Mechanistic Analysis of Iridium Heteroatom C−H Activation: Evidence for an Internal Electrophilic Substitution Mechanism

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Summary: The mechanism responsible for C−H activation in $Ir(acac)_2(OCH_3)(C_6H_6)$ has been identified and described as an internal electrophilic substitution (IES) mechanism, on the basis of orbital changes and predicted reactivity. In this IES mechanism, the lone pair on a M−X ligand forms an X−H bond, while the orbital making up the M−X bond turns into a coordinating lone pair.

There has been great progress in the development of new alkane activation catalysts based on mechanisms ranging from oxidative addition (OA) to *σ*-bond metathesis (SBM) and electrophilic substitution (ES). However, a commercially viable catalyst has yet to be announced. We analyze here the mechanism responsible for C−H activation in a recent system published by us and identify it as an internal electrophilic substitution (IES). On the basis of this IES mechanism, we suggest guidelines for choices in metals and ligands expected to have activation barriers lower than those of currently known catalysts.

Recently, we published a joint experimental/theoretical account of the first intermolecular C−H activation reaction with a late metal−alkoxo complex, (acac-O,O)$_2$Ir^{III}(OMe)(Py) (**1**).[1] The mechanism for the C−H activation step was tentatively described as a SBM, on the basis of the geometry of the reacting atoms in the transition state (**TS1**; see Figure 1). Gunnoe and Cundari studied the H/D exchange for a similar reaction catalyzed by TpRu(PMe$_3$)(OH) (**2**)[2] and also proposed that the operative mechanism resembles SBM.[2a]

However, a more detailed analysis of **TS1** shows that this earlier assignment was incorrect. We report here the computational analysis of **TS1** plus a more detailed study of a simplified model system. This shows that the mechanism is not traditional SBM; rather, it reacts through a mechanism we denote as internal electrophilic substitution (IES). This is most likely analogous to the mechanism for metal-catalyzed dihydrogen cleavage,[3] as postulated by Gunnoe et al.[4] In addition, Gunnoe
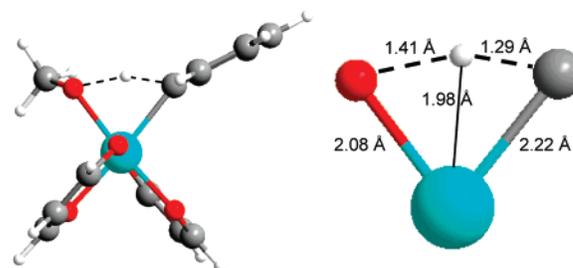

Figure 1. (left) C−H activation transition state **TS1**, where a hydrogen is transferred from a benzene to a methoxo group. (right) Close-up of the four relevant atoms in **TS1**.

et al. pointed out the possibility that the lone pair could be important for this type of transformation,[4] although, to the best of our knowledge, no orbital analysis of either H−H or C−H cleavage under these conditions has been conducted. Also, it might be related to the well-known early-metal M=NR$_2$ type C−H activation, which reacts through a [1,2]-insertion mechanism.[5]

The calculations were performed using the B3LYP functional with the LACVP** basis and effective core potential treatment of the Ir (17 explicit electrons), as implemented by the Jaguar 6.5 program package.[6] Orbital analysis was performed by localizing orbitals using the Pipek−Mezey (PM) methodology as well as single-point GVB calculations. Although only the PM orbitals are shown in this report, both sets of orbitals agree.

To ensure that the calculated mechanism is not a computational artifact, we compared calculated and experimental deuterium kinetic isotope effects (KIE). The computationally predicted KIE (k_H/k_D) for **TS1** was calculated to be 3.2.[7] The experimental KIE was determined to be 3.04 ± 0.20 by reaction of **1** with neat 1,3,5-trideuteriobenzene (see the Supporting Information for details), in very good agreement with the theoretical KIE. It should be noted that we do *not* expect to be able to differentiate between, for example, SBM and IES solely on the basis of the predicted KIE. However, the convergence

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(1) Tenn, W. J., III; Young, K. J. H.; Bhalla, G.; Oxgaard, J.; Periana, R. A.; Goddard, W. A., III. *J. Am. Chem. Soc*. **2005**, *127*, 14172.
(2) (a) Feng, Y.; Lail, M.; Foley, N. A.; Gunnoe, B.; Barakat, K. A.; Cundari, T. A.; Petersen, J. L. *J. Am. Chem. Soc*. **2006**, *128*, 7982. (b) Feng, Y.; Lail, M.; Barakat, K. A.; Cundari, T. R.; Gunnoe, T. B.; Petersen, J. L. *J. Am. Chem. Soc*. **2005**, *127*, 14174.
(3) (a) Kubas, G. J. *Catal. Lett*. **2005**, *104*, 79. (b) Hedberg, C.; Kallstrom, K.; Arvidsson, P. I.; Brandt, P.; Andersson, P. G. *J. Am. Chem. Soc*. **2005**, *127*, 15083. (c) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc*. **2000**, *122*, 1466. (d) Fryzuk, M. D.; Montgomery, C. D.; Rettig, S. J. *Organometallics* **1991**, *10*, 467. (e) Fryzuk, M. D.; Bhangu, K. *J. Am. Chem. Soc*. **1988**, *110*, 961. (f) Joubert, J.; Delbecq, F. *Organometallics* **2006**, *25*, 854.

(4) Conner, D.; Jayaprakash, K. N.; Cundari, T. R.; Gunnoe, T. B. *Organometallics* **2004**, *23*, 2724.
(5) (a) Hoyt, H. M.; Michael, F. E.; Bergman, R. G. *J. Am. Chem. Soc*. **2004**, *126*, 1018. (b) Fulton, J. R.; Holland, A. W.; Fox, D. J.; Bergman, R. G. *Acc. Chem. Res*. **2002**, *35*, 44. (c) Cundari, T. R.; Klinckman, T. R.; Wolczanski, P. T. *J. Am. Chem. Soc*. **2002**, *124*, 1481. (d) Bennett, J. L.; Wolczanski, P. T. *J. Am. Chem. Soc*. **1997**, *119*, 10696. (e) Bennett, J. L.; Wolczanski, P. T. *J. Am. Chem. Soc*. **1994**, *116*, 2179. (f) Cummins, C. C.; Baxter, S. M.; Wolczanski, P. T. *J. Am. Chem. Soc*. **1988**, *110*, 8731. (g) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc*. **1988**, *110*, 8729.
(6) Jaguar 6.5; Schrodinger, Inc., Portland, OR, 2005.
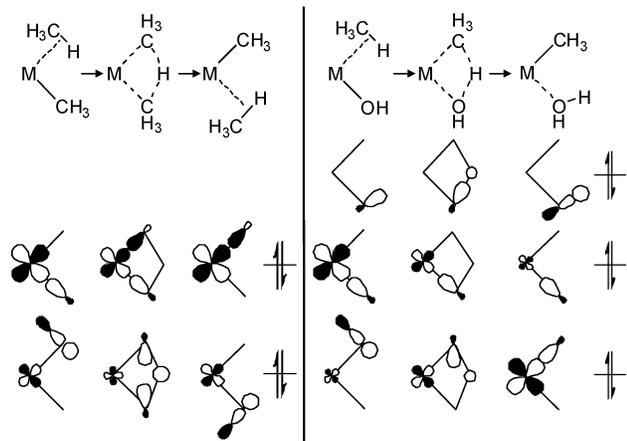(7) For further computational details, see the Supporting Information.

Figure 2. Conceptual orbital view of σ-bond metathesis (left) and internal electrophilic substitution (right)

between experimental and theoretical KIE's strongly indicates that the theoretical description of the transition state is correct.

The impetus for this investigation was the question of whether the lone pair of the alkoxo group participates in the reaction, as illustrated in Figure 2. In this conceptual view, we expect that the M−O bond is transformed into an oxygen lone pair (which eventually coordinates to an empty d orbital on the metal) while the O−H bond is formed from one of the lone pairs. This is unlike SBM, where the X−H bond is based on the same orbital as the X−M bond (Figure 2, left).[8] The formerly bonding C−H orbital, on the other hand, should in the transition state be delocalized over both the breaking C−H bond and the forming M−C bond, as would be expected from a traditional SBM TS. Finally, in the IES mechanism, the migrating hydrogen must cross an orbital's nodal plane during the reaction, while in SBM it does not.

Orbital analysis of the transition state shows that the forming O−H bond is not based on the same orbital as the breaking O−Ir bond. To illustrate the orbital interactions more clearly, calculations on a model compound were carried out. The complex $Ir(CH_3)_2(NH_3)_2(OH)(CH_4)$, where the two NH_3 ligands are in equatorial positions with regard to OH and CH_4, was chosen to minimize interference from lone pairs on the spectator ligands. The energetics from the model transformation are reasonably similar ($\Delta H = -8.6$ kcal/mol, $\Delta H^{\ddagger} = 14.5$ kcal/mol, as compared to -16.7 and 8.4 kcal/mol for the $Ir(acac)_2$-$(OMe)(C_6H_6)$ system). A model compound with an even closer energetic profile could most likely be found, but we do not expect this to make any difference to our conclusion, especially since our calculations on **TS1** exhibit a similar orbital picture, albeit with significant interference from the π orbitals on the acacs.

The reacting localized orbitals are shown in Figure 3 and clearly correspond well to the conceptual orbitals shown in Figure 2. Particularly interesting is the lack of sign change in the reacting orbitals, which is contrary to the SBM mechanism (see Figure 2, left).

The bottom left orbital in Figure 3 corresponds to the bonding CH_3−H orbital that donates to an empty d orbital on the metal in the form of a σ complex. During the reaction coordinate this orbital swells out to allow for a bonding interaction with both the metal and the H and eventually shrinks back to form a bonding M−CH_3 orbital. Even though the orbital is chiefly centered on the ligand, it is clear that some electron density has been donated to the metal d orbital in the top right structure.

The changes in the other two orbitals are less obvious. The oxygen lone pair changes spatial direction due to the changes in geometry during the reaction but retains its overall shape.
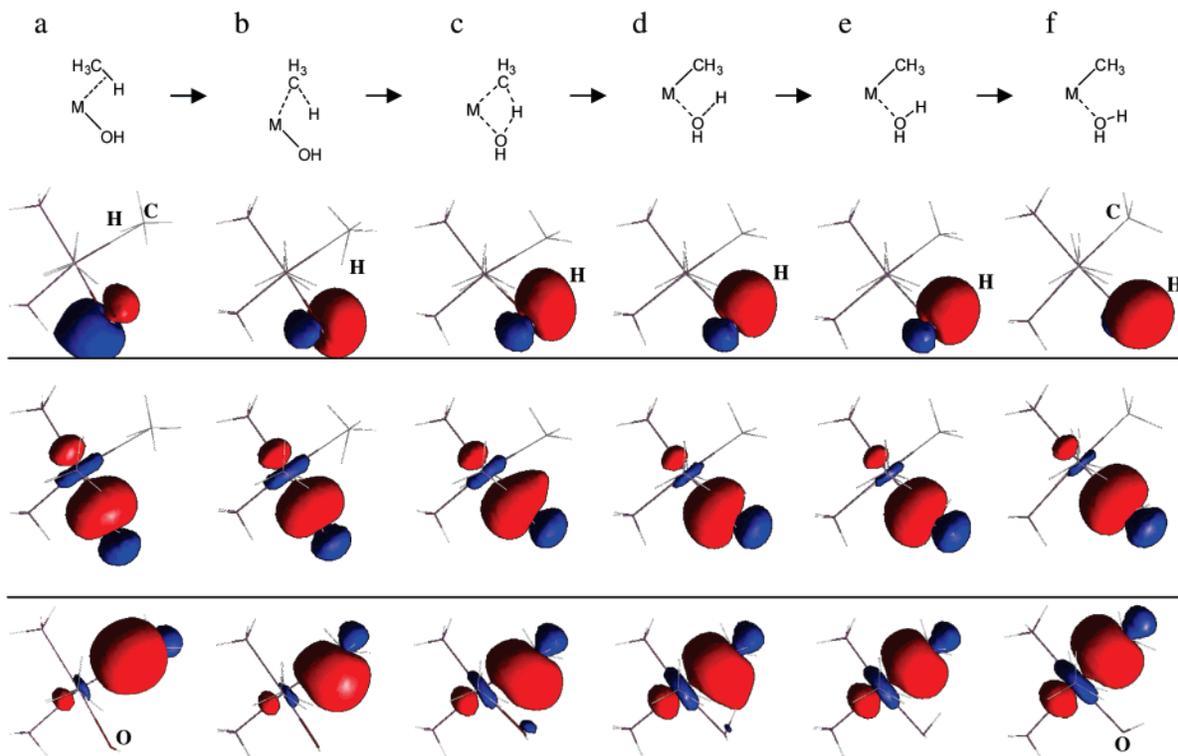

Figure 3. Pipek−Mezey localized orbitals during the IES transformation. In the reactant (a), the σ-complexing C−H bond is pointing left, down and out of the plane, while the noncoordinating O−H bond is pointing right, down and into the plane. In the product (f), one of the O−H bonds points up, right and parallel to the plane, while the other points straight into the plane. The three rows of reacting orbitals are in the same order as the conceptual orbitals in Figure 2.
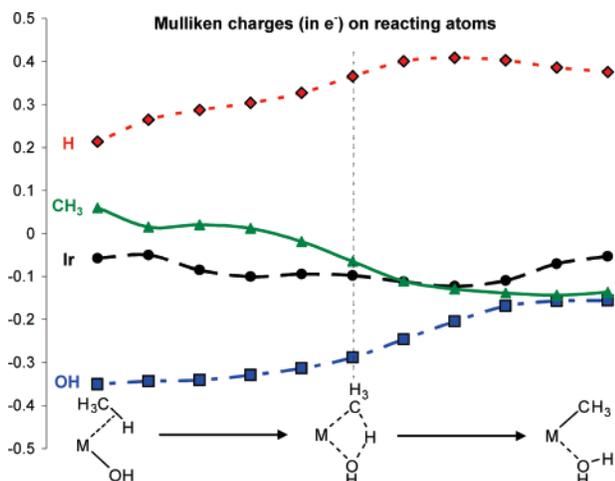
Figure 4. Mulliken charges (in electrons) on the reacting moieties Ir (black circles), H (red diamonds), CH₃ (green triangles), and OH (blue squares) during the IRC of the model reaction.

The same is true for the bonding M−O orbital, although there appears to be some bonding character to the H in the transition state.

By following the charges on the four reacting atoms during the transformation (Mulliken charges on select IRC points shown in Figure 4), we see that some charge reorganization occurs, particularly in the hydrogen, which goes from 0.21 e in the starting material, through 0.37 e in the TS and ending at 0.38 e in the product. Intriguingly, the charge on H is actually greater just *after* the TS, peaking at ∼0.41 e. The charge on the iridium, on the other hand, changes very little, from −0.06 e through −0.10 e to −0.05 e. The methyl group develops more negative character in the TS, from 0.06 e to −0.06 e, and reaches −0.14 e in the product. The OH group changes little before the TS (from −0.35 e to −0.29 e) but becomes significantly more positive after the TS, ending up at −0.16 e in the product. The balance of charge is donated to the spectator ligands, with no particular concentration. Overall, electron density is thus transferred mainly from the hydrogen and the OH group to the methyl group and the spectator ligands, the latter presumably through the iridium.

On the basis of this analysis, it appears that an electrophilic metal activates the C−H bond by generating a positively charged hydrogen. This type of mechanism is well-known in related mechanisms involving platinum,[9] palladium,[10] and gold[11] and is normally referred to as "electrophilic substitution".[12] None of the previously known systems are directly bonding to the base which abstracts the hydrogen, however, which is a marked distinction, and we thus label this variant of the mechanism "internal electrophilic substitution", or IES.

It should be noted that an analogue of the IES mechanism has been known for quite some time in the field of metal-catalyzed dihydrogen activation, where it is referred to as "heterolytic cleavage".[3] This appears to be an overly broad term,

however, as there does not appear to be a consensus regarding the details of this mechanism. Indeed, while the possibility that the lone pair does play a major role has been pointed out,[4] the transition state has also been described as a quadropolar ionic transition state or as a SBM.[2a,3a] We expect that the mechanistic analysis presented for the CH₄ case is equally valid for H₂ (which would rule out SBM), and we are currently investigating suitable systems for a detailed analysis. Furthermore, despite the small peak in charge reorganization in the latter part of the IES, it is more reminiscent of an asymmetric sigmatropic rearrangement than a quadropolar transition state (which, in our view, implies a mainly ionic transition state) and we thus do not believe this term is fitting for the current mechanism.

While the definition of precise language regarding mechanisms is worthwhile in its own right, the ultimate utility is whether it provides sufficient insight into the chemistry to suggest improved catalysts. We expect that the internal aspect of the IES would not benefit from changes due to substitutions in the M−XR moiety, as a change affecting the energy of the lone pair would equally affect the energy of the M−X bond. Indeed, preliminary calculations on $Ir(acac)_2(X)(C_6H_6)$, where X = OCH_3, OCF_3, NH_2, indicates that this assumption is correct, as the barriers change less than 2 kcal/mol.

Conversely, making the metal more electrophilic by removing electron density should promote the transfer of the hydrogen, thereby reducing the barrier. Preliminary calculations on the analogous fluorinated model complex $Ir(CH_3)_2(NF_3)_2(OH)(CH_4)$ show that replacing the NH_3 groups with NF_3 groups reduces the barrier by 6.8 kcal/mol.

Furthermore, the use of the lone pair might require a d^6 (or higher) metal, since a lower d occupation on the metal could stabilize the lone pair through the formation of an oxo species. Indeed, preliminary calculations on a singlet d^4 $Re(acac)_2$ system shows that the barrier for C−H activation increases by up to 20 kcal/mol. (However, we have not yet established that the higher barrier is caused by stabilization of the lone pair.)

On the basis of the IES mechanism we can now suggest strategies for the design of more reactive M−X type C−H activation catalysts. First, we suggest focusing on d^6 and higher metals, preferably with highly donating d orbitals that are expected to repulse the M−X lone pair. Second, low electron density on the metal is advantageous, which would suggest Pt^{II} and Pd^{II} centers. However, since the d orbitals on these systems are not particularly donating, it is possible that a compromise must be found between the electrophilic center and the energy of the d orbital. Thus, in addition to the reported systems featuring Ir^{III} and Ru^{II}, we suggest Os^{II} and possibly Re^{I} as likely candidates. Finally, regardless of which metal is used, it is clear that ligands with low electron-donating character are beneficial. Thus, we predict that replacing the acacs in **1** with an electron-withdrawing analogue (1,1,1,5,5,5-hexafluoropentane-2,4-dionate) or replacing the PMe₃ group in **2** with PF₃ or OH₂ would improve the barriers by 3−4 kcal/mol.

Supporting Information Available: Text, figures, and tables giving computational and experimental details, geometries, absolute energies, ZPE's, frequencies, and orbital coefficients. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Ziegler, T.; Folga, E.; Berces, A. *J. Am. Chem. Soc.* **1993**, *115*, 636.

(9) (a) Shilov, A. E. *Activation of Saturated Hydrocarbons by Transition Metal Complexes*; Reidel: Dordrecht, The Netherlands, 1984. (b) Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560.

(10) Periana, R. A.; Mironov, O.; Taube, D.; Bhalla, G.; Jones, C. J. *Science* **2003**, *301*, 814.

(11) Jones, C. J.; Taube, D.; Ziatdinov, V. R.; Periana, R. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 4626.

(12) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.