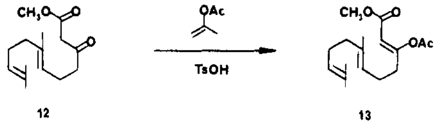
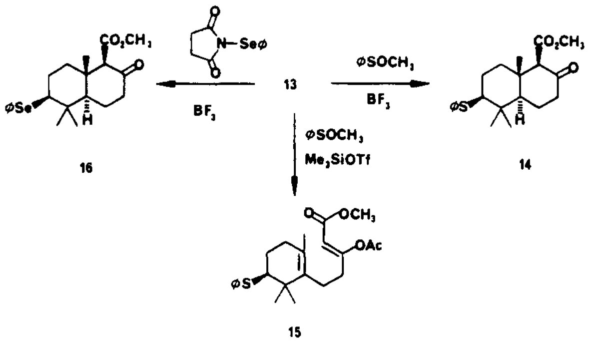
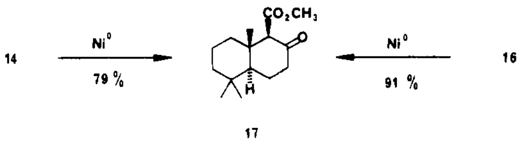
β-keto ester **12** with isopropenyl acetate in the presence of TsOH.[16] Addition of the acetoxy enoate **13** over 1 h via a mechanical syringe to 1.10 equiv of PhSOCH$_3$ and 2.20 equiv of BF$_3$ (as a 0.80 M solution in CH$_3$NO$_2$) [CH$_2$Cl$_2$–CH$_3$NO$_2$ (2:1), −78 °C (1 h)] gave rise to the anticipated cyclized adduct **14** (mp 122–124 °C) in 53% recrystallized yield. In contrast to the results involving cyclization in the presence of BF$_3$, other Lewis acids proved less effective in promoting the formation of bicyclic products. Accordingly, treatment of **13** with PhSOCH$_3$ and Me$_3$SiOTf[6] led to the formation of the monocyclic derivative **15** in 46% yield. The existance of the monocycle **15** as an intermediate enroute to **14** in the PhSOCH$_3$·BF$_3$-mediated cyclization of **13** was ruled out by the exposure of **15** to 2 equiv of BF$_3$ or BF$_3$·CH$_3$OH complex [CH$_3$NO$_2$–CH$_2$Cl$_2$, −78 °C]. Under these sets of conditions the formation of **14** was not observed and the quantitative recovery of the monocycle **15** was realized.





We have recently disclosed that selenylative carbocycle annulations can be readily accomplished by the treatment of appropriate substrates with *N*-(phenylseleno)succinimide (PSS) in the presence of Lewis acids.[7,8] The utility of PSS–Lewis acid binary systems for initiating representative polyene annulations was demonstrated in the following way. Addition of the (*Z*)-acetoxy enoate **13** over 1 h via mechanical syringe to 1.10 equiv of PSS and 2.20 equiv of BF$_3$ [CH$_2$Cl$_2$–CH$_3$NO$_2$ (2:1), −78 °C (1 h)] provided the crystalline bicyclic keto ester **16** (mp 128–130 °C) in 47% chromatographed yield.

Evidence for the equatorial disposition of the pendant phenylthio and phenylseleno moieties of **14** and **16** was provided by the coupling constants observed for the associated C-3 methine protons. Specifically, these methines appeared as doublets of doublets possessing a characteristic *axial* coupling constant in each instance [(**14**: $J = 12.3$ and 4.6 Hz); (**16**: $J = 12.0$ and 4.8 Hz)]. The relative stereochemistry at the ring junctions of **14** and **16** was deduced by comparison of the spectral and physical properties of the corresponding reduction product **17** to those reported in the literature (mp **17**: 85–87 °C; lit. mp 85.5–87 °C).[9]



The foregoing studies clearly indicate the potential that episulfonium and episelenonium ion initiated polyene cyclizations hold for the elaboration of natural products. The application of this methodology to the synthesis of the taxodione and totarolone ring systems will be described in the future.

Acknowledgment. Support for this research by a grant from the National Institutes of Health is gratefully acknowledged. This communication is dedicated to the memory of Professor Robert V. Stevens.

Registry No. **5a**, 106625-34-7; **5b**, 106625-35-8; **6a**, 106625-36-9; **6b**, 106625-37-0; **7a**, 106625-38-1; **7b**, 106625-39-2; **8**, 106708-95-6; **9**, 106708-96-7; **10**, 106625-40-5; **11**, 106625-41-6; **12**, 56523-17-2; **13**, 106625-42-7; **14**, 106625-43-8; **15**, 106625-44-9; **16**, 106625-45-0; **17**, 65794-68-5; PhSOCH$_3$, 1193-82-4.

Eric D. Edstrom, Tom Livinghouse*
Department of Chemistry
University of Minnesota
Minneapolis, Minnesota 55455

Received August 28, 1986

---

[16] Casey, C. P.; Marten, D. F. *Synth. Commun.* **1973**, *3*, 321.

Stability Relationships of Decalindiones. Modified MM2 Force Field Calculations

Summary: Calculations of the steric energies of decalindiones using standard MM2 parameters lead to predictions of greater stability for the cis isomers. Experimental equilibration studies demonstrate that the trans isomers are favored at equilibrium. Modified MM2 parameters lead to improved predictions of isomer ratios.

Sir: Molecular mechanics is an important and useful technique for the calculation of molecular properties.[1] The technique has seen increasing use in the prediction of favored geometries and the reactive stereochemistry of conformationally mobile systems,[2] transition state geometries,[3] and product vs. reactant energies.[4] The force fields and parameters developed by Allinger and co-workers and utilized through the MM2 program[1] have proven to be powerful tools in synthetic organic chemistry.[5] We wish to report, however, a significant problem with the application of currently available molecular mechanics programs to the calculation of steric energies of cyclic ketones.[6]

Our interest in the area of molecular modeling stems in part from work directed toward the total synthesis of clerodane antifeedant diterpenes.[7] One approach to the clerodanes, compounds featuring substituted decalin structures, involves the use of bicyclic Diels–Alder adducts of general structure **1** as synthetic intermediates.[8] We

---

[1] Burket, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, 1982. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

[2] (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257.

[3] (a) Moreland, D. W.; Dauben, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2264. (b) DeTar, D. F.; Tenpes, C. J. *Ibid.* **1976**, *96*, 4567. (c) Still, W. C.; Galynker, I. *Ibid.* **1982**, *104*, 1774.

[4] Boeckman, R. K.; Flann, C. J.; Poss, K. M. *Ibid.* **1985**, *107*, 4359.

[5] For recent examples, see: Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Tetrahedron* **1984**, *40*, 2275. Kuroda, C.; Hirota, H.; Takahashi, T. *Chem. Lett.* **1982**, 249. Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058.

[6] Allinger and co-workers have noted previously that calculations of cyclic ketones may give erroneous answers. Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron* **1972**, *28*, 1173.

[7] Kubo, I.; Kido, M.; Fukuyama, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 897. Kubo, I.; Lee, U-W.; Balogh-Nair, V.; Nakanishi, K.; Chapya, A. *Ibid.* **1976**, 949.

[8] Goldsmith, D. J.; Srouji, G.; Kwong, C. *J. Org. Chem.* **1978**, *43*, 3182.

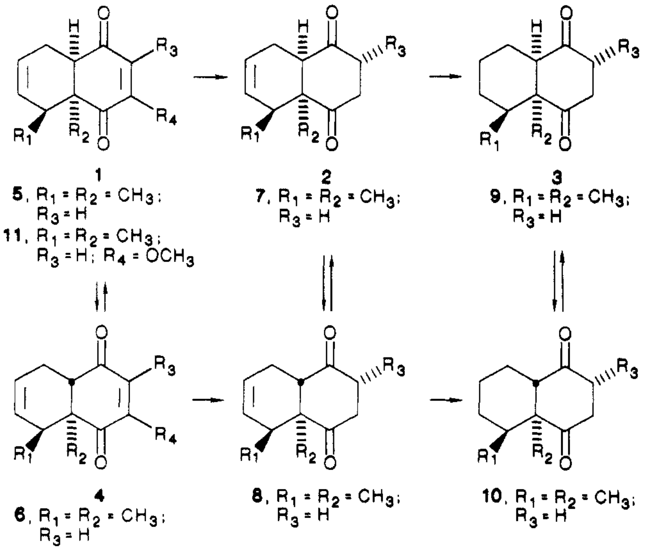
0022-3263/87/1952-0951$01.50/0

Table I. Modified MM2 Parameters

	original parameters			refined parameters		
torsional array[a]	V1	V2	V3	V1	V2	V3
H–C(sp^3)–C(sp^2)–C(sp^3)	0.0	0.0	0.13	–0.145	0.0	0.211
H–C(sp^3)–C(sp^2)═O	–0.167	0.0	–0.10	0.281	0.755	–0.126
C(sp^3)–C–(sp^3)–C(sp^2)–C(sp^3)	0.55	–0.18	0.40	0.879	0.00	–0.275
C(sp^3)–C(sp^3)–C(sp^2)═O	–0.30	1.20	–0.35	–0.286	1.365	–0.301
H–C(sp^3)–C(sp^2)–H	0.18	0.0	0.275	0.113	0.0	0.287
C(sp^3)–C(sp^3)–C(sp^2)–H	0.35	0.0	0.25	0.319	0.0	0.287
value of error function		122			19	
rms error (kcal/mol)		0.68			0.26	
largest error		2.02			0.64	

[a] MM2 atom types: H = 5, C(sp^3) = 1, C(sp^2) = 3, O = 7.

have prepared a series of adducts of this type[9] and in each case reduced them in stepwise fashion to diketones **2** and **3**. In every instance equilibration of the cis adduct, **1**, generates a mixture in which the trans isomer **4** predominates. MM2 calculations[10] of the energy relationships of the cis and trans isomers of the cycloadducts and their B-ring dihydro derivatives are generally in good agreement with experimental values. For example, the calculated equilibrium ratio (including both cis forms) of **6**:**5** is 9:1. Epimerization of **5** with DABCO in $CHCl_3$ or C_6H_6 yields a mixture containing greater than 97% of **6**. In contrast, a comparison of the calculated and experimental energies and equilibrium constants for the isomerizations of the tetrahydro compounds (general structure **3**) shows a serious discrepancy. *The trans isomers in these cases are invariably found to be the more stable ones empirically, but the cis forms are consistently predicted from molecular mechanics calculations using the standard force fields.* We describe in this communication the detailed results for one study of this problem. Dienedione **5** is formally a Diels–Alder adduct of piperylene and toluoquinone. It cannot be prepared in this manner since the cycloaddition reaction of toluoquinone occurs exclusively at the unsubstituted double bond.[11] Compounds **5** and **6**, therefore, were prepared indirectly by reduction–elimination of adduct **11**.[12] Reduction of **6** with Zn in HOAc gave **8**. Equilibration of the latter in the presence of DABCO in $CHCl_3$ then afforded a 95:5 mixture of **8**:**2**. Standard MM2 and MacroModel calculations are in good agreement with this result, 94:6 and 92:8, respectively.



For the tetrahydro compounds, diketones **9** and **10**,[13] the cis isomer is relatively more important, both experimentally and by calculation, than it is in the case of the adducts or dihydro compounds. However, the predominant isomer at equilibrium in $CHCl_3$ is still the trans one, in this case in a proportion of 76:24. In contrast, *standard* MM2 calculations yield a trans to cis (**10**:**9**) ratio of 19:81,[14] equivalent to a difference of ca.1.5 kcal/mol between the calculated and experimental values. This amount though not large in absolute terms, effectively serves to limit even

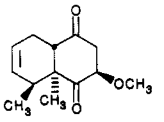
---

(9) (a) These include **1a** ($R_1 = R_2 = R^3 = CH_3$, R^4 = H) **1b** ($R_1 = CH_3$, $R_2 = CO_2CH_3$, $R_3 = R^4$ = H); **1c** ($R_1 = R_3 = CH_3$, $R_2 = CO_2CH_3$, R_4 = H), **1d** ($R_1 = CH_2OAc$, $R_2 = CH_3$, $R_3 = R_4$ = H), **1e** ($R_1 = CH_2OAc$, $R_2 = CO_2CH_3$, $R_3 = CH_3$, R_4 = H). For another published example, see ref 7. (b) The cis isomers of the adducts generally prefer the conformation in which both methyl groups are axial. This is readily observed in the ^1H NMR spectrum of **7** in which the C-8 methyl group is observed at 0.89 ppm. The MM2 calculated ratio for the two cis conformers of **7** is 93:7 in favor of the diaxial conformation. For another reported example of this conclusion see: Bohlmann, F.; Mathar, W.; Schwarz, H. *Chem. Ber.* **1977**, *110*, 2028. (c) All new compounds have been fully characterized by spectroscopic means and combustion analysis.

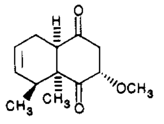
(10) (a) Standard MM2 calculations were carried out by using Quantum Chemistry Program Exchange Program Number 395, Indiana University. (b) The MacroModel MM2 field differs from the standard field in that it uses the point charge electrostatic model with partial charges derived from the MM2 bond dipoles whereas the standard MM2 electrostatic treatment uses a dipole–dipole model. These calculations were performed by using a distance-dependent dielectric (Q_1Q_2/R^2). Note that while the the absolute energies differ from those of QCPE 395 MM2, the relative energies of the conformers are essentially the same.

(11) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1951**, *73*, 2043, 3547, 3548.

(12) Reduction of **11** with $TiCl_3$ in aqueous acetone at pH 1 affords **6** (24%) plus i (57%). The latter is converted into **6** by treatment with *p*-TsOH. At pH 6 **11** yields ii in the presence of $TiCl_3$. The latter upon reduction with lithium and ammonia followed by oxidation with PCC (buffered with NaOAc) yields **5**.



i

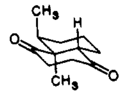
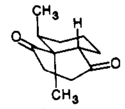
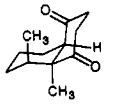
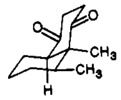
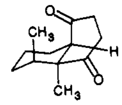
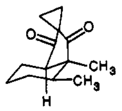


ii

(13) The assignment of stereochemistry to these compounds was based initially on their NMR spectra. The latter were measured at 360 MHz with a Nicolet NT360 spectrometer and gave the following values for **9** and **10**. **9**: δ 1.06 (3 H, d, *J* = 7 Hz, C-8-CH_3), 1.30 (3 H, s, C-9-CH_3), 2.42 (1 H, dd, *J* = 5.4, 8.7 Hz, C-5-H). **10**: δ 0.96 (3 H, d, *J* = 6.9 Hz, C-8-CH_3), 1.02 (3 H, s, C-9-CH_3), 3.01 (1 H, dd, *J* = 3.8, 11.2 Hz, C-5-H). As noted, complete confirmation of this assignment was achieved by a crystal structure determination of **10**. (b) Equilibrium ratios were obtained from the measurement of integrated intensities of methyl resonance peaks in the ^1H NMR spectra of the isomer mixtures. In all cases there was complete resolution of all methyl peaks at 360 MHz. Equilibria were typically carried out under nitrogen or argon in an NMR tube at 60 °C until no further change took place. Measurements in methanol solution generally led to slightly higher percentages of trans isomers.

(14) This value is based on including 4% of the ring-B boat conformer of **10** in the Boltzmann distribution for the equilibrium of the tetrahydro compounds. On the basis of the classical phrase "From the examination of molecular models..." (i.e., mechanical molecules) one is also drawn to the conclusion that the cis isomer **9**, despite the usual mind set in favor of *trans*-decalins, should be strongly favored "vis â vis" **10**. Mechanical molecules, furthermore, do not inspire the consideration of twist/boat forms for **10**.

Table II. Calculated Conformer Energies and Populations[a]

	steric energy (population at 25 °C)		
structure	QCPE 395 MM2	MacroModel MM2	MacroModel MM2 (new ketone parameters)
	21.74 (15%)	18.48 (15%)	20.21 (17%)
	22.45 (4%)	19.18 (5%)	17.93 (39%)
	23.75 (<1%)	20.47 (<1%)	21.51 (2%)
	20.76 (79%)	17.50 (79%)	19.86 (31%)
	23.45 (<1%)	20.14 (<1%)	20.53 (10%)
	24.15 (<1%)	20.87 (<1%)	21.85 (1%)

[a] Energies in kcal/mol and populations calculated by a standard Boltzmann distribution at 25 °C.

the qualitative application of currently available molecular mechanics calculations to the prediction of decalin ketone geometries.

The problem with obtaining reasonable steric energies for these decalin diketones appears to reside in the MM2 treatment of highly substituted ketones.[15] Recent ab initio results[16] with isopentanone indicate that the original parameterization of MM2, based on the conformational energies of acetaldehyde, propionaldehyde, and butyraldehyde, is not adequate for isopropyl ketones. To incorporate this new data into the MM2 force field, we used experimental rotational[17] barriers for acetone and acetaldehyde and ab initio[16] relative energies for butanone, isopentanone, propionaldehyde, and isobutyraldehyde to define an error function equal to the sums of the squares of the individual errors in relative conformational energies. We then iteratively refined the relevant MM2 torsional parameters[18] to minimize the error function using the Polak–Ribiere conjugate gradient method.[19] Results of the refinement are shown in Table I (see also supplementary paragraph at the end of the paper).

Our modified force field was then applied to the calculation of steric energies for **9** and **10**. The results from both standard and modified MM2 calculations for principal conformations of each of the configurational isomers are shown in Table II. Using the modified force field an equilibrium ratio of 65:34 in favor of the trans isomer is found for the **10** to **9** interconversion. Not only is a more accurate measure of the relative energies of the cis and trans isomers found by this calculation but the favored conformer of **10** is correctly predicted to be the B-ring boat form (conformer b, Table II). This structural prediction (*made prior to obtaining the experimental result*) is borne out by the crystal structure for **10**.

The results described herein illustrate two salient features of the calculational approach to molecular modeling. Molecular mechanics calculations clearly cannot be applied without the foundation of experimental verification of basic parameters. Given the appropriate modifications and reevaluations that result from empirical and other calculational results, however, the molecular mechanics approach can yield results for the steric energies of complex molecule that cannot be acheived readily by other means.

Registry No. **5**, 106588-82-3; **6**, 106588-83-4; **9**, 106588-80-1; **10**, 106588-81-2.

Supplementary Material Available: Data used for the refinement of ketone and aldehyde parameters and single-crystal X-ray (crystal and data collection parameters, perspective view, atom coordinates and temperature factors, bond lengths and angles) for **10** (9 pages). Ordering information is given on any current masthead page.

David J. Goldsmith,* Joel Phillip Bowen
Emad Qamhiyeh

Department of Chemistry
Emory University
Atlanta, Georgia 30322

W. Clark Still

Department of Chemistry
Columbia University
New York, New York 10027

Received October 7, 1986

---

(15) We have been informed by Professor Allinger that he has also looked into the modification of the standard MM2 force field to accommodate cyclic ketones. Reports of these changes as well as a general revision of the molecular graphics programs (MM3) will be forthcoming from his laboratories. We appreciate his commentary on the results reported herein.

(16) We wish to thank Professor K. B. Wiberg, Yale University for providing his ab initio results prior to publication.

(17) Krishner, L. C.; Sagebarth, E. *J. Chem. Phys.* **1971**, *54*, 4533.

(18) Since there is not enough data to define all 18 torsional parameters, V2 barriers for interactions not directly involving a carbonyl group were arbitrarily set to zero.

(19) For a related MM2 force field refinement, see: Jaime, C.; Osawa, E. *Tetrahedron* **1983**, *39*, 1983.