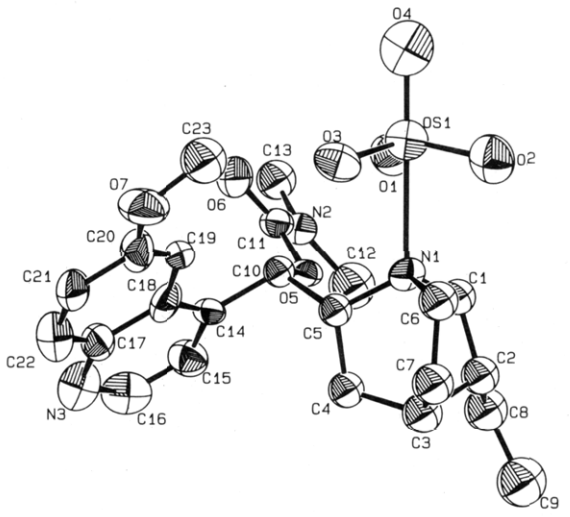


Figure 1. ORTEP view of the osmium tetraoxide complex of (dimethylcarbamoyl)dihydroquinidine (1).

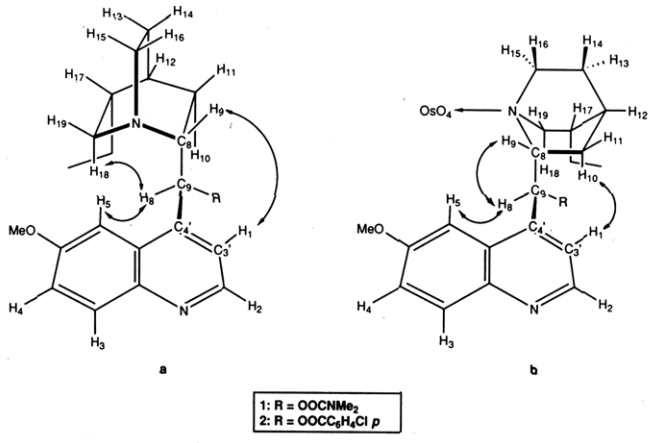


Figure 2. Atom numbering and important NOE's in the (a) closed and (b) open conformation of the cinchona alkaloids. Curved arrows indicate important NOE's.

by changes in the NOE connectivity pattern. Irradiation of H-8 in the complex yielded strong enhancements at H-5 and H-9, suggesting that these three nuclei are close to each other. A significant NOE was also observed between H-10 and H-1, which can only be accounted for by an "open" conformation. Additional substantiation of the conformational change was the disappearance of NOE's involving the pairs H-8, H-18 and H-9, H-1 upon complexation of the alkaloid to OsO_4.

Several important differences in the chemical shift values between free and complexed alkaloids, which could not be accounted for by direct shielding contributions from the heavy metal oxo species, can be explained by the change in the alkaloid conformation upon binding to osmium. In the transition from the "closed" to the "open" conformation, the quinuclidine ring rotates around the C-9–C-8 bond, changing the position of H-10 and H-11 relative to the quinoline ring. In the "open" conformation, H-11 is positioned in the shielding cone above the quinoline ring and experiences a strong upfield shift, whereas H-10, being in the same plane as the quinoline ring, suffers a downfield shift.

This NMR study reveals that the structure of the alkaloid–osmium tetraoxide complex in solution closely resembles the solid state structure in Figure 1. Since the 1:1 complex is known to oxidize a wide range of unfunctionalized olefins to their corresponding osmate esters with good to excellent levels of asymmetric induction, we hoped to be able to derive a coherent stereochemical model for the reaction from the data presented here. However, we find instead that the chiral centers in the alkaloid ligand are quite remote from the oxo ligands, and there is no clear indication of how chirality might be transmitted to the substrate. This is exacerbated by the fact that there is still very little known about the mechanism for the addition of osmium tetraoxide to olefins.[1a,12] One important piece of information obtained from the NMR studies may bear some relevance to the asymmetric dihydroxylation. The alkaloids which are effective ligands in the process all exist in a "closed" conformation in their uncomplexed state, whereas ineffective ligands (1, R = OH, OMe, $OSiMe_3$, H) all exist in an "open" conformation. The exact significance of this difference is not obvious, particularly since upon complexation to osmium tetraoxide all ligands adopt an "open" conformation. In any event, it is apparent that the steric and/or electronic factors governing the asymmetric osmylation reaction are extremely subtle and require considerably closer investigation. In this vein, solid state and solution studies of the corresponding osmate ester–alkaloid complexes are currently under way.

Acknowledgment. Financial support was provided by the National Science Foundation (Grant CHE-8303355) and Eli Lilly & Co. E.N.J., J.S.S., and K.B.S., respectively, thank the National Institutes of Health, the Royal Norwegian Council for Scientific and Industrial Research, and the John Simon Guggenheim Foundation for fellowships.

Supplementary Material Available: Tables of atomic positions, bond lengths and angles, anisotropic temperature factors, and calculated hydrogen atom positions for 1–OsO_4 and chemical shift values for **1**, **2**, and **3** and of their osmium tetraoxide complexes. ^1H NMR spectra of **2** before and after addition of OsO_4 (27 pages). Ordering information is given on any current masthead page.

J. S. Svendsen, István Markó, Eric N. Jacobsen
Ch. Pulla Rao, Simon Bott, K. Barry Sharpless*
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received December 27, 1988

(12) For some recent discussions, see: Wallis, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 8207. Jørgensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, *108*, 1867. Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 573.

Acid–Base Controlled Torquoselectivity: Theoretical Predictions of the Stereochemical Course of the Electrocyclic Reactions of Cyclobutene-3-carboxylic Acid and the Conjugate Base and Acid

Summary: Ab initio calculations using the 3-21G and 6-31G* basis sets were carried out on the electrocyclic reactions of cyclobutene-3-carboxylic acid and its protonated and deprotonated forms. The calculations predict that the stereochemistry of the cyclobutene-3-carboxylic acid ring opening can be reversed from outward to inward rotation by protonation of the acid.

Sir: Substituted cyclobutenes undergo thermally allowed conrotatory ring opening by inward or outward rotation

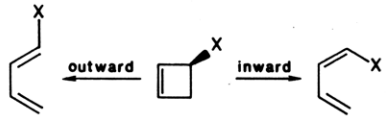
0022-3263/89/1954-2264$01.50/0

Table I. Activation Energies (kcal/mol) of Ring Openings of Cyclobutene-3-carboxylic Acid (B), the Conjugate Base (A) and Acid (C), Methyl Cyclobutene-3-carboxylate, and Lithium Cyclobutene-3-carboxylate

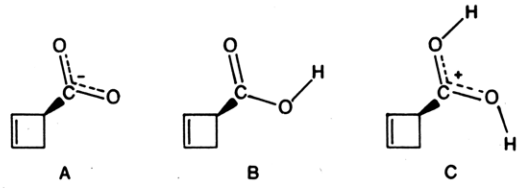
substituent	method	orientation	$\Delta E^{\ddagger}$ in	$\Delta E^{\ddagger}$ out	$\Delta\Delta E^{\ddagger}_{rel}$ in	$\Delta\Delta E^{\ddagger}_{rel}$ out
CO_2H	3-21G	syn[a]	40.0	38.5	1.5	0.0
	3-21G	anti[a]	40.9	39.1	2.4	0.6
	6-31G*//3-21G	syn[a]	44.2	41.9	2.3	0.0
	6-31G*//3-21G	anti[a]	44.4	42.7	2.5	0.8
CO_2^-	3-21G		42.1	37.2	4.9	0.0
	6-31G*//3-21G		47.1	39.8	7.3	0.0
$C(OH)_2^+$	3-21G	endo[b]	23.3	29.6	0.0	6.3
	3-21G	exo[b]	28.1	31.8	4.8	8.5
	6-31G*//3-21G	endo[b]	31.5	35.2	1.1	4.8
	6-31G*//3-21G	exo[b]	30.4	36.0	0.0	5.6
CO_2CH_3	3-21G[c]	syn[a]	40.3	38.6	1.7	0.0
		anti[a]	41.5	39.2	2.9	0.6
CO_2Li	3-21G[d]		43.1	39.3	3.8	0.0

[a] Syn indicates the carbonyl oxygen is pointed toward the ring, while anti indicates the carbonyl oxygen pointed away from the ring. [b] Exo indicates the anti CCOH part in C points away from the ring and endo points toward the ring. [c] A standard methyl replaced the H in the acid TS.[13] [d] Only the position of Li^+ was optimized.

of the substituent, X. According to the theoretical predictions, the tendency for outward rotation is increased as X is made a better π-electron-donating group, and inward rotation occurs only when X becomes a very strong π-electron-withdrawing group like BH_2 or CHO.[2-4] We



recently predicted that 3-cyano- and 3-formylcyclobutene should give outward and inward rotation, respectively.[3] The σ_R parameters for CN, CHO, and COOH groups suggest that the π-electron-withdrawing ability of the carboxylic acid group is intermediate between that of the cyano and formyl groups.[5] The mild electron-withdrawing character of the carboxylic acid group can be changed by deprotonation to form a group with weak donor character. By protonation of the acid, a strong electron-withdrawing group is formed.[5] If the protonation effects are large enough, alteration of the stereochemistry of the cyclobutene ring openings should be observed. We have investigated this qualitative argument by quantitative computations.



Calculations employed the GAUSSIAN 82[6] and 86[7] series of programs. The geometries of the ground states (GS) and transition states (TS) were fully optimized with the ab initio RHF method by using the split-valence 3-21G basis set.[8] The transition structures were found starting from the cyclobutene case, replacing the appropriate hydrogen with the substituent. From these geometries, second-derivative techniques converge on the stationary points quite rapidly. Vibrational frequencies were computed for each of the stationary points; zero or one imaginary frequency were found for reactants or transition structures, respectively. Finally, 6-31G* single-point calculations[9] on 3-21G geometries were carried out. This

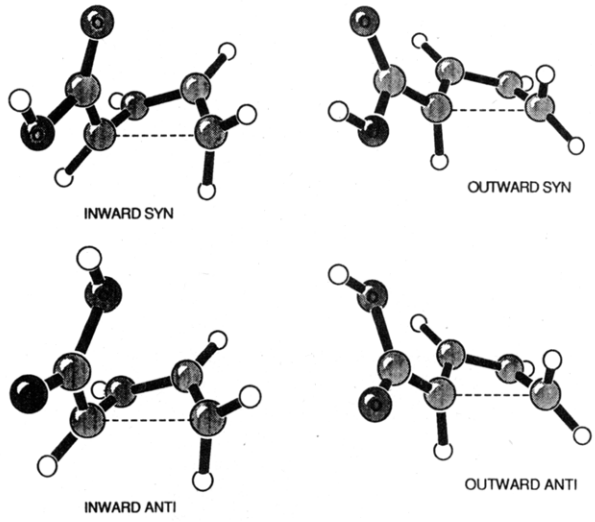


Figure 1. 3-21G optimized transition structures for cyclobutene-3-carboxylic acid electrocyclic reactions.

Table II. 6-31G*//3-21G Activation Energies (kcal/mol) for Electrocyclic Reactions of Cyclobutene-3-carboxylic Acid and the Conjugate Base and Acid Relative to the Calculated Activation Energy for Cyclobutene Opening[14]

substituent	in	out	in − out
CO_2H	−2.0	−4.3	2.3
CO_2^-	+0.9	−6.4	7.3
$C(OH)_2^+$	−15.8	−11.0	−4.8

(1) On leave from the Jagiellonian University, Krakow, Poland.
(2) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.
(3) Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708.
(4) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125.
(5) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley and Sons: New York, 1979.
(6) Binkley, J. S.; Frisch, M.; Raghavachari, K.; DeFrees, D. J.; Schlegel, H. B.; Whiteside, R.; Fluder, E.; Seeger, R.; Pople, J. A. *GAUSSIAN 82: Release E and H*; Carnegie-Mellon University: Pittsburgh, PA.
(7) Frisch, M.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; DeFrees, D. J.; Seeger, R.; Whiteside, R.; Fox, D. J.; Fluder, E. M.; Pople, J. A. *GAUSSIAN 86*; Carnegie-Mellon Publishing: Pittsburgh, PA, 1984.
(8) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

method was used previously to predict successfully the stereochemistry of 3-formylcyclobutene and other ring openings.[3,4] Correlation energy corrections were found to be unimportant in stereochemical predictions for other substituents and were not made for these cases.

The accurate transition structures for cyclobutene-3-carboxylic acid ring openings are shown in Figure 1, and the activation energies for ring openings of A, B, and C are collected in Table I. Activation energies relative to that for the conrotatory ring opening of cyclobutene are given in Table II.

The calculated 3-21G activation energies of cyclobutene-3-carboxylic acid ring openings with *outward* rotation of the carboxylic acid group are very close to the corresponding activation energies for 3-formylcyclobutene.[3] All are about 39 kcal/mol, about 10 kcal/mol higher than experimental values expected.[3,4] The activation energies for the *inward-syn* TS of 3-formylcyclobutene and both of the carboxylic acid TSs are about 40 kcal/mol. The acid has a slight preference for outward rotation. On the contrary, the activation energy of the *inward-anti* TS for 3-formylcyclobutene (35 kcal/mol) is significantly lower than the other TS energies. In the *inward-anti* TS, the formyl oxygen is pointed away from the cyclobutene ring, and the steric interactions or secondary orbital interactions between oxygen and the ring are much smaller than for the TS with the *inward-syn* conformation, which has the oxygen atom pointed toward C_2 of the cyclobutene ring. The syn and anti TS's of 3-cyclobutenecarboxylic acid are similar to each other because both forms have one oxygen pointed toward the ring. It may be concluded that both formyl and acid groups display the same stereoelectronic preference for inward rotation during cyclobutene ring openings, but the stronger steric interaction between the acid group and the cyclobutene ring disfavors this rotation. The acid is predicted to rotate outward with only 1.5–2.3 kcal/mol preference over the inward rotation. This predicts that the ratio of outward to inward rotation will be 7:1 (3-21G)–19:1 (6-31G*) at 100 °C.

The steric interactions between the acid group and the cyclobutene moiety for the conjugate base, A, and conjugated acid, C, should be very similar to those of the free acid. Differences in the stereochemistries of the ring openings should be related to changes in stereoelectronic effects. Deprotonation of the acid to form the carboxylate, A, increases the inward activation energy, since the π-acceptor character is diminished. The activation energy for outward rotation is further decreased, so the difference between outward and inward rotation is higher than for the carboxylic acid group. Therefore, only the outward product should be observed for carboxylate A. This contrasts to the experimental results reported by Trost et al., in which a carboxylate shows only a slight preference for outward rotation as compared to an ester.[10,11] Perhaps the strong preference for the outward product calculated for the gas phase becomes much smaller upon ion pairing in solution. In order to estimate the importance of solvation effects for the ring opening of an anion, single-point calculations for the lithium salt of A were performed.[12] The outward rotation for the chelate is still favored over the inward one by 3.8 kcal/mol, but this preference is smaller than for A.

For the protonated cyclobutene-3-carboxylic acid, C, however, the activation energies for ring opening are significantly smaller than for A and B. The 16 kcal/mol predicted decrease in activation energy implies that the protonated acid should open at room temperature with a barrier of only 16 kcal/mol. The calculations predict that the protonated acid group will rotate inward, and there is about a 5 kcal/mol preference for this stereochemistry. The calculated energetic preference for inward rotation of C is similar to that for 3-formylcyclobutene (4.5 kcal/mol) for which it was shown experimentally that the cyclobutene ring opening gives only one product with the formyl group rotated inward.[3] The dramatic decrease in activation energy, and the preference for inward rotation, is the result of the low π^*_{COO} acceptor orbital energy in the protonated acid. We have shown elsewhere that substituents with low-lying vacant orbitals rotate inward to maximize stabilizing cyclic two-electron interactions.[3,4]

The ab initio calculations suggest that the stereochemistry of the 3-cyclobutenecarboxylic acid ring opening will vary with the protonation of the acid group. Theoretical predictions on cyclobutene-3-carboxylic acid methyl ester ring openings were also performed. Single-point RHF/3-21G calculations were carried out using the optimized structures of cyclobutene-3-carboxylic acid with the acid hydrogen substituted by the methyl group.[13] The approximate activation energies obtained in this way are shown in Table I. The calculations predict that the methyl ester group should rotate outward, but with a preference of only 1.7 kcal/mol over inward rotation. This predicts a ratio of outward to inward products of 9:1 at 120 °C. In an accompanying paper, Piers reports a substituted case which gives experimental results in reasonable agreement with this prediction.[15] Our own experimental data on cyclobutenes and benzocyclobutenes provides further support, and will be reported in due course.[11]

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research and to the Harris Corporation for the grant of a computer system to UCLA. We thank Dr. David Eaton of Du Pont for suggesting the use of Lewis acids to increase π-electron withdrawal by carbonyl groups.

Andrzej B. Buda,[1] Ying Wang, K. N. Houk*

Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, California 90024

Received December 30, 1988

(9) Hariharan, P. C.; Pople, J. A. *Theor. Chem. Acta* **1973**, *28*, 213.
(10) Trost, B. M.; McDougal, P. G. *J. Org. Chem.* **1984**, *49*, 458.
(11) Experiments are under way in our laboratories to test these prediction, Wang, Y.; Houk, K. N., unpublished results.
(12) The position of the lithium atom was found by the geometry optimization of the lithium salt of cyclobutene-3-carboxylate anion. The optimal position was found in the plane of the carboxylic acid group, 1.84 Å from the oxygen atoms.
(13) The geometry of the methyl group was taken from the optimized 3-21G structure of methyl formate: Whiteside, R. A.; Frisch, M. J.; Pople, J. A. *The Carnegie-Mellon Quantum Chemistry Archive*; Carnegie-Mellon University, 1983.
(14) Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3412.
(15) Piers, E.; Lu, Y.-F. *J. Org. Chem.*, following paper in this issue.