and thus competing more favorably at low [CH_2O] with the Cannizzaro (bimolecular) reaction. It was also determined that as the concentration of base increases, the hydrogen yield increases (Table III). These results are attributed to the fact that when [OH^-] increases, the concentration of free aldehyde (which is necessary for the Cannizzaro reaction) decreases (eqs 2, 3), thus allowing the hydrogen-producing reaction (eq 4) to compete even at high formaldehyde concentration.

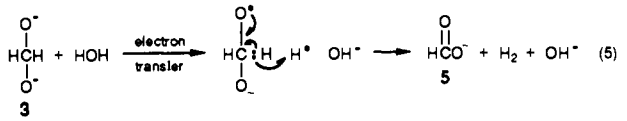
It is interesting to note that other aldehydes that do not possess α hydrogen atoms (e.g., benzaldehyde, glyoxylic acid, pivalaldehyde) produced hydrogen in 17, 29, and 30% yield, respectively, under the same conditions (Table I, second entry) reported for formaldehyde (41% H_2).

Proposed Mechanism. The proposed mechanism for the formation of H_2 involves the formation of the Cannizzaro intermediate **3** (eq 2), which reacts as a hydride ion donor with a water molecule, to produce hydrogen and sodium formate (eq 4).[12] When the concentration of base is high and the concentration of formaldehyde is low, the probability of a bimolecular reaction of the Cannizzaro intermediate with a formaldehyde molecule (eq 3) is small. Instead, intermediate **3** reacts with water to produce H_2 (eq 4). These latter conditions are those believed to be present in nuclear waste storage tanks where small, steady-state concentrations of formaldehyde can form by radiolysis or thermal decomposition of organic complexants and other decomposition products.

Conclusions. Formaldehyde and other aldehydes that do not possess α hydrogen atoms are very likely intermediates for the generation of H_2 during the storage of alkaline nuclear waste. The data reported herein suggests that formaldehyde and water each provide one hydrogen atom in the formation of H_2.

Acknowledgment. We wish to thank Westinghouse-Hanford and the Department of Energy for support of this work.

(12) The transfer of hydrogen from the Cannizzaro intermediate (**3**) to H_2O can take place as a hydride ion (H^-) or a hydrogen atom ($H^\bullet$) (eq 5).



(5)

[2.2]Orthoparacyclophane: The Last and Most Strained [2.2] Cyclophane

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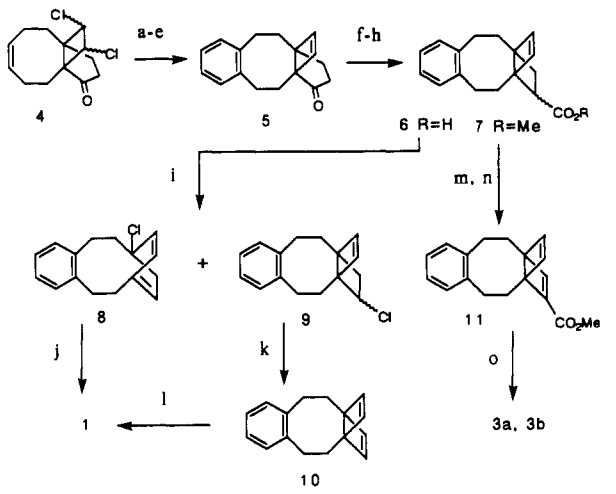
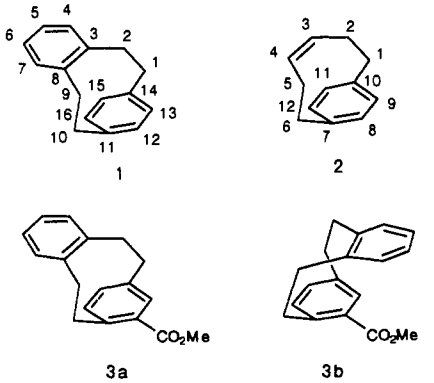
[2.2] cyclophanes can be regarded as prototype members of the cyclophane class and can serve as a good basis for developments in this field.[1] Of the six conceivable [2.2] cyclophane isomers, four relatively unstrained members are known.[2] The highly strained [2.2]orthometacyclophane was recently synthesized by Hopf and co-workers.[3] The last member of this family of compounds, [2.2]orthoparacyclophane (**1**), has been estimated from MM2 calculations to be the most strained[1b,4] and until now has eluded synthesis.[5]

Scheme I[a]



[a] Conditions: (a) LAH, Et_2O, 98%; (b) tetrachlorothiophene dioxide, toluene, 120 °C, 2 h, 91%; (c) Na, NH_3, Et_2O; (d) Na, *t*-BuOH, THF, 52% for two steps; (e) CrO_3, pyridine, 64%; (f) HCO_2Et, NaOEt, benzene; (g) TsN_3, Et_3N, CH_2Cl_2; (h) *hν*, H_2O/THF for **6** (34% from **5**) or *hν*, MeOH for **7** (40% from **5**); (i) $Pb(OAc)_4$, LiCl, DMSO, room temperature; (j) *t*-BuOK (3 equiv), DMSO, room temperature, 44%; (k) *t*-BuOK (50 equiv), DMSO, room temperature, 100%; (l) heat (50 °C), $CDCl_3$; (m) LDA, Ph_2Se_2, HMPA, THF, −78 °C, 73%; (n) H_2O_2, pyridine, CH_2Cl_2, 88%; (o) heat (40 °C), 1,2-dichloroethane, 47%.

We envision **1** as a benzo-fused homologue of (*Z*)-[6]paracycloph-3-ene (**2**), which was previously prepared in this laboratory.[6] However, in view of the foregoing work on **1**[5] and [3.2]orthopara-,[7] [3.3]orthopara-,[8] and [2.2]orthometacyclophane,[3] the incorporation of two ethylene bridges in the orthopara system should greatly enhance the propensity of the ethylene bond toward homolytic cleavage, generating a pair of benzyl radicals. With those precautions in mind, extension of the synthetic methodology that we used for **2** (thermal or cationic cleavage of the central bond in [6.2.2]propellanes) has led to the synthesis of **1** and its methoxycarbonyl derivatives **3a** and **3b**.



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(1) (a) *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vols. I and II. (b) Hopf, H.; Marquard, C. *Strain and Its Implications in Organic Chemistry*; de Meijere, A., Blechert, S., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1989; p 297.
(2) See refs 2-7 in ref 5.
(3) Bodwell, G.; Ernst, L.; Haenel, M. W.; Hopf, H. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 455.
(4) MM3 calculations reveal that **1** is the most strained isomer. The ranking of the strain energies of the parapara and orthometa isomers is reversed in the MM3 calculations from the order obtained by the MM2 calculations (Hopf, H.; Marquard, C. Unpublished results). We are grateful to Professor Hopf for informing us of the results of the MM3 calculations.
(5) Bodwell, G.; Ernst, L.; Hopf, H. *Chem. Ber.* **1989**, *122*, 1013.
(6) Tobe, Y.; Ueda, K.; Kaneda, T.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *J. Am. Chem. Soc.* **1987**, *109*, 1136.
(7) Jenneskens, L. W. Ph.D. Thesis, Vrije Universiteit te Amsterdam, Amsterdam, 1986, p 67.
(8) Asami, M.; Krieger, C.; Staab, H. A. *Tetrahedron Lett.* **1991**, *32*, 2117.

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Table I. Parameters for AM1 Optimized Geometries of 1 and 2

	1	2[a]
deformation of para-bridged benzene ring		
α,[b] deg	24.2	23.6 (20.5)
β,[c] deg	21.9	21.6 (24.1)
relative geometries between two π systems		
dihedral angle,[d] deg	20.3	18.6 (17.7)
distance,[e] Å	3.12	3.05 (3.03-3.04)

[a] Experimental values determined by X-ray structure analysis of the bismethoxycarbonyl derivative are given in parentheses (ref 6). [b] The out-of-plane bending angle of the para carbons. [c] The out-of-plane bending angle of the benzyl carbons. [d] Angle between the plane C-(12)-C(13)-C(15)-C(16) and the plane C(2)-C(3)-C(8)-C(9) for 1; angle between the plane C(8)-C(9)-C(11)-C(12) and the plane C-(2)-C(3)-C(4)-C(5) for 2. [e] Nonbonded distance C(3)···C(15) or C-(8)···C(16) for 1 and C(3)···C(11) or C(4)···C(12) for 2.

Preparation of benzo-fused propellanone 5 from the enone dichloroethylene photoadducts 4[6] was accomplished using the tetrachlorothiophene dioxide[9] benzoannelation method followed by sequential dechlorination. Ring contraction of 5 afforded acid 6 or ester 7. Although in low yield, chlorinative decarboxylation[10] of 6 gave the expected chloride 8 (9%) and the ring-unopened chloride 9 (7%). The low yield of 8 is due to its lability under the reaction conditions. Dehydrochlorination of 8 proceeded smoothly to give cyclophane 1 as an unstable solid (mp 168-170 °C).[11] Thermal isomerization of 10,[12] a Dewar type valence isomer of 1 prepared by treatment of 9 with excess base, also yielded cyclophane 1 (Scheme I).

As shown in Table I, semiempirical AM1 optimized geometries[13] of 1 and 2 are similar. The only discrepancy is that the bridge π bond of 1 (C(3)-C(8) = 1.41 Å) is considerably longer than that of 2 (C(3)-C(4) = 1.34 Å). Spectroscopic data support this calculation; the coupling constants of the vicinal methylene protons in the ^{1}H NMR spectra of compounds 1 and 2[11] are nearly equal. Additionally, the longest wavelength absorptions (310 nm in cyclohexane) in the UV spectra of both compounds are identical. These data imply that the para-bridged benzene ring of 1 is as deformed as in 2, which contains one of the most severely distorted benzene rings known. Spectroscopically, the only difference between 1 and 2 is the paramagnetic shielding effect exerted by the ortho-bridged ring. In the ^{1}H NMR spectrum of 1, the syn protons (H(15), H(16), δ 6.27) appear at about 1 ppm higher field than the anti protons (H(12), H(13), δ 7.32).

Mutual syn/anti isomerization of the methoxycarbonyl derivatives of [6]paracyclophene 2 took place near room temperature ($\Delta G^{\ddagger}_{25°C}$ = 24.6 kcal/mol), giving an equilibrium mixture composed of equal amounts of the isomers ($K_{25°C}$ = 0.97).[5] In order to investigate the conformational behavior of the [2.2]ortho-paracyclophane system, the methoxycarbonyl-substituted derivatives 3a and 3b were prepared (Scheme I). Heating (dichloroethane, 40 °C, 17 h) the Dewar isomer 11 afforded a mixture of 3a and 3b in a ratio of 2:5 in 47% yield.[11] In contrast to the [6]paracyclophene system, no isomerization was observed when 3a or 3b was heated to 50 °C for 48 h. Higher temperatures only resulted in the rapid decomposition of 3a and 3b. Consequently, benzoannelation of 2 brings about a substantial barrier to this dynamic process, although the most stable conformations of 1 and 2 are similar.[14]

(9) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856.

(10) (a) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279. (b) Tobe, Y.; Takahashi, T.; Ishikawa, T.; Yoshimura, M.; Suwa, M.; Kobiro, K.; Kakiuchi, K.; Gleiter, R. *J. Am. Chem. Soc.* **1990**, *112*, 8889.

(11) The spectral properties of 1, 3a, and 3b are given in the supplementary material.

(12) The isomerization of 10 ($k_{50°C}$ = 1.4 × 10^{-5} s^{-1} in $CDCl_3$) proceeded about 4 times slower than the isomerization of the Dewar isomer of 2.

(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. The calculations were performed using MOPAC Ver. 5.00 (QCPE No. 445): Stewart, J. J. P. *QCPE Bull.* **1989**, *9*, 10. Hirano, T. *JCPE Newsl.* **1989**, *1*, 36. Revised as Ver. 5.01 for OS/2 personal computers (NEC PC-9801): Toyoda, J. *JCPE Newsl.* **1990**, *2* (1), 56.

(14) A similar benzoannelation effect was observed for [2.2]orthometacyclophane (ref 3).

Acknowledgment. We thank the Instrumental Analysis Center of the Faculty of Engineering, Osaka University, for the use of NMR and MS facilities.

Supplementary Material Available: Listings of spectral properties for compounds 1, 3a,b, and 5-11 (3 pages). Ordering information is given on any current masthead page.

A New Class of Proteinase Inhibitor. Cyclopropenone-Containing Inhibitor of Papain

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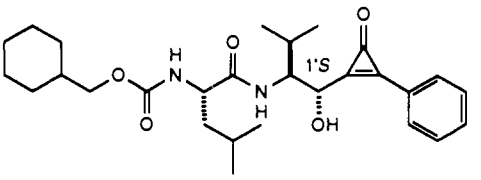
The rational design and synthesis of inhibitors of proteolytic enzymes have recently attracted the attention of bioorganic chemists. We report an entirely new class of molecules that effectively inhibit the action of papain (EC 3.4.22.2), an archetypal cysteine proteinase,[1,2] with a K_i of submicromolar level. The new class of molecules—a cyclopropenone-containing enzyme inhibitor (CCI)—consist of a cyclopropenone structure and a dipeptide moiety connected by a C-C bond as shown in structure 1.



1: 1'*S*
2: 1'*R*-epimer

Cyclopropenone is a highly intriguing system due to its amphiphilic properties: it can act either as an electrophile, owing to the electrophilicity of the olefinic and the carbonyl carbons, or as a proton acceptor, since protonation generates a 2π-aromatic hydroxycyclopropenylium structure.[3] Although the biological properties of a few cyclopropenones have been studied previously,[4] there has been no systematic effort to use the cyclopropenone structure as a design tool in bioorganic chemistry. Here we report the results of our studies in this area[5] on the synthesis of a new and potent papain inhibitor.

The synthesis of 1 was achieved in a straightforward manner as shown in Scheme I. The right-hand side of 1, which may be crucial for the biological activity of the molecule, was synthesized according to the general synthesis of cyclopropenones that we reported recently.[6] Thus, 2-phenylcyclopropenone acetal 3, prepared from 1,3-dichloroacetone in three steps in 76% overall yield, was lithiated,[7] and the resulting vinyllithium reagent was

(1) Cf.: Drenth, J.; Jansonius, J. N.; Koekoek, R.; Wolthers, B. G. *Adv. Protein Chem.* **1971**, *25*, 79.

(2) Reviews on inhibition of cysteine proteinases: Rich, D. H. In *Proteinase Inhibitors*; Barrett, A. J., Salvesen, G., Eds.; Elsevier: Amsterdam, 1986; p 153.

(3) Cf.: Potts, K. T.; Baum, J. S. *Chem. Rev.* **1974**, *74*, 189.

(4) Okuda, T.; Shimma, N.; Furumai, T. *J. Antibiot.* **1984**, *37*, 723. Tokuyama, H.; Isaka, M.; Nakamura, E.; Ando, R.; Morinaka, Y. *J. Antibiot.* **1992**, *45*, 1148 and references cited therein.

(5) For more "chemical" aspects of the work at Tokyo Institute, see: Tokuyama, H.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 5523. Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428.

(6) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045. Isaka, M.; Ando, R.; Morinaka, Y.; Nakamura, E. *Tetrahedron Lett.* **1991**, *32*, 1339.

0002-7863/93/1515-1174$04.00/0