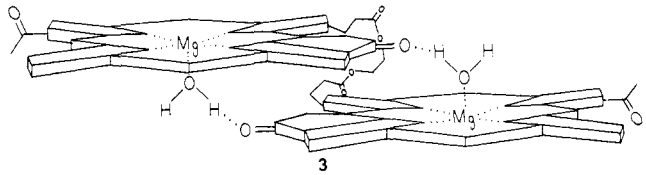
little from its position in the unfolded, linked dimer.[18] As the changes in chemical shift are due to the influence of the ring current of one macrocycle on its dimeric partner, the ^{1}H NMR data suggest that the macrocycles are, on the average, parallel to each other with the III and V rings of each macrocycle experiencing the greatest interannular overlap, and that the acetyl groups do not participate in folding the dimer through hydrogen-bonding interactions. Thus, the evidence suggests that the Bchlide a covalent dimer folds into a structure, **3**, essentially similar to that previously proposed for the special pair of Chl a.[5,6,19]



3

Illumination of a 10^{-5} M solution of **2** in water-saturated toluene containing an equivalent of I_2 with red light ($\lambda > 648$ nm) resulted in complete bleaching of the 803-nm band in <30 s and the appearance of a new absorption band at 1150 nm. This behavior closely mimics the in vivo bleaching of P865,[20] which results in a species absorbing at 1250 nm.[1-3,21] This long wavelength absorption is usually ascribed to the cation radical of the Bchl a special pair. If the same experiment using 10^{-3} M covalent dimer is performed in the cavity of an ESR spectrometer, a Gaussian photo-ESR signal with a linewidth of 10.6 ± 0.3 G is observed at $g = 2.0027$. An identical ESR signal is obtained by oxidation of **2** in water-saturated toluene with $ZnTPP^+ \cdot ClO_4^-$ according to the method of Fajer et al.[22] Since the line width of the ESR signal of monomeric Bchl $a^+ \cdot$ is ~13 G, the narrowing of the signal of the folded cation radical of **2** indicates that the folded structure of the linked Bchl a model special pair has the ability to delocalize an unpaired spin over both macrocycles, as does the in vivo special pair.[7-9]

While our covalently linked Bchl a model mimics the properties of oxidized bacterial photoreaction center special pair chlorophyll, it nevertheless absorbs at 803 nm instead of 865 nm. It is known that reaction center preparations contain at least four bacteriochlorophyll and two bacteriopheophytin molecules.[1-3] Interaction of the in vivo bacteriochlorophyll special pair with additional Bchl a and Bpheo a molecules may shift the special pair transition to longer wavelength. Our model bacterial special pair does not use its two acetyl groups in folding into its photoactive conformation, and these groups could interact with additional Bchl a molecules either through direct acetyl C=O···Mg coordination or via hydrogen bonding to yield an aggregate with an environmentally shifted optical transition. *The additional Bchl a molecules need not be involved in the delocalization of the unpaired spin in the oxidized special pair.* Thus, an important consequence of the work reported here is that the ESR and optical properties of bacterial reaction center probably involve different numbers of Bchl a molecules.

Acknowledgment. This work was performed under the auspices of the Division of Physical Research of the U.S. Energy Research and Development Administration. We thank Dr. M. H. Studier for obtaining the mass spectrum of diester **1**.

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Synthesis of a Chiral Pyridoxal Analogue as a Potential Catalyst for Stereospecific Nonenzymatic Reactions

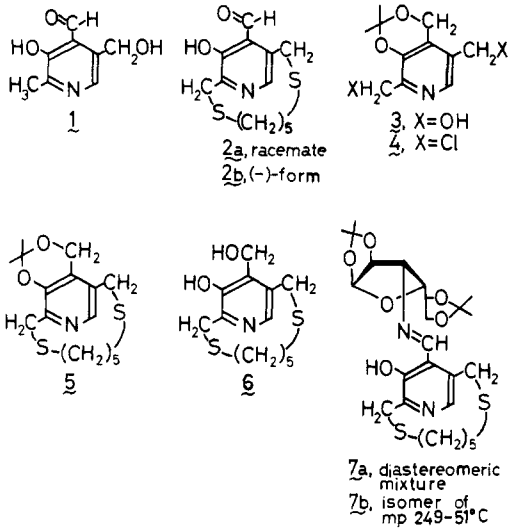
Sir:

Many reactions of amino acids that are catalyzed by pyridoxal phosphate containing enzymes have been duplicated by nonenzymatic model reactions in which pyridoxal (**1**) and a suitable metal salt serve as catalysts.[1] It is generally accepted that these enzymatic and nonenzymatic reactions proceed by closely similar mechanisms.[2]

The stereochemical aspects of these two types of reactions are, however, quite different. While enzymes carry out stereospecific reactions due to their apoenzymes, the nonenzymatic model reactions are not stereospecific. The only reported instance of apparent stereospecificity in model reactions has been attributed to the asymmetry in the substrate.[3] If chirality can be introduced into the pyridoxal molecule without loss of the catalytic activity, we might have a useful novel catalyst for stereospecific reactions that can differentiate between enantiomeric substrates.

From this point of view, we have tried to derive an ansa compound which has planar chirality from **1**, using the methyl group at position 2 and the hydroxymethyl group at position 5 for formation of the "ansa chain", since neither of these groups seems to play any role for the catalytic activity in **1**.[4] Here we report the synthesis of (−)-15-formyl-14-hydroxy-2,8-dithia[9](2,5)pyridinophane (**2b**), which proved to be potential catalyst for stereospecific nonenzymatic reactions.

3,4′-*O*-Isopropylidene-2′-hydroxypyridoxine (**3**) prepared from pyridoxine in 55% overall yield by modifications of a known procedure[5] was treated with thionyl chloride at 0 °C. Removal of excess thionyl chloride followed by neutralization with sodium bicarbonate gave **4**, mp 89–91 °C, in 67% yield.



Condensation of **4** with pentane-1,5-dithiol[6] was performed by slow addition of benzene solution of both reactants to a dilute solution of sodium ethylate in ethanol at 0 °C. Workup and chromatographic purification gave **5** (mp 109–111 °C; NMR (100 MHz, $CDCl_3$, δ) 5.27 (1 H, d, J = 16 Hz), 4.78 (1 H, d, J = 16 Hz), 4.28 (1 H, d, J = 13 Hz), 3.69 (1 H, d, J = 14 Hz), 3.53 (1 H, d, J = 13 Hz), 3.48 (1 H, d, J = 14 Hz)) in 90% yield. After removal of the isopropylidene group by acidic hydrolysis followed by neutralization, the resulting crude **6** was oxidized in benzene–pyridine (2:1 v/v) with commercial manganese dioxide at 80 °C in the presence of a primary amine.[7] The crude oxidation product (Schiff base produced from the amine employed and the resulting **2a**)[8] was hydrolyzed in *p*-dioxane with aqueous hydrochloric acid. Extraction of the mixture at pH 3 with ethyl acetate and subsequent purification by chromatography afforded the racemate (**2a**) (mp 89–92 °C; NMR (100 MHz, $CDCl_3$, δ) 4.48 (1 H, d, J = 13 Hz), 4.30 (1 H, d, J = 14 Hz), 3.71 (1 H, d, J = 14 Hz), 3.58 (1 H, d, J = 13 Hz); UV max (EtOH) 359, 306, nm; IR (KBr) 1660 cm^{-1}) in 60% yield from **5.**

The first attempt of optical resolution of **2a** via formation of Schiff base by treatment with commercial (+)- or (−)-α-methylbenzylamine failed because the Schiff base resisted crystallization. In contrast, condensation of **2a** with 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose[9] gave quantitatively a mixture of diastereomeric Schiff bases (**7a**) which easily crystallized. One diastereomer (**7b**) (mp 249–251 °C dec; $[\alpha]^{22}D$ −307° (c 0.621, $CHCl_3$); NMR (100 MHz, $CDCl_3$, δ) 6.09 (1 H, d, J = 4 Hz), 4.64 (1 H, d, J = 4 Hz);[10] UV max (EtOH) 351, 250 nm; IR (KBr) 1625 cm^{-1}) was isolated by fractional crystallization from cyclohexane–benzene (3:1 v/v) in 61% yield on the base of half of **7a.** Hydrolysis of **7b** with hydrochloric acid and subsequent extraction with ethyl acetate at pH 3 gave the optically active pyridoxal analogue (**2b**)[11] ($[\alpha]^{24}D$ −366° (c 0.666, $CHCl_3$); UV max (EtOH) 359, 306 nm; IR (film) 1660 cm^{-1}) in 81% yield. Compound **2b** did not show any mutarotation.

We also synthesized in a similar way a homologue of **2b** having six methylene groups between two sulfur atoms which, however, underwent complete racemization at room temperature within a few days in contrast to **2b.**[12]

The stereospecific pyridoxal-like activity of **2b** was polarimetrically examined in racemization reaction of L- and D-glutamic acids catalyzed by **2b** (or **1** for comparison) in the presence of cupric ion. It was expected that the asymmetric structure of the catalyst would bring about differences in the stabilities or in the rates of the formation of the intermediates,[13] and that those differences would appear as differences in the racemization rates between L- and D-amino acids.

Table I. The Observed Rate Constants (min^{-1}) of Racemization of L- or D-Glutamic Acid at 25 °C, pH 10.2

Substrate	Catalyst	
	2b	**1**
L-glutamic acid	5.5×10^{-4} [a]	3.3×10^{-4} [b]
D-glutamic acid	4.1×10^{-4} [b]	

[a] The rate constant in the period of 0–40 h. [b] The rate constant in the period of 0–72 h.

Aliquots of buffered mixture (pH 10.2) of the amino acid, cupric sulfate, and the catalyst (300:6:5 in molar ratio)[14] were kept at 25 °C. An aliquot was taken out every 8 h and the reaction was stopped by addition of hydrochloric acid (6 N). The optical rotation $\alpha_t^{mix.}$[15] and uv spectrum of the resulting solution were examined. Because the invariable uv spectra observed suggested the stability of **2b** under these conditions, it was assumed that the rotation contributed by **2b** was constant throughout the reaction. The rotation contributed by the amino acid α_t^{amn} was calculated by using the following equation: $\alpha_t^{amn} = \alpha_t^{mix.} - \alpha_0^{cat.}$ where $\alpha_0^{cat.}$ is the rotation contributed by **2b** in the mixture at $t = 0$.[16]

In accordance with the previous studies on racemization,[17] plots of $\log \alpha_0^{amn} - \log \alpha_t^{amn}$ vs. t were linear, suggesting that racemization catalyzed by **2b** also obeys first-order kinetics. Table I shows values of the observed rate constants k_{obsd} calculated from the slopes of those linear plots.[18,19] These results confirmed the ability of **2b** as a pyridoxal-like catalyst with stereospecificity, and also suggested the possibility of application of **2b** to another type of pyridoxal 5′-phosphate reactions. The greater rate of racemization with **2b** than with **1** may be attributable to the fact that **2b,** unlike **1,** cannot form a hemiacetal.[2]

The chemical stability of **2b** under basic conditions can also be regarded as an advantage as a catalyst, because many pyridoxal analogues including pyridoxal itself are rather labile under those conditions.

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(6) Dithiol compound was chosen for the strong nucleophilicity of sulfur atom.
(7) Presence of primary amines was found to be efficient for accelation of the oxidation reaction. Furthermore, it resulted in marked increase of the yield of the product. Both aliphatic and aromatic amines such as methylamine, 3,*N*′,*N*′-dimethylamino-1-propylamine, and 4-ethoxyaniline were used.
(8) The oxidation was performed with concomitant removal of the resulting water by azeotropic distillation.
(9) This compound is readily obtained by catalytic hydrogenation of the corresponding 3-azido-3-deoxy derivative. For the latter compound, see W. Meyer zu Reckendorf, *Chem. Ber.*, **101,** 3802 (1968).
(10) These signals were assigned respectively to protons at C-1 and C-2 of the amino sugar moiety and employed as a criterion for the purity of **7b** because there was a little difference in the chemical shifts of these protons between two diastereomers included in **7a.**
(11) Although the racemate (**2a**) easily crystallized, **2b** resisted crystallization.
(12) This fact indicates that number of the methylene groups must be less than five for optically stable enantiomers.
(13) These intermediates include Schiff bases formed with **2b** and the substrates and their chelate derivatives with the metal.
(14) The catalyst (0.283 g, $1/1000$ M) was dissolved in a mixture of Sörensen borate buffer and ethanol (4:1 v/v, pH 10.2). The total volume of the solution was made to be 150 mL. Amino acid (14.7 g, $1/10$ M) and $CuSO_4 \cdot 5H_2O$ (0.500 g, $1/500$ M) were suspended in a small volume of water and adjusted to pH 10.2 with aqueous sodium hydroxide. The total volume of the solution was adjusted to 100 mL by addition of water. When the catalyst solution (5 mL)

was mixed with the amino acid solution (2 mL) at 25 °C, measurement of time was started ($t = 0$).

(15) The optical rotation was measured with a Perkin-Elmer Model 241 MC polarimeter. In regard to the optical rotation, the following abbreviations are used: mixture, mix.; catalyst, cat.; amino acid, amn. The subscript t indicates the time when the reaction was stopped.

(16) A solution of the racemic catalyst **2a** with the same concentration as that of the solution of **2b** was also prepared and mixed with L- or D-amino acid solution. The difference in the observed $\alpha_0^{mix.}$ values between the mixture containing **2b** and that containing **2a** was regarded as $\alpha_0^{cat.}$.

(17) For example, see M. Ando and S. Emoto, *Bull. Chem. Soc. Jpn.*, **42**, 2628 (1969).

(18) The calculation is based on the following equation: $K_{obsd} \times t = 2.30 \times (\log \alpha_0^{amn} - \log \alpha_t^{amn})$.

(19) When the racemization yield calculated as $100(\alpha_0^{amn} - \alpha_t^{amn})/\alpha_0^{amn}$ reached 70% ($t = 40$ h), the racemization rate of L-glutamic acid with **2b** decreased to the almost equal value to that of D-glutamic acid.

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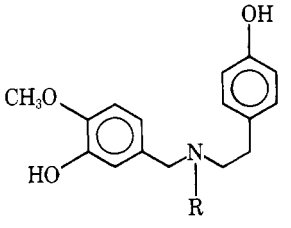
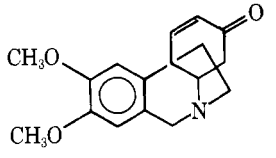
Regiocontrolled Aromatic Palladation

Sir:

The intramolecular coupling of phenols occupies a central position in the biosynthesis of a large number of structurally diverse natural products.[1] For example, *O*-methylnorbelladine (**1a**) is converted in vivo to oxomaritidine (**2**), and *O,N*-dimethylnorbelladine (**1b**) serves as precursor to narwedine (**3**).[2] Much progress toward the laboratory emulation of these conversions has been made in recent years,[3] but, as yet, no rational methodology exists to allow selective ortho coupling of substrates such as **1**.



1a, R = H
b, R = CH_3



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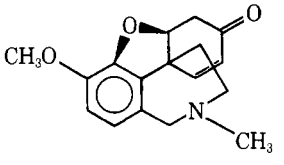
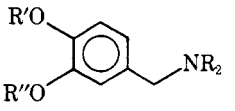
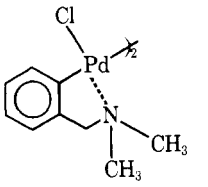


3

Our approach to this problem involves the development of procedures to allow the regiospecific activation of 3,4 dioxygenated benzylic amines (e.g., **4**) at either C-2 or C-6, followed by intramolecular replacement of activating functionality by an appropriate carbon moiety. We report herein the experimental realization of the first of these goals.



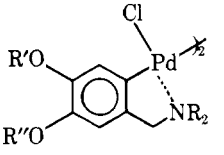
4a-g



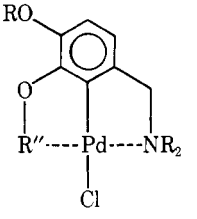
5

We initially dismissed the potential use of lithium[4] or copper as such activating groups, owing to their high reactivity toward a variety of functionality.[5] Instead, our attention was attracted to the facile electrophilic palladation of dimethylbenzylamine, giving rise to the stable ortho palladated complex **5** in high yield.[6,7]

Palladation of benzylic amines **4a-g** by lithium tetrachloropalladate (1 mol equiv) in methanol containing excess triethylamine or diisopropylethylamine gave complexes **6a-g** in high yield, as summarized in Table I. These complexes are

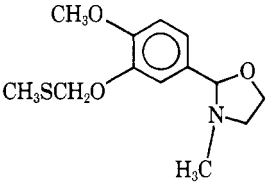


6a-e

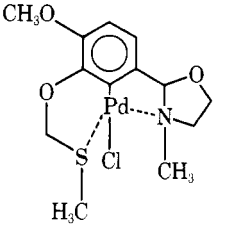


6f-g

creamy yellow crystalline solids, remarkably stable to air and moisture, withstanding shelf storage without noticeable decomposition for indefinite periods of time. That palladation is tolerant of a range of functionality is indicated by the facile formation of complex **6b**, containing a free phenolic hydroxyl group. We have detected no side products from the reaction: complete material balance was realized through unreacted benzylic amine; yields based on recovered starting benzylic amine are virtually quantitative in all cases.



4h



6h

Table I. Regiospecificity of Ortho Palladation

Benzylic amine[8]				Palladium complex[8]				
No.	R	R′	R″	No.	6 isomer, %[a]	2 isomer, %[a]	% yield[b]	Mp,[c] °C
4a	C_2H_5	$-CH_2-$		**6a**	100	0	98	183-185[d]
4b	C_2H_5	CH_3	H	**6b**	100	0	95	158-160[d]
4c	C_2H_5	CH_3	$COCH_3$	**6c**	100	0	52	177-178[d]
4d	C_2H_5	CH_3	CH_2OCH_3	**6d**	100	0	85	155-156[d]
4e	C_2H_5	CH_3	$CH_2C_6H_5$	**6e**	100	0	58	165-167[d]
4f[9]	C_2H_5	CH_3	$CH_2SC_6H_5$	**6f**	0	100	42	197-199.5[d]
4g[10]	C_2H_5	CH_3	CH_2SCH_3	**6g**	0	100	95	150-152
4h[11]				**6h**			93	235-237[d]

[a] Determined by NMR analysis; limit of detection of minor isomer: ~4%. [b] Yields of isolated, crystalline, chromatographically and spectrally homogeneous material. Reported yields are *not* based on recovered starting benzylic amine. [c] Uncorrected. [d] Decomposition.