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Oxidative Addition Reaction of 1,3-Dialkyl-5-fluoro-6-iodouracils to Low-valent Transition Metal Complexes

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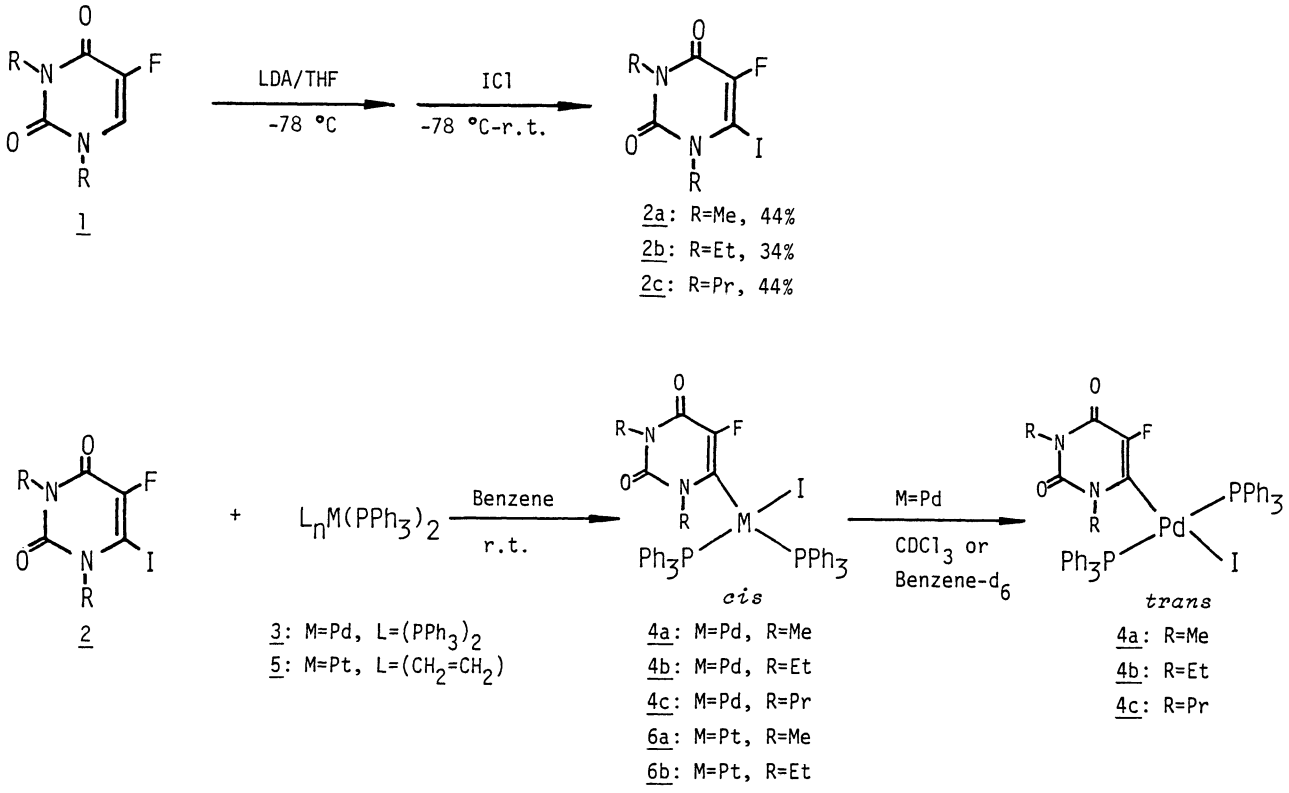
cis-Oxidative adducts are isolated by the reaction of Pd(0) complexes or $Pt(CH_2=CH_2)(PPh_3)_2$ with 1,3-dialkyl-5-fluoro-6-iodouracils, and in palladium cases *cis*-adducts further isomerize to *trans*-ones in solution completely.

Recently, many attentions have been focused on transition metal complexes for their biological activities. For example, it has been shown that *cis*-diaminedichloroplatinum(II) called cisplatin binds covalently to nucleobases in chromosomal DNA by releasing chloride ligands and inhibits the affected DNA from replicating, thus showing the potent cytotoxicity.[1] While continuing our studies on the syntheses and physiological properties of a series of fluorine-containing nucleobases,[2,3] we have taken an interest in group VIII transition metal complexes bearing 5-fluorouracils as ligand. Because these complexes are expected to have dual effects on the DNA and RNA syntheses. That is, they may release 5-fluorouracils on binding to DNA, and free 5-fluorouracils thus formed may be incorporated into RNA to produce "false RNA", which inhibits the protein-synthesis.[4] Here, we wish to describe the preparation and properties of 6-transition metal-substituted 5-fluorouracils as model compounds.

As a method for their syntheses, we chose the oxidative addition reaction[5] of 5-fluoro-6-iodouracils (**2**) to low-valent palladium and platinum complexes. Compounds **2** could be prepared from the corresponding 5-fluorouracils (**1**) as shown in Scheme 1.[6] The reaction of 1,3-dimethyl-5-fluoro-6-iodouracil (**2a**) with tetrakis(triphenylphosphine)palladium (**3**) in benzene at room temperature afforded the adduct, iodo(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-fluoro-6-pyrimidinyl)bis(triphenylphosphine)palladium (**4a**), in 83% yield as yellow needles. Surprisingly, *cis*-configuration of the product was identified by its ^{31}P and ^{19}F NMR spectra, indicating two distinguishable triphenylphosphine groups are present in the complex (see Table 1). To our knowledge this can be the first example that *cis*-isomer of Pd(II) complex is exclusively isolated in the oxidative addition of organic halides to coordinatively saturated Pd(0) species.[7] We also found that this complex easily isomerized to *trans*-one (**4a**-*trans*) in $CDCl_3$ or benzene-d_6 solution. The configuration of **4a**-*trans* was confirmed by its ^{31}P and ^{19}F NMR spectra (Table 1), and also it was isolated as cream prisms by recrystallization from CH_2Cl_2/*n*-pentane.



Scheme 1.

For clarification of this isomerization step of **4a**, we have investigated kinetic studies by means of NMR technique. It was observed that the isomerization obeyed first-order kinetics with respect to a concentration of complex **4a**-*cis*, and the rate constant (k_{obsd}) measured by ^{1}H NMR at 38°C in $CDCl_3$ solution (2.8 x 10^{-2} M) was 2.78 x 10^{-5} s^{-1}. Isomerization rate dramatically decreased in the presence of additional phosphine; for example, the presence of 0.1 equivalent of triphenylphosphine afforded value of a rate constant, k_{obsd} = 5.28 x 10^{-6} s^{-1} (at 2.3 x 10^{-2} M of the complex in $CDCl_3$ at 38°C), which is about five times smaller than that in the absence of free phosphine. Although several plausible mechanisms in the cis-trans isomerization steps of square planar complexes have been proposed,[8] the present isomerization may proceed *via* phosphine-dissociated three-coordinate intermediate.

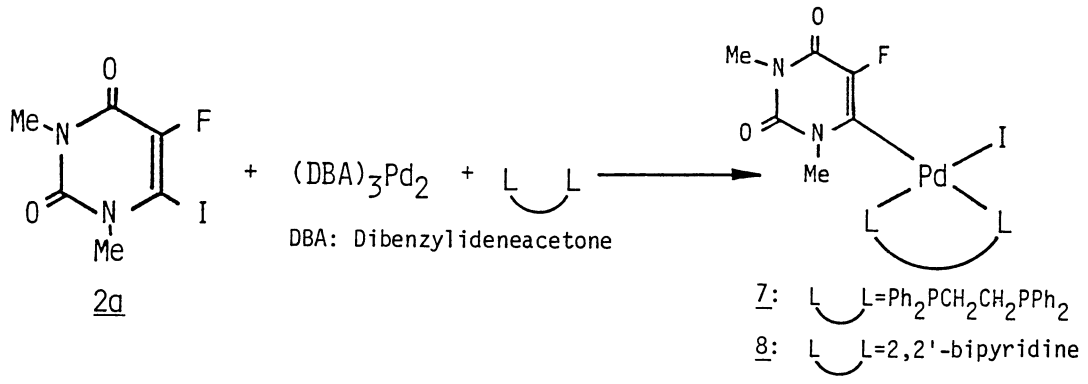
When other 1,3-dialkyl-5-fluoro-6-iodouracils (**2b** and **2c**) were employed as substrates, initial formation of *cis*-adducts (**4b**- and **4c**-*cis*) was also recognized by their NMR spectra. However, they could not be isolated in pure form because of their rapid isomerization to *trans*-ones. Thus, the complexes **4b** and **4c** were obtained as the mixture of *cis* and *trans* forms in 88% and 99% yields, respectively. They also isomerized to *trans*-ones (**4b**- and **4c**-*trans*) completely on standing in solution. Oxidative addition of 1,3-dimethyl-5-fluoro-6-iodouracil (**2a**) to (η^2-ethylene)bis(triphenylphosphine)platinum (**5**) in benzene at room temperature also afforded *cis*-iodo(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-fluoro-6-pyrimidinyl)bis(triphenylphosphine)platinum (**6a**-*cis*) in 64% yield as colorless needles. Diethyl analogue (**2b**) also reacted with Pt(0) complex **5** to

Table 1. Spectral data of Pd complexes 4a-*cis* and 4a-*trans*

	cis form	*trans* form
IR (KBr)	ν(C=O) 1692 and 1642 cm^{-1} ν(C=C) 1590 cm^{-1}	ν(C=O) 1695 and 1642 cm^{-1} ν(C=C) 1592 cm^{-1}
^1H NMR ($CDCl_3$, TMS)	δ3.01(3H, s), 3.65(3H, s), 7.1-7.8(30H, m).	δ2.83(3H, s), 3.40(3H, s), 7.3-7.6(18H, m), 7.6-7.9(12H, m).
^{19}F NMR ($CDCl_3$, $CFCl_3$)	δ-146.9(dd, $^4J_{F-P}$=8.4 and 6.5 Hz).	δ-147.2(t, $^4J_{F-P}$=6.7 Hz).
^{31}P NMR ($CDCl_3$, PPh_3)	δ20.8(dd, $^2J_{P-P}$=29 Hz, $^4J_{P-F}$=6.5 Hz), 31.9(dd, $^2J_{P-P}$=29 Hz, $^4J_{P-F}$= 8.4 Hz).	δ26.4(d, $^4J_{P-F}$=6.7 Hz).
^{13}C NMR ($CDCl_3$, TMS)		δ27.03(3N-Me), 40.93(1N-Me), 139.03 (C-5, dt, $^1J_{C-F}$=196 Hz, $^3J_{C-P}$= 4 Hz), 150.12(C-2), 153.72(C-4, d, $^2J_{C-F}$=33 Hz), 167.42(C-6, dt, $^2J_{C-F}$= 65 Hz, $^2J_{C-P}$=6 Hz).

give the corresponding *cis*-adduct (**6b**-*cis*) in lower yield, probably because of its steric hindrance. Physical and spectral data of **6a** and **6b** are consistent with *cis*-configurations.[9] In sharp contrast with Pd complexes, *cis* Pt complexes did not isomerize to *trans*-ones. The *cis*-adducts bearing 1,2-bis(diphenylphosphino)-ethane (**7**, 88%) or 2,2'-bipyridine (**8**, 44%) as ligand were also prepared from **2a** and tris(dibenzylideneacetone)dipalladium(0) in the presence of these bidentate ligands, respectively (Scheme 2). Further detailed kinetic studies are now in progress in order to make the oxidative addition and isomerization mechanisms clearer.

Finally, it is noteworthy that all of these oxidative adducts of Pt and Pd



Scheme 2.

complexes obtained here have moderate to high antitumor activities against P388 leukemia cell (*in vitro*).

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6) All our attempts to synthesize 5-fluoro-6-iodouracil (**2**, R = H) according to several routes have resulted in failure. We found that all of 1,3-dialkyl-5-fluoro-6-iodouracils exhibit potent cytotoxicity against P388 leukemia cell (*in vitro*) similar to 5-fluorouracil itself. Thus, we used these substituted-uracils (**2**, R = alkyl) as starting materials.

7) The oxidative-addition of a number of organic halides, such as iodobenzene, methyl iodide, acetyl chloride, to $(Ph_3P)_4Pd$ forms the corresponding *trans* complexes; P. Fitton, M. P. Johnson, and J. E. McKeon, Chem. Commun., 1968, 6

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9) Spectral data for the all new complexes are consistent with thier structures, and typical data are described below; **6a**: IR(KBr) ν(C=O) 1690 and 1640 cm^{-1}, ν(C=C) 1590 cm^{-1}; ^1H NMR ($CDCl_3$, TMS) δ3.05(3H, s), 3.65(3H, s), 7.1-7.7(30H, m); ^{13}C NMR ($CDCl_3$, TMS) δ27.31(3N-$\underline{C}H_3$), 41.36(1N-$\underline{C}H_3$, $^3J_{C-Pt}$=50 Hz), 139.74(C-5, d, $^1J_{C-F}$=197 Hz, $^2J_{C-Pt}$=22 Hz), 151.48(C-2, d, $^4J_{C-P}$=6 Hz, $^3J_{C-Pt}$=40 Hz), 155.25(C-4, dd, $^2J_{C-F}$=32 Hz, $^4J_{C-P}$=5 Hz, $^3J_{C-Pt}$=21 Hz), 158.09(C-6, dd, $^2J_{C-P}$=122 Hz, $^2J_{C-F}$=60 Hz, $^1J_{C-Pt}$=844 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ-148(dd, $^4J_{F-P}$=8.2 and 4.0 Hz, $^3J_{F-Pt}$=231 Hz); ^{31}P NMR ($CDCl_3$, PPh_3) δ16.3(*trans* to C-6, dd, $^2J_{P-P}$=17.6 Hz, $^4J_{P-F}$=8.2 Hz, $^1J_{P-Pt}$=2121.1 Hz), 17.4(*trans* to I, dd, $^2J_{P-P}$=17.6 Hz, $^4J_{P-F}$=4.0 Hz, $^1J_{P-Pt}$=3749.6 Hz).

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