## Concluding Remarks

We have been able to witness some interesting reactions of trifluoromethyl groups in heteroaromatic compounds with nucleophilic reagents. These results will assist understanding of other types of reactions of trifluoromethyl groups in organic chemistry and of the biochemical reactions of trifluoromethyl compounds, which now find some use in medicine. Concerning the latter point, Santi[20] recently proposed a mechanism for inhibition of thymidylylase by trifluorothymine, which is used as an antitumor agent, as shown in Chart IX. This mechanism is comparable to our type 3 mechanism of 3-(trifluoromethyl)quinoline (Chart II). Thus, the results of these experiments will help to understand the mechanisms of biological action, metabolism, and toxicity of some trifluoromethyl compounds.

(20) D. V. Santi and T. T. Sakai, *Biochemistry*, 10, 3598 (1971).

# Metal-Induced Rearrangements and Insertions into Cyclopropyl Olefins

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The birth of small-ring chemistry was both difficult and painstaking. Because of numerous failures, the great masters of the time, Victor Meyer, Emil Fischer, and Baeyer, were firmly persuaded that carbocycles with fewer than six carbon atoms in a ring could not be capable of existence. The major breakthrough in this area was due to Perkin who in 1883 furnished a general approach for the synthesis of three-, four-, and five-membered ring compounds.

Earlier, Meyer advised young Perkin to abandon the idea of trying to prepare small rings and "work at something more promising and more likely to give positive results".[1b]

Perkin's findings stimulated von Baeyer to consider the ease of formation of small-ring compounds. He reasoned that because of angle strain ease of ring formation should follow the order 3 < 4 < 5. This evolved in his "Spannungs Theorie",[1a] the now famous "strain theory".

Cyclopropane is a molecule of great interest, both experimentally and theoretically. A major advance in explaining bonding in this unusual molecule was made by Walsh[2] and by Coulson and Moffitt.[3]

The Walsh model of cyclopropane describes the higher occupied molecular orbitals (HOMO) as largely p orbital in character and suitable for overlap with adjacent $\pi$ electrons of a double bond, as in the case of vinylcyclopropane. In analogy with dienes, the interaction between the $\pi$ and $\sigma$ bonds could be detected by analysis of bond properties associated with either the central single bond (C2–C3) or the outer double bond (C1–C2) and the cyclopropane bond.[4,5]

The cyclopropane bonds are known to be weaker than normal $\sigma$ bonds and are consequently susceptible to attack by reagents which attack double bonds. An extra dimension was added to the similarity between cyclopropane and olefins when Tipper[6] reported that cyclopropane yields a dichloroplatinum complex (1)
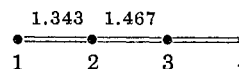


1
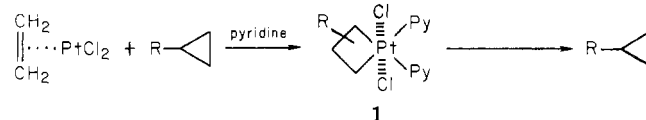
(1) (a) A. von Baeyer, *Ber.*, 18, 2278 (1885); (b) W. H. Perkin, *J. Chem. Soc.*, 1347 (1929).
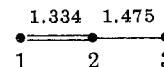
(2) A. D. Walsh, *Trans. Faraday Soc.*, 45, 179 (1949).

(3) C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, 40, 1 (1949).

(4) Electron-diffraction measurements [A. de Meijere and W. Luttke, *Tetrahedron*, 25, 2047 (1949)] indicate that the C2–C3 bonds both in butadiene
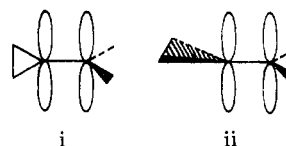


and in vinylcyclopropane



are significantly shorter than the normal $\sigma$ bond (1.522 Å), possessing 15 and 13% double-bond character, respectively.

(5) (a) MO calculations [P v. R. Schleyer and V. Buss, *J. Am. Chem. Soc.*, 91, 5880 (1969)] indicate extremes of stabilization of 9–26 kcal/mol between bisected (i) and perpendicular (ii) conformations. See also: J.



i                          ii

Wolf, P. G. Harch, R. W. Taft, and W. J. Hehre, *J. Am. Chem. Soc.*, 97, 2903 (1975); H. C. Brown and M. Ravindranathan, *ibid.*, 97, 2895 (1975), and references cited therein. (b) The $\pi,\sigma$ interaction detected in the vinylcyclopropanes is further manifested by their ability to enter into cycloaddition reactions with electron-deficient olefins and dienophiles [see (a) R. Askani and J. P. Chesick, *Chem. Ber.*, 106, 8 (1973); (b) S. Sarel, A. Felzenstein, and J. Yovell, *J. Chem. Soc., Chem. Commun.*, 753 (1974); 918 (1975); and references therein; *Tetrahedron Lett.*, 451 (1976); (c) S. R. Tanny and F. W. Fowler, *J. Org. Chem.*, 39, 2715 (1974); (d) A. Padwa and Carlsen, *J. Am. Chem. Soc.*, 97, 3862 (1975).

(6) G. F. H. Tipper, *J. Chem. Soc.*, 2045 (1955).

Shalom Sarel was born and educated in Jerusalem. He received the M.Sc. degree from the Hebrew University, and returned there as a member of the faculty in 1946 after earning the Ph.D. at the Daniel Sieff Institute in Rehovot with F. Bergmann. Following 2 years of postdoctoral work at Ohio State University with M. S. Newman, Professor Sarel was assigned, in 1956, to form a new Department of Pharmaceutical Chemistry at Hebrew University, which he now heads. His research interests center around strained small rings, organometallics, stereochemistry, and reaction mechanisms.

which was subsequently shown[7] to arise as a result of insertion of a $PtCl_2$ residue into a carbon–carbon bond.

The displacement reaction was shown[8] to depend on the electron-donor capacity of the cyclopropane ring and on the electrophilic nature of the $H_2PtCl_2$ residue.[9] This and the related reaction of cyclopropane with tetracarbonyldichlorodirhodium $[Rh(CO)_2Cl]_2$ which yields rhodacyclopentanone (**2**)[10] (a metal–acyl insertion



rhodacyclobutane
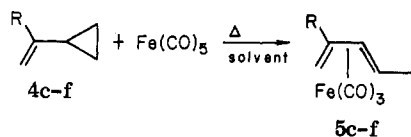


**2**

rhodacyclopentanone
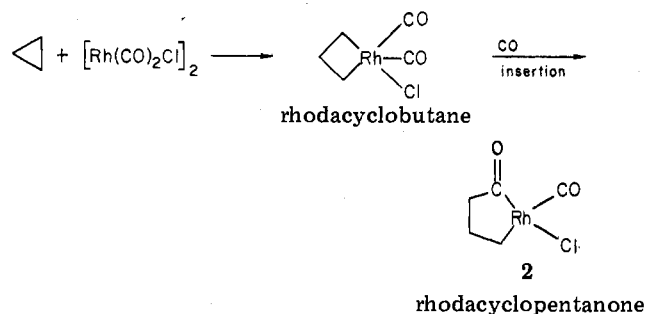
product) have become the precedents for a wide range of insertions and isomerizations of strained cyclohexenones.[11] They clearly indicate the polarizability of the cyclopropane $\sigma$ bonds, resulting in a tendency to undergo electrophilic attack by coordinatively unsaturated transition-metal species.[12]

From the dramatic developments in the field of diene–iron $\pi$ complexes initiated by Hallam and Pauson[13] arose the interesting question whether, in analogy to dienes, vinylcyclopropanes (VCP) can be induced to form VCP–iron $\pi$ complexes of structure **3** by zerovalent transition metals such as $Fe(CO)_5$. With this objective
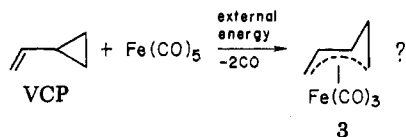


we initiated a study aimed at establishing whether, in analogy to 1,3-dienes, vinylcyclopropanes (VCP) could also provide a ligand of four $\pi$ electrons for metal coordination. Our studies led to the discovery of four distinctly different modes of metal-mediated reactions of VCP depending on substrate and reaction parameters. They are the following:

(a) heat-induced rearrangement of VCP to diene $\pi$ complexes[14]



**5c–f**

(b) photoinduced carbonyl insertions across the VCP system to form cyclohexenones ($4 \to 7 + 8$)[15]



**a**, $R = CH_3$; **b**, $R = C_2H_5$; **c**, $R = C_6H_5$; **d**, $R = p\text{-}ClC_6H_4$;
**e**, $R = p\text{-}CH_3OC_6H_4$; **f**, $R = $ cyclopropyl; **g**, $R = \alpha\text{-}C_4H_3S$

(c) metal insertion into the VCP system to form a $\sigma,$-$\pi$-allyl complex[16]



**9**, semibullvalene                **10**

(d) photoinduced acyl-metal insertions across the VCP system[17]



**11**, $\alpha$-thujene



**12**

In the course of these studies we became concerned with the problem whether divinylcyclopropanes and dicyclopropylacetylene could behave as six $\pi$-electron ligands for coordination with metal. We shall refer briefly to this later in the present Account.

## Vinylcyclopropane Diene Rearrangements

Our first endeavor in this field related to the exposure of para-substituted styrenes (**4c–e**) to the action of



**13**           **4c–e**           **5c–e**

**c**, $X = H$; **d**, $X = Cl$; **e**, $X = OCH_3$
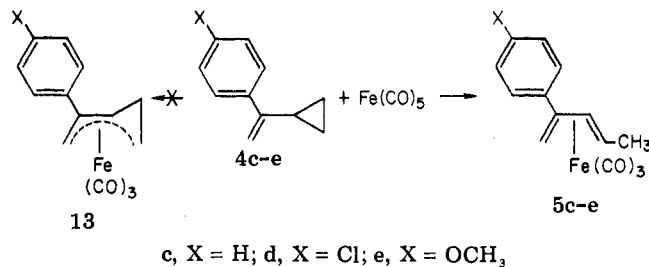
$Fe(CO)_5$ in high-boiling ethers. Study[14] has shown that the desired $VCP–Fe(CO)_3$ $\pi$ complex **13** could not be obtained. Instead, we were able to isolate (2-aryl-1,3-*trans*-pentadiene)iron carbonyl complexes (**5**) in 72–75% yield. Evidently, the cyclopropyl group of the substrate underwent (i) ring opening and (ii) hydrogen

(7) D. M. Adams, J. Chatt, R. G. Guy, and N. Sheppard, *J. Chem. Soc.*, 738 (1961); N. A. Bailey, R. D. Gillard, M. Keeton, R. Mason, and D. R. Russell, *Chem. Commun.*, 396 (1966); S. E. Binns, R. H. Cragg, R. D. Gillard, B. T. Heaton, and M. F. Pillbrow, *J. Chem. Soc. A*, 1227 (1969); J. A. McGinnety, *J. Organometal. Chem.*, **59**, 429 (1973).

(8) W. J. Irwin and F. J. McQuillin, *Tetrahedron Lett.*, 1937 (1968); D. B. Benson, *J. Organometal. Chem.*, **24**, 787 (1970).

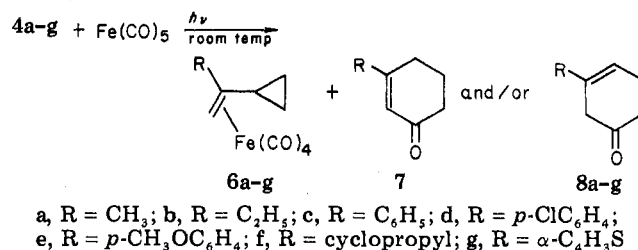(9) F. J. McQuillin and K. G. Powell, *J. Chem. Soc., Dalton Trans.*, 2123, 2129 (1972).

(10) D. M. Roundhill, D. N. Lawson, and G. Wilkinson, *J. Chem. Soc. A*, 845 (1968).

(11) L. Cassar and J. Halpern, *Chem. Commun.*, 1082 (1970); L. Cassar, P. E. Eaton, and J. Halpern, *J. Am. Chem. Soc.*, **92**, 3515 (1970); P. G. Gassman, T. J. Atkins, and F. J. Williams, *J. Am. Chem. Soc.*, **93**, 1812 (1971); **92**, 7631 (1970).
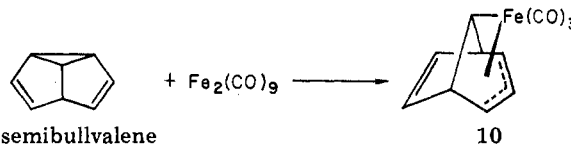
(12) For recent reviews see: (a) K. C. Bishop III, *Chem. Rev.*, **76**, 461 (1976); (b) A. P. Kozikowski and H. F. Wetter, *Synthesis*, 561 (1976).

(13) (a) B. F. Hallam and P. L. Pauson, *J. Chem. Soc.*, 642 (1958); (b) P. L. Pauson, "Organometallic Chemistry", Arnold, London, 1967.
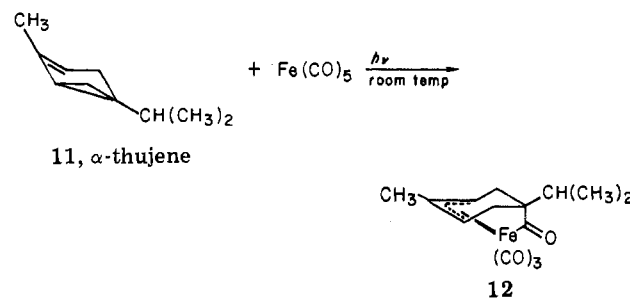
(14) (a) S. Sarel, R. Ben-Shoshan, and B. Kirson, *J. Am. Chem. Soc.*, **87**, 2517 (1965); (b) *Israel J. Chem.*, **10**, 787 (1972).

(15) (a) R. Ben-Shoshan and S. Sarel, *J. Chem. Soc., Chem. Commun.*, 883 (1969); (b) R. Victor, R. Ben-Shoshan, and S. Sarel, *Tetrahedron Lett.*, 4253 (1970).

(16) R. M. Moriarty, L. L. Yeh, and K. C. Ramey, *J. Am. Chem. Soc.*, **93**, 6709 (1971).

(17) The product from $\alpha$-thujene induced by $Fe(CO)_5$ photolysis [S. Sarel and G. Chriki, work to be published] is thermostable (mp 106–107 °C; IR $(C_6H_{14})$ 2005, 2020, 2080 $cm^{-1}$).

**Scheme I**
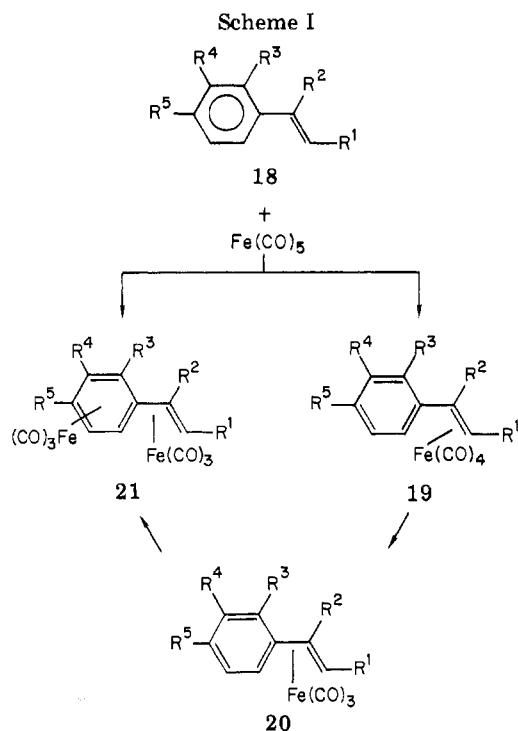


migration to form the 1,3-pentadienyl ligand with (iii) metal coordination. Significantly, the cis isomers of **5c–e** could not be isolated from these reactions, implying stereospecificity in either or in both modes of the ring opening and the hydrogen migration. These findings furnished the first examples where the VCP system behaves as a four π-electron ligand suitable for metal coordination. As a consequence, we wondered whether 1,1-dicyclopropylethylene (**4f**) would behave as a four or possibly as a six π-electron ligand.
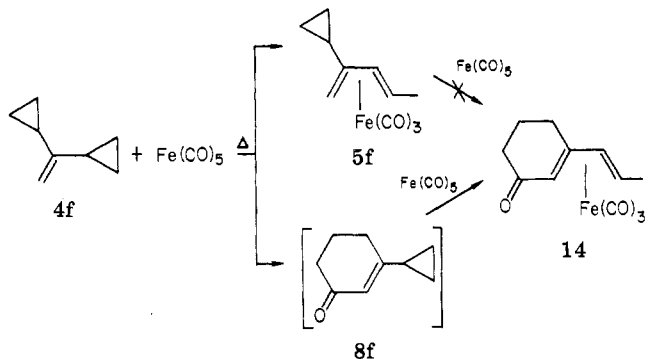


The Fe(CO)$_5$-mediated thermolysis of **4f** led to a quite unexpected product of structure **14** together with the respective diene π complex **5f**.[15a] Formation of **14** must have involved opening of one of the cyclopropyl groups, with carbon monoxide insertion across the homodienic system at some stage of the reaction. We were able to ascertain that this could not have occurred via **5f**, since its cyclopropyl residue proved to be inert to the action of Fe(CO)$_5$ even at elevated temperatures. By implication, the reaction was assumed to follow the route **4f → 8f → 14**. It was not possible however to test this experimentally due to stringent reaction conditions which did not allow isolation of unstable intermediates. We became therefore interested in exploring reaction conditions which could permit mechanistic studies. In this context the low-temperature irradiation of 4 seemed highly promising since the photolysis of Fe(CO)$_5$ could

generate the coordinatively unsaturated Fe(CO)$_4$ species[18] similar to that arising from Fe(CO)$_5$ thermolysis.

## Cyclohexenones from Photoreaction of VCP with Fe(CO)$_5$

The photolysis of a wide range of substituted VCP (**4a–g**) in the presence of a 5-fold excess of Fe(CO)$_5$ in
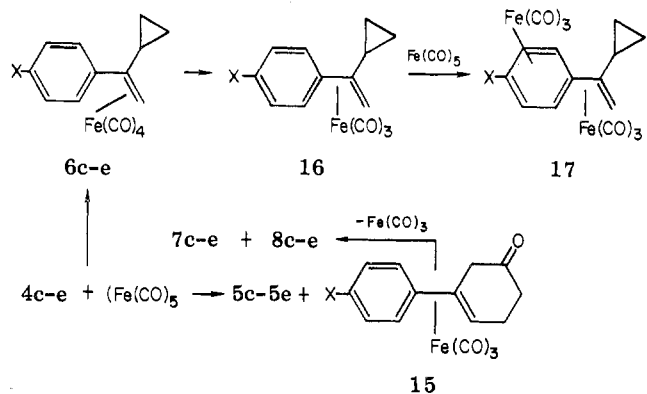


inert solvents at room temperature led to formation of the corresponding cyclohexenones (**7** and **8**) as the major products,[15b] together with minor quantities of π complexes of structure **6**. In the cases of α-cyclopropylstyrenes (**4c–e**) it was also possible to isolate unstable organometallic complexes of structure **15**, and stable complexes of structure **17** as minor products.[20]

(18) The photolysis of Fe(CO)$_5$ in low-temperature matrices was shown to give rise to reactive species such as Fe(CO)$_4$:[19]

$$\text{Fe(CO)}_5 \xrightleftharpoons[h\nu\,(\text{near-IR, vis})]{h\nu\,(\text{UV})} \text{Fe(CO)}_4 + \text{CO}$$
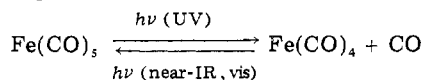
similarly to the species arising from Fe(CO)$_5$ thermolysis.

(19) M. Poliakoff and J. J. Turner, *J. Chem. Soc., Dalton Trans.*, 1351 (1973); 2276 (1974). See also: (a) J. J. Turner, J. K. Burdett, R. N. Perutz, and M. Poliakoff, *Pure Appl. Chem.*, **49**, 271 (1977); (b) E. A. K. von Gustorf, L. H. G. Leenders, I. Fischler, and R. N. Perutz, *Adv. Inorg. Chem. Radiochem.*, **19**, 65 (1976).

(20) Unlike vinylcyclopropane derivatives, cyclopropylbenzene (iii)
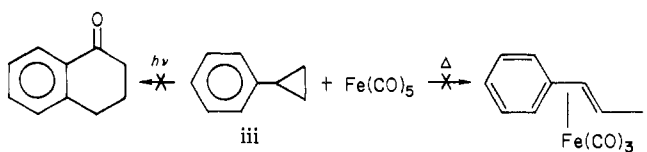


exhibits no tendency to react with Fe(CO)$_5$ either on thermolytic or on photolytic conditions [compare H. W. Voigt and J. A. Roth, *J. Catal.*, **33**, 91 (1974)]. Likewise, the prolonged photolysis of dicyclopropyl ketone (iv) in presence of Fe(CO)$_5$ failed to produce the corresponding unsaturated
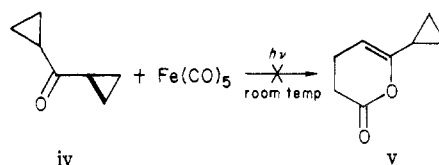


lactone v (unpublished results from this laboratory). These results indicate that the vinylic π electrons in the vinylcyclopropane systems serve as the initial site of coordination to iron from which the cyclopropane ring-opening follows. Analogously, the tendency of the aromatic double bonds in benzene to form diene–iron carbonyl complexes is remarkably enhanced upon introduction of vinyl groups which affords a more reactive center for initial metal complexes [see ref 22c and references therein cited]. The metal, then, is in an advantageous position to draw electrons from the benzene system for further coordination. The loss of benzene resonance is a prerequisite for the formation of diene–iron carbonyl type complexes [see (a) R. E. Davis and R. Pettit, *J. Am. Chem. Soc.*, **92**, 716 (1970); (b) F. H. Herbstein and M. G. Reisner, *J. Chem. Soc., Chem. Commun.*, 1077 (1972); *Acta Crystallogr., Sect. B*, **33**, 3304 (1977); (c) R. Victor, R. Ben-Shoshan, and S. Sarel, *Tetrahedron Lett.*, 4253 (1970)].

Yields of the corresponding cyclohexenones (**7** + **8**) increase on passing from **8a** (37%) to **8b** (50–60%) and decrease on going from **8c** (37%) to **8d–f** (25%) to **8g** (11%),[21] illustrating the range of sensitivity of the photochemical CO insertion to substitution factors.

Of particular interest are the minor products arising from coordination of the metal to eight π electrons of the styrenes, yielding the two novel types of iron tricarbonyl π complexes: the monoiron tricarbonyl π complex **16** and the bis(iron tricarbonyl) complexes **17**. The former was shown to originate photochemically from **6** and its remaining four π electrons were shown to react further with Fe(CO)₅ to produce a second diene π complex (**17**), leaving the cyclopropyl group intact.

More detailed study has shown that the photoreaction of substituted styrenes devoid of cyclopropyl groups at the α position (**18**) gives rise to three distinctly different types of metal π complexes in which the metal coordinates (i) to two (**19**), (ii) to four (**20**), and (iii) to eight electrons (**21**) of the eight π-electron system in the vinylbenzene.[22] The reaction was found to be general for alkyl or aryl substitution at α and β positions ($R^1$ and $R^2$) and on the phenyl ring at positions 2, 3, and 4 of the styrene skeleton (see Scheme I).[22c]

From conformational considerations we had deduced that the photoreaction of the spiro compound **22** should
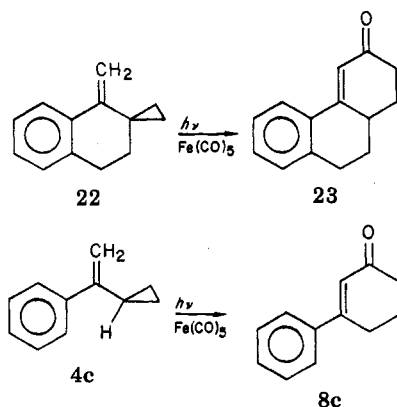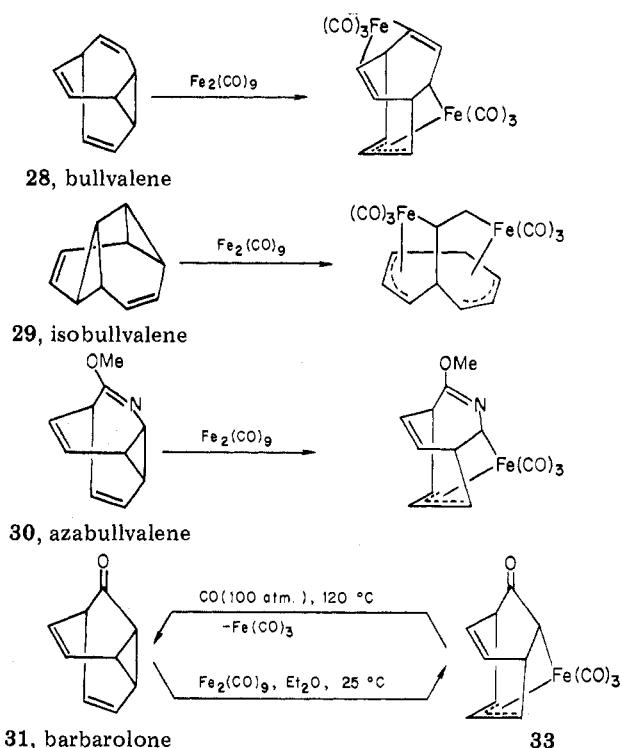


result in higher yield of the carbonyl insertion product (**23**) as compared to a similar reaction with its unbridged form (**4c → 8c**). Indeed, the observed yield of **23** was 75–80% as compared to 37% in the case of **8a**, manifesting the importance of conformational effects on the ease of cyclohexenone formation.[23]

This was not, however, the case with the dispiro-[2.1.2.3]decane **24** (the bridged form of **4f**) which yielded, as a major product, a tricarbonyliron σ,π complex of structure **25** of remarkable chemical stability. A minor product of this reaction was the carbonyl insertion product **26**, leaving the second cyclopropyl group intact. The latter could be induced by Fe(CO)₅ to rearrange to the diene π complex (**27**) but *not* to σ,π-allyl complex (**25**).[24]

The striking chemical stability of **25** resembles very closely that of the σ,π-allyl complexes resulting from the action of Fe₂(CO)₉ on cyclopropane-containing
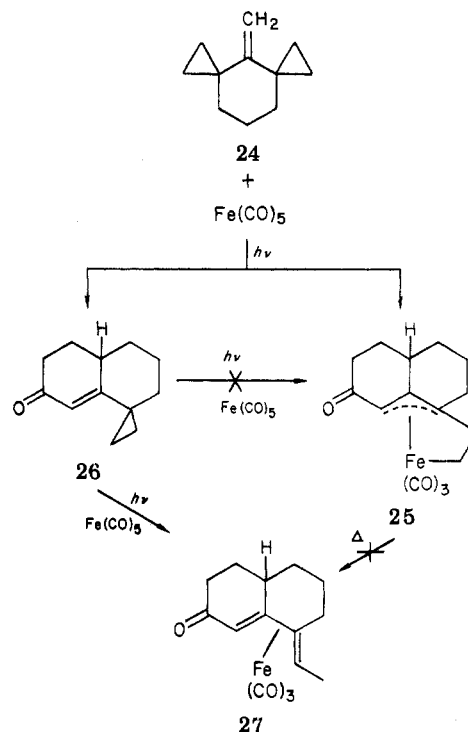


polycyclic olefins such as semibullvalene (**9**),[25] bullvalene (**28**),[26] isobullvalene (**29**),[26] azabullvalene (**30**),[27]



barbarolone (**31**),[28] and homosemibullvalene (**32**).[29]

(21) R. Victor, R. Ben-Shoshan, and S. Sarel, results to be published.

(22) (a) R. Victor, R. Ben-Shoshan, and S. Sarel, *Tetrahedron Lett.*, 4253 (1970); (b) *Chem. Commun.*, 1680 (1970); (c) *J. Org. Chem.*, **37**, 1930 (1972).

(23) S. Sarel and S. Blum, results to be published.

(24) S. Sarel, A. Felzenstein, R. Victor, and J. Yovell, *J. Chem. Soc., Chem. Commun.*, 1025 (1974).

(25) (a) B. F. C. Johnson, J. Lewis, and S. W. Tamm, *J. Organometal. Chem.*, **105**, 271 (1973); (b) S. W. Tamm, *Tetrahedron Lett.*, 2385 (1974); (c) R. M. Moriarty, L. L. Yeh and K. C. Ramey, *J. Am. Chem. Soc.*, **93**, 6709 (1971); R. M. Moriarty, C. L. Yeh, K. N. Chen and R. Srinivasan, *Tetrahedron Lett.*, 5325 (1972); R. M. Moriarty, C. L. Yeh, K. N. Chen, E. L. Yeh, K. C. Ramey and C. W. Jefford, *J. Am. Chem. Soc.*, **95**, 4756 (1973); R. M. Moriarty, K. N. Chen, C. L. Yeh, J. L. Flippen and J. Karle, *ibid.*, **94**, 8944 (1972).

(26) R. Aumann, *Angew. Chem., Int. Ed. Engl.*, **10**, 188, 189, 190 (1971).

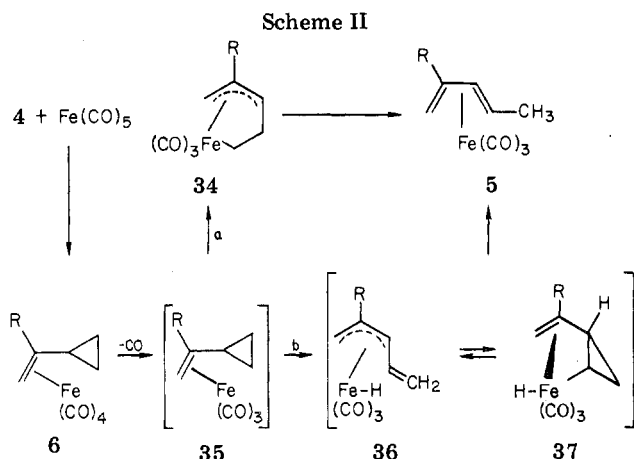(27) Y. Becker, A. Eisenstadt, and Y. Shvo, *Chem. Commun.*, 1156 (1972).

(28) (a) A. E. Eisenstadt, *Tetrahedron Lett.*, 2005 (1972); (b) *J. Organometal. Chem.*, **60**, 335 (1973); (c) B. F. G. Johnson, J. Lewis, D. J. Thompson, and B. Heal, *J. Chem. Soc., Dalton Trans.*, 1268 (1975).

**Scheme II**



In contrast to **28–33** in which the bridgehead hydrogens are structurally precluded from undergoing a shift because this would lead to anti-Bredt bridgehead olefins, there is no obvious reason why the $\sigma,\pi$-allyl complex **25** could not be induced to rearrange into the diene $\pi$ complex **27**. The $\sigma,\pi$-allyl complex from the parent vinylcyclopropane (**34**, R = H) was reported to collapse readily into the respective isomers of 1,3-pentadiene $\pi$ complex (**5h**, R = H).[30]
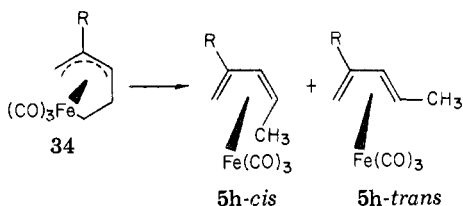


## Mechanism of Vinylcyclopropane–Diene Rearrangement

The Fe(CO)$_5$-mediated (**4 → 5**) conversions entail: (i) fission of one $\sigma$ bond coupled with (ii) 1,2-hydrogen shift, and (iii) stereoselective formation of a new $\pi$ bond with metal coordination to the resulting dienic system. This can be rationalized in terms of two alternative mechanisms: (a) and (b), which involve the participation of the metal as delineated in Scheme II.

The reaction is envisioned to arise from complexation of the metal to the vinylic double bond to form first the (ligand)tetracarbonyliron **6** which, on losing carbon monoxide, gives the coordinatively unsaturated complex **35**, tending to undergo cyclopropane ring opening with hydrogen migration.[20] Pathway a implies metal-promoted rupture of the cyclopropane ring with formation of one $\pi$-allyl and one $\sigma$ bond attached to the metal (**35 → 34**). In the absence of stabilizing features the latter (**34**) rearranges to the more stable diene $\pi$-complex **5** via hydrogen migration to the terminal $\sigma$-bonded carbon atom.[14] Pathway b suggests a hydrogen shift to the metal upon cyclopropane ring opening with formation of a $\pi$-allyl hydride intermediate (**36**). The latter could also rearrange into **37**, a hydride complex containing $\pi$ and $\sigma$ components. Transformation of **36** to **5** involves: (i) the shift of metal-bonded hydrogen to the terminal olefinic carbon with (ii) the concomitant shifting of the uncomplexed

double bond.[14b,31] On the other hand, transformation of **37** to **5** should involve: (i) ring opening at the bond across the ring with (ii) transfer of the hydrogen from the metal to the terminal carbon atom $\sigma$-bonded to the metal.[32] The driving force in either mode evidently springs from stability of the diene $\pi$ complex **5**.

## $\pi$-Allyl–Acyl Complexes

In parallel to the conversion, **22 → 23**, high yields of the conjugated enone **39** were obtained from the
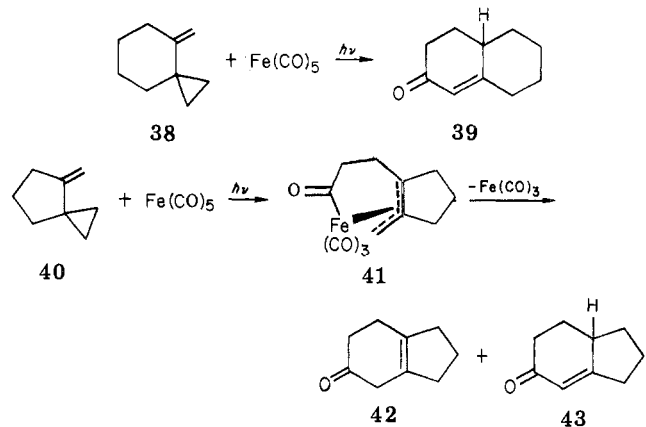


metal-mediated photolysis of **38**.[24,33] Unlike the latter, the photoreaction of the lower homologue **40** led to isolation of an air-sensitive metal–acyl–$\pi$-allyl complex of structure **41**, exhibiting high tendency to lose Fe(CO)$_3$, producing a 1:4-mixture of **42** and **43**, respectively.

In contrast to **22, 38,** and **40**, the planes of the double bond and of the cyclopropane rings in bicyclo[3.1.0]-hex-2-ene (**44**) and in $\alpha$-thujene (**11**) do not assume the
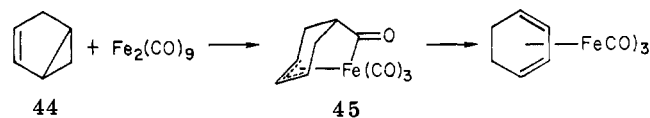
(29) B. F. G. Johnson, J. Lewis, D. L. Thompson, and V. Heill, *J. Chem. Soc., Dalton Trans.*, 567 (1975), observed that the $\sigma,\pi$-allyl complex **33** could be converted in 93% yield back to barbarolone **31**, demonstrating the reversibility of this reaction.

(30) R. Aumann, *J. Am. Chem. Soc.*, **96**, 2631 (1974).

(31) Pathway b bears analogy to related hydrogen transfers in iron-carbonyl complexes [see W. T. Hendrix, F. G. Cowherd, and J. L. von Rosenberg, *Chem. Commun.*, 97 (1968), and references cited therein] first suggested by C. H. DePuy, V. M. Kobal, and D. H. Gibson, *J. Organometal. Chem.*, **13**, 266 (1968), and favored by T. Katz and S. A. Cerefice, *J. Am. Chem. Soc.*, **93**, 1049 (1971).

(32) The ring opening in the path **35 → 36 → 37 → 5** bears analogy to the case of metal-induced cleavage of the cyclopropane during hydrogenation [see (a) F. D. Mango, *Adv. Catal.*, **20**, 291 (1969); (b) R. Pettit, H. Sugahora, J. Wristers, and W. Merk, *Discuss. Faraday Soc.*, **71** (1969); (c) F. D. Mango and J. H. Schacht-Schneider, *J. Am. Chem. Soc.*, **89**, 2484 (1967); (d) J. A. Roth, *ibid.*, **92**, 6658 (1970)]. Neither of these pathways (a or b) could be applied to the [Rh(CO)$_2$Cl]$_2$-induced rearrangement of the vinylcyclopropane moiety in 7-vinylbicyclo[4.1.0]heptanes which gives rise to unconjugated 1,4-diene rather than to conjugated 1,3-dienes. Compare R. G. Salomon, M. F. Salomon, and L. C. Kachinski, *J. Am. Chem. Soc.*, **99**, 1043 (1977).

(33) The $\sigma,\pi$ system in **38** appears to be highly sensitive to substitution effects. The inclusion of electron-withdrawing groups such as CN on either the cyclopropane ring (vi) or on the terminal olefinic carbon (vii) endows
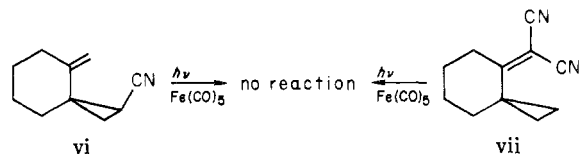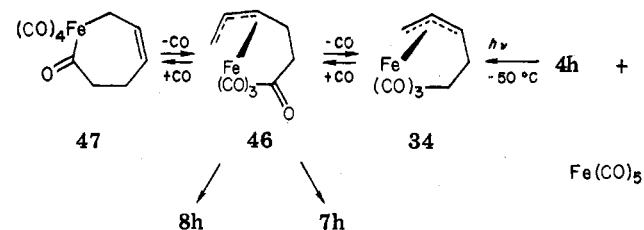
the small ring resistance to attack by Fe(CO)$_5$ on photochemical conditions (unpublished results from this laboratory). In general, the inclusion of electron-withdrawing groups should enhance the reactivity of the cyclopropane ring to nucleophilic attack and favor interaction with metals in low oxidation states [see K. G. Powell, F. J. McQuillin, *Tetrahedron Lett.*, 3313 (1971); *Chem. Commun.*, 931 (1971)]. The lack of reactivity of Fe(CO)$_5$ toward **38a** is at variance with the conclusion derived from substitution effects on the reactivity of cyclopropane–platinum(II) complexes (see ref 25a,b).

**Scheme III**
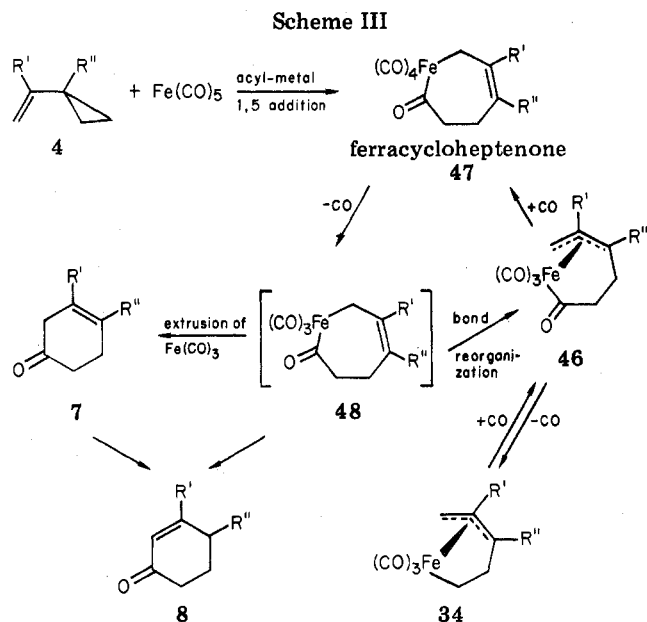


energetically most favorable bisecting conformation. The photolyses of either $44$[34] or $11$[17] did not lead to carbonyl insertions but rather to acyl–metal insertions affording metal–acyl–$\pi$-allyl complexes of considerable chemical stability, $45$ or $12$.[35]

Of particular interest is the finding that the photoreaction of $11$ occurs in both a stereospecific and a regiospecific manner. The site of attachment of the acyl–metal residue onto the vinylcyclopropane moiety of $\alpha$-thujene occurs at the highly branched cyclopropane carbon bearing the isopropyl group, whereas the metal coordination occurs at the less hindered site adjacent to the $\pi$-electron system. More examples of acyl–metal insertions into VCP systems are accumulating.[36,37]

In the low-temperature ($-50$ °C) photolysis of $4h$ in the presence of $Fe(CO)_5$, it was possible to show that under high pressure of CO the $\sigma,\pi$-allyl complex $34$



successively inserts two CO molecules to form the ferracycloheptenone $47$. This follows the sequence $34 \rightarrow 46 \rightarrow 47$, and $46$ easily loses $Fe(CO)_3$ to yield cyclohexenones ($7h$, $8h$).

## Mechanism of Carbonyl Insertion

To encompass all the data now at hand, a mechanism for the reaction path to cyclohexenones is delineated in Scheme III. Unlike the concurrent path leading to diene $\pi$ complexes, the carbonylation path can be viewed to arise from an oxidative cycloaddition of an iron carbonyl bond [Fe=C=O] to the conjugated $\sigma,\pi$ electrons of the vinylcyclopropane system[5b] to form a labile, spectroscopically identifiable metallacyclic species of the ferracycloheptenone structure $47$.[38a] The latter is postulated to lose reversibly carbon monoxide to give a nonisolable, coordinatively unsaturated metallacycloalkenone ($48$). This can be stabilized by undergoing either (i) bond reorganization into an isolable, coordinatively saturated species of the acyl–$\pi$-allyl structure $46$[38b] or (ii) cyclization with expulsion of iron to yield the products $7$ and/or $8$. The $\sigma,\pi$-allyl species $46$ could also reversibly lose carbon monoxide to yield the isolable, well-characterized $\sigma,\pi$-allyl iron tricarbonyl complex $34$.[38b] The initial stage $4 \rightarrow 47$ resembles in pattern the "homodienic reaction" in which iron pentacarbonyl appears as a genuine "homodienophile"[39] featuring high stereo- and regiospecificity, and the vinylcyclopropane system provides a novel source of four $\pi$ electrons for metal coordination.

## Cyclooctadienones from Divinylcyclopropanes

The divinylcyclopropane units in the spiro[2.x]alkanes of structure $49$ (where $n$ equals 1, 2, and 3) were

(38) (a) Although the parent ferracycloheptanone $47$ could not be isolated from the exposure of $46$ to the action of carbon monoxide at high pressure,[30] due to its instability, its formation could be deduced however from NMR and IR spectroscopy [2066, 2064, 2008, 2005 cm$^{-1}$ (Fe–CO) and 1665 cm$^{-1}$ (C–CO)]. (b) The acyl–metal complex $46$, exhibiting IR absorptions at 2064, 2005 (Fe–CO), and 1665 cm$^{-1}$ (C–CO), readily loses CO to yield the $\sigma,\pi$-allyl species $34$ (2053, 1994, and 1989 cm$^{-1}$ (Fe–CO)].[30] (c) The formation of rhoda-$\beta$-tetralone species [xi, IR 1700 and 2050 cm$^{-1}$; $\delta$ 2.28 and 2.37 (s)] was observed by R. F. Heldeweg and H. Hogeveen, *J. Am. Chem. Soc.*, **98**, 6040 (1976), in the course of rhodium-catalyzed insertion of carbon monoxide across the diene x with formation of five-membered ring ketone xii. (d) To explain the formation of the cyclohexenones (xvi, R = CH$_3$; C$_2$H$_5$) from the photoreaction of norbornadiene and alkyl propiolates in presence of Fe(CO)$_5$, K. Hayakawa and H. Schmid, *Helv. Chim. Acta*, **60**, 2160 (1977), invoked the intermediacy of the ferracyclohexene species xv.



x    xi



xii

(39) It is widely believed [see E. W. Abel and F. G. A. Stone, *Q. Rev. Chem. Soc.*, **23**, 325 (1969)] that the bonding between CO and a metal is a combination of $\sigma$ and $\pi$ bonding as diagrammed in xiii.
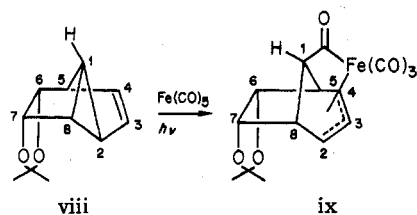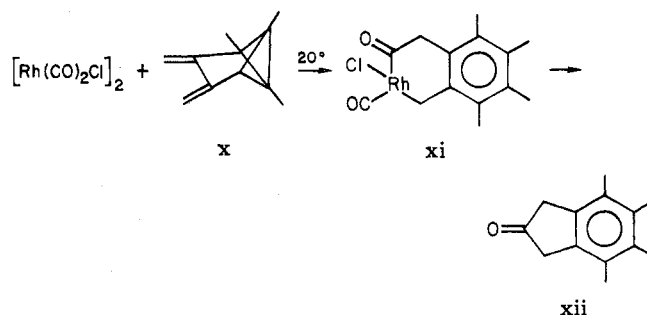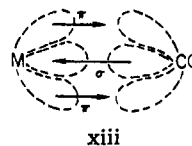


xiii

(34) R. Aumann, *J. Organometal. Chem.*, **47**, C29 (1973).

(35) In contrast to $44$, which was reported[34] to decompose thermally to yield cyclohexadiene, neither diolefin nor a bicyclic enone could be obtained from thermolysis of $12$.[17]

(36) (a) R. M. Moriarty and co-workers, *J. Am. Chem. Soc.*, **96**, 3661 (1974); (b) P. Eilbracht, *Chem. Ber.*, **109**, 1429, 3136 (1976).

(37) The Fe(CO)$_5$-mediated photochemical acyl–metal insertion (viii → ix) across the vinylcyclopropane system in the acetonide of *endo*-6,7-dihydroxy-6,7-dihydrosemibullvalene (viii) was shown by H. D. Scharf

viii    ix

and J. Mattay, *Tetrahedron Lett.*, 401 (1977), to occur from the exo side, opposite to the acetonide group. The acyl–metal residue is attached to C-1 in viii and the metal coordination occurs at the side adjacent to the $\pi$-electron system with rupture of the 1,2 $\sigma$ bond in viii.

shown to undergo a ready 1,7 cycloaddition with tetracyanoethylene (TCNE) to yield the bicyclic system containing a cyclononadiene unit.[40]  Another type of 1,7 cycloaddition of carbon monoxide across the vinylcyclopropane system in 49 was discovered when the



**49**

**50**

$$[C_{n+10}H_{2n+14}Fe_2(CO)_6]$$
$$+ [C_{n+10}H_{2n+14}Fe_2(CO)_3] +$$
$$n = 1, 2, 3$$

**51**
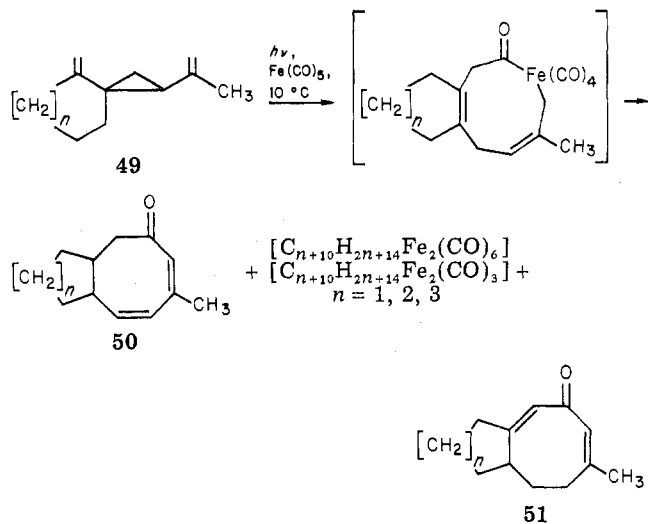
latter were photolyzed in the presence of $Fe(CO)_5$. It furnished novel examples of bicyclic systems 50 and 51 which contain cyclooctadienone units.  They are assumed to be formed via insertion of an acyl-metal entity across the divinylcyclopropane system to yield a ferracyclononadiene species which upon subsequent losses of carbon monoxides and $Fe(CO)_3$, coupled with $Fe(CO)_5$-induced double-bond migration, furnishes the isomeric cyclooctadienones.  This demonstrates the ability of the divinylcyclopropane system to act as a six $\pi$-electron donor ligand in organometallic reactions.[41,42]

### Dicyclopropylacetylene as a Multi-$\pi$-Electron Ligand

Adding extra unsaturation to the original C–C $\pi$ linkage in VCP was shown to render the cyclopropyl group inert to attack by iron carbonyls.  The photoreaction of cyclopropylacetylene (52) with $Fe(CO)_5$ gave



**52**

**53**                    **54**
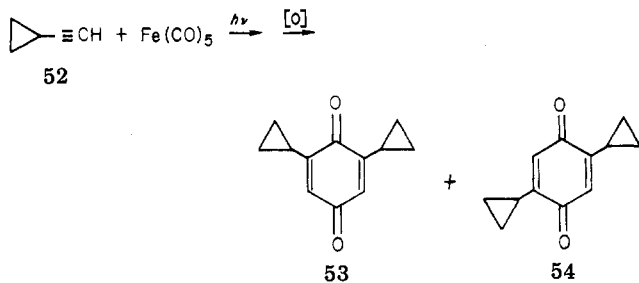
(40) S. Sarel and M. Langbeheim, *J. Chem. Soc., Chem. Commun.*, 593 (1977), have shown that the TCNE adducts had the structure:
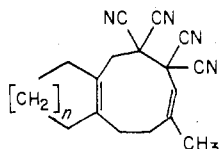


(41) S. Sarel and M. Langbeheim, *J. Chem. Soc., Chem. Commun.*, 827 (1977).
(42) For discussion of the metal-catalyzed Cope rearrangement, see V. Aris, J. M. Brown, J. A. Conneely, B. T. Golding, and D. H. Williamson, *J. Chem. Soc., Perkin Trans. 2*, 4 (1975).

rise to precursors of the dicyclopropylbenzoquinones 53 and 54 originating from the insertion of carbonyls between the molecules of acetylene while leaving the cyclopropane ring itself intact.[43]

In contrast to 52, the photoreaction of dicyclopropylacetylene (55) with iron carbonyl was found to take a number of pathways yielding some ten different



**56**            **57***            **58**

**55**

**59a**                    **59b**
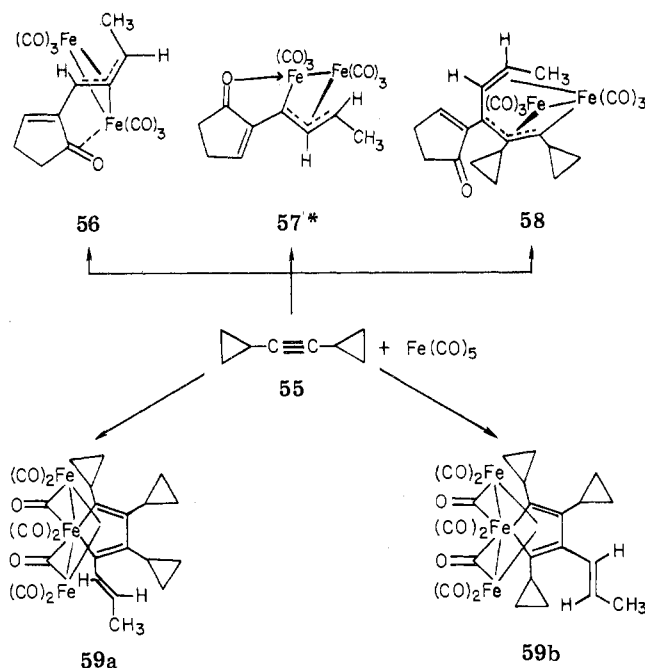
products, depending upon the reagent and the reaction conditions.  Of particular interest are the complexes of types $56 \rightarrow 59$ which emerged from the photoreaction of 55 with $Fe(CO)_5$ in solution[44] and which illustrate the propensity of the multi-$\sigma,\pi$-electron system to enter into a novel carbonyl insertion with ring opening to afford cyclopentenones.  These complexes find models in the above described reactions of VCP with $Fe(CO)_5$.  In analogy to 1,1-dicyclopropylethylene (4f), the opening of one of the cyclopropane rings in 55 has been coupled with carbonyl insertion, leading to cyclopentenone formation, while the opening of a second ring occurs with a hydrogen shift and metal coordination to the resulting open chain.  Unlike the $4f \rightarrow 7f + 8f$ conversion, the $55 \rightarrow 56$–$59$ process gives rise to a five-membered ring rather than to a six-membered one.  Indeed, the dicyclopropylacetylene system emerged as a novel donor of six $\pi$ electrons for coordination with metals.

### Conclusion

In the final analysis, the various modes of reaction of vinylcyclopropanes with $Fe(CO)_5$ spring from two distinctly different reaction routes which could be labeled the $\pi$ and the $\sigma,\pi$ routes.  In the "$\pi$ route" the vinylic $\pi$ electrons of the VCP system serve as the initial site of coordination to iron from which follows cyclopropane ring opening with hydrogen migration to generate diene $\pi$ complexes.  The "$\sigma,\pi$ route" involves interaction between the $\sigma,\pi$ electrons of the homodienic

(43) R. Victor, R. Ben-Shoshan, and S. Sarel, *Tetrahedron Lett.*, 4211 (1973).
(44) R. Victor, V. Usieli, and S. Sarel, *J. Organometal. Chem.*, **129**, 387 (1977).

system with the $\pi$ electrons of the Fe–C bond to form a ferracycloalkenone adduct from which follow generation of acyl $\pi$ complexes, $\sigma,\pi$-allyl complexes, and/or cycloalkenones.

Thus, iron pentacarbonyl emerged as a genuine and most efficient "homodienophile" of remarkable stereospecific and regiospecific characteristics. Vinylcyclopropanes and divinylcyclopropanes, on the other hand, emerged as novel sources of four and six $\pi$ electrons suitable for metal coordination.

The novel features characterizing the interaction between zerovalent transition-metal and multi-$\sigma,\pi$-electron systems opens a new vista of chemical research of great synthetic interest.

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# Platinum Complexes: Probes of Polynucleotide Structure and Antitumor Drugs

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The study of biological macromolecules is facilitated by the attachment of metal ions that serve to probe their structures and dynamic properties. Examples include paramagnetic shift reagents,[1] fluorescent probes,[2] and energy-transfer donor–acceptor metal ion pairs.[3] Metal ions may serve[4] as substitution probes, illustrated by the replacement of zinc in metalloenzymes with magnetically and spectroscopically more rich metals such as cobalt or copper,[5] or as addition probes, exemplified by the use of electron-dense metals to assign phases during protein x-ray crystal structure determinations.[6] Heavy metal reagents may also be employed as electron microscope stains. A long-standing objective has been to sequence DNA by first attaching a heavy metal to a base-specific site in the polymer, for example all the guanine residues, and then to read the positions of the labeled bases along the polymer chain by electron microscopy.[7] Successive application of this method to other bases would provide the entire sequence.[8]

Platinum complexes offer certain advantages as biological probe reagents. They are moderately soluble in water, are kinetically stable, and, unlike some earlier third-row transition metals, do not form insoluble hydrated oxides at neutral pH. The known chemistry of platinum in the +2 and +4 oxidation states is extensive,[9] and it is now relatively easy to design and synthesize complexes having desired properties. Platinum also appears to be better behaved in the electron microscope than other heavy metals, notably mercury.

Interest in the aqueous chemistry of platinum and its binding to polynucleotides was greatly aroused by the discovery that *cis*-dichlorodiammineplatinum(II), DDP,

has antitumor properties.[10] This simple compound, which has no carbon atoms, is currently used in many hospitals throughout the world in the treatment of ovarian, testicular, and other forms of cancer.[11] Although studies have shown that DDP inhibits DNA synthesis,[12] the primary site of action in the cell is unknown. Nevertheless, attention has focused on platinum–DNA interactions about which there now exists a substantial and still growing body of knowledge.

Three specific themes will be discussed in this Account. Connecting these themes is the basic coordination chemistry of platinum, an essential ingredient in each. The major objectives are (1) to sequence polynucleotides by electron microscopy following heavy metal attachment at base-specific sites and (2) to understand the mode of action of the antitumor platinum drugs. As with the Holy Grail of medieval

(1) (a) K. G. Morallee, E. Nieboer, F. J. C. Rossotti, R. J. P. Williams, A. V. Xavier, and R. A. Dwek, *Chem. Commun.*, 1132 (1970); (b) C. R. Jones and D. R. Kearns, *J. Am. Chem. Soc.*, 96, 3653 (1974).

(2) J. M. Woolfson and D. R. Kearns, *Biochemistry*, 14, 1437 (1975).

(3) W. DeW. Horrocks, Jr., B. Holmquist, and B. L. Vallee, *Proc. Natl. Acad. Sci. U.S.A.*, 72, 4764 (1975).

(4) S. J. Lippard, *Prog. Inorg. Chem.*, 18, vi (1973).

(5) B. L. Vallee, J. F. Riordan, J. T. Johansen, and D. M. Livingston, *Cold Spring Harbor Symp. Quant. Biol.*, 36, 517 (1971).

(6) R. H. Stanford, Jr., and R. B. Corey in "Structural and Molecular Biology", A. Rich and N. Davidson, Eds., W. H. Freeman, San Francisco, Calif., 1968.

(7) (a) M. Beer and C. R. Zobel, *J. Mol. Biol.*, 3, 717 (1961); (b) M. Beer and E. N. Moudrianakis, *Proc. Natl. Acad. Sci. U.S.A.*, 48, 409 (1962).

(8) Great progress has recently been made in the chemical/enzymatic sequencing of DNA: (a) F. Sanger and A. R. Coulson, *J. Mol. Biol.*, 94, 441 (1975); (b) A. Maxam and W. Gilbert, *Proc. Natl. Acad. Sci. U.S.A.*, 74, 560 (1977).

(9) F. R. Hartley, "The Chemistry of Platinum and Palladium", Wiley, New York, N.Y., 1973.

(10) (a) B. Rosenberg, L. Van Camp, J. E. Trosko, and V. H. Mansour, *Nature (London)*, 222, 385 (1969). (b) B. Rosenberg and L. Van Camp, *Cancer Res.*, 30, 1799 (1970). (c) For a review, see J. M. Hill, E. Loeb, A. MacLellan, N. O. Hill, A. Khan, and J. J. King, *Cancer Chemother. Rep.*, 59, 647 (1975).

(11) The most recent reports of the clinical status of the drug appear in a two-part issue of *J. Clin. Hematol. Oncol.*, 7 (1977).

(12) (a) H. C. Harder and B. Rosenberg, *Int. J. Cancer*, 6, 207 (1970); (b) J. A. Howle and G. R. Gale, *Biochem. Pharmacol.*, 19, 2757 (1970).