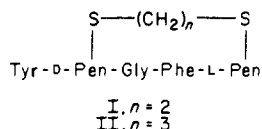


allowable positions in the linear sequence for substitution by amino acids with sulfhydryl side chains are limited. Since readily available amino acids with sulfhydryl side chains are limited to cysteine and penicillamine (β -sulfhydryls) and homocysteine (γ -sulfhydryl) one is restricted, for fixed substitution within the primary sequence, to cyclic structures of n to $n + 2$ atoms where n is determined by the number of intervening amino acid residues in the primary sequence. Thus even in cases in which a folded conformation may be biologically important the disulfide cyclization may impose too severe a conformational constraint. We present here a more general approach which allows the examination of a larger set of cyclized peptides by utilizing sulfhydryl side chains to form dithioethers. This variable conformational restriction approach can be employed to evaluate the importance of folded structures for bioactivity of a given native peptide and to develop cyclic analogues in which the appropriate degree of folding is stabilized.



[D-Pen²,L-Pen⁵]Enkephalin (Tyr-D-Pen-Gly-Phe-L-Pen), a cyclic disulfide-containing analogue of the native, linear enkephalins, Tyr-Gly-Gly-Phe-Met (or Leu), which is highly selective for the δ opioid receptor,⁵ served as the parent peptide for the present study. The protected, resin-bound pentapeptide *N*-(*tert*-butyloxycarbonyl)-Tyr-D-Pen(*S-p*-MeBzl)-Gly-Phe-L-Pen(*S-p*-MeBzl)-resin was synthesized by solid-phase methodologies using Merrifield resin (chloromethylated polystyrene cross-linked with 1% divinylbenzene) as previously described.⁵ Cleavage from the resin and concomitant deprotection were achieved by reaction with anhydrous HF containing 10% anisole at 0 °C for 1 h. Following evaporation the peptide was extracted from the resin with 50% acetic acid and the solution freeze dried. The cyclic dithioether-containing peptides I and II were obtained by modification of the procedure employed by Frankel and Gertner for the synthesis of homologues of djenkolic acid.⁶ The free sulfhydryl-containing peptide (0.1 mmol) was added to 400 mL of anhydrous liquid ammonia and treated with sufficient sodium to maintain a blue color for 90 s. The solution was decolorized by addition of NH₄Cl and 0.12 mmol of 1,2-dibromoethane (for I), or 1,3-dibromopropane (for II) dissolved in 10 mL of anhydrous ether was added dropwise over 0.5 h. The solution was allowed to reflux for 2 h and then evaporated under a nitrogen stream. The product was dissolved in 30% acetic acid and purified by HPLC (Vydac C-18 column, 1 cm \times 25 cm) using the solvent system 0.1% trifluoroacetic acid in H₂O/0.1% trifluoroacetic acid in acetonitrile (75/25). Yields of 20% were obtained for both I and II and in each case unreacted, free sulfhydryl-containing peptide was the major component recovered.

The purified products, I and II, were tested for the presence of free sulfhydryls through reaction with 5,5'-dithiobis(2-nitrobenzoic acid)⁷ with and without prior incubation with disulfide-reducing agents (2-mercaptoethanol, dithiothreitol, or NaBH₄). In all cases these tests were negative, indicating the absence of free sulfhydryls or disulfides. Analysis by fast atom bombardment mass spectrometry yielded the appropriate molecular weights for I (MW = 673) and II (MW = 687).

To the best of our knowledge, I and II constitute the first examples of the use of dithioether bridges to form cyclic peptides. This approach should be of general utility in the design and

synthesis of cyclic peptides with variable ring size. Pharmacological and conformational analyses of I and II are in progress.

Acknowledgment. We thank Brian Musselman and the NIH Mass Spectrometry Facility at Michigan State University for providing the fast atom bombardment mass spectra. This study was supported by USPHS Grant NS20428 and by a University of Michigan Rackham Faculty Grant.

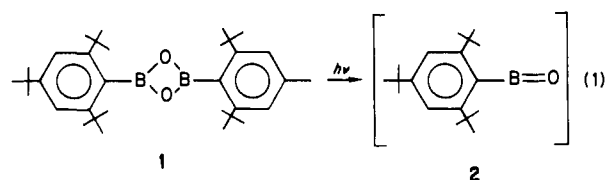
Synthesis of a 1,3-Dioxa-2,4-diboretane: An Oxoborane Precursor

Bernd Pachaly and Robert West*

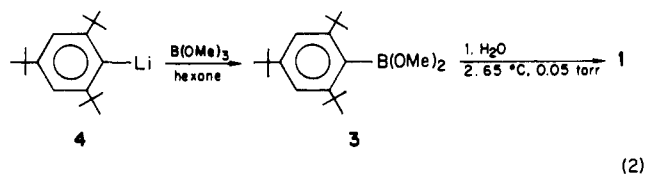
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We report here the synthesis of a 1,3-dibora-2,4-dioxetane 1 and its photolysis to give trapping products consistent with intermediate formation of the oxoborane 2 (eq 1).



Although there is much current interest in species containing multiple bonds to boron,¹ no reports of oxoboranes (boranones, RB=O) have yet appeared.² Photolytic cleavage of a 1,3-dioxa-2,4-diboretane seemed a likely route to boranones, but these compounds were also unknown, except for a coordination compound with bridging methoxyl groups.³ Dehydration of organodihydroxyboranes usually leads to the six-membered ring boroxines;⁴ when very bulky groups are attached to boron dehydration may not take place.⁵ However, hydrolysis and dehydration of (2,4,6-tri-*tert*-butylphenyl)dimethoxyborane (3), prepared from (2,4,6-tri-*tert*-butylphenyllithium) (4) and trimethoxyborane, led to dioxadiboretane 1 (eq 2).



In a typical experiment 5.2 g of 3 was stirred in a mixture of 50 mL of heptane, 50 mL of toluene, and 100 mL of water with 20 mg of tetrahexylammonium bromide for 48 h at 25 °C. The organic layer was separated and the solvents were evaporated under vacuum; heating of the residue to 65 °C at 0.05 torr produced 3.3 g (76%) of nearly pure 1 as a yellowish oil.⁷ The same

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(2) Unsuccessful attempts to obtain boranones in matrix have been reported: see: Paetzold, P.; Weber, G.; Reinards, R.; Fenrich, H.; Sockel, K.-H. *Forschungsber. Landes Nordrhein-Westfalen* **1975**, No. 2476. Boron-oxygen double bonds were also postulated in cations containing a [$\text{N}=\text{B}=\text{O}$] unit: Nöth, H.; Weber, S.; Rasthofer, B.; Narube, C.; Konstantinov, A. *Pure Appl. Chem.* **1983**, *55*, 1453.

(3) Goubeau, J.; Lücke, K. E. *Liebigs Ann. Chem.* **1952**, *575*, 37. A compound for which a 1,3-dioxa-2,4-diboretane structure was originally proposed (Hawkins, R. T.; Lennarz, W. J.; Synder, H. R. *J. Am. Chem. Soc.* **1960**, *82*, 3053) was later shown to have the common six-membered ring boroxine structure.⁴

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(5) Hunter, D.; Steinberg, H. U.S. Patent 3359298, 1969; *Chem. Abstr.* **1969**, *70*, 353.

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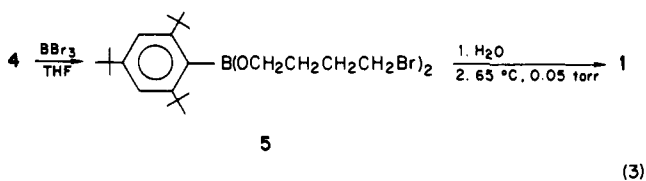
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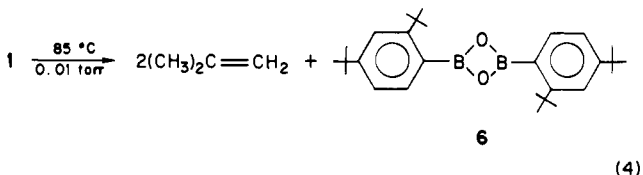
(6) Frankel, M.; Gertner, D. *J. Chem. Soc.* **1960**, 898-899.

(7) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70-77.

product is obtained upon similar hydrolysis and dehydration of bis(4-bromobutoxy)(2,4,6-tri-*tert*-butylphenyl)borane (**5**), obtained by the reaction of **4** with boron tribromide in tetrahydrofuran (eq 3).⁸

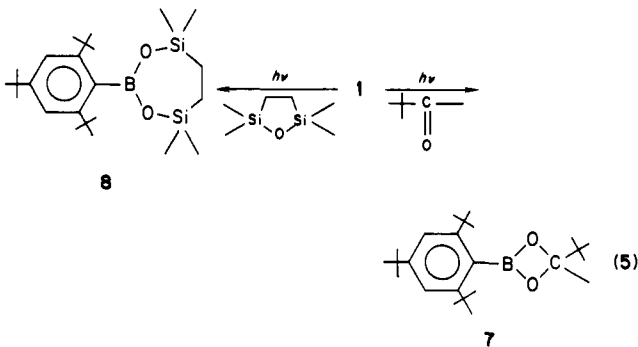


Compound **1** reacts with water and oxygen; when heated to 85 °C it decomposes with loss of two molecules of 2-methylpropene to form a second diboradioxetane, **6**, also a pale yellow oil (eq 4).⁹ Both **1** and **6** show rather positive ¹¹B chemical shift values,



+32.37 and 33.01 ppm, respectively. The deshielding of the boron nucleus in these species is consistent with a strained ring structure.¹⁰ The Raman spectrum of **1** exhibits a strong line at 905 cm⁻¹ with satellites at 927 and 944 cm⁻¹, assigned to the symmetric ring stretching of the B₂O₂ framework. These frequencies are about 100 cm⁻¹ higher than for related six-membered rings, R₃B₃O₃.¹¹

Photolysis of **1** in the presence of trapping agents led to products which may arise from the intermediate oxoborane **2**.¹² Thus irradiation at 254 nm of a solution of **1** in *tert*-butyl methyl ketone produced the dioxaboretane **7**,¹³ and similar photolysis in the presence of 2,2,4,4-tetramethyl-2,4-disila-1-oxacyclopentane gave the product **8**¹⁴ (eq 5), both in nearly quantitative yields.



(7) ¹H NMR δ 1.43 (s, 9), 1.59 (s, 18), 7.56 (s, 2); ¹¹B NMR 32.37 ppm; UV, hexane λ_{max} 268, 232, 220 cm⁻¹; Raman 905, 927, 944 (16:4:1). Molecular weight 544.4623 (calcd), 544.4755 (found); MS, *m/e* 544 (M⁺, 0.9%), 489 (1.9), 418 (7.8), 272 (0.6), 256 (50.3), 57 (100.0), 54 (43.8). In repeated mass spectral and GC-MS experiments under various conditions, no peaks with higher mass were ever detected.

(8) Kuchen, W.; Brinckmann, R. D. *A. Anorg. Allg. Chem.* **1963**, 325, 225. (9) ¹H NMR δ 1.32 (s, 9), 1.52 (s, 9), 7.25 (m, 1), 7.53 (m, 1), 7.72 (m, 1); ¹¹B NMR 33.01 ppm; molecular weight 432.3371 (calcd), 432.3370 (found); MS, *m/e* 432 (M⁺, 5.7%), 417 (1.5), 303 (6.1), 288 (5.7), 216 (7.7), 171 (5.0), 57 (100.0).

(10) Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*, Springer-Verlag, Berlin, 1978.

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(13) ¹H NMR δ 0.95 (s, 3), 1.40 (s, 9), 1.55 (s, 18), 1.79 (s, 9), 7.59 (s, 2); ¹¹B NMR 33.52 ppm; molecular weight 315.2495 (M - 57 calcd), 315.2337 (M - 57 found); MS 372 (M⁺ - 15, 1.3%), 315 (M⁺ - 57, 7.7), 300 (3.0), 256 (1.5), 245 (23.7), 71 (11.7), 57 (100.0), 56 (18.3), 43 (47.2).

(14) ¹H NMR δ 0.15 (s, 12), 0.73 (s, 4), 1.38 (s, 9), 1.52 (s, 18), 7.52 (s, 2); ¹¹B NMR 30.48 ppm; molecular weight 432.3051 (calcd), 432.3011 (found); MS, *m/e* 432 (M⁺, 2.9%), 417 (1.2), 360 (1.0), 245 (4.5), 231 (19.7), 187 (9.8), 115 (10.4), 72 (14.6), 57 (100.0).

Irradiation of **1** at -196 °C in 3-methylpentane glass led to formation of a weak UV absorption band at 314 nm which may be due to free **2**. Further investigations of this new species are being carried out.

Acknowledgment. This work was supported by a NATO scholarship through the German Academic Exchange Service (DAAD) to B.P. and by the Air Force Office of Scientific Research Air Force Systems Command, USAF, under Contract F49620-83-C-0044. The United States Government is authorized to reproduce and distribute reprints for governmental purposes notwithstanding any copyright notation thereon.

Highly Efficient Sensitization of Titanium Dioxide

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Received December 6, 1984

The photosensitization of wide-bandgap oxide semiconductors is the subject of an intensive investigation, mainly due to its importance for solar energy conversion.² Of particular interest is the combination of chromophores such as Ru(bpy)₃²⁺ with TiO₂ or SrTiO₃ since this offers the possibility to shift the water cleavage activity of these oxides into the visible.³ However, the efficiencies achieved so far with such devices have been disappointingly low, mainly due to poor light energy harvesting and small quantum yields for charge injection. We have achieved strikingly high efficiencies in the sensitization of colloidal anatase particles and polycrystalline electrodes using tris(2,2'-bipyridyl-4,4'-dicarboxylate)ruthenium(II) dichloride⁴, (**1**) as a sensitizer.

(1) Visting scientist from the Heyrovsky Institute of Physical Chemistry and Electrochemistry, 10200 Prague, 10, CSSR.

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