Table I. Comparative in Vitro Activity of Neamine 5,6-Dideoxyneamine and 3′,5,6-Trideoxykanamine A against *Bacillus subtilis* and *E. coli*

compd	MIC, μg/mL	
	Bacillus subtilis	*E. coli*
neamine	0.25	3
5,6-dideoxyneamine	0.25	4
3′,5,6-trideoxykanamine A	0.5	20

Table II. Antimicrobial Activity of Kanamine, Neamine, and 3′,5,6-Trideoxykanamine A against *Pseudomonas aeruginosa* (ATCC 10145)

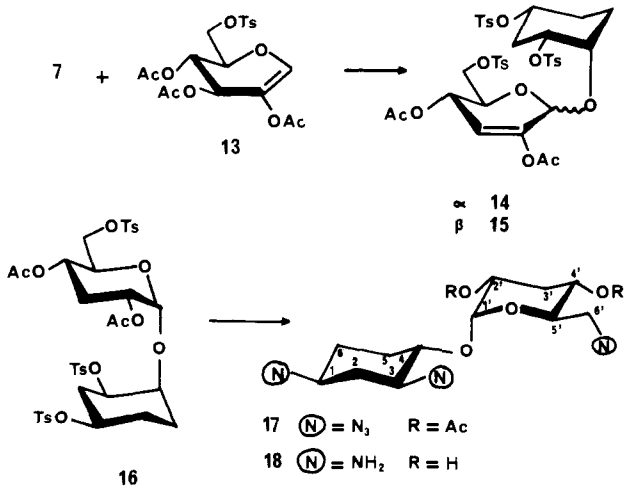
concn, mg/mL	diameter of inhibition zone in mm, by the paper disk method		
	kanamine	neamine	3′,5,6-trideoxy-kanamine A
0.5	0	0	6
1	0	0	8
2	0	0	10

the recently reported subunit assembly for the butirosins.[12]

In general, mutasynthesis provides vital information concerning the structural modification allowed for the aglycone moiety of amino glycosides.[1-3,13] **11** exhibits broad-spectrum antibacterial activity (Table I) comparable with that of neamine.[10] Consequently, the chemical synthesis of other pseudodisaccharides having 2,5,6-trideoxystreptamine as an aglycone, with altered amino sugar subunit, was considered.

A recently described[14] extension of Ferrier's reaction, leading to cyclitol α-glycoside, was used as glycosylation procedure. This method gives stereoselectively the α-glycosidic bond in high yield (70–80%) and simultaneously provides 3′-deoxyaminocyclitol glycosides, an important feature regarding enzymatic inactivation.

Addition of the glycal **13** (1.5 equiv) to a dichloroethane solution of **7** containing a catalytic amount of boron trifluoride etherate as described previously[14] furnished in 95% yield an anomeric mixture of unsaturated derivatives **14** and **15** in a ratio of 7:3, respectively, as shown by ^{13}C NMR: $\delta(C_{1'\beta})$ 94.9,



$\delta(C_{1'\alpha})$ 91.6 ppm. From the mixture the β-glycoside **15** could be isolated by crystallization, mp 156–157 °C, $[\alpha]_D$ +58° (*c* 1.6, $CHCl_3$). The reduction of the syrupy α-glycoside **14**, as noted previously,[14] proceeded regiospecifically giving the required compound **16** (65% overall yield based on **7**), mp 179–180 °C, $[\alpha]_D$ +79° (*c* 1.34, $CHCl_3$), with the D-ribo configuration as confirmed by ^1H and ^{13}C NMR [$J_{1',2'}$ = 3.5, $J_{2',3'a}$ = 12, $J_{2',3'e}$ = 5 Hz; δ 92.9 ($C_{1'}$) and 67.9 ($C_{5'}$)].

Azidolysis of **16** yielded the unstable oily triazide **17**. Sequential deacetylation and catalytic reduction gave the 3′,5,6-trideoxykanamine A **18** characterized as its trihydrochloride salt, mp 214–220 °C, $[\alpha]_D$ +67° (*c* 0.83, H_2O). Anal. Calcd for $C_{12}H_{28}Cl_3N_3O_4$: C, 37.46; H, 7.34; Cl, 27.65; N, 10.92. Found: C, 37.17; H, 7.47; Cl, 27.41; N, 10.72.

The structure of **18** was assigned[16] on the basis of its ^{13}C NMR spectrum [$\delta(C_1 \rightarrow C_6)$ 48.2, 33.3, 52.5, 74.7, 26.5, 28.2; $\delta(C_{1'} \rightarrow C_{6'})$ 93.7, 66.6, 34.8, 66.6, 69.9, 41.3] and chemical ionization mass spectrometry[9] [*m/e* 276 (MH^+), fragments 146 and 131].

The antibacterial activity of 3′,5,6-trideoxykanamine A is comparable with that of kanamine A against a variety of strains.[15] Surprisingly 3′,5,6-trideoxykanamine A exhibited activity against *Pseudomonas aeruginosa* (ATCC 10145), a great advantage over the parent kanamine A and also neamine (Table II).

Extension of this work is continuing in our laboratories.

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(16) Satisfactory ^1H and ^{13}C NMR, IR, and mass spectral and analytical data were obtained on chromatographically homogenous samples of all synthetic intermediates described herein.

Claudine Colas, Béatrice Quiclet-Sire
Jeanine Cléophax, Jeanne-Marie Delaumény
Anne-Marie Sepulchre, Stephan D. Géro*
Institut de Chimie des Substances Naturelles, CNRS
91190 Gif-sur-Yvette, France
Received August 6, 1979

Synthesis and Structure of a Bis[terpyridineplatinum(II)] Complex and Its Evaluation as a Metallointercalator

Sir:

Intercalation is a mode of binding of flat molecules to nucleic acids.[1] Numerous organic dyes and drugs[2] as well as platinum complexes[3] such as **1** intercalate into DNA and RNA. X-ray crystallographic investigations have elucidated the geometry

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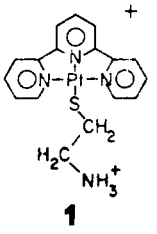

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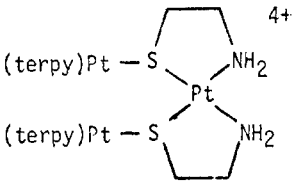
of several products obtained from the cocrystallization of planar dyes, drugs, and metallointercalators with self-complementary fragments of polynucleotides.[4] A preliminary crystallographic study of the reaction product of **1** and deoxymethoxy-pTpA revealed the presence of an unexpected triplatinum complex, **2**.[5] This complex apparently formed from



2

three moles of **1**, one of which lost its ligands during the 2-week period in which crystals of the deoxymethoxy-pTpA adduct were grown. In these crystals, A-T base pairs are stacked on either side of **2** but do not form a miniature double helix since it is sterically impossible for a dinucleotide duplex to span the "double thick" (6.8 Å) bis[terpyridineplatinum(II)] moiety. Here we report the synthesis of **2** as the tetrafluoroborate salt, its structural characterization by X-ray diffraction, an interesting form of isomerism exhibited by **2**, and its failure to intercalate into closed circular pSM1 DNA.

To a stirred solution of $[(terpy)PtCl]Cl\cdot 2H_2O$[6] (0.1 g, 0.19 mmol) in 20 mL of water were added 2-aminoethanethiol hydrochloride (0.02 g, 0.18 mmol) in 20 mL of water and 0.185 mmol of NaOH in 10 mL of water. Up to this stage all solutions were continuously flushed with nitrogen, a precaution not employed in subsequent steps.[7] Dropwise and simultaneously to the stirred mixture, made up to 300 mL with water, were added K_2PtCl_4 (0.04 g, 0.095 mmol) in 100 mL of water and 0.185 mmol of NaOH in 100 mL of water over a period of 45 min. The resulting solution was stirred for 2 h and the volume was reduced to ~30 mL by lyophilization. Addition of 20 mL of an aqueous solution of tetramethylammonium tetrafluoroborate (0.24 g, 1.49 mmol) immediately produced 15 mg of a red precipitate that was removed by filtration. Slow evaporation of the yellow filtrate in air produced orange crystals of the tetrafluoroborate salt of **2**.

The compound crystallizes in the monoclinic system, space group $I2/c$ or Ic, with four formulas in a unit cell of dimensions $a = 21.924\ (3)$, $b = 13.416\ (4)$, $c = 15.241\ (8)$ Å; $\beta = 97.89\ (1)°$; $\rho_{calcd} = 2.320$, $\rho_{obsd} = 2.32\ (1)$ g/cm^3. The structure was solved by direct methods with MULTAN-76 and refined using 3093 independent reflections [$2\theta \leq 60°$, $I_0 > 3\sigma(I_0)$] collected on an Enraf-Nonius CAD-4 κ diffractometer at 25 °C using graphite monochromatized Mo Kα radiation. The value for the conventional discrepancy index, $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, at the present stage of refinement in $I2/c$ is 0.044. Full details will be reported elsewhere at a later date.

As shown in Figure 1a, the structure of **2** consists of three square-planar platinum(II) atoms, two of which [Pt(1) and Pt(1′)] are coordinated by tridentate terpyridine ligands and the sulfur atom of a 2-aminoethanethiolate ligand. The third, unique platinum atom, Pt(2), lying on a crystallographic twofold axis, is coordinated by the sulfur and nitrogen atoms of each of two 2-aminoethanethiolate ligands. Each sulfur atom

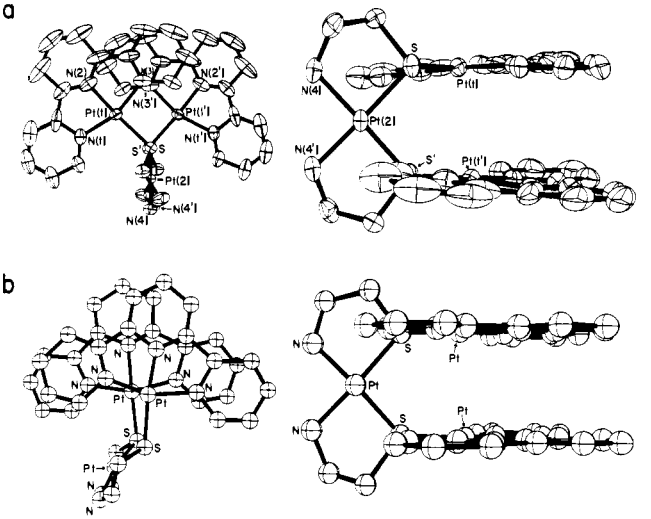


Figure 1. Perpendicular views of the structure of **2** (a) in the tetrafluoroborate salt showing the 40% probability thermal ellipsoids [selected bond lengths (in ångstroms; esd, ~0.01 Å) for this enantiomer are Pt(1)-S, 2.295; Pt(2)-S, 2.263; Pt(1)-N(1), 2.03; Pt(1)-N(2), 1.94; Pt(1)-N(3), 2.03; Pt(2)-N(4), 2.07; Pt(1)-Pt(1′), 4.420; Pt(1)-Pt(2), 3.880 Å. The primed and unprimed atoms are related by a crystallographically required twofold axis.]; (b) in the adduct with deoxymethoxy-pTpA[5] showing isotropic thermal ellipsoids fixed at 5 Å^2.

thus bridges two platinum atoms. The coordination plane of Pt(2) is approximately perpendicular to the coordination planes of the other two platinum atoms. The two latter planes correspond to the planes of the terpyridine ligands which are stacked on one another and are approximately parallel. Figure 1a reveals that the two (terpy)Pt^{II} moieties are only partially overlapping, a situation reminiscent of the partial stacking of terpyridineplatinum(II) units in adjacent unit cells in the structure of $[(terpy)Pt(HET)](NO_3)$ (HET = 2-hydroxyethanethiolate).[7] In the region of ring overlap the thickness of the cation, defined as the interplanar separation plus the van der Waals radii of two terpyridineplatinum(II) units, is 6.8 Å.

The cis configuration of ligands about Pt(2) is expected by analogy to numerous bisthiolate complexes, for example, bis(6-mercapto-9-benzylpurine)palladium(II).[8] Because of the sp^3 hybridization at the bridging sulfur atoms, an interesting kind of stereoisomerism is possible for **2**, which occurs as enantiomers in the crystal lattice. A meso isomer can be generated from the racemic isomer shown in Figure 1a by inversion of configuration at one of the bridging sulfur atoms. This meso diastereomer is actually manifest in the adduct of **2** with deoxymethoxy-pTpA,[5] as shown in Figure 1b. Here the overlap between the two (terpy)Pt^{II} units is nearly complete, closely resembling the head-to-head stacking found in the 2:2 chloroterpyridineplatinum(II)-adenosine 5′-monophosphate intercalation complex.[9] The interconversion of the diastereomers in solution is under investigation. The anisotropic thermal ellipsoids of the racemic isomer of **2** (Figure 1a) clearly reveal the graphite-like vibrational motion of the stacked (terpy)Pt^{II} moieties in their respective coordination planes.

Studies of the band sedimentation behavior of a mixture of nonsupercoiled closed and nicked circular pSM1 DNAs[10] revealed no separation in the presence of 2.6 or 6.4 μM of **2** as the tetrafluoroborate salt in 90% D_2O by volume, 0.2 M NaCl, 4 mM Tris·HCl, pH 7.4, at 20 °C. In a control experiment under identical conditions, complete separation was induced by 6.3 μM ethidium bromide. The sedimentation coefficient of supercoiled pSM1 DNA was unaffected by **2**. These results rule out intercalative binding of **2** to these DNAs,[11] as expected

for a cation having twice the thickness of a normal metallointercalator.[3] From an examination of space-filling models of **2** and the DNA double helix it is apparent that base pair displacement would have to occur to accommodate intercalative binding of the bis[terpyridineplatinum(II)] reagent. The triplatinum(II) complex might therefore be used to identify base substitution mutations.[12] Because of its high electron density, it might also prove to be useful in preparing heavy-atom derivatives of biological molecules.

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John C. Dewan, Stephen J. Lippard*
Department of Chemistry, Columbia University
New York, New York 10027

William R. Bauer
Department of Microbiology, State University of New York
Stony Brook, New York 11794

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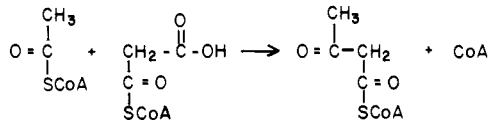
Copper(I) Promoted Acylation Reactions. A Transition Metal Mediated Version of the Friedel–Crafts Reaction

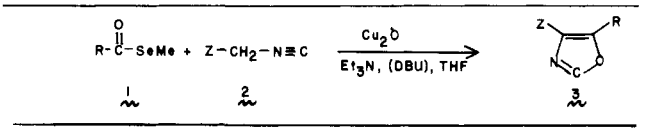
Sir:

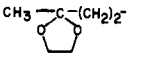
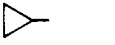
Thioesters of coenzyme A are important intermediates in carboxylic acid metabolism. They serve as "activated" acid derivatives, keying, for example, the important carbon–carbon-bond-forming reaction in the synthesis of acetoacetyl CoA.[1]



Studies conducted in our laboratories have now revealed that selenol esters[2] can, in analogy to the actual role played by thioesters in the biochemical process cited above, be used in carbon–carbon-bond-forming reactions. This work was originally initiated to achieve a new synthesis of 2-unsubstituted oxazoles. We had envisaged that selenol esters could replace acid chlorides in the assembly of these heterocycles from activated isonitriles, if these reactions were conducted in the presence of a soft metal ion showing a strong affinity for selenium. This process would thus serve as a useful modification to the standard Schöllkopf oxazole synthesis.[3]

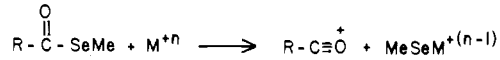
Table I. Synthesis of 2-Unsubstituted Oxazoles



1 (R)	2 (Z)	Base	Reaction Time (h)	Isolated Yield (%)
Ø-	CO_2Et	Et_3N	14	60
	CO_2Et	Et_3N	11	92
	CO_2Et	Et_3N	6	61
$CH_3(CH_2)_6$-	CO_2Et	Et_3N	12	85
$CH_3(CH_2)_6$-	Tos	DBU	20	40

Our hopes were nicely realized, for simply stirring the selenol ester and isonitrile (Z = CO_2Et or Tos) at room temperature for 6–20 h in the presence of 1.5 equiv of Et_3N or DBU and 1.5 equiv of anhydrous cuprous oxide affords in good yield the 2-unsubstituted oxazole **3** by a process presumably proceeding through an intermediate β-ketoisonitrile (Table I). The cuprous oxide functions as an efficient reagent for complexation to the selenium moiety.

With this information in hand, we now considered the possibility that selenol esters might be able to participate in other processes, such as the Friedel–Crafts acylation of aromatics, thus providing a new source of oxocarbenium ions. We imagined that a system could be properly designed which might allow acylation reactions to proceed under relatively mild (neutral) conditions using metal salts which did not possess the high Lewis acidity characteristic of the main group catalysts. Again, one would rely on a soft-soft-type metal–selenium interaction to key the desired bond-forming process.[4]



While our previous studies had revealed that Hg(II) and Cu(II) salts were effective for the conversion of selenol esters to amides, esters, and acids,[2] we found these salts to be ineffectual in the attempted acylation of the electron-rich aromatic anisole in benzene or THF as solvent. Although mercuric trifluoroacetate and cuprous trifluoroacetate offer the advantage of being partially soluble in organic solvents, these salts led only to partial conversion of the selenol ester into its corresponding acid. No traces of the desired acylation products could be detected. Heterogeneous reaction mixtures using mercuric chloride, silver nitrate, cupric chloride, and cuprous oxide were also examined, but again acylation of anisole was not observed.

In contrast, use of the highly reactive crystalline complex of copper(I) triflate and benzene [$(CuOTf)_2PhH$], a reagent first described by Kochi and Salomon, does readily induce the desired transformation.[5] The reaction (entry 6, Table II), which was complete within minutes at room temperature in benzene as solvent, afforded an 81% isolated yield of the acylated product which was found to consist of >95% para isomer by VPC and ^1H NMR analysis. Other examples of this process are displayed in Table II.

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