Metal-Stabilized Rare Tautomers of Nucleobases. 6.† Imino Tautomer of Adenine in a Mixed-Nucleobase Complex of Mercury(II)

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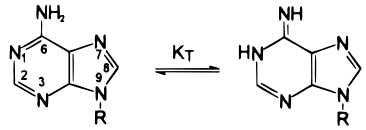
Received September 20, 1996[⊗]

(1,3-Dimethyluracil-5-yl)mercury(II), (1,3-DimeU-*C5*)Hg^{II}, reacts with the model nucleobase 9-methyladenine (9-MeA) to give the mixed-nucleobase complex [Hg(1,3-DimeU-*C5*)(9-MeA-*N6*)]$NO_3 \cdot H_2O$. Hg(II) binds to the adenine via the N6 position with N1 being protonated. The neutral adenine nucleobase is therefore present in its imino form, which represents the rare tautomer form of this nucleobase. The X-ray crystal structure analysis reveals an *anti* orientation of the (1,3-DimeU-*C5*)Hg^{II} entity with respect to N1 of 9-MeA and substantial differences in nucleobase geometry as compared to the amino tautomer form of 9-MeA. These differences refer to both the pyrimidine and the imidazole rings of the purine base. The possible relevance of this compound with regard to nucleobase cross-linking in DNA and nucleobase mispairing is discussed. Attempts to demonstrate mispairing between the metalated rare tautomer and "the wrong" bases 1-methylcytosine (1-MeC) and 9-ethylguanine (9-EtGH) in DMSO-d_6 proved unsuccessful due to a ligand exchange process at the heavy metal.

Introduction

It is estimated that the amino tautomer of the nucleobase adenine (A) exceeds the rare imino form (A*) by a factor of 10^4-10^5 (Scheme 1).[2] In principle, the rare tautomer can mispair either with cytosine, with adenine in its *syn* form, or with guanine in its *syn* form.[3] If not repaired, this may lead to spontaneous substitution mutations, specifically to transitions in the case of the A*C mispair and transversions with the purine−purine mispairs A^*A_{syn} and A^*G_{syn}. In many cases metal ions capable of covalently binding to DNA prove mutagenic.[4] One possibility for nucleobase mispairing, among others, involves a metalated rare tautomer. We have been studying this question in a number of cases.[5] With adenine we have tried to estimate the effect of Pt(II) binding to the N7 position on the tautomer equilibrium K_T but found the effect at most to be marginal.[6] We have now isolated a mixed 9-methyladenine (9-MeA), 1,3-dimethyluracil (1,3-DimeU) complex of Hg(II) which contains the imino tautomer form of 9-MeA exclusively. Generation of the metalated rare tautomer has been accomplished by Hg(II) binding to the exocyclic amino group of the adenine with a simultaneous proton shift from N6 to N1. The adenine thus remains in a neutral state, unlike in related complexes of CH_3Hg^{II}, where the nucleobase becomes anionic.[7] The only other structurally characterized complexes that appears to be relevant to our compound are those of a Mo_2 complex containing neutral 9-ethyladenine, $[Mo_2(CHF_2CO_2)_2(9\text{-EtA-}N7,N6)_2(MeCN)_2](BF_4)_2$, in which the dinuclear metal core spans across the N7 and N6 positions,[8] and of a CH_3Hg^{II} complex of neutral 9-methyl-8-azaadenine, in which the mercury is bonded to the exocyclic amino group and oriented *syn* with respect to N1.[9]

Scheme 1



A A*

Experimental Section

Preparation of Starting Compounds. The starting materials (OAc)Hg(1,3-DimeU-*C5*)[10] and 9-methyladenine (9-MeA)[11] were prepared as previously described. 1,3-Dimethyluracil (1,3-DimeU) was purchased from Sigma, and $Hg(OAc)_2$ from Fluka.

Preparation of [(1,3-Dimethyluracil-*C5*)Hg(9-MeA)]$NO_3 \cdot H_2O$. The compound was prepared by reacting (OAc)Hg(1,3-DimeU-*C5*) (0.07 mmol) with 9-MeA (0.07 mmol) in 1.5 mL of water with the pH adjusted to *ca.* 1.2 by means of 1 N HNO_3. After 3 days the crystals formed were filtered off, washed with water, and dried at 40 °C overnight. Anal. Calcd (found) for $C_{12}H_{16}N_8O_6Hg$: C, 25.3 (25.1); H, 2.8 (2.8); N, 19.7 (19.9). Yield: 30%. ^{1}H NMR (D_2O, pH* 2.4): 8.44, 8.29, 7.44, 3.90, 3.40, 3.30 ppm. ^{199}Hg NMR (D_2O, pH* 2.0): −1347 ppm, $^3J(^1H-^{199}Hg)$ 185 Hz. IR selected data (KBr; cm^{-1}): 3317 m, 1688 s, 1665 s, 1324 s, 651 m.

Instrumentation. IR spectra (KBr pellets) were recorded on a Perkin-Elmer 580B spectrometer. ^{1}H and ^{199}Hg NMR spectra (200.13, 35.79 MHz) were recorded on a Bruker AC200 instrument. Chemical shifts are given in ppm and are referenced to internal TSP (D_2O) and TMS (DMSO-d_6) (^{1}H) and external $HgMe_2$ (^{199}Hg), respectively. $J(^{199}Hg-^1H)$ values in complexes were determined with help of nondecoupled ^{199}Hg NMR spectra and/or taken directly from ^{1}H NMR spectra. pK_a values (in D_2O) were determined by plotting ^{1}H NMR chemical shifts *vs* the uncorrected pH (pH*).

† For part 5, see ref 5.

⊗ Abstract published in *Advance ACS Abstracts,* March 1, 1997.

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S0020-1669(96)01167-6 CCC: $14.00

Table 1. Crystallographic Data

formula	$C_{12}H_{16}N_8O_6Hg$
fw	568.90
cryst dimens, mm	0.08 × 0.09 × 0.17
cryst syst	monoclinic
space group	$P2_1/c$ (No. 14)
a, Å	11.976(3)
b, Å	6.958(2)
c, Å	20.550(6)
β, deg	106.31(2)
V, Å^3	1644(2)
d(calcd), g cm^{-3}	2.31
Z	4
μ(Mo Kα), cm^{-1}	94.11
temp, °C	−120
$2\theta_{max}$	46°
no. of reflecs measd	total: 2013
no. of indep reflecs ($I > 3\sigma(I)$)	1254
no. of variables	165
final R;[a] R_w[a]	0.028; 0.036
goodness of fit	1.02
max peak in final diff map, e/Å^3	0.6

[a] $R = \sum(|F_o|) - |F_c|)/\sum|F_o|$; $R_w = [\sum w(|F_o|) - |F_c|)^2/\sum|F_o|^2]^{1/2}$.

Table 2. Positional Parameters and *B*(eq) (Å^2) Values

atom	*x*	*y*	*z*	*B*(eq)[a]
Hg	0.10281(4)	0.20204(7)	−0.00318(3)	1.32(3)
O(1W)	−0.2503(7)	0.771(1)	0.0852(5)	2.4(4)
O(2U)	0.4376(7)	−0.078(1)	0.2597(4)	2.2(4)
O(4U)	0.3749(6)	0.052(1)	0.0356(4)	1.5(4)
O(11)	−0.1925(7)	0.035(1)	0.2338(5)	2.3(4)
O(12)	−0.0625(7)	−0.074(1)	0.1885(5)	2.1(4)
O(13)	−0.0262(7)	−0.063(1)	0.2978(4)	2.0(4)
N(1U)	0.2620(7)	0.042(1)	0.02021(5)	1.4(2)
N(1A)	−0.2172(8)	0.409(2)	−0.1340(6)	1.6(2)
N(3U)	0.4076(8)	−0.007(1)	0.1478(6)	1.7(2)
N(3A)	−0.3598(8)	0.443(1)	−0.0767(5)	1.6(2)
N(6A)	−0.0257(8)	0.296(2)	−0.0867(6)	1.8(2)
N(7A)	−0.1035(8)	0.254(1)	0.0401(6)	2.0(2)
N(9A)	−0.2834(8)	0.337(1)	0.0411(6)	1.5(2)
N(11)	−0.0921(8)	−0.036(1)	0.2407(7)	1.7(2)
C(2U)	0.374(1)	−0.017(2)	0.2069(8)	1.7(2)
C(2A)	−0.327(1)	0.460(2)	−0.1311(7)	1.5(2)
C(4U)	0.337(1)	0.056(2)	0.0858(8)	1.5(2)
C(4A)	−0.277(1)	0.375(2)	−0.0212(7)	1.4(2)
C(5U)	0.2188(9)	0.113(2)	0.0845(7)	1.2(2)
C(5A)	−0.1639(9)	0.327(2)	−0.0217(6)	1.2(2)
C(6U)	0.188(1)	0.107(2)	0.1413(7)	1.9(2)
C(6A)	−0.128(1)	0.341(2)	−0.0803(7)	1.3(2)
C(7U)	0.224(1)	0.029(2)	0.2635(7)	2.1(3)
C(8U)	0.528(1)	−0.067(2)	0.1534(7)	2.3(3)
C(8A)	−0.177(1)	0.268(2)	0.0799(8)	1.8(3)
C(10A)	−0.389(1)	0.358(2)	0.0640(7)	2.3(3)

[a] $B_{eq} = 8\pi^2/3[U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}\ aa^*bb^* \cos\gamma + 2U_{13}aa^*cc^* \cos\beta + 2U_{23}bb^*cc^* \cos\alpha]$.

X-ray Crystal Structure Determinations. All X-ray measurements were carried out on a Rigaku AFC6S diffractometer using Mo Kα radiation ($\lambda = 0.710\,69$ Å). Calculations were performed on a VAX station 3520 computer by using the TEXSAN 5.0 software[12] and in the later stages on a Silicon Graphics Personal Iris 4D35 computer with the teXsan 1.7 package.[13]

Relevant crystallographic data are listed in Table 1, and positional parameters are in Table 2. Unit cell dimensions were determined by applying the setting angles of 25 high-angle reflections. Three standard reflections were monitored during the data collection showing no significant variance. The intensities were corrected for absorption by applying ψ scans of several reflections with the transmission factors ranging from 0.88 to 1.00.

The structure was solved by Patterson and Fourier techniques. Full-matrix least-squares refinement with anisotropic displacement parameters for the Hg and O yielded the final R of 0.028 ($R_w = 0.036$). All hydrogen atoms were found in difference Fourier maps and refined with isotropic thermal parameters, except for the hydrogen atoms of the methyl groups which were treated as fixed contributions to the refinement. The final difference map was essentially featureless with the highest peak of 0.6 e/Å^3.

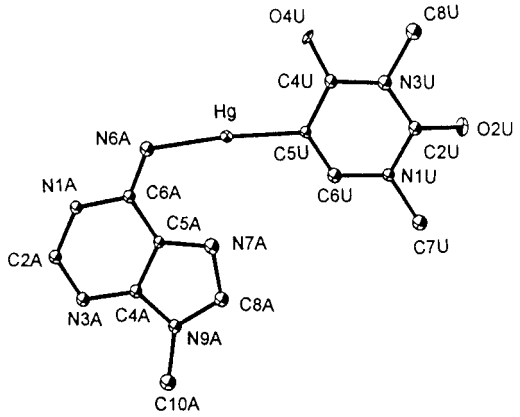

Figure 1. View of molecular cation of [(1,3-DimeU-*C5*)Hg(9-MeA-*N6*)]$NO_3 \cdot H_2O$ with atom-numbering scheme.

Table 3. Selected Bond Lengths (Å) and Angles (deg) of the Hg Coordination Sphere

Hg−N6A	2.06(1)	N6A−Hg−C5U	174.6(4)
Hg−C5U	2.04(1)	Hg−N6A−C6A	120(1)
Hg−O1W	2.769(9)	Hg−C5U−C4U	121(1)
Hg−N7A	2.87(1)	Hg−C5U−C6U	120.2(8)

Results and Discussion

Structure of the Title Compound. Figure 1 gives a view of the cation of [Hg(9-MeA-*N6*)(1,3-DimeU-*C5*)]$NO_3 \cdot H_2O$. Selected interatomic distances and angles are provided in Table 3. Hg is bound to the N6 position of the 9-methyladenine and C5 of the uracil ring. Bond lengths are in the normal range for Hg−N[14] and Hg−C bonds.[10,15,16] Relative to the N1 site of adenine the heavy metal is in an *anti* orientation. Since the adenine-N1 position is protonated, 9-MeA is present in its imino form, mercurated at the exocyclic amino group in the 6-position. The coordination geometry of Hg is not exactly linear (angle 174.6(4)°), probably because of a weak interaction with the water molecule (Hg−O1W 2.769(9) Å). Although the N7A··· Hg distance is only slightly longer (2.87(1) Å), the direction of the folding angle at Hg seems to rule against any substantial Hg−N7 bonding. In a 2-fold mercurated complex, [$(HgCH_3)_2$-(9-MeA-*N6*,*N1*)]$^+$, virtually the same Hg−N7 separation (2.86-(7) Å) is seen.[17] Binding to the 1,3-dimethyluracil ring is through the 5-position. The title compound thus represents another example of a crystallographically confirmed metal binding pattern to the C5 position of an uracil nucleobase.[10,15,16] There are no unusual features as far as bond lengths and angles of the uracil nucleobase are concerned. The two nucleobases are close to planar, except for some of the exocyclic groups of the 1,3-DimeU (maximum deviation of O2U, 0.047 Å) and are almost coplanar with each other, the dihedral angle being 2.9°. The Hg(II) is slightly out of the plane of the two bases, by 0.06 Å from 1,3-DimeU and by 0.09 Å from 9-MeA. The proton at C6U is pointing in the direction of N7A, but the distance C6U···N7A is too long (3.67(2) Å) for H bond formation. Intermolecular H bond formation of less then 3 Å occurs between the water molecule and O4U (2.80(1) Å) as well as

(12) TEXSAN 5.0: Single Crystal Structure Analysis Software. Molecular Structure Corp., The Woodlands, TX 77381, 1989.
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Table 4. Comparison of 9-MeA Geometries of the Title Compound and Amino Tautomer Form

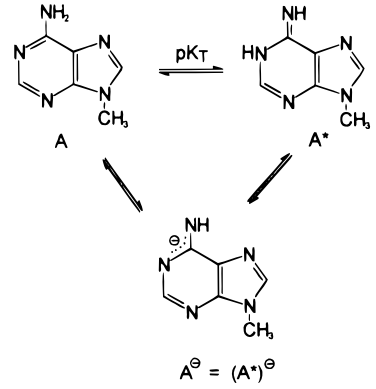
	title compd	amino tautomer[18a]
N1−C2	1.38(1)	1.335(2)
C2−N3	1.29(1)	1.326(2)
N3−C4	1.37(1)	1.351(2)
C4−C5	1.40(2)	1.380(2)
C5−C6	1.39(2)	1.411(2)
C6−N1	1.39(1)	1.357(2)
C5−N7	1.37(2)	1.389(2)
N7−C8	1.37(2)	1.311(2)
C8−N9	1.38(1)	1.365(2)
N9−C4	1.33(1)	1.370(2)
C6−N6	1.31(1)	1.329(2)
N9−C10	1.48(2)	1.453(3)
N1−C2−N3	123(1)	129.9(2)
C2−N3−C4	115(1)	110.0(1)
N3−C4−C5	124(1)	127.4(1)
C4−C5−C6	122(1)	116.8(1)
C5−C6−N1	111(1)	117.3(1)
C6−N1−C2	126(1)	118.7(1)
C5−N7−C8	105(1)	103.5(1)
N7−C8−N9	109(1)	114.4(2)
C8−N9−C4	109(1)	105.4(1)
N9−C4−C5	106(1)	106.4(1)
C4−C5−N7	110(1)	110.3(1)
N6−C6−C5	127(1)	124.3(1)
N6−C6−N1	122(1)	118.4(1)
C8−N9−C10	126(1)	128.4(1)
C10−N9−C4	125(1)	126.1(1)

nitrate oxygen O12 (2.84(1) Å) and between the nitrate oxygen O11 and the proton at N1A (2.84(2) Å).

Geometry of the Rare Tautomer. In Table 4, geometries of the normal amino tautomer of 9-MeA, as based on an accurate X-ray diffraction study,[18] and the imino tautomer ligand in our Hg(II) complex are compared. Despite the lower accuracy of the present structure determination, a number of significant[19] differences in the geometries exist. In the metal complex, the N1−C2 and N1−C6 bond lengths increase by 0.045 Å (4.5σ) and 0.033 Å (3.3σ), respectively, while C2−N3 and C4−C9 bonds become shorter, by 0.036 Å (3.6σ) and 0.040 Å (4.0σ). Almost all internal ring angles undergo significant changes. The most prominent change is the increase in the internal ring angle C2−N1−C6 from 118.7(1) to 126(1)°, corresponding to 7.3 σ. This change is clearly consistent with a proton sitting at the N1 position,[20,21] hence proving the imino tautomer structure. H bond formation with a nitrate oxygen (cf. above) further agrees with this interpretation. The increase of the internal ring angle at N1 is accompanied by a decrease in the adjacent ring angles N1−C6−C5 (by 6.3°, 6.3σ) and N1−C2−C3 (by 6.9°, 5.1σ). Qualitatively, these changes follow the trend seen in Pt complexes of the rare iminooxo tautomer form of cytosine.[5,22] Moreover, both the C2−N3−C4 (by 5°, 5σ) and the C4−C5−C6 angles (by 5.2°, 5.2σ) open up. An effect is even seen in the imidazole ring: The internal ring angle at C8 gets reduced (by 5.4°, 5.4σ) while that at N9 becomes larger (by 3.6°, 3.6σ). The increase of the external angle N1−C6−N6 (by 3.6°, 3.6σ) is possibly related to the heavy metal coordination at N6.

As we have previously discussed in detail for cytosine,[22] heavy metal binding to an exocyclic group of a nucleobase has a very minor effect on the overall geometry of the heterocyclic ring of the base. To a first approximation, the geometry of the 9-MeA ligand found in our complex can therefore be taken as that of the free imino tautomer of this nucleobase.

Scheme 2



Effect of Hg(II) on the Acidity of A*. The acidity of the free imino tautomer of 9-MeA (A*) can be estimated from the cycle outlined in Scheme 2 taking into account the reported pK_a of 16.7 [23] or 17.0 [24] for the deprotonation of the amino group of 9-MeA and assuming a $K_T = 10^{-5}$. Then,

$$pK_{A^*,A^{*\ominus}} = pK_{A,A^{*\ominus}} - pK_{A,A^*}$$

gives $pK_{A^*,A^{*\ominus}} \approx 12$.

Experimentally, the acidity of the proton at N1 of the Hg(II) complex has been determined by pH-dependent ^{1}H NMR spectroscopy (vide infra). Its value of p$K_a \approx 4.5$ is virtually identical with that of the free nucleobase (pK_a of 9-MeAH$^+$ = 4.4 ± 0.1 [6]). The effect of Hg(II) in our compound in increasing the acidity by 7.5 log units is thus higher than that of Pt(IV) (increase by 6.9 and 4.5 log units[22]) and that of Pt(II) (increase by 3 log units[5]) in similar iminooxo cytosine complexes. In essence, the electronic effect exercised by the (1,3-dimethyluracil-5-yl)mercury(II) entity is comparable with that of a proton. A strongly acidifying effect of Hg(II) is also observed in aqua complexes of Hg(II), for which pK_a values of 2.6−3.7 [25] have been measured.

NMR Spectra. The ^{1}H NMR spectra of the title compound in D_2O consist of single, sharp resonances of the aromatic and aliphatic protons in the pH range 1−12. Above pH 9 some precipitation of an unknown species occurs. Since the chemical shifts of the adenine resonances in our complex and the pH dependence of these resonances are very similar to those of free 9-MeA, the possibility of complex decomposition and formation of [(1,3-DimeU-*C5*)Hg(H_2O)]$^+$ was considered. However, neither the chemical shift of the ^{199}Hg resonance nor the coupling constant $^3J(^1H(6)-^{199}Hg)$ of 185 Hz, visible at least up to pH* 7.6, is consistent with an oxygen donor being *trans* to C5. Then J values of ≥200 Hz are to be expected.[15] Rather, this coupling constant is close to that observed for [(1,3-DimeU-*C5*)Hg(1-MeC-*N4*)]$^+$ (179 Hz).[15] Moreover, the ^{1}H NMR spectrum in DMSO-d_6 provides no indication of complex decomposition (*vide infra*). We therefore conclude that the (1,3-DimeU-*C5*)Hg^{II} in fact resembles a proton as far as the effects on acid/base equilbria and chemical shifts are concerned. There is no indication from ^{1}H NMR spectra in D_2O for any dismutation of our complex with formation of {[(1,3-DimeU-*C5*)Hg]$_2$(9-MeA)} and free 9-MeA, as is typical of CH_3Hg^{II}

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(19) σ defined as $\sigma = (\sigma_1^2 + \sigma_2^2)^{1/2}$ with σ_1 and σ_2 being the errors in bond lengths and angles that are compared.
(20) Singh, C. *Acta Crystallogr.* **1965**, *19*, 861.
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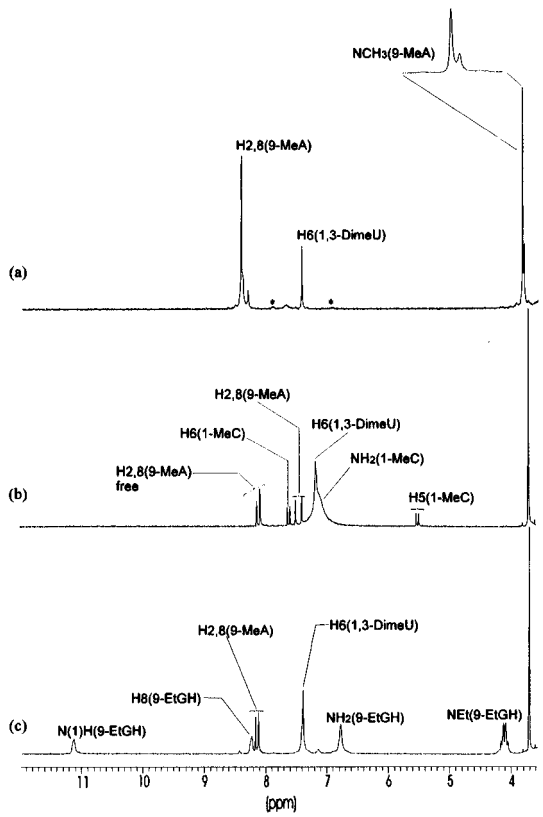


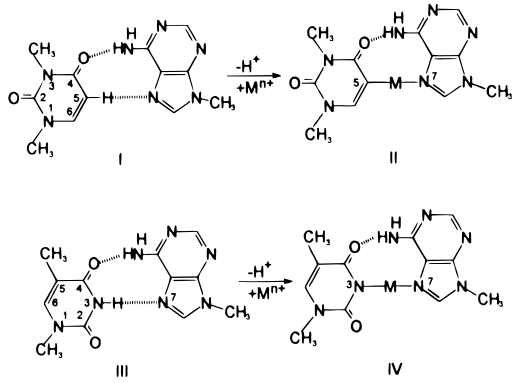
Figure 2. Sections of ^{1}H NMR spectra (200 MHz, DMSO-d_6) of (a) the title compound, (b) the title compound in the presence of an equivalent amount of 1-MeC, and (c) the title compound in the presence of an equivalent amount of 9-EtGH.

complexes of 9-MeA[7] and 9-methyl-8-azaadenine[9] in DMSO. Moreover, no doubling of resonances is observed in D_2O that could be interpreted in terms of slow *syn* ⇌ *anti* equilibrium, hence rotation of the Hg entity about the C6−N6 bond. Again, this phenomenon is seen with CH_3Hg^{II} complexes.[7,9,24] Our observation also holds up for the neutral and basic pH range, where the N1 position becomes deprotonated and the double-bond character of C6−N6 is expected to diminish.

The ^{1}H NMR spectrum in DMSO-d_6 is likewise relatively simple (Figure 2a). Compared to spectra of related nucleobase complexes of CH_3Hg^{II} in this solvent[7,9,24] it is also less informative. Neither the N(1)H nor the N(6)H protons are observed, probably because of rapid exchange with residual water, and the two aromatic protons H2 and H8 coincide at 8.43 ppm. However, the N−CH_3 resonance of the adenine is split (3.84 and 3.81 ppm, 4:1) and there are two weak resonances at 8.31 and 8.37 ppm which, on the basis of their relative intensities, could be due to aromatic protons of a second species. Since resonances due to free 9-MeA are absent, we propose that slow rotation of a Hg entity about the C6−N6 bond takes place, leading to *syn* and *anti* rotamers.

Using ^{1}H NMR spectroscopy with DMSO-d_6 as solvent, we have also tried to detect H-bonding interactions between the Hg(II) complex and 1-MeC as well as 9-ethylguanine in attempt to model base mispairing between the metalated rare 9-MeA* tautomer and a "wrong" base (see also the section "Relevance"). However, the dynamics of the complex do not permit this aspect to be studied. Our findings indicate that with these two nucleobases adenine substitution takes place. Thus, addition of 1-MeC to the Hg(II) complex leads to partial displacement of the adenine nucleobase (Figure 2b). 1-MeC resonances are different from those in the absence of the Hg(II) complex, and variation of the amount of 1-MeC added indicates rapid exchange of free and coordinated cytosine on the NMR time scale. The cytosine −NH_2 resonance is broad and overlaps with the H6 resonance of the 1,3-DimeU. No statement concerning a possible structure of the new compound can be made. However, the fact that two sets of aromatic 9-MeA resonances are observed, free and complexed, with the latter displaying shifts that are not identical with those of the compound in the absence of 1-MeC, tentatively suggests that Hg has extended its coordination sphere and that a compound containing 9-MeA, 1-MeC, and 1,3-DimeU may have formed. In D_2O (pH* 6.3), displacement of the adenine ligand by 1-MeC (added in equimolecular concentration) is complete. The chemical shifts of the 1-MeC resonances (CH_3, 3.41 ppm; H5, 6.11 ppm, d, ^3J 7.4 Hz; H6, 7.66 ppm) clearly indicate complex formation, and Hg is still bound to the uracil ligand (H6, 7.49 ppm; $^3J(^1H(6)-^{199}Hg)$ 190 Hz). The data appear not to be inconsistent with N4 binding of 1-MeC.[15]

Scheme 3



In the presence of 9-EtGH (DMSO-d_6) rapid exchange between the two different purine nucleobases takes place, leading to sharp resonances in the ^{1}H NMR spectrum (Figure 2c). Compared to free 9-EtGH in the same solvent, all resonances are strongly shifted downfield. At Hg:9-EtGH = 1:1 these shifts are ca. 0.07 ppm for CH_3, 0.19 for CH_2, 0.52 ppm for NH_2, 0.62 ppm for H8, and 0.69 ppm for N(1)H.

Relevance. Our original attempt was to prepare a metal-modified analogue (Scheme 3, II) of a hypothetical base pair between 1,3-DimeU and 9-MeA in which we had replaced the aromatic C5 proton by a linear Hg(II) entity (Scheme 3, I). Although CH···N hydrogen bonds among nucleobases are rare,[26] we have recently demonstrated their existence in a metalated nucleobase quartet.[27] This metal-modified base pair would have had a close similarity with the metalated analogue (IV) of the Hoogsteen pair between adenine and thymine (III). The corresponding with M = *trans*-Pt$(NH_3)_2$ has recently been described by us.[28] To our surprise, Hg binding at pH 1 does not occur at N7 of the 9-MeA but rather at the exocyclic N6 amino group with a proton shift to N1. This finding thus confirms a similar observation made with CH_3Hg^{II} and 9-methyl-8-azaadenine.[9] With 1-methylcytosine (1-MeC) instead of 9-MeA we had recently observed a similar reaction, again at the exocyclic amino group rather than at the endocyclic N3 position. Both findings are surprising in view of reports that CH_3Hg^{II} binds to the exocyclic ring nitrogens of these nucleobases at high pH only.[24,29] The question may be raised if the possibility of the proton switch to N3, hence generation of a metalated rare tautomer, had been overlooked. On the other hand, a recent NMR study on the interaction of $Hg(ClO_4)_2$ with

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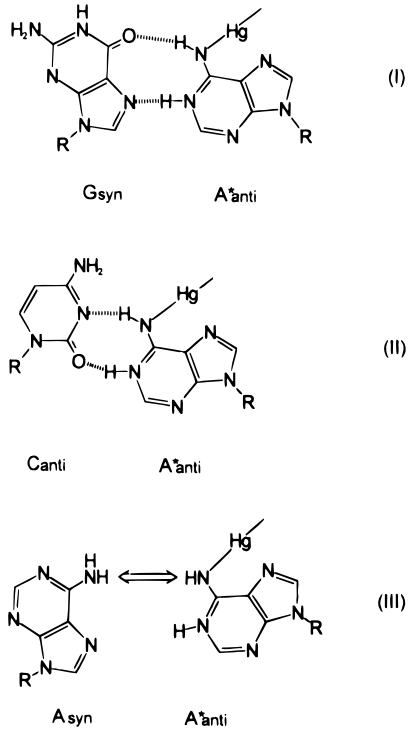
Scheme 4

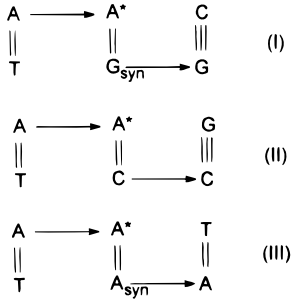


the adenine,thymine pair in a DNA dodecamer carried out at pH 7 had been interpreted in terms of Hg(II) cross-linking the exocyclic amino group of adenine and O4 of thymine, with the adenine rather than the thymine deprotonated.[30] A major difference between this proposed model and our model compound, apart from uracil being bound to Hg via the C5 position instead of O4, refers to the fact that both nucleobases have switched from the normal *anti* to *syn* orientations.[31] As a consequence of the purine rotation, the distance between the groups corresponding to the C1′ atoms of the sugars in double-stranded nucleic acids becomes quite short, 7.69(2) Å for C7U−C10A. This compares with *ca.* 8.65 Å for the Hoogsteen pair between T and A.[32] The N9A−C10A−C7U and N1U−C7U−C10A angles likewise change from 56 and 44° in the Hoogsteen pair[32] to 50 and 90° in our complex.

As to possible mispairing schemes of the title compound, the following ones are feasible (Scheme 4): First, a mispair with guanine in a *syn* and A* in the normal *anti* orientation (I); second, a mispair between cytosine and A* with both bases in the normal *anti* conformation (II).

The existence of A*, G_{syn} has been postulated as a central mispairing step during the transversion of an AT pair to a CG pair[3] (Scheme 5, I). The geometry of this mispair should be virtually identical with that between neutral guanine in a *syn* orientation and protonated adenine in the normal *anti* orientation, G_{syn}, HA^{+}_{anti}, the existence of which has been established in mismatched DNA fragments using X-ray diffraction[33] and NMR spectroscopy.[34] The interglycosidic bond separation of 10.8 Å in this mismatch is close to that of standard Watson−Crick pairs and therefore would fit well into DNA. The heavy metal entity would be easily accommodated in the major groove.

Scheme 5



The A*, C mispair could account for the mispairing step that causes transitions of type AT → GC [3] (Scheme 5, II). This mismatch has been proposed to involve two H bonds between N1H of A* and N3 of C as well as between N6 of A* and N4H of C, with the imino proton at A* not involved and oriented toward N7.[3] An analogous scheme could not be accomplished with our metal compound since there the imino proton of A* points toward the mismatched base. There is, however, the alternative possibility of a mismatch geometry (Scheme 4, II) as established by X-ray crystallography in a duplex DNA dodecamer containing a mismatch between a cytosine and an adenine protonated at N1,[35] with the cytosine somewhat slipped and two H bonds between O2 of C and N1H of HA^{+} as well as between N3 of C and N6H of HA^{+}. While the pseudo-2-fold axis of the Watson−Crick pairs is lost in this mismatch, the interglycosidic distance of 10.3 Å still permits accommodation in the double helix. Again, the Hg(II) ion would sit in the major groove and be capable of carrying any other ligand.

A third mismatch, involving A* and A_{syn} during the AT → TA transversion (Schemes 4 and 5, III),[3,6] cannot be realized with metalated A* if the metal, as in our compound, is *anti* to the N3 site.

Conclusion

A mixed nucleobase complex of Hg(II) has been prepared which contains the rare imino tautomer form of the model nucleobase 9-MeA. The geometry of the rare tautomer in its uncomplexed form is expected to be very similar to that found in the metal complex. On the basis of geometrical considerations, nucleobase mismatches between the metalated imino tautomer and guanine of cytosine are feasible, which could very well be relevant to the mutagenic potential of Hg(II) compounds. We are aware, that other sources of mutagenic events exist as well, e.g. formation of wobble pairs that include ionized nucleobases.

Acknowledgment. The work has been supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Human Capital and Mobility program.

Supporting Information Available: Tables of thermal displacement parameters, including those of H atoms, bond lengths and angles, least-squares planes, and intermolecular distances and a figure showing a packing scheme (8 pages). Ordering information is given on any current masthead page.

IC961167P

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