acetate and adjacent methyl groups is indicated by the small (2 Hz) coupling between the H geminal to the acetate and the H geminal to the methyl group (equatorial–axial coupling). Mass spectrum (70 eV) *m/e* (realtive intensity) 284 (M, 3), 224 (M – HOAc, 2), 181 (47), 164 (62), 150 (22), 149 (66), 123 (45), 105 (100), 95 (37), 59 (20), 55 (25); high-resolution mass spectrum (M) calcd for $C_{14}H_{20}O_6$ 284.1260, found 284.1238.

Methyl 1,2-Diacetoxy-3-methyl-5-oxocyclohexanecarboxylates (25). Ozonolysis of methylene triesters **24** afforded keto triesters **25**.

General Procedure. Methylene cyclohexane derivative **24d** (10 mg, 0.35 mmol) was dissolved in dry methylene chloride (5 mL) and cooled to –78 °C. Ozone was bubbled into the solution until the blue color of excess ozone persisted in the solution. The ozone stream was removed and a stream of nitrogen was bubbled through the solution at –78 °C until the solution became colorless. After the solution turned colorless, the nitrogen stream was continued for 5 min. Acetic acid (0.25 mL, 4 mmol) was added to the flask followed by zinc dust (13 mg, 0.2 mmol). The solution was allowed to warm to room temperature and stirred for 1 h. The solution was filtered and extracted with ether (3 × 10 mL) and the combined extracts were washed with water (2 × 10 mL), saturated aqueous sodium bicarbonate (2 × 10 mL), water (10 mL), and saturated sodium chloride (2 × 10 mL), dried ($MgSO_4$) and rotary evaporated to afford **25d** (9.7 mg, 97%). The keto diacetates **4** and **25b-d** were fully characterized by ^1H NMR and high-resolution mass spectra as described below.

Methyl 1,*cis*-2-Diacetoxy-*trans*-3-methyl-5-oxocyclohexanecarboxylate (4). The keto diacetate **4** (89% from **24a**) obtained after removal of solvents was quite pure according to ^1H NMR analysis. ^1H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz, $CHCH_3$), 1.96 (3 H, s, OAc), 2.03 (3 H, s, OAc), 1.9–2.6 (3 H, m), 2.53 (1 H, d, J = 15 Hz), 3.47 (1 H, d partly buried, J = 15 Hz), 3.68 (3 H, s, OMe), 5.27 (1 H, br d, J = 8 Hz, *CH*OAc); mass spectrum (70 eV) *m/e* (relative intensity) no parent peak, 226 (M – HOAc, 5.5), 185 (37), 184 (75), 167 (53), 166 (67), 144 (39), 146 (36), 142 (27), 126 (15) 125 (100), 103 (21), 99 (30), 82 (22), 79 (16), 69 (48), 60 (25), 59 (29), 58 (16), 57 (53), 55 (47); high-resolution mass spectrum (M – HOAc), calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0830.

Further purification of **4** was attempted with preparative TLC (0.25 mm, 1:1 ethyl acetate:hexane). No **4** was recovered from the plate. Only the acetic acid elimination product, methyl *trans*-6-acetoxy-5-methyl-3-oxo-1-cyclohexenecarboxylate (R_f 0.53–0.67), was obtained. NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 7 Hz, $CHCH_3$), 2.10 (3 H, s, OAc), 2.3–2.8 (3 H, m), 3.85 (3 H, s, OMe), 5.76 (1 H, br d, J = 4 Hz, *CH*OAc), 6.80 (1 H, s, olefinic).

Methyl 1,*trans*-2-Diacetoxy-*trans*-3-methyl-5-oxocyclohexanecarboxylate (25b). The keto diacetate **25b** (82% from **24b**) obtained after removal of solvents was quite pure according to ^1H NMR analysis. ^1H NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 6 Hz, $CHCH_3$), 1.8–2.2 (3 H, m), 1.96 (3 H, s, OAc), 2.12 (3 H, s, OAc), 2.48 (1 H, d, J = 15 Hz), 3.28 (1 H, d, J = 15 Hz), 3.68 (3 H, s, OMe), 5.46 (1 H, narrow m, whh = 4 Hz, CHOAc); mass spectrum (70 eV) *m/e* (relative intensity) 226 (M – HOAc, 12), 185 (41), 184 (91), 167 (45), 166 (61), 144 (42), 143 (32), 142 (29), 126 (18), 125 (100), 103 (25), 99 (28), 82 (25), 79 (20), 69 (40), 55 (39); high-resolution mass spectrum (M – HOAc), calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0853.

Methyl 1,*trans*-2-Diacetoxy-*cis*-3-methyl-5-oxocyclohexanecarboxylate (25c). The keto diacetate **25c** (95% from **24c**) obtained after removal of solvents was quite pure according to ^1H NMR analysis. ^1H NMR ($CDCl_3$, 100 MHz) δ 1.07 (3 H, d, J = 7 Hz, $CHCH_3$), 2.0–2.8 (4 H), 2.11 (3 H, s, OAc), 2.12 (3 H, s, OAc), 3.27 (1 H, d, J = 13 Hz), 3.70 (3 H, OMe), 5.22 (1 H, d, J = 10 Hz, *CH*OAc); mass spectrum (70 eV) *m/e* (relative intensity) no parent peak, 226 (M – HOAc, 11), 202 (23), 185 (84), 184 (100), 167 (61), 166 (62), 146 (33), 145 (21), 144 (49), 143 (53), 142 (40), 126 (22), 125 (83), 103 (40), 99 (36), 85 (33), 83 (23), 82 (30), 79 (26), 71 (22), 69 (80), 60 (20), 59 (25), 56 (43), 55 (56); high-resolution mass spectrum (M – HOAc), calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0825.

Methyl 1,*cis*-2-Diacetoxy-*cis*-3-methyl-5-oxocyclohexanecarboxylate (25d). The keto diacetate **25d** (97% from **24d**) obtained after removal of solvents was quite pure according to ^1H NMR analysis. ^1H NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 6 Hz, $CHCH_3$), 2.05 (3 H, s, OAc), 2.13 (3 H, s, OAc), 1.9–2.6 (3 H, m), 2.97 (1 H, slightly br d, J = 15 Hz), 3.25 (1 H, d, J = 15 Hz), 3.68 (s, OMe), 5.38 (1 H, narrow m, whh = 4 Hz, *CH*OAc); mass spectrum (70 eV) *m/e* (relative intensity) 286 (M, 0.5), 226 (M – HOAc 24) 185 (36) 184 (100), 167 (15), 166 (19), 144 (29), 143 (29), 142 (47), 125 (31), 110 (16), 103 (16), 99 (24), 83 (15), 82 (26), 77 (17), 69 (19), 55 (17); high-resolution mass spectrum (M), calcd for $C_{13}H_{18}O_7$ 286.1052, found 286.1034.

Acknowledgment. We thank the American Cancer Society for support of our research on the structure of leucogenenol and Dr. F. A. H. Rice for helpful discussions and attempts to isolate a sample of leucogenenol.

Registry No. 1, 29101-95-9; **4**, 80448-38-0; **7**, 71435-90-0; **10**, 71435-91-1; **11**, 71435-95-5; **12**, 80448-39-1; **13**, 80448-40-4; **14**, 80448-41-5; **15**, 80448-42-6; **17**, 80448-43-7; **18**, 80482-92-4; **19**, 80482-93-5; **23a**, 80448-44-8; **23b**, 80482-94-6; **23c**, 80482-95-7; **23d**, 80482-96-8; **24a**, 80448-45-9; **24b**, 80482-97-9; **24c**, 80482-98-0; **24d**, 80482-99-1; **25b**, 80483-00-7; **25c**, 80483-01-8; **25d**, 80483-02-9; 4-methoxy-3-methylbenzyl chloride, 60736-71-2; methyl *trans*-6-acetoxy-5-methyl-3-oxo-1-cyclohexenecarboxylate, 80448-46-0.

Low-Temperature Reactions of Metal Atoms with Methyl Bromide

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Received June 8, 1981

Abstract: The atoms of a series of metals were codeposited with CH_3Br under matrix isolation conditions (argon diluent at 12 K and pure CH_3Br at 77 K). Oxidative addition of CH_3Br to Fe, Co, Ni, and Pd did not occur upon simple codeposition or upon matrix photolysis, which is rationalized by the formation of a favored CH_3Br–M complex. Cu, Ag, and Au behaved similarly. Main-group metals Mg, Al, Ga, and In did react to form CH_3MBr whereas Zn, Tl, Ge, Sn, and Pb did not. For the group 1B–4B (Cu, Zn, B, C) families the most important reactivity parameter is a low ionization potential. However, a high heat of vaporization of the element also has a positive effect on reactivity. In the case of Mg, clusters may be necessary for high reactivity.

Introduction

Ault[1] has recently provided convincing evidence that Mg atoms react in a low-temperature argon matrix at 15 K with methyl halides to yield CH_3MgX species. This finding seemed remarkable to us in light of the extremely low temperature employed and the report of Skell and Girard[2] suggesting that Mg atoms deposited with pure alkyl halides at 77 K did not yield oxidative addition products (nonsolvated Grignard reagents) until the matrix was

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(1) Ault, B. *J. Am. Chem. Soc.* **1980**, *102*, 3480.

(2) Skell, P. S.; Girard, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 5518.

0002-7863/82/1504-1013$01.25/0 © 1982 American Chemical Society

warmed. Furthermore, with transition-metal atoms and organohalides we have concluded on numerous occasions that oxidative addition does not take place until the matrix is well above 77 K.[3] And finally, Ozin and co-workers[4] have found allyl chloride–Ni atom oxidative addition does not take place as high as 120 K (in pure allyl chloride) and have suggested the possibility of Ni clusters being necessary for the formation of the oxidative addition product, $(\eta^3\text{-}CH_2CHCH_2NiCl)_2$.

More examination of these interesting processes is clearly needed. Our initial approach has been to choose one model system, CH_3Br, and determine what metal atoms are reactive under matrix isolation conditions (12 K in argon and 77 K in pure CH_3Br).[5] Both main-group and transition-metal atoms have been studied and the results are reported herein.

Experimental Section

Our matrix isolation apparatus is modeled after that of Hauge, Kauffman, and Margrave.[5] Reflectance IR studies were possible with a four-sided polished copper block which could be cooled with an Air Products Displex cooling unit or with liquid nitrogen. (A Beckman IR-12 with a mirror system set up for reflectance was used in this work.) In the argon dilution experiments the ratios used were generally Ar:CH_3Br = 16:1 although ratios greater than 130:1 were used on occasion. The metal flux could be varied at will by changing the furnace temperature. The matrix gas:metal mole ratios were 10^3–10^4, which were determined by carefully weighing the furnace before and after the experiment and calculating how much of the vapor escaping the furnace would pass through the slit leading to the cold copper block.

The argon dilution experiments were done at 12 K and usually each matrix was then annealed at 30 K, where spectra were also recorded. The 77 K experiments were done with pure CH_3Br.

A 140-W mercury UV lamp was used with no filters for the photolysis experiments. The light was admitted through a quartz window directly onto the matrix, usually for 30 min but sometimes longer.

The metals were vaporized from *Al_2O_3* tubular furnaces. In the case of Al, a *BN tubular furnace* was used. Deposition times were 1–2 h and the furnace temperatures were occasionally monitored with an optical pyrometer although the more usual procedure was to visually monitor the matrix color and darkness and adjust the furnace temperature as needed. The metals were obtained from the following sources: Fe, Cu, and Pb, Fisher Scientific; Co, Ni, and Pd, Materials Research Corp.; Ag, Alfa Inorganics; Au, Research Organic and Inorganic Chemicals; Al, J. T. Baker; Ga, In, and Tl, CERAC, Inc.

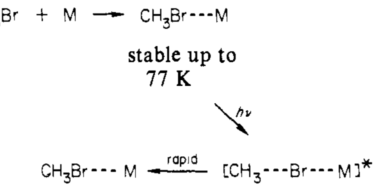
Perdeuteriomethyl bromide (99.5%) was obtained from Merck and methyl bromide was obtained from Matheson Gas Products. These were freeze–thaw–degassed and mixed with argon (obtained from Linde and passed through a 77 K trap before use) in a 3.5-L bulb on the vacuum line. The gases were thoroughly mixed with convection heating and the bulb was kept covered with metal foil to protect it from light.

Infrared band assignments were made based on prior literature as discussed in the text. Attempts to pinpoint the ν_{M-Br} frequency in the far-IR region were made but were unsuccessful apparently due to the low intensity of this absorption. Similar results have been obtained by Ault[1] and Tan and Pimentel[6] for their CH_3MgX and methyl alkali halide species.

Results

Transition Metals (Fe, Co, Ni, and Pd). It is known that CH_3Br reacts when codeposited at 77 K with Fe, Ni, or Pd atoms followed by matrix warmup.[3,7-9] However, the resultant products (probably CH_3MBr) are very unstable and decompose to a mixture of CH_4, C_2H_4, C_2H_6, and MX_2. These reactions and subsequent decompositions must occur at well above 77 K since under matrix isolation conditions we now find no evidence for reaction products at 77 K or in argon matrices at 12 K with widely varying concentrations of metal and CH_3Br (as judged by IR spectroscopy). Only the spectrum of seemingly unperturbed CH_3Br was observed in the frozen matrices, and upon warming these matrices, we observed no evidence for reaction up to the point where matrix boil off (argon, > 30 K) or CH_3Br sublimation (150 K) allowed for no more spectral data to be collected. Furthermore, UV photolysis of the matrices after completion of the decomposition did not produce product bands.[10] This finding is particularly interesting since it is known that Fe–H_2O/argon and Fe–CH_4/argon matrices at 12 K upon photolysis yield HFeOH and $HFeCH_3$.[11-13] Thus, UV-excited Fe atoms attack bonds that are thermodynamically much stronger than C–Br. We do not observe formation of species such as $HFeCH_2Br$ either, so we draw the conclusion that the CH_3Br–Fe and CH_3Br–Fe* reactant pairs are unproductive. A possible explanation is as follows.

CH_3Br–Fe(Co)(Ni)(Pd). Since codeposition yields colored matrices, it is probable that a weak CH_3Br–M complex forms that is stable until considerably higher temperatures are attained, whereupon reaction occurs to yield unstable organometallic products. Furthermore, the CH_3Br–M complex does not react upon photolysis because the light may go into a charge-transfer band that does not lead to bond breaking.[14] Alternatively, the CH_3Br molecule is large enough to rapidly dissipate and thereby quench the excess energy possessed by M*, or, if bond breaking does occur, the Br species, is too large to migrate rapidly enough and far enough to allow formation of CH_3M–Br. Hydrogen from H_2O[11] or CH_4[12] would be capable of moving much more readily.



Group 2B (Cu, Ag, and Au). Earlier reports show that Cu, Ag, and Au atoms react with CH_3Br by abstraction processes where M–Br is formed with the subsequent formation of CH_3 radicals, which eventually yield hydrocarbon products.[3,15] These reactions must occur on matrix warmup since with Cu, Ag, and Au we did not observe reaction products in the matrix as monitored by IR. Photolysis also *yielded no products*, and since Ozin and co-workers have reported that CH_4–Cu matrices react upon photolysis,[16] we can invoke a rationale similar to that previously discussed for Fe, Ni, and Pd.

Main-Group Metals Mg, Al, Ga, In, Tl, Fe, Sn, and Pb. Ault's[1] CH_3Br–Mg work is completely reproducible. However, we do note that rather high concentrations of Mg in the matrix are necessary for a successful experiment.[17] It is not yet clear if this means Mg clusters are necessary or not, and further work is in progress.[17] It is important to gain a better understanding of this particular reaction in light of recent reports by Whitesides[18] demonstrating that alkyl halide–Mg surface reactions occur at transport-limited rates in ether solvents. This, of course, suggests

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(3) See Klabunde for discussion and references: Klabunde, K. J. "Chemistry of Free Atoms and Particles"; Academic Press: New York, 1980; p 86.

(4) Ozin, G. A.; Power, W. J. *Inorg. Chem.* **1978**, *17*, 2836.

(5) Hauge, R. H.; Kauffman, J. W.; Margrave, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 6005 and references therein.

(6) Tan, L. Y.; Pimentel, G. C. *J. Chem. Phys.* **1968**, *48*, 5202.

(7) Klabunde, K. J.; Roberts, J. S. *J. Organomet. Chem.* **1977**, *137*, 113.

(8) Klabunde, K. J. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 287.

(9) Klabunde, K. J.; Low, J. Y. F. *J. Am. Chem. Soc.* **1974**, *96*, 7674.

(10) A 140-W mercury UV lamp was used. See Experimental Section for more details.

(11) Hauge, R. H.; Margrave, J. L., unpublished results.

(12) Billups, W. E.; Konarski, M. M.; Hauge, R. H.; Margrave, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7393.

(13) We have found that H_2O impurity in an alkyl halide/argon matrix reacts photolytically with Fe atoms as shown for a H_2O/argon matrix.[10]

(14) Private communications with Professor G. Ozin.

(15) Timms, P. L. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 273.

(16) Ozin, G. A.; McIntosh, D. F.; Mitchell, S. A.; Garcia-Prieto, J. *J. Am Chem. Soc.* **1981**, *103*, 1574.

(17) For each M–CH_3Br system, several experiments were carried out at different furnace temperatures (different metal fluxes) with constant matrix gas inlet. Increased metal flux led to uniform increases in product bands. Therefore, for all metals studied, except Mg, the metal/matrix gas ratio did not appear to have a critical effect. This would suggest that clusters of Mg may be necessary for the oxidative addition reaction to occur, and this is supported by Ault's[1] observation and our observation of deeply colored CH_3Br/Mg matrices that could be due to $(Mg)_x$ species. We plan to carry out UV–visible spectroscopy studies of these and related reactions soon.

(18) Rogers, H. R.; Hill, C. L.; Fujiwara, Y.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 217 and accompanying papers.

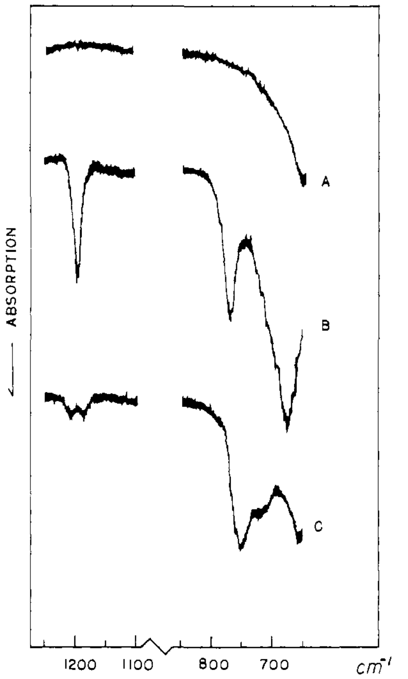

Figure 1. Partial infrared spectra of M/CH_3Br matrices at 77 K: (A) CH_3Br; (B) Al + CH_3Br; (C) Ga + CH_3Br.

Table I. Absorption Frequencies for CH_3MBr Species for Mg, Al, Ga, and In

species	codep temp, K	$\delta_{sym}(CH_3)$, cm^{-1}	$\delta_{asym}(CH_3)$, cm^{-1}	ref
CH_3AlBr	12	678	1200	this work
	77	675, 780	1200	
CD_3AlBr	77	540, 620	947	
CH_3GaBr	12	712, 750, 770	1208	this work
	77	720, 752	1179, 1203	
CD_3GaBr	77	570[a]	927, 942	
CH_3InBr	12	744		
	77	738		this work
CD_3InBr		b		
CH_3MgBr	15	541		1
CD_3MgBr	15	418		

[a] Approximate value; obscured by a parent band. [b] The yield was especially very low at 77 K, and with CD_3Br or in CD_3Br + CH_3Br reactions no clear bands were obtained.

that Mg clusters may be extremely reactive even in frozen matrices.

Other main-group metals are also reactive with CH_3Br. These metals include Al, Ga, and In, while Tl, Ge, Sn, and Pb did not reactive under 12 K/argon or 77 K/pure CH_3Br conditions in our hands. (Ault[1] reports that Ca atoms are reactive and Zn atoms are not.)

Figures 1 and 2 show the spectra obtained when CH_3Br–Al, CH_3Br–Ga, CD_3Br–Al, and CD_3Br–Ga codepositions are carried out. Equal mixtures of CH_3Br and CD_3Br yield spectra that are overlays of the spectra obtained separately, and we conclude that the product for each reaction contains just one methyl group. Table I records the absorption frequencies observed along with those observed by Ault[1] for CH_3MgBr. As expected there are shifts in the C–H bending modes upon change in metal, but the bands observed compare sensibly with those recorded by Ault. Due to these similarities and the CH_3Br/CD_3Br results, we assign our product bands to CH_3MBr species:

$$M + CH_3Br \rightarrow CH_3MBr$$

$$M = Al, Ga, In$$

The absorption intensities of product bands relative to parent bands were in the order Al > Ga > In. In the 12 K reactions, product bands for Ga and In increased in intensity upon UV irradiation while those for Al remained unchanged. The 77 K matrices showed no spectral changes upon irradiation. These data would suggest that Al atoms react most efficiently and completely whereas Ga and more so In only partially react under the 12 K conditions, but all three metals react completely at 77 K. Tl did not react. In the case of Ga/CH_3Br at 12 K three bands were observed instead of the usual one or two. We do not know what species these bands represent, but it is very likely an intermediate en route to CH_3GaBr since upon photolysis the 712- and 770-cm^{-1} bands decreased while the 750-cm^{-1} band increased. In 30 min of photolysis only one band was left centered at 750 cm^{-1}, which we attribute to CH_3GaBr.

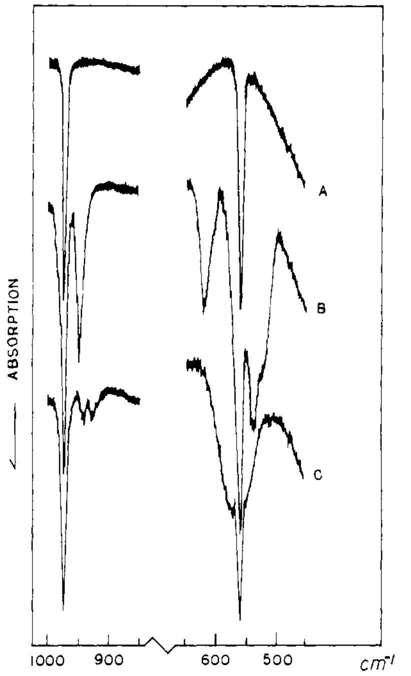

Figure 2. Partial infrared spectra of M/CD_3Br matrices at 77 K: (A) CD_3Br; (B) Al + CD_3Br; (C) Ga + CD_3Br.

During photolysis of the 12 K matrices with Al, Ga, and In, a band grew at 618 cm^{-1}. This band was totally absent in the transition-metal atom reactions even after photolysis. This band can be assigned to the free CH_3 radical[19] and must form during secondary photolysis of the CH_3MBr product, similar to what Ozin and co-workers found for CH_3CuH.[16]

Discussion

Although in a general way these results further demonstrate the remarkable reactivity of bare metal atoms/clusters at extremely low temperatures, they also indicate peculiar selectivities. If Mg is not included, it appears that two logical explanations can be given for the high reactivities of Al, Ga, and In: (1) These elements possess very low first ionization potentials. Thus, Al, Ga, In, and Tl metals have IPs around 6 V whereas all the other metals have IPs > 7.3 V. This is a striking difference. (2) Diatomic molecule bond energies for M–Br are highest for M = Al, Ga, In, and Tl.[20] In a way both arguments reflect the same idea. The lower IPs lead to more ionic M–Br bonding and thus stronger bonds. However, further rationale is needed for the Al > Ga > In >> Tl reactivity trend we observed. Heats of vaporization also are in that order and it is reasonable that reactivity would be governed partially by the energy put into the system during vaporization. So the Al, Ga, In, and Tl reactivity data

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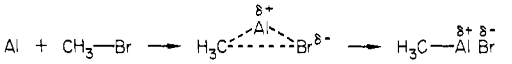
(19) (a) Andrews, L.; Pimentel, G. C. *J. Chem. Phys.* **1967**, *47*, 3637. (b) Milligan, D. E.; Jacox, M. E. *Ibid.* **1967**, *47*, 5146. (c) Andrews, L. In "Cryochemistry"; Ozin, G. A., Moskovits, M., Eds.; Wiley-Interscience: New York, 1976; 197.

(20) "Handbook of Chemistry and Physics", 56th ed.; CRC Press: Cleveland, Ohio, 1975–1976; p F-215.

can be rationalized by low IPs for all but higher potential energies due to heat of vaporization differences.[21]

Since low IP does seem to be important, a polar reaction mechanism would seem reasonable, perhaps as follows for Al:



Complete electron transfer may occur during the reaction, and only one Al (or Ga or In) atom is involved. In the case of Mg the reaction must be more complex and Mg clusters may be involved. In the case of transition metals, high IPs, low M–Br bond strengths, and unfilled d orbitals lead to the preference of CH_3Br---M complexation rather than oxidative addition.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work. Numerous discussions with Dr. R. Hauge of Rice University and G. A. Ozin of the University of Toronto have been very helpful.

Registry No. CH_3Br, 74-83-9; Al, 7429-90-5; Ga, 7440-55-3; In, 7440-74-6; Mg, 7439-95-4; Fe, 7439-89-6; Cu, 7440-50-8; Pb, 7439-92-1; Co, 7440-48-4; Ni, 7440-02-0; Pd, 7440-05-3; Ag, 7440-22-4; Au, 7440-57-5; Tl, 7440-28-0; Ge, 7440-56-4; Sn, 7440-31-5.

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[21] Professor P. S. Skell has found a similar reactivity dependency in M–H_2O reactions (28th IUPAC Congress, Aug 16–21, 1981, Vancouver, B.C., Canada, paper IN 002) and has used the term "atom potential" to describe this inherent reactivity.

Mechanism of the Cyanide-Induced Formation of Methyl Acetate from [(Methoxycarbonyl)methyl]cobalamin[1]

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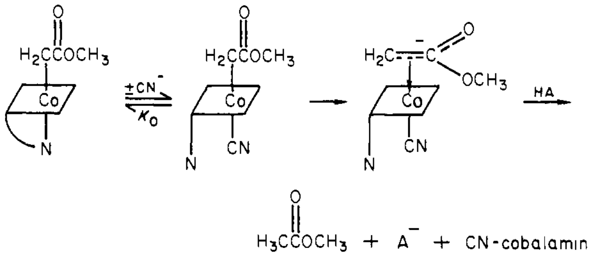
Contribution No. 1389 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254. *Received July 6, 1981*

Abstract: The addition of cyanide to [(methoxycarbonyl)methyl]cobalamin (MeO_2CCH_2Cbl, $MCMB_{12}$) results in the rapid, reversible formation of a cyanide addition compound ($K_0 = 0.044$ M), followed by cleavage of the carbon–cobalt bond and protonation to give methyl acetate. An analogous, slower reaction occurs with (carboxymethyl)cobalamin ($K_0 = 0.77$ M). At pH <8 the reaction of $MCMB_{12}$ occurs through specific-acid catalysis, with $k_{DOD}/k_{HOH} = 2.7$. This inverse isotope effect, the small normal solvent isotope effect of $k_{HOH}/k_{DOD} = 1.4$ at pH >9, and the absence of general-acid catalysis show that protonation of the leaving carbon atom does not occur in the rate-determining step. There is discrimination against the incorporation of tritium from the solvent into the product, with $[^1H]/[^3H] = 4.3$–4.9 at pH >9 and $[^1H]/[^3H] = 8.6$ at pH 1. These isotope effects establish a stepwise reaction mechanism, in which protonation of the intermediate occurs after the rate-determining step. α-Deuterium isotope effects of $k_{2H}/k_{2D} = 1.19 \pm 0.06$ at pH 11.4 and $k_{2H}/k_{2D} = 1.11 \pm 0.06$ at pH 0.9 demonstrate a significant change toward sp^2 hybridization of the α-carbon atom in the rate-determining transition state. Partial inversion of configuration at the α-carbon atom in the methyl acetate produced from (R)-$[^2H]MCMB_{12}$ in tritiated water shows that protonation must occur, at least in part, before separation of the enolate from cobalamin and provides evidence that the intermediate is a π complex with a lifetime of $>10^{-6}$ s. The small equilibrium isotope effect of $K_{HCN}/K_{DCN} = 2.3$ for the dissociation of hydrogen cyanide is attributed to the low bending frequency of the C–H bond.

The ability of adenosylcobalamin and other alkylcobalamins to undergo both cleavage and formation of carbon–cobalt bonds with remarkable ease is probably responsible for the biological activity of these compounds in mediating reactions that cannot be brought about by the simpler chemistry utilized by other coenzymes. This facile carbon–cobalt bond cleavage occurs to give electron-deficient, radical, or carbanionic products, depending on the ability of substituents on carbon to stabilize one or another of these species. The ease with which these different reactions occur reflects the easy accessibility of the three oxidation states of the products, Cob(I)alamin, Cob(II)alamin, and Cob(III)alamin, that are formed in the three modes of cleavage. The expulsion of leaving groups with a pair of electrons, leaving behind a Cob(III)alamin, is greatly facilitated by the addition to the trans position of cyanide anion or other groups that increase the electron density on cobalt.[2]

The experiments described here were undertaken in order to learn more about the chemistry of heterolytic carbon–cobalt bond cleavage. Adenosylcobalamin and [(methoxycarbonyl)methyl]cobalamin ($MCMB_{12}$) undergo cyanide-induced fragmentations that give Cob(III)alamin products and appear to proceed through the electron-rich, carbanionic class of mechanism.[3-5] It has been proposed that the cleavage of $MCMB_{12}$, to give methyl acetate as the product, proceeds through a direct, front-side displacement to expel the enolate anion of methyl acetate[4] or through an intermediate adduct in which cyanide ion adds to the α (trans) position, replacing the dimethylbenzimidazole ligand[5] (eq 1, in



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