Mechanisms of Intramolecular Activation of C–H Bonds in Transition-Metal Complexes

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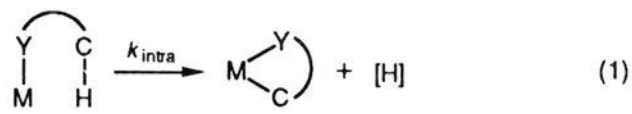
Alexander Dmitreyevich Ryabov was born in Moscow in 1953 and educated at Moscow State University. He graduated in 1976, obtained a Phil.D. degree in 1979, working with Professor A. K. Yatsimirsky on palladium-promoted oxidative coupling of alkenes and arenes, and, finally, received a Doctor of Sciences degree for studies of mechanisms of the formation and conversion of palladacycles. He is now at the Division of Chemistry, G. V. Plekhanov Institute of National Economy, where he is Professor of Chemistry. His present interests are focused on the coupling of transition-metal complexes and enzymes.

I. Introduction

The chemistry of cyclometalated complexes is undoubtedly one of the most advanced areas of modern organometallic chemistry. The evidence is both a number of special reviews[1-10] and a monograph,[11] which are, in general, preparatively oriented. It is now clear why metallacycles have attracted so much attention in the past two decades. The compounds are successfully used in organic synthesis,[12] catalysis,[13-15] asymmetric synthesis,[16] and photochemistry.[17-19] They mimic some key intermediates in catalytic transformations[1,20] and are rather promising as potential biologically active materials[21] and constituents of ordered mesophases.[22] The rapid growth of the chemistry of cyclometalated complexes stimulates the fundamental investigations aimed, in particular, at elucidation of the basic mechanisms of the formation of metallacycles, among which the most attractive are those involving direct metalation of the C–H bonds (eq 1). Here, Y is any center either



(1)

coordinating with or forming a covalent bond with the central metal. Designation of the leaving hydrogen as [H] reflects the fact that at present we specify neither the nature of the leaving atom (proton, hydride, or radical) nor whether it remains bound to the metal or dissociates with the appropriate ligand. These points will be discussed in this review, the main goal of which is to provide a general look at mechanisms of cyclometalation associated with C–H bond cleavage. In contrast to all previous surveys,[1-12] the backbone of this review is built on thermodynamic and kinetic data of reactions of type 1 supported by the corresponding stereochemical results as well as by the common chemical evidence relevant to reaction mechanisms.

Evidently, the intramolecular activation of C–H bonds (eq 1) is closely related to the corresponding

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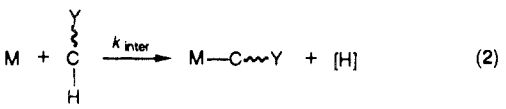
intermolecular activations (eq 2). The latter processes



(2)

are now so much investigated and spoken about (for reviews, see refs 23–29) that no comments are required but one. Whitesides wrote recently:[30] "The problem of activating alkanes via soluble metal complexes is similar to solving Rubik's cube: there are many solutions, none of which is particularly obvious until after the fact". It is clear that the purpose of mechanistic studies of both intra- and intermolecular C–H bond metalations is to correct such an unfortunate situation by finding out general principles of handling it. It is also clear that mechanisms of reactions 1 and 2 have much in common and, thus, must and will (in reasonable proportion) be treated together. Besides, it should always be remembered that if, for example, reaction 1 is of interest and intramolecular metalation is carried out in a solvent with C–H bonds, external metalation is always probable. On the other hand, when reaction 2 is under study, the concurrent intramolecular cyclometalation of adjacent ligands is possible, if those have proper C–H bonds. The interrelation between intra- and intermolecular C–H bond activation is also under discussion in this review.

II. Cyclometalation: Questions To Be Answered

The most intriguing, key questions providing a complete mechanistic picture of cyclometalation are probably the following:

1. How does a metal complex prepare for subsequent intramolecular activation of C–H bonds? Do the vacant coordinative sites develop in the course of cyclometalation, and what is the driving force for their formation?
2. What can be said about the intimate mechanism of the C–H bond cleavage by the central atom? Does oxidative addition or electrophilic substitution occur, or does cyclometalation occur through some third pathway?
3. How large is the activity of reactive complexes in the intermolecular metalation of C–H bonds of related molecules which do not form kinetically significant associates with the central atom?
4. Are there any approaches to asymmetric and/or regioselective cyclometalation of complex organic molecules?

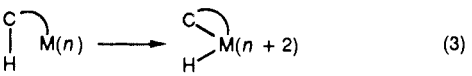
Only the last question needs no comments. The remaining ones require some explanations, which are given below.

A. Adjustment of Complexes for Subsequent Activation

Equation 1 formally claims that the coordination number of the central atom may increase on cyclometalation by one unit at the expense of the formation of a novel carbon–metal bond. If the leaving hydrogen [H] binds to the metal, the coordination number increases by two units. Hence, cyclometalation may be accompanied by significant alteration, "perestroika" of the coordination sphere. The oxidation state of the central atom could be unchanged in the course of cyclometalation, or, more precisely, the oxidation state of the metal in the initial and final states could be the same. In this case the complex, before or in the course of cyclometalation, by necessity must part with one ligand if the leaving hydrogen dissociates, or with two, if the hydrogen binds directly to the metal, since the coordination number of the complex does not usually change when the oxidation state remains the same. At the same time a complex must often throw off some ligands to create the vacant sites in its coordination sphere which are necessary for the ready cleavage of C–H bonds. An ability of complexes to become coordinately unsaturated is sometimes an important prerequisite of cyclometalation.

B. The Mode of the C–H Bond Cleavage

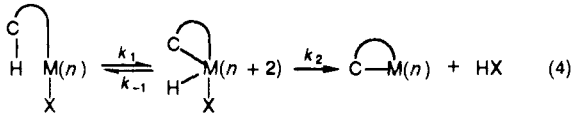
There are three generally accepted mechanisms of C–H bond cleavage:[23-29] oxidative addition, electrophilic substitution, and the so-called multicentered pathway. The following features are typical of the first one. For a facile reaction of type 3 the reactive complex must have an empty σ-type MO and a high-energy MO containing the lone pair which will be transferred into the σ^* orbital of the H–C bond during the oxidative addition reaction.[29] The C–H bond formally receives two electrons from the central atom, the oxidation state of the metal (n) increasing by two units:



(3)

If the hydride remains in the coordination sphere after the cleavage of the C–H bond, one may with confidence speak about oxidative addition as a mechanism of cyclometalation. The metal can be considered here as a nucleophilic center. Pathway 3 is therefore referred to as nucleophilic.

The absence of hydride in the coordination sphere of the product of cyclometalation, unfortunately, does not rule out oxidative addition, since subsequent reductive elimination of the hydride with suitable ligand X is possible:



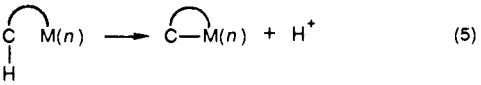
(4)

The observed first-order rate constant, k_{obsd}, is then given by

$$k_{obsd} = \frac{k_1 k_2}{k_{-1} + k_2}$$

If $k_2 \gg k_{-1}$, one obtains $k_{obsd} \approx k_1$, and if formally the "nonoxidative addition" product is formed, the reaction rate is determined by the nucleophilic, oxidative addition step.

In straightforward electrophilic mechanisms metal hydrides do not form, the central atom does not change its oxidation number, and hydrogen dissociates as a free or bound proton:



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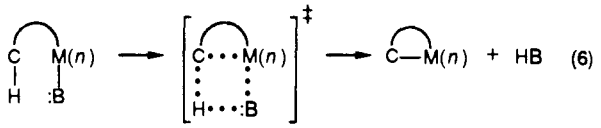
Electrophilic reactions of type 5 are often nucleophilically assisted by coordinated or free bases B:, which

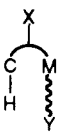
accept the leaving proton, for example:



Generally speaking, the discrimination between the mechanistic pathways "oxidative addition/reductive elimination" and "electrophilic substitution" appears to be rather complicated and has been discussed in the literature.[31] It is also a problem in cyclometalation.

Formally multicentered pathways can be written as nucleophilically assisted electrophilic ones (eq 6). The principal difference is that alkyl, benzyl, or phenyl groups (R) must be present instead of the base B. For the multicentered pathway to occur, the reactive species need only have empty acceptor MOs, at least one, to stabilize the entering σ-bond electron pair in the transition state.[29] This condition can be achieved for d^0 L_mM–R compounds having $m < 7$ such as Cp_2M–R ($m = 6$) or Cp_2MRR' ($m = 7$), i.e., where the metal has a total coordination number lower than 9.[29]

In order to characterize the reactivity of the central atom in cyclometalation, investigators often use the terms "nucleophile" and "electrophile", tacitly assuming that nucleophilic and electrophilic pathways are typical of the former and the latter, respectively. Therefore, it seems necessary to define these terms in some detail. The thermodynamic or, better to say, regioselectivity criterion was first used for this purpose: where a metal is located in the product when several, usually two, pathways of cyclometalation are possible. If the metal is σ bound to the carbon of highest electron density, the pathway was termed electrophilic, but if to the most electron-deficient, the pathway was termed nucleophilic. The kinetic criterion, based on comparison of the *rates* of activation of C–H bonds, was for some time not taken into account, but is used in this review. It should be remembered, however, that the rate constants of cyclometalation may not give straightforward Hammett plots for the following reason. Consider an imaginary complex shown below in which the substituents are attached to the ligand undergoing cyclometalation, for certainty, via oxidative addition. The substituent X can affect both the reaction sites, i.e., the metal center and the C–H bond. An increase in the electron-donating power of X would favor the oxidative addition by increasing electron density at the metal but may disfavor it by increasing electron density at the C–H bond. Which, if either, of the "electronic flows", to the metal or to the C–H bond, will dominate depends on a particular system. One can partly rule out this ambiguity by varying substituents Y in auxiliary ligands that are not cyclometalated. In this case one may expect larger changes of the electron density at the metal than at the C–H bond.



C. "Effective Molarities" in Cyclometalation

Intuition suggests that intramolecular reactions proceed faster than their intermolecular counterparts. The quantitative measure of the rate difference[32] is the ratio of the first-order rate constant of the intramolecular reaction and the second-order rate constant of the corresponding intermolecular reaction. In terms of the present article, this is the ratio of the rate constants of reactions 1 and 2, i.e., k_{intra}/k_{inter}. The ratio is called "the effective molarity".[32] The effective molarity is measured in M, and its physicochemical meaning is apparent: it is that concentration of the intermolecular reagent [Y~C–H] at which the second-order rate constant of the intermolecular reaction (k_{inter}[Y~C–H]) is equal to the first-order rate constant of the intramolecular reaction. This can be alternatively expressed by saying that the effective concentration (molarity) of C–H bonds in the intramolecular reagent is equal to [Y~C–H].[33] This approach, very visual, in particular, for understanding the high catalytic activity of enzymes, has been recently introduced into organometallic chemistry.[34,35] The values of effective molarities are of predictive value. If lower than 10 M, one can expect both inter- and intramolecular activation of C–H bonds. If the effective molarity is much higher than 10 M, the intermolecular processes become less probable, and only cyclometalation is observed.

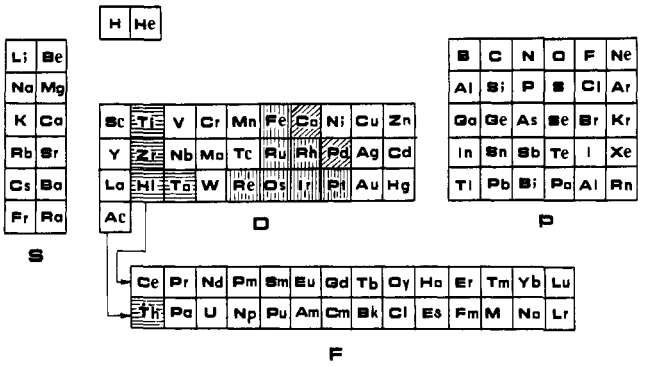


Figure 1. The elements of Mendeleev's table carrying out cyclometalation via nucleophilic (▥), electrophilic (▨), and multicentered (▤) pathways.

III. Cyclometalation: Systems Studied

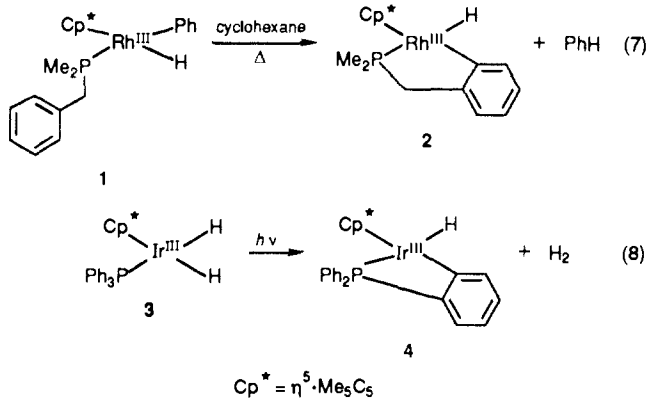
Figure 1 shows the elements of Mendeleev's table, the reactivity of which in cyclometalation is characterized by thermodynamic and kinetic data. The number of these is not, evidently, very impressive, but the variety of the mechanisms encompassed is substantial.

It is the mechanism of the C–H bond cleavage (see section II.B) that seems to be the most convenient for the systematization of the material which then logically splits into three large classes: complexes reacting by nucleophilic (oxidative addition), electrophilic, and multicentered pathways.

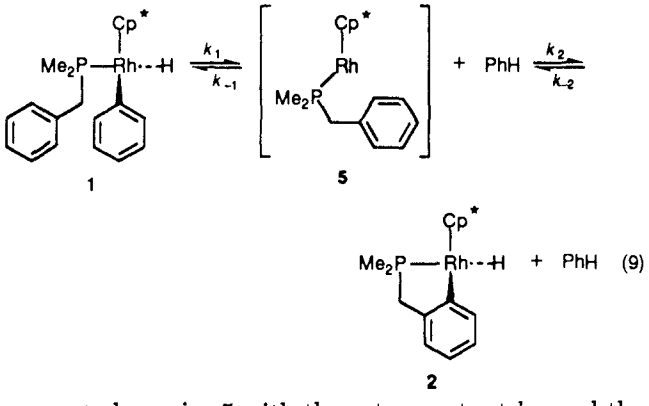
IV. Cyclometalation: Nucleophilic Pathways

A. d^8 Complexes of Rhodium(I), Iridium(I), and Ruthenium(0)

Consider reactions 7[34] and 8[36] as the most representative. The stoichiometry of both necessitates the involvement of d^6 metal complexes in the cleavage of the aromatic C–H bonds. In fact, the carbon–hydrogen



bonds are activated by d^8 species. This comes from the facts that reaction 8, for example, is triggered by photolysis of **3**, which induces reductive elimination of dihydrogen to afford the coordinately unsaturated d^8 intermediate $Cp^*Ir(PPh_3)$.[36] Similarly, photolysis of $C_6H_6RuH_2(P\text{-}i\text{-}Pr_3)$, but not its osmium analogue, in a number of solvents provides initial loss of dihydrogen, and a d^8 coordinately unsaturated intermediate formed rearranges into the four-membered metallacycle $C_6H_6(H)RuCH_2CH(Me)P\text{-}i\text{-}Pr_2$.[37] In the case of rhodium complex **1**, the reactive species are produced on thermolysis, which at 58 °C in cyclohexane-d_{12} leads to reductive elimination of benzene to give the d^8 complex $Cp^*Rh(Me_2PCH_2Ph)$.[34] The reductive elimination also occurs at 51 °C in benzene, but the reaction does not go to completion and affords the equilibrium mixture of **1** and **2** in the ratio 2.65:97.3. Equilibrium 9 is the key for understanding the chemistry observed, the equilibrium constant $K_9 = [2][C_6H_6]/[1]$ being equal to 397 M. Thermolysis of **1** leads to coordinately unsaturated species **5** with the rate constant k_1, and the value of k_1 can be evaluated in C_6D_6 by integrating the signals from ortho protons of the phenyl group of **1**. Measuring an area under the Cp* methyls of **1**, one can obtain the rate of conversion of **1**, which, applying the steady-state approximation with respect to **5**, is equal to



$$-d[1]/dt = k_1[1] - k_{-1}[C_6H_6](k_1[1] + k_{-2}[2])/(k_{-1}[C_6H_6] + k_2) \quad (10)$$

Since $K_9 = 397$ M, one can neglect the contribution from k_{-2} in the numerator of eq 10 and obtain the following expression for the observed rate constant of conversion of **1**:

$$k_{obsd} = -\{1/[1]\}\, d[1]/dt = k_1k_2/(k_{-1}[C_6H_6] + k_2) \quad (11)$$

TABLE I. Rate Constants k_1 (in C_6D_6) and k_{obsd} (in 95:5 C_6H_6:C_6D_6) for the Conversion of Complex **1**[a]

T, K	k_{obsd}, s^{-1}	k_1, s^{-1}
295.5	4.06×10^{-7}	1.09×10^{-6}
310.7	7.27×10^{-6}	1.72×10^{-5}
320.0	2.86×10^{-5}	7.09×10^{-5}
324.4	6.72×10^{-5}	1.36×10^{-4}
332.0	3.10×10^{-4} [b]	3.10×10^{-4} [b]
332.0	1.86×10^{-4}	3.265×10^{-4}

[a] From ref 34. [b] Reaction in C_6D_{12}.

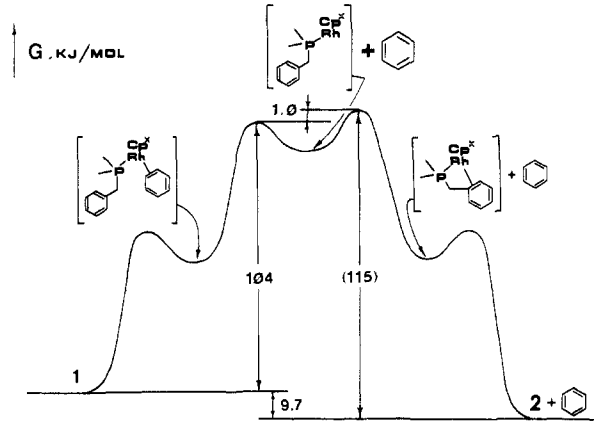
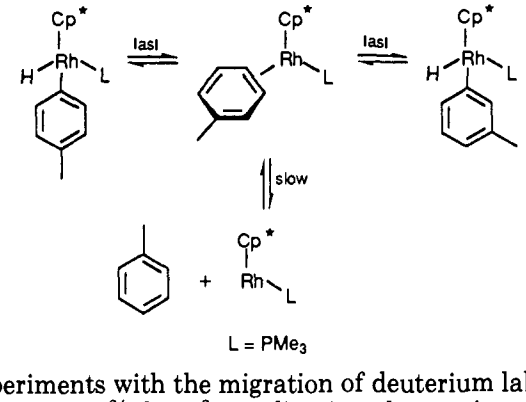


Figure 2. Free energy profile for the conversion of $(C_5Me_5)Rh(PMe_2CH_2Ph)(Ph)(H)$ at 51.2 °C in benzene. Reprinted from ref 34; copyright 1985 American Chemical Society.

Evidently, in this case the ratio $rate_{intra}/rate_{inter} = k_2/k_{-1}[C_6H_6]$. It comes from eq 11 that $k_2/k_{-1}[C_6H_6] = k_{obsd}/(k_1 - k_{obsd})$. The latter equation and the data in Table I allow the calculation of the ratio of the rates of intra- and intermolecular reactions, which is as low as 1.34 at 332 K.

The cleavage of the aromatic C–H bonds by rhodium(I) undoubtedly occurs as oxidative addition since the hydride is bound to the metal.[34] Surprisingly, this step is not rate determining. It has been previously shown[33] that in the related intermolecular activation of sp^2 C–H bonds by $Cp^*Rh(PMe_3)$ the slow step is the formation of η^2-bound intermediates:



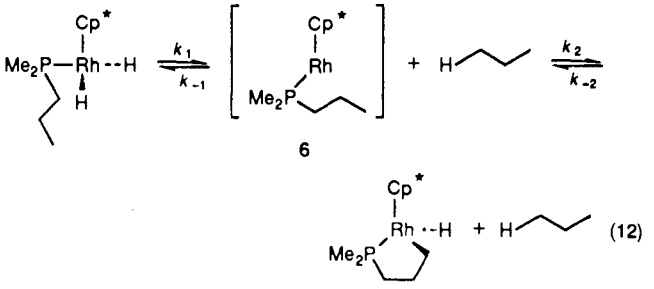
Experiments with the migration of deuterium label in **2** have shown[34] that η^2-coordination plays an important role in this case, too. All kinetic and thermodynamic results are available to construct the energy profile of the transformations of $Cp^*Rh(Me_2PCH_2C_6H_5)(C_6H_5)H$ (Figure 2), which leads to two important conclusions.

1. For these d^8 coordinately unsaturated systems reacting via oxidative addition, the cyclometalation is of no kinetic advantage over the intermolecular metalation, and the energy barrier of the former is 1.05 kJ/mol higher than that of the latter.

2. The thermodynamic picture is the reverse: the cyclometalation is more favorable by 9.66 kJ/mol.

The contributions of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ (the difference between activation parameters of the k_{-1} and k_2 pathways) to $\Delta\Delta G^{\ddagger}$ = 1.05 kJ/mol (51.2 °C), equal to 7.1 kJ/mol and +18.8 J/(K mol), respectively, show that the intramolecular C–H bond activation is more favorable in entropy, but the enthalpy term levels off this advantage.

It is interesting to note that the same tendencies are seen in the "sp^3 C–H" version of the system, equilibrium 12. The cyclometalation is by 2.5 kJ/mol less favorable



(12)

kinetically, but by 18.8 kJ/mol more favorable thermodynamically.[34] The energy profile is, naturally, similar to that in Figure 2 without, however, local minima due to η^2-coordination. It should be pointed out, however, that later Bergman suggested and provided evidence for η^2-coordination of C–H bonds of alkanes with rhodium[39a] and of alkenes with iridium.[39b]

For reaction proceeding in pure solvent, multiplication of the ratio $rate_{intra}/rate_{inter}$ and the solvent concentration (of benzene in this case), taking into account the statistical correction (six and two sites of benzene and Me_2PCH_2Ph, respectively, are attacked), gives the value of the effective molarity. Its numerical values are equal to 5.5 and 3.3 for complexes **5** and **6**, respectively. Qualitatively, the effective molarity is also low in the rhodium(I) complex $[Rh\{N(CH_2CH_2PPh_2)_3\}]^+$, since both intra- and intermolecular arene metalation can be achieved by slight variation of reaction conditions.[40] Remarkably, the intermolecular C–H activation dominates in the case of (trifluoromethyl)benzene as expected for C–H activation by oxidative addition. One may approximately estimate the value for the Ir(I) complex $Cp^*Ir(PPh_3)$, the intermediate in reaction 8, by comparing the relative yields of **4** and $Cp^*Ir(PPh_3)(Ph)(H)$ in benzene.[36] It should be, however, assumed that the product distribution is kinetically controlled. The effective molarity is then 12.6 M and only slightly higher than that for Rh(I) complexes. The complexes considered are thus excellently arranged for easy intermolecular metalation of various C–H bonds.

Earlier an attempt was made to follow the substituent effect on the rate of cyclometalation in $[IrCl\{P(C_6H_4X\text{-}p)_3\}_3]$.[41] The reaction affords $[IrCl](H)\{(XC_6H_3)P(C_6H_4X\text{-}p)_2\}\{P(C_6H_4X\text{-}p)_3\}_2]$ and has a small kinetic isotope effect, and its rate increases in the order F < H < OMe < Me, the influence being, however, small. The dependence obtained suggests an electrophilic character of oxidative addition, but in light of the results presented above, one should treat these data with care, since predissociation of the phosphine ligand may contribute to the overall rate. Thus, the effect observed may not directly refer to the C–H bond cleavage. On the other hand, we will see later that oxidative addition

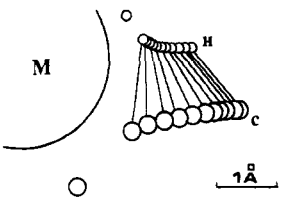
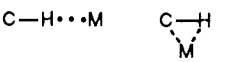


Figure 3. Reaction trajectory for C–H + M → C–M–H. Isolated circles are the final positions of C and H in the product alkyl hydride. Reprinted from ref 46a; copyright 1985 American Chemical Society.

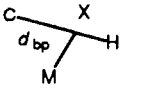
at platinum can occur without preequilibrium loss of the bound phosphine ligand. Therefore, the question of predissociation needs special attention when mechanisms of cyclometalation are under investigation.

There is another remarkable pathway of cyclometalation at iridium(I) centers.[42] Surprisingly, it is acid catalyzed. In contrast to oxidative addition, cyclometalation of $[(cod)Ir\{P(OC_6H_4Me\text{-}o)_3\}_2]^+$, where cod = 1,5-cyclooctadiene, to give $[(cod)Ir(H)\{(MeC_6H_3O)P(OC_6H_4Me\text{-}o)_2\}\{P(OC_6H_4Me\text{-}o)_3\}]^+$ can proceed by a catalytic pathway ($k_{obsd} = k[H^+] = kK_a^{1/2}[HClO_4]_{tot}^{1/2}$ in acetone) that entails oxidation of Ir(I) by external protons, affording $[(cod)Ir(H)\{P(OC_6H_4Me\text{-}o)_3\}_2]^{2+}$ prior to the cyclometalation step. Ring closing, as suggested,[42] most probably occurs by an electrophilic displacement mechanism as the oxidative addition pathway would require an Ir(V) dihydride intermediate, which seems unlikely.

We now discuss the dynamics of nucleophilic cleavage of C–H bonds by metal centers and the mutual orientation of the metal and C–H bond during the cleavage. From the theoretical standpoint of interest is the geometry, linear ("open", end-on approach) or triangular ("closed", side-on approach), of the transition state of the C–H bond cleavage.[43] The aspects of the transi-

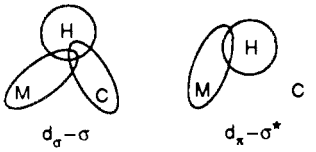


tion-state structure are closely linked with the now very popular problem of agostic contacts.[44] They are the nonbonding interactions between C–H bonds and metal centers registered by spectral or crystallographical means. With care they can be treated as inverted, reverse hydrogen bonds since the electron density from C–H bonds can be transferred to a metal. The energy of agostic contacts is also close to that of normal hydrogen bonds. For instance, the stabilization of Cp_2WMe_2 due to the agostic interaction of one methyl group with tungsten reaches 11.3 kJ/mol.[45] The dynamics of the C–H bond cleavage by nucleophilic metal centers has recently been considered in detail by Crabtree.[46a] Valuable information, as suggested, may be gained from analyses of the d_{bp} distance between the metal and the bonding pair of electrons (bp) of the C–H bond, point X. The latter corresponds to the point of

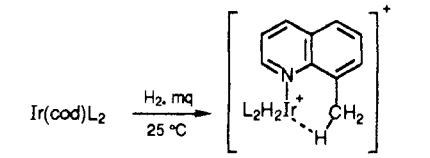


meeting of covalent radii of atoms C and H. To minimize the effect of the metal nature on d_{bp}, the parameter r_{bp} was introduced: $r_{bp} = d_{bp} - r_M$, where r_M is the covalent metal radius. The value of r_{bp} is thus characterizing the effective covalent radius. If the value of

r_{bp} is large (≈1.0–1.5 Å), one can speak about weak agostic interactions; if r_{bp} is small (≈0.4–0.5 Å), strong contacts are implied. If r_{bp} exceeds 1.9 Å, these are the trivial van der Waals interactions. The dependencies of both d_{bp} and the angles MHC on r_{bp} can shed some light on the C–H + M → C–M–H reaction trajectory by using the method of Burgi and Dunitz.[47] As seen from Figure 3, the C–H bond is not significantly lengthened until the C–H bond approaches very close to the metal. This implies a late transition state. The M–H–C angle at H, 130° (not 180°) at large r_{bp}, falls rapidly as r_{bp} decreases. This implies that at the transition state considerable steric interference between the ligands at the metal and the substituents at the carbon of the C–H bond is to be expected. This may be the reason for the high activation barriers of nucleophilic cyclometalation observed in rhodium(I) complexes (Figure 2). The angle of 130° reflects the most favorable mutual arrangement of the C–H bond and the metal for the interaction of both the d_σ metal orbital with the bonding pair of electrons of the σ C–H bond and the d_π orbital with the σ* orbital of the C–H bond (back-donation). The interactions of both types favor C–H bond breaking. This discussion supports the triangular geometry of the transition state of nucleophilic cyclometalation. At the same time, it is obvious that in such systems the rigid orientation of the reacting fragments may result in a pronounced strain in complexes, which seems to be very unfavorable for intramolecular metalations, thus opening channels for intermolecular processes.



There is another important point in cyclometalation by any centers, i.e., the question of aromatic versus aliphatic C–H bond activation.[25,26] It is generally agreed that examples of C–H bond oxidative addition are much more numerous for aromatic than for aliphatic or benzylic C–H groups. According to Crabtree,[46b] two types of explanations can be advanced to account for this observation. One suggestion, based on kinetic arguments, is that the arene group can bind to the metal, for example, in an η^2 fashion[38] followed by oxidative addition. A second explanation is thermodynamic. In this idea, the deciding factor is the greater bond strength for an M–C(aryl) over M–C(alkyl) or M–C(benzyl) bond. A recent report from Crabtree's group has shed some light on this problem[46b] by a comparative study of reactions 13 and 14. The former, involving 8-methylquinoline, leads to a compound with a C–H···Ir bridge, while the latter affords a cyclometalated derivative of 7,8-benzoquinoline. The latter ligand, when it binds through the quinoline nitrogen presents an aromatic C–H bond to the metal in an end-on C–H···M fashion. Initial η^2-binding is considered[46b] to be very unlikely. However, the cyclometalation of 7,8-benzoquinoline as well as the formation of the C–H···M bridge in reaction 13 occurs rapidly, suggesting that the discrimination is not kinetic in nature. Note that the 8-methyl group of 8-methylquinoline is isotopically labeled over ca. 90 min at 25 °C by exposure of the complex to D_2, indicating oxidative addition of the agostic



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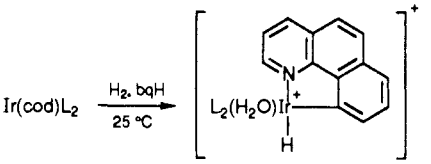
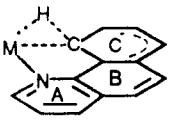


(14)

mq = 8-methylquinoline, bqH = 7,8-benzoquinoline, L = PPh_3, cod = 1,5-cyclooctadiene

C–H proton to the metal. These results confirm the importance of thermodynamic rather than kinetic factors in C–H activation.

Since free arenes are not activated by $Ir(cod)L_2$ under these conditions (the effective molarity is high in this case), it is reasonable to imagine that the quinoline nitrogen of 7,8-benzoquinoline binds before aryl C–H bond cleavage. η^2 intermediates are unlikely because this would lead to unacceptable strain in the chelate ring. As long as the arene remains planar, the C–H bond can only approach the metal end on rather than side on. However, as discussed above, the transition state must be of the side-on type. A possible way out of this contradiction is to allow the ligand to twist as shown in the following diagram:

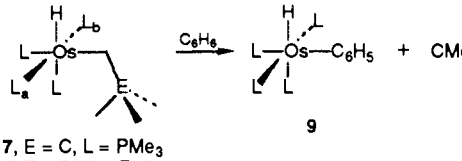


Partial rehybridization of the C–H carbon toward sp^3 in the transition state may be involved here, and this shows a possible bridge between oxidative addition and arene electrophilic substitution mechanisms.

B. d⁶ Complexes of Rhenium(I), Osmium(II), and Other Species

The d^6 osmium(II) and rhenium(I) systems have much in common with d^8 complexes of rhodium(I) and iridium(I) described in the previous section. The identity arises from the common nucleophilic pathways of the C–H bond cleavage and an ability to metalate both internal and external carbon–hydrogen bonds. Dissimilarities concern the preparation of the complexes for the C–H bond activation. The coordinately unsaturated 16-electron species of osmium(II) are generated on thermolytic phosphine dissociation, while 15-electron complexes of rhenium(I) are produced on photolytic departure of coordinated trimethylphosphine.

The following transformations occur in octahedral osmium(II) complexes.[48] Neopentyl hydridic complex 7 is cleanly thermolyzed in benzene at 80 °C according to eq 15. The reaction is strongly retarded in the

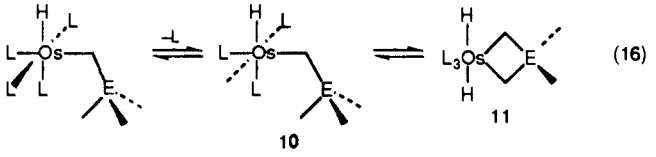


(15)

7, E = C, L = PMe_3
8, E = Si, L = PMe_3

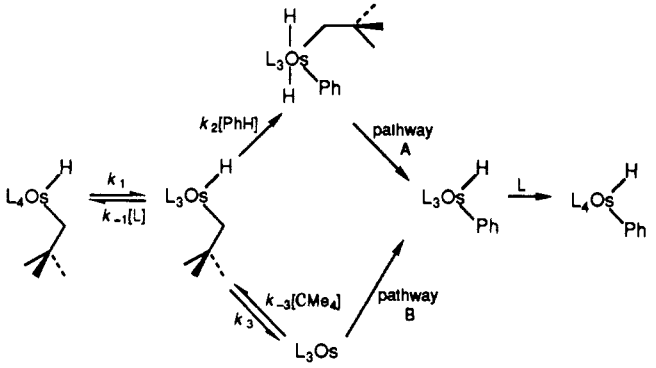
9

presence of added trimethylphosphine, indicating the necessity of its preequilibrium departure. Experiments with $P(CD_3)_3$ have revealed that the deuterium-labeled ligand is first introduced into positions a and b; i.e., the phosphine ligands mutually trans are the most labile. Besides, thermolysis of $L_4Os(H)[CH_2C(CH_3)(CD_3)_2]$ in C_6H_{12} leads to randomization of the deuterium label. This is a consequence of reversible cyclometalation of the neopentyl ligand as shown in eq 16. Qualitative

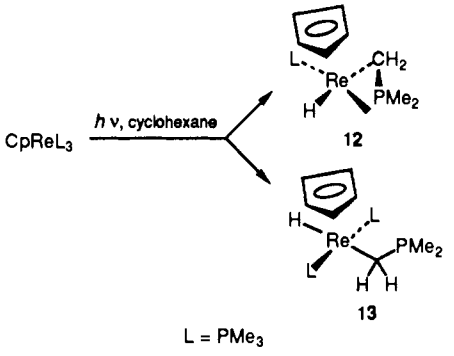


(16)

rate measurements by dynamic ^1H NMR have demonstrated that the rate of cyclometalation is somewhat lower than that of the exchange of the phosphine ligands but higher than that of intermolecular metalation of benzene. Evidently, both the benzene metalation affording **9** and the cyclometalation to give **11** involve the common intermediate **10**. The kinetic study of the formation of **9** allowed discrimination between the two principally different mechanisms of the C–H bond activation: by d^6 osmium(II) complexes (pathway A) or by d^8 osmium(0) complexes (pathway B). The absence of both the inhibition of the reaction by CMe_4 and intermolecular activation of added CMe_4 is indicative of pathway A. The osmium(II) complex does not increase its nucleophilicity prior to reaction by reductive elimination of CMe_4, as complexes of rhodium(III) and iridium(III) do (section IV.A).



Similar reactivity trends can be followed in rhenium(I) complexes.[49] Irradiation of $CpReL_3$ (L = PMe_3) even at 5–10 °C in cyclohexane gives two similar complexes **12** and **13**. In solvents more useful for intermolecular



C–H bond activations compared with cyclohexane, the irradiation, as expected, affords complexes such as $CpRe(H)L_2(R)$, where R = Ph, $HC{=}CH_2$, c-C_3H_5, and n-C_6H_{13}. It should also be pointed out that thermolytic activation of **12** in the corresponding solvent also provides the products of intermolecular metalation, $CpRe(H)L_2(R)$.

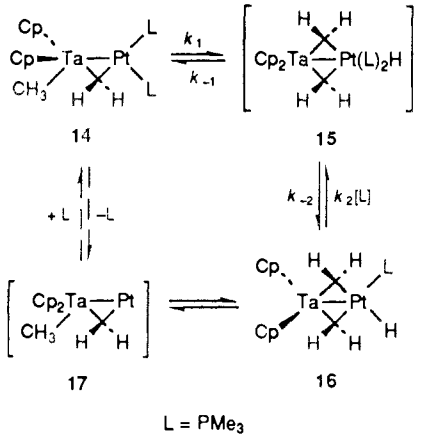
"Coordinative holes" in the rhenium complexes, where initial reductive elimination is principally impossible, may be created in two ways: via dissociation of L or $\eta^5 \rightarrow \eta^3$ isomerization of the cyclopentadienyl ligand. The latter was ruled out on the basis of the study of deuterium distribution in the products.

The unique feature of these systems is the formation of **13**. Three possible routes to the compound are discussed:[49] (i) via clear-cut intermolecular activation of PMe_3 by the coordinately unsaturated intermediate; (ii) via intramolecular activation of the C–H bond without preliminary dissociation of trimethylphosphine; and (iii) via intermolecular nucleophilic attack of complex **12** on trimethylphosphine. The second pathway was found to be operative.

It should be emphasized that both complexes of osmium(II) and rhenium(I) were constructed as *intermolecular* "activators" of the C–H bonds. The ligands that underwent cyclometalation, especially in the case of rhenium complexes, were far from being the most convenient for internal metalation. Nevertheless, cyclometalation still occurs. Intermolecular processes become dominating only at lowered temperatures when kinetic control plays the key role.[49]

It would be erroneous to associate oxidative addition cyclometalation solely with complexes of metals in low oxidation states. A striking example is the reactivity of the d^2 rhenium(V) complex $ReH_5(Pcy_3)_2$ (cy = cyclohexyl) formed on mild (60 °C, benzene) thermolysis of the fluxional complex $ReH_7(Pcy_3)_2$.[50] This species exchanges hydrogen with hexadeuteriobenzene. Remarkably, deuterium is incorporated into the complex not only as hydride ligands but also selectively at the C2 and C3 carbons of all cyclohexyl rings, indicating cyclometalation. Only one of the two methylene hydrogens at each of these carbons is exchangeable, the rate at C3 being higher than at C2. Oxidative addition of the corresponding C–H bonds is believed to be involved, and the formation of the five-membered metallacycle (metalation at C3) is faster than the four-membered one (metalation at C2).

It would also be erroneous to think that cyclometalation via oxidative addition is always associated with the formation of coordinately unsaturated intermediates. It is a rare example in platinum chemistry when rapid, reversible intramolecular C–H oxidative addition in heterodinuclear transition-metal complex **14** occurs without dissociation of PMe_3 from the metal.[51a] Thermal conversion of **14** to **16** is a smooth first-order process ($k = 3.3 \times 10^{-4}$ s^{-1} in benzene at 40 °C), with $\Delta H^{\ddagger} = 97.8$ kJ/mol and $\Delta S^{\ddagger} = 1.4$ J/(K mol). The near-zero value for $\Delta S^{\ddagger}$ is consistent with a nondissociative rate-determining step. The arguments against **17** as a possible intermediate were based on the rate measurements of both the reversible reaction, i.e., the phosphine-induced **16** → **14** rearrangement (first order in PMe_3), and the conversion of **16** to **17**. The former reaction is by a factor of 36 faster than the latter, indicating different intermediates. Therefore, it was suggested that **14** undergoes cyclometalation through



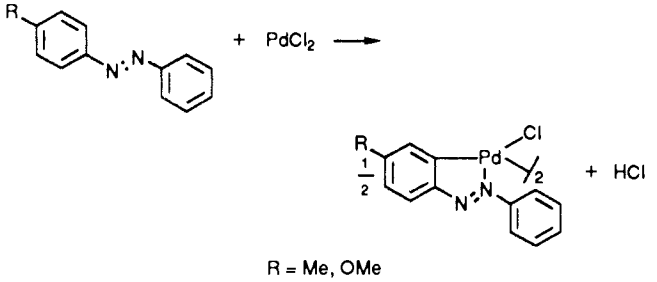
15 in a way the reverse reaction does.

The rearrangement of binuclear complex 14 is the only example of cyclometalation involving clusters considered in this review. Evidently, mechanisms operating here are generally more complicated than those observed at mononuclear species (see, for example, ref 51b). It is clear that cyclometalation involving clusters needs separate treatment, which is beyond the scope of the present review.

V. Cyclometalation: Electrophilic Systems (d^8 Complexes of Palladium(II) and d^6 Complexes of Cobalt(III))

The chemistry of cyclopalladated compounds is very rich. Launched by Cope,[52] it grew very rapidly because of the reasons stated in the Introduction. Dunina has recently devoted a special review with 232 references to these particular compounds.[10] The reader will find there numerous examples of cyclopalladation with various ligands. Although practically every report on cyclopalladation concluded with mechanistic discussion, only a few of them were directly aimed at elucidation of intimate mechanisms and supported by kinetic data. Therefore, it seems reasonable to concentrate attention here on pure mechanistic aspects of cyclopalladation provided by the references to the previous works which go in line with present methodology.

As an agent for the intramolecular activation of C–H bonds, palladium(II) was historically classified as a typical electrophile.[52-55] Such a conclusion has been made on the basis of general properties of this element and its location in the products of cyclopalladation of complex molecules (section II.B). In particular, Tsuji was first to report[53] that cyclopalladation of asymmetrically substituted azobenzenes leads to a palladium–carbon σ bond formed preferentially with the benzene ring having an electron-donating group:



A similar study on fluoro-substituted azobenzenes was reported by Bruce.[54] Hiraki presented a typical exam-

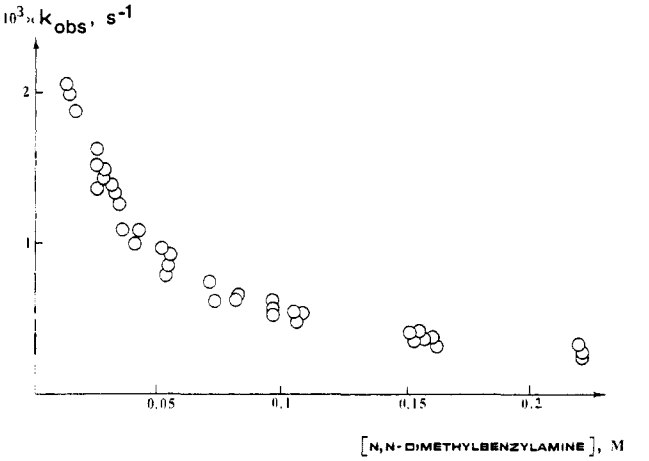
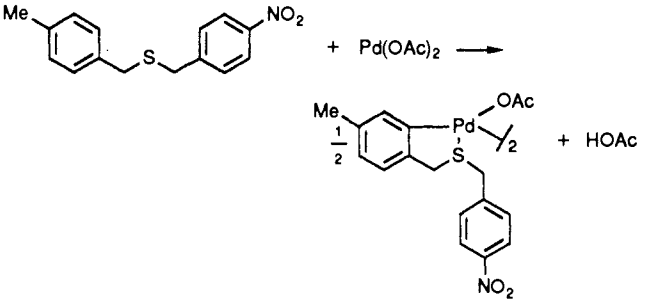


Figure 4. Pseudo-first-order rate constants k_{obsd} of reaction 17 plotted against the *N,N*-dimethylbenzylamine concentration (25 °C, chloroform). Reprinted from ref 35; copyright 1985 Royal Society of Chemistry.

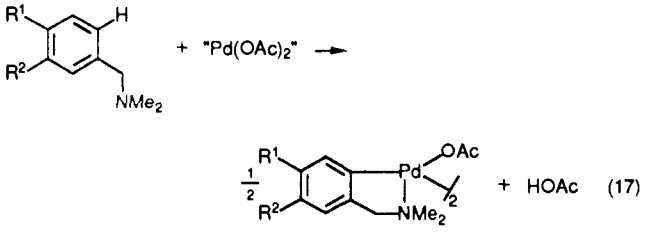
ple utilizing asymmetrically substituted dibenzyl sulfide:[55]



Some other examples are discussed in section V.D. Recent studies have demonstrated that the single word "electrophilic" does not encompass the entire "cyclochemistry" of palladium(II). Examples are given below of instances where this "typical electrophile", on the basis of kinetic and thermodynamic evidence, behaves as a nucleophilic center in its reactions with aromatic C–H bonds.

A. Mechanism of Cyclopalladation (Exemplified by Substituted *N,N*-Dimethylbenzylamines)

With the indulgence of other authors, historical aspects are not included in this section, and for convenience, the discussion is concentrated around the kinetic investigation of reaction 17 carried out in the laboratory of the author.[35]



R^1, R^2 = Cl, H, Me, OMe

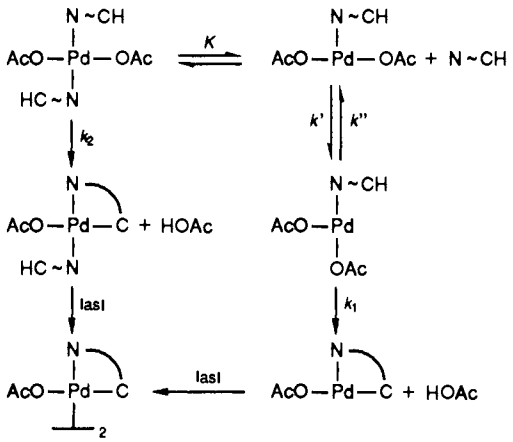
Reaction in Chloroform. As is known[56,57] palladium(II) acetate exists as the $Pd_3(OAc)_6$ trimer in the majority of solvents, including chloroform. In the presence of an excess of amines (N∼CH), the trimers are depolymerized into the monomers *trans*-$[Pd(N{\sim}CH)_2(OAc)_2]$.[58-60] If amines undergo cyclopalladation, the

TABLE II. Equilibrium and Kinetic Parameters of Reaction 17[a]

amine	$[Pd(OAc)_2(N\sim CH)_2]$ 298 K 10^2K, M	10^3k_1, s^{-1}	$Na_2Pd_2(OAc)_6$ 323 K 10^4k_{21}, s^{-1}
$3,4\text{-}(MeO)_2C_6H_3CH_2NMe_2$	2.7	6.1[b]	4.4
$4\text{-}Me_{C6}H_4CH_2NMe_2$	1.5	5.0	4.2
$C_6H_5CH_2NMe_2$	1.35	4.3	7.6
$4\text{-}MeOC_6H_4CH_2NMe_2$	2.0	2.7	3.5
$4\text{-}ClC_6H_4CH_2NMe_2$	2.9	1.0	14.8

[a] From ref 35. [b] Statistically corrected doubled value.

SCHEME I



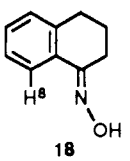
latter complexes transform into the palladacycles $[Pd(N\sim C)(OAc)]_2$.[35,59] Consequently, at least in an excess of amines, the monomers *trans*-$[Pd(N\sim CH)_2(OAc)_2]$ should be considered as starting materials in cyclopalladation.

Figure 4 shows the dependence of k_{obsd} of reaction 17 as a function of *N,N*-dimethylbenzylamine concentration.[35] We will also meet such plots when cycloplatination is considered. Kinetic eq 18, corresponding

$$k_{obsd} = \frac{k_1K + k_2[N\sim CH]}{K + [N\sim CH]} \qquad (18)$$

to Figure 4, reflects the fact that cyclopalladation occurs via two parallel routes through the coordinately unsaturated 14-electron complex $[Pd(N\sim CH)(OAc)_2]$ (k_1) and the coordinately saturated 16-electron complex $[Pd(N\sim CH)_2(OAc)_2]$ (k_2). In the case of *N,N*-dimethylbenzylamine at 25 °C, $k_1 = 4.3 \times 10^{-3}$ s^{-1}, while $k_2 = 3.1 \times 10^{-5}$ s^{-1}; i.e., $k_1 \gg k_2$. In other words, the 16-electron pathway is practically insignificant when comparable concentrations of palladium(II) and metalating ligand are employed. Scheme I shows the corresponding mechanism of cyclopalladation.[35]

The reversible dissociation of amine producing the 14-electron reactive intermediate plays the key role in Scheme I. The necessity of the latter was first postulated by Deeming,[61,62] who studied the regioselectivity of cyclopalladation (see section IV.D.2). Nielson[63] arrived at the same conclusion, performing a ^1H NMR investigation on the cyclopalladation of 1-tetralone oxime (18) by Li_2PdCl_4. It has also been proposed that



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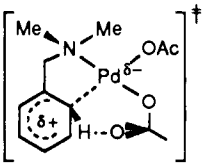
the bis-adduct $[PdCl_2(N\sim CH)_2]$ is not on the reaction coordinate, but the true intermediate is the 14-electron complex *cis*-$[PdCl_2(N\sim CH)]$, isolated as the tetraaqua solvate. In addition, another remarkable feature has been noted. The proton H^8 in $[PdCl_2(N\sim CH)_2]$ is deshielded and lies over the palladium plane. In the reactive 14-electron intermediate *cis*-$[PdCl_2(N\sim CH)]$, this proton, on the contrary, is shielded and localized in the palladium plane. The facts described convincingly show that cyclopalladation most readily occurs in the palladium plane of a 14-electron intermediate.

Let us return to Scheme I. After the dissociation and isomerization of the T-shaped intermediate (which proceeds very fast in the square-planar complexes[64,65]), the rate-limiting C–H bond breaking takes place. The kinetic isotope effect $k_1(H)/k_1(D)$ is 2.2.[35] Kinetically, this step is electrophilic since the rate constants k_1 progressively increase as the donor strength of the ring substituents in *N,N*-dimethylbenzyl amines increases (the slope of the corresponding Hammett plot is −1.6 against σ_m) (Table II). The activation parameters of the rate-limiting step, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, are 11 kJ/mol and −254 J/(K mol), respectively, and are in accord with "early", highly ordered transition state **19**, in which the bond making dominates and the leaving proton is accepted by a base, acetate in particular. Such a ra-



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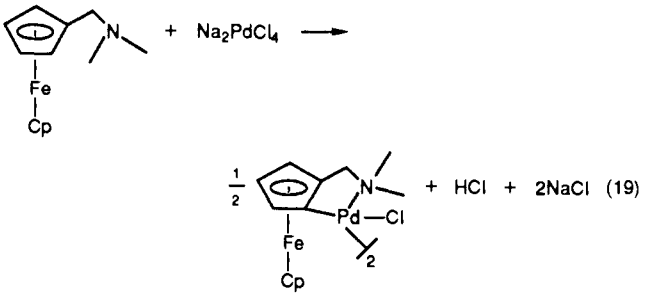
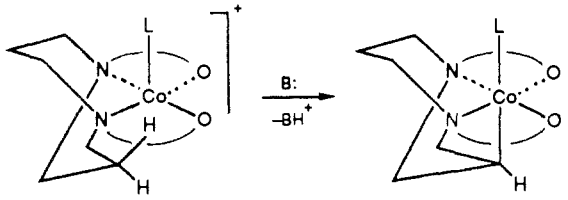
tionalization of the rate-limiting step of cyclopalladation is strongly supported by the accepted views on cyclopalladation as an electrophilic process,[53-55,66,67] direct evidence for the general-base catalysis in orthopalladation of azobenzene,[68] and asymmetric induction during palladation of ((dimethylamino)methyl)ferrocene in the presence of the sodium salt of (*S*)-(+)-*N*-acetylvaline[69] (eq 19). Incorporation of the optically active carboxylate in the transition state of type



20

19 results in the formation of the (*R*)-(+) enantiomer of 20. The base catalysis is even more pronounced in intramolecular metalation involving the d^6 complex of cobalt(III).[70] Here a base effectively removes the leaving proton from the agostic C–H bond to afford cobaltacycle 21:



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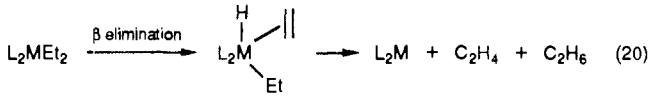
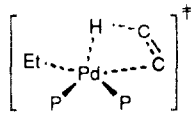
We have already mentioned that the 16-electron pathway of cyclopalladation governed by the rate constant k_2 from the practical point of view is much less important than the 14-electron one (k_1). But from a theoretical standpoint the pathway is worth mentioning, since its nature is still poorly understood. Actually, for reaction 17 it is only known that such a pathway does in fact exist and it is by a factor of 100 less effective than the 14-electron one. There are, however, some helpful analogies in the literature, for example, the thermolysis of the diethylpalladium(II) complexes *trans*-[$PdEt_2(PR_3)_2$] liberating a mixture of ethane and ethene as the major organic products.[71] Unexpectedly, the excess of the corresponding phosphine PR_3 only slightly retards the thermolysis, and at high [PR_3] the reaction rate levels off. The inhibitory effect decreases in the series $PEtPh_2 > PMePh_2 > PEt_2Ph$, i.e., with a lowering of the Tolman cone angles of the phosphines,[72] but in the case of PMe_2Ph, there is no retardation at all. The thermolysis rate also decreases in this series. The thermolysis proceeds mainly through a 16-electron pathway, occurring as a typical β elimination (eq 20)



(20)

without deuterium scrambling, and is characterized by a kinetic isotope effect $k(H)/k(D)$ of 1.4. To achieve the favorable interaction between the β hydrogen and the axial palladium(II) site, both the lengthening of the Pd–C bond and the bending of the Pd–C^α–C^β angle are necessary. By bending away the two phosphine ligands from the plane and allowing the approach of a β hydrogen of one of the ethyl groups toward palladium through the space above the molecular plane, the complex is brought to a configuration close to trigonal-bipyramidal 22.



22

This 16-electron pathway seems to be rather general for reactions of square-planar complexes, including cyclopalldation. Whether it will occur probably depends on the ability to undergo a transition from the square-planar configuration with a hint of even weak axial agostic C–H···M contacts to a trigonal-bipyramid. The isomerization may relieve strain of the coordination sphere and create a center for the C–H bond cleavage. To some extent the isomerization may be considered as an alternative to the ligand dissociation in the 14-electron pathways. The necessary but not sufficient condition for its realization is the existence of the axial agostic contacts in 16-electron complexes [$PdX_2(Z{\sim}CH)_2$]. Such contacts are in fact observed in the azobenzene complex [$PdCl_2(PhN{=}NPh)_2$],[73] which more likely undergoes cyclopalladation through the 16-electron pathway.[68] A similar mechanism was suggested to account for cyclopalladation of the *tert*-butyl group in the hydride complex *trans*-PdH(X)(P-*t*-$Bu_3)_2$ (X = Cl, CF_3COO) which is accompanied by evolution of H_2.[74] At the same time several related structures with agostic contacts have been reported[75] that do not undergo further cyclopalladation.

Reaction in Acetic Acid. A remarkable feature of reaction 17 is observed when the process is performed in acetic acid solvent: palladium(II) is no longer a "typical electrophile" in this medium.[35] In the presence of NaOAc, when the dominating species is $Na_2Pd_2(OAc)_6$,[76] the reaction rate is given by

$$\text{rate} = k_{21}[\text{amine}][\text{Pd(II)}]/[\text{NaOAc}] \qquad (21)$$

where the rate constants k_{21} increase upon increasing the electron-withdrawing properties of the ring substituents of the *N*,*N*-dimethylbenzylamines. The corresponding Hammett coefficient ρ is now equal to +1.4 (σ_p).[35] It should be pointed out, however, that under these conditions, the cleavage of the ortho C–H bonds is not rate determining ($k(H)/k(D) = 1.05$). The same is likely true for palladation of 3,2′-annelated 2-phenylpyridines by palladium(II) acetylacetonate.[77] In these cases the ligand environment around palladium is very large and thick. Hence, the rate-limiting steps are associated with the necessity of its rupture.

B. Effective Molarities in Cyclopalladation

The intermolecular activation of benzene by palladium(II) is much more difficult than its intramolecular activation. Until recently, there were no such examples in aprotic solvents. The first reported activation by palladium(II) was carried out in benzene at 70 °C in the presence of dialkyl sulfides to afford the trimer [$(R_2S)PhPd(\mu\text{-}OAc)_2Pd(\mu\text{-}OAc)_2PdPh(SR_2)$], where R = *t*-Bu and *t*-$BuCH_2$.[78] The reactions proceeding in acetic and trifluoroacetic acid media were studied in much more detail.[79-82] In aqueous acetic acid the reaction between benzene and palladium(II) gives biphenyl as a final organic product, but the rate-limiting step is $PhH + Pd(II) \rightarrow PhPh^+ + H^+$.[79] The estimate of the corresponding second-order rate constant in pure HOAc at 25 °C, when $Pd(OAc)^+$ is the reactive species, is 3.7×10^{-5} M^{-1} s^{-1}.[35,79] If one uses the value of k_1 for $PhCH_2NMe_2$ from Table II as the rate constant for the corresponding intramolecular process and takes into account the statistical correction, it is possible to estimate the lower limit for $k_{intra}/k_{inter} = 3.6 \times 10^2$ M. The real effective molarity is even higher, since the intermolecular process under the intramolecular conditions used simply does not occur and the rate constant cannot be measured. Thus, in electrophilic cyclometalation the effective molarities are large, accounting for the readiness of intramolecular processes.

TABLE III. Stability Constants of the Complexation of Ag(I) with Various Butylamines at 25 °C[a]

amine	log K_1	log K_2
n-$BuNH_2$	3.43	4.05
i-$BuNH_2$	3.38	3.86
t-$BuNH_2$	4.01	4.25
$(n$-$Bu)_2NH$	3.14	3.42
$(s$-$Bu)_2NH$	3.38	2.94
$(n$-$Bu)_3N$	2.22	1.60

[a] Taken from: Sillen, L. G.; Martell, A. E. *Stability Constants of Metal-Ion Complexes*; The Chemical Society: London, 1964.

C. Comment on One Old Problem (Why Tertiary Amines Are the Best)

There is a fundamental rule in the chemistry of orthopalladated compounds: direct activation of C–H bonds by palladium(II) to afford corresponding palladacycles is the most feasible in the case of tertiary amines, whereas primary and secondary amines are usually inert toward such activation.[52b] Recent findings of Dunina,[83] who developed a procedure to orthopalladate secondary amines via C–H bond cleavage, and Avshu,[84] who showed a way to palladacycles with primary amines, did not, however, change the general situation, since both approaches have obvious limitations.

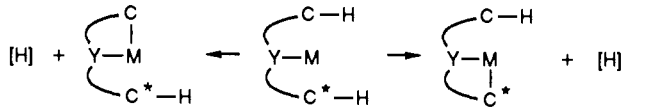
The unique properties of tertiary amines were first accounted for in terms of stronger binding to the metal of primary and secondary amines compared with tertiary ones, thus preventing effective electrophilic attack of palladium(II) on the aromatic ring.[52b] Shaw, on the contrary, has suggested[85] that steric factors are not less important than electronic factors. By analogy with known phenomena in organic chemistry, the *gem*-dialkyl effect was proposed to play a major role, since polysubstituted compounds lose less internal entropy on cyclization compared with the parent compounds. Although both explanations seemed reasonable, one could hardly imagine their mechanistic nature, since neither was bound to a true mechanism of orthopalladation.

The mechanism of cyclopalladation in Scheme I, precisely its "dissociative" 14-electron pathway, allows one to propose the kinetic–thermodynamic rationalization of the phenomena. Its quintessence is in the following: tertiary amines are, at least partly, the best for cyclopalladation because they have the most favorable equilibrium constants K to provide the reactive coordinately unsaturated species. Unfortunately, there are no appropriate literature data to support this statement in palladium chemistry. The corresponding data for the complexation of Ag(I) with various butylamines (Table III) do, however, support it. Silver(I) forms linear bis(amine) complexes that can mimic the square-planar Pd(II) species, since the behavior of only trans-coordinated amines is of particular interest now.

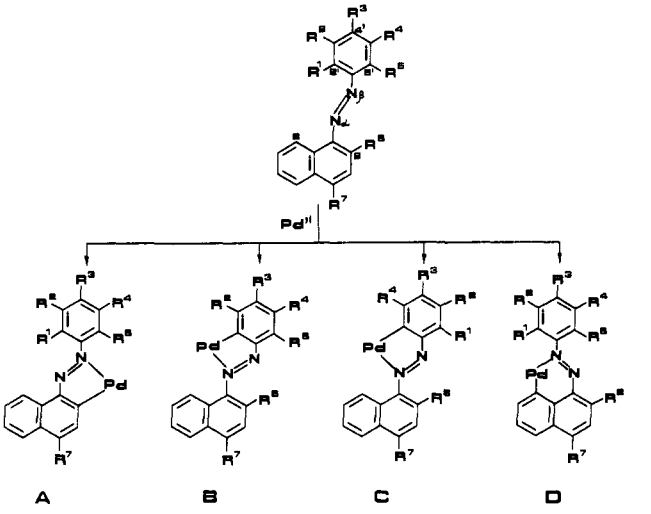
Inspection of Table III clearly shows that log K_1 values are almost independent of the nature of the amines. Only a small decrease in log K_1 is observed for $(n$-$Bu)_3N$. The situation is reversed for log K_2. The latter drops from 4.05 to 1.60 on going from n-$BuNH_2$ to $(n$-$Bu)_3N$. It is noteworthy that log K_2 decreases to 2.94 for the branched secondary amine as well. These data demonstrate that tertiary amines have an evident tendency to form weak bis complexes and can easily provide coordinately unsaturated species. The same is probably true for highly branched secondary amines, the steric crowding of which lowers log K_2, providing a channel for subsequent orthopalladation.

Data in Table III also reveal that the pathway in question is impossible for primary amines: the second amine has no tendency to dissociate because of too strong binding to the metal. However, the vacant coordination site at palladium in this case can be alternatively generated by removing one acido ligand X, as has been recently shown.[84] Abstraction of iodide by Ag(I) from *trans*-$[Pd(PhCH_2NH_2)_2I_2]$ in EtOAc initiates orthopalladation of the primary amine undoubtedly via the formation of a three-coordinate intermediate.

SCHEME II



SCHEME III



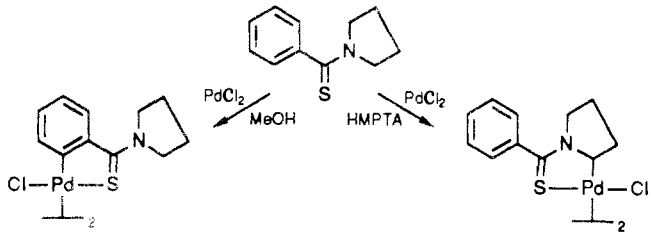
D. Regioselectivity of Cyclopalladation

A ligand may have two or more activated C–H bonds (Scheme II). If metalation of several C–H bonds can occur, the problem of regioselectivity of cyclometalation, which has two different levels, arises. The first, more trivial level will be referred to as *enforced* regioselectivity when electronic, steric, or other factors make only some one route of cyclometalation possible. The second level, referred to as *regulated* regioselectivity, has the advantage that by changing the reaction conditions one may drive cyclometalation along any path available.

1. Enforced Regioselectivity

Cyclopalladation, as was mentioned above, for a long time was thought to be an electrophilic process. This was concluded from studies of enforced regioselectivity. In particular, substituted azobenzenes were cyclopalladated at the electron-rich rings.[53,54] A similar study was carried out on 4-methyl-4′-nitrodibenzyl sulfide,[55] and results of an exhaustive investigation of various aspects of enforced cyclopalldation are depicted in Scheme III.[66] There are four possible ways to palladate 1-arylazonaphthalenes. The unsubstituted molecule (R^1–R^7 = H) gives complex A in accordance with the highest electron density at ^{2}C-H. Even strong donors

SCHEME IV



at position 4′ (R^3 = Me, OH, OMe) enhancing the electron density at N^α do not change the reaction pathway. Only when position 2 (R^6 = Me) is protected does attack at the phenyl ring provide isomer B. Further, elimination of C–H bonds at positions 2′, 6′, and 2 ($R^1 = R^5 = R^6$ = Me) gives only complex D if R^3 = OH. One can deactivate position 2 by electronic factors. If R^3 = OMe and $R^7 = NO_2$ (remaining R = H), the ratio of isomers A and B is equal to 33:67, but if R^3 = OH, R^5 = Me, and $R^7 = NO_2$, complex B is exclusively formed (an interesting effect of the OH group). As shown here and from other data, the regioselectivity of cyclopalladation of aromatic azo compounds is governed by (i) the relative nucleophilicities of the aromatic palladation sites and (ii) the relative affinities of palladium(II) toward nitrogen donors N^α and N^β. This can be achieved by (i) introduction of strong donors or acceptors, (ii) shielding of one of the two nitrogens of the azo bridge, and (iii) blocking C–H bonds by such groups that cannot be readily palladated.[66]

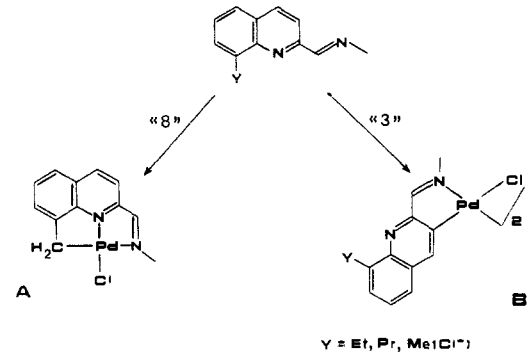
Another way to achieve enforced regioselectivity is associated with the presence of strong donor centers in molecules that on complexing with palladium(II) can crucially affect the course of cyclopalladation.[86]

2. Regulated Regioselectivity

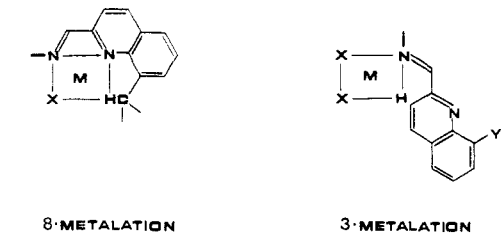
Consider first the examples when palladium(II) attacks either sp^2 or sp^3 C–H bonds. The reaction between *N*-thiobenzoylpyrrolidine and $PdCl_2$ leads in methanol to the palladation of the phenyl ring, while in hexamethylphosphorous triamide (HMPTA), the saturated cycle is metalated[87] (Scheme IV). The authors provided no explanation for this remarkable effect. The situation is more apparent in methanol solvent, where the electrophilic activation is probably realized and, hence, aromatic C–H bonds appear to be more reactive than the aliphatic ones. Due to the high donicity of HMPTA,[88] palladium(II) chloride must exist as the solvate $Pd(HMPTA)_2Cl_2$ in the medium. Therefore, the electrophilic strength of the metal should be considerably decreased, eliminating the sp^2 pathway. The unresolved question is now why the activation of the pyrrolidine ring takes place. One of the possible reasons is an increase of the C–H acidity of the α C–H bond of the pyrrolidine cycle in very polar HMPTA, which facilitates palladation.

The competition between sp^2 and sp^3 C–H bonds manifests itself also in cyclopalladation of 8-methylquinoline-2-carboxaldehyde *N*-methylimine by palladium(II) acetate[62,89] (Scheme V). In methanol 8-metalation occurs, giving complex A. Addition of Cl^- stimulates the formation of B, only the latter isomer being formed in a 52% yield when $[Cl^-]:[Pd(II)] = 5.5$.[62] Note that if 8-R = Et or *i*-Pr, only the products of 3-metalation are produced; i.e., enforced regioselectivity

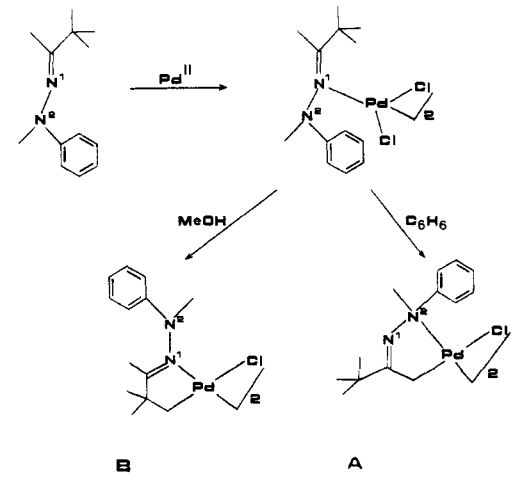
SCHEME V



SCHEME VI



SCHEME VII

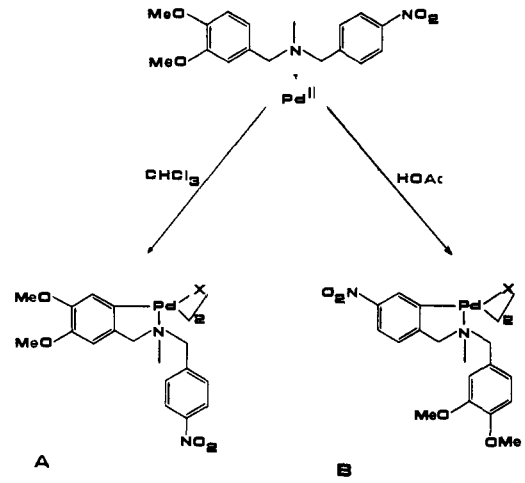


is realized. The chemistry in Scheme V is in full accord with the mechanism of cyclopalladation discussed above. Its postulates about the 3-coordinate intermediate and the metalation in the palladium plane perfectly account for the effect of added chloride (Scheme VI).

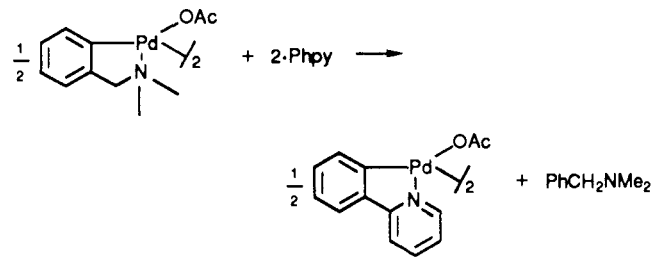
Next come the reactions in which C–H bonds of the same nature are cyclopalladated. Activation of aliphatic C–H bonds of the methylphenylhydrazone of pinacolone follows the formation of the dimeric complex with the Pd–N^1 bond[90] (Scheme VII). The latter in benzene or methylene chloride rearranges to metallacycle A in which the methyl group is activated and N^2 is the donor center. On the contrary, in methanol in the presence of NaOAc the *tert*-butyl group undergoes palladation to form B. The rationalization involved the equilibrium between the N^1- and N^2-bound coordination complexes.[90]

Solely the nature of solvent is responsible for the regioselectivity of cyclopalladation of the bifunctional dibenzylamine[91,92] (Scheme VIII). In chloroform, in which palladium(II) acetate exhibits electrophilic properties, the cyclopalladation is aimed at the dimethoxy-substituted ring, while in acetic acid the ni-

SCHEME VIII



tro-substituted ring is metalated. Moreover, if isomer A is thermolyzed in HOAc at 70 °C for 4 h, it quantitatively rearranges into B. The formation of B in HOAc is run by both the kinetic[35] and thermodynamic[91] affinity of palladium(II) to electron-poor aromatic rings of amines in acetic acid solvent. The intramolecular isomerization of A into B, related to various intermolecular ligand-exchange processes,[93] exemplifies the electrophilic version of the σ C–H bond metathesis.[94] As an example of intermolecular exchange process, consider the palladium(II) migration from cyclopalladated *N,N*-dimethylbenzylamine to 2-phenylpyridine that takes place on mild thermolysis in acetic acid:[91]



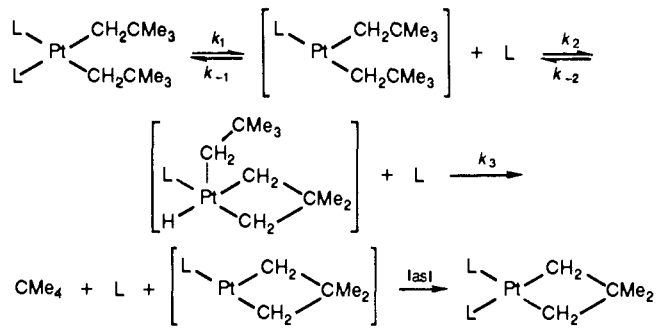
The mechanism of this exchange is dissociative; i.e., the cleavage of the starting palladacycle occurs in the transition state but not the formation of a new Pd–C bond.

VI. Cyclometalation: Masked Nucleophilic Pathways

A. Mechanism of Thermal Metalation in Dineopentylbis(triethylphosphine)platinum(II) and Related d^8 Complexes

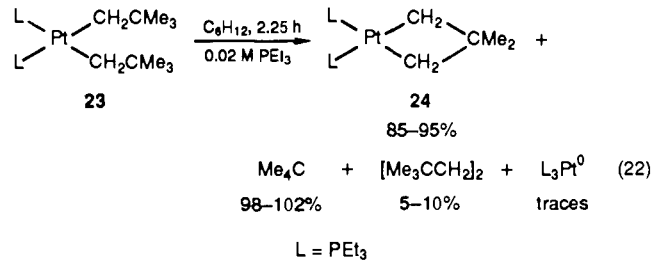
The ardent debates on mechanisms of C–H bond cleavage by platinum started after Shilov and coworkers reported on the activation of alkanes by solutions of platinum(II) chlorides.[95] Even now, after 20 years, one can neither define the nature of the rate-limiting step nor discriminate between oxidative addition, electrophilic substitution, or multicentered routes. This is also true for intramolecular metalation by platinum(II). Sometimes platinum(II) displays electrophilic features, for example, on cyclometalation of azobenzene[52a] and *N,N*-dimethylbenzylamine,[52b] but sometimes it reacts via oxidative addition[96] (see also

SCHEME IX



section IV.B). There are examples when nothing can be said about its nature in cyclometalation.[67] Valuable mechanistic information on cycloplatination can be found in a family of kinetic investigations of mechanisms of reactions, of platinum(II) complexes performed by Whitesides' group.[97–100]

At 157 °C in cyclohexane, i.e., under rather vigorous conditions, dialkylplatinum(II) complexes are thermolyzed as follows:[98,99]



The following main features are typical of this cycloplatination reaction:

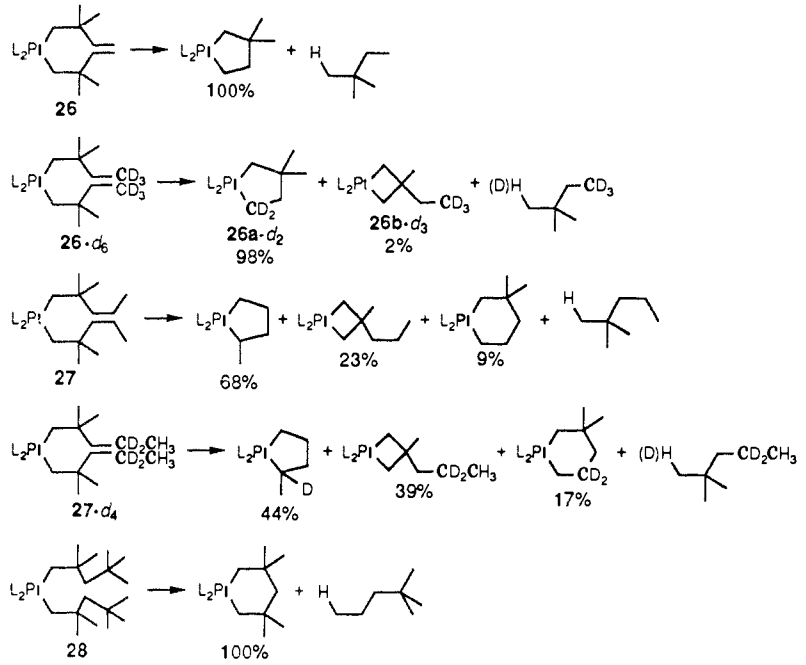
1. There is the intramolecular hydrogen transfer from the methyl group of the first neopentyl ligand to the methylene group of the second.
2. The hydrogen atom transfer is characterized by a kinetic isotope effect $k(H)/k(D)$ of ca. 3.
3. The reaction follows rate law 23, indicative of the intermediate formation of the three-coordinate complex $LPtR_2$.

$$-d[\mathbf{23}]/dt = k_{23}[\mathbf{23}][L]^{-1} \qquad (23)$$

4. Neopentyl radicals are not the intermediates.
5. Methylene and methyl groups of the neopentyl ligand do not interchange in the course of reaction 22.

The mechanism of reaction 22 based on this information is shown in Scheme IX. Its key steps are the reversible dissociation of the phosphine ligand, oxidative addition of the C–H bond to the coordinately unsaturated three-coordinate complex, rate-limiting reductive elimination of neopentane, and reassociation of triethylphosphine. The first step of the mechanism, i.e., the phosphine dissociation, resembles that in Scheme I, where the amine departure is necessary. Thus, this platinum case again demonstrates the importance of coordinative unsaturation in square-planar complexes in order for cyclometalation to occur. Moreover, dramatic changes in reactivity patterns take place when a complex cannot adopt the intermediate three-coordinate configuration. In particular, *cis*-[bis(dicyclohexylphosphino)ethane]hydridoneopentylplatinum(II) (**25**), which is structurally related to **23** but contains the bidentate phosphine, thus precluding the dissociation of the coordinated phosphorus atom, is not

TABLE IV. Formation of Various Platinacycloalkanes in Cyclohexane (L = PEt_3)[a]



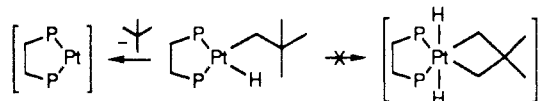
[a] From ref 100.

TABLE V. Activation Parameters, Relative Rates (87 °C), and Kinetic Isotope Effects of the Cycloplatination in L_2PtR_2 in the Presence of 0.019–0.022 M PEt_3 (L)[a]

complex	$\Delta H^{\ddagger}$, kJ/mol	$\Delta S^{\ddagger}$, J/(K mol)	k(H)/k(D)	k_{rel}
$L_2Pt(CH_2CMe_3)_2$ (23)	202	126	3.0	1
$L_2Pt(CH_2CMe_2CH_2Me)_2$ (26)	172	126	3.2	9500
$L_2Pt(CH_2CMe_2CH_2CH_2Me)_2$ (27)	176	126	2.8	50
$L_2Pt(CH_2CMe_2CH_2CMe_3)_2$ (28)				8000

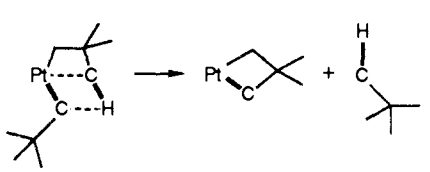
[a] From ref 100.

involved, if thermolyzed, in cyclometalation of the neopentyl ligand[101] (cf. with the osmium(II) case (eq 16) or the iridium(I)[102] case), but rather reductively eliminates neopentane to give [bis(dicyclohexylphosphino)ethane]platinum(0), the latter intermediate being able to cleave a variety of C–H bonds.[30]



25

There is an obvious alternative to the mechanism shown in Scheme IX frequently realized in cyclometalation at titanium(IV), thorium(V), and other high-valent metal centers discussed in the succeeding section. This is the already-mentioned multicentered concerted pathway, sometimes called electrophilic, the typical features of which are great activation enthalpies $\Delta H^{\ddagger}$ (>80 kJ/mol) and large and negative activation entropies $\Delta S^{\ddagger}$ (ordered transition states).[103] Note in reaction 22 the value of $\Delta H^{\ddagger}$ is unprecedentedly large (206 kJ/mol), while $\Delta S^{\ddagger}$ is high and positive (126 J/(K mol)). It has been argued[99] that a multicentered mechanism 24 in the platinum case is inconsistent with the positive value of $\Delta S^{\ddagger}$.



(24)

It should be emphasized that despite the fact that complexes **23** readily rearrange to **24**, the three-coordinate intermediates $LPtR_2$ do not activate external C–H bonds of the solvent in particular. Their effective molarities are thus very high. This inertness is thought to be due to unfavorable steric hindrance in the ground state.[99]

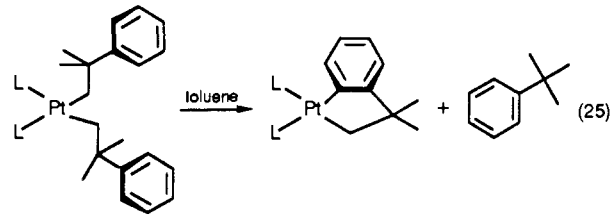
The influence of the nature of R in the L_2PtR_2 complexes on cyclometalation is exemplified by the compounds included in Table IV. All the complexes undergo cycloplatination according to rate law 23, and the relative rates together with activation parameters are summarized in Table V.

As seen from Table IV, complexes **26**-d_6, **27**, and **27**-d_4 produce several, as shown[100] *kinetically* controlled, products. The similarity of the activation parameters (Table V) suggests a common mechanism. If the mechanism in Scheme IX is realized, the following generalization can be made.[100] Since the platinacycloalkanes seem to be fully formed before the rate-limiting transition states and since each reaction expels a similar alkane moiety in the transition state, the relative rates of formation of the metallacycles should reflect directly their relative strain energies. That is, to a first approximation, $\Delta\Delta G^{\ddagger} \approx \Delta\Delta G$, where $\Delta\Delta G^{\ddagger}$ is the difference in activation free energy for two reactions forming platinacycles and $\Delta\Delta G$ is the difference in the strain energy of these rings. The estimate for the conversion of **26**-d_6, based on the assumptions that **26a**-d_2 and **26b**-d_3 are formed with the rate constants k_1 and k_2, respectively, and k_1/k_2 = [**26a**-d_2]/[**26b**-d_3]

and $\Delta\Delta G^{\ddagger} = RT \ln (k_1/k_2)$, taking into account statistical corrections and the value of the kinetic isotope effect, show that the strain energy for the four-membered metallacycle of **26b**-d_3 is 19.3 kJ/mol larger than that of the five-membered metallacycle of **26a**-d_2. This is maximal of the known strain energies in these complexes.

Thermal decomposition of *trans*-chloroneopentylbis(tricyclopentylphosphine)platinum(II) to yield *trans*-[PtCl(H)L_2] and 1,1-dimethylcyclopropane proceeds through intermediate cyclometalation of the neopentyl group after reversible loss of the phosphine ligand.[104] The mechanism is a copy of that in Scheme IX but reductive elimination of 1,1-dimethylcyclopropane is rate determining.

Aromatic C–H bonds can also be activated in the same way (eq 25). An extensive mechanistic study of this reaction reported by Young[105] revealed that the above-discussed aliphatic and this aromatic cycloplatinations have much in common. For instance,



(25)

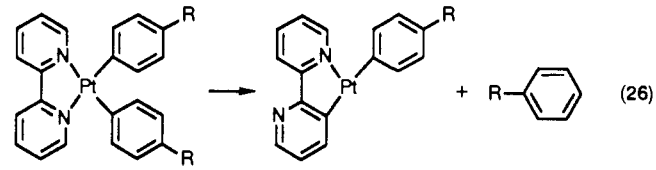
L_2 = dipy, 2, 2′-dipyrimidyl, phen, 1, 7-Ph_2phen, 1, 4, 7, 10-Me_4phen, $[PEt_3]_2$, $[PPh_3]_2$

complexes with monodentate phosphine ligands are the most labile. When L = PEt_3, the reaction is first order and a plot of the reciprocal of the rate constant against the phosphine concentration is linear. Both in the presence and in the absence of PEt_3 $k(H)/k(D) = 3.40$. The activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, are 174 kJ/mol and 248 J/(K mol) at [PEt_3] = 0 and 193 kJ/mol and 239 J/(K mol) at [PEt_3] = 0.037 M. The coordinative unsaturation is achieved by reversible loss of the coordinated phosphine, and the reductive elimination is believed to be rate limiting. In the case of bidentate N donors, the vacant site is formed via the rate-limiting Pt–N bond rupture. As a result, the kinetic isotope effect drops 1.26 (L_2 = dipy). We see here that *N,N*-platinum chelates, in contrast to the *P,P*-platinum ones, can provide coordinative unsaturation for subsequent cyclometalation.

B. Other Examples

Examples considered in this section were not as thoroughly mechanistically studied as the above transformations of the platinum(II) complexes, and the data are consistent with several pathways. Therefore, together with the original proposals, other possibilities will be briefly discussed where necessary.

A very interesting example is a "rollover" thermal 3-metalation of coordinated 2,2′-dipyridyl which transforms complexes **29** into a mixture of polymeric products where every dipy ligand is dimetalated.[106] The reaction occurs in toluene and proceeds without both the formation of biaryls and the incorporation of deuterium into arenes formed in toluene-d_8 as solvent. It is believed that the first step of the reaction is given by eq 26 followed by cyclometalation of the second pyri-



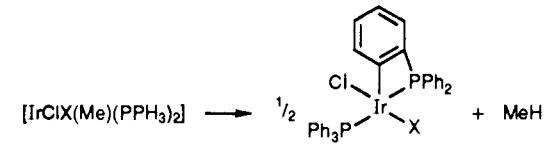
(26)

29 **30**

R = H (**a**), CMe_3 (**b**), CF_3 (**c**)

dine ring of dipy either in the monomeric product **30** or in various binuclear species. Details of this C–H bond-breaking process are unknown and a number of speculations are possible, but the cyclometalation is nucleophilic in nature since the comparison of the first-order rate constants shows that **29b** reacts 62 times faster than **29c**.

The next is the iridium(III) case.[107] The Ir(III)–dinitrogen complexes [$IrCl(O_3SY)Me(N_2)(PPh_3)_2$] (Y = F, CF_3) react with anions in methanol to give five-coordinate Ir(III) species having the formula [IrClX(Me)$(PPh_3)_2$] (X = Cl, Br, I, etc.). The coordinately unsaturated chloro and bromo complexes undergo ready cyclometalation to afford **31** both in solution (1,2-Cl_2-C_2H_4) and in the solid state:

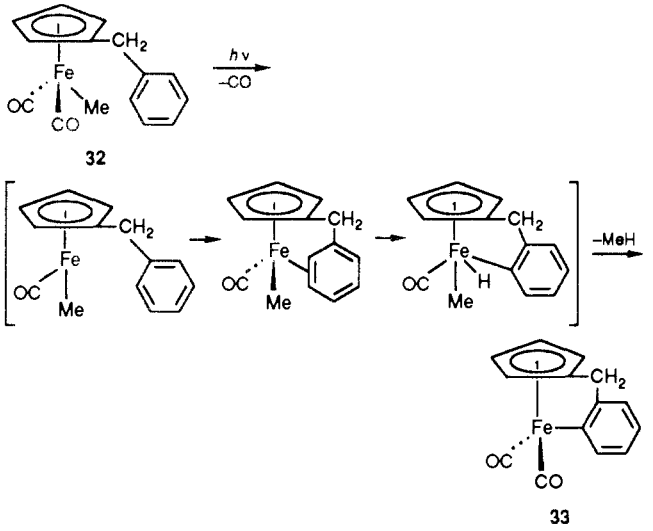


31

The solid-state cyclometalation is exothermic, $\Delta H° = -10.9$ kJ/mol (X = Cl). The reaction in solution is unimolecular and only slightly retarded by added triphenylphosphine. The bromo complex reacts twice as fast as the chloro complex, and the kinetic isotope effects $k(H)/k(D)$ are 1.2 and 1.5, respectively. $\Delta H^{\ddagger}$ is ca. 80 kJ/mol for both complexes, while $\Delta S^{\ddagger}$ is negative, −64 and −38 J/(K mol) for the chloro and bromo complexes, respectively.

The original mechanism involved oxidative addition to form a seven-coordinate intermediate of Ir(V) followed by reductive elimination of methane. As mentioned above, the Ir(V) intermediate is confusing. In the late seventies, the multicentered pathways were unknown and, hence, were not considered by the authors. The data, however, could be accounted for in terms of such a pathway. Some objections can be raised due to the small isotope effects but the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are consistent with the multicentered mechanism.

The third example is another extreme. At first glance the methyl ligand in iron(II) complex **32** perfectly suits it for the multicentered mechanism but an oxidative addition mode of the C–H bond cleavage is realized instead.[108] Near-UV irradiation of [(η^5-$C_5R_4CH_2Ph$)-$Fe(CO)_2Me$] (R = Me, H) yields both loss of CO and methyl radicals, although loss of CO dominates. In the absence of two-electron donor ligands, the CO loss product undergoes oxidative addition to yield finally the cyclometalated product **33**.

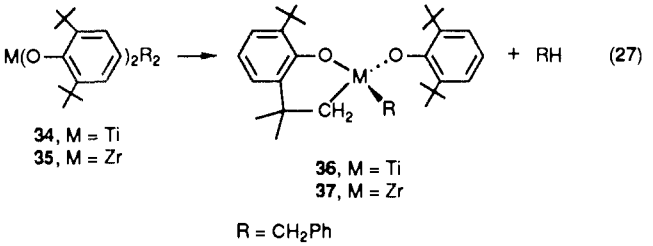


There are other examples where cyclometalation proceeds in transition-metal complexes bearing alkyl leaving groups and where mechanisms are uncertain.[54,109] The principal difficulty here is to make a choice between nucleophilic and multicentered pathways.

VII. Cyclometalation: Multicentered Pathways

A. d^0 Complexes of Titanium(IV) and Zirconium(IV)

The C–H bond activation in the complexes of four-valent titanium and zirconium cannot be realized as oxidative addition/reductive elimination, since in the absence of readily eliminating groups one would assume at least intermediate formation of the six-valent species. Therefore, the nucleophilic pathways (sections IV and VI) must be excluded from consideration. Two distinct mechanistic possibilities remain for the conversion of these slightly distorted tetrahedral[110] complexes of titanium **34** and zirconium **35** into the respective metallacycles **36** and **37**, which readily occur in toluene at 73–130 °C[103] (eq 27). Two distinct mechanisms are



plausible. The first involves the homolytic or radical pathway in which the breaking of the metal–benzyl bond occurs in the activation step to generate a benzyl radical, presumably caged, which then abstracts hydrogen from one of the *tert*-butyl groups of an aryl oxide ligand followed by ring closure to the product. The second, already briefly discussed, envisages a multicenter transition state in which the new M–C bond is being formed at the same time that the leaving group–metal bond is being broken.

Reaction 27 strictly follows first-order kinetics, and the rate constants together with the corresponding activation parameters can be found in Table VI. The mechanistic choice has been made here on the basis of the similarity of $\Delta H^{\ddagger}$ for the titanium and zirconium

TABLE VI. Rate Constants and Activation Parameters of the Cyclometalation of Complexes of Ti, Zr, and Ta with 2,6-di-*tert*-Butylphenolato (OAr) Ligand in Toluene[a]

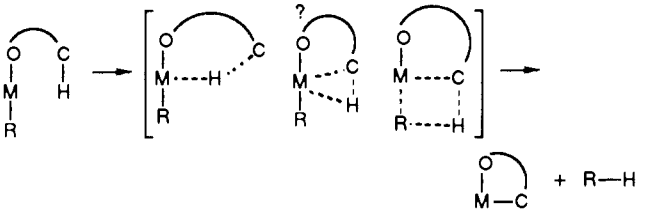
complex	T, °C	10^5k, s^{-1}	$\Delta H^{\ddagger}$, kJ/mol	$\Delta S^{\ddagger}$, J/(K mol)
$Ti(OAr)_2(CH_2Ph)_2$ (**34**)	114	126.0	97	-55
$Zr(OAr)_2(CH_2Ph)_2$ (**35**)	114	32.3	91	-80
$Zr(OAr)_2(CH_2C_6H_4Me\text{-}4)_2$	114	39.2		
$Zr(OAr)_2(CH_2C_6H_4F\text{-}4)_2$	114	45.8		
$Zr(OAr)_2(CH_2C_6H_4F\text{-}3)_2$	114	18.4		
$Ta(OAr)_2Me_3$ (**39**)	106	13.0	111	-29
$Ta(OAr)(OCH_2)Me_2$ (**40**)	106	0.42	124	-25
$Ta(OAr)_2(=CH_2)Me$ (**42**)	27	4.3	60	-130

[a] From refs 103 and 117.

complexes.[103] If the homolysis were rate limiting, one would expect basically different values of $\Delta H^{\ddagger}$ for complexes **34** and **35**,[111] since there is a significant increase in the values of mean bond dissociation energies on going from first-row d-block elements to their second-row analogues.[112] In the case of homoleptic benzyls, the value of $D(M\text{–}CH_2Ph)$ has been measured as 206 kJ/mol for M = Ti and 252 kJ/mol for M = Zr.[113] The radical mechanism of reaction 27 is thus hardly acceptable. The multicentered mechanism is additionally supported by rather large and negative activation entropies $\Delta S^{\ddagger}$ (Table VI).

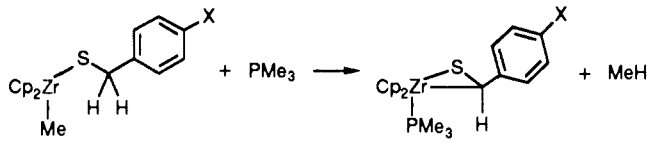
The rate of metalation at titanium is faster than at zirconium, and analysis of the data shows that this rate difference is entropically based and can be rationalized in terms of the relative sizes of the coordination spheres of the two metals. The covalent radius of titanium is normally 0.14 Å smaller than that of zirconium. Hence, the coordination sphere is more crowded in the titanium case and hence presumably less freedom of motion of the aryl oxide ligands will be present in the ground state. Slightly less entropy will, therefore, be lost on going to the four-centered transition state. (One may note that there are polar views on the role of steric factors in nucleophilic and multicentered cyclometalations. The steric crowding is believed to be unfavorable in oxidative addition (see above), but it entropically favors multicentered activation as suggested here).

An attempt to shed light on the effect of substituents in reaction 27 was without success. Data in Table VI are poorly informative and provide no evidence concerning the nature of the metal center in cyclometalation 27. It has been speculated[103] that an end-on or linear interaction between the metal and the C–H bond is more favorable. However, one could imagine that the linear interaction could then lead to a side-on bonding mode with the metal now interacting directly with the carbon and hydrogen atoms as shown in the following:



It was also pointed out[103] that the overall sequence might be an S_E2 displacement of the proton by the metal center, although this was considered unlikely.

Electronic effects in cyclometalation at zirconium(IV) centers are much better seen in reaction 28, showing internal metalation in (substituted benzylthio)methylzirconocene complexes **38**.[114] At 75–90 °C in



38 (28)

X = CF_3, Cl, H, OMe, NMe_2

C_6H_6, reaction 28 is first order in the complex, and added trimethylphosphine has no effect on its rate. If X = H, the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, are equal to 78.1 kJ/mol and −87.4 J/(K mol), respectively, while the kinetic isotope effect measured by Cp_2Zr-(Me)SCH(D)Ph is large: 5.2 at 80 °C and 7 at 25 °C (estimated value). The latter clearly show that the hydrogen is transferred in the rate-limiting step. Contrary to the systems considered above, a straightforward substituent effect is seen here, the reaction rate steadily increasing on going to the complexes with electron-withdrawing substituents. The slope of the corresponding Hammett plot is +0.39, and the value should not be treated as very low, since the reaction center is significantly separated from the X group. The mechanistic analysis, as above, drives to the concerted four-center process in which the transition state is polarized so that the hydrogen moves as a proton, the metal being positive.

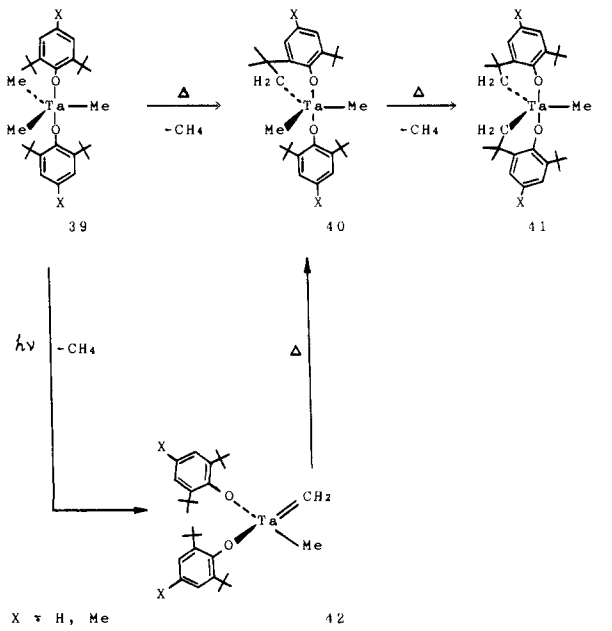
Interestingly, corresponding main-group complexes of tin(IV), namely, $SnMe_n(OAr\text{-}2,6\text{-}Ph_2)_{4-n}$ (n = 2, 3), failed to undergo multicentered cyclometalation.[115] Extended thermolysis of these species at temperatures up 250 °C did not give any evidence of cyclometalation occurring with loss of either methane or 2,6-diphenylphenol. At the same time, $SnCl_4$ or $Sn(NMe_2)_4$ did give the cyclometalated derivatives of 2,6-diphenylphenol under much milder conditions. A possible reason is that the multicentered pathway is no longer operative and the cyclometalations proceed by some other, plausibly electrophilic mechanism, as previously suggested for orthometalation in (benzylideneimino)tin(IV) halides, $SnCl_3(N{=}CPh_2)$, on the basis of a qualitative study of a substituent effect in the phenyl ring.[116]

B. d^0 Complexes of Tantalum(V)

The trigonal-bipyramid complexes of tantalum(V) **39** with aryl oxide axial ligands give cyclometalated products by many routes as shown in Scheme X.[117] Thermolysis of **39** in toluene at 90 °C for 24 h gives monocyclometalated complex **40**. At temperatures higher than 100 °C, the latter transforms into dimetallacycle **41**. At the same time, on UV irradiation at 10 °C **39** almost quantitatively rearranges to methylidene complex **42**.[117,118] In turn, **42** transforms into **40** at room temperature.

The kinetics of each step in Scheme X was independently studied to reveal that the transformations **39** → **40**, **40** → **41**, and **42** → **40** follow first-order kinetics. The rate constants and corresponding activation parameters are summarized in Table VI. The kinetic data and the experiments with deuterium-labeled compounds have demonstrated that the mechanism operating in this case is indistinguishable from the mechanism of cyclometalation in the aryl oxide complexes of titanium and zirconium. It should only be pointed out that reactions of methyl complexes of tantalum(V) are characterized by higher values of $\Delta H^{\ddagger}$ and less negative values of $\Delta S^{\ddagger}$ compared with those of tetravalent titanium and zirconium. An increase in $\Delta S^{\ddagger}$ is accounted for in terms of higher steric demands of the five-coordinate sphere around tantalum. This means that the limitation of the mobility of the *tert*-butyl groups of the aryl oxide ligand around tantalum should compensate for the lowering of the rotational entropy on the formation of a more ordered transition state.[117]

SCHEME X

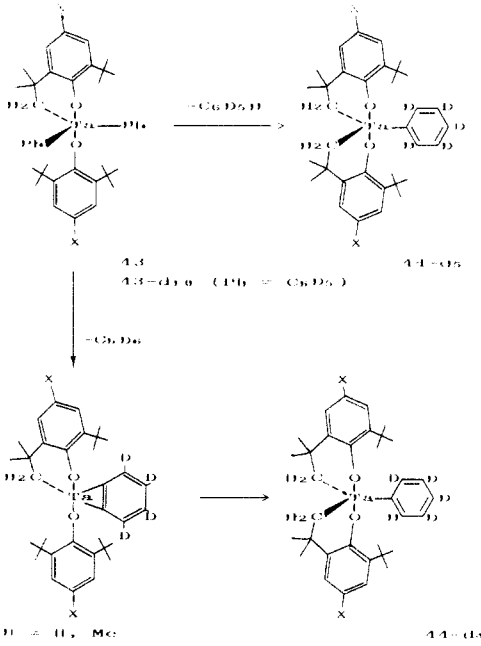


Of interest is a dramatic decrease in $\Delta H^{\ddagger}$ in the process **42** → **40** involving the methylidene complex, which is, however, partly compensated for by a decrease in the entropy of activation. The decrease in $\Delta S^{\ddagger}$ could have a number of explanations. First, **42** is not a five-coordinated complex, as **39**, but a four-coordinated complex. Therefore, a fixation of the required position of the *tert*-butyl group undergoing activation in the transition state is less favorable entropically. Nevertheless, the value of $\Delta S^{\ddagger}$ is still more negative compared with the reactions at four-coordinate titanium and zirconium. Therefore, the activation entropy is additionally lowered at the expense of the necessity of rigid orientation of the C–H bond to be cleaved with the methylidene π bond and because there is no extra particle, a methane molecule, formed in the process **42** → **40** as observed in all other cases. Despite all this, the rate of C–H bond activation in the methylidene complex **42** is a factor of 2.4×10^3 higher than in **39**, suggesting a high potential of the $=CH_2$ group in promoting cyclometalation.

Kinetic isotope effects in cyclometalation at tantalum(V) centers were measured by the phenyl analogue of **40**, the transformations of which are presented in Scheme XI.[119] Additionally, the reactions revealed one more interesting detail.

Comparing the rates of cyclometalation of **43** and **43**-d_{10} shows a definite, although rather slight, retardation of the rate of cyclometalation of the second aryl

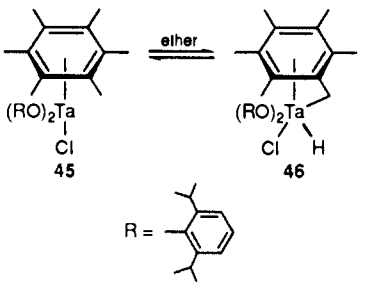
SCHEME XI



oxide ligand. Mass spectrometric analysis of the product of thermolysis of **43**-d_{10} at 118 °C showed a mixture of **44**-d_5 (92%) and **44**-d_4 (8%) indicative of the two biscyclometalated, monophenyl compounds. One involves direct combination of the *tert*-butyl C–H bond hydrogen atom with the Ta–Ph leaving group ("classical" multicentered mechanism) with $k(H)/k(D)$ = 2.3, while the other involves the formation of an intermediate benzyne (*o*-phenylene) functionality with $k(H)/k(D)$ = 4.1. The latter pathway was confirmed by the thermolysis of deuteriated aryl oxide compound $[TaOC_6D_2Bu^t(CD_3)_2CD_2\text{-}4\text{-}CH_3](OC_6D_2Bu^t{}_2\text{-}4\text{-}CH_3)(C_6H_5)_2$.

The use of substituted aryl leaving groups (3-Me, 4-Me, 3-F, and 4-F) shows the cyclometalation to exhibit a negligible substituent effect. A pathway in which the hydrogen atom of the activated C–H bond is transferred to the aryl ipso carbon as an incipient proton to generate a "metallo-Wheland" intermediate can be ruled out.[119]

The question that may arise here is how complexes of tantalum in lower oxidation states will react. An example from tantalum(III) chemistry indicates that these d^2 complexes lose the ability to undergo multicentered cyclometalation. In particular, **45** does not cyclometalate the isopropyl groups, but rather undergoes oxidative addition to form an unprecedented d^0 "tucked-in" hexamethylbenzene compound **46**, which was trapped by $Me_3CC{\equiv}CH$ and $H_2C{=}CHCH_2Cl$.[120]



The intramolecular metalation of a methyl C–H bond in **46** and the existence of a hydridic intermediate are also inferred from various deuterium-labeling and kinetic studies. Disappearance of **45** follows first-order kinetics and apparently oxidative addition does not require coordinative unsaturation.

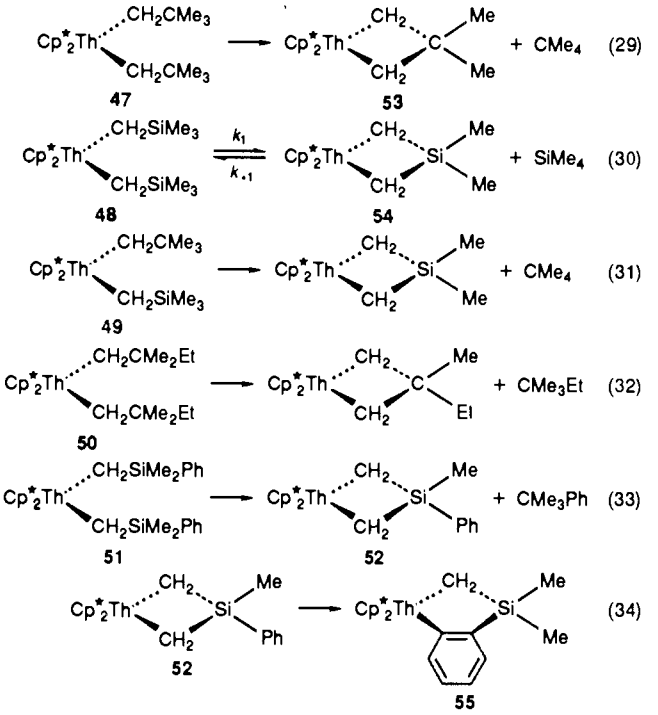
TABLE VII. Rate Constants and Activation Parameters of Unimolecular Reactions 29–33 in C_6D_{12}[a]

reaction	10^5k, s^{-1}	$\Delta H^{\ddagger}$, kJ/mol	$\Delta S^{\ddagger}$, J/(K mol)
29	7.3	89	−67
30	0.39	105	−44
31	8.4	81.5	−87
32	8.2	78	−101
33	0.61	90	−84

[a] From ref 121.

C. d^0f^0 Complexes of Thorium(IV)

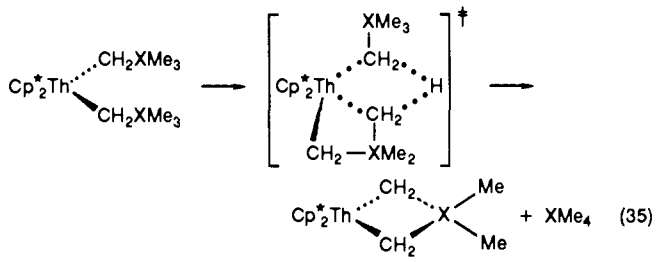
Thorium(V) complexes, eq 29–34, also do not contain easily dissociable ligands, and, thus, multicentered mechanisms of cyclometalation appear probable.



Triggered thermally, reactions 29–34 are all first-order processes, with the parameters presented in Table VII.[121] The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ obtained correspond adequately to those expected for the multicentered pathways. Other data for these endothermic[122] reactions support the same pathway. In particular, the reactions of $Cp^*{}_2Th(CHDSiMe_3)_2$ and $Cp^*{}_2Th(CD_2CMe_3)_2$ afford $Cp^*{}_2ThCH_2Si(CHD)Me_2$ + Me_3SiCH_2D and $Cp^*ThCH_2C(CD_2)Me_2$ + Me_3CCD_2H, with the isotopic purity of volatile products exceeding 98%. The kinetic isotope effect measured by $Cp^*{}_2Th[CH_2Si(CD_3)_3]_2$ is also impressive, being equal to 10.0 and 8.5 at 85 and 115 °C, respectively.

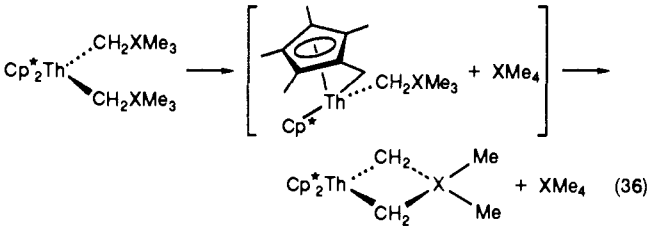
According to the study of **47** by neutron diffraction techniques,[121] the cyclometalation occurs in the strongly sterically distorted molecule. The neopentyl ligands are markedly asymmetric, Th–C(α) = 2.543 and 2.456 Å, Th–C(α)–C(β) = 132.1 and 158.2°. Consequences of these distortions include the acute angles Th–C(α)–H(α) = 84.4 and 87.1° in the ligand with Th–C(α)–C(β) = 158.2°. One must also pay attention to the significant interligand C(α)–C(γ) interaction which involves the

groups engaged in the hydrogen transfer. It is tempting to accept that this ground-state structure to a great extent mimics the transition state of pathway 35.



(35)

Thermolysis of $Cp^*_2Th[CH_2Si(CD_3)_3]_2$ leads to formation of both $(CH_2D)Si(CD_3)_3$ (65%) and $(CH_3)Si(CD_3)_3$ (35%), showing that reaction 30 only partly (65%) follows pathway 35 and the other reaction flow proceeds through a secondary mechanism involving rate-limiting abstraction of a hydrogen atom from a Cp* ring, followed by hydrogen (deuterium) atom transfer from the remaining alkyl ligand to an intermediate η^5,η^1-$(CH_3)_4C_5CH_2$ species (eq 36). Similar complicated pathways are realized in some other systems,[123,124] and one should take this into account when complexes with Cp* ligands are mechanistically investigated (see also section VII.D).

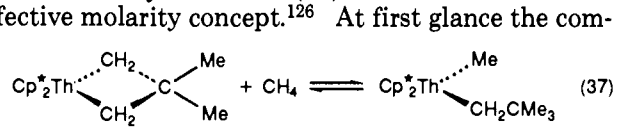


(36)

One of the most remarkable features of reactions 29–34 is their regioselectivity. The latter arise from the kinetic control governing the reactions and is somehow related to the large negative activation entropies and, hence, to the highly ordered transition states. Consequently, the complex $Cp^*_2Th(CH_2CH_2Me)_2$ is inert to cyclometalation, while **50** affords exclusively the four-membered metallacycle rather than the five-membered one as does the platinum complex **26** from Table IV. The selectivity in conversion of **49** is due to both the difference in $D(Th–CH_2CMe_3)$ and $D(Th–CH_2SiMe_3)$ (ca. 302 and 336 kJ/mol, respectively) and the difference in the strain energy of metallacycles **53** and **54** (67 and 33.5 kJ/mol, respectively). The resulting gain in energy in the rearrangement of complex **49** into **54** rather than into **53** is approximately 67 kJ/mol.

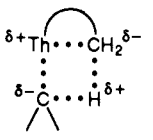
Reactions 33 and 34 exemplify the regulated selectivity. Thermolysis of **51** in toluene at 80 °C for several days affords the "kinetic" product **52** in 64% yield.[121] Under the same conditions, but at 100 °C, in a week complex **52** isomerizes into the "thermodynamic" product **55** in 75% yield. The rearrangement is driven by the bond energy difference: the stability of Th–Ph is higher than that of $Th–CH_2SiMe_3$ by 38 kJ/mol.[122,125]

The ability of some thorium cyclobutanes to react with hydrocarbons by eq 37[122] allows the consideration of the reactivity of thorium(IV) centers in terms of the effective molarity concept.[126] At first glance the comparison of reactions 29–34, on the one hand, and reaction 37, on the other, is of no virtue since it is much less visual than in the case of the rhodium complexes considered above. Nevertheless, it is justified. In fact, instead of the reaction between external hydrocarbon and the complex $Cp^*_2Th(R')(CH_2CR_3)$, we consider the reaction of its analogue $Cp^*_2ThCH_2CR_2CH_2$. In order to obtain the effective molarity accepting this approach, the direct and reverse rate constants of reaction 30 should be compared.[126] In this case the effective molarity is equal to the ratio $k_1/k_{-1} = K$ multiplied by the statistical correction (4/3). The equilibrium constants K increase with the temperature, but even at 100 °C, the K is only 8.4 M, the effective molarity being 11.2 M! It should be, however, mentioned that related reaction 29 is so much shifted to the right that the rate of the reverse process (similar to the platinum(II) case) cannot be measured. Therefore, only a rough estimate for **47** is available ($K > 75$ M at 60 °C). The effective molarity in this case is therefore higher than 100 M!



(37)

In conclusion, let us sum up the features typical of thorium centers in cyclometalation. These are unimolecular kinetics, kinetically controlled regioselectivity, congested ground-state structures, large and negative activation entropies, and an apparent absence of a high-energy, thorium-centered HOMO. They implicate a highly organized, sterically constrained, electrophilic transition state **56**.[121]



56

D. Chain Mechanisms of C–H Bond Cleavage

What is the chain mechanism of C–H bond cyclometalation? It is such when the final C–H bond cyclometalation is preceded by activation of one or more C–H bonds of adjacent ligands. We have already come across such pathways (see Scheme XI or eq 36, for example) but some emphasis is needed, since the pathways in question could be crucial for further progress in both cyclometalation and intermolecular activation of C–H bonds by metal centers. The chain pathways have clear-cut advantages. As in catalysis, a concerted process with a high energy barrier is replaced by several related reaction activation barriers that are significantly lower (such a case is shown in Figure 5).

Consider first the cyclometalation of the methyl group of the Cp* ligand at the zirconium(IV) center (eq 38).[124a]

$$Cp^*_2Zr(C_6H_5)_2 \rightarrow Cp^*Zr(C_6H_5)(\eta^5,\eta^1\text{-}Me_4C_5CH_2) + C_6H_6 \quad (38)$$

57

Reaction 38 follows first-order kinetics in toluene-d_8 at 50–104 °C and is characterized by the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, equal to 94.5 kJ/mol and −50 J/(K mol), respectively. Measured by $Cp^*_2Zr(C_6D_5)_2$, the kinetic isotope effect is 13.5 at 25 °C! The results strongly implicate a benzyne complex as the initial thermolysis product:

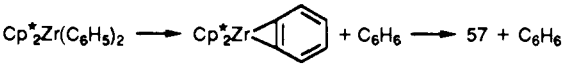


TABLE VIII. An Attempt To Summarize the Most Typical Features of Cyclometalation by Oxidative Addition, Electrophilic Substitution, and Multicentered Mechanisms

feature	mechanism		
	oxidative addition	electrophilic substitution	multicentered activation
metal complexes involved	transition metals in low oxidation states	palladium(II)	early transition metals in highest oxidation states
observed kinetics	inhibition by added ligands (coordinative unsaturation is commonly needed)	inhibition by added ligands; general-base catalysis	strict first-order kinetics unaffected by added ligands
activation parameters	*a*	*a*	large $\Delta H^{\ddagger}$; large and negative $\Delta S^{\ddagger}$ (ordered transition states)
kinetic isotope effects (k_{C-H}/k_{C-D})	from low to moderate (1–3)	*a*	usually very high (>5)
effective molarity	usually low	high	variable

[a] More data are needed for generalizations.

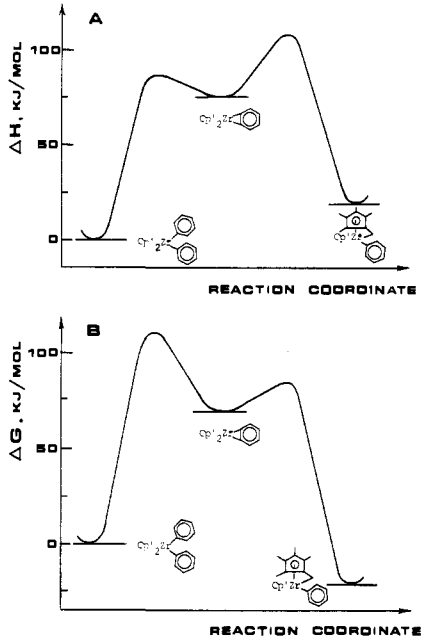


Figure 5. (A) Enthalpy profile for the thermolytic transformations of $Cp^*_2ZrPh_2$ based upon experimental bond enthalpy and kinetic data. (B) Free energy profile for the thermolytic transformations of $Cp^*_2ZrPh_2$ at 350 K based upon experimental bond enthalpy and kinetic data. The $T\Delta S$ contribution to ΔG for all processes creating (consuming) a particle is estimated to be −37.6 kJ/mol (+37.6 kJ/mol). In both profiles, the position of the benzyne intermediate is approximate. Reprinted from ref 124a; copyright 1987 American Chemical Society.

Analysis of the temperature dependence of $k(H)/k(D)$ indicates a symmetrical transition state of the initial step with possible tunneling.[124a] Both kinetic[124a] and thermochemically derived bond enthalpy data[124b] were used to make the enthalpy and free energy profile for the $Cp^*_2Zr(C_6H_5)_2$ thermolytic chemistry shown in Figure 5. It should be pointed out that benzyne transition-metal complexes may appear very powerful for both intra- and intermolecular metalation.[127]

The next example is taken from hafnium(IV) chemistry.[125] Thermal decomposition of $Cp^*_2Hf(CH_2C_6H_5)_2$ in benzene-d_6 cleanly affords toluene and hafnabenzocyclobutane $Cp^*_2HfCH_2$-*o*-C_6H_4. Deuterium labeling of the benzyl ligands indicates that decomposition of $Cp^*_2Hf(CY_2C_6H_5)_2$ (Y = H, D) proceeds primarily by α-H abstraction to form a permethylhafnocene-benzylidene intermediate [$Cp^*_2Hf{=}CHC_6H_5$], which rapidly rearranges to the metalated cyclopentadienyl or "tucked-in" benzyl complex $Cp^*(\eta^5,\eta^1\text{-}Me_4C_5CH_2)HfCH_2C_6H_5$. Finally, the latter rearranges to the observed product $Cp^*_2HfCH_2$-*o*-C_6H_4. Thus, there are three steps in the chain! The last one, eq 39, has been mechanistically probed in detail. If X = H, the values

$$Cp^*(\eta^5,\eta^1\text{-}Me_4C_5CH_2)Hf(CH_2C_6H_4X\text{-}m) \longrightarrow Cp^*_2HfCH_2\text{-}o\text{-}C_6H_3X\text{-}m \quad (39)$$
$$R = CF_3, H, Me, NMe_2$$

of $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $k(H)/k(D)$ are equal to 84.8 kJ/mol, −71.8 J/(K mol), and 9.6, respectively. (For comparison, the primary α-H abstraction step is characterized by 143 kJ/mol, 4 J/(K mol), and 1.07, respectively.) The slope of the Hammett plot ρ has been found to be −0.2, too low, as suggested, to accept an electrophilic aromatic substitution mechanism. The multicentered pathway with highly ordered transition state seems to be the only possibility. This is a magnificent chain system with three C–H bond-breaking processes, two of which have been kinetically characterized!

VIII. Conclusion

It is the goal of this survey to cover the main, known, updated mechanisms of cyclometalation. Rather than trying to compile as many examples as possible, only the most representative ones are cited. This review also touches the general problem of C–H bond activation by metal centers from the standpoint of cyclometalation, a problem in which the author has been involved for many joyful years.

In Table VIII an attempt is made to sum up the features typical of the mechanistic patterns discussed in the present review. It is, of course, an oversimplification since one must keep in mind that only the first steps in elucidating mechanisms of cyclometalation have been made and more data are evidently needed for disclosing some reactivity patterns. It should also be remembered that several borderline mechanisms may be operative as well. The task of evaluating such mechanisms of intramolecular metalation is difficult, but it would be even much more difficult if the data on the most typical, "limiting" mechanism of cyclometalation are left without some sort of generalization.

IX. References

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