reaction intermediate. The design sequence starts with determining the critical diffusion distances in the binary diffusion couples. A ternary composite is then prepared such that all of the diffusion distances are subcritical, the layer sequence is chosen so as to control the interdiffusion process,[32] and the stoichiometry is selected to be that of the desired ternary compound. Upon heating, this composite should form a homogeneous, ternary, amorphous alloy.[33]

The key to obtaining the desired compound is controlling the nucleation of this amorphous alloy. There are several approaches which can be used to achieve this goal. Stoichiometry has been shown to control the phase which nucleates from the amorphous alloy.[13] Since the amorphous alloy contains three elements, nucleation of binary compounds should be suppressed and should favor the nucleation of ternary compounds. Additional experimental variables which can be used to influence nucleation temperatures include the crystal structure of the substrate surface[34] and the addition of controlled impurities acting as nucleation agents.[35] This synthetic sequence, separating the mixing of the elemental reactants from nucleation of crystalline compounds, should permit the synthesis of ternary compounds which are unstable with respect to competing binary phases. Work toward this goal is in progress.

## Conclusion

We have shown that the course of a solid-state reaction can be controlled by varying the length scale of the initial composite. A mechanism for the solid-state reaction of ultrathin films is presented. The synthetic importance of using diffusion distances to control the intermediates of the solid-state reaction is emphasized. Further work based upon the proposed mechanism is focused upon directly nucleating ternary compounds from amorphous precursors and controlling nucleation and the synthesis of single-crystal thin films from the homogeneous, amorphous alloy intermediate.

**Acknowledgment**. We acknowledge the assistance of T. Novet, J. McConnell, and C. Grant for helpful discussions and advice. This work was supported in part by a Young Investigator Award from the Office of Naval Research (No. N0014-87-K-0543). Support by the National Science Foundation (DMR-8704652), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Oregon is also gratefully acknowledged.

**Registry No.** Mo, 7439-98-7; Se, 7782-49-2; $MoSe_2$, 12058-18-3.

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(32) The interdiffusion process can be controlled by choosing the layering sequence of the modulation composite such that those elements that form very stable binary compounds do not have a change to interact directly. An example of this for ternary phases is the layering sequence Cu–Mo–Cu–Se instead of the layering sequence of Mo–Cu–Mo–Se. In the first example, the copper alloys almost immediately with the selenium and it is this compound that then interdiffuses with the molybdenum. In the second, the molybdenum and selenium alloy below the interdiffusion temperature of molybdenum and copper.

(33) Work in progress.

(34) Tung, R. T. *J. Vac. Sci. Technol. A* **1987**, *5*, 1840–1844.

(35) Glass ceramics are formed by the controlled crystallization of a glass such that many nuclei are formed. The resultant fine grained ceramics have very high strength and adjustable thermal expansion coefficients.

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# Ag(I) Modified Base Pairs Involving Complementary (G, C) and Noncomplementary (A, C) Nucleobases. On the Possible Structural Role of Aqua Ligands in Metal-Modified Nucleobase Pairs†

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*Received November 18, 1991*

**Abstract:** Two Ag(I) complexes containing the model nucleobases 1-methylcytosine (1-MeC), 9-methyladenine (9-MeA), and 7,9-dimethylguanine (7,9-DimeG) have been prepared and studied: $[Ag(1\text{-MeC-}N^3)(9\text{-MeA-}N^7)(H_2O)]NO_3$ (**2**) crystallizes in the space group $P2_1/a$, $a = 11.167$ (2) Å, $b = 13.437$ (2) Å, $c = 11.520$ (2) Å, $\beta = 109.79$ (2)°, $V = 1626$ (1) Å$^3$, $Z = 4$. Ag has a severely distorted trigonal-planar coordination geometry with two strong bonds (2.128 (2) Å and 2.120 (2) Å) to the nitrogens of the nucleobases and a weak bond (2.664 (2) Å) to a water molecule. The N–Ag–N vector is markedly nonlinear (angle at Ag 165.8 (1)°). Both nucleobases and the water molecule are virtually coplanar. Intramolecular H bonding is between O(2) of 1-MeC and N(6) of 9-MeA (3.053 (3) Å) as well as between N(4) of 1-MeC and the aqua ligand (2.894 (4) Å). Structural details of the structure of **2** clearly demonstrate that the water molecule is an integral part of the "metal-modified" base pair. A second mixed-nucleobase complex of composition $[Ag(1\text{-MeC})(7,9\text{-DimeG})NO_3]_2\cdot[(1\text{-MeC})(7,9\text{-DimeGH})PF_6]\cdot 10H_2O$ (**3**) has been prepared and characterized by elemental analysis and $^1H$ NMR spectroscopy. On the basis of the structure of **2** an alternative model to existing hypotheses on Ag–DNA interactions is put forward which considers the "insertion" of a metal-aqua entity into an existing base pair.

## Introduction

Ever since interactions between metal ions and nucleic acids or their constituents, the nucleobases, became of general interest, Ag(I) has played a major role in such studies.[2-15] At an early stage it became evident, that Ag(I) has a distinct preference for binding to endocyclic ring nitrogen atoms, even with displacement of protons, e.g., N(3)H of thymine (uracil) and N(1)H of inosine.[7,11] Studies involving isolated nucleobases and models

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† Dedicated to Prof. Wolfgang Beck.

(1) (a) University of Dortmund. (b) University of Virginia.

(2) Yamane, T.; Davidson, N. *Biochim. Biophys. Acta* **1962**, *55*, 609 and 780.

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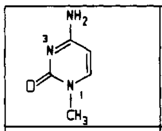
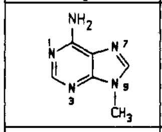
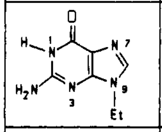
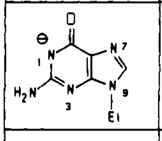
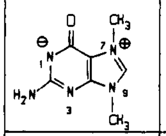
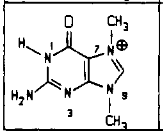
0002-7863/92/1514-4644$03.00/0 © 1992 American Chemical Society

**Chart I**

| | Name | Abbreviation | Charge |
|---|---|---|---|
|  | 1-methylcytosine | 1-MeC | neutral |
|  | 9-methyladenine | 9-MeA | neutral |
|  | 9-ethylguanine | 9-EtGH | neutral |
|  | [9-ethylguanine] anion | $[9\text{-EtG}]^-$ | anionic |
|  | 7,9-dimethylguanine | 7,9-diMeG | zwitterionic |
|  | [7,9-dimethylguaninium] cation | $[7,9\text{-diMeGH}]^+$ | cationic |

thereof,[16-26] in particular those that included X-ray structure analysis,[18-22] have contributed much to the present understanding of Ag(I) nucleobase complex formation. Without exception, these model studies were performed on binary systems, containing a single nucleobase and a single metal (Ag(I)). Consequently, the models derived from these studies appear to be relevant primarily for ordered structures of the respective homooligonucleotides in the presence of Ag(I) only, yet of limited usefulness for the question of Ag(I)–DNA complex formation.

**Table I.** Crystallographic Data for **2**

| | |
|---|---|
| **A. Crystal Data** | |
| empirical formula | $AgO_5N_9C_{11}H_{16}$ |
| formula wt | 462.17 |
| crystal color, habit | colorless, needle |
| crystal dimensions (nm) | 0.410 × 0.280 × 0.220 |
| crystal system | monoclinic |
| no. reflecns used for unit cell determination ($2\theta$ range) | 25 (28.0–32.0°) |
| lattice parameters | |
| $a$, Å | 11.167 (2) |
| $b$, Å | 13.437 (2) |
| $c$, Å | 11.520 (2) |
| $\beta$, deg | 109.79 (2) |
| $V$, Å$^3$ | 1626 (1) |
| space group | $P2_1/a$ (no. 14) |
| Z value | 4 |
| $D_{calc}$, g/cm$^3$ | 1.887 |
| $F_{000}$ | 928 |
| $\mu_{(MoK\alpha)}$, cm$^{-1}$ | 12.71 |
| **B. Intensity Measurements** | |
| diffractometer | Enraf-Nonius CAD-4 |
| radiation | Mo K$\alpha$ ($\lambda$ = 0.71069 Å) |
| temperature | −120 °C |
| scan type | $\omega$–$2\theta$ |
| scan width | (0.75 + 0.35 tan $\theta$) ° |
| $2\theta_{max}$ | 50° |
| no. of reflctns measd | total: 3148<br>unique: 2990 ($R_{int}$ = 0.018) |
| corrections | Lorentz–polarization<br>absorption<br>(trans. factors: 0.82–1.38) |
| **C. Structure Solution and Refinement** | |
| structure solution | Patterson method |
| refinement | full-matrix least-squares |
| function minimized | $\sum w(\lvert F_o\rvert - \lvert F_c\rvert)^2$ |
| least-squares weights | $4F_o^2/\sigma^2(F_o^2)$ |
| $p$-factor | 0.05 |
| anomalous dispersion | all non-hydrogen atoms |
| no. observations ($I > 3.00\sigma(I)$) | 2351 |
| no. variables | 299 |
| reflcn/parameter ratio | 7.86 |
| residuals: $R$; $R_w$ | 0.023; 0.032 |
| goodness of fit indicator | 1.05 |
| maximum peak in final diff. map | 0.31 e$^-$/Å$^3$ |

We have previously reported on ternary and quaternary systems containing two different metals, including Ag(I)[27] and one or two (different) model nucleobases.[28] In these compounds, the inert Pt(II) was fixed to ring N atoms of the nucleobase first, followed by attachment of the labile (Ag(I) at exocyclic oxygens adjacent to the metal binding site.

In the ternary complexes described in this work two *different* nucleobases are connected by the Ag(I) via ring nitrogen atoms. The resulting compounds can be considered metal-modified base pairs[29] with the metal formally replacing a proton in a hydrogen bond between two nucleobases.

Chart I lists structures and abbreviations of the model nucleobases applied in this work.

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(28) Schöllhorn, H.; Thewalt, U.; Lippert, B. *Inorg. Chim. Acta* **1987**, *135*, 155.

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**Table II.** Positional Parameters and *B*(eq) for **2**[a]

| atom | *x* | *y* | *z* | *B*(eq) |
|---|---|---|---|---|
| AG | 0.00489 (2) | 0.28142 (2) | 0.24387 (2) | 1.91 (1) |
| O1N | 0.1452 (3) | 0.7336 (2) | 0.0478 (3) | 3.8 (1) |
| O1W | 0.1528 (2) | 0.4007 (2) | 0.1662 (2) | 2.7 (1) |
| O2C | −0.0793 (2) | 0.0761 (1) | 0.2847 (2) | 2.02 (7) |
| O2N | 0.1251 (2) | 0.5760 (2) | 0.0285 (2) | 3.1 (1) |
| O3N | 0.0563 (3) | 0.6530 (2) | 0.1568 (3) | 4.8 (1) |
| N1A | −0.2739 (2) | 0.3504 (2) | 0.5070 (2) | 2.09 (9) |
| N1C | 0.0211 (2) | −0.0333 (2) | 0.1996 (2) | 1.72 (8) |
| N1N | 0.1086 (2) | 0.6540 (2) | 0.0790 (2) | 2.13 (9) |
| N3A | −0.2485 (2) | 0.5260 (2) | 0.4772 (2) | 1.85 (9) |
| N3C | 0.0507 (2) | 0.1397 (2) | 0.1877 (2) | 1.59 (8) |
| N6A | −0.1799 (3) | 0.2263 (2) | 0.4282 (3) | 2.1 (1) |
| N4C | 0.1812 (3) | 0.2003 (2) | 0.0869 (2) | 2.2 (1) |
| N7A | −0.0646 (2) | 0.4010 (2) | 0.3230 (2) | 1.68 (8) |
| N9A | −0.1109 (2) | 0.5569 (2) | 0.3571 (2) | 1.63 (8) |
| C2A | −0.2936 (3) | 0.4473 (2) | 0.5202 (3) | 2.1 (1) |
| C2C | −0.0058 (2) | 0.0623 (2) | 0.2262 (2) | 1.7 (1) |
| C4A | −0.1738 (3) | 0.4967 (2) | 0.4137 (2) | 1.5 (1) |
| C4C | 0.1311 (3) | 0.1224 (2) | 0.1244 (2) | 1.8 (1) |
| C5A | −0.1449 (3) | 0.3997 (2) | 0.3926 (2) | 1.5 (1) |
| C5C | 0.1597 (3) | 0.0237 (2) | 0.0985 (3) | 2.0 (1) |
| C6A | −0.1990 (3) | 0.3232 (2) | 0.4420 (2) | 1.7 (1) |
| C6C | 0.1038 (3) | −0.0510 (2) | 0.1364 (3) | 1.9 (1) |
| C7C | −0.0376 (4) | −0.1169 (2) | 0.2427 (3) | 2.5 (1) |
| C8A | −0.0483 (3) | 0.4955 (2) | 0.3042 (3) | 1.8 (1) |
| C9A | −0.1162 (4) | 0.6650 (2) | 0.3490 (3) | 2.4 (1) |

[a] Positional parameters for protons and anisotropic thermal parameters of the heavy atoms are given in the supplementary material.

## Experimental Section

1-Methylcytosine (1-MeC),[30] 9-methyladenine (9-MeA),[31] and [Ag(1-MeC)]$NO_3$ (**1**)[19] were prepared as described in the literature; 9-ethylguanine (9-EtGH) and 7,9-dimethylguanine (7,9-DimeG) were purchased from Chemogen, Konstanz (FRG).

[Ag(1-MeC)(9-MeA)($H_2O$)]$NO_3$ (**2**) was prepared as follows: 1 mmol of **1** was dissolved in 20 mL of $H_2O$ at 50 °C (pH 6–7) and 1 mmol of 9-MeA, dissolved in 25 mL of $H_2O$ at 50 °C, was added. The warm solution was filtered from a small amount of undissolved material and cooled to room temperature. The white gel that formed was kept in air for several days and eventually formed colorless, transparent crystals in over 80% yield. Anal. Calcd for $AgC_{11}H_{16}N_9O_5$: Ag, 23.19; C, 28.40; H, 3.47; N, 27.75. Found: Ag, 23.4; C, 28.5; H, 3.6; N, 27.7.

[Ag(1-MeC)(7,9-DimeG)($NO_3$)]$_2$·[(1-MeC)(7,9-DiMeGH)$PF_6$]·$10H_2O$ (**3**) was obtained by mixing 1 mmol of **1** and 1 mmol of 7,9-DimeG in 40 mL of $H_2O$ at 40 °C (pH 5.5–6) and adding 150 mg of $KPF_6$ to the solution. Crystallization, which was performed at 90 °C, gave 180 mg (34%) of colorless crystals of **3**. Without addition of $KPF_6$, the relatively poorly soluble starting compound **1** crystallized preferentially. The IR spectrum of **3** was consistent with both $NO_3^-$ and $PF_6^-$ being present. Anal. Calcd for $Ag_2C_{36}H_{69}N_{26}O_{22}PF_6$: C, 27.39; H, 4.41; N, 23.07; Ag, 13.66. Found: C, 27.8; H, 3.8; N, 23.4; Ag, 13.3.

IR spectra of **1–3** were recorded as KBr pellets on a Perkin-Elmer 580 instrument. There were no signs of formation of AgBr. Raman spectra were recorded on a Coderg PH1 spectrometer with Kr laser excitation (647.1 nm). $^1H$ NMR spectra were recorded both on Jeol JNM-FX 60 and Bruker AC200 instruments in $Me_2SO$-$d_6$ with TMS as internal reference. $Me_2SO$-$d_6$ was kept over molecular sieves prior to use or used as obtained.

Experimental details of the X-ray data collection, the structure solution, and refinement as well as crystal data of **2** are compiled in Table I. The structure was solved by heavy atom methods (Patterson and Fourier maps) in TEXSAN 5.0.[32] Absorption corrections were applied by using the DIFABS program.[33] Final atomic coordinates and equivalent isotropic temperature factors are given in Table II. The anisotropic thermal parameters are included in the supplementary material.

## Results

**Formation and Characterization of AgCA (2).** The title compound [Ag(1-MeC-$N^3$)(9-MeA-$N^7$)($H_2O$)]$NO_3$ (**2**) was obtained by mixing aqueous solutions of Ag(1-MeC)$NO_3$ (**1**) and 9-MeA in 1:1 ratio. The viscous gel that formed immediately, solidified to give crystalline **2** within a few days. While elemental analysis and $^1H$ NMR spectroscopy (vide infra) confirmed the composition of **2**, the metal binding site at the 9-MeA ligand was uncertain. Raman spectra, which proved of diagnostic value in identifying Pt(II) binding sites 9-MeA,[34,35] were of no help in the present case.[36]

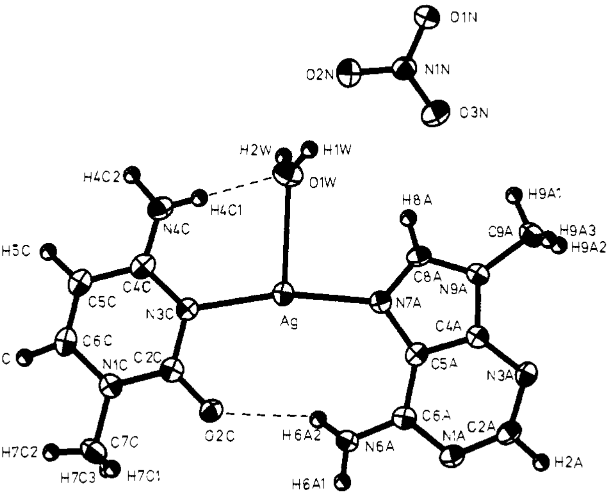

**Figure 1.** ORTEP drawing (50% probability ellipsoids) of the asymmetric unit of the [Ag(1-MeC)(9-MeA)($H_2O$)]$NO_3$ (**2**) structure.

**Table III.** Selected Interatomic Distance (Å) and Angles (deg) in **2**

| | | | |
|---|---|---|---|
| Ag–N3C | 2.128 (2) | N3C–C4C | 1.355 (3) |
| Ag–N7A | 2.120 (2) | N6A–C6A | 1.338 (4) |
| Ag–O1W | 2.664 (2) | N4C–C4C | 1.326 (4) |
| O2C–C2C | 1.240 (3) | N7A–C5A | 1.391 (3) |
| N1A–C2A | 1.339 (4) | N7A–C8A | 1.312 (4) |
| N1A–C6A | 1.348 (3) | N9A–C4A | 1.373 (3) |
| N1C–C2C | 1.377 (4) | N9A–C8A | 1.353 (3) |
| N1C–C6C | 1.377 (4) | N9A–C9A | 1.455 (4) |
| N1C–C7C | 1.468 (4) | C4A–C5A | 1.384 (4) |
| N3A–C2A | 1.336 (4) | C4C–C5C | 1.419 (4) |
| N3A–C4A | 1.342 (3) | C5A–C6A | 1.405 (4) |
| N3C–C2C | 1.366 (4) | C5C–C6C | 1.332 (4) |
| N1N–O1N | 1.241 (3) | N1N–O2N | 1.243 (3) |
| N1N–O3N | 1.224 (3) | | |

| | | | |
|---|---|---|---|
| N3C–Ag–N7A | 165.80 (8) | O2C–C2C–N1C | 119.6 (2) |
| N3C–Ag–O1W | 101.28 (9) | O2C–C2C–N3C | 121.7 (3) |
| N7A–Ag–O1W | 92.73 (8) | N1C–C2C–N3C | 118.6 (2) |
| C2A–N1A–C6A | 118.9 (2) | N3A–C4A–N9A | 126.8 (2) |
| C2C–N1C–C6C | 120.9 (2) | N3A–C4A–C5A | 126.7 (2) |
| C2C–N1C–C7C | 118.9 (2) | N9A–C4A–C5A | 106.6 (2) |
| C6C–N1C–C7C | 120.2 (2) | N3C–C4C–N4C | 118.0 (3) |
| C2A–N3A–C4A | 110.6 (2) | N3C–C4C–C5C | 120.7 (2) |
| Ag–N3C–C2C | 113.4 (2) | N4C–C4C–C5C | 121.3 (2) |
| Ag–N3C–C4C | 126.1 (2) | N7A–C5A–C4A | 108.9 (2) |
| C2C–N3C–C4C | 120.5 (2) | N7A–C5A–C6A | 133.8 (3) |
| Ag–N7A–C5A | 129.8 (2) | C4A–C5A–C6A | 117.4 (2) |
| Ag–N7A–C8A | 124.8 (2) | C4C–C5C–C6C | 118.1 (2) |
| C5A–N7A–C8A | 105.1 (2) | N1A–C6A–N6A | 118.9 (2) |
| C4A–N9A–C8A | 106.3 (2) | N1A–C6A–C5A | 117.4 (2) |
| C4A–N9A–C9A | 127.1 (2) | N6A–C6A–C5A | 123.7 (2) |
| C8A–N9A–C9A | 126.5 (2) | N1C–C6C–C5C | 121.1 (3) |
| N1A–C2A–N3A | 129.1 (2) | N7A–C8A–N9A | 113.2 (2) |
| O1N–N1N–O2N | 118.4 (2) | O2N–N1N–O3N | 121.1 (3) |
| O1N–N1N–O3N | 120.5 (3) | | |

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(36) Two intense 9-MeA modes at 717 and 762 cm$^{-1}$ did not fit the pattern of Pt(II) to either N1 or N7 binding. The intense 1-MeC ring mode at 790 cm$^{-1}$ was at a position close to that of Pt(II) compounds with N(3) bound 1-MeC, see e.g.: Faggiani, R.; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1982**, *21*, 3210.

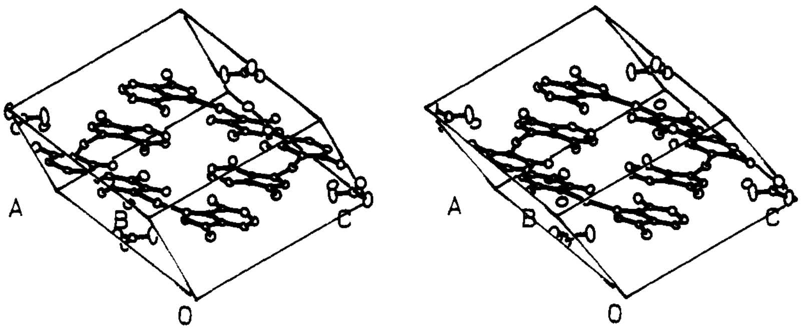

**Figure 2.** Packing diagram of **2**.

Figure 1 illustrates the molecular cation of **2** and the nitrate anion. Relevant distances and angles are given in Table III. Ag(I) binding is through N(3) of the cytosine base and N(7) of the adenine, with an additional weak bond (2.664 (2) Å) to a water oxygen. The orientation of the two bases is *anti* with respect to the N–Ag–N entity. Formally, the cation may be considered an analogue of a reversed Hoogsteen base pair between an adenine and a protonated cytosine, with the proton displaced by Ag(I). Except for the presence of the aqua ligand in **2**, the overall structure of the cation of **2** is similar to that of *trans*-$[(NH_3)_2Pt(1\text{-MeC-}N^3)(9\text{-MeA-}N^7)](ClO_4)_2$.[29b] Remarkable features of the X-ray structure of **2** are the nonlinear N(3)–Ag–N(7) bond (angle at Ag 165.8 (1)°) and the presence of an aqua ligand. The deviation of N–Ag–N from linearity is such as to permit hydrogen bond formation between the exocyclic groups, O(2) of C and $NH_2(6)$ of A (3.053 (3) A), and is supported by the presence of the weakly bonding aqua ligand. As a consequence of the H bond, the two nucleobases are close to planar, the dihedral angle being 4.0°. Despite its relatively long bond, the aqua ligand appears to be an *integral part* of the metal-modified base pair in that it is essentially coplanar with Ag and the two N-donor atoms and forms a hydrogen bond of 2.894 (4) Å with the exocyclic amino group N4C of the cytosine ring.

The Ag–N bonds in **2** are significantly shorter than in the starting compound $Ag(1\text{-MeC})NO_3$ (2.225 (2) Å),[19] comparable to those in a bis(9-methylhypoxanthine) complex (2.13 (1) Å)[21] and the polymeric 9-MeA complex (Ag–N(7), 2.16 (1) Å),[18] but longer than in Ag(I) complexes containing anionic 1-methylthyminate (2.08 (1) Å)[20] or 1-methyluracilate (2.08 (3) Å)[22] ligands. A comparison of bond lengths and angles of the nucleobases in **2** with those of the free ligands 1-MeC[37] and 9-MeA[38b] reveals a few minor changes. For example, both N3–C4 and N1–C6 bonds are somewhat longer (0.023 and 0.020 Å, corresponding to 6–5 $\sigma$) in **2**, while N1–C2 is shorter by 0.018 Å (4$\sigma$). Of the internal ring angles of 1-MeC in **2**, only that at C4 is somewhat smaller (1.1°, 5$\sigma$) as compared to free 1-MeC. With the 9-MeA ligand in **2**, only the two internal ring angles of the imidazole entity at C5 and N7 are affected by $Ag^+$ binding: While C5–N7–C8 expectedly increases by 1.6° (7$\sigma$) on metal complexation, the N7–C5–C4 angle decreases to a similar extent (1.4°, 6$\sigma$).

A packing diagram of **2** is given in Figure 2. Pairs of cations of **2**, virtually planar and connected by a hydrogen bond of 3.109 (3) Å between N6A of one cation and N3A of an adjacent one, are stacked in such a way that each cytosine overlaps with an adenine of the next layer.

Apart from the intramolecular H bonds between N6A and O2C as well as N4C and O1W and the intermolecular one between two adenines already mentioned, several additional H bonds of less than 3 Å exist: between $H_2O$ and O2N of the nitrate anion, between O1N and N4C of the symmetry related molecule at $^1/_2 - x$, $^1/_2 + y$, and $-z$, and between water and O2C of the molecule at $^1/_2 + x$, $^1/_2 - y$, and $+z$. A complete list of short contacts is given in the supplementary material.

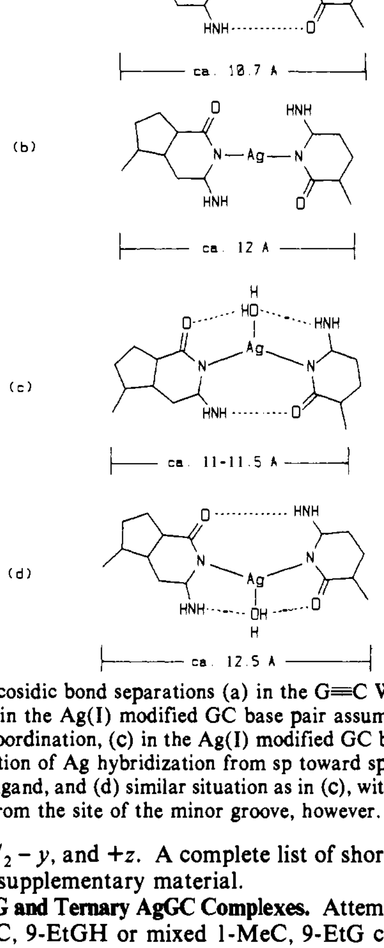

**Figure 3.** Glycosidic bond separations (a) in the G≡C Watson–Crick base pair, (b) in the Ag(I) modified GC base pair assuming a strictly linear Ag(I) coordination, (c) in the Ag(I) modified GC base pair with a strong deviation of Ag hybridization from sp toward $sp^2$ and a coordinated aqua ligand, and (d) similar situation as in (c), with aqua ligand approaching from the site of the minor groove, however.

**Binary AgG and Ternary AgGC Complexes.** Attempts to isolate mixed 1-MeC, 9-EtGH or mixed 1-MeC, 9-EtG complexes of Ag(I) in analogy to **2** from water failed.[39] The precipitated compounds analyzed as $[Ag(9\text{-EtGH})_2]NO_3$ (aq)[40,41] and Ag(9-EtG), respectively.

With 7,9-dimethylguanine instead of 9-ethylguanine, a crystalline product of composition $[Ag(1\text{-MeC})(7,9\text{-DimeG})NO_3]_2\cdot[(1\text{-MeC})(7,9\text{-DimeGH})PF_6]\cdot 10H_2O$, **3**, was obtained. The somewhat unusual composition of **3** was confirmed by a combination of $^1H$ NMR spectroscopy (C and G in 1:1 ratio) and elemental analysis (Ag) and was found to be fully reproducible. We assume that Ag(I) binding to 7,9-DimeG is via N(1) since

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(37) Rossi, M.; Kistenmacher, T. J. *Acta Crystallogr., Sect. B.* **1977**, *B33*, 3962.

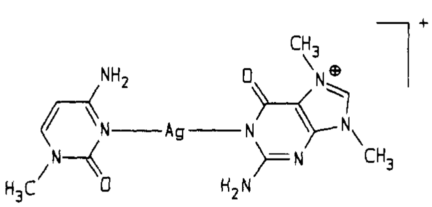
(38) (a) McMullan, R. K.; Benci, P.; Craven, B. M. *Acta Crystallogr. Sect. B.* **1980**, *B36*, 1424. (b) Kistenmacher, T. J.; Rossi, M. *Acta Crystallogr., Sect. B* **1977**, *B33*, 253.

(39) It appears that due to largely different solubilities of the desired ternary complexes and the binary Ag(9-EtGH)/(9-EtG) compounds in water, the equilibrium is shifted toward the least soluble species.

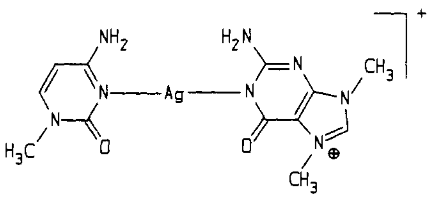
(40) Elemental analyses of several samples were somewhat variable in their $AgNO_3$ and $H_2O$ contents, e.g., $(9\text{-EtGH})_2\cdot nAgNO_3\cdot mH_2O$ ($n$ = 1–1.3, $m$ = 1.5–2.5). Changing the anion gave different stoichiometries, e.g., $(9\text{-EtGH})\cdot 1.1AgClO_4$, $(9\text{-EtGH})\cdot 0.85AgBF_4$, and $(9\text{-EtGH})\cdot 0.55Ag_2SO_4$.

(41) Applying a mixed solvent system (ethanediol/$H_2O$) $[Ag(9\text{-EtGH-}N^7)_2]NO_3$ has now been obtained as crystals suitable for X-ray crystallography.

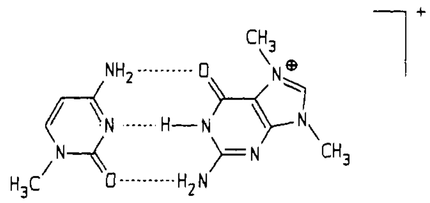
**Chart II**



(A)

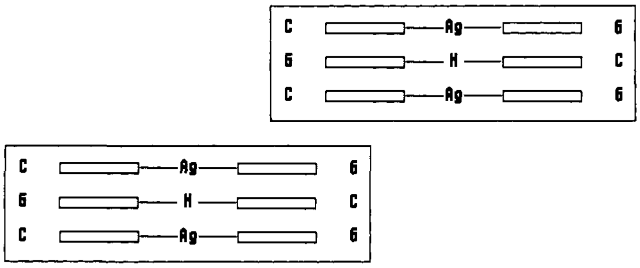


(B)

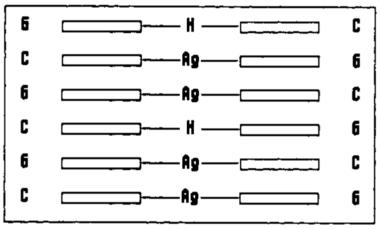


(C)

**Chart III**



(D)



(E)

this is the most basic site (p$K_a$ of 7,9-DimeGH$^+$ is 7.2[42]), and Pt(II) binding has been demonstrated to occur there before.[43] Two possible arrangements of the metalated bases in **3**, which correspond to a Watson–Crick (A) and a reversed Watson–Crick (B) arrangement, respectively, are given in Chart II. Provided a strictly linear geometry is realized, no H bonding interactions between exocyclic groups of the two nucleobases in the Ag complex are expected to occur. Alternatively, as with **2**, a shift toward sp$^2$ hybridized Ag in conjunction with binding of a water molecule could lead to a pattern with the bound aqua ligand taking part in H bonding with one or both bases. This possibility is not shown in Chart II but will be further discussed below. The two arrangements A and B can be interchanged by either ligand rotation about a Ag–N bond or a dissociative process. The protonated 1-MeC/7,9-DiMeGH$^+$ pair most likely adopts a Watson–Crick pairing pattern (C, chart II).

It is tempting to speculate on the possible solid-state structure of **3**. On the basis of the stoichiometry and taking into consideration the pronounced tendency of nucleobases to stack, at least two basic arrangements can be anticipated (Chart III): Isolated stacks consisting of three base pairs (metalated or protonated) each (D) or a polymeric stack with a Ag$_2$H sequence (E). A third possibility, an adduct of a dinuclear [Ag$_2$(1-MeC)$_2$]$^{2+}$ macrochelate[19] with a hemiprotonated (7,9-DimeG)·(7,9-DimeGH)$^+$ entity cannot be excluded, even though it appears unlikely that a ligand (7,9-DimeG) of higher basicity than 9-MeA should be unable to displace the O2 of 1-MeC in the macrochelate.

**$^1$H NMR Spectra.** $^1$H NMR spectra of the free ligands and of the Ag(I) compounds in Me$_2$SO-$d_6$ have been recorded. Chemical shifts and signal assignments are given in the supplementary material. With Ag(1-MeC)NO$_3$ (**1**), all 1-MeC resonances are shifted downfield relative to free 1-MeC by 0.24 (H(5)), 0.22 (H(6)), 0.11 (CH$_3$), and 0.87 ppm (av, NH$_2$). The magnitude of the downfield shift is a clear indication for the considerable thermodynamic stability of this complex in Me$_2$SO. The NH$_2$ resonance, which in the free ligand is a broad singlet, is split in two broad singlets (half-width ca. 30 Hz each) in [Ag(1-MeC)]$^+$. The splitting could be a consequence of increased hindrance to rotation about the C(4)–N(4) bond on Ag(I) binding[44] or, alternatively/additionally, intramolecular H bonding between Ag coordinated Me$_2$SO or water molecule and one of the two NH$_2$ protons (supplementary material). Salts that might cause splitting[45] are absent.

When free 1-MeC is added to a solution of Ag(1-MeC)NO$_3$, the averaged 1-MeC resonances move upfield and the two original NH$_2$ resonances coalesce to a single broad peak, suggesting rapid exchange between free and bound 1-MeC.

With the mixed cytosine, adenine complex **2**, 1-MeC resonances are close to those of the binary complex **1**. Again, the NH$_2$ resonance of 1-MeC is split in a 1:1 ratio, unlike the NH$_2$ resonance of 9-MeA. Adenine H2 and H8 resonances of **2** occur downfield relative to the free ligand (supplementary material). Addition of either 1-MeC or 9-MeA to a solution of **2** results in signal averaging of the respective bound and free nucleobase, as expected. The use of moist Me$_2$SO-$d_6$ or deliberate addition of H$_2$O (100-fold excess over **2**) does not markedly change the spectrum. The use of moist Me$_2$SO-$d_6$ as a solvent, to which 3 Å molecular sieves had been added to remove the water, had a distinct effect on the spectrum, however. In a slow reaction (hours), formation of a second species was observed (supplementary material). Upon subsequent warming to 60 °C, the spectrum had changed again, then exhibiting single nucleobase resonances of the free bases (NH$_2$ of C not split), which were somewhat shifted downfield, however. At present, we cannot safely assign the intermediate, which is inert on the NMR time scale, even though we are certain that its formation relates to basic reaction conditions, with base generated via anion exchange (H$^+$ from water vs alkali) from zeolite. Deliberate addition of NaOD to a Me$_2$SO-$d_6$ solution of **2** (Me$_2$SO not treated with molecular sieves) had a similar effect. Heating apparently removes Ag$^{I}$ (as an oxide or hydroxide?) from the equilibrium. In fact, formation of some dark, insoluble material was observed.

As mentioned above, relative intensities of purine (7,9-DimeG) and pyrimidine (1-MeC) resonances of **3** in Me$_2$SO-$d_6$ are consistent with a 1:1 ratio of the two nucleobases. It must be taken into consideration that chemical shifts of 1-MeC resonances of **3**, although close to those of **1** and **2**, are averaged over the protonated G,C and the Ag,G,C complex. The fact that, in contrast to **1**, the cytosine NH$_2$ signal is not split in **3**, certainly is inconsistent with the assumption that **3** represents a mixture of two binary compounds, [Ag(1-MeC)]$_2$$^{2+}$ and [(7,9-Di-

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meG)(7,9-DimeGH)]$^+$ and rather points toward the proposed structure (Charts II and III). There is no immediate evidence for Ag(I) binding to N1 of 7,9-DimeG, although it is the most likely one from the point of view of basicity (see above). Certainly, the effect of Pt$^{II}$ electrophiles[43] on the resonances of 7,9-DimeG in **3** is consistent with N1 binding of Ag(I). Binding to N3 of the guanine ligand can safely be excluded since it should dramatically affect the N(9)CH$_3$ resonance.[46] Addition of either 1-MeC or 7,9-DimeG(H) to a solution of **3** in Me$_2$SO-$d_6$ leads to rapid exchange with the respective bound nucleobase. There is no indication from the $^1$H NMR spectra that binary bis(nucleobase) complexes are formed preferentially under conditions of moderate excess of one of the two nucleobases.

## Discussion

Interactions between Ag(I) and DNA have been classified (types I, II, and III) according to stoichiometry, the pH at which reaction occurs, and whether or not Ag(I) binding is accompanied by nucleobase deprotonation.[5,6] Many models have been proposed to account for the physicochemical changes observed. Most models center around one bound Ag(I) per two bases,[2,5,6,12,14] but there is also the hypothesis that two Ag(I) per two bases are feasible with formation of an eight-membered metalamacrocycle.[19] A very similar binding pattern has recently been found in Tl(1-MeC)-NO$_3$.[48]

We have now prepared and studied two mixed nucleobase complexes Ag(I), [Ag(1-MeC)(9-MeA)(H$_2$O)]$^+$ (**2**), and [Ag-(1-MeC)(7,9-DimeG)]$^+$ (**3**) which bear relevance to the question of how Ag(I) could cross-link DNA. We feel that the X-ray structure of the mixed nucleobase complex **2**, despite the fact that it has no model character for any presently established Ag–DNA interaction, provides a basis for speculations on the nature of Ag(I)–DNA adducts, which differs from the hypotheses put forward in the past. We herewith propose that a *metal-coordinated water* molecule (or possibly even a hydroxo ligand) might become an *integral part* of the Ag–nucleobase complex. We further propose that adduct formation of this type is favored if the the two bases bound to Ag(I) are *different* rather than identical. In the latter case a strictly linear coordination geometry about the Ag is to be expected.[49] The "insertion" of a silver aqua species from the major groove of DNA into a complementary base pair with substitution of a hydrogen bonded proton by Ag$^+$ might be achieved without major distortion of DNA. At the same time it would open many possibilities for the stabilization of base pairs between complementary bases and noncomplementary ones during DNA replication. Clearly, this possibility is not restricted to Ag(I) but in principle is also possible for other metal ions with the capability to adopt flexible coordination geometries.[50] In this context, it should be pointed out, that the inclusion of water molecules that stabilize the H bonding pattern of base-pair mismatches has been recognized.[51]

We have not been able to obtain the mixed guanine, cytosine complex **3** in a form suitable for X-ray structural work. Therefore we cannot comment on the topic raised but nevertheless would like to briefly speculate on its structure and possible relevance in Ag(I)–DNA binding. Formation of a Ag(I) cross-link between N3 of cytosine and N1 of guanine with a strictly linear coordination geometry of the metal would cause an increase in the separation between the glycosidic bonds of the two bases from 10.7 Å (Watson–Crick pair, Figure 3a) to at most 12 Å (Figure 3b) in the metal-modified base pair. In this case, no H-bonding interaction between the exocyclic groups of the two bases is to be expected. From structural data obtained from a double helix incorporating a guanine, adenine mispair,[52] it is obvious that this widening of the glycosidic bond separation could be easily tolerated by DNA. Considering the ability of Ag(I) to change its coordination geometry from strictly linear toward distorted trigonal-planar (cf. N3C–Ag–N7A in **2**, 165.8°; N7A–Ag–N1A in [Ag(9-MeA)]$^+$,[18] 161.8°; 171.3°) or ideally trigonal-planar,[53] however, the actual change in glycosidic bond separation on Ag(I) binding might be quite small (Figure 3c), provided the Ag(H$_2$O)$^+$ inserts from the side of the major groove. In fact, maintenance of one of the three original hydrogen bonds between G and C could be possible. A water ligand, coordinated to Ag, could effectively stabilize such an arrangement through H bonding to O6 of guanine and/or N4 of cytosine. Although insertion of Ag(H$_2$O)$^+$ from the side of the minor groove (Figure 3d) could leave the O(6)-G···N(4)CH bond intact, it would probably cause an even larger separation of the glycosidic bonds than the estimated 12 Å in the case of a strictly linear coordination geometry about the metal.

## Conclusion

The mixed cytosine, adenine complex **2** examplifies a novel view of possible metal ion–nucleobase interactions: Rather than considering binding of an isolated metal ion to one or more nucleobases, binding of a metal–aqua entity as a whole to the nucleobase(s) is considered. Thus the aqua ligand is a *structurally determining factor* rather than a *merely stabilizing* one. In **2**, the weakly bound aqua group "imposes" a coordination geometry on the metal ion, which in silver–nucleobase chemistry is rare[18] as compared to strictly linear and/or distorted tetrahedral geometries usually found.[19-22] While metal–aqua–nucleobase complexes with hydrogen bonding of an aqua ligand to the nucleobase have been reported in many cases,[54] in none of these examples is the regular coordination geometry of the metal affected by such a stabilizing interaction.

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

**Supplementary Material Available:** Listings of positional and thermal parameters of **2**, intramolecular distances, and H bonding distances, $^1$H NMR chemical shifts (Me$_2$SO-$d_6$) of **1**, **2**, and **3**, $^1$H NMR spectra of **2** in Me$_2$SO-$d_6$, and possible structures of **1** in Me$_2$SO (13 pages); tables of observed and calculated structure factors (16 pages). Ordering information is given on any current masthead page.

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(49) The bis(9-methylhypoxanthine)Ag complex with head–head arranged ligands is an exception (cf. ref 21).

(50) We consider it to be unlikely, however, in the case of square-planar Pt(II) complexes, as confirmed by X-ray structures of related mixed-nucleobase complexes of *trans*-(NH$_3$)$_2$Pt$^{II}$ (see ref 29).

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