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On the Mechanism of Pd(0)-Catalyzed, Cu(I) Carboxylate-Mediated Thioorganic-Boronic Acid Desulfitative Coupling. A Non-innocent Role for Carboxylate Ligand

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Abstract

Computational studies of the mechanism of the Pd-catalyzed, Cu(I)-carboxylate-mediated desulfitative coupling of thioorganics with boronic acids have determined that the requisite Cu(I)-carboxylate plays multiple important roles. The Cu(I)-carboxylate enhances both the transmetalation and the C-C reductive elimination steps: it acts as a reactive transmetalation center and it provides a vital carboxylate ligand. The carboxylate ligand functions not only as an activator for the boronic acid, but it also displaces a phosphine ligand at the palladium center generating a catalytically competent mono-phosphine-palladium intermediate.

Keywords

Cu(I) carboxylate; density functional calculations; transmetalation; thioorganic-boronic acid coupling; non-innocent carboxylate

Alone or in combination with other metals, copper increasingly plays a central role in many modern metal-mediated organic reactions.¹ Of the various copper co-catalysts, copper(I)-carboxylate cofactors have been essential to the development of a relatively new and quite general family of efficient palladium-catalyzed desulfitative couplings of thioorganics with boronic acids that take place at neutral pH.² To date all information on the mechanistic role of the Cu(I) carboxylate in these transformations has been limited to circumstantial speculation derived from control experiments. Herein we describe the results of computational studies that have uncovered specific attributes of the Cu(I) center and an important, unanticipated mechanistic role for the carboxylate counterion.

Thioorganics do not react directly with boronic acids, neither in the presence nor absence of palladium or nickel catalysts. The addition of a stoichiometric quantity of a Cu(I) carboxylate cofactor renders the palladium-catalyzed system highly effective.² The bottleneck of the palladium-catalyzed desulfitative coupling reaction was been assumed to be the transmetalation step because the poorly electrophilic organopalladium intermediate $L_2PdR^1(SR^2)$ (generated upon thioorganic oxidative addition to $L_nPd(0)$, where $L = PR_3$) does not react with weakly nucleophilic reagents like boronic-acids. The addition of a stoichiometric quantity of a Cu(I)-carboxylate, *but not a Cu(I) halide*, to the $L_nPd(0)$ -catalyst overcomes this

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SUPPORTING INFORMATION PARAGRAPH (total 3 pages). Complete Reference for Gaussian_03, and Cartesian coordinates and total energies of all discussed structures.

problem and facilitates the coupling of thioorganics and boronic acids at neutral pH (Scheme 1).

An understanding of the mechanism and the factors that govern this reaction is important in light of the increasing relevance of Cu in many catalytic processes. A firm understanding of mechanism will likely aid the development of a more general, truly catalytic and efficient process for thioorganic–boronic acid cross-couplings that occur at or near neutral pH.

In order to guide experimental efforts a computational (DFT) study³ of the mechanism and factors controlling the component reactions (Scheme 1, Eqns 1-3) of the palladium-catalyzed, Cu(I)-carboxylate mediated coupling of thioorganics with boronic acids has been carried out. We report herein our findings on the transmetalation (Eqn 2) and reductive elimination (Eqn 3) steps, only. In these studies the organopalladium intermediate $L_nR^1Pd(\mu_2-SR^2)$ was modeled using both 4- and 3-coordinated Pd-complexes, $L_2MePd(\mu_2-SH)$ and $LMePd(\mu_2-SH)$ (where $L = PH_3, PMe_3$ and PPh_3) in order to mimic bisphosphine and monophosphine ligand environments at the Pd-center, respectively. Cu(HCOO) was used as a model for the Cu(I)-carboxylate. We note that the Cu(I)-mediated transmetalation may proceed via two distinct mechanisms, either through a stepwise transfer from $R^4-B(OH)_2$ to Cu(I) to produce Cu- R^4 , which subsequently transmetalates to $L_nR^1Pd(\mu_2-SR^2)$, or by *prior* activation of the C-B bond of the boronic acid in a pre-reaction complex, $L_nR^1Pd(\mu_2-SR^2)Cu(R^3COO)$, formed from the Cu(I)-carboxylate and $L_nR^1Pd(\mu_2-SR^2)$. Since previous experimental results are not consistent with the stepwise mechanism,⁴ we report here a study of only the concerted mechanism of the reactions (2) and (3).

The first step of this mechanism, the addition of Cu(HCOO) to $L_nMePd(\mu_2-SH)$ ($n = 1$ and 2), is a highly exothermic process and leads to the formation of the 4- and 3-coordinate pre-reaction complexes $L_2MePd(\mu_2-SH)Cu(HCOO)$, **I**, and $LMePd(\mu_2-SR^2)Cu(HCOO)$, **Ia**, which are depicted in Figure 1.⁵ The resulting complexes **I** and **Ia** may exist in numerous isomeric forms, but we report only those isomers which are connected to the corresponding intermediates and transition states of the studied reactions, confirmed by the intrinsic reaction coordinate (IRC) method.

As seen in Figure 1, the calculated Pd-O² bond distance is significantly longer in the 4-coordinated complex **I** than in the 3-coordinated complex **Ia**, suggesting that the carboxylate may facilitate displacement of a phosphine ligand from the Pd center. The calculated energy of the reaction **I** $\rightarrow$ **Ia** + PR_3 , " $\Delta(PR_3)$ ", for the complexes, $(PR_3)_2MePd(\mu_2-SH)$, $(PR_3)_2MePd(\mu_2-SH)Cu(HCOO)$, and $(PR_3)_2MePd(\mu_2-SH)CuCl$ (the latter complex is included for comparison to the carboxylate ligand) supports this conclusion: for $R = H, Me$ and Ph , respectively, the $\Delta(PR_3)$'s presented as $\Delta E/\Delta H$ are 10.8/(8.9), 13.0/(11.1) and 14.2(12.7) kcal/mol for complex $(PR_3)_2MePd(\mu_2-SH)$; 10.1/(8.1), 14.3/(12.3) and 16.1(14.5) kcal/mol for complex $(PR_3)_2MePd(\mu_2-SH)CuCl$; and 5.1/(3.2), 9.8/(8.0) and 12.1/(10.7) kcal/mol for complex $(PR_3)_2MePd(\mu_2-SH)Cu(HCOO)$. For $R = H, Me$ and Ph , respectively, the inclusion of entropy effects into the calculations (those data are shown in brackets) makes the PR_3 dissociation exothermic by: $\Delta G = [2.6], [2.1]$ and $[1.6]$ kcal/mol for complex $(PR_3)_2MePd(\mu_2-SH)$; $[2.7], [0.8]$ and $[3.8]$ kcal/mol for complex $(PR_3)_2MePd(\mu_2-SH)CuCl$; and $[8.5], [5.6]$, and $[4.4]$ kcal/mol for complex $(PR_3)_2MePd(\mu_2-SH)Cu(HCOO)$. Thus, $\Delta(PR_3)$ diminishes via the sequence $(PR_3)_2MePd(\mu_2-SH) \geq (PR_3)_2MePd(\mu_2-SH)CuCl > (PR_3)_2MePd(\mu_2-SH)Cu(HCOO)$. These findings indicate that the carboxylate ligand plays an unexpected, non-innocent role in the Pd-catalyzed, Cu-mediated cycle. It facilitates displacement of a phosphine ligand from the Pd-center and generates a catalytically competent (less hindered and more electrophilic) monophosphine-Pd intermediate. One should note that inclusion of solvent effects into the calculations may change the above reported energetics, but it will not alter the presented trends and conclusions. Indeed, for $R = H$ and Me , single point PCM calculations of

complexes **I** and **Ia** and ligand PR_3 (at their gas-phase optimized geometries) reduce the calculated energy of the reaction $\text{I} \rightarrow \text{Ia} + \text{PR}_3$ from 5.1 and 9.8 kcal/mol to 2.2 and 7.1 kcal/mole, respectively.

As seen from Figure 1, the boronic acid, $\text{H}_3\text{C}^2\text{-B(OH)}_2$, may undergo transmetalation with **I** and **Ia** via both “*Pd-side*” and “*Cu-side*” pathways. In the *Pd-side* pathway, the Pd and O^2 centers [from the $\text{O}^2=\text{C(H)O}^1$ - ligand] act cooperatively to cleave the B- C^2 bond of boronic acid, while in the *Cu-side* pathway the Cu and O^1 centers [from the $\text{O}^2=\text{C(H)O}^1$ - ligand] perform the same function. The transition states (**TS1_Pd**, **TS1a_Pd**, **TS1_Cu**, and **TS1a_Cu**) corresponding to these $\text{H}_3\text{C}^2\text{-B(OH)}_2$ activation are also presented in Figure 1.

The nature of these transition states was confirmed by performing vibrational normal mode analysis and intrinsic reaction coordinate (IRC) calculations.⁶ As seen from Scheme 2 and Scheme 3, the calculated barriers (based on their enthalpy ΔH values,³) associated with the *Pd-side* and *Cu-side* transmetalations are (33.0) and (21.7) kcal/mol for the 4-coordinate complex **I** ($\text{R}=\text{H}$), and (19.4) and (22.2) kcal/mol for the 3-coordinate complex **Ia** ($\text{R}=\text{H}$), respectively. These values are slightly higher for the complexes with $\text{R} = \text{Me}$ and Ph (second and third lines in these Figures), especially for *Pd-side* transition states. In other words, for the 4-coordinated Pd-complex **I** (modeling a bisphosphine ligand environment), the *Cu-side* transmetalation is more favorable than the *Pd-side* transmetalation (Scheme 2). For the 3-coordinated Pd-complex **Ia**, the *Pd-side* and *Cu-side* transmetalations by boronic acid occur with similar energy barriers (Scheme 3). Perhaps not surprisingly, an increase in size of the phosphine ligands favors a *Cu-side* over a *Pd-side* transmetalation. This trend is also partially affected by an increase in the Pd- PR_3 bonding energy via $\text{PR}_3 = \text{PH}_3 < \text{PMe}_3 < \text{PPh}_3$ (see discussion, above), which is due to a change in the electronic nature of phosphine ligands.

Comparison of the calculated barrier heights for the B- C^2 bond activation by 4-coordinate complex **I** and 3-coordinate complex **Ia** (Scheme 2 and Scheme 3, respectively) shows that dissociation of one of the PR_3 groups from **I** clearly enhances the *Pd-side* transmetalation step. As demonstrated above, the presence of a hemilabile carboxylate ligand⁷ assists the displacement a phosphine ligand from the Pd-center and facilitates the generation of **Ia**. Furthermore, analysis of the geometries of the transition state structures **TS1_Pd**, **TS1a_Pd**, **TS1_Cu**, and **TS1a_Cu** show that one of the O-atoms of the carboxylate ligand is directly involved in the B-C bond activation simultaneously with the corresponding transition metal centers (Pd or Cu). Previously, a similar result was reported by Sakaki and co-workers for mononuclear complexes $\text{M}(\eta^2\text{-O}_2\text{CH})$ of Pd and Pt, where the formate ligand assists benzene and methane C-H bond activation.⁸

As seen in Scheme 2 and Scheme 3 the reductive elimination, which occurs at the Pd-center regardless of the site of transmetalation, is the rate-determining step for both the *Pd-side* and *Cu-side* transmetalation pathways of the reaction involving **I**, and for the *Pd-side* transmetalation pathway of the reaction involving **Ia**. For the reaction involving the 4-coordinated reactant **I** (Scheme 2), the reductive elimination occurs directly from the *Pd-side* transmetalation product, while in the *Cu-side* pathway, reductive elimination also occurs at Pd, but prior to reductive elimination, the transmetalation product, $(\text{PR}_3)_2(\text{CH}_3)\text{Pd}(\mu_2\text{-SH})\text{CuMe}$, must dissociate one of PR_3 -groups from Pd and generate the bridging Me intermediate $(\text{PR}_3)(\text{CH}_3)\text{Pd}(\mu_2\text{-SH})(\mu_2\text{-Me})\text{Cu}$. In contrast, in the case of the reaction involving the 3-coordinated reactant **Ia** (Scheme 3), reductive elimination occurs directly from the transmetalation products for both the *Pd-side* and *Cu-side* pathways. In general, the reductive elimination from the 3-coordinated Pd-complex **Ia** is favorable, especially for the *Cu-side* pathway, which occurs only (20.3) and (23.3) kcal/mol overall barrier for $\text{R} = \text{H}$ and Me , respectively.

In summary, the current results show that the requisite Cu(I) carboxylate cofactor present in Pd-catalyzed, Cu-mediated desulfurative couplings plays multiple roles. The Cu-center of the complexes **I** and **Ia**: (i) functions as a lynch-pin that both coordinates to thiolate sulfur and provides a carboxylate ligand that facilitates phosphine dissociation from the palladium center; (ii) enhances thermodynamicity for the transmetalation step by forming a strong (*ca* 45–55 kcal/mol⁵) Cu-S bond; (iii) acts as a reactive transmetalation center for the boronic acid (the calculated B-C activation barriers are significantly smaller for *Cu-side* pathway than *Pd-side* one), especially for 4-coordinated complex **I**; and (iv) facilitates reductive elimination by forming a strong bond with the thiolate sulfur. The carboxylate ligand enhances the transmetalation step by facilitating the displacement of a phosphine ligand from the Pd-center thus generating a catalytically competent monophosphine-Pd intermediate, as well as by acting as a reactive transmetalation center for the boronic acid.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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larger than that in the solution, where the real reaction takes place, here we do not discuss the entropy corrections, while the calculated gas-phase ΔG values are given in Schemes 2 and 3. Inclusion of solvent effects (italic numbers in Schemes 2 and 3) leads qualitatively to the same conclusions, and therefore will not be discussed either.

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Scheme 1.

The Component Reactions of the Pd(0)-catalyzed, Cu(I)-Carboxylate Mediated Desulfurative Coupling of Thioorganics with Boronic acids.

Figure 1.

Calculated Important Bond Distances^a of the Complexes I and Ia, and Transmetalation Transition States TS1_Pd, TS1a_Pd, TS1_Cu and TS1a_Cu.

^a Bond Distances in Å. The numbers in the first and second lines are for R = H and Me, respectively. To minimize clutter in this Figure, values for R = Ph are provided in the Supporting Information.

Scheme 2.

Potential Energy Surface of the Reactions (2) and (3) for 4-Coordinated Complex I.a

^a Presented energies are relative to the reactants **I** + MeB(OH)₂ and are given in the following order, ΔE/(ΔH)/[ΔG]/PCM. Numbers in the first, second and third lines are for R = H, Me and Ph, respectively.

Scheme 3.

Potential Energy Surface of the Reactions (2) and (3) for 3-Coordinated Complex **Ia**.^a

^aPresented energies are relative to the reactants **Ia** + MeB(OH)₂ and are given in the following order, ΔE/(ΔH)/[ΔG]/PCM. Numbers in the first, second and third lines are for R = H, Me and Ph, respectively