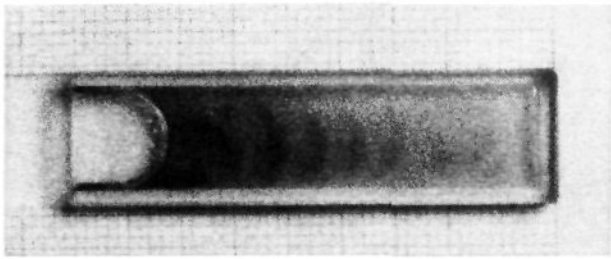

Figure 3. Typical set of traveling waves (dark regions) in an open cell with 2-mm path length, which is placed horizontally on a thermostated plate (65 ± 1 °C). Initial reactant concentrations: [PhCHO] = 0.15 M; [Co(III)] = 0.0020 M; [Co(II)] = 0.0065 M. The photograph was taken 1 h after mixing the reactants. Green waves of Co(III) emerge periodically from the region near the gas–liquid interface, where oxygen from air is absorbed, and propagate through the solution toward the closed end of the cell. Wave velocity: 2.0–2.5 mm/min. Cell length: 4.5 cm.

detailed mechanistic studies. In addition, the hydrogen isotope effect may provide a valuable tool for testing mechanistic models.

Our chemical oscillator consists of benzaldehyde (PhCRO, R = H or D), Co(III),[24] Co(II), and elemental oxygen. The reaction takes place at 60 °C in an acetic acid medium, either in a closed, thermostated 1-cm square spectrophotometer cell where oxygen may be taken up from the remaining head-space gas volume (closed system) or in an open cell where oxygen from the air may be absorbed at the liquid surface of the motionless reaction mixture (open system). The final oxidation product is benzoic acid. The oscillating behavior is recorded with a UV/VIS spectrophotometer (Shimadzu UV-260) by measuring the absorbance of Co(III) at 620 nm.

Figure 1a shows the typical oscillatory pattern of the closed and unstirred reaction system containing PhCDO. After the concentration of Co(III) has reached a maximum, a spontaneous oscillation sets in with a characteristic frequency of 6.0×10^{-3} s^{-1}. Due to the limited amount of oxygen in the closed system, the oscillations are highly damped. It is interesting to note that, if PhCDO is replaced by PhCHO and the other conditions are unchanged, the oscillating behavior is hardly noticeable (Figure 1b).

When the oxidation is carried out in an open system and at sufficiently low conversion, an almost sustained oscillatory behavior is observed for PhCDO as well as for PhCHO, with characteristic oscillation frequencies for the given reaction conditions of 6.0×10^{-3} and 6.7×10^{-3} s^{-1}, respectively (Figure 2).

In the closed as well as in the open reaction systems, the average Co(III) concentration during oscillation is much higher in the case of PhCDO than in the case of PhCHO. Furthermore, it is noteworthy that after allowing for an appropriate induction period, the average concentration of Co(III) in the open system slightly increases or decreases with time, depending on whether the deuterated (Figure 2a) or the nondeuterated (Figure 2b) benzaldehyde is oxidized. The hydrogen isotope effect is further confirmed by a competitive reaction experiment in which the ratio of the oxidation rates of PhCHO and PhCDO was determined to be 3.8.

The spatial periodicity in our system manifests itself not by a single reaction front,[23] but rather by periodically self-generating waves. Figure 3 shows a typical set of such traveling waves. Under the conditions given, self-generated waves are propagating at the velocity of about 2–2.5 mm/min. The nature of these waves and the hydrogen isotope effect in the wave propagation are under investigation and will be reported elsewhere.

(24) The Co(III) complex used in our system was prepared by O_2 oxidation of $Co(AcO)_2$ in AcOH in the presence of methyl ethyl ketone. The cobalt complexes were then isolated and dried after removing the solvent under vacuum. The total cobalt content was determined by atomic absorption spectroscopy. The concentration of Co(III) was measured spectrophotometrically.[21]

Model for a Platinated DNA Triplex: Watson–Crick and Metal-Modified Hoogsteen Pairing†

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Received August 5, 1991

Nucleobase triples between adenine (A) and two thymines (T) or between guanine (G), neutral cytosine (C) and protonated cytosine (CH^+) combine Watson–Crick and Hoogsteen base pairing patterns (Figure 1).[2] Formation of such base triples occurs naturally in DNA (H-DNA[3]) or spontaneously (disproportionation) in RNA[4] and represents the basis for numerous site-specific manipulations of DNA which include cleavage,[5-7] nonenzymatic oligonucleotide ligation,[8] and sequence-specific alkylation,[9] for example. Oligonucleotide specificity could feasibly be applied to regulate or inhibit transcription of DNA to RNA, thereby providing a rationale for treatment of viral diseases.[10]

Similarly, the principle of Watson–Crick base pairing and duplex formation between mRNA and a synthetic oligonucleotide is the basis of antisense oligonucleotide chemistry and its possible therapeutic uses.[10]

Both approaches face major challenges as far as future clinical applications are concerned, e.g., (i) the question of oligonucleotide transport into cells, (ii) the danger of enzymatic degradation of the oligonucleotide, or (iii) the problem of persistent fixation of the oligonucleotide to the target sequence. There are many efforts to overcome these inherent problems.[10] As to item iii, attempts have been made to increase the oligonucleotide affinity by various methods such as manipulations of its charge,[11] via linked intercalators,[12] through photocross-linking,[13] or covalent bond formation, e.g., alkylation[14] or cross-linking via Pt(II).[15]

† Dedicated to Prof. B. Rosenberg on the occasion of his 65th birthday.

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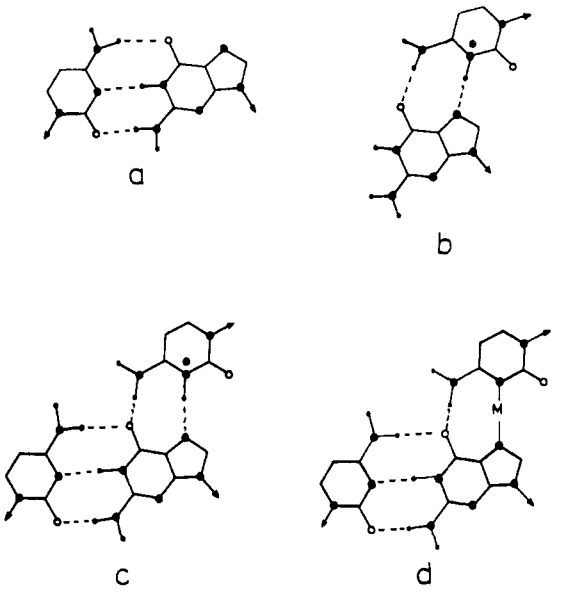

Figure 1. Schematic representation of base-pairing schemes between guanine and cytosine: (a) Watson–Crick, (b) Hoogsteen, (c) triple, and (d) metal-modified triple. Reversed Watson–Crick and reversed Hoogsteen pairs are not shown. Full circles denote N atoms; empty circles, O atoms.

We have been interested in models for "metal-modified base pairs" in which a metal entity with a linear coordination geometry, e.g., *trans*-$(NH_3)_2Pt^{II}$ or Ag^I, formally replaces a hydrogen bond between two bases, thereby keeping the two bases in a nearly planar arrangement.[16] Specifically, combination between the complementary bases G and C[17] as well as A and T[18] had been of interest, since they represent metal analogues of Hoogsteen,[17,18] Watson–Crick,[18] or reversed Hoogsteen[18] base pairs. We herewith report a model for a platinated DNA triplex in which a normal Watson–Crick pair between 9-methylguanine and 1-methylcytosine is complemented by a *trans*-$(CH_3NH_2)_2Pt^{II}$(1-methylcytosine-*N3*) entity bound to the guanine via N7 in a Hoogsteen fashion. In addition, the crystal lattice contains a hemiprotonated 1-methylcytosine with three hydrogen bonds between two cytosines.

The title compound (**2**) was obtained by cocrystallization of *trans*-$[(CH_3NH_2)_2Pt$(1-MeC-*N3*)(9-MeGH-*N7*)$]Cl_2$ (**1**)[19-21] and 1-MeC at pH 5–5.5.[22] Colorless crystals of **2** were isolated in 36% yield and proved to be of composition $\{[(CH_3NH_2)_2Pt(1\text{-}MeC)(9\text{-}MeGH)]Cl_2\cdot(1\text{-}MeC)\}\cdot 0.5\{[(1\text{-}MeCH)\cdot(1\text{-}MeC)]Cl\}\cdot 4.5H_2O$.[23,24] Figure 2 depicts the platinated base triple, and in

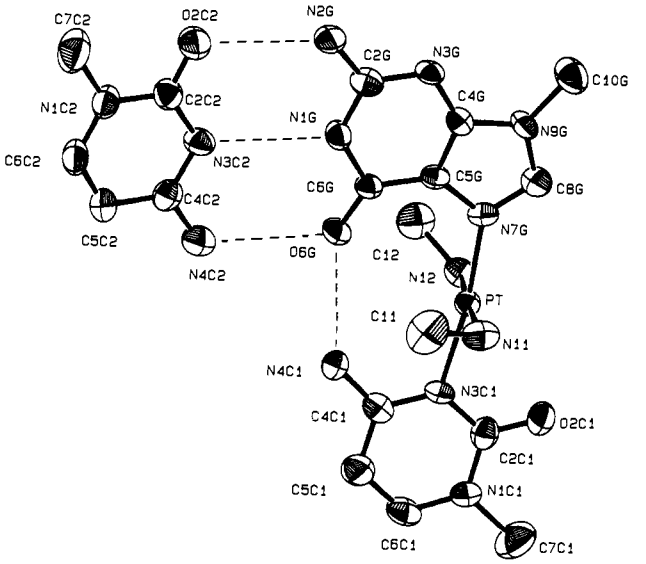

Figure 2. ORTEP drawing (50% probability ellipsoids) of *trans*-$\{[(CH_3NH_2)_2Pt$(1-MeC-*N3*)(9-MeGH-*N7*)$](1\text{-}MeC)\}^{2+}$. The hemiprotonated 1-methylcytosine (C3 ring), Cl^- anions, and water molecules are not shown.

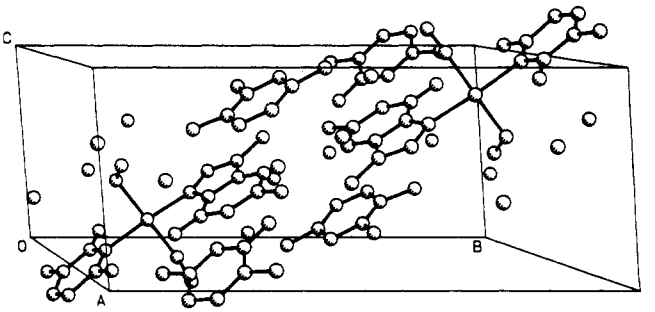

Figure 3. The unit cell viewed along the *a* axis. The hemiprotonated 1-methylcytosine is virtually parallel to the platinated guanine.

Figure 3 the unit cell as viewed along the *a* axis is given. The Pt coordination geometry is a bit unusual in that the N3C1–Pt–N7G angle deviates markedly from linearity [172.5 (3)°].[25] Pt–N distances are normal, but unlike in *trans*-$(CH_3NH_2)_2PtCl_2$,[26] the two methyl groups of CH_3NH_2 are on the same side of the Pt coordination plane. The orientation of the two nucleobases coordinated to Pt and the geometries of the two bases are very similar to those of *trans*-$[(NH_3)_2Pt$(1-MeC)(9-EtGH)$]^{2+}$.[27] The two bases in **2** form a slight propeller twist (10.4°) and are connected by a hydrogen bond between the exocyclic NH_2(4) of cytosine and O(6) of guanine [2.99 (1) Å]. As compared to the Watson–Crick GC base pair,[28] the separation between the exocyclic methyl groups, which in DNA corresponds to the interglycosidic distance between the C(1′) positions, is slightly shorter

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(19) Abbreviations used: 1-MeC = neutral 1-methylcytosine ($C_5H_7N_3O$); 1-MeCH$^+$ = 1-methylcytosinium; 9-MeGH = neutral 9-methylguanine ($C_6H_7N_5O$).

(20) **1** was prepared from *trans*-$[(CH_3NH_2)_2Pt$(1-MeC)Cl$]Cl\cdot H_2O$[21] and 9-MeGH (water, 4 days, 40 °C). Then 1-MeC (3 equiv) was added, and the pH was found to be 5–5.5. Slow evaporation at 3 °C gave initially 1-MeC and eventually **2**.

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(23) Elemental analytical data for **2** and ^1H NMR intensities between 1-MeC and 9-MeGH resonances were in agreement with this formulation.

(24) Crystallography (**2**): $[C_{13}H_{24}N_{10}O_2Pt]Cl_2\cdot C_5H_7N_3O\cdot 0.5[C_{10}H_{15}N_6O_2]Cl\cdot 4.5H_2O$; M = 979.54; triclinic, space group $P\bar{1}$ (No. 2); a = 14.058 (3) Å, b = 18.481 (4) Å, c = 7.783 (2) Å, α = 93.78 (2)°, β = 92.26 (2)°, γ = 72.41 (2)°, V = 1945 (2) Å^3, Z = 2, d_{calcd} = 1.67 g cm^{-3}. The structure was solved by Patterson and Fourier techniques using TEXSAN 5.0. Full-matrix least-squares refinement gave $R(F)$ = 0.034 and $R_w(F)$ = 0.043 for 4184 absorption-corrected reflections with $I > 3\sigma(I)$ measured up to 2θ = 46° on a Rigaku AFC6S diffractometer at −120 °C (Mo Kα radiation, λ = 0.71069 Å).

(25) We note that, in a related compound of composition *trans*-$[(NH_3)_2Pt$(1-MeC)(9-MeA)$]^{2+}$ (9-MeA = 9-methyladenine), a similar deviation from linearity [175.6 (3)°] at the Pt is observed, probably also assisted by a H bond between exocyclic nucleobase groups (O2 of 1-MeC, N6 of 9-MeA). See: Beyerle-Pfnür, R.; Brown, B.; Faggiani, R.; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1985**, *24*, 4001.

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(10.44 Å vs 10.72 Å[28b] or 10.64 Å in the Watson-Crick pair of **2**). The geometry of the Watson-Crick base pair between the G and the C2 ring is, except for the somewhat larger propeller twist (11.9°), very similar to that observed in (9-EtGH)·(1-MeC)[28a] or $(GpC)_2$.[28b] The base pair between the neutral and the protonated C3 rings is normal.[29] The latter is virtually parallel to the guanine (dihedral angle 1.5°) and almost parallel to the platinated C1 ring and the hydrogen-bonded C2 ring (dihedral angles 9° and 12.1°, respectively). Within the crystal, platinated base triples and the (1-MeC)(1-MeCH)$^+$ base pairs occur in alternating layers, with considerable stacking between the heterocyclic rings. The chloride anions as well as the water molecules are involved in extensive hydrogen bonding with no unusual features apparent.

The (metal-modified) nucleobase triple observed in **2** represents, to the best of our knowledge, the first example of its kind and is different from tertiary base pairs found in tRNAs.[30] The results of the X-ray structure determination strongly suggest that covalent binding of a pyrimidine oligonucleotide strand to a DNA duplex via a linear *trans*-a_2Pt^{II} entity (a = NH_3 or amine) is sterically feasible. We assume that, provided the oligonucleotide is sufficiently long, recognition and H-bond formation with the target sequence will be much faster than covalent binding of the Pt to the target. Thus, specific rather than unspecific binding of a platinated oligonucleotide to DNA appears to be possible. Work in our laboratory is in progress to apply this binding principle to oligonucleotides.

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

Supplementary Material Available: Experimental details for the structure determination of **2** and tables of atomic positional and thermal parameters, bond distances and angles, intermolecular distances and angles, and least-squares planes for **2** (13 pages); listing of F_o and F_c for **2** (29 pages). Ordering information is given on any current masthead page.

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Enantiomeric Cholesterol as a Probe of Ion-Channel Structure

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ent-Cholesterol has been prepared for the first time as a single isomer to probe the role of sterols in ion-channel formation.[2,3] It was prepared by enantioselective total synthesis and shown to have >97% ee by optical rotation and Mosher's ester analysis[4] of the intermediate *ent*-testosterone.[5] Cholesterol is a vital component of mammalian membranes that is required for proper membrane protein function[6,7] and plays an important role in human health. Its primary activity is to stabilize membranes and mediate their fluidity.[8] *ent*-Cholesterol can be used to probe the role of cholesterol in biological systems. Wherever cholesterol binding is important, substitution by *ent*-cholesterol will lead to diastereomeric interactions resulting in measurably different behavior.

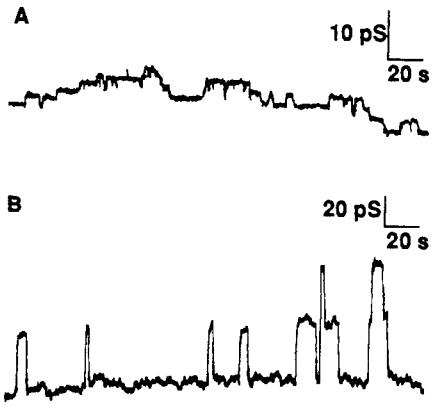

Figure 1. Amphotericin B ion channels in soy azolecithin with cholesterol. (A) Cholesterol, 5% in azolecithin, 2×10^{-8} M amphotericin B, 2 M KCl, 0.1 M HEPES buffered to pH 7.0, 120 mV. (B) *ent*-Cholesterol, 5% in azolecithin, 2×10^{-7} M amphotericin B, 2 M KCl, pH 7.0, 120 mV. Membranes were formed by painting lipid solutions across a 0.1-mm hole in a Teflon partition. Membrane-forming solutions were 1-5% lipid in decane (w/v), doped with 5% (w/w) cholesterol to lipid. Membranes were formed in the presence of amphotericin B. All records were filtered at 20 Hz.

Enantiomers can be used to distinguish between specific binding interactions and nonspecific associations. Enantiomers will have identical physical properties in an achiral environment, but can often be distinguished through diastereomeric complex formation with a chiral probe molecule. This is the basis for enantiomer analysis by NMR spectroscopy using chiral shift reagents[9] and for chromatographic resolutions using chiral stationary phases.[10] The same strategy can be used to test for binding between chiral components in a complex system. If each enantiomer of a biologically active compound has identical properties in a complex environment like a cell, then the biological activity does not result from a specific binding interaction. For example, the two enantiomers of the antibiotic lasalocid A have identical biological properties, and thus their biological activity does not involve specific binding to a receptor or any other chiral cellular component.[11] On the other hand, the *R* and *S* enantiomers of carvone smell like spearmint and caraway, respectively, and this alone demonstrates that the sense of smell involves specific binding.[12,13]

Amphotericin B is a polyene macrolide antibiotic used to treat life-threatening systemic fungal infections that are often found in patients with impaired immune systems. Its activity is attributed to the formation of ion channels in cell membranes containing sterols.[14] In the most widely accepted model, amphotericin B and the membrane sterol from a complex, and several complexes assemble in the membrane to form an ion channel.[15,16] This model

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