Bio-organometallic Organosulfur Chemistry. Transition Metal-Catalyzed Cross-Coupling Using Coenzyme M or Thioglycolic Acid as the Leaving Group

Jiri Srogl, Wansheng Liu, Daniel Marshall, and Lanny S. Liebeskind*

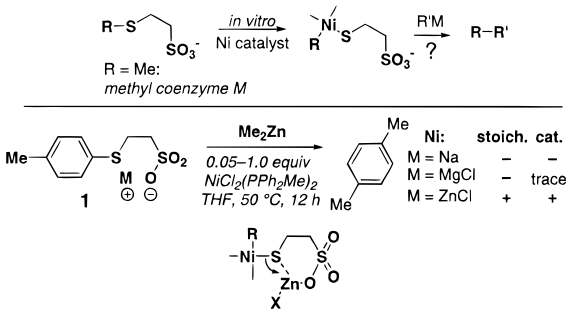
Sanford S. Atwood Chemistry Center, Emory University, 1515 Pierce Drive, Atlanta, Georgia 30322

Received May 18, 1999

Metal−thiol and −thiolate interactions occur commonly and are of seminal importance in the biochemistry of life-sustaining processes.[1] Given the stability of the bond between a mercaptide ligand and various redox-active metals, it is of interest that Nature has evolved significant metalloenzymatic processes, which use key interactions of sulfur-containing functionalities with metals such as Ni, Co, Cu, and Fe (methanogenesis,[2] acetyl CoA synthesis,[3] biological methyl transfers,[4−6] and the mediation of metal bioavailability by metallothioneins[7−9]). From a chemical perspective, it is striking that these metals can function as robust biocatalysts in vivo, even though they are often "poisoned" as catalysts in vitro through formation of refractory metal thiolates. Insight into the nature of this chemical discrepancy is essential for a more complete understanding of biochemical processes and could open the way to new procedures in synthetic organic and organometallic chemistry.

Consider, for example, metal-catalyzed cross-coupling protocols.[10−15] Although some examples are known,[16−19] thioorganic compounds do not participate in as wide a range of metal-catalyzed cross-coupling reactions as do iodoorganics. Why? Both iodoorganics and thioorganics undergo oxidative addition reactions with low-valent metals,[20−24] so the answer must reside in the difference between the metal−iodide and metal−thiolate bond strengths. The metal−iodide bond is relatively weak and easily substituted, whereas the metal−thiolate bond is strong. It resists substitution and therefore retards catalysis, except under reaction conditions where thiolate displacement from the metal is favored, such as with potent nucleophilic reagents (RMgX).[25]

Scheme 1



How might refractory metal thiolates be activated *under mild conditions* and thus ensure the robust behavior of metal catalysts in thiol/thiolate-rich environments? Transfer of thiolate to a metal of greater thiophilicity has clear support in the domain of biochemistry. For example, Zn(2+), a ubiquitous, non-redox-active metal, is found throughout biological systems, and, of the biologically relevant divalent metals, it has an affinity for thiolate second only to that of copper.[26] Therefore, the equilibrium M−SR + Zn^{2+} = M^+ + Zn^+SR can be displaced toward the zinc mercaptide with liberation of the metal M. Examples of this principle are found in biology, medicine, and chemistry.[27−29]

We demonstrate herein a new synthetic process that uses the above-mentioned principle and has its conceptual basis in a bioorganometallic transformation with presumed primordial origins; namely, the putative final steps in methanogenesis, the production of methane from methyl coenzyme M ($CH_3SCH_2CH_2SO_3^-$) mediated by methyl coenzyme M reductase.[2,30] In this remarkably efficient process, a nickel hydrocorphinoid cofactor (F_{430}) ruptures the CH_3−S− bond of $CH_3SCH_2CH_2SO_3^-$, generating a CH_3−Ni intermediate, which subsequently suffers protonation to methane. If the C−S cleavage of *S*-substituted coenzyme M derivatives by nickel catalysts a general process, then inhibition of the biologically relevant protonation might allow interception of the organonickel intermediate for alternative processes, such as the formation of carbon−carbon bonds by way of a cross-coupling protocol (Scheme 1).

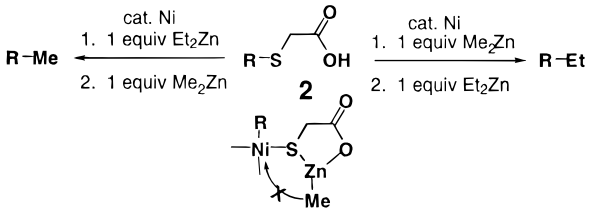
To test this hypothesis, salts of *S*-(*p*-tolyl)thioethanesulfonate (**1**) were prepared and assayed as substrates in nickel-catalyzed

* To whom correspondence should be addressed. Tel.: (404) 727-6604. Fax: (404) 727-0845. E-mail: CHEMLL1@emory.edu.

(1) *Handbook of Metal−Ligand Interactions in Biological Fluids*; Berton, G., Ed.; Marcel Dekker: New York−Basel−Hong Kong, 1995.
(2) Ermler, U.; Grabarse, W.; Shima, S.; Goubeaud, M.; Thauer, R. K. *Science (Washington, D.C.)* **1997**, *278*, 1457.
(3) Ragsdale, S. W.; Kumar, M. *Chem. Rev.* **1996**, *96*, 2515−2539.
(4) Matthews, R. G.; Goulding, C. W. *Curr. Opin. Chem. Biol.* **1997**, *1*, 332−339.
(5) Goulding, C. W.; Matthews, R. G. *Biochemistry* **1997**, *36*, 15749−15757.
(6) Jablonski, P. E.; Lu, W.-P.; Ragsdale, S. W.; Ferry, J. G. *J. Biol. Chem.* **1993**, *268*, 325−329.
(7) Jacob, C.; Maret, W.; Vallee, B. L. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3489.
(8) Maret, W.; Vallee, B. L. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3478.
(9) Kägi, J. H. R.; Schäffer, A. *Biochemistry* **1988**, *27*, 8509−8515.
(10) Beletskaya, I. P. *Pure Appl. Chem.* **1997**, *69*, 471.
(11) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L., Ed.; John Wiley & Sons: New York, 1997; Vol. 50, pp 1−652.
(12) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(13) Erdik, E. *Tetrahedron* **1992**, *48*, 9577−9648.
(14) Hatanaka, Y.; Hiyama, T. *SynLett* **1991**, 845−853.
(15) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.-i.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958−1969.
(16) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189−3192.
(17) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637−638.
(18) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43−46.
(19) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112* , 7050.
(20) Planas, J. G.; Hirano, M.; Komiya, S. *Chem. Lett.* **1998**, 123.
(21) Jones, W. D.; Dong, L. *J. Am. Chem. Soc.* **1991**, *113*, 559−564.
(22) Shaver, A.; Uhm, H. L.; Singleton, E.; Liles, D. C. *Inorg. Chem.* **1989**, *28*, 847−851.
(23) Osakada, K.; Maeda, M.; Nakamura, Y.; Yamamoto, T.; Yamamoto, A. *J. Chem. Soc., Chem. Commun.* **1986**, 442−443.
(24) Dobrzynski, E. D.; Angelici, R. J. *J. Organomet. Chem.* **1974**, *76*, C53−C55.
(25) Metal-catalyzed cross-coupling between Grignard reagents and aryl and alkenyl sulfides and various dithiane derivatives is known: Fiandanese, V.; Marchese, G.; Naso, F.; Ronzini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 647. Wenkert, E.; Leftin, M.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1984**, 617. Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. Luh, T. Y. *Acc. Chem. Res.* **1991**, *24*, 257.
(26) Bertini, I.; Briganti, F.; Scozzafava, A. In *Handbook of Metal−Ligand Interactions in Biological Fluids*; Berton, G., Ed.; Marcel Dekker: New York−Basel−Hong Kong, 1995; Vol. 1, p 176.
(27) Mathews, A. P.; Walker, S. *J. Biol. Chem.* **1989**, *6*, 299.
(28) Korbashi, P.; Katzhendlers, J.; Saltman, P.; Chevion, M. *J. Biol. Chem.* **1989**, *264*, 8479.
(29) Cheng, C.-C.; Lu, Y.-L. *J. Chem. Soc., Chem. Commun.* **1998**, 253−254.
(30) Hausinger, R. P. In *Biochemistry of Nickel*; Plenum Press: New York, 1993; pp 147−180.
(31) Please refer to the Supporting Information for experimental procedures.
(32) Typical experimental procedure: Under argon in a 50-mL Schlenk tube, a solution of 3-carboxymethylsulfanyl benzoic acid ethyl ester (74 mg, 0.307 mmol) and $NiCl_2(PPh_2Me)_2$ (7.4 mg, 0.014 mmol, 0.05 equiv) in dry, degassed THF (4 mL) was treated with di-*o*-tolylzinc (2.1 mL of a solution prepared from 0.7 mL of 1.0 M $ZnCl_2$ and 1.4 mL of 1.0 M *o*-tolylMgCl). After 14 h at 50 °C, the reaction mixture was allowed to cool and diluted with 20 mL of Et_2O. The organic layer was washed with 20 mL of saturated NH_4Cl and 20 mL of brine, dried ($MgSO_4$), filtered, and concentrated to a viscous yellow oil. Preparative thin-layer chromatography (20% Et_2O/hexanes) provided 2′-methylbiphenyl-3-carboxylic acid ethyl ester (54 mg, 0.226 mmol, 74%) as a colorless oil. Refer to the Supporting Information for details.

10.1021/ja991654e CCC: $18.00
Published on Web 09/28/1999

Scheme 2



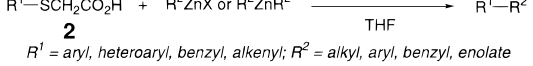
cross-coupling with Me_2Zn) and $(MePPh_2)_2NiCl_2$, a useful surrogate for the Ni hydrocorphinoid that is the actual catalyst in methanogenesis (Scheme 1).[2] Reactions both stoichiometric and catalytic in nickel showed a striking dependence on the sulfonate counterion. *The efficient formation of p-xylene (the product from coupling of Me_2Zn with the anticipated p-tolylnickel intermediate, which formed upon cleavage of the C−S bond by the reduced nickel reagent) was observed only in the presence of a Zn(2+) counterion!* Neither Na^+ nor $MgCl^+$ counterions led to any significant formation of *p*-xylene. These observations are consistent with effective activation of the nickel thiolate by Zn(2+), but not by the other metal ions.

Control experiments demonstrated an important role for the ethanesulfonate motif in this process. Treatment of the simple thioether *p*-tolyl methyl sulfide with 2.2 equiv of Me_2Zn in the presence of 4 mol % $(MePPh_2)_2NiCl_2$ gave only 8% of *p*-xylene after 16 h at 50 °C. The sluggishness of this control reaction is remarkable in contrast to the efficient coupling of *p*-tolyl$S(CH_2)_2$-SO_3ZnCl with Me_2Zn. Similarly, only a trace amount (4%) of 4-methylbenzonitrile was detected from a reaction of 4-(methylthio)benzonitrile with Me_2Zn in the presence of nickel catalyst at 50 °C after 43 h (96% recovered starting material). The importance of the *intramolecular* nature of the zinc effect was established by carrying out the reaction of *p*-tolyl methyl sulfide with Me_2Zn and catalytic $(MePPh_2)_2NiCl_2$ in the presence of 2.2 equiv of $Zn(OAc)_2$. Only 2% of *p*-xylene was detected after 21 h at 50 °C. These collective experiments suggest a significant acceleration of the rate of cross-coupling by an *internal, ligand-bound* zinc ion, which presumably activates the nickel thiolate ligand and thus facilitates transmetalation, as depicted in the bottom figure of Scheme 1. Effective scavenging of the thiolate by Zn(2+) may also be a contributing factor, since the presence of 5 equiv of $(PhS)_2Zn$ had no deleterious effect on the nickel-catalyzed cross-coupling of *S*-(*p*-tolyl)thioethanesulfonate with Me_2Zn. Thiolate scavenging by Zn(2+) may be an important factor in Fukuyama's Pd-catalyzed synthesis of ketones from thioesters and organozinc reagents (boronic acids are ineffective).[16]

To render this process synthetically versatile, the principle of nickel-catalyzed cross-coupling by metal thiolate activation was extended from the coenzyme M system to the more accessible *S*-(substituted)thioglycolate series. *S*-Substituted thioglycolic acids (**2**, Table 1) were readily synthesized as robust crystalline solids with indefinite shelf lifes,[31] and they participated in a general, nickel-catalyzed cross-coupling reaction with different organozinc reagents (2−5% $(MePPh_2)_2NiCl_2$ in THF between ambient temperature and ∼50 °C).[32]

A number of control experiments were conducted with the thioglycolate system. Again, zinc was an essential cofactor for efficient reaction. The high-yielding reaction of dimethylzinc with bromozinc *S*-(*p*-tolyl)thioglycolate, but not with the corresponding *tert*-butyl ester, supports an essential role (activation of the Ni−S bond toward substitution) for an internal, ligand-bound zinc ion in the cross-coupling process. Crystal structure studies support such simple zinc chelates in the solid state.[33−36]

Table 1. Ni-Catalyzed Cross-Coupling Reactions of Thioglycolic Acids with Organozinc Reagents[a]



R[1] = aryl, heteroaryl, benzyl, alkenyl; *R*[2] = alkyl, aryl, benzyl, enolate

entry	thioglycolate, R^1	organozinc, R^2	conditions	yield (%)[b]
1	*p*-tolyl	Me	50 °C, 12 h	80
2	2-methoxyphenyl	*o*-tolyl	50 °C, 20 h	40
3	3-methoxyphenyl	*o*-tolyl	50 °C, 20 h	74
4	2-carbomethoxyphenyl	*o*-tolyl	50 °C, 14 h	100
5	3-carbomethoxyphenyl	*o*-tolyl	50 °C, 14 h	74
6	1-naphthyl	3,4-dimethoxyphenyl	50 °C, 14 h	49
7	2-naphthyl	3,4-dimethoxyphenyl	50 °C, 14 h	70
8	benzyl	Me	50 °C, 18 h	63
9		Et	rt, 10 h	84
10	5,5-dimethylcyclohex-2-enon-3-yl	Me	rt, 43 h	64
11	2-methyl-1,3,4-thiadiazol-5-yl	Et	50 °C, 16 h	93
12	2-pyridyl	*o*-tolyl	50 °C, 14 h	94
13	3-pyridyl	*o*-tolyl	50 °C, 14 h	97
14	4-pyridyl	*o*-tolyl	50 °C, 14 h	100
15	6-methyl-2-pyrimidinyl	*p*-tolyl	50 °C, 8 h	79
16	6-methyl-2-pyrimidinyl	Me	50 °C, 8 h	66
	Organozinc as XZnR			
17	2-carbomethoxyphenyl	$BrZnCH_2Ph$	55 °C, 14 h	76
18	benzoxazol-2-yl	$BrZnCH_2CO_2Et$	50 °C, 20 h	54

[a] Between 2 and 4 equiv of R_2Zn or RZnX was used. Refer to the Supporting Information for details. [b] Yields for entries 1 and 8 were determined by quantitative GLC. All other yields are for isolated products.

Three experiments provided good support for a transmetalation from an external zinc reagent to nickel, rather than from the "internal" organozinc R group that is bound to the thioglycolate or thioethylsulfonate (Scheme 2). Vigorous gas evolution was observed upon treatment of thioglycolic acid **2** (R = 5,5-dimethylcyclohex-2-enon-3-yl) with 1 equiv of Me_2Zn in the presence of catalytic $(MePPh_2)_2NiCl_2$, but no cross-coupling product was produced after 50 h at room temperature. Upon addition of a second equivalent of Me_2Zn to the same reaction mixture, the cross-coupling product R−Me was obtained in good yield. Treatment of the preformed MeZn carboxylate of the same thioglycolate with Et_2Zn in the presence of nickel catalyst gave R−Et as the major product, while reaction of the preformed EtZn carboxylate with Me_2Zn gave R−Me as the major product. These results suggest that the preformed alkylzinc thioglycolates are relatively stable and that an "external" zinc reagent is mainly responsible for the transmetalation process.

In conclusion, *S*-substituted coenzyme M and thioglycolate derivatives were investigated in Ni-catalyzed cross-coupling reactions and a unique role for a Zn(2+) cofactor was identified. It is clear from this and other work[37] that the misconception regarding poisoning of metal catalysts by organosulfur compounds can be misleading and is without full merit.

Acknowledgment. The National Cancer Institute, DHHS, supported this investigation through Grant No. CA40157. We thank Dr. Paul Rieder of Merck Pharmaceutical Co. for his interest in and support of this work.

Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991654E

(33) Ohba, S.; Saito, Y. *Acta Crystallogr., C* **1984**, *40*, 398.
(34) Ogawa, T.; Shimoi, M.; Ouchi, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 126.
(35) Ouchi, A.; Shimoi, M.; Takeuchi, T.; Saito, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2290.
(36) Ogawa, T.; Shimoi, M.; Ouchi, A. *Acta Crystallogr., Sect. B* **1980**, *36*, 3114.
(37) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108−5114.