added to a solution of 2-protoadamantanone,[17] **1d** (300 mg, 2 mmol), in carbon tetrachloride (5 mL) and stirred at 0 °C. The reaction mixture was stirred for additional hour at this temperature and overnight at room temperature and then poured onto ice (10 g). The resulting mixture was extracted with pentane (2 × 20 mL). The extracts were combined, washed with saturated $NaHCO_3$ solution (2 × 10 mL), and dried ($MgSO_4$). The solvent was evaporated, and the residue was sublimed in vacuo to give **1f** (348 mg, 87%; 95% pure by ^{13}C NMR): ^{13}C NMR ($CDCl_3$) δ 101.2 (s), 52.4 (d, 2 C), 37.4 (t), 35.0 (t), 33.7 (d), 32.7 (t), 28.0 (t), 27.6 (d), 21.1 (t); ^1H NMR ($CDCl_3$) δ 3.05-2.7 (m, 1 H) 2.7-2.2 (m, 3 H), 2.2-1.15 (m, 10 H); IR (KBr) 2940, 2860, 1460, 920, 895, 880, 805, 760, 740 cm^{-1}; MS, m/z 206 (M^+, 3%), 204 (M^+, 5), 171 (34), 170 (29), 169 (100), 168 (54), 133 (60), 91 (51), 79 (44), 77 (26). Anal. ($C_{10}H_{14}Cl_2$) C, H.

10,10-Dichloroprotoadamantane (**4f**) was prepared in 84% yield from 10-protoadamantanone[17] (**4d**) following the procedure described above. However, the reaction mixture was stirred at room temperture for 4 h rather than overnight. **4f** (95% pure by ^{13}C NMR): ^{13}C NMR ($CDCl_3$) δ 101.4 (s), 53.8 (d), 46.9 (d), 39.0 (t), 33.8 (t), 32.9 (d), 32.4 (d), 29.2 (t), 23.9 (t), 23.5 (t); ^1H NMR ($CDCl_3$) δ 2.85-1.35 (m, 14 H); IR (KBr) 2940, 2880, 1460, 830, 817, 804, 767, 748 cm^{-1}; MS, m/z 206 (M^+, 10%) 204 (M^+, 15) 171 (21), 170 (35), 169 (61), 168 (88), 133 (55), 121 (100), 95 (67), 91 (67) 79 (46) 77 (49). Anal. ($C_{10}H_{14}Cl_2$) C, H.

Protoadamantane-*2,2-d*$_2$ (1c) and -*10,10-d*$_2$ (4c). Lithium (70 mg, 10 mmol) and *tert*-butyl-*O*-*d*[35] alcohol (2.0 mL, 20 mmol) were added to a solution of geminal dichloride **1f** (348 mg, 1.7 mmol) in THF (7 mL, freshly distilled from $LiAlH_4$). The reaction mixture was refluxed with stirring overnight and then cooled to room temperature and poured into water (20 mL). The resulting suspension was extracted with pentane (2 × 30 mL). The extracts were combined, washed with water (2 × 40 mL), and dried ($MgSO_4$). The solvent was evaporated, and the crude product was sublimed in vacuo to give **1c** (202 mg, 86%; ≥98% pure by GC, DEGS, 100 °C; deuterium content: d_2 84%, d_1 15%, d_0 1%).

Protoadamantane-*10,10-d*$_2$ (**4c**) was obtained in 84% yield from **4f** by the procedure described above (≥97% pure by GC, DEGS, 100 °C; deuterium content: d_2 82%, d_1 16%, d_0 2%).

Protoadamantane-*6-d*$_1$ (5) was prepared in 88% yield by reduction of 6-bromoprotoadamantane[23] with lithium in *tert*-butyl-*O*-*d*[35] alcohol following the procedure described for preparation of **1c** (≥95% pure by GC, DEGS, 100 °C; deuterium content: d_1 88%, d_0 12%).

Acknowledgment. This work was supported by a grant from the Research Council of the Republic of Croatia (SIZ II). We thank Professors J. W. Larsen and M. M. Kreevoy for critical reading of the manuscript and Dr. Z. Meić for recording the ^2H NMR spectra.

Registry No. 1a, 94596-80-2; **1b**, 94668-58-3; **1c**, 94596-81-3; **1e**, 94596-88-0; **1f**, 94596-91-5; **2a**, 94596-82-4; **2b**, 94668-59-4; **2c**, 94596-83-5; **2e**, 33801-02-4; **3a**, 94596-84-6; **3b**, 94668-60-7; **3c**, 94596-85-7; **3e**, 94596-89-1; **4a**, 94596-86-8; **4b**, 94668-61-8; **4c**, 94596-87-9; **4e**, 94596-90-4; **4f**, 94596-92-6; **5**, 94596-95-9; $(PhCO_2)_2BH$, 94596-93-7; $(PhCO_2)_2BD$, 94596-94-8; D_2, 7782-39-0.

Cyclization of Acetylenic Carbonyl Compounds via Their Silyl Enol Ether Derivatives: A New Intramolecular C-Vinylation Induced by Mercury(II) Salts. Stereochemistry and Functionalization of the Intermediate Vinylmercurial

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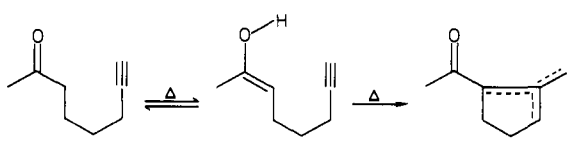
Abstract: By treatment with mercury(II) chloride (1.1 equiv) in the presence of HMDS (0.2 equiv), at room temperature followed by acidification with aqueous HCl–NaI, silyl enol ethers **2**, **5**, and **7** of ϵ-acetylenic ketones or aldehydes are cyclized in high yield into 2-alkylidene-1-oxocyclopentanes: silyl enol ethers of 4′- and 5′-alkyn-2-ylcycloalkanones **9** and **11** lead to spiro compounds, a methylene–cyclopentane and –cyclohexane unit, respectively, being formed in the reaction. In all products, the exocyclic position of the C=C double bond so formed is fully maintained. The reaction is multistep: a transient α-mercury carbonyl compound is formed, leading, via an intramolecular cis addition, to a vinylmercurial which can be functionalized by electrophilic substitution of the mercury atom with retention of configuration.

The thermal cyclization of unsaturated carbonyl compounds involving at first enolization and then an ene-type reaction, in which the shifted hydrogen is the enol one, is a well-known reaction (for a review, see ref 1). It has been extended to various types of carbonyl compounds, e.g., enones, enals, dienones, ynones, and diynones in particular,[1] but the high temperature necessary causes some compounds (e.g., most of the aldehydes)[2] to decompose or to resinify and an exocyclic double bond, when formed in the process, to migrate.[2,3]



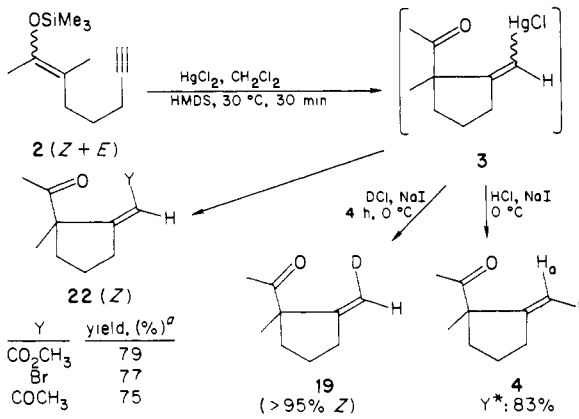
In our continued effort to find conditions under which the reaction temperature of these cyclizations could be lowered, we have shown that mercury(II) salts are efficient catalysts for the cyclization of easily enolizable acetylenic carbonyl compounds;[4] most monoketones react sluggishly, however, suggesting that enolization is rate limiting and the products suffer isomerization of their exocyclic double bond, as in the thermal cyclization.

In this article, we report the *fast regio- and stereospecific room-temperature cyclization* of some representative *acetylenic carbonyl compounds, via their trimethylsilyl enol ethers*, by treatment with mercury(II) chloride, followed by acidification with aqueous HCl–NaI[5] and observations bearing on the *mechanism of this reaction*, and exploit the *completely stereoselective functionalization of the vinylmercurial produced in the reaction.*

(1) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1.
(2) Bloch, R.; Le Perchec, P.; Rouessac, F.; Conia, J. M. *Tetrahedron* **1968**, *24*, 5971.
(3) Schostarez, H.; Paquette, L. A. *Tetrahedron* **1981**, *37*, 4431.
(4) Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801.
(5) Beletskaya, I. P.; Myshkin, A. E.; Reutov, O. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1965**, 226.

0002-7863/85/1507-1726$01.50/0

Scheme I. Mercury(II) Chloride Induced Regiospecific Cyclization of an ε-Acetylenic Ketone via Its Silyl Enol Ethers and Stereospecific Deuteration and Functionalization of the Cyclized Product



Y	yield, (%)[a]
CO_2CH_3	79
Br	77
$COCH_3$	75

[a] Isolated yield.

Results and Discussion

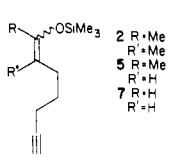
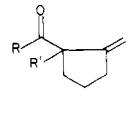
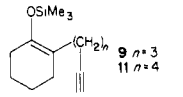
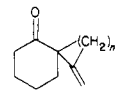
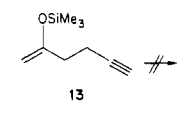
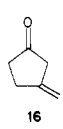
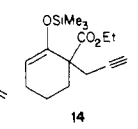
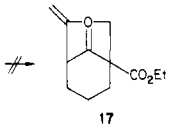
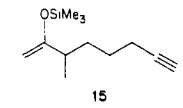
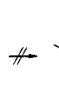
When, in a typical NMR experiment, the trimethylsilyl enol ether **2** ($Z + E$) of 3-methyloct-7-yn-2-one (**1**) and $HgCl_2$ (1 equiv) were mixed in $CDCl_3$, a fast reaction occurred without the need of any additive (e.g., water or ethanol[6]): at 30 °C, the singlet δ 0.40 for $OSi(CH_3)_3$ entirely disappeared within 30 min, while a singlet δ 0.60 for $(CH_3)_3SiCl$ appeared; a vinylic hydrogen signal also appeared at δ 5.85, supporting the presence of a vinylmercurial **3** in the solution (see, for instance, ref 8). This fast reaction strongly contrasts with the inertness, toward $HgCl_2$, of the silyl enol ethers of the corresponding saturated ketone 2-octanone and ethylenic ketone oct-7-en-2-one which remain unchanged after 6 h under the same conditions.

The behavior of the enol ethers **2** with $HgCl_2$, the formation of the vinylmercurial **3**, and its hydrolysis to the cyclized ketone **4** have been investigated in detail by GLC, using an internal standard (Scheme I). When the mixture of enol ethers **2** was added to a suspension of anhydrous $HgCl_2$ in CH_2Cl_2 containing hexamethyldisilazane (HMDS) (0.2 equiv),[9] both isomers disappeared within less than 5 min. The maximum yield of **4** (>96.5%) was obtained when a 30-min cyclization step (**2** → **3**) was followed by a 2-h hydrolysis step (**3** → **4**). Conditions of hydrolysis were found to be critical in many respects: when 5 M aqueous HCl (2 equiv) alone was used, the hydrolysis was very slow (~24 h) and use of a 8 M acid solution led to the isomerization of the double bond; but when NaI[10-13] (2 equiv) was added to the 5 M acid solution, a large enhancement of the hydrolysis rate was observed, without migration of the ethylenic double bond.

A variety of acetylenic carbonyl compounds were prepared and converted into their trimethylsilyl enol ethers **2**, **5**, **7**, **9**, and **11** (see Table I) and these were subjected to reaction with $HgCl_2$ and then with HCl–NaI under standard conditions.

The data of Table I reveal this cyclization to be a powerful and highly regioselective method with specific limitations. In all cases, the new carbon–carbon bond was formed between the enol carbon atom and the nonterminal sp carbon, leading to the formation of five-membered rings from **2**, **5**, **7**, and **9** and a six-membered ring from **11**. These cyclizations, termed α-type,[1] were faster in the reactions leading to the five-membered ring products. On the other hand, α′-type cyclizations, which would have led to **16**, **17**, and **18**, failed. These failures, though in line with the known difficulty of the α′-type thermal cyclization,[1] are in sharp contrast with the easy Pd(II)-promoted α′-type cyclizations of ethylenic silyl enol ethers described by Kende[14] and Saegusa.[15]

Table I. Mercury(II)-Induced Cyclization of Silyl Enol Ethers

enol ether[a,b]	product	isolated yield (%)
 2 R=Me, R′=Me; 5 R=Me, R′=H; 7 R=H, R′=H	 4 R=Me, R′=Me; 6 R=Me, R′=H; 8 R=H, R′=H	(83); (89); (60)[c]
 9 n=3; 11 n=4	 10 n=3; 12 n=4	(>90); (>80)
 13	 16	
 14	 17	
 15	 18	

[a] The enol ethers 2 and 5 were prepared by following general experimental procedures from ref 11 ($Me_3SiCl/Et_3N/DMF/120$ °C/7 days) or ref 12 (Me_3SiI/HMDS/room temperature/7 days): 7, 9, 11, and 14 by following ref 13 ($Me_3SiCl/Et_3N/NaI/CH_3CN$/room temperature/15 min and, for 7, then 70 °C/2 h); 14 and 15 by following ref 13 (90 °C/3 h). [b] For cyclization conditions, see the Experimental Section. [c] In this particular case, the NMR spectrum showed that 17% of the original ynal was present. Yield corrected for recovered ynal is 72%.

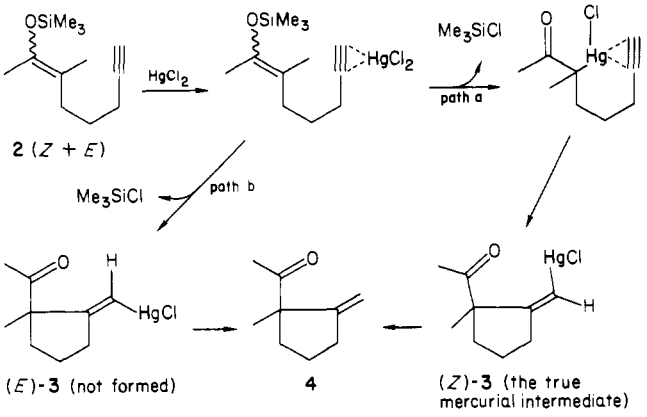
The α-type mercury-induced cyclization of silyl enol ether **7** gave the carboxaldehyde **8** in moderate yield (60%); however, all the intermediates in this reaction were found to be very unstable, and **8** itself cannot be chromatographed. When the cyclization step was lengthened, the NMR spectrum of the crude mixture showed a rapid decrease of the aldehydic hydrogen signal.

Finally, it is noteworthy that the hydrolysis conditions retain the thermodynamically unfavored exocyclic position of the ethylenic double bond, even for compounds **6** and **8** where conjugation might be very easy, and give a rare opportunity to prepare this kind of carbonyl compounds.

This intramolecular C-vinylation, is, to our knowledge, an unprecedented reaction. It results in a new cycloalkenylation which, in some respects, may be related to the palladium(II)-mediated cycloalkenylation of ethylenic trimethylsilyl enol ethers.[14,15] Two different mechanisms have been proposed for this latter reaction: (a) a fast oxo-π-allylpalladium(II) complex formation followed by a rate-determining cyclization[16] and (b) an intramolecular attack of the palladium-coordinated olefin on the electron-rich silyl enol ether.[17] A priori, mechanisms related to mechanism a or b above may also be proposed for the mercury(II)-induced cyclization of the silyl enol ethers of acetylenic carbonyl compounds. To shed light on this mechanism, the following observations are valuable: The acetylenic enol ether **2** ($Z + E$), when stirred with 1 equiv of $HgCl_2$, disappears com-

(6) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. T. *J. Org. Chem.* **1973**, *38*, 514.
(7) No ^{199}Hg H coupling was observed in this compound.
(8) Wells, F. R.; Kitching, W. *Aust. J. Chem.* **1964**, *17*, 1204.
(9) When the use of such an acid scavenger was omitted, the reaction ended up with 5–15% of the ynone **1**.
(10) Jensen, F. R.; Rickborn, B. "Electrophilic Substitution of Organomercurials"; McGraw-Hill: New York, 1968; pp 39 and 64.
(11) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. *J. Org. Chem.* **1969**, *34*, 2324.
(12) Miller, P. D.; McKean, D. R. *Synthesis* **1979**, 730.
(13) Cazeau, P.; Moulines, F.; Laporte, D.; Duboudin, F. *J. Organomet. Chem.* **1980**, *201*, C9–C13.
(14) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784.
(15) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494.
(16) Ito, Y.; Aoyama, H.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 4519.
(17) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808.

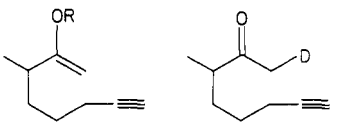
Scheme II. Possible Reaction Paths for the Reaction of Acetylenic Silyl Enol Ethers with Mercury(II) Chloride



pletely within 5 min; immediate hydrolysis affords **4** in only 50% (GC) yield (with recovered ynone **1**), whereas the (GC) yield is >96.5% when hydrolysis is carried out after 30 min of reaction. These results imply a fast first step, leading to an α-mercury ketone followed by a rate-determining cyclization step (see Scheme II, path a) clearly resembling mechanism a above. If the reaction took place via path b, then the yield of **4** would be maximum after 5 min, since the cyclized product **3** would be directly formed from the enol ether **2** and the configuration of the vinylmercurial **3** should be *E*.

It has been possible to determine which vinylmercurial ((*Z*)-**3** or (*E*)-**3**) is formed in the following way (see Scheme I): we know that electrophilic substitutions of vinylmercurials occur with retention of configuration at the carbon atom,[10] and we observed that the NMR signals of the two vinylic hydrogens of **4** appear fairly well separated at δ 4.95 (H_a) and δ 4.78 (H_b). Therefore, the intermediate vinylmercurial ((*Z*)-**3** or (*E*)-**3**) has been deuterolyzed. Mass spectrometric analysis of the product showed ~96% deuterium incorporation,[18] and the signal for the vinyl proton H_a at 4.95 ppm was reduced to ~8% of the normal value from its NMR spectrum; from these results a ratio (*Z*)-**19**:(*E*)-**19** >95:5 was deduced. Such a high ratio of (*Z*)-**19**:(*E*)-**19** is indicative of a cis addition on the triple bond as in Scheme II, path a, and is consistent with the formation *of a transient* α-mercury ketone, which may either add directly on the triple bond (four-centered mechanism) or transfer its mercury atom via a six-centered transition state involving an unstable O-mercury enolate.[19,20]

To further demonstrate the formation of an α-mercury ketone in the reaction, the isomer **20b**[21] of the enol ethers **2** was reacted with $HgCl_2$. It disappeared more slowly than **2** (~10 vs. ~5 min) but did react, Me_3SiCl being formed simultaneously. The NMR spectrum of the product, even after 24 h of reaction, showed no vinylic hydrogen, and deuterolysis afforded as the only product the uncyclized 1-deuterio-3-methyloct-7-yn-2-one (**21**) whose mass spectrum showed a parent peak at *m/e* 44 (DCH_2CO^+) and not at 43. Therefore, **20b** also gives an α-mercury ketone when treated with $HgCl_2$. Whereas the α-mercury ketone formed from **2** is short-lived ($t_{1/2}$ ~ 5 min at 30 °C), that from **20b** is stable for days, suggesting that seven-membered cycloalkanones will be hard to get through this reaction, as they are from **20a**, by simple heating.[1]



20a R=H
20b R=$SiMe_3$

21

Functionalization of vinylmercurials being readily effected,[22] the formation of **3** as an intermediate was likely to give an opportunity of great synthetic value for the preparation of functionalized cyclized compounds. In some preliminary experiments, compounds functionalized (**22** in Scheme I, with Y = CO_2CH_3, Br, and $COCH_3$) have been obtained in 79%, 77%, and 75% yield by treatment of **3** with CO + CH_3OH, NBS, and CH_3COCl, respectively, following the methods described in ref 22a,b and 22c. Only one isomer was found in all cases, and it is reasonable to assume that the compounds (*Z*)-**22** were formed.

These results merit some comments: (a) the good yield and the total stereospecificity of the functionalizations are obviously of synthetic value; (b) such a complete stereospecificity of the functionalizations confirms the formation of a single vinylmercurial intermediate, which must be (*Z*)-**3**.

In summary, $HgCl_2$ induces a fast room-temperature regioselective cyclization of acetylenic silyl enol ethers, leading stereospecifically by a cis addition on the triple bond into δ-oxocycloalkylidene mercurials, which may be hydrolyzed into β,γ-enones without isomerization of the exocyclic ethylenic double bond or further functionalized with retention of stereochemistry.

Experimental Section

General. ^1H NMR spectra were obtained at 90 MHz (or 60 MHz) in $CDCl_3$ on a Perkin-Elmer R 32 (or R 12A) spectrometer with tetramethylsilane as internal standard. Chemical shift values are reported as parts per million on the δ scale. IR spectra were recorded on a Perkin-Elmer 682 spectrometer. GCMS data were collected at 70 eV on a Girdel-Nermag R10-10 mass spectrometer. Gas chromatographic analyses were performed on an Intersmat IGC 120FB. GC yields were obtained by using an internal standard and predetermined response factors. Product yields are based on the weighted amount of silyl enol ether. All compounds, but **8**, were isolated by column chromatography over SiO_2, using pentane/ether (100:0 to 50:50) as the eluant.

Typical Experimental. To a well-stirred suspension of $HgCl_2$ (476 mg, 1.65 mmol) (dried over P_2O_5 under vacuum, 1 torr) in CH_2Cl_2 (8 mL) maintained at 30 °C, under a nitrogen atmosphere, was added a solution of 6-methyl-7-(trimethylsiloxy)oct-6-en-1-yne (**2**) (315 mg, 1.50 mmol) and hexamethyldisilazane (HMDS) (48 mg, 0.30 mmol) in CH_2Cl_2 (1 mL). After 30 min, the flask was cooled to 0 °C and HCl 5 M, 0.55 mL, aqueous solution and NaI (450 mg, 3.00 mmol) were added. Stirring was continued for 3 h, and the mixture was neutralized (solid $NaHCO_3$), filtered, dried (Na_2SO_4), and concentrated. Column chromatography of the residue over SiO_2 (5 g) using ether/pentane (0:100 to 50:50) as the eluant provided 172 mg (1.25 mmol, 83%) of 1-acetyl-1-methyl-2-methylenecyclopentane (**4**) (R_f = 0.49, ether/pentane 30:70): ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.3–1.9 (m, 4 H), 2.05 (s, 3 H), 2.1–2.6 (m, 2 H), 4.78 (t, J = 2 Hz, 1 H), 4.95 (t, J = 2 Hz, 1 H); IR (CCl_4) 3080 (w), 1710 (vs), 1650 (s); mass spectrum, *m/e* 138 (M^+), 95 (100%), 67, 55, 43.

Other Important Experimental Conditions are as follow: cyclization—**7** (0.25 h), HMDS (1 equiv); **11** (4 h); hydrolysis—**5** (3 h, −15 °C).

1-Acetyl-2-methylenecyclopentane (6). ^1H NMR 1.5–2.1 (m, 4 H), 2.18 (s, 3 H), 2.5–2.6 (m, 2 H), 3.4 (m, 1 H), 4.95 (t, J = 2 Hz, 1 H), 5.05 (t, J = 2 Hz, 1 H); IR (neat) 3080 (w), 1710 (vs), 1650 (s).

2-Methylenecyclopentanecarboxaldehyde (8). ^1H NMR 1.4–2.9 (m, 6 H), 3.35 (m, 1 H), 5.05 (m, 1 H), 5.25 (m, 1 H), 9.50 (d, J = 3 Hz, 1 H); IR (neat) 3080 (w), 2720 (m), 1720 (vs), 1650 (s).

10 and **12**: Spectral data in agreement with ref 23.

1-Acetyl-1-methyl-2(*Z*)-(deuteriomethylene)cyclopentane (19). ^1H NMR 1.20 (s, 3 H), 1.30–1.90 (m, 4 H), 2.08 (s, 3 H), 2.15–2.60 (m, 2 H), 4.78 (t, J = 2 Hz, 1 H); IR (CCl_4) 3050 (vw), 2260 (w), 1710 (vs)

(18) The deuterolysis being found about 2 times slower than the protolysis and the D content of the DCl solution being 99%, the formation of **4** (4%) should arise from a competitive protolysis to an extent of 2%, the remaining 2% arising from a late hydrolysis of some residual **3**.

(19) Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761. Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(20) As stressed by one of the referees, a number of mechanisms could fulfill the syn selectivity observed in the cyclization and especially an "ene reaction of a transient oxygen bound mercury analogous to the protic case". We fully agree with this statement and would not infer any mechanistic speculation about the cyclization step from the present results.

(21) **20b** was isolated by GLC from a nonequilibrated mixture of **2** + **20b**.

(22) (a) Larock, R. C. *J. Org. Chem.* **1975**, *40*, 3237. (b) Riedicker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842. (c) Larock, R. C.; Bernhart, J. C. *Tetrahedron Lett.* **1976**, *36*, 3097. (*The reaction time was lengthened to 4 h.*)

(23) Mandville, G.; Leyendecker, F.; Conia, J. M. *Bull. Soc. Chim. Fr.* **1973**, 963.

1650 (s); mass spectrum, *m/e* 139 (M^+), 96 (100%), 68, 67, 56, 55, 39.

1-Acetyl-1-methyl-2(*Z*)-(methylcarboxymethylene)cyclopentane (22) (Y = CO_2CH_3). ^1H NMR 1.27 (s, 3 H), 1.40–2.0 (m, 4 H), 2.10 (s, 3 H), 2.7–3.2 (m, 2 H), 3.68 (s, 3 H), 5.65 (t, J = 2 Hz, 1 H); IR ($CDCl_3$) 1715 (vs), 1650 (s); mass spectrum, *m/e* 165, 154 (100%), 122, 95, 79, 77, 43.

1-Acetyl-1-methyl-2(*Z*)-(bromomethylene)cyclopentane (22) (Y = Br). ^1H NMR 1.30 (s, 3 H), 1.45–2.00 (m, 4 H), 2.12 (s, 3 H), 2.20–2.80 (m, 2 H), 6.05 (t, J = 2 Hz, 1 H); IR ($CDCl_3$) 3080 (w), 1705 (vs), 1635 (m); mass spectrum, *m/e* 175, 173, 137, 93, 91, 77, 43 (100%), 39.

1-Acetyl-1-methyl-2(*Z*)-(acetylmethylene)cyclopentane (22) (Y = $COCH_3$). ^1H NMR 1.25 (s, 3 H), 1.35–2.05 (m, 4 H), 2.10 (s, 3 H), 2.7–3.1 (m, 2 H), 6.05 (t, J = 2 Hz, 1 H); IR ($CDCl_3$) 1710 (vs), 1690 (s), 1615 (vs), 1250 (vs); mass spectrum, *m/e* 180 (M^+), 138, 95, 80, 43 (100%).

Purification Technique for Compound 8: After workup, the crude mixture was distilled bulb to bulb (room temperature, 0.08 torr, dry ice cooling). Enal **8** and its precursor, hept-6-ynal were collected altogether.

Acknowledgment. M.A.B gratefully acknowledges a grant of the CAPES (Centre de Aperfeicoamento de Pressoal de Ensino Superior do Brasil). Support of this research by the CNRS and Université de Paris-Sud with Research grants to UA 478 is acknowledged.

Registry No. (*E*)-**2**, 94645-03-1; (*Z*)-**2**, 94645-04-2; **4**, 88459-76-1; **5**, 94645-05-3; **6**, 54683-73-7; **7**, 94645-06-4; **8**, 94645-07-5; **9**, 94645-08-6; **10**, 42988-49-8; **11**, 94645-09-7; **11**, 42797-98-8; **19**, 94645-10-0; **20b**, 94645-11-1; **21**, 94645-12-2; **22** (Y = CO_2CH_3), 94645-13-3; **22** (Y = Br), 94645-14-4; **22** (Y = $COCH_3$), 94645-15-5; NBS, 128-08-5; CO, 630-08-0; CH_3OH, 67-56-1; CH_3COCl, 75-36-5; $HgCl_2$, 7487-94-7.

The Structure of a B_{12} Coenzyme: Methylcobalamin Studies by X-ray and NMR Methods

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Abstract: The B_{12} coenzyme methylcobalamin crystallizes in the orthorhombic space group $P2_12_12_1$, with Z = 4 and a = 17.887 (6) Å, b = 32.68 (1) Å, c = 17.447 (5) Å, V = 10197 (6) Å^3. The structure was determined by X-ray diffraction methods. The cobalt atom was located from the Patterson map, and lighter atoms were located from subsequent electron density maps. The final R value, after least-squares refinements, is 0.146 based on 4254 observed intensities (diffractometer data) and 538 parameters (isotropic refinement except for Co and P which were refined anisotropically). Many hydrogen atoms in the methylcobalamin molecule, including those in the methyl group attached to the cobalt atom, were located from difference electron density maps. Approximately 40 sites for water molecules (many disordered) plus one disordered molecule of acetone of crystallization were located. The structure of methylcobalamin is very similar to that of cyanocobalamin (vitamin B_{12}), although in methylcobalamin there is some disorder in the area of the phosphate group. The orientation of the benzimidazole group and the conformations of most side chains are remarkably similar in the two molecules, with the exception of the orientations of the amide groups at the ends of side chains. These apparently can rotate to accommodate nearby hydrogen-bonding groups. The Co–C (methyl) bond length is 1.99 (2) Å, the Co–N (Bzm) bond length is 2.19 (2) Å, and the four Co–N (equatorial) bond lengths are 1.88 (2), 1.97 (2), 1.93 (2), and 1.89 (2) Å. The corrin ring system is not folded about the Co–C(10) line as much as in 5′-deoxyadenosylcobalamin (coenzyme B_{12}). The ^1H NMR and ^{31}P NMR spectra of a series of cobalamins with H_2O, CN, CH_2CN, CH_2CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, and 5′-deoxyadenosyl as (upper) axial ligands are reported. The H(BC7) of the benzimidazole group, H(RC1), and ^{31}P resonances (except in the case of charged H_2O cobalamin) follow reasonable trends with respect to the donor ability of the alkyl group. These resonances also suggest that in the compound containing the bulky axial $CH_2CH(CH_3)_2$ group, there are some steric interactions with the corrin side chains. Thus, NMR techniques may prove useful in assessing conformational and structural changes in cobalamins in much the same way that such spectroscopic methods have proved to be useful with B_{12} model compounds. The structural and NMR studies reveal no particular steric interactions involving the methyl group of methylcobalamin. Furthermore, the similarity in structure of the nonalkyl portion of coenzyme B_{12} and methyl B_{12}, one with a bulky and one with a small alkyl ligand, suggests that the bulkiness of the alkyl substituent in coenzyme B_{12} is not a main structural determinant.

According to Halpern,[1] the B_{12} prosthetic group, coenzyme B_{12} or 5′-deoxyadenosylcobalamin (DBC), can be considered to be an "organic radical carrier" much as the heme group in hemoglobin is a dioxygen carrier. In both types of protein systems, the conformation of the protein influences the ability of the metal center to bind the carried species (radical or dioxygen);[2-4] therefore, the relationship between the structure at the metal center and its function is both intriguing and important. In many B_{12} holoenzymes, the Co–C bond in coenzyme B_{12} is readily cleaved to produce, eventually, a protein-bound substrate radical. This protein-bound radical then undergoes rearrangement reactions that are often not favored by the analogous (unbound) free radical. In a similar way, in hemoglobin the affinity for ligands other than oxygen and the irreversible oxidation of the heme groups are greatly modulated by the protein.

Recently, Finke[5-7] has critically reviewed aspects of the B_{12}

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(1) Halpern, J. *Pure Appl. Chem.* **1983**, *55*, 1059.
(2) Toscano, P. J.; Marzilli, L. G. *Prog. Inorg. Chem.* **1984**, *31*, 105.
(3) Dolphin, D., Ed. "B_{12}"; Wiley-Interscience: New York, 1982; 2 volumes.
(4) Glusker, J. P. In "B_{12}"; Dolphin, D., Ed.; Wiley: New York, 1982; Vol. 1, p 23.
(5) Finke, R. G.; Schiraldi, D. A.; Mayer, B. J. *Coord. Chem. Rev.* **1984**, *54*, 1.
(6) Finke, R. G.; McKenna, W. P.; Schiraldi, D. A.; Smith, B. L.; Pierpont, C. *J. Am. Chem. Soc.* **1983**, *105*, 7592.
(7) Finke, R. G.; Schiraldi, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 7605.

0002-7863/85/1507-1729$01.50/0