error, production of V was completely stereospecific in all media. The value of the ratio of V to VI for *threo*-IV changed from 49 in pure dimethyl sulfoxide at 25° to 19 in tetrahydrofuran at 25° to 7 in water at 132°, whereas for *erythro*-IV the values with the corresponding solvents and temperatures were 16, 19 and 11. The reactions were cleanly first order in substrate. The reaction proceeded at a convenient rate *at 25° in dry dimethyl sulfoxide and tetrahydrofuran*[8] to give 80–90% yields of product, whereas temperatures of 132–138° were required in water, and yields were inferior due to polymerization of IV. Rate comparisons for *threo*-IV at 25° are (the rate in water at 25° had to be estimated by extrapolation from higher temperature): $k_{\text{DMSO}}/k_{\text{water}} \sim 10^5$; $k_{\text{tetrahydrofuran}}/k_{\text{water}} \sim 10^6$. For erythro-IV at 25°, the values were $k_{\text{DMSO}}/k_{\text{water}} \sim 10^4$; $k_{\text{tetrahydrofuran}}/k_{\text{water}} \sim 10^5$. For each isomer, addition of 10 mole % water to tetrahydrofuran depressed the rate by a factor of approximately 200, whereas similar treatment of dimethyl sulfoxide gave a decrease of only a factor of 5 to 10.

These data indicate that the activity of the negative oxygen of the amine oxide is subject to considerable variation, depending on whether it is hydrogen-bonded. The rate is higher in dry tetrahydrofuran than dry dimethyl sulfoxide because less solvation energy of the dipole has to be overcome in tetrahydrofuran in going to the transition state (charge is more dispersed in the transition state). The rate is higher in wet dimethyl sulfoxide than in wet tetrahydrofuran because unlike tetrahydrofuran, dimethyl sulfoxide acts as an internal drying agent, and competes with amine oxide for hydrogen bonds with the water present.

These results should find practical applications in synthetic and degradative chemistry in which low temperatures are required for the Wolff–Kishner or internal elimination reactions.

[8] Runs in anhydrous tetrahydrofuran and dimethyl sulfoxide were made by dissolving hydrated amine oxide in the dry solvent and drying out the water with Molecular Sieves (at 80° in the case of tetrahydrofuran).

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SPECIES EQUILIBRIA IN NICKEL(II) PORPHYRIN SOLUTIONS: EFFECT OF PORPHYRIN STRUCTURE, SOLVENT AND TEMPERATURE[1]

Sir:

We wish to report our finding that nickel (II) porphyrins in basic solvents capable of acting as ligands (*e.g.*, pyridine and *n*-butylamine) can exist as an equilibrium mixture of two spectrally distinct species and that the relative concentrations of the two species are dependent upon porphyrin structure, solvent basicity, and temperature but, over the range of concentrations studied, are independent of nickel(II) porphyrin concentration.

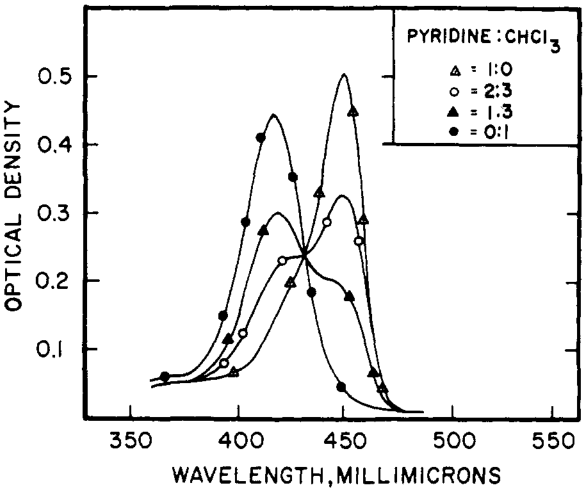

Fig. 1.

Among the nickel(II) porphyrins that have been prepared from the metal-free porphyrin and nickel acetate in acetic acid solution, purified chromatographically, and crystallized out of chloroform-methanol are: Ni(II) mesoporphyrin IX dimethyl ester (Cpd. 1, m.p. 189°, *Anal.* Calcd. for $C_{36}H_{40}O_4N_4Ni$: C, 66.37; H, 6.05; N, 8.60. Found: C, 66.25; H, 6.40; N, 8.61), Ni(II) deuteroporphyrin IX dimethyl ester (Cpd. 2, m.p. 202°, *Anal.* Calcd. for $C_{32}H_{32}O_4N_4Ni$: C, 64.56; H, 5.42; N, 9.41. Found: C, 64.75, 64.55; H, 5.56, 5.60; N, 9.36, 9.66), Ni(II) 2,4-bis-(2-carboxycyclopropyl)-deuteroporphyrin IX, 2,4-diethyl ester 6,7-dimethyl ester (Cpd. 3, m.p. 99–101°, *Anal.* Calcd. for $C_{44}H_{48}N_4O_8Ni$: C, 64.41; H, 5.90; N, 6.38. Found: C, 64.19; H, 6.05; N, 7.02). Ni(II) 2,4-diacetyldeuteroporphyrin IX dimethyl ester (Cpd. 4, m.p. 204–205°, *Anal.* Calcd. for $C_{36}H_{36}O_6N_4Ni$: C, 63.64; H, 5.34; N, 8.64. Found: C, 63.79; H, 5.58; N, 8.31; Ni, 8.55), and Ni(II) 2,4-diformyldeuteroporphyrin IX dimethyl ester (Cpd. 5, m.p. 270°, *Anal.* Calcd. for $C_{34}H_{32}N_4O_6Ni$: C, 62.70; H, 4.95; N, 8.60. Found: C, 62.37; H, 5.24; N, 8.57).

The spectrum of a given nickel(II) porphyrin in solution can differ with solvent and temperature. As shown in Fig. 1 for Cpd. 4 ($2.0 \times 10^{-6} M$) in pyridine–chloroform mixtures (v./v.) at 30°, these spectra are characterized by isosbestic points indicative of an equilibrium between two, and only two, species. In solvents of low basicity (*e.g.*, chloroform, benzene, 1,2-dichloroethane and dioxane) only one species (I) is observed; in more basic solvents a second species (II) appears whose spectrum has a Soret band maximum at about 30 mμ longer wave length and other differences. The D_{II}/D_{I} values[2] for Cpd. 2 ($2.0 \times 10^{-5} M$) at 30° are 0.05, 0.09, 0.19, 0.62 and 2.33 in chloroform, pyridine–water (1:1), pyridine–chloroform (1:1), pyridine and *n*-butylamine, respectively. The lower is the temperature the greater is the relative amount of Species II present. In pyridine, Cpd. 2 ($3.7 \times 10^{-5} M$) exhibits D_{II}/D_{I} values of 0.62, 0.93 and 1.44 at 30°, 20° and 10°, respectively; for Cpd. 4 ($5.7 \times 10^{-5} M$), D_{II}/D_{I} is 1.0 at 83° and 3.0 at 30°.

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[1] Presented in part at the 138th National Meeting, American Chemical Society, New York, N. Y., 1960.

[2] D_I and D_{II} represent optical densities at Soret band maxima of Species I and Species II, respectively.

The position of the equilibrium is sensitive to the type of substituents at the periphery of the porphyrin ring. The more effectively electron-withdrawing (as reflected in basicity of the nitrogen atoms in metal-free porphyrins) is a substituent in the 2 and 4 positions,[3] the greater is the proportion of Species II relative to Species I (Table I).

TABLE I

Compound	2,4-Substituent	D_{II}/D_I[a]	pK_3[b] ($\pm$0.1)
1	Ethyl	0.28	5.8
2	Hydrogen	0.62	5.5
3	2-Ethoxycarbonylcyclopropyl	0.74	4.8
4	Acetyl	2.63	3.4
5	Formyl	3.33	2.8

[a] $2.0 \times 10^{-5} M$ in pyridine at 30°. [b] These data pertain to the equilibrium between neutral metal-free porphyrin and monocation in 2.5% sodium dodecyl sulfate at 25° (J. N. Phillips and W. S. Caughey, unpublished; *cf.* J. N. Phillips, *Revs. Pure Appl. Chem.*, **10**, 35 (1960)).

The position of the equilibrium is independent of Ni(II) porphyrin concentration over the concentration ranges studied. For example, D_{II}/D_I values obtained for Cpd. 2 in pyridine at 30° are 0.623, 0.617, 0.625 and 0.621 at molar concentrations of 3.3×10^{-4}, 3.3×10^{-5}, 3.3×10^{-6} and 6.5×10^{-7}, respectively.

That basic solvent molecules are serving as ligands at the nickel atom giving rise to Species II is consistent with an increase in the proportion of Species II with increasing solvent basicity and decreasing temperature and porphyrin basicity. Solute–solute interactions observed in "magnetically anomalous" nickel complexes[4] evidently are not important here since the position of the equilibrium is independent of solute concentration. Also, an equilibrium between square-planar and tetrahedral complexes can be excluded in view of the high stability[5] and planarity[6] of Ni(II) porphyrins. A difference in spin-state with Species I diamagnetic, as it is in the solid,[7] and Species II paramagnetic (high-spin) might be expected on theoretical grounds[8] and in view of the magnitude and direction of spectral shifts[9] and findings with other nickel complexes.[4] Preliminary magnetic susceptibility studies in 0.01 *M* solutions do show pyridine solutions to be paramagnetic with respect to chloroform solutions to a degree consistent with such a spin-state difference.

These data, interpreted on the basis of solvent perturbation effects,[10] suggest Species I is a highly tetragonal complex experiencing weak perturbation along the d_{z^2} axis perpendicular to the prophyrin plane and Species II is a less tetragonal complex experiencing strong axial perturbation. Separation between d_{z^2} and $d_{x^2-y^2}$ energy levels increases with increasing porphyrin basicity and decreases with increasing solvent basicity. However, as yet conclusive evidence of the number of solvent ligands involved in these species has not been obtained.

The structural differences among the porphyrin moieties of hemoproteins and heme enzymes, particularly in the cytochromes,[11] suggest corresponding ligand field differences of the same order of magnitude as those encountered in this study.[12]

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[3] Each of the porphyrins are 2,4-disubstituted derivatives of deuteroporphyrin IX or 1,3,5,8-tetramethylporphin-6,7-dipropionic acid.

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[11] S. Granick and D. Mauzerall in Greenberg, "Metalobic Pathways," Vol. 2, Academic Press, Inc., New York, N. Y., 1961, p. 554.

[12] The dimethyl esters of protoporphyrin IX and chlorocruoroporphyrin have pK_3 values of 4.8 and 3.7, respectively.

[13] Initial experiments at Monadnock Research Institute were supported under Cancer Chemotherapy National Service Center Contract No. SA-43-ph-1914, National Cancer Institute, National Institutes of Health; completing experiments were supported by United States P.H.S. Grant No. H-6079.

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STEROIDS. CXCVII.[1a] SPECTRA AND STEREOCHEMISTRY. PART II.[1b] LONG-RANGE SPIN–SPIN COUPLING BETWEEN FLUORINE AND STEROID ANGULAR METHYL PROTONS

Sir:

Recently reports have appeared of resolvable long-range coupling between protons separated by four or more bonds. In some cases coupling takes place through the agency of sigma bond electrons alone,[2–4] whereas in others "communication" of spin state information also involves π bond electrons, though the π bond itself may,[5,6] or may not,[7] be a direct link in the connective bond chain between the coupling protons. Long-range spin–spin coupling of proton and fluorine also has been reported with comments on the importance of the stereochemical relationship of the coupling nuclei.[4] We are independently examining this problem and record here our results for a number of fluorinated steroids of known stereochemistry. In each of five cases spin–spin coupling of the protons at C_{19} with fluorine leads to splitting of the characteristic 10-methyl three-proton singlet into a resolvable doublet (Table I).[8]

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[8] N.m.r. spectra have been taken at 60 Mc. in carbon tetrachloride or purified chloroform solutions using tetramethylsilane as an internal reference. Varian HR-60 and A-60 instruments have been employed.