.

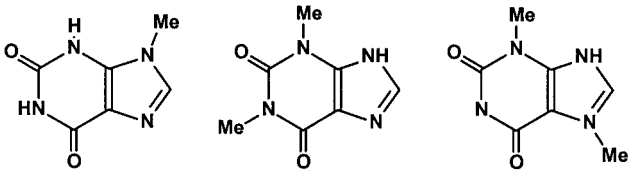
Xanthine

The xanthine-derived nucleoside xanthosine has already been incorporated in a TpZn complex, the structure of which (with zinc attachment at N7) was assigned as follows:[21]



$Tp^{Cum,Me}$Zn-Xao

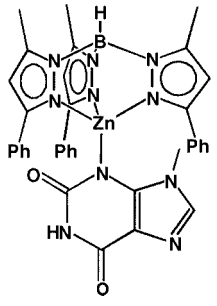
The nucleobase xanthine with three NH functions permits various N-alkylations, allowing us to probe the variation of its metal binding properties. The simplest xanthosine analogue is 9-methylxanthine, while some of the other methylated xanthines are well-known purine alkaloids. For example, caffeine (1,3,7-trimethylxanthine), theophylline (1,3-dimethylxanthine) and theobromine (3,7-dimethylxanthine) are the stimulating ingredients of coffee, tea, and cocoa, respectively. Amongst these, 9-methylxanthine, theophylline and theobromine were chosen for this investigation.



9-methylxanthine theophylline theobromine

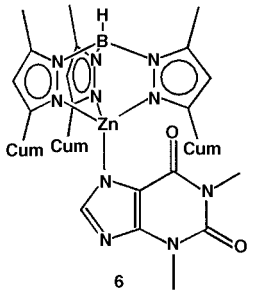
9-Methylxanthine and **1a** yielded **5**. The NMR spectrum of **5** indicates that the attachment of the nucleobase to the zinc is different from that in the xanthosinate complex (see

above). The strongest indicator is the C8-H signal at δ = 6.92 ppm, representing an upfield shift of ca. 1 ppm relative to free 9-methylxanthine. However, in all TpZn complexes of purine bases which are coordinated to zinc via N7 or N9, the C8-H resonance experiences an upfield shift of ca. 2 ppm due to the location of C8-H inside the pocket between the three phenyl groups of the Tp ligand.[1,20,21] Thus, while the C8-H proton resonance excludes N7 coordination, the N9-methyl resonance speaks against N1 coordination and favours N3 coordination. The upfield shift for this resonance, relative to that of free 9-methylxanthine, is ca. 1 ppm, which is typical for methyl groups in the Tp ligand pocket, while for N1 coordination the methyl group would point away from the Tp ligand and experience only little shielding from it. Thus the most likely structure for **5** is the following:



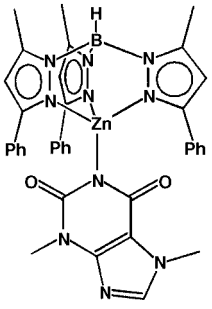
5

Anionic theophylline has been well-investigated as a ligand, showing a pronounced preference to coordinate via N7.[41,42] This was reproduced here with the complex, **6**, resulting from **1b** and theophylline. Again, NMR spectroscopic data allow a reliable structural assignment. While the 2 ppm upfield shift of the C8-H resonance indicates coordination via N7 or N9, the proton resonances of the two methyl groups make the assignment clear: the N3-methyl resonance is shifted upfield by 0.3 ppm and that of the N1-methyl group by 0.9 ppm. This places the N1-methyl group deeper into the Tp ligand pocket, which calls for attachment of theophylline to zinc via N7. Confirmation of this structural assignment also comes from the structure determination of the related $Tp^{Ph,Me}$Zn complex of 1-methyl-3-isobutylxanthine.[43]



6

In anionic theobromine N1 and N9 are available for coordination to zinc. This was tested by the formation of **7** from **1a** and theobromine. In the NMR spectrum of **7** the C8-H resonance is shifted upfield by only 0.3 ppm relative to free theobromine. Thus a coordination via N9 is unlikely, but the 0.5 ppm upfield shifts for both N-methyl resonances favour coordination via N1.



7

The assignment was confirmed by the structure determination of **7** (Figure 3). There are two independent molecules of **7** in the asymmetric unit, differing in the orientation of the purine base in the $Tp^{Ph,Me}$ ligand-pocket, but not in the relevant intramolecular bonding distances and angles. The theobrominate ligand is monodentate, and the two carbonyl functions flanking N1 are not within bonding range of the zinc ion. Correspondingly the Zn−N1 bond is quite short. As two of the three nitrogen atoms of theobromine pointing outward from the TpZn unit are methylated, there exists no possibility for the dimerization of **7** by means of hydrogen bonds. In all these respects complex **7** is unique, as no metal complex with N1-bound theobromine has been reported so far.

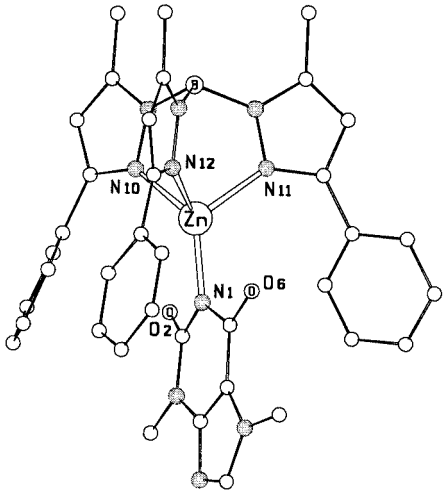


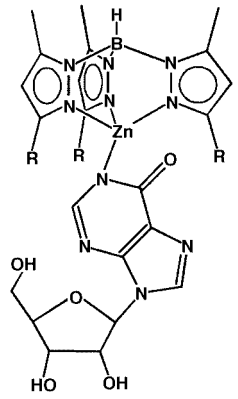
Figure 3. Molecular structure of **7** (one of the two independent molecules in the asymmetric unit); relevant atomic distances (average values, Å): Zn−N1 1.905(3), Zn−N10 2.065(4), Zn−N11 2.030(4), Zn−N12 2.010(4), Zn···O2 2.913(5), Zn···O6 2.943(5)

In all the zinc complexes of xanthine derivatives described here, the nucleobase has two or three nitrogen atoms available for zinc coordination (four in free xanthine). Xanthine, xanthosine and theophylline use N7, 9-methylxanthine uses N3, and theobromine uses N1. We see no consistent interpretation of this in the steric or electronic environment of the xanthine derivatives themselves. There-

fore we think that secondary interactions like base pairing or π-stacking favour the observed constitutions.

Hypoxanthine

The nucleoside of hypoxanthine is inosine. It reacted cleanly with **1a** and **1b**, producing complexes **8a** and **8b** of which **8a** could be subjected to a structure determination. Having achieved this, it was no longer necessary to resort to alkylated hypoxanthine derivatives as inosine analogues.



8a: R = Ph, **8b:** R = Cum

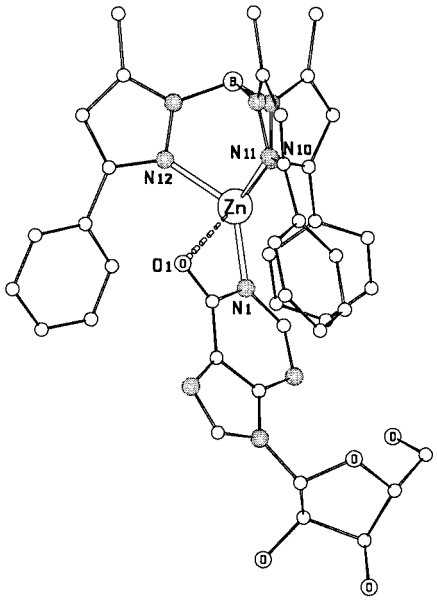


Figure 4. Molecular structure of **8a** (conformer **8a.4**); relevant bond lengths (average values, Å): Zn−N1 1.968(8), Zn−O1 2.528(8), Zn−N10 2.059(8), Zn−N11 2.031(8), Zn−N12 2.019(8)

The structure determination of **8a** was plagued by the fact that the asymmetric unit contains four independent complex units, i.e. the conformational freedom of the molecules is displayed even in the solid state. Even though enantiomerically pure D-inosine is present, its orientation in the Tp ligand-pocket yields two conformers, each of which is obtained with two different conformations of the sugar moiety. Although this generates a large amount of structural data, the essential part of the structures, i.e. the interaction between the zinc ion and the anionic nucleobase, varies very little.

In **8a** the nucleobase binds to zinc via N1, which is the nitrogen bearing the proton in neutral inosine. The negative charge in anionic inosine is presumed to rest on N1, N3 and mostly O6.[41,44] This makes O6 a potential donor atom, as is observed in the structure of **8a** by clearly noticeable Zn···O interactions (2.53−2.76 Å), creating a four-membered chelate ring. These Zn···O interactions are intermediate between the very weak ones in **2** and the very strong ones in **4′′**. Accordingly the ν(CO) IR bands for the coordinating carbonyl functions appear at 1670 cm^{-1} for **2** and at 1632 cm^{-1} for **8a**, but are absent from the IR spectrum of **4′′**. For this reason it is not appropriate to consider zinc as five-coordinate in **2** and **8a**, which is also reflected by the fact that the Zn−N1 bond in **8a** is close to the trigonal axis of the TpZn unit. There seems to be a relation, however, between the strengths of the Zn−N(nucleobase) and the Zn−O(nucleobase) interactions: in **2** and **7**, where the the Zn−O interactions are very weak, Zn−N is very short; in **8a**, where the Zn−O interactions are intermediate, it is elongated; and in **4′′**, where the Zn−O interactions are strong, Zn−N is unusually long.

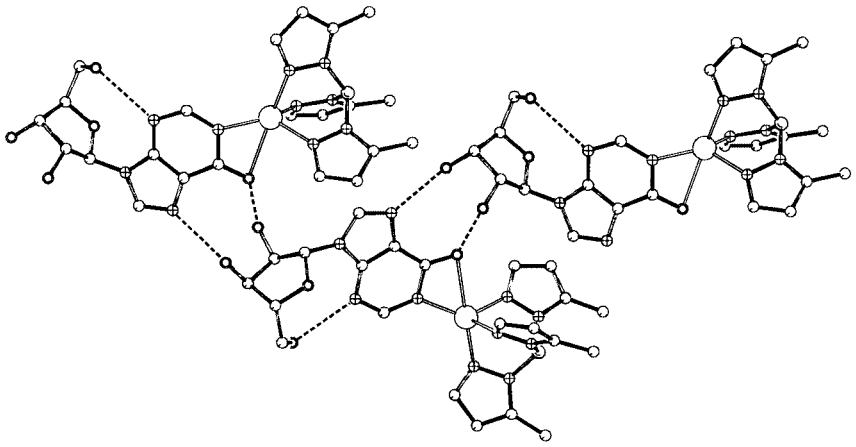


Figure 5. Hydrogen-bonding network for the conformer **4** of complex **8a**

We are not aware of any other zinc complexes of anionic hypoxanthine or inosine. There is a bis(methylmercury) complex of inosinate which has mercury attached at N1 and N7.[45] Inosinemonophosphate also coordinates to zinc via N7.[46]

Like in the other compounds described here, the zinc ion in **8a** is not necessarily attached to the point of highest electron density in the nucleobase. One factor supporting the observed zinc-nucleobase interaction is certainly the additional bonding interaction with the carbonyl oxygen. In addition, like many other of these zinc complexes **8a** displays various kinds of hydrogen bonding which may contribute significantly to the overall stability. Each of the four individual conformers of **8a** is linked to its symmetry-related neighbours by one or two hydrogen bonds such that infinite chains result. Figure 5 displays this for the conformer **8a.4**, for which the linking consists of hydrogen bonds between the 2′-OH group and the carbonyl oxygen as well as between the 3′-OH group and N7.

Conclusions

This study brings our investigation on pyrazolylboratozinc complexes of nucleobases, nucleosides and analogues thereof to completion. Of the nine nucleobases applied[20] only guanine evaded zinc complexation. Of the four nucleosides used, three (uridine, xanthosine, inosine) could be attached to zinc. The alkylated nucleobases filled the gaps. In addition, a small number of nucleotide analogues[21] and of sugar phosphates[47] were included.

In all cases the advantage of encapsulating pyrazolylborate ligands, i.e. the limitation of the coordination space at the zinc ion, could be exploited. In all but a few cases the nucleobase-derived substrates are attached to zinc in a monodentate fashion, thereby showing their preferred donor site which is always located at a nitrogen atom. The other advantage of the Tp ligands, i.e. the preference for monoanionic coligands, which results in the formation of uncharged (and hence easily isolable) zinc complexes, could also be put to use.

The latter aspect requires, however, all the nucleobase-derived coligands to be anionic. This limits their selection to those which have at least one NH or OH function in their uncharged forms. It also means that the nitrogen atom that binds to zinc is not necessarily the one which was deprotonated. Moreover, it also means that in the free nucleobases "unnatural" coordination to zinc can occur via that nitrogen atom which bears the sugar moiety in the nucleosides; we found that this is actually the preferred bonding mode.

In the nucleosides and nucleoside analogues which are the subject of this paper "natural" binding to zinc must occur. In the pyrimidine-derived nucleobases (substituted uracil and thymine) there is only one possible donor atom, N3, which is used. In all the other (purine-derived) nucleobase derivatives there are three or more possible nitrogen donors. We have observed that the choice of the actual donor site cannot be predicted from the acid/base, electron density, or from the geometrical properties of the substrates. Instead additional bonding interactions seem to control the zinc-substrate connectivity. Thus in **4** and **8** the coordination of a carbonyl oxygen to zinc, in other cases hydrogen-bonding patterns, and possibly in all cases, π-stacking between the nucleobases of adjacent molecules or between the nucleobases and the phenyl substituents of the Tp ligands offer major contributions to the overall stability and hence to the choice of the zinc-binding nitrogen donor.

Conversely, according to the specific modes of attachment, the zinc ions can exert different kinds of influence on the electronic nature and hence the reactivity of the bound substrates. This in turn might be of use for an understanding of the modes of action of the various zinc enzymes along the metabolic pathways of the nucleobases, the nucleosides and the nucleotides.

Experimental Section

General: Reactions were performed under a nitrogen atmosphere in anhydrous solvents. The TpZn-OH complexes were prepared as described.[48,49] All other starting materials were obtained commercially. The analytical equipment was as described previously.[50]

Complex 2: A solution of **1b** (207 mg, 0.30 mmol) and 1-methyluracil (45 mg, 0.36 mmol) in 160 mL of benzene was refluxed for 3 days in a Soxhlet extractor filled with 4 Å molecular sieves. After reducing in vacuo to 40 mL and cooling to 4 °C a precipitate of unused starting materials was formed. After filtration the solution was evaporated to dryness. The residue was dissolved in a minimum amount of benzene which was layered with heptane. Within one week 128 mg (53%) of **2** had separated as colourless crystals. M.p. 211 °C. $C_{44}H_{51}BN_8O_2Zn$ (800.14): calcd. C 66.05, H 6.42, N 14.00; found C 66.11, H 6.16, N 13.70. IR (KBr): $\tilde{\nu}$ = 2547 cm^{-1} (m, BH), 1646 (vs, CO). ^1H NMR ($CDCl_3$): δ = 1.19 [d, *J* = 6.9 Hz, 18 H, Me(*i*Pr)], 2.51 [s, 9 H, Me(pz)], 2.57 (s, 3 H, MeN), 2.84 [sept, *J* = 6.9 Hz, 3 H, CH(*i*Pr)], 5.04 (d, *J* = 7.5 Hz, 1 H, C5H), 6.12 [s, 3 H, CH(pz)], 6.52 (d, *J* = 7.5 Hz, 1 H, C6H), 7.06 (d, *J* = 8.1 Hz, 6 H, Ph), 7.45 (d, *J* = 8.1 Hz, 6 H, Ph) ppm.

Complex 3: Like **2**, from **1a** (400 mg, 0.73 mmol) and 1-methylthymine (102 mg, 0.73 mmol). Yield: 386 mg (77%) of **3** as colourless crystals; m.p. 257 °C (dec.). $C_{36}H_{35}BN_8O_2Zn$ (687.93): calcd. C 62.86, H 5.13, N 16.29; found C 62.65, H 5.28, N 16.35. IR (KBr): $\tilde{\nu}$ = 2544 cm^{-1} (w, BH), 1655 (vs, CO). ^1H NMR ($CDCl_3$): δ = 1.41 (d, *J* = 1.1 Hz, 3 H, C5-Me), 2.53 [s, 9 H, Me(pz)], 2.63 (s, 3 H, NMe), 6.16 [s, 3 H, H(pz)], 6.43 (d, *J* = 1.1 Hz, 1 H, C6H), 7.16 (m, 9 H, Ph), 7.55 (m, 6 H, Ph) ppm.

Complex 4: $Tp^{Ph,Me}$Zn-H (133 mg, 0.24 mmol) and 9-isobutylguanine (50 mg, 0.24 mmol) in 30 mL of dichloromethane were stirred for 24 h. The solvent was removed in vacuo, the residue dissolved in 15 mL of benzene, filtered and layered with heptane. Within a short time a fluffy precipitate was formed, followed slowly by the growth of small evenly shaped crystals. After 2 days the heterogeneous mixture was separated by vigorous stirring and decanting of the solution in which the fluffy precipitate was suspended. The remaining crystals were washed with a small amount of heptane and dried in vacuo. 95 mg (45%) of **4′′·1.5C$_6$H$_6$** remained as colourless crystals. M.p. 203 °C. $C_{39}H_{40}BN_{11}OZn{\cdot}1.5C_6H_6$ (755.02 + 117.17): calcd. C 66.10, H 5.66, N 17.67; found C 65.53, H 5.68, N 17.77. IR (KBr): $\tilde{\nu}$ = 3471 cm^{-1} (s, NH), 2533 (m, BH), 1638

Table 1. Crystallographic data

	2	**4"**	**7**	**8a**
Empirical formula	$C_{44}H_{51}BN_8O_2Zn$	$C_{39}H_{40}BN_{11}OZn{\cdot}1.5\ C_6H_6$	$C_{37}H_{35}BN_{10}O_2Zn$	$C_{40}H_{39}BN_{10}O_5Zn$
Molecular mass	800.14	755.02 +117.17	727.95	816.01
Crystal size [mm]	0.5 × 0.3 × 0.2	0.2 × 0.2 × 0.55	0.15 × 0.2 × 0.3	0.15 × 0.35 × 0.55
Space group	$P2_1/n$	$C2/c$	$P2_1/c$	$P2_1$
Z	4	8	8	8
a [Å]	17.664(4)	29.879(7)	20.271(5)	21.572(9)
b [Å]	12.824(3)	18.191(4)	13.907(3)	16.128(7)
c [Å]	18.882(4)	19.470(5)	24.912(6)	22.806(10)
α [°]	90	90	90	90
β [°]	98.64(3)	118.834(4)	91.657(5)	103.658(10)
γ [°]	90	90	90	90
V [Å^3]	4228.7(16)	9271(4)	7020(3)	7710(1)
D(calc) [gcm^{-3}]	1.26	1.25	1.38	1.41
μ(Mo-K_α) [mm^{-1}]	0.63	0.58	0.75	0.70
hkl range	*h:* 0 to 21	*h:* −39 to 38	*h:* −27 to 25	*h:* −23 to 23
	k: −15 to 0	*k:* −24 to 24	*k:* −18 to 16	*k:* −17 to 17
	l: −23 to 23	*l:* −25 to 25	*l:* −32 to 32	*l:* −25 to 25
Measured reflections	8566	69233	62688	54436
Independent reflections	8294	11199	17031	22152
Observed refl. [$I>2\sigma(I)$]	5541	6414	6107	14627
Parameters	505	578	927	2053
Refined reflections	8294	11199	17031	22152
R_1 (obs.refl.)	0.049	0.055	0.070	0.062
wR_2 (all refl.)	0.155	0.176	0.178	0.157
Residual electron density [e/Å^3]	+0.6/-0.4	+0.5/-0.8	+0.7/-1.1	+0.5/-0.4

(s, CO). ^{1}H NMR ($CDCl_3$): δ = 0.87 [d, J = 6.8 Hz, 6 H, Me(*i*Bu)], 2.05 [m, 1 H, CH(*i*Bu)], 2.56 [s, 9 H, Me(pz)], 3.31 (s, 2 H, NH_2), 3.60 [d, J = 7.2 Hz, 2 H, CH_2(*i*Bu)], 6.21 [s, 3 H, H(pz)], 6.99−7.17 (m, 9 H, Ph), 7.30 (s, 1 H, C8H), 7.34 (s, 9 H, C_6H_6), 7.60 (d, J = 6.8 Hz, 6 H, Ph) ppm.

The decanted suspension was filtered and the precipitate dried in vacuo, leaving behind 33 mg (18%) of **4′** as colourless needles. M.p. 216 °C. $C_{39}H_{40}BN_{11}OZn$ (755.02): calcd. C 62.04, H 5.34, N 20.41; found C 61.87, H 5.64, N 20.27. IR (KBr): $\tilde{\nu}$ = 3414 cm^{-1} (m, NH_2), 2548 (w, BH), 1692 (s, CO). ^{1}H NMR ($CDCl_3$): identical to the spectrum of **4′′**.

Complex 5: Complex **1a** (28.5 mg, 0.05 mmol) and 9-methylxanthine (8.4 mg, 0.05 mmol) in 10 mL of dichloromethane were stirred for 2 days. The solvent was removed in vacuo and the residue dissolved in 8 mL of benzene and 2 mL of dichloromethane. Slow evaporation yielded 18 mg (50%) of **5** which, after drying in vacuo, was isolated as a colourless powder. M.p. 158 °C. $C_{36}H_{33}BN_{10}O_2Zn$ (713.92): calcd. C 60.57, H 4.66, N 19.62; found C 60.17, H 5.01, N 18.50. IR (KBr): $\tilde{\nu}$ = 2550 cm^{-1} (m, BH), 1673 (vs, CO). ^{1}H NMR ($CDCl_3$): δ = 2.54 (s, 3 H, NMe), 2.58 [s, 9 H, Me(pz)], 6.23 [s, 3 H, H(pz)], 6.92 (s, 1 H, C8H), 7.12 (m, 9 H, Ph), 7.46 (m, 6 H, Ph), 7.71 (s, 1 H, N3H) ppm.

Complex 6: Complex **1b** (200 mg, 0.29 mmol) and theophylline·H_2O (58 mg, 0.29 mmol) in 50 mL of dichloromethane were stirred for 36 h. After filtration the volume was reduced to 10 mL in vacuo. Cooling to 4 °C yielded colourless crystals. The solvent was decanted and the crystals dried in vacuo, leaving behind 125 mg (50%) of **6** as a colourless powder. M.p. 241 °C. $C_{46}H_{53}BN_{10}O_2Zn$ (854.19): calcd. C 64.68, H 6.25, N 16.40; found C 64.48, H 6.24, N 16.29. IR (KBr): $\tilde{\nu}$ = 2540 cm^{-1} (m, BH), 1698 (s, CO). ^{1}H NMR ($CDCl_3$): δ = 1.12 [d, J = 7.0 Hz, 18 H, Me(-*i*Pr)], 2.55 [s, 9 H, Me(pz)], 2.63 (s, 3 H, NMe), 2.75 [sept, J = 7.0 Hz, 3 H, CH(*i*Pr)], 3.37 (s, 3 H, NMe), 6.04 (s, 1 H, C8H), 6.14 [s, 3, H(pz)], 6.91 (d, J = 8.0 Hz, 6 H, Ph), 7.20 (d, J = 8.0 Hz, 6 H, Ph) ppm.

Complex 7: A solution of **1a** (213 mg, 0.38 mmol) in 20 mL of dichloromethane was added to a suspension of theobromine·3H_2O (86 mg, 0.37 mmol) in 30 mL of methanol. After stirring for 12 h and filtration, the solution was evaporated to 30 mL. Upon cooling to 4 °C a fine precipitate of impure product was formed. This was filtered off and the filtrate evaporated to 10 mL. Further cooling to 4 °C yielded 156 mg (58%) of **7** as colourless crystals. M.p. 244 °C. $C_{37}H_{35}BN_{10}O_2Zn$ (727.95): calcd. C 61.05, H 4.85, N 19.24; found C 60.93, H 5.07, N 18.98. IR (KBr): $\tilde{\nu}$ = 2547 cm^{-1} (m, BH), 1655s, 1632 (vs, CO). ^{1}H NMR ($CDCl_3$): δ = 2.54 [s, 9 H, Me(pz)], 3.00 (s, 3 H, NMe), 3.52 (s, 3 H, NMe), 6.17 [s, 3 H, H(pz)], 7.10 (m, 9 H, Ph), 7.22 (s, 1 H, C8H), 7.56 (m, 6 H, Ph) ppm.

Complex 8a: A suspension of inosine (150 mg, 0.56 mmol) in 30 mL of methanol was treated with a solution of **1a** (316 mg, 0.56 mmol) in 40 mL of dichloromethane. After stirring for 12 h and filtration, the solution was evaporated to 20 mL. Cooling to 4 °C yielded colourless crystals. The solution was decanted and the residue dried in vacuo, leaving behind 325 mg (71%) of **8a** as colourless crystals. M.p. 320 °C (dec.). $C_{40}H_{39}BN_{10}O_5Zn$ (816.01): calcd. C 58.88, H 4.82, N 17.16; found C 58.66, H 4.81, N 17.28. IR (KBr): $\tilde{\nu}$ = 3274 cm^{-1} (broad OH), 2546 (m, BH), 1632 (vs, CO). ^{1}H NMR ([D_6]DMSO, assignments by COSY): δ = 2.58 [s, 9 H, Me(pz)], 3.49−3.72 (m, 2 H, C5′H_2), 3.95 (m, 1 H, C4′H), 4.11 (m, 1 H, C3′H), 4.45 (m, 1 H, C2′H), 5.16 (d, J = 4.8 Hz, 1 H, O3′H), 5.21 (d, J = 6.1 Hz, 1 H, O5′H), 5.36 (d, J = 6.4 Hz, 1 H, O2′H), 5.74 (d, J = 6.0 Hz, 1 H, C1′H), 6.09 (s, 1 H, C2H), 6.44 [s, 3 H, H(pz)], 7.11 (m, 9 H, Ph), 7.41 (m, 6 H, Ph), 7.96 (s, 1 H, C8H) ppm.

Complex 8b: Like **8a**, from inosine (32 mg, 0.31 mmol) and **1b** (212 mg, 0.31 mmol). Yield: 240 mg (83%) of **8b** as colourless needles. M.p. 206 °C. $C_{49}H_{57}BN_{10}O_5Zn$ (942.25): calcd. C 62.46, H

6.10, N 14.87; found C 61.90, H 6.01, N 14.49. IR (KBr): $\tilde{\nu}$ = 3430 cm^{-1} (broad, OH), 2542 (m, BH), 1639 (vs, CO). ^1H NMR ([D_6]DMSO, assignments by COSY): δ = 1.02 [d, J = 6.9 Hz, 18 H, Me(*i*Pr)], 2.56 [s, 9 H, Me(pz)], 2.69 [sept, J = 6.9 Hz, 3 H, CH(*i*Pr)], 3.46−3.70 (m, 2 H, C5′H_2), 3.90 (m, 1 H, C4′H), 4.09 (m, 1 H, C3′H), 4.37 (m, 1 H, C2′H), 5.13 (m, 2 H, O3′H and O5′H), 5.25 (d, J = 6.1 Hz, 1 H, O2′H), 5.68 (d, J = 5.0 Hz, 1 H, C1′H), 6.12 (s, 1 H, C2H), 6.39 [s, 3 H, H(pz)], 6.94 (d, J = 8.1 Hz, 6 H, Ph), 7.33 (d, J = 8.1 Hz, 6 H, Ph), 7.97 (s, 1 H, C8H) ppm.

Structure Determinations:[51] Crystals were obtained as described in the Exp. Sect.. Diffraction data were recorded at 180 K (**7**) and at room temp. (**2, 4′′, 8a**) on a Nonius CAD4 (**2**) or a Bruker Smart CCD diffractometer (**4′′, 7, 8a**). Empirical absorption corrections were applied for **4′′, 7** and **8a**. The structures were solved with direct methods and refined anisotropically with the SHELX program suite.[52] Hydrogen atoms were included with fixed distances and isotropic temperature factors 1.5 times those of their attached atoms. Parameters were refined against F^2. The R values are defined as $R_1 = \Sigma|F_0 - F_c|/\Sigma F_o$ and $wR_2 = [\Sigma[w(F_0^2 - F_c^2)^2]-\Sigma[w(F_0^2)^2]]^{1/2}$. Drawings were produced with SCHAKAL.[53] Table 1 lists the crystallographic data.

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