^{11}B and ^{13}C NMR spectra were obtained on a Varian FT-80A instrument. ^1H NMR spectra were recorded on a Varian T-60 (60 MHz) instrument. GC analyses were carried out on a Hewlett-Packard 5750 equipped with a thermal conductivity detector and connected to a Hewlett-Parkard integrator for determining peak areas. GC columns used were as follows: $^1/_4$ in. × 6 ft 10% SE-30 on 60/80 mesh Chromosorb W and $^1/_4$ in. × 6 ft 15% Carbowax 1540 on 60/80 mesh Chromosorb W.

Procedures. The determination of the kinetics of haloalkyne hydroboration was carried out by the quantitative IR method.[5b] The alkene/haloalkyne pairs studied by competitive hydroboration include cyclohexene/1-chloro-1-hexyne, *cis*-4,4-dimethyl-2-pentene/1-bromo-1-hexyne, 2-methyl-2-butene/1-iodo-1-hexyne, cyclohexene/1-chloro-1-octyne, *cis*-3-hexene/1-bromo-1-octyne, 2-methyl-2-butene/1-iodo-1-octyne, methylcyclohexene/chlorophenylacetylene, cyclohexene/bromophenylacetylene, cyclohexene/iodophenylacetylene, *cis*-3-hexene/1-bromo-1-butyne, 2-methyl-2-butene/1-bromo-3-methyl-1-butyne, and 2-methyl-2-butene/1-bromo-3,3-dimethyl-1-butyne. The relative reactivities of the alkenes used have been determined previously.[5] The results are summarized in Table II.

Acknowledgment. We gratefully acknowledge the National Science Foundation, Grant CHE 76-20846, for support of this work. Thanks are due also to Dr. K. K. Wang for stimulating discussions.

Registry No. 9-BBN, 280-64-8; $(9\text{-BBN})_2$, 70658-61-6; $H_2C{=}CH(CH_2)_3CH_3$, 592-41-6; $HC{\equiv}C(CH_2)_3CH_3$, 693-02-7; $IC{\equiv}C(CH_2)_3CH_3$, 1119-67-1; $IC{\equiv}C(CH_2)_5CH_3$, 81438-46-2; $IC{\equiv}CPh$, 932-88-7; $BrC{\equiv}CCH_2CH_3$, 50405-39-5; $BrC{\equiv}C(CH_2)_5CH_3$, 38761-67-0; $BrC{\equiv}CCH(Me)CH_3$, 54105-74-7; $BrC{\equiv}CC(Me)_2CH_3$, 13601-86-0; $BrC{\equiv}C(CH_2)_3CH_3$, 1119-64-8; $ClC{\equiv}C(CH_2)_5CH_3$, 64531-26-6; $ClC{\equiv}C(CH_2)_3CH_3$, 1119-66-0; $BrC{\equiv}CPh$, 932-87-6; $ClC{\equiv}CPh$, 1483-82-5; $HC{\equiv}C(CH_2)_7CH_3$, 764-93-2; $HC{\equiv}CPh$, 536-74-3; $HC{\equiv}CCH(Me)CH_3$, 598-23-2; $HC{\equiv}CC(Me)_2CH_3$, 917-92-0; $HC{\equiv}C(CH_2)_5CH_3$, 629-05-0; $HC{\equiv}CCH_2CH_3$, 107-00-6; (*E*)BrC(9-BBN)=CHBu, 82415-27-8; (*E*)ClC(9-BBN)=CHBu, 82415-28-9; (*E*)IC(9-BBN)=CHBu, 82415-29-0; (*Z*)BrCH=CHBu, 13154-12-6; (*Z*)ClCH=CHBu, 50586-18-0; (*Z*)ICH=CHBu, 16538-47-9.

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Cobalt-Mediated 1,4-Acylation/Alkylation of 1,3-Dienes

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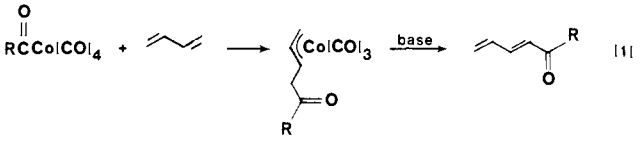
Abstract: Acylcobalt complexes prepared from $NaCo(CO)_4$ and organic halides reacted with butadiene, isoprene, and allene to form (acyl-π-allyl)cobalt complexes. Reaction of these with stabilized carbanions resulted in alkylation at the unsubstituted π-allyl terminus. The procedure provides an overall 1,4-acylation/alkylation of 1,3-dienes in which three carbon–carbon bonds are formed in a one-pot, four-step reaction sequence.

The cobalt carbonyl anion, $[Co(CO)_4]^-$, is a weak base ($pK_a \sim 1$) but a modest nucleophile. It reacts with active organic halides (primary and secondary alkyl, allyl, benzyl) and tosylates by an S_N2 process to generate alkylcobalt carbonyl complexes, $RCo(CO)_4$, which readily insert carbon monoxide under mild conditions to produce acylcobalt carbonyl complexes, $RCOCo(CO)_4$. When treated with an alcohol, these cleave to produce esters, resulting in the overall conversion of an organic halide to an ester.[1] Acylcobalt complexes react with 1,3-dienes to produce π-allylcobalt complexes by insertion of the diene into the cobalt–acyl carbon bond. These acylated π-allylcobalt complexes react with base to regenerate the diene, resulting in an acyldiene synthesis (eq 1).[2]



[1]

A number of π-allylmetal complexes react with nucleophiles at the π-allyl ligand, resulting in transfer of the allyl group from the metal to the nucleophile. This process is particularly well-developed for π-allylpalladium complexes. Both carbon[3] and nitrogen[4] nucleophiles react cleanly, and the process has been used extensively in the synthesis of a variety of natural products.[5] Other π-allylmetal complexes have been much less studied in their re-

Table I. Acylation/Alkylation of 1,3-Butadiene (Eq 3)

RX	W	Y	Z	procedure	products (% yield)[a]
CH_3I	CO_2Me	CO_2Me	H	A	1 (20), 2 (10)
CH_3I	CO_2Me	CO_2Me	H	B	1 (39), 2 (23)
CH_3I	CO_2Et	CO_2Et	Me	A	1 (17)[b]
CH_3I	CO_2Et	CO_2Et	Me	B	1 (49)
CH_3I	COMe	CO_2Et	H	A	1 (35)
CH_3I	COMe	CO_2Et	H	B	1 (43)
CH_3I	CN	CO_2Et	H	A	1 (3), 2 (14)[c]
CH_3I	CN	CO_2Et	H	B	1 (5),[d] 2 (44)[d]
$PhCH_2Br$	CO_2Et	CO_2Et	Me	A	1 (7)
$PhCH_2Br$	CO_2Et	CO_2Et	Me	B	1 (18)
$PhCH_2COCl$	COMe	CO_2Et	H	A	1 (39)
$BrCH_2CO_2Et$	CO_2Me	CO_2Me	H	A	1 (47)
$BrCH_2CO_2Et$	CO_2Me	CO_2Me	H	B	1 (35)

[a] Yields are for isolated purified material. [b] With 1 equiv of added H_2O, the yield was 40%. [c] A third product, 1 bearing a methyl group at the enol position, was isolated in 17% yield. [d] These materials were not separated from each other. The reported isomer distribution is calculated from NMR data. Upon separation, 2% of 1 and 26% of 2 was obtained. The $NaCo(CO)_4$ was prepared by the reaction of $Co_2(CO)_8$ with NaOH in THF. This gives $NaCo(CO)_4$ with 0.80 equiv of H_2O/Co. For procedure A, the water was removed by treatment with NaH. For procedure B, the water was not removed.

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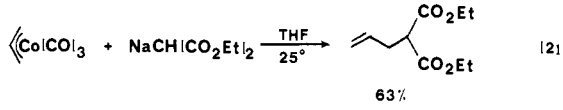
actions with nucleophiles. Neutral π-allyliron dicarbonyl nitrosyl complexes react with stabilized carbanions (e.g., malonate anion) to give good yields of monoalkylated organic products.[6] The corresponding anion, $NaFe(CO)_3NO$, catalyzed the allylic alkylation of allyl acetates by stabilized carbanions via the π-allyliron complex.[7] This same paper claimed catalysis by both $NaCo(CO)_4$ and π-allylcobalt carbonyl complexes, but yields of allylic alkylation with these catalysts were low.[8] π-Allylcobalt tricarbonyl has been reported to react with sodium methoxide to produce allyl methyl ether (no yield reported).[9] In this paper, we report the development of the alkylation of π-allylcobalt tricarbonyl complexes with stabilized carbanions and its combination with the cobalt-assisted acylation of 1,3-dienes to result in the 1,4-acylation/alkylation of 1,3-dienes.

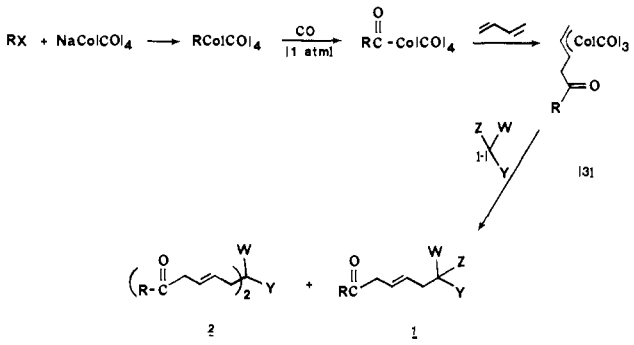
Results and Discussion

In the course of a general study of the reactions of nucleophiles with π-allylmetal complexes, it was noted that π-allylcobalt tricarbonyl complexes reacted with stabilized carbanions in the absence of added ligands to produce allylic alkylation products in good yield (eq 2). This reaction was combined with the



[2]

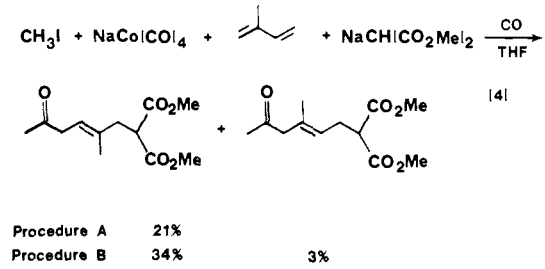
cobalt-assisted acylation of dienes to form acylated π-allylcobalt complexes, producing an overall 1,4-acylation/alkylation of 1,3-dienes (eq 3). The results are summarized in Table I.



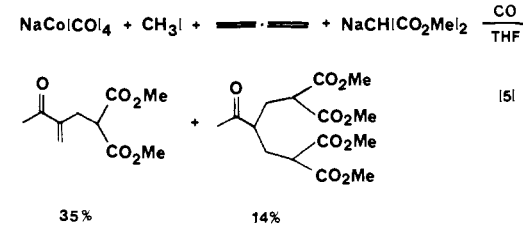
The $NaCo(CO)_4$ used in these reactions was prepared from $Co_2(CO)_8$ and sodium hydroxide in THF solution.[10] This procedure produces $NaCo(CO)_4$ containing 0.8 equiv of water/$NaCo(CO)_4$. For procedure A, this water was removed by treatment with sodium hydride, while for procedure B, wet $NaCo(CO)_4$ was used. For water-stable substrates, the wet $NaCo(CO)_4$ resulted in a higher overall yield of desired product than did the dry $NaCo(CO)_4$. (For the third entry of the table, addition of 1 equiv of water to the dried cobalt reagent resulted in an increase in yields of 2.5-fold.) Since the first step of this reaction is formation of the alkylcobalt complex by an S_N2 displacement, the source of the acyl group in the final product was limited to rather reactive halides. Thus methyl iodide and ethyl bromoacetate reacted well. Surprisingly, benzyl bromide gave only low yields of desired product. However, the same product was available in considerably better yield from the corresponding acid halide, phenylacetyl chloride. This reactivity of acid halides is useful, since it should permit acyl groups from normally unreactive halides (aryl, vinyl, secondary and tertiary alkyl) to be incorporated into the final product via their acid halides.

Stabilized carbanions ($pK_a \simeq 10$–15) were most effective for the alkylation step of the reaction. Unsubstituted malonate esters gave the highest yield, while methyl-substituted malonates were less effective. Ethyl acetoacetates reacted in fair yield, but the methyl-substituted analogue of this anion gave only low yields of the desired product. Ethyl cyanoacetate reacted in fair yield, but dialkylation was the major process observed , as is typical for cyano-stabilized carbanions. Less stabilized (more basic) carbanions such as ester or ketone enolates did not alkylate the acylated π-allylcobalt complexes. Rather, proton abstraction to generate the acyldiene (eq 1)[2] ensued. Thus, a competition between nucleophilic attack and proton abstraction interferes with the desired reaction using nonstabilized carbanions.

Few dienes have been examined in this reaction. The results for butadiene are shown in Table I. Isoprene also undergoes the process in eq 3, with the product distribution depending on the source of $NaCo(CO)_4$ used (eq 4). With dry $NaCo(CO)_4$, a low

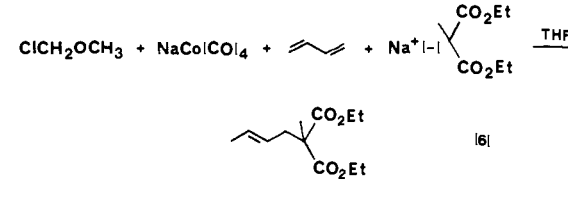


yield of the isomer resulting from insertion of the (expected) *less* substituted olefin of the diene into the cobalt–carbon bond was obtained. With wet $NaCo(CO)_4$, the yield of this isomer was substantially higher, and a minor isomer corresponding to acylation of the *more* substituted olefin was obtained. Allene also underwent this acylation/alkylation reaction, giving a 1,2-addition product resulting from acylation at the central carbon of this diene (eq 5). In this case, the initially formed conjugated ketone underwent



a further Michael addition with malonate to give some dialkylation product. Cyclohexadiene underwent the acylation process, but reaction with malonate anion produced the acyldiene (eq 1) rather than the desired alkylation product.

This same procedure affords a method for 1,4-hydroalkylation of 1,3-dienes. In an attempt to use chloromethyl methyl ether as the electrophile in eq 3, with the $NaCo(CO)_4$ containing water, we found that the sole product was the hydroalkylated diene (eq 6). It is likely that the water present hydrolyzed the chloromethyl



methyl ether, generating HCl and thence $HCo(CO)_4$. Addition of $HCo(CO)_4$ to the diene generated the π-crotylcobalt carbonyl complex,[11] which underwent alkylation exclusively at the *less* substituted terminus. Indeed, reaction of butadiene with HCo-

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(11) Reference 1a, pp 376–377.

$(CO)_4$ followed by malonate anion led to the same product. This procedure should be a general method for the alkylation of 1,3-dienes.

Although the formation of (1-acyl-π-allyl)cobalt carbonyl complexes from 1,3-dienes and acylcobalt tricarbonyl is a well-established process and requires no further comment, the reaction of π-allylcobalt tricarbonyl complexes with carbanions has several interesting aspects. In contrast to related π-allylpalladium complexes,[3] π-allylcobalt tricarbonyl complexes react with carbanions cleanly and rapidly in the absence of added ligands. Since $[Co(CO)_4]^-$ is a good leaving group and a stable compound in its own right, added ligands are not necessary for stabilization, as is the case with the palladium complexes. In fact, addition of 1 equiv. of triphenylphosphine to the reaction mixture just prior to the addition of the malonate anion completely suppressed the alkylation reaction. Under these conditions, the major product was that resulting from oxidative coupling of the malonate anion, $[CH(CO_2Me)_2]_2$, during isolation, rather than acylation/alkylation of the diene. Virtually no product containing the diene was obtained under these conditions. The regiochemistry of alkylation, in all cases studied, was cleanly attacked at the unsubstituted π-allyl terminus. With π-allylpalladium complexes, the regioselectivity is strongly dependent on the particular system studied, but high regioselectivity is often observed. The initial site of nucleophilic attack on the π-allylcobalt complexes is not presently known. Addition of the carbanion to the π-allylcobalt tricarbonyl solution results in the immediate formation of a deep red color, which gradually fades to a pale yellow over the course of the reaction (1–3 h). This implies the formation of some intermediate complex. Its nature awaits further studies.

The *overall* yields of this acylation/alkylation reaction are only modest. However, the process reported involves *four* sequential reactions and makes three carbon–carbon bonds, in a one-pot, 2–5-h reaction sequence requiring no isolation of any of the intermediates. Each step of the process must have proceeded in >80% yield to obtain the observed yields. Thus, the overall process is reasonably efficient.

Experimental Section

General Procedures. Melting points were taken with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on either a Beckman Acculab 3 or Beckman 4240 spectrometer. ^1H NMR spectra were recorded with either a Varian T-60 or EM360A spectrometer with tetramethylsilane as an internal standard and are reported in δ. Analytical preparative vapor-phase chromatography was performed on a Bendix Model 2300 gas chromatograph equipped with a 4 ft × 0.25 in. column (SE-30, 15% on Chromosorb W NAW 60–80 mesh). Liquid chromatography was performed under moderate (40–80 psi) pressures with either 15 × 250 mm or 37 × 180 mm columns of Woelm Type 206 silica gel. Preparative layer chromatography was carried out by using 20 × 20 cm plates coated with EM Laboratories 60 PF-254 silica gel. Microanalyses were performed by Midwest Microanalytical Laboratory, Indianapolis, IN. Mass spectra were measured by Mass Spectrometry Service Laboratory, University of Nebraska, Lincoln, NE. All manipulations of the cobalt complexes were carried out under an argon atmosphere.

Materials. The complex $NaCo(CO)_4$ was synthesized from $Co_2(CO)_8$ and solid NaOH[10] in THF. For procedure A (Table I), the resulting solution was dried over excess NaH for 2 h and then filtered. For procedure B, the solution was used without further treatment. The amount of cobalt carbonyl anion formed was determined by adding excess I_2 to the reaction mixture and then measuring the amount of evolved carbon monoxide by a gasometric procedure.[12] THF was heated at reflux over sodium metal/benzophenone and distilled before use. Butadiene (Matheson) and allene (ICN) were used without further purification. Isoprene was distillled at atmospheric pressure. All the alkyl halides and the acid halides used were distilled except chloromethyl methyl ether.

Preparation of the Carbanions. Sodium hydride (50% mineral oil suspension) was washed with dry petroleum ether or hexane under an inert atmosphere. Most of the petroleum ether was removed with a syringe. The remaining petroleum ether was removed carefully by evaporation under reduced pressure. The carbanion solution was made by adding the appropriate substrate to the sodium hydride-THF suspension (2 mL/mmol) at 0 °C. Potassium carbanions were prepared from potassium hydride by the same procedure.

Reaction of π-Allylcobalt Tricarbonyl with Sodium Diethyl Malonate. π-Allylcobalt tricarbonyl was synthesized from cobalt octacarbonyl and allyl bromide under phase-transfer conditions[13] and isolated by distillation under reduced pressure. A 10-mL portion of a 0.1 M THF solution of π-allylcobalt tricarbonyl was placed in a 50-mL airless flask. Sodium diethyl malonate (1.1 mmol) in 2.2 mL of THF was added dropwise under a CO atmosphere at room temperature. Immediately a deep red color appeared. As the reaction proceeded, the color gradually faded. After 17.5 h, the mixture was warmed to 50 °C and stirred for 4 h. At that time, the color of the solution was light orange. The mixture was then poured into ice water and 1 mL of concentrated HCl and ether (ca. 100 mL) were added. The mixture was stirred until the organic phase became transparent. The organic phase was separated and dried over $MgSO_4$. Isolation by preparative layer chromatography (silica gel, 1:1 hexane–ether, R_f 0.4) gave 0.13 g (63%) of diethyl allylmalonate, identical in all respects with authentic material prepared from allyl bromide and diethyl malonate.

Preparation of (1-(Acetylmethyl)-π-allyl)cobalt Tricarbonyl (3).[2b] Into a 100-mL airless flask was placed solvent (THF) and a THF solution of 3.0 mmol of $NaCo(CO)_4$ under Ar (the total amount of THF was 30 mL). Methyl iodide (0.187 mL, 3 mmol) was added, and the resulting solution was exposed to gaseous butadiene (balloon) with stirring for 0.5 h at room temperature to give an amber-orange solution of **3**.

Reaction of 3 with Carbanions. The anion (6 mmol) in 12 mL of THF was added to the THF solution of **3** (3 mmol) under a CO atmosphere at room temperature. In many cases, the color of the solution became red when the anion was added, and the color gradually faded as the reaction proceeded. When the red color disappeared, the reaction was stopped by adding saturated NH_4Cl solution. Then I_2 in ether was added to decompose any remaining cobalt carbonyl species present. The mixture was stirred until the brown color remained for at least 0.5 h. The brown mixture was washed with brine. Excess I_2 was reduced with 1 M $Na_2S_2O_3$ solution. The organic layer was washed with water once and dried over $MgSO_4$.

Reaction of 3: With Sodium Dimethyl Malonate (Procedure A) (1-h Reaction Time). Isolation by preparative layer chromatography (1:1 hexane–ethyl acetate, R_f 0.54) gave 135 mg (20%) of methyl 2-carbomethoxy-7-oxo-*trans*-4-octenoate: NMR (CCl_4) δ 2.04 (s, 3, $COCH_3$), 2.51 (t, J = 7 Hz, 2, $=CHCH_2CH$), 2.97 (d, J = 5 Hz, 2, $=CHCH_2COMe$), 3.28 (t, J = 7 Hz, 1, $CH(COOMe)_2$), 5.37 (m, 2, CH=CH); IR (neat) 1728 (ester C=O), 1710 (ketone C=O), 969 (CH=CH, trans) cm^{-1}. An analytically pure sample was obtained by further preparative layer chromatography as a colorless oil. Anal. ($C_{11}H_{16}O_5$) C, H.

In addition, 48 mg (10%) of 2,12-dioxo-7,7-dicarbomethoxy-*trans*,-*trans*-4,9-tridecadiene (R_f 0.36) was obtained as a pale yellow oil: NMR (CCl_4) δ 2.04 (s, 6, CH_3CO), 2.50 (d, J = 6 Hz, 4, $=CHCH_2C(COOMe)_2$), 3.00 (d, J = 6 Hz, 4, $=CHCH_2CO$), 3.58 (s, 6, $COOCH_3$), 5.32 (m, 4, $CH=CH$); IR (neat) 1725 (ester C=O), 1710 (ketone C=O), 969 (CH=CH, trans) cm^{-1}; mass spectrum, calcd for $C_{17}H_{24}O_6$, m/e 324.1576 (M^+); found, m/e 324.1573.

A small amount (10 mg, 1%) of tetramethyl ethane-1,1,2,2-tetracarboxylate was also obtained as white crystals: mp 137–138 °C (lit.[14] 138 °C); NMR ($CDCl_3$) δ 3.80 (s, 12, $COOCH_3$), 4.21 (s, 2, $CH(COOMe)_2$); IR (KBr) 1734 (ester C=O) cm^{-1}. Anal. ($C_{11}H_{14}O_9$) C, H.

With Sodium Dimethyl Malonate (Procedure B). (1-h Reaction Time). Isolation by medium-pressure LC (5:4 hexane–ethyl acetate) gave 267 mg (39%) of methyl 2-carbomethoxy-7-oxo-*trans*-4-octenoate. 2,12-Dioxo-7,7-dicarbomethoxy-*trans*,*trans*-4,9-tridecadiene (116 mg; 23%) was isolated by column chromatography (silica gel, ethyl acetate).

With Sodium Diethyl Methylmalonate (Procedure A) (3-h Reaction Time). Isolation by preparative layer chromatography (5:3 hexane–ethyl acetate, R_f 0.47) gave 139 mg (17%) of ethyl 2-methyl-2-carboethoxy-7-oxo-*trans*-4-octenoate: NMR (CCl_4) δ 1.34 (t, J = 7 Hz, 6, CH_2CH_3), 1.38 (s, 3, $CH_3C(COOEt)_2$), 2.10 (s, 3, CH_3CO), 2.56 (d, J = 6 Hz, 2, $=CHCH_2(CH_3)$), 3.07 (d, J = 6 Hz, 2, $=CHCH_2CO$), 4.13 (q, J = 7 Hz, 4, CH_2CH_3), 5.47 (m, 2, $CH=CH$); IR(neat) 1721 (ester C=O), 1709 (ketone C=O), 967 (CH=CH, trans) cm^{-1}. Anal. ($C_{14}H_{22}O_5$) C, H.

With Sodium Diethyl Methylmalonate in the Presence of Added Water (Procedure A) (3-h Reaction Time). Water (54 mg, 3 mmol) was added to a THF solution of 3.0 mmol of $NaCo(CO)_4$. Preparation of **3** and the

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following alkylation were done as usual. Isolation by preparative layer chromatography (5:3 hexane–ethyl acetate) gave 325 mg (40%) of ethyl 2-methyl-2-carboethoxy-7-oxo-*trans*-4-octenoate.

With Sodium Diethyl Methylmalonate (Procedure B) (3-h Reaction Time). Isolation by medium-pressure LC (1:1:0.1 hexane–ether–methanol) gave 398 mg (49%) of ethyl 2-methyl-2-carboethoxy-7-oxo-*trans*-4-octenoate.

With Sodium Ethyl Acetoacetate (Procedure A) (2-h Reaction Time). Isolation by preparative layer chromatography (5:3 hexane–ethyl acetate, R_f 0.33) gave 236 mg (35%) of ethyl 2-acetyl-7-oxo-*trans*-4-octenoate: NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3, CH_2CH_3), 2.03 (s, 3, CH_3CO), 2.12 (s, 3, CH_3CO), 2.47 (t, J = 6 Hz, 2, $=CHCH_2CH(COOEt)$), 2.98 (d, J = 6 Hz, 2, $=CHCH_2COCH_3$), 3.33 (t, J = 7 Hz, 1, $CH(COMe)(COOEt)$), 4.09 (q, J = 7 Hz, 2, CH_2CH_3), 5.40 (m, 2, $CH=CH$); IR (neat) 1730 (ester C=O), 1709 (ketone C=O), 968 (CH=CH, trans) cm^{-1}. Anal. ($C_{12}H_{18}O_4$) C, H.

With Sodium Ethyl Acetoacetate (Procedure B) (2-h Reaction Time). Isolation by medium-pressure LC (5:4 hexane–ethyl acetate) gave 289 mg (43%) of ethyl 2-acetyl-7-oxo-*trans*-4-octenoate.

With Sodium Ethyl Cyanoacetate (Procedure A) (1-h Reaction Time). The crude products were treated with 1 M Na_2CO_3 solution to remove most of the unreacted ethyl cyanoacetate. Isolation by preparative layer chromatography (5:2 hexane–ethyl acetate, R_f 0.18) gave 21 mg (3%) of ethyl 2-cyano-7-oxo-*trans*-octenoate: NMR (CCl_4) δ 1.39 (t, J = 6 Hz, 3, CH_2CH_3), 2.14 (s, 3, CH_3CO), 2.68 (t, J = 6 Hz, 2, $=CHCH_2CH(CN)$), 3.11 (d, J = 6 Hz, 2, $=CHCH_2COMe$), 3.45 (t, J = 6 Hz, 1, $CH_2CH(CN)(COOEt)$), 4.25 (q, J = 6 Hz, 2, CH_2CH_3), 5.62 (m, 2, $CH=CH$); IR (CCl_4) 2225 (CN), 1740 (ester C=O), 1717 (ketone C=O), 966 (CH=CH, trans) cm^{-1}. Anal. ($C_{11}H_{15}NO_3$) C, H, N.

Also, 112 mg (17%) of ethyl 2-methyl-2-cyano-7-oxo-*trans*-4-octenoate (R_f 0.30) was obtained: NMR (CCl_4) δ 1.34 (t, J = 6 Hz, 3, CH_2CH_3), 1.56 (s, 3, $CH_3C(CN)$), 2.06 (s, 3, CH_3CO), 2.56 (m, 2, $=CHCH_2CCN$), 3.10 (d, J = 6 Hz, 2, $=CHCH_2CO$), 4.17 (q, J = 6 Hz, 2, CH_2CH_3), 5.56 (m, 2, $CH=CH$); IR (neat) 2235 (CN), 1736 (ester C=O), 1711 (ketone C=O), 968 (CH=CH, trans) cm^{-1}. Anal. ($C_{12}H_{17}NO_3$) C, H, N.

Also, 66 mg (14%) of 2,12-dioxo-7-cyano-7-carboethoxy-*trans,trans*-4,9-tridecadiene (R_f 0.12) was obtained: NMR (CCl_4) δ 1.30 (t, J = 7 Hz, 3, CH_2CH_3), 2.08 (s, 6, CH_3CO), 2.51 (d, J = 6 Hz, 4, $=CHCH_2CCN$), 3.09 (d, J = 6 Hz, 4, $=CCH_2CO$), 4.17 (q, J = 7 Hz, 2, CH_2CH_3), 5.55 (m, 4, CH=CH); IR (neat) 2235 (CN), 1735 (ester C=O), 1712 (ketone C=O), 970 (CH=CH, trans) cm^{-1}; mass spectrum, calcd for $C_{17}H_{23}NO_4$, m/e 305.1628 (M^+) missing; 276.1236 ($M^+ - C_2H_5$), found 276.1220; 262.1441 ($M^+ - CH_3CO$), found 262.1442; 222.1131 ($M^+ - CH_3COCH_2CH{=}CH$), found 222.1129; 220.1339 ($M^+ - CCOOEt$); found 220.1341; 208.0978 ($M^+ - CH_3COCH_2CH{=}CHCH_2$), found 208.0965.

With Sodium Ethyl Cyanoacetate (Procedure B) (1-h Reaction Time). The crude products were treated with 1 M Na_2CO_3 solution (50 mL). Isolation by preparative layer chromatography (5:2 hexane–ethyl acetate, R_f 0.21) gave 15 mg (2%) of ethyl 2-cyano-7-oxo-*trans*-4-octenoate and 44 mg (7%) of ethyl 2-methyl-2-cyano-7-oxo-*trans*-4-octenoate (R_f 0.31). Also, 120 mg (26%) of 2,12-dioxo-7-cyano-7-carboethoxy-*trans,trans*-tridecadiene was isolated by another preparative layer chromatography (1:2 hexane–ethyl acetate, R_f 0.52).

With Potassium Ethyl Phenylacetate (Procedure A) (19-h Reaction Time). Starting material was recovered unchanged.

With Lithium Enolate of Cyclohexanone (Procedure A). An anion was prepared from cyclohexanone (0.623 mL, 3 mmol) and LDA (3 mmol) in THF (6 mL) at −78 °C for 0.5 h. All the solvent was evaporated off under reduced pressure at room temperature, and THF (6 mL) was added. This was used for the subsequent reaction (2.5 h). There was no expected product. Only 1-acetyl-1,3-butadiene[2c] was detected by NMR (21%).

Preparation of (1-(Acetylmethyl)-2-methyl-π-allyl)cobalt Tricarbonyl (4).[2a] This was prepared by the same procedure as described for that of **3**[2] by using 0.6 mL (6 mmol) of isoprene instead of butadiene.

Reaction of 4: With Sodium Dimethyl Malonate (Procedure A) (1.5-h Reaction Time). Isolation by preparative layer chromatography (5:3 hexane–ethyl acetate, R_f 0.45) gave 155 mg (21%) of methyl 2-carbomethoxy-4-methyl-7-oxo-4-octenoate: NMR (CCl_4) δ 1.65 (s, 3, CH_3), 2.09 (s, 3, CH_3CO), 2.58 (d, J = 7 Hz, 2, $=CCH_2CH(CO_2Me)_2$), 3.04 (d, J = 7 Hz, 2, $=CHCH_2COMe$), 3.47 (t, J = 7 Hz, 1, $CH(CO_2Me)_2$), 3.70 (s, 6, CH_3O), 5.32 (t, J = 7 Hz, 1, CH=C); IR (CCl_4) 1740–1710 (ester and ketone C=O) cm^{-1}. Anal. ($C_{12}H_{18}O_5$) C, H.

With Sodium Dimethyl Malonate (Procedure B) (2-h Reaction Time). Isolation by medium-pressure LC (1:1 hexane–ethyl acetate) gave 266 mg (37%) of the product. From the NMR data, the isomer distribution was calculated as follows: methyl 2-carbomethoxy-4-methyl-7-oxo-4-octenoate (92%) and methyl 2-carbomethoxy-5-methyl-7-oxo-4-octenoate (8%).

Preparation of (1-((Phenylacetyl)methyl)-π-allyl)cobalt Tricarbonyl (5) from Benzyl Bromide.[2c] This was prepared by the same procedure as described for that of **3** by using benzyl bromide (0.356 mL, 3 mmol) instead of methyl iodide.

Reaction of 5: With Sodium Diethyl Methylmalonate (Procedure A). (9-h Reaction Time). Isolation by preparative layer chromatography (5:1 hexane–ethyl acetate, R_f 0.26) gave 72 mg (7%) of ethyl 2-carboethoxy-2-methyl-7-oxo-8-phenyl-*trans*-4-octenoate: NMR (CCl_4) δ 1.04 (t, J = 7 Hz, 6, CH_2CH_3), 1.10 (s, 3, CH_3), 2.17 (d, J = 6 Hz, 2, $=CHCH_2C(CH_3)(COOC_2H_5)_2$), 2.80 (d, J = 6 Hz, 2, $=CHCH_2C(=O)$), 3.33 (s, 2, $PhCH_2CO$), 3.89 (q, J = 7 Hz, 4, CH_2CH_3), 5.19 (m, 2, $CH=CH$), 6.92 (s, 5, C_6H_5); IR (neat) 1726 (ester C=O), 1712 (ketone C=O), 1493 (aromatic), 972 (CH=CH, trans) cm^{-1}; mass spectrum, calcd for $C_{20}H_{26}O_5$, m/e 346.1781; found, 346.1793 (M^+).

With Sodium Diethyl Methylmalonate (Procedure B) (2-h Reaction Time). Isolation by preparative layer chromatography (5:2 hexane–ethyl acetate, R_f 0.52) gave 184 mg (18%) of ethyl 2-carboethoxy-2-methyl-7-oxo-8-phenyl-*trans*-4-octenoate.

Preparation of (1-((Phenylacetyl)methyl)-π-allyl)cobalt Tricarbonyl (5) from Phenylacetyl Chloride.[2c] This was prepared by the same procedure, reacting 1 h as described for **3**, but using phenylacetyl chloride (0.398 mL, 3 mmol) instead of methyl iodide.

Reaction of 5: With Sodium Ethyl Acetoacetate (Procedure A) (2.5-h Reaction Time). Isolation by preparative layer chromatography (5:1 hexane–ethyl acetate, R_f 0.20) gave 353 mg (39%) of ethyl 2-acetyl-7-oxo-8-phenyl-*trans*-4-octenoate: NMR (CCl_4) δ 1.28 (t, J = 7 Hz, 3, CH_2CH_3), 2.17 (s, 3, CH_3CO), 2.52 (t, J = 6 Hz, 2, $=CHCH_2CHCOCH_3$), 3.05 (d, J = 6 Hz, 2, $=CHCH_2COCH_2Ph$), 3.38 (t, J = 6 Hz, 1, $CHCOCH_3$), 3.60 (s, 2, $PhCH_2$), 4.11 (q, J = 7 Hz, 2, CH_2CH_3), 5.42 (m, 2, $CH=CH$), 7.17 (s, 5, C_6H_5); IR (neat) 1730 (ester C=O), 1706 (ketone C=O), 966 (CH=CH, trans) cm^{-1}. Anal. ($C_{18}H_{22}O_4$) C, H.

Preparation of (1-((Carboethoxyacetyl)methyl)-π-allyl)cobalt Tricarbonyl (6).[2c] This was prepared by the same procedure as described for that of **3** by using ethyl bromoacetate (0.333 mL, 3 mmol) instead of methyl iodide.

Reaction of 6: With Sodium Dimethyl Malonate (Procedure A) (3-h Reaction Time). Isolation by preparative layer chromatography (5:2 hexane–ethyl acetate, R_f 0.25) gave 423 mg (47%) of methyl 2-carbomethoxy-7-oxo-8-carboethoxy-*trans*-4-octenoate: NMR (CCl_4) δ 1.30 (t, J = 7 Hz, 3, CH_2CH_3), 2.56 (t, J = 6 Hz, 2, $=CHCH_2CH(COOMe)_2$), 3.16 (d, J = 7 Hz, 2, $=CHCH_2C=O$), 3.32 (s, 2, $COCH_2COOEt$), 3.36 (t, J = 6 Hz, 1, $CH(COOMe)_2$), 3.65 (s, 6, $COOCH_3$), 4.13 (q, J = 7 Hz, 2, CH_2CH_3), 5.50 (m, 2, $CH=CH$); IR (neat) 1730 (ester C=O), 1710 (ketone C=O), 970 (CH=CH, trans) cm^{-1}. Anal. ($C_{14}H_{20}O_7$) C, H.

With Sodium Dimethyl Malonate (Procedure B) (3-h Reaction Time). Isolation by medium-pressure LC (1:1:0.1 hexane–ethyl acetate–methanol) gave 315 mg (35%) of methyl 2-carbomethoxy-7-oxo-8-carboethoxy-*trans*-4-octenoate.

Preparation of (1-((Methoxyacetyl)methyl)-π-allyl)cobalt Tricarbonyl (7).[2c] This was prepared by the same method as described for that of **3** by using chloromethyl methyl ether (242 mg, 3 mmol) instead of methyl iodide and reacting for 1 h. The chloromethyl methyl ether was passed through a column packed with basic alumina before use to remove any HCl that might be contained.

Attempted Preparation of (1-((Methoxyacetyl)methyl)-π-allyl)cobalt Tricarbonyl and Reaction with Sodium Dimethyl Methylmalonate (Procedure B) (18-h Reaction Time). Isolation by preparative layer chromatography (10:1 hexane–ethyl acetate, R_f 0.35) gave 383 mg (56%) of ethyl 2-methyl-2-carboethoxy-*trans*-4-hexenoate: NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 6, CH_2CH_3), 1.28 (s, 3, CH_3), 1.66 (d, J = 5.2 Hz, 3, $CH_3CH=$), 2.43 (d, J = 6 Hz, 2, $=CHCH_2C-$), 4.08 (q, J = 7 Hz, 4, CH_2CH_3), 5.33 (m, 2, $CH=CH$); IR (neat) 1727 (ester C=O), 966 (CH=CH, trans) cm^{-1}.

Preparation of π-Allylcobalt Tricarbonyl Derivative (8) from $NaCo(CO)_4$, MeI, and 1,3-Cyclohexadiene.[2c] This was prepared by the same procedure as described for that of **3** by using 481 mg (6 mmol) of 1,3-cyclohexadiene and reacting at 40–50 °C for 0.5 h.

Reaction of 8: With Sodium Ethyl Acetoacetate (Procedure A) (1-h Reaction Time). The NMR spectrum of the crude products shows that there is no expected product, but 1-acetyl-1,3-cyclohexadiene[2c] is formed in 46% yield.

Preparation of (2-Acetyl-π-allyl)cobalt Tricarbonyl (9).[15] Into a 100-mL airless flask was placed the solvent (THF) and a THF solution of 3.0 mmol of $NaCo(CO)_4$ under Ar (the total amount of THF was 30 mL). Methyl iodide (0.187 mL, 3 mmol) was added, and subsequently 100 mL of gaseous allene (4.1 mmol at 24 °C) was contacted. The

reaction mixture was stirred at 0 °C for 6 h to give a yellow-amber solution of **9**.

Reaction of 9: With Sodium Dimethyl Malonate (Procedure A) (20-min Reaction Time by Using 3 mmol of Sodium Dimethyl Malonate Instead of 6 mmol). Isolation by preparative layer chromatography (5:3 hexane–ethyl acetate, R_f 0.39) gave 226 mg (35%) of methyl 2-carbomethoxy-4-methylene-5-oxohexanoate: NMR (CCl_4) δ 2.23 (s, 3, CH_3CO), 2.70 (d, J = 8 Hz, 2, $CH_2CH(COOMe)_2$), 3.43 (t, J = 8 Hz, 1, $CH_2CH(COOMe)_2$), 3.60 (s, 6, $COOCH_3$), 5.72 and 5.88 (2s, 2, CH_2=C); IR (CCl_4) 1750 (ester C=O), 1732 (ester C=O), 1678 (ketone C=O) cm^{-1}. Analytically pure sample was obtained by further preparative gas chromatography (SE-30, 180 °C, retention time 7 min). Anal. ($C_{10}H_{14}O_5$) C, H.

In addition, dimethyl 2,6-dicarbomethoxy-4-acetylheptanedioate, a Michael addition product (R_f 0.19, 141 mg, 14%), was obtained: NMR (CCl_4) δ 2.16 (s, 3, CH_3CO), 1.30–2.90 (m, 5, $CH_2CH(COCH_3)CH_2$), 3.31 (t, J = 7 Hz, 2, $CH(COOMe)_2$), 3.66 and 3.70 (2 s, 12, $COOCH_3$); IR (neat) 1750–1710 (ester and ketone C=O), cm^{-1}; mass spectrum, calcd for $C_{15}H_{22}O_9$, m/e 346.1264 (M^+) missing; 315.1080 ($M^+ - CH_3O$), found 315.1075; 303.1080 ($M^+ - CH_3CO$), found 303.1090; 215.0192 ($M^+ - CH(COOCH_3)_2$), found 215.0915.

Reaction of Hybridocobalt Tetracarbonyl with Butadiene and Dimethyl Malonate. Wet $NaCo(CO)_4$ (3 mmol) in 4.4 mL of THF was added to a flask containing THF (25 mL). The flask was cooled to 0 °C. HCl gas (75 mL at 24 °C, 3.08 mmol) was added by syringe and stirred for 0.5 h to give a light yellow-green solution and white precipitate. Butadiene was contacted for 0.5 h at 0 °C and then 10 min at 25 °C to give a dark amber solution. Then the anion of dimethyl malonate (6 mmol) in 12 mL of THF was added at 25 °C under CO to give a light red solution immediately. The red color faded into light amber (~5 min). After 1 h, the mixture was shaken with saturated NH_4Cl solution. The organic layer was separated. Iodine in ether was added to decompose any cobalt carbonyl species. Excess I_2 was removed by washing with aqueous $Na_2S_2O_3$ solution. The organic layer was dried over $MgSO_4$.

NMR spectrum of the crude products indicated the formation of methyl 2-carbomethoxy-*trans*-4-hexenoate (35% based on the Co). There is no indication of the formation of methyl 2-carbomethoxy-3-methyl-4-pentenoate.

Reaction of 3 with Sodium Dimethyl Malonate in the Presence of Triphenylphosphine (Procedure B). The solution of **3** was transferred by needlestock into a 100-mL airless flask containing triphenylphosphine (0.786 g, 3 mmol). The reaction foamed, and the mixture was stirred for 20 min to give a red-orange solution. Then sodium dimethyl malonate (6 mmol) in 12 mL of THF was added at room temperature under CO atmosphere. A deep red solution resulted. It was stirred for 17.5 h to give a brown-red solution. Worked up as usual, the resulting triphenylphosphine oxide was removed by column chromatography (silica gel 60–200 mesh, 5:4 hexane–ethyl acetate). Isolation by medium-pressure LC (5:3 hexane–ethyl acetate) gave 358 mg (41%) of tetramethyl ethane-1,1,2,2-tetracarboxylate.

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Registry No. 1, 82545-55-9; **2**, 82545-56-0; **3**, 82554-91-4; **4**, 82554-92-5; **5**, 82554-93-6; **6**, 82554-94-7; **7**, 82554-95-8; **8**, 82554-96-9; **9**, 36485-11-7; π-allylcobalt tricarbonyl, 12144-85-3; cobalt octacarbonyl, 10210-68-1; allyl bromide, 106-95-6; diethyl allylmalonate, 2049-80-1; sodium tetracarbonylcobalt, 14878-28-5; methyl iodide, 74-88-4; sodium dimethyl malonate, 18424-76-5; tetramethyl ethane-1,1,2,2-tetracarboxylate, 5464-22-2; sodium diethyl methylmalonate, 18242-77-6; ethyl 2-methyl-2-carbethoxy-7-oxo-*trans*-4-octenoate, 82545-57-1; sodium ethyl acetoacetate, 19232-39-4; ethyl 2-acetyl-7-oxo-*trans*-4-octenoate, 82545-58-2; sodium ethyl cyanoacetate, 18852-51-2; ethyl 2-cyano-7-oxo-*trans*-4-octenoate, 82545-59-3; ethyl 2-methyl-2-cyano-7-oxo-*trans*-4-octenoate, 82545-60-6; 2,12-dioxo-7-cyano-7-carbethoxy-*trans*,*trans*-4,9-tridecadiene, 82545-61-7; potassium ethmhyl phenylacetate, 82545-62-8; lithium cyclohexanone enolate, 21300-30-1; 1-acetyl-1,3-butadiene, 2957-06-4; isoprene, 78-79-5; butadiene, 106-99-0; methyl 2-carbomethoxy-4-methyl-7-oxo-4-octenoate, 82545-63-9; methyl 2-carbomethoxy-5-methyl-7-oxo-4-octenoate, 82545-64-0; benzyl bromide, 100-39-0; ethyl 2-carbethoxy-2-methyl-7-oxo-8-phenyl-*trans*-4-atenoate, 82545-65-1; phenylacetyl chloride, 103-80-0; ethyl 2-acetyl-7-oxo-8-phenyl-*trans*-octenoate, 82545-66-2; ethyl bromoacetate, 105-36-2; methyl 2-carbomethoxy-7-oxo-8-carbethoxy-*trans*-4-octenoate, 82545-67-3; chloromethyl methyl ether, 107-30-2; ethyl 2-methyl-2-carbethoxy-*trans*-4-hexenoate, 82545-68-4; 1,3-cyclohexadiene, 592-57-4; 1-acetyl-1,3-cyclohexadiene, 53329-13-8; allene, 463-49-0; methyl 2-carbomethoxy-4-methylene-5-oxohexanoate, 82545-69-5; dimethyl 2,6-dicarbomethoxy-4-acetylheptanedioate, 82545-70-8; dimethyl malonate, 108-59-8; methyl 2-carbomethoxy-*trans*-4-hexenoate, 82545-71-9.

Kinetics and Mechanism of the Stepwise Dissociation of Iron(III) from Ferrioxamine B in Aqueous Acid

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Abstract: Deferriferrioxamine B (H_3DFB) is a linear trihydroxamic acid siderophore with molecular formula $NH_2(CH_2)_5[N(OH)C(O)(CH_2)_2C(O)NH(CH_2)_5]_2N(OH)C(O)CH_3$. In aqueous solution at pH 5, the siderophore forms a hexadentate chelate with iron(III), ferrioxamine B ($Fe(HDFB)^+$), in which the terminal amine group is protonated. The aquation reaction of ferrioxamine B has been investigated over the $[H^+]$ range 0.03–1.0 M at 25.0 °C and ionic strength 2.0 ($NaClO_4/HClO_4$). The dissociation reaction, which may be represented as $Fe(HDFB)^+ + 3H_{aq}^+ \rightleftharpoons Fe_{aq}^{3+} + H_4DFB^+$, is observed to proceed in four kinetically distinguishable stages. The microscopic rate constants for the first three steps are 2.9×10^2 s^{-1}, 1.4×10^1 s^{-1}, and 1.8×10^{-1} s^{-1}. The final dissociation step proceeds by parallel $[H^+]$-dependent and $[H^+]$-independent paths, with rate constants of 1.9×10^{-3} M^{-1} s^{-1} and 2.1×10^{-3} s^{-1}, respectively. Equilibrium quotients have also been determined for various stages of the reaction. Ferrioxamine B formation rate constants are computed to be 2×10^{-1} M^{-1} s^{-1} and 2×10^2 M^{-1} s^{-1} for the reactions of H_4DFB^+ with $Fe(H_2O)_6^{3+}$ and $Fe(H_2O)_5OH^{2+}$, respectively. Five intermediate species between fully coordinated reactant and completely dissociated products are detectable by spectral and/or kinetic techniques. A mechanism is proposed whereby the intermediates correspond to the stepwise unwrapping of deferriferrioxamine B from iron(III), starting with the N–O oxygen atom at the protonated amine end of the linear trihydroxamic acid ligand. Careful analysis of the aquation reaction suggests that the detailed mechanism for mono(hydroxamato)iron(III) dissociation is applicable to the dissociation of each hydroxamate group of deferriferrioxamine B, including the important role of coordinated H_2O cis to the dissociating hydroxamate group, acid dependencies, and the role of the hydroxamate group in the transition state of the dissociating complex. The importance of mechanistic information for iron release from ferrioxamine B in understanding siderophore-mediated iron transport is discussed.

Iron is an essential nutrient for microorganisms, but due to hydrolysis is insoluble at physiological conditions. Consequently, microorganisms synthesize iron(III)-specific chelating agents (siderophores) in order to solubilize iron from the environment

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