Table I. Radical Complex Species, P_n^{+y} [a] (P = Py· = 1-alkyl-4-carbomethoxypyridinyl)

	y				
n	0	1	2	3	4
1	P	P^+			
2	P_2	P_2^+	P_2^{2+}		
3			P_3^{2+}		
4			P_4^{2+}	P_4^{3+}	
5					
6					P_6^{4+}

[a] The species described in the communication are isomeric forms of P_3^{2+}. Entries have been made in the table only for complexes for which there is some spectroscopic evidence.

established as a complex of two pyridinium rings and one pyridinyl radical by titrating the cation radical $(Py\cdot)_2^+$ with pyridinium ion, $(Py\cdot)^+$. Addition of the pyridinium ion caused the near-infrared band to increase in intensity (λ_m 1360 nm, ϵ_m 350) along with the ultraviolet band. The absorption curve at a 1:1 ratio of $(Py\cdot)_2^+$ to $(Py\cdot)^+$ was similar to but different from the curve observed for the combination of $(Py\cdot)_2^{2+}$ and $(Py\cdot)$ in intensity. For clarity and simplicity, we shall indicate the rings as either + or ·. Heating the solution of ++· for 18–20 h at 50–60° changed the absorption spectrum into that found for +·+, while heating the latter for many hours had no effect. Thus, the unsymmetrical complex is converted into the symmetrical complex by heating[14a] (eq. 1).

$$++ \text{ and } \cdot \rightarrow ++\cdot \rightarrow +\cdot+ \leftarrow +\cdot \text{ and } + \qquad (1)$$

The near-infrared transition is identified as an intervalence transition on the basis of (1) position and intensity, (2) band widths of ca. 3200 cm^{-1} (calculated for the high-temperature limit according to Hush,[1c] 4100 cm^{-1}), (3) substantial temperature sensitivities (thus, associated with a complex and favored by decreased relative motion of the components to a greater extent than local electronic transitions) (40% increase for ++·, ca. 20% increase for +·+ in ϵ_{max} for a shift from +29 to −29 °C), and (4) similarity to bands noted for polyferrocene (nII, III) ions.[2a]

The ++· complex is produced in the same way from iodide, bromide, and perchlorate. A similar complex is formed from a biscation containing an *o*-xylylene group in place of a trimethylene group, but is not observed for a biscation connected by a tetramethylene group, implying that the complex requires rather precise orientation of the rings. The ++· complex is not stable if the acetonitrile is replaced by 2-methyltetrahydrofuran. The salt which separates is a mixture of both possible salts, the bissalt predominating because of solubility.

The cation radical $(Py\cdot)_2^+$ itself dimerizes to yield either +·+· or +··+ which accounts for the weak intravalence absorption cited above. Itoh[13] noted the visible absorption at 77 K, but made no reference to its presence at 25 °C. It seems likely that the dimer is responsible for the low radical concentrations reported by Itoh, and that the dimer structure may be different in acetonitrile and methyltetrahydrofuran.[14b]

A summary (Table I) indicates that a number of relatively simple complexes and their surprisingly slow interconversions remain to be explored. A moderate number of analogous TCNQ complexes involving the neutral TCNQ molecules and the $TCNQ\cdot^-$ anion radical could be listed in a parallel fashion, including (for T = TCNQ) T, T^-, T_2^-, T_2^{2-}, T_3^{2-}, and T_4^{2-}.[5,6] Relating the properties of such complexes to those of component species may be fruitful for the design of complexes with desirable solid-state properties, through the probable relationship between the occurrence of the IT bands and conductivity.

Kinetic studies on the interconversions of the complexes are possible,[14a] and it will be of special interest to probe possible differences between solids obtained from solutions containing different but isomeric complexes.

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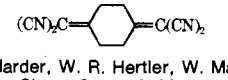

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(9) We have utilized the convention that the neutral radical (Py·) is taken as the base for the formulation of structures, and have chosen to explicitly indicate the radical to create a clear distinction between this formula and Py, commonly used for pyridine. Then, in analogy for the metal to metal ion conversions (e.g., $M \rightarrow M^+$), the positive ion is formed by writing a positive sign, with the loss of the electron being implicit. Thus, $(Py\cdot)_2 \rightarrow (Py\cdot)_2^+$ expresses the conversion of a pyridinyl diradical to a pyridinyl radical–pyridinium ion combination. The specific structure can be further defined by (a) indicating the order of radical and charge where appropriate and (b) writing regular structural formulas.

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(11) All solutions were prepared in all-glass apparatus and used after sealing off from a vacuum line. Bispyridinium salts were the gift of Dr. P. K. Huang. Spectroscopic measurements were made with a Cary 17 spectrophotometer.

(12) The properties of the $(Py)_2^{2+}$–$(Py\cdot)_2$ solutions will be communicated separately.

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(14) (a) Detailed kinetic studies are under way. (b) Further details will be furnished with the related ++·· stoichiometry for the solutions noted in footnote 12.

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Synthesis of C-5 Substituted Pyrimidine Nucleosides via Organopalladium Intermediates

Sir:

We wish to report a facile method for the introduction of carbon chains at the C-5 position of pyrimidine nucleosides. We have found that substitution at the C-5 position of uridine and 2′-deoxyuridine may be effected by reaction of olefins with organopalladium intermediates generated in situ from mercurinucleosides.

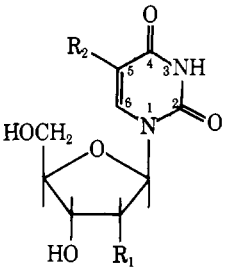
Arylpalladium compounds (which may be prepared in

situ from an appropriate inorganic palladium complex and either arylmercury salts or aryl halides) react readily with unactivated olefins, generating carbon–carbon bonds.[1-3] Two particularly important features of this approach are (1) the reaction may be carried out under exceedingly mild conditions, and (2) a wide variety of common functional groups are unreactive toward organopalladium intermediates.[2] In light of these considerations it seemed to us that an opportunity existed for creation of carbon–carbon bonds to unprotected nucleosides.

Uridine and related nucleosides substituted by various functional groups at the pyrimidine C-5 position represent an intriguing class of compounds. A representative example is 2′-deoxy-5-ethyluridine, a thymidine analogue which shows significant activity against herpes viruses.[4] 5-(4,5-Dihydroxypentyl)uracil is a major constituent of the DNA of the *B. subtilis* phage SP-15.[5,6] Although not yet proven it is most likely bonded normally to 2′-deoxyribose within the DNA. The 2′-deoxyribonucleoside would be a useful intermediate en route to synthetic polynucleotides incorporating this modified base. With few exceptions,[7] past synthesis of pyrimidine nucleosides with a carbon chain at the C-5 position has been accomplished by way of a condensation reaction between the protected, activated sugar and the C-5 substituted base. In the case of derivatives of 2′-deoxyuridine, the synthesis and purification have normally proven difficult. The use of organopalladium intermediates, derived from unprotected nucleosides, in forming carbon–carbon bonds at the C-5 position completely circumvents these difficulties.

The reaction of phenylmercuric chloride with $LiPdCl_3$ and ethylene in acetonitrile gives styrene in good yield.[2] When 5-chloromercuriuridine[8] was subjected to the same reaction in acetonitrile, methanol, or water, the expected product 5-vinyluridine[9] was not obtained. In methanol the major product, on the basis of preliminary spectral data, is most likely 5-(1-methoxyethyl)uridine. Since our initial goal was to establish a synthetic route to 5-alkyluridines, we did not, in this and other related reactions, attempt to purify the intermediates but reduced them directly to the 5-alkylnucleosides by catalytic hydrogenolysis. Furthermore, we have made no attempt to isolate and characterize the nucleoside-derived organopalladium intermediates. In analogy to other arylpalladium compounds we have assumed that they exist only as unstable transient intermediates.[1,2]

Details of the synthesis of 5-ethyluridine from 5-chloromercuriuridine illustrate the facility with which this and related transformations may be accomplished. 5-Chloromercuriuridine[8] (1.37 mmol) and 0.1 M Li_2PdCl_4 in MeOH (13.7 ml) were stirred under an atmosphere of ethylene for 3 h at room temperature. The mixture was filtered and the filtrate treated with $NaBH_4$ (100 mg) to reduce the soluble mercury salts. After refiltration, 10% Pd/C (100 mg) was added to the filtrate and the mixture stirred under hydrogen at room temperature for 16 h. The methanol-soluble residue was chromatographed on silica gel (50 g) in a 2-cm diameter column eluting with 3:1 ethyl acetate–ethanol. Fractions 14–28 (7-ml fractions) were combined, the solvent was evaporated, and the last traces of solvent were removed under vacuum to give 5-ethyluridine (86% yield). Recrystallization from acetone gave analytically pure 5-ethyluridine,[10] mp 186–187° (lit.[11] mp 184–186°). Following a nearly identical procedure 2′-deoxy-5-ethyluridine (**2**) was obtained in 68% overall yield from 2′-deoxyuridine. Analytically pure **2** after recrystallization from acetone melted at 153–153.5° (lit.[12] mp 152–153°). Reaction of 2′-deoxy-5-acetoxymercuriuridine with 1-benzyloxy-4-penten-2-ol[13] and Li_2PdCl_4 in methanol gave, after hydrogenolysis and chromatography on silica gel, 2′-deoxy-5-(4,5-dihydroxypentyl)uridine (**3**) (57% yield): mp 151–152°; NMR (D_2O, δ values relative to sodium 3-(trimethylsilyl)propionate-*2,2,3,3-d*$_4$) δ 1.52 (4 H, m), 2.37 (4 H, m), 3.56 (3 H, m), 3.82 (2 H, m), 4.04 (1 H, m), 4.49 (1 H, dd), 6.28 (1 H, t, J = 7 Hz), 7.71 (1 H, s); uv (H_2O) 267 nm (ϵ 9100). The peaks from δ 3.82 to 6.28 correspond closely to the 2′-deoxyribosyl proton resonances found in the NMR spectrum of thymidine.[14]



1, R_1 = OH; R_2 = CH_2CH_3
2, R_1 = H; R_2 = CH_2CH_3
3, R_1 = H; R_2 = $CH_2CH_2CH_2CHOHCH_2OH$
4, R_1 = OH; R_2 = $CH{=}CHCO_2CH_3$
5, R_1 = OH; R_2 = $CH_2CH{=}CH_2$

The reaction between methyl acrylate, 5-chloromercuriuridine, and Li_2PdCl_4 in methanol was worked up by saturation of the reaction mixture with H_2S to remove palladium and mercury salts as their insoluble sulfides. The methanol-soluble residue was recrystallized from ethanol to give methyl *trans*-3-(5-uridylyl)propenoate (**4**) in 57% yield: mp 202–204°; NMR (TFA) δ 3.97 (3 H, s), 7.09 (1 H, d, J = 16.5 Hz), 7.68 (1 H, d, J = 16.5 Hz), 8.35 (1 H, s), in addition to the expected resonances due to the ribosyl protons; uv (H_2O) 300 nm (ϵ 19 900).

Allyl chlorides have been found to react with arylpalladium chlorides by a mechanism which regenerates palladium chloride and produces allyl aromatic derivatives.[3] Reaction of nucleoside-derived organopalladium compounds with allyl chloride also proceeds by this mechanism. 5-Chloromercuriuridine, allyl chloride (ninefold excess), and Li_2PdCl_4 (25 mol %) reacted rapidly at room temperature in methanol. Treatment of the reaction mixture with H_2S followed by chromatography on silica gel gave 5-allyluridine (**5**) in 78% yield. Recrystallization from acetone gave analytically pure product melting at 175.5° (lit.[15] 175–176°).

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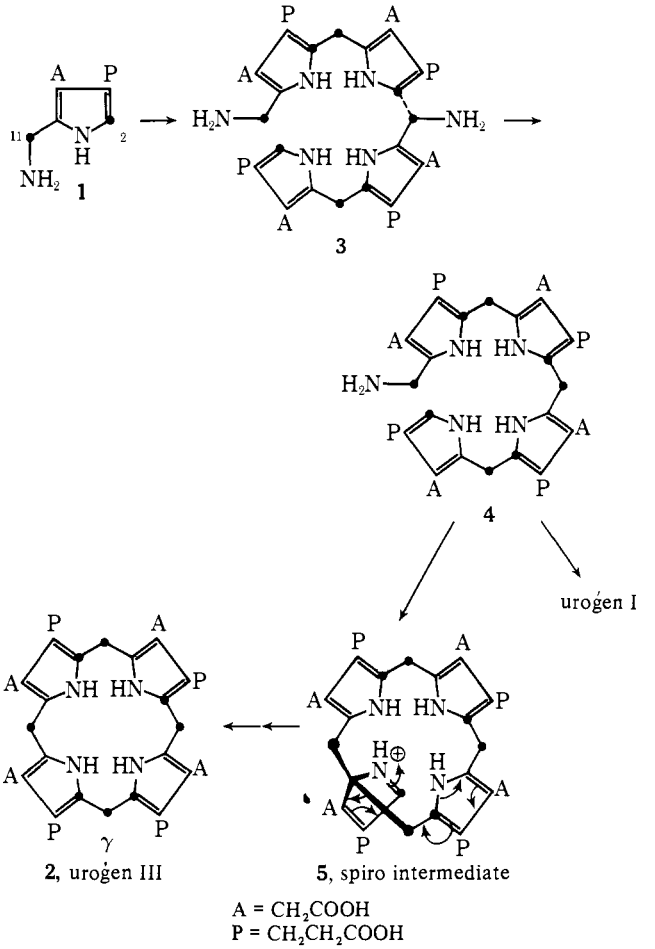
Biosynthesis of Uroporphyrinogen III from Porphobilinogen. Resolution of the Enigmatic "Switch" Mechanism

Sir:

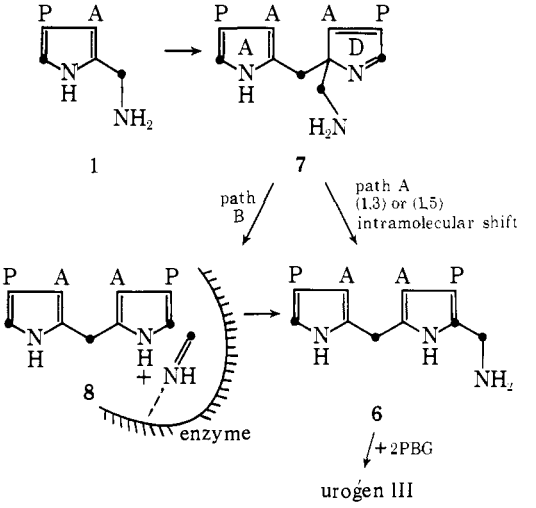
A long-standing problem in the biosynthesis of the ubiquitous porphyrins, which play a vital role in the architecture of heme, chlorophyll, cytochrome *c*,[1] and vitamin B_{12},[2] concerns the fascinating mechanism[1d] whereby the combined action of two enzymes, porphobilinogen deaminase and modifying cosynthetase, transforms the monomeric pyrrole (PBG, **1**) to the unsymmetrical uroporphyrinogen (uro'gen) III (**2**). In the type III structure one of the PBG units (ring D) appears to have been "switched" with respect to a head-to-tail polymerization sequence, an event which has given rise to more than 20 published speculations[3] and some 200 experimental papers[1] designed to solve this mystery. The stage has now been reached where the evidence for what happens is secure; i.e., an *intra*molecular process (clearly defined by the elegant kinetic work of Bogorad)[4] is responsible for transforming four molecules of PBG to a mixture of uro'gens I and III and the liberation of 4 mol of ammonia. Within the experimental error (ca. 10%) of a ^{13}C NMR experiment, the work of Battersby[5] has confirmed not only the intramolecular nature of the switch mechanism, but has rigorously defined the new location of the mobile amino methyl carbon from C-11 of one PBG unit as it finds its way into the γ position of protoporphyrin IX, according to Scheme I. In order to recognize the timing and nature of the mechanism, the use of specifically labeled dipyrrylmethanes has been undertaken recently in two laboratories. According to the Cambridge group,[6] the dipyrrylmethane (DPM) **3** serves as a good precursor for the type III porphyrins via the linear bilane **4**, and the spiro intermediate **5**; i.e., the switch takes place after the head-to-tail condensation of 4 PBG units. On the other hand, the Frydmans' work supports a mechanism in which "switching" occurs at the first head-on encounter of two PBG molecules under the influence of the deaminase-cosynthetase system to afford the DPM **6** (Scheme II) followed by addition of two more PBG units to complete the type III macrocycle.[1d] Thus although both groups have secured evidence that aminomethyldipyrrylmethanes are involved, different conclusions were reached about the timing of the rearrangement process, and it was clearly recognized that verification of either the Corwin (Scheme I) or Rimington-Johnson (Scheme II) hypothesis[7] was fraught with an overwhelming experimental difficulty associated with the in vitro chemistry of the DPM systems **3** and **6** which necessitates not only subtraction of a chemical blank (up to 80% in some cases) from the enzymatic yield, but also the development of analytical systems for the biologically irrelevant or "nonsense" type IV porphyrins generated from **3**.[11] We have devised a new approach toward the solution of this problem which, by removing the in vitro chemistry of the aminomethyl side chain, provides for the first time a clear mechanistic distinction between Schemes I and II and sets the stage for more advanced enzymological studies.

Scheme I. The Corwin Hypothesis[a]



[a] Heavy circles in Schemes I and II denote the sites of ^{13}C enrichment from a sample of 2,11-[$^{13}C_2$]PBG.[5]

Scheme II. Rimington–Johnson Hypothesis



Consideration of a mechanism such as that depicted in Scheme II reveals that, although the reaction may be deemed *intra*molecular in the chemical sense, i.e., via concerted rearrangement **7** → **6** (path A), the operation of enzymatic intramolecular transfer **7** → **8** → **6** (path B) cannot be excluded. We were, therefore, led to a simple experiment in which a *labeled* sample of DPM **8**[12,16] which has