way in our laboratory to elucidate the mechanistic basis of this stereoselectivity and demonstrate the utility of the (trimethylsilyl)cyclopentene annulation in the synthesis of polyquinane natural products.

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(18) The stereochemistry of bicyclo[3.3.0]octanes **19** and **20** was assigned by analysis of carbon-13 spectral data.[19] ^{13}C NMR ($CDCl_3$) δ **19**: 21.7 (exo CH_3), 27.8 (C_3); **20**: 15.4 (endo CH_3), 21.8 (C_3).

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In Vitro Reactivity of the Meso and *dl* Dimers of the 3,5,5-Trimethyl-2-oxomorpholin-3-yl Radical with Adriamycin and Daunomycin

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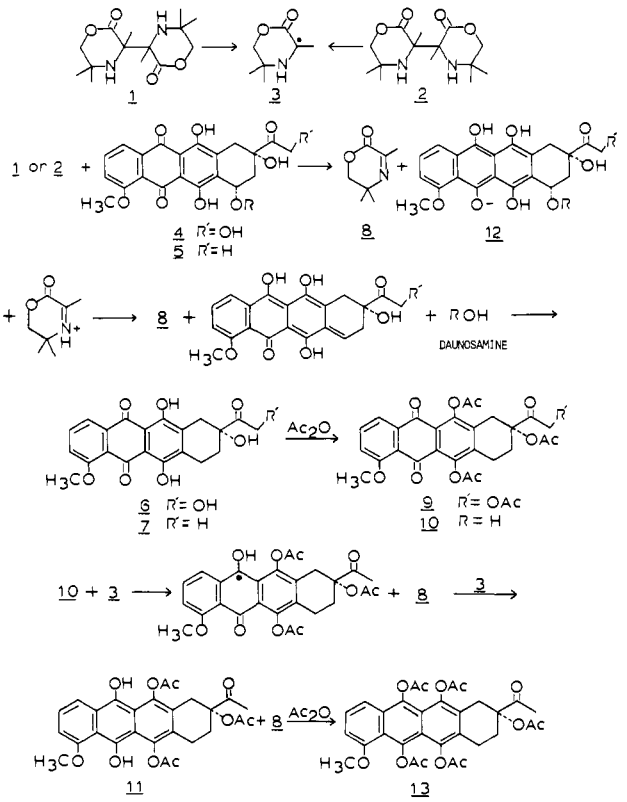
We have recently noted that the meso and *dl* dimers (**1** and **2**) of the 3,5,5-trimethyl-2-oxomorpholin-3-yl radical (**3**) dramatically reduce the toxicity in mice of the anthracycline, antitumor drug adriamycin hydrochloride (**4**).[1] This observation coupled with our recent report that **3**, which results from homolytic cleavage of **1** and **2**, reacts as a mild one-electron reducing agent[2] prompted us to study the in vitro reactivity of **1** and **2** with both adriamycin hydrochloride and daunomycin hydrochloride (**5**).

We now report that a mixture of the stereoisomeric radical dimers (**1** and **2**) react with adriamycin and daunomycin hydrochlorides in near quantitative yield to give the corresponding 7-deoxyaglycons (**6** and **7**) characterized as their tetraacetate and triacetate derivatives, respectively (**9** and **10**). The triacetate of **7** reacts further with **1** and **2** to give the hydroquinone **11** characterized as the pentaacetate **13**. This reactivity parallels the reactivity of adriamycin and daunomycin with nicotinamide adenine dinucleotide phosphate (NADPH) in rat liver microsomes and heart sarcosomes under anerobic conditions as proposed by Bachur and co-workers.[3,4] The reduction of daunomycin hydrochloride by the *dl* dimer **2** occurs faster than the rate of bond homolysis of **2** and is at least predominantly bimolecular.

A mixture of **1** and **2** in a freeze–pump–thaw degassed methanol solution reduced the anthracyclines **4** and **5** to their 7-deoxyaglycons **6** and **7** in excellent yields. In a typical experiment 2 equiv of the radical dimers and 1 equiv of anthracycline in absolute methanol were reacted in the dark at ambient temperature for 1 h. The 7-deoxyaglycons precipitated as red crystalline solids and were collected in greater than 90% yield. The only product observed by ^1H NMR spectroscopy from the dimers was 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**8**).[5] The 7-deoxyaglycons were characterized as their tetraacetate and triacetate derivatives, respectively (**9** and **10**). The derivatives were prepared in greater than 87% yield by reaction of the 7-deoxyaglycons with acetic anhydride in dry pyridine. The tetraacetate and triacetate were identical in all respects with those prepared by catalytic hydrogenation of adriamycin (**4**) followed by acetylation[6] and sodium dithionite reduction of daunomycin (**5**) followed by acetylation.[7]

Scheme I



The 7-deoxyaglycons appeared to react further with the dimers **1** and **2** in methanol solvent. The reaction was slow due in part to the low solubility of **6** and **7**. Consequently, this reactivity was examined further by using the triacetate of the 7-deoxyaglycon of daunomycin (**10**) which is soluble in organic solvents. An NMR sample tube was charged with a deuteriochloroform solution of **1**, **2**, and **10**, freeze–pump–thaw degassed, and sealed. When the solution was left in the dark for several hours at 25 °C it became visibly fluorescent. The ^1H NMR spectrum indicated that the dimer had oxidized to **8** and that **10** had disappeared. When the sample was exposed to air, the fluorescence rapidly disappeared and the 7-deoxyaglycon triacetate reappeared as indicated by ^1H NMR spectroscopy. When the reaction of **10** with **1** and **2** was allowed to occur in the presence of acetic anhydride and a catalytic amount of dry pyridine, the pentaacetate **11** was formed, isolated in 53% yield as a stable yellow crystalline material (mp 148 °C dec), and characterized from spectral data.[8]

The hydrogenolysis of adriamycin and daunomycin most likely proceeds via formation of the anion **12** as shown in Scheme I. Elimination followed by tautomerization gives the 7-deoxyaglycons and an amino sugar, daunosamine, which was not isolated or characterized. Initially we presumed that anion **12** was formed by electron transfer followed by proton transfer from two oxomorpholinyl radicals **3**, analogous to the mechanism for reaction of **3** with other substrates as proposed earlier.[2,9] We also presumed that the rate-controlling step would be homolysis of the radical dimer (Scheme I) as observed in the reaction between the radical dimers and *N*-methylisatin.[9]

The hydrogenolysis of daunomycin hydrochloride (**5**) by the *dl* dimer **2**, however, proceeds at least eight times faster than the

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(8) The pentaacetate **13** gave the following spectral absorptions: IR ($CHCl_3$) 5.66 (br) and 5.76 (br) μm; UV (CH_3OH) (log ϵ) 266 (5.6), 356 (4.2), 375 (4.4), 395 (4.4), and 417 nm (4.3); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.16 (s, 3 H), 2.36–2.46 (overlapping s, 12 H), 2.56–3.30 (m, 4 H), 6.63–7.53 (m, 3 H); mass spectrum (70 eV), *m/e* (relative intensity) 594.9 (12), 553.0 (9), 512.0 (8), 511.0 (25), 468.8 (24), 408.8 (16), 366.8 (27), 365.7 (35), 324.6 (12), 323.6 (39), 43 (100).

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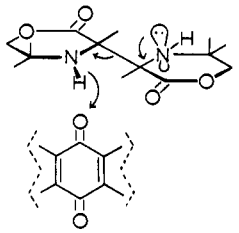
homolysis of **2** in methanol solvent under the reaction conditions. The rate constant for bond homolysis of **2** in methanol solvent at 9.9 ± 0.1 °C is (5.17 ± 0.02) × 10^{-4} s^{-1} and in methanol-*d* solvent (4.19 ± 0.04) × 10^{-4} s^{-1}. The homolysis rate constants were determined by using *N*-methylisatin as a trapping agent for the oxomorpholinyl radical **3**. The experimental technique was analogous to that previously described[9] in chloroform solvent except the destruction of *N*-methylisatin was monitored by visible spectroscopy at 420 nm. The hydrogenolysis of daunomycin hydrochloride by **2** in methanol solvent at 9.7 ± 0.2 °C is first order in daunomycin hydrochloride (**5**) and first order in *dl* dimer **2** when daunomycin hydrochloride is 1–2 × 10^{-4} M and occurs with a rate constant of 43 ± 7 M^{-1} s^{-1}. In methanol-*d* solvent at 9.8 ± 0.1 °C the rate constant is 8.1 ± 1.3 M^{-1} s^{-1}. The two rate constants yield a deuterium kinetic isotope effect of 5.3 ± 1.7. Destruction of daunomycin hydrochloride was monitored spectrophotometrically at 475 or 480 nm. The error in the measurements of the bimolecular rate constants resides predominantly in the determination of the infinity point. Each rate constant is the average of four measurements which followed bimolecular kinetics with correlation coefficients of better than 0.9995 for more than 70% of the reaction.

In the daunomycin hydrochloride concentration region of 1–2 × 10^{-4} M especially in methanol-*d* solvent, competitive first- and second-order reaction mechanisms can logically be inferred from the magnitude of the rate constants. The second-order rate constants were recalculated by using the integrated rate expression for competitive first- and second-order processes, the measured first-order rate constant for bond homolysis, and an iterative procedure. The data fit the competitive first- and second-order mechanisms as well as the second-order mechanism. The recalculated second-order rate constants in methanol and methanol-*d* solvents are 38 ± 6 and 4.4 ± 1.2 M^{-1} s^{-1}, respectively, giving a deuterium kinetic isotope effect of 8.6 ± 2.7.

Although the isotope effect for the bimolecular mechanism includes contributions from exchange of the various remote acidic protons of daunomycin hydrochloride with the solvent and a solvent isotope effect, the magnitude is still suggestive of cleavage of an N–H bond of the dimer in the transition state of the rate-controlling process. Note that the isotope effect for homolysis of



2, which also includes a solvent isotope effect, is only 1.23 ± 0.03. The N–H bond cleavage probably involves either a hydrogen atom or a hydride transfer, both facilitated by cleavage of the central 3,3′ C–C bond. If hydrogen atom transfer occurs, a subsequent electron transfer from radical **3** would be required to generate anion **12**.

The reduction of the 7-deoxyaglycon triacetate to the hydroquinone most likely occurs via a series of electron transfer followed by proton-transfer steps from radical **3** (Scheme I), since this reduction is visibly slower than bond homolysis of **1** or **2**. The process of electron transfer from radical **3** is analogous to that proposed earlier for the reduction of the carbon–nitrogen double bond of 5,6-dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one,[2] the reduction of benzil to benzoin,[2] and the reductive dimerization of isatin to isatide[9] by the radical **3**.

Recently, Bachur and co-workers have proposed that the quinone-containing anticancer drugs including adriamycin (**4**) and daunomycin (**5**) serve as electron-transfer catalysts for the reduction of oxygen to superoxide by NADPH.[3,4] Since **4** and **5** bind effectively to DNA, probably by intercatalation, the toxicity and/or activity in chemotherapy has been proposed to result from the production of superoxide and subsequently peroxide and hydroxyl radicals in the vicinity of the DNA. In an anerobic environment **4** and **5** are reductively cleaved by NADPH to the 7-deoxyaglycons **6** and **7**, respectively, analogous with the reductive cleavage described here. The dramatic reduction in the toxicity of adriamycin by **1** and **2** may then result from the reductive cleavage reaction. Although the 7-deoxyaglycons themselves should be capable of serving as catalysts for the reduction of oxygen to superoxide, reactivity should be severely inhibited by solubility.

The reactivity of both the radical dimers (**1** and **2**) and the oxomorpholinyl radical **3** appear to resemble the reactivity of NADPH. The reactivity of the dimers might parallel the reactivity of NADPH in hydride donation, and the reactivity of the oxomorpholinyl radical **3** appears to parallel the free-radical reactivity of NADPH in electron transfer.[2,10,11]

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Exchange Interaction Contribution to Energy Transfer between Ions in the Rapid-Diffusion Limit[1]

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Energy transfer is enhanced by translational diffusion occurring during the excited state lifetime of the fluorescent donor.[2,3] The increase in transfer efficiency becomes maximal when $D\tau/s^2 \gg 1$, where D is the sum of the diffusion coefficients of the donor and acceptor, τ is the lifetime of the donor, and s is the mean donor–acceptor distance. This rapid-diffusion limit has been experimentally realized[3] by the use of terbium chelates as long-lived energy donors ($\tau \sim 1$ ms). An attractive feature of rapid-diffusion transfer is its very strong dependence on the distance of closest approach of the donor and acceptor. Consequently, this technique can be used to ascertain the depths of chromophores in biological macromolecules and membrane systems.[4] The

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