Mechanism of the 1,3-Sigmatropic Shift of 2-Vinylcyclobutanol Alkoxides

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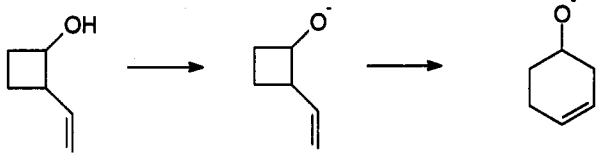
Abstract: The rate of rearrangement of 2-vinylcyclobutanol was studied in dimethyl sulfoxide and tetrahydrofuran solvents. Rearrangement to 3-cyclohexenol in 1% aqueous DMSO is catalyzed by lithium hydroxide. When lithium bromide is added to this medium, the rate is diminished by a factor of 17, due to the effect of added lithium cation on the ion-pairing equilibrium. Disappearance of the potassium salt (*E* isomer) in THF at −22 °C shows first-order behavior over four half-lives, but the first-order rate constant varies inversely with starting alkoxide concentration, suggesting that an ion pair dissociation equilibrium precedes rearrangement. The rearrangement of the potassium salt in 10:1 THF/HMPA is accelerated 11-fold over the rate in pure THF, due to specific solvation of the cation by HMPA. At 2 °C in THF the sodium salt of (*Z*)-2-vinylcyclobutanol epimerizes to the *E* isomer at a rate 36-fold faster than the *E* alkoxide rearranges to the product. The potassium (*E*)-2-(2-propenyl)cyclobutoxide salt rearranges 17 times slower than potassium 2-vinylcyclobutoxide, in agreement with a previous comparison of rates of fragmentations of homoallylic alkoxides. Secondary deuterium kinetic isotope effect (kie) measurements were made by rearranging mixtures of deuterated and nondeuterated potassium vinylcyclobutoxides at 0 °C in diethyl ether and analyzing the extent of reaction by GC and the isotopic content of the mixture by proton NMR. The large normal kie (k^H/k^{D2} = 1.34 ± 0.04) at the terminal vinyl positions and the small normal kie at the carbinol position (k^H/k^D = 1.12 ± 0.06) are explainable if an allyl anion/aldehyde intermediate species is formed. *Ab initio* calculations suggest that such an intermediate can exist in several possible conformations and should be nearly as stable in the gas phase as the starting vinylcyclobutoxide.

The alkoxide from 2-vinylcyclobutanol, **1**, rearranges to 3-cyclohexen-1-ol alkoxide in a 1,3-sigmatropic shift.[1]



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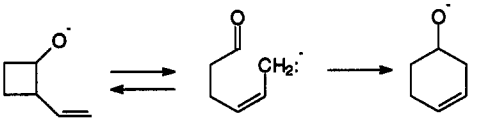
This reaction is related to other anionic "charge-accelerated" rearrangements such as the oxy-Cope rearrangement of 1,5-hexadien-3-ol alkoxides, **2**,[2,3] and the Ireland Claisen rearrangement of allyl ester enolates, **3**.[4]

2

3

The 1,3-rearrangements of 2-vinylcyclobutanols and 2-vinylcyclopropanol alkoxides are synthetic routes to six- and five-membered rings, respectively.[5,6] In this work the mechanism of the rearrangement of vinylcyclobutanol alkoxide was studied.

In a study of the anionic oxy-Cope rearrangement[3] secondary deuterium kinetic isotope effects were used as a probe of transition state structure.[7] It was found, perhaps not surprisingly, that rearrangement of 3-methyl-1,5-hexadien-3-ol alkoxide has a greater amount of doubly allylic, C3–C4, bond cleavage and a smaller extent of bond formation between the terminal carbons, C1 and C6, at the transition state than that for the ordinary Cope rearrangement.[8] It was anticipated that the 1,3-shift of 2-vinylcyclobutanol alkoxide might proceed through a nonconcerted mechanism involving an intermediate allyl anion, **4**.[6,9]



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The 1,2-bond cleavage of 2-vinylcyclobutanol alkoxide is more favorable than that of other homoallylic alkoxides[1a,9,10] due to

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(2) (a) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609–626 and references therein. (b) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766. (c) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 785–826. For oxy-Cope rearrangements of 1,2-divinylcyclobutanols see: (d) Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268–2275. (e) Miller, S. A.; Gadwood, R. C. *J. Org. Chem.* **1988**, *53*, 2214.

(3) Gajewski, J. J.; Gee, K. R. *J. Am. Chem. Soc.* **1991**, *113*, 967–971.

(4) (a) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650–657. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452.

(5) (a) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *J. Am. Chem. Soc.* **1981**, *103*, 2443–2446. (b) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943–3950. (c) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1340–1341. (d) Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579–4581. (e) Cohen, T.; Bhupathy, M.; Matz, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 520–525.

(6) (a) Bhupathy, M.; Cohen, T. *J. Am. Chem. Soc.* **1983**, *105*, 6978–6979. (b) Cohen, T.; Yu, L.-C.; Daniewski, W.M. *J. Org. Chem.* **1985**, *50*, 4596–4600. (c) Snider, B. B.; Niwa, M. *Tetrahedron Lett.* **1988**, *29*, 3175–3178.

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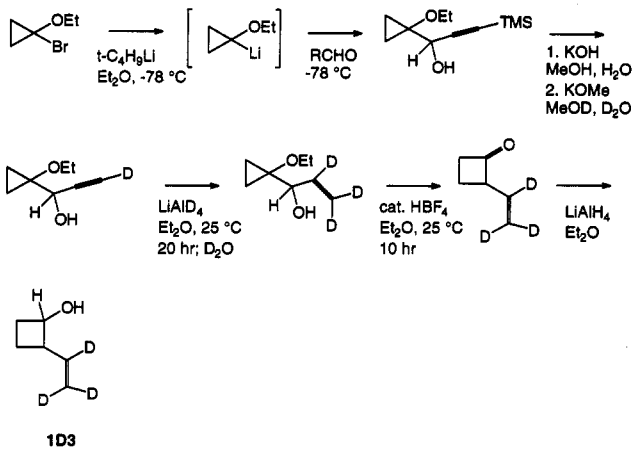
Scheme 1. Synthesis of 2-Vinylcyclobutanol-d_3, **1d3**



the release of ring strain.[11] This, therefore, is why this rearrangement takes place more readily than other oxyanionic 1,3-shifts.[1a]

The solvents used for study of the 1,3-shift are dimethyl sulfoxide, tetrahydrofuran, and diethyl ether. To study rates in DMSO, the alkoxide was formed using aqueous lithium hydroxide as a basic catalyst. In THF and ether the alcohol was completely converted to the potassium or sodium salt using the appropriate metal hydride. DMSO is a stronger Lewis base with a higher dielectric constant than the ether solvents, factors which favor greater dissociation of the alkali alkoxide ion pair and consequently a faster rearrangement in DMSO than in the ether solvents.[12]

Results

Syntheses. Synthesis of 2-vinylcyclobutanol, **1**, was accomplished by Gadwood's method,[13] starting from the commercially available [(1-ethoxycyclopropyl)oxy]trimethylsilane. (1-Ethoxycyclopropyl)lithium was generated by metal-halogen exchange of 1-bromo-1-ethoxycyclopropane with *tert*-butyllithium in ether solution.[14] The organolithium was then condensed with acrolein, and the resulting cyclopropylcarbinol was rearranged to 2-vinylcyclobutanone by treatment with a catalytic amount of fluoroboric acid in ether (see Scheme 1 for related transformations).[15] The 2-vinylcyclobutanone was reduced with lithium aluminum hydride (LAH) in ether to give a mixture of (*Z*)- and (*E*)-2-vinylcyclobutanols, with the ratio (*E*)-**1** to (*Z*)-**1** being 82:18, as determined by capillary GC analysis of the trimethylsilyl derivatives. The only important contaminants were solvent (diethyl ether, 5 mol %) and a *tert*-butyl-containing impurity, which was the 1,2-adduct of *tert*-butyllithium with acrolein (5–10 mol %). Cohen obtained an 82:18 ratio of *E* and *Z* isomers in the LAH reduction of 2-(4-(2-propenyl)cyclohexen-1-yl)-cyclobutanone.[5e,16] Only with the sterically bulky reducing agent K-Selectride could Cohen obtain exclusively the *Z* isomer.[5e] The vinylcyclobutanol isomers were distinguished by their proton NMR spectra.[17] The allylic and terminal vinylic proton multiplets for the *E* isomer appear at δ 2.7 and 5.0 ppm, while for the *Z* isomer the same multiplets appear downfield at δ 3.2 and 5.2 ppm. A sample of pure (*E*)-**1** was isolated by preparative GLC, but the *Z* isomer rearranged in the injection port of the chromatograph at 190 °C and could not be isolated. The thermal rearrangement product from (*Z*)-**1** was identified by carbon-13 NMR, proton NMR, and low-resolution mass spectrometry as *cis*-4-hexenal, which presumably is formed by a retro-ene ring-opening reaction.[18]

2-(2-Propenyl)cyclobutanol, **5**, was prepared in a manner similar to that for preparation of 2-vinylcyclobutanol. The 1-ethoxycyclopropylcarbinol prepared from methacrolein and (1-ethoxycyclopropyl)lithium was rearranged to 2-(2-propenyl)-cyclobutanone with a catalytic amount (but 5 times more than with the parent compound) of fluoroboric acid in ether, and the ketone was reduced with LAH to a mixture of (*Z*)- and (*E*)-2-(2-propenyl)cyclobutanols. The pure (*E*)-propenylcyclobutanol isomer was obtained by preparative GC. Once again the *Z* isomer rearranged completely in the GLC injector port, giving 5-methyl-4-hexenal.

The two compounds *trans*-2-(1′,2′,2′-trideuterioethenyl)cyclobutanol, (*E*)-**1d3**, and 1-deuterio-*trans*-2-vinylcyclobutanol, (*E*)-**1d1**, were synthesized for the purpose of observing the secondary kinetic isotope effects for bond breaking and bond making, respectively.[7,8] The latter compound was made by reducing 2-vinylcyclobutanone with $LiAlD_4$. The strategy for synthesis of (*E*)-**1d3** (Scheme 1) was the same as for the synthesis of **1**. (1-Ethoxycyclopropyl)lithium was condensed with 3-(trimethylsilyl)propynal. The trimethylsilyl group was removed by treatment with methanolic sodium methoxide in methanol-*O*-*d* and deuterium oxide (1:2 v/v). The propargyl alcohol was then reduced to the allylic alcohol with $LiAlD_4$ in ether, and the organoaluminum intermediate was quenched with D_2O.[19] The reduced alcohol underwent acid-catalyzed rearrangement to 2-vinylcyclobutanone-d_3. From integration of the proton NMR spectrum this ketone had 0.10 residual proton distributed at the two terminal vinyl positions.

Kinetic Studies. To study the kinetics of the 1,3-shift of 2-vinylcyclobutanol alkoxides, reaction solutions were prepared, and samples were removed at various time intervals. The mixture of reactant and product alcohols in the samples was converted to the trimethylsilyl derivatives[20] and analyzed by capillary GLC (see the Experimental Section). The first-order rate for disappearance of vinylcyclobutanol was computed by least squares analysis. For several experiments 1-pentanol was added to the reaction medium to serve as an internal standard. In all reactions, except where noted, only the 1,3-shift product is formed.

The rearrangement was observed for 0.04 M solutions of **1** in DMSO at ambient temperature with aqueous lithium hydroxide

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(8) (a) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693–6704. (b) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 2747–2748.

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(11) Diggle, A. W.; Griffiths, G.; Young, D. J.; Stirling, C. J. M. *Bull. Soc. Chim. Fr.* **1988**, No. 2, 317–321 and references to previous work therein.

(12) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988.

(13) Miller, S. A.; Gadwood, R. C. *Organic Syntheses*; Wiley: New York, 1989; Vol. 67, pp 210–219.

(14) Gadwood, R. C.; Rubino, M. R.; Nagarajan, S. C.; Michel, S. T. *J. Org. Chem.* **1985**, *50*, 3255–3260.

(15) A number of similar syntheses of cyclobutanones have been developed. See: Cohen, T.; Brockunier, L. *Tetrahedron* **1989**, *45*, 2917–2924 and references therein.

(16) The preferred attack by LAH at the sterically more hindered face of the ketone is also observed in the reductions of 2-methylcyclohexanone and 2-methylcyclopentanone. The stereoselectivity is opposite of that predicted on the basis of *steric approach control*. See: Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53.

(17) Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910–7925.

(18) (a) Barnier, J. P.; Ollivier, J.; Salaün, J. *Tetrahedron Lett.* **1989**, *30*, 2525–2528. (b) The thermal homodienyl [1,5]hydrogen shift also takes place with 2-methylvinylcyclobutane and 2-methylvinylcyclopropane. See: Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; pp 81, 82, 178.

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Table 1. First-Order Rate Constant for Rearrangement of (*E*)-2-Vinylcyclobutanol, **1**, under Various Conditions (*n* is Number of Data Points, *r* is Correlation Coefficient)

method	solvent	10^3k (s^{-1})	*n*	*r*
A[a]	DMSO (28)	0.25 ± 0.03	4	0.980
B[b]	DMSO (20)	0.014 ± 0.001	10	0.984
C[c]	THF (–22)	2.36 ± 0.03	22	0.998
D[d]	THF (–22)	1.26 ± 0.03	21	0.993
E[e]	THF (0)	0.0053 ± 0.0006	8[g]	0.959
F[f]	THF/HMPA (–42)	0.94 ± 0.07	9	0.983

[a] DMSO, 0.90% water (w/w), 0.014 M LiOH. [b] DMSO, 0.90% water (w/w), 0.016 M LiOH, 0.0045 M LiBr. [c] THF, excess KH, 0.035 M substrate. [d] THF, excess KH, 0.070 M substrate. [e] THF, excess NaH. [f] THF/HMPA (10:1), excess KH. [g] Each point an average of three samples.

added as a basic catalyst. In solutions containing 0.90% water and 0.014 mol/kg LiOH the rearrangement was followed over two half-lives with a first-order rate constant for disappearance of **1** (*E* and *Z* isomers) of about 0.25×10^{-3} s^{-1} (Table 1). The rates varied widely for different runs (see the Experimental Section) possibly due to destruction of the base by carbon dioxide or oxygen. When lithium bromide was present in the reaction medium at 1.4×10^{-3} mol/kg, the rate was diminished by a factor of 17. For several experiments in DMSO an internal standard was employed. These runs seemed to show that 2-vinylcyclobutanol was not converted exclusively to 3-cyclohexenol under these conditions.[6,21] However, the potassium salt of **1** was formed in dry solvents (diethyl ether, THF, mixed THF/DMSO, or DMSO) in the presence of an internal standard, and GC analysis showed complete rearrangement to product for these cases. These results in dry solvents suggest some systematic error for the experiments in aqueous DMSO. Perhaps this error can be traced to inefficiency of the silylation procedure[20] due to the presence of 1% water in the reaction medium. Aqueous sodium or potassium hydroxide was used in place of lithium hydroxide as a catalyst, resulting in rearrangement which was too fast to follow by removing aliquots at timed intervals.

Disappearance of the potassium salt of (*E*)-**1** in THF at –22 °C showed first-order behavior over four half-lives. However, the observed rate constant changed from 0.0024 to 0.0013 s^{-1} when the starting concentration of alkoxide was changed from 0.035 to 0.070 M (Table 1). In the mixed solvent 10:1 THF/HMPA the rearrangement of the potassium alkoxide was too fast to follow at –22 °C. At –42 °C in the mixed solvent the rate constant was 0.94×10^{-3} s^{-1}.

Several experiments were performed to measure the rate for rearrangement of the sodium salt of **1** at 0 °C in THF. Disappearance of (*Z*)-**1** (as the sodium salt) proceeded with a first-order rate constant of 1.9×10^{-4} s^{-1} at 0 °C starting with a mixture containing the (*E*)-**1** and (*Z*)-**1** isomers in an 82:18 ratio. It appeared that the fraction of (*E*)-**1** increased over the first 10 000 s, no doubt resulting from epimerization of the *Z* isomer.[5e,6,22] However, even after 50% or more of the total (*E* plus *Z*) reactant was converted to 3-cyclohexenol a small amount of (*Z*)-**1** (ca. 2% relative to the *E* isomer) was present. The disappearance of the sodium salt of (*E*)-**1** was 36 times slower than disappearance of the *Z* isomer, with $k = 0.5 \times 10^{-5}$ s^{-1}. The presence of a small amount of (*Z*)-**1** throughout the rearrangement was also seen for the rearrangements of the potassium salt in THF at –22 °C and the lithium salt in DMSO at ambient temperature.

The ratio of rate for rearrangement of (*E*)-**1** relative to the rate of rearrangement of (*E*)-**5** was measured by adding a mixture of the two substrates to excess potassium hydride in diethyl ether at 0 °C. Analysis by GLC showed that (*E*)-2-vinylcyclobutanol rearranged 17-fold more rapidly than (*E*)-2-(2-propenyl)cyclobutanol under these conditions.

Kinetic Isotope Effects. Kinetic isotope effects for disappearance of (*E*)-**1** were measured by adding a 1:1 mixture of deuterio and protio 2-vinylcyclobutanols to a suspension of potassium hydride in diethyl ether at 0 °C. After one to two half-lives the potassium alkoxides were quenched with aqueous ammonium chloride, and the fraction of remaining starting material was determined by capillary GC analysis of the reaction mixture. The remaining starting material was then recovered by preparative GC and analyzed by proton NMR to determine the isotope content.

To calculate the kinetic isotope effects, it is useful to label the mole fractions of unlabeled 2-vinylcyclobutanol alkoxide at time zero and after some amount of reaction as x^{H}_0 and x^{H}, respectively, and the fractions of labeled 2-vinylcyclobutanol alkoxide at time zero and after some amount of time as x^{D}_0 and x^{D}, respectively; these were determined by NMR integrations. In addition, α is the fraction of total 2-vinylcyclobutanol alkoxide remaining after the reaction is stopped; this was measured by capillary GC. These quantities are related to the concentrations [H] and [D] by

$$\alpha = \frac{H+D}{C},\ x^{H}_0 = \frac{H_0}{C},\ x^{D}_0 = \frac{D_0}{C},\ x^{D} = \frac{D}{H+D},\ x^{H} = \frac{H}{H+D}$$

where *C* is the concentration of total alkoxide. Using these relations, the kinetic isotope effect can be expressed in terms of experimentally measurable quantities as

$$\frac{k^H}{k^D} = \frac{\ln(\alpha x^H/x^H_0)}{\ln(\alpha x^D/x^D_0)}$$

The error in the determination of the isotope effect arises mainly from errors in the measurements of the mole fractions. To minimize the error, it is desirable to observe the mole fractions after most of the reactant is converted to product (i.e., for small α); however, because of the need to recover enough starting material for an NMR analysis, the experiments were limited to α values larger than 0.3.

The secondary deuterium kinetic isotope effect at the carbinol position (C1) was $k^H/k^D = 1.12 \pm 0.06$ (average from two trials), and the isotope effect at the terminal vinyl positions was $k^H/k^{D2} = 1.34 \pm 0.04$, or 1.16 per deuterium (average from two trials).[22]

Computational Studies

The energy change for fragmentation of sodium or lithium vinylcyclobutoxide to an allylmetal/aldehyde intermediate in the gas phase was estimated as shown in Scheme 2. The value of ΔE_1 was computed from molecular mechanics calculations of heats of formation of the reactant and product (the semiempirical AM1 method[23] gave $\Delta E_1 = -12.3$ kcal/mol). The value of ΔE_2 in Scheme 2 was estimated from the difference in gas-phase acidities of propene (390 kcal/mol) and 2-propanol (375 kcal/mol).[24] The value for ΔE_3 in Scheme 2 was determined by *ab initio* calculations,[25] at the MP2/6–31+G*//MP2/6–31+G* level, of the energy change for the following reaction:

(21) (a) Hoffman, T. D.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 1000–1008; (b) *Ibid.* **1969**, *91*, 1009–1020.

(22) By using the notation k^H/k^{D2}, we are implying that the substitution of deuterium for hydrogen at the internal vinyl position has no effect on the reaction rate. That is, the internal vinyl C–H bonds in the starting species and the allylic intermediate are very similar. See: Takada, T.; Dupuis, M. *J. Am. Chem. Soc.* **1983**, *105*, 1713–1716.

(23) Dewar, M. J. S.; et al. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

(24) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. 1.

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$$CH_3O^-Na^+(Li^+) + CH_2CHCH_2^- \rightleftarrows CH_3O^- + CH_2CHCH_2^-Na^+(Li^+)$$

The calculated energy difference (ΔE_3) shows that pairing of a sodium and especially a lithium cation with a localized alkoxide ion is stronger than pairing with a delocalized allyl anion.

Experimentally observed results show that the fragmentation of the alkoxide or alkoxide salts has a much lower kinetic barrier than fragmentation of the parent alcohol, even though the computations show that the retro-ene cleavage of the alcohol (ΔE_1) is thermodynamically most favorable.[26] The experimental results also show that decreased association of the alkoxide with the counterion kinetically favors cleavage. That is, the rates of cleavage are in the order free alkoxide > sodium salt > lithium salt >> alcohol.[2b,10,27]

The sum ($\Delta E_1 + \Delta E_2 + \Delta E_3$) gives the estimated changes in energy for the fragmentations of sodium and lithium vinylcyclobutoxide as +10 and +13 kcal/mol, respectively. Finally, ΔE_4 in Scheme 2 is the energy for complexation of the cation with the aldehyde oxygen. Calculations at the 3-21G level[25b] for energies of complexation of formaldehyde with allylsodium and allyllithium give ΔE_4 = −19.1 and −21.2 kcal/mol, respectively (corrected for zero-point energy differences). These complexation energies are overestimated by a small basis set lacking polarization functions, particularly for the lithium case.[28] In any event, the energy for this complexation is unimportant in a donor solvent.

The lifetime of the suspected allylic anion/aldehyde species must be short enough to avoid intermolecular reactions (such as enolate formation) in the highly basic medium, so it must have an energy far above the starting alkoxide, the difference being close to the activation barrier. For the potassium alkoxide we estimate (vida infra) that the barrier to rearrangement is 19 kcal/mol, and from comparing rates in THF the barrier for sodium vinylcyclobutoxide is about 4 kcal/mol higher. Using a 23 kcal/mol barrier and the energy ($\Delta E_1 + \Delta E_2 + \Delta E_3$) calculated in Scheme 2, it seems that the sodium alkoxide would be stabilized relative to the intermediate in going from the gas phase to a polar solvent by about 13 kcal/mol. It is important to distinguish between bulk solvent polarity and solvent basicity or donor ability, since the experimental observations show that increased solvent basicity destabilizes the alkoxide relative to the fragmentation products and transition state.

Model studies were done by *ab initio* RHF calculations with the 3-21G basis set[25b] to study the structure of a possible intermediate in the rearrangement of sodium 2-vinylcyclobutoxide. The 45 geometric variables were fully optimized with no constraints in locating six distinct allyl anion/aldehyde species as minima on the potential energy surface. ORTEP renderings of four of the intermediates are depicted in Figure 1. These four intermediates have similar energies and are about 20 kcal/mol more stable than the two intermediates not shown in Figure 1, which have open-chain geometries with no coordination between the carbonyl oxygen and the sodium cation. The intermediates have the geometric characteristics expected for allyl anion/aldehyde species, such as wide (ca. 128°) C4–C5–C6 bond angles,[29] short (ca. 122 pm) C–O bonds, and two nearly equal allylic C–C bond lengths of around 140 pm. The intermediates I1 and I3 have *trans* geometries about the allylic C4–C5 bonds, and the intermediates I2 and I4 have *cis* geometries (see Figure 1).

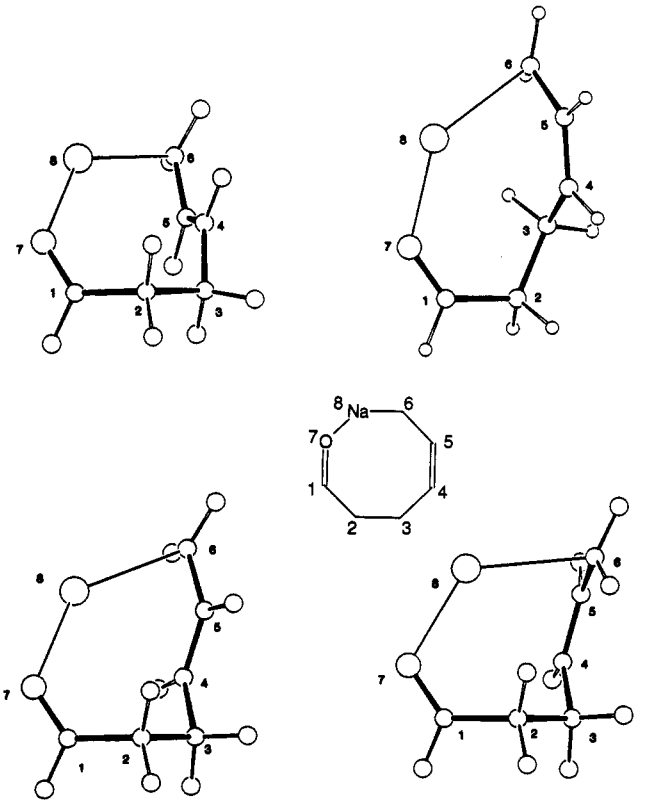
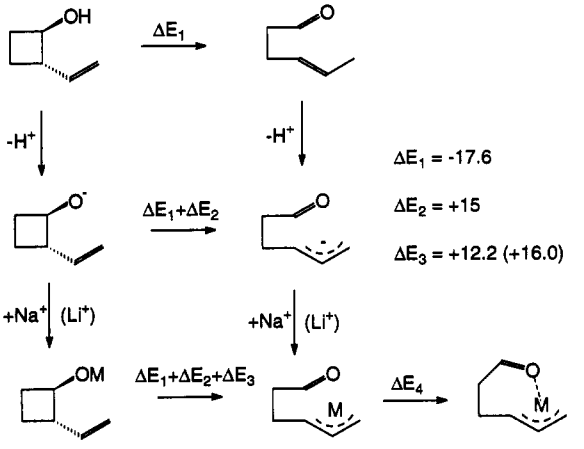


Figure 1. ORTEP plots of 3-21G geometries for intermediates from fragmentation of sodium vinylcyclobutoxide: I1 (top left), I2 (top right), I3 (bottom left), I4 (bottom right).

Scheme 2. Energies (kcal/mol) for Fragmentation of 2-Vinylcyclobutoxide



It is expected that the barrier for rotation about the C4–C5 bonds in these intermediates is too large for interconversion between *cis* and *trans* forms, so that the product is formed from the *cis* intermediates, and the *trans* intermediates can only reclose to the starting alkoxide. In Cohen's study of the rearrangements of *trans*- and *cis*-2-(1-cyclohexenyl)cyclobutoxide, the stereochemistry of the products changed depending on reaction conditions.[6a] To explain the results, a cyclic intermediate similar to I2 or I4 was invoked. The two intermediates I2 and I4 differ in the facial orientation of the aldehyde with respect to the allyl anion, so that closure of these intermediates could give products differing in the configuration at C1 (the carbinol carbon).

A mechanism involving cleavage to an intermediate allyl anion was also suggested for the anionic 3,3-rearrangements of *trans*-1,2-divinylcyclobutanols.[2d] It is likely that an allylic anion intermediate is also formed in Danheiser's highly stereoselective rearrangements of 2-vinylcyclopropanol alkoxides.[5] In this case

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cleavage of the C1–C2 bond of the lithium alkoxide to give a seven-membered *cis* intermediate similar to I2 or I4 would be followed by intramolecular condensation to give the five-membered ring of the product. A cleavage followed by recombination is consistent with observations of *cis–trans* epimerization and fragmentation of vinylcyclobutoxides and similar alkoxides,[5d,6,21] and with the general tendency for strained homoallylic alkoxides to undergo fragmentation.[1a,9,10,27]

Discussion

The 1,3-shift of 2-vinylcyclobutanol alkoxide responds not only to different solvents and different metal counterions but also to added metal common ions. Thus, with 0.0045 *m* lithium bromide added to the medium of aqueous LiOH in DMSO the first-order rate constant decreased about 15-fold, in agreement with Watt's observations.[27] In DMSO the lithium alkoxide ion pair or its dimer is in equilibrium with the lithium cation[27] and the alkoxide ion or alkoxide ion triad, with the latter anions being much more reactive.[2b,3,10,30]

At –22 °C in THF the rearrangement of the potassium alkoxide followed first-order kinetics, but the rate constant varied inversely with alkoxide concentration. As suggested earlier in a study of alkoxide-induced 3,3-shifts in DMSO,[3] ion pair dissociation as a preequilibrium step can explain this curious phenomenon provided that the product alkoxide has the same dissociation constant as the starting alkoxide.[30,31]

$$(\mathrm{ROK})_{n-1}\mathrm{RO}^- + \mathrm{K}^+ \underset{\text{rds}}{\rightarrow} (\mathrm{ROK})_{n-1}\mathrm{R'O}^- + \mathrm{K}^+ \rightleftarrows (\mathrm{ROK})_{n-1}\mathrm{R'OK}$$

The situation is complex since the potassium alkoxide exists as one or more aggregated forms in THF,[32] meaning that ion pair dissociation would form the THF-solvated potassium cation and an anionic aggregate.[3] Tests of the effect of added potassium cation on the rate are desirable, but such studies are problematic since strong potassium electrolytes are insoluble in THF (for example, the solubility of potassium tetraphenylborate in THF at ambient temperature is only ca. 0.002 M). In the earlier study[3] the rate for 3,3-rearrangement in THF was independent of the potassium alkoxide concentration. Perhaps the different dependence on starting alkoxide concentration for the 3,3-rearrangement and the 1,3-rearrangement is related to the difference in ion-pairing behavior of the products. The product in 3,3-shift of **2** is a potassium enolate, which should be more dissociated than the starting alkoxide, but in the 1,3-shift of **1** the product is a potassium alkoxide, which should resemble the reactant in ion-pairing behavior.

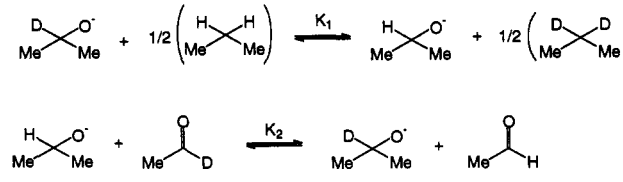
If it is assumed[33a] that the Arrhenius preexponential term is 10^{14}, then it is possible to estimate the activation energy for rearrangement of the potassium salt of **1** in THF as about 19 kcal/mol. This barrier is some 31 kcal/mol lower than that for thermal rearrangement of vinylcyclobutane. Indeed this barrier is an upper limit, since the free alkoxide is at least 100-fold more reactive than the potassium alkoxide ion pair.[27] When 10% HMPA is added, the barrier is lowered by about 1.2 kcal/mol, corresponding to an 11-fold acceleration at –22 °C over the rate in pure THF, which is probably the result of specific interactions between the strong donor HMPA and the potassium ion.

In experiments with the sodium salts in THF at 0 °C the (*Z*)-**1** alkoxide epimerized to the *E* isomer.[5e,6,21] A small amount of (*Z*)-**1** (ca. 2% of the concentration of the *E* isomer) was detected throughout the course of kinetic experiments, even after disappearance of more than half of the starting alkoxide, and even in experiments starting with the pure (*E*)-**1** isomer. These observations suggest that the *E* and *Z* alkoxides equilibrate rapidly compared to the overall rate of rearrangement to 3-cyclohexenol. The *Z* alcohol may rearrange directly to 3-cyclohexen-1-ol as well as epimerize. The scheme is similar to that for thermal rearrangement of vinylcyclobutanes, in which *cis–trans* isomerization, 1,3-rearrangement, and fragmentation (to butadiene plus ethylene) are competing processes.[33]

Rearrangement of a mixture of potassium salts of (*E*)-2-vinylcyclobutanol and (*E*)-2-(2-propenyl)cyclobutanol in ether at 0 °C showed the former alkoxide rearranged 17-fold more rapidly, corresponding to an activation free energy difference of $\Delta\Delta G^{\ddagger} = 1.5$ kcal/mol at 273 K. Frey found[33a] that in the rearrangements of 2-(2-propenyl)cyclobutane and 2-vinylcyclobutane at 350 °C the latter compound rearranged faster, with a relative rate constant $k_{rel} = 1.59$, corresponding to $\Delta\Delta G^{\ddagger} = 0.6$ kcal/mol. Snowden et al. studied fragmentation of tris(homoallylic) potassium alkoxides in HMPA at 80 °C and found that the 2-propenyl group was cleaved faster than the 2-methyl-2-propenyl group, with $k_{rel} = 4.5$.[9a] The faster rate for cleavage of the 2-propenyl group was attributed to the difference in stabilities of the allyl and 2-methylallyl anions.[9a,34]

The kinetic isotope effects provide an important insight into the transition-state structure. The kie (kinetic isotope effect) at C1 is normal but small. Fractionation factors[35] suggest that the equilibrium isotope effect between a C1 deuterium substituted cyclobutanol and an aldehyde with an aldehydic deuterium is 1.43, favoring the former, provided that the force constants of CH bonds α to the alkoxide group are the same as those α to alkoxy groups. Thus if the rate-determining step in the rearrangement involved complete cleavage to an aldehyde, the normal secondary deuterium kinetic isotope effect at C1 would be 1.43. The smaller isotope effect observed suggests either that cleavage does not occur to a great extent or that the assumption of near-equivalent frequencies of α CH bonds in alcohols and alkoxides is in error. The latter is probably the case, considering the lower bond strength of groups attached to alkoxide-bearing carbon.[10] Evidence is an experimental determination of the fractionation of deuterium between trideuteriomethoxide and methanol with methoxide and trideuteriomethanol in the gas phase, which gave $K_{eq} = 1.32/\mathrm{D}$.[35b]

The equilibrium constants K_1 and K_2 for the reactions below can be estimated by *ab initio* calculations of the harmonic frequencies of each species and application of the Bigeleisen equation.[36]



Calculated frequencies at the MP2/6–31+G* level give $K_1 = 1.27$ and $K_2 = 1.00$. The large value for K_1 shows that the oxyanion substituent causes fractionation of deuterium from substantial lowering of the C–H stretching and bending force constants. This oxyanion effect contrasts with the effect of electronegative substituents such as the neutral hydroxyl group.[35] The calculated

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value for K_2 suggests that a small isotope effect (or no effect at all) is expected at the carbinol carbon in fragmentation to an aldehyde. This is unusual since ordinarily $k^H/k^D > 1$ for a change from sp^3 to sp^2 hybridized carbon. Ion-pairing would decrease the ability of the oxyanion to act as a donor[10] and so decrease the calculated value of K_1 and increase the value of K_2. The C1 isotope effect for fragmentation of vinylcyclobutoxide might also be affected by the unusual hybridization of cyclobutane-type carbon. Clearly, some experimental determination of the equilibrium isotope effect in alkoxides in various solutions is in order. Finally, one pathway that is ruled out by the kie at C1 is a concerted rearrangement with increased bonding to C1, which should result in an inverse kie.

The kinetic isotope effect at the terminal carbon of the vinyl group is large and normal. This is a surprise if it is assumed that the terminal carbon becomes involved in bonding to C1 at the transition state. If this were the case, the secondary deuterium kinetic isotope effect should be inverse! There are two circumstances where the kie at the terminal carbon could be large and normal. One possibility for the normal kie at the terminal vinyl position is that complete cleavage to an allyl anion and an aldehyde occurs in the rate determining step. Then the looser C–H bending modes of the allylic species relative to those in the starting vinyl group would provide the necessary zero-point energy change to result in a normal kie. This type of kie was recently observed by Olson, who studied the Cope rearrangements of *trans*-1,2-divinylcyclopropane and *trans*-1,2-bis(2′,2′-dideuteriovinyl)-cyclopropane.[7a] Here a normal isotope effect of 1.08 per deuterium was observed (extrapolated to 25 °C) at the terminal vinyl positions. This effect was attributed to a loosening of C–H bending vibrations in the intermediate allyl radicals. In the present case, an isotope effect of $k^H/k^{D2} = 1.33$ at 0 °C was found at the terminal vinyl positions. The effect suggests again that C–H bending motions of the allylic anion intermediate are substantially looser than those of an ordinary olefinic C–H bond.[22]

The second possibility for the origin of a normal kie at the terminal vinyl position is a rotational isotope effect. If the terminal vinyl carbon was becoming bonded to C1 in the rate-determining step, there must be a rotation of the exomethylene carbon. With deuterium substitution, this could result in a normal isotope effect as large as 1.414 due to the mass effect of deuterium.[37]

To distinguish between the two possibilities, recourse to the origin of the kie at C1 suggests that simultaneous bonding between C1 and the exomethylene does not occur since an inverse kie at C1 might be expected. Further, the alternative interpretation of the kie at C1, namely, complete cleavage starting from a loosely vibrating hydrogen at C1 of the reactant and generating an allyl anion in the transition state, is more consistent with the observation that geometric isomerization precedes rearrangement in this 2-vinylcyclobutanol alkoxide system. The geometric isomerization, while not necessarily providing information about the structural rearrangement, gives credibility to intervention of the cleavage–recombination pathway ... after, of course, reversible dissociation of the metal counterion.

Experimental Section

4-(Trimethylsiloxy)-3-penten-2-one. 4-(Trimethylsiloxy)-3-penten-2-one was prepared as described by Veysoglu.[20] The silyl enol ether was stored in a desiccator in a dry vial covered with a septum. ^{1}H NMR ($CDCl_3$) δ: 5.26 and 5.58 (1 H), 2.12 and 2.26 (6 H), 0.28 and 0.32 (9 H).

3-(Trimethylsilyl)-2-propyn-1-ol. The title compound was prepared as described by Denmark.[38] ^{1}H NMR ($CDCl_3$) δ: 4.25 (d, 2 H), 1.63 (t, 1 H), 0.181 (s, 9 H). ^{13}C NMR δ: 104.2, 90.4, 51.5, –0.1.

3-(Trimethylsilyl)propynal.[39a,b] A solution of 3-(trimethlylsilyl)-2-propyn-1-ol (16.0 g, 0.125 mol) in 25 mL of dry CH_2Cl_2 was added dropwise from an addition funnel to a stirred suspension of pyridinium chlorochromate[39c] (PCC, 40.4 g, 0.187 mol) in dry CH_2Cl_2 (100 mL). The solution was stirred for 2.5 h at room temperature. An NMR spectrum of an aliquot showed oxidation was not complete. More PCC (7.8 g) was added, and the mixture was stirred for 1.5 h. The oxidation was still not complete. A third portion of PCC (3.1 g) was added, and the mixture was stirred for 1.5 h longer. Dry diethyl ether (200 mL) was added, and the solution was filtered through Florisil. The filtrates were concentrated, and the remaining liquid was distilled through a 15-cm Vigreaux column under aspirator vacuum (52–57 °C, 30 mm) to give 10.2 g (0.081 mol, 65%) of colorless liquid. ^{1}H NMR ($CDCl_3$) δ: 9.16 (s, 1 H), 0.26 (s, 9 H). ^{13}C NMR δ: 176.6, 102.9, 102.2, –0.9.

2-Vinylcyclobutanone. 1-(Ethoxycyclopropyl)lithium was prepared as described by Gadwood,[13,14] from the reaction of 1-bromo-1-ethoxycyclopropane[13,14] (0.034 mol) with *tert*-butyllithium (1.7 M in pentane, 36 mL, 0.062 mol) in ether (80 mL) at –78 °C, and the organolithium was condensed with acrolein (1.12 g, 0.020 mol).[13,14] The resulting 1-ethoxy-1-(1-hydroxy-2-propenyl)cyclopropane was stirred in dry ether (100 mL) containing concentrated fluoroboric acid (48% aqueous HBF_4, 1.3 mL), as described by Gadwood.[13,15] Under these conditions the reaction required ca. 10 h for completion. The crude product was distilled under aspirator vacuum at 70 °C (bath temperature), giving 1.30 g (0.013 mol, 68% based on acrolein) of 2-vinylcyclobutanone.[18a,40] ^{1}H NMR ($CDCl_3$) δ: 5.80–6.0 (m, 1 H), 5.18 (dt, J = 7,2, 1 H), 5.13 (d, J = 2, 1 H), 3.92–4.04 (m, 1 H), 2.91–3.17 (m, 2 H), 2.22–2.35 (m, 1 H), 1.89–2.02 (m, 1 H). ^{13}C NMR δ: 208.0, 132.6, 116.6, 63.7, 44.9, 16.4. Lit.[40] ^{1}H NMR ($CDCl_3$) δ: 5.60–6.20 (m, 1 H, olefinic), 5.30–4.95 (m, 2 H, olefinic), 3.65–4.20 (m, 1 H), 1.55–3.20 (m, 4 H, cyclobutyl). Mass spectrum (70 eV): *m/e* (%) 96.0 (6.4), 80.9 (5.6), 68.0 (64), 67.0 (21), 54.0 (100), 39.0 (84). Lit.[40] *m/e* (%): 96 (11, M^+), 81 (5, $M^+ - CH_3$), 68 (49, $M^+ - CO$), 67 (16), 54 (100, $M^+ - CH_2CO$), 53 (21), 42 (14, C_3H_6), 41 (11), 39 (58).

2-Vinylcyclobutanol (1). The title compound was prepared by reduction of 2-vinylcyclobutanone (135 mmol) with $LiAlH_4$ (9.5 mmol) in ether (40 mL), as described by Cohen,[5e] to give 0.89 g (9.1 mmol, 67%) of a 82:18 mixture of (*E*)-**1** and (*Z*)-**1**. A pure sample of the (*E*)-**1** isomer was obtained by preparative GLC (Carbowax, 170 °C). The (*Z*)-**1** isomer isomerized in the GLC injector port at 200 °C to 4-hexenal. IR (neat): 3350, 3100, 3000, 1650, 990, 915, 800 cm^{-1}.

E isomer: IR (neat) 3350, 3100, 3000, 990, 910, 790 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 5.89 (m, 1 H), 4.96–5.06 (m, 2 H), 3.92 (m, 1 H), 2.68 (m, 1 H), 2.25 (br s, 1 H, hydroxyl), 2.12–2.22 (m, 1 H), 1.67–1.91 (m, 2 H), 1.25–1.38 (m, 1 H). ^{13}C NMR δ: 139.6, 114.1, 72.2, 50.5, 29.8, 17.8.

Z isomer: ^{1}H NMR (from spectrum of *Z*/*E* mixture in $CDCl_3$) δ 5.97–6.09 (m, 1 H), 5.16–5.29 (2 H), 4.33 (m, 1 H), 3.14 (broad, 1 H), 1.7–2.3 (5 H). ^{13}C NMR (from spectrum of *Z*/*E* mixture) δ: 136.4, 117.2, 68.1, 45.9, 31.1, 18.9.

4-Hexenal: ^{1}H NMR ($CDCl_3$) δ 9.78 (t, J = 2, 2 H), 5.58–5.45 (m, 1 H), 5.40–5.31 (m, 1 H), 2.48 (m, 2 H), 2.37 (m, 2 H), 1.63 (m, 3 H). ^{13}C NMR δ: 202.3, 128.1, 125.6, 43.7, 19.8, 12.8. Mass spectrum (70 eV): *m/e* (%) 98.0 (13), 97.0 (5).

3-Cyclohexenol. Using a pasteur pipet, 10 drops of 35% KH suspension in mineral oil was placed in a dry 15-mL flask containing a stir bar. The mineral oil was rinsed off with pentane. The flask was covered with a septum and flushed with nitrogen. Dry ether (10 mL) and then **1** (100 μL) were added. The solution was stirred under nitrogen for 3 h and then quenched with 25% aqueous NH_4Cl. The ether layer was removed, dried ($MgSO_4$), and filtered. The solvent was removed, and the residue was purified by preparative GLC (Carbowax, 170 °C). ^{1}H NMR ($CDCl_3$) δ: 5.65 (m, 1 H), 5.59 (m, 1 H), 4.05–3.95 (m, 1 H), 2.4–1.8 (5 H), 1.72–1.56 (2 H). ^{13}C NMR δ: 126.5, 124.8, 65.1, 34.3, 31.1, 23.8.

2-(2-Propenyl)cyclobutanone. 1-Ethoxy-1-(1′-hydroxy-2′-methyl-2-propenyl)cyclopropane was prepared as described by Gadwood,[13] by condensation of (1-ethoxycyclopropyl)lithium (0.100 mol) with methacrolein (5.6 g, 0.080 mol) in dry ether (250 mL) at –78 °C. The resulting (1′-hydroxy-2′-methyl-2-propenyl)cyclopropane (0.07 mol) was dissolved in dry ether (150 mL) containing concentrated fluoroboric acid (48% aqueous HBF4, 10 mL), where it was converted to 2-(2-propenyl)-

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cyclobutanone, as described by Gadwood.[13,15] Under these conditions the reaction required ca. 10 h for completion. The crude product was distilled under aspirator vacuum (75–85 °C, 20 mm) and then chromatographed on silica gel with 6:1 pentane/diethyl ether, giving 2.94 g of 2-(2-propenyl)cyclobutanone.[18a] Analysis by capillary GLC showed 33% of an impurity was present, which was also apparent from the ^{1}H NMR spectrum. The ketone was further purified by preparative GLC (Carbowax, 150 °C). IR (neat) 2960, 1790, 1680, 900, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 4.86 (m, 1 H), 4.82 (m, 1 H), 3.92 (m, 1 H), 3.13–2.87 (2 H), 2.28–2.16 (m, 1 H), 2.09–1.99 (m, 1 H), 1.79 (s, 3 H). ^{13}C NMR δ: 140.1, 110.9, 66.8, 44.5, 21.3, 15.5.

(E)-2-(2-Propenyl)cyclobutanol ((*E*)-5). The title compound was prepared by reduction of 2-(2-propenyl)cyclobutanone (0.59 g, 5.4 mmol) with $LiAlH_4$ (0.57 g, 5.4 mmol) in ether (45 mL), as described by Cohen,[5e] to give 0.55 g (92% crude) of clear liquid. Pure (*E*)-**5** was obtained by preparative GLC (Carbowax, 170 °C). The (*Z*)-**5** isomer rearranged in the GLC injector port at 200 °C to 5-methyl-4-hexenal.

(*E*)-5: ^{1}H NMR ($CDCl_3$) δ 4.74 (m, 1 H), 4.70 (m, 1 H), 3.98 (m, 1 H), 2.64 (m, 1 H), 2.20–2.12 (m, 1 H), 2.0–1.5 (3 H), 1.74 (s, 3 H), 1.44–1.30 (m, 1 H). ^{13}C NMR δ: 146.3, 108.7, 71.5, 53.4, 29.3, 20.6, 16.8.

5-Methyl-4-hexenal: IR (neat) 2900, 2730, 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.75 (t, *J* = 2, 1 H), 5.07 (t, *J* = 7, 1 H), 2.43 (tt, *J* = 7, 2, 2 H), 2.30 (m, 2 H), 1.68 (s, 3 H), 1.60 (s, 3 H). ^{13}C NMR δ: 202.5, 133.2, 122.1, 43.9, 25.6, 20.9, 17.6.

3-Methyl-3-cyclohexenol. The title compound was prepared from (*E*)-**5** by the method described above for preparation of 3-cyclohexenol. ^{1}H NMR ($CDCl_3$) δ: 5.37 (m, 1 H), 3.97 (m, 1 H), 2.30–1.75 (5 H), 1.66 (br s, 3 H), 1.62–1.50 (2 H). ^{13}C NMR δ: 131.3, 120.5, 67.4, 39.1, 30.5, 23.5, 23.1.

1-Ethoxy-1-(1′-hydroxy-3′-trimethylsilyl-2-propynyl)cyclopropane. The title compound was prepared as described by Gadwood,[13] by condensation of (1-ethoxycyclopropyl)lithium (0.101 mol) with 3-(trimethylsilyl)-propynal (8.20 g, 0.065 mol) in ether (200 mL) at −78 °C. ^{13}C NMR ($CDCl_3$) δ: 103.6, 90.3, 65.1, 64.2, 63.7, 15.8, 11.3, 9.6, −0.3.

1-Ethoxy-1-(1′-hydroxy-2-propynyl)cyclopropane. To a solution of 1-ethoxy-1-(1′-hydroxy-3′-trimethylsilyl-2-propynyl)cyclopropane (0.065 mol) in methanol (130 mL) was added 65 mL of 5% aqueous KOH. The solution was stirred overnight. The methanol was evaporated, and the remaining liquid was extracted with ether (4 × 150 mL). The ether solution was dried ($MgSO_4$) and filtered, and the solvent was evaporated, affording 6.86 g (0.049 mol, 75%) of crude 1-ethoxy-1-(1′-hydroxy-2-propynyl)cyclopropane. ^{1}H NMR ($CDCl_3$) δ: 4.65 (br s, 1 H), 3.92 (q, *J* = 7, 2 H), 3.67 (m, 1 H), 2.73 (br s, 1 H), 2.43 (d, *J* = 2, 1 H), 1.17 (t, *J* = 7, 3 H), 0.86–0.92 (m, 4 H). ^{13}C NMR δ: 82.0, 73.6, 64.7, 64.1, 63.9, 15.8, 11.3, 9.7.

1-Ethoxy-1-(3′-deuterio-1′-hydroxy-2-propynyl)cyclopropane. A solution was prepared containing potassium methoxide (1.0 g, 14 mmol), methanol-*d* (25.0 g, 99.5% d), and D_2O (50 g, 98% d). 1-Ethoxy-1-(1′-hydroxy-2-propynyl)cyclopropane (6.8 g, 0.048 mol) was added. After stirring for 2 h, the base was neutralized with glacial acetic acid (1 mL), and the solution was poured into ether (300 mL). The ether layer was washed with 5% aqueous NaCl, and the solvent was evaporated. The residue was again taken up in ether (200 mL) and washed with 5% aqueous NaCl. The ether layer was dried ($MgSO_4$) and filtered and the solvent evaporated. The brown residue was distilled under vacuum (0.5 mm) through a short-path apparatus, giving 4.87 g (34 mmol, 71%) of clear liquid. The NMR spectrum showed no acetylenic proton was present. IR (neat): 3400, 2590, 1980 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 4.64 (br s, 1 H), 3.66 (q, *J* = 7, 2 H), 2.55 (br s, 1 H), 1.17 (t, *J* = 7, 3 H), 0.86–0.92 (m, 4 H).

1-Ethoxy-1-(2′,3′,3′-trideuterio-1′-hydroxy-2-propenyl)cyclopropane. 1-Ethoxy-1-(3′-deuterio-1′-hydroxy-2-propynyl)cyclopropane (4.87 g, 34 mmol) was added to a suspension of $LiAlD_4$ (2.0 g, 48 mmol) in dry ether (150 mL) under nitrogen at 0 °C. The suspension was stirred mechanically for 20 h, quenched by slow addition of D_2O (4.43 g, 0.221 mol), and then stirred an additional 2 h. The solution was filtered and dried over $MgSO_4$. The solvent was removed, and the crude product (3.91 g, 27 mmol, 78%) was filtered through silica gel with ether and used directly in the next step.

2-(1′,2′,2′-Trideuterioethenyl)cyclobutanone (Vinylcyclobutanone-d_3). The title compound was prepared as described by Gadwood,[13,15] from 1-ethoxy-1-(2′,3′,3′-trideuterio-1′-hydroxy-2-propenyl)cyclopropane (27 mmol) in dry ether (90 mL) containing concentrated fluoroboric acid (48% aqueous HBF4, 1.2 mL). Under these conditions the reaction required ca. 10 h for completion, to give 1.30 g (12.9 mmol, 48%) of vinylcyclobutanone-d_3 after distillation. The ^{1}H NMR spectrum showed the presence of ca. 0.10 residual proton distributed at the terminal vinyl positions and no proton at the internal vinyl position. IR (neat): 3000, 2960, 2930, 2220, 1780, 1580, 1400, 1200, 1070, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 5.30 (0.07 H), 5.10 (0.03 H), 3.92–4.04 (m, 1 H), 2.91–3.17 (m, 2 H), 2.22–2.35 (m, 1 H), 1.89–2.02 (m, 1 H). ^{13}C NMR ($CDCl_3$) δ: 208.0, 131.9 (m), 63.5, 44.8, 16.3. Mass spectrum (70 eV): *m/e* (%) 99.1 (8.0), 98.1 (0.8), 97.0 (0.0), 57.0 (100).

(*E*)-2-(1′,2′,2′-Trideuterioethenyl)cyclobutanol ((*E*)-1d3). The title compound was prepared by reduction of 2-vinylcyclobutanone-d_3 (1.1 g, 11.1 mmol) with $LiAlH_4$ (0.97 g, 26 mmol) in ether (60 mL), as described by Cohen,[5e] to give 0.736 g (73 mmol, 66% crude) of clear liquid. The pure (*E*)-**1d3** isomer was obtained by preparative GLC (Carbowax, 170 °C). IR (neat): 3350, 3000, 2250, 2220, 1590, 990, 930, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 5.06–4.96 (0.1 H), 3.94 (m, 1 H), 2.68 (m, 1 H), 2.25 (br s, 1 H, hydroxyl), 2.12–2.22 (m, 1 H), 1.67–1.91 (m, 2 H), 1.25–1.38 (m, 1 H).

(*E*)-1-Deuterio-2-vinylcylobutanol ((*E*)-1d1). Lithium aluminum deuteride (1.0 g, 0.024) was added to a solution of 2-vinylcyclobutanone (1.47 g, 0.0153 mol) in ether (45 mL) at 0 °C. The remaining procedure was carried out as described by Cohen,[5e] giving 1.07 g (0.0107 mol, 70%) of clear yellow liquid. The proton NMR spectrum indicated complete deuteration (>95%) at the 1-position. The pure *E* isomer was isolated by preparative GLC (Carbowax, 170 °C). ^{1}H NMR ($CDCl_3$), mixture of *Z* and *E* isomers, δ: 5.78–6.10 (1 H), 4.91–5.31 (2 H), 2.59–3.21 (1 H), 1.25–2.36 (6 H).

General Procedure for Sampling and Analysis for Kinetics Experiments. Samples (usually 0.20 mL) were withdrawn from the reaction flask by syringe at appropriate time intervals and added to the silylating reagent (50 μL of 4-(trimethylsiloxy)-3-penten-2-one[20]). The samples were stirred briefly, diluted with pentane (0.50 mL), and washed with water or 10% aqueous NH_4Cl (0.20 mL). The pentane layer was analyzed by capillary GLC. Analysis of the silylated alcohols was on a Varian 3700 GC with a 50 m × 0.25 mm DB-5 capillary column using a flame ionization detector and a Hewlett-Packard HP-3390 recorder. The reactant and product eluted with a column temperature of 70 °C (isothermal). The (*E*)-**1** and (*Z*)-**1** silyl ethers eluted 0.3 min apart at 14 min, and the product eluted at 19 min. For several experiments 1-pentanol was added to serve as an internal standard. First-order rate constants were computed using the method of least squares with appropriate weighting.

Rearrangement Using Aqueous Lithium Hydroxide in Dmso. Aqueous 1.5 M LiOH solution (21 mg) was added to degassed DMSO (2.1 g) under nitrogen at ambient temperature. The standard (1-pentanol, 5 μL) and then the substrate (**1**, 15 μL) were added. Four aliquots (0.10 mL) were withdrawn at appropriate time intervals.

Results from seven trials are summarized in Table 2. C_{LiOH} denotes the concentration of LiOH in moles/kilogram, *k* is the first-order rate constant, *n* is the number of samples taken, and *r* is the correlation coefficient for least squares analysis. The solvent contained 0.90 ± 0.05% water by weight for each trial.

Another set of experiments was done under similar conditions, except lithium bromide was added. Results from 10 trials are summarized in Table 3.

Rearrangement Using Potassium Hydride in THF. Eight drops of the 35% KH suspension in oil (100 mg, 0.9 mmol) was placed into a dry 5-mL flask. The mineral oil was removed with pentane washes, and the flask was flushed with nitrogen. Freshly distilled tetrahydrofuran (4.00 mL) was added by syringe. The flask was immersed in a bath of freezing carbon tetrachloride (−22 °C). After 15 min, the substrate (30 μL, 27 mg, 0.28 mmol, mixture of (*E*)-**1** and (*Z*)-**1**) was added to the stirred solution. A sample was taken after 10 min (sufficient time for disappearance of the *Z* isomer), and kinetic timing was begun. Seven more samples were removed at timed intervals using a chilled syringe.

Table 2. Kinetics Experiments in Aqueous DMSO

$100C_{LiOH}$	*T* (°C)	10^3k (s^{-1})	*n*	*r*
1.53	30.5	0.33 ± 0.04	4	0.988
1.48	28.5	0.27 ± 0.03	4	0.991
1.48	29.0	0.20 ± 0.02	4	0.992
1.47	28.5	0.25 ± 0.03	4	0.980
1.42	29.0	0.22 ± 0.04	4	0.968
1.39	27.5	0.33 ± 0.04	4	0.984
1.38	24.5	0.23 ± 0.04	4	0.967

Table 3. Kinetics Experiments in Aqueous DMSO with Added Lithium Bromide

$100C_{LiOH}$	$100C_{LiBr}$	T (°C)	10^4k (s^{-1})	n	r
1.35	0.044	24.0	0.61 ± 0.07	4	0.987
1.35	0.097	24.0	1.70 ± 0.2	4	0.986
1.28	0.109	20.5	0.92 ± 0.13	4	0.980
1.29	0.169	20.5	0.46 ± 0.03	4	0.995
1.35	0.165	21.0	1.3 ± 0.2	4	0.967
1.34	0.342	20.0	0.33 ± 0.03	4	0.993
1.36	0.324	20.0	0.70 ± 0.10	4	0.981
1.33	0.616	20.5	0.35 ± 0.03	4	0.992
1.32	0.610	21.0	0.31 ± 0.05	4	0.973
1.60	0.447	20	0.143 ± 0.001	10	0.983

The fraction x of starting material remaining at time t was computed from

$$x = (A_1/(A_1 + A_2))_t/(A_1/(A_1 + A_2))_0$$

where A_1 and A_2 are the GC peak areas for the reactant (vinylcyclobutanol) and product (3-cyclohexenol), the numerator is at time t, and the denominator is at time 0 (for the first sample $x = 1.00$). The experiment was repeated three additional times. Data from one of the runs were rejected. The combined data for the other three runs were subjected to least squares analysis and gave a first-order rate constant for disappearance of the potassium salt of (*E*)-2-vinylcyclobutanol of (1.26 ± 0.03) × 10^{-3} s^{-1} ($n = 21$, $r = 0.993$). The experiment was repeated, except the volume of added substrate was decreased to 15 μL (0.14 mmol). Combined data from three kinetic runs at the lower concentration gave a first-order rate constant of (2.36 ± 0.03) × 10^{-3} s^{-1} ($n = 22$, $r = 0.998$).

Rearrangement Using Potassium Hydride in THF/HMPA. The rate for rearrangement was measured in the mixed solvent THF/HMPA (10:1) at −42 °C (freezing acetonitrile bath) with an alkoxide concentration of 0.045 M. The method was the same as that described above for rearrangement in pure THF. The first sample (0.40 mL) was removed after 10 min (sufficient time for disappearance of the (*Z*)-**1** isomer), and kinetic timing was begun. Four more samples were removed 815, 1545, 2280, and 3100 s after the first sample. A second trial was done, with the first sample taken after 10 min and four more samples at 485, 1035, 1560, and 2065 s after the first sample. The combined data for the two runs gave a first-order rate constant k = (0.94 ± 0.07) × 10^{-3} s^{-1} ($n = 9$, $r = 0.983$).

Rearrangement Using Sodium Hydride in THF. Eight sealed, evacuated 6-mm tubes were prepared, each containing ca. 10 mg of sodium hydride and 0.20 mL of a THF solution of **1** (0.07 M, mixture of *E* and *Z* isomers) and 1-pentanol (0.03 M). The tubes were kept below −70 °C at all times to prevent any rearrangement to 3-cyclohexenol. The time was noted, and six of the tubes were shaken and placed in an ice bath. The other two tubes (controls) were cooled in liquid nitrogen, cracked open, covered with septa, warmed to −78 °C, and sampled for GC analysis. After 1.406 × 10^5 s, two tubes were withdrawn from the ice bath and cooled in liquid nitrogen, cracked open, warmed to −78 °C, and sampled for GC analysis. After 2.645 × 10^5 sec, three more tubes were withdrawn, cooled, cracked open, and sampled. (The last tube had cracked while still in the ice bath and could not be used.) The sealed tube experiment was repeated several times giving the following data points: 1.406 × 10^5 s (two duplicate samples), 2.645 × 10^5 s (three duplicate samples), 1.013 × 10^5 s (three duplicate samples), 0.968 × 10^5 s (three duplicate samples), 1.567 × 10^5 s (five duplicate samples), 1.499 × 10^5 s (three duplicate samples), 3.385 × 10^5 s (three duplicate samples), 3.359 × 10^5 s (three duplicate samples, no control). The combined data gave a first order rate constant for rearrangement of the sodium salt of (*E*)-2-vinylcyclobutanol in THF at 0 °C of (0.53 ± 0.06) × 10^{-5} s^{-1} ($n = 8$, $r = 0.959$).

A second set of experiments which gave the rate for disappearance of (*Z*)-**1** was done as follows. Sodium hydride (60% in mineral oil, 65 mg) was placed in a 5-mL flask and washed free of mineral oil with pentane. The flask was capped with a septum and flushed with nitrogen. Dry THF (2.00 mL) was added, and the vessel was cooled to 0 °C. After 15 min, **1** (15 μL, mixture of *E* and *Z* isomers) was added. Six samples (0.10 mL) were taken at 1430, 5295, 8250, 11 905, 62 020, and 68 435 s. The experiment was repeated with three samples taken at 760, 2710, and 8290 s. The combined data (excluding the last two points of the first run) gave a first-order rate constant for disappearance of (*Z*)-2-vinylcyclobutanol of (1.91 ± 0.08) × 10^{-4} s^{-1} ($n = 7$, $r = 0.994$).

Rearrangement Using Potassium Hydride in Dmso or THF/DMSO. Measurement of the Fraction of Conversion of Vinylcyclobutanol to 3-Cyclohexenol. Potassium hydride suspension (3 drops) was placed in a 5-mL flask, which was covered with a septum and flushed with nitrogen. The KH was rinsed with pentane and the flask again flushed with nitrogen. Degassed DMSO (1.00 mL) was added by syringe. Evolution of hydrogen gas occurred immediately. The mixture was stirred until a homogeneous solution formed (a few minutes). Using a 50-μL syringe, 10 μL of a premixed solution of **1** (mixture of *E* and *Z* isomers) and 1-pentanol (internal standard) was added. Samples from both the premixed solution and the reaction mixture were analyzed by capillary GLC. The ratio of GLC peak areas for 3-cyclohexenol (the product) and 2-vinylcyclobutanol (the reactant) was computed. For two trials the fraction of **1** which was converted to 3-cyclohexenol was determined to be 0.95 and 1.00.

Similar experiments were carried out at 0 °C, substituting the mixed solvent THF/DMSO (10:1) for pure DMSO. The reaction was complete in less than 10 min. For two trials the fraction of conversion to product was determined to be 1.00 and 1.00.

Rearrangement of (*E*)-1/(*E*)-5 Mixtures Using Potassium Hydride in Diethyl Ether. Potassium hydride (35% in mineral oil, 10 drops) was placed in a 5-mL flask containing a stirring bar. The hydride was rinsed with pentane, and the flask was capped with a septum and flushed with nitrogen. Freshly distilled diethyl ether (5.00 mL) was added by syringe. The flask was cooled to 0 °C and a mixture of (*E*)-**1** (25 μL, 22 mg, 0.24 mmol) and (*E*)-**5** (25 μL, 22 mg, 0.20 mmol) was added. Samples (0.50 mL) were removed with a chilled syringe at 540, 930, 11 320, and 11 550 s. The flask was warmed to ambient temperature, and a fifth sample was taken after 2 h. The samples were quenched with silylating reagent (50 mL), diluted with pentane (0.50 mL), washed with 20% aqueous NH_4Cl, and analyzed by capillary GLC at a constant column temperature of 75 °C. The six-carbon alcohols **1** and 3-cyclohexenol eluted at 10.7 and 16.0 min, and the seven-carbon alcohols **5** and 3-methyl-3-cyclohexenol eluted at 17.6 and 25.2 min. The ratio of peak areas for six-carbon and seven-carbon alcohols was 0.57 (samples 1 and 2), 0.56 (samples 3 and 4), and 0.58 (sample 5). For samples 3 and 4 (at 11 320 and 11 550 s) k_{rel} was computed from the ratio

$$\ln(A_1/(A_1 + A_2))/\ln(B_1/(B_1 + B_2))$$

where A_1, A_2, B_1, and B_2 are the GLC peak areas for **1**, 3-cyclohexenol, **5**, and 3-methyl-3-cyclohexenol. This gave 15.6 ± 0.1 for the rate of rearrangement of (*E*)-2-vinylcyclobutanol relative to the rate of rearrangement of (*E*)-2-(2-propenyl)cyclobutanol. The experiment was done twice more giving k_{rel} = 17.7 ± 0.4 and k_{rel} = 16.6 ± 0.2. The average for the three trials was k_{rel} = 16.6 ± 1.0.

Rearrangement Using Potassium Hydride in Diethyl Ether. Measurement of Secondary Kinetic Isotope Effects. A potassium hydride suspension (13 drops) was placed in a dry 15-mL flask and washed free of mineral oil with pentane. The flask was covered with a septum and flushed with nitrogen. Freshly distilled diethyl ether (10.0 mL) was placed in the flask by syringe. The flask was cooled to 0 °C (bath temp) and 100 μL of a 1:1 mixture of (*E*)-**1** and (*E*)-**1d3** was added to the stirred solution. After 104 min, the reaction was halted by rapidly adding 1.0 mL of 25% aqueous NH_4Cl. The ether layer from the quenched reaction solution was removed and washed with 3% aqueous NaCl (2 mL) and dried ($MgSO_4$). The solution was then analyzed by capillary GLC using a 60 m × 0.25 mm Supelcowax 10 column. The reactant and product eluted at column temperatures of 140 and 150 °C, respectively. The fraction of starting material remaining after quenching the reaction was determined from $\alpha = A_1/(A_1 + A_2)$, where A_1 and A_2 are the GLC peak areas for reactant and product. This measurement gave $\alpha = 0.562$. The experiment was repeated with a reaction time of 135 min, resulting in $\alpha = 0.445$.

After the GC analysis, the ether solution was filtered and the solvent removed by distillation through a 15-cm Vigreaux column. The unreacted starting material was recovered by preparative GLC and analyzed by proton NMR.

The integrals were recorded for the regions δ 6.01–5.80, 5.14–4.90, and 4.07–3.82 for 1% solutions in $CDCl_3$ of the recovered material and the starting material. A 15-s pulse delay was used to ensure time for relaxation of the vinyl protons between pulses. Integrations for the starting mixture gave the mole fractions $x^{H}_0 = 0.480$, $x^{D3}_0 = 0.500$, and $x^{D2}_0 = 0.020$ for 2-vinylcyclobutanol, 2-(1′,2′,2′-trideuterioethenyl)cyclobutanol, and 2-(1′,2′-dideuterioethenyl)cyclobutanol, respectively. The fraction of total deuterated material ($x^{D2}_0 + x^{D3}_0$) was $x^{D}_0 = 0.520$. The same

fractions were determined for the recovered starting material from the two trials, and the data are tabulated below.

trial	x^H	x^{D3}	x^{D2}	$x^D(x^{D3} + x^{D2})$	α
1	0.440	0.526	0.033	0.559	0.562
2	0.417	0.551	0.031	0.582	0.445

The kie was computed from

$$k^H/k^D = \ln(\alpha x^H/x^H{}_0)/\ln(\alpha x^D/x^D{}_0)$$

which gave $k^H/k^{D2} = 1.31_6$ (trial 1) and 1.36_5 (trial 2).[22,41]

The same method was used to find the isotope effect at the carbinol carbon using a mixture of (*E*)-**1** and (*E*)-**1d1**. The mole fractions of protio material at the start ($x^H{}_0$) and at the time of quenching (x^H) were determined from the ratio of the integrated NMR signals at δ 4.07–3.82 and 6.01–5.80, and the fraction of deuterio material was computed from $x^D = 1 - x^H$. Results for two trials are tabulated below.

trial	$x^H{}_0$	x^H	α	k^H/k^D
1	0.506	0.480	0.289	1.08_7
2	0.502	0.456	0.285	1.15_8

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(41) The fraction $x^D = x^{D3} + x^{D2}$ could be measured with greater accuracy than the individual fractions x^{D3} and x^{D2}, and so we chose to compute k^H/k^{D2} based on x^D rather than x^{D3}. If the isotope effect k^H/k^{D2} is calculated using the fraction x^{D3} instead of x^D, the values of k^H/k^{D2} are a little smaller (1.260 and 1.334 instead of 1.316 and 1.365). These two methods for computing k^H/k^{D2} give discordant values; we would expect that the inverse isotope effect computed using x^D would be a little smaller than that computed using x^{D3}.