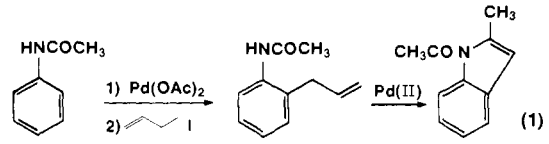

(1)

Two possible mechanisms of the ortho-methylation reaction are considered in Scheme I. The first step of this reaction involves the well-precedented ortho-metalation of acetanilides.[6] We found that the metalation reaction occurred readily with a variety of acetanilides including ortho-substituted compounds, even though it was reported that ortho-substituted acetanilides could not be metalated with $Pd(OAc)_2$.[6] Under our reaction conditions, the metalated products, such as A, could be isolated by omitting the alkylating agents. It was also found that the metalation reaction was inhibited by donor solvents such as DMF, DMA, and acetonitrile; this inhibiting effect allowed the synthesis of exclusively monomethylacetanilides (see Table I).

The alkylation step may involve either an electrophilic attack of MeI on the Pd–carbon bond[7] or a Pd^{IV} intermediate[8] as depicted by Scheme I. These mechanistic pathways are supported by the following observations: (1) EtI reacted 5.5 times slower than MeI at 50 °C in a competition experiment with complex A yielding, respectively, *o*-ethyl- and *o*-methylacetanilide. (2) Complex A was alkylated with methyl triflate and dimethyl sulfate. These reactivity patterns are consistent with an S_N2 mechanism and not a radical pathway.[9,10]

The following observations suggest that the slow step of the ortho-methylation reaction is the ortho-metalation step: (1) The rate of methylation of complex A was much faster than the overall rate of methylation of acetanilide with CH_3I and palladium acetate. (2) The overall rate of the reaction was increased by a factor of 12 when the more electrophillic palladium trifluoroacetate was used instead of palladium acetate.

One of the most interesting features of the ortho-methylation reaction is the observation that the oxidation state of palladium is conserved in the +2 state.[11] We considered the possibility of producing a catalytic cycle. When 4 equiv of acetanilide were reacted with 1 equiv of $Pd(OAc)_2$ and 10 equiv of MeI at 100 °C in HOAc, 1.5 turnovers/Pd^{2+} were obtained in 2.5 h. The only observed products of this reaction were *o*-methylacetanilide and palladium diiodide. When the above reaction was performed with palladium trifluoroacetate in trifluoroacetic acid, 1.8 turnovers/Pd^{2+} were achieved in 5.0 min. Further support for catalysis was demonstrated in the reaction of excess acetanilide, $Pd(OAc)_2$, and MeI in trifluoroacetic at 100 °C in the presence of excess AgOAc. Under these conditions 10 turnovers/Pd^{2+} were achieved in 10 min. Since PdI_2 (formed after the methylation step) does not metalate acetanilide under our reaction conditions, AgOAc was used to regenerate the more electrophillic $Pd(OAc)_2$ catalyst.

The results described in this manuscript demonstrate the feasibility of practical carbon–carbon bond formation that utilizes an ortho-metalation reaction in conjuction with electrophilic alkylating agents and avoids the need for Pd^0 to Pd^{II} recycle. We are presently studying the scope and mechanism of this reaction.

Acknowledgment. We are grateful to Drs. Clark Landis, Patrick Lennon, and Don Morris for helpful discussions and Dr. Robert Kaley, Jim Scanlon, and Dr. Don Willis for technical assistance.

Registry No. PhNHAc, 103-84-4; *m*-MeC_6H_4NHAc, 537-92-8; *p*-MeC_6H_4NHAc, 103-89-9; *o*-$MeOC_6H_4NHAc$, 93-26-5; *o*-$CF_3C_6H_4NHAc$, 344-62-7; *o*-MeC_6H_4NHAc, 120-66-1; *o*-EtC_6H_4NHAc, 33098-65-6; $Pd(OAc)_2$, 3375-31-3; *o*-acetamidophenylpalladium acetate dimer, 72573-63-8; *N*-(2,5-dimethylphenyl)acetamide, 2050-44-4; *N*-(2,4-dimethylphenyl)acetamide, 2050-43-3; *N*-(2,6-dimethylphenyl)acetamide, 2198-53-0; *N*-(2-methoxy-6-methylphenyl)-acetamide, 50868-76-3; *N*-[2-(trifluoromethyl)-6-methylphenyl]acetamide, 91759-50-1; *N*-[2-(2-propenyl)phenyl]acetamide, 68267-69-6; 1-acetyl-2-methyl-1*H*-indole, 37842-85-6.

(7) (a) Grove, D. M.; Van Koten, G.; Louwen, J. N.; Noltes, J. G.; Spek, A. L.; Offels, H. J. C. *J. Am. Chem. Soc.* **1982**, *104*, 24, 6609. (b) Ho, S. C. H.; Straus, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1984**, *106*, 1533–1534.

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(11) A Pd^0 intermediate has been ruled out for the following reasons: (1) The well-precedented ortho-metalation step (first step) has been characterized as an electrophilic attack of Pd^{2+} on the aromatic ring. (2) The alkylation step of complex A (Pd^{II}) with CH_3I proceeds readily under mild conditions (25 °C in toluene) where reduction of Pd^{2+} to Pd^0 is unlikely to occur. (3) Rigorous exclusion of air or deliberate inclusion of air have no effect on the reaction.

Aza Macrocycle That Selectively Binds Lithium Ion with Color Change

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As a part of program directed to a study of the aza macrocyclic compounds related to porphyrines and phthalocyanines, new deeply colored tetraaza macrocycles have been synthesized. We have recently reported a synthesis and tautomerism, shown by Scheme I, of a hexaaza macrocycle containing four pyridine rings connected by two nitrogen bridges.[1] In this paper we report the synthesis and a survey of the complexing properties of the related tetraaza macrocycles. Borror and Haeberer had shown that 2–chloroquinoline reacted with α-cyanoacetamide to give 2-quinolyl-2(1*H*)-quinolylideneacetonitrile.[2] We then applied this reaction to 6,6′-dibromo-2,2′-bipyridine to gain a macrocycle involving pyridine rings connected by carbon bridges.

α-Cyanoacetamide in DMF was treated with sodium hydride to give the sodium salt to which was added 0.25 mol equiv of 6,6′-dibromo-2,2′-bipyridine.[3] The deep-red suspension obtained was stirred for 6 h at 120 °C, water was added then filtered, and the precipitate was washed with acetone to furnish the red fine needles. The spectral data obtained with these crystals clearly indicate that it exists as the fully conjugated form composed of two 2-pyridyl-2(1*H*)-pyridylideneacetonitrile residues (**1**) (20% yield, mp >400 °C dec)[4,5] (Scheme II).

Dicyano macrocycle **1** can be hydrolyzed by 70% sulfuric acid at 120 °C to give dark-red tetraaza macrocycle **2**. ^1H NMR spectrum shows a singlet (2 H) of strongly hydrogen-bonded NH protons at δ 14.9. The tautomerism of a series of dipyridylmethanes has been studied by Daltrozzo, Scheibe, et al.[6] It is noteworthy that while *meso*-cyanodi-2-pyridylmethane is colorless and therefore the dipyridylmethane form predominates over the methine form,[7] deep-red fully conjugated methine forms are favored for our cyclic derivatives (**1** and **2**).

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(4) Satisfactory elemental analysis and mass spectral data were obtained for all new compounds.

(5) The IR spectrum shows conjugated nitrile absorption at 2180 cm^{-1}. The electronic spectrum points to a highly conjugated system, showing absorption maxima at 357 (ε 36600), 375 (37000), 508 (7000), 541 (5600), and 592 nm (3000) in 1-chloronaphthalene. No ^1H NMR data are available owing to the poor solubility of the product.

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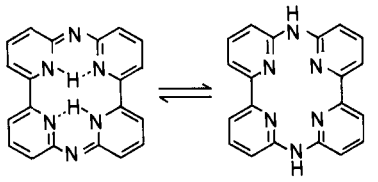
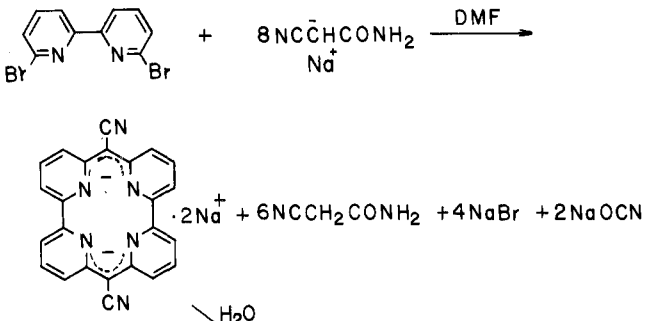
Scheme I



Scheme II



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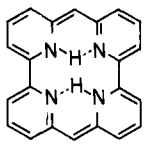
Alkylation of **1** was successful by treatment with butyl iodide and sodium hydride in DMF at 80 °C to afford colorless dibutyl dicyano macrocycle **3** in 30% yield, along with red monoalkylated



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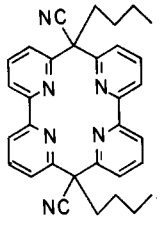
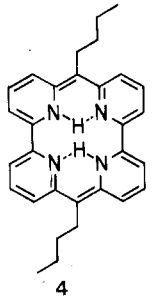


3

product in 60% yield, after chromatography on alumina (chloroform). We regard **3** as being a mixture of cis–trans isomers which can be separated as colorless needles and plates by crystallization from chloroform. Details of these structures will be reported elsewhere.

When the mixture of **3** was treated with 70% sulfuric acid, it gave the red dibutyl macrocycle **4**, mp 154–155 °C, in essentially quantitative yield. The great difference from **2** is that the electronic spectrum of **4** is remarkably solvent dependent: red in methylene chloride and colorless in methanol (Figure 1). Fully conjugated 2(1*H*)-pyridylidene structure **4** is thought to predominate in nonpolar solvent, whereas pyridine structure **5** predominates in polar solvent.[8]



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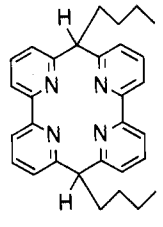

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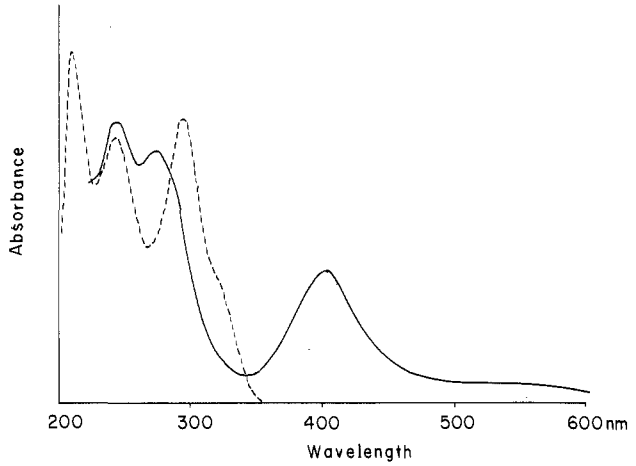


Figure 1. Absorption spectra of dibutyl macrocycle in methylene chloride (—) and in methanol (---).

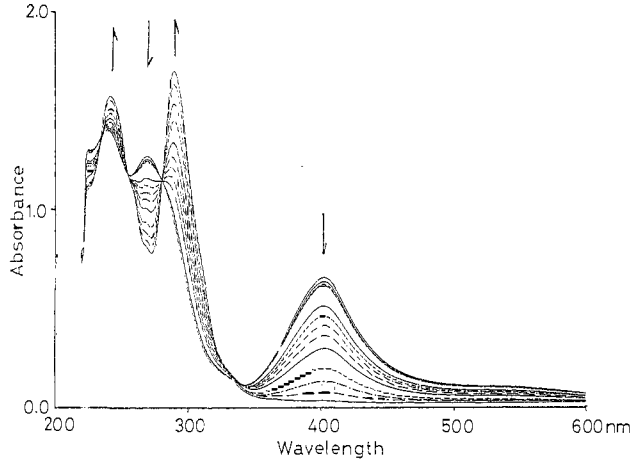


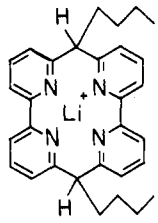
Figure 2. Spectral change of **4** in methylene chloride contacted with LiCl. Arrows indicate the direction of the absorption changes.

The most striking characteristic of this compound is that the electronic spectrum changes remarkably when the solution contacts lithium salt. Figure 2 shows the spectral change of **4** in methylene chloride in contact with solid lithium chloride. When lithium chloride was added to the red solution of **4** in methylene chloride with stirring, the spectrum changed cleanly with good isosbestic behavior. This change in the spectrum, which is also visually observable as color change from red to colorless, can be accounted for by the formation of Li complex **6** which brings the deduction of the conjugated system.[9] When Na or K ion was added to the solution of **4**, spectral change was not observed at all, and hydrogen-bonded NH observed at δ 15.0 did not disappear. No alkaline-earth metal ions were extracted either. Both isomers of **3** were also found to complex preferentially with Li ion with spectral change and gave similar spectra.[10] That the spectra of Li complexes of **3** are quite similar to the spectrum of Li complex of **4** supports the structure of **6**. The following two reasons are thought to support the high selectivity of these macrocycles toward Li ion: (1) The macrocyclic rings are not flexible enough and the cavity sizes are too small to bind other alkali and alkaline-earth ions. (2) The coordination force of nitrogen toward alkali and alkaline-earth metal ions is much weaker than that of oxygen of

(8) The fading of color in methanol was not caused by aggregation because the spectra of **5** followed Beer's law in methanol.

(9) Although the inner NH protons disappeared by adding Li salt, the bridged protons of **6** have not yet been assigned by broadening of the bands because **6** might be a mixture of trans and cis isomers.

(10) Each isomer of **3** shows a small spectral change by adding Li salt because conformation changes occur by the formation of Li complexes.



6

crown ethers, and the cavity size takes a very important part for complexation of metal ions.

Further studies toward additional structural analysis and variations of the macrocycle are now in progress.

Different Isotope Effects for Parallel Pathways of Enzyme-Catalyzed Transmethylation[1]

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Catechol O-methyltransferase[2] (EC 2.1.1.6, COMT) is one of the rare enzymes that catalyze parallel reactions of natural substrates, the methyl group of *S*-adenosylmethionine being simultaneously transferred to the *m*- and *p*-hydroxyl groups of dopamine, for example.[3] We now report that the kinetic isotope effects at pH 7.6 for the formation of these two products from *S*-adenosylmethionine labeled in the methyl group with ^3H and ^{14}C are quite different: $k_T/k_{14} = 1.16 \pm 0.07$ for meta methylation, $k_T/k_{14} = 1.35 + 0.05$ for para methylation. The value for para methylation agrees with an estimate of 1.29 ± 0.12 for S_N2 methyl transfer as purely rate determining. The smaller value for meta methylation, which is around 3-fold faster, indicates incursion of "physical steps" into determining the rate. A different transition-state structure for methyl transfer would also be in principle possible but is excluded by the further observation that at pH 6.2 both isotope effects become equal: 1.32 ± 0.10 (meta), 1.30 ± 0.06 (para).

The isotope effects were measured by allowing a mixture of *S*-adenosyl[*methyl*-^{3}H]methionine and *S*-adenosyl[*methyl*-^{14}C]-methionine (total concentration 0.03–0.05 mM) to methylate dopamine at 37 °C, pH 7.6, in Hepes buffer with 7.0 mM Mg^{2+}, with catalysis by rat-liver COMT. Dopamine was present in excess at concentrations of 0.25–7.5 mM. The meta and para products were isolated at various times by HPLC,[4] and the isotopic ratio $^3H/^{14}C$ was determined by liquid scintillation counting. The counts from the two isomeric products were pooled and the isotope ratio at various fractions of reaction was treated as usual[5] to obtain the isotope effect $k_T/k_{14} = J$. J is then a weighted average of effects for meta and para pathways (eq 1 and 2). To obtain the

$$J = W_m^{14} J_m + (1 - W_m^{14}) J_p \quad (1)$$

$$W_m^{14} = (m/p)_{14}/[1 + (m/p)_{14}] \quad (2)$$

individual isotope effects J_m and J_p, the separated meta and para products were counted, yielding $(m/p)_T = 2.77 \pm 0.05$; $(m/p)_{14} = 3.14 \pm 0.13$. Since it is also true that $J_m/J_p = (m/p)_T/(m/p)_{14}$, we can calculate J_m and J_p from the data.

J_m and J_p themselves vary[6] with dopamine concentration B, because the COMT mechanism is ordered with *S*-adenosylmethione binding first.[7] This binding is reversible at low B, allowing later steps to participate in limiting the rate, but becomes irreversible at high B. In Figure 1, J_m and J_p are extrapolated to $B = 0$ to obtain the *overall* isotope effects $J_{ovm} = 1.16 \pm 0.07$ and $J_{ovp} = 1.35 \pm 0.05$ and to $B = \infty$ to obtain a measure of the isotope effect for the "on reaction" of *S*-adenosylmethionine. The right-hand intercepts must be corrected for branching (see caption) but then yield the expected small or absent isotope effect for the binding step: $J_{on} = 1.03 \pm 0.03$ (meta); 1.02 ± 0.03 (para).

J_{ovm} and J_{ovp} can be compared to an expected value for fully rate-limiting S_N2 methyl transfer. This estimate can be made

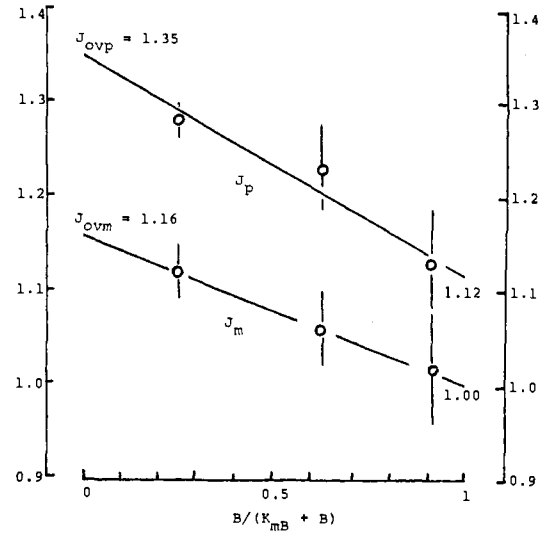

Figure 1. Plot of the observed isotope effects J_p (for para product) and J_m (for meta product), measured at various concentrations of dopamine (concentration = B) vs. a saturation function in B. The expected dependence of J on B (given by Northrop[6] in slightly different algebraic form) is:

$$J = (1 - F)J_{ov} + (F)J_{on}(\beta_T/\beta_{14})$$

where β_T and β_{14} are branching ratios between meta and para products, and $F = B/([K_{mB}k_2/k_5] + B)$ with k_2 measuring the off rate of *S*-adenosylmethionine from its binary complex with enzyme and k_5/K_{mB} the continuation rate of the binary complex on to products ($K_{mB} = 0.75$ mM).[3] The ratio β_T/β_{14} is 0.970 (meta) and 1.095 (para). In the figure, we have taken $k_2 \sim k_5$ so that $F = B/(K_{mB} + B)$; if this is correct, then the intercepts at $F = 1$ for J_m and J_p, when corrected by the branching ratios, will yield the same value of J_{on}. This is found, $J_{on} = 1.03 \pm 0.03$ (meta) and $J_{on} = 1.02 \pm 0.03$ (para), confirming that $k_2 \sim k_5$. The intercepts at $F = 0$ yield $J_{ovp} = 1.35 \pm 0.05$ and $J_{ovm} = 1.16 \pm 0.07$.

(1) This research was supported by the National Institutes of Health through research Grants GM-20199, GM-29332, and NS-10918 and by the National Science Foundation through the award of a Graduate Fellowship to W.P.H.

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