strength and improved probe design, better accuracy and sensitivity can presumably be obtained.[78]

(iii) Proton exchange does not create significant problems so that studies in aqueous solution are feasible.

(iv) ^{17}O shifts of carbonyl oxygens are more sensitive to large hydrogen-bonding perturbations than the corresponding carbonyl ^{13}C shifts.

The important specific findings from the present research include the following:

(i) IPU in CH_3CN forms primarily cyclic dimers through the C(4)=O(4) carbonyls of both molecules.

(ii) The hydrogen bonding of water to IPU in CH_3CN occurs mainly through two equilibrium processes. In low concentrations of water, one water molecule hydrogen bonds to O(4) with K_{1W} = 0.29 M^{-1} at 29 °C and ΔH = −5.2 kcal/mol. At higher concentrations of water, a second process becomes significant in which one water molecule hydrogen bonds to each of the O(4) lone pairs, with K_{1WW} = 0.061 M^{-1} at 29 °C and ΔH = −11.0 kcal/mol.

(iii) The carbonyl O(2) of IPU in CH_3CN participates relatively weakly in H_2O hydrogen bonding and may be weakly intramolecularly hydrogen bonded to the 5′OH.

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Registry No. [4-^{17}O]-2′,3′,5′-Tri-*O*-benzoyluridine, 86392-68-9; 2′,3′,5′-tri-*O*-benzoyl-4-chlorouridine, 4418-14-8; [4-^{17}O]-uridine, 86392-69-0; [4-^{17}O]-2′,3′-*O*-isopropylideneuridine, 86392-70-3; [2-^{17}O]-2′,3′-*O*-isopropylideneuridine, 86392-71-4; [2-^{17}O]-uridine, 86392-72-5; [2-^{17}O]-5′-iodo-5′-deoxy-2′,3′-*O*-isopropylideneuridine, 86392-73-6; [2-^{17}O]-5′-deoxy-2′,3′-*O*-isopropylideneuridine, 86409-51-0.

(77) For example, ^{15}N shifts of no more than 8 ppm have been observed for cytidine–guanosine hydrogen bonding: Dyllick-Brensinger, C.; Sullivan, G. R.; Pang, P. P.; Roberts, J. D., *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 5580–5582. For derivatives of uridine–adenosine base pairs, limiting shifts of 4.7 and 3.5 ppm for ^{15}N and ^{1}H, respectively, have been reported: Poulter, D.; Livingston, C. L. *Tetrahedron Lett.* **1979**, *755–758*.

(78) Spectra taken on the XL-200 (27.1 MHz for ^{17}O) referred to in Table I could be obtained in about one-tenth of the time required by using the 60-MHz spectrometer. Improvement in both signal to noise and chemical shift accuracy were greatly enhanced as well as enabling larger line widths (i.e., in Me_2SO, $W \sim 1800$ Hz) to be accurately observed.

Communications to the Editor

7-Deoxydaunomycinone, a Catalyst for Achieving a Two-Electron Reduction with a One-Electron Reducing Agent[1]

Don L. Kleyer and Tad H. Koch*

Department of Chemistry, University of Colorado Boulder, Colorado 80309

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7-Deoxydaunomycinone (**1**) is the product of reductive elimination of daunosamine from the antileukemic drug daunomycin (**2**).[2] The reductive cleavage process leads to reactive intermediates[3] that are proposed to combine with DNA to give **1** covalently bound to DNA.[4,5] Subsequent chemistry of bound **1** as a redox catalyst likely leads to cell death.[6]

Previously we demonstrated that the reducing agent *dl*-bi-(3,5,5-trimethyl-2-oxomorpholin-3-yl) (**3**) reduces **2** to **1** via the transient semiquinone and hydroquinone of **2** and a tautomer of **1**.[3] The reducing agent was 3,5,5-trimethyl-2-oxomorpholin-3-yl (**4**) from bond homolysis of **3**.[7] We now report the anaerobic

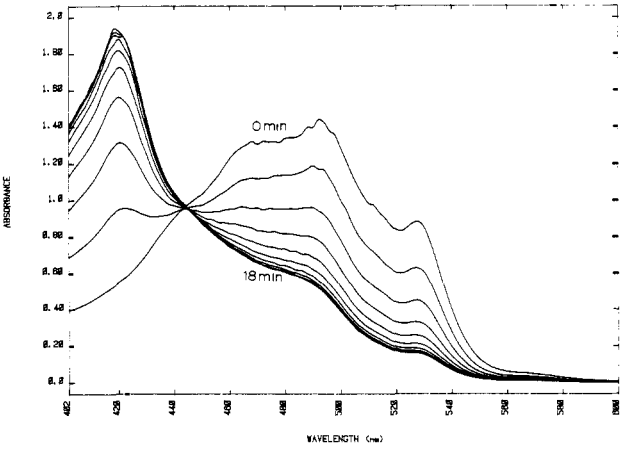
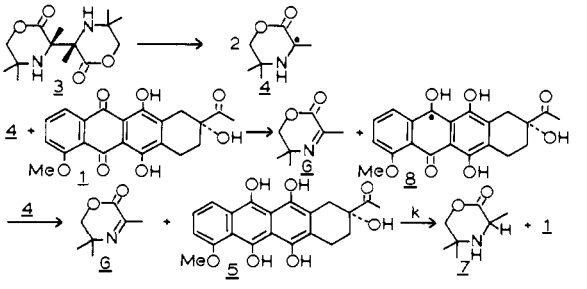


Figure 1. Visible absorption of a rigorously oxygen-degassed methanol solution 1.39 × 10^{-4} M in **1**, 1.39 × 10^{-3} M in **3**, and 2.0 × 10^{-3} M in Trizma buffer at 25.3 ± 0.1 °C as a function of time. Scans were 1 s in duration and occurred every 2 min in the time period 0–18 min.

Scheme I



reduction of **1** to 7-deoxydaunomycinone hydroquinone (**5**) by **4** in one-electron steps and the subsequent reduction of 5,6-dihydro-3,5,5-trimethyl-2-oxazinone (**6**), the product of oxidation of **4**, to 3,5,5-trimethyl-2-oxomorpholine (**7**) by **5** in a two-electron step (Scheme I).

(1) This investigation was facilitated by the following support: PHS Grant CA-24665, DHHS; University of Colorado, CCRW faculty fellowship: Developmental Therapeutics Program, NCI; 3M Co.

(2) Smith, T. H.; Fujiwara, A. N.; Henry, D. W.; Lee, W. W. *J. Am. Chem. Soc.* **1976**, *98*, 1969. Marshall, V. P.; Reisender, E. A.; Reineke, L. M.; Johnson, J. H.; Wiley, P. F. *Biochemistry* **1976**, *15*, 4139. Felsted, R. L.; Gee, M.; Bachur, N. R. *J. Biol. Chem.* **1974**, *249*, 3672. Karnetova, J.; Mateju, J.; Sedmera, P.; Vokoun, J.; Vanek, Z. *J. Antibiot.* **1976**, *29*, 1199. Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassinelli, G.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334.

(3) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1983**, *105*, 2504.

(4) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249. Sinha, B. K.; Gregory, J. L. *Biochem. Pharmacol.* **1981**, *30*, 2626. Sinha, B. K. *Chem.-Biol. Interact.* **1980**, *30*, 67. Ghezzi, P.; Donnelli, M. G.; Pantarotto, C.; Facchinetti, T.; Garattini, S.; *Biochem. Pharmacol.* **1981**, *30*, 175.

(5) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc.*, in press.

(6) Bachur, N. R.; Gordon, S. L.; Gee, M. V. *Mol. Pharmacol.* **1977**, *13*, 901. Bachur, N. R.; Gordon, S. L.; Gee, M. V. *Cancer Res.* **1978**, *38*, 1745. Lown, J. W.; Chen, H.-H. *Can. J. Chem.* **1981**, *59*, 390.

(7) Burns, J. M.; Wharry, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 849.

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Two freeze-pump-thaw-sonicate degassed 2.5-mL methanol solutions each 1.39×10^{-4} M in **1**, 2.75×10^{-4} M in **3**, and 2.0×10^{-3} M in Trizma buffer (1:1 Tris/Tris-HCl) at ambient temperature for 24 h yielded $(6.7 \pm 0.1) \times 10^{-7}$ mol (100%) of **7**, $(7.0 \pm 0.3) \times 10^{-7}$ mol (100%) of **6**, and $(3.6 \pm 0.1) \times 10^{-7}$ mol (100%) of recovered **1**. Yields for **6** and **7** were determined by GLC with a 10% SE-30 on 100/120-mesh Chromasorb W column at 150 °C and for **1** by HPLC with a RSIL-phenyl column eluting with 40% THF 60% aqueous buffer (0.1% ammonium formate adjusted to pH 4.0 with formic acid)[8] and detecting at 480 nm. ^{1}H NMR analysis of the reaction mixture confirmed the chromatographic results and showed that no other products were formed. A similar solution with 5 times higher concentration of **3** gave the visible spectral changes shown in Figure 1 as a function of time. The spectrum of the reaction solution was observed every 2 min. During the period 0-18 min, the absorption of **1** at 480 nm dropped and the absorption at 420 nm assigned to the hydroquinone **5** rose. Over a subsequent time period 18-240 min, the band at 420 nm dropped and the band at 480 nm rose. Subtraction of the absorption at 420 nm predicted to result from residual **1** at 18 min gave an extinction coefficient for **5** at 420 nm of 12000. Fisher and co-workers have assigned a band at 407 nm to enzyme-bound **5** at pH 7.0 from sodium dithionite reduction of enzyme-bound 2 in sodium phosphate buffer.[9]

The semiquinone of **1** (**8**) was never present at high enough concentration in these reaction solutions to appear significantly in the visible spectrum. An EPR signal for **8** was observed for a degassed methanol solution of **1** and **3** at -20 °C; however signal strength and anisotropic effects precluded an assignment of the splittings. In Me_2SO at 40 °C the signal for **8** was stronger because a higher concentration of **1** could be achieved, and the spectrum was characterized by the following parameters: g = 2.0037, splittings 5.80 (1:1), 3.06 (1:1), 2.32 (1:1), 1.18 (1:1), 0.59 (1:3:3:1).

The rate of decay of the absorption at 420 nm at 25 ± 0.1 °C was studied in methanol solutions 2.04×10^{-4} M in **1** and **3** and 8.0×10^{-3} M in Trizma buffer. The decay after 10 half-lives of **3** (2040 s) followed clean second-order kinetics, first order in both **5** and **6**. A nonlinear least-squares fitting of the data to the integrated rate law, correcting for absorption by **1**, gave a rate constant of 2.06 ± 0.02 M^{-1} s^{-1} for reduction of **6** by **5** and an extinction coefficient for **5** at 420 nm of 12700 ± 400. The same experiment in methanol-*d* solvent gave a rate constant of 0.69 ± 0.01 M^{-1} s^{-1}. The deuterium kinetic isotope effect is 3.0, consistent with breakage of a bond to hydrogen in the transition state. Reaction of **5** with **6** was further established by the observation of a complete suppression of spectral changes at 420 nm by inclusion of 220 mol equiv of **6** in the original reaction mixture.

A control experiment showed that the rate of disproportionation of **4** to **6** and **7** in methanol in the absence of **1** is very slow. A solution 5.56×10^{-2} M in **3** in methanol-d_4 solvent showed no disproportionation after 135 h at 35.0 ± 0.1 °C by ^{1}H NMR spectroscopy. The deuterium kinetic isotope effect of deuterated solvent on bond homolysis of **3** and on disproportionation of **4** in the absence of a catalyst is small.[3,7]

On the basis of these data and previous work on the mechanism of reduction of daunomycin by **3**,[3] we conclude that the 7-deoxydaunomycinone-catalyzed disproportionation of **3** occurs via reduction of **1** in single-electron steps to give hydroquinone **5** followed by transfer of a hydride from **5** to **6**. Thus, catalysis occurs because a one-electron reducing agent creates a two-electron reducing agent. The hydride transfer appears to be mechanistically related to some quinone-substrate dehydrogenation reactions.[10] The intracellular function of free or DNA-bound **5** as a two-electron reducing agent is unknown; however, it may be expressed in the interior of a tumor that is hypoxic. The two-electron-two-proton reduction potential of **1** is sufficiently negative, -0.66 V vs. SCE,[11] that **5** is thermodynamically capable of reducing many cellular constituents.

Registry No. 1, 32384-98-8; **3**, 53153-53-0; **4**, 57765-64-7; **5**, 86632-73-7; **6**, 53153-46-1; **7**, 86632-74-8; **8**, 86667-95-0; methanol-*d*, 1455-13-6; deuterium, 7782-39-0.

(8) Andrews, P. A.; Brenner, D. E.; Chou, F. E.; Kubo, H.; Bachur, N. *Drug Metab. Dispos.* **1980**, *3*, 152.
(9) Fisher, J.; Ramakrishnan, K.; McLane, K. E. *Biochemistry* **1982**, *21*, 6172.
(10) Becker, H.-D. In "The Chemistry of Quinoid Compounds"; Patai, S., Ed.; Wiley: New York, 1974; pp 335-423.
(11) Rao, G. M.; Lown, J. W.; Plambeck, J. A. *J. Electrochem. Soc.* **1978**, *125*, 534.

Novel Synthesis and Reactivity of 4-Azahomoadamant-3-ene and 4-Aza-4-homobrend-3-enes via Intramolecular Aza-Wittig Reactions

Tadashi Sasaki,* Shoji Eguchi, and Takashi Okano

Institute of Applied Organic Chemistry
Faculty of Engineering, Nagoya University
Furo-cho, Chikusa-ku, Nagoya 464, Japan

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A variety of synthetic methods for preparation of carbocyclic bridgehead olefins have been developed recently,[1,2] whereas only two such methods for bridgehead imines have appeared. These are the photorearrangement of bridgehead azides[3] and lead tetraacetate oxidation of the parent azapolycycles.[4] The former method provides a general route to bridgehead imines but suffers serious disadvantages since unsymmetrical azides generally afford a mixture of bridgehead imines due to nonregioselective ring expansion;[3a,c] moreover the reagents applicable to generated imines are restricted to photostable ones. The latter oxidation method is only useful for limited precursors. In view of the above, the development of regiospecific routes to bridgehead imines is desirable. We would like to report a novel method for generation of bridgehead imines from keto azides and oxoacyl azides, respectively, utilizing the Staudinger reaction followed by an intramolecular aza-Wittig reaction.[5]

When an equimolar mixture of keto azide **1**[6-8] and triphenylphosphine (TPP) in methanol was heated to reflux for 3 h, **1** was converted smoothly into methoxyamine **5a**, which was

(1) (a) For a recent review, see: Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. (b) For stability and reactivity, see: Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.
(2) For some of recent leading references, see: (a) Shea, K. J.; Wise, S.; Burke, L. D.; Davis, P. D.; Gilman, J. W.; Greeley, A. C. *J. Am. Chem. Soc.* **1982**, *104*, 5708. (b) Sellers, S. F.; Klebach, T. C.; Hollowood, F.; Jones, M., Jr.; Schleyer, P. v. R. *Ibid.* **1982**, *104*, 5492.
(3) (a) For a review, see: Lwowski, W. In "Reactive Intermediates"; Jones, M., Jr., Moss, R. A., Ed.; Wiley-Interscience: New York, 1978; Vol. 1, p 198. (b) Quast, H.; Eckert, P. *Liebigs Ann. Chem.* **1974**, 1727. (c) Quast, H.; Seiferling, B. *Ibid.* **1982**, 1553. (d) Becker, K. B.; Gabutti, C. A. *Tetrahedron Lett.* **1982**, *23*, 1883. (e) Sasaki, T.; Eguchi, S.; Okano, T. *Ibid.* **1982**, *23*, 4969.
(4) (a) Toda, Y.; Hirata, Y.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1597. Toda, Y.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1972**, *28*, 1477. (b) Toda, Y.; Niwa, H.; Ienaga, Y.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1972**, 335.
(5) For related reviews, see: (a) Golobov, Y. G.; Zhmurova, I. N.; Kosukhin, L. F. *Tetrahedron* **1981**, *37*, 437. (b) Cadogan, J. I. G.; Mackie, R. K. *Chem. Soc. Rev.* **1974**, *3*, 87. For synthesis of bridgehead olefins via the intramolecular Wittig reaction, see: (c) Becker, K. B. *Tetrahedron* **1980**, *36*, 1717.
(6) All new isolable compounds were characterized by elemental analysis and by IR, NMR, and mass spectra (see the supplementary material).
(7) Ethyleneketalization of 7-*endo*-((acetylamino)methyl)bicyclo[3.3.1]-nonan-3-one (ref 8) followed by alkaline hydrolysis gave the corresponding aminomethyl ketal, mp 126-128 °C, which was converted to azidomethyl ketal by the diazo transfer method (NaH-TsN_3-THF). Hydrolysis (1 N HCl-Et_2O) of the azido ketal gave the azido ketone **1** as on oil (54%).
(8) Padegimas, S.; Kovacic, P. *J. Org. Chem.* **1972**, *37*, 2672.

0002-7863/83/1505-5912$01.50/0