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Free Energy *ab Initio* Metadynamics: A New Tool for the Theoretical Study of Organometallic Reactivity? Example of the C−C and C−H Reductive Eliminations from Platinum(IV) Complexes

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Metadynamics and static DFT calculations have been performed on the C−H and C−C reductive elimination from Pt(IV) octahedral complexes $L_2Pt(CH_3)_3X$ (X = H or CH_3, L_2 = diphosphine ligand, viz., a model of a dppe and dppbz ligand). The use of metadynamics simulations is shown to be a powerful tool to describe the reactivity of organometallic compounds and provide us with the activation free energy of the different processes involved in these reactions: ligand dissociation; C−C and C−H formation. The computational results bring to the fore three mechanisms: direct and dissociative pathways, but also a concomitant mechanism with a simultaneous C−H formation and Pt−P dissociation. The dissociative pathway, which proceeds through a five-coordinate intermediate, is favored for the C−C reductive elimination, whereas the two other mechanims are observed for the C−H reductive elimination. The basicity of the phosphine used as much as its intrinsic rigidity strongly influences the mechanism of the C−H reductive elimination: direct or with concomitant dissociation of one arm of the diphosphine ligand. On the contrary, it has no influence on the C−C reductive elimination. The computed free activation energies from metadynamics calculations are in good agreement with experimental values measured for the different complexes. We also report computed activation free energy with inclusion of the entropy effect for the dissociation of the diphosphine ligand, a necessary step for the C−C reductive elimination.

Introduction

Reductive elimination leading to a carbon−carbon or carbon−hydrogen bond is the usual product-forming step in organometallic catalytic cycles to generate various organic compounds. Like its microscopic reverse, the oxidative addition of a carbon−carbon or carbon−hydrogen bond, reductive elimination is a key activation step of metal-mediated organic transformations, both stoichiometric and catalytic.[1] Thus, the quest for the understanding of the mechanism of these bond cleavage/formation processes from Pt complexes has produced a large amount of experimental and theoretical studies.[2−4] Despite all these efforts, the detailed mechanism for this reaction especially for the Pt(IV) octahedral complex is still a matter of intense debate.[2,3a] The key question concerns the initial ligand dissociation and the formation, or not, of an intermediate prior to the reductive elimination.

The lack of unambiguous evidence for a direct elimination for reductive C−H and C−C elimination from d^6 octahedral Pt(IV) complexes has strongly supported the belief that such reductive eliminations occur only in conjunction with ligand dissociation and formation of a five-coordinate intermediate. For C−C reductive elimination from octahedral Pt(IV) complexes with phosphine ligands, the inhibition role of added phosphine has been early[5] interpreted as a clue in favor of formation of a five-coordinated intermediate prior to the reductive elimination. In the presence of a chelating diphosphine ligand, reductive elimination still occurs through a five-coordinate intermediate but with dissociation of the X^- group (with $X^- = I^-$ or carboxylate, for example) for *fac*-(diphosphine)−$PtMe_3X$ complexes[6] or dissociation of an arm of the diphosphine ligand for (diphosphine)−$PtMe_4$ systems.[2,4a] C−H reductive elimination was not supposed to proceed through a different mechanism, and most of the proposed mechanisms

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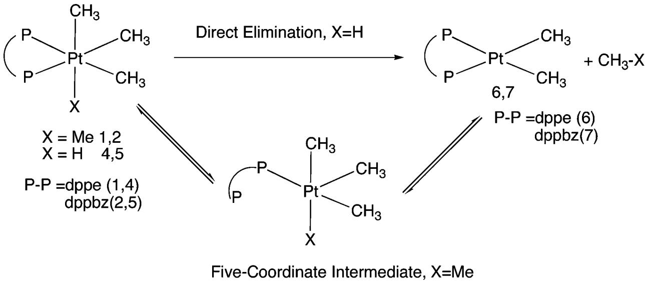
Scheme 1. Postulated Pathways for C−H and C−C Reductive Eliminations



indeed suggest a dissociative pathway.[7] This hypothesis was highly supported by the discoveries of thermally stable hydride alkyl Pt(IV) compounds.[8] The synthesis of these compounds seems related to the use of chelating ligand, which does not easily undergo dissociation and so prevents the system from forming the necessary five-coordinate intermediate. However Crumpton-Bregel and Goldberg[2] opened a breach in this belief: they focused on the comparison between Me−H and Me−Me reductive eliminations from octahedral Pt(IV) complexes with two different chelating diphosphine ligands: L_2-$PtMe_3R$ (R = Me or H) with L_2 = dppe (bis(diphenylphosphino)-ethane, $PPh_2(CH_2)_2PPh_2$) or dppbz (*o*-bis(diphenylphosphino)benzene, *o*-$PPh_2(C_6H_4)PPh_2$), which is a less fluxional ligand compared to dppe because of its benzene backbone. The difference in reactivity between C−H and C−C reductive elimination and from one chelating phosphine to the other one led them to the mechanistic assumptions summarized in Scheme 1.

These conclusions were motivated by converging observations. A dramatic temperature difference between C−H and C−C reductive elimination is observed: for methane elimination, whatever the ligand used, a rate constant of 1×10^{-4} s^{-1} is achieved at 50 °C versus 4.2×10^{-6} s^{-1} at 150 °C for ethane elimination from (dppe)$PtMe_4$ **1**. Moreover, the C−C reductive elimination is strongly dependent on the phosphines used: if the more rigid chelating ligand dppbz is used, no elimination is observed. Therefore, a prior dissociation of the phosphine is necessary but impossible with this rigid ligand and prevents the ethane elimination from (dppbz)$PtMe_4$ **2**. On the other hand, the rate constant of C−H elimination from (dppe)$PtMe_3H$ **4** or (dppbz)$PtMe_3H$ **5** is not sensitive to the use of one phosphine compared to the other one, and similar activation parameters ($\Delta H^\ddagger \approx 26$ kcal·mol^{-1} and $\Delta S^\ddagger \approx 3$−6 cal·mol^{-1}·K^{-1}) are observed for both rigid and nonrigid ligands. This seems to imply that the phosphine ligand does not play any role in these C−H reductive elimination reactions. Thus, a dissociative mechanism was assumed for C−C reductive elimination and a direct mechanism for the C−H reductive elimination.

From a general point of view, this work provides pertinent and accurate experimental data (choice of the complexes, activation enthalpy, activation entropy, and X-ray data), which can allow comparisons with theoretical free energy calculations. To study these reactions and to introduce entropy effects which come along with a possible ligand dissociation, these reactions have been studied by *ab initio* metadynamics[9] as implemented in the DFT CP2K-QuickStep code using Gaussian plane waves (GPW) orbitals and by quantum chemistry methods with the Gaussian03 code. With such a theoretical strategy, we study the mechanism of the C−H and C−C reductive eliminations, we analyze the role played by the biphosphine ligand, and we investigate the mechanistic assumptions of Crumpton-Bregel and Goldberg.[2] Indeed, for such reactions, which can occur with or without ligand dissociation, the knowledge of the minimum reaction path and of the free energy along this pathway can be crucial. Moreover, due to the heights of the barriers, a spontaneous reaction cannot be realistically observed during the finite simulation time of an ordinary molecular dynamics simulation. Thus, the use of metadynamics appears to be a natural choice.

In this paper, we report the results of our *ab initio* metadynamics calculations and compare them with the experimental data on the C−C and C−H reductive eliminations from octahedral diphosphine Pt(IV) complexes. The novelty of the application of this method to organometallic reactivity suggests comparing the *ab initio* metadynamics calculations to standard static calculations. On the basis of those results, we present possible pathways for these reactions and discuss the origin of the observed differences between C−C and C−H reductive elimination in conjunction with the chelating ligand used.

Computational Details

The *ab initio* Born−Oppenheimer dynamics calculations were performed using the CP2K-QuickStep program[10] at the DFT level with the BLYP[11] functional. QuickStep is an implementation of the Gaussian Plane Waves (GPW) method based on the Kohn−Sham formulation of the density functional theory (DFT). It is a hybrid method using a linear combination of Gaussian-type orbitals to describe the Kohn−Sham orbitals, whereas an auxiliary plane waves basis set is employed to expand the electronic charge density. The basis set used was a double-ζ valence set of Gaussian orbitals[12] with a set of polarization added for all atoms except platinum in conjunction with the Goedecker−Teter−Hutter[13] pseudopotentials. The auxiliary PW basis set was defined by a cubic box of 12 Å[14] and by a density cutoff of 300 Ry for the larger grid. The quantum chemistry calculations were carried out with both the CP2K-QuickStep program and the Gaussian03[15] program. With this latter code, we used both the BLYP and B3LYP[16] functional with the

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sdd[17] basis sets, and a set of polarization functions[18] was added for all atoms, platinum included. In this article, this level of calculation will be referred to as B3LYP/sdd*.

To understand the role of the diphosphine ligands, especially the benzene backbone versus the substituants on the phosphorus, we used different model complexes. The simplest one uses $H_2P(CH_2)_2PH_2$ and $H_2P(CH)_2PH_2$ to model dppe and dppbz, respectively. Since it was previously shown[4b] that the model of the phosphine can influence strongly the mechanism, we also used the same model but with CH_3 to model the phenyl substituents: $(CH_3)_2P(CH_2)_2P(CH_3)_2$ and $(CH_3)_2P(CH)_2P(CH_3)_2$ as dppe and dppbz ligands, respectively. As the benzene backbone is supposed to prevent the ring opening of the chelating ligand, we have also used the previous models but with explicit inclusion of the benzene. To identify these complexes, we followed the nomenclature presented in Scheme 1 for the numbering of the complexes followed by **m** if the simplest model is used and followed by **Me** if the phenyl group of the phosphine ligand is modeled by a Me group. We added **bz** when the benzene backbone of the dppbz ligand is included in the model.

Metadynamics has been used to overcome the problem of observing rare events in conventional molecular dynamics and of finding the reaction coordinate. A series of small repulsive Gaussian potentials centered on the values of some collective variables are added during the dynamics, preventing the system from revisiting the same points in configurational space and creating a history-dependent multidimensional biasing potential. A time step of 1 fs is used for the dynamics, and the hills were added every 10 fs.

In the present study, we explicitly considered coordination numbers (cn) as collective variables instead of selected bond distances in order to avoid enforcing a specific reaction pathway. Following Ensing et al.,[19] the coordination number between atoms a and atoms b is defined as $c_{ab} = (1/N_a)\sum_a(1/N_b)\sum_b[(1 - (r_{ab}/r_0)^p)/(1 - (r_{ab}/r_0)^q)]$, where r_{ab} is the distance between the two atoms and p and q are set equal to 3 and 6, respectively, except for the study of Pt−P dissociation, where they are set equal to 4 and 8, respectively. We used two different sets of collective variables for the models of type **4** and **5**. The set (a) is built from two collective variables and does not contain explicitly the Pt−P bond. The first collective variable is the coordination number **cn(H,Ceq)** between the H atom linked to the Pt atom and the C atoms of the equatorial methyls, which favors C−H bond formation. The second collective variable of set (a) is the dihedral angle **P−P−C−C**. In the set (b), we replaced the dihedral angle P−P−C−C by the coordination number **cn(Pt,P)** between Pt atom and P atoms. We have to choose two others sets to study the elimination of ethane from complexes **1** and **2**. The first one, set (c), is the coordination number **cn1-(Pt,P)** between the Pt atom and one of the P atoms, which was aimed at studying the Pt−P dissociation. For the C−C bond formation from the pentacoordinate complex we used two collective variables designed to avoid any predetermination of the reactant methyls. The first collective variable is the coordination number **cn(Ceqs)** between the three C atoms in the equatorial position. The second one is the coordination number **cn(Cax,Ceqs)** between the C atom of the axial methyl, *trans* to the phosphine ligand, and the C atoms of the equatorial methyls. These different sets of collective variables can be visualized in Figure 1. Constant temperature *T* has been enforced by velocity rescaling.

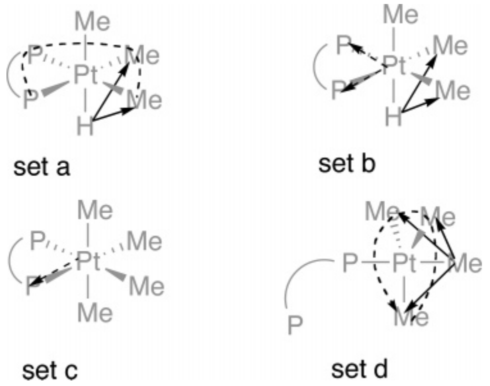

Figure 1. Sets of collective variables used for the metadynamics simulation.

The kinetic study was carried out using the RRK and RRKM approximation. Calculations were performed with the freely available MassKinetics program.[20] The algorithm was originally developed for modeling complex reaction kinetic systems for mass spectrometry[21] (i.e., for nonthermal, nonequilibrium situations), but can be used for thermal systems as well. Energy differences and vibrational frequencies necessary for RRKM were extracted from the DFT calculations at the B3LYP/sdd* level.

Results and Discussion

Characteristics of the Complexes. As presented in the Computational Details part, the complexes have been optimized using different levels of calculations and software. The results are shown Table 1. The agreement between the X-ray data, the CP2K BLYP GPW method, and the B3LYP and BLYP functionals as implemented in CP2K and Gaussian03 is excellent. The agreement between the theoretical results is also remarkable for the thermodynamic data shown in Table 2. Another striking fact is the exothermicity of the reductive elimination, which remains the same around −33 kcal·mol^{-1} whatever the reductive elimination performed, C−H or C−C, and the ligand used.[22] Test calculations performed without any modelization of the ligand show that the exothermicity remains similar, with values of −35.4 and −35.8 kcal·mol^{-1} with the dppe and dppbz ligand, respectively, for the C−H reductive elimination and −39.2 and −39.9 kcal·mol^{-1} for the C−C elimination. Also the comparison of the dynamics of the **1m** and **4m** complexes and of the **2m** and **5m** complexes exhibits no obvious difference in the behavior of the chelate ligand. But, the similarity of the thermodynamic costs with the strongly different kinetic experimental data supports two different mechanisms.

Mechanism of the Reactions: C−H Reductive Elimination. We have performed metadynamics at 350 K using set (a) as collective variables, namely, C−H coordination between the hydride and the carbon atoms in the equatorial plane and the dihedral P−P−C−C angle. For **4m** and **5m**, the C−H elimination is effectively directly observed at 350 K with an activation free energy of ∼16 kcal·mol^{-1} starting from the **4m** complex and ∼17 kcal·mol^{-1} from the **5m** complex. But surprisingly, this C−H elimination occurs with the simultaneous ring opening of the diphosphine chelate ligand dppe for **4m** and dppbz ligand for **5m**, although the Pt−P bonds were *not* defined as a collective variable. This fact proves the efficiency of the

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Table 1. Selected Bond Lengths (Å) and Angles (deg) for the dppePtMe4 Complex and for Its Simplest Model 1m at Various Levels of Calculations

	1m			dppePtMe4		
	BLYP/GTH-DZVP	BLYP/sdd*	B3LYP/sdd*	BLYP/GTH-DZVP	BLYP/sdd*	X-ray
Pt−Cax	2.220	2.200	2.175	2.139	2.206	2.139(7)
Pt−Ceq	2.144	2.124	2.101	2.129	2.115	2.115(6)
Pt−P	2.394	2.414	2.394	2.441	2.458	2.3359(7)
bite	3.199	3.222	3.198	3.320	3.320	
P−Pt−P	83.9	83.7	83.8	85.5	85.1	85.94(5)

Table 2. Reaction Energy (kcal·mol^{-1}) of the Reductive Elimination from the Simplest Model Complexes

	BLYP/GTH-DZVP	BLYP/sdd*	B3LYP/sdd*
1m	−33.4	−30.3	−32.4
1Me	−33.4	−30.4	−31.8
1	−39.2		
2m	−34.0	−31.0	−32.9
2mbz	−33.3	−31.0	−32.9
2Me	−33.7	−30.8	−32.4
2Mebz	−35.0	−31.2	−32.8
2	−39.9		
4m	−33.4	−31.4	−32.3
4Me	−33.8	−30.3	−30.9
4	−35.4		
5m	−34.4	−32.0	−32.9
5mb	−33.6	−32.6	−32.9
5Me	−32.5	−30.8	−31.5
5Mebz	−32.3	−31.0	−31.7
5	−35.8		

metadynamics simulations for the understanding of reactivity. The simultaneousness of these two actions can be easily perceived from the evolution of the Pt−P and C−H distances presented in Figure 2. Such a mechanism with bond dissociation concomitant with the C−H bond formation was already suggested by Borden et al.[4b] but with different Pt(IV) complexes and with a loss of chlorine *trans* to the Pt−H bond. Starting from the metadynamics's guess, transition state (TS) structures have been obtained at the B3LYP/sdd* level using Berny's algorithm[23] and are shown in Figure 3. Indeed they present an important contribution of the Pt−P bond in the reactive coordinate computed from a harmonic vibrational analysis. No transition state without Pt−P contribution, namely, through a direct pathway, has been found for both **4m** and **5m** complexes. This fact was also confirmed by the metadynamics calculations performed using set (b) as collective variables (C−H and Pt−P coordination number). Indeed the use of these two coordination numbers allows the free energy surface as a function of the two chemically important parameters to be reconstructed and more insight into the pathway to be gained. The comparison of the *ab initio* activation energy with the free energy barriers gives values in the same range of energy: 18.5 and 18.6 kcal·mol^{-1} for the dppe and dppbz ligands, respectively, at the B3LYP/sdd* level. Finally, the trajectories started from the transition state like structure have also confirmed the role of the dissociation of the platinum−phosphorus bond. Thus, from a computational point of view, the metadynamics has proved to be an efficient method to determine the pathway of a reaction, even if one of the key contributions is *not* included in the collective variables. From a chemical point of view, with these not strongly basic chelating ligands, the formation of the C−H bond occurs simultaneously to the dissociation of the platinum−phosphore bond *trans* to the forming C−H bond. The possibility of a five-coordinated intermediate complex induced by Pt−P dissociation has also been investigated: none of the resulting five-coordinate complexes was found to be a minimum of the potential energy surface, and the C−H reductive elimination took place from all the starting geometries investigated. The C−H bond formation concomitant with the Pt−P opening was observed for the two diphosphine ligands with similar activation free energy, which is in agreement with the kinetic data of Crumpton-Bregel and Goldberg,[2] but seems to be in disagreement with the assumption of an impossible dissociation of the dppbz ligand prior to the C−C reductive elimination. Thus the benzene backbone was included in the model since it seems responsible for preventing ring opening. The results obtained with the **5mbz** complex are similar to those obtained without the introduction of the benzene backbone but with a computed barrier of 19.7 kcal·mol^{-1} at the B3LYP/sdd* level with a Pt−P bond distance of 3.23 Å and a free energy barrier of 17.5 kcal·mol^{-1} at 350 K using set (a) as collective variables.

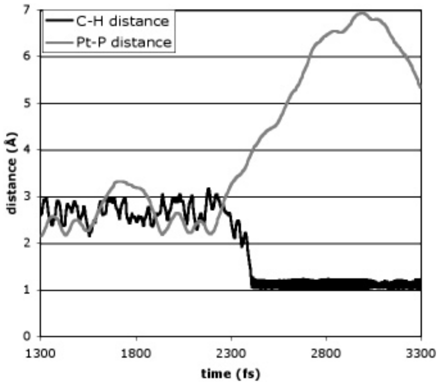

Figure 2. Time evolution of C−H and Pt−P bonds of **4m** during metadynamics at 350 K using set (a) of collective variables.

Since it was also shown[24] that the basicity of the phosphine ligands has an important role, and that the use of a not sufficiently basic phosphine favors the dissociative pathway, we have also studied the reactivity of the **4Me** and **5Me** complexes.

For **4Me**, the metadynamics performed at 350 K with set (a), so without the inclusion of the Pt−P bond distance as collective variable, gives a C−H reductive elimination occurring with ring opening and a computed free energy of around 20 kcal·mol^{-1}. The inclusion of the Pt−P bond distances as a collective variable, set (b), gives a free energy in the same range, 23 kcal·mol^{-1}, with a concomitant C−H bond formation and Pt−P dissociation. In this complex, preventing the Pt−P collective variable from reaching dissociation by means of a repulsive wall, we were able to compute the free energy activation of the C−H reductive elimination without Pt−P dissociation. The barrier found at 350 K using the same parameters is higher in energy: 28 kcal·mol^{-1}. This is in agreement with the previous metadynamics calculations, which had no restriction on Pt−P values. We used the guesses from these metadynamics calculations to perform the B3LYP TS

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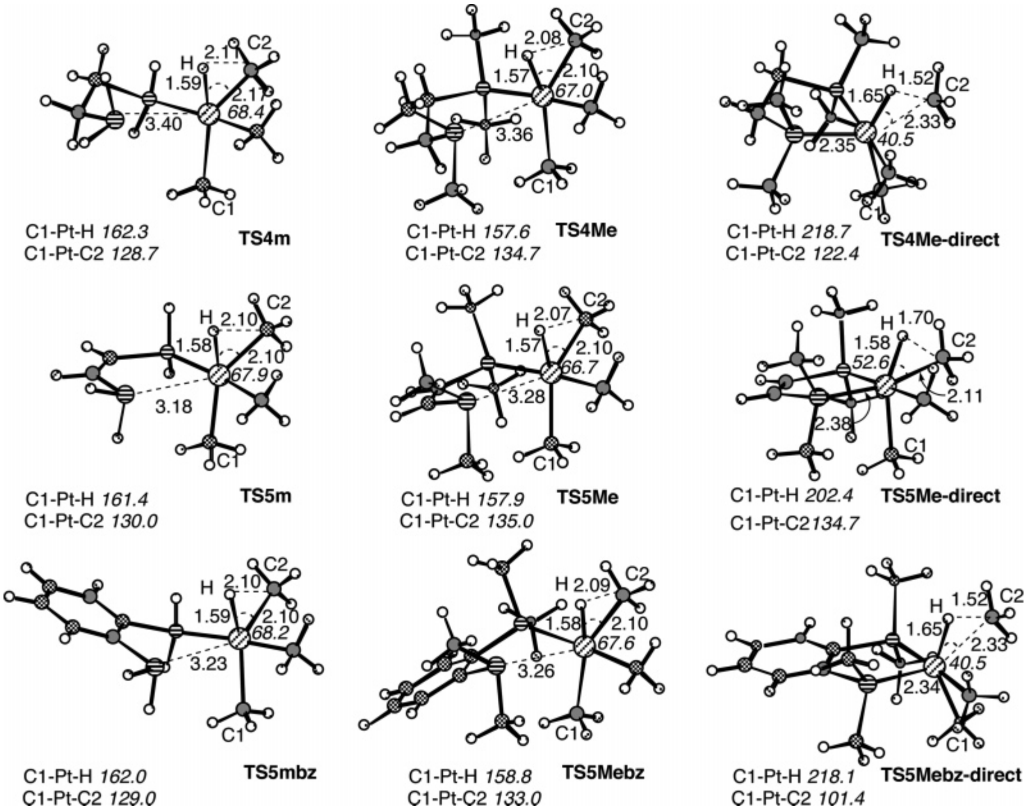

Figure 3. Transition state structures leading to reductive elimination of methane at the B3LYP/sdd* level. Distances are indicated in Å, angles in deg.

Table 3. Energy Activation and Free Energy Activation of Reductive Elimination of Methane from 4 and 5 Type Complexes (kcal·mol^{-1}) (values in parentheses correspond to the direct mechanism)

	BLYP/DZVP-GTH metadynamics set (b) 350 K	BLYP/sdd*	BLYP/sdd*	B3LYP/sdd*	B3LYP/sdd*	exptl data, ref 2
	$\Delta F^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	
4m	16[a]	16.2	13.2	18.6	14.6	
5m	17[a]	16.2	13.8	18.5	15.7	
5mbz	16	17.2	15.4	19.7	17.6	
4Me	23 (28)	22.7 (26.9)	20.1 (24.6)	25.0 (28.7)	22.4 (26.2)	
5Me	22	21.9	20.6	25.1 (28.5)	23.6 (26.52)	
5Mebz	(27)	25.0 (26.6)	24.2 (25.1)	28.0 (28.5)	26.1 (26.1)	
4						22.6−26.7
5						23.4−25.6

[a] Set (a) used.

optimizations. Two TSs were indeed identified: one corresponding to a direct mechanism and the other one with the C−H bond formation occurring simultaneously with the Pt−P dissociation. The energy values calculated follow the same pattern of the free energy. The B3LYP activation energy of the combined pathway is 25.0 kcal·mol^{-1}, which is 3.7 kcal·mol^{-1} lower than that of the direct mechanism. The agreement between the free energy calculations and the B3LYP static calculations seems to tip the balance in favor of the pathway including the Pt−P dissociation even if the existence of an alternative direct mechanism cannot be excluded.

For **5Me**, the same kind of results were obtained: metadynamics using the set (a) of collective variables gives a C−H formation concomitant with the Pt−P bond dissociation and a free energy of 18 kcal·mol^{-1} at 350 K. The B3LYP results also give similar results with two TS structures characterized: one corresponding to the combined pathway with an activation barrier of 25.1 kcal·mol^{-1} and the other one corresponding to a direct mechanism with a barrier of 28.5 kcal·mol^{-1}. We also included explicitly the benzene backbone in the **5Me** complex. The results in the **5Mebz** complex are the following. At 350 K, using set (b), thus with the Pt−P explicitly included, the metadynamics calculation gives a free energy activation of about 27 kcal·mol^{-1} but via a *direct* pathway. The B3LYP results for the two TS structures give an energy activation of 28.0 kcal·mol^{-1} for the combined pathway and 28.5 kcal·mol^{-1} for the direct pathway. Thus, the direct mechanism is only observed in the **5Mebz** complex but not in the **5mbz** and **5Me** complexes. This highlights the necessity of both the benzene backbone and of proper phosphorus substituents to determine its reactivity.

From these different calculations, we can see that metadynamics is an efficient tool to describe the reactivity of organometallic compounds and is quite able to deal with the complexity of the reactive coordinates. The different types of calculations of Table 3 show that the metadynamics values obtained are consistent with the different data available both experimentally and theoretically. Similarly, the order of reactivity is well reproduced compared to the free Gibbs energy

Table 4. Energy Activation and Free Energy Activation of Reductive Elimination of Ethane from 1 and 2 Opened Type Complexes (kcal·mol^{-1})

	BLYP/DZVP-GTH metadynamics set (d) 300 K	B3LYP/sdd* static	B3LYP/sdd* static
	$\Delta F^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$
1m	9	12.7	13.1
2m	14	12.4	13.4
2mbz	11	12.9	13.1
1Me	17	16.3	17.6
2Me	16	14.4	15.4
2Mebz	12	8.6	7.7

obtained at the B3LYP or BLYP level. From this table, it can also be shown that BLYP/sdd* results underestimate activation values compared to the corresponding B3LYP results. From a chemical point of view, the reductive elimination from **4** occurs with a concomitant Pt−P bond dissociation, whereas for complex **5**, a direct pathway is preferred. The computed BLYP free energy barriers between 20 and 25 kcal·mol^{-1} at 350 K are in very good agreement with the experimental Gibbs energy, which range between 22 and 27 kcal·mol^{-1} at the same temperature.

Mechanism of the Reactions: C−C Reductive Elimination. Metadynamics calculations performed at different temperature, until 450 K, on **1m** and **2m**[25] using the same type of collective variables as for **4m** and **5m**—number of coordination of C−C bonds and dihedral angle P−P−C−C—did not lead to a reductive elimination or dissociation but to a Berry pseudorotation. This pseudorotation of the Me groups is in agreement with the observations of Crumpton-Bregel and Goldberg on complex **3** of ref 2, a tetraalkyl complex similar to **1m**, (dppe)-PtMe$_3$Et, which coexists in a *fac* and *mer* conformation. Thus from this type of metadynamics, no direct or kinetically favored pathway for reductive elimination has been observed. Similarly, no pathway with a Pt−P dissociation concomitant to a C−C bond formation was found whatever the set of collective variables used. On the other hand, switching to the dissociative pathway, five-coordinated complexes can be optimized and characterized as minima on the potential energy surface. Metadynamics performed on these open structures can undergo reductive elimination. At 300 K, we used the two collective variables described previously in the Computational Details part, namely, the coordination number between the three equatorial carbons and the coordination number between the axial and the equatorial carbons. The corresponding activation barriers are 9 and 14 kcal·mol^{-1} for **1m** and **2m**, respectively, and 17 and 16 kcal·mol^{-1} for **1Me** and **2Me**, respectively, at 300 K. Compared to the experimental activation energies of around 40 kcal·mol^{-1}, these results seem much too small, but it should be pointed out that this computed barrier does not include the cost for the Pt−P dissociation. As for the C−H reductive elimination, we have also performed the corresponding static calculations at the B3LYP/sdd* level. The results for the different models are gathered in Table 4, and the TS structures are represented in Figure 4. The striking facts are as follows: first, the similarity of the results between the two complexes **1m** and **2m** and the absence of influence of the ligands used, while the experimental reactivity is quite different; second, the agreement between static and metadynamics calculations; third and last the “apparent disagreement” with the experimental data: the apparent one-step activation enthalpy of 43 kcal·mol^{-1} determined with complex **1** and the nonreactivity observed for complex **2**.

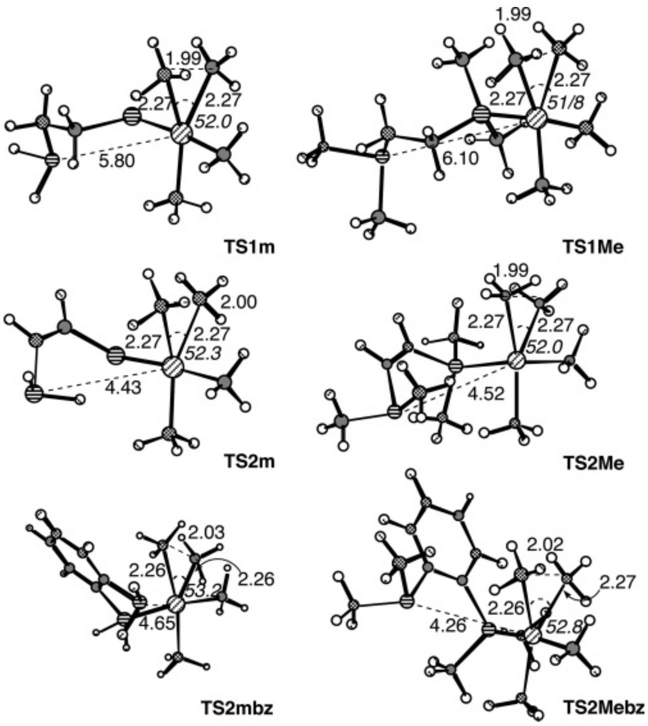

Figure 4. Transition state structures leading to reductive elimination of ethane at the B3LYP/sdd* level. Distances are indicated in Å, angles in deg.

Table 5. Thermodynamic Cost of Ring Opening of a Diphosphine Ligand for 1 and 2 Type Complexes (kcal·mol^{-1})

	BLYP/DZVP-GTH static	B3LYP/sdd[a] static
	ΔE	ΔE
1m	16.9	17.7
2m	15.6	18.4
2mbz	18.7	19.4
1Me	19.4	23.2
2Me	24.6	26.0
2Mebz	26.7	34.0
1	16.3	20.0[a]
2	28.5	32.4[a]

[a] B3LYP calculations on the optimized structures at the BLYP/DZVP-GTH level.

To explain this disagreement, one can compute the dissociation cost of the phosphine arm (see Table 5). This cost is nearly the same for **1m** and **2m** with an energy difference of only 2 kcal·mol^{-1}. But as expected, switching to more realistic model for the calculations of the platinum−phosphorus bond dissociation (see Table 5), we clearly see the influence of the model for the type **2** complexes, whereas its influence for the type **1** complexes is less important. The inclusion of both methyl substituents and benzene backbone is necessary for a proper description of the dppbz ligand, whereas for complex **1**, the dppe ligand is already well reproduced by the simplest model. Indeed **2m** exhibits a thermodynamic dissociation cost of 16 kcal·mol^{-1}, compared with a cost for the real complex of around 30 kcal·mol^{-1}. For complex **1m**, the cost reaches ~17 kcal·mol^{-1}, quite close to the value of the real complex, which is between 17 and 20 kcal·mol^{-1}. These results also corroborate the results obtained for the **4** and **5** type complexes and the C−H reductive elimination: for complex **4**, the simplest model is already a good approximation, whereas modeling the dppbz ligand is more demanding.

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(25) The same results are observed with **1Me** and **2Me**.

Finally, we have also computed, by *ab initio* metadynamics, the free energy cost of the Pt−P bond dissociation. The free energy barriers at 100 K[26] are 19 kcal·mol^{-1} for **1Me** and 31 kcal·mol^{-1} for the **2Mebz** complex. Compared to the thermodynamic dissociation cost, the free energy activation costs are only a few kcal·mol^{-1} higher in energy, which corresponds to a nearly barrierless process. From the energy profile obtained by metadynamics, we were able to determine the Pt−P distances around the TS-like structure. The Pt−P distance is 3.4 and 4.2 Å for the **1Me** and **2Mebz**, respectively. The longer distance found for the **2Mebz** compound is in accordance with the higher computed barrier. To our knowledge, this is one of the first calculations of a dissociation activation process that give both an estimation of the activation free energy including entropic effects and an estimation of the transition state structure.[27]

Thus concerning the mechanism of C−C reductive elimination, we can see that whatever the ligand used, labile or nonlabile, the C−C reductive elimination occurs through a two-step pathway via the formation of a five-coordinate complex successive to a ligand's dissociation.[28] These results are in accordance with some recent experimental results,[3a] which propose for C−C bond formation from cationic Pt(IV) complexes the same two-step pathway, viz., dissociation of one ligand to form a five-coordinate intermediate prior to C−C bond formation. They also revisited some earlier results[29] and suggested that these results could be explained in terms of dissociative pathways rather than in terms of some assumed direct C−C reductive elimination pathways. We propose a two-step mechanism, a Pt−P dissociation with a free energy cost ranging from 19 to 31 kcal·mol^{-1} depending on the ligand and a C−C bond formation from the five-coordinate complex of around 12−17 kcal·mol^{-1}. To reconcile these computed results with the apparent one-step experimental kinetic data for **1** and the absence of reactivity for **2**, kinetic modeling has been carried out. The RRK/RRKM modeling of the theoretical two-step mechanism of **1Me**, dissociation followed by reductive elimination with an activation energy of 20 and 14 kcal·mol^{-1}, respectively, can be reproduced by a RRKM modeling of a theoretical one-step reaction of **1Me** but with one activation barrier of 44 kcal·mol^{-1}. The inclusion of the first demanding step of complex **2** did not allow the reaction to produce a significant yield.

Thus, this two-step mechanism is in good agreement with the experimental data for complexes **1** and **2**.

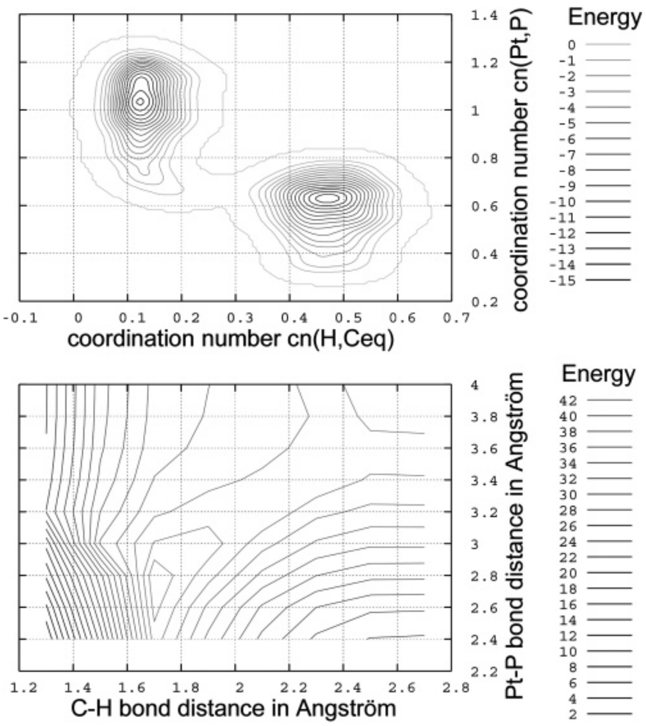

Figure 5. (a) Free energy surface of **4m** reconstructed by metadynamics at 350 K within set (b) of collective variables. (b) B3LYP/sdd* energy surface. Energy in kcal·mol^{-1}.

Role of the Pt−P Dissociation. Two different mechanisms, direct and dissociative, were postulated by Crumpton-Bregel and Goldberg, but metadynamics calculations have brought to the fore a third mechanism: the concomitant mechanism with a simultaneous C−H formation and Pt−P dissociation. That is why we wanted to gain more chemical insight into this latter mechanism and understand the role of the Pt−P dissociation using the convergent data given by the dynamic and static calculations. First, we wanted to check if a synergy exists between the C−H formation and the Pt−P dissociation for the **4m** and **5m** complexes. The optimizations of the **4m**, or **4Me**, complex with C−H or Pt−P constrained distances confirmed that there was no synergy between these two bonds and that there is no transition state for a direct C−H reductive elimination. When the C−H is shortened to 1.7 Å, no dissociation of the Pt−P is observed and the energy of the complex is approximately 4 kcal·mol^{-1} higher than the energy of the transition state structure. When the C−H is finally shortened even further to 1.4 Å, the optimization leads to the Pt(II) complex plus methane, giving the appearance of a cliff to the energy potential surface shown in Figure 5. The energy surface computed at the B3LYP/sdd* level and the free energy surface lead to the same conclusion that the reactive pathway is through a dissociative structure.

If no *trans/cis* effect confers a synergy between the C−H bond and the Pt−P bond, why cannot this C−H reductive elimination proceed through a six-coordinate structure for these model complexes? A close examination of the structures and of the metadynamics trajectory shows a significant modification of the reactive H−Pt−C part of the complex going from the six-coordinate structure with a constrained C−H distance of ∼2.0 Å to the TS structure and to the reactive complexes' structure along the metadynamics trajectory (see Figure 3). The six-coordinate structure exhibits an octahedral-like structure, whereas the TS structure has for the reactive part H−Pt−C a more Y-shaped structure. This difference is also obvious if we compare the structure of the two TSs obtained for the two mechanisms, direct and concomitant, obtained for the **1Me** complex (see Figure 3). The TS structure **TS1Me** for the concomitant mechanism exhibits a H−Pt−C angle of 67° and the H−Pt−C1 and C−Pt−C1 angle values are close to the ideal values (∼150°) for a Y-structure with values of 158° and 135°, respectively. This Y structure compared to the octahedral one can undergo reductive elimination, as it presents a clearly more favorable molecular orbital (MO) diagram. The simplified correlation diagram for the reductive elimination of a C−H bond is represented in Figure 6.[30]

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(26) At higher temperature the velocities of the atoms were too high to obtain a precise enough estimation of the barriers.

(27) Estimations of transition state structure for CO dissociation have already been computed; for example see: Sztaray, B.; Baer, T. *J. Am. Chem. Soc.* **2000**, *122*, 9219.

(28) A direct mechanism was found using **1Me** but with an energy barrier of 57.7 kcal·mol^{-1} (B3LYP/sdd*), obviously less favorable than the two-step mechanism proposed.

(29) Dücker-Benfer, C.; van Eldik, R.; Canty, A. J. *Organometallics* **1994**, *13*, 2412.

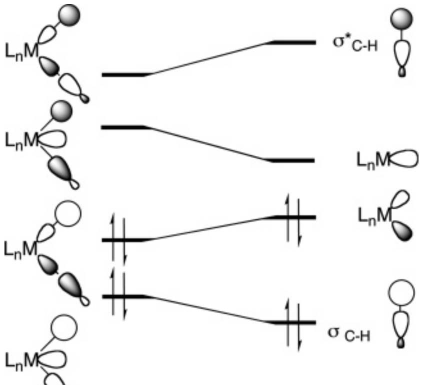

Figure 6. Simplified correlation diagram of C−H reductive elimination.

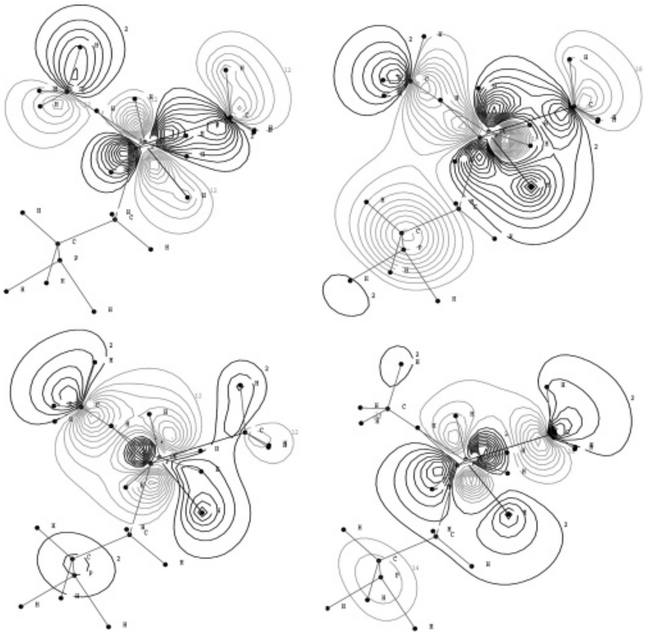

Figure 7. Molecular orbitals of **TS4m** involved in the reductive elimination of methane.

These orbitals exist as d orbitals in a five-coordinate complex in a Y conformation: they are the contributions of the d_{xy} and $d_{x^2-y^2}$ orbitals. These contributions can clearly be seen form the cross section of the molecular orbitals[31] of the TS structure **TS1m** represented in Figure 7. Reductive elimination can also be obtained from an octahedral complex,[32] but in this case, some of the orbitals involved are lower in energy,[33] and the cost is higher.[34]

This Y-shaped structure can only be obtained from the octahedral Pt(IV) complex through at least a partial but yet important dissociation of the Pt−P bond or, of course, directly through a five-coordinate complex with such a Y-shaped structure or after deformation from a T structure. Effectively, two main conformers exist for the five-coordinate complex: Y and T structures. It is worth noting that for a five-coordinate complex in a T conformation the d orbitals are less favorable for a reductive elimination. But, depending on the ligand sphere, the deformation cost to join the two conformers Y and T can be very low or quite high especially for bulky ligands involved in agostic interactions with the metal center.

Thus, the calculations of ref 4 starting from the five-coordinate complex present TS structures that have such a Y-shape and exhibit long C−H distances and early TS structures in accordance with the low barriers found. Low barriers are especially expected for reductive elimination from a Y-shaped five-coordinate complex.[35] But even if the C−H reductive elimination should proceed very easily from a five-coordinate complex or with a five-coordinate TS structure, the cost of the dissociation necessary to obtain the five-coordinate complex should be added. In the case of the concomitant Pt−P opening and C−H bond formation observed for the **4**-type complexes and for some models of complex **5**, the computed total barrier can be seen as an important contribution from the P−P opening and a smaller contribution from the C−H formation as the long C−H distance observed in the TS structure indicates. The comparison of the Pt−P bond distance in the TS structure of the Pt−P dissociation from the **1Me** complex and in the TS of the concomitant Pt−P opening/C−H reductive elimination from **4Me**, around 3.4 Å in both cases, supports this assumption. When R−PH$_2$ ligands are used, the cost of the ring opening of the chelate ligand is not important, and no alternative direct mechanism can be found, whereas when the more basic R−PMe$_2$ ligand is used, the balance between the two mechanisms is subtler. As can be seen from the calculations (see Table 5) of the cost of the ring opening of the chelating ligand for the **1** and **2** type compounds, the cost for the dppe ligand is around 3 kcal·mol^{-1} higher than for the simplest model, for a total cost of 20 kcal·mol^{-1}. On the contrary, for the dppbz ligand the simplest model underestimates this cost by 13 kcal·mol^{-1}, to finally reach a total cost of around 30 kcal·mol^{-1}. This large difference explains the direct mechanism found for the C−H reductive elimination for complex **5**, whereas for complex **4**, the concomitant pathway is more likely due to the lower cost of dissociation. This difference also explains the nonreactivity of complex **2** toward C−C reductive elimination compared to complex **1**, which can undergo the successive steps: ring opening of the chelate ligand to give the suitable five-coordinate complex and C−C formation.

Conclusions

Detailed theoretical studies have been performed in order to understand the reactivity of platinum(IV) complexes toward C−H and C−C reductive elimination. Free energy metadynamics barriers have been computed for all the reactions involved: C−H and C−C bond formations and ring opening of the chelate ligand. These results have been compared both to the available experimental data and to static B3LYP/sdd* calculations. The agreement between the experimental and theoretical data is excellent and proves metadynamics to be a powerful and useful tool for the study of larger inorganic compounds. In particular, we have been able to compute free energy activation not only

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[30] (a) Jean, Y. *Les orbitales moléculaires dans les complexes*; Les éditions de l'école Polytechnique: Palaiseau, 2003. (b) Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; John Wiley & Sons: New York, 1985. (c) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Soc. Chim. Jpn.* **1981**, *54*, 1857.

[31] Drawings done thanks to Molden: Schaftenaar G.; Noordik, J. H. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 123.

[32] Akermark, B.; Ljungqvist, A. *J. Organomet. Chem.* **1979**, *182*, 59.

[33] Some orbitals involved are the ligand orbitals lower in energy than the d orbitals.

[34] The cost of a reductive elimination is higher from the six-coordinate complex than from a five-coordinate complex. But from a global mechanistic point of view, to conclude about the favored pathway for the reactions under study, the cost of the dissociation to obtain the five-coordinate complex should be taken into account.

[35] Y structures are usually favored by π-donor ligands such as Cl$^-$, for example, structure **12b** of ref 4b, whereas T structures are favored by π-acceptor ligands such as phosphine ligands. Riehl, J.-F.; Yves, J.; Eisenstein, O.; Pélissier, M. *Organometallics* **1992**, *11*, 729.

for the C−H and C−C reductive elimination but also for the dissociation of one arm of the diphosphine ligand. We were able to estimate the free energy cost thus including entropy effects and the Pt−P distance of the TS structure. From a mechanistic point of view, the C−C reductive elimination occurs through a two-step dissociative pathway with barriers of around 19 and 16 kcal·mol^{-1} when the less rigid ligand dppe is used. Kinetic simulations have shown that this combination of values gives results comparable to a first-order kinetics with a barrier of around 40 kcal·mol^{-1}. When the more rigid ligand, dppbz, is used, the increase of the dissociation cost prevents the system from being reactive. For C−H reductive elimination, we found two mechanisms, the direct one previously postulated and a new one: the concerted mechanism discovered thanks to metadynamics. In the concomitant mechanism the platinum−phosphorus bond formation occurs simultaneously to the C−H bond formation. Depending on the cost of the phosphine dissociation, the direct or the concomitant mechanism is observed. Thus, this reaction is strongly influenced by the basicity of the phosphine as much as by its intrinsic rigidity, which both increase the cost of dissociation and therefore favor the direct pathway. Finally, we would like to emphasize the efficiency of the *ab initio* metadynamics calculations both to determine some new pathways and to compute accurate free energy barriers even for extremely difficult cases, such as the dissociation of ligands.

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Supporting Information Available: Cartesian coordinates of the different complexes and the different parameters used for the metadynamics calculations. This material is available free of charge via the Internet at http://pub.acs.org.

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