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Reaction Mechanisms |*Hot Paper*|

Single-Electron Transfer between CuX_2 and Thiols Determined by Extended X-Ray Absorption Fine Structure Analysis: Application in Markovnikov-Type Hydrothiolation of Styrenes

Hong Yi+,[a] Chunlan Song+,[a] Yiying Li,[a] Chih-Wen Pao,[c] Jyh-Fu Lee,[c] and Aiwen Lei*[a, b]

Abstract: Transition-metal mediated C–S bond formation using thiol compounds has been widely used in recent years. However, there has been less focus on the interaction between the metal and thiol compounds. In this work, we have successfully evidenced the single-electron transfer between CuX_2 and thiophenol utilizing EXAFS. The fitting EXAFS results reveal that two halide anions are coordinated with the Cu^I center, whereas no sulfur atom is observed in the first coordination sphere. This Cu^I ate complex serves as the key intermediate for the proton transfer in the application of Markovnikov-type hydrothiolation reactions.

Thiol compounds widely exist in nature and occupy an important role in organic synthesis.[1] The construction of C–S bonds using thiol compounds is a significant goal in synthetic chemistry due to the widespread utility of numerous organosulfur compounds as synthetic intermediates, bioactive compounds, and functional materials.[1d,2] The addition reaction of organosulfur compounds to unsaturated bonds presents a very attractive strategy for C–S bond formation, and great progress has been achieved in recent decades.[3] The thiol–ene "click" reaction is well established and has served as a powerful tool in organic synthesis.[2d] The *anti*-Markovnikov addition of thiols to alkenes was achieved in high selectivity.[4] A radical-type mechanism was involved and promoted by initiators, such as AIBN, peroxides, or photochemistry. However, Markovnikov-type hydrothiolation of alkenes is relatively less developed. Although several examples have been demonstrated, excess strong acid, alkenes, or conjugated olefins are always needed.[5] Recently, some examples have been accomplished using catalytic Pd or Cu to achieve the Markovnikov-type hydrothiolation.[6] In these reported examples, the olefins are always alkenes bearing heteroatoms and the detailed mechanism between metals and thiols remains unclear.[1g] Though interaction between Cu^{II} species and thiols is a known process and has been studied,[1g,j] a detailed mechanism and determination of the Cu^I species generated still remains unknown. In this work, we employed extended X-ray absorption fine structure (EXAFS) and EPR analyses to study the single-electron transfer between CuX_2 and thiophenol, which provides direct evidence of this reductive process. This formed Cu^I ate complex serves as the key intermediate in unprecedented Markovnikov-type hydrothiolation of alkenes with thiophenols.

EPR spectroscopy has been used to probe the Cu^{II} species present in different reactions.[7] Initially, we applied EPR spectroscopy to investigate this reaction between $CuBr_2$ and *p*-MePhSH. As shown in the EPR spectra (Figure 1), an EPR silent species was generated after adding the *p*-toluenethiol in $CuBr_2$ solution. These results may indicate that the Cu^{II} species can be reduced by thiophenol compounds.

To further probe this process, we used XAS spectroscopy, which has served as a powerful tool for determination of the local structure of metal species,[8] to investigate the reaction between CuX_2 ($X = Br$, Cl) and *p*-toluenethiol under nitrogen atmosphere. As shown in the XANES spectra (Figure 2 A, black

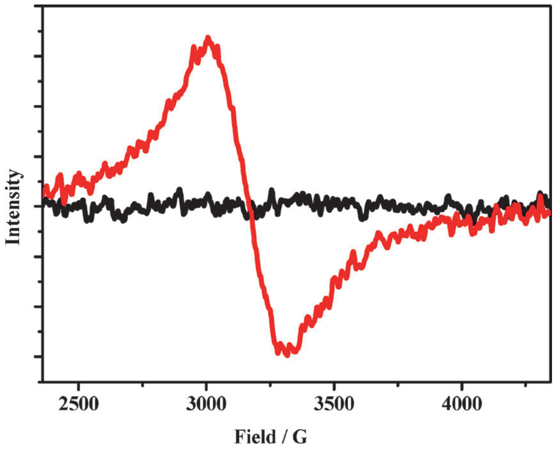

Figure 1. EPR spectra of the reaction between $CuBr_2$ (0.5 mmol) and *p*-toluenethiol (1.0 mmol) in 5.0 mL DMF for 5 min. Red line: $CuBr_2$ in DMF; black line: reaction system.

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[a] H. Yi,+ C. Song,+ Y. Li, Prof. Dr. A. Lei
College of Chemistry and Molecular Sciences
The Institute for Advanced Studies (IAS)
Wuhan University, Wuhan, Hubei 430072 (P.R. China)
E-mail: aiwenlei@whu.edu.cn
Homepage: http://aiwenlei.whu.edu.cn/Main Website/

[b] Prof. Dr. A. Lei
State Key Laboratory and Institute of Elemento-Organic Chemistry
Nankai University, Tianjin 300071 (P.R. China)

[c] Dr. C.-W. Pao, Prof. Dr. J.-F. Lee
National Synchrotron Radiation Research Center
Hsinchu 30076 (Taiwan)

[+] These authors contributed equally to this work.

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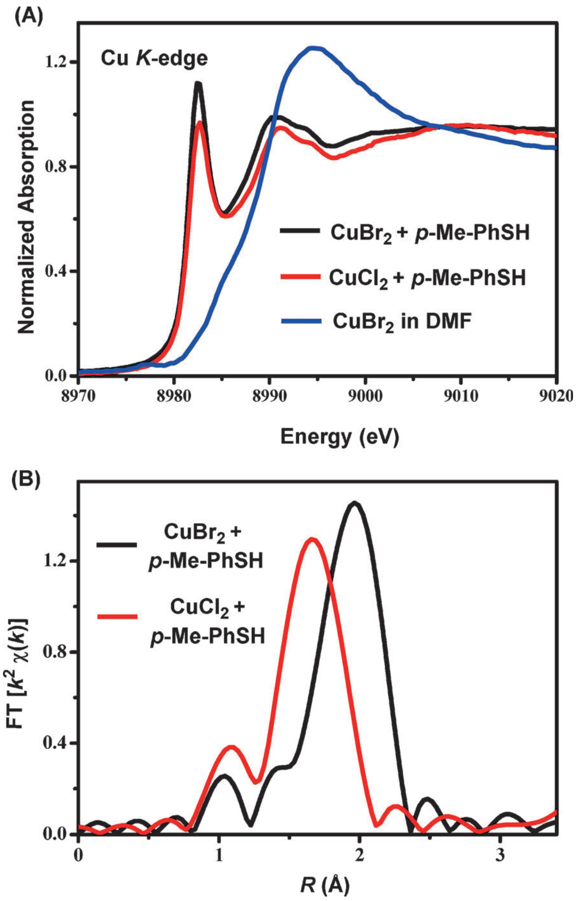


Figure 2. XANES and EXAFS spectra. Black line: $CuBr_2$ (0.5 mmol) and p-toluenethiol (1.0 mmol); red line: $CuCl_2$ (0.5 mmol) and p-toluenethiol (1.0 mmol); blue line: $CuBr_2$ (0.5 mmol) in DMF at room temperature.

line), the obtained copper species has an edge energy of 8981.6 eV. Therefore, it could be concluded that the obtained Cu species is Cu^I. In addition, the reaction of $CuCl_2$ and p-toluenethiol was also demonstrated (Figure 2A, red line). A nearly identical XANES spectrum revealed that the geometry and oxidation specification of both generated Cu^I species were similar. As shown in Figure 2B, the EXAFS spectrum of the reaction between $CuBr_2$ and p-toluenethiol is very different from the reaction between $CuCl_2$ and p-toluenethion, indicating that the halide ion with different bond length may coordinate with the formed Cu^I species and no sulfur atom is coordinated. The fitting results showed that two bromide ions coordinated with Cu^I species (Figure S1 in the Supporting Information). The average distance of the Cu–Br bond is 2.24 Å (Table 1). We also fitted the data with a $[CuBrSPh]^-$ structure for comparison (Figure S2 in the Supporting Information). However, the Debye–Waller factor of the Cu–S bond is relatively large. Furthermore, we also isolated, in quantitative yield, the homocoupling product of p-toluenethiol. Therefore, we determined the obtained Cu^I complex to be $(CuBr_2)^-H^+$.[7a] In addition, we also fitted the EXAFS of the reaction between $CuCl_2$ and p-toluenethiol (Figure S2). The fitting results revealed that two Cl ions coordinated with the Cu^I species and the average bond distance of the Cu–Cl bond is 2.11 Å, which we proposed to be the $(CuCl_2)^-H^+$ complex, in accordance with the single-crystal structure reported in the literature.[9] Based on these results, we think that the $[X\text{-}Cu\text{-}X]^-H^+$ ate complex is the most probable structure for the Cu^I species generated through the reduction process between CuX_2 (X = Br or Cl) and thiols.

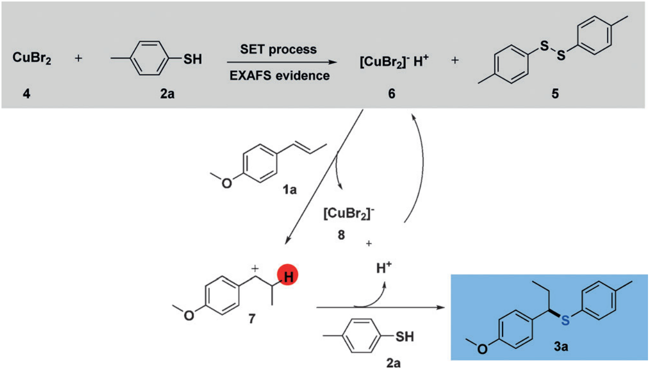
Table 1. Summary of EXAFS first shell-fitting results.[a]

	edge energy (eV)	OS	coordination atom	CN	d [Å]
$CuBr_2$ + p-toluenethiol (DMF solution)[b]	8981.6 (edge)	+1	Br	2	2.24
$CuCl_2$ + p-toluenethiol (DMF solution)[c]	8981.6 (edge)	+1	Cl	2	2.11

[a] OS: oxidation state; CN: coordination number; d: bond length. [b] Fitting results of the R-Space EXAFS spectrum of $CuBr_2$ + p-toluenethiol in DMF solution (FT: 3.00–13.98 $Å^{-1}$, fitting range: 1.22–2.37 Å, Debye–Waller factor: 0.0034. [c] Fitting results of the R-Space EXAFS spectrum of $CuCl_2$ + p-toluenethiol in DMF solution (FT: 1.84–10.53 $Å^{-1}$, fitting range: 1.34–2.04 Å, Debye–Waller factor: 0.001.

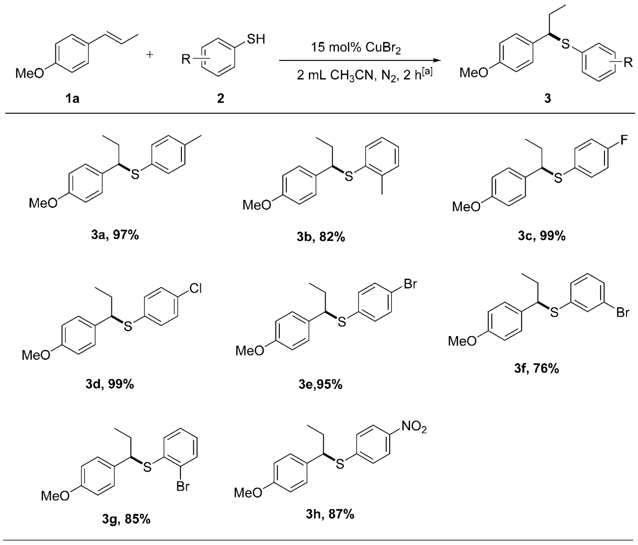
Based on the above results, thiophenol can serve as the reductant to transfer one electron to Cu^{II}, furnishing the reduced Cu^I complex and the thiyl radical. We hoped to add one olefin to trap the formed thiyl radical. Initially, we used *trans*-anethole **1a** as the trapping substrates (Scheme 1). However, no desired anti-Markovnikov product was detected, whereas 70% yield of Markovnikov-type product **3a** was generated. A plausible mechanism for this hydrothiolation process is proposed in Scheme 2. As evidenced by EXAFS and EPR studies, the initial step is the single-electron transfer between $CuBr_2$ and thiophenol, generating the $[CuBr_2]^-H^+$ species. Almost quantitative yield of the homocoupling product of thiophenol was formed during this single-electron transfer (SET) process. The $[CuBr_2]^-H^+$ ate complex **6** then transfers one proton to the olefin, forming the cation intermediate **7** and complex **8**. Finally, the p-toluenethiol attacks this intermediate **7** to form the desired hydrothiolation product with the loss of one proton. The $[CuBr_2]^-H^+$ ate complex **6** can be regenerated through the combination of complex **8** and proton. In this hydrothiolation process, the $[CuBr_2]^-H^+$ ate complex serves as the key intermediate for the proton transfer. In addition, we found that the HBr acid could also promote this reaction, which is further evidence that the Cu^I ate complex acted as a proton-transfer intermediate.

Scheme 1. The reaction between 4-methylbenzenethiol and p-toluenethiol promoted by $CuBr_2$.



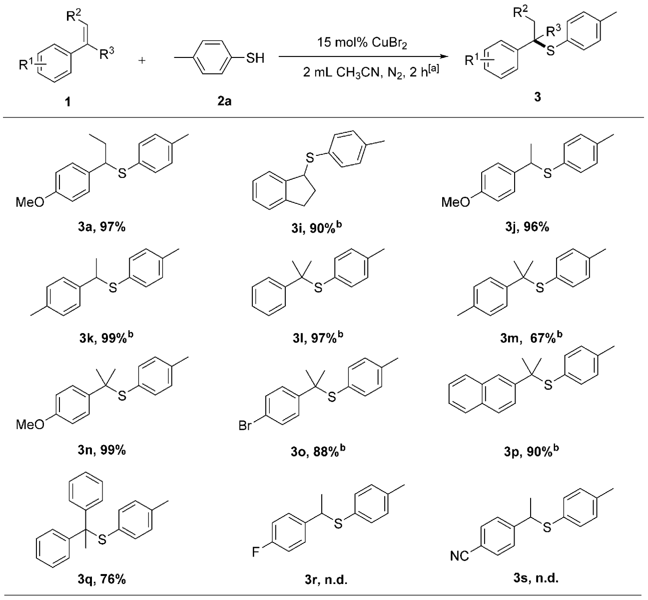
Scheme 2. The proposed mechanism of single-electron transfer between CuX$_2$ **4** and *p*-toluenethiol **2a**, and application in hydrothiolation reaction.

We found that almost quantitative yield of the hydrothiolation product was achieved when employing CH_3CN as solvent and $CuBr_2$ as the catalyst (see the Supporting Information, Table S1, entry 2). In addition, we investigated the effect of different copper salts on this hydrothiolation reaction. It was found that $CuBr_2$ showed the best catalytic activity. In the control experiments, no desired product was detected without the addition of $CuBr_2$, confirming that the copper salt was essential to this transformation (Table S1, entry 7). With the optimized conditions established, we turned to explore the generality of this copper-promoted hydrothiolation reaction in the synthesis of sulfanes. As shown in Scheme 3, the benzenethiols **2** with different electron-withdrawing and electron-donating substituents reacted efficiently to afford the corresponding sulfanes (**3a**–**3h**) in good to excellent yields. Benzenethiols with *p*-methyl and *o*-methyl groups gave the desired product in good yields (**3a** and **3b**). Notably, halide substituents on the aromatic ring were well-tolerated in this transformation and afforded moderate to good yields (**3c**–**3g**). The thiols substituted with -bromo, *m*-bromo, and *o*-bromo gave the desired products in 95, 76, and 85 % yields, respectively, indicating that steric effects have little impact on this transformation. Moreover, 87 % yield was obtained when using a strong electron-withdrawing substituent like nitro on the benzenethiols (**3h**).



Scheme 3. Copper-promoted hydrothiolation reaction between anethole **1a** and different thiophenol derivatives **2**. [a] Reactions were conducted at RT for 2 h using **1a** (0.50 mmol), **2** (1.0 mmol), and $CuBr_2$ (15 mol %) in CH_3CN (2.0 mL) under N_2 atmosphere. Isolated yields are shown.

Subsequently, the reaction was expanded for the synthesis of sulfanes using different olefins (Scheme 4). Besides **3a**, other kinds of external alkene like indene could also tolerate this transformation (**3i**). The terminal alkenes that included different substituent groups reacted effectively to afford the corresponding products in excellent yields (**3j**–**3q**). Styrenes substituted with methyl and methoxy groups were almost quantitatively converted into the desired products (**3j** and **3k**). However, the styrenes substituted with electron-withdrawing groups such as F and CN did not produce the desired products.



Scheme 4. Copper-promoted hydrothiolation reaction between *p*-toluenethiol **2a** and different alkene derivatives **1**. [a] Reactions were conducted at RT for 2 h using **1** (0.50 mmol), **2a** (1.0 mmol), and $CuBr_2$ (15 mol %) in CH_3CN (2.0 mL) under N_2 atmosphere. Isolated yields are shown. [b] The reaction time is 12 h.

In conclusion, we have observed and provided evidence for the single-electron transfer between CuX_2 and thiophenol using EXAFS and EPR spectroscopy. The formed Cu^I species was assigned as the Cu^I ate complex, which serves as the key intermediate for the proton transfer in the application of hydrothiolation reaction. These spectroscopic analyses for the observation of single-electron transfer between Cu^{II} and thiophenol will not only be helpful for mechanistic understanding in copper catalysis but will also benefit further reaction design.

Experimental Section

General procedure: A Schlenk tube equipped with a stir bar was loaded with 16.7 mg (15 mol %, 0.75 mmol) of $CuBr_2$, 0.5 mmol olefins **1a** and 1.0 mmol 4-methylbenzenethiol **2a** in 2.0 mL degassed acetonitrile under N_2 atmosphere. The solution was then stirred at room temperature for 2 h. After the completion of the reaction, the products were determined by TLC. The solvent was removed under reduced pressure by an aspirator, then the pure product was obtained by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 50:1) to afford **3a** in 132.2 mg (97 %, 0.5 mmol scale) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.16–7.12$ (m, 4H), 6.98 (d, $J = 7.6$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 3.95 (dd, $J = 9.0$, 5.9 Hz, 1H), 3.72 (s, 3H), 2.25 (s, 3H), 2.09–1.644 (m, 2H), 0.87 ppm (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 158.3$, 136.9, 133.9, 132.8, 131.3, 129.3, 128.8, 113.5, 55.0, 54.9, 29.2, 21.0, 12.2 ppm. HRMS (EI^+) m/z calcd for $C_{17}H_{20}OS$: 272.1235 $[M]^+$; found: 272.1239.

Acknowledgements

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Keywords: copper catalysis · copper reduction · C–S bond formation · hydrothiolation · synchrotron

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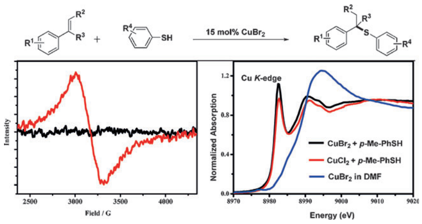

Reaction Mechanisms

*H. Yi, C. Song, Y. Li, C.-W. Pao, J.-F. Lee, A. Lei**

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