



# Theoretical investigation on the mechanism of iron catalyzed cross coupling reactions via ferrate intermediates



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## ABSTRACT

Iron is a versatile catalyst for cross coupling reactions. These reactions may proceed either via classical redox cycles involving low-valent iron species or via highly alkylated organoferrate complexes. Experimentally, it is difficult to trap reactive intermediates, but it has been possible to prepare iron complexes similar to the supposed active catalyst that are able to methylate activated electrophiles (J. Am. Chem. Soc. 130 (2008) 8773–8787). Motivated by these experiments we studied the methylation of 4-chlorobenzoyl chloride by the organoferrate complex  $[(\text{Me})_4\text{Fe}(\text{MeLi})][\text{Li}(\text{OEt}_2)]_2$  employing density functional theory at the OPBE/6-311+G\*\* level, as well as B3LYP/6-311+G\*\* calculations with explicit inclusion of dispersion and solvent effects (describing iron with the QZVP basis and SDD pseudopotential). In the preferred mechanism, methyl transfer takes place via substitution at the organoferrate complex, with the leaving methyl group being replaced by chloride. In line with the experimental findings, up to four methyl groups can be transferred in this manner. By locating all conceivable transition states and intermediates, the calculations shed light on the relative ease of substitution at the various positions of the organoferrate complex, both in the first and subsequent methyl transfers. Transition states for an alternative redox mechanism could not be located.

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## 1. Introduction

In recent years iron has emerged as a versatile catalyst in cross coupling reactions [1–9]. In contrast to cross coupling reactions catalyzed by *e.g.* palladium or copper, the underlying mechanisms are not yet well understood in the case of iron. There is consensus that the mechanism may vary depending on reagents and precursors [10–13]. Generally speaking, there are two main alternatives: either so-called -ate mechanisms involving highly alkylated iron species [14] or catalytic redox cycles consisting of up to three formal steps: oxidative addition, transmetalation, and reductive elimination. For the latter, different experimental and computational studies proposed different oxidation states for the low-valent iron center [11,15–22].

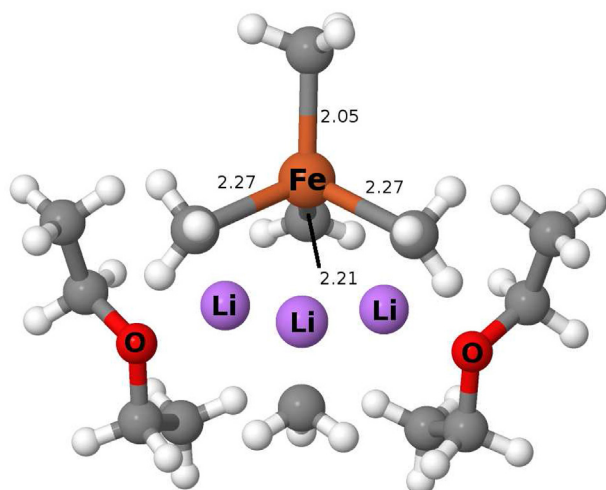
Experimentally, the mechanisms of iron catalyzed cross coupling reactions are difficult to elucidate because any reactive intermediates formed in situ are expected to be unstable and short-lived. Fürstner and coworkers succeeded in synthesizing several

iron complexes believed to be similar to the reactive intermediates and tested their activity in cross coupling reactions [23]. Among others, they prepared the organoferrate complex **1**,  $[(\text{Me}_4\text{Fe})(\text{MeLi})][\text{Li}(\text{OEt}_2)]_2$  (*cf.* Fig. 1), which could be crystallized for structure determination and was shown to transfer one or several methyl groups to activated substrates such as acid chlorides and enol triflates [23,24]. The methylation may proceed either by a substitution reaction, in which the methyl group is directly transferred to the substrate, or by a two-step reaction with an oxidative addition and a reductive elimination step. Motivated by the experimental findings on complex **1** [23], we decided to analyze the mechanism of the corresponding methyl transfers using density functional theory (DFT).

To choose the most suitable DFT level for this ferrate complex, we first tested several functionals and basis sets, and we also identified the most probable spin state. The findings from this initial stage are included in the next section describing the computational methodology. Thereafter we present our computational results on the mechanism of methylation.

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**Fig. 1.** Crystal structure of organoferrate complex **1** from Ref. [23] (color code: carbon atoms in gray, hydrogen atoms in white). Key distances are given in Å. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

## 2. Computational methods

We performed DFT calculations to investigate the iron complex **1** and its reactions. Previous DFT benchmarks on transition metal complexes [25,26], in particular iron complexes, suggested that the OPBE functional gives a good description of spin states [27,28]. We thus initially adopted the OPBE functional and applied it in combination with the 6-311+G\*\* basis set [29–31], while using the LANL2DZ pseudopotential and basis set for the iron atom [32–34].

To determine the preferred spin state, complex **1** was optimized as singlet, triplet, and quintet, starting in each case from the crystal structure. Table 1 lists the resulting relative energies and the RMSD values (root mean square deviations) relative to the crystal structure; the selected bond lengths and angles included in the RMSD evaluation are given in the Supporting Information, Table SI-1. The quintet state is lowest in energy followed by the triplet state and, still higher, the singlet state. The RMSD values clearly show that the computed geometry of the quintet is closest to the crystal structure, whereas the geometries of the singlet and triplet deviate strongly. Hence, the ground state of complex **1** is a quintet (consistent with an oxidation state of +2 for iron).

For further validation, we tested additional functionals that are recommended in the literature for transition metal complexes [35–39]: M06 [40], B3LYP [41,42], B3LYP+D with D3 dispersion corrections [38], and TPSSh [43]. Complex **1** was optimized in the quintet state using these functionals. We again chose the 6-311+G\*\* basis set for all atoms except iron, which was described by the SDD basis set and pseudopotential [44]. All optimizations were started from the crystal structure. Table 2 collects the RMSD values for the same set of bond lengths and angles as before (mainly around the central iron-methyl tetrahedron, see Table SI-1).

**Table 1**  
Energies and free energies (relative to the quintet state) and RMSD values of the optimized geometries with respect to the crystal structure of complex **1** (OPBE/6-311+G\*\*, Fe: LANL2DZ).

Spin state	Singlet	Triplet	Quintet
E (kcal/mol)	34.56	17.24	0.00
G (kcal/mol)	39.93	20.66	0.00
RMSD bonds (Å)	0.19	0.13	0.07
RMSD angles (°)	13.5	15.5	4.7

**Table 2**

RMSD values of the optimized quintet geometries with respect to the crystal structure of complex **1** for various functionals (basis set: 6-311+G\*\*, SDD for iron).

Functional	OPBE	M06	B3LYP	B3LYP+D	TPSSh
RMSD bonds (Å)	0.07	0.13	0.09	0.11	0.13
RMSD angles (°)	4.7	5.7	4.7	5.6	6.0

The smallest errors in geometry (compared to the crystal structure) are indeed found for the quintet structures computed with the OPBE functional closely followed by B3LYP. Larger deviations, especially for bond angles, are obtained with M06, B3LYP+D, and TPSSh. Given these results we decided to perform geometry optimizations using the OPBE functional employing the LANL2DZ basis set and pseudopotential for iron; for brevity this standard computational setup is termed OPBE-level.

For further analysis the geometries optimized at the OPBE-level were used for single-point calculations with several other functionals (BP86, B3LYP, B3LYP+D, TPSSh, M06) and/or larger basis sets such as QZVP [45] or SDD [32,46] for iron (SDD pseudopotential as well). When appropriate, solvent effects were taken into account by using the polarizable continuum model (PCM) [47] with THF as solvent (as in the experiment). All calculations were carried out using the Gaussian09 program package, revision D.01 [48]. Harmonic frequencies were calculated for all stationary points to confirm them as minima (no imaginary frequency) or transition states (one imaginary frequency) and to compute zero-point energy corrections (at 238.15 K, the temperature used in the experiments). Additionally, intrinsic reaction coordinate calculations (IRC) [49] were performed to ensure that the transition states connect to the expected reactants and products, taking 30 IRC steps in each direction with subsequent optimization of the resulting geometry. This always led to the correct minimum structures of reactants and products.

## 3. Results and discussion

As exemplary reaction we first studied the transfer of a methyl group from complex **1** to 4-chlorobenzoyl chloride **2**, see Scheme 1. As can be seen, **1** carries in total five methyl groups. Four of them are directly bound to the central iron atom forming a tetrahedral coordination sphere. The fifth methyl group is farther away from the central iron atom (3.84 Å compared to 2.05 to 2.27 Å) being coordinated to the three lithium atoms in-between. To distinguish these five methyl groups they are colored differently in Scheme 1. The black methyl group is in the top position (in short: to), the two red ones are equivalent by symmetry and occupy the back position (ba), the blue one is in the front position (fr), and the green one is located below the lithium atoms in the bottom position (bo).

For the oxidative addition-reductive elimination mechanism, we located an intermediate with the substrate **2** being attached to the iron complex **1**, both in the triplet and quintet state (Fig. 2). The free energy relative to the separated reactants is 1.11 kcal/mol for the quintet species and 0.45 kcal/mol for the triplet species (*i.e.* 0.66 kcal/mol lower in free energy). In both cases, the carbonyl carbon C1 is bound to the central iron atom (Fe–C1: quintet, 1.98 Å; triplet: 1.81 Å), thereby distorting the tetrahedral coordination sphere around iron, while the chlorine atom binds to the free lithium atom (Li–Cl: quintet, 2.13 Å; triplet, 2.10 Å); the pertinent Li–O distances are similar (quintet, 2.08 and 2.16 Å; triplet, 2.12 and 2.17 Å). In the quintet intermediate the iron atom remains almost at the center of a distorted tetrahedron, whereas in the triplet state the Fe[Me]<sub>4</sub>-unit with the attached substrate is turned away from the center of the lithium triangle. We did not manage to locate any

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