studies of the reactions of $1^{\bullet+}$ and $2^{\bullet+}$ with a common reactant, ethyl diazoacetate, under aminium salt conditions, which effects the cyclopropanation of $1^{\bullet+}$ and $2^{\bullet+}$ (with second-order rate constants k_{CP1} and k_{CP2}, respectively) in competition with the respective intramolecular cycloadditions.[13] The experimentally determined ratio $k_{DA1}/k_{CP1} = 20$ affords $k_{CP1} = 1.5 \times 10^6$ M^{-1} s^{-1}. If we assume $k_{CP1} = k_{CP2}$ (the hole sites in $1^{\bullet+}$ and $2^{\bullet+}$ are essentially identical), the observed minimum ratio $k_{CB2}/k_{CP2} \geq 2000$ affords $k_{CB2} \geq 3 \times 10^9$ s^{-1}. The accuracy of this latter estimate of the minimum cyclobutanation rate constant rests upon the assumption that the *relative* rate ratios k_{DA1}/k_{CP1} and k_{CB2}/k_{CP2} (hence k_{DA1}/k_{CB2}), which are measured in dichloromethane, are not substantially different in acetonitrile, the solvent in which k_{DA1} was measured. This key assumption is supported by additional studies of the competitive dimerization(k_{CB5})/cyclopropanation(k_{CP5}) of *trans*-anethole (**5**). The rate ratio $k_{CB5}/k_{CP5} = 2$ affords $k_{CB5} = 3 \times 10^6$ M^{-1} s^{-1}, in reasonable agreement with the value previously derived from quenching studies in acetonitrile.[12] In like manner, the lower limit estimated for the rate constant for the cyclization of $3^{\bullet+}$ is $k_{CB3} \geq 3 \times 10^9$ s^{-1}. The reaction $4^{\bullet+} + 4$ has previously been found to have a rate constant $k_{DA4} = 3 \times 10^8$ M^{-1} s^{-1}.

Substrates **1–4** were then used to investigate the hypothetical electron-transfer (ET) mechanism of metalloporphyrin (MP)-catalyzed epoxidation. According to this mechanism, an alkene molecule undergoes ET to the metal oxene to give the corresponding alkene cation radical, which is then rapidly epoxidized by the reduced metal oxene. The ease of ionization of **1–3** should make them especially amenable to an ET mechanism if this were operable, and the cation radicals $1^{\bullet+}$–$3^{\bullet+}$ should be *relatively* long lived and thus especially susceptible to detection. The monoepoxides of **1–3** and of the cyclized form **1′** were first characterized by MCPBA epoxidation. The MP-catalyzed epoxidations of **1–3** were then examined using M = Fe(III) and Mn(III) (as the chlorides) and P = 5,10,15,20-tetraphenylporphyrin and also 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin in dichloromethane and in acetonitrile/water (90:10) with iodosylbenzene as the oxidant. Reactions were carried out to ~10% conversions to the epoxides, and material balances were ≥99%. In every instance only unreacted **1–3** and the corresponding (uncyclized) epoxides were found. Specifically, no **1′–3′** or their corresponding epoxides or other oxidation or dehydrogenation products were formed. It was established that such products would have been detectable in amounts at least as small as 0.5% of the uncyclized epoxide product. Similarly, the MP-catalyzed epoxidation of 1,3-cyclohexadiene (M = Mn, Fe) yielded only 3,4-oxidocyclohexene and none of the Diels–Alder dimer of **4** or the epoxide of the latter even when carried out in a 2.0 M solution of **4** in acetonitrile/dichloromethane solution.

Free cation radicals are clearly not formed in these epoxidations, even in the relatively more polar solvent. To the extent that cation radicals in the coordination sphere of iron resemble free cation radicals in their reactivity (this should be especially true in polar solvents), narrow limits can be defined for the maximum lifetime of any such cation radical intermediate. Using **1** as a probe ($k_{DA1} = 3 \times 10^7$ s^{-1}) and the indicated detectability limits of cation radical products (0.5%), a cation radical intermediate would have been detected if its rate constant for epoxidation were $\leq 6 \times 10^9$ s^{-1}. With **2** or **3** as the probe ($k_{CB2}, k_{CB3} \geq 3 \times 10^9$ s^{-1}), a cation radical process with a rate constant of up to 6×10^{11} s^{-1} would have been detected. Finally, with **4** as the probe a cation radical process of rate constant 3×10^{11} s^{-1} would have been detected. For comparison, the rate constant for the quasi-intramolecular hydroxylation of alkyl radicals in P-450-catalyzed hydroxylation is just 2×10^{10} s^{-1}.[14]

The failure to detect cation radical intermediates using rather sensitive intramolecular clock probes which present relatively ionizable functionalities significantly limits the tenable role of cation radicals in MP-catalyzed epoxidation.

Acknowledgment. The authors thank the National Science Foundation (CHE-8822051) for support of this research.

Supplementary Material Available: Experimental details of the epoxidation reactions mentioned in the text (14 pages). Ordering information is given on any current masthead page.

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On the Potential Energy Surface for Ring Inversion in Cyclohexene and Related Molecules

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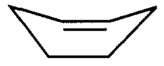
The conformations of cyclohexene and related monounsaturated heterocyclic six-membered rings have been extensively investigated by spectroscopic and molecular mechanics methods.[1] Cyclohexene (**I**) itself exists in the half-chair conformation (C_2 point group) and undergoes ring inversion (**Ia** ⇄ **Ib**) with the boat form (**II**, C_s point group) as a presumed transition state. The barrier for this process is 4.2–7.9 kcal/mol as calculated by molecular mechanics with more than half a dozen different force fields.[1] The free energy barrier ($\Delta G^{\ddagger}$) has been measured to be 5.3 ($CBrF_3$ solution) and 5.4 kcal/mol (vinyl chloride–chlorotrifluoroethylene solution) by dynamic NMR of partially deuteriated **I** at −165 °C.[1,2] In a recent paper,[3] Laane and co-workers have deduced a potential energy surface for ring inversion in **I** from an analysis of the ring bending and twisting vibrations in the gas-phase infrared spectrum of **I**. The analysis is based on a two-dimensional model describing the ring inversion energy surface as a quartic in ring bending and twisting coordinates.[4] The potential energy barrier for ring inversion in cyclohexene corresponding to this surface is 10.3 kcal/mol.[3] These authors discount the much lower barriers obtained previously by NMR and molecular mechanics for reasons that are unconvincing to us.[5,6] We now present results from (i)

Ia   **Ib**



II

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[1] For a review, see Anet, F. A. L. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P. W., Ed.; VCH Publishers: New York, 1987; Chapter 1.

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[3] Rivera-Gaines, V. E.; Leibowitz, S. J.; Laane, J. *J. Am. Chem. Soc.* **1991**, *113*, 9735–9742. These authors discuss the possibility that the barrier might be 1–2 kcal/mol lower than their best estimate, but they do not seem to put much weight on such a possibility, and no such qualification is made in the abstract or conclusion sections of their paper.

[4] This model has been applied previously to related heterocyclic molecules. (a) Tecklenberg, M. M. J.; Laane, J. *J. Am. Chem. Soc.* **1989**, *111*, 6920–6926. (b) Tecklenberg, M. M. J.; Villarreal, J. R.; Laane, J. *J. Chem. Phys.* **1989**, *91*, 2771–2775.

[5] Molecular mechanics force fields are, with a few exceptions, parametrized as much on energy as on geometry and generally reproduce conformational barriers, including gas-phase values (Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, 1982), in contrast with the views expressed by Laane and co-workers.[3] The geometry and barriers to planarity and pseudorotation in four- and five-membered rings are reasonably well predicted by MM2 (Rasas, R. L.; Cooper, C.; Laane, J. *J. Phys. Chem.* **1990**, *94*, 1830–1836).

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Table I. Ab Initio Energies for Cyclohexene

level	half-chair (C_2)[a]	barrier[b]	barrier (incl ZPE)[b]
RHF/3-21G	−231.72915	5.51	5.38
RHF/6-31G*	−233.01965	6.56	6.28
MP2/6-31G*	−233.82056	5.70	5.33
MP2/6-31G*[c]	−233.79140	5.70	5.33
MP4SDQ[c]	−233.85277	6.07	5.70
QCISD[c,d]	−233.85565	6.05	5.68
QCISD(T)[c,d]	−233.88371	5.87	5.50

[a] In Hartrees. [b] Difference between boat and half-chair energies, in kcal/mol. [c] Computed in the frozen core approximation with the MP2/6-31G* geometries and zero point energies (ZPE). [d] Quadratic configuration interaction calculations.[8]

ab initio quantum mechanical calculations, (ii) molecular mechanics (MM3) calculations, and (iii) low-temperature gas-phase NMR measurements. These investigations show that the ring inversion barrier is in fact much lower than that deduced from infrared frequencies,[3] and an origin for this discrepancy is suggested.

Table I summarizes ab initio calculations on **I**.[7,8] The barriers show very little dependence on the level of the calculation and should be particularly reliable because the half-chair and boat forms are simple closed-shell hydrocarbon molecules. At the MP2/6-31G* level, the boat is a transition state (but with an unscaled imaginary frequency of only 28i cm^{-1}), although at the lower RHF/3-21G level it is a shallow local minimum. At the highest level, QCISD(T)/6-31G*,[8] the ring inversion energy barrier with zero point energies and geometries determined at the MP2/6-31G* level is 5.5 kcal/mol.

The allylic torsional parameters in MM2 have been criticized for giving a poor fit to conformational energy differences in some simple alkenes, and modifications to this force field have been proposed.[9] The parameters in MM3 are better than those in MM2, and the (steric) energy barrier for ring inversion in cyclohexene with this force field has been reported to be 6.6 kcal/mol with the boat being the transition state.[10] Our MM3 calculations are in agreement with the published barrier,[10] but the boat (**II**) is actually a (very shallow) local energy minimum with MM3 (lowest vibrational frequency of 64 cm^{-1}); the (unsymmetrical) transition state (imaginary frequency of 90i cm^{-1}) lies 0.08 kcal/mol above the symmetrical boat. The MM3 free energy barrier ($\Delta G^{\ddagger}$) for ring inversion in **I** at −170 °C is 5.6 kcal/mol.

The potential energy profile for the ring inversion in cyclohexene as a function of the CH_2–CH_2–CH_2–CH_2 ring torsional angle (ω_{3456}), as calculated by molecular mechanics, is shown in Figure 1. Selected RHF ab initio points also shown in that figure were geometrically optimized with only ω_{3456} constrained. The profiles are all flat topped, and those for MM3 and RHF/6-31G* are remarkably similar despite relatively large differences in the transition structures.[11]

Table II. NMR Line Widths of the Homoallylic Proton Resonance in Gaseous I

temp (°C)	line width at half-height[a] (Hz) sample A[b]	line width at half-height[a] (Hz) sample B[c]
−62	4.7 ± 1.6	2.7 ± 0.5
−68	5.3 ± 0.7	2.9 ± 0.8
−73	4.4 ± 2.0	3.2 ± 1.2

[a] At 500 MHz with the allylic protons decoupled, errors are 95% confidence limits. [b] Sample also contains 1 atm of CO_2. [c] Sample also contains about 2 atm of CO_2.

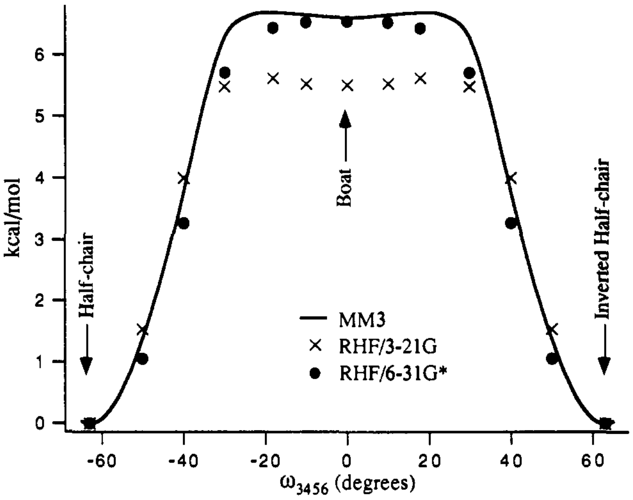

Figure 1. Potential energy profiles for ring inversion in cyclohexene as a function of ω_{3456}. All the calculations are for fully optimized geometries under the single torsional constraint (ω_{3456}) employed.

We have been able to observe the homoallylic proton signal in the 500 MHz spectrum of **I** in the gas phase down to −73 °C; below this temperature the vapor pressure of the compound was too low for an accurate measurement of the NMR signal. The line width (Table II) remains essentially constant between −62 and −73 °C, so that any broadening that can be ascribed to a slowing down of ring inversion at −73 °C must be less than 1 Hz. With an axial–equatorial chemical shift difference of 140 Hz at 500 MHz, this experiment shows that *k* (ring inversion) is greater than 30 000 s^{-1} and thus an upper limit for $\Delta G^{\ddagger}$ in the gas phase at −73 °C is 7.45 kcal/mol.[12] After allowing for ZPE and entropy differences the best experimental upper limit for the potential energy barrier in **I** becomes 7.95 kcal/mol.[13]

A major problem with the approach used by Laane and coworkers is that the observed infrared transitions in **I** correspond to energies less than 3 kcal/mol above the half-chair and are

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(6) Solution ($\Delta G^{\ddagger}$ = 10.1 kcal/mol) and gas-phase ($\Delta G^{\ddagger}$ = 10.4 kcal/mol) NMR data for the ring inversion barrier in *cyclohexane* are in good agreement, and the difference (0.3 kcal/mol) can be ascribed to a change in molecular volume between the initial and the transition states: Anet, F. A. L.; Bourn, A. J. *J. Am. Chem. Soc.* **1967**, *89*, 760–767. Ross, B. D.; True, N. S. *J. Am. Chem. Soc.* **1983**, *105*, 4871–4875. These free energies of activation are also in good agreement with recent ab initio calculations: Dixon, D. A.; Komornicki, A. *J. Phys. Chem.* **1990**, *94*, 5630–5636. Calculations show that the half-chair and boat forms of I have virtually the same volumes. Thus, it is unreasonable to expect that the barriers for ring inversion of I in the solution and gas phases could differ by 4 or 5 kcal/mol, as claimed by Laane and co-workers.[3]

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(11) For the MM3 calculations, the cyclohexene conformation has C_2 symmetry for $-34° \langle \omega_{3456} \rangle 34°$, but it is otherwise unsymmetrical, except for the boat form at $\omega_{3456} = 0$.

(12) For I in $CBrF_3$, we find that $\Delta\nu$ (the axial–equatorial chemical shift difference of the homoallylic protons) at 500 MHz is 148 ± 1 Hz between −172 and −155 °C ($\Delta G^{\ddagger}$ = 5.5 kcal/mol at −151 °C), from which we conservatively estimate that $\Delta\nu$ is at least 140 Hz at −70 °C. In the fast exchange region, $k = \pi(\Delta\nu)^2/2W_{1/2}$, where $W_{1/2}$ is the ring inversion contribution to the line width at half height (Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982). The NMR samples contained a small amount of ethylene as a reference line for the gas phase ($W_{1/2}$ = 2.6 ± 0.3 Hz for sample A and 3.3 ± 0.5 Hz for sample B), a centered capillary containing CD_2Cl_2 as a lock and CO_2 as an inert gas to ensure first-order kinetics for ring inversion[6] and to prevent broadening by spin-rotation relaxation. Liquid I was present at low temperatures as a film or fine droplets on the side of the 5-mm NMR tube, but its resonances are about 2 ppm more shielded than those of gaseous I, with which it is in *slow* exchange. Liquid I thus does not affect any broadening from ring inversion of the gas-phase molecules, although it lowers the achievable resolution to a slight extent that varies from experiment to experiment.

(13) A zero-point energy (ZPE) difference of 0.4 kcal/mol (Table I) and an entropy of activation ($\Delta S^{\ddagger}$) of 0.6 eu (from molecular mechanics) are assumed.

J. Am. Chem. Soc. **1992**, *114*, 10971-10972

geometrically far removed on the potential energy surface from the boat form (**II**), as is shown in Figure 1. Much extrapolation is then needed to determine the energy of the boat form, and the results therefore depend strongly on the nature of the model used. A quartic model for the potential energy surface may be satisfactory for four- and five-membered rings,[14] which have low barriers, but we believe that it is too restrictive and therefore unsatisfactory for describing the *entire* ring inversion energy surface in cyclohexene, even though it may be excellent in the vicinity of the half-chair. On the other hand, a less restrictive model would probably have too many adjustable parameters for the available data, so that a meaningful ring inversion energy surface is unlikely to be obtainable purely from an analysis of infrared frequencies. The present results also cast doubts on the energy surfaces for ring inversion in heterocyclic analogs of cyclohexene determined by Laane and co-workers from infrared data,[4] as the torsional constraints in all these molecules are similar; the calculated inversion barriers are also substantially higher than those obtained by MM2 calculations and by dynamic NMR.[4]

Acknowledgment. We are grateful to the National Science Foundation for support of this research. Computations were supported by a Joint Study grant from the IBM Corporation and the UCLA Office of Academic Computing on an IBM ES/9000 Model 900 computer.

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A 10-Step, Asymmetric Synthesis of (*S*)-Camptothecin

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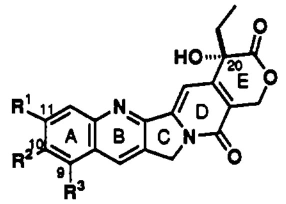
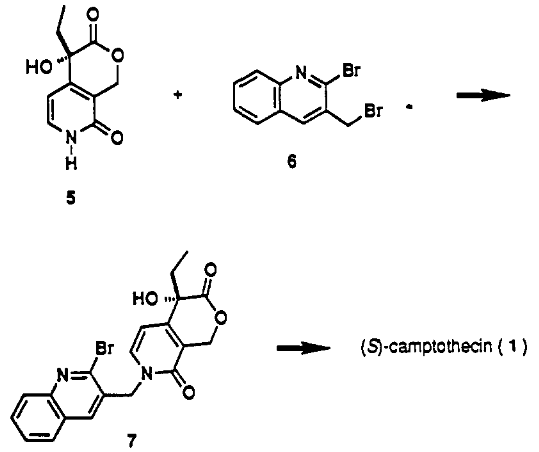
(*S*)-Camptothecin (**1**), a pentacyclic alkaloid isolated from *Camptotheca acuminata* by Wall and co-workers in 1966, continues to be one of the most important lead compounds among the anticancer natural products.[1] A number of promising analogs have been prepared that show improved solubility, low overall toxicity, and impressive in vivo activity against certain solid tumors.[2] Some of the more active derivatives include 9-aminocamptothecin[2a] (**2**), 10,11-(methylenedioxy)camptothecin[2a,3] (**3**), and (20*S*)-9-[(dimethylamino)methyl]-10-hydroxycamptothecin[2b] (**4**). Analog **4** is currently undergoing phase I clinical trials in cancer patients. The camptothecins' mode of action has been demonstrated to involve inhibition of DNA relaxation through interference with topoisomerase I function.[4] This novel activity and a recent report of potent anti-retroviral activity[5] for (*S*)-camptothecin have reenergized interest in this family of alkaloids.



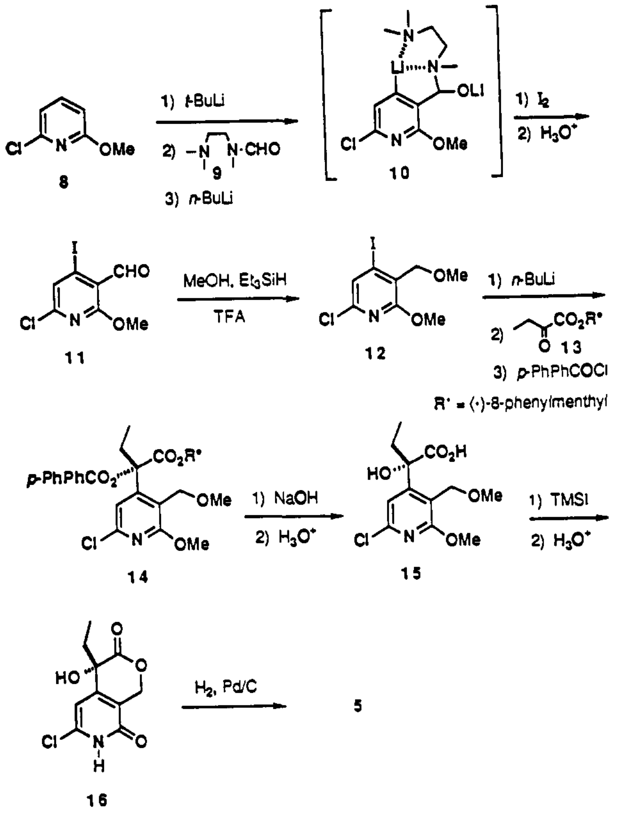
1, $R^1, R^2, R^3 = H$ (*S*)-camptothecin
2, $R^1, R^2 = H, R^3 = NH_2$
3, $R^1, R^2 = \text{-}OCH_2O\text{-}, R^3 = H$
4, $R^1 = H, R^2 = OH, R^3 = CH_2NMe_2$

Although much beautiful synthetic work has been reported in this area,[1,6] most of the syntheses are racemic and not attractive

Scheme I



Scheme II



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