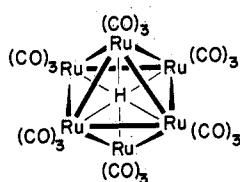


Theoretical Organometallic Chemistry

Roald Hoffmann

Modern organometallic chemistry is the realm of the possible, in several senses. Out of the collection of molecules in Fig. 1, none was known 30 years ago. Over these years our knowledge of the decisive role of metal ions at the active sites of many enzymes, a function that has evolved over millennia, has increased tremendously. There is some connection, of course, between this natural metal-based chemistry and the multitude of new inorganic compounds. But the latter are, by and large, the handiwork of man. Not that they are necessarily made by the most rational means. Nevertheless, they are creatures of the laboratory, owing their existence to the

plicity and there from complexity. We could not have foretold that a hydrogen atom would find its way smack in the middle of an octahedron of ruthenium atoms (1) a structure utterly simple in its



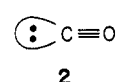
1 $\text{H Ru}_6(\text{CO})_{18}^-$

Cartesian geometry (2). Nor would we have predicted, yet we cannot help but appreciate, the staggering variety of

Ligands and Orbitals

In the organometallic molecules in Fig. 1 we perceive one or more transition metal atoms and some attached groups. These groups are termed ligands. They span a range of complexity from simple atoms such as Cl^- , through diatomic molecules such as carbon monoxide or carbonyl (CO), nitric oxide, and molecular nitrogen, larger groupings such as phosphines (PR_3) and alkyls (CH_3), to still larger, more complicated, clearly organic moieties endowed with substantial stability on their own such as ethylene ($\text{H}_2\text{C}=\text{CH}_2$) or groupings that kinetically are not very stable at all such as methylene (CH_2) or allyl ($\text{H}_2\text{C}=\text{CH}-\text{CH}_2$).

All the ligands must possess an electronic arm by which they attach themselves to the metal. This is their basicity, their donor function, and it consists of one or more pairs of electrons used for bonding to the metal. To display the donor function explicitly, I introduce the convention of displaying the donor's electrons in pairs. A negative charge is thereby imposed on some of these donors: CO is neutral (2), but a methyl group is anionic (3), which makes it anal-



Summary. Organometallic chemists have synthesized a remarkable variety of new structural types. In these structures ligands, which are organic or inorganic molecules of variable independent stability, bind to one or more transition metal atoms. An approach to an understanding of the electronic structure, geometrical preferences, and reactivity of these complexes may be made if the molecule is "decomposed" conceptually into a metal fragment, ML_n , and a ligand. A library of the molecular orbitals of these fragments is becoming available. One then "reconstructs" the molecule by examining the interaction of the orbitals of the ligand, typically an organic molecule, with the orbitals of the ML_n fragment.

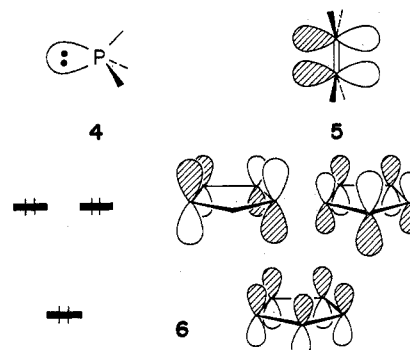
flask and the dry box and often incapable of withstanding the rigors of an aqueous, oxygen-rich, biological or geochemical environment (1).

Organometallic complexes of the transition metals are also in the realm of the possible because there seems to be no limit to their geometrical and stereochemical beauty, derived here from sim-

ways that a metal cluster, $\text{Ru}_3(\text{CO})_{12}$, has of binding, dismembering, and reassembling acetylenes (3) (Fig. 2).

The admission that we lack predictive power in this field is a reaffirmation of the experimental nature of chemistry, and a challenge. The challenge is to use the apparatus of modern quantum mechanics, perforce in approximate form, to achieve some degree of understanding of the electronic structure of organometallic molecules.

ogous to a phosphine (4). The quantum mechanical description of a donor or base is a doubly occupied orbital (indicated by the broad horizontal bar with two strokes through it, standing for the electron pair), at relatively high energy. The C_2H_4 molecule carries its donor function in a π orbital (5), whereas the ubiquitous cyclopentadienyl (6) has three such orbitals and so is counted as C_5H_5^-



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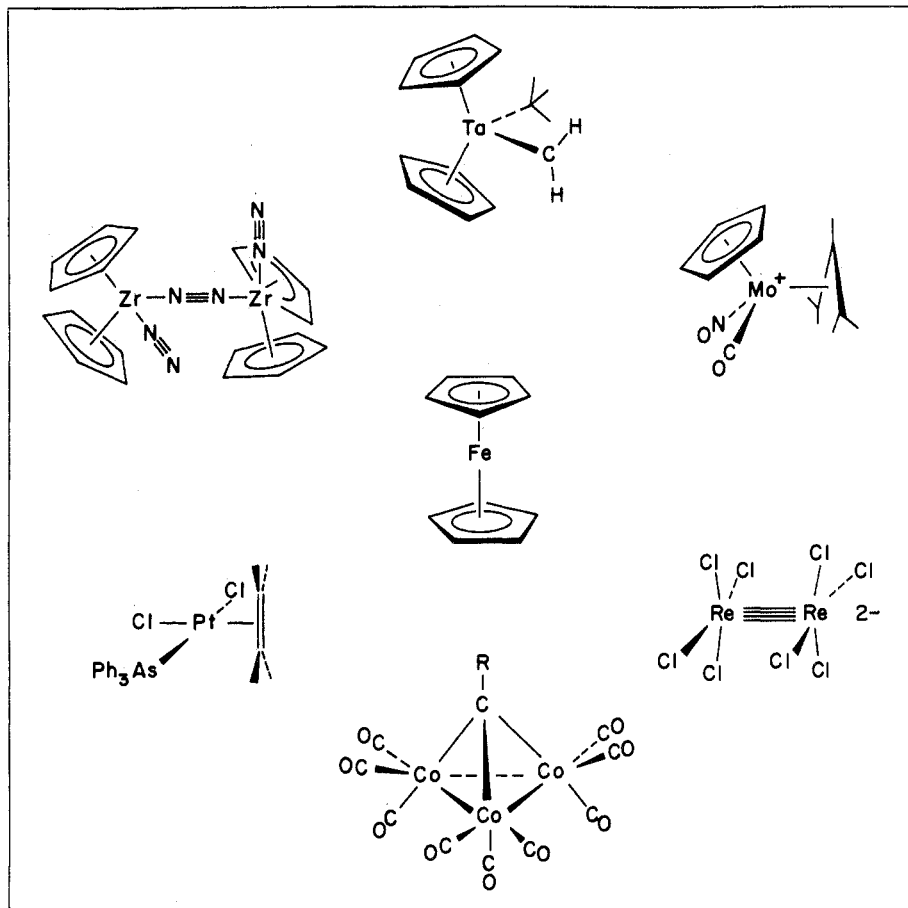
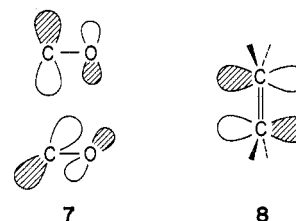


Fig. 1 (top). Some typical organometallic complexes. Purists may carp at the inclusion of $\text{Re}_2\text{Cl}_8^{2-}$, but it is so pretty that, despite the lack of carbon, I like to think of it as an honorary organometallic molecule. Fig. 2 (bottom). Those products of the reaction of various acetylenes with $\text{Ru}_3(\text{CO})_{12}$ whose structures are established. The structures shown by no means exhaust the total set of complex products of these reactions.

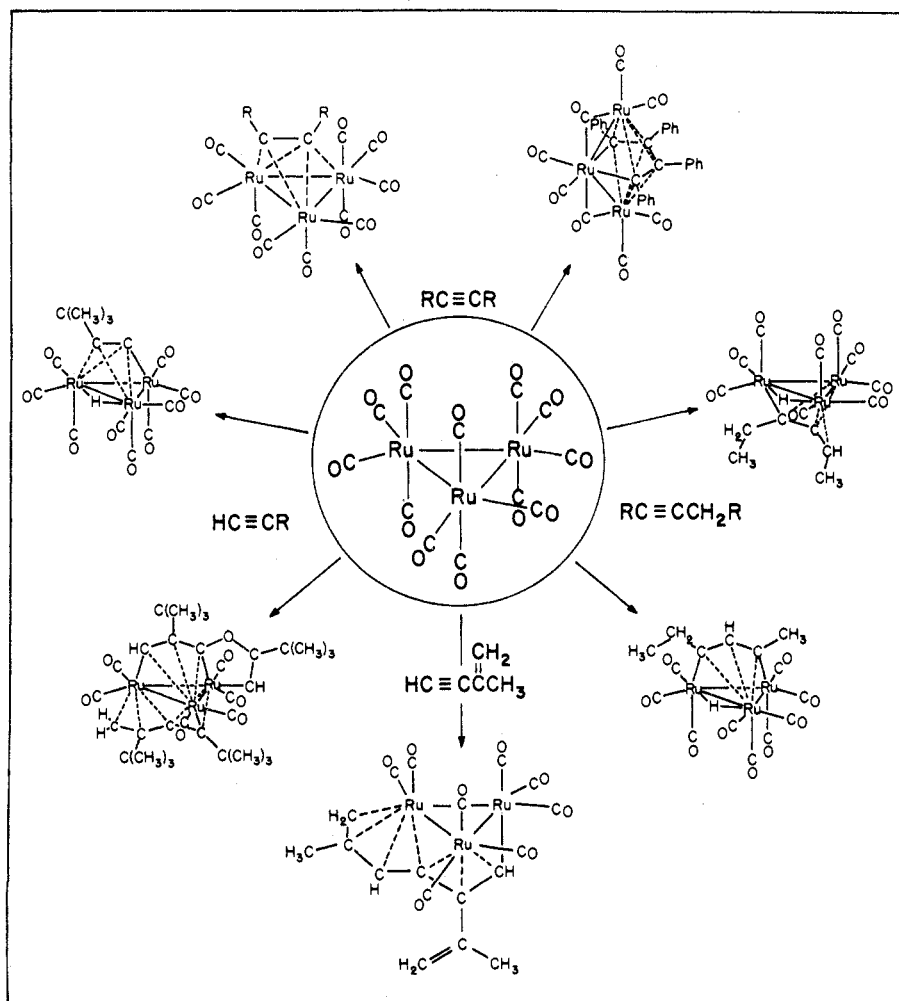
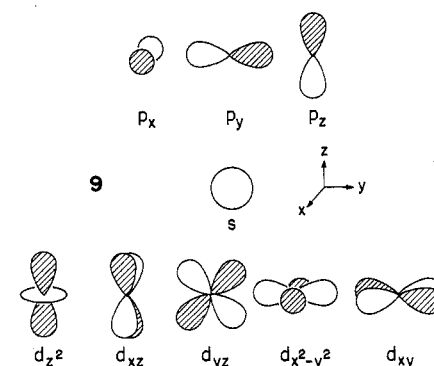
(Cp^-) (4). In 5 and 6, I introduce a graphic notation that will be used throughout this article: shading or lining of an orbital lobe implies the positive phase of the wave function, and no shading means the negative phase.

Some ligands, indeed the best ones, are also Lewis acids, carrying an acceptor function as well. In orbital language what makes for an acceptor is a relatively low-energy unfilled orbital. Those of methyl are too high in energy, but CO and C_2H_4 both have π^* orbitals that serve very well (7 and 8):



The ability to both donate electrons to the metal and accept other electrons back is the hallmark of the strongest bonding ligands. Still another determinant of a good ligand is its size, to be precise the size of its orbitals, relative to a typical metal atom. This is what makes the Cp unit, an aromatic system but nevertheless not very stable on its own, such a common ligand in organometallic compounds. Its diameter, 2 to 3 angstroms, matches very well the span of a typical transition metal d orbital.

The center of all the activity is the metal atom. The three transition metal series (Fig. 3) provide the same set of valence orbitals, albeit differing in principal quantum number. These frontier orbitals are the five nd ($3d$ or $4d$ or $5d$, depending on the transition series), one $(n+1)s$, and three $(n+1)p$. With these nine orbitals (9), the metal brings a variable



4	5	6	7	8	9	10
Ti	V	Cr	Mn	Fe	Co	Ni
Zr	Nb	Mo	Tc	Ru	Rh	Pd
Hf	Ta	W	Re	Os	Ir	Pt

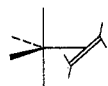
Fig. 3. That portion of the periodic table containing the transition elements. The number heading each column is the number of electrons available for bonding in the neutral form of the atom.

number of electrons, indicated by the numeral above each column in Fig. 3.

The versatility of the transition metals is now fully displayed. There is spatial flexibility—enough orbitals to provide bonding in just about any direction—and there is electronic tuning—the possibility of modifying the electronic count, sometimes drastically, by moving across the periodic table. Still greater freedom (and control) is provided by the potential of adjusting orbital size by changing the metal, its oxidation state, or switching from the first transition series to the second or third. No wonder that the variety of geometry, bonding strength, and function in organometallic complexes seems to be infinite.

Interaction Diagrams, Fragments, and a Molecular Orbital Theory of Bonding

Let us investigate a specific and typical organometallic molecule and determine what holds it together. The example is $\text{Fe}(\text{CO})_4(\text{C}_2\text{H}_4)$, iron tetracarbonyl ethylene, an iron complex typical in that it contains several CO groups and an olefin ligand. It is a relatively unstable orange-yellow oil, first made around 1963 (5). The geometry of the molecule, known from the crystal structures of the parent molecule and numerous derivatives (6), is shown in 10.



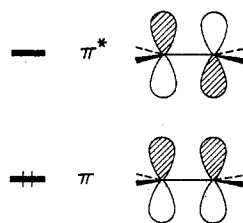
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It may be described alternatively as a trigonal bipyramid (two CO groups along the axis, two CO groups and the C_2H_4 carbons in the equatorial plane) or as an octahedron, the two C_2H_4 carbons approximately completing this common coordination polyhedron.

The C_2H_4 in this complex has its C-C bond stretched ($\sim 1.42 \text{ \AA}$) (6), and its hydrogens somewhat pinned back. Yet it is clearly recognizable as the C_2H_4 unit that it was in the free state, and indeed it may

be set free under suitable conditions. The fact that this transition metal complex contains a C_2H_4 ligand suggests a partitioning of the molecule into $\text{Fe}(\text{CO})_4$ and C_2H_4 . This is a theoretical fragmentation. It may not be the way the molecule is made, but we are not barred from constructing the compound in our minds, on paper, or in a computer in this way.

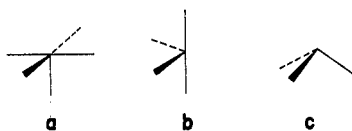
In order to examine how this molecule is made, we need to write down the orbitals of C_2H_4 and $\text{Fe}(\text{CO})_4$ and then allow them to interact. The orbitals of C_2H_4 are well known (4): crucial to any bonding scheme are the frontier π and π^* levels of 11



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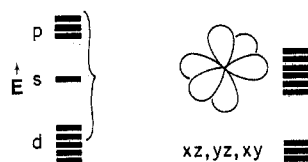
What about the orbitals of $\text{Fe}(\text{CO})_4$, the inorganic moiety? This fragment, as well as other typical ML_n components of organometallics shown in Fig. 1, is made up of a metal atom and several ligands. The orbitals of such ML_n fragments are very easy to construct, in either a molecular orbital or a valence bond way (7). Let us do so.

In the geometry it displays in the olefin complex, $\text{Fe}(\text{CO})_4$ clearly looks like an octahedron with two *cis* ligands missing (12b). Most other popular fragments, for example, square pyramidal ML_5 (12a) and pyramidal ML_3 (12c), may also be re-



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lated geometrically to an octahedron. So let us prepare a metal center for octahedral bonding. From its nine valence orbitals (9) one may form six equivalent hybrids pointing toward the vertices of an octahedron. These are d^2sp^3 hybrids, that is, they use up two d functions and all of the s and p orbitals (8). The hybrids are shown schematically in 13, along



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with the three d orbitals, d_{xy} , d_{xz} , and d_{yz} , that remain unhybridized.

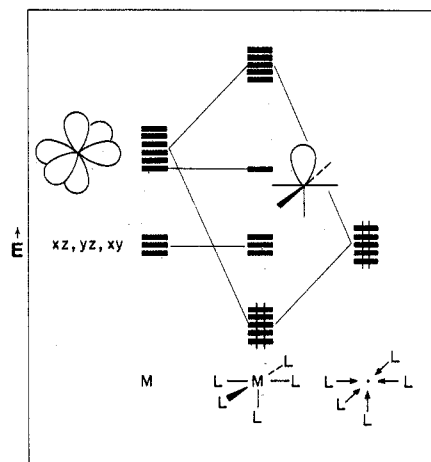
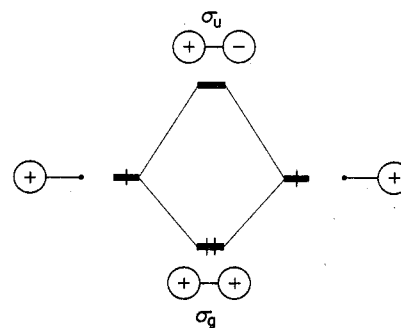


Fig. 4. Five ligands, Lewis bases, are at right. At left are the valence orbitals of a typical transition metal center prepared for octahedral bonding. The five ligands come in along five of the six octahedral directions. The resultant orbitals of ML_5 are shown in the center.

Now suppose we need to know the orbitals of the ML_5 fragment (12a). The unspecified ligand L is so far characterized only by a directed orbital containing two electrons—it could be any of the Lewis bases (2 through 5). Five such ligands coming in along the octahedral directions interact with five of the six hybrids, as shown in Fig. 4.

“Interaction” is an important word in our quantum chemical vocabulary. It has the sense of forming from two initially isolated wave functions, orbitals, two new combinations. One is a bonding, in-phase combination, and the other is an antibonding, out-of-phase, noded mixture. The simplest manifestation of this most familiar phenomenon is the formation of H_2 (14), where the bonding combination is σ_g and the antibonding combination is σ_u .



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As shown in the center of Fig. 4, five metal-ligand bonding combinations with reduced energies carry the ten electrons that the five bases bring to the metal. Five metal-ligand antibonding combinations have increased energies. One hybrid orbital remains unused, along with the three unhybridized d functions.

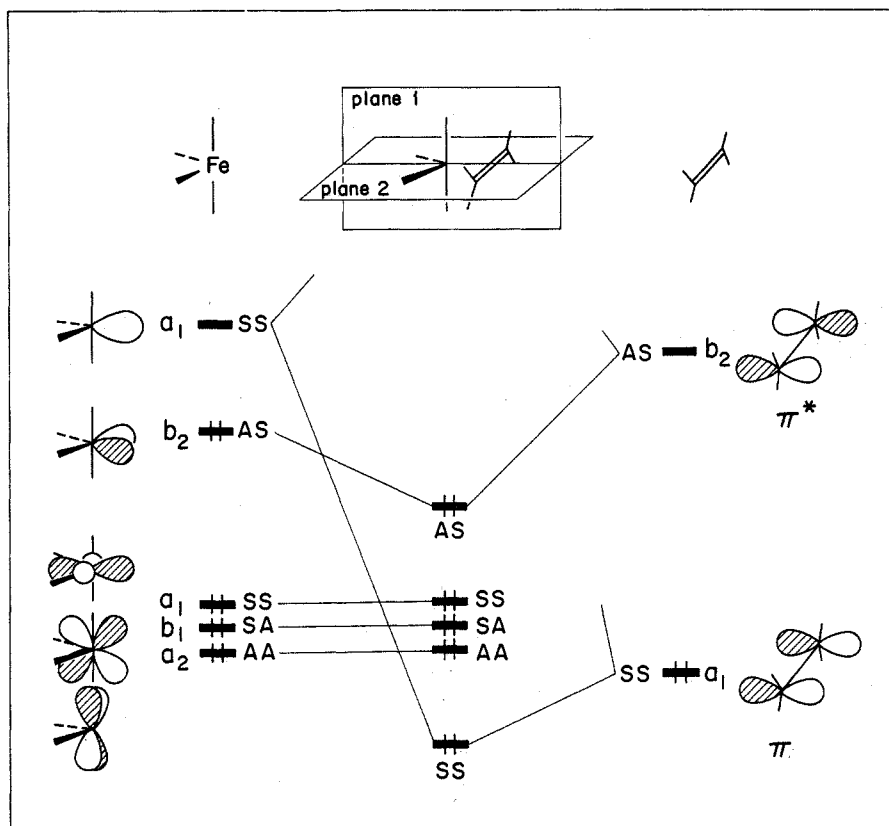
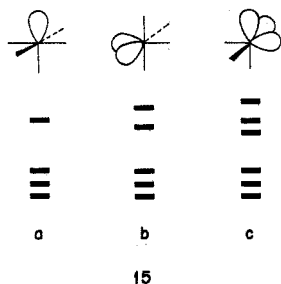


Fig. 5. Interaction diagram for $\text{Fe}(\text{CO})_4(\text{C}_2\text{H}_4)$. The C_2H_4 is at right, the $\text{Fe}(\text{CO})_4$ fragment at left. The orbitals are classified in two ways, according to their symmetry properties in the C_{2v} group of the complex or, equivalently, according to their reflection properties in the two indicated planes.

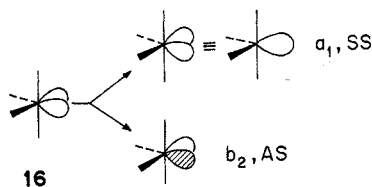
These four orbitals are the valence or frontier levels of the ML_5 fragment. They carry all the metal d electrons (precisely how many depends on the metal), and they will interact with any other ligands that come near.

The patterns of interaction for ML_4 and ML_3 are no different. Four or three bases come up, interacting with four or three of the octahedral hybrids of structure 13, leaving two or three hybrid orbitals, respectively, untouched. The primitive picture, not a bad one at that, of ML_5 , ML_4 , and ML_3 is then given in 15. In each ML_n fragment there are three orbitals of lower energy, essentially xz , yz , and xy , and $6-n$ hybrids of higher energy, pointing toward the octahedral sites.



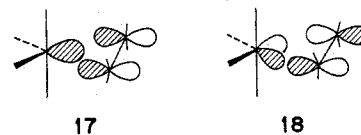
One additional bit of preparation is still needed before we proceed with our analysis of the attraction of $\text{Fe}(\text{CO})_4$ for

C_2H_4 . The two higher-lying hybrids in 15b are localized. They must be prepared for bonding by the formation of delocalized combinations. In the jargon of the trade, the orbitals need to be symmetry-adapted. In this particular case nothing more complicated than taking a sum and a difference of the localized orbitals is required, as in 16 (9).



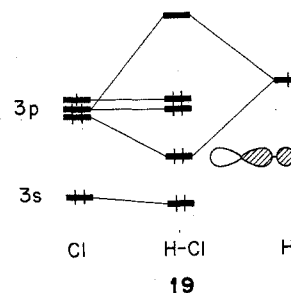
Group theory, that marvelous mathematical edifice which combines elegance with labor saving, makes the work of constructing the interaction diagram of Fig. 5 easier (10). The orbitals are classified both in their appropriate C_{2v} symmetry and according to their reflection properties (S = symmetric, A = anti-symmetric) in the two mirror planes. The metal fragment b_1 and a_2 orbitals do not have the correct symmetry to mix with either π or π^* of C_2H_4 . There are two metal-based a_1 orbitals that are of the same symmetry as the C_2H_4 π . The upper orbital, $2a_1$, a hybrid of d , s , and p on the metal, is better disposed for

interaction with the C_2H_4 π than the lower $1a_1$, primarily metal d . Thus one bonding interaction is between the π of C_2H_4 and $2a_1$, another between C_2H_4 π^* and $\text{Fe}(\text{CO})_4$ b_2 . The lower-energy component of each interaction is sketched in 17 and 18. All that remains is to place ten



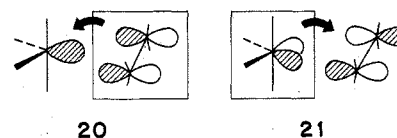
electrons in the final level scheme, two from the C_2H_4 π and eight from the iron atom. These electrons fill five orbitals, two of which are bonding (17, 18) and three of which are nonbonding. There is a substantial gap between filled and unfilled levels, a sign of kinetic and thermodynamic stability in organic and inorganic molecules.

The nature of the bonding in this organometallic complex differs in no substantial way from the bonding in any molecular aggregate. For instance, the H-Cl bond in hydrogen chloride forms by the interaction of a chlorine $3p$ orbital with a hydrogen $1s$ orbital, placing an electron pair in the bonding combination, as in 19.



Two chlorine lone pairs remain unperturbed by this σ bonding. In $\text{Fe}(\text{CO})_4(\text{C}_2\text{H}_4)$, two bonds form between the metal fragment and the C_2H_4 , and three lone pairs remain essentially unaffected.

A certain perceptual shading of the bonding picture of $\text{Fe}(\text{CO})_4(\text{C}_2\text{H}_4)$ is worth pursuing. Let us redraw the bonding combinations 17 and 18 in 20 and 21.



The box outlines signify the parentage of these orbitals. In our conceptual fragmentation of Fig. 5 the two electrons in 20 initially belonged entirely to the C_2H_4 . The resultant bonding molecular orbital (20) still is occupied by two electrons, but now they are delocalized over both fragments. Thus some electron density has been shifted to the $\text{Fe}(\text{CO})_4$ in the

course of bond formation. Similarly the two electrons in **21** initially were assigned to the $\text{Fe}(\text{CO})_4$ fragment; bonding has shifted some electron density in the reverse direction, from the metal to the olefin.

Forward and back donation have been part of the theoretical framework of inorganic chemistry from the early 1950's. The picture I have just described is the Dewar-Chatt-Duncanson model of olefin bonding (11). In the 1950's several intellectual streams combined into a torrent—the renaissance of modern inorganic and organometallic chemistry. The Dewar-Chatt-Duncanson model was one of the streams. My choice of the other rivers includes the metallocenes, the rediscovery of crystal field theory, Ziegler-Natta catalysis, and three-dimensional crystal structure determination.

Geometries and Conformations

One may inquire whether the geometry we assumed for $\text{Fe}(\text{CO})_4(\text{C}_2\text{H}_4)$, **10**, is preferred to one in which the C_2H_4 is twisted by 90° around the metal to the C_2H_4 midpoint axis, as in **22**. This is a



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conformational question, a query regarding the equilibrium or most stable geometry of the complex. Once one has used the fragment decomposition to analyze the bonding in **10**, the approach to the alternative geometry is evident. One uses the same fragments and reconstructs **22**. There had better be a difference, and Fig. 6 shows what it is.

The C_2H_4 π interacts with $\text{Fe}(\text{CO})_4$ a_1 (10) approximately to the same extent in the two conformations. A differential is provided by the C_2H_4 acceptor function, the π^* orbital, of b_2 symmetry (10) in **10**, b_1 in **22**. Orbital interactions are governed by the usual perturbation theoretical expression (4, 12)

$$\Delta E = \frac{|H_{ij}|^2}{E_i - E_j}$$

which says that the extent of interaction between two orbitals i and j is determined by a quotient. The numerator is the matrix element of the interaction squared. This matrix element H_{ij} is a function of the overlap between the two orbitals. If not directly proportional to the overlap, H_{ij} is at least large when the overlap of orbitals i and j is large and

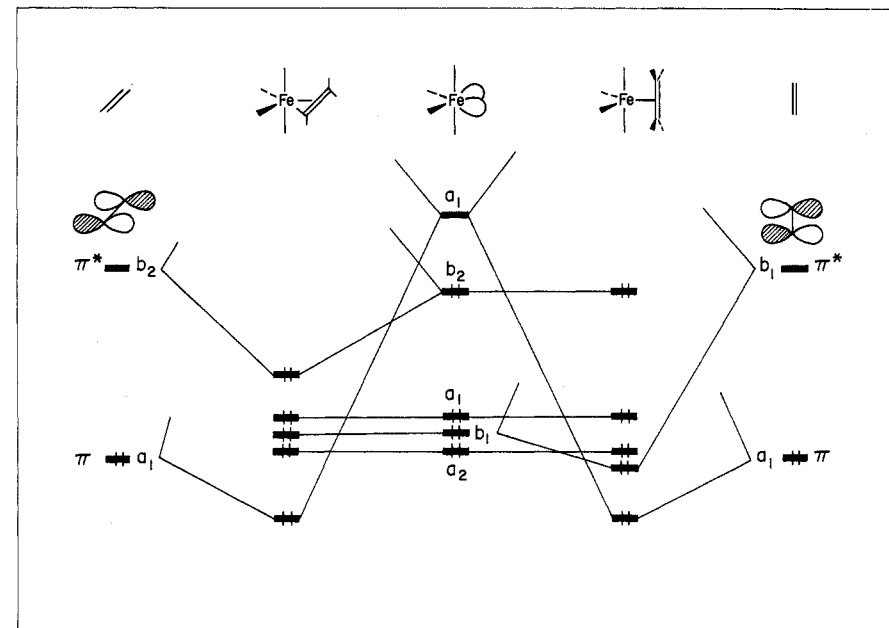
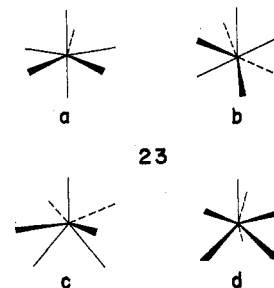


Fig. 6. Interaction diagram for two conformations of $\text{Fe}(\text{CO})_4(\text{C}_2\text{H}_4)$, differing in the rotational disposition of the C_2H_4 ligand.

small when it is small. The denominator of the perturbation expression makes ΔE inversely proportional to the difference in energy between the levels so that the closer two energy levels are, the more strongly they will interact (4, 12). On both counts the C_2H_4 π^* interaction in the initial conformation **10** is better. The $\text{Fe}(\text{CO})_4$ orbital that it mixes with is higher in energy, closer to π^* of C_2H_4 . And the overlap is better; the b_2 hybrid of $\text{Fe}(\text{CO})_4$ is nicely directed away from the metal, toward the C_2H_4 , whereas b_1 is an unhybridized, mainly d orbital. The "backbonding" b_2 interaction in the conformation in which C_2H_4 lies in the equatorial plane is better. There is a substantial rotational barrier in these complexes, 10 to 15 kilocalories per mole (13, 14).

This brief introduction to one methodology of analyzing preferred geometries of molecules in no way exhausts the geometrical richness of inorganic stereochemistry. In addition to orientational degrees of freedom of coordinated groups, one has in complexes every type of isomerism—positional, geometrical, optical—in detail the equivalent of the same beautiful, inherently chemical phenomena in organic chemistry. But one has an added range of coordination number and geometry. Not just two, three, or four atoms may be bound to a central one, but five, six, seven, and eight, or even more ligands are commonplace. Each coordination number has associated with it several polyhedral shapes. For instance, in 7-coordination, a typical environment for molybdenum, tungsten,

and uranium, one finds geometries as seemingly diverse (but in fact very closely related to each other) as a pentagonal bipyramid (**23a**), a capped octahedron (**23b**), and two kinds of capped trigonal prisms (**23c** and **23d**). The stereochemical diversity of these structural types is fascinating (15).



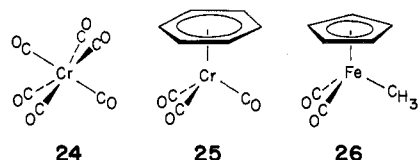
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Fragments at Work

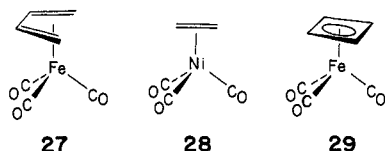
The fragment approach is one theoretical tool, one piece of interpretative machinery, that many investigators (16) have found useful in trying to make sense of the immense variety of complex structures that have poured forth from the cornucopia of the synthetic organometallic chemist. By way of example, let me trace the multitudinous uses to which my collaborators and I have put one such fragment, ML_3 .

The orbitals of a C_{3v} ML_3 fragment were sketched in **15c**. There are three low-energy orbitals and three hybrids above. This fragment comes in complexes with from zero to ten electrons. Here are some of the things that can be done with it.

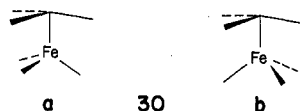
1) Once the lower three orbitals are occupied by six electrons, the fragment seeks three bases (six electrons) to interact with the upper three hybrids. These six electrons may come from the ligands, as in the restored octahedron $\text{Cr}(\text{CO})_6$ (24) or from a six-electron organic donor, as in (arene) $\text{Cr}(\text{CO})_3$ (25), or $\text{CpFe}(\text{CO})_2\text{CH}_3$ (26) (here we have for-



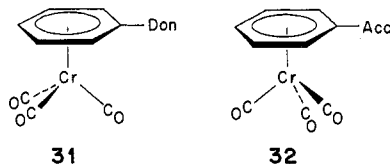
mally a Cp^- and a CH_3^- , which makes the iron Fe^{2+} , d^6). Or some of the electrons may come from the metal and some from the ligand, as in the complexes 27 through 29. The last compound is an example of the remarkable capability of transition metal fragments to stabilize unstable organic moieties (17).



2) Conformational preferences and rotational barriers spanning a wide energy range may be explicated (18). Trimethylenemethane iron tricarbonyl prefers geometry 30b over 30a by nearly 20 kcal/mole (19).



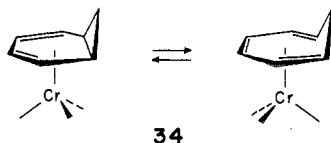
The barrier to internal rotation in benzene chromiumtricarbonyl (25) is small. However, when a donor is substituted on the benzene ring, the equilibrium conformation is 31, but, when an acceptor is substituted, it is 32. In each case substantial barriers to internal rotation appear (18).



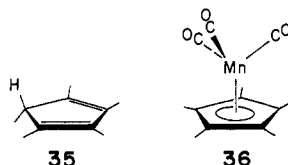
The preferred geometry of polyene- ML_3 complexes is 33, one arm of the tricarbonyl under the "open" end of the polyene, unless the metal is electron-



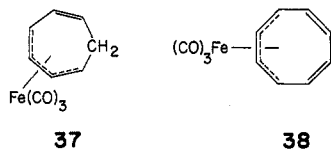
deficient. Then the preferred conformation changes. Thus a $\text{Cr}(\text{CO})_3$ orientation may be coupled with the norcaradiene-cycloheptatriene equilibrium, as in 34 (20).



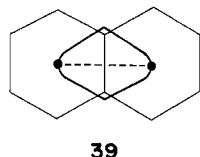
3) A proton moving across the face of a cyclopentadienyl ring "sits down" directly above a carbon atom (cyclopentadiene, 35) and moves about, with substantial activation energy, by a sequence of 1,5 sigmatropic shifts (21). So do a methyl and other group IV ER_3 groups (where $\text{E} = \text{Si}, \text{Ge}, \text{Sn}, \text{or Pb}$), the activation energy for the process falling as one descends group IV (22). In contrast, an $\text{Mn}(\text{CO})_5^+$ group places itself directly over the center of the ring (36). So do CuL^+ , BeR^+ , Li^+ , Tl^+ , and In^+ .



More complicated patterns of equilibrium placement and mobility occur with larger rings. Sometimes the barriers to rearrangement are substantial [22 kcal/mole in 37 (23)], whereas in not distantly related molecules they are much smaller [~ 8 kcal/mole in 38 (24)]. A fragment analysis will explain this trend (25).

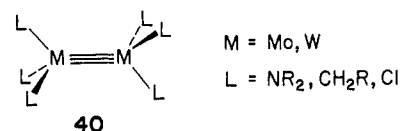


Tours of ML_n groups across the face of larger organic ligands may be subject to substantial symmetry-imposed barriers (26). For instance, the rearrangement of naphthalene- $\text{Cr}(\text{CO})_3$, in which the $\text{Cr}(\text{CO})_3$ moves in a least-motion way from one ring to another (dashed line in 39), should not be as easy as the round-about excursion marked by the solid lines (25).

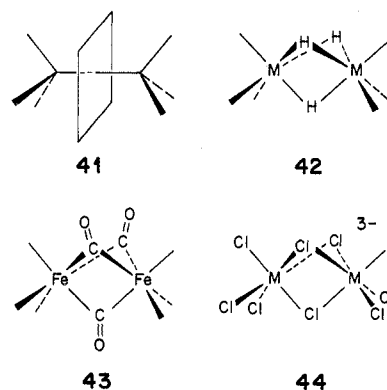


4) Two ML_3 groups brought up to each other make M_2L_6 . For a d^3 electron count, these are the remarkable d^3 triple-bonded complexes (40) of Chisholm and

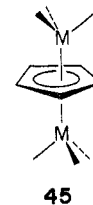
Cotton (27). We think that with small ligands these might be eclipsed (28), but others do not agree (29).



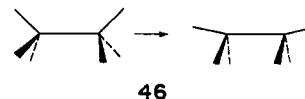
Next one can insert other atoms or molecules in the middle, in the plane marked in 41. The insertion of three hydrides gives rise to 42, a reasonably well-known structural type for d^8 and d^7 metal centers ($\text{M} = \text{Co}, \text{Fe}, \text{Ir}, \text{Re}$) (30). Incorporation of three CO groups produces the d^8 $\text{Fe}_2(\text{CO})_9$ (43). If three chlorides are inserted, we have the remarkable d^3 series $\text{M}_2\text{Cl}_9^{3-}$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) (44), in which a striking range of metal-metal bonding is traversed as one scans down the group, from $\text{M} = \text{chromium}$ where there is no metal-metal bond, six unpaired electrons, and an elongated biotetrahedron, to $\text{M} = \text{tungsten}$, with a triple bond, diamagnetic properties, and a squashed biotetrahedron (30).



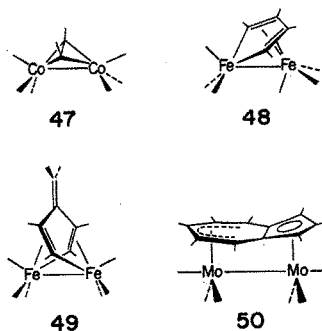
Sandwich molecules, with a metal atom between two organic fragments, exemplified by ferrocene, should appear on any flag of modern inorganic chemistry. It occurred to my colleagues and me that an organic ligand could be inserted in between the $\text{M}(\text{CO})_3$ units as well, to give the inverse sandwich (45), stable for certain electron counts (31). Remarkably, several of these molecules have been made (32).



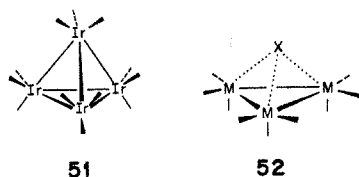
5) The M_2L_6 unit, bent back a little (46), serves as a building block for an



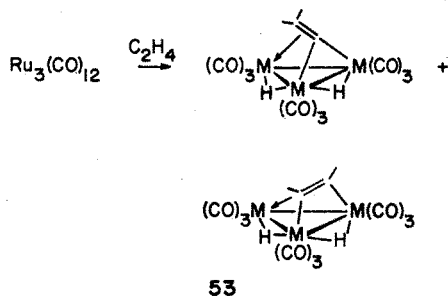
enormous variety of M_2L_6 (ligand) complexes. The acetylene complex (47), the ferrole (48), the flyover bridge (49), and the azulene complex (50) are examples (33). Each molecule has intriguing conformational choices available to it.



6) Four $Ir(CO)_3$ fragments may be combined to give an inorganic tetrahedrane (51). A general theory of bonding in this and substantially more complicated clusters, developed by Wade [see (16)] and Mingos [see (16)], is one of the most important conceptual developments in modern inorganic theory. Three $M(CO)_3$ units may be combined to form an $M_3(CO)_9$ fragment (52) that can be



capped in many ways, by a chalcogen atom, by CR, by a Cp ring, or by another metal (34). An isoelectronic Co_3Cp_3 unit can split an acetylene and keep the two CR pieces thereof as caps (35); $Ru_3(CO)_{12}$ can dismember C_2H_4 in at least two distinct ways (53) (36). It seems



likely that we will eventually find out how these extreme disruptions of bonding occur. For the moment, the theoretical analysis is limited to the geometrical preferences of the products (34).

An understanding of bonding and equilibrium structure has been the main subject of this discussion. Only the simplest reaction type, unimolecular rearrangement, has figured in the above examples. Yet chemistry is in large part molecules in motion, it is chemical reactivity. Some

progress has been made in the analysis of simple organometallic reactions (37). But the broad outlines of a theory of organometallic reactivity, the kind of framework that would allow us to anticipate approximately the range of products exhibited in Fig. 2, is still lacking. Our relative ignorance in this area is not a cause for despair. On the contrary, it makes theoretical work in this realm of the possible a great deal of fun.

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38. Many people, able young scientists all, have participated in the work of the Cornell group over

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Clocked Cell Cycle Clocks

Leland N. Edmunds, Jr., and Kenneth J. Adams

Our understanding of the cell cycle has come a long way since Howard and Pelc (1) more than 25 years ago divided it into four consecutive intervals— G_1 , S, G_2 , and M—where G_1 and G_2 , respectively, designated the gaps in time between the completion of cell division and the onset of DNA synthesis, and between the end of replication and the onset of mitosis

self a part of the clocked division cycle in the sense that the timer is replicated with each round of division. After reviewing some of the major notions of the cell division cycle and different types of cell cycle oscillators, we examine the void between cell cycles and circadian clocks (3, 4). Finally, we address the basic problem of variability in cell cycle gener-

Summary. The cell division cycle of both mammalian cells and microorganisms, which apparently has both deterministic and probabilistic features, is a clock of sorts in that the sequence of events that comprise it measures time under a given set of environmental conditions. The cell division cycle may itself be regulated by a programmable clock that, under certain conditions, can generate circadian periodicities by interaction with a circadian pacemaker. These clocks must insert time segments into the cell division cycle in order to generate the observed variability in cellular generation times.

(M). Advances have not been confined, however, to a mere filling in of these gaps and subdividing them into smaller steps. Rather, recent experimental and theoretical work has emphasized the mechanisms controlling the cell cycle and, indeed, has indicated that a single "cell cycle" may be somewhat of a misnomer. Finally, perhaps there is no such thing as the cell division cycle; the final event would be merely the end of a sequence of events and the beginning of nothing (2).

The cell division cycle—a clock in the sense that it measures time under a given set of environmental conditions—may be governed by an underlying oscillatory mechanism or timing device, which is it-

ation times, a major challenge in constructing models for cell cycle regulation, and explore new molecular approaches for the insertion of time segments into the cell cycle.

Models of the Cell Cycle:

Deterministic and Probabilistic

Attempts to describe the cell division cycle (CDC) have been (i) deterministic and (ii) indeterminate or probabilistic. Within the former, there are two possible types of mechanism for ordering a fixed sequence of cell cycle events relative to each other (5, 6). There may be a direct causal connection between one event

and the next so that it would be necessary for the earlier event in the CDC to be completed before the following could occur. Hartwell and co-workers (7) have referred to this notion as the "dependent pathway" model and have analyzed the "circuitry" of the CDC of the budding yeast, *Saccharomyces cerevisiae*, using temperature-sensitive mutants whose CDC is blocked at various stages. In contrast to this sequential type of approach, there is the possibility that no direct causal connection exists between any two events but that they are ordered by some master timing mechanism that operates on one or more key events ("control points") of the CDC, such as the initiation of DNA synthesis or mitosis. In this "independent pathway" model (7), the accumulation of a mitogen or other substance, the completion of a "division protein" structure, or the attainment of a critical ratio of DNA to mass or nuclear volume may initiate a new CDC state. Obviously, it is possible, even likely, that the CDC is controlled by a combination of these types of mechanism.

Such deterministic models, however, do not adequately account for the large variances commonly observed in generation time (as great as 20 percent of the mean in mammalian cell systems), rendering timekeeping relatively imprecise and leading to the rapid decay of synchrony in phased cultures (8). In an effort to explain this variability, other attempts to characterize the cell cycle traverse have considered a portion of the CDC to be indeterminate (9) or have turned to probabilistic descriptions (10–12). Thus, Smith and Martin (11), observing that the number of cells that have divided as time progresses decreases exponentially, have suggested that the S and G_2 portions of the CDC (which they

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