causing this band at 1060 cm^{-1}.

To summarize our preliminary observations on the $MnBr_2PMe_3$ system: (1) the complex does exist in the solid state in accord with claims by McAuliffe; (2) the dioxygen is present as a superoxide species in the solid state leaving Mn with a III oxidation state as claimed by Green; (3) although reversible oxygenation/evacuation cycling has been reported for some complexes,[1] this process is very slow if present at all in the solid state for the $MnBr_2PMe_3 \cdot O_2$ complex and is accompanied by slow irreversible transformation to the inactive phosphine oxide complex. We have learned that the relative rates of the competing process of reversible interaction with dioxygen and irreversible formation of a phosphine oxide complex for $MnLX_2$ complexes in the solid state are highly dependent on the nature of the phosphine employed.[4]

Acknowledgment. We are grateful to the Research Corp., the National Science Foundation through Grant CHE-7920825, and the Auburn University Energy Grant-in-Aid program for partial support for this work.

Control over Site of Alkylation in Iron Acylate Complexes: General Preparation and Reactions of Alkylidene–Iron Tetracarbonyl Complexes

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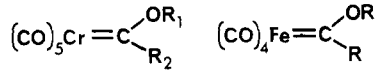
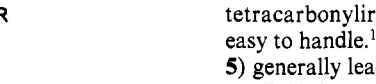
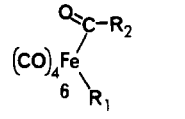
Fischer-type carbene metal complexes[1] of iron (e.g., **1**) have



2: R_1 = alkyl; R_2 = alkyl, aryl
3: R_1 = Li, Na



1: R_1 = Et; R_2 = Ph
4: R_1 = Li; R_2 = alkyl, aryl
5: R_1 = Na; R_2 = alkyl, aryl
7: R_1 = Et; R_2 = tBu
8: R_1 = Et; R_2 = nBu
9: R_1 = Et; R_2 = Me



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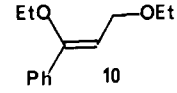
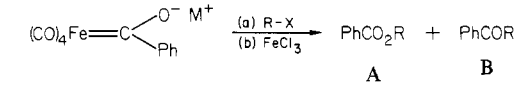


10

been relatively inaccessible,[2-4] and little information on the pattern of reactivity has been reported.[7] The analogous chromium complexes (**2**) are well-known, from alkylation of acylate salts (**3**), and show reactivity of significant potential in organic synthesis.[8,9]

Table I. Reaction of Iron Acylate Salts with Alkylating Agents



A B

entry	M^+	R–X	solvent	yield,[a] %	ratio A:B
1	Li	$EtOSO_2F$	ether/HMPA (4:1)[b]	80	89:11
2	Li	$EtOSO_2F$	ether	70	24:76
3	NMe_4[c]	$EtOSO_2F$	CH_2Cl_2	78	64:36
4	Li	$EtOSO_2F$	CH_2Cl_2	57	16:84
5	Li	$MeOSO_2F$	ether/HMPA (4:1)	79	14:86
6	NMe_4[c]	$MeOSO_2F$	CH_2Cl_2	61	10:90
7	Li	$EtOSO_2$tol	THF/HMPA (1:1)[d]	20	90:10
8	Li	EtI	THF/HMPA (1:1)[e]	53	0:100

[a] The yields were determined by quantitative GLPC analysis using standard samples of the products for calibration. [b] The reagents were mixed at −78 °C and stirred for 4 h and then allowed to warm to 25 °C over 2.0 h. [c] The ammonium salt was prepared by metathesis with tetramethylammonium bromide (see ref 10). [d] Heated at 65 °C/18 h. [e] 25 °C/24 h.

We were drawn to consider the iron analogue **1** for several reasons. The iron acylate salts (e.g., **4** and **5**) can be prepared by reaction of organolithium[10] or organomagnesium derivatives[11] with $Fe(CO)_5$, by reaction of carboxylic acid chlorides with tetracarbonyliron(II) dianion,[12] and by addition of an alkyl halide to the dianion followed by migratory insertion of CO.[12,13] The tetracarbonyliron(II) dianion is readily available and relatively easy to handle.[12] However, alkylation of iron acylate salts (**4** and **5**) generally leads not to alkylidene complexes (i.e., **1**) but instead to alkylation at iron (to give **6**) and subsequent coupling to form unsymmetrical ketones (Collman's reaction).[4,12]

We analyzed the problem using the hard–soft acid–base picture, which serves to rationalize O- vs. C-alkylation in enolate anions.[14]

(1) For reviews, see: (a) Cardin, D. J.; Cetinkaya, B.; Lappert, M. F. *Chem. Rev.* **1972**, *72*, 545–574. (b) Fischer, E. O. *Adv. Organomet. Chem.* **1976**, *14*, 1–32. (c) Fischer, E. O. *Rev. Pure Appl. Chem.* **1972**, *30*, 353. (d) Fischer, E. O. *Angew, Chem.* **1974**, *86*, 651.

(2) Complexes of type **1** have been prepared by photochemical exchange of a CO ligand in $Fe(CO)_5$ with an alkylidene ligand in a molybdenum complex: (a) Fischer, E. O.; Beck, H.-J.; Kreiter, C. G.; Lynch, J.; Müller, J.; Winkler, E. *Chem. Ber.* **1972**, *105*, 162–172. (b) Fischer, E. O.; Beck, H. J. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 72–74.

(3) Special examples of Fischer-type carbene complexes of iron are known: (a) Nakatsu, K.; Mitsudo, T.; Nakanisi, H.; Watanabe, Y.; Takegami, Y. *Chem. Lett.* **1977**, 1447–1448. (b) Petz, W.; Schmid, G. *Angew. Chem., Int. Ed.* Engl. **1972**, *11*, 934–935. (c) Darensbourg, D. J.; Darensbourg, M. Y. *Inorg. Chem.* **1970**, *9*, 1691–1694. (d) Petz, W.; Jonas, W. *J. Organomet. Chem.* **1976**, *120*, 423–432.

(4) Systematic attempts at O-alkylation of tetracarbonyliron acylate anions were generally unsuccessful. In certain special cases, reaction of trimethyloxonium fluoroborate in dichloromethane gave the desired methoxyalkylidene–iron species.[5] In a study concerning several aspects of the reaction of iron acylate anions with alkylating agents, with emphasis on (phosphine)tricarbonyliron acylates, H. Conder and M. Darensbourg considered the effect of leaving group on the efficiency of O-alkylation.[6] This work showed that complexes in the series $L(CO)_3Fe{=}C(OEt)Ph$ could be prepared where L = various phosphines using triethyloxonium fluoroborate and methyl fluorosulfonate; the parent compound with L = CO appears as an entry in a table without experimental detail. No alkyl-substituted alkylidene ligands were prepared.

(5) In special cases, the alkylation of analogues of **5** has been successful: Fischer, E. O.; Beck, H. J.; Kreiter, C. G.; Lynch, J.; Muller, J.; Winkler, *Chem. Ber.* **1972**, *105*, 162.

(6) Condor, H. L.; Darensbourg, M. Y. *Inorg. Chem.* **1974**, *13*, 506–511.

(7) We are aware of no systematic study or isolated example pertaining to the reactivity pattern of complex **1** nor of the previously more accessible analogue with a phosphine ligand replacing CO.[6]

(8) (a) For a review, see: Casey, C. P. In "Transition Metal Organometallics in Organic Synthesis"; Alper, H., Ed.; Academic Press: New York, 1976; Vol. 1, pp 190–234. (b) An extensive study of reactions of **2** with alkynes has been initiated by K. H. Dötz and co-workers. For a recent paper and leading references, see: Dötz, K. H.; Pruskil, I.; Mühlemeir, J. *Chem. Ber.* **1982**, *115*, 1278–1285. For a recent application in β-lactam synthesis, see: McGuire, M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 5538–5540.

(9) An obvious alternate preparation of **3** from reaction of pentacarbonyl chromium(+II) dianion with a carboxylic acid chloride has not been reported. We studied this possibility using benzoyl chloride and $Cr(CO)_5^{2-}$, generated by several different procedures: (a) Ellis, J. E.; Hentges, S. G.; Kalina, D. G.; Hagen, G. P. *J. Organomet. Chem.* **1975**, *97*, 79. (b) Ellis, J. E.; Hagen, G. P. *J. Am. Chem. Soc.* **1974**, *96*, 7825. (c) Maher, J. M. PhD Thesis, Harvard University, 1981. We thank Dr. Maher for this procedure: (d) Maher, J. M.; Beatty, R. P.; Cooper, J. M. *Organometallics* **1982**, *1*, 215. Under the best conditions, the salt (**3**, R_1 = Na; R_2 = Ph) was obtained and methylated to give **2** (R_1 = Me; R_2 = Ph) in 50% yield, using $Cr(CO)_5^{2-}$ from reduction of $Cr(CO)_6$ with sodium in liquid ammonia. Rigorous air-free work is necessary to minimize the formation of polynuclear anionic complexes.

(10) Fischer, E. O.; Kiener, V. *J. Organomet. Chem.* **1970**, *23*, 215.

(11) For a recent example and leading references, see: Yamashita, M. Miyoshi, K.; Nakazono, Y.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1663–1664.

(12) For a review, see: Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342–356.

(13) Collman, J. P.; Finke, R. G.; Cawsi, J. N.; Brauman, J. I. *J. Am.* Chem. *Soc.* **1977**, *99*, 2515–2526.

(14) HSAB theory successfully correlates trends in the effect of leaving group on C- vs. O-alkylation of enolate anions: Pearson, R. G.; Songstad, J. *J. Org. Chem.* **1967**, *34*, 2899; *J. Am. Chem. Soc.* **1967**, *39*, 1827. For a general discussion of factors influencing O- vs. C-alkylation, see: House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: New York, 1972; pp 522–529.

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Table I presents the results from variation of cation (Li^+ and $^+NMe_4$),[10] alkylating agent (methyl and ethyl, various leaving groups), and solvent (ether, HMPA, THF, dichloromethane). In this series, with an oxidative isolation procedure,[15] the formation of the ketone is taken as a measure of alkylation at iron while the benzoate derivatives are suggested to arise from oxidation of the alkylidene form (e.g., **1**). Ether and dichloromethane both tend to favor reaction at iron, but addition of HMPA to an ether solution (compare entries 1, 2, and 4) strongly favors O-alkylation (alkylidene formation). The change from lithium cation to the tetramethylammonium ion (entry 3 vs. 4) again changes the selectivity toward O-alkylation. There is a strong dependence on the size of the alkylating agent, with the larger group (Et) favoring O-alkylation (entries 1 and 5, 3 and 6).[16] The soft iodide leaving group produces only the ketone (alkylation at iron) even in the presence of HMPA, while the relatively unreactive *p*-toluenesulfonate leaving group gives predominately O-alkylation (at low conversion, entry 7). Overall, these results give a picture entirely consistent with the familiar chemistry of enolate anions and allow a choice of conditions to favor either ketone products or alkylidene-iron complexes.[17]

We have used the optimum conditions (ethyl fluorosulfonate, ether-HMPA) to generate the complex **1** (64-72% yields), as well as new examples with R_2 = *t*-Bu (**7**), *n*-Bu (**8**), and CH_3 (**9**). The complexes are deep red oils with characteristic IR absorptions and other spectral data.[18] A typical procedure follows. To a solution of $Fe(CO)_5$ (5.88 g, 30.0 mmol) in ether (160 mL) was added dropwise PhLi (33 mmol in cyclohexane solution) at -78 °C under argon. The solution was allowed to warm to O °C over ca. 2 h, HMPA (40 mL) was added, and the deep brown solution was returned to -78 °C. Ethyl fluorosulfonate (14.5 mL, 150 mmol) was added dropwise with vigorous stirring. After being stirred at -78 °C for 4 h, the mixture was warmed slowly to 25 °C and partitioned between hexane and saturated aqueous sodium bicarbonate. After the usual washing, drying, and concentrating of the hexane solution, the residue was chromatographed (silica gel, hexane, under argon) to give 6.53 g (72%) of tetracarbonyl(ethoxyphenylmethylidene)iron, **1** (R_1 = Et, R_2 = Ph).[18,19]

Preliminary tests of the reactivity of **1** suggest some differences with the Cr analogue. Reaction of **1** with excess ethyl vinyl ether under 55 psi of CO at 50 °C for 1.0 h gave a mixture from which the major product (76% yield after isolation) has been shown to be **10**.[20] While reactions of an alkylidene-tantalum complex with alkenes is known to give products of the type represented by **10**,[21] this pathway is not significant with the chromium series and has not been tested previously with iron. The mechanisms and scope of the reactions of alkynes and alkenes with the alkylidene iron complexes are under study.

Acknowledgment. We are pleased to acknowledge financial support from the National Science Foundation (CHE-82-04339) and helpful discussions with Professors A. Mayr and J. Schwartz and J. W. Herndon at Princeton.

(15) Several techniques have been used to oxidize chromium derivatives such as **2**, replacing the carbon-chromium bond with a carbon-oxygen double bond: (a) Fischer, E. O.; Riedmüller, R. *Chem. Ber.* **1974**, *107*, 915. (b) Casey, C. P.; Burkhardt, T. J.; Bunnell, C. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 2127. We are employing a procedure previously used to detach 1,3-dienes from $Fe(CO)_3$: Emerson, G. F.; Mahler, J. F.; Kochbar, R.; Pettit, R. *J. Org. Chem.* **1964**, *29*, 3620. The reaction mixture was diluted with acetone at 25 °C, and a GC standard (*p*-chloroacetophenone) was added. Then solid ferric chloride was added in small portions until gas evolution ceased. The resulting mixture was partitioned between ether and saturated aqueous sodium carbonate solution; the ether solution was washed repeatedly with brine and concentrated carefully at reduced pressure. GC analysis for methyl and ethyl benzoates and acetophenone was calibrated with pure samples of the products.

(16) The effect of steric size in the alkylating agent for Me, Et, and *i*-Pr is observed in alkylation of β-dicarbonyl compounds: (a) Chatterjee, A.; Banerjee, E.; Banerje, S. *Tetrahedron Lett.* **1965**, 3851. (b) Yoffe, S. T.; Vatsuro, K. V.; Kugutcheva, E. E.; Kabachnik, M. I. *Ibid.* **1965**, 593. (c) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: New York, 1972; pp 526-527.

(17) It is of interest to see if the reactivity of the chromium acylate anions can be manipulated in the same way, to develop a chromium analogue of Collman's reaction. In a preliminary study, we find that acylate salt **2** (R_1 = Li) reacts with excess allyl iodide in a mixture of THF/HMPA to give phenyl propenyl ketones (mixture of α,β and β,γ isomers) in 17% yield. Similarly, benzyl iodide reacts slowly with **2** (R_1 = Li) to give phenyl benzyl ketone (deoxybenzoin) in 12% yield. These "soft" alkylating agents appear to enhance the tendency toward alkylation at the metal, but the process seems unlikely to be preparatively useful.

(18) **1**:[5,10] ^1H NMR (acetone-d_6) δ 7.50 (s, 5 H), 5.21 (q, *J* = 7.2 Hz, 2 H), 1.69 (t, *J* = 7.2 Hz, 3 H); IR[6] (hexane) 2055, 1988, 1962, 1945 cm^{-1}; MS, calcd 301.9878, found 301.9882. **7**: ^1H NMR δ 5.30 (q, *J* = 7.2 Hz, 2 H), 1.67 (t, *J* = 7.2 Hz, 3 H), 1.34 (s, 9 H); IR 2053, 1986, [1954 and 1941 maxima on one broad band] cm^{-1}; MS, calcd 282.0191, found 282.0196. **8**: ^1H NMR δ 5.17 (q, *J* = 7.2 Hz, 2 H), 3.43 (t, *J* = 7.5 Hz, 2 H), 1.63 (t, *J* = 7.2 Hz, 3 H), 1.85-1.04 (m, 4 H), 0.92 (t, *J* = 6.4 Hz, 3 H); IR 2056, 1992, [1960 and 1950 maxima on one broad band] cm^{-1}; MS, *m/e* 282 (P, 4.5% of base at 85), 254 (14) 226 (3.4), 198 (19), 170 (10), 142 (21), 114 (31), 99 (21), 85 (100). **9**: ^1H NMR δ 5.04 (q, *J* = 7.2 Hz, 2 H), 3.17 (s, 3 H), 163 (t, *J* = 7.2 Hz, 3 H); IR 2056, 1995, 1961, 1948 cm^{-1}. **9** was too unstable to obtain meaningful composition data.

(19) The complexes **1** and **7**, derived from phenyllithium and *tert*-butyllithium, respectively, are relatively air stable at 25 °C; they can be handled as neat oils and in solution without special precautions. However, the complexes **8** and **9** are considerably more sensitive to oxidation and have been manipulated in an argon atmosphere. In general, the hexane and aqueous solutions used in the extraction procedure were saturated with argon by bubbling the gas into the liquid for a few minutes. No effort was made to rigorously exclude oxygen during the isolation procedures.

(20) **10**: The product is homogeneous as judged by ^{13}C NMR and analytical chromatographic data; however, we have not established whether it is the *E* or *Z* isomer; ^1H NMR (acetone-d_6) δ 7.61-7.24 (m, 5 H), 5.46 (t, 1 H, *J* = 6.9 Hz), 4.19 (d, 2 H, *J* = 6.9 Hz), 3.69 (q, 2 H, *J* = 7.5 Hz), 3.48 (q, 2 H, *J* = 7.5 Hz), 1.23 (t, 3 H, *J* = 7.5 Hz), 1.15 (5, 3 H, *J* = 7.5 Hz); IR (neat) 1664 (s), 1079 (vs) cm^{-1}; MS, *m/e* 206 (P, 9.7% of base at 105), 177 (6.1), 161 (23), 133 (20), 115 (10), 105 (100), 91 (9.0), 77 (51).

(21) The formation of **10** can be rationalized by rearrangement of an initial ferrocyclobutane species, following the reactivity pattern of alkylidene niobium and tantalum complexes: McLain, S. M.; Wood, C. D.; Schrock, R. R. *J. Am. Chem. Soc.* **1977**, *95*, 3519-3520.

Design of a Peptide Hormone: Synthesis and Characterization of a Model Peptide with Calcitonin-like Activity

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Calcitonin is a peptide hormone produced by the parafollicular cells, which are scattered throughout the thyroid in mammals but which constitute a distinct organ, the ultimobranchial body, in lower animals. The common form of the hormone consists of 32 amino acids, has a disulfide bridge between the cysteine residues at positions 1 and 7, and ends at the carboxyl terminus with the amide of proline (Figure 1).

While calcitonins from at least nine different species have been sequenced and characterized biologically and a number of synthetic analogues have been studied, few clear correlations have been made between structure and biological activity. From studies of peptide models of apolipoprotein A-I, the bee venom toxin melittin, and most recently, the peptide hormone β-endorphin the importance of amphiphilic helical regions to the biological activities of a variety of peptides and proteins that interact with lipid and/or protein surfaces has been shown.[1] When the amino acid sequences of natural variants of calcitonin in the region from residues 8 to 22 were viewed as axial projections of α-helices (as in Figure 1B),

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† Department of Chemistry, The University of Chicago.
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(1) Taylor, John W.; Osterman, David G.; Miller, Richard J.; Kaiser, E. T. *J. Am. Chem. Soc.* **1981**, *103*, 6965.

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