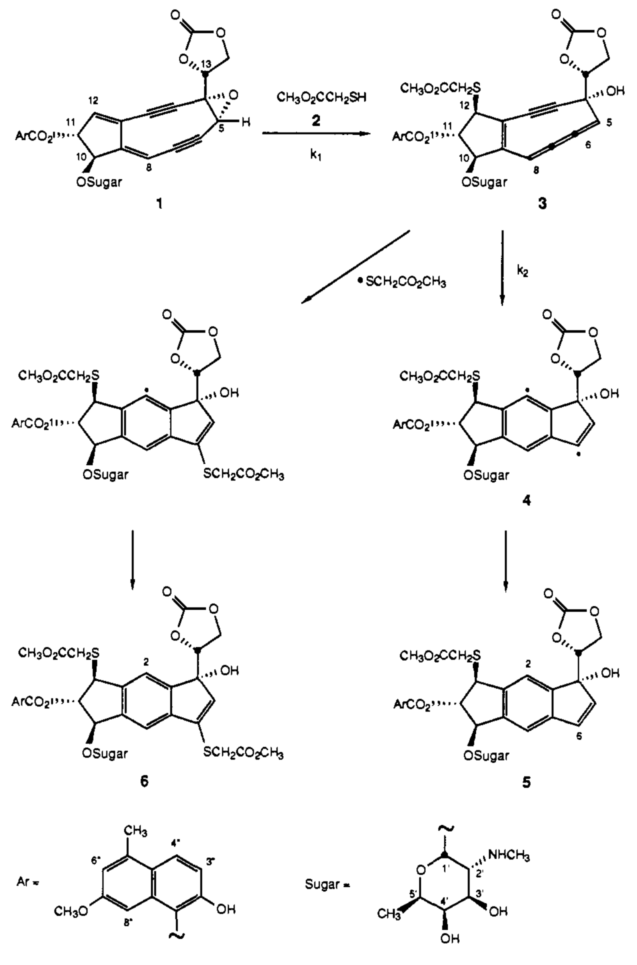
Scheme I



from consideration in light of more rapid trapping of **4** by solvent and we thus conclude that $k_{obsd} = k_2$ (Scheme I) and that $\Delta G^{\ddagger}$ for the process **3** → **4** is 18.0 ± 0.1 kcal/mol.[7]

While the conditions of the experiments outlined above are far from physiological, our results bear on questions regarding the relevance of pathways such as that outlined in Scheme I to the mechanism of action of neocarzinostatin in vivo. In the initial activation event, it is clear that **1** possesses a remarkable affinity for thiols, combining readily with methyl thioglycolate (30 mM, pK_a = 7.9)[8] at −70 °C. Glutathione (pK_a = 8.7), present in mammalian cells at concentrations of 0.5–10 mM,[9] has been strongly implicated as the activating nucleophile in studies of neocarzinostatin toxicity in intact cells.[10] With regard to the second event in activation, aromatization of a thiol–chromophore adduct such as **3** to the corresponding tetrahydroindacenediyl, we calculate a half-life of ~0.5 s for the transformation of **3** to **4** at 37 °C.[11]

Acknowledgment. Generous financial assistance from the National Institutes of Health (CA-47148-01) and Merck & Co., Inc., a Dreyfus New Faculty Award (to A.G.M.), and a National Science Foundation predoctoral fellowship (to P.J.P.) are gratefully acknowledged. We are indebted to our colleague Professor Dennis Dougherty for many helpful discussions.

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(7) The rate of trapping of **4** can be estimated by the rate of reaction of phenyl radical with diphenylmethane (7.7 × 10^6 M^{-1} s^{-1} at 60 °C): Lockhart, T. P.; Mallon, C. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5976. Ingold, K. U. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. I, Chapter 2.

(8) Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 4433.

(9) Meister, A.; Anderson, M. E. *Annu. Rev. Biochem.* **1983**, *52*, 711.

(10) DeGraff, W. G.; Russo, A.; Mitchell, J. B. *J. Biol. Chem.* **1985**, *260*, 8312.

(11) This assumes a (likely) weak temperature dependence of $\Delta G^{\ddagger}$.

Nonplanarity in Hückel 2π Aromatic Systems. An NMR-IGLO-ab Initio Proof of the Puckered Structure of Cyclobutadiene Dications

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Although numerous derivatives of the cyclobutadienyl dication (**1** and **2**) have been characterized by NMR spectroscopy in super acid media[1]—the tetramethyl-substituted dication (**1b** and **2b**) was prepared by Olah et al. 20 years ago[1a]—the structures of these species have not been established experimentally.[2]

In contrast to the expectation that 2π electron Hückel aromatics should prefer planar geometries **1**,[1e,3] ab initio calculations predict puckered structures **2** to be more stable.[4] The same preference also was forecast for isoelectronic 1,3-diboracyclobutadiene **3**;[4c] this was verified, subsequently by X-ray crystallography on derivatives[5] and by further ab initio calculations.[6]

We now present evidence, based on comparison of the chemical shifts calculated (IGLO)[7] for **1b** and **2b** with the experimental values, which establishes the nonplanar structure **2b** for the tetramethylcyclobutadienyl dication conclusively.

The fully optimized 6-31G* geometries were employed not only for the parent dication (**1a** and **2a**)[4] but also for the tetramethyl derivatives (**1b** and **2b**). Experience has shown that carbocation structures of at least this quality are desirable for the IGLO calculations, in order to obtain the best comparison with experimental chemical shifts.[7-9]

The symmetries chosen, C_{4h} for **1b** and D_{2d} for **2b**, were based on the methyl group conformational preferences found at 3-21G//3-21G. Frequency analyses at 6-31G* establish **2a** (D_{2d}) to be a minimum and **1a** (D_{4h}) to be the transition structure for ring inversion (one imaginary frequency). We assume the same to hold for **2b** and **1b**. As is shown in Table I, which also summarizes the earlier work, the barrier as well as the puckering angle increase somewhat at higher levels of theory. On the basis of the trends in the **1a**–**2a** energy differences, we estimate an inversion barrier of about 7 kcal/mol for **1b**–**2b**.

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(1) (a) Olah, G. A.; Bollinger, J. M.; White, A. M. *J. Am. Chem. Soc.* **1969**, *91*, 3667. (b) Olah, G. A.; Mateescu, G. P. *Ibid.* **1970**, *92*, 1430. (c) Olah, G. A.; Liang, G. *Ibid.* **1976**, *98*, 3033. (d) Olah, G. A.; Liang, G. *Ibid.* **1977**, *99*, 6045. (e) Olah, G. A.; Staral, J. S. *Ibid.* **1976**, *98*, 6290. See, also: Maier, G. *Angew. Chem.* **1988**, *100*, 317.

(2) Attempts to establish the nonplanarity of cyclobutadiene dications by use of prochiral substituents were unsuccessful, see: Brendel, D. Dissertation, Erlangen, 1985.

(3) See, e.g.: Pittman, C. U., Jr.; Kress, A.; Kispert, L. D. *J. Org. Chem.* **1974**, *39*, 378. Radom, L.; Schaefer, H. F., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 7522.

(4) (a) Krogh-Jespersen, K.; Schleyer, P. v. R.; Pople, J. A.; Cremer, D. *J. Am. Chem. Soc.* **1978**, *100*, 4301. (b) Chandrasekhar, J.; Schleyer, P. v. R.; Krogh-Jespersen, K. *J. Comput. Chem.* **1981**, *2*, 356. (c) Krogh-Jespersen, K.; Cremer, D.; Dill, J. D.; Pople, J. A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 2589. (d) Hess, B. A. Jr.; Ewig, C. S.; Schaad, L. J. *J. Org. Chem.* **1985**, *50*, 5809.

(5) Hildenbrandt, M.; Pritzkov, H.; Zeuneck, U.; Siebert, W. *Angew. Chem.* **1984**, *96*, 371; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 371.

(6) (a) Schleyer, P. v. R.; Budzelaar, P. H. M.; Cremer, D.; Kraka, E. *Angew. Chem.* **1984**, *96*, 374; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 374. (b) Budzelaar, P. H. M.; Krogh-Jespersen, K.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1985**, *107*, 2773. (c) Budzelaar, P. H. M.; Kraka, E.; Cremer, D.; Schleyer, P. v. R. *Ibid.* **1986**, *108*, 563.

(7) Schindler, M. *J. Am. Chem. Soc.* **1987**, *109*, 1020.

(8) Bremer, M.; Schleyer, P. v. R.; Schötz, K.; Kausch, M.; Schindler, M. *Angew. Chem.* **1987**, *99*, 795; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 761.

(9) (a) Schleyer, P. v. R.; Laidig, K.; Wiberg, K. B.; Saunders, M.; Schindler, M. *J. Am. Chem. Soc.* **1988**, *110*, 300. (b) Laidig, K.; Saunders, M.; Wiberg, K. B.; Schleyer, P. v. R. *Ibid.* **1988**, *110*, 7652. (c) Koch, W.; Liu, B.; Schleyer, P. v. R., submitted for publication. (d) Schötz, K.; Fleischer, U.; Bremer, M.; Schleyer, P. v. R., to be submitted for publication.

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

	barrier puckered-planar		puckering angle	
theoretical level	**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]			

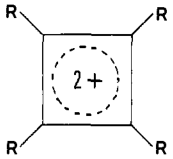
[a] Reference 4. [b] This work. [c] Zero point energy (6-31G*) corrections are negligible.

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.

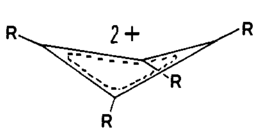
The IGLO ^{13}C chemical shifts were calculated for the $C_4H_4^{2+}$ geometries with double-ζ (DZ) and polarized (TZ + P, II) basis sets[7] (Table II). The variation was small (6–7 ppm). In contrast, the δ ^{13}C difference between the planar **1a** and puckered **2a** structures was an order of magnitude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



1

1a: R = H

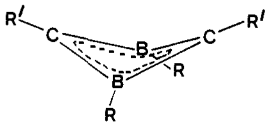
1b: R = CH_3



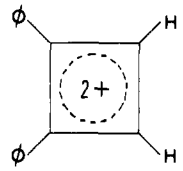
2

2a: R = H

2b: R = CH_3



3



4

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-dehydro-adamant-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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(3) Abdella, B. R. J.; Fisher, J. *Environ. Health Perspect.* **1985**, *64*, 3.

(4) Powis, G. *Pharm. Ther.* **1987**, *35*, 57.

(5) Moore, H. W. *Science (Washington, D.C.)* **1977**, *197*, 527. Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.

(6) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1984**, *106*, 2380.

(7) Kleyer, D. L.; Gaudiano, G.; Koch, T. H. *J. Am. Chem. Soc.* **1984**, *106*, 1105.

(8) Boldt, M.; Gaudiano, G.; Koch, T. H. *J. Org. Chem.* **1987**, *52*, 2146.

(9) Fisher, J.; Abdella, B. R. J.; McLane, K. *Biochemistry* **1985**, *24*, 3562.

0002-7863/89/1511-1148$01.50/0