Table I. Planar Inversion Barriers (kcal/mol) and Puckering Angles (deg) for Cyclobutadiene Dications

theoretical level	barrier puckered-planar		puckering angle	
	2a–1a	**2b–1b**	**2a**	**2b**
STO-3G//STO-3G	2.8[a]	2.3[a]	33.2[a]	25.4[a]
3-21G//3-21G	5.2[b]	3.7[b]	39.6[b]	37.8[b]
4-31G//4-31G	4.6[a]		35.8[a]	
6-31G*//6-31G*	7.5[a,c]	5.0[b]	42.6[a]	39.0[b]
MP4SDTQ/6-31G*//6-31G*	9.6[b,c]			

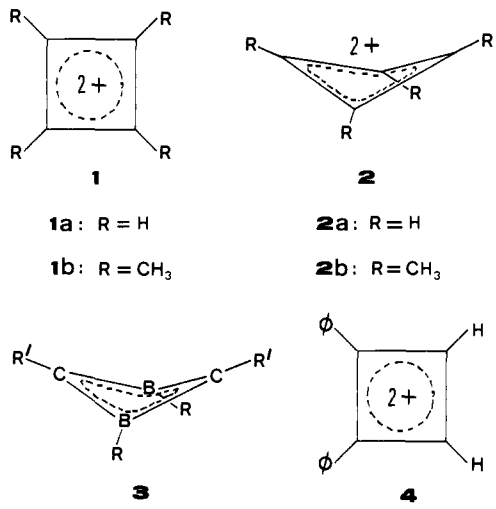
[a] Reference 4. [b] This work. [c] Zero point energy (6-31G*) corrections are negligible.

Table II. Comparison of IGLO Calculated and Experimental ^{13}C Chemical Shifts, ppm (vs TMS) (6-31G* Geometries)

	1a	**2a**	**1b**		**2b**	
	ring-*C*	ring-*C*	ring-*C*	*C*H$_3$	ring-*C*	*C*H$_3$
IGLO						
DZ basis[a]	261	193	263	25.2	209	18.7
II (DZ + P) basis[b]	255	186				
expt		182.1[c,d]			209.7[d]	18.8[d]

[a] Double ζ basis set. [b] Triple ζ + polarization basis set; see ref 7. [c] For the 1,2-diphenylcyclobutadiene dication **4**; see text. [d] Reference 1c–e.

The IGLO ^{13}C chemical shifts were calculated for the $C_4H_4^{2+}$ geometries with double-ζ (DZ) and polarized (TZ + P, II) basis sets[7] (Table II). The variation was small (6–7 ppm). In contrast, the δ ^{13}C difference between the planar **1a** and puckered **2a**



structures was an order of magnitude larger (68–69 ppm). Experimental data for $C_4H_4^{2+}$ are not available. However, Olah has reported[1e] δ ^{13}C = 182.1 ppm for the four-membered ring CH carbons in the 1,2-diphenylcyclobutadiene dication **4**. The chemical shift agrees with the calculated value for **2a** but not for **1a**. This suggests that **4** favors a nonplanar geometry.

A direct comparison between theory and experiment is provided by the $(CCH_3)_4^{2+}$ δ ^{13}C values, both for the ring and the methyl carbons (Table II). The IGLO (DZ) (209 and 18.7 ppm, respectively) and experimental (209.7 and 18.8 ppm, respectively) chemical shifts for the puckered geometry (**2b**) are nearly identical! Although this high degree of agreement must be to some extent fortuitous (e.g., only the DZ and not the II basis could be employed, and no solvent corrections were made), the planar structural alternative (**1b**) can be ruled out with certainty (Tables I and II).

It is now conclusive: four-membered 2π electron Hückel ring systems do *not* prefer to be planar.[4-6] However, we do not agree that this puckering is "perhaps the best evidence for the lack of strong π stabilization".[4d] As discussed in detail elsewhere,[4a-c,6] the energies of the π MO's are lowered by the orbital mixing possible in lower symmetry and from the shorter C–C distances in the nonplanar form. The π systems in **2a** and **2b** enjoy 1,3- as well as 1,2-stabilizing interactions and strive to achieve the three-dimensional aromaticity exemplified by the 1,3-dehydroadamant-5,7-diyl dication.[8] The stabilization energies for four-membered ring 2π electron systems are evaluated to be quite large,[4c,6c,11] and the same is true for the planar form.

As these and related investigations continue to demonstrate,[7-9] an important new tool is now available to the structural chemist. Ab initio geometries (even quite subtle features!) can be related to molecular structures in solution by comparing calculated and experimental NMR chemical shifts.[12]

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(10) The relationship of the ^{13}C chemical shifts and the π electron density for *planar* aromatic systems, first proposed by Spieseke and Schneider (Spiesecke, H.; Schneider, W. G. *Tetrahedron Lett.* **1961**, 468) has been extended by employing data for cyclobutadiene dications.[1b] However, the apparent agreement is thrown into question by our data. Table II shows the chemical shift for the *planar* forms of these dications to be 54–68 ppm *higher* than the experimental values.

(11) Also, see: Clark, T.; Wilhelm, D.; Schleyer, P. v. R. *Tetrahedron Lett.* **1982**, *23*, 3547.

(12) The GIAO (gauge-invariant atomic orbital)-based program of Pulay, Hinton, and Wolinski (Pulay, P.; Hinton, J. F.; Wolinski, K., private communication) predicts δ ^{13}C values (vs CH_4) of 187.6 (6-31G) and 180.3 ppm (6-31G**) for **2a**, 258.8 (6-31G) and 245.3 ppm (6-31G**) for **1a**, 266.6, 23.0 (4-31G), 252.0, 20.4 ppm (6-31G*) for **1b**, and 209.7, 15.9 (4-31G), 200.9, 13.7 ppm (6-31G*) for **2b**. These are comparable to the IGLO results in Table II. We thank Professor Pulay and his associates for these data.

Leucodaunomycin, a Tautomer of Daunomycin Hydroquinone[1]

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Daunomycin (**1**) and structurally related anthracylines such as adriamycin and aclacinomycin A are important antitumor drugs whose mechanism of action has been extensively investigated.[3,4] They are thought to attack nucleic acids, cell membranes, and proteins such as topoisomerase.[3] Of continued interest is possible covalent binding to DNA through bioreductive activation.[5] Reduction produces a reactive quinone methide intermediate from rapid glycosidic cleavage at the hydroquinone redox state.[6-9] A dilemma in understanding covalent binding to DNA is that in vitro experiments indicate that the quinone methide intermediate has

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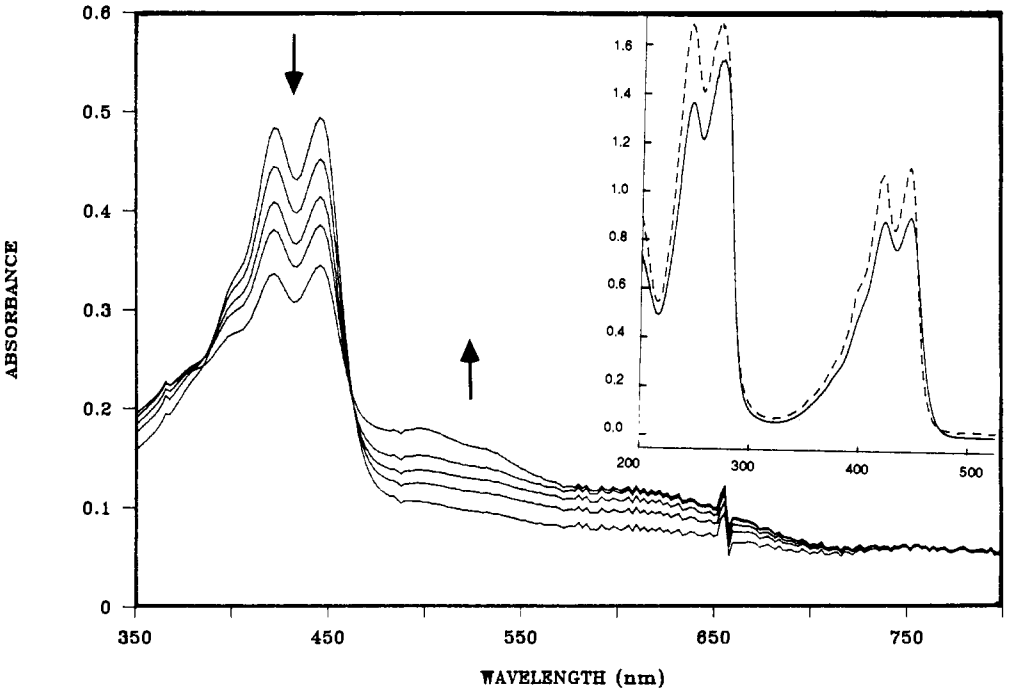
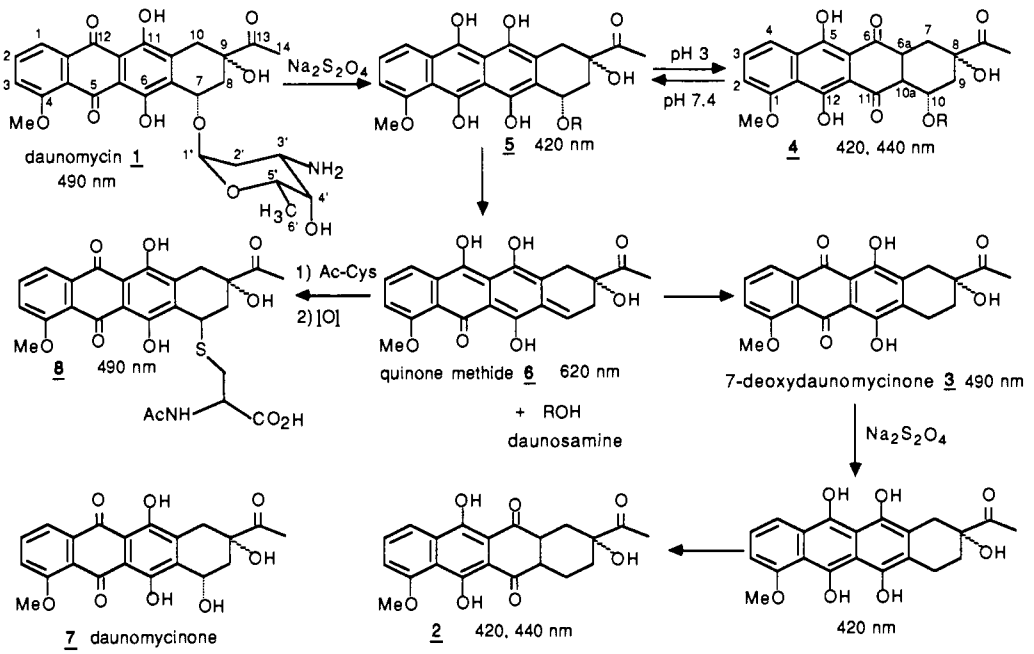


Figure 1. UV–vis absorption spectra of a 4.40×10^{-5} M, anaerobic, aqueous solution of isomer A of leucodaunomycin **4** adjusted to pH 7.4 at 25 °C as a function of time. Scans were 1 s in duration and occurred at the following times after adjusting the pH: 15, 25, 35, 45, and 65 s. The inset shows UV–vis absorption spectra of a 7.14×10^{-5} M solution of isomer A of **4** (—) and a 7.71×10^{-5} M solution of isomer C of **4** (– –) in pH 3 water.

Scheme I



a half-life of only 22 s at 25 °C in aqueous medium[9] and is only moderately reactive with nucleophiles. Although the anthracylines, especially adriamycin, are strong DNA intercalators[10] and intercalation might provide a good reaction geometry for the quinone methide, intercalation inhibits reductive activation.[11] We report here that a possible explanation for this dilemma is the formation of a tautomer of daunomycin hydroquinone whose stability with respect to glycosidic cleavage is pH dependent.

Anaerobic reduction of daunomycin hydrochloride with 1 equiv of sodium dithionite in aqueous medium followed by immediate addition of 0.25 equiv of deoxygenated hydrochloric acid (pH 0.7) to lower the pH to 3 yielded two major (A and C) and two minor (B and D) isomeric products in the ratio 2.9:1.0:4.7:1.2 in order of increasing retention time as indicated by C18 reverse phase HPLC. Diode array UV–vis spectroscopic analysis of the products as they eluted from the chromatograph suggested that they all had a chromophore identical with that of the diastereoisomers of leuco-7-deoxydaunomycinone **2** first characterized by Brand and Fisher;[12] however, retention times distinguished them from the diastereoisomers of **2**. The leuco-7-deoxydaunomycinones **2** were formed by reduction of either daunomycin or 7-deoxydaunomycinone (**3**) with dithionite at pH 7.4.[12] The two major isomers, A and C, formed when the pH was lowered to 3 im-

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mediately after reduction, were isolated in small quantity by C18 reverse phase flash chromatography eluting with a step gradient of methanol and 1.5% aqueous formic acid, and they were characterized as stereoisomers of leucodaunomycin, (8*S*-*cis*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxohexopyranosyl)-oxy]-6a,7,8,9,10,10a-hexahydro-5,8,12-trihydroxy-1-methoxy-6,11-naphthacenedione (**4**), from spectroscopic, chemical, and kinetic data. The major isomers (A and C) gave UV-vis absorptions as shown in the inset of Figure 1, and isomer C was further characterized from mass spectral and NMR data.[13]

Isomer A was reacted anaerobically in aqueous solution by adjusting the pH to 7.4 with Trizma buffer, and the course of the reaction was monitored spectrophotometrically. The spectra showed a rise (Figure 1) and a fall in the absorption at 618–622 nm consistent with slow back tautomerization to daunomycin hydroquinone (**5**) followed by rapid elimination of daunosamine to form the quinone methide **6** and slow tautomerization of **6** to 7-deoxydaunomycinone (**3**) as shown in Scheme I. The absorption at 618–622 nm versus time data for the early part of the reaction were fit by nonlinear least squares to a consecutive first-order rate law correcting for end absorption by **3**. Absorption at later times was obscured by precipitation of **3**. The integrated rate law was as follows:

$$A_t = \frac{[4]_0}{k_1 - k_2}\{(k_1\epsilon_6 - k_2\epsilon_3)e^{-k_1 t} + (k_1\epsilon_3 - k_1\epsilon_6)e^{-k_2 t} + \epsilon_3(k_2 - k_1)\}$$

where A_t is the absorbance at 618–622 nm at time t, $[4]_0$ is the initial concentration of **4**, k_1 is the pseudo-first-order rate constant for tautomerization of **4**, k_2 is the pseudo-first-order rate constant for tautomerization of **6**, and ϵ_6 and ϵ_3 are the molar extinction coefficients for **6** and **3** at 618–622 nm. The calculated rate constants k_1 and k_2 were $(1.0 \pm 0.1) \times 10^{-2}$ and $(3.3 \pm 0.02) \times 10^{-2}$ s^{-1}, respectively, where the errors are given as the average deviation from the mean of two measurements. Reverse phase HPLC analysis of the product mixture showed 97% 7-deoxydaunomycinone (**3**) and 3% daunomycinone (**7**). In a separate experiment the rate constant for decay of quinone methide **6** generated by anaerobic reduction of **1** at pH 7.4 with sodium dithionite was determined to be 3.2×10^{-2} s^{-1}. Reverse phase HPLC analysis of this reduction showed 98% **3** and 2% **7**.

Similar spectroscopic monitoring of reaction of isomer C of **4** at pH 7.4 did not show the build up of absorption at 618–622 nm but only decay of the leucodaunomycin bands with formation of predominantly the quinone band of **3**. A sharp isosbestic point appeared at 454 nm. The decay of the 440-nm band of **4** was first order, and least-squares treatment of $\ln(A - A_\infty)$ versus time data gave k_1 equal to 1.3×10^{-3} s^{-1} with a correlation coefficient of 1.00. Reverse phase HPLC analysis showed 96% **3** and 4% **7**. The quinone methide band was not observed because the rate constant for tautomerization of isomer C to hydroquinone **5** is too small, 25 times smaller than the rate constant for destruction of **6**.

Isomer A was also reacted with a 60-fold excess of *N*-acetyl-L-cysteine at pH 7.4 to give 86% **3** and 14% of a 2:1 mixture of the diastereomers from quinone methide nucleophilic trapping followed by oxidation, 7-(*N*-acetyl-L-cystein-*S*-yl)-7-deoxydaunomycinone (**8**). The structure for **8** was established by comparison with authentic material produced by reduction of daunomycin in the presence of *N*-acetyl-L-cysteine.[14]

The leucodaunomycins **4** were also produced by reduction of daunomycin with the organic reducing agent bi(3,5,5-trimethyl-2-oxomorpholin-3-yl) (TM-3 dimer)[5,15] in the aprotic solvent anhydrous acetonitrile. Formation of **4** from daunomycin hydroquinone (**5**) in acetonitrile solvent and in protic solvent at low pH in preference to glycosidic cleavage is consistent with glycosidic cleavage occurring at an anionic state of **5**.

In summary, daunomycin hydroquinone (**5**) tautomerizes at the B-ring to leuco isomers in competition with glycosidic cleavage when the pH is rapidly reduced from 7 to 3. The leuco isomers are stable at low pH but revert to daunomycin hydroquinone at pH 7.4. If leucodaunomycins are formed in vivo as transient metabolites by reduction of daunomycin in hydrophobic regions or in regions of low pH, subsequent reaction with biological macromolecules would not require reduction but only a change in pH and hydrophobicity. The leucodaunomycins may also be interesting pharmaceutical materials because they are anthracyclines which do not require bioreductive activation to reach the quinone methide state; furthermore, isomer C has a relatively long half-life at biological pH.

(13) FAB (positive ion) m/z 552 (100, M + Na$^+$), 530 (80, M + 1), 401 (27); (negative ion) m/z 529 (100, M); 300 MHz ^{1}H NMR δ 1.22 (d, J = 6.5 Hz, 5′-CH$_3$), 1.79–2.18 (m, 2′-H, 7-H, 9-H), 2.28 (s, 8-COCH$_3$), 3.60 (m, 3′-H, 6a-H), 3.73 (m, 4′-H, 10a-H), 3.98 (s, 1-OCH$_3$), 4.13 (q, J = 6.5 Hz, 5′-H), 4.72 (m, 10-H), 4.94 (m, 1′-H), 7.30 (d, J = 7.6 Hz, 4-H), 7.71 (t, J = 7.7 Hz, 3-H), 7.93 (d, J = 7.4 Hz, 2-H).

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Ligand Substitution Reactions of 17-Electron Transition-Metal Carbonyl Anions: An Electron-Transfer Mechanism

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Seventeen-electron metal complexes have been recognized as intermediates in catalytic, photochemical, and electrochemical reactions.[1] An important aspect of their reactivity is their substitutional lability. In general 17-electron complexes are more reactive than 18-electron complexes and more selective in their reactivity than 16-electron complexes. Reaction of a 17-electron metal complex with a two-electron donor by an associative mechanism usually involves delocalization of electron density from the metal onto the ligands. This avoids a high-energy 19-electron transition state and is postulated to be important in the very facile ligand substitution reactions of $Mn(CO)_5$,[2] for example. We report here facile gas-phase ligand substitution reactions of the isoelectronic $Cr(CO)_5^-$. These reactions provide an interesting example of the selectivity with which 17-electron complexes can react. They proceed selectively with ligands of high electron affinity. This suggests a mechanism in which the metal transfers an electron to the attacking ligand, and the resulting 16-electron metal complex can then accept two electrons from a donor group on the ligand to form a low-energy 18-electron transition state. Charge transfer is thought to be involved in some reactions of more unsaturated metal carbonyl anions,[3,4] but reactions of 17-electron metal carbonyl anions have generally been interpreted in terms of other mechanisms.[4,5]

The gas-phase reactions involve $Cr(CO)_5^-$ and a series of organic ligands. Examination of the reactions has produced two kinds of evidence supporting the charge-transfer mechanism: (1) The variation of rates of the reaction with electron affinity of the ligand and (2) the distinctive nature of the products of certain reactions, in particular the reactions of the bromonitrobenzene isomers.

The total reaction rate constants for reactions of $Cr(CO)_5^-$ with a series of organic ligands were measured by using FTICR techniques on a Nicolet FTMS-2000 instrument.[6] The anion reactant was formed by low-energy electron attachment to Cr-

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