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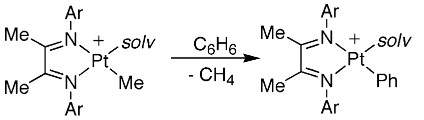
Correspondence

C−H Activation by Platinum(II): What Do Gas-Phase Studies Tell Us about the Solution-Phase Mechanism?

Sir: During the past 5 years the Bercaw/Labinger and Tilset groups (henceforth abbreviated BLT) have reported mechanistic studies on the reaction shown in eq 1, where *solv* = water or 2,2,2-trifluoroethanol (TFE), that implicate a pathway involving associative, solvent-assisted displacement of a water ligand by benzene, with either that step or the subsequent C−H cleavage being rate-determining, depending upon the steric nature of the ancillary diimine ligand N−N.[2] Recently Gerdes and Chen (GC) published the results of mass spectrometric gas-phase studies (along with a more limited set of solution-phase experiments) that they interpret as demonstrating that solvent does *not* participate at all in the rate-determining transition state and, therefore, that the BLT mechanistic proposals must be incorrect.[3] While we have no reason to doubt the validity of their gas-phase experiments or solution-phase experiments separately, we believe that their case for linking them to one another, and to our solution chemistry, is seriously flawed and that their inferences from one regime to the other do not in fact apply. Since this disagreement is relevant to two areas of considerable current activity—the mechanism of C−H activation by transition-metal complexes and the general issue of what implications gas-phase studies can have for solution-phase chemistry—we felt it would be worthwhile to present our detailed arguments in this forum.

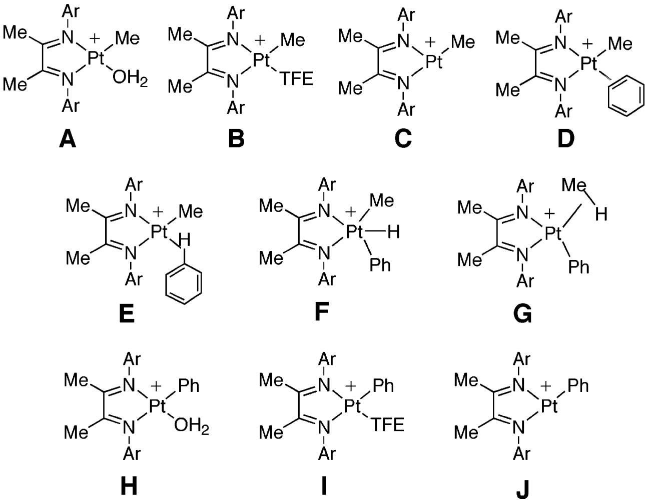


(1)

We begin with a brief restatement of the two contesting positions, followed by our commentary on the various components of the GC claims. For convenience, the various species (observed and hypothesized) involved are represented in Chart 1. The discussion pertains primarily to species involving N−N systems for which Ar (eq 1) = 2,6-$Me_2C_6H_3$ ($N^{Me}-N^{Me}$) or 2,6-$Cl_2C_6H_3$ ($N^{Cl}-N^{Cl}$).

BLT Studies and Conclusions. When the (N−N)Pt(*solv*)Me^+ cation is prepared from (N−N)$PtMe_2$ by protonolysis using an aqueous acid,[4] the starting position is shown clearly by NMR to involve an equilibrium between **A** and **B**, with the former strongly favored ($K_{eq} > 10^2$; the exact value depends on the electronic nature of N−N). Reaction with benzene leads to a corresponding equilibrium mixture of **H** and **I**.[2b]

Chart 1



Detailed kinetics studies yield a rate law that is approximately first-order in [benzene] and inverse first-order in [water]. When N−N contains relatively bulky (ortho-disubstituted) aryl groups, the kinetic isotope effect (KIE) is close to unity (1.06 ± 0.05), and reactions of deuterated benzene with ordinary Pt−Me result in virtually complete statistical isotopic scrambling among the various possible product positions. In contrast, when N−N contains no such bulky aryls, a substantial KIE (around 2) is observed, along with only limited isotope scrambling.[2e,5]

We account for these observations in terms of the sequence of steps shown in eq 2. For bulky N−N, step 1 (**B** → **D**) is rate-determining (RDS); this involves no C−H bond cleavage, and so no large KIE would be expected. Assuming k_1' is (symmetrically) relatively slow, steps 2 and 2′, which effect isotopic scrambling, will be fast compared to loss of hydrocarbon. For less bulky N−N, k_2 (which *does* involve C−H cleavage) is rate-determining; hence, the larger KIE and less extensive scrambling. **D**, the π-benzene complex, can be generated by an alternate route and observed by NMR at low temperature.[2b,6] (It seems likely that there would be a σ-C−H−benzene complex **E** intermediate between **D** and **F**, but we have no evidence on

$$\mathbf{A} \underset{H_2O}{\overset{TFE}{\rightleftarrows}} \mathbf{B} \underset{TFE,\ k_{-1}}{\overset{C_6H_6,\ k_1}{\rightleftarrows}} \mathbf{D} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathbf{F} \underset{k_{-2}'}{\overset{k_2'}{\rightleftarrows}} \mathbf{G} \underset{CH_4,\ k_{-1}'}{\overset{TFE,\ k_1'}{\rightleftarrows}} \mathbf{I} \underset{TFE}{\overset{H_2O}{\rightleftarrows}} \mathbf{H} \quad (2)$$

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[1] (a) California Institute of Technology. (b) University of Oslo.

[2] (a) Johansson, L.; Ryan, O. B.; Tilset, M. *J. Am. Chem. Soc.* **1999**, *121*, 1974−1975. (b) Johansson, L.; Tilset, M.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 10846−10855. (c) Johansson, L.; Tilset, M. *J. Am. Chem. Soc.* **2001**, *123*, 739−740. (d) Johansson, L.; Ryan, O. B.; Rømming, C.; Tilset, M. *J. Am. Chem. Soc.* **2001**, *123*, 6579−6590. (e) Zhong, H. A.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 1378−1399.

[3] Gerdes, G.; Chen, P. *Organometallics* **2003**, *22*, 2217−2225.

[4] Anhydrous solutions of **B** can be prepared by an alternate route (Heyduk, A. F.; Driver, T. G.;. Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2004**, *126*, 15034−15035) and exhibit the enhanced reactivity toward C−H activation predicted from the BLT mechanistic picture.

[5] GC do not address this case. Indeed, from comments in their paper it is not at all clear whether they even recognized that there *are* two different cases.

[6] An analogous species has been characterized crystallographically in a different system: Reinartz, S.; White, P. S.; Brookhart, M.; Templeton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 12724−12725.

10.1021/om0502638 CCC: $33.50

that score, and the question does not appear to have any significant consequences for the overall analysis.)

The rate law is consistent with the solvent-assisted associative pathway shown in eq 2, where the inverse water dependence is a consequence of the equilibrium between **A** and **B**. However, it would also be compatible with a dissociative pathway involving the equilibrium between **A** and three-coordinate **C**. The latter seems a priori less likely but cannot be ruled out. Dissociative substitution for square-planar Pt(II) is rare but not unknown.[7] The rate law for the latter case should exhibit saturation in [benzene], which was not observed, but that could be due to the inability to attain sufficiently high benzene concentrations.

However, positive evidence for an associative route was obtained from the observation that adding a better ligand, CH_3CN, suppresses the degree of isotopic scrambling in these studies[2c,e] and also reduces the extent of isomeric rearrangement in related systems involving substituted benzenes.[2d] Such behavior indicates that external ligand accelerates the loss of hydrocarbon (steps −1 and 1′) relative to scrambling (2, −2, 2′, −2′), which requires that the entering ligand be present in the transition state for the former steps. By microscopic reversibility, the leaving ligand must be present in the transition state for hydrocarbon coordination—i.e., an associative process. This conclusion is also supported by high-pressure studies that give a negative activation volume.[8,9]

GC Studies and Conclusions. Mass spectrometric studies were carried out using the ortho-disubstituted aryl diimine ligand $N^{Cl}-N^{Cl}$. Electrospraying a TFE solution of the corresponding Pt−Me cation gives ions whose *m*/*z* values correspond to **A**−**C**, which are mass-selected and allowed to react with benzene. **A** and **B** are not very reactive under these conditions, but **C** reacts efficiently to give an ion with an *m*/*z* value consistent with any of the species (or a rapidly interconverting mixture thereof) **D**, **F**, and **G**, along with product ion **J**. By substitution with C_6D_6 an overall KIE value of 1.18 ± 0.06 for the overall transformation of **C** to **J** was determined. A separate experiment revealed that the conversion of **C** to (**DFG**) exhibited no detectable isotope effect, so that the observed value must be attributed to the transformation (**DFG**) to **J**. The product ion **J** obtained from the reaction of **C** with C_6D_6 shows nearly statistical isotopic scrambling, as in the solution studies.

(**DFG**) undergoes collision-induced loss of hydrocarbon—methane or benzene—to give the corresponding ions **J** and **C**, respectively. The ratio of **J** to **C** is around 84:16 and is independent of the colliding species, whether the latter is argon, TFE, or 1,1,1,2-tetrafluoroethane. For the case of TFE as colliding species, no TFE-containing ions (**B**, **I**) are detected as products. Also, the overall product yield depends only on the energy, not the identity, of the collision gas.

Solution kinetics were also carried out in both TFE and wet benzene, for complexes with $N^{Cl}-N^{Cl}$ as well as $N^{Me}-N^{Me}$. For both complexes the rate constants, defined as $k = k_{obs}[\text{water}]/[\text{benzene}]$, were nearly the same in both media. Furthermore, the results for the $N^{Me}-N^{Me}$ complex in TFE were quite similar to those previously reported by BLT.

From these findings GC conclude that TFE does not participate at all in the rate-determining step for C−H activation, that it is nothing more than an “inert diluent”, that “TFE gives no acceleration at all”, that “a putative solvent-assisted associative mechanism cannot be the explanation for the facile C−H activation reaction”, and that “While it is on one hand disappointing that the claimed facilitation of C−H activation by solvent assistance by TFE is not supported by the present experimental data, it is on the other hand encouraging that extremely rapid C−H activation...may be achieved in ordinary solvents as long as the solvent is not strongly coordinating.”

On the Role of TFE. The GC claim that TFE is an *inert* diluent is plainly incorrect, as TFE clearly does coordinate to Pt in **B**. The role of TFE in “accelerating” C−H activation consists of nothing more or less than to act as a weakly coordinating, readily displaceable ligand. We have formulated this role in terms of an associative displacement pathway, but the situation would be *no different* if it were a dissociative pathway, as the concentration of the key (in that model) intermediate **C** would be strongly affected by the coordination ability of the solvent. Even if we were to accept GC’s apparent position that the substitution is associative but the rate-determining step lies further along the reaction profile, after TFE has departed (see below), it would still be the case that **B**, not **A**, undergoes such displacement, or else the inverse [water] dependence and the relationship between rates and equilibrium position[2e] could not be explained. That is *by definition* a solvent-assisted pathway.[10]

GC are quite correct that equally high activity may be achieved by an “ordinary” solvent that is not strongly coordinating, with the proviso that the solvent also must support dissolution of an ionic complex. Wet benzene will accomplish this up to concentrations sufficient for UV/visible spectroscopic studies (we doubt whether it can extend to synthetically useful concentrations), but the choice of “ordinary” solvents that satisfy both requirements and also do not cause undesirable side reactions is not large, and TFE is the best we have found so far. It *does* give acceleration, in the sense of being more weakly coordinating than most polar solvents (for example, higher temperatures are required for similar reactions in pentafluoropyridine[11]), and that is the *only* sense in which we have ever suggested it has any special powers. GC apparently have misunderstood the significance of TFE as a solvent for C−H activation and have (willfully or otherwise) misconstrued our interpretation thereof.

On the Similarity between Rate Constants in TFE and Wet Benzene. GC claim this implies zero-order dependence on TFE and essentially identical behavior in the two solvents. The rate constant in wet benzene was calculated by assuming the same rate law as in TFE. However, since only one experiment was carried out, at a single water concentration, this is just an assumption; the actual rate law is unknown. How *does* the reaction proceed under these conditions? There are several possibilities, depending on the speciation.

1. The primary solution species is the π-benzene complex **D**, and the RDS is C−H cleavage. This seems least likely, but if it were the case there would be no inverse [water] dependence and it would make no sense to multiply the observed rate constant by [water]. Hence, the calculated rate constant would not be meaningful.

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[7] Romeo, R. *Comments Inorg. Chem.* **1990**, *11*, 21−57.

[8] Procelewska, J.; Zahl, A.; van Eldik, R.; Zhong, H. A.; Labinger, J. A.; Bercaw, J. E. *Inorg. Chem.* **2002**, *41*, 2808−2810.

[9] GC include an additional intermediate between **B** and **D**, corresponding to the five-coordinate species obtained by adding benzene to **B**. However, that species might instead be a transition state, which would amount to an associative interchange rather than a “true” associative mechanism. All arguments (on both sides) apply equally well to either case; thus, we have left it out in the interests of simplicity.

[10] See for example: Tobe, M. L.; Burgess, J. *Inorganic Reaction Mechanisms*; Addison-Wesley Longman: New York, 1999; pp 74−79.

[11] Holtcamp, M. W.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1997**, *119*, 848−849.

2. The primary solution species is the aquo complex **A**, and the RDS is associative displacement of water by benzene. Again, there would be no inverse [water] dependence.

3. The primary solution species is **A**, and the RDS is dissociative displacement of water by benzene. In this case the overall rate would be determined by the competition of water and benzene for coordinatively unsaturated **C**, and there would be an inverse [water] dependence. However, TFE clearly does coordinate as well; thus, if the mechanism is the same in TFE solution (as GC argue), then TFE would also be competing for **C** and there would also be an inverse [TFE] dependence. Hence, at the same [benzene]:[water] ratio the rate constant calculated by assuming no dependence on [TFE] should be considerably *larger* in wet benzene than in wet TFE, not the same.

4. The complex exists as a mixture of **A** and **D** in fast equilibrium (with the former strongly favored), and the RDS is C−H activation, to give **F**, with the overall rate proportional to the concentration of **D**. Here again TFE would reduce the latter by forming **B**, with the same consequence as in possibility 3 above.

There is thus *no* set of circumstances in which the similarity of calculated rate constants supports GCs conclusion. The similarity *is* a bit surprising—one might well have expected the large difference in polarity to have a more dramatic effect, no matter what the detailed mechanism happens to be—but it does not prove anything mechanistically. Presumably the various effects of solvent polarity (TFE vs benzene) and leaving group coordination ability (TFE vs water) more or less offset each other. Certainly further studies (e.g., the [water] dependence in benzene, the effect of added TFE in wet benzene) are required before any interpretation beyond coincidence can be justified.

On the Relevance of Gas-Phase Studies to Solution Mechanism. The first mechanistically relevant point is that the gas-phase study involves neither **A** nor **B**, which are relatively unreactive toward benzene, but the coordinatively unsaturated ion **C**, which is almost surely *not* involved in solution (unless the arguments for an associative pathway are wrong, which GC do not claim). GC note that the collision-induced reactions of (**DFG**) to **C** + **J** proceed identically whether the collision gas is TFE or something else, indicating TFE is not present in the transition state of these reactions. By microscopic reversibility, they argue, the reverse reactions cannot have TFE bound in the transition state either. Nobody could disagree with that: the reverse reactions are **C** + benzene → (**DFG**) and **J** + methane → (**DFG**), which do not involve TFE at all! Furthermore, the fact that these are collision-induced begs the question of how closely related they are to solution chemistry. It seems to us at least plausible to ascribe the facts that the cross-section depends only on energy, not identity, of the colliding species and that TFE does not end up bound in any products to the particular nature of high-energy, collision-induced gas-phase chemistry. (The low probability of a TFE collision in the correct orientation for coordination—O-end first, presumably—compared to all the other possible configurations, may also contribute to the explanation of why TFE behaves no differently from other colliding species.)

GC do acknowledge the need to establish firmer connections between gas and solution phases and offer four arguments for mechanistic similarity that they feel justify extending the gas-phase conclusion —that TFE is not present in the transition state for the reactions—to the solution phase.

1. The gross overall reactions are identical.

2. The overall KIEs—1.18 ± 0.06 in the gas phase and 1.06 ± 0.05 in solution—are similar.

3. Near-statistical isotope scrambling of deuterium from C_6D_6 is observed in both phases.

4. The branching ratio of (**DFG**) to **J** + **C** is very similar in the gas phase (84:16) to that for **H** + **A** in solution (82:18).

Let us take these in turn.

1. The gross overall reactions are identical. This carries no weight at all (except for the obvious point that if they were *not* the same reactions we would never have had this discussion in the first place). The organo-transition-metal chemistry literature is replete with examples of closely related reactions, giving identical stoichiometry and yet proceeding by different (in some cases drastically so) mechanisms. To cite just one case (from one of our pasts), the oxidative addition of alkyl iodide to $IrCl(CO)(PMe_3)_2$ proceeds cleanly and rapidly to the same trans addition product, $IrClIR(CO)(PMe_3)_2$, for both R = Me and R = Et; however, the first reaction goes by an S_N2 pathway and the second by a radical-chain pathway.[12] It is clear that there is often a multiplicity of energetically fairly similar reaction pathways for a given system, such that small perturbations can cause an abrupt switch from one to another. Mechanistic inferences from stoichiometry are not justified.

2. The overall KIEs are similar. This argument has two problems. First, while similar *large* KIE values might well have mechanistic significance, it is highly doubtful that comparing two such *small* KIEs (and they are not even all that similar, considering the given uncertainties) can tell us anything at all, beyond the fact that neither appears to involve extensive C−H bond breaking in the transition state. Presumably they reflect secondary isotope effects, which can arise from a number of quite different factors. Two mechanistically very different reactions (e.g., the Ir case cited in the above paragraph) might well also exhibit KIEs in the same range.

The second problem is even more serious. GC argue that the KIEs result from the same process in both media, but they have completely overlooked the significance of their finding: that the gas-phase KIE applies to the transformation of (**DFG**) to **J**, *not* to the reaction of **C** + benzene to give (**DFG**). The gas-phase KIE must therefore reflect either a step *within* (**DFG**)—that is, the observed species is actually **D** (or **F**) and the KIE refers to its conversion to **F** (or **G**) followed by fast conversion to **J**—or the loss of methane from (**DFG**) to give **J**. But *neither* of these can possibly be the RDS in solution—and in solution, of course, the KIE must reflect what happens in the RDS. In the first case, an RDS within (**DFG**), isotope scrambling could not be fast compared to other processes. In the second case, for methane loss to be rate-determining, the barrier for (**DFG**) to **J** (+methane) would have to be higher than that leading to **C** (+benzene), the opposite of what is actually observed. Hence, the gas-phase and solution-phase KIEs are probing two completely different steps of the overall reaction sequence. Any similarity between them (which is marginal at best) must be purely coincidental.

3. The near-statistical isotope scrambling of deuterium from C_6D_6 is identical. This demonstrates that **D**, **F**, and **G** are in rapid equilibrium in both the gas and solution phases. The latter conclusion was reached in the original BLT studies. It says *nothing* about the processes leading up to and away from these species, except that they are slower than the scrambling.

*4. The branching ratio of (**DFG**) to **J** + **C** in the gas phase (84:16) is very similar to that for **H** + **A** in solution (82:18).* The solution branching ratio was determined by protonating $(N^{Me}-N^{Me})PtMePh$.[2b] When it is carried out using aqueous

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[12] Labinger, J. A.; Osborn, J. A.; Coville, N. J. *Inorg. Chem.* **1980**, *19*, 3236−3243.

HBF_4 at room temperature in TFE, this reaction gives **H** and **A** in an 82:18 ratio, as cited by GC. In contrast, when the protonation is carried out at −78 °C in dichloromethane, a stable solution of **D** is obtained. When the temperature is raised to −23 °C, again loss of methane + benzene and formation of phenyl and methyl complexes are observed. However, under these conditions, the ratio of the latter is 60:40, not 82:18. This shows that the partition is dependent on solvent, anion (triflic acid was used to protonate), and/or temperature. If solvent dependence is the case, then GC's contention that the loss of hydrocarbon is independent of entering group is clearly incorrect. If temperature dependence is operative, then the gas-phase ratio should be compared with the solution ratio obtained at the temperature that best corresponds to the state of the ions upon collision. What is that temperature? We have no idea. Given that the gas-phase reaction is induced by an energetic collision, it seems unlikely that room temperature is the most appropriate comparison to choose. In any case, yet again the result cannot be taken to establish any connection between the two realms.

On the Overall Reaction Sequence. GC's claim that there is no TFE in the transition state requires either a dissociative mechanism for replacement of solvent by benzene (the step labeled k_1 in eq 2) or location of the RDS to the right of that step. They apparently do not want to argue for the first, presumably finding the evidence cited above for associative displacement convincing. However, the RDS must be to the left of intermediate **D**, as the interconversion between **D**, **F**, and **G** is rapid. Hence, they are forced to postulate an additional intermediate (call it **X**), of unknown structure, with the RDS being the conversion of **X** to **D**. By symmetry there must be a new intermediate between **G** and **I** (eq 3).

$$\mathbf{A} \underset{H_2O}{\overset{TFE}{\rightleftarrows}} \mathbf{B} \underset{TFE,\ k_{-1}}{\overset{C_6H_6,\ k_1}{\rightleftarrows}} \mathbf{X} \overset{\mathbf{RDS}}{\rightleftarrows} \mathbf{D} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathbf{F} \underset{k_{-2}'}{\overset{k_2'}{\rightleftarrows}}$$

$$\mathbf{G} \rightleftarrows \mathbf{X'} \underset{CH_4,\ k_{-1}'}{\overset{TFE,\ k_1'}{\rightleftarrows}} \mathbf{I} \underset{TFE}{\overset{H_2O}{\rightleftarrows}} \mathbf{H} \quad (3)$$

Unfortunately, this proposal *completely* fails to account for the very evidence that supports an associative mechanism: the fact that added ligand reduces the degree of scrambling (isotopic or isomeric) in eliminated hydrocarbon. If adding a good ligand exerts an effect by accelerating the elimination relative to other steps, elimination must be slower—i.e., rate determining—in the absence of those ligands. However, the GC model places the RDS for activation *after* the departing ligand is gone; thus (by microscopic reversibility, and also concluded from their gas-phase studies), the RDS for elimination *precedes* the entry of incoming ligand. In this scenario the isotope/isomer distribution would be fixed before any participation of incoming ligand could exert any effect, in contradiction to the observations.

Conclusions. While the GC gas-phase studies lead to an interesting and plausible mechanistic picture of the behavior of these organoplatinum ions in the gas phase, their case for applying that picture to reactions in solution breaks down at every point. Their proposal fails even to account for the full set of observations in the BLT studies, let alone to stand as adequate grounds for rejecting the mechanism based on those observations. Of course mechanistic demonstrations are never final or unequivocal, and we could certainly imagine results that would lead us to rethink our ideas; however, we believe the above discussion shows clearly that GC have generated no such results.

We are in full agreement with GC that mass spectrometric studies of organometallic reaction mechanisms in the gas phase are of interest in their own right and have unquestioned potential for shedding light upon related solution-phase chemistry. At the same time, it must be recognized that there *are* clear differences between the two realms, and connecting them needs to be based on careful and rigorous reasoning, rather than on superficial similarities, facile assumptions, and convenient neglect of obvious inconsistencies. In the present case, it seems to us much more likely that the gas-phase data pertain to a mechanism wherein the key intermediates are accessed via the coordinatively unsaturated, three-coordinate species **C**, resulting in *major* differences from the C−H activation observed in solution, where **C** plays no significant role.

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