Communications to the Editor

Synthetic Oxygen Carrier. A Dioxygen Adduct of a Manganese Porphyrin

Sir:

In the past 5 years studies on the properties of cobalt(II) oxygen carriers[1] have afforded an excellent opportunity to attack some of the central questions regarding biological oxygen carriers. More recently, it has been found that synthetic iron(II) systems can be reversibly oxygenated,[2] offering further opportunities of characterizing transition metal-dioxygen interactions. We now have investigated the interaction of dioxygen with *meso*-tetraphenylporphyrin(pyridine)manganese(II), Mn(TPP)(py), and report the first observations of reversible adduct formation between a manganese porphyrin and dioxygen.

The pyridine adduct of Mn(TPP) was isolated as a solid after the method of Kobayashi and Yanagawa.[3] A water-free toluene solution of this complex, prepared under nitrogen without added pyridine, is exposed to molecular oxygen at −79°. Figure 1 shows the resulting spectral changes.[4] The decrease in optical density, splitting of the Soret peak, and growth of a band at ~470 nm are all similar to the spectral changes observed on going from Mn^{II}(TPP) to a Mn^{III}(TPP) species.[5] The effect of oxygenation occurs within the time required to record the visible spectrum (several minutes after the addition of O_2). Removal of dioxygen (effected by bubbling rigorously dried and deoxygenated N_2 through the solution) largely returns the spectrum to that initially observed. It is possible to go through several such oxygenation-deoxygenation cycles, indicating that the pyridine adduct of Mn(TPP) reacts reversibly with O_2 in toluene at −79°. Under these same conditions, after 14 hr of exposure to 1 atm of O_2, 70% of the initial manganous complex can be regenerated.

Qualitatively, the affinity of M(TPP)(py) for O_2, as a function of the metal, increases in the order Co(II) < Fe(II) < Mn(II). Under 1 atm of oxygen in toluene at −79°, the cobalt system shows only a slight tendency to form an adduct;[6] the iron complex is partially converted to the dioxygen adduct,[2d] whereas the manganese compound is almost totally in the form of the dioxygen complex. Such a result is in accord with the ease of oxidation of analogous metalloporphyrins,[7] M(II) → M(III), which also increases in the order Co(II) < Fe(II) < Mn(II). This suggests that the corresponding Cr(II) complex could be an even more efficient oxygen carrier, and work is in progress to test this hypothesis.

The upper portion of Figure 2 presents the EPR spectrum of the pyridine adduct of Mn(TPP). The observed axial g values, $g_{\perp}^{Mn} = 5.96$ and $g_{\parallel}^{Mn} = 2.0$, are typical of a high spin ($S = \frac{5}{2}$) d^5 system with zero field splitting (D) greater than the microwave quantum (~0.3 cm^{-1}); experiments at higher frequencies (~1.2 cm^{-1}) show that $D^{Mn} \sim 0.55$ cm^{-1}.[8] The hyperfine splittings from ^{55}Mn are essentially isotropic, $a^{Mn} = 74$ G.[8] The large-D value for a Mn(II) ion, the lack of variation of the spectrum with base concentration, and the similarity to spectra of Mn-substituted hemoglobin[9,8] all show this spectrum to be associated with the five-coordinate Mn(TPP)(py).[10]

In the presence of O_2 and excess pyridine (10–100% v/v) the Mn(TPP)(py) complex is stable at room temperature for as long as several hours, and the 77 K EPR spectrum (Figure 2, upper) is not affected by O_2. However, when Mn(TPP)(py) is dissolved in toluene, exposed to O_2 at −79°, and frozen, the lower spectrum of Figure 2 appears, with features at $g = 1.45$, ~2, and ~5.4–5.5 (see Figure 3 and discussion below). In some samples an additional weak complicated spectrum with $g \simeq 2$, associated with an uncharacterized dimeric species, overlaps the broad $g \sim 2$ absorption. Reevacuation restores the Mn(TPP)(py) spectrum, with a slight irreversible increase of the multiline $g \simeq 2$ spectrum. This cycling can be repeated, indicating that the lower spectrum in Figure 2 is that of a reversible dioxygen adduct.

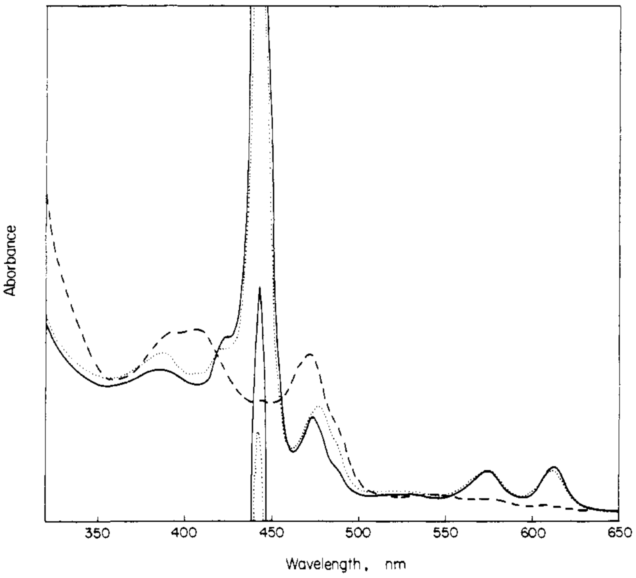


Figure 1. Visible spectrum of ~1 × 10^{-6} *F* Mn(TPP)(py) in toluene at −79°: (—) under nitrogen, (- - -) under oxygen, (···) under nitrogen after oxygenation-deoxygenation cycle.

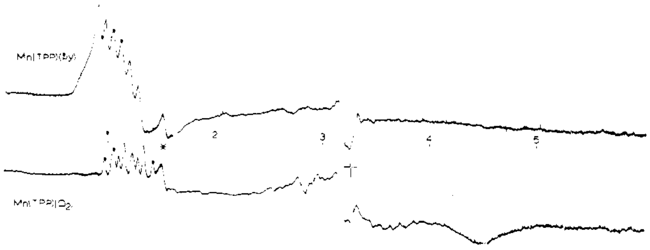


Figure 2. EPR spectrum of Mn(TPP)(py) in degassed toluene at −196°. Mn(TPP)(O_2) in toluene with O_2 at −196°. Field calibration indicated in kG. "*" indicates signal from rhombic iron in quartz.

The low field portion of the dioxygen-adduct spectrum (Figure 3) is found to consist of an overlapping of one sextet of equal intensity lines having ($g_1 = 5.470$, $A_1^{Mn} = 57$ G), with another sextet having ($g_2 = 5.424$, $A_2^{Mn} = 88$ G). This observation of sextets, rather than 11-line pattern with unequal intensity, indicates that the species formed is a 1:1 complex of manganese and dioxygen. Temperature-dependent EPR studies and the successful interpretation of the spectra in terms of a single Mn (vida infra) further oppose a bridged, dimeric species. The above noted competition be-

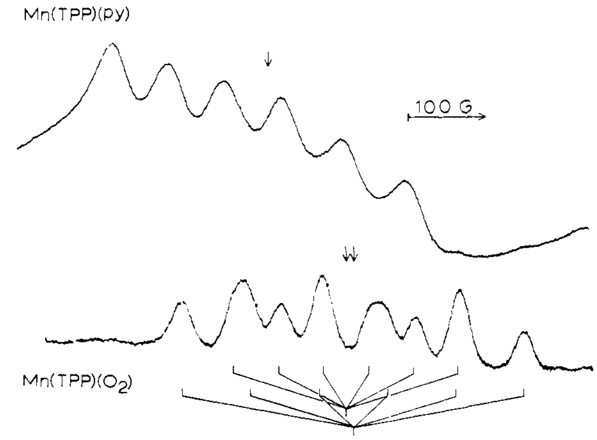
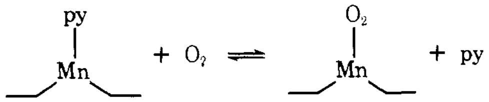


Figure 3. Low field portion of EPR spectrum of Mn(TPP)(py) in degassed toluene (upper) and Mn(TPP)(O_2) in toluene with oxygen (lower) (−196°. The position of $g_\perp$ for Mn(TPP)(py) and the overlapping sextets in the Mn(TPP)(O_2) spectrum are indicated.

tween pyridine and dioxygen additionally shows that the reaction is *not* O_2 addition to five-coordinate Mn. Rather, the observed process is that shown in eq 1. This conclusion



$$\overset{\text{py}}{\text{Mn}} + O_2 \rightleftharpoons \overset{O_2}{\text{Mn}} + \text{py} \qquad (1)$$

explains why manganese(II) hemoglobin does not bind O_2 reversibly.[11] The protein provides an adjacent imidazole as ligand to the Mn(II) porphyrin. With this high effective local concentration of coordinating base, the equilibrium (1) is driven to the left.

There are numerous electronic structures which may be conceived for this dioxygen adduct. The lower spectra of Figures 2 and 3 are wholly different from those observed for O_2^- and for cobalt dioxygen adducts which are formulated as Co(III)-O_2^-.[1f] This fact, plus the large ^{55}Mn hyperfine splittings and the absence of spin transfer to dioxygen which we find in experiments with 50% ^{17}O enriched O_2 rule out a formulation as low-spin Mn(III)-O_2^-. In addition, the trio of g values calculated from the observed peak positions can be shown by Blumberg's technique[12] to be inconsistent with any combination of crystal field parameters describing a low spin ($S = \frac{1}{2}$) d^5 Mn(II) ion.

The overall pattern of the lower spectrum in Figure 2 does appear under cursory inspection to be compatible with that expected of a high-spin ($S = \frac{5}{2}$) Mn(II) with a slight rhombic splitting ($\Delta g_\perp{}^{\text{MnO}_2} = g_1 - g_2 > 0$) and D decreased from that of Mn(TPP)(py) ($\bar{g}_\perp{}^{\text{MnO}_2} = \frac{1}{2}(g_1 + g_2) = 5.436 < g_\perp{}^{\text{Mn}} = 5.96$). This led us to initially formulate the dioxygen adduct as Mn$^{\text{II}}$(TPP) ($^1O_2$).[13] However, $\bar{g}_\perp{}^{\text{MnO}_2} = 5.436$ requires[14] $D \approx 0.26$ cm^{-1}, which is inconsistent[15] with the existence of the feature at 4500 G ($g = 1.45$). Further, the features at g_1 and g_2 when blown up (Figure 3) do not have the appropriate shapes to be "perpendicular" resonances. Thus we discard the formulation "high-spin Mn$^{\text{II}}$(TPP)($^1O_2$)".

With the above formulations excluded, and noting the similarity of the present spectra to those of certain (d^3) $S = \frac{3}{2}$ Cr(III) systems[16] (neglecting hyperfine splitting), we are led to consider the adduct as an $S = \frac{3}{2}$ system with large axial splitting, $D \gg 0.3$ cm^{-1}, and also a large rhombic distortion $E/D > 0.3$). Calculations based on this assumption are completely successful in explaining these 77 K spectra of Mn(TPP)(O_2), as well as spectra taken at 4.2 K.[17]

Although the optical spectrum of Mn(TPP)(O_2) resembles that of Mn$^{\text{III}}$(TPP), both the existence of three unpaired electrons ($S = \frac{3}{2}$) in the oxygen adduct and other considerations[17] lead us to suggest the *formal* description "Mn$^{\text{IV}}$(TPP)(O_2^{2-})", rather than "spin-coupled Mn$^{\text{III}}$(TPP)(O_2^-)" (or less satisfactory, "intermediate-spin Mn$^{\text{II}}$(TPP)(O_2)"). Although an unsymmetrically bonded O_2, as in cobalt and iron dioxygen complexes[18] cannot be ruled out at this time, again for chemical reasons, and by analogy to other "O_2^{2-}" complexes,[19] we suggest that the O_2 is in a symetrically bonded peroxide-like structure (ethylene structure). The powerful perturbation of the manganese is reflected in the quite unusual anisotropy of the ^{55}Mn hyperfine splitting of the dioxygen adduct. Confirmation of these interpretations through detailed calculations and ir observations of the O-O stretch are in progress. However, we note that this formulation suggests that the manganese porphyrin-dioxygen adducts may be useful models for the compound II of peroxidases.[20]

In summary, both by optical and EPR measurements at low temperatures, we have observed for the first time the reversible coordination of dioxygen to a manganese(II) porphyrin. The resulting species is quite different from the corresponding cobalt and iron porphyrin adducts. The adduct formed is Mn(TPP)(O_2) and has three unpaired electrons; there is no appreciable spin transfer to O_2; the manganese thus appears to achieve a formal Mn(IV) valency and is tentatively proposed to be symmetrically bonded to a peroxidelike dioxygen fragment. Work is in progress to further examine the nature of this system and its chemical reactivity and to prepare other Mn(II) complexes capable of reversibly adding dioxygen.

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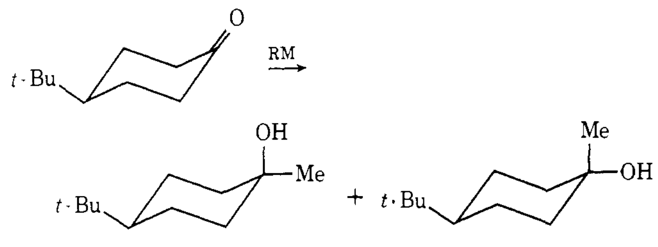
Organocuprates. A Stereoselective Synthesis of Axial Alcohols

Sir:

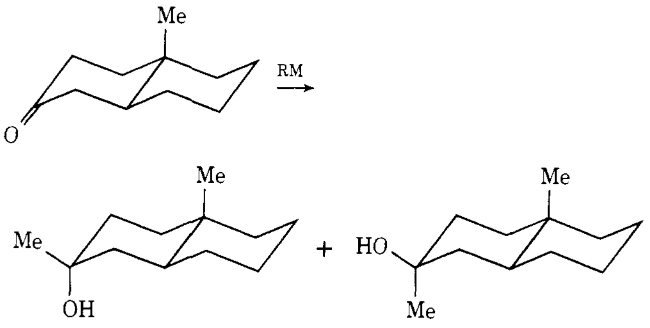
The addition of nucleophiles to ketones is an important method for the introduction of stereochemistry into organic molecules. In contrast to the numerous highly stereoselective reducing agents which have been developed,[1] the availability of reagents for the addition of unhindered alkyl nucleophiles to ketones with high stereoselectivity is limited.[2] We wish to report here that the reagent prepared by mixing lithium dimethylcuprate[3] with methyllithium reacts with cyclohexanones to produce axial alcohols with high stereoselectivity and in high yield.

The addition of a primary organolithium or Grignard reagent to an unhindered cyclohexanone generally results in a mixture of epimeric products. For example, 4-*tert*-butylcyclohexanone reacts with methyl magnesium iodide, methyllithium, or dimethylmagnesium to give only 51–70% axial alcohol.[4] In an effort to improve the stereoselectivity of this reaction, a new approach to the problem was considered. We reasoned that if an organocuprate could be induced to react with a saturated ketone,[5] those factors which give high stereoselectivity to the reaction of cuprates with enones[6] might allow a stereospecific synthesis of substituted alcohols. While a variety of methods for effecting this transformation may be envisioned, we have examined an organocuprate-mediated addition of methyllithium to a number of cyclohexanones at low temperature.[7] When 4-*tert*-butylcyclohexanone was treated with a 3:2 mixture[8] of lithium dimethylcuprate and methyllithium, a crystalline product was isolated in 91% sublimed yield. This material contained no starting ketone and consisted of a mixture of epimeric methyl carbinols, 94% of which was the expected *trans*-4-*tert*-butyl-1-methylcyclohexanol.[9] This result compares with other organometallic methylations as shown below.



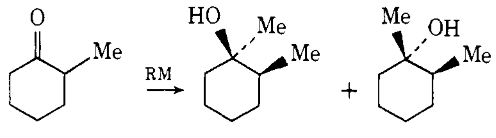
RM		
RM = MeMgI (5°)^{4a}	51%	49%
= Me_2Mg^{4b}	70%	30%
= MeLi (5°)^{4}	65%	35%
= MeLi (−78°)	79%	21%
= MeLi-Me_2CuLi (−70°)	94%	6%

We have also observed a similar improvement in stereochemical control for the methylation of 4a-methyl-*trans*-2-decalone[10]



RM		
RM = MeLi (−78°)	76%	24%
= MeLi-Me_2CuLi (−70°)	90%	10%

and 2-methylcylohexanone



RM		
RM = MeMgI (0°)^{11}	84%	16%
= MeLi (−78°)	92%	8%
= MeLi-Me_2CuLi (−70°)	97%	3%

Interestingly, MeLi-Me_2CuLi provides no stereochemical improvement over methyllithium in its reaction with 2-methylcyclopentanone. Both reagents give approximately 70% attack trans to the methyl substitutent at −70°.

In each case, the epimeric methyl carbinols were the only products detected at greater than 95% conversion of starting ketone. Thus, MeLi-Me_2CuLi offers a distinct stereochemical advantage over conventional methylating reagents and appears to be the reagent of choice for the high yield equatorial methylation of unhindered cyclohexanones. Alternatively it should be noted that improved stereoselectivity in ethereal methyllithium additions may be obtained by conducting the reaction with ketones at low temperature.[12]

The detailed structure of this new reagent remains obscure. However, neither dimethylcuprate nor methyllithium alone can account for our results since 4-*tert*-butylcyclohexanone is recovered unchanged from treatment with the former reagent at low temperature and gives different stereochemical results with the latter compound. We feel that the most reasonable explanation is that lithium dimethylcuprate and methyllithium react to form low concentrations of a bulky, highly reactive cuprate having the stoichiometry Me_3CuLi_2 or Me_4CuLi_3.[13] The formation of such higher ate complexes has been supported by NMR studies[5a] and by isolation of the corresponding acetylide complexes, $(RC{\equiv}C)_3CuK_2$.[14] In addition, a reagent having the stoichiometry Ph_3CuLi_2 appears to be more reactive than Ph_2CuLi in metal-halogen exchange reactions and coupling with aryl bromides.[15] The reaction of a ketone with a dianionic trialkylcuprate (or a related higher ate complex) should be facilitated since the increased charge on copper should enhance either an oxidative addition–reductive elimination sequence[16] or an electron transfer process.[17] Whatever the mechanism, it must be fast relative to carbonyl attack by methyllithium since the same high stereoselectivity is obtained by the slow addition of methyllithium to a mixture of the ketone and lithium dimethylcuprate at −70°.

The experimental procedure is straightforward and is detailed here for 4-*tert*-butylcyclohexanone. Cuprous iodide (5.70 g, 30 mmol) was suspended in 100 ml of anhydrous ether at 0° under nitrogen. Ethereal (80 mmol) methyllithium (approximately 2 *M*) was added and the light tan solution was stirred for 10 min before cooling to −70°.[18] 4-*tert*-Butylcyclohexanone (1.54 g, 10 mmol) in 25 ml of anhy-