Acknowledgment. We thank Professors K. P. C. Vollhardt, R. Bergman, and T. Vermeulen for helpful comments concerning this research project. We also wish special thanks to Dr. H. Heinemann of LBL for encouragement and support of this project. The constructive comments of one of the referees was also greatly appreciated by the authors. This study was jointly support by the Director, Office of Energy Research, Office of Basic Energy Science, Chemical Sciences Division, and the Assistant Secretary of Fossil Energy, Office of Coal Research, Liquefaction Division of the U.S. Department of Energy through the Pittsburgh Energy Technology Center under Contract No. DE-AC03-76SF00098.

Reglstry No. 1, 120-12-7; **2**, 85-01-8; **3**, 129-00-0; **4**, 85-02-9; **5**, 230-27-3; **6**, 229-87-8; **7**, 260-94-6; **8**, 91-22-5; **11**, 781-43-1; **12**, 82706-19-2; **13**, 82706-20-5; **15**, 2141-42-6; **16**, 5223-80-3; **17**, 40174-35-4; H_2O, 7732-18-5; $Mn_2(Co)_8(Bu_3P)_2$, 15609-33-3; $Fe(CO)_4(Bu_3P)$, 18474-82-3; $Co_2(CO)_6(Ph_3P)_2$, 24212-54-2; $Fe(CO)_5$, 13463-40-6; $H_4Ru_4(CO)_{12}$, 34438-91-0; $RuCl_2(CO)_2(Ph_3P)_2$, 14564-35-3; $Ru_3(CO)_{12}$, 15243-33-1; $RhCl_2(py)_2(dmp)BH_4$, 24436-16-6; $Rh_6(CO)_{16}$, 28407-51-4; $Cr(CO)_6$, 13007-92-6; $Mo(CO)_6$, 13939-06-5; $W(CO)_6$, 14040-11-0; $Mn_2(CO)_{10}$, 10170-69-1; $Co_2(CO)_8$, 10210-68-1; $Re_2(CO)_{10}$, 14285-68-8; $Mo(CO)_5(Bu_3P)$, 15680-62-3; $Os_3(CO)_{12}$, 15696-40-9; 9,10-dihydrophenanthridine, 82692-08-8; 9,10-dihydroacridine, 92-81-9; 1,2,3,4-tetrahydroquinoline, 635-46-1; 5,6,7,8-tetrahydroquinoline, 10500-57-9.

Deglycobleomycin: Total Synthesis and Oxygen Transfer Properties of an Active Bleomycin Analogue

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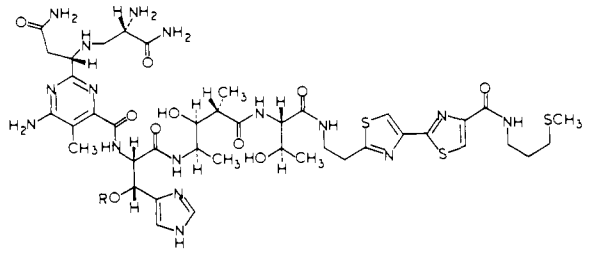
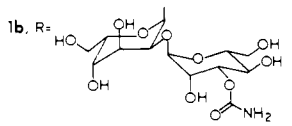
Received April 13, 1982

Bleomycin is the generic name that has been given to a family of clinically useful antitumor antibiotics.[1,2] The bleomycins are believed to mediate their therapeutic effect via oxidative degradation of DNA.[1] This transformation has been investigated intensively, in part because such studies may permit the design of structurally simpler congeners of bleomycin having analogous biological properties. Presently, we describe a practicable total synthesis of deglycobleomycin (**1a**),[3] a redox-active analogue of bleomycin (**1b**) capable of oxidative degradation of DNA.[4] Also reported is the anaerobic activation of Fe(III) and Cu(II) deglycobleomycin by iodosobenzene and the abilility of the active species to degrade DNA and to transfer oxygen to simple olefins in analogy with cytochrome P-450.

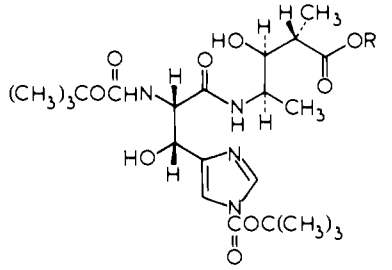


1a, R = H



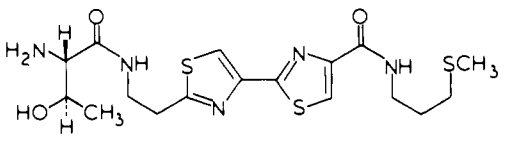
1b, R =

Coupling of N^{α},N^{im}-di-*tert*-butoxycarbonyl-L-erythro-β-hydroxyhistidine[5] and benzyl (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvalerate[5] (DCC, HOBt, DMF, 25 °C, 16 h) provided dipeptide **2a** as a glassy solid in 62% yield, $[\alpha]^{24}_D$ +20.3° (*c* 2.72, CH_3OH).[6] Following hydrogenolysis of the dipeptide (1 atm H_2, 10% Pd/C, 1.5 h), **2b**[6] was condensed with bithiazole derivative **3**[7] via the agency of DCC–HOBt (DMF, 40 h), to provide the N-protected derivative of **4** as a glassy solid after chromatographic purification on silica gel (yield 56%), $[\alpha]^{24}_D$ +15.1° (*c* 1.50, CH_3OH).[6] The carbamate protecting groups were removed



2a, R = $CH_2C_6H_5$

2b, R = H



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* To whom correspondence should be addressed at the Department of Chemistry.

(1) (a) Umezawa, H. *Biomedicine* **1973**, *89*, 459. (b) Umezawa, H. In "Bleomycin: Current Status and New Developments"; Carter, S. K.; Crooke, S. T.; Umezawa, H., Eds.; Academic Press: New York, 1978; p 15 ff. (c) Hecht, S. M. In "Bleomycin: Chemical, Biochemical and Biological Aspects"; Hecht, S. M., Ed.; Springer-Verlag: New York, 1979; p 1 ff.

(2) (a) Umezawa, H. *Prog. Biochem. Pharmacol.* **1976**, *11*, 18. (b) Ichikawa, T. *Ibid.* **1976**, *11*, 143. (c) Carter, S. K.; Blum, R. H. *Ibid.* **1976**, *11*, 158. (d) Bonadonna, G.; Tancini, G.; Bajetta, E. *Ibid.* **1976**, *11*, 172. (e) Depierre, A. *Ibid.* **1976**, *11*, 195. (f) Rygard, J.; Hansen, H. S. *Ibid.* **1976**, *11*, 205. (g) Rathert, P.; Lutzeyer, W. *Ibid.* **1976**, *11*, 223.

(3) Other workers have recently described what is presumably a relay synthesis of deglycobleomycin A_2. See: Saito, S.; Umezawa, Y.; Morishima, H.; Takita, T.; Umezawa, H.; Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 529.

(4) Oppenheimer, N. J.; Chang, C.; Chang, L.-H.; Ehrenfeld, G.; Rodriguez, L. O.; Hecht, S. M. *J. Biol. Chem.* **1982**, *257*, 1606.

(5) N^{α},N^{im}-Di-*tert*-butoxycarbonyl-L-erythro-β-hydroxyhistidine was formed by treatment of L-erythro-β-hydroxyhistidine (Hecht, S. M.; Rupprecht, K. M.; Jacobs, P. M. *J. Am Chem .Soc.* **1979**, *101*, 3982) with *tert*-butyl azidoformate (DMF, 25 °C, 20 h, 66%); benzylation ($C_6H_5CH_2OH$, HCl, 25 °C, 12 h) of (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvaleric acid (Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 1232) provided the requisite ester in quantitative yield as a glassy solid.

(6) (Partial) ^1H NMR spectra: **2a** ($CDCl_3$–D_2O, $(CH_3)_4Si$) δ 1.00 (d, 3), 1.18 (d, 3), 1.36 (s, 9), 1.54 (s, 9), 2.47 (m, 1), 3.73 (m, 1), 3.89 (m, 1), 4.41 (q, 1), 4.88 (d, 1), 5.05 (s, 2), 5.93 (d, 1), 6.74 (d, 1), 7.28 (s, 6), 7.96 (s, 1); **2b** ($CDCl_3$–D_2O, $(CH_3)_4Si$) δ 1.05 (d, 3), 1.15 (d, 3), 1.31 (s, 9), 1.55 (s, 9), 2.3–2.6 (m, 1), 3.7–4.0 (m, 2), 4.37 (d, 1), 4.81 (d, 1), 7.30 (s, 1), 8.00 (s, 1); **3** (D_2O, DSS) δ 1.75 (t, 2), 1.98 (s, 3), 2.45 (t, 2), 7.69 (s, 1), 7.86 (s, 1); di-*N*-BOC-**4** ($CDCl_3$–D_2O, $(CH_3)_4Si$) δ 1.40 (s, 9), 1.60 (s, 9), 1.94 (t, 2), 2.11 (s, 3), 2.58 (t, 2), 4.49 (d, 1), 4.90 (d, 1), 7.37 (s, 1), 7.81 (s, 1), 8.02 (s, 1), 8.08 (s, 1); **4** (D_2O, DSS) δ 1.81 (t, 2), 2.01 (s, 3), 2.51 (t, 2), 7.11 (s, 1), 7.73 (s, 1), 7.90 (s, 1), 8.00 (s, 1).

(7) Bithiazole derivative **3** was formed in analogy with tripeptide S (Levin, M. D.; Subrahamanian, K.; Katz, H; Smith, M. B.; Burlett, D. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1452), by treatment of the acid chloride of 2′-(2-(trifluoroacetamido)ethyl)-2,4′-bithiazole-4-carboxylic acid with 3-(methylthio)propylamine (CH_2Cl_2, Et_3N, DMAP). The fully blocked product was isolated as colorless crystals from CH_2Cl_2–hexane (67%, mp 126–128 °C) and converted to the free amine by treatment with aqueous NH_4OH in CH_3OH. The amine was isolated as a colorless oil in 87% yield (NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.66 (br s, 2), 1.90 (m, 2), 2.10 (s, 3), 2.57 (t, 2), 3.17 (m, 4), 3.53 (m, 2), 7.66 (br s, 1), 7.87 (s, 1), 8.10 (s, 1)) and condensed with 2,4-dinitrophenyl-*N*-(*o*-nitrophenylsulfenyl)threoninate to give the NPS derivative of **3** (68%, mp 108 °C). Conversion to **3** was accomplished by treatment of the blocked derivative with concentrated HCl in 1:1 $CHCl_3$–CH_3OH at 25 °C. Compound **3** (·HCl) was obtained as a pale yellow glass in 94% yield.[6]

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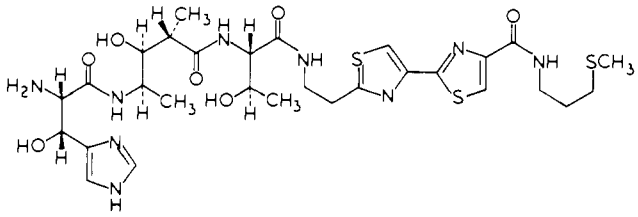
(CF_3COOH, CH_3SCH_3, 0 °C, 1 h), and the product was purified by chromatography on Amberlite XAD-2, affording **4** as a pale



4

yellow foam in 87% yield; $[\alpha]^{25}_D$ +7.3° (*c* 1.0, CH_3OH).[6] Compound **4** was condensed with BOC–pyrimidoblamic acid[8] by using diphenylphosphoryl azide in DMF (Hünigs base, 25 °C, 36 h). Following extractive workup, the product was deblocked (3:5 CH_3SCH_3–CF_3COOH, 0 °C, 1 h) and purified chromatographically[9] to afford deglycobleomycin demethyl A_2 in 36% overall yield from **4**. The product was identical with authentic deglycobleomycin demethyl A_2,[10,11] as judged by comparison of chromatographic properties on TLC and CM-Sephadex C-25, as well as the 360-MHz ^1H NMR spectra of the two.[4] Synthetic deglycobleomycin also mediated O_2-dependent degradation of *E. coli* [^3H]DNA, as reported[4] for authentic deglycobleomycin, and was shown to have the same oxygen-transfer properties as the authentic material, as judged by the criteria discussed below.

Although many congeners of bleomycin have been tested for their ability to degrade DNA and to inhibit the growth of transformed mammalian cells in vitro,[12] only those species modified at the C terminus have shown significant activity relative to bleomycin at concentrations limiting for activity of the parent antibiotic. In this sense deglycobleomycin is unique, as it has been shown to degrade DNA about half as well as bleomycin[4] over a range of concentrations (Ehrenfeld, G., unpublished result). Deglycobleomycin is also known to form a Fe(II)·CO complex having fundamentally different geometry than bleomycin·Fe(II)·CO,[4] the latter of which is thought to be analogous in structure to the species formed from bleomycin·Fe(II) and O_2 during aerobic activation of bleomycin.[13] In an effort to define further the functional relationship between bleomycin and deglycobleomycin activity, we sought to compare the two in additional assay systems. Recent experiments have established that bleomycin·Fe(III) and bleomycin·Cu(II) can be activated anerobically in the presence of iodosobenzene and that the activated compounds transfer oxygen to *cis*-stilbene but not to *trans*-stilbene and also mediate the release of [^3H]thymine from radiolabeled *E. coli* DNA.[14] Comparative experiments were carried out by using deglycobleomycin.

Admixture of iodosobenzene to an anerobic methanolic solution containing synthetic deglycobleomycin demethyl A_2, Fe(III), and *cis*-stilbene resulted in formation of *cis*-stilbene oxide as the major product (29% conversion, based on C_6H_5IO).[15,16] Also produced to a lesser extent was *O*-methylhydrobenzoin (<5%), whose formation from *cis*-stilbene oxide can be demonstrated under the reaction conditions. Essentially identical results were obtained by using naturally derived deglycobleomycin demethyl A_2. The same two products were obtained when Cu(II) was used in place of Fe(III) in these experiments, although *O*-methylhydrobenzoin was the predominant product. Consistent with observations made for bleomycin, deglycobleomycin would not oxidize *trans*-stilbene. Moreover, no epoxidation of *cis*-stilbene was observed in control experiments that lacked deglycobleomycin.

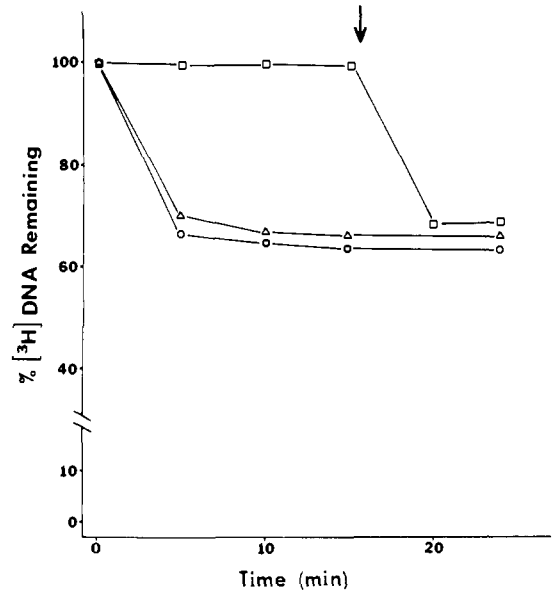


Figure 1. Release of [^3H]thymine from radiolabeled *E. coli* DNA in the presence of deglycobleomycin B_2. Reaction mixtures (1.0 mL) contained 50 mM, Na^+–cacodylate buffer, pH 7.0, 2.5 μM *E. coli* [^3H]DNA (specific activity 145 Ci/mol), 25 μM deglycobleomycin B_2, and either 25 μM $FeCl_3$ (○) or 25 μM $CuCl_2$ (△). Prior to the initiation of the reactions by dropwise addition of a solution of iodosobenzene (final concentration 100 μM), the reaction mixtures were purged with oxygen-free argon for 10 min. The incubations were maintained at 25 °C, and aliquots were removed at predetermined time intervals, diluted with unlabeled calf thymus DNA, and added to 1.0 mL of cold 10% trichloroacetic acid. The precipitated DNA was collected by filtration and used for determination of radioactivity. A control incubation employing 25 μM $Fe(NH_4)_2(SO_4)_2$ (but no iodosobenzene) was assayed initially in the absence of oxygen (□); this reaction mixture was opened to the atmosphere after 15 min (arrow), and additional aliquots were removed for assay.

Deglycobleomycin was next tested for its ability to degrade DNA. In the presence of iodosobenzene and Cu(II) or Fe(III), an anaerobic solution of deglycobleomycin B_2 effected the release of [^3H]thymine from radiolabeled *E. coli* DNA (Figure 1) and concomitant DNA strand scission (Ehrenfeld, G., unpublished result). A control experiment utilizing deglycobleomycin B_2·Fe(II), but no iodosobenzene, was shown to require O_2 for DNA degradation and to mediate that transformation to about the same extent as the anaerobic systems. Repetition of these experiments with other deglycobleomycins gave the same results.

Thus, in common with bleomycin, deglycobleomycin is capable of transferring oxygen in a fashion reminiscent of oxygenated

(8) (a) Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umezawa, H.; Kobayashi, S.; Otsuka, M.; Narita, M.; Ohno, M. *J. Am. Chem. Soc.* **1980**, *102*, 6631. (b) Arai, H.; Hagmann, W. K.; Suguna, H.; Hecht, S. M. *Ibid.* **1980**, *102*, 6633.

(9) Following desalting on Amerblite XAD-2, the product was converted to the Cu(II) salt and applied to a column of CM-Sephadex C-25 (1.4 × 78 cm). The column was washed with a linear gradient of NaCl (0–1.0 M) containing 0.05 M citrate buffer, pH 4.5. The fractions containing the desired product were treated with 1.0 g of disodium EDTA and again applied to an XAD-2 column for desalting and demetalation.

(10) Muraoka, Y.; Suzuki, M.; Fujii, A.; Umezawa, Y.; Naganawa, H.; Takita, T.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 353.

(11) Deglycobleomycin demethyl A_2 can be converted to deglycobleomycin A_2 by methylation with methyl iodide (Aoyagi, Y., unpublished results) and should provide access to many other C-terminal analogues of deglycobleomycin via the intermediacy of deglycobleomycinic acid (Tanaka, W.; Takita, T. *Heterocycles* **1979**, *13*, 469).

(12) See, e.g.: Takahashi, K.; Ekimoto, H.; Aoyagi, S.; Koyu, A.; Kuramochi, H.; Yoshioka, O.; Matsuda, A.; Fujii, A.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 36.

(13) Burger, R. M.; Horwitz, S. B.; Peisach, J.; Wittenberg, J. B. *J. Biol. Chem.* **1979**, *254*, 12299.

(14) Murugesan, N.; Ehrenfeld, G. M.; Hecht, S. M. *J. Biol. Chem.* **1982**, *257*, 8600.

(15) In a typical experiment, an anerobic solution containing 50 μg (0.096 μmol) of $Fe(ClO_4)_3$ and 100 μg (0.07 μmol) of deglycobleomycin in 45 μL of 65% aqueous methanol was treated with 2 mg (11.1 μmol) of *cis*-stilbene in 100 μL of methanol. Iodosobenzene (0.5 mg, 2.3 μmol) was then added dropwise (microsyringe) from a 20-μL solution over a period of 8 min. After 2 h at 25 °C, the reaction mixture was concentrated, and the products were purified by chromatography (silica gel TLC). The products were analyzed by HPLC vs. authentic samples and by 360-MHz ^1H NMR spectroscopy.

(16) The formation of *cis*-stilbene oxide occurred via a(n unstable) ternary complex formed from deglycobleomycin, Fe(III), and iodosobenzene; iodobenzene was isolated as a byproduct of this process.

cytochrome *P*-450[17] and of effecting DNA degradation via aerobic or anerobic activation. It seems reasonable to conclude that deglycobleomycin represents an attractive lead structure for synthetic modification, as well as a species that can help to define the range of metal-coordination geometries consistent with the expresion of bleomycin–like activity. The ability of deglycobleomycin to inhibit the growth of transformed mammalian cells via degradation of intracellular DNA is under active investigation.

Acknowledgment. We thank Professor Iwao Tabushi for a helpful discussion during the course of this work. This investigation was supported by PHS Research Grants CA27603 and CA-29235.

Registry No. 1a, 82691-97-2; deglycobleomycin A_2, 78193-35-8; **2a**, 82691-98-3; **2b**, 82691-99-4; **3**, 82692-00-0; **3**·NPS derivative, 82692-06-6; **3**·HCl, 82692-07-7; **4**, 82692-01-1; **4** di *N*-BOC, 82692-02-2; **4** BOC-pyrimidoblamic acid, 82692-05-5; N^{α},N^{im}-di-*tert*-butoxycarbonyl-L-erythro-β-hydroxyhistidine, 82692-03-3; benzyl (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvalerate, 82692-04-4; BOC-pyrimidoblamic acid, 75452-30-1; 2′-[2-(trifluoroacetamido)ethyl]-2,4′-bithiazole-4-carbonyl chloride, 76275-92-8; 3-(methylthio)propylamine, 4104-45-4; 2′-[2-(*tert*-butoxycarbonylamino)ethyl]-4-[3-(methylthio)propylaminocarbonyl]-2,4′-bithiazole, 78175-35-6; 2′-(2-aminoethyl)-4-[3-(methylthio)aminocarbonyl]-2,4′-bithiazole, 78175-36-7; 2,4-dinitrophenyl-*N*-(*o*-nitrophenylsulfenyl)threoninate, 82730-85-6; Fe(III), 20074-52-6; Cu(II), 15158-11-9; O_2, 7782-44-7.

(17) (a) Groves, J. T.; Krichan, S.; Avaria, G. E.; Nemo, T. E. In "Biomimetic Chemistry"; American Chemical Society: Washington, D.C., 1980; Adv. Chem. Ser. No. 191, p 227 ff. (b) Tabushi, I.; Koga, N. *Ibid.*, p 291 ff.

[1.1.1]Propellane†

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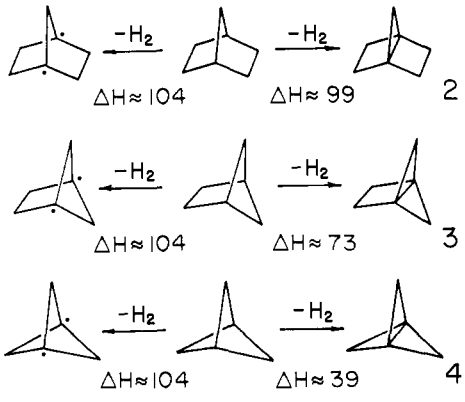
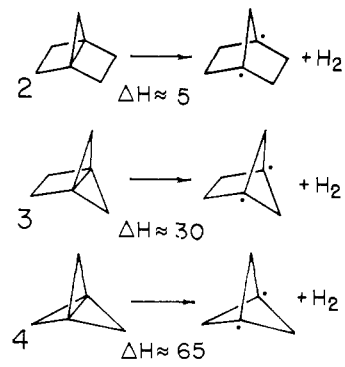
Received June 21, 1982

The propellanes having three small rings have been of considerable recent interest. Besides being the subject of a number of theoretical calculations,[1-3] both a [2.2.2]propellane (**1**) derivative[4] and the [2.2.1]propellane (**2**)[5] have been prepared. We have been interested in the possibility of preparing the [2.1.1]- (**3**) and



[1.1.1]propellanes (**4**). In this connection, we have estimated the enthalpies of hydrogenolysis of **2**–**4** via extended basis set (6-31G*) ab initio calculations.[6] We may also estimate the energies of converting the bicycloalkanes to the corresponding bridgehead diradicals by using an approximate C–H bond dissociation energy of 104 kcal/mol.[7]

Scheme I



The strain energies of **2**–**4** were found to be approximately equal, whereas the strain energies of the corresponding bicycloalkanes change markedly.[8] This leads to the large difference in the enthalpies of hydrogenolysis. The formation of the propellanes from the corresponding bridgehead substituted bicycloalkanes[5] is essentially the reverse of this reaction, and the calculations suggest that this type of process should be considerably more facile for **4** than for either **2** or **3**.

Although the values are approximate, the energies of dissociating the central bond of the propellanes are quite instructive (see Scheme I).[9] The [4.1.1]-,[10] [3.1.1]-,[11] and [2.2.1]propellanes[5] undergo rapid polymerization, presumably via a free-radical process. Our calculations suggest that [1.1.1]propellane will be relatively stable and unreactive. The activation energy for initiating a free-radical polymerization should be related to the energy of forming the diradical and will be relatively high for **4**. Similarly, the addition of a free radical to **4** will be much less exothermic than the corresponding reactions of **2** and **3**. The thermolysis of **4** also may have a relatively high activation energy since the energy of dissociating one of the side bonds also should be on the order of 60 kcal/mol.[12] Thus, **4** may be considerably less reactive than

† Dedicated to Professor William v. E. Doering on his 65th birthday.

(1) Newton, M. D.; Schulman, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 773.
(2) Stohrer, W.-D.; Hoffmann, R. *J. Am. Chem. Soc.* **1972**, *94*, 779.
(3) Newton, M. D.; Schulman, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 4391.
(4) Eaton, P. E.; Temme, G. H., III *J. Am. Chem. Soc.* **1973**, *95*, 7508.
(5) Wiberg, K. B.; Walker, F. H.; Michl, J. *J. Am. Chem. Soc.* **1982**, *104*, 2056.

(6) Newton and Schulman[1] calculated the energies of bicyclo[1.1.1]pentane and [1.1.1]propellane with partial geometry optimization (the gradient method was not then available) using the 4-31G basis set. They found a central C–C bond length of 1.600 Å. With complete geometry optimization using the 6-31G* basis set, we obtain for bicyclopentane, $E = -193.90568$ hartrees, and for [1.1.1]propellane, $E = -192.69106$ hartrees, with a central bond length of 1.543 Å. Polarization functions were needed to properly describe the propellane. The reported enthalpy changes include corrections for zero-point energies and the change in enthalpy on going from 0 to 298 K. The details of these calculations will be reported separately.

(7) The bridgehead C–H bond dissociation energies are known to be larger than for normal tertiary bonds and larger even than for secondary C–H bonds. Thus, norbornane (Kooyman, E. C.; Vegter, G. C. *Tetrahedron* **1958**, *4*, 382) and bicyclo[2.1.1]hexane (Srinivasan, R.; Sonntag, F. I. *J. Am. Chem. Soc.* **1967**, *89*, 407) are halogenated exclusively at the methylene positions, and bicyclo[1.1.1]pentane (Wiberg, K. B.; Williams, V. Z. *J. Org. Chem.* **1970**, *35*, 369) has been found to be much less reactive than cyclohexane in halogenation. We have assumed that the bridgehead C–H bond dissociation energies are similar to that for methane (104 kcal/mol: Chupka, W. A. *J. Chem. Phys.* **1968**, *48*, 2337).

(8) Wiberg, K. B.; Wendoloski, J. *J. Am. Chem. Soc.* **1982**, *104*, 0000.

(9) Our conclusions concerning [1.1.1]propellane were in part anticipated by Newton and Schulman,[1] who calculated the energy of the triplet diradical derived from **4** to lie about 51 kcal/mol above the ground state. Similarly, they calculated the triplet formed by cleaving one of the side bonds to lie about 30 kcal/mol above the ground state. One would expect the singlet and triplet diradicals to have similar energies. Inclusion of polarization functions in the calculations will presumably increase the values by up to 20 kcal/mol (the extra stabilization of the [1.1.1]propellane by including these functions).

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