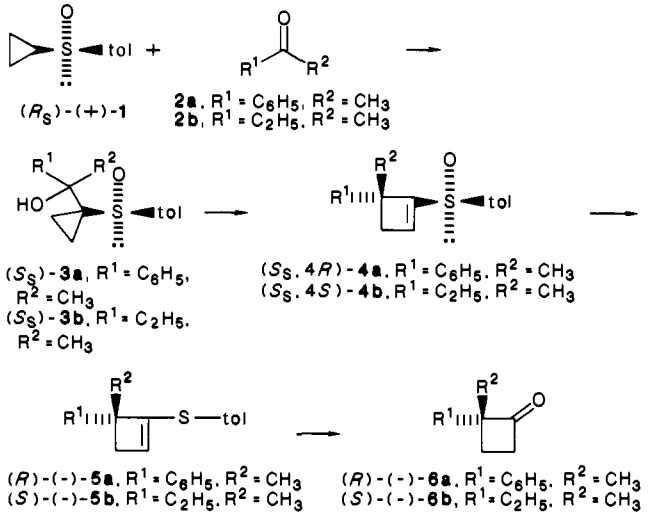
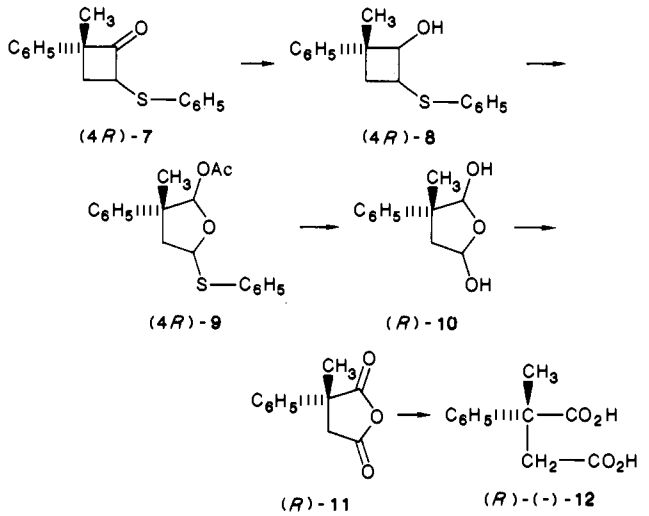
Scheme I



Scheme II



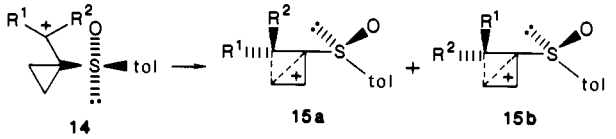
phenylcyclobutanone (**6a**) ($[\alpha]^{20}_D$ −9.6° (*c* 3.0, EtOH)) in 86% yield (Scheme I).

The absolute configuration and the enantiomeric excess of the product **6a** were determined as (*R*)-(−)-**6a** and 94.0% ee by chemical correlation of (−)-**6a** with (*R*)-(−)-2-methyl-2-phenylsuccinic acid (**12**) of known configuration[7] as follows. Sulfenylation of the ketone (−)-**6a** obtained above with diphenyl disulfide followed by sodium borohydride reduction of **7** produced an α-phenylthio alcohol **8**. Alcohol **8** upon treatment with lead tetraacetate in toluene–acetic acid (4:1) at 0 °C for 8 h underwent an oxidative cleavage[8] to give a thioacetal acetate **9**. Hydrolysis of this acetate **9** with potassium hydroxide in methanol at room temperature gave a hemiacetal **10**. Oxidation of this hemiacetal **10** with chromic acid in aqueous sulfuric acid–acetone at 0 °C produced 2-methyl-2-phenylsuccinic anhydride (**11**), which upon hydrolysis with potassium hydroxide in refluxing methanol gave (*R*)-(−)-**12** ($[\alpha]^{20}_D$ −18.8° (*c* 3.5, EtOH), 94.0% ee)[7] (Scheme II). The reaction sequences starting with ethyl methyl ketone (**2b**) were successfully executed in the same way.

Addition of the α-carbanion of (R_S)-(+)-**1** (100% ee)[4] to **2b** gave (S_S)-**3b** in 72% yield (the diastereomers of **3b** (ratio 3:2) were unseparable). The thermal rearrangement of (S_S)-**3b** thus obtained was carried out by treatment with *p*-toluenesulfonic acid in refluxing benzene for 3.5 h to furnish a cyclobutene derivative (S_S)-**4b** in 65% yield. Reduction of the sulfoxide (S_S)-**4b** with acetyl chloride followed by hydrolysis of the enol thioether (−)-**5b**

(7) Abbayes, H.des.; Dabard, R. *Tetrahedron* **1975**, *31*, 2111.
(8) Trost, B. M.; Hiroi, K. *J. Am. Chem. Soc.* **1975**, *97*, 6911.

Scheme III



produced (*S*)-(−)-2-ethyl-2-methylcyclobutanone (**6b**). The absolute configuration and the enantiomeric excess of the product **6b** were determined as (S)-(−)-**6b** and 73.3% ee by transformation of **6b** into 4-methyl-4-hexanolactone (**13**) of known configuration;[9] Baeyer–Villiger oxidation of (−)-**6b** (H_2O_2–NaOH in aqueous methanol) followed by lactonization by heating in refluxing benzene with a catalytic amount of *p*-toluenesulfonic acid led to (*S*)-(−)-**13** ($[\alpha]^{23}_D$ − 6.3° (*c* 3.0, $CHCl_3$), 73.3% ee).[9]

On the basis of the above experimental results, the asymmetric inductions in these thermal 1,2-rearrangements of **3a,b** to **4a,b** were determined to give 94.0% and 73.3% optical yields, respectively.

From these stereochemical results, the mechanistic pathway for this asymmetric induction would be represented as follows. In the acid-catalyzed thermolysis, the carbonium ion **14** would be formed initially. The 1,2-migration of a carbon–carbon bond of the cyclopropane ring would occur via a transition state **15**, and a new asymmetry would be induced at this stage. The degree of asymmetric induction would depend on the difference between the thermodynamical stability of **15a** and **15b**, that is, on the difference of the steric interference between R^1 or R^2 and the lone pair or the oxygen atom of the chiral sulfoxide (Scheme III).

The easy access to the starting chiral sulfoxide and the high degree of asymmetric induction in this thermal rearrangement represent a potentially great advantage for the construction of asymmetric quaternary carbons. Furthermore, this method provides a facile entry to chiral cyclobutane derivatives, which have usually been hard to access.

(9) Mayer, H.; Schudel, P.; Ruegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 963.

Biosynthesis of the Modified Peptide Antibiotic Nosiheptide in *Streptomyces actuosus*

David R. Houck, Li-Chun Chen, Paul J. Keller, John M. Beale, and Heinz G. Floss*

Department of Chemistry, The Ohio State University Columbus, Ohio 43210

Received August 4, 1986

Nosiheptide (**1**),[1,2] a metabolite of *Streptomyces actuosus*, is a member of a broader class of highly modified, sulfur-rich peptide antibiotics, which also includes thiostrepton,[3] micrococcin,[4] the thiopeptins,[5] and several other compounds. Compound **1** inhibits protein synthesis in Gram-positive bacteria by binding to the 50S ribosomal subunit;[6] it is used as an animal-feed additive to increase weight gains.[7] Nosiheptide contains several structural elements

(1) Pascard, C.; Ducruix, A.; Lunel, J.; Prange, T. *J. Am. Chem. Soc.* **1977**, *99*, 6418 and references therein.
(2) Endo, T.; Yonehara, H. *J. Antibiot.* **1978**, *31*, 623.
(3) Anderson, B.; Crowfoot-Hodgkin, D.; Visuramitra, M. A. *Nature (London)* **1970**, *225*, 233.
(4) Walker, J.; Olesker, A.; Valente, L.; Ranabal, R.; Lukacz, G. *J. Chem. Soc., Chem. Commun.* **1977**, 706.
(5) Hensens, O. D.; Albers-Schönenberg, G. *J. Antibiot.* **1983**, *36*, 814.
(6) Cundliffe, E.; Thompson, J. *J. Gen. Microbiol.* **1981**, *126*, 185.
(7) Benzaet, F.; Cartier, M.; Florent, J.; Godard, C.; Jung, G.; Lunel, J.; Maney, D.; Pascal, C.; Renaut, J.; Tarridec, P.; Theilleux, J.; Tissier, R.; Dubost, M.; Ninet, L. *Experientia* **1980**, *36*, 414.

0002-7863/87/1509-1250$01.50/0

Table I. ^{13}C NMR Assignments and ^{13}C Enrichments in **1** Derived from ^{13}C-Labeled Precursors

^{13}C chem shift,[b] ppm	assignment	^{13}C enrichments,[a] % J_{cc} in **1** derived from			
		DL-[3-^{13}C]cysteine	L-[CH_3-^{13}C]methionine	L-[3-^{13}C]serine	DL-[1-^{13}C]serine
12.23	Indole-CH_3 (C-3′)			2.8	
29.49	Cys-C3	7.2			
65.90	Indole-CH_2O (C-4′)		28.6	3.4	
103.60	Deala-C3			6.7	
119.98	Thz(4)-C5	9.5		2.2	
124.45	Thz(2)-C5	9.9		2.9	
125.25	Thz(3)-C5	9.9		2.8	
125.98	Thz(1)-C5	8.1		2.4	
126.80	Thz(5)-C5	8.3		2.8	
127.12	Pyr-C4			3.3 (66 Hz)	
150.80	Pyr-C3			3.1 (66 Hz)	
142.52	Pyr-C6				3.6
158.20	Thz-CO				3.0
159.45	Thz-CO				2.4
159.60	Thz-CO				4.0
159.80	Thz-CO				3.9
163.85	Thz(1)-C2				6.3
165.00	Deala-CO				5.4
167.10	Thz(5)-C2				4.2
168.98	Thz(4)-C2				3.4
181.60	Indole-CO(C-2′)				6.2

[a] Signals of the other 30 carbons were not significantly enriched. [b] Signal assignments are based on chemical-shift theory, multiplicity, ^1H-^{13}C correlations, long-range couplings, NOE effects, and various other techniques. The four amide carbonyl groups at C-4 of the thiazole rings have not yet been differentiated.

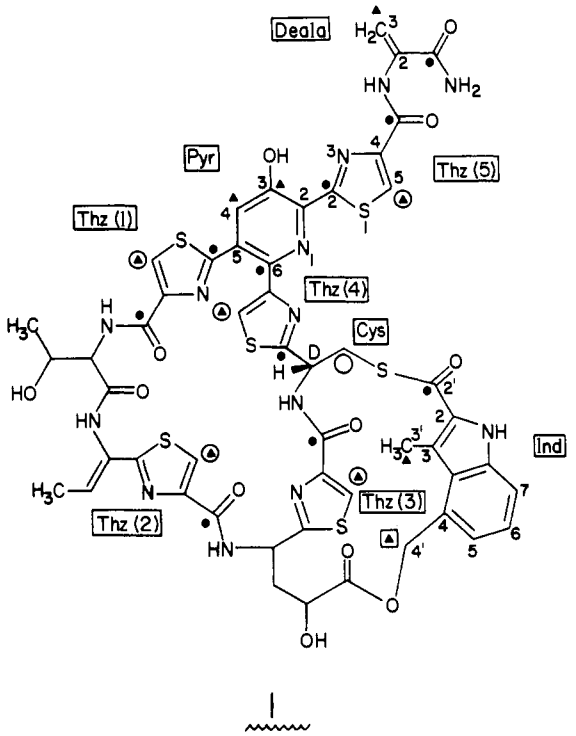


Figure 1. Structure of nosiheptide, including the sites of ^{13}C labeling from DL-[3-^{13}C]cysteine(○), L-[3-^{13}C]serine (▲), DL-[1-^{13}C]serine (•), and L-[methyl-^{13}C]methionine (□). Symbols are superimposed for carbons labeled by two precursors (◉ and ▣) in separate experiments.

with biosynthetic origins that were of interest to us, notably a 2,3,4-trisubstituted indole, five thiazole rings, and a trisubstituted pyridine.

Cultures[8] of *S. actuosus* were fed labeled substrates after 32 h of growth, and **1** was extracted from the mycelium 48–72 h later and purified (precipitation from tetrahydrofuran/hexane, CH_2Cl_2/EtOH, HPLC) for radioactivity (Beckman LS 7500) or ^{13}C NMR (Bruker WM-300, 7.1 T, Me_2SO-d_6) analysis. The

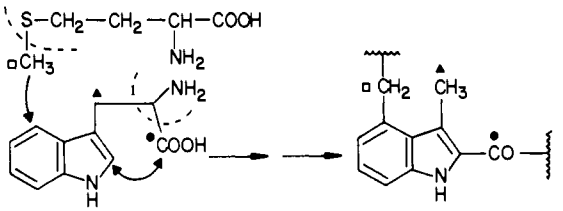


Figure 2. Biosynthetic origin of the indolic acid moiety of nosiheptide.

results of the stable isotope experiments are summarized in Table I and Figure 1.

The structure of the thiazole rings suggests origin from cysteine, which provides the sulfur, the nitrogen, C-5, C-4, and the attached carboxyl group; C-2 comes from the carboxyl group of another amino acid. Consistent with this notion, DL-[3-^{13}C]cysteine (97% ^{13}C, 50 mg/L) labeled C-5 of the thiazole rings. C-3 of the D-cysteine moiety was also labeled but not C-3 of the dehydroalanine portion. The latter is not derived from alanine (1.3% specific incorporation for L-[U-^{14}C]alanine vs. 37% for L-[U-^{14}C]serine). Its origin from serine is confirmed by labeling of C-1 from DL-[1-^{13}C]serine (99% ^{13}C, 200 mg/600 mL) and C-3 from L-[3-^{13}C]serine (93% ^{13}C, 126 mg/600 mL).

C-1 of serine, as expected, labeled the carboxyl carbons attached to C-4 of the five thiazole rings. One of these forms part (C-6) of the pyridine moiety. C-3 of L-serine labeled all the carbons enriched by C-3 of DL-cysteine except, notably, C-3 of the D-cysteine moiety. Since C-2 of the thiazole(4), the carboxyl carbon of this D-cysteine moiety, is labeled by DL-[1-^{13}C]serine, one must conclude that the D-cysteine moiety is efficiently derived from D- but not L-serine, presumably via D-cysteine. The pyridine ring is formed, rather uniquely, from the carboxyl group of one cysteine (C-6) and from two molecules of serine, which are connected "tail to tail", i.e., through their methylene carbons, to form the C-3/C-4 connectivity (Figure 2). The mechanism of this intriguing transformation will require further study.

Our initial working hypothesis for the origin of the indole moiety was cyclization of phenylalanine and methylation at C-3 and C-4. The observed labeling of both indole C-3′ and C-4′ by C-3 of serine is consistent with this idea.[9] However, L-[methyl-^{13}C]methionine (90% ^{13}C, 200 mg/L) labeled exclusively C-4′ and hence, only

(8) Cultures were grown in 40 mL of medium (4% glucose, 0.5% L-glutamate, 0.1% L-aspartate, 0.1% L-arginine, 0.2% Na_2SO_4, 0.1% $MgSO_4$, 0.05% K_2HPO_4, 0.3% $CaCO_3$, 0.001% $ZnSO_4$, 0.002% $FeSO_4$) in 250-mL Erlenmeyer flasks at 27 °C with rotary shaking (300 rpm).

(9) C-3 of serine gives rise, via the tetrahydrofolate pathway, to the methyl group of methionine.[10]

(10) Matthews, R. G. In *Folates and Pterins*; Blakely, R. L., Benkovic, S. J., Eds.; Wiley: New York, 1984; Vol. 1, pp 497–553.

the $-CH_2O$ group at indole C-4 is derived by methylation. It is noted, however, that the 2-carboxyl group of the indole moiety was labeled extensively by C-1 of serine. Since the alanine side chain of tryptophan is derived from L-serine,[11] this suggests that the indole moiety may arise by cyclization of tryptophan, connecting indole C-2 with the carboxyl group, followed by excision of the side-chain carbon atom 2 plus its attached nitrogen and methylation of indole C-4 (Figure 2). Consistent with this hypothesis, DL-[7a-^{14}C]tryptophan (0.5 mmol/L, 10% and 8% specific incorporation), L-[methylene-^{14}C]tryptophan (0.5 mmol/L, 7% and 12% specific incorporation) and [2-^{14}C]indole (1 mmol/L, 13 and 8% spec. incorp.) were efficiently incorporated into **1**. Nonincorporation of DL-4-methyl[methylene-^{14}C]tryptophan[12] suggests that methylation of the indole is not the first step in the reaction sequence.

On the basis of the above results and reasonable extrapolations, one may speculate that **1** arises from a dodecapeptide H_2N-L-Ser-L-Cys-L-Thr-(L?)-Thr-L-Cys-L-Glu-L-Cys-D-Cys-L-Cys-L-Ser-L-Cys-L-Ser-COOH through connection of the carbon atoms 3 of ser(3) and ser(12) and attachment of a (modified) tryptophan.

Acknowledgment. This work was supported by the National Institutes of Health (Grant AI 20264) and by Merck and Co. (paid leave of absence for D.R.H.). We also are grateful to Dr. J. Lunel of Rhone-Poulenc for providing samples of nosiheptide and the producing culture.

(11) Miles, E. W. *Adv. Enzymol.* **1979**, *49*, 127.
(12) Synthesized from 4-methylindole and $^{14}CH_2O$ via the gramine route.[13]
(13) Weygand, F.; Linden, H. *Z. Naturforsch., B: Anog. Chem., Org. Chem., Biochem., Biophys., Biol.* **1954**, *9*, 682.

Gas-Phase Observation and CO Substitution Kinetics of *cis*-$Cr(CO)_4(C_2H_4)_2$ by Time-Resolved IR Absorption Spectrometry†

Bruce H. Weiller‡ and Edward R. Grant*

Department of Chemistry, Purdue University
West Lafayette, Indiana 47907
Received September 11, 1986

Olefin complexes of metal carbonyl fragments have theoretical importance[1] and play a role in numerous catalytic systems.[2] Theory suggests an interesting trend in bond strengths for the bis-olefin and diene complexes of the 16-electron group VI (group 6) carbonyl fragments.[1d] Bis-olefin complexes of $M(CO)_4$ (M = Cr, Mo, W) are generally thought to be more stable than η^4-diene complexes. Experiments show that the mono- and bis-olefin complexes of molybdenum and tungsten carbonyls are quite stable[3] but such examples for chromium are rare. Only one $Cr(CO)_4(olefin)_2$ complex is known and it is stabilized by relief of ring strain in the uncomplexed olefin.[4] Interestingly, the analogous η^4 complexes of nonconjugated dienes are generally quite stable for all three rows of group VI (group 6).[5]

This paper reports the first gas-phase observation and infrared spectral characterization of $Cr(CO)_4(C_2H_4)_2$. This complex is unstable and reacts with CO by dissociative substitution. We follow the kinetics of this process by time-resolved IR absorption spectrometry, extracting a unimolecular decay constant orders of magnitude larger than the reported solution value for $Cr(CO)_4(\eta^4$-butadiene),[6] in an apparent conflict with elementary theory as cited above.

Our apparatus[7] and the technique of time-resolved IR absorption spectrometry as applied to organometallics[8] have recently

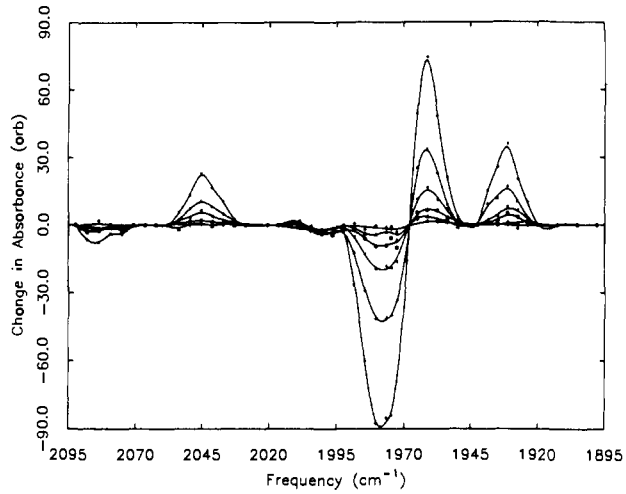


Figure 1. Transient IR absorption spectrum obtained following photolysis of a mixture of $Cr(CO)_5(C_2H_4)$ (0.12 torr), CO (0.56 torr), and C_2H_4 (500 torr). The initial spectrum (largest amplitude) corresponds to an observation time of 30 μs following the laser pulse. Subsequent spectra are separated in time by 13.7 ms. The instrumental resolution is 5 cm^{-1}.

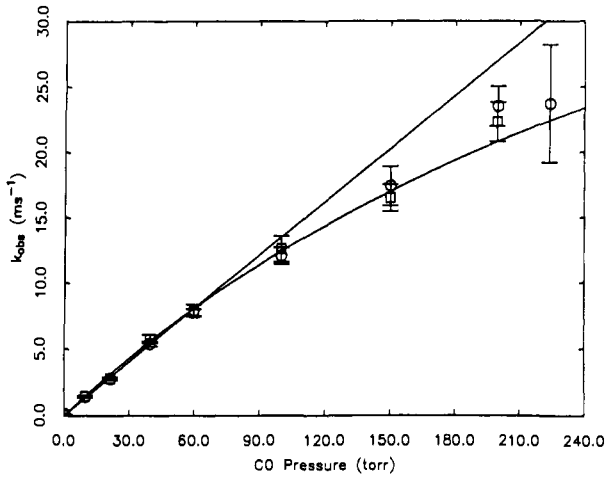


Figure 2. CO pressure dependence of k_{obsd} at 1975 (□) and 1961 cm^{-1} (○) for a constant C_2H_4 pressure of 300 torr. The straight line is the weighted fit to the data below 60 torr of CO. The curved line is the weighted nonlinear least-squares fit to all the data.

† In this paper the periodic group notation in parentheses is in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is eliminated because of wide confusion. Groups IA and IIA become groups 1 and 2. The d-transition elements comprise groups 3 through 12, and the p-block elements comprise groups 13 through 18. (Note that the former Roman number designation is preserved in the last digit of the new numbering: e.g., III → 3 and 13.)

‡ Present address: Argonne National Laboratory, Chemistry Division, Argonne, IL 60439.

(1) (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C79. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939. (c) Ittel, S. D.; Ibers, J. A. *Adv. Organomet. Chem.* **1976**, *14*, 33. (d) Elian, M.; Hoffmann, R. *Inorg. Chem.* **1975**, *14*, 1058. (e) Albright, T. A.; Hoffmann, R.; Thibeault, J. C.; Thorn, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 3801. (f) Rosch, N.; Hoffmann, R. *Inorg. Chem.* **1974**, *13*, 2656. (g) Stockis, A.; Hoffmann, R. *J. Am. Chem. Soc.* **1980**, *102*, 2952 and references therein. (h) Bachman, C.; Demuynck, J.; Veillard, A. *J. Am. Chem. Soc.* **1978**, *100*, 2366. (i) Basch, H.; Newton, M. D.; Moskowitz, J. W. *J. Chem. Phys.* **1978**, *69*, 584. (j) Swope, W. L.; Schaefer, H. F., III *Mol. Phys.* **1977**, *34*, 1037. (k) J. Garcia-Prieto and O. Novaro, Molec. Phys. 41, 205 (1980).

(2) (a) Parshall, G. W. *Homogeneous Catalysis*; Wiley: New York, 1980. (b) Moggi, L.; Juris, A.; Sandrini, D.; Manfrin, M. F. *Rev. Chem. Intermed.* **1981**, *4*, 171.

(3) Stolz, I. W.; Robson, G. R.; Sheline, R. K. *Inorg. Chem.* **1963**, *2*, 1264. Grevels, F. W.; Lindemann, M.; Benn, R.; Goddard, R.; Kruger, C. *Z. Naturforsch., B* **1980**, *35B*, 1298.

(4) Grevels, F. W.; Skibbe, V. *J. Chem. Soc., Chem. Commun.* **1984**, 681.

(5) (a) Bennett, M. A.; Pratt, L.; Wilkinson, G. *J. Chem. Soc.* **1961**, 2037. (b) Darensbourg, D. J.; Nelson, H. N., III; Murphy, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 896. (c) Fischer, E. O.; Frohlich, W. *Chem. Ber.* **1959**, *92*, 2995. (d) Bennett, M. A.; Wilkinson, G. *Chem. Ind.* **1959**, 1516. (e) Manuel, T. A.; Stone, F. G. A. *Chem. Ind.* **1959**, 1349. (f) Leigh, G. J.; Fischer, E. O. *J. Organomet. Chem.* **1965**, *4*, 461. (g) Zingales, F.; Conziani, F.; Basolo, F. *J. Organomet. Chem.* **1967**, *7*, 461. (h) Zingales, F.; Granziani, M.; Belluco, U. *J. Am. Chem. Soc.* **1967**, *89*, 256.

(6) Dixon, P. T. ; Burkinshaw, P. M.; Howell, J. A. S. *J. Chem. Soc., Dalton Trans.* **1980**, 2237.

(7) Weiller, B. H.; Grant, E. R., submitted for publication in *J. Am. Chem. Soc.*

0002-7863/87/1509-1252$01.50/0