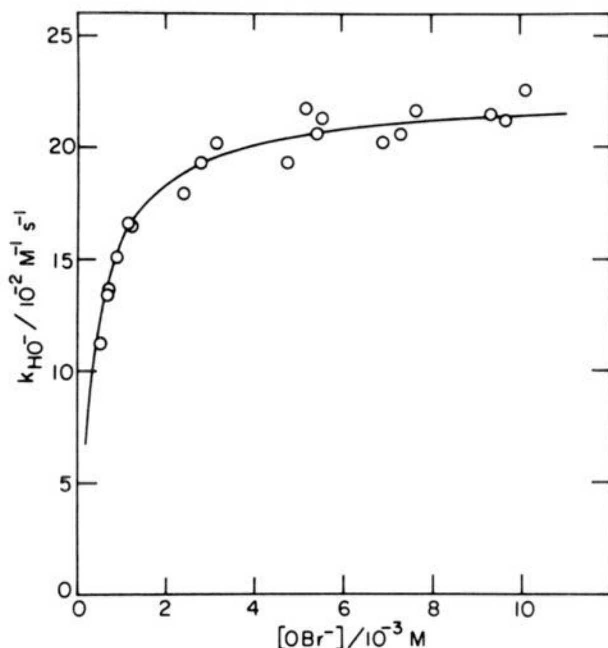
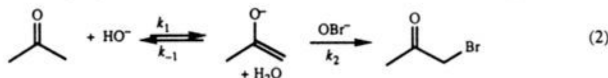


Figure 2. Relationship between [OBr⁻] and apparent rate constants for the enolization of acetone determined by bromine scavenging in aqueous solution at 25 °C, ionic strength = 0.10 M (NaCl).

In the original work,[1] hydroxide ion catalytic coefficients for the protium and deuterium reactions were determined by bromine scavenging of the acetone enolate ion as it formed, eq 2. This



technique requires the scavenging reaction to be sufficiently faster than re-formation of acetone, $k_2[OBr^-] \gg k_{-1}$, but it seems likely, now that k_{-1} is known,[7] that this condition was not fulfilled. We have found that apparent rate constants for the enolization of protioacetone, determined at scavenger concentrations normally used in enolization studies, depend on [OBr⁻] as shown in Figure 2. This is the behavior expected under conditions of inadequate scavenging. Least-squares fitting of the data to the rate law that applies under these conditions, eq 3, gave the true enolization

$$k_{obsd} = k_1/(1 + k_{-1}/k_2[OBr^-]) \quad (3)$$

catalytic coefficient $k^{H}_{HO^-}$ ($=k_1$) = $(2.24 \pm 0.03) \times 10^{-1}$ M^{-1} s^{-1} and the ratio $k_{-1}/k_2 = (4.62 \pm 0.20) \times 10^{-4}$ M. Combination of this ratio with the known value of k_{-1} ($=5.0 \times 10^4$ s^{-1})[7] gives $k_2 = (1.08 \pm 0.06) \times 10^8$ M^{-1} s^{-1}, which is consistent with a previous estimate of this rate constant, $k = 1.4 \times 10^8$ M^{-1} s^{-1}.[8] Our new catalytic coefficient for the enolization of protioacetone is 40% greater than the value reported before,[1] and we conclude that inadequate scavenging did lead to errors in the previous study. This new catalytic coefficient for the protium reaction, when combined with our rate constant for tritioacetone, gives the isotope effect $k_H/k_T = 19.2 \pm 0.7$; this is nearly twice the previously published result.[1]

There is available a value of the hydroxide ion catalytic coefficient for enolization of deuterioacetone that was obtained from mass spectrometric measurement of deuterium-exchange rates, and this rate constant is consequently not subject to errors introduced by inadequate scavenging.[9] When this result, $k^{D}_{HO^-}$ = $(3.10 \pm 0.08) \times 10^{-2}$ M^{-1} s^{-1}, is combined with our value of $k^{H}_{HO^-}$, the isotope effect $k_H/k_D = 7.24 \pm 0.21$ is obtained. Comparison of this with our newly determined tritium isotope effect gives the Swain–Schaad exponent $x = 1.49 \pm 0.07$; this agrees well with Swain and Schaad's prediction, $x = 1.44$, and also falls within the range expected from higher level theory, $x = 1.33$–1.58.

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Registry No. Acetone, 67-64-1; deuterium, 7782-39-0; tritium, 10028-17-8.

(7) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460–462.
(8) Data of Taphui and Jencks (Taphui, E.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 5758–5765) recalculated in the following: Keeffe, J. R.; Kresge, A. J. *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, Chapter 7.
(9) Hine, J.; Kaufmann, J. C.; Cholod, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 4590–4595.

Cyclodextrin–B_{12}, a Potential Enzyme–Coenzyme Mimic

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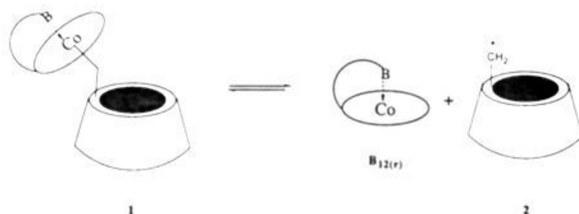
Since it was suggested[1] that the homolysis of the carbon–cobalt bond of adenosylcobalamin coenzyme (coenzyme B_{12}) was the first step in the process that led to product formation in its dependent enzymes, the study of its radical chemistry has been extensive.[2] The standard mechanism for rearrangements catalyzed by this coenzyme is as follows: (a) homolysis to form $B_{12(r)}$ and the enzyme-bound deoxyadenosyl radical, followed by (b) hydrogen atom transfer from the bound substrate to this radical to form a substrate radical. Then (c) the derived substrate radical rearranges, followed by (d) hydrogen atom transfer back to reform the deoxyadenosyl radical, which then couples with $B_{12(r)}$ to reform the coenzyme. Although a number of model systems exist that mimic some of the rearrangement steps of such processes,[3] there are not yet examples in which a substrate and B_{12} or a surrogate are bound together in a receptor site, such that intracomplex atom transfers to the carbon radical can mimic the opening stages of this general mechanism.

It seemed to us that the attachment of cobalamin by a direct cobalt–carbon bond to the primary carbon of β-cyclodextrin should lead to a compound (**1**) with very interesting potential. Homolysis of the carbon–cobalt bond would generate $B_{12(r)}$ and a primary cyclodextrin radical (**2**) of a glucose unit[4] strongly related to the primary ribose radical formed from the true coenzyme. In water, hydrophobic substrates will bind into the cyclodextrin cavity, so that **2** could perform an intracomplex atom transfer to generate a substrate radical (Figure 1). We have prepared compound **1** and shown that its properties are very promising.



(1) Abeles, R. H. *Proc. Robert A. Welch Found. Conf. Chem. Res.* **1972**, *15*, 113. See also: Breslow, R. *Ibid.* **1972**, *15*, 119–120.
(2) For a recent review, see: Finke, R. G. In *Molecular Mechanisms in Biological Processes*; Bleasdale, C., Golding, B., Eds.; Royal Society of Chemistry: Cambridge, England, 1990; p 344.
(3) Choi, G.; Choi, S.-C.; Wilk, B.; Dowd, P. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3174.
(4) Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957–2958.

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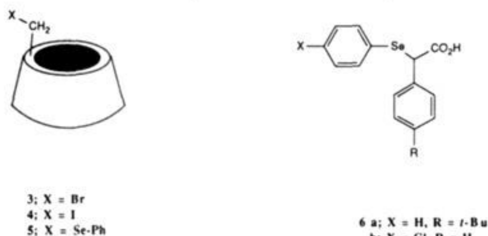
Figure 1.

Treatment of **3** with cob(I)alamin, in a manner similar to that described[5] for the preparation of other cobalamins, yields **1** in the "base-off" form as a purified yellow powder [MS (FAB) 2447 ($M^+ + 1$); UV-vis[6] $\lambda_{max(1\ M\ HCl)}$ 340 (1.00), 405 (0.61), 450 (0.64), $\lambda_{max(pH\ 7)}$ 370 (1.00), 425 (0.61), 477 (0.81), 510 (0.81)]. The compound must be almost pure, as judged from the greater than 90% yield of reaction product **5** (vide infra). Treatment of **1** with I_2 afforded **4**.

In this form **1** may be handled briefly in air. In neutral 0.05 M phosphate buffer, however, it is quite reactive; its pseudo-first-order aerobic decomposition[7] has a half-life of 152 ± 13 min at 25 °C in the absence of light. This compares with 5 min for the same process in benzylcobalamin and 75 min for neopentylcobalamin.[7] The aerobic decomposition of adenosylcobalamin itself is too slow to be measured in the absence of the enzyme under these conditions, and dissociation requires heating or irradiation.[8] Since the bonding in adenosylcobalamin is similar to that in **1**, we ascribe the greater reactivity of **1** to steric crowding by the cyclodextrin system. Thus **1** is in rapid equilibrium with $B_{12(r)}$ and the cyclodextrinyl radical (**2**) and is actually a better model for the reactive coenzyme-enzyme complex than is adenosylcobalamin itself. In 1 M HCl, where the benzimidazole group of **1** is not coordinated with the cobalt, decomposition is much slower.

Reaction of **1** in the dark with benzyl or *tert*-butylbenzyl iodide in aqueous deoxygenated neutral 0.05 M phosphate buffer at room temperature and then quenching with air in the dark produces **4** and the corresponding benzaldehyde, probably from air oxidation of the product benzylcobalamin. Attempts to detect selective reaction for the more strongly binding 4-*tert*-butylbenzyl iodide, or bromide, were hampered by problems with solubility, hydrolysis, and radical exchange. These were overcome with the selenide (**6a**), which underwent group transfer to **2** under the above conditions and afforded a 95 ± 5% yield, based on **1**, of the cyclodextrin selenide **5**. Competition between **6a** and the weaker-binding **6b** showed a preference for reaction with **6a** of greater than 10-fold, as judged by the relative yields of **5** and of the corresponding *p*-chloro derivative. As expected, if this preference reflects binding, the addition of 20% ethanol decreased the preference to less than 2-fold by decreasing the effectiveness of hydrophobic binding to the cyclodextrin cavity. A similar decrease in selectivity between **6a** and **6b** was seen if an excess of *p*-*tert*-butylbenzoate ion, a competitive binder, was present.



X– –Se– CO₂H, R

6 a; X = H, R = *t*-Bu
b; X = Cl, R = H

To look for rearrangements, we examined cyclizations of the type demonstrated by Curran[9] but with substrates carrying a hydrophobic binding group. Reaction did not occur exclusively within the cavity, but there was instead a radical atom transfer chain process in free solution initiated by **1**. It is interesting that in some enzymatic reactions coenzyme B_{12} may also be serving only as a chain initiator,[10] rather than performing all the atom transfers described above. Thus we have not yet mimicked all the steps of B_{12} catalysis. However, the properties of cyclodextrin-B_{12} (**1**), with a carbon-cobalt bond labile under physiological conditions and a binding site in the resulting radical, make it a very attractive candidate for further enzyme model studies.

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(5) Blaser, H.-U.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 1684-1689.
(6) All intensities are relative.
(7) Schrauzer, G. N.; Grate, J. H. *J. Am. Chem. Soc.* **1981**, *103*, 541-546.
(8) Pratt, J. M. In *B_{12}; Volume 1: Chemistry*; Dolphin, D., Ed.; Wiley Interscience: New York, 1982; p 364.
(9) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140-3157.
(10) Stubbe, J. *Biochemistry* **1988**, *27*, 3893-3900.

Preparation of Highly Functionalized Magnesium, Zinc, and Copper Aryl and Alkenyl Organometallics via the Corresponding Organolithiums

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Organometallics bearing electrophilic functionalities are versatile intermediates for the synthesis of a wide range of highly functionalized organic molecules,[2,3] including important biologically active compounds.[4] The readily prepared alkyl[2] and benzylic[2d,5] organozinc halides, in particular, have found widespread applications and were shown to be compatible with most organic functionalities.[2-6] Their relatively low reactivity can be dramatically enhanced by transmetalation to copper[2-6] organometallics or by using a palladium(0) catalyst.[7] Unfortunately, the preparation of polyfunctionalized alkenyl and aryl organometallics is less straightforward, as a direct metal insertion can be troublesome. The use of highly activated metals (zinc,[3] copper[8]) or polar solvents is required to perform a metal insertion into the

(1) Present address: Prof. P. Knochel, Philipps-Universität Marburg, Fachbereich Chemie, Hans Meerwein Strasse, D-3550 Marburg, Germany.
(2) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799. (c) Retherford, C.; Yeh, M. C. P.; Schipor, I.; Chen, H.-G.; Knochel, P. *J. Org. Chem.* **1989**, *54*, 5200. (d) Berk, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053. (e) Chou, T.-S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 4791. (f) Knochel, P. *J. Am. Chem. Soc.* **1990**, *112*, 7431. (g) Yeh, M. C. P.; Chou, H.-G.; Knochel, P. *Org. Synth.* **1991**, *70*, 195. (h) Retherford, C.; Knochel, P. *Tetrahedron Lett.* **1991**, *32*, 441. (i) AchyuthaRao, S.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735.
(3) (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (b) Rieke, R. D.; Li, P. T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323. (c) Rieke, R. D.; Uhm, S. J.; Hudnall, P. M. *J. Chem. Soc., Chem. Commun.* **1973**, 269. (d) Zhu, L.; Rieke, R. D. *Tetrahedron Lett.* **1991**, *32*, 2865.
(4) (a) Tsujiyama, H.; Ono, N.; Yoshino, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1990**, *31*, 4481. (b) Tanaka, T.; Bannai, K.; Hazato, A.; Koga, M.; Kurozumi, S.; Kato, Y. *Tetrahedron* **1991**, *47*, 1861.
(5) (a) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789. (b) Chen, H.-G.; Hoechstetter, C.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4795.
(6) (a) Knoess, H. P.; Furlong, M. T.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 5974. (b) Knochel, P.; Rozema, M. J.; Tucker, C. E.; Retherford, C.; Furlong, M. T.; AchyuthaRao, S. *Pure Appl. Chem.* **1992**, *64*, 361.
(7) (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (b) Negishi, E.; Matsushita, H.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett.* **1983**, *24*, 3823. (c) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393. (d) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683.
(8) (a) Rieke, R. D.; Wehmeyer, R. M.; Wu, T.-C.; Ebert, G. W. *Tetrahedron* **1989**, *45*, 443. (b) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1988**, *53*, 4482. (c) Rieke, R. D. *Science* **1989**, *246*, 1260. (d) O'Brien, R. A.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 788. (e) Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* **1991**, *113*, 4672. (f) Ebert, G. W.; Klein, W. R. *J. Org. Chem.* **1991**, *56*, 4744.

0002-7863/92/1514-3983$03.00/0 © 1992 American Chemical Society