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# Mechanistic Studies into the Oxidative Addition of Co(I) Complexes: Combining Electroanalytical Techniques with Parameterization

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**ABSTRACT:** The oxidative addition of organic electrophiles into electrochemically generated Co(I) complexes has been widely utilized as a strategy to produce carbon-centered radicals when cobalt is ligated by a polydentate ligand. Changing to a bidentate ligand provides the opportunity to access discrete Co(III)–C bonded complexes for alternative reactivity, but knowledge of how ligand and/or substrate structures affect catalytic steps is pivotal to reaction design and catalyst optimization. In this vein, experimental studies which can determine the exact nature of elementary organometallic steps remain limited, especially for single-electron oxidative addition pathways. Herein, we utilize cyclic voltammetry combined with simulations to obtain kinetic and thermodynamic properties of the two-step, halogen-atom abstraction mechanism, validated by analyzing kinetic isotope and substituent effects. Complex Hammett relationships could be disentangled to allow understanding of individual effects on activation energy barriers and equilibrium constants, and DFT-derived parameters used to build predictive statistical models for rates of new ligand/substrate combinations.

# 1. Introduction

The oxidative addition of an electron-rich metal center into a carbon–heteroatom bond is a ubiquitous organometallic step involved in numerous key synthetic transformations.<sup>1</sup> The mechanism of oxidative addition is highly dependent on both the metal complex and substrate involved and can proceed through a variety of polar and/or radical intermediates. Thereby, knowledge of the mechanism enables the prediction of reactivity.

For example, the application of modern one-electron processes in nickel catalysis, including photoredox catalysis and electrocatalysis, has facilitated the development of a range of nickel-catalyzed synthetic transformations, which proceed through radical intermediates.<sup>2</sup> Two-electron processes have also been widely implicated for the oxidative addition of nickel into alkyl-heteroatom bonds, and the dichotomy of these pathways has been extensively studied by DFT.3-5 However, identifying experimental techniques to probe these distinctions remains a challenge, owing to the multiple reaction steps involved. In this context, Diao and co-workers recently provided the first experimental evidence that Xantphos-ligated Ni(I) complexes react with unactivated alkyl bromides by halogen-atom abstraction, interrogated using a range of kinetic studies, and supplemented by DFT computations.<sup>6</sup> 

As part of our emerging program to investigate the subtle effects of molecular structure on fundamental organometallic reactivity, we herein leverage electroanalytical techniques to study how the reactivity of Co(I) complexes compares mechanistically to nickel systems. While Co(I) complexes ligated by polydentate ligands have been broadly used as a source of carbon-centered radicals in solution,<sup>7,8</sup> comparatively little is understood about the modes of activation of cobalt complexes with bidentate ligands.<sup>9</sup> In analogy to similar reactivities of Ni/Pd/Cu species, it is feasible that several different mechanisms could be in operation: concerted polar oxidative addition, S<sub>N</sub>2-type oxidative addition, outer-sphere electron transfer, or halogen-atom abstraction (Scheme 1).<sup>6,10,11</sup>

Scheme 1. (a) Study into the mechanism of oxidative addition of Co(I) complexes. (b) Possible transition states/intermediates for oxidative addition processes.



Having previously studied how electronic manipulations of the N,N-bidentate ligand structure reduces deleterious disproportionation reactions of Co(I) complexes,<sup>12</sup> we identified that pyridine-oxazoline (pyrox) ligands are promising candidates for designing electrocatalytic systems. Nevertheless, without knowledge of the mechanism of the fundamental organometallic steps that occur in a catalytic cycle, it is difficult to predict combinations of substrate and catalyst that are kinetically and thermodynamically facile for applications in catalysis. Indeed, to gain a complete picture of the complex oxidative addition mechanism unveiled herein, it was necessary to employ a combination of electroanalytical measurements and simulations,<sup>13</sup> along with modern physical organic tools,<sup>14</sup> to disentangle multiple reaction steps. With the ultimate goal of designing new catalytic transformations in mind, the techniques developed throughout this study are widely applicable to investigating the intricate factors which lead to catalytic activity across a number of organometallic systems.

#### 2. Results and Discussion

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2.1. Determination of Oxidative Addition Rate Constants. In order to determine the rate constant for oxidative addition, we conducted cyclic voltammetric (CV) studies with a solution containing 1 equiv of CoBr<sub>2</sub>, 1 equiv of pyrox ligand and 1 equiv of benzyl bromide substrate, using a boron-doped diamond working electrode. Boron-doped diamond was used due to the high overpotential for the hydrogen evolution reaction at the electrode surface.<sup>15</sup> According to our previous study.<sup>12</sup> we first used square wave voltammetry to ascertain the concentration of mono-ligated complex in solution. Next, we conducted a series of CVs performed at various scan rates across an electrochemical window limited to the Co(II)/Co(I) redox couple of the mono-ligated complex. Comparing the ratio of peak currents in the forward  $(i_{pc})$ and reverse  $(i_{pa})$  scans enables calculation of the quantity of Co(I) complex consumed by oxidative addition during the CV scan.<sup>8b</sup> Altering the scan rate of the CV changes the time allowed for the oxidative addition between the two peak-current measurements, thus changing the ratio of peak currents (Figure 1). Plotting multiple peak-current ratios vs. time according to standard second-order kinetics thereby facilitates measurement of the oxidative addition rate constant. For a more detailed explanation of this technique, we direct the reader to previous studies.<sup>8b,12,16</sup> Measurements of oxidative addition in this manner can be rapidly ascertained (average time for collection of one rate constant of 15-30 minutes), and we collected repeat measurements for each substrate/ligand complex studied. We note that the measurement of the rate constant in this manner can only be made in scenarios where the oxidative addition is significantly faster (ideally at least one order of magnitude) than disproportionation of the



**Figure 1.** The variation in peak-current ratio  $(i_{pa}/i_{pc})$  as a function of scan rate enables measurement of the rate constant of oxidative addition occurring during the CV scan. CVs of 1.0 mM Co(I) complex in the presence of 1.0 mM benzyl bromide at varying scan rates in a 100 mM solution of Bu<sub>4</sub>NPF<sub>6</sub> in acetonitrile, using a 0.071 cm<sup>2</sup> boron-doped diamond working electrode. CVs are plotted in polarographic notation with positive currents corresponding to reduction.

reactive Co(I) complex. Additionally, when the oxidative addition is too fast such that the reverse peak cannot be observed even at very fast scan rates, this technique is no longer applicable. This can also occur when the oxidative addition is catalytic, reforming a Co(II) species following reaction with the substrate such that a catalytic current is observed (an EC' mechanism was observed with 2,2'-bipyridyl ligated Co(I) complexes<sup>12</sup>). Under these conditions, one can use the shift in peak potential to measure reaction rates (see Section 2.3).<sup>8d,13a</sup>

**2.2. Hammett Studies.** Having determined the relative rate constants for a variety of *para*- and *meta*-substituted benzyl bromides, we performed a Hammett-type analysis by comparing correlations with various tabulated Hammett  $\sigma$  values.<sup>17</sup> With cyano-substituted pyrox ligand **1**, we observed the best fit for separately correlating electron-rich substrates with  $\sigma^+$ , and electron-deficient substrates with  $\sigma^-$  (Figure 2.a). A similar pair of correlations was observed with trifluoromethyl-substituted pyrox ligand **2** (Figure 2.b), except that the rate constants for oxidative addition were determined to be a factor of four greater on average, which is in agreement with a more electron-rich ligand increasing the rate for oxidation of nucleophilic Co(I) to Co(III).

The contrasting behaviors with electron-rich and electron-deficient substrates suggest a change in mechanism between stabilization of a positive and negative charge in the transition state, respectively. Previously, curved and broken Hammett relationships have been observed for  $S_N2$  reactions at benzylic sites as

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**Figure 2.** Hammett plots for oxidative addition into benzyl bromides by LCo(I)Br ligated by (a) 5CN-substituted pyrox 1 and (b) 5CF<sub>3</sub>-substituted pyrox 2. The lines with negative correlations use  $\sigma^+$  values, while the lines with positive correlations use  $\sigma^-$  values (taken from the pK<sub>a</sub> of the corresponding aniline or phenol).<sup>17a,18</sup> Error bars depict the standard error of the mean for between 2–5 measurements. (c) Trends and anomaly in oxidative addition rate constants observed from the Hammett plots, with selected example substrates depicted.

a result of structural variations in the transition state,<sup>19</sup> and also for organometallic reactions involving a change in rate-determining step between oxidative addition and reductive elimination.<sup>20</sup> While a break in a Hammett relationship between separate correlations using  $\sigma$  and  $\sigma^+$ parameters or *para*- and *meta*-substituents are not uncommon,<sup>21</sup> a break between  $\sigma^+$  and  $\sigma^-$  is very unusual.

Alternatively, the deviation in the Hammett relationship may be a consequence of the stabilization of a radical intermediate, which would yield increased rate constants with either mesomerically-donating or withdrawing groups. However, generally poor correlations were observed when using a variety of radical-based substituent parameters ( $R^2 < 0.75$  in all cases, as an average for the two ligands, see Supporting Information),<sup>22</sup> suggesting against singular stabilization of a radical intermediate (see Section 2.7 for further information).

36 Additionally, in both Hammett studies, we observed the 37 same outlier - para-COPh benzyl bromide (8, depicted in 38 red). The presence of this outlier suggests an additional 39 mechanism may be in operation. Benzophenone is a 40 known reductive mediator,<sup>23</sup> and we determined the half-41 peak potential  $(E_{p/2})^{13a,24}$  for this bromide substrate to be 42 570 mV more negative than the Co(II)/Co(I) redox couple 43 with ligand 2, which by itself appears to contradict an 44 electron-transfer mechanism. However, it is important to 45 consider that this heterogeneous electron transfer at the 46 boron-doped diamond working electrode may be 47 kinetically slow, leading to a large overpotential for 48 substrate reduction. It is therefore feasible that the 49 thermodynamic reduction potential lies close to or less 50 negative than the Co(II)/Co(I) couple, and a single 51 electron-transfer mechanism should not be discounted at 52 this stage. Furthermore, it is possible that this electron 53 transfer is induced photochemically by the formation of a 54 charge-transfer complex<sup>25</sup> or reduction of a photoexcited 55 state;<sup>26</sup> however, this scenario was discounted by 56

measuring the same rate constant with and without visible light.

**2.3. Dependence of Peak Current and Potential on Substrate Concentration.** To provide further insight into the different oxidative addition mechanisms, we next conducted CV experiments with varying concentrations of substrate. In this experiment, if Co(II) is returned in the reaction, one would expect to observe a sequential increase in current as more benzyl bromide is added, indicative of an EC' (catalytic) mechanism, which we had previously observed with 2,2'-bipyridyl (bpy) as the ligand for cobalt.<sup>12</sup> This behavior was not observed for any substrate with either pyrox ligand, and the peak current was found to be minimally dependent on substrate concentration.

In contrast to electrochemical catalysis, the peak potential for an EC mechanism (electrochemical reduction, 'E', followed by a chemical step directly forming Co(III). 'C'), should display an anodic shift (to less negative potentials) with increasing substrate concentration. This is indicative of depleting the solution near the electrode of Co(I) and shifting the Nernstian equilibrium accordingly.<sup>8d</sup> However, we observed the opposite -acathodic shift with increasing substrate concentration is displayed by all the substrate-catalyst combinations tested (Figure 3). This data points to an alternative mechanism entirely to the postulated EC process, and suggests a second electrochemical or chemical step is involved in the oxidative addition mechanism. Since the rate constants  $(k_{obs})$  correlated above are then compounded rate constants of multiple reaction steps, this is in agreement with the unusual broken Hammett relationships observed.

In order to identify the nature of the multiple-step reaction, simulations using DigiSim 3.03b software were performed to determine the magnitude of the cathodic shift, in combination with the simulated overall rate constant,  $k_{obs}$ . Electrochemical finite element and finite difference simulations are used to formulate a theoretical



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**Figure 3.** Cathodic shift of peak cathodic potential for the Co(II)/Co(I) couple ligated by 5CN-Pyrox 1 with successive increases in benzyl bromide (5) concentration is not consistent with an EC mechanism. CVs run with 1.0 mM CoBr<sub>2</sub> with 1.0 mM 1 at varying equivalents of 5 in a 100 mM solution of  $Bu_4NPF_6$  in acetonitrile, using a 0.071 cm<sup>2</sup> boron-doped diamond working electrode at a scan rate of 100 mV s<sup>-1</sup>. CVs are plotted in polarographic notation with positive currents corresponding to reduction.

response as a function of experimental conditions and physical knowns and unknowns.<sup>13a,27</sup> Although multiple assertions are required to estimate some values that are inputs in the simulation (see Supporting Information for details), comparing trends in the theoretical response against experiment (e.g., the magnitude of the cathodic shift VS. equivalents of substrate) facilitates approximation of the physical unknowns – in this case. the kinetics and thermodynamics of various reaction steps, which can be validated by simulated cyclic voltammograms under different conditions (concentrations, scan rate, etc.).

36 Using this method, possible scenarios involving the 37 presence of comproportionation steps<sup>2c,28</sup> and/or a second 38 electrochemical step could be discounted. A good match 39 with the experimental data was observed for an initial 40 formation of CoBr<sub>2</sub> and a carbon-centered benzylic 41 radical, followed by an equilibrium for Co(III)-C bond 42 formation (Figure 4). The equilibrium formation of 43 Co(III)–C explains differences in CV responses with bpy 44 and pyrox – for pyrox ligands, the equilibrium lies 45 towards the formation of Co(III) leading to EC-type CV 46 responses, while with bpy the equilibrium shifts to favor 47 Co(II). Since the Co(II) at the electrode becomes rapidly 48 reduced back to Co(I), this results in catalysis (EC' CV 49 response) with increasing currents as the substrate 50 concentration increases.<sup>12</sup> 51

Additionally, these simulations provide plausible changes
in Gibbs free energies for the various steps (oxidative addition of benzyl bromide 5 with Co(I) ligated by 5CNPyrox 1) – an activation energy barrier of 14.9 kcal mol<sup>-1</sup>
for the initial oxidative addition step, and a subsequent
barrier of 11.0 kcal mol<sup>-1</sup> for addition of the benzylic



Figure 4. (a) Proposed oxidative addition mechanism, with (b) experimental results in agreement with simulation (error bars represent one standard deviation from 3-6 repeat experiments, Co(I) ligated by 5CN-Pyrox 1 in the presence of 5).

radical to Co(II), with a -6.8 kcal mol<sup>-1</sup> exergonic reaction to form Co(III).<sup>29</sup> Deriving thermochemical data directly from simulating experimental outputs in this manner provides direct access to information on the intricate factors that affect multiple sequential reactions, while changing the CV scan rate alone only identifies the net kinetic result.

These results can be compared with DFT computations derived for similar oxidative additions of nickel and subsequent reversible Ni(III)-C bond formation/cleavage.<sup>4b,6,30</sup> Indeed, the low (4 kcal mol<sup>-1</sup>) barrier for addition of benzylic radicals to a Ni(bpy)PhBr complex determined by the groups of Kozlowski and Molander enables a dynamic kinetic resolution (DKR) to induce the formation of enantioenriched products from racemic starting materials in the presence of a chiral bioxazoline ligand.<sup>30a</sup> Since our simulated barrier is greater than this, DKR is possible but less kinetically facile with this cobalt catalyst system than with chiral derivatives of Ni(bpy)PhBr.

Overall, at this stage, concerted polar or  $S_N 2$  reaction mechanisms can be ruled out as the intermediacy of a discrete carbon-centered radical is consistent with the data. This provides indirect evidence that either a halogen-atom abstraction (inner-sphere) mechanism, or an outer-sphere electron transfer, is operational.

2.4. Analyzing the Impact of Electronics on the Individual Mechanistic Steps. As a consequence of the thermochemical data, which is available through simulation of experimental voltammetric results, we next conducted a series of experiments to ascertain the impact of changing the substrate and/or ligand on the two steps in the overall reaction: (a) formation of the benzylic radical, and (b) the reversible combination of the benzylic radical with Co(II) to afford a Co(III)–C bond. A subset of the substrate Hammett series was selected – namely, selecting electron-rich, -neutral, and -deficient substrates (Figure 5).

Comparing the substrate effects on the formation of the benzylic radical, the activation barrier is lowered by either adding an electron-donating methyl or electron-withdrawing cyano-group on the aromatic, consistent with stabilization of the resulting radical (Scheme 2.a). This suggests that the rate is not determined by an initial outer-sphere electron transfer, where one would expect the methyl group to raise the LUMO of the aromatic ring and slow the electron transfer. Similarly, the rate of the addition of the benzylic radical is also determined by radical stability – the least stabilized radical derived from substrate 5 has the lowest barrier to addition to cobalt (Scheme 2.b). 

In contrast to the activation energy barriers, the exergonicity of the formation of the terminal Co(III)–C complex appears to be controlled more by electron density on the benzylic carbon rather than radical stability – removing electron density by replacing an electron-donating substituent with an electron-withdrawing substituent shifts the equilibrium towards the initial benzylic radical. This suggests that the thermodynamics of this step are controlled by aspects of nucleophilicity – the electron-withdrawing cyano-substituent of substrate 7 reduces the stabilization afforded by binding to the cobalt center, since the partial negative charge is in conjugation with the electron-withdrawing group.



**Figure 5.** Graphical depiction of free-energy data for the two steps of the oxidative addition process derived from CV simulations. OA is the formation of benzylic radicals, and Co–C the subsequent formation of the Co(III) complex.

Scheme 2. Ligand and substrate effects on (a) the formation of the benzylic radical, and (b) the equilibrium formation of Co(III)–C.





Comparing the effect of the two ligands, the more electron-withdrawing ligand (1) increases both activation barriers as well as increasing the exergonicity of the equilibrium. As discussed above (Section 2.2), the reduced rate with ligand 5CN-Pyrox 1 is indicative of a less nucleophilic Co(I) complex that slows oxidative addition. The shift in the equilibrium position is in agreement with greater stabilization of the more electrophilic Co(II) center by an additional X-type benzyl ligand.

**2.5. Secondary Substrates.** To understand the precise nature of the first step in the oxidative addition, the formation of a benzylic radical, we next chose to study the effect of changing from a primary to a secondary and tertiary benzylic substrate (Table 1). It was found that secondary bromide substrates consistently react with a greater rate constant than their primary counterparts. This is not consistent with either an  $S_N2$  or concerted polar-type oxidative addition, which would both proceed through more sterically hindered transition states than for **Table 1. Relative rate constants for primary, secondary and tertiary substrates.**<sup>4</sup>

Ligand	Substrate	$k_{2^{\circ}}/k_{1^{\circ}}$	$k_{3^{\circ}}/k_{1^{\circ}}$
5CN-Pyrox (1)	5	$2.24 \pm 0.44$	n.d.
5CN-Pyrox (1)	7	$1.51 \pm 0.03$	n.d.
5CN-Pyrox (1)	8	$3.21 \pm 0.10$	n.d.
5CF <sub>3</sub> -Pyrox (2)	5	$2.36 \pm 0.37$	n.d.
5CF <sub>3</sub> -Pyrox ( <b>2</b> )	7	$1.14 \pm 0.32$	n.d.
5CF <sub>3</sub> -Pyrox ( <b>2</b> )	BnCl (9)	$1.30 \pm 0.35$	$1.65 \pm 0.35$
H 5	NC 7 F	PhOC 8	H 9

<sup>a</sup>Error bars are one standard deviation based on the variance of the secondary/tertiary substrate rate constant (for 3-5 repeat experiments). *n.d.* = not determined.

primary substrates, in agreement with the one-electron mechanism determined by simulating the CVs above. An outer-sphere electron transfer is also not supported by this mechanism, since electron donation from the methyl group makes the aromatic ring less electron-deficient by raising the LUMO.

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To interrogate these results further, we turned our attention to the chloride series, given that the tertiary bromide is highly unstable to E1 elimination. The parent primary benzyl chloride (9) reacts with the Co(I) complex ligated by 2 with a substantially reduced rate compared to benzyl bromides as a consequence of the greater C-Cl bond strength. Upon changing to a secondary and tertiary substrate respectively, the rate increases consecutively. The smaller effect of the secondary substrate in rate enhancement observed with benzyl chloride in comparison with the bromide analogue suggests that the transition state is earlier in the case of chloride due to the greater C-Cl bond strength. In this scenario, the reaction coordinate from starting material to an early transition state is accompanied by a reduced change in hybridization from  $sp^3$  to  $sp^2$ , thereby diminishing the stabilization afforded by hyperconjugation from the methyl substituents.22a

Finally, we also investigated the effect of changing benzophenone substrate 8 to the corresponding secondary analogue. Given that we earlier proposed that an outersphere electron transfer is in operation for this anomalous substrate, our hypothesis was that the secondary substrate would react with a reduced rate, consistent with the higher LUMO. Upon testing this, we determined that, with 5CN-Pyrox 1,  $k_{2^\circ}/k_{1^\circ} = 3.21 \pm 0.10$ , in direct contradiction with our expectation for an outer-sphere electron transfer. Indeed, this evidence points towards a halogen-atom transfer mechanism, even though this substrate was found to be anomalous in the Hammett plots. The reasoning behind this discrepancy was discovered through our multivariable linear-regression studies, see Section 2.8.

**2.6. Kinetic Isotope Effect Study.** Further validation of the halogen-atom abstraction mechanism was provided by studying the secondary kinetic isotope effect (KIE)<sup>31</sup>

of replacing protons with deuterium nuclei bonded to the benzylic carbon, which provides information on changes in hybridization in the transition state. Studies of various oxidative addition<sup>32</sup> and organohalide reduction<sup>33</sup> mechanisms by this technique have previously been used to differentiate between mechanisms based upon the magnitude of the KIE.

Investigating the combination of substrate 7 and its deuterated analogues  $7-d_1$  and  $7-d_2$  in the presence of  $CoBr_2$  ligated by 5CF<sub>3</sub>-pyrox 2, a normal (>1.0) secondary KIE was observed (Figure 6.a), indicative of a change from sp<sup>3</sup> to sp<sup>2</sup> hybridization. The average KIE of  $1.52 \pm 0.28$  is larger than a standard secondary KIE, and approaches or exceeds the theoretical maximum value of  $\sim$ 1.4 derived from changes in the out-of-plane CH<sub>2</sub> bending vibration.<sup>34</sup> This observation is in agreement with our proposed two-step mechanism, in which not only is the KIE of the first step resulting in a change in the rate constant, but additionally an equilibrium isotope effect (EIE) of the second step modifies the overall magnitude of the observed rate constant.<sup>35</sup> The latter effect results from the preferential stabilization of deuterium in a bond with the greatest force constant.<sup>36</sup>

To identify the contributing factors of these two steps to the overall KIE, we analyzed and simulated the CVs upon sequentially adding more 7- $d_2$ , in combination with cobalt ligated by 5CF<sub>3</sub>-pyrox 2. The deuterated substrate displayed an activation energy barrier of 13.6 kcal mol<sup>-1</sup> for the oxidative addition, a barrier of 9.9 kcal mol<sup>-1</sup> for the addition of the benzylic radical to Co(II), with a -5.5 kcal mol<sup>-1</sup> exergonic reaction to form Co(III) (Figure 6.b).

In comparison with the data for the protonated analogue (7), the deuterated substrate has a higher activation barrier for the formation of the radical and a lower activation barrier for the combination with Co(II). Consequently, there is a normal secondary KIE in the first step (Figure 6.c), consistent with a change in hybridization from sp<sup>3</sup> to sp<sup>2</sup> in the formation of the radical. Contrastingly, an inverse (<1.0) secondary KIE is observed in the second step, in which the sp<sup>2</sup> hybridized benzylic radical



Figure 6. (a) Trend in rate constants for protonated and deuterated analogues of substrate 7, with  $5CF_3$ -pyrox 2. For raw data and comparisons with other deuterated substrate/ligand combinations, see Supporting Information. (b) Result of simulations comparing substrate 7 and 7- $d_2$ . (c) Change in hybridization leading to a normal KIE in the formation of the benzylic radical. (d) KIE and EIE effects in radical combination with Co(II) to form a Co(III)–C complex. OA is the formation of benzylic radicals, and Co–C the subsequent formation of the Co(III) complex.

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undergoes a change to partial sp<sup>3</sup> character in the transition state towards the Co(III)–C complex (Figure 6.d). The EIE shows a small shift in the equilibrium position towards the starting benzylic radical for the deuterated substrate, consistent with favoring the sp<sup>2</sup> hybridized carbon center in which the C–D bond has more s-character, giving rise to a stronger bond.

Conducting CV simulations in this manner, thereby, allows the determination of the intricate factors affecting multiple kinetic steps, including changes in hybridization with KIE studies, which otherwise remain allusive with traditional techniques.

12 2.7. Analysis of Compounded Rate Constants with 13 Hammett Parameters. With knowledge of the proposed 14 mechanism involving halogen-atom abstraction and 15 subsequent radical trapping by Co(II), we returned to the 16 Hammett study to delineate the two effects. In the first 17 step, abstraction of the bromine atom occurs with the 18 buildup of both charge and radical character at the 19 benzylic carbon. In comparable systems, it has been 20 determined that for hydrogen-atom abstraction, 21 correlations with  $\sigma^+$  are observed – electron-donating 22 groups stabilize the buildup of positive charge at the 23 benzylic carbon atom upon the abstraction of a hydrogen 24 atom by an electrophilic radical, such as a bromine or 25 *N*-oxyl radical.<sup>37</sup> Conversely, correlations with  $\sigma^-$  are 26 observed where the radical is nucleophilic, as seen with 27 bromine-atom abstraction by tin- and silicon-centered 28 radicals.38 29

30 Importantly, improved correlations are frequently 31 observed when separating the atom abstraction processes 32 into two components – a polar term for the development 33 of partial charges in the transition state, and a distinct 34 radical term for the delocalization of spin density.<sup>22d</sup> In 35 this vein, Jiang et al. paired two terms to describe the 36 effects of bromine-atom abstraction from benzyl 37 bromides by silyl radicals.<sup>38a,39</sup> The relative magnitudes 38 of the  $\rho$ -value for each term then provides a reaction 39 specific comparison of polar to spin stabilization effects, 40 a concept which has been used in a number of recent 41 mechanistic investigations.40 42

When we applied this technique to our system, we observed an excellent correlation with the combination of  $\sigma^-$  and a conjugation parameter derived by Jackson,<sup>41</sup>  $|(\sigma^{\pm}-\sigma)/n|$ , where *n* is a classification term used to determine the number of stabilizing electrons (Figure 7). The Jackson conjugation parameter was selected since the value of  $\sigma^{\bullet}$  has not been tabulated for all our substituents, so that we could identify a model with all the available data. However, it should be noted that this term assumes that *meta*-substituents provide no (de-)stabilization of spin density, an approximation which does not entirely account for *meta*-effects.<sup>42</sup>

The positive coefficient for  $\sigma^-$  in the correlation is in agreement with a halogen-atom abstraction in which the high-spin (triplet-state)<sup>12</sup> Co(I) is reacting as a



**Figure 7.** Unified Hammett model for the oxidative addition with both pyrox ligands, split into charge and radical stabilization terms. *n* is a classification term for the number of stabilizing electrons,<sup>40</sup> and Lig is a binary term included to account for the differential rate constants with the two pyrox ligands. Results of benzophenone-derived substrate **8** with two different ligands depicted as open circles.

nucleophilic radical, as one would expect for an electronrich metal center (Scheme 3). By comparing the relative magnitude of the coefficients for the two terms, we can observe that the stabilization of spin density is most significant.<sup>43</sup> Additionally, the model has a higher weight for radical stability than one-step bromine-atom abstractions by either silicon<sup>38a,b</sup> or tin<sup>38c</sup> radicals, matching the two-step mechanism proposed herein.

Scheme 3. Halogen-atom abstraction favored by stabilization of both negative charge and spin density.



2.8. Parameterization of Substrates and Modeling of Kinetic Data. As part of our program on utilizing multiple DFT-derived parameters to model complex chemical outcomes through multivariable linearregression analysis,<sup>14</sup> including within the setting of Hammett-type analysis,<sup>44</sup> we next sought to determine whether we could model the kinetic outcome with only computationally-derived parameters.<sup>45</sup> The reasons for this were three-fold: (a) first, we questioned whether parameters determined by DFT would allow delineation of the stabilization of charge and spin density; (b)  $\sigma$ values are not available for all our substituents, and therefore we wanted a model that could better account for all the possible groups, especially *meta*-substituents (which are not sufficiently modeled by Jackson's conjugation parameter<sup>41,42</sup>); and, (c) to allow prediction of more complicated multi-substituted benzyl bromides. Specifically, we hoped our model could enable prediction of 3,4- and 3,5-disubstituted aromatic rings: while the additivity of Hammett  $\sigma$ -values is successful in some scenarios,<sup>46</sup> it has several limitations.<sup>47</sup>

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Considering the impact of the stabilization of both charge and radical character at the benzylic carbon in the transition state of the halogen-atom abstraction (c.f., Scheme 3), we proposed that partial charge according to NBO and spin density at the benzylic carbon would appropriately describe both of these parameters, respectively. Upon computing a range of properties for the anion, cation and radical, we determined a model incorporating the combination of the partial charge according to NBO of the radical at the benzylic carbon and the spin density according to NBO of the same carbon (Figure 8.a). It is noteworthy that the  $R^2 = 0.83$  and 0.86 for this combination of parameters with subsets of data corresponding to ligands 1 and 2, respectively.

The statistics of this model is substantially perturbed by the clustering of the data – two clusters are observed for the two ligands in the reaction with a range of largely electron-neutral substrates. To combat this, we added an

additional ligand (5- $CO_2Me$  substituted pyrox, 10) to provide a better spread of data by measuring the rate constants for the Co(I) oxidative addition with a smaller subset of benzyl bromides. A good model using the same substrate descriptors plus the Hammett  $\sigma^-$  value of the substituent on the pyridine was found (Figure 8.b). This  $\sigma^{-}$  parameter describes the electron-withdrawing nature of the ligand and is also correlated with the energy of the ligand's LUMO (see Supporting Information), indicative of modulation of the nucleophilicity of the Co(I)complex. Interestingly, the Co(II)/Co(I) redox potential of the complex does not prove to be an appropriate parameter for modeling the rate constant, in contrast to previous reports of the S<sub>N</sub>2-type oxidative addition of macrocyclic Co(I)<sup>8b</sup> and Fe(I)<sup>48</sup> complexes to alkyl halides. Furthermore, substrate 8 is no longer a significant outlier in this model, a result that is discussed in detail in Section 2.9.

In line with our goals for the parameterization study, we utilized a set of multi-substituted benzyl bromides to validate the statistics of the model. Sixteen validation



**Figure 8.** Multivariable linear-regression models for the Hammett series kinetic data. (a) Correlation with charge (NBO) and radical (spin) stabilization parameters in combination with a binary term (Lig) to differentiate the two ligands. Results of benzophenone-derived substrate **8** with two different ligands depicted as open red circles. (b) Addition of third ligand into the model (open blue diamonds) and validation with multi-substituted benzyl bromides (closed red diamonds). (c) Alternative model with bond-dissociation energy as a parameter, including validation (closed red diamonds). (d) Description of parameters and ligands utilized within Figure 8.

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points constructed from different combinations of substrates and ligands were tested (see Supporting Information for details), resulting in a validation  $R^2 =$ 0.73, demonstrating the efficacy of the model to account for the effect of multiple electronic variations on reaction kinetics.

6 Moving aside from molecular descriptors that are directly 7 analogous to Hammett parameters, we also identified a 8 second model with similar statistics using the 9 combination of the bond-dissociation energy (BDE) and 10 the spin density (Figure 8.c). These two terms could 11 describe the halogen-atom transfer and radical 12 combination steps discretely; wherein, the kinetics of the 13 first step is modeled by the BDE, and the spin density is 14 a correction factor for the combination of the kinetic and 15 thermodynamic effects of the second step. Indeed, the 16 simulated activation energy barriers for radical formation 17 were found to be highly correlated ( $R^2 > 0.99$ ) with the 18 bond-dissociation energy, validating the results of the CV 19 simulations (see Supporting Information). 20

**2.9.** Solving Hammett Anomalies, Guided by Multivariable Linear-Regression Models. The models in Figure 8 demonstrate one major difference to those derived from the initial Hammett studies in Figures 2 and 7 – the rate data for the benzophenone substrate 8 is no longer statistically anomalous, consistent with this substrate undergoing the same halogen-atom transfer mechanism as the other compounds. Indeed, it was an error in the effective  $\sigma^-$  Hammett value that results in a break in the linear free-energy relationship for this substrate.

32 To investigate the origin of this, we correlated DFT-33 computed gas-phase acidities of various para-substituted 34 phenols (from which  $\sigma^{-}$  values are derived), as well as 35 *para*-substituted toluene derivatives, against the  $\sigma^{-}$  values 36 (see Supporting Information). Consequently, we 37 determined that the acidity of the *para*-COPh toluene is 38 not appropriately predicted by the  $\sigma^-$  value. The reason 39 for this was found to be a change in the conformation of 40 both the anion and conjugate acid depending on the nature 41 of the atom (O in the case of phenols, or C in the case of 42 toluenes). Conformational variations and their resultant 43 perturbation in conjugation are a significant reason for the 44 failings of Hammett correlations to account for ortho-45 substituents,<sup>44</sup> but the effect of conjugation on distal 46 groups is less common.

47 Benzophenone demonstrates a contorted conformation 48 with changing dihedrals in the ground state, excited state, 49 and radical anion as a result of sterics between the two 50 aromatic rings inhibiting planarity, which favors 51 delocalization into the carbonyl (Figure 9).49 However, 52 altering the substituents manipulates the competition 53 between sterics and conjugation. For instance, we 54 calculated that the carbonyl group lies 24° out of the plane 55 of a para-hydroxy substituted ring, but a larger 27° out of 56 the plane for a *para*-methyl substituent. In this case, the 57



**Figure 9.** Conformation of *para*-COPh substituent (substrate **8**) for toluene before and after deprotonation.

delocalization of the oxygen lone pair favors conjugation and reduces the dihedral angle. Upon deprotonation, the dihedral angle is reduced in both cases in order to delocalize the charge onto the carbonyl oxygen. However, this effect is significantly greater for the benzylic anion (9° dihedral) than the phenoxide (12° dihedral), as a consequence of the oxygen electronegativity changing the charge distribution.

Nominally, these differences in conformation appear modest, but for the toluene gas-phase acidity series we derive a  $\sigma^{-}$  value for substrate 8 of 0.99 (see Supporting Information), significantly larger than the phenol value of 0.83. This difference explains why substrate 8 appears as an anomaly in the Hammett relationship  $-\sigma^{-}$  is only an appropriate value for this substituent when considering reactivity of phenols. When corrected using the adjusted  $\sigma^{-}$  value, substrate 8 no longer appears as an anomaly in the Hammett plots of Figures 2 and 7 (see Supporting Information). Through the parameterization program, we are able to observe the true result of this substrate, showing the power of this underlying technique. Additionally, we caution the future use of a COPh substituent as a point in a Hammett series without further analysis of conformational bias, as this may mislead the researcher to propose an alternative mechanistic rationale.

**2.10. Beyond Hammett Relationships – Correlations Including Diverse Substrates.** Given the parameters in the model in Figure 8.c, we questioned whether this would allow extrapolation to alternative substrate classes. In the first instance, we were intrigued by modeling our data on the benzyl chloride (9) oxidative addition (see Section 2.5). While Hammett models and other traditional linear free-energy relationships can only correlate the changes in aromatic substitution, and our first model in Figure 8.a/b utilizes parameters from only the benzylic radical (thereby, not encoding the nature of starting material halide), the bond-dissociation energy term in Figure 8.c was ideal to describe the nature of the halide leaving group in the halogen-atom abstraction.

Additionally, we were able to incorporate a range of secondary and tertiary substrates (studied in Section 2.5), as well as benzhydryl bromide (13), into the model (Figure 10). To add these substrates, we observed that the introduction of a new parameter  $-\omega$ , the electrophilicity



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**Figure 10.** Multivariable linear-regression model allows extrapolation to alternative substrate classes (depicted as open red circles, see Supporting Information for full list of substrate/ligand combinations).  $R^2_{\text{Valid.}} = 0.77$ ; validation points not shown for simplicity.

index of the radical (a measurement of the energy stabilization upon acquiring additional electron density)<sup>50</sup> – was beneficial, presumably due to the large extrapolations in the parameters for bond-dissociation energy and spin density when including the benzyl chlorides and benzhydryl bromide, respectively. This parameter has been reported to classify the nucleophilicity of a radical,<sup>51</sup> which was also found to be integral to the exergonicity of the radical combination step in the CV simulations (Section 2.4).

The new model allows comparisons between the kinetics of multiple substrate classes, beyond the correlations of a Hammett series with a single variable. Noticeably, some of these substrates represent significant extrapolations from other results with the same ligand – the combination of benzyl chloride (9) with ligand 2 has a rate constant 0.8 log units smaller than any benzyl bromides with the same ligand, while benzhydryl bromide (13) with ligand 1 has a rate constant 0.7 log units larger than any of the rate constants in Figure 2.a.

Further applications towards expanding the scope of substrates studied in this manner could therefore theoretically allow the prediction of any oxidative addition kinetics that occur with pyrox-ligated Co(I) complexes through a halogen-atom abstraction pathway.

#### 3. Conclusion

In conclusion, we have investigated the mechanism of oxidative addition of Co(I) complexes into a variety of substituted benzyl bromides. The rate constants for the

oxidative addition processes are readily determined by cyclic voltammetry at various scan rates, allowing rapid assessment of a Hammett relationship to evaluate electronic effects on the reaction. Further analysis of the cyclic voltammograms obtained with varying equivalents of substrate determined that the reaction is not a single transformation of Co(I) to Co(III)–C, but rather a two-step mechanism involving the initial formation of a benzylic radical, and the subsequent reversible formation of the Co(III)–C bond.

From these experiments, we propose that the mechanism proceeds through a halogen-atom abstraction process, a pathway found to be in agreement with kinetic isotope effects and the comparison between primary, secondary and tertiary substrates. As a consequence, the complex, two-line Hammett plot can then be delineated as a combination of polar and radical stabilization effects according to the experimentally determined rate constant. compounded value arising from the two-step а mechanism. Finally, DFT-computed parameters can be utilized as diagnostic terms in place of Hammett parameters to successfully correlate calculated features of the benzyl halides to the observed rate constant. Furthermore, the multivariable statistical models allowed for rationalization of the anomalous points in the Hammett correlation which arose from distal conformational differences between molecules.

The mechanistic knowledge gained in this study is integral to designing novel reaction methodologies with cobalt catalysts. Notably, although Co(III)–C complexes can be afforded by oxidative addition and employed in further transformations, the existence of the equilibrium poses challenges for preventing catalytic turnover of benzyl bromides to their corresponding radicals. This challenge is a direct consequence of rapid reduction of any Co(II) within the electrode double layer under bulk electrolysis conditions. With an improved understanding of the principles behind these organometallic reaction steps, one can design new catalytic applications. Specifically, the multivariable correlation in Figure 10 facilitates the prediction of kinetic behavior for new substrate/ligand combinations outside the remit of the traditional Hammett series ubiquitous in physical organic chemistry.

Ultimately, we believe the techniques developed herein are of wide utility for the study of fundamental organometallic mechanisms. By simulating the cyclic voltammograms, we were able to obtain experimental values of multiple activation energies and equilibrium constants simultaneously, a significant challenge in complex, multi-step processes such as those investigated. Therefore, these principles will be relevant in a range of applications for the purpose of disentangling complex reaction mechanisms.

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#### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Materials and methods, experimental and simulated cyclic voltammograms and kinetic data, parameters used in the modeling, additional models and correlations, discussion of gas-phase acidity computations, experimental procedures, characterization data and spectra for the synthesis of ligands and substrates, and coordinates of DFT-optimized structures. (PDF)

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The authors declare no competing financial interest.

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