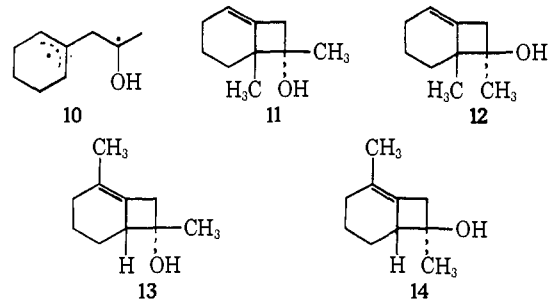
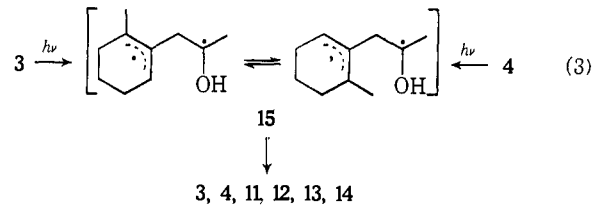


mass spectra.[19] The nmr of **13** and **14** show no vinyl hydrogens, while the third product has absorpion for one vinyl hydrogen at $\delta$ 5.3. Each product has two methyl singlets in the nmr with the position being as follows: for **13**, $\delta$ 1.52 and 1.35; for **14**, 1.52 and 1.14; and for **11** or **12**, 1.35 and 1.18. The 1.52 singlet in **13** and **14** is assigned to the vinylic methyl. The structures of compounds **13** and **14** are then assigned on the basis of the upfield shift of the remaining $CH_3$ singlet in **14** relative to **13**, in analogy with the chemical shifts for the methyls in **5** and **6**.

The production of nearly identical ratios of the three cyclobutanols upon photolysis of both **3** and **4**[18] clearly rules out a concerted mechanism for cyclobutanol formation and requires the intermediacy of a biradical, **15**, whose lifetime is long relative to the rate of rotation about the $\beta$ bond (see eq 3).



(3)

This leaves the question of whether the intramolecular hydrogen abstraction is occurring from the excited singlet or the excited triplet state of these $\beta,\gamma$-unsaturated ketones. Irradiation of a benzene solution (0.5 *M*) of **2** at 313 nm with added 1,3-pentadiene (1 *M*) resulted in no quenching of cyclobutanol formation, suggesting that the reaction occurs either from the singlet state or from a short-lived triplet state.[20] Irradiation of solutions (0.5 *M*) of **2** and **4** in acetone at 313 nm yielded mostly polymer and only small amounts of cyclobutanols. The sensitized product ratios differed from those in the direct irradiation, implying that in the direct irradiation cyclobutanol formation is occurring predominantly through the excited singlet state in analogy with the results of Engel and Schexnayder.[6] This interpretation is further verified by our observation that the fluorescence efficiencies of **2**, **3**, and **4** are all very low, at leat ten times lower than that of methyl allyl ketone, a $\beta,\gamma$-unsaturated ketone containing no allylic $\gamma$ hydrogens.

(19) **13**: oil; mass spectrum (70 eV), *m/e* (relative intensity) 152 ($M^+$, 9), 109 (100), 67 (45), 43 (61); ir ($CCl_4$) 3500, 1670 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.0–2.25 (13 H, m, with singlets at 1.35 and 1.52), 2.52 (3 H, m). **14**: oil; mass spectrum 152 ($M^+$, 11), 109 (100), 67 (46), 43 (53); ir ($CCl_4$) 3500, 1670 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 0.9–2.2 (12 H, m, with singlets at 1.14 and 1.52), 2.6 (3 H, m), 2.8 (1 H, s, OH). **11** or **12**: oil; mass spectrum 152 ($M^+$, 7), 109 (100), 67 (39), 43 (81); ir ($CCl_4$) 3500, 1660 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.0–2.8 (14 H, m, with singlets at 1.18 and 1.35), 4.55 (1 H, s), 5.3 (1 H, m).

(20) The lack of 1,3-pentadiene quenching also rules out any triplet sensitization by benzene.

Thus, we conclude that cyclobutanol formation is occurring from the n,$\pi^*$ excited singlet state of $\beta,\gamma$-unsaturated ketones **2**, **3**, and **4** with the intermediacy of a relatively long-lived biradical, **15**. This is quite different behavior from that observed for intramolecular $\gamma$-hydrogen abstraction reactions from the $S_1$ state of saturated alkanones for which the evidence to date rules out a biradical intermediate with a lifetime long relative to the time required for bond rotation[21,22] although there is some evidence that relatively short-lived biradical intermediates may exist.[21b,c] It may be that allylic stabilization of the biradical generated from $\beta,\gamma$-unsaturated ketones leads to a substantial increase in its lifetime.[23]

**Acknowledgments.** The authors wish to make acknowledgment to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Hoffmann-La Roche Foundation for partial support of this research.

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## Reversible Binding of Nitric Oxide and Carbon Monoxide to Iron Porphyrins. Assessment of the Role of the Protein in Hemoglobin

*Sir:*

Iron porphyrins provide one model for the active heme group in hemoglobin (Hb). However, the porphyrins differ in some important respects from the active site in hemoglobin. In the deoxy protein the iron exists as five-coordinate high-spin Fe(II) which reversibly binds one molecule of $O_2$ per iron.[1] Outside the protein, six-coordinate low-spin Fe(II) porphyrins may be obtained;[2,3] these do not bind oxygen reversibly but rather are rapidly oxidized to Fe(III) in aqueous media.[4–6] While iron porphyrins do not bind $O_2$ reversibly, we find that they do bind NO and CO reversibly. The binding of CO to heme has been reported in aqueous solution,[7] and the influence of pyridine on the extent of CO binding has been described.[8] The only report of the interaction of NO with hemes

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outside of a protein environment concerns an esr study on reactions with iron(III) hemes.[9] Here we present preliminary results on the equilibrium constants for the reversible binding of NO and CO to iron(II) protoporphyrin IX (FePpIX) and iron(II) tetraphenylporphyrin (FeTPP) in piperidine (pip). These data in conjunction with those reported for the hemoglobin system enable us to assess the effect of the protein on the heme reaction.

$$\mathrm{Fe(CO)} + \mathrm{NO} \rightleftharpoons \mathrm{Fe(NO)} + \mathrm{CO} \qquad (1)$$

Reaction of ClFeP (P = porphyrin) with piperidine results in rapid and complete reduction of the high-spin Fe(III) to a diamagnetic low-spin iron(II) complex, $(\mathrm{pip})_2\mathrm{FeP}$.[10] Addition of NO to piperidine solutions of this complex results in rapid formation of (pip)FeP(NO), readily identified by its esr spectrum in frozen solution. The three $g$ values ($g_1 = 2.079$, $g_2 = 2.005$, $g_3 = 1.979$) are similar to those reported for nitrosyl complexes of hemoglobin and other heme proteins[11] and are also identical with those reported for products of the reaction of iron(III) porphyrins with NO.[9]

The equilibrium constant $K_{NO}$ for reaction 2 was

$$(\mathrm{pip})_2\mathrm{FeP} + \mathrm{NO} \overset{K_{NO}}{\rightleftharpoons} (\mathrm{pip})\mathrm{FeP(NO)} + \mathrm{pip} \qquad (2)$$

measured by following the change in visible spectrum at low NO pressures (NO diluted with $N_2$). The spectra show good isosbestic points, and the spectra of the PpIX system are virtually identical with those reported by Chien for hemoglobin.[12] At 23°, the values of $P_{NO}(1/2)$, the pressure for 50% nitrosylation, are 0.18 and 0.40 Torr for the PpIX and TPP complexes, respectively; the stronger binding to the PpIX complex seems reasonable since the higher electron density with this more basic porphyrin would favor formal oxidation to a $Fe^{III}NO^-$ complex. The NO stretching frequency for the (pip)FeTPP(NO) complex at 1680 $cm^{-1}$ (KBr) is similar to that reported for other $Fe^{III}$-$NO^-$ complexes.[13] The spectral changes upon addition of NO are reversible, but a number of freeze–pump–thaw cycles over a period of several hours is required.

The equilibrium constant $K_{CO}$ for reaction 3 was also

$$(\mathrm{pip})_2\mathrm{FeP} + \mathrm{CO} \overset{K_{CO}}{\rightleftharpoons} (\mathrm{pip})\mathrm{FeP(CO)} + \mathrm{pip} \qquad (3)$$

obtained in piperidine, by following changes in visible spectra with CO pressure. The changes were readily reversible upon pumping. At 23°, values of $P_{CO}(1/2)$ were 5.8 and 75 Torr for the PpIX and TPP complexes, respectively, the greater binding again occurring with the more basic PpIX system. The $K$(PpIX)/$K$(TPP) ratio for NO binding (~2.2) is considerably less than for CO binding (~13), suggesting that backbonding is more important in the carbonyl system. This observation also favors the bent configuration for NO.[14]

Direct comparison of the equilibrium constants for NO (and CO) binding to the heme inside and outside of the protein environment suffers from differences in iron(II) coordination number and spin state which are difficult to assess, although estimates of thermodynamic contributions due to these differences can be made.[15] However, if the ratio of the binding constants $K_{NO}/K_{CO}$ is considered, the differences between the iron porphyrin model and the protein vanish.

$$(\mathrm{pip})\mathrm{FePpIX(CO)} + \mathrm{NO} \overset{K = K_{NO}/K_{CO}}{\rightleftharpoons} (\mathrm{pip})\mathrm{FePpIX(NO)} + \mathrm{CO} \qquad (4)$$

$$\mathrm{Hb(CO)} + \mathrm{NO} \rightleftharpoons \mathrm{Hb(NO)} + \mathrm{CO} \qquad (5)$$

Both the above equilibria involve conversion of a six-coordinate diamagnetic carbonyl to a six-coordinate paramagnetic nitrosyl complex. Except for the sixth coordination site (piperidine *vs.* imidazole), the only difference between the two equilibria is the environment surrounding the heme: piperidine solvent in reaction 4 and the hydrophobic pocket provided by the globin in reaction 3. The relative binding constants for sheep hemoglobin are $K_{NO}/K_{CO} = 1500$ from competition experiments[16] which compare with a value of ~30 for the free heme in piperidine. Therefore, we assign a factor of 50 to the difference in the heme environment in the two cases.

Preliminary data on the temperature dependence of reaction 4 indicate that $\Delta H$ is comparable with that reported[16] (2–3 kcal $mol^{-1}$) for reaction 5, and thus we suggest that the difference between reactions 4 and 5 lies in the entropies of solvation in the model system. An unfavorable effect of greater ordering of solvent around the polar $Fe^{III}NO^-$ product compared to the $Fe^{III}CO$ reactant would be unimportant in the protein system, where an essentially rigid preformed pocket accommodates the gaseous molecules. The observed effect of the protein is comparable with similar data for the difference in the reversible binding of oxygen by cobalt porphyrins and coboglobin,[17–19] where the oxygen complex is best formulated as a $Co^{III}O_2^-$ species.

Preliminary studies on the competition between NO and CO indicate a greater amount of the NO complex is formed initially than that expected from the separate equilibrium constants, but on standing the relative amounts of NO and CO complexes reach their expected equilibrium concentrations. Kinetic measurements show that the addition reactions involve five-coordinate intermediates,[20] and qualitative observations are in agreement with the reported kinetics of addition of NO and CO to hemoglobin.[16] Of all ligand reactions with hemoglobin studied to date, NO has the largest $k_{on}$ and the smallest $k_{off}$.

These preliminary thermodynamic and kinetic measurements appear to provide the best example yet of a model system for a naturally occurring protein in terms of both structural similarity at the active site and undergoing an identical reaction with that occurring in the protein. Such systems provide the only

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direct means of assessing the role of the globin on the reactivity of the heme group.

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## Isolation and Characterization of a Kinetically Stable Transition Metal Formyl Complex

*Sir:*

Acyl complexes are well known, synthetically useful organotransition metal derivatives;[1-7] however, corresponding formyl complexes have not been characterized.[8] Herein we report the preparation and characterization of a kinetically stable formyl complex, **1**.

Of the two obvious methods for preparing formyl complexes, (a) migratory insertion of a metal carbonyl hydride in the presence of an external ligand such as CO[8] and (b) formylation of a nucleophilic saturated metal carbonyl, we chose the latter because the equilibrium in (a) apparently lies far to the left or the forward rate is imperceptibly slow (eq 1). Previously we had isolated acyl tetracarbonylferrates(0)[3] and found their rate of CO exchange to be very slow.[9] This result suggested that the corresponding formyl tetracarbonylferrate(0) **1** would be kinetically stable with respect to decarbonylation.

Treatment of $Na_2Fe(CO)_4$ with acetic formic anhydride[10] in THF under Ar at 25° cleanly afforded the desired formyl complex $(CO)_4Fe(CHO)^-$ (**1**) which was isolated as the $N(PPh_3)_2^+$ salt.[11] *Anal.* Calcd for $C_{41}H_{31}FeNO_5P_2$: C, 66.95; H, 4.25; N, 1.90. Found: C, 66.94; H, 4.47; N, 1.93.

$$HFe(CO)_4^- + CO \underset{(b)}{\overset{(a)}{\rightleftharpoons}} \underset{\mathbf{1}}{HCFe(CO)_4^-} \xleftarrow{HCOCCH_3} Fe(CO)_4^{2-} \quad (1)$$

The ir and cmr spectra of **1** closely resemble those of the analogous acyl derivatives $(CO)_4Fe(COR)^-$ (**2**).[12] In addition, the spectra of both **1** and **2** are markedly dependent on the nature of the cation and its state of solvation. The acyl and formyl frequencies in **1** and **2** are raised by 30 $cm^{-1}$ in the ir and their acyl and formyl cmr resonances are shifted upfield by $\delta$ 18 and 16, respectively, upon changing the counterion from $Na^+$ to $N(PPh_3)_2^+$ (Table I). The addition of strongly coordinating solvents such as HMPA or crown ethers to THF solutions of the $Na^+$ salt of **1** and **2** cause shifts to values near those observed with the $N(PPh_3)_2^+$ counterion. The methyl cmr signal in **2** (R = $C_2H_5$) is insensitive to these changes ($\Delta\delta < 0.1$) exemplifying the small solvent shifts normally associated with cmr. Terminal carbonyls in **1** and **2** show smaller shifts in the ir (5–15 $cm^{-1}$) and slight cmr shifts ($\Delta\delta < 1$), in each case in the opposite direction from the acyl or formyl shifts.[12,13] These solvent- and cation-induced shifts strongly suggest ion pairing involving primarily association through the acyl or formyl oxygen.[14] Earlier we demonstrated the role of ion pairing in migratory insertion reactions leading to **2**.[17]

**Table I.** Ir and Cmr Spectra of $Z^+[(YCO)Fe(CO_4)]^-$

| Solvent | $Z^+$ | $\nu$(YC=O), $cm^{-1}$ Y = H | Y = $CH_3$ | $^{13}C$ nmr ($\delta$ TMS) Y = H | Y = $C_2H_5$ |
|---|---|---|---|---|---|
| THF | $Na^+$ | 1577 | 1580 | 275.8 | 279.7 |
| THF–HMPA | $Na^+$ | 1610 | 1610 | 257.6 | 260.2 |
| THF | $N(PPh_3)_2^+$ | 1607 | 1609 | 260.1 | 261.5 |

Although similarities between **1** and **2** have been emphasized, there are important differences. Only the formyl complex **1** exhibits aldehydic $\nu_{CH}$ (2690 and 2540 $cm^{-1}$). The cmr resonance for the formyl carbon in **1** but not acyl carbons in **2** shows nuclear Overhauser enhancement with proton noise decoupling. With off-resonance decoupling the formyl carbon signal is split into a doublet by the aldehydic proton. The pmr spectrum of **1** exhibits a sharp singlet at very low fields ($\delta$ 14.95, TMS, in THF).[18]

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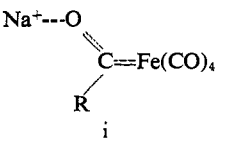
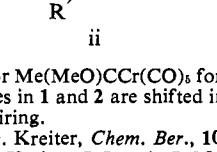
(14) Tightly ion paired acyls i would be structurally similar to carbene



i

complexes[14] ii. Carbene complexes have characteristic cmr resonances



ii

at very low field ($\delta$ 362.3 for Me(MeO)CCr(CO)$_5$ for example).[15,16] The formyl and acyl frequencies in **1** and **2** are shifted in this direction under conditions favoring ion pairing.
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