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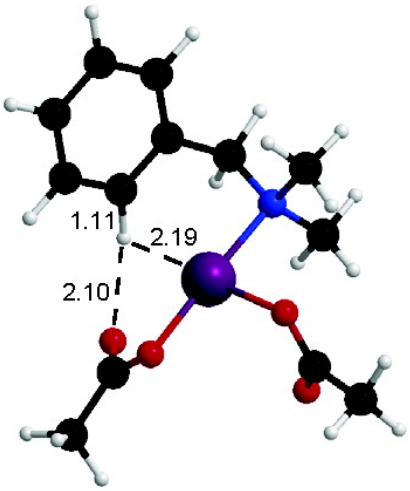
cyclometallation transition state

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# Computational Study of the Mechanism of Cyclometalation by Palladium Acetate

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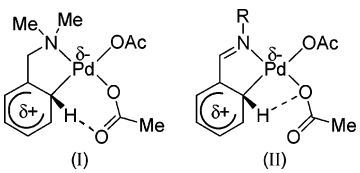
C−H activation is an extremely important process, not only for its fundamental scientific interest but also because of its potential for producing functionalized hydrocarbons.[1,2] To date, most success in this area has been achieved using functionalized aromatic compounds, for example, ruthenium- or rhodium-catalyzed reactions of aromatic ketones with alkenes or alkynes.[3] In these cases, the C−H activation step is believed to be a cyclometalation reaction which proceeds via oxidative addition. Arene C−H activation has also been studied with electrophilic late transition metal centers,[4a−c] and very recently, cyclometalation at $Pd^{2+}$ has been combined with oxidation to give catalytic functionalization of aromatic and $sp^3$ C−H bonds.[4d−g]

Three broad classes of C−H activation have been identified, oxidative addition, $\sigma$-bond metathesis, and electrophilic activation, though the dividing line between these is sometimes rather blurred. Distinguishing between these possibilities experimentally can be extremely difficult; however, insight can often be gained from computational methods which can even put forward novel C−H activation mechanisms, such as Goddard's recent suggestion of "oxidative hydrogen migration".[5]

The mechanism of palladium-promoted cyclometalation of dimethylbenzylamine (DMBA-H) was investigated by Ryabov and co-workers.[2,6] They proposed an electrophilic mechanism via a metal arenium (Wheland) intermediate which transfers a proton to a bound acetate via a highly ordered six-membered transition state (I). Thus, the palladium acetate is thought to play a dual role of electrophilic activation of the arene and intramolecular base for the deprotonation. Subsequent studies on imine cyclometalations reached similar conclusions but suggested a four-membered transition state (II).[7] The possibility of an oxidative addition pathway with or without assistance by acetate has also been considered.[8] Alternatively, it has been suggested that intramolecular arene C−H activation may occur via an agostic intermediate or transition state.[9] Indeed, Milstein et al. have isolated a rhodium complex with an $\eta^2$ agostic aromatic C−H bond which undergoes deprotonation by external base to form a PCP pincer complex; both the X-ray structure and calculations on model complexes showed that the agostic complex had little if any contribution from an arenium structure.[10]




To our knowledge, there are no computational studies of the important Pd cyclometalation reaction. In this paper, we employ density functional calculations[11] to probe the role of acetate and to assess various pathways for the cyclometalation of DMBA-H with palladium acetate.[12] Our results show that an acetate-assisted H-transfer process involving a six-membered transition state is the most accessible route, but that this proceeds via an agostic C−H intermediate rather than the generally assumed arenium structure.

The monomeric square-planar complex $Pd(OAc)_2$(DMBA-H), **1**, has been previously identified as a key intermediate in the $Pd(OAc)_2$/DMBA-H cyclometalation reaction.[6] We calculate **1** to have both $\eta^2$- and $\eta^1$-acetate ligands and find that it can adopt a number of different conformations. H-transfer via a six-membered transition state originates from one of these, **1a** (Figure 1), and is initiated by displacement of one arm of the $\eta^2$-acetate by one *ortho*-C−H bond. This occurs via $\mathbf{TS_{1a-2a}}$ ($E = +13.0$ kcal/mol) and leads to an agostic intermediate, **2a** ($E = +11.0$ kcal/mol). **2a** also exhibits a H-bonding interaction between the *ortho*-H and the displaced acetate (C−H···O═C = 2.04 Å) and is, therefore, ideally set up for H-transfer, which occurs with a minimal activation barrier via $\mathbf{TS_{2a-3a}}$ ($E = +11.1$ kcal/mol). In the cyclometalated product, **3a**, the H-acceptor acetate twists away from the new Pd−C bond and ultimately donates the transferred hydrogen to the second acetate ligand. The formation of **3a** ($E = -13.2$ kcal/mol) is both thermodynamically favored and kinetically accessible, the overall activation barrier relative to **1a** being only 13.0 kcal/mol.

The alternative intramolecular C−H activation pathways of H-transfer via a four-membered transition state and oxidative addition have also been considered, but prove far less accessible with computed barriers of +34.3 and +25.7 kcal/mol, respectively.[13] One key feature of these processes is that during C−H bond cleavage the *ortho*-H and displaced acetate arm are on opposite sides of the Pd coordination plane. The reason H-transfer via a six-membered transition state is much more accessible is because the *ortho*-H remains in the proximity of the pendant acetate arm, which is therefore in a position to facilitate H-transfer (cf. structure **2a**).

Our computed activation barrier of 13 kcal/mol for the H-transfer pathway via a six-membered transition state compares well with experimental values in the range of 11−18 kcal/mol for a variety of palladium-acetate-promoted cyclometalations.[2,5,6] Experimentally, a small H/D kinetic isotope effect (KIE) and the increased rate of cyclometalation with electron-donating arene substituents have been used as evidence of a conventional electrophilic aromatic substitution mechanism,[2,6] though the slope of the Hammett plot (−1.6) is much less than usual. However, the formation of an agostic complex in the rate-determining step is also consistent with these facts, as it involves some elongation of the C−H bond and is facilitated by electron-donating groups. Calculations based on the free energy change between **1a** and $\mathbf{TS_{1a-2a}}$ confirmed a small value for the H/D KIE (1.2) and qualitatively reproduced the substituent effect implicit in the Hammett plot.[14]

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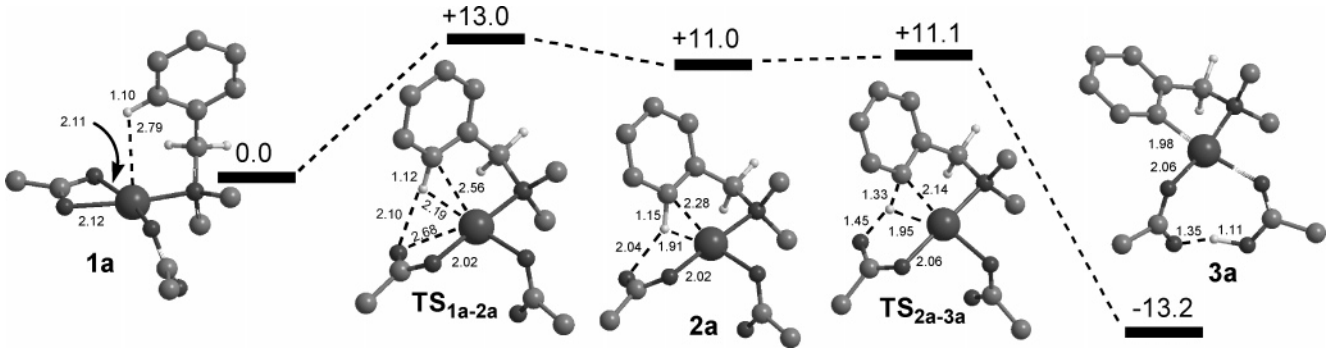


***Figure 1.*** Computed reaction profile (kcal/mol) and key distances (Å) for the cyclometalation of $Pd(OAc)_2$(DMBA-H) via a six-membered transition state. Methyl and nonparticipating phenyl hydrogens are omitted for clarity.

The detailed picture of the cyclometalation process differs from the generally assumed electrophilic attack via a Wheland (arenium) intermediate. First, **2a** exhibits a short Pd···H contact (1.91 Å) and elongated C−H distance (1.15 Å), indicative of an agostic complex. Second, major changes in the calculated natural atomic charges for species **1a** to $\mathbf{TS_{2a-3a}}$ occur only at the activating C−H bond, the negative charge at C increasing by −0.14, while H becomes more positive by +0.09. There is little evidence for any contribution from a Wheland intermediate as the maximum increase in positive charge on any of the ring carbons is only +0.05 and Pd experiences only a slight decrease in positive charge (from +0.75 to +0.72). Finally, the geometry of the agostic interaction in **2a** is very similar to that in the crystallographically characterized rhodium pincer complex mentioned previously[10] (**2a**: Pd···C = 2.28 Å and Pd···H = 1.91 Å, cf. Rh···C = 2.273(5) Å and Rh···H = 1.95 Å; the agostic hydrogen is also displaced out of the aromatic plane to a similar extent in both systems, ca. 18°).

Although the formation of the agostic species **2a** is the rate-determining step in our computed cyclometalation pathway, for this to be productive, deprotonation must subsequently occur. The presence of an appropriately oriented acetate to act as an intramolecular base via a six-membered transition state allows deprotonation to occur with very little distortion of the system and so virtually no activation barrier. In contrast, the four-membered transition state is much higher in energy as it requires a significant lengthening of the Pd−O bond (from 2.02 Å in **2b** to 2.19 Å in $\mathbf{TS_{2b-3b}}$) to accept the transferring hydrogen. Although Milstein et al. have shown that agostic coordination of an arene C−H bond renders it susceptible to deprotonation by an external base,[10] we do not believe this is important in the current case, as the experimental mechanistic data indicate that external amine is not involved in the transition state.[6]

In summary, density functional calculations on the palladium-promoted cyclometalation of (DMBA-H) suggest that the reaction proceeds via an agostic C−H complex, rather than a Wheland intermediate. This is followed by a facile intramolecular H-transfer via a six-membered transition state to coordinated acetate. Thus, the amphiphilic palladium acetate provides electrophilic activation of a C−H bond and acts as an intramolecular base for the deprotonation. The acetate may also play a role in stabilizing the key agostic intermediate through hydrogen bonding. Recently, calculations on palladium-catalyzed alcohol oxidation have also suggested a role for hydrogen bonding to acetate in directing the incoming substrate.[15] At present, it is not clear whether our arguments extend beyond $Pd(OAc)_2$; however, it is noteworthy that many palladium-catalyzed processes employ bases, such as carbonate and phosphate, and it is possible that these also act as intramolecular bases in a similar way to acetate.[16] We are currently investigating this possibility.

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**Note Added after ASAP Publication.** After this paper was published ASAP on September 17, 2005, a typographical error in ref 16 was corrected on September 21, 2005.

**Supporting Information Available:** Computed Cartesian coordinates and energies of all stationary points and full listings of computed natural atomic charges. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Frisch, M et al. *Gaussian 98*, revision A.11.4; Gaussian, Inc: Pittsburgh, PA, 2001. Calculations used the BP86 functional. Pd was described using the Stuttgart RECPs and the associated basis sets; 6-31G** basis sets were used for C, N, O, and H atoms. Quoted energies include a correction for zero-point energies. See Supporting Information for full details.
(12) While the C−H bond activation step is rate-determining in chloroform, the kinetics are very different in acetic acid. Our calculations should, therefore, only be taken to represent the situation in low polarity media.
(13) Full details, including all stationary points, are illustrated in Figures S1 and S2 in the Supporting Information.
(14) The computed KIE was based on $Pd(OAc)_2(Me_2NCH_2C_6H_5)$ versus $Pd(OAc)_2(Me_2NCD_2C_6D_5)$ as in ref 6, with relative rates based on the Eyring equation. Free energies of activation (kcal/mol) for $Pd(OAc)_2(Me_2NCH_2$-*p*-$C_6H_4$-X) species were 15.0 (X = Cl), 14.2 (X = H), and 13.2 (X = Me).
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(16) Indeed, the process described herein may not be limited to aryl-C−H activation. Preliminary results with $Me_2N^nPr$ indicate that alkyl-C−H activation proceeds with a barrier of only 20 kcal/mol.

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