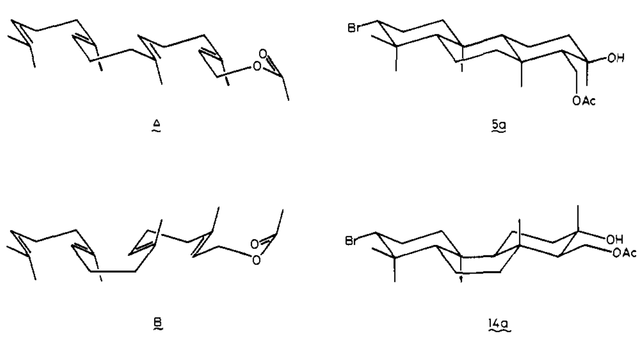
Chart II



yield from **10**), were isolated as crystals. The latter product, **14a**, afforded ^{1}H NMR, IR, and mass spectra entirely superimposable with those of natural isoaplysin-20 acetate. Hydrolysis of **14a** ($NaOH/C_2H_5OH$, 0 °C, 10 min) gave a diol, **14**, which was again identified with the natural isoaplysin-20 in all respects. Since no more sample of isoaplysin-20 is available, the correct structure was established through the X-ray crystallography of our synthetic material **14a**, which was crystallized from methanol.

It should be noted that the perhydrophenanthrene system of this compound involves in an anti/syn/anti ring juncture, which forces the ring system to take a chair/boat/chair conformation. Observed dihedral angles show that some distortion is presented in all three rings, and, particularly, the ring B takes a skew-boat rather than a boat conformation. The bond distances of C-9/C-10 (1.579 (8) Å) and C-8/C-14 (1.575 (8) Å) are rather long. The lengthening of these distances is mainly due to the intramolecular H-1α/H-11α and C-16/C-17 repulsions.

By consideration of this biomimetic olefin cyclization, the following assumption would be required for the reasonable reaction pathway. The major carbinol product **5a** must be derived by the consecutive four-ring formation via all chair folding (A) of (*E,E,E*)-geranylgeranyl chain including acetoxyl group participation, while **14a** should be formed from chair/boat/chair folding (B) (Chart II).. Even though the latter path (B) is more strained, this arrangement would release an apparent three successive 1,3-diaxial interaction originated from four methyl groups in A. Anyhow, this provides the clear experimental evidence to produce a perhydrophenanthrene derivative with the boat form B ring by means of the biomimetic cyclization of (*E,E,E*)-geranylgeraniol derivative.[11] The reaction pathway is somewhat similar to that of the Lewis acid or enzyme catalyzed cyclization of 2,3-oxidosqualene.[12]

Acknowledgment. We are indebted to Professor S. Yamamura of Keio University for a generous supply of spectral charts of natural isoaplysin-20 and its acetate, Dr. Y. Fujita of Kuraray Co. LTD for the gift of pure (*E,E,E*)-geranylgeraniol, and the Crystallographic Research Center, Institute for Protein Research, Osaka University, for computer calculations. This study is supported by the Grant-in-Aid for Special Project Research (1983), No. 582180024) from the Ministry of Education, Science and Culture of Japanese Government.

Supplementary Material Available: IR, ^{1}H NMR, ^{13}C NMR, mass spectra, analytical data, and details of X-ray analysis including an ORTEP drawing (14 pages). Ordering information is given on any current masthead page.

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(10) The minor product **13** showed a different ^{1}H NMR spectrum in its methyl region (δ 0.94 (3 H), 1.05 (3 H), 1.24 (3 H), and 1.27 (6 H)) from those of **5a** and **14a**, and preparation of good crystals for X-ray diffraction analysis is still in effort.

(11) A nonenzymic biogenetic-type conversion of a geranylgeraniol-type tetraene oxide to 24,25-dihydroprotosterol and 24,25-dihydroparkeol, both of which possess the boat form B ring, has been recorded previously: van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8225.

(12) van Tamelen, E. E.; Leopold, E. J.; Marson, S. A.; Waespe, H. R. *J. Am. Chem. Soc.* **1982**, *104*, 6479. Review: van Tamelen, E. E. *Acc. Chem. Res.* **1975**, 152.

Are π-Complexes Intermediates in Halocarbene Cycloadditions?

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Halocarbenes are electrophilic species, undergoing faster cycloadditions with electron-rich alkenes than with electron-deficient alkenes. We recently showed that the room-temperature selectivities of carbenes in cycloadditions to a series of alkylethylenes[1] are linearly related to carbene stabilities.[2] This normal reactivity–selectivity relationship implies that variations in activation enthalpy control selectivity. However, it has been known since the work of Skell and Cholod in 1969 that the relative rates of CCl_2 cycloadditions to alkylethylenes parallel the differences in entropies of activation, while differences in activation enthalpies are negligible.[3] Giese and co-workers have thoroughly documented this "entropy control" of selectivity for cycloadditions of highly reactive carbenes (CCl_2, CBrCl, CBr_2). All halocarbenes exhibit identical selectivities at 360 K, while selectivity reversal occurs at higher temperatures.[4] Several experimental reports of zero or negative activation energies for carbene cycloadditions have also appeared.[5,6] It is usually concluded that an intermediate (π-complex, or "loose charge-transfer complex"[6]) is formed and that the conversion of this complex to products involves a barrier that is below the energy of the reactants.[4-6] A cage complex or proximity pair is also compatible with the observed kinetics.[6a] Zero or negative activation energies, and entropy control of reactivity also have been interpreted as evidence for the formation of intermediates in singlet oxygen reactions,[7] in quenching of ketone triplet excited states by alkenes,[8] in nitrile ylide cycloadditions,[9] and in a Diels–Alder reaction.[10]

In this and the following communication, we present a new interpretation of these results. We describe (1) calculations which suggest that the most reactive halocarbenes do not form stable π-complexes with alkenes, (2) computations of ΔH and ΔS at several points upon the potential energy surface, which show a simple relationship between ΔS and reaction progress, (3) models for ΔH and ΔS that parallel experimental data for carbene cycloadditions and provide a new explanation of how negative activation energies and entropy control of reactivity arise, and (4) a generalization of these results for other fast reactions.

Ab initio calculations were carried out on the cycloadditions of CCl_2 and CF_2 to ethylene. Structures of stationary points obtained at the 3-21G[11] level with gradient optimization[12] are shown in Figure 1. Energies at 3-21G, 6-31G*[13] and MP2/3-21G[14] levels are given in Table I.

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(1) Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58 and references therein.

(2) Rondan, N. G.; Houk, K. N.; Moss, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1770.

(3) Skell, P. S.; Cholod, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 7131.

(4) Giese, B.; Meister, J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 595. Giese, B.; Lee, W.-B. *Ibid.* **1980**, *19*, 835. Giese, B.; Lee, W. B.; Meister, J. *Liebigs Ann. Chem.* **1980**, 725; *Chem. Ber.* **1981**, *114*, 3306. Giese, B.; Lee, W.-B.; Neumann, C. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 310; *Tetrahedron Lett.* **1982**, *23*, 3557.

(5) Wong, P. C.; Griller, D.; Scaiano, J. L. *Chem. Phys. Lett.* **1981**, *103*, 2423.

(6) (a) Turro, N. J.; Lehr, G. F.; Butcher, Jr.; Moss, P. A.; Guo, W. *J. Am. Chem. Soc.* **1982**, *104*, 1754. (b) Moss, R. A.; Perez, L. A.; Turro, N. J.; Gould, I. R.; Hacker, N. P. *Tetrahedron Lett.* **1983**, *24*, 685.

(7) Gorman, A. A.; Lovering, G.; Rodgers, M. A. J. *J. Am. Chem. Soc.* **1979**, *101*, 3050. Gorman, A. A.; Gould, I. R.; Hamblett, *Ibid.* **1982**, *104*, 7098. Schuster, G. B.; Hurst, J. R. *Ibid.* **1982**, *104*, 6854.

(8) Maharaj, U.; Winnick, M. A. *J. Am. Chem. Soc.* **1981**, *103*, 2328.

(9) Turro, N. J.; Hrovat, D. A.; Gould, I. R.; Padwa, A.; Dent, W.; Rosenthal, R. J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 625.

(10) Kiselev, V. D.; Miller, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 4036.

(11) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(12) (a) Binkley, J. S.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; Defrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. GAUSSIAN80, Carnegie-Mellon University, Pittsburgh, PA. We thank Professor Pople for the use of GAUSSIAN82 for some of these calculations.

(13) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta*, **1973**, *28*, 213.

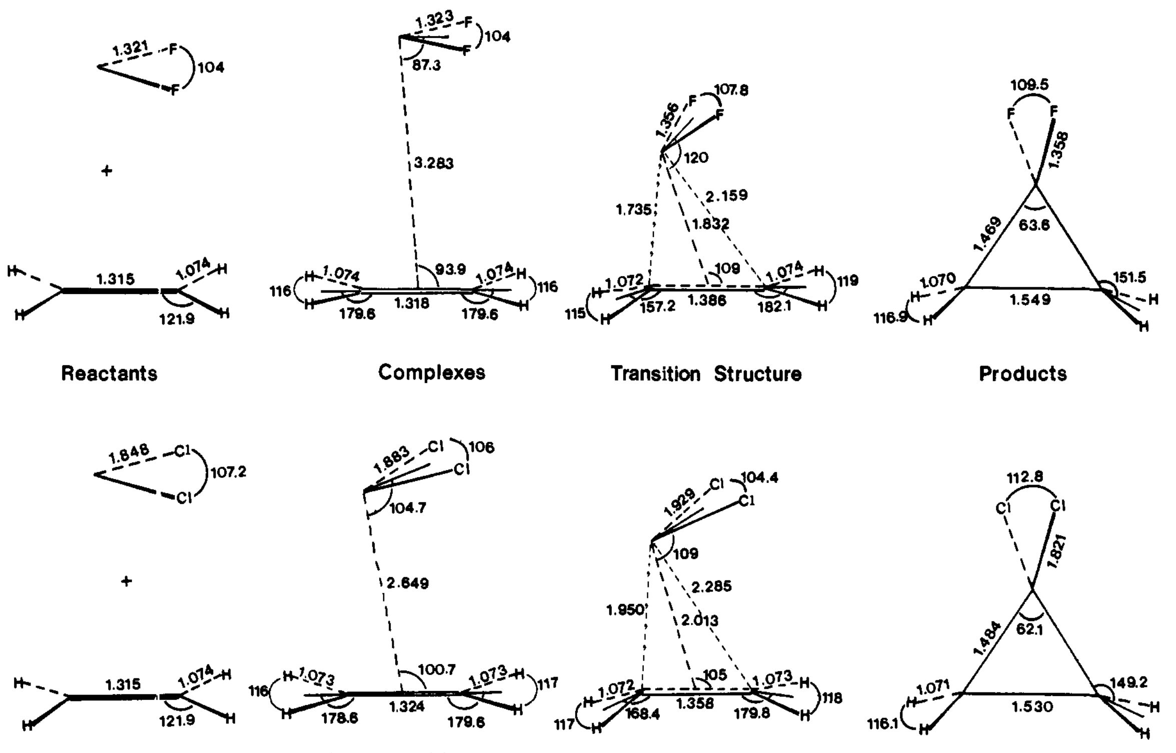

Figure 1. 3-21G structures of reactants, complexes, transition structures, and products in the reactions of CCl_2 and CF_2 with ethylene. The complex and transition structure for the CCl_2 reaction are not stationary points at higher computational levels.

Table I. Energies of Reactants, Intermediates, Transition Structures, and Products (au)[a]

	CF_2			CCl_2	
	3-21G	6-31G*	MP2/3-21G	3-21G	MP2/3-21G
CX_2 + ethylene	−312.975 80 (0)	−314.689 54 (0)	−313.469 01 (0)	−1029.704 79 (0)	−1030.063 51 (0)
intermed	−312.978 92 (−2.0)	−314.690 98 (−0.9)	−313.472 07 (−1.9)	−1029.708 31 (−2.2)	−1030.070 33 (−4.3)
transitn struct	−312.932 94 (+26.9)	−314.640 33 (+30.9)	−313.447 25 (+13.7)	−1029.706 80 (−1.3)	−1030.079 13 (−9.8)
dihalocyclopropane[b]	−313.045 34 (−43.6)	−314.762 89 (−46.0)	−313.542 32 (−46.0)	−1029.820 59 (−72.7)	−1030.183 24 (−75.1)

[a] Relative energies (kcal/mol) are given in parentheses; all calculations were carried out at 3-21G geometries. [b] Heats of reaction have been estimated as −46 and −70 kcal/mol for CF_2 and CCl_2, respectively.[2]

Intermediates are found for both of these reactions at the 3-21G level. Each complex consists of an essentially undistorted ethylene arranged in a plane nearly parallel to that of the slightly distorted singlet carbene. At the 3-21G level, the transition structure for CCl_2 cycloaddition has an energy that is lower than that of the reactants. A negative activation energy is predicted, apparently in good accord with the experimental results on PhCCl[6] and inferences about CCl_2.[3,4] However, with inclusion of correlation energy, even at the MP2/3-21G level, the complex disappears, and no barrier at all to cycloaddition is predicted![15] We also studied the reactions of CCl_2 with propene and isobutene. Even at the 3-21G level, no stable complexes and no activation barriers are predicted for these cycloadditions. At optimized geometries corresponding to the (artifactual) 3-21G transition state for the CCl_2–ethylene reaction [r(reaction coordinate) = 2.013 Å], CCl_2–propene and CCl_2–isobutene are 4.0 and 6.6 kcal/mol more stable than the isolated reactants.

At all levels explored, CF_2 and ethylene form a complex. The relatively large activation energy for cycloaddition, which is approximately correct[2] at the MP2/3-21G level, is a result of the large stabilization of the carbene by the fluoro substituents.[2] Thus, although a weakly bound complex is predicted for CF_2, none is predicted for CCl_2.

Table II. ΔH, ΔS, and ΔG from 3-21G Calculations for CX_2–Ethylene Reactions[a]

	ΔE	ZPE[b]	ΔH[c]	$\Delta S^{298\,K}$[d]	$-T\cdot\Delta S^{298\,K}$	ΔG
CCl_2 + ethylene	0.0	36.8	0.0	116.1	0.0	0.0
π-complex[e]	−2.2	38.0	−1.6	83.0	10.1	8.6
transitn state	−1.3	39.0	0.3	79.3	11.0	11.3
CF_2 + ethylene	0.0	39.2	0.0	109.6	0.0	0.0
π-complex	−2.0	39.8	−0.9	87.3	6.7	5.6
transitn state	26.9	41.4	28.2	71.7	11.4	39.6

[a] Energies, geometries and vibrational frequencies (ν_i) from 3-21G calculations; energies and enthalpies in kcal/mol; entropies in eu (Gibbs/mol). [b] ZPE = $^1/_2\sum h\nu_i$. The imaginary frequency is neglected in the transition-state calculation. [c] $\Delta H^{298\,K} = \Delta E + \Delta(\mathrm{ZPE}) + 4RT + \sum h\nu_i/(e^{h\nu_i/(kT)} - 1)$. Values of the last term range 3.4–4.7 kcal/mol at 298 K. [d] Evaluated from mass, moments of inertia, and vibrational frequencies according to ref 16. Electronic entropies were neglected. For comparison, experimental entropies are 116.1 eu for CCl_2 + ethylene and 109.9 eu for CF_2 + ethylene.[16a] Estimated entropies for difluorocyclopropane and dichlorocyclopropane are 68.7 and 73.3 eu, respectively, using Benson's tables.[16a] [e] ν were estimated.

Enthalpies and entropies of the 3-21G stationary points were calculated by using standard formulas for partition functions and the masses, 3-21G moments of inertia, and 3-21G harmonic vibrational frequencies.[16,17] The results are listed in Table II. In

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(14) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. Binkley, J. S.; Pople, J. A. *Int. J. Quantum. Chem., Symp.* **1975**, *9*, 229. Pople, J. A.; Binkley, J. S.; Seeger, R. *Ibid.* **1976**, *10*, 1. Krishnan, R.; Pople, J. A. *Int. J. Quantum Chem.* **1978**, *14*, 91.

(15) Higher level calculations on the H_2O–$^1CH_2$ complex indicate that more flexible basis sets and correlation energy decreases the stability of complexes. With zero-point corrections, the complexes are less stable than the reactants: Harding, L. B.; Schlegel, H. B.; Krishnan, R.; Pople, J. A. In "Potential Energy Surfaces and Dynamics Calculations"; Truhlar, D. G., Ed.; Plenum Press: New York, 1981; p 169. Calculations of our systems with the 6-21G basis set give decreases of complex stabilities, implying that part of the stabilization is due to basis-set superposition error.

each case, the largest portion of the negative ΔS is caused by the decrease in translational entropy (−35 eu). The smaller differences between the entropies of complexes, transition states, and products result from increasing vibrational frequencies primarily associated with the increasing force constants for CC stretching and CCC bending as bonds are formed. The experimental entropies of reaction of CH_2, CF_2, and CCl_2 with ethylene are all essentially identical (−42 ± 1 eu),[16a] so that the change in entropy is a function of the reaction coordinate but is independent of the identity of the carbene.

Even using the crude 3-21G values of ΔE, the ΔG values in Table II indicate that the complexes are not likely to be free energy minima at room temperature. Furthermore, the ether or halocarbon solvents often used for such reactions should be better Lewis basic coordinators than alkenes.[18] Complexes of CCl_2 or CF_2 with H_2O are calculated to be 23.6 and 9.7 kcal/mol, respectively, more stable than the separated species at the MP2/3-21G level. On the basis of these admittedly nondefinitive calculations, we conclude that no complexes, other then possible solvent "cage" complexes, are formed between the more reactive halocarbenes and alkenes in solution.

The following communication shows how this conclusion is compatible with the experimental observations of negative activation energies and entropy control of reactivity.

Acknowledgment. We are grateful to the National Science Foundations of the USA (Grant CHE-8213329 to K.N.H. and equipment grant to the University of Pittsburgh) and Switzerland (Postdoctoral Fellowship to J.M.) for financial support of this research and to Professors J. A. Pople and B. Giese for helpful comments.

Registry No. CCl_2, 1605-72-7; CF_2, 2154-59-8; ethylene, 74-85-1.

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(16) (a) Benson, S. W. "Thermochemical Kinetics", 2nd ed.; Wiley-Interscience: New York, 1976. (b) Lewis, G. N.; Randall, M. "Thermodynamics"; Pitzer, K. S., Brewer, L., Eds.; McGraw-Hill: New York, 1961; pp 419–448. Knox, J. H. "Molecular Thermodynamics"; Wiley: New York, 1978; pp 95–143.

(17) The vibrational frequencies obtained with a split-valence basis set are usually approximately 10% too large: Yamaguchi, Y.; Schaefer, H. F., III. *J. Chem. Phys.* **1980**, *73*, 2310.

(18) A variety of carbene complexes are known. For leading references, see: Lambert, J. B.; Larson, E. G.; Bosch, R. J. *Tetrahedron Lett.* **1983**, *24*, 3799.

Origin of Negative Activation Energies and Entropy Control of Halocarbene Cycloadditions and Related Fast Reactions

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The previous communication describes calculations which indicate that stable π-complexes are not formed in the reactions of relatively unstabilized carbenes with alkenes.[1] If stable complexes are not formed, how can negative activation energies and entropy control of selectivity be explained? We abandon calculations at this point and develop a new hypothesis to show how negative activation energies and entropy control of reactivity can arise in fast reactions having no inherent potential energy barrier. This hypothesis is based upon the well-known principle that the transition state of a reaction is the point where the free energy is a maximum separating reactants and products.[2] Both enthalpy and entropy changes contribute to the location of this maximum.[3]

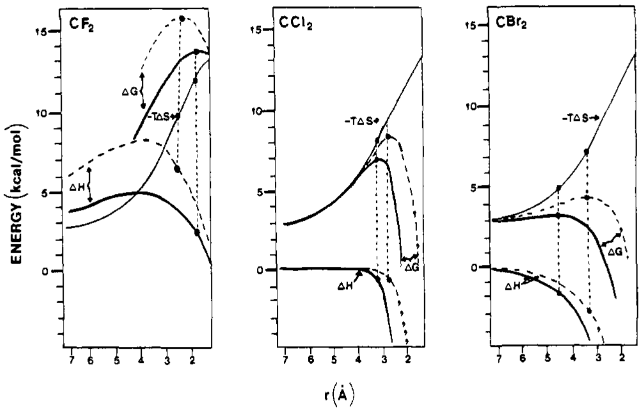

Figure 1. Model ΔH, $-T\Delta S$(298 K), and ΔG(298 K) profiles for the reactions of CF_2, CCl_2, and CBr_2 with isobutene (DME) and tetramethylethylene (TME). The $-T\Delta S$ curve is the same for both alkenes and all three carbenes. The full lines represent the TME potentials, and the dashed lines represent the DME potentials. The vertical dashed lines pass through the value of r at the transition states and intercept the ΔH and $-T\Delta S$ curves at the values of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ at 298 K.

We have also constructed numerical model potential functions for the reactions of CF_2, CCl_2, and CBr_2. For conceptual simplicity, we have expressed these functions in terms of familiar transition-state theory quantities,[2] in spite of the limitations of this treatment.[4] The functions used to model ΔH are inverted Morse functions, $\Delta H = -\Delta H_{\max}(1 - e^{-\beta(r-r')})^2$, where r is the value of the reaction coordinate, r' is the value of r at the maximum value of ΔH, and $\Delta H_{\max}$ is the maximum of ΔH along the reaction coordinate. β controls the curvature of the function. $\Delta H_{\max}$ and r' were estimated using the information obtained from calculations or from calculated guesses.[5] Figure 1 shows plots of ΔH, $-T\Delta S$ (at 298 K), and ΔG for the reactions of three carbenes with two alkenes (DME = isobutene = 1,1-dimethylethylene; TME = tetramethylethylene). The $-T\Delta S$ functions were obtained from the linear correlation of 3-21G $-T\Delta S$ values vs. the reaction coordinate, r, in the region of r = 1.2–4 Å.[1] From 4 to 7 Å, $-T\Delta S$ is assumed to decay in a smooth fashion to a value of 2.7 kcal/mol at 7 Å. The quantity $-T\Delta S$ is assumed to be independent of the identity of the carbene or the alkene and becomes increasingly positive as the distance between the alkene and carbene decreases. This is a consequence of the increases in vibrational frequencies associated with forming bonds as r decreases. The ΔG ($=\Delta H - T\Delta S$) curves show that the free energy maxima (vertical dashed lines) do not correspond to the ΔH maxima. The ΔG maximum is, however, the energy corresponding to the "transition state" (TS)[2] or, in dynamics terminology,[6] the critical point dividing the reactants from products. Each reaction has a "dynamical bottleneck", which becomes the primary determinant of the position of the TS when there is no enthalpic barrier. Because $-T\Delta S$ is linearly related to T, the position of the TS varies with temperature, becoming earlier (larger value of r) with lower temperature.

For CF_2, the TS for the less reactive alkene (DME) occurs earlier along the reaction coordinate than the TS for the more reactive alkene (TME), even though the ΔH maxima are assumed to be at the same value of r. This explains why $-T\Delta S^{\ddagger}$ favors the less reactive alkene. By plotting $-\Delta G^{\ddagger}/(2.303RT)$ (equivalent to log k(TME)/k(DME)), obtained from these functions, vs. $1/T$, we obtain values of $\Delta\Delta H^{\ddagger}$(theor) and $\Delta\Delta S^{\ddagger}$(theor) to compare

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(1) Houk, K. N.; Rondan, N. G.; Mareda, J. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107.

(3) We thank Dr. Charles Doubleday, Jr., for enlightening discussions on this point. For a related case of entropy effects producing a free energy minimum, see: Doubleday, C., Jr.; Camp, R. N.; King, H. F.; McIver, J. W., Jr.; Mullaly, D.; Page, M. *J. Am. Chem. Soc.* **1984**, *106*, 447.

(4) For example, see: Menzinger, M.; Wolfgang, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 438.

(5) Details about these potential functions will be reported in detail: Houk, K. N.; Rondan, N. G.; Mareda, J. "Tetrahedron Symposium-In-Print"; Platz, M., Ed., in press.

(6) Truhlar, D. G.; Garrett, B. C. *Acc. Chem. Res.* **1980**, *13*, 440. Hase, W. B. *Ibid.* **1983**, *16*, 258, and references therein.

0002-7863/84/1506-4293$01.50/0