Intriguingly, *DXPas34*, a region downstream from the *Tsix* promoter, is hypermethylated on strong *Xce* alleles (*8*). Recent experiments have shown that *Tsix* transcription from both X chromosomes before initiation of X inactivation suppresses *Xist*, thereby preventing X-chromosome silencing. As a result, *Tsix* may maintain the active state of the two X chromosomes before the onset of silencing (*1*). Genetic evidence suggests, however, that the function of *Tsix* extends beyond this simple model. *Tsix* also regulates X-chromosome choice, making it the third element within the *Xic*, along with *Xce* and *Xist*, postulated to act in this process (*1*).

Chao *et al.* (*3*) tackle this poorly understood stage of the inactivation pathway by searching for trans-acting molecules. Most models of X-chromosome choice invoke trans-acting blocking factors that protect the future X_a from silencing (*2*). The authors applied computational analysis to the *Tsix* promoter/*DXPas34* region and identified a mouse-specific cluster of binding sites for the ubiquitous chromatin insulator and transcription regulator CTCF. Insulators, first described in *Drosophila*, are defined operationally by their ability to protect genes against position effects and to prevent interactions between promoters and enhancers when positioned between them (*9*). In vertebrates, CTCF operates at the chicken β-globin gene locus (*10*) and at the imprinted *H19-Igf2* locus in the mouse (*11*). The current understanding of insulators is incomplete, however, and their mechanism of action remains obscure.

The investigators propose that CTCF and *Tsix* work together to direct X-chromosome choice. According to their model, CTCF binds first to one of the two X chromosomes, designating it as the future X_a and preventing *Xist* transcription. Allelic methylation differences within a proposed differentially methylated region (DMR) would enable discrimination of the X chromosomes and binding of CTCF to only one allele of the *Tsix*. Suppression of *Xist* by binding of the CTCF to the X_a could be achieved by direct activation of its repressor, *Tsix*, or by blocking access to putative enhancers located downstream (see the figure). The model proposed by Chao *et al.* provides an alluring solution to the long-standing dilemma of how a cell could discriminate between two seemingly equivalent X chromosomes. In an elegant portrayal of an epigenetic switch, it fulfills many of the requirements of X-chromosome choice. The model is consistent with the authors' previous observation that deletion of the CTCF array results in nonrandom inactivation of mutated X (*1*). Importantly, the study encourages the discovery of additional trans-acting factors, including those involved in the proposed blocking complex.

Nevertheless, questions remain about the specific function of CTCF in this setting, and the proposed enhancer and DMR have yet to be identified. Fortunately, many details of the epigenetic switch model are testable. For example, although Chao *et al.* demonstrate that the sites could bind CTCF in vitro and in vivo, it remains to be seen whether binding of CTCF is limited to one allele. If proven, how is monoallelic binding achieved in a developmentally specific and dosage-sensitive manner? How does the *Xce* effect on choice correlate with that of CTCF binding? Does hypermethylation of *DXPas34* affect CTCF binding? Does CTCF operate similarly in the human, where *Tsix* structure has been shown to vary from that of the mouse and where there is no known *Xce* effect? Could CTCF bind biallelically but invoke distinct allele-specific regulatory effects? One could envision an alternative model in which CTCF binds and functions secondarily after blocking complex–induced silencing of the *Xic* on the X_a (see the figure). Now that the gates to the garden of trans-acting factors have been thrown open, details of the epigenetic-switch model should rapidly follow.

The identification of CTCF as a trans-acting factor in the X-inactivation pathway provides not only significant insight into X-chromosome selection, but also raises awareness about the universality of epigenetic gene regulation. In the postgenomics era, genetic and epigenetic studies will once again become critical to understanding how exquisitely specific effects are achieved with global factors like CTCF. As additional facets of the pathway are revealed, X-chromosome inactivation will continue to provide an exceptional paradigm for gene regulation.

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PERSPECTIVES: CHEMISTRY

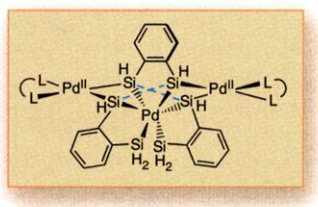
A New Oxidation State for Pd?

Robert H. Crabtree

The discovery of a new oxidation state of a transition metal element is rare. It is even more unexpected in the case of a long-studied metal like palladium (Pd). This precious metal of the platinum group forms exceptionally efficient catalysts (*1*) for a wide variety of organic reactions. Either as a Pd compound or as the finely divided element, these catalysts are widely used, for example, in the pharmaceutical industry.

Knowledge of the range of oxidation states accessible to an element is crucial in characterizing the mechanisms of catalytic reaction cycles. For a mechanism to be plausible, all postulated intermediates in such a cycle have to be assigned to a known metal oxidation (or valence) state.

In the late 1970s and early 1980s, only Pd(0) and Pd(II), with oxidation states 0 and +2, respectively, were believed to form in organic reaction cycles catalyzed by Pd. Pd(IV) was known in inorganic compounds such as PdO_2 or PdF_4, but these compounds are quite unlike the organometallic species, with Pd-C bonds, that are typically formed in catalytic cycles. Historically, the highest oxidation states had been seen with electronegative ligands, such as O and F (*2*). Organometallic compounds tended to have lower oxidation states and more electropositive ligands, such as C or Si.



The structure of the new Pd(VI) compound as determined by Chen *et al.* (*5*).

In the past 15 years, it has become fully accepted that organometallic compounds can contain Pd(IV) (*3*). Such compounds can be formed not just as unstable intermediates but as species stable enough for their structures to be determined by x-ray crystallography—the gold standard of chemical structure determination. But no definitive evidence for an organometallic Pd(VI) species has been presented (*4*).

On page 308 of this issue, Chen *et al.* (*5*) report the synthesis and x-ray crystallographic characterization of such a

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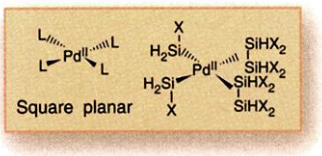
species (see the first figure). Surprisingly, their compound does not have an electronegative ligand, but a silicon one. This feature makes it organometallic at least in spirit, because Si is the nearest chemical relative of carbon.



The geometry typically found for Pd(II) and the Pd(II) model of the present compound. L, ligand on Pd; X, non-hydrogen substituent on silicon.

To assign an integer oxidation state to an atom in a compound can be difficult, however. It requires clear-cut situations with a well-defined number of bonds between atoms. Consider the hypothetical species PdH_6, which contains Pd(VI). H–H bond formation could in principle give $Pd(H_2)H_4$ with oxidation state Pd(IV), $Pd(H_2)_2H_2$ with Pd(II), and $Pd(H_2)_3$ with Pd(0). Each time we replace two M–H bonds by a neutral H_2 ligand, the oxidation state of Pd decreases by two.

Oxidation state ambiguity (*6*) can arise in organometallic species because they often show structures with partial bonds. A structure partway between PdH_6 and $Pd(H_2)H_4$—for example, with a long H···H bond—leads to one such ambiguity. The same can happen if we replace the M–H bonds by M–SiX_3 and consider formation of X_3Si–SiX_3 ligands, although such a ligand has never previously been seen.

The new compound described by Chen *et al.* is frozen partway between the $Pd(SiX_3)_6$ and $Pd(X_3Si–SiX_3)_2(SiX_3)_2$ forms. Two Si···Si distances in the ligand sphere (dashed in the first figure) are about 2.5 Å, too close to be considered nonbonding but too far to be pure Si–Si bonds. The compound thus has some Pd(VI) and some Pd(II) character. The limiting Pd(II) form (see the second figure) has the square planar geometry typical of Pd(II). Which model is most appropriate, Pd(VI) (first figure) or Pd(II) (second figure), will require further study. But both are unprecedented. Changing the X groups on Si should push the compound toward one or the other limiting structure. This a likely topic for future work.

Chen *et al.*'s work not only opens up what may be a wide field of such high valent organometallic compounds and of Si–Si complexes but allows us to consider Pd(VI) and Si–Si complexes as intermediates in certain catalytic reaction mechanisms. The work also justifies a half-serious comment (*7*) once made by J. C. Bailar of the University of Illinois (1904–1991), an early pioneer in the area. Bailar quipped that the advent of organometallic chemistry had simplified the lives of students because they no longer had to learn the permitted valence states of the metals: It could be safely assumed that for organometallic compounds all valence states were now possible.

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PERSPECTIVES: SYNTHETIC CHEMISTRY

The Key to Successful Organic Synthesis Is...

William D. Jones

The ability to selectively form carbon-carbon bonds between organic fragments has been crucial to the development of synthetic organic chemistry. Complex molecules held together largely by carbon-carbon bonds can be synthesized through careful planning and execution of a series of chemical reactions that build up the desired structure step by step. This approach is used, for example, in the chemical synthesis of natural product molecules for use in the pharmaceutical industry.

Existing methods are not perfect, however, and complex synthetic routes may be required to reach a desired product. New methodologies for the formation of carbon-carbon bonds therefore continue to be important. On page of 305 of this issue, Cho *et al.* report such a new methodology. They catalytically convert aromatic compounds into precursors that can facilely form bonds between unsaturated carbon centers (*1*). The method is versatile and selective and promises to be widely used in organic synthesis.

Three methods have proven particularly valuable for the formation of bonds between unsaturated carbon atoms (see left panel in the figure). Heck coupling is typically used to join alkenes with halide-functionalized benzene (aryl halides) or alkenes (vinyl halides) with a palladium catalyst. Stille coupling is also catalyzed by palladium; here, a tin compound, trialkyltin, carries one of the two organic units that are to be joined. Suzuki coupling is similar to Stille coupling, except that a borylate group, $B(OR)_2$, is used instead of trialkyltin to carry the aryl or vinyl group.

These methods have gained widespread use because they can be applied to a wide range of reactions and do not form undesired side products (*2*). They have proven to be superior to earlier methods in the syntheses of several organic compounds (*3*–*5*). The particularly successful Suzuki coupling (*6*) has been adapted to solid-phase synthesis (*7*), two-phase catalysis (*8*), and industrial applications (*9*) and has led to breakthroughs in the synthesis of polyarylene polymers (*10*).

All of these couplings, however, require one or both of the coupling partners to carry a functional group (halogen, trialkyltin, or borylate). This can require additional reaction steps in the preparation of the starting materials.

Smith and co-workers and Hartwig and co-workers have reported progress toward overcoming this problem. Using transition metal compounds as catalysts, they have prepared aryl and alkyl borylates that can be used in Suzuki couplings of unfunctionalized arenes and alkanes (*11*, *12*). Smith and co-workers showed that several unfunctionalized arenes could be catalytically converted to borane derivatives by activating the aromatic C–H bond and substituting with boron. Cho *et al.* now report several major steps beyond this previous work.

First, their new iridium-based catalyst system gives high yields and high turnovers. The catalyst (see right panel in the figure) is readily synthesized from commercially available starting materials in one step. In the presence of a chelating phosphine (dppe), it can convert arenes with fluoro-, chloro-, and even bromo-substituents to the arylboronate products. The reaction is highly selective for meta substitution (two atoms removed from the halogen group, see the figure), while the halogen group re-

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