

Figure 1. The dependence of the pseudocontact chemical shifts, in hertz, of the cyclopropane protons in amines 5-7 on the metal/ligand mole ratio is illustrated.

amino group and the methylene protons in 6 and 7 enables the assignment of the signal experiencing the larger pseudocontact shift to the endo protons and the less shifted signal to the exo protons of the cyclopropane ring as shown in Table I.

The contact chemical shifts were measured in chloroform solution,⁷ with a low nickel acetylacetonate/amine ratio,^{5b} and relative to internal tetramethylsilane. The observations for the endo and exo protons of 5-7 are illustrated in Figure 2 and the results are summarized in Table II.

Table II. Relative Contact Chemical Shifts for Aniline Derivatives

Amine	Relative contact shift ^a			
	H ₂	H ₃	H _β	H _γ
1	1.00	-0.47	-1.08	
2	1.00	-0.45	-0.82	-0.007
3	1.00	-0.43	-0.45	-0.036
4	1.00	-0.46		-0.039
5	1.00	-0.42	-0.34	0.048 (endo)
				-0.034 (exo)
6	1.00	-0.45		0.090 (endo)
				-0.120 (exo)
7	1.00	-0.45		0.079 (endo)
				-0.095 (exo)

^a The relative contact shift, $\Delta H_i/\Delta H_2$. The contact shift for the ortho proton is positive in each case.

The contact shifts for the ortho protons (positive), the meta protons (negative), and the β protons (negative) are in complete accord with prior sign determinations with a negative sign for the epr coupling constant a_2 and positive signs for a_3 and a_β .⁸ The shifts for the γ protons of the alkyl groups in 2-4 are small and negative, indicative of positive a_γ values. In contrast, both positive and negative contact shifts are observed for the γ methylene protons of the cyclopropyl ring. The shifts for the endo protons of 5 and 7 are positive, whereas the shifts for the exo protons are negative.

(7) W. D. Perry and R. S. Drago, *J. Amer. Chem. Soc.*, **93**, 2183 (1971).

(8) J. E. Wertz and J. R. Bolton, "Electron Spin Resonance," McGraw-Hill, New York, N. Y., 1972, Chapter 6.

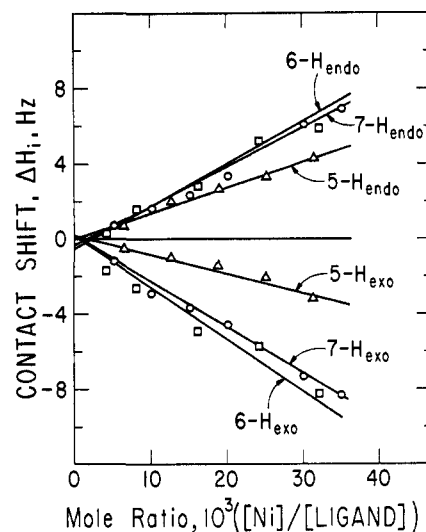


Figure 2. The dependence of the contact chemical shifts, in hertz, of the cyclopropane protons in amines 5-7 on the metal/ligand mole ratio is illustrated.

The nickel reagent also separates the singlet of 6 into an upfield and a downfield component. To assign these resonance signals, we added incremental amounts of nickel acetylacetonate to a solution of 6 and the rare earth pseudocontact shift reagent. The resonances of the methylene protons remained sharp indicating that fast exchange was realized. As the nickel reagent was added, the upfield (endo) signal of 6 shifted further upfield while the downfield (exo) signal shifted further downfield. The results for 5-7 establish that a_{endo} and a_{exo} differ only modestly in magnitude, but that a_{endo} is negative and a_{exo} is positive.

These findings are consistent with the spin density distribution in strained bicyclic molecules observed by Morishima and Yonezawa^{5b} and by Rassat and his group.⁹ We note that the spin polarization models apparently have limited utility compared with the INDO model. Our observations concerning the spin density distribution in the unstrained isopropyl group as well as the strained cyclopropyl group agree well with the predictions of the latter theory.¹⁰

(9) A. Rassat and J. Ronzaud, *J. Amer. Chem. Soc.*, **93**, 5041 (1971).

(10) Theoretical results for cyclopropylcarbinyl radical, 4-nitrocyclopropylbenzene anion radical, and related compounds are presented in ref 2d and in W. C. Danen, C. T. West, T. T. Kensler, and T. J. Tipton, *ibid.*, **94**, 4830 (1972).

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5 vs. 4a Addition to Isoalloxazines

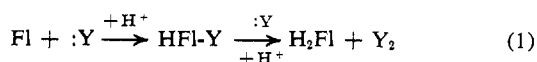
Sir:

It has been suggested, as a general concept, that flavin-mediated oxidation reactions should be considered to occur *via* the formation of covalent intermediates.^{1,2} The most important question as to the

(1) G. A. Hamilton, *Progr. Bioorg. Chem.*, **1**, 83 (1971).

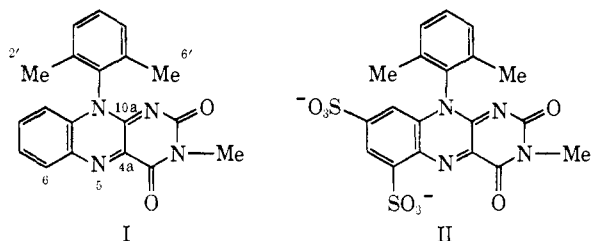
(2) P. Hemmerich, *Chimia*, **26**, 149 (1972).

positions of the isoalloxazine ring involved in catalysis remains to be answered. The 10a, 8, 5, and 4a positions have received consideration as those involved in the formation of HF1-Y. Though numerous covalent



adducts to isoalloxazines are available through photocatalytic reactions,³ only one example of a nucleophilic addition (dark) to a flavin has been reported.⁴ We wish to report herein that the position of addition of SO_3^{2-} may, dependent upon steric and electrostatic factors, be to either the 5 or 4a positions of an isoalloxazine.

Substrates employed in the present investigation are I⁵ and II.⁶ In I and II the 2,6-dimethylphenyl



substituent at N(10) of the isoalloxazine system provides steric hindrance to nucleophilic attack at the 10a position. By use of I the 10a position has previously been eliminated as a site for catalysis in several flavin mediated reactions.⁵ In II, not only is the 10a position hindered but approach of a negatively charged nucleophile (SO_3^{2-}) to the 5 position should be disfavored due to charge and steric repulsion by the SO_3^- substituent at the 6 position.

I was found to react with the SO_3^{2-} component of sulfite buffers to provide a product with λ_{max} 307 nm (ϵ_{max} 8700) at pH 7.1. Under the same conditions, II provides an adduct with λ_{max} 367 nm (ϵ_{max} 3460) and a shoulder at 300 nm. The numerous 4a and 5 adducts previously synthesized by photochemical reactions and indirect routes have invariably been found to be differentiable by their characteristic uv-visible spectra. Thus, for 16 odd 5 adducts, λ_{max} is characteristically^{4,7} between 296 and 330 nm and for 15 odd 4a adducts the λ_{max} values are invariably between 360 and 370 nm with shoulders near 300 nm.^{7c,8} The

(3) See, for example: (a) W. H. Walker, P. Hemmerich, and V. Massey, *Eur. J. Biochem.*, **13**, 258 (1970); (b) M. Brüstlein, W.-R. Knappe, and P. Hemmerich, *Angew. Chem., Int. Ed. Engl.*, **10**, 804 (1971).

(4) F. Müller and V. Massey, *J. Biol. Chem.*, **59**, 1295 (1970).

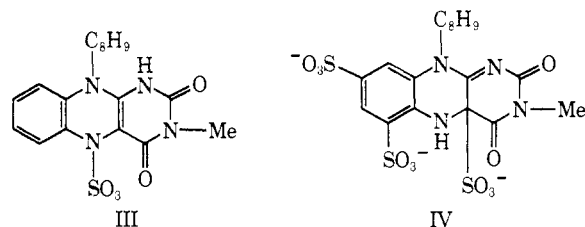
(5) T. C. Bruice, L. Main, S. Smith, and P. Y. Bruice, *J. Amer. Chem. Soc.*, **93**, 7327 (1971); (b) L. Main, G. Kasperek, and T. C. Bruice, *Chem. Commun.*, 847 (1972).

(6) II: *Anal.* Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_5\text{S}_2 \cdot 4\text{H}_2\text{O}$: C, 40.42; H, 4.28; N, 9.93; S, 11.36. Found: C, 40.39; H, 4.26; N, 9.93; S, 11.16. Neutral equivalent: calcd, 2.0; found, 2.05. As the dipotassium salt: *Anal.* Calcd for $\text{C}_{19}\text{H}_{13}\text{O}_8\text{N}_5\text{S}_2\text{K}_2 \cdot 4\text{H}_2\text{O}$: C, 35.62; H, 3.46; N, 8.74; S, 10.01; K, 12.21. Found: C, 34.97; H, 3.62; N, 8.95; S, 10.25; K, 11.66. The nmr spectrum in DMSO-*d*₆ solution (δ ppm) showed: 1.93 (s, 6 H), 3.28 (s, 3 H), 7.00 (d, 1 H), 7.43 (s, 3 H), 8.33 (d, 1 H). The two doublets ($J = 2$ Hz) arise from the aromatic hydrogens of the isoalloxazine ring in meta position.

(7) (a) K. H. Dudley, A. Ehrenberg, P. Hemmerich, and F. Müller, *Helv. Chim. Acta*, **47**, 1354 (1964); (b) M. Brüstlein and P. Hemmerich, *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, **1**, 335 (1968); (c) P. Hemmerich, S. Ghisla, U. Hartmann, and F. Müller, "Flavins and Flavoproteins," H. Kamin, Ed., University Park Press, Baltimore, Md., 1971, p 83.

(8) (a) W. H. Walker, P. Hemmerich, and V. Massey, *Helv. Chim. Acta*, **50**, 2269 (1967); (b) M. Brüstlein, Ph.D. Thesis, University of Konstanz (Germany), 1971; (c) W.-R. Knappe, Ph.D. Thesis, University of Konstanz (Germany), 1971.

spectra of the adducts of I and II are, therefore, as anticipated for III and IV, respectively. Finally, nmr (D_2O) splitting of absorption of the 2'- and 6'-methyl groups (112 and 137 Hz) conclusively establishes IV. In IV a differential magnetic environment is provided for the 2'- and 6'-methyl groups due to an asymmetrically substituted 4a carbon. We conclude that the adduct of I possesses structure III and that of II, structure IV. The reversible formation of 5 ad-



ducts in reactions of SO_3^{2-} with flavinium salts has been most conclusively established.⁴ The readily reversible formation of the 4a adduct IV establishes that the $\Delta\Delta F^\circ$ for formation of the 5 and 4a adducts is not prohibitive. Our results also establish that 5 and 4a adducts, depending upon the nucleophile, may accompany one another in which case the minor constituent cannot be dismissed as not being along the reaction path (eq 1). One can envision steric and electrostatic hindrance at an enzyme site which could control the direction of nucleophilic addition.

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Total Synthesis of *dl*-Dendrobine

Sir:

Dendrobine is the main alkaloid obtained from *Dendrobium nobile* L.¹ with biological activities similar to those of picrotoxin.² By chemical and spectral means the structure³ of dendrobine was determined to be **1** possessing a picrotoxane skeleton.

The result of our synthetic study on dendrobine was published previously,⁴ and we are reporting here the total synthesis of (\pm)-dendrobine. An ingenious method of constructing a *cis*-hydrindan system stereoselectively by intramolecular Michael addition was thoroughly studied by Johnson and his coworkers⁵ and was employed in the present work. 3,4-Dihydro-7-

(1) H. Suzuki and I. Keimatsu, *Yakugaku Zasshi*, **52**, 1049 (1932); *Chem. Abstr.*, **27**, 1886 (1933).

(2) L. A. Porter, *Chem. Rev.*, **67**, 441 (1967), and the references cited therein.

(3) S. Yamamura and Y. Hirata, *Tetrahedron Lett.*, **79** (1964); T. Onaka, S. Kamata, T. Maeda, Y. Kawazoe, M. Natsume, T. Okamoto, F. Uchimaru, and M. Shimizu, *Chem. Pharm. Bull.*, **12**, 506 (1964); Y. Inubushi, Y. Sasaki, Y. Tsuda, B. Yasui, T. Konita, J. Matsumoto, E. Katarao, and J. Nakano, *Tetrahedron*, **20**, 2007 (1964); Y. Inubushi, E. Katarao, Y. Tsuda, and B. Yasui, *Chem. Ind. (London)*, 1689 (1964).

(4) Y. Hayakawa, H. Nakamura, K. Aoki, M. Suzuki, K. Yamada, and Y. Hirata, *Tetrahedron*, **27**, 5157 (1971).

(5) W. S. Johnson, S. Shulman, K. L. Williamson, and R. Pappo, *J. Org. Chem.*, **27**, 2015 (1962).