5,5′-Diuracilyl Species from Uracil and $[AuCl_4]^-$: Nucleobase Dimerization Brought about by a Metal**

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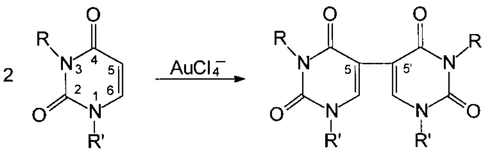
Dedicated to Professor Dr. Friedo Huber on the occasion of his 70th birthday

The mutagenic and carcinogenic potential of pyrimidine nucleobase photoproducts is an area of substantial interest. Thymine, for example, forms dimers of the cyclobutane type with twofold C5,C5′ and C6,C6′ bond formation or those of the 6,4′-(pyrimidine-2′-one)thymine type with C6,C4′ cross-linking.[1–3] Mixed thymine/cytosine photoproducts are likewise known.[4] Here we report the ready formation of C5,C5′-diuracil products directly from the corresponding uracil bases in water and at room temperature with light excluded (Scheme 1). We believe that this is the first reported example



R	R′
H	CH_3
CH_3	CH_3
H	$C_5H_9O_4$

Scheme 1.

of a nucleobase dimerization brought about by a metal species. It appears to be of interest with regard to the photosensitization of DNA by $[AuCl_4]^-$[5] and to speculations that anti-arthritic Au^I drugs may be activated in vivo to Au^{III} metabolites that are responsible for undesired side effects.[6]

According to ^1H NMR spectroscopy $Na[AuCl_4]$ reacts with 1-methyluracil (1-MeUH; R = H, R′ = CH_3) in D_2O (22 °C) over a period of hours to days (pH value drops) to give a variety of soluble products, which have been separated in part by semipreparative HPLC and identified by ^1H NMR spectroscopy (pH dependence of uracil resonances; comparison with samples prepared in an alternative fashion). Accordingly, at least $[Au(1\text{-MeU-}N3)Cl_3]^-$, $[Au(1\text{-MeU-}C5)Cl_3]^-$, $[(AuCl_3)_2(1\text{-MeU-}C5,N3)]^{2-}$, and 5-Cl-1-MeUH are formed in addition to the major product di(1-methyluracilyl-*C5*,*C5′*) **1a** which is not detected by NMR spectroscopy as a result of its extremely poor solubility. However, **1a** can be isolated in good yield and characterized by a variety of methods (see Experimental Section). $[Na(1\text{-MeUH-}O4)_4][AuCl_4]$, which crystallizes as a uracil quartet,[7] is not obtained at the pH used. Compound **1a** does not form if 5-Cl-1-MeUH is used instead of 1-MeUH.

A similar multitude of products is formed when uridine (R = H, R′ = $C_5H_9O_4$) is used instead of 1-MeUH. However, the H6 singlet of di(uridinyl-*C5*,*C5′*) **1b** at $\delta = 8.24$ (D_2O, pD ≈ 1) is observed for at least two days prior to precipitation of **1b**.

With 1,3-dimethyluracil (1,3-DimeU; R = R′ = CH_3) fewer products are detected in solution by ^1H NMR spectroscopy. Di(1,3-dimethyluracilyl-*C5*,*C5′*) **1c** has been isolated in crystalline form as the $NaAuCl_4$ adduct **1c** · 0.5 $NaAuCl_4$ (**1d**), and characterized by X-ray analysis.[8]

Figure 1 gives a view of the chiral dimerization product **1c** of 1,3-dimethyluracil. Two 1,3-dimethyluracilyl residues are joined by a C5–C5′ bond (1.478(5) Å) and display a propeller

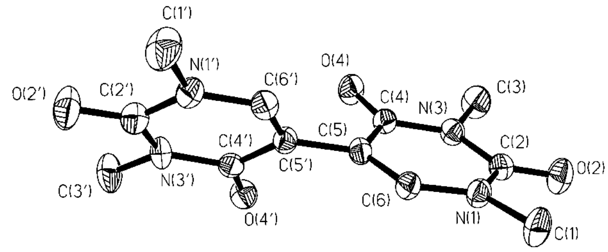


Figure 1. View of the C5,C5′ dimerization product of 1,3-DimeU (**1c**).

twist of 56.9(1)°. To a first approximation the exocyclic O(4) oxygen atoms adopt a head–head orientation. The two halves of the compound are identical within standard deviations and do not differ significantly from the parent compound 1,3-dimethyluracil,[11] except for the interior ring angle at C5, which is smaller in the dimerization product (118.8(3), 118.6(3)° versus 120.4(2)°; 4.4–5σ).

A section of the zigzag chain of **1d** that is formed by linking the diuracilyl entities **1c** by Na^+ cations is shown in Figure 2. Each Na^+ ion in **1d** is octahedrally coordinated by pairs of O4

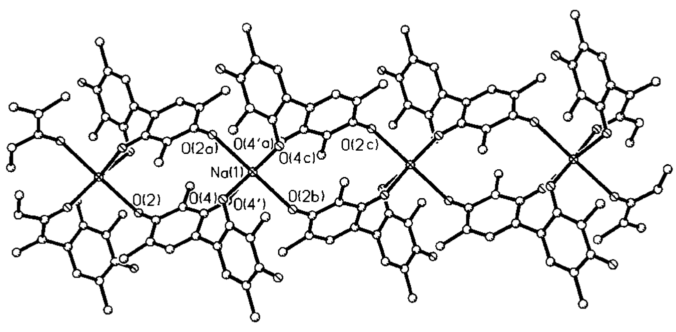


Figure 2. Section of the solid-state structure of adduct **1c** · 0.5 $NaAuCl_4$ (**1d**). The view is along the *y* axis. The pyrimidine rings of the two enantiomers (with O(2a), O(2) and O(2b), O(2c), respectively) are stacking.

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oxygen atoms of the diuracilyl entity (in plane) and O2 oxygen atoms in the axial positions. The observed deviations of some angles from 90° about the Na atom are not unusual. The Na–O distances (2.344(3) – 2.508(3) Å) are likewise not unexpected. The overall arrangement is stabilized by intermolecular base stacking (approximately 3.4 Å).

We assume that formation of the diuracilyl products is the consequence of a reductive elimination process of two *cis*-oriented uracil entities, each bonded to the Au^{III} center through C5. Similar reactions are documented for Au^{III} alkyl compounds[12] as well as a compound of 2-(2′-thienyl)pyridine.[13] Formation of the 5-chlorouracil species could occur in an analogous manner. We have no indication of the formation of twofold coordinate Au^{I} species, most probably because it rapidly disproportionates to Au^{0} and Au^{III}. Moreover, the absence of EPR signals during the dimerization processes is inconsistent with a radical mechanism. Finally, our recent findings on the formation of a Au^{III}–C bond in *trans*-$K[Au(CN)_2Cl$(1,3-DimeU-*C5*)][14] lend further support to such a mechanism. We plan to further study whether other pyrimidine bases behave similarly.

Experimental Section

$C_{10}H_{10}N_4O_4$ (**1a**): $NaAuCl_4 \cdot 2H_2O$ (397.8 mg, 1 mmol) and 1-MeUH (252 mg, 2 mmol) were dissolved in H_2O (100 mL) and the sample kept in a stoppered flask with daylight excluded. After 40 d the precipitate consisting of **1a** and Au^0 was filtered off and treated with NaOH (50 mL, pH 12) for 10 min. Following filtration of Au^0 the pH was brought to 7 (HNO_3). Compound **1a** precipitated as a colorless material (140 mg, 0.56 mmol, 56%). Better yields (64%) were obtained under slightly modified conditions (2 mmol reactants each, 20 mL H_2O, 11 d, 40 °C). Correct elemental analysis data for C, H, N. ^{1}H NMR (Na^+ salt, D_2O, pD 11, sodium 3-(trimethylsilyl)propanesulfonate (TSP)) $\delta = 7.46$ (s, 1H; H6), 3.35 (s, 3H; CH_3); ^{13}C NMR (Na^+ salt, D_2O, pD 11): $\delta = 39.6$ (CH_3), 163.1 (C2), 178.0 (C4), 111.3 (C5), 148.4 (C6); DEPT: C5 quaternary; MS: *m/z*: 250; IR (KBr): $\tilde{\nu} = 1668$vs, 1607s, 1470s, 1442s, 1416s, 1333s, 1317s, 1181s, 1069s, 941s, 875s,b, 755s, 640s, 573s, 483s, 421s; Raman (solid state): $\tilde{\nu} = 1626$vs, 794vs, 79vs.

$C_{18}H_{22}N_4O_{12} \cdot 1.2H_2O$ (**1b**): The compound was obtained together with Au^0 from an analogous reaction to **1a** after 3 d at 40 °C (1 mmol reactants each, 15 mL H_2O). Work up as with **1a**, or alternatively by simple treatment of the precipitate with hot water and filtration of Au^0, gave **1b** (250 mg, 0.51 mmol, 51%). Correct elemental analysis data for C, H, N. Mass loss is 4.4% at 91 °C; ^{1}H NMR (Na^+ salt, D_2O, pD 12.9, TSP): $\delta = 7.71$ (s, 1H, H6), 5.87 (d, $J = 5.3$ Hz, 1H; H1′), 4.3 – 3.7 (m, 5H; other sugar protons); ^{1}H NMR ([D$_6$]DMSO): $\delta = 11.56$ (s, 1H; N(3)H), 8.21 (s, 1H; H6), 5.84 (d, 5.3 Hz, 1H; H1′), 5.41, 5.15, 4.95, 4.06, 3.96, 3.85, 3.56 (OH and H2′ – H5′); ESI-MS: *m/z*: 509 [**1b**+Na^+]; IR (KBr): $\tilde{\nu} = 1717$vs, 1654vs, 1476s, 1431s, 1272s, 1133m, 1089s, 1059s, 1028m, 589m; Raman (solid state): $\tilde{\nu} = 1653$vs, 1332s, 1262s, 1218s.

$C_{12}H_{14}N_4O_4$ (**1c**): Reaction was carried out in an analogous manner to **1b** and Au^0 was filtered off after 3 d (no precipitate of **1c**). The remaining solution was evaporated to dryness and treated with acetone (15 mL). The residue, consisting of **1c**, a small amount of Au^0 and NaCl was filtered off and recrystallized from H_2O to give pure **1c** (60 mg, 0.22 mmol, 22%). Correct elemental analysis data for C, H, N. Slow evaporation of the acetone solution yielded additional **1c**; ^{1}H NMR (D_2O, pD 8.5, TSP): $\delta = 7.74$ (s, 1H; H6), 3.45 (s, 3H), 3.33 (s, 3H); IR (KBr): $\tilde{\nu} = 1693$vs, 1647vs, 1448s, 1342s, 766s, 752s, 486s, 425s; Raman (solid state): $\tilde{\nu} = 1629$vs, 787s.

$C_{12}H_{14}N_4O_4 \cdot 0.5NaAuCl_4$ (**1d**): A procedure analogous to **1c** was followed, but the residue was extracted several times with $CHCl_3$ instead of being treated with acetone. The residue was subsequently recrystallized from H_2O. Orange – red crystals of **1d** were obtained in low yield (6%). Correct elemental analysis for C, H, N.

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[8] Crystal data for **1d**: $AuCl_4C_{24}H_{28}N_8O_8Na$ ($M_r = 918.33$), monoclinic, space group *C2/c*; $a = 27.578(6)$, $b = 7.917(2)$, $c = 14.678(3)$ Å, $\beta = 90.88(3)°$, $V = 3204.3(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.912$ g cm^{-3}, $F(000) = 1816$, $\mu = 4.998$ mm^{-1}, 3802 observed reflections with $I > 2\sigma(I)$, $R_1 = 0.0277$, $\omega R_2 = 0.0627$, max/min. residual electron density: 0.75/ – 0.66 e Å^{-3}, Siemens P4 diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å), graphite monochromator, absorption correction ψ scans; structure solved with SHELXS-86,[9] refined by least-squares method.[10] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-114368. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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