

B₁₂ Mimicry in a Weak Ligand Environment: Oxidation and Alkylation of Thiolst

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The first examples of alkylation and oxidation of thiols by cobalt in weakly coordinating ligand (MeCN) environment is presented as a mimic to B₁₂-dependent nonenzymatic reaction.

Over three decades ago it was demonstrated that (a) vitamin B₁₂ (Factor B) and aquocobalamin mediate the oxidation of thiols in sulfur containing amino acids at pH ≥ 6¹ and (b) aquocobalamin can be methylated² by MeI-RSH while thiolate ions can be alkylated³ by alkylcobalamin at ambient conditions (eqns. 1, 2).



These and subsequent demonstrations have played a pivotal role in the understanding of B₁₂-dependent bioalkylation reactions and in correlating the likely early origins of B₁₂ vs. the significant role of S-containing compounds in the primitive environment.⁴ In the intervening years several research groups⁵ including ours⁶ have established the far-reaching potential of B₁₂ and its model compounds in mediating various important organic transformations. The success of these investigations were attributed to the delicate stereoelectronic balance arising between equatorial ligands like corrin, glyoxime, bis(salicylidine)ethylenediamine *etc.*; and the axial base ligands such as benzimidazole, pyridine *etc.*⁷ We became interested in assessing the role of the 'naked cobalt' in mediating established nonenzymatic B₁₂ reactions and in this communication wish to report our results on the title reactions catalysed by cobalt(II) chloride in the weakly coordinating ligand environment acetonitrile. This investigation led to novel and synthetically attractive methodologies for even the most deactivated aromatic disulfides, which otherwise require drastic conditions, and for unsymmetrical sulfides.

Thus reactions of alkyl, allyl, benzyl and aromatic thiols (RSH) in the presence of cobalt(II) chloride (10 mol %) in acetonitrile at ambient temperature and under an inert atmosphere affords the corresponding disulfides in >85% isolated yields after 0.5–5 h (Table 1). Reactions in the absence of nitrogen also afford similar results. Cobalt(II) chloride (5 mol%) catalysed reactions of RSH with alkyl, allyl and benzyl iodides in the presence of pyridine (1 equiv.) under constant visible irradiation (500 Watt sunlamp) proceeds to completion in 0.25–5 h giving rise to >87% yields of unsymmetrical sulfides RSR' (Table 2). It is also observed that pyridine inhibits disulfide formation and enhances the rate of alkylation of thiols [footnote (d) Table 2]. In control experiments the effects of various parameters have been studied; most significant is the drastic lowering in reaction rates in the dark and in the presence of air. These results clearly

Table 1 Conversions of sulfides to disulfides (2RSH → RSSR) with CoCl₂ in acetonitrile

R	Isolated yield (%)
Me(CH ₂) ₁₁	95
HOCH ₂ CH ₂	97
AcOCH ₂ CH ₂	97
CH ₂ =CHCH ₂	90
PhCH ₂	88
Ph	95
2,5-Me ₂ C ₆ H ₃	88
4-NO ₂ C ₆ H ₄	99
2,4-(NO ₂) ₂ C ₆ H ₃	95
4-NO ₂ , 5-CH ₂ CO ₂ HC ₆ H ₃	92
4-NO ₂ , 5-CH ₂ CO ₂ MeC ₆ H ₃	89

demonstrate the inherent potential of 'naked cobalt' to mimic the B₁₂-dependent oxidation and alkylation of thiols; even in a weakly coordinating and nonaqueous solvent like acetonitrile.‡

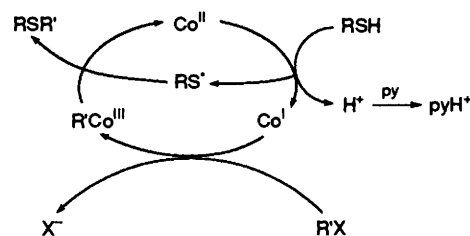
While detailed investigations are being pursued in this laboratory, a working hypotheses for formation of sulfides and disulfides are presented in Schemes 1 and 2. The formation of disulfides in B₁₂-mediated reactions is believed^{9,10} to involve a cobalt(I) species; in which the metal, being in a spin-paired d⁸ configuration, behaves as a strong nucleophile. We are unaware, at present, as to the existence and lifetime of a high-spin cobalt(I) species such as [Co(MeCN)₄Cl₂]⁻. The mediation of such a species is invoked in the mechanism of sulfide (RSR') formation which involves alkylation§ of [Co^I] by R'X followed by homolytic displacement (S_H2) of [Co^{II}] from R'-[Co^{III}] by a thiyl radical RS•. There is substantial literature evidence^{5,6,11} for each of these reactions in pre-formed organocobalt complexes containing equatorial chelating nitrogen and oxygen donor ligands. Further support to the mechanism comes from the experimental observations *i.e.* (a) decreased order of reactivity for X = I > Br > Cl and for R' = Me > allyl > *n*-butyl > benzyl in accordance with the nucleophilic displacement step and (b) drastic reduction in the yields of RSR' in the presence of oxygen¶ as well as in the dark.

The exact mechanism of disulfide formation appears to be more complex in view of the experimental observation that the reaction proceeds either in the presence or absence of oxygen

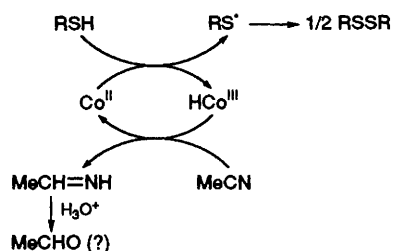
Table 2 Formation of unsymmetrical sulfides RSR' from RSH and R'X by CoCl₂ in acetonitrile^a

R	R'	X	Isolated yield (%)
HOCH ₂ CH ₂ -	PhCH ₂	Br	95
4-NO ₂ C ₆ H ₄	Me	I	85 ^b
	PhCH ₂	Br	88
2,5-Me ₂ C ₆ H ₄	Me	I	87 ^b
Ph	Me	I	90 ^b
	EtCO ₂ CH ₂	Br	97
	CH ₂ =CHCH ₂	Br	92
	PhCHCHCH ₂ OC(=O)CH ₂	Cl	42 ^c
	PhCH ₂	I	96 ^b
		Br	88
			24 ^d
		Cl	57 ^c

^a After photoirradiation for 1 h. ^b Photoirradiation for 15 min. ^c Photoirradiation for 4 h. ^d In the absence of pyridine; other products RSSR (7%), RSH (21%), RBr (40%).



Scheme 1 Alkylation of RSH



and is catalytic with respect to cobalt.† An electrobalanced equation ($2\text{RSH} \rightarrow \text{RSSR}$) needs to incorporate the fate of $\text{H}^\bullet/\text{H}^+$. Evolution of molecular hydrogen has been observed¹³ in the reaction of thiols with cobaloxime(II), an established B_{12} model. However, several attempts by us to detect hydrogen (by GC and chemical trapping) in our system proved to be futile. It is further noticed that the reaction is slowed down in solvents such as THF and DME. This leads us to envisage the participation of the nitrile ligand in the reaction; a parallel has been found in the literature.¹⁴ Corroborating the above facts, a hypothetical mechanism of disulfide formation is presented in Scheme 2.

Although there is a large armoury of reagents available to an organic chemist for thiol to disulfide formation,¹⁵ the synthetic usefulness of the present route lies in its compatibility to a wide variety of functional groups, notably base-sensitive and readily oxidizable functionalities and deactivated aromatic thiols. The significance of the latter can, at once, be viewed from the fact that aerobic oxidation of 4-nitrothiophenol cannot be effected¹⁶ even in NaOH or NaOMe media; only strong oxidizing agents like DEAD can mediate this transformation (EtOH, 8 h, 93%).¹⁷ Similarly, the synthesis of unsymmetrical sulfides provides a good alternative pathway to existing methodologies.¹⁸ Moreover, complete *S*-selectivity is obtained in the alkylation of 2-mercaptoethanol (Table 2). Further scope and mechanistic studies of these reactions are under investigation. In conclusion, the present study calls for a resurging investigation of various other B_{12} -reactions with weakly coordinating ligand environments around the metal.

S. C. thanks UGC for the award of a Junior Research Fellowship. We thank Dr A. V. Rama Rao for encouragement and support.

Received, 17th January 1994; 4/00242C

Footnotes

† IICT communication no. 3229. Presented in part at the Winter School-Cum-Workshop on Organometallic Chemistry, IIT Delhi, India, December 6th–8th, 1993.

‡ Conversion of cysteine to cystine in the presence of a stoichiometric excess of aqueous cobalt(II) [ref. 8(a)] and the formation of PhSSPh in 30% yield in cobalt catalyzed reaction of oxiranes and thiophenol [ref. 8(b)] have been reported previously.

§ An alternate pH-independent mechanism involving $[\text{RSH-Co}^{\text{II}}]\text{-MeI}$ as recently proposed by Pratt *et al.*⁹ is equally probable.

¶ Oxygen insertion into the cobalt–carbon bond under photo-stimulated conditions is well known.¹²

|| We thank one of the referees for this suggestion.

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