Medium Effects on the Rates of Stereomutation of a Pair of Diastereomeric Cyclopropanones. Ground State Stabilization in Nucleophilic Solvents Induces Deviation from Solvent Polarity Controlled Behavior

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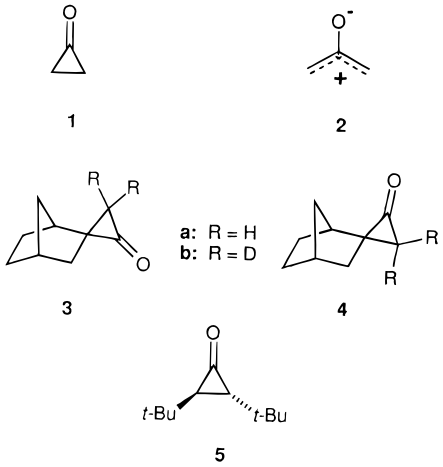
Abstract: The synthesis of the two stereoisomers of spiro(bicyclo[2.2.1]heptane-2,1′-cyclopropan)-2′-one, **3a** and **4a**, from diazomethane and the ketene 2-carbonylylbicyclo[2.2.1]heptane in ether at 195 K yields a ∼1.6 to 1 ratio. At 245 K, the ratio changes in a first-order manner, with an observed rate constant of 1.7×10^{-4} s^{-1}, to an equilibrium ratio of 0.8 to 1. The temperature dependence of the interconversion of **3a** and **4a** (GC method) and that of their dideuterio derivatives **3b** and **4b** (NMR method) have been determined and yield activation parameters $E_a = 16.3 \pm 1.4$ kcal/mol and log $A = 10.4 \pm 1.4$ (A in s^{-1}) (GC method) and $E_a = 15.3 \pm 1.4$ and log A = 9.6 ± 1.4 (NMR method). The free energies of activation at 239 K have been determined in four solvents: dichloromethane (16.1 kcal/mol), acetone (17.7), hexane (17.9), and ether (19.1). The solvent dependence does not correlate well with commonly used measures of solvent polarity, and the reaction is unexpectedly slow in acetone and ether. This deceleration is explained in terms of nucleophilic association of these solvents with the carbonyl groups in the cyclopropanones, leading to a ground state stabilization.

Three overlapping motivations sustain the current interest in cyclopropanone (**1**) and its ring-opened isomer oxyallyl (**2**): computational efforts to solve the difficult quantum mechanical problems of π-conjugated non-Kekulé molecules,[1−5] mechanistic scrutiny of thermal valency tautomeric reactions,[1,6−11] and synthetic applications of the Favorskii rearrangement of α-halo ketones, a reaction in which important mechanistic roles for **1** and **2** derivatives have been discerned but not entirely elucidated.[12−20] The present paper extends the previous study[1b] of solvent effects on the stereomutation of the isomeric cyclopropanones **3** and **4**, compares the experimental data with the results of computational treatments[2a] of similar reactions, and provides an explanation for the different nature of the solvent effects in the stereomutations of **3** and **4** as compared to those seen[10,11] in the case of *trans*-2,3-di-*tert*-butylcyclopropanone (**5**).



Selection of the System To Be Studied. The choice of **3** and **4** as a pair of epimeric cyclopropanones for this diverse

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(6) Sorensen, T. S.; Sun, F. *J. Am. Chem. Soc.* **1995**, *117*, 5592 and references cited therein.

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(8) (a) Pazos, J. F.; Greene, F. D. *J. Am. Chem. Soc.* **1967**, *89*, 1030. (b) Pazos, J. F.; Pacifici, J. G.; Pierson, G. O.; Sclove, D. B.; Greene, F. D. *J. Org. Chem.* **1974**, *39*, 1990.

(9) Greene, F. D.; Camp, R. L.; Kim, L.; Pazos, J. F.; Sclove, D. B.; Wilkerson, C. J. *Proc. Int. Congr. Pure Appl. Chem., 23rd* **1971**, *2*, 325.

(10) (a) Sclove, D. B.; Pazos, J. F.; Camp, R. L.; Greene, F. D. *J. Am. Chem. Soc.* **1970**, *92*, 7488. (b) Although the observed stereomutation in the *trans*-2,3-di-*tert*-butyl case **5a**−**5b** formally could result from reversible cleavage of the C_1-C_2 (or C_1-C_3) bond accompanied or followed by internal bond rotations in a biradical intermediate, the mechanism of Scheme 3 was preferred.[10a]

(11) Camp, R. L.; Greene, F. D. *J. Am. Chem. Soc.* **1968**, *90*, 7349.

(12) Wasserman, H. H.; Berdahl, D. R.; Lu, T.-J. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley and Sons: New York, 1987.

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(14) Baretta, A.; Waegell, B. *React. Intermed. (Plenum)* **1982**, *2*, 527−585.

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(16) Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307−4315.

(17) House, H. O.; Gilmore, W. F. *J. Am. Chem. Soc.* **1961**, *83*, 3980−3985.

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(19) Skrobek, A.; Tchoubar, B. *Compt. Rend.* **1966**, *263*, 80.

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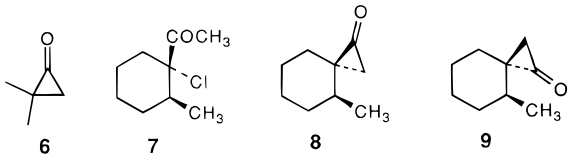
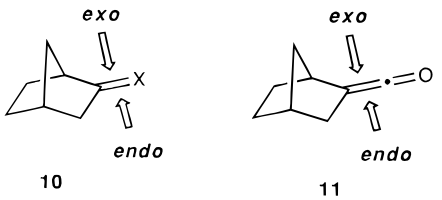
group of objectives was intended to provide a closer comparison to the relatively unhindered 2,2-dialkylcyclopropanones widely used in earlier work. Thus, the cycloaddition studies of Edelson and Turro[7] centered on 2,2-dimethylcyclopropanone (**6**), and some of the classic experiments on the stereochemistry of the Favorskii rearrangement started from the chloro ketone **7**,[11−15] whose corresponding cyclopropanones **8** and **9** are probably intermediates.



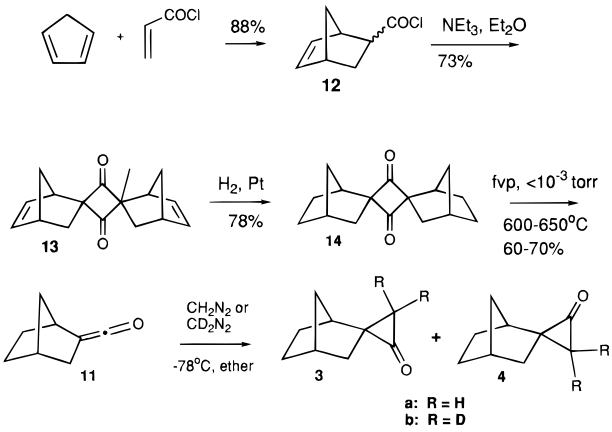
Further, structural analogy between **3** and **4** and the small, computationally manageable system **6**[2a] offers a link to quantitative theoretical investigations and should provide a meaningful theory−experiment dialogue on the cyclopropanone−oxyallyl energy gap.

Beyond this, several practical considerations affect the choice. For example, if one is to monitor the course of stereomutation by conventional kinetic observation[21] of the change in concentration over time, the reaction must be started with a non-equilibrium ratio, preferably one far from equilibrium. In the case of the sterically protected *trans*-di-*tert*-butylcyclopropanone **5**,[8−11] Greene and co-workers achieved this through partial resolution of the two enantiomers, which allowed for the observation of racemization by optical rotation measurements. Since the benefits of steric bulk cannot be afforded under the present goals, the synthesis must furnish the required non-equilibrium ratio directly, and the cyclopropanones must be handled in solution, at low temperature, and with a minimum of manipulation.

In the case of 2,2-dialkylcyclopropanones the only known synthesis involves the reaction of diazomethane with a dialkylketene.[22] This process is known to proceed rapidly at 195 K, so that at least the requirement of a rapid synthetic reaction should be met. Prediction of the degree and direction of stereochemical bias to be expected in this step is difficult, since the mechanism of diazomethane's addition to ketenes is not known. We chose the norbornyl moiety present in **3** and **4** as a stereochemical element which is not prohibitively bulky. Derivatives of the type **10** are known[23−27] to prefer addition from the exo rather than the endo face, and we hoped that a similar kinetic preference would prevail in ketene **11**. We also hoped that the equilibrium composition **3**:**4** might be close to 50:50.



Scheme 1



On the other hand, these hopes must be tempered by the realization that if the mechanism in fact resembles a nucleophilic attack on the carbonyl carbon, as considered by Turro and Hammond,[22] the initial approach of diazomethane to **11** would be neither endo nor exo but *lateral* with respect to the two faces, making the ultimate stereochemical preference difficult to predict.

To reach the cyclopropanones **3** and **4**, ketene dimer **14**, synthesized according to Scheme 1, was subjected to flash vacuum pyrolysis to ketene **11** which could be trapped on a liquid nitrogen cold finger. Solutions of **11** were obtained by removal of the liquid nitrogen and rinsing of the cold finger with dry diethyl ether into a collection flask at 195 K. Finally, cold (195 K) diazomethane in dry ether (dried over KOH pellets) was introduced under nitrogen atmosphere to give a mixture of cyclopropanones **3a** and **4a** in ether. These samples exhibited the characteristic high frequency IR signal of cyclopropanones at 1822 cm^{-1}.[28−30] Like most unhindered cyclopropanones, **3** and **4** were unstable in moderately concentrated solution at room temperature and were reactive toward water or other hydroxylic species. Samples for further study were prepared fresh as described in the Experimental Section. For reasons given below, the dideuterated derivatives **3b** and **4b** also were prepared from ketene **11** and CD_2N_2.

Direct observation of the ratio of **3a** and **4a** initially produced by the diazomethane addition was not straightforward. The compounds were unlikely to survive GC or HPLC, they were not readily differentiable by IR, and application of NMR methods required significant manipulation or isotopic labeling (see below). Accordingly, we turned to derivatives of the cyclopropanones to lock the desired stereochemical information into a stable, readily analyzable form. Quenching of aliquots of the cyclopropanone/ether solution in methanol/ether at −78 °C gave, by addition of methanol to the carbonyl group, four epimeric *hemiketals*,[22,28,31,32] two from **3a** and two from **4a**. These possessed the structures **15**−**18** (see Scheme 2) and appeared as a group of four peaks on a capillary gas chromatogram. In the ^1H NMR spectrum, the cyclopropyl methylene proton resonances appeared at 1.0 to 0.4 ppm.

Experimental Detection of the Cyclopropanone Stereomutation. The distribution of the hemiketal products depended

(21) The recent study of Sorensen and Sun[6] used dynamic NMR spectroscopy, a basically different method, to detect the site-equilibration of the diastereotopic methyl groups in *cis*-2,3-di-*tert*-amylcyclopropanone, which presumably occurs by ring-opening but does not involve a change in concentration of the reactant. This stereomutation occurs with $\Delta G^{\ddagger} = 11.3$ kcal/mol, in contrast to that of the trans di-*tert*-butyl derivative **5**,[8−11] for which $\Delta G^{\ddagger} \sim 28$ kcal/mol.

(22) Turro, N. J.; Hammond, W. B. *Tetrahedron* **1968**, *24*, 6017.

(23) Review: Berson, J. A. In *Molecular Rearrangements;* de Mayo, P., Ed.; Interscience: New York, 1963, Part 1, Chapter 3.

(24) Brown, H. C.; Hammar, W. J.; Kawakami, J. H.; Rothberg, I.; VanderJagt, D. L. *J. Am. Chem. Soc.* **1967**, *89*, 6381.

(25) Brown, H. C.; Kawakami, J. H.; Ikegami, S. *J. Am. Chem. Soc.* **1970**, *92*, 6914.

(26) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.

(27) Lasne, M. C.; Ripoll, J. L.; Denis, J. M. *Tetrahedron* **1981**, *37*, 503.

(28) Turro, N. J.; Hammond, W. B. *J. Am. Chem. Soc.* **1966**, *88*, 3672.

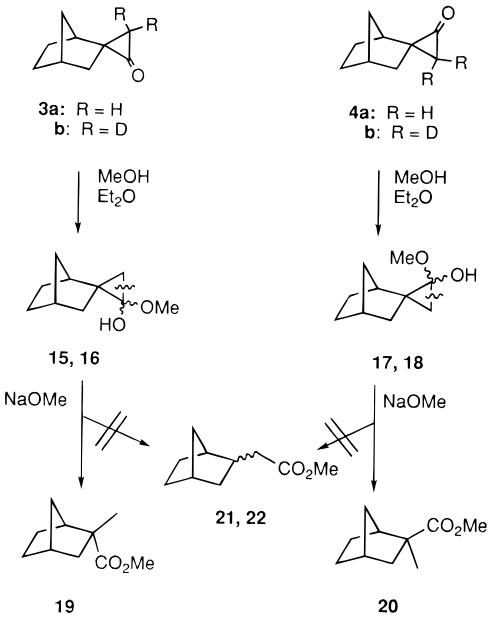
(29) Ohno, A.; Grosse, D. J.; Davis, R. E. *Tetrahedron Lett.* **1968**, 959.

(30) van Tilborg, W. J. M. *Tetrahedron Lett.* **1973**, 523.

(31) Salaun, J. *Chem. Rev.* **1983**, *83*, 619.

(32) Wasserman, H. H.; Clagett, D. G. *J. Am. Chem. Soc.* **1966**, *88*, 5368.

Scheme 2



upon the thermal history of the cyclopropanone solution prior to quenching (and, as will be described later, on the temperature at which the quench was run). For instance, if after synthesis the solution of **3a** and **4a** was held at −78 °C, the quenching experiment gave a GC trace showing two pairs of peaks. Although the ratio of the individual members of a pair did not vary with conditions, the ratio of the summed intensity of the early-emergent pair to that of the late-emergent pair depended on whether the cyclopropanone preparation was quenched at 195 K or was first allowed to warm to 298 K, re-cooled to 195 K, and then quenched. The first experiment typically gave a ratio two early:two late of 1.6−1.65:1, the second a ratio of 0.8 to 1.

The obvious interpretation of this result is that the early-emergent pair of hemiketals is associated with one cyclopropanone epimer, and the late-emergent pair with the other. Presumably through thermal equilibration upon warming, the ratio of cyclopropanones **3** to **4** varies between the first and second quench experiments, and the hemiketal composition reflects this change. Although some hemiketals have been shown to exchange one alcohol for another on standing for weeks at room temperature, presumably through prior reversion to the cyclopropanone,[32] hemiketal formation here appears relatively irreversible, since **15**−**18** are stable to GC and are observable in different ratios. The variation in hemiketal product composition provides a way of assigning each pair to a particular cyclopropanone epimer. Further transformation of **15**−**18** by sodium methoxide smoothly gives the known "Favorskii" esters **19** and **20** (see Scheme 2). The esters **21** and **22**, which could result from cleavage of the cyclopropanone toward the tertiary α-carbon, are not observed. 2,2-Dimethylcyclopropanone (**16**) gives an analogous result.[33] Because none of the bonds to the carbon at the 2-position of the norbornane are disturbed by the rearrangement to ester, the ratio of esters **19** to **20** should report faithfully the ratio of hemiketals from capture of **3** to those from capture of **4**. In fact, one can verify this experimentally, since the relative amounts of **19** and **20** do vary as the ratio of the short to long retention time pairs of hemiketals. The short retention time pair are apparently the precursors of **19**, and are therefore assigned structures **15** and **16**, in no particular order. The long retention time pair of hemiketals then have structures **17** and **18**.

(33) Hammond, W. B.; Turro, N. J. *J. Am. Chem. Soc.* **1966**, *88*, 2880.

Since it is possible to obtain different compositions of methanol quench products under the same quenching conditions, it appears that the trapping of cyclopropanones **3a** and **4a** preserves, at least in part, whatever ratio **3a**:**4a** is present at the time. Such irreversible methanolysis holds within it the promise of utility in an indirect kinetic measurement of the rate of interconversion of cyclopropanones **3a** and **4a**.

In experiments of this kind, different samples of the same initial ratio **3a**:**4a** were stored at a single temperature (in the range 235−257 K) for various lengths of time and then quenched into methanol/ether at 195 K. The results were striking. Referenced to an equilibrium (infinite time) measurement, a clean first-order change was observed in the ratio of **15** and **16** (from **3a**) to **17** and **18** (from **4a**). This number changed from an initial value of ∼1.6:1 to an equilibrium value of ∼0.8:1. The analysis also includes 5−10% of the Favorskii esters **19** and **20**, which appeared to result from thermal rearrangement in the GC injection port. The signal due to these compounds was added to that from their respective hemiketals to give the overall ratio. The kinetic data for the change correponded well ($r = 0.99929$) to an observed first-order rate constant of 1.8×10^{-4} s^{-1} at 245.6 K.

The material balance remained essentially constant throughout such runs, so that the change cannot be attributed to a selective decomposition of **3** relative to **4**. In fact, the only cogent interpretation of the data is that **3** and **4** are interconverting during the run and, upon methanol capture, are leaving a traceable stereochemical legacy in the form of **15**−**18**, that is, the rate constant for the hemiketal compositional change is actually a rate constant for the interconversion of **3a** and **4a**.

Direct confirmation of this hypothesis is provided by 500 MHz ^{2}H NMR experiments on deuterated compounds **3b** and **4b**. Initially, we had hoped to use ^{1}H NMR on protio compounds **3a** and **4a** themselves, but the proton spectrum is complex (see Experimental Section) and also must be obtained on a solution of **3a** and **4a** in a deuterated solvent. These considerations prompted the use of deuterated cyclopropanones **3b** and **4b**, which were synthesized by the procedures described in Scheme 1 with substitution of CD_2N_2 for CH_2N_2. The needed CD_2N_2 of 97−98% isotopic purity in ether solution was prepared by base-catalyzed exchange of CH_2N_2 under phase transfer conditions.[34]

Nevertheless, in the synthetic application here, we encountered some difficulty in obtaining solutions dry enough for use in the preparation of the extremely hydrophilic cyclopropanones. Drying in the undeuterated case could be done easily by storage of the ethereal solutions over KOH pellets. In the deuterated case, however, the same procedure caused unacceptably rapid exchange of protium for deuterium. To circumvent this problem, the CD_2N_2 in ether was stirred over anhydrous Na_2CO_3 for 30 min and then transferred into the ketene solution by a variant of the aeration method developed for CH_2N_2 by Bush and Sanders-Bush.[35] In this process, the labeled compound was passed from the source flask in a stream of dry nitrogen through a drying tube containing KOH pellets. As opposed to the solution phase attempt, the brief contact of the deuterated diazomethane gas with solid KOH resulted in a much smaller loss of isotopic purity. By chemical derivatization and GC-MS analysis of the resulting cyclopropanones, the final deuterium content was found to be 91−95% d_2.

(34) (a) Markey, S. P.; Shaw, G. J. *J. Org. Chem.* **1978**, *43*, 33−34. (b) Damtoft, S.; Jensen, S. R.; Nielsen, B. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1943−1948.

(35) Bush, M. T.; Sanders-Bush, E. *Anal. Biochem.* **1980**, *106*, 351−362.

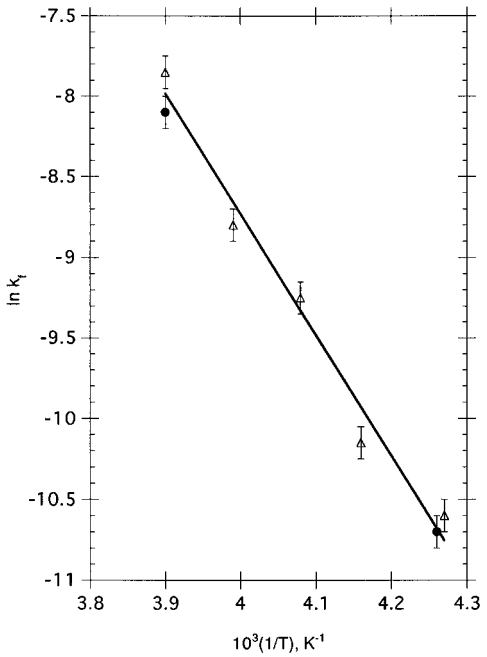


Figure 1. Arrhenius plot for GC kinetics of interconversion of **3a** and **4a** in ether (triangles) and, for comparison, two runs conducted in the presence of Proton Sponge (closed circles).

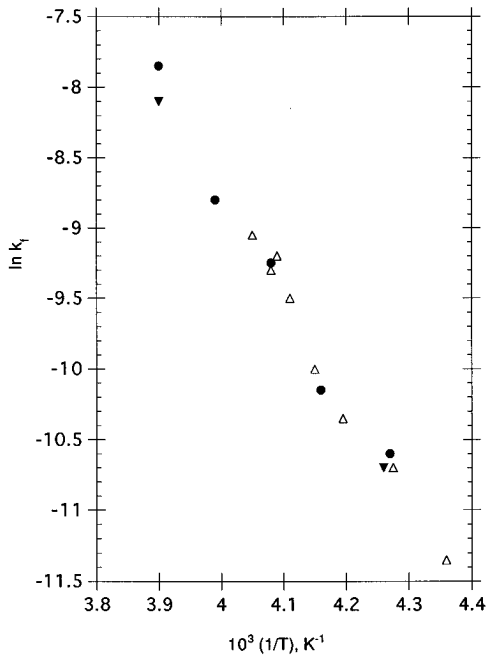


Figure 2. All kinetic data for the interconversion of **3a** and **4a** or **3b** and **4b** in diethyl ether plotted together. The GC and ^{2}H NMR data are shown as open triangles and closed circles, respectively. The ^{2}H NMR data in the presence of Proton Sponge are shown as closed triangles.

The behavior of **3b** and **4b** as observed directly by 500 MHz ^{2}H NMR closely paralleled the indirect GC results. From the data (see Supporting Information) for approach to an equilibrium ratio of ~0.8 from an initial **3b:4b** ratio of ~1.6 at 245.3 K the rate constant $k_{obs} = 1.7 \times 10^{-4}$ s^{-1} was derived from the areas of the two most upfield peaks. The value of k_{obs} is given by the slope of the plot of ln[(**4**$_e$)/(**4**$_e$ − **4**)] *vs t*. This plot has an intercept of ln[(**4**$_e$)/(**4**$_e$ − **4**$_0$)], where **4**$_e$, **4**$_0$, and **4** represent the signal intensities of **4b** at equilibrium, at time zero, and at time *t*, respectively. Alternatively, one may plot ln[(**4**$_e$ − **4**$_0$)/(**4**$_e$ − **4**)], which has a zero intercept but the same slope. The value of k_{obs} agrees well with the GC value of 1.8×10^{-4} s^{-1} in the undeuterated case at 245.6 K. The data probably are not accurate enough to detect a secondary isotope effect with confidence, but if such an effect is present, it appears to be small.

Temperature-dependence data for the stereomutation process were obtained by GC experiments over the range 235−256 K and by NMR experiments over the range 229−247 K. Figure 1 shows an Arrhenius plot for the GC method, based on eq 1

$$\ln k_f = \ln A - E_a/RT \quad (1)$$

where the rate constant k_f for the forward reaction **3** → **4** is defined in eq 2.

$$k_f = (k_{obs}K_e)/(1 + K_e) \quad (2)$$

Also included in Figure 1 are runs conducted in the presence of Proton Sponge (1,8-bis(dimethylamino)naphthalene), an acid scavenger. These showed reasonable agreement with the data from unprotected runs in both rate and temperature dependence.

Temperature dependence data for runs followed by the NMR method (plotted in the Supporting Information) agreed with those from the GC method to within 20% for the rate constants and 5% for the equilibrium constants. Finally, to illustrate the good overall agreement, Figure 2 shows all of the temperature dependence data plotted together.

By the GC method, the Arrhenius parameters (A in s^{-1}) for the reaction in ether are $E_a = 16.3 \pm 1.3$ kcal/mol and log A = 10.4 ± 1.4 (the two GC runs with Proton Sponge gave E_a = 15.6 kcal/mol and log A = 9.8). By the NMR method, they are $E_a = 15.3 \pm 1.4$ kcal/mol and log $A = 9.6 \pm 1.4$. Within experimental error (partially attributable to the narrow range of ratios of **3** and **4** experimentally accessible with our samples), the results of both methods are essentially the same. The average of the two gives $E_a = 15.8$ kcal/mol and log $A = 10.0$. This in turn gives a $\Delta H^‡$ of 15.3 kcal/mol and $\Delta S^‡$ of −14 eu for the forward process converting **3** to **4**.

Table 1. Summary of Temperature-Dependence Data for the Interconversion of Cyclopropanes **3a** and **4a** or **3b** and **4b**[e]

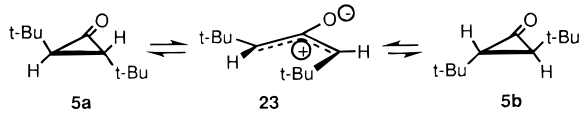
solvent	method	E_a ($\Delta H^‡$)[a]	log A ($\Delta S^‡$)[b]
ether	GC	16.3 (15.8)	10.4 (−12)
ether prot. sp.	GC	15.6 (15.1)	9.8 (−14)
ether	^{2}H NMR[c]	15.3 (14.8)	9.6 (−14)
CD_2Cl_2/prot. sp.	GC, ^{1}H NMR[d]	12.4 (11.9)	9.9 (−13)

[a] $\Delta H^‡ = E_a - RT$. [b] $\Delta S^‡ = R[\ln(hA/\kappa k_b T) - 1]$,where k_b is the Boltzmann constant. The $\Delta S^‡$ values were calculated for the middle of the experimental temperature range, and κ was assumed equal to 1. [c] Peak intensity analysis. [d] Line broadening analysis. [e] The experimental errors in E_a and log A are estimated to be ±1.3 kcal/mol and ±1.4 units, respectively.

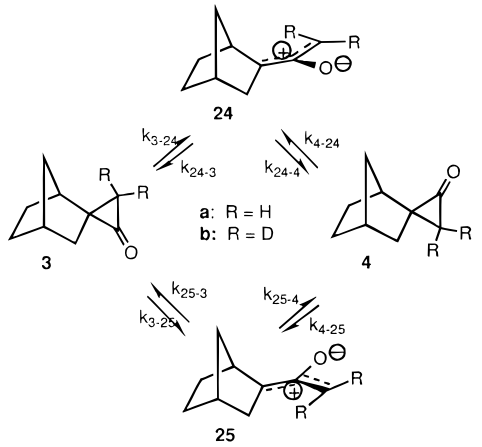
The observed log A values of 9−10 (±1.4 units) and derived $\Delta S^‡$ values of −12 to −15 eu (Table 1) for the **3** → **4** stereomutation are surprisingly low for a simple unimolecular ring-opening process[36a] and raise the possibilities that the mechanistic description may be inadequate or the experimental results may be suspect. Among the mechanistic reasons we have considered and discussed in the Supporting Information are solvent electrostriction and spin or dynamics prohibition in the transition state for ring-opening. The evidence now available is inconclusive on these points. The experimental issue of greatest concern is whether the ring-opening may be catalyzed by some adventitious hydroxylic species.[10,36b,c] If a hydrogen-bonded association or actual proton transfer preceded ring-opening, a more negative observed activation entropy and thus

(36) (a) Willcott, M. R.; Cargill, R. L.; Sears, A. B. *Prog. Phys. Org. Chem.* **1972**, *9*, 25. (b) Olah, G.; Calin, M. *J. Am. Chem. Soc.* **1968**, *90*, 938. (c) Turro, N. J.; Hammond, W. B. *Tetrahedron* **1968**, *24*, 6029, 6035.

Scheme 3



Scheme 4



a low log *A* value would result. Considerations given in the Supporting Information lead us to think that such explanations for the low $\Delta S^{\ddagger}$ values are very unlikely.

Kinetics and Mechanism of the Cyclopropanone Stereomutation. As a framework for rationalizing our kinetic data, we adopt the basic mechanistic hypothesis for the stereomutation of *trans*-2,3-di-*tert*-butylcyclopropanone (**5a**) proposed by Greene et al:[10] disrotatory cleavage of the C_2-C_3 ring bond to form a planar oxyallyl **23**, followed by disrotatory closure to the stereoisomeric cyclopropanone **5b** (Scheme 3). Attempts to trap the presumed intermediate oxyallyl **23** in the di-*tert*-butyl case were unsuccessful.[10a] In the case of the cyclopropanones of the present study, cycloaddition products of structure appropriate to trapping the oxyallyl intermediate now have been found.[1c] Epimerization of **3** and **4** occurs more rapidly than adduct formation, consistent with the competitive fast closure and slow capture of oxyallyl intermediates.

On the assumption that cyclopropanones **3** and **4** interconvert by a disrotatory ring-opening mechanism to the oxyallyls **24** and/or **25** (Scheme 4), the rate data now can be used to deduce information about the absolute free energy differences between the cyclopropanone and the oxyallyl. Appendix A contains a full discussion of the derivations involved. Whether an intermediate or transition state, the more stable of the oxyallyls **24** and **25** can lie no higher in free energy than ΔG(**3**−**24** or **25**) $\leq RT[\ln(k_f/2) - \ln(RT/Nh)] \leq 19.1$ kcal/mol above cyclopropanone **3** in solvent diethyl ether at 247 K. In general, Gibbs free energies of activation reported in this section are derived from this relationship, which accounts for the existence of two possible oxyallyls, **24** and **25**. It gives the larger of the free energy differences between the reactant and the two physically distinct transition states leading to the two oxyallyls. However, where activation energies (E_a) and log *A* values, and the associated Eyring parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, are discussed, they are derived simply from the forward rate k_f from **3** to **4**.

In addition to the determinations in diethyl ether, we have measured the rate of interconversion of **3a** and **4a** in three other solvents, acetone, methylene chloride, and hexane, all by the GC method. This was accomplished by synthesizing **3a** and **4a** in ether as usual, removing the solvent under vacuum at low temperature, and introducing a second solvent via vacuum transfer. Of the four solvents studied, ether produced the slowest rate, which corresponded to $\Delta G^{\ddagger} = 19.2$ kcal/mol at 239 K. A remarkable acceleration was observed in methylene chloride, for which $\Delta G^{\ddagger} = 15.3$ kcal/mol at 191 K. Extrapolated to a common temperature of 239 K from the Arrhenius parameters given below, the ratio of rate constants in CH_2Cl_2 and ether was 1114. The epimerization proceeded at nearly equal rates in acetone and hexane, for which the $\Delta G^{\ddagger}$ were 17.7 and 17.9 kcal/mol at 239 K, respectively. In part because of some loss of stereochemical integrity during replacement of the ether, these methods unfortunately were not of sufficient accuracy in any of the latter three solvents to permit meaningful assessments of the activation parameters E_a, log *A*, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$.

Table 2. Solvent Dependence of the Reaction Barriers for Interconversion of **3** and **4** at 239 K

		solvent parameters[a]		
solvent	$\Delta G^{\ddagger}$, kcal/mol	E_T	π^*	β
dichloromethane	16.1	41.1	0.82	0.00
acetone	17.7	42.2	0.72	0.48
hexane	17.9	30.9	−0.08	0.00
ether	19.2	34.1	0.27	0.47

[a] E_T is the Reichardt-Dimroth polarity parameter (refs 40 and 41); π^* and β are parameters expressing solvent dielectric and nucleophilic properties, respectively (ref 51).

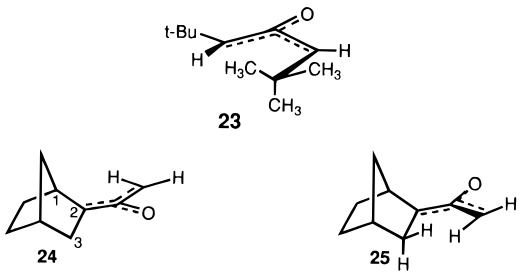
It was possible, however, to take advantage of the relatively rapid equilibration of **3a** and **4a** in deuterated methylene chloride (CD_2Cl_2) to obtain approximate rates by the method of ^{1}H NMR line broadening, since chemical exchange between **3a** and **4a** in this solvent is of sufficient velocity at room temperature (of the order of $k_f = 1-5$ s^{-1}). Details of the procedures are given in the Supporting Information. A rate constant at 297 K was extracted from the change in line width relative to the line widths in a sample at 267 K, where the chemical exchange is slow on the NMR time scale. Proton Sponge was included in the solutions to suppress acid catalysis. On the assumption that no significant solvent isotope effect was active, the NMR lineshape rate constant at 297 K in CD_2Cl_2 was combined with the GC rate constant at 191 K in CH_2Cl_2 and subjected to a two-point Arrhenius analysis to yield the activation parameters listed in Table 1, which summarizes the temperature-dependence data for both solvents. Finally, adjustment of the reaction barriers in ether and dichloromethane to 239 K, the temperature of the acetone and hexane measurements, gives the free energies of activation for all the solvents (Table 2), which are displayed along with some relevant solvent parameters (to be discussed below).

We are now in a position to compare all of our results with those of Greene and co-workers[9,10] for the di-*tert*-butyl system **5**, and with the theoretical work of Lim et al.[2a] on parent cyclopropanone and 2,2-dimethyl analog **6**.

The experimental observation that **3** and **4** interconvert readily at subambient temperatures with free energy barriers of 16-19 kcal/mol in four solvents at 239 K is in reasonable agreement with the prediction by Lim et al. of a ∼20 kcal/mol free energy barrier for the disrotatory opening of the model compound 2,2-dimethylcyclopropanone to 1,1-dimethyloxyallyl at 298 K in the gas phase. This agreement strongly supports the participation of oxyallyls in cyclopropanone ring-openings and, for the present, constitutes the closest available approach to a direct comparison of experimental and theoretical work on a cyclopropanone−oxyallyl valence tautomeric system.

The interconversions of **3** and **4** are much faster than those of *trans*-2,3-di-*tert*-butylcyclopropanone system **5**,[9,10] where a cyclopropanone ring-opening barrier of 27.4−29.2 kcal/mol in five solvents at 80 °C (351 K) was observed. In considering the mechanisms of cyclopropanone reactions, therefore, the use

Scheme 5



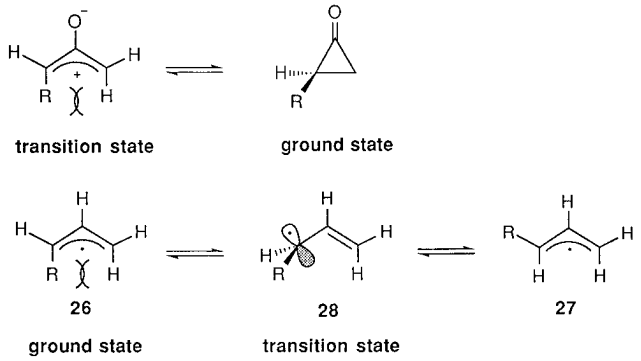
of the rate of stereomutation of *trans*-2,3-di-*tert*-butylcyclopropanone **5** as a model for the stereomutation rate of a typical cyclopropanone would be seriously misleading. The current data on **3** and **4**, and the accord with theoretical work, compel the conclusion that in many systems, cyclopropanone−oxyallyl interconversion will be fast at room temperature in solution. As is discussed elsewhere,[1c] this significantly affects, for example, the interpretations of experiments designed to elucidate the mechanisms of cyclopropanone cycloadditions and the Favorskii rearrangement.

Several structural differences may contribute to the ∼10 kcal/mol lowering of the barrier for stereomutation of **3** and **4** relative to that of **5**. Ground state spirocyclic strain in **3** and **4** and, perhaps, more effective hyperconjugative stabilization of the oxyallyls by the norbornane system than by *tert*-butyl groups probably contribute to a small extent, but a more obvious source is steric hindrance in the transition state for ring-opening of *trans*-2,3-di-*tert*-butylcyclopropanone (**5**). In a disrotatory mechanism, ring-opening of any of these cyclopropanones **5**, **3**, or **4** forces one alkyl group into a 1,3-*cis*-allylic interaction with a hydrogen atom in the ring-opened product oxyallyl (see Scheme 5). In **24** and **25**, the oxyallyls derived from **3** and **4**, the relevant alkyl groups are C_1 (secondary) and C_3 (primary), whereas in **23**, the oxyallyl from **5**, the alkyl group is tertiary. However, the steric effects in **24** and **25** cannot be compared to those of ordinary secondary and primary alkyl groups. Because the rigid norbornane ring prevents rotation about C_2-C_1 and C_2-C_3, the effective size of these groups is smaller than those of freely rotating analogs. In the 1,3-*cis*-allylic interactions in **24** and **25**, the ring structure always requires a ring hydrogen to be turned toward the oxyallyl hydrogen. As a rough guess of the effective size of these groups in this context, we suggest that it is comparable to that of methyl and should produce only a minor rate effect. In contrast, all rotational conformations of the oxyallyl **23** from *trans*-2,3-di-*tert*-butylcyclopropanone (**5**) have a methyl group turned toward the oxyallylic hydrogen in the crucial 1,3-*cis*-allylic interaction, and the *tert*-butyl group exerts its full steric effect. Consequently, we expect a substantial retardation of the stereomutation.

In attempting to estimate more quantitatively how large such an effect should be, we find little literature precedent. The *syn* to *anti* isomerization of 1-alkylallyl radicals (conversion of **26** to **27** via transition state **28**, Scheme 6) may represent the closest analogy available.

The size of the steric requirements of this reaction should be similar to those for the cyclopropanone ring-openings, with the difference that the effect is in the transition state in the cyclopropanone case and in the ground state in the allyl stereomutation. That is, an oxyallyl-like transition state for disrotatory cyclopropanone ring-opening (with one alkyl group turned inward) should sterically resemble the *syn*-alkylallyl ground state (**26**) in the radical isomerization in that both will possess 1,3-*cis*-allylic interactions. Likewise, both the ground state cyclopropanone and the twisted allyl transition state **28**

Scheme 6



lack such steric strain. Thus, because of ground state destabilization, *syn*-1-*tert*-butylallyl radical (**26**, R = *t*-Bu) should show fast conversion to the *anti* form **27**, relative to the analogue where R = Me. This expectation is in fact fulfilled. The conversion of **26** (R = *t*-Bu) to **27** occurs with a barrier of 10 kcal/mol,[37] but the interconversion of the nearly equienergetic radicals **26** and **27** (R = Me) has a barrier of 14.3 or 21 kcal/mol (two different measurements).[38,39] If the 4−11-kcal/mol difference here is a proper measure of the added strain of a *tert*-butyl/hydrogen relative to a methyl/hydrogen 1,3-interaction, then the observed increase of ∼10 kcal/mol for the barrier to the cyclopropanone stereoisomerizations of **5** relative to those of **3** and **4** may well be entirely the result of such an effect.

Solvent Effects on the Rates of Stereomutation 3 → 4. Greene's racemization data (351 K) for *trans*-2,3-di-*tert*-butylcyclopropanone (**5**) in five solvents correlates reasonably well with empirical measures of solvent polarity, such as the solvatochromic parameter E_T,[40,41] as shown in Figure 3. If the intuition is correct that the oxyallyl transition state is more polar than the cyclopropanone ground state, preferential solvation of the transition state would be expected and would result in the observed rate ordering. The rates span 1.8 kcal/mol of activation free energy, from the nonpolar isooctane to the polar acetonitrile.

Monte Carlo (MC) statistical mechanics fluid simulations by Lim et al.[2a] of the disrotatory ring-opening of cyclopropanone and 2,2-dimethylcyclopropanone in four solvents track the results for *trans*-1,2-di-*tert*-butylcyclopropanone (**5**) quite well (see Figure 3). For the unsubstituted cyclopropanone itself, for example, computations using either CHELPG or Mulliken charges show a 2 kcal/mol difference between the reaction barrier in propane and that in acetonitrile (Figure 5C shows the Mulliken results). The correlation with E_T is much like that for **5**.

As is evident from Figure 3, the data for the two spirocyclopropanones **3** and **4** are not correlated with the experimental data for **5**, with E_T, or with the values predicted computationally for the parent or for 2,2-dimethylcyclopropanone. The rate of equilibration for **3** and **4** is substantially slower in ether than in hexane, and it is also slower in acetone than in methylene chloride. The difference between ether, the slowest solvent, and methylene chloride, the fastest solvent, corresponds to $\Delta\Delta G^{\ddagger}$ of more than 3 kcal/mol at 239 K, much larger than would be predicted on the basis of Greene's results or the computations (Figure 3),which would call for a difference of <1 kcal/mol.

(37) Sustmann, R.; Brandes, D. *Chem. Ber.* **1976**, *109*, 354−8.
(38) Gorton, P. J.; Walsh, R. *Chem. Commun.* **1972**, 783.
(39) Crawford, R. J.; Hamelin, J.; Strehlke, B. *J. Am. Chem. Soc.* **1971**, *93*, 3810.
(40) Kosower, E. *Physical Organic Chemistry;* Wiley: New York, 1968; Chapter 2.6.
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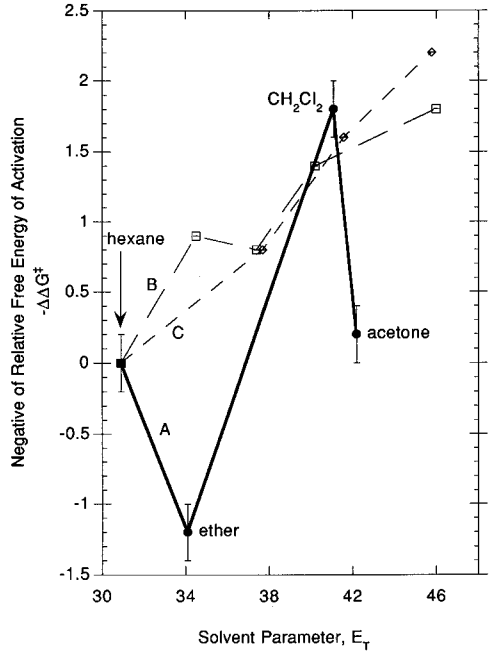

Figure 3. Solvent dependence of the rate of stereomutation. The solvent term E_T is the Dimroth−Reichardt parameter.[40,41] The ordinate shows the negative of the free energy of activation ($-\Delta\Delta G^{\ddagger}$) relative to that in hexane taken as zero. (A) Data points at 239 K for the stereomutation of **3** and **4** studied in the present work. (B) Data points at 351 K for the racemization of *trans*-di-*tert*-butylcyclopropanone measured by Greene et al.[9] (C) Values at 298 K calculated for the ring-opening of cyclopropanone by Lim et al.[2a]

In examining possible reasons for this unanticipated result, we note first that certain aspects of the solvent effects in the present work are *not* anomalous. If one simply compares the rate of interconversion of **3** and **4** in hexane with that in methylene chloride, the difference at 239 K is 1.8 kcal/mol, a value in reasonable accord with that predicted by the (rough) slope of the solvent polarity−rate relationship observed in Figure 3. Likewise, the difference between ether and acetone of 1.4 kcal/mol is easily understandable in the same terms.

Apparently, relative to hexane and methylene chloride, the barriers in ether and acetone are both about 1.5 kcal/mol too high for a good overall correlation with E_T. The common feature of the "slow" solvents, ether and acetone, is the presence of an oxygen atom. Yet no indication of such an oxygen effect is seen in the experimental data for *trans*-1,2-di-*tert*-butylcyclopropanone (**5**)[9,10] or in the MC simulations on cyclopropanone and the 2,2-dimethyl derivative,[2a] even though both studies include tetrahydrofuran as one of the solvents.

We suggest that the structural feature in **3** and **4** that accounts for the discrepancies is the presence of a sterically accessible, nucleophilically vulnerable carbonyl carbon. A carbonyl group in a three-membered ring generates hybridization strain, which must be responsible for a large part of the 18 kcal/mol increment of empirical strain energy of cyclopropanone over that of cyclopropane.[42] The strain increment can be released by nucleophilic addition to the carbonyl carbon.[12] In consequence, as is indicated, for example, by a recent *ab initio* study,[43] the gas-phase free energy of hydration of cyclopropanone is much lower than that of acetone, or of any other investigated ketone.

Even if a nucleophile does not bond covalently to a carbonyl compound to give a tetrahedral adduct, attractive interactions still exist between nitrogen and oxygen lone pairs and carbonyl carbons, even for unstrained ketones. The extensive crystal structure studies of Bürgi, Dunitz, and co-workers show pyramidalization of the ligands attached to the carbonyl carbon in the direction away from the attacking nucleophile.[44−49] In a cyclopropanone, the pyramidalization should have a much smaller cost due to the compensating diminution of hybridization strain. One then expects that, just as cyclopropanones accept explicit covalent carbonyl addition more readily than unstrained ketones, they also should experience stronger Bürgi−Dunitz attractions at a given Nu···C═O distance. We suggest therefore that ether and acetone would selectively stabilize the cyclopropanone ground state and cause a slowing of the interconversion of **3** and **4**. This extra stabilization should be diminished after ring-opening of a cyclopropanone to an oxyallyl, which relieves the hybridization strain and with it the carbonyl's high incentive to pyramidalize.

How can this difference contribute to the overall solvent effect but nevertheless be invisible to the Monte Carlo statistical mechanics fluid simulations of Lim et al?[2a] The cyclopropanone−oxyallyl system used in these computations is represented as a collection of charges and Lennard-Jones terms based on a gas phase *ab initio* geometry and wave function.[50] The method is not "self-consistent" in that it involves no adjustment of any of these terms in response to the presence of solvent. If a solvent−solute interaction exists which perturbs the energy of either species in a way that depends on a geometric change, it will not be treated by the calculation in any explicit sense, and will appear implicitly only insofar as it is averaged into the parametrization of the solvent model.

In spite of this limitation, MC statistical mechanics calculations of this type are often highly successful at treating specific solvent−solute interactions, because many such interactions are quite well described by Coulombic and dispersion forces or are well accounted for in the solvent parametrization. Further, in cases where the specific solvation of a reactant and product or transition state are similar, errors due to the lack of self-consistency tend to cancel. As noted, however, we believe that in the current work, the specific solvation of the ground state cyclopropanone is more (perhaps much more) important than that of the transition state or oxyallyl.

In contrast, the racemization of di-*tert*-butylcyclopropanone **5** does not seem to be anomalously slow in nucleophilic solvents (Figure 3). One of the reasons for this difference in behavior is probably the steric shielding of the carbonyl carbon by the flanking *tert*-butyl groups. In this context, it is significant that addition of methanol to **5**[8] is much slower than we observe for addition to **3** and **4**. The same hindrance should serve to shield **5** from van der Waals contact with solvent lone-pairs, thus attenuating any ground state stabilization.

It should also be noted that all of the more polar solvents investigated for **5**, namely THF, pyridine, and acetonitrile, possess nitrogen or oxygen lone pairs, whereas the less polar solvents, isooctane and benzene, do not. In the case of the polar solvents, the rate-enhancing effect of polarity thus may be partially canceled by nucleophilic stabilization of the ground

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(43) Morgan, K. M. Ph.D. Dissertation (with K. B. Wiberg), Yale University, New Haven, CT, 1994.
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(45) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *Acta Crystallogr.* **1974**, *B30*, 1517.
(46) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.
(47) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.
(48) Kaftory, M.; Dunitz, J. D. *Acta Crystallogr.* **1975**, *B31*, 2912, 2914.
(49) Schweizer, W. B.; Procter, G.; Kaftory, M.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2783.
(50) Jorgensen, W. L. *Acc. Chem. Res.* **1989**, *22*, 184.

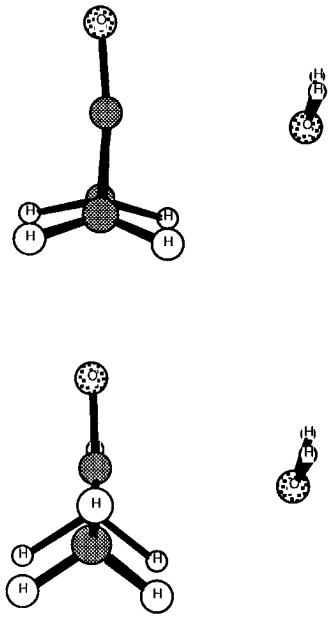
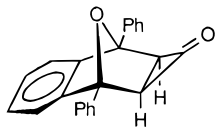


Figure 4. Cyclopropanone−water (top) and acetone−water (bottom) Bürgi−Dunitz complexes as derived by 6-31+G* ab initio calculations. The water oxygen to carbonyl carbon distance was fixed at 2.6 Å. The angle of approach (water oxygen−carbonyl carbon−carbonyl oxygen angle) was fixed at 98°.

state. Although weak relative to that in an unhindered cyclopropanone, this interaction could produce an apparent net low sensitivity of the rate to solvent polarity.

Experimental evidence of an *intramolecular* ether oxygen−cyclopropanone carbonyl attractive interaction is available from the X-ray crystal structure analysis[1b] of adduct **29** of cyclopropenone and 1,3-diphenylisobenzofuran, which shows a significant pyramidalization of the ligands on the cyclopropanone carbonyl carbon.



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Ab initio calculations[1c] confirm the anticipation that the interaction of a nucleophile with a cyclopropanone is stronger (at a given distance) than is the interaction with a simple ketone. Figure 4 shows 6−31+G* structures computed for comparable cyclopropanone−water and acetone−water complexes at O···C=O angles of 98° (a reasonable Bürgi−Dunitz angle) and distances of 2.6 Å (near van der Waals contact). The pyramidalization at this geometry, as measured by the distance between the C atom and the plane of its three covalently bonded neighbors, is roughly half again as great for cyclopropanone as for acetone. The energy of the complex is also lower, relative to the free ketone and a water molecule, by about 1 kcal/mol. Variation of the distance of the interaction reveals that as the extents of pyramidalization increase, so does the associated energy gap between the two complexes. As anticipated, cyclopropanone allows a closer approach than does acetone.

Ostensibly, a multiparametric treatment, considering both the relative ground state stabilization by nucleophilic solvation and the relative transition state/oxyallyl stabilization by dielectric solvation, should give a more satisfactory account of the solvent effects on the interconversion of **3** and **4**. Data for only four solvents, however, seem to be insufficient to justify a two parameter correlation, and we do not venture here to attempt any exact quantification of the two effects on such a basis.

A brief analysis, however, shows the utility of the the two-effect model. Table 2 includes E_T, π^*, and β parameters for hexane, ether, methylene chloride, and acetone as measures of the dielectric and nucleophilic qualities of each solvent, respectively. The latter two are part of the Kamlet−Abboud−Taft system,[51a] one of the most thorough attempts at a multiparametric treatment[51b] of solvent effects using solvatochromic methods. The π^* and E_T (used for the correlations in Figure 3) parameters are somewhat comparable. Indeed the trends are very similar for these four solvents, so that these two parameters π^* and E_T may be used interchangeably here.

The similarity of the β values for ether and acetone indicates comparable propensities for nucleophilic solvation (more precisely, β is a measure of hydrogen bonding basicity), and predicts that the oxygen lone pairs in each will produce similar ground state stabilization. Both methylene chloride and hexane, on the other hand, have β values of zero. This all-or-nothing nucleophilic effect nicely explains the zigzag appearance of the data plot for the **3**−**4** stereomutation shown in Figure 3. An alternating difference of about 0.5 in β values produces a zigzagging approximately 1.5 kcal/mol in amplitude here.

The dielectric solvation corresponds to ca. 1.5 kcal/mol per roughly ten E_T, or 0.5−0.75 π^* units, so that the two effects seem to be of comparable magnitude within this limited group of solvents. In sum, an understanding of the solvent effects on the interconversion of **3** and **4** cannot be achieved through a model based on simple stabilization of a somewhat dipolar oxyallyl-like transition state; the novel response of the cyclopropanone ground state to solvent is important as well.

Conclusions. The solvent and temperature dependencies of the interconversion of **3** and **4** are intriguing, and certain aspects of the results remain mysterious. For reasons already given, however, we are reasonably confident that none of the unexplained phenomena, *e.g.*, the low Arrhenius *A* values, are experimental artifacts. The major finding of our work is the unusual rate retardation by oxygenated solvents, which we attribute to ground state stabilization produced by their interaction with the nucleophilically vulnerable cyclopropanone carbonyl carbon. This type of stabilization generally has not been been incorporated explicitly into Monte Carlo calculations of solvent effects on reaction rates. It emerges experimentally because the cyclopropanone ring is highly strained and because the carbonyl carbons of **3** and **4** are sufficiently unhindered to permit close approach of the solvent.

Experimental Section

Syntheses. The syntheses of cyclopropanones **3a** and **4a** (Scheme 1) and their deuterated derivatives **3b** and **4b**, as well as the identification of the hemiketals and the Favorskii esters of Scheme 2, already have been described in the Supporting Information to a preliminary communication.[1a]

Instrumentation and General Equipment. Standard experimental procedures, which are described in the Supporting Information, were employed.

Epimerization Studies. Preparation of Solutions of 3 and 4 in Solvents Other Than Ether. Solutions of **3** and **4** in hexane, acetone, and methylene chloride were obtained beginning from a solution in ether, using an evaporation/vacuum transfer technique. In early studies, the new solvent was introduced by cannulation rather than vacuum transfer, but we came to favor the latter technique, described in detail below, because it appeared to yield drier solutions.

(51) (a) Kamlet, M. J.; Abboud, J. L. M.; Taft, R. W. *Prog. Phys. Org. Chem.* **1981**, *13*, 485. For other such approaches, see: (b) Gajewski, J. J. *J. Org. Chem.* **1992**, *57*, 5500 and references cited therein.

The flask containing the cyclopropanones in ether, immersed in dry ice/acetone, was placed on one port of a vacuum manifold (connected to both a rough pump and a diffusion pump) under nitrogen atmosphere, with the stopcock closed. On another port was placed a flask of hexane with sodium hydride, acetone with Linde type 4Å molecular sieves, or methylene chloride with calcium hydride as an appropriate drying agent. Both the hexane and methylene chloride were distilled from calcium hydride previously.

The stopcock on the solvent port was closed, the nitrogen supply was closed, and the manifold was opened to the rough pump. When the pressure reached $<10^{-3}$ Torr, the stopcock on the cyclopropanone flask was opened. When the pressure again reached $<10^{-3}$ Torr, the diffusion pump was opened. At 10^{-5} to 10^{-6} Torr, the dry ice/acetone bath was removed from the cyclopropanone flask and replaced with either an acetonitrile/liquid N_2 slush (nominal −42 °C) or a *m*-xylene/liquid N_2 slush (nominal −47 °C). We measured the *m*-xylene bath temperature at −56 to −60 °C.

The ether then began to evaporate from the cyclopropanone solution. Because it was essential that the solution be stirred efficiently in order to remove all of the ether, the *m*-xylene or acetonitrile bath was best kept in a very shallow Dewar flask. In *m*-xylene/liquid N_2, approximately 1.5−2 h were required to remove all of the ether. Somewhat less time was required with acetonitrile/N_2. Results varied, but *m*-xylene usually afforded better preservation of the original ratio of **3** to **4**, so that if time was not important, it was usually preferable.

When the ether had all evaporated, the flask stopcock was closed, and the bottom of the flask was immersed in liquid nitrogen. The diffusion pump was closed and the rough pump opened. Now, the flask containing the solvent to be transferred was cooled with a dry ice/acetone bath, and the stopcock on its manifold port was opened. When the pressure dropped to $<10^{-3}$ Torr, the manifold was closed off from the pump, the dry ice/acetone bath was removed, and the stopcock on the cyclopropanone flask was opened. As the solvent warmed, transfer to the cyclopropanone flask at liquid nitrogen temperatures occurred. When approximately 10 mL had come over, the stopcock on the cyclopropanone flask was closed again, the vacuum manifold was back-flushed with nitrogen, and the flask was removed, stoppered, and taken to the hood at liquid nitrogen temperature for thawing and further manipulation.

Analytical Procedures. **Determination of the Isotopic Purity of Diazomethane-$^2H_2$ and 3b and 4b.** The determination of isotopic incorporation levels in deuterated diazomethane and in the deuterated cyclopropanones involved three steps. First, the species of interest were derivatized to produce compounds more amenable to direct analysis. Then, mass spectra were obtained for these compounds and for the unlabeled versions. Finally, the unlabeled spectrum was used in a computer simulation of the labeled spectrum, yielding best fit percent levels of the components corresponding to undeuterated, singly deuterated, and doubly deuterated diazomethane or cyclopropanone. These procedures are described in detail in the Supporting Information.

^{2}H NMR Kinetic Analyses of the Interconversion of 3b and 4b. Sample tubes were prepared by fusing several inches of 6-mm Pyrex tubing onto the end of a 5-mm NMR tube. These were dried by brief storage in an oven, followed by nitrogen flushing upon removal and immersion in dry ice/acetone. Approximately 0.5 mL of a solution of ca. 100 mg of **3b** and **4b** in diethyl ether maintained at −78 °C containing 10−15 μL of benzene-d_6 as an internal standard was then cannulated (18 gauge, 24 in., double tapered) rapidly under N_2 pressure into the NMR tube. The tube was placed on a vacuum line under N_2 at −78 °C, evacuated for several minutes, and sealed.

The temperature of the probe of the 500 MHz spectrometer was lowered to the desired value using nitrogen gas cooled by passage through copper coils immersed in liquid nitrogen. Once the spectrometer had been allowed to equilibrate and had been shimmed, a methanol sample was used to measure the probe temperature.[52] Five separately phased and analyzed scans were acquired, and the difference in ppm between the two resonances was noted. This procedure was repeated after the run was finished as well, to ensure that the probe temperature had not changed. The determinations from the ten different scans were averaged to yield the run temperature.

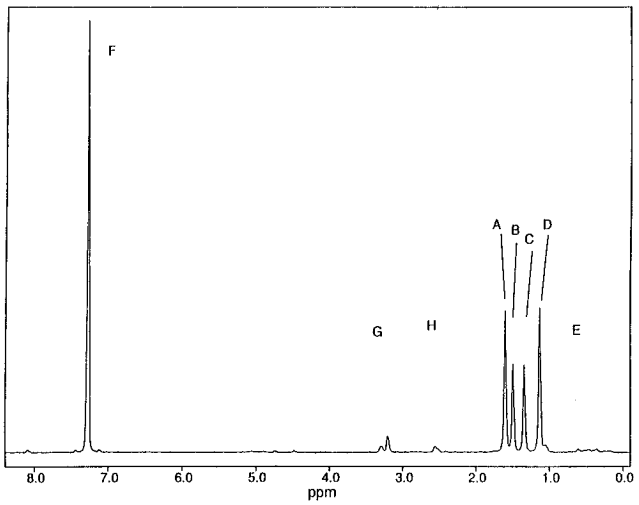


Figure 5. ^{2}H NMR spectrum of **3b** and **4b** in diethyl ether prior to equilibration. Peak assignments are given in the text.

To conduct the actual run, a sample of **3b** and **4b** in diethyl ether, kept in dry ice/acetone or dry ice/methanol, was removed from its bath, quickly wiped with a tissue, and inserted into the spinner. The end of the tube was then reimmersed in the cooling bath to ensure maintenance of very low temperature. After about 10 s, the tube was removed again and wiped again with a tissue, then the spinner height was quickly adjusted. Again the sample was reimmersed in the cooling bath for a short time. Finally, it was removed, wiped once more with a tissue, carried to the magnet, and lowered into the cooled probe and spun.

The sample was allowed to equilibrate to the probe temperature for approximately 2−3 min. During this time, a brief shim adjustment was performed using the proton FID. Then, the run itself was conducted using a simple automation program, available with the Bruker AM500 instrument and listed in the Supporting Information to this paper.

Because the nucleus being monitored was deuterium, which is much less sensitive than protium, a fairly large number of scans (256) was necessary to acquire a spectrum with reasonable signal-to-noise ratio. These scans could be acquired rather rapidly (approximately every 2 s) due to the fast quadrupolar relaxation of deuterium, but about 8 min of acquisition were required per point. Since there were 10 min between points, this meant that most of the time of the run was spent in acquisition. Under these conditions, one assigns the time between points under the assumption that the course of the reaction (fractional change per unit time) was linear over the 8 min of acquisition. In the present case, any errors from this approximation will be negligible, as each half-life contains at least five points in all runs. We were, however, limited to accurate measurements at temperatures where the reaction half-life was nearly an hour or more.

Another consequence of the use of deuterium as the observed nucleus was that runs had to be performed without the aid of a deuterium lock. All care was taken to avoid moving large objects in the vicinity of the magnet during the run.

After the run was over, the sample was removed and immersed in a 0−5 °C bath for about 30 min to allow for the establishment of equilibrium. Then, the sample was returned to the cooled magnet, and a final equilibrium point was acquired.

Each run was stored as a serial file and the FIDs were processed using the Felix 2.05 program on an SGI Personal IRIS. The processing included zero-filling, Fourier transform, phasing, and baseline correction, and occurred with the same parameters for each FID in a given run. After processing, the spectra have the appearance of Figure 5.

The two outer peaks (A and D) corresponded to **3b** and the two inner peaks (B and C) to **4b**. Peak F was the benzene-d_6 standard.

(52) Ammann, C.; Meier, P. F.; Merbach, A. E. *J. Magn. Reson.* **1982**, *46*, 319.

(53) Benson, S. W.; O'Neal, H. E. *Kinetic Data on Gas Phase Unimolecular Reactions*, NSRDS-NBS 21, National Bureau of Standards: Washington, DC, 1970; p 8.

The small shoulder on the upfield side of peak D consisted of natural abundance deuterium signals from the ether solvent. The smaller of the peaks labeled G was also due to ether solvent. The larger has not been identified. H was very likely D_2O or DOH (a spectrum of D_2O in ether had a single peak in this region). The small peaks labeled E were probably due to cyclopropanone hydrate, which can occur in these runs in up to about 10% of the combined area of cyclopropanone resonances.

The areas of each of the four cyclopropanone peaks were determined by fitting the spectrum to a Lorentzian model using a simulated annealing minimization routine, as was the area of the benzene-d_6 internal standard. Rather than use all four cyclopropyl peaks to determine the rate constant, we have used only C and D, the two most upfield peaks, which were the best resolved of the four. The concentration of **4b** for a particular point was determined as the area of peak C over the combined areas of C and D.

$$[\mathbf{4b}]_t = \text{area C}/(\text{area C} + \text{area D})$$

In other words, it is expressed as a fraction of the total cyclopropanone concentration. The infinite time value $[4b]_{eq}$ is then determined from the spectrum of the cyclopropanones equilibrated at 0−5 °C, adjusted to the run temperature. The adjustment is made using the equation

$$\ln(K_{2eq}/K_{1eq}) = T_1/T_2$$

where K_{2eq} = area D/area C in the spectrum of the equilibrated sample. Then, $[\mathbf{4b}]_{eq} = 1/(1 + K_{1eq})$. The correction assumes the free energy difference between the cyclopropanones to be temperature independent. This assumption is justified by a rough van't Hoff analysis, both by GC and NMR, of the temperature dependence of the equilibrium constant.

Finally, the data are plotted according to the relation

$$\ln\{[\mathbf{4b}]_{eq}/([\mathbf{4b}]_{eq} - [\mathbf{4b}]_t)\} = k_{obs}t + C$$

yielding the observed rate constant $k_{obs} = k_f + k_r$, the sum of the forward and reverse rate constants. Here $[\mathbf{4b}]_{eq} = 1/(1 + K_{eq})$.

This analysis depends on the constancy of the total cyclopropanone concentration over the course of the run. As determined by comparison of the cyclopropanone peak integrals to the internal standard integral, the material balance in all runs is 95% or better, justifying this approximation.

Our decision to use only peaks C and D in the kinetic analysis is based on a perceived higher accuracy for these peaks, which one might expect due to the higher resolution. We have compared analyses based on all possible two peak combinations (a total of four analyses), and that from C and D most often gives the highest correlation coefficient (five out of eight runs, R values ranging from 0.996 to 0.999) in the kinetic plot. The overall Arrhenius plot using this method also has the highest correlation coefficient of any of the four ($R = 0.991$). Figure 6 contains a compilation of the four two-peak analyses over the eight runs. It is seen that the rate constants and Arrhenius parameters do not vary widely (they are within the assessed experimental error), so that in any case the particular choice of which peaks to use in the analysis makes little difference. The eight runs have an average starting ratio of **3b** to **4b** of 1.59, ranging from 1.69 to 1.43. The average K_{eq} is 0.845 (not temperature corrected, 273−277 K), and the values range from 0.824 to 0.858. If peaks A−D are all included, the mean K_{eq} is 0.824, perhaps a more accurate absolute number.

Indirect Hemiketal-Based Gas Chromatographic Kinetic Analyses. Details are given in the Supporting Information.

Sources of Error. We have assessed the error in the rate constants and in the Arrhenius parameters in the NMR runs using the method discussed by Benson and O'Neal.[53] For details, see Supporting Information. Two major sources of error have been considered in assessing the uncertainty of each measured rate constant. First, the error in the measured temperature for the run is considered to be ±0.6 °C. Second, each of the peaks (C and D, Figure 5) used is assigned an integration error of 1%. Errors in peak fitting due to deviations from Lorentzian line shape should generally cancel. Integration error in the equilibrium constant is considered to contribute 5% uncertainty to each rate constant. Propagation of all of these errors gives an overall rate constant uncertainty of 11−12% in all of the runs. When figuring the error in the Arrhenius parameters, an additional 3% is assigned to the rate constants in order to account for any inaccuracies in applying temperature adjustments to the equilibrium constants. The final Arrhenius parameters computed are $E_a = 15.3 \pm 1.4$ kcal/mol and log $A = 9.6 \pm 1.4$ s^{-1}.

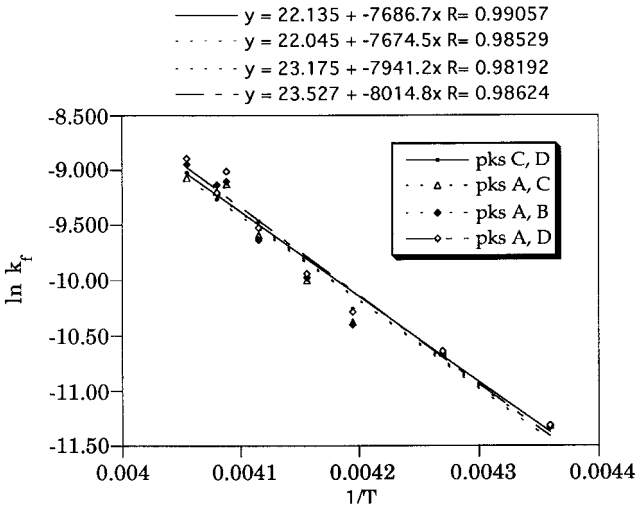


Figure 6. Arrhenius plots for four different two-peak analyses of the interconversion of **3b** and **4b**.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for grants in support of this research. M.H.J.C. held a National Science Foundation Graduate Fellowship.

Appendix. Absolute Rate Theory: Determination of Symmetry-Corrected Activation Free Energies from Observed Rate Constants

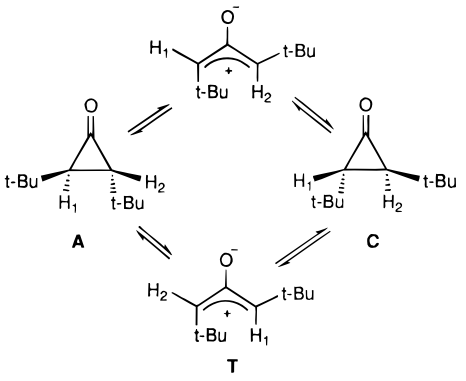
Absolute rate theory requires the consideration of reaction path degeneracies in the determination of barrier heights ($\Delta G^{\ddagger}$) from forward and reverse rate constants. Often, $\Delta G^{\ddagger}$ incorrectly calculated without such symmetry considerations differs only slightly from the properly calculated value, but it is advisable to make the correction for the sake of a clear definition. Pollak and Pechukas[54] have outlined a method based on symmetry numbers, where the symmetry number corresponding to a given structure is determined in the following manner.

First, one supposes that all atoms of a given type are distinguishable by labeling. The number of different structures generated in this manner is equal to $\prod_i N_i!$ where N_i equals the number of atoms of type i in the structure. The symmetry number may be obtained by dividing this number by the number of physically distinct structures generated by the labeling. The term "physically distinct" denotes structures which are not superimposable by a simple translation and/or rotation.

To analyze the rate of racemization of 2,3-*trans*-di-*tert*-butylcyclopropanone, we first assume that a planar oxyallyl species mediates the process, that ring-opening is exclusively disrotatory, and that the oxyallyl is the transition state (see Scheme 7). The latter assumption allows for the greatest ease of analysis and yields a maximum value for the relative free energy of the oxyallyl.

(54) Pollak, E.; Pechukas, P. *J. Am. Chem. Soc.* **1978**, *100*, 2984.

Scheme 7. Physically Distinct Species Generated by Labeling of the Two α-Carbonyl Hydrogens in the Racemization of *trans*-2,3-Di-*tert*-butylcyclopropanone



In all possible species two configurations are generated by permutation of the two α-carbonyl hydrogens. These yield one physically distinct structure for each enantiomeric cyclopropanone, and two for the oxyallyl species. The corresponding symmetry numbers are 2 for each cyclopropanone and 1 for the oxyallyl. The Pollak−Pechukas formula states that

$$k_f = \frac{kT}{h}\frac{Q_T^o/\sigma_T}{Q_A^o/\sigma_A}$$

The Q^o are partition functions evaluated without symmetry numbers, and the σ are symmetry numbers. One finds that the overall forward rate is actually twice the forward rate through one of the physically distinct labeled transition states (k_{abs}):

$$k_f = \frac{2kT}{h}\frac{Q_T^o}{Q_A^o} = 2k_{abs}$$

The rate k_{abs} translates, through the Eyring equation, into the absolute free energy of activation for the reaction, where this quantity is defined as the free energy difference between one physically distinct labeled ground state and one of the physically distinct transition states. For a reaction of this type, the observed macroscopic rate constant for the racemization is equal to the sum of the forward and reverse rate constants.

$$k_{rac} = \frac{1}{t}\ln\frac{\alpha_o}{\alpha} = k_f + k_r$$

In this case K_{eq} is 1 and thus $k_f = k_r$. Therefore

$$k_{rac} = 2k_f = 4k_{abs}$$

For example, Greene reports the racemization to occur with $k_{rac} = 8 \times 10^{-5}$ s^{-1} in tetrahydrofuran at 353 K. Since

$$k_{abs} = \frac{kT}{h}e^{-\Delta G^{\ddagger}_{abs}/RT}$$

$$\Delta G^{\ddagger}_{abs} = 28.5 \text{ kcal/mol}$$

This value is to be compared with the uncorrected value $\Delta G^{\ddagger} = 27.5$ kcal/mol calculated from k_{rac}.

For the case of cyclopropanones **3a** and **4a**, a symmetry number analysis is not necessary since all species involved have a symmetry number of 1. However, the existence of two possible planar oxyallyls complicates the kinetic analysis. Scheme 4 shows the possible reaction pathways for the stereomutation. Again we assume the exclusive mediation of the reaction by a planar oxyallyl transition state and the exclusive operation of a disrotatory ring-opening mechanism.

Again, the observed rate constant for stereomutation must first be translated into the forward and reverse rate constants for reaction. This is accomplished in a similar manner as for the Greene case, except that since $K_{eq} \neq 1$, $k_{obs} \neq 2k_f$.

$$k_{obs} = \frac{1}{t}\ln\frac{[\mathbf{4a}]_{eq}}{[\mathbf{4a}]_{eq} - [\mathbf{4a}]} = k_f + k_r = \left(1 + \frac{1}{K_{eq}}\right)k_f$$

At this point, we recognize that k_f is actually the sum of the two forward rate constants corresponding to the two possible directions of ring-opening (see Scheme 4).

$$k_f = k_{3-24} + k_{3-25}$$

There is no way, from the data at hand, to determine the individual values of the two rate constants. However, we may say that the minimum value of the faster forward rate constant is equal to $k_f/2$. This value may be converted into the maximum free energy of activation for the favored forward reaction pathway.

If one were to model the oxyallyls as intermediates rather than as transition states, it would become impossible to determine their free energies even in the case where one knew the individual forward rate constants k_{3-24} and k_{3-25}. However, if one could obtain such a value (for the more stable oxyallyl) from the kinetic analysis, it would never be higher than the free energy obtained from the analysis above. Therefore, the value of $\Delta G^{\ddagger}$ derived from $k_f/2$ stands as the maximum free energy of the more stable of the two oxyallyls, relative to the less stable cyclopropanone.

Supporting Information Available: A listing of the kinetic measurements of the stereomutation of **3a** and **4a** determined by the indirect hemiketal GC method and a description of the method; evaluation of experimental errors in the kinetic measurements; details of kinetics by NMR line-broadening experiments (47 pages). See any current masthead page for ordering information.

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