Table II. Reaction of *tert*-Butylmagnesium Chloride with Benzophenone

Expt	Magnesium purity[d]	Grignard prepared in excess	Solvent	Grignard concn (*M*)	G/K ratio	% 1,6-addition	% 1,2-addition	% benzopinacol
15	SC	*t*-BuCl	Ether	0.188	1.5	48.0	42.3	9.7
16	GGT	Mg	Ether	0.188	1.5	50.0	40.3	9.7
17	GGT	Mg	Ether	0.188	20	48.5	40.7	10.8
18	GGT	Mg	Ether	0.230	121	50.0	42.2	8.8
19	SC	*t*-BuCl	Ether	0.033	0.05	43.8	31.2	25.0
20	GGT	Mg[a]	Ether	0.188	1.5	49.1	38.2	12.7
21	SC	*t*-BuCl	THF	0.208	1.68	41.3	47.0	11.7
22	SC	*t*-BuCl[b]	THF	0.188	1.5	47.4	45.3	7.3
23	SC	*t*-BuCl	HMPA	0.188	1.5	26.0	72.3	<1.7
24	SC	*t*-BuCl[c]	HMPA	0.188	1.5	20.8	77.8	<1.4

[a] With 400 ppm $FeCl_3$. [b] With 4000 ppm $FeCl_3$ added. [c] With 2500 ppm $FeCl_3$, $CoCl_2$, CuCl, and $CrCl_3$ added. [d] Key: GGT = Grignard Grade turnings, SC = single crystal, G = Grignard, K = Ketone.

proceeds predominantly, if not entirely, through a SET mechanism.[1e] Since the purity of the magnesium was shown to be important with CH_3MgBr, it was considered necessary to determine whether or not their findings were the result of a transition metal catalyzed reaction. We have found that the reaction of *t*-C_4H_9MgCl with benzophenone in diethyl ether gives from 48.0 to 50.0% conversion to 1,6-addition products, 38.2 to 42.3% conversion to 1,2-addition product, and 8.8 to 12.7% conversion to benzopinacol, regardless of the grade of Grignard reagent used, the ratio of G/K (if Grignard is in excess), or the presence of 400 ppm $FeCl_3$ (Table II). This is sufficient indication that the reaction of *t*-BuMgCl with benzophenone in diethyl ether proceeds predominantly through a SET mechanism even in the most favorable case when the Grignard reagent was prepared from single crystal magnesium in excess *t*-C_4H_9Cl. Again, experiment 19 shows that in a reaction which is already proceeding predominantly through SET, the presence of a more polar compound in the ether (in this case the excess benzophenone) evidently stabilizes the ketyl radical anion and aids in escape from the solvent cage, forming a larger percentage of benzopinacol. In THF solvent, 41.3% 1,6-addition product, 47.0% 1,2-addition product, and 11.7% benzopinacol was formed. The same reaction in HMPA gave 26.0% 1,6-addition product, >72.3% 1,2-addition product, and <1.7% benzopinacol. No real information can be drawn from the iron doped experiment in HMPA. The doped experiment in THF (experiment 22) gives less 1,2-addition product than the undoped one (experiment 21). This trend is in the right direction to indicate a shift away from a polar mechanism, but the magnitude of the change is too small to be significant and most likely the mechanism is SET in each case. The importance of the *t*-BuMgCl–$Ph_2C{=}O$ reaction lies in the fact that in ether the product ratio does not depend on the "purity" of the magnesium used to prepare the Grignard reagent. It appears, then, that the reaction, when compared to the work of Holm and Crossland,[1e] proceeds through a SET mechanism, even when the best grade of magnesium available is used to prepare the Grignard.

It is clear from all these data that CH_3MgBr addition to benzophenone in ether solvent is proceeding predominantly, if not entirely, by a polar mechanism whereas the reaction of *t*-C_4H_9MgCl under the same conditions is proceeding by a SET pathway. It is also clear that a reaction that would normally proceed by a polar mechanism can proceed by a SET pathway, if the magnesium used to prepare the Grignard reagent contains parts per million of transition metal impurities. Further work is underway to determine the effect of other transition metals and the nature of the ketone in affecting the mechanism of reaction of Grignard reagents with ketones.

(5) We are grateful to the National Science Foundation for support of this work and to Professor Holm for sending us nmr spectra to compare with spectra obtained in this work.

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Reduction of Coordinated O_2 by Organic Substrates

Sir:

The recent preparation[1] of functionally active cobalt-containing analogs of hemoglobin (Hb) and myoglobin (Mb) suggests that further study of the reactions of mononuclear Co–O_2 adducts (best formulated as $Co^{III}O_2^-$, but here written $Co^{II}O_2$ for the sake of simplicity) may contribute to an understanding of the mechanisms whereby the protein can either "stabilize" the O_2 coordinated to iron(II) porphyrins, as in Hb and Mb, or conversely "activate" it, as in the enzyme cytochrome oxidase. We report here some results on the "activation" of O_2 coordinated to Co(II) complexes.

We have previously noted[2a] that the autoxidation of the Co(II) corrinoid vitamin B_{12r} in aqueous solution at room temperature is accelerated by the addition of *p*-dihydroxybenzene (QH_2), thiols, ferrocyanide, and other reducing agents and have ascribed this to the occurrence of the following type of reaction involving a transient $Co^{II}O_2$ complex

$$\underset{(\text{or } QH^-)}{Co^{II}O_2 + QH_2} \longrightarrow \underset{(\text{or } Q\cdot^-)}{Co^{III}O_2H^- + QH\cdot} \qquad (1)$$

We have now studied directly the reaction of QH_2, etc., with the fully formed O_2 adducts of [Co(II) 3-methoxy-

(1) B. M. Hoffman and D. H. Petering, *Proc. Nat. Acad. Sci. U. S.*, **67**, 637 (1970); G. C. Hsu, C. A. Spilburg, C. Bull, and B. M. Hoffman, *ibid.*, **69**, 2122 (1972).
(2) J. M. Pratt, "Inorganic Chemistry of Vitamin B_{12}," Academic Press, London, 1972, (a) Chapter 11, (b) Chapter 5.

salen][3] (I) in pyridine and of vitamin B_{12r} (II) in methanol. The solutions were thermostated at −35 to 40° and the reactions followed either by uv–visible spectrophotometry in a Beckmann/RIIC low-temperature cell or, after freezing aliquots to −180°, by epr spectroscopy.

The uptake and release of O_2 by I was completely reversible during at least three cycles spread over 1 hr (λ_{max}: Co^{II}, 364 nm; $Co^{II}O_2$, 382 nm), and full formation (>95%) of the O_2 adduct appeared to be achieved under 1 atm of oxygen. This $Co^{II}O_2$ complex is readily decomposed by the addition of reducing agents such as QH_2, ascorbic acid, thiols, and *N,N'*-tetramethyl-*p*-phenylenediamine (TMPD); since TMPD has no significant ligand properties but Wurster's Blue radical cation is formed, as confirmed by esr and uv, this strongly suggests that the reaction does not require prior coordination of the reducing agent to the cobalt. The reaction of 3.0×10^{-3} *M* $Co^{II}O_2$ with the same concentration of QH_2 showed no induction period, but gave a good isosbestic point and followed approximately second-order kinetics for *ca.* 25 min before becoming complex; this represents about 70% of the reaction. The Co(III) species produced was essentially aquocobalamin,[2] but the final organic products were not fully characterized. The epr spectra of samples taken at intervals from the reaction of 2.6×10^{-3} *M* $Co^{II}O_2$ with five times the concentration of QH_2 showed the gradual disappearance of $Co^{II}O_2$ together with the rise (maximum after ~10 min) and subsequent fall in concentration of the semi-quinone radical anion ($Q\cdot^-$). The only simple explanation[4] involves the initial donation of an electron or hydrogen atom by the free QH_2 or QH^- to the coordinated O_2 as in eq 1, followed by further reactions of $QH\cdot$, $Q\cdot^-$, HO_2^-, etc.

The O_2 adduct of II can be formed below room temperature by the reaction either of O_2 with the Co^{II} complex[5] or of free superoxide ion (O_2^-) with the Co^{III} complex.[6] We found that yellow solutions of II in MeOH at −80° react reversibly with O_2 giving good isosbestic points to yield a red complex with a spectrum (bands at 529, 502, and 352 nm; see Figure 1) similar to those of the $Co^{III}OH_2$ and $Co^{III}OH^-$ complexes (see ref 2b), which supports its formulation as $Co^{III}O_2^-$. Solutions of this $Co^{II}O_2$ complex in MeOH also reacted with QH_2 at −40° to give the radical $Q\cdot^-$ (epr) and the Co^{III} complex (uv–visible).[4]

It appears that reaction 1 is typical of $Co^{II}O_2$ complexes and can occur in both protic and aprotic solvents and at very low temperatures.

The reaction of coordinated O_2 with an uncoordinated organic substrate has been postulated for many metal-catalyzed autoxidations[7] and the present example is in accord with this view for a simple, protein-free complex. It also demonstrates that the combination of a metallic and an organic reducing agent can convert the unfavorable one-equivalent reduction of O_2 into the much more favorable two-equivalent reduction[8] and hence, if the reduced forms of the metallic and organic components can be regenerated (or replenished), provide a mechanism for catalyzing the reduction of O_2.

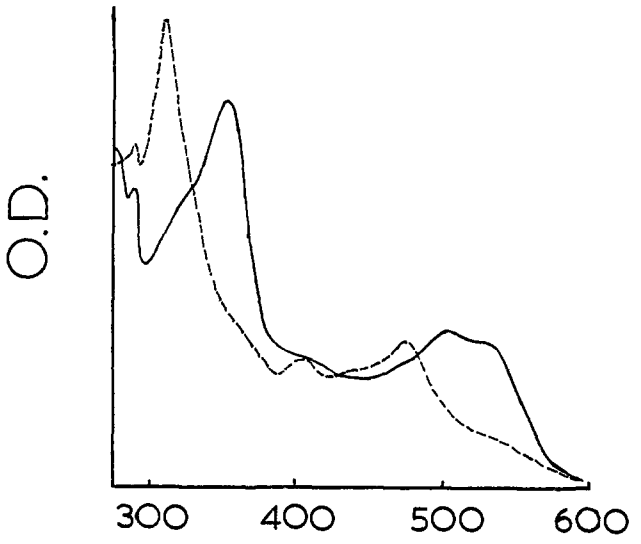

Figure 1. Spectra of vitamin B_{12r} (Co^{II}) in methanol at −80° (---) and of the product ($Co^{III}O_2^-$) formed under 1 atm of oxygen (——). Arbitrary optical density units.

The mechanism of action of cytochrome oxidase is still far from clear.[9] It is generally assumed that reducing equivalents are transferred only by the metals and only along a simple pathway (*e.g.*, cyt.a → Cu → cyt.a_3 → O_2). But there is considerable controversy as to whether the $Fe^{II}O_2$ complex of cyt.a_3 is a true intermediate, since the first detectable change in cyt.a_3 on admitting O_2 to the reduced enzyme is a change from Fe^{II} to Fe^{III}, while the complex considered to be $Fe^{II}O_2$ only appears subsequently. Our results suggest that one should consider the possibility that reducing equivalents are also transferred to the coordinated O_2 by a second, purely organic redox group such as a cysteine or tyrosine residue (both present in the enzyme) by mechanisms analogous to eq 1 and that the supply of electrons to two such separate sites might require the existence of a more complex path of electron transfer within the enzyme. Such a scheme would, in fact, explain the anomalously late appearance of the supposed $Fe^{II}O_2$, since it requires that the $Fe^{II}O_2$ complex will be most rapidly destroyed and hence least readily detected when the rate of supply of electrons from the second site is greatest, *i.e.*, immediately after admitting O_2 to the reduced enzyme.

(3) C. Floriani and F. Calderazzo, *J. Chem. Soc. A*, 946 (1969); D. Diemente, B. M. Hoffman, and F. Basolo, *Chem. Commun.*, 467 (1970).
(4) No reaction was observed between Co(II) and QH_2 alone under nitrogen (uv–visible) and no radical formed by the reaction of QH_2 alone with O_2 in the absence of Co(II) (epr).
(5) J. H. Bayston, N. K. King, F. D. Looney, and M. E. Winfield, *J. Amer. Chem. Soc.*, 91, 2775 (1969).
(6) J. Ellis, J. M. Pratt, and M. Green, *J. Chem. Soc., Chem. Commun.*, 781 (1973).
(7) For examples see the recent review by R. A. Sheldon and J. K. Kochi, *Oxid. Combust. Rev.*, 5, 135 (1973).
(8) See the redox potentials given by P. George in "Oxidases and Related Redox Systems," T. E. King, H. S. Mason, and M. Morrison, Ed., Wiley, New York, N. Y., 1965, p 3.
(9) D. C. Wharton in "Inorganic Biochemistry," Vol. 2, G. L. Eichhorn, Ed., Elsevier, Amsterdam, 1973, p 955.
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