shift with 4-vinylpyridine suggests that it is a stronger σ-bonding ligand than pyridine and lack of oxidation shows that it is sterically unfavorable for the vinyl group in the 4 position to π bond with the iron. Intramolecular oxidation would also be unfavorable.

It is interesting to note that the spectral shift indicative of the Fe(II) oxidation is to the blue while for Co(II) oxidation, it is to the red. These shifts have been explained by electronic[22] and steric factors[8,19] and more recently by stereoelectronic factors,[23] but the main assignments of the spectra as to Co(II), Co(III), Fe(II), or Fe(III) remain unchanged.

(22) M. Gouterman, *J. Chem. Phys.*, **30**, 1139 (1959).
(23) A. H. Corwin, A. B. Chivvis, R. W. Poor, D. G. Whitten, and E. W. Baker, *J. Am. Chem. Soc.*, **90**, 6577 (1968).

Reactions of Cobalt(I) Supernucleophiles. The Alkylation of Vitamin B_{12s}, Cobaloximes(I), and Related Compounds[1]

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Abstract: Results of kinetic measurements are presented which indicate that the reactions of alkyl halides with vitamin B_{12s}, cobaloximes(I), and other Co(I) chelates proceed by a classical SN2 mechanism, the Co(I) centers being some of the most powerful nucleophiles known. The evidence for this mechanism providing the dominant reaction pathway is based mainly on the analysis of substrate structural effects on the substitution rates. Although the *absolute* reactivities of the Co(I) nucleophiles are up to 10^7 times greater than those, *e.g.*, of iodide ion, the relative reactivities with various substrates are very similar. Surprisingly, the rates of reactions of the alkyl halides studied are no more sensitive to steric effects of the corrin ligand system than to those of the cobaloxime moiety. Steric hindrance by out-of-plane corrin ligands appear in later stages of the Co–C bond formation process, as evidenced by the instability of secondary alkyl cobalamins in contrast to the corresponding cobaloxime derivatives. The factors influencing the nucleophilicity of the Co(I) chelates, in particular, the effects of axial bases, ligand structure, and possible mechanistic alternatives of the alkylation reactions are discussed. The presence of the coordinated 5,6-dimethylbenzimidazole does not cause a substantial change of the Co(I) nucleophilicity of vitamin B_{12s}.

The reaction of vitamin B_{12s} with alkylating agents is of fundamental biochemical importance and constitutes the most versatile method of synthesizing organocobalamins (eq 1),[3] We have recently[4] presented

$$(Co^{I})^{-} + R\text{-}X \longrightarrow \overset{R}{\underset{|}{(Co)}} + X^{-} \qquad (1)$$

evidence indicating that this reaction (where RX is an alkyl halide) follows an SN2 mechanism involving the powerfully nucleophilic Co(I) derivative of vitamin B_{12} (vitamin B_{12s}). It was also indicated that cobaloxime(I) derivatives react with alkyl halides by the same mechanism, thus providing the basis for a systematic quantitative comparison of the alkylation reactions of vitamin B_{12s} with those of simple, well-defined vitamin B_{12} model compounds. In the present paper we describe the results of detailed kinetic and mechanistic studies on the reactions of vitamin B_{12s} and "cobaloximes" with alkyl halides.

(1) Supported by Grant GB 6174 of the National Science Foundation, and in part, Grant No. 3486/A3 from the Petroleum Research Fund, administered by the American Chemical Society.
(2) National Institutes of Health Postdoctoral Fellow, 1967–1968, Contract No. 7-F2-6M-29, 156-01A1.
(3) E. L. Smith, L. Mervyn, P. W. Muggleton, A. W. Johnson, and N. Shaw, *Ann. N. Y. Acad. Sci.*, **112**, 565 (1964).
(4) G. N. Schrauzer, E. Deutsch, and R. J. Windgassen, *J. Amer. Chem. Soc.*, **90**, 2441 (1968).

The Nature and Reactions of Co(I) Nucleophiles

Vitamin B_{12} and other strong field planar cobalt chelates form spin-paired Co(I) (d^8) derivatives on reduction. The Co(II)/Co(I) reduction potentials of vitamin B_{12} and of several other cobalt chelates have been estimated[4,5] to be in the order of -0.59 to -0.80 V (at equilibrium with 1 atm of H_2 and a platinum catalyst) and were found to depend on the effective coordinating power of the in-plane ligands and the donor–acceptor bonding properties of the axial ligands. The highest occupied orbital in the reduced cobalt species is the weakly antibonding d_{z^2} orbital,[4,6] whose directional characteristics and high charge density are responsible for the high nucleophilicity perpendicular to the plane of the molecule. The occurrence of the macrocyclic "loop" in the molecule of vitamin B_{12} implies that the coordination of the Co(I) ion by the axial base (*i.e.*, 5,6-dimethylbenzimidazole) could serve the specific purpose of increasing the nucleophilicity of the Co(I) ion. To answer this question we have therefore studied the effect of axial bases on the reactivity of the Co(I) nucleophiles. The alkylation reac-

(5) G. N. Schrauzer, J. W. Sibert, and R. J. Windgassen, *ibid.*, **90**, 6681 (1968).
(6) G. N. Schrauzer, R. J. Windgassen, and J. Kohnle, *Chem. Ber.*, **98**, 3324 (1965).

Table I. Rates of Reaction of Tributylphosphine–Cobaloxime$_s$ + Alkyl Halides[a]

Alkyl halide	T, °C[b]	k^{2nd}, M^{-1} sec^{-1}	Alkyl halide	T, °C[b]	k^{2nd}, M^{-1} sec^{-1}
CH_3Cl	Amb	8.5×10^{-1}	CH_3Br[c]	25.0	2.2×10^{2}
CH_3CH_2Cl	Amb	9.0×10^{-3}	CH_3CH_2Br	Amb	1.6
$CH_3CH_2CH_2Cl$	Amb	6.3×10^{-3}	$CH_3CH_2CH_2Br$	Amb	1.5
$CH_3CH_2CH_2Cl$	48	3.6×10^{-2}	$(CH_3)_2CHBr$	Amb	1.1×10^{-1}
$CH_3(CH_2)_3Cl$	Amb	7.3×10^{-3}	$(CH_3)_2CHCH_2Br$	Amb	2.8×10^{-1}
$CH_3(CH_2)_4Cl$	Amb	6.7×10^{-3}	$(CH_3)_3CCH_2Br$	Amb	9.6×10^{-4}
$CH_3(CH_2)_5Cl$	Amb	6.3×10^{-3}	$(CH_3)_3CCH_2Br$	48	7.7×10^{-3}
$(CH_3)_2CHCl$	Amb	3.2×10^{-4}	$(CH_3)_2CHCH_2CH_2Br$	Amb	1.1
$(CH_3)_2CHCl$	48	4.0×10^{-3}	$CH_3CH_2CH_2CH(CH_3)Br$	Amb	3.2×10^{-2}
$(CH_3)_2CHCH_2Cl$	Amb	7.7×10^{-4}	c-C_3H_5Br	Amb	1.0×10^{-5}
$(CH_3)_2CHCH_2Cl$	48	5.9×10^{-3}	c-C_4H_7Br	Amb	1.1×10^{-1}
$NCCH_2Cl$	Amb	1.6×10^{3}	c-C_5H_9Br	Amb	2.0×10^{-1}
CH_3OCH_2Cl	Amb	$>1.0 \times 10^{4}$	c-$C_6H_{11}Br$	Amb	1.2×10^{-2}
$H_2NC(O)CH_2Cl$	25.0	1.4×10^{1}	c-$C_7H_{13}Br$	Amb	5.4×10^{-2}
$H_2C{=}CHCH(CH_3)Cl$	25.0	6.0	c-$C_8H_{15}Br$	Amb	3.0×10^{-2}
$C_6H_5CH_2Cl$[c]	25.0	4.4×10^{2}	$HOCH_2CH_2Br$	Amb	8.9×10^{-1}
$C_6H_5CH_2Cl$[c]	33.0	5.1×10^{2}	$Cl(CH_2)_4Br$	Amb	5.3
$C_6H_5CH_2Cl$[c]	13.0	2.3×10^{2}	$Br(CH_2)_4Br$	Amb	3.2[e]
p-t-$C_4H_9C_6H_4CH_2Cl$[c]	25.0	7.5×10^{2}	$^-OOCCH_2Br$	Amb	3.4
p-t-$C_4H_9C_6H_4CH_2Cl$[c]	19.0	4.2×10^{2}	$C_6H_5CH_2Br$[c]	25.0	1.9×10^{4}
p-t-$C_4H_9C_6H_4CH_2Cl$[c]	13.0	2.3×10^{2}	CH_3I[c]	25.0	2.3×10^{3}
$(C_6H_5)_2CHCl$	Amb	1.0	$(CH_3)_2CHI$	Amb	3.2
$C_6H_5CH(CH_3)Cl$	Amb	2.3	$(CH_3)_2CHCH_2I$	Amb	8.4
1-$C_{10}H_7CH_2Cl$[d]	Amb	1.4×10^{3}	$CH_3CH_2CH(CH_3)I$	Amb	8.2×10^{-1}
			$^-OOCCH_2I$[c]	25.0	2.5×10^{1}

[a] In methanol, 0.10 F in NaOH. [b] Amb indicates reaction was done at ambient temperature, 25 ± 2°. [c] Measured by stopped-flow technique. [d] 1-chloromethylnaphthalene. [e] Rate constant corrected for statistical factor of 2.

tions of these highly reactive reduced cobalt species will be described first.

The Mechanism of Alkylation

The occurrence of characteristic low-energy d–d transitions in the spectra of all Co(I) chelates[6,7] (their colors are blue to blue green, depending on the axial components) was utilized as a convenient indicator of the concentration changes of the Co(I) species in the rate studies. All alkylation reactions of the type defined by eq 1 follow a simple second-order rate law, $-d[Co^I]/dt = k^{2nd}(RX)(Co^I)$, over a wide concentration of RX relative to (Co^I). Rate constants of cobaloxime(I) and of vitamin B_{12s} alkylation reactions are summarized in Tables I and II. The reactions of the Co(I) nucleophiles with primary alkylating agents are known to yield *n*-alkylcobalt complexes in often quantitative yields, whose chemical and physical properties are well documented.[8,9] Cobaloximes(I) also react with secondary alkyl halides forming *sec*-alkylcobaloximes, but most tertiary alkyl halides react without allowing the isolation of *t*-alkylcobaloximes. Thus, *t*-butyl chloride with pyridine–cobaloxime(I), yields cobaloxime(II) and isobutylene. The instability of *t*-alkylcobaloximes is undoubtedly due to steric hindrance, which is even more dominant in the cobalamins. Thus *sec*-alkylcobalamins (and -cobinamides) are quite unstable.[10,11]

Table II. Rates of Reaction of Vitamin B_{12s} + Alkyl Halides[a]

Alkyl halide	T, °C[b]	k^{2nd}, M^{-1} sec^{-1}
CH_3Cl	Amb	5.0
CH_3CH_2Cl	Amb	4.7×10^{-2}
$CH_3CH_2CH_2Cl$	Amb	3.7×10^{-2}
$CH_3(CH_2)_3Cl$	Amb	2.8×10^{-2}
$CH_3(CH_2)_4Cl$	Amb	2.5×10^{-2}
$CH_3(CH_2)_5Cl$	Amb	2.6×10^{-2}
$(CH_3)_2CHCH_2Cl$	Amb	4.1×10^{-3}
CH_3Br[c]	25.0	1.6×10^{3}
CH_3CH_2Br	Amb	3.1×10^{1}
$CH_3CH_2CH_2Br$	Amb	1.4×10^{1}
$(CH_3)_2CHBr$	Amb	1.8
$(CH_3)_2CHCH_2Br$	Amb	2.1
$(CH_3)_3CCH_2Br$	Amb	9.6×10^{-2}
$(CH_3)_2CHCH_2CH_2Br$	Amb	5.2
CH_3I[c]	25.0	3.4×10^{4}
CH_3I[c]	15.7	3.0×10^{4}
$(CH_3)_2CHI$	Amb	2.3×10^{2}
$CH_3CH_2CH_2Cl$[d]	30	3.5×10^{-2}

[a] In methanol, 0.10 F in NaOH. [b] Amb indicates reaction was done at ambient temperature, 25 ± 2°. [c] Measured by stopped-flow techniques. [d] Rate of reaction with reduced cyano(aquo)-cobinamide (factor B_s).

The steric arguments concerning the substituents apply mainly to alkyl groups on the α-carbon atom. Smaller substituents, *i.e.*, chlorine or cyanide, are permissible as evidenced by the existence of β-cyanoisopropylcobaloxime[12] or of chloromethylcobalamin[13] and other cobaloxime derivatives.[14]

The Mechanism of Alkylation

The observed second-order rate law eliminates the possibility of a SN1 mechanism operative in the reactions studied, but does not discriminate between a

(7) G. N. Schrauzer, *Ann. N. Y. Acad. Sci.*, in press.

(8) See, for example, (a) E. L. Smith, "Vitamin B_{12}," 3rd ed, Methuen and Co., New York, N. Y., 1965; (b) K. Bernhauer, O. Müller, and F. Wagner, *Angew. Chem.*, 75, 1145 (1964); *Angew. Chem. Int. Ed. Engl.*, 3, 200 (1964); (c) R. Bonnett, *Chem. Rev.*, 63, 573 (1963), and references cited therein.

(9) G. N. Schrauzer, *Accounts Chem. Res.*, 1, 97 (1968), and references cited therein.

(10) Isopropyl*cobinamide* is said to be very unstable, decomposing even on storage under nitrogen.[11] Isopropylcobalamin cannot be isolated (see Experimental Section).

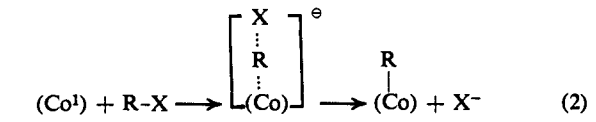
(11) R. A. Firth, H. A. O. Hill, B. E. Mann, J. M. Pratt, R. G. Thorp, and R. J. P. Williams, *J. Chem. Soc., A*, 2419 (1968).

(12) G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, 89, 1999 (1967).

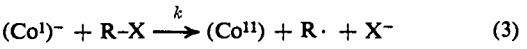
(13) J. M. Wood, F. S. Kennedy, and R. S. Wolfe, *Biochemistry*, 7, 1707 (1968).

(14) Unpublished work, with L. P. Lee and J. W. Sibert.

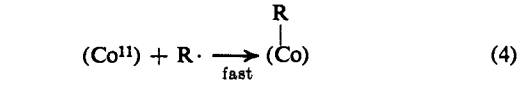
classical SN2 mechanism (eq 2) and an electron-transfer process involving free radicals as intermediates (eq 3 and 4). Such a free-radical mechanism, though less likely in the systems involving the Co(I) nucleophiles, must be considered as an alternative possibility since it has been shown[15,16] that the reaction of pentacyanocobalt(II) with alkyl halides is likely to proceed in the analogous fashion (eq 5 and 6). Furthermore, it is probable that in aprotic solvents cobaloximes(II) react with benzyl bromide by this mechanism.[17] Electron transfer as the first step in nucleophilic substitution is expected to become important in all cases in which stable free-radical species can be formed by one-electron-transfer reactions. Evidence for organic reactions of the type symbolized by eq 7 and 8 has recently been compiled by Bilevitch, *et al.*[18] A more detailed consideration of the mechanism of cobalt alkylation reactions thus appeared to be warranted. An SN2 mechanism can be conclusively demonstrated by showing that reaction at a nucleophilic center gives a product with complete inversion of configuration. Initial studies of the reaction of asymmetric substrates with cobaloximes(I) indeed indicate that this mechanistic criterion is fulfilled.[19] However, even without the results of these experiments, the analysis of the data reported in Tables I and II indicate very strongly that the reactions of vitamin B_{12s} and of cobaloximes(I) with alkyl halides proceed by a classical SN2 mechanism, and reduced cobalt centers behaving as exceptionally strong nucleophiles. The reasoning that leads to this conclusion is based on a comparison of relative rates observed in this work with those of known SN2 and free-radical processes.



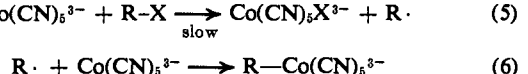
$$(Co^{I}) + R\text{-}X \longrightarrow \left[X \cdots R \cdots (Co) \right]^{\ominus} \longrightarrow \overset{R}{|}(Co) + X^- \qquad (2)$$



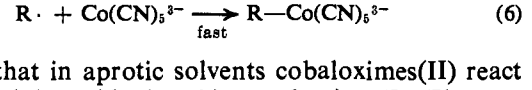
$$(Co^{I})^- + R\text{-}X \xrightarrow{k} (Co^{II}) + R\cdot + X^- \qquad (3)$$



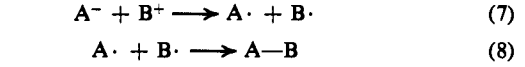
$$(Co^{II}) + R\cdot \xrightarrow[\text{fast}]{} \overset{R}{|}(Co) \qquad (4)$$



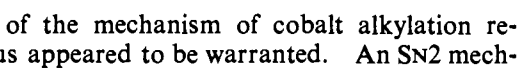
$$Co(CN)_5^{3-} + R\text{-}X \xrightarrow[\text{slow}]{} Co(CN)_5X^{3-} + R\cdot \qquad (5)$$



$$R\cdot + Co(CN)_5^{3-} \xrightarrow[\text{fast}]{} R\text{—}Co(CN)_5^{3-} \qquad (6)$$



$$A^- + B^+ \longrightarrow A\cdot + B\cdot \qquad (7)$$



$$A\cdot + B\cdot \longrightarrow A\text{—}B \qquad (8)$$

(a) It is well established that for both SN2 and free-radical displacements of alkyl halides the order of leaving group effectiveness is I > Br > Cl,[20,21] and that the rate of displacement roughly varies as the inverse of the C–X bond strength. Streitwieser[20] has tabulated relative rates of typical organic SN2 reactions and calculated average values of k_{Cl}/k_{Br} and k_I/k_{Br} as 0.02 and 3, respectively. Table III shows that the Co(I) reactions are in general about the factor 10 more sensitive to leaving group effects than a typical SN2 reaction. The range of observed rates overlaps with the range tabulated by Streitwieser, for SN2 reactions, implying that a similar mechanism is operative. The alkylation of pentacyanocobaltate(II) ion with alkyl halides is 100 times more sensitive to the nature of the leaving group than are the Co(I) reactions, suggesting that these occur by a different (*i.e.*, free-radical) mechanism.[15,16]

Table III. Relative Rates of Alkyl Halide Reactions[a]

Reaction	R	Cl	Br	I
Tributylphosphine[b]–cobaloxime$_s$ + RX (25°, methanol)	CH_3	0.0039	1.0	10
	CH_3CH_2	0.0057	1.0	
	$CH_3CH_2CH_2$	0.0042	1.0	
	$(CH_3)_2CH$	0.0029	1.0	29
	$(CH_3)_2CHCH_2$	0.0028	1.0	30
	$C_6H_5CH_2$	0.023	1.0	
	$^-OOCCH_2$		1.0	7.4
Vitamin B_{12s} + RX[b] (25°, methanol)	CH_3	0.0031	1.0	21
	CH_3CH_2	0.0015	1.0	
	$CH_3CH_2CH_2$	0.0026	1.0	
	$(CH_3)_2CHCH_2$	0.0019	1.0	
$Co(CN)_5^{3-}$ + RX[c] (25°, water)	$^-OOCCH_2$	0.00071	1.0	3200
	$H_3COOCCH_2$	0.000029	1.0	2600
	$H_2NC(O)CH_2$	0.000037	1.0	1800
	$^-OOCCH_2CH_2$		1.0	680

[a] Rates relative to alkyl bromide. [b] This work. [c] J. Halpern and J. P. Maher, *J. Amer. Chem. Soc.*, 87, 5361 (1965).

(b) From tabulated[22] data on relative reaction rates of alkyl halides it is furthermore known that the order of reactivity of differently substituted substrates undergoing SN2 displacements is fairly constant and independent of the nature of the leaving group or attacking nucleophile. For example, adding methyl groups at the α- or β-carbon atom of the substrate has always the same effect on the relative displacement rates, independent of the nature of the leaving group or the nucleophile. Average relative rates, as compiled by Streitwieser, give a measure of relative average reactivity and are shown together with the relative reaction rates of vitamin B_{12s} and of tributylphosphine–cobaloxime(I) in Figure 1. It is immediately seen that the three sets of data give the same rate profile.

Substitution of hydrogen by one or two methyl groups on the carbon, or substitution of two or three methyl groups on the α carbon, produces a large decrease in rate, but rates are unaffected by lengthening of a linear alkyl chain. This similar sensitivity to structural features of alkyl-type substrates clearly indicates a classical SN2 mechanism. If a free-radical mechanism were operative, secondary alkyl halides would be expected to react faster than primary ones,[23] whereas *n*-propyl, isobutyl, and neopentyl halides would all react at about the same rate,[24] thus producing an entirely different profile from that shown in Figure 1.

(c) The relative rate data for the reaction of various substituted alkyl halides with tributylphosphine–cobaloxime(I) shown in Table IV, lead to the following generalizations. (1) Groups that are not directly

(15) J. Halpern and J. P. Maher, *J. Amer. Chem. Soc.*, 87, 5361 (1965).
(16) J. Kwiatek and J. K. Seyler, *J. Organometal. Chem.*, 3, 421 (1965).
(17) P. W. Schneider, P. F. Phelan, and J. Halpern, *J. Amer. Chem. Soc.*, 91, 77 (1969).
(18) K. A. Bilevitch, N. N. Pubnov, and O. Yu. Okhlobystin, *Tetrahedron Lett.*, 3465 (1968).
(19) Unpublished experiments with L. P. Lee and J. W. Sibert.
(20) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 29–31.
(21) A. F. Trotman-Dickenson, "Free Radicals," Methuen and Co., London, 1959.
(22) Reference 20, pp 12–13.
(23) E. Warhurst, *Quart. Rev.* (London), 5, 44 (1951).
(24) Reference 21, p 82.

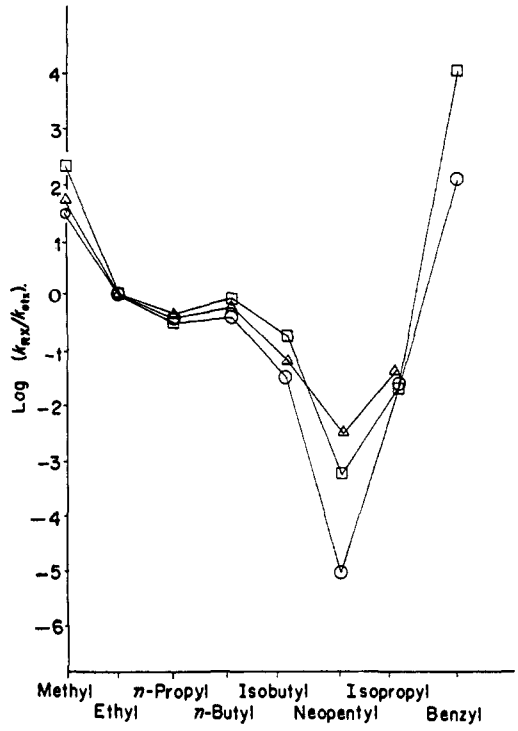


Figure 1. Rate profile for SN2 reactions on alkyl halide substrates: O, average relative rate data tabulated in ref 20, pp 12-13, for a variety of SN2 reactions in different solvents at different temperatures; □, cobaloxime$_a$ + RX; Δ, B_{12a} + RX.

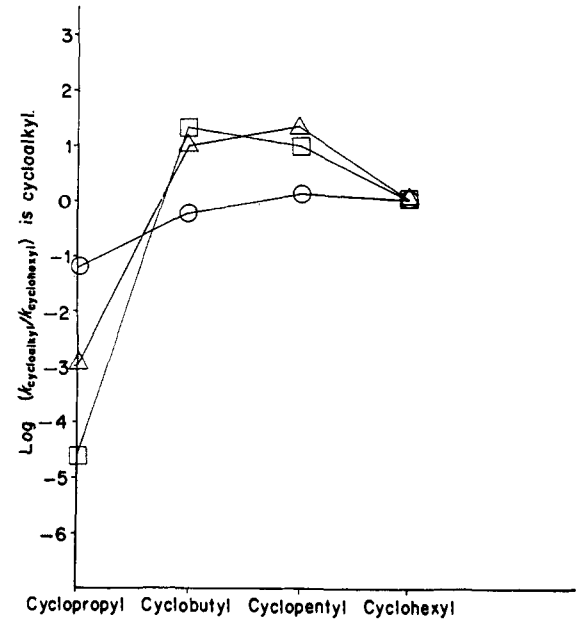


Figure 2. Rate profiles for SN2 and free-radical reactions on cycloalkyl substances: O, average relative rates for cycloalkyl free-radical reactions (values calculated from data in Table V); □, average relative rates for cycloalkyl SN2 reactions (values calculated from data in Table V); Δ, relative rates of cobaloxime$_a$ + cycloalkyl bromide reactions.

bonded to the α-carbon atom do not significantly affect the rate. (2) Groups that are capable of delocalizing and stabilizing the charge developed in the transition state enhance observed rates considerably. These groups include NC, H_3CO, C_6H_5, $C_{10}H_7$, NH_2C-(O), and ^-OOC. In the last case mentioned the effect is overridden by a rate decrease caused by the electrostatic repulsion due to the negative charges on both substrate and nucleophile. (3) Allylic double bonds cause a rate enhancement. (4) While one phenyl group increases the observed rate, two phenyl groups provide enough steric hindrance in the transition state to cause chlorodiphenylmethane to react at 1% the rate of benzyl chloride. The observation that 1-chloroethylbenzene reacts slightly faster than chlorodiphenylmethane supports the conclusion that the second phenyl group provides almost no delocalization in the transition state. (5) A naphthyl group is slightly more effective than a phenyl group in stabilizing the transition state. (6) The observed rate is not very sensitive to alkyl substitution in the *para* position of benzyl compounds.

Table IV. Relative Rates of Reaction of Tributylphosphine–Cobaloxime$_a$ with Substituted Alkyl Halides[d]

Alkyl group	Rel rate[a]	Log rel rate
$BrCH_2CH_2CH_2CH_2$	2.0	0.30
$ClCH_2CH_2CH_2CH_2$	3.3	0.52
$HOCH_2CH_2$	0.56	−0.25
$NCCH_2$	1.8×10^5	5.22
H_3COCH_2	$>1.1 \times 10^6$	>6.05
$H_2NC(O)CH_2$	1.9×10^3	3.19
$^-OOCCH_2$	2.1	0.33
$C_6H_5CH_2$	4.9×10^4	4.69
$C_6H_5CH_2$	4.9×10^4	4.69
p-t-$C_4H_9C_6H_4CH_2$	8.3×10^4	4.92
$(C_6H_5)_2CH$	1.1×10^2	2.05
$C_6H_5CH(CH_3)$	2.5×10^2	2.41
1-$C_{10}H_7CH_2$[c]	1.6×10^5	5.19
$H_2C{=}CHCH(CH_3)$	1.9×10^4[b]	4.27
$C_6H_5CH(CH_3)$	7.2×10^3[b]	3.86

[a] Rates relative to ethyl compound except for last two entries. [b] Rates relative to isopropyl compound. [c] 1-Chloromethylnaphthalene. [d] 25°, 0.1 *F* NaOH in methanol.

(d) Table V shows that when cycloalkyl halides react by a free-radical mechanism, under a wide variety of conditions, the relative reactivities of the halides remain roughly constant. The variation of reactivity with ring size is readily explainable by the I strain theory.[28] When the average (free-radical) reactivities are plotted *vs.* ring size a characteristic pattern emerges (see Figure 2) which is significantly different from the reac-

While all these observations are completely consistent with an SN2 mechanism, agreeing with substituent effects observed in classical SN2 reactions,[25,26] they are not necessarily inconsistent with a free-radical mechanism. For example, the rates of both SN2 and free-radical reactions are increased by allyl groups, methoxy groups, etc., and both are relatively insensitive to *para* substituents in benzyl compounds.[15,27] However, in general, free-radical reactions are if anything more sensitive to substituents on the α-carbon[15] than are SN2 reactions,[25] and since the cobaloxime(I) reactions are if anything more sensitive to α substituents than the reactions tabulated by Streitwieser, it is reasonable to conclude that these cobaloxime(I) displacements proceed *via* a genuine SN2 mechanism.

(25) Reference 20, pp 13-29.
(26) C. A. Bunton, "Reaction Mechanisms in Organic Chemistry," Vol. 1, Elsevier Publishing Co., Amsterdam, 1963, pp 33-38.
(27) J. K. Kochi and D. D. Davis, *Nature*, 202, 690 (1964).
(28) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Amer. Chem. Soc.*, 73, 212 (1951).

Table V. Relative Rates of Cycloalkyl Reactions[a]

Reaction	T, °C	Conditions	c-C_3	c-C_4	c-C_5	c-C_6	Ref
		Free Radical					
$Na + RBr = NaBr + R\cdot$	247	Gas phase	0.027	0.63	2.2	1.0	*i*
$CH_3\cdot + RH = CH_4 + R\cdot$	182	Gas phase	0.12	0.83	1.4	1.0[b]	*j*
$H\cdot + RH = H_2 + R\cdot$	25	Gas phase	0.083	0.50	2.7	1.0[b]	*j*
$CD_3\cdot + RH = CHD_3 + R\cdot$	327	Gas phase	0.021	0.36	0.84	1.0[b,c]	*k*
$Cl\cdot + RH = HCl + R\cdot$	68	CCl_4 solution	0.10	0.67	0.84	1.0[b]	*l*
$Cl\cdot + RH = HCl + R\cdot$	0	CCl_4 solution	0.048	0.84	0.95	1.0[b]	*l*
$Cl\cdot + RH = HCl + R\cdot$	68	C_6H_6 solution	0.14	0.75		1.0[b]	*l*
$(CH_3)_3CO\cdot + RH = (CH_3)_3COH + R\cdot$	68	$CFCl_3$ solution	0.027	0.71[d]	1.04[e]	1.0[b]	*l*
$(CH_3)_3CO\cdot + RH = (CH_3)_3COH + R\cdot$	0	$CFCl_3$ solution	0.010	0.51	0.89[e]	1.0[b]	*l*
$RCOOOOCR = 2CO_2 + 2R\cdot$	70	CCl_4 solution	0.013	0.12	0.53	1.0	*m*
		SN2					
$HOAc + ROTs = HOTs + ROAc$	60	HOAc solution	0.00002	14	16	1.0	*n*
$H_2O + RCl = HCl + ROH$	95	50% EtOH-H_2O	*f*	41	15	1.0	*n*
$I^- + RBr = Br^- + RI$	90	Acetone solution	*g*	1.4	5.7[h]	1.0	*n*
$(Co^I)^- + RBr = Br^- + (Co)$-R	25	Methanol solution	0.0009	9.8	22	1.0	This work

[a] Rates relative to cyclohexyl compound. [b] Rates calculated per hydrogen atom. [c] Rates calculated from observed activation parameters. [d] Ratio determined at 40°. [e] CCl_4 solution. [f] No measurable reaction under these conditions, although some solvolysis took place at 200°. [g] No measurable reaction under these conditions. In addition, cyclopropyl chloride (0.02 F) was found to give no measurable reaction with 0.01 *F* potassium iodide in acetone in 8 hr at 200°. [h] c-C_5 rate determined at 60.5°. [i] N. J. Friswell, B. G. Gowenlock, and K. E. Thomas, *J. Chem. Soc.*, 6323 (1965). [j] Reference 21, p 85. [k] A. S. Gordon and S. R. Smith, *J. Phys. Chem.*, **66**, 521 (1962). [l] C. Walling and P. S. Fredericks, *J. Amer. Chem. Soc.*, **81**, 1485 (1959). [m] H. Hart and D. P. Wyman, *ibid.*, **81**, 4891 (1959). [n] J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5034 (1951).

tivity patterns of all SN2 reactions, although it still to some extent follows the trends predicted by the I strain theory. This difference is most obvious in the cyclopropyl reactions where I strain affects the attainment of the SN2 transition state much more than in the free-radical reaction.

The relative rates of the cycloalkyl bromide reactions with cobaloxime$_s$ shown in Figure 2 are nevertheless typical of an SN2, and not of a free-radical reaction.

(e) Initial determinations of the activation parameters for the alkylation of cobalt(I) species with alkyl halides indicate that the observed rate differences are largely due to variations in $\Delta H^{\ddagger}$, and that in general $\Delta S^{\ddagger}$ is large and negative (−20 to −30 eu). A negative entropy change implies increased order in the transition state, and the large change observed in these reactions probably reflects the increased coordination number of the metal ion in the activated complex. This is consistent with the cobalt center being pentacoordinate in the starting material and hexacoordinate in the product and hence is in better agreement with a one-step SN2 mechanism (eq 2) rather than the two-step radical mechanism (eq 3), for which one would have to assume that the coordination of the metal ion is not increased in the rate-determining step.

(f) The data in Table VI show that there is no large solvent dependence for the alkylation of cobalt(I) species by alkyl halides. While this is definitely consistent with a SN2 reaction between an ion and a neutral molecule,[29] it is not clear whether or not a different effect would be expected in a free-radical mechanism. The higher rates in water as compared to in methanol may be due to water or OH^- acting as an axial base; this effect will be discussed in the next section.

Table VI. Solvent Dependence of Some Cobalt(I) + Alkyl Halide Reactions

Reaction[a]	Solvent	Rel rate[b]
$B_{12s} + CH_3Cl$	Methanol	1.0
$B_{12s} + CH_3Cl$	Water	6.2
$(n\text{-}C_4H_9)_3P$-cobaloxime$_s$ + CH_3CH_2Br	Methanol	1.0
$(n\text{-}C_4H_9)_3P$-cobaloxime$_s$ + CH_3CH_2Br	50% methanol-water	6.6
$(n\text{-}C_4H_9)_3P$-cobaloxime$_s$ + CH_3CH_2Br	Ethanol	2.1
$(n\text{-}C_4H_9)_3P$-cobaloxime$_s$ + CH_3CH_2Br	1-Propanol	1.4

[a] 25°, 0.1 *F* NaOH. [b] Rate relative to reaction in methanol.

Effects of Axial Bases

Cobaloximes(I) are known to form 1:1 adducts with a variety of Lewis bases.[6] The dominant form of vitamin B_{12} is probably pentacoordinated or at least in equilibrium with pentacoordinated species due to the presence of the 5,6-dimethylbenzimidazole sugar phosphate "loop." The axial coordination of a strong electron donor to the planar tetracoordinated Co(I) ion is expected to increase the antibonding character of the $3d_{z^2}$ orbital and could therefore have the effect of increasing the nucleophilicity. On the other hand, if the axial ligand possesses low-lying unoccupied π or d orbitals, the nucleophilicity of the Co(I) ion may decrease due to electron back-donation to the axial ligand *via* the d_{xz},d_{yz} orbitals. The data in Table VII show that both effects are observed, the rate of reaction of cobaloxime(I) with ethyl bromide increasing with base strength, and decreasing with the back-bonding ability, of the added axial base.

The interpretation of the rates given in Table VII is complicated due to the dependence of the rates on the concentration of added ligand. A satisfactory description of at least some of the phenomena observed is possible by considering the equilibria between the original reduced cobalt species and the 1:1 base adduct, *i.e.*, eq 9 (the 1:1 base adduct is assumed to be the only adduct formed). Assuming that equilibrium 9 is

(29) Reference 26, p 112.

Table VII. Effect of Axial Bases on the Reaction of Cobaloximes(I) with CH_3CH_2Br (25°, 0.1 F NaOH in Methanol)

Axial base added	(base)/(cobaloxime)	$k_{obsd}{}^{2nd}$, M^{-1} sec^{-1}
None[a]		10
Water	1100	11
Pyridine	500	5.9
Pyridine	20	7.2
Pyridine	10	7.8
Pyridine	5	8.3
2-Picoline	500	6.0
2-Picoline	10	12
2,6-Lutidine	500	4.8
2,6-Lutidine	10	11
Aniline	10	5.9
Cyclohexylamine	500	10
Cyclohexylamine	10	8.1
4-Cyanopyridine	500	5.3
4-Cyanopyridine	10	5.4
Triphenylphosphine	10	0.30
Triphenylarsine	10	1.3
Triphenylstibine	10	1.9
Tributylphosphine	10	1.7
Tributylphosphine	1	1.6
	0.5	2[b]
Dimethyl sulfide	500	3.5
Dimethyl sulfide	10	3.0
Cyanide ion	1	11
Cyclohexylisocyanide	10	0.54

[a] Conditions with no axial base added: (Co) = 7×10^{-4} F; (Cl) = 2(Co); (H_2O) = 320(Co); (OH^-) = 0.1 F. [b] Two rates are observed—one fast with k^{2nd} about 10 M^{-1} sec^{-1} and one slow with k^{2nd} as reported here.

attained rapidly compared to the alkylation of $(Co^I)^-$ and B-$(Co^I)^-$, the second-order rate constant, k^1, of the alkylation reaction is given by eq 11. From eq 11

$$B + (Co^I)^- \underset{}{\overset{K}{\rightleftharpoons}} B\text{-}(Co^I)^- \quad (9)$$

$$K = \frac{[B\text{-}(Co^I)^-]}{[B][(Co^I)^-]} \quad (10)$$

$$k^1 = \frac{k_1 + k_2K[B]}{1 + K[B]} \quad (11)$$

the dependence of the observed specific rates on added base can be calculated if B is pyridine and assuming that $k_1 = 9.6$, $k_2 = 5.9$ mol l.$^{-1}$ sec^{-1}, respectively, and K-(pyridine) is 150. The agreement between the calculated and observed rate constants, k^1, at various concentrations of pyridine is satisfactory (Table VIII).

Table VIII. Calculated and Observed Alkylation Rates of Cobaloxime(I) with CH_3CH_2Br (k^{obsd} from Table VII)

	$k^{calcd} = [9.6 + (5.9)(150)(\text{pyridine})]/[1 + 150(\text{pyridine})]$	
(Pyridine), M	k^{obsd}, M^{-1} sec^{-1}	k^{calcd}, M^{-1} sec^{-1}
0.0035	8.3	8.3
0.0070	7.8	7.7
0.0140	7.2	7.1
0.350	5.9	5.9

Using tributylphosphine as the added base the condition that equilibrium is established rapidly is no longer fulfilled. It appears that the formation of the base adduct is in fact slow as compared to the alkylation and that $k_1 > k_2$. Thus, if 0.5 mol of tributylphosphine is added per mole of Co(I) derivative present, a rate plot is obtained which shows two straight line portions. From these k_1 and k_2 are calculated to about 10 and 2 mol l.$^{-1}$ sec^{-1}, respectively (each for 50% of the reaction). If tributylphosphine is used in equimolar amounts, the observed rate corresponds to that given by the magnitude of k_2.

Intermediate situations where equilibrium is attained at a rate comparable to the rate of disappearance of cobalt(I) species undoubtedly occur, but need not be discussed here. However, it should be pointed out that by varying the concentration and nature of RX the rate of consumption of cobalt(I) can be varied over a wide range and thus different equilibria can be studied at one or both of the limits described above.

Below is a list of rate constants observed at a constant concentration of added axial base (tenfold excess over cobaloxime) in order of increasing effectiveness in reducing the nucleophilic character of the Co(I) center (rate constants in mol l.$^{-1}$ sec^{-1} are noted in parentheses: the estimated average error in the rate constants is ±8%): no base (OH^-?) (10); 2.6-lutidine (11); 2-picoline (11); cyclohexylamine (8.1); pyridine (7.8); aniline (5.9); 4-cyanopyridine (5.4); dimethyl sulfide (3.0); triphenylstibine (1.9); tributylphosphine (1.7); triphenylarsine (1.3); cyclohexylisocyanide (0.54); triphenylphosphine (0.30).

The observed sequence corresponds approximately to one of decreasing donor strength and increasing acceptor character of the base components added. However, the position of some of the ligands is also determined by the magnitude of the equilibrium constant, K (eq 10). Thus, the sterically hindered bases, 2-picoline and 2,6-lutidine, depress the rate of alkylation only in high concentration (500-fold excess) and are ineffective at 10-fold excess. 4-Cyanopyridine appears later on the list than pyridine. This ligand binds to cobalt more strongly than pyridine, since increasing its excess from 10- to 500-fold has no effect on the rate. The rate constants for pyridine and cyanopyridine furthermore are numerically nearly identical ($k_{py} = 5.9$; $k_{4\text{-}NC\text{-}py} = 5.4$ M sec^{-1}). Table IX shows that adding 1000-fold excesses of axial bases to solutions of vitamin B_{12s} has little or no effect on the initial rates. This indicates that at the concentrations applied (0.16 F) these bases do not effectively compete with the 5,6-dimethylbenzimidazole ligand. This is presumably due to its attachment to the corrin ring by the sugar phosphate loop, and suggests that the displacement reactions with these bases, if they occur, must be relatively slow. Reduced aquo(cyano)-

Table IX. Effect of Axial Bases on the Reaction of Vitamin B_{12s} with CH_3CH_2Br (25°, 0.1 F NaOH in Methanol)

Axial base added	(Base)/(vitamin B_{12s})	$k_{obsd}{}^{2nd}$, M^{-1} sec^{-1}
None[a]	1000	31 ± 2
Tributylphosphine	1000	27 ± 2[b]
Cyclohexylisocyanide	1000	26 ± 3[b]
4-Cyanopyridine	1000	27 ± 3[b]

[a] Conditions with no axial base added; (Co) = 1.6×10^{-4} F; (H_2O) = 1400(Co); (OH^-) = 0.1 F. [b] Serious tailing present in rate plots; error range is the average deviation from the median of five determinations of initial slopes.

Table X. Second-Order Rate Constants (M^{-1} sec^{-1}) of the Reactions of Miscellaneous Co(I) Chelates with Alkyl Halides[a] at 30°

Chelate[b]	Alkyl halide	None	Bases added (100-fold excess)[c] Pyridine	$(CH_3)_2S$	$(n\text{-}C_4H_9)_3P$
I	n-C_3H_7Cl	7.4×10^{-2}	2.3×10^{-2}	1.45×10^{-2}	7.7×10^{-3}
II	n-C_3H_7Cl	6.6×10^{-3}	1.5×10^{-3}	1.6×10^{-3}	3.4×10^{-3}
III	CH_3I	*d*	*d*	*d*	4.3
IV	n-C_3H_7Cl	5.7×10^{-2} [e]	5.0×10^{-3}	2.1×10^{-3}	1.2×10^{-3}
V	n-C_3H_7Cl	3.0×10^{-2} [e]	2.9×10^{-3}	2.2×10^{-3}	6.9×10^{-4}
VI	CH_3Cl	8.4×10^{-3}			
VI	C_2H_5Br	6.3×10^{-2}			
VII[f]	n-C_3H_7Cl	4.4×10^{-3}			6.0×10^{-4}
VIII	n-C_3H_7Cl	1.2×10^{-2}	1.3×10^{-4}	5.6×10^{-5}	2.7×10^{-6}
CoSalen[g]	n-C_3H_7Cl	1.2			
	CH_3Cl	10^2			

[a] If not stated otherwise, in methanol. [b] Roman numerals of chelates identified in the text. [c] Tributylphosphine excess only tenfold. [d] Co(I) derivative unstable. [e] A small amount of NH_3 solution added to stabilize Co(I) Species. [f] Approximate values. [g] Rates determined in methanol containing 80 g of 50% aqueous NaOH/l.

cobinamide ("Factor B"), which does not contain 5,6-dimethylbenzimidazole, reacts with *n*-propyl chloride about as fast as vitamin B_{12s}. The addition of bases (in 100-fold excess) in this case causes slightly greater inhibiting effects, Base added: none (3.5×10^{-2} *M* sec^{-1}), pyridine (2.9×10^{-2}), cyclohexylisocyanide (1.8×10^{-3}).

The important conclusion is, however, that the presence of the coordinated benzimidazole evidently does not substantially increase the nucleophilicity of the Co(I) ion in vitamin B_{12s}.

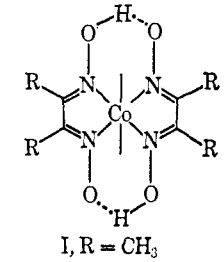
Chelate Structure and Co(I) Nucleophilicity

The nucleophilicity of the Co(I) chelates is determined by the absolute energy of the $3d_{z^2}$ orbital and the charge density on the cobalt atom and therefore also depends on the structure of the in-plane ligands. To explore the magnitude of these effects, the nucleophilicities of the Co(I) ions in chelates I–VIII were determined under comparable conditions. Rates observed are given in Table X from which the average nucleophilicities were calculated (Table XI).

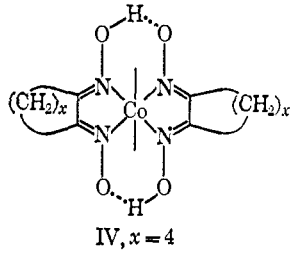
Table XI. Average Nucleophilicities of Co(I) Chelates in Methanol (at 30°) with Values of Vitamin B_{12s} and Reduced Cobinamide for Comparison

Compd	None	Py	Axial base added[a] $(CH_3)_2S$	$(n\text{-}C_4H_9)_3P$	$C_8H_{11}NC$[b]
Vitamin B_{12s}	14.4	14.4	14.4	14.4	14.4
Cobinamide(I)	14.4	14.4	14.4	*c*	14.1
Chelate I	14.3	13.8	13.6	13.3	13.1
II	13.7	13.1	13.0	12.9	
III	*d*	*d*	*d*	10.5	*c*
IV	14.1	13.5	13.1	12.9	*c*
V	13.9	13.3	13.1	12.4	*c*
VI	12.2	11.7	*c*	*c*	*c*
VII	13.2	*c*	*c*	12.3	*c*
VIII	13.8	11.9	11.5	11.1	*c*

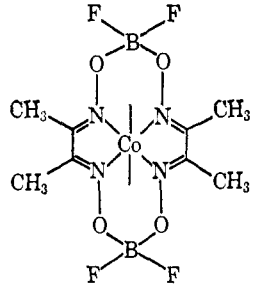
[a] Excess employed as indicated in Table X. [b] Employed in 10–100-fold excess. [c] Not determined. [d] Co(I) species unstable.



I, R = CH_3
II, R = C_6H_5
III, R = H



IV, $x = 4$
V, $x = 3$



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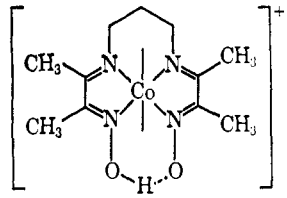
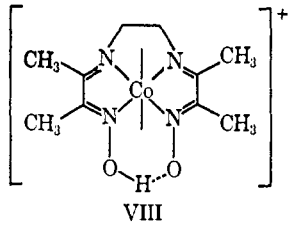


VII



VIII

The nucleophilicity of vitamin B_{12s} is 14.4, if defined according to Pearson[30] as $n_{CH_3I} = \log (k_Y/k_{CH_3OH})$, where k_Y and k_{CH_3OH} are, respectively, the second-order specific rate constants for attack by a nucleophile Y and methanol on the substrate CH_3I, at 25° in methanol as the solvent. This compares well with the values of 14.3 observed for aquocobaloxime.[30a] However, the nucleophilicities of the other cobaloximes studied decrease in the sequence I > IV > V > II > (III) for reasons to be outlined in the following. The *dimethylglyoxime* ligands evidently coordinate to the cobalt ion more strongly than the other substituted dioximes, mainly due to the inductive effect of the methyl groups. Diphenylglyoxime and glyoxal–dioxime, accordingly, product Co(I) derivatives with lower nucleophilicity. Among the two cyclic *vic*-dioximes studied, 1,2-cyclopentanedione dioxime is a somewhat weaker ligand than 1,2-cyclohexanedione dioxime, which is not unexpected

(30) R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, **90**, 319 (1968).

(30a) NOTE ADDED IN PROOF. W. W. Miller and J. H. Richards [*ibid.*, **91**, 1498 (1969)] have recently suggested that certain cobaloxime reactions may differ from those of cobalamins because of the diminished tendency of cobaloximes to stabilize the d^8 (Co^I) valence state as compared to vitamin B_{12}. The observed near-identity of the nucleophilicities indicates that this suggestion is not substantiated.

in view of the angular dependence of the overlap integrals between the nitrogen sp^2 and the cobalt orbitals. The substitution of the oxime hydrogen atoms by BF_2 groups is known to reduce the electron density on the nitrogen atoms and the central metal ion.[31] Although the formation of the chelate ring system may also cause slight changes in the Co–N distances, the overriding effect is inductive and leads to a considerable decrease in the Co(I) nucleophilicity (Table XI).

The substituted cobaloximes VII and VIII have somewhat smaller nucleophilicities mainly for electrostatic reasons, their Co(I) derivatives being electroneutral rather than uninegative. The substitution of the N–O··H–O–N grouping in the cobaloximes by the $N(CH_2)_3N$ or $N(CH_2)_2N$ chain otherwise has only a minor effect on the coordinating power of the in-plane ligand nitrogen atoms as is evidenced by the similarity of the Co(III)/Co(I) reduction potentials.[5] Preliminary measurements with Co(I)bis(salicylaldehyde)ethylenediimine (Co(I)Salen) indicate even a somewhat greater nucleophilicity than that of the cobaloximes or of vitamin B_{12s}. However, the measurements with Co(I)Salen had to be performed in a different solvent mixture to obtain the Co(I) nucleophile and hence are not directly comparable with values determined for the other Co(I) derivatives. A similar situation exists in the case of cobalt porphyrins, where Co(I) nucleophilicities also appear to be greater than those of cobaloximes(I) or of vitamin B_{12s}.

The formation of the Co–C bond from the Co(I) derivatives is accompanied by a change of the formal cobalt valence from +I to +III. This change in the oxidation state on product formation explains the high Co(I) nucleophilicity in terms of the oxibase concept,[32] since the energy term, E, in the expression defining the oxibase scale, *i.e.*, $\log (k/k_0) = \alpha E + \beta H$, must be significant.

Conclusion

The cumulative evidence presented in this paper forces us to conclude that vitamin B_{12s} and the other Co(I) chelates studied react with alkyl halides by a classical SN2 mechanism, the only point of difference with typical nucleophilic reactions being the exceptionally high reactivity of the Co(I) species. This property of the Co(I) ion in planar ligand environments is a direct consequence of the shape and antibonding energy of the $3d_{z^2}$ orbital, the highest occupied orbital in these systems. In-plane ligand effects are important in determining the nucleophilicity of the Co(I) center inasmuch as they influence the charge density on the cobalt ion. By selecting suitable ligand systems it thus becomes possible to obtain Co(I) derivatives covering a range of reactivities. Axial bases accepting charge *via* π-electron back-donation from the cobalt atom have the effect of *reducing* the Co(I) nucleophilicity. Strong, "hard" bases in the axial position increase it. The coordinated 5,6-dimethylbenzimidazole in vitamin B_{12s} does not change the Co(I) nucleophilicity substantially.

One of the more surprising results of the present study is that vitamin B_{12s} reactions with the alkylating agents are not subject to greater steric hindrance than those of cobaloximes, and, in fact, of simple nucleophiles such as iodide ion. This is the more remarkable as the alkylcobalamins, which should form in the reactions with secondary alkyl halides, are unstable, decomposing into B_{12r} and olefin. Most corresponding cobaloximes, on the other hand, can be isolated. Nevertheless, the relative rates of reactions of Co(I) nucleophiles of both vitamin B_{12s} and the cobaloximes(I) with secondary alkyl halides are quite similar. This indicates that the maximum of the potential energy profile of the SN2 transition state is largely dominated by contributions due to bond breaking. Steric effects of the corrin ligand evidently become important only after the passage of the energy maximum. This observation will be of significance in future interpretations of vitamin B_{12} dependent enzyme reactions, since steric considerations in SN2 transition states can be minimized.

The enormous nucleophilicity of vitamin B_{12s} explains its unique selectivity for methylcarbonium ions; reactions with corresponding ethyl- or higher alkylcarbonium ion releasing agents take place at only about 1% of the rate observed with methyl derivatives. This observation provides a fundamental explanation for the established involvement of vitamin B_{12} in one-carbon metabolism, *e.g.*, in methane, acetic acid, and methionine biosynthesis. Few cases are known in which comparatively simple model compounds duplicate reactions and reactivities of complicated natural products. The extent with which such coincidences are observed between cobaloximes and vitamin B_{12} is for this reason even more remarkable.

Experimental Section

Solvents and Starting Materials. All reactions, except those concerned with solvent effects, were run in reagent grade methanol as the solvent. Varying the quality of the methanol (technical, reagent, spectrophotometric grades, etc.) had no effect on the observed reaction rates. No attempt was made to keep the solvent anhydrous since it was observed that water concentrations up to 2% of the methanol had no effect on the rates. In fact, the methanol in almost all cases was made to contain 0.4% water, since 50% NaOH solution was used to make the reaction solutions 0.1 *F* in NaOH. Other solvents were of reagent grade; the water was deionized.

Alkyl Halides. Nearly all alkyl halides were commercially available compounds that were purified by repeated distillation or crystallization where applicable. Such purification was found to be absolutely necessary in almost every case because of oxidizing impurities. The purity of the final product was confirmed by comparing its boiling or melting point to literature values, and in many cases by nmr spectroscopy and gas chromatography.

Commercially available cyclopropyl bromide (Aldrich, bp 69.0°) is very difficult to purify by distillation since it contains both allyl and *n*-propyl bromide (bp 71.3 and 70.9°, respectively). However, by refluxing this commercial product in 2-heptanone saturated with potassium iodide, the impurities can be converted into alkyl iodides without affecting the cyclopropyl bromide.[33] Distillation of this mixture yields a pure sample of cyclopropyl bromide. Cyclobutyl bromide was prepared according to Cason and Way.[34]

p-t-Butylbenzyl chloride was prepared by the chloromethylation of *t*-butylbenzene according to the method of Kosolapoff.[35] Its isomeric purity was confirmed by nmr analysis; bp 113° (10 mm).

Axial Bases. Pyridine, 2-picoline, 2,6-lutidine, aniline, and tributylphosphine were commercial materials that were purified by distillation (the last under argon). 4-Cyanopyridine, obtained from Reilly Tar & Chemical Corp., was purified by crystallization from toluene–hexane. Cyclohexylamine, dimethyl sulfide, tri-

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(32) R. E. Davis in "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience Publishers, New York, N. Y., 1967, pp 311–328.
(33) J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, 73, 5034 (1951).
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(35) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 68, 1670 (1946).

phenylphosphine, triphenylarsine, triphenylstibine, and KCN were commercial materials that were used without purification. Cyclohexyl isocyanide was freshly prepared according to Ugi.[36]

Sodium Borohydride. Commercial sodium borohydride usually contains substantial amounts of metal impurities which were found to seriously affect the course of the reactions studied by catalyzing the reductive cleavage of the Co–C bond of the organocobalt products. (This effect of trace metal ion impurities was demonstrated by independent experiments in which small amounts of, *e.g.*, cupric ion were added to a solution of an alkylcobaloxime in the presence of excess pure $NaBH_4$. Whereas alkylcobaloximes are stable to $NaBH_4$ over several hours of standing in the dark, decomposition is quite fast in the presence of traces of copper. This effect of trace metal impurities can in part be reduced through the addition of EDTA to the $NaBH_4$ solution prior to its addition to the organocobalt compound.) Therefore, a thorough purification of the $NaBH_4$ was necessary, recrystallization from diglyme according to the procedure of Brown[37] yielding samples of adequate purity.

Cobaloximes and Other Cobalt Chelates. Tributylphosphine-bis(dimethylglyoximato)cobalt(III) chloride, bis(dimethyglyoximato)cobalt(III) chloride, hydrochloride salt, and most other cobalt chelates were prepared by published procedures.[38] The preparation of the cobaloxime derived from 1,2-cyclopentanedione dioxime has not yet been described but is achieved just like that of the derivatives of dimethylglyoxime.

Vitamin B_{12} Compounds. Vitamin B_{12} (cyanocobalamin) and factor B (aquocyanocobinamide) were supplied by Merck Sharp and Dohme Research Laboratories, Rahway, N. J. Vitamin B_{12a} (aquocobalamin) was prepared by reducing vitamin B_{12} with sodium borohydride and then degassing the methanol–water solution to remove the HCN formed; after air oxidation the solution was extracted with 50% (w/w) phenol–chloroform and water added and the phenol extracted into ether. Vitamin B_{12a} was crystallized from the water layer and then recrystallized from water. The spectra of this vitamin B_{12a} and the vitamin B_{12s} obtained therefrom on reduction were identical with published spectra.

Solution Preparation. Enough 50% NaOH solution and cobalt compound were weighed out and diluted with methanol in a volumetric flask to make the final concentration of cobalt about 10^{-4} *F* and the concentration of NaOH 0.10 *F*. In most runs the cobalt complex used was either vitamin B_{12a} or tributylphosphine-bis(dimethylglyoximato)cobalt(III) chloride, but in the axial base studies factor B, vitamin B_{12a}, or bis(dimethylglyoximato)cobalt(III) chloride, hydrochloride salt, was used along with a weighed amount of the appropriate axial base. An aliquot of this alkaline, methanolic cobalt complex solution was pipetted into a spectrophotometric cell (path length usually 1 cm) and deoxygenated with an argon stream that had been saturated with methanol vapor. Solid, recrystallized sodium borohydride was added (2–3 mg/ml of solution) and the cell was capped with a rubber serum stopper. Reduction of the cobaloximes to the Co(I) derivatives was usually complete within 30 min (reduction times vary somewhat due to the presence of ultramicroquantities of catalytically active metals in the reagents). Reduction of vitamin B_{12a} under these conditions usually does *not* take place unless a trace of a heavy metal catalyst is present and therefore reduction was usually initiated by adding a trace (1 μl of 0.1% solution) of K_2PdCl_4 or K_2PtCl_4. The presence of these catalysts were found to have no effect on the initial rates of reaction of vitamin B_{12s} with alkyl halides, but their presence accentuated the tailing of the rate curves in later stages of the alkylation reaction. As was mentioned above, this tailing is attributed to the reductive cleavage of the alkylcobalt reaction product, yielding a hydrocarbon and the original Co(I) starting material. A subsequent glpc analysis of the reaction solution gas phase revealed the presence of significant amounts of hydrocarbon derived from the original alkyl halide.

Kinetic Measurements. Kinetic runs with half-lives greater than 15 sec were followed on a Cary recording spectrophotometer at a wavelength in the visible region characteristic for the Co(I) derivative (usually 690 mμ for cobaloxime$_s$ and 700 mμ for vitamin B_{12s}). Either the pure halide or a solution of the halide in deoxygenated methanol was injected into the spectrophotometric cell with a syringe, the cell quickly shaken placed into the cell compartment of the spectrophotometer and the decrease in absorbance of the solution monitored as a function of time. Usually the halide was employed in 15- to 100-fold excess to make the reaction pseudo first order. Some reactions were also run under second-order conditions (3–10-fold excess of halide over cobalt complex) and a few runs were done with cobalt in excess over alkyl halide.

Reactions with half-lives of less than 15 sec were followed by using a stopped-flow apparatus kindly loaned by Professor Henry Taube (Stanford). The construction, theory, and use of this instrument are described elsewhere.[39,40]

Kinetic runs that were followed using the stopped-flow apparatus were thermostated to ±0.3°, while runs on the Cary, at high temperatures, were controlled to ±0.5° using equipment kindly loaned by Professor Joe Watson (UCSD). Room temperature Cary runs were not thermostated and were performed in the temperature range 25 ± 2°, even though the temperature of any one set of runs remained constant to ±0.5°. Thus, although the precision of any set of runs is almost always better than ±8%, the inherent inaccuracy of these kinetic measurements if ±15%, assuming an activation enthalpy of 15 kcal/mol.

Treatment of Data. The reactions performed under pseudo-first-order conditions (excess alkyl halide) gave straight log ($OD_t - OD_\infty$) *vs.* time plots, usually, but not always, with some tailing after two or three half-lives. As was mentioned above, this tailing is due to reductive cleavage of the organocobalt bond of the product, yielding the Co(I) starting material, and the rate of this process is dependent upon many variable factors. All rates reported in this paper were calculated either from the initial slopes of the rate plots, or by a Guggenheim treatment of the data[41] for which infinity OD values are not needed. Second-order specific rate constants were calculated from the expression

$$k^{2nd} = \frac{-2.303(\text{slope})}{[b - (a/2)]}$$

where b and a are the initial concentrations of alkyl halide and Co(I), respectively, and the slope has units of sec^{-1}.

Runs done under second-order conditions also frequently showed tailing, and again the second-order specific rates reported here were calculated from the initial slopes of plots of

$$\log \frac{OD_t + OD_0[(b/a) - 1] - (b/a)OD_\infty}{OD_t - OD_\infty}$$

vs. time by the equation

$$k^{2nd} = \frac{-2.303(\text{slope})}{(b - a)}$$

The specific rate constants reported in this paper are the median of at least five determinations, the average deviation from the median always being better than ±8% and usually with ±5%. As mentioned previously, the runs done at ambient temperature have an inherent inaccuracy of ±15%.

Reaction Conditions. Unless otherwise noted, all reactions reported in this paper were run with Co(I) nucleophiles that were produced by sodium borohydride reduction in a methanolic solution that contained 0.4% water and was 0.1 *F* in NaOH. Various control experiments were performed in order to determine the effects of varying these conditions, and the following results show that the reactions studied are remarkably insensitive to ionic strength (which is expected since one of the reactants is neutral), solvent composition, base concentration (as long as there is enough base present to stabilize the reactants), and the method of preparation of the Co(I) nucleophile.

No effect on the rate of reaction of *n*-propyl chloride with either vitamin B_{12s} or cobaloxime$_s$ was detected by (1) varying the water concentration of the solvent from 0 to 2%, (2) varying the concentration of NaOH (and hence the ionic strength) from 0.02 to 1.0 *F*, (3) varying the amount of $NaBH_4$ added from 1.0 to 16 mg/ml, (4) using hydrogen gas (with a noble metal catalyst) instead of sodium borohydride to reduce the cobalt chelates, (5) varying the amount of time waited between complete reduction and beginning the kinetic run, and (6) adding varying amounts of sodium borate to the reaction solution (sodium borate, the final product of $NaBH_4$ hydrolysis, could possibly exert a salt or similar effect on the rate).

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(38) (a) G. N. Schrauzer, "Inorganic Syntheses," Vol. XI, W. L. Jolly, Ed., New York, N. Y., 1968; pp 61–69; (b) L. Tshugaev, *Chem. Ber.*, **40**, 3498 (1907); (c) see ref 9, and literature cited therein.
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Rate Law. All the alkylation reactions studied in this paper followed the simple second-order rate law $-d(Co^I)/dt = k^{2nd}(RX)(Co^I)$. In every case the first-order dependence on alkyl halide was checked by varying the concentration of RX by at least a factor of 4, and in many cases by a factor of 20. In one instance, the reaction of *n*-propyl chloride with a 3×10^{-4} *F* solution of cobaloximes, varying the concentration of RX from 0.02 to 0.92 *F* had no effect on the second-order rate constant calculated from the above expression (this experiment also provides additional evidence for the insensitivity of these reactions to medium effects, since the most concentrated solution was about 10% halide in methanol). The first-order dependence on $(Co^I)^-$ is shown by the linearity of the rate plots, which are straight over at least a factor of 4 in the concentration of Co(I) and are often linear for four half-lives.

Product Analysis

The reactions studied in most cases yield isolable organocobalamins or -cobaloximes. An identification of the products formed was necessary in certain doubtful cases, *i.e.*, the reaction of vitamin B_{12s} with secondary alkyl halides or those of cobaloximes with tertiary alkyl halides.

a. Reaction of Isopropyl Iodide with Vitamin B_{12s}. The *sec*-alkyl halide was very carefully purified to eliminate any possible contamination by primary halides.

Its reaction with vitamin B_{12s} under various conditions is slow, yielding vitamin B_{12r} and yellow corrin reduction products which are also obtained on prolonged reduction of vitamin B_{12a} with sodium borohydride. Organocobalamins could not be detected among the reaction products.

b. Reaction of *t*-Butyl Chloride with Cobaloxime(I). Solutions of cobaloxime(I) were prepared by reducing chloro(pyridine)cobaloxime with $NaBH_4$ in methanol. After destroying the excess of borohydride with acetone, carefully distilled *t*-butyl chloride was added under argon. After 1 hr the blue-green solution of the cobaloxime(I) was brown, and crystals of pyridine–cobaloxime(II) (recognized by its color and oxygen sensitivity in the methanolic suspension) had separated. Glpc analysis of the gas phase revealed the presence of isobutylene. No organocobaloxime could be detected in the reaction solution. In the cobalamin series optical absorption spectra were run to identify the reaction products. The initial reaction product with *t*-butyl chloride resembles vitamin B_{12r}. On prolonged standing under reducing conditions yellow, air-stable, reduced corrins are formed.

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Synthesis of Oligothymidylates *via* Phosphotriester Intermediates[1]

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Abstract: A procedure is described for the large-scale preparation of β-cyanoethyl ester derivatives of 5′-O-monomethoxytrityl TpT, TpTpT, and TpTpTpT. The essential feature is a double phosphorylation, the first step of which involves reaction of a terminal 3′-OH of a nucleoside with β-cyanoethyl phosphate and mesitylenesulfonyl chloride and the second step, condensation of the resulting phosphodiester with thymidine in the presence of triisopropylbenzenesulfonyl chloride. The products are separated by chromatography on silica gel with ethyl acetate and tetrahydrofuran. They may be converted in high yield to the corresponding demethoxytritylated derivatives and thence to TpT, TpTpT, and TpTpTpT, respectively, by successive treatment with aqueous acetic acid and ammonium hydroxide.

With the synthesis of 5′-O-trityldeoxycytidylyl-(3′–5′)-thymidine and related compounds two features were introduced in the methodology of oligonucleotide syntheses: (1) the nucleotide chains were constructed on an insoluble polymer support, which facilitated the separation of intermediates from solvents and soluble by-products; and (2) the nucleosides were joined by reactions designed to yield β-cyanoethyl phosphotriester links ($ROP(O)(OR')OCH_2CH_2CN$), which in a final alkaline treatment could be converted to phosphodiester salts.[2] The present set of papers reports the further elaboration of these techniques. In the first paper are described experiments adapting the β-cyanoethyl phosphotriester method to the synthesis of oligothymidylate derivatives in solutions in the absence of a polymer support. These experiments were stimulated both by the wish to elucidate the chemistry of the triester intermediates and by the hope that the homogeneous solution approach could be developed into a useful method in its own right. The second paper reports research on new blocking groups designed to meet the specific demands imposed by the phosphotriester approach, and the third paper describes procedures for synthesizing β-cyanoethyl phosphotriester derivatives of all four common nucleosides, making use of the new blocking groups.

Phosphotriester Method. The procedure for synthesizing oligonucleotides directly by condensation of 3′-O-protected nucleoside 5′-phosphates, or oligonucleotides bearing 5′-phosphomonoester groups, with nucleotides or oligonucleotides possessing a free ter-

(1) Part XIII in a series of nucleotide chemistry. A preliminary account has been published: R. L. Letsinger and K. K. Ogilvie, *J. Am. Chem. Soc.*, 89, 4801 (1967). For part XII see R. L. Letsinger, P. S. Miller, and G. W. Grams, *Tetrahedron Letters*, 2621 (1968).

This research was supported by the Division of General Medical Sciences, National Institutes of Health (GM 10265).

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