A biomimetic methyl transfer from amine to thiol

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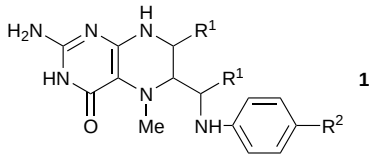
A biomimetic methyl transfer, analogous to a tetrahydrofolate-to-homocystein transfer, is simulated by the reaction of methylammonium salts with arylthiolatocobaloxime; the mechanism proposed is an electron transfer from the cobaloxime to the ammonium ion followed by radical substitution of the methyl group.

Biological methyl transfers often occur *via* methionine, $(HO_2C)(NH_2)CHCH_2CH_2SMe$,[1] and methyl coenzyme-M, $^{-}O_3SCH_2CH_2SMe$.[2] Methyl groups in these cofactors originate from N^5-methyl derivatives of tetrahydropteridine, *i.e.* N^5-methyltetrahydrofolic acid **1a**, (R^1 = H, R^2 = CONH–glutamate)[3] and N^5-methyltetrahydromethanopterin **1b**, [R^1 = Me, R^2 = $CH_2(CHOH)_3CH_2OPO_2HOCH(CO_2H)(CH_2)_2CO_2H$].[4]



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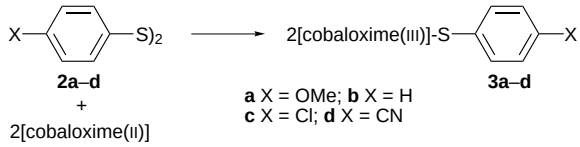
These methyl transfers from amine to sulfur are mediated by coenzyme-B_{12} and its congener,[5] but the participation mode of the cobalt complexes has not been clarified as yet.[6,7] The direct methyl transfer from a methyl ammonium salt to a thiolate anion is known[8] but the cobalt mediated biological methyl transfer is much faster than the direct biological methyl transfer from nitrogen to sulfur.[9]

We report here a biomimetic N–S methyl transfer which is assisted by a cobalt complex. Coenzyme-M was originally isolated in the disulfide form.[10] Thiol and disulfide forms both exist in biological systems because they are interconvertible *via* a simple biochemical redox process. We therefore started the model reaction from a disulfide and bis(dimethylglyoximato)(4-*tert*-butylpyridine)cobalt(II) [cobaloxime(II)]. Thus diaryl disulfides **2** were treated with cobaloxime(II) (0.5 equiv.) to produce arylthiolatocobaloxime(III) **3** in fair yields (Scheme 1).

Reaction† of phenylthiolatocobaloxime(III) **3b** with a trimethylanilinium salt **4** gave methyl sulfide **5** in addition to diphenyl disulfide **6**. The reaction of **3b** with a methylpiperidinium salt **7** yielded the corresponding phenyl sulfide **8** and disulfide **6** (Scheme 2).

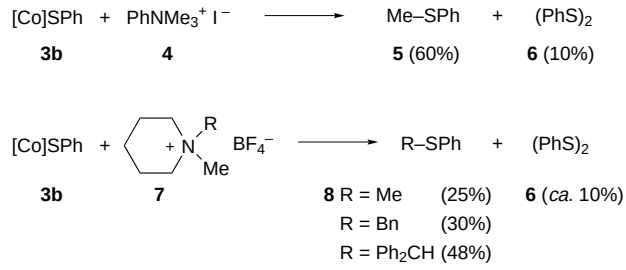
We then tested the effect of a *para*-substituent on the phenyl group of **3** and the benzyl group of ammonium salt **9**. The ammonium salt **9** having an electron-withdrawing substituent gave higher yields of the products **10** (Scheme 3 and Table 1).



2a–d + 2[cobaloxime(II)] → **3a–d**

a X = OMe; **b** X = H
c X = Cl; **d** X = CN

Scheme 1

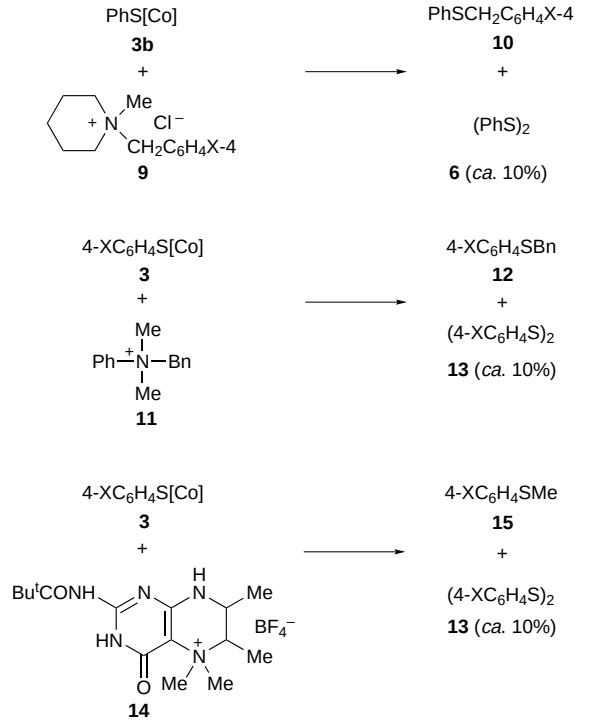


Scheme 2

On the other hand, arylthiolatocobaloxime(III) **3** having an electron-donating substituent showed higher reactivity towards benzyldimethylanilinium salt **11** to yield benzyl sulfide **12** selectively (Scheme 3). Similarly, the reaction with a folate coenzyme model **14**[8] produced methyl sulfide **15**. The time course of the reaction of **3** with benzylammonium salt **11** clearly shows the relationship between the relative rate of product formation and the substituent on **3** (Fig. 1).

The substituent effect envisages nucleophilic attack of the arylthiolate anion at the methyl or benzyl group without the assistance of the cobalt complex, as reported by Hilhorst *et al.*[8] However, the formation of the thiolate anion from arylthiolatocobaloximes **3** must precede the nucleophilic attack, and the electron-withdrawing substituent on **3** is expected to accelerate this heterolysis, contrary to the experimental findings.

If these methyl and benzyl transfer reactions start with the initial homolysis of the sulfur–cobalt bond of **3**,‡ the reactivity



Scheme 3

Table 1 Substituent effect on methyl transfer from an ammonium ion to arylthiolatocobaloximes

Starting material	Ammonium ion	X	Product	Yield (%)
3b	**9a**	OMe	**10**	19
3b	**9b**	H	**10**	30
3b	**9c**	NO_2	**10**	38
3a	**11**	OMe	**12a**	77
3b	**11**	H	**12b**	72
3c	**11**	Cl	**12c**	70
3d	**11**	CN	**12d**	65
3a	**14**	OMe	**15a**	61
3b	**14**	H	**15b**	51
3c	**14**	Cl	**15c**	48
3d	**14**	CN	**15d**	44

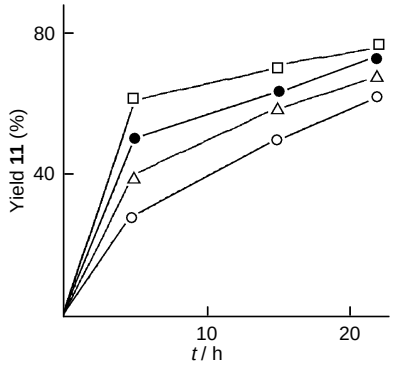


Fig. 1 Time course of the reaction of arylthiolatocobaloximes **3** with benzyldimethylammonium salt **11**: (□) **3a**, (●) **3b**, (△) **3c** and (○) **3d**

of **3** must be inversely proportional to the bond strength and hence the bond distance of the sulfur–cobalt bond. X-Ray crystal analyses[11] determined the Co–S distance of **3** as shown in Table 2. However, this correlation between the oxidation potential (E_{ox}) and the bond distance (d_{Co-S}) breaks down upon moving from **3c** and **3d**. The X-ray analysis unexpectedly showed the Co–S bond in 4-chlorophenylthiolatocobaloxime(III) **3c** to be shorter than the others. As we pointed out earlier,[12] the strength of the cobalt–sulfur bond is a consequence of the donation and back-donation from sulfur to cobalt. Cyclic voltammetry of arylthiolatocobaloximes **3a–d** showed a reversible oxidation wave as shown in Table 2, and the reactivity of the present methyl and arylmethyl group transfer has a trend parallel with the oxidation potential (E_{ox}) of **3a–d**; a lower oxidation potential results in higher reactivity.

The substituent effects on both sides of the reactants suggest a single electron transfer (SET) mechanism. The intermediacy of the arylthiyl radical is supported by the formation of diaryl disulfide in all the reactions. As one of the plausible mechanisms for the methyl transfer, we propose a homolytic substitution by an arylthiyl radical on the methyl group of the zwitterionic species formed by SET [Scheme 4, (*a*)].‡ The migrations of the benzyl and diphenylmethyl groups are considered to proceed *via* a radical coupling mechanism

Table 2 Oxidation potentials and bond lengths of arylthiolatocobaloxime(III) **3**

Compound	X	E_{ox}/V[a]	*d*(Co–S)/Å
3a	OMe	+0.483	2.291
3b	H	+0.542	2.280
3c	Cl	+0.563	2.261
3d	CN	+0.777	2.274[b]

[a] Pt electrodes; voltage *vs.* $Ag/AgNO_3$; **3a–d** (0.2 mmol dm^{-3}), Bu_4NClO_4 (0.1 mol dm^{-3}) in MeCN; scan rate, 0.100 V s^{-1}. The voltages were referenced to ferrocene (E_{ox} = 0.083 V). [b] Mean value of two independent molecules in the asymmetric unit.

(*a*)

$$ArS[Co^{III}] + Me-\overset{+}{N}R_2-Ar \xrightarrow{SET} ArS^{\bullet} + Me-\overset{+}{N}R_2-Ar^{\bullet -}$$

$$\downarrow$$

$$ArS-Me + R_2NAr + [Co^{III}]^+$$

(*b*)

$$ArS[Co^{III}] + R_3\overset{+}{N}-CH_nPh_{3-n} \longrightarrow ArS^{\bullet} + R_3\overset{+}{N}-CH_nPh_{3-n}^{\bullet -} + [Co^{III}]^+$$

$$\downarrow$$

$$ArS-CH_nPh_{3-n} + NR_3 + [Co^{III}]^+ \longleftarrow ArS^{\bullet} + {}^{\bullet}CH_nPh_{3-n} + NR_3 + [Co^{III}]^+$$

Scheme 4

[Scheme 4, (*b*)] because these migrations occur in preference to methyl group migration in spite of greater steric hindrance. In accordance with the SET mechanism, the reactions proceed more efficiently in polar MeCN than in less polar $CHCl_3$ or protic MeOH.

Direct methyl transfer to a thiolate anion[8] *via* an S_N2 mechanism cannot explain the involvement of coenzyme-B_{12} in enzymatic processes. The present experimental findings account for assistance by a cobalt complex and suggest a possible scheme for the enzymatic process, in which N^5-protonated-N^5-methyltetrahydrofolic acid and homocysteinylthiolato–coenzyme B_{12} complex are reaction partners.

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Footnotes and References

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† Reaction conditions were the same for all reactions of **3**. A mixture of **3** (0.2 mmol) and an ammonium salt (0.25 mmol) in MeCN (10 cm^3) was heated to 80 °C for 22 h and then concentrated to 1 cm^3. The concentrated mixture was subjected to Florisil chromatography (hexane–CH_2Cl_2) to remove polar non-volatile materials. The yields of **5** were obtained by GC analyses of the eluate using an internal standard, and those of **8**, **10**, **12** and **15** refer to the isolated products. In most cases the starting materials persisted but the reactions were stopped after 22 h to assess the relative reactivities.

‡ The direct attack of the arylthiyl radical on ammonium salts is ruled out by the lack of reactivity of the arylthiyl radical generated by PhSH–AIBN or photolysis of $(PhS)_2$.

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