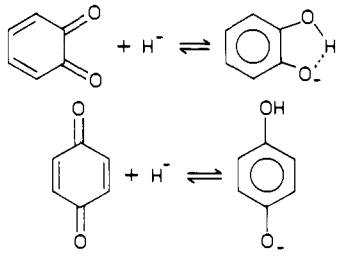

(11)

(12)

of the same magnitude as the present measured difference in stabilization energies of *o*- and *p*-hydroxyphenoxy radicals (4.6 kcal). Linstead explained these differences in reactivity in terms of intramolecular H bonding in the species generated by H addition to the *o*-quinones. Linstead, however, argued that anionic intermediates are involved. In this case, one might conclude that *o*-hydroxyphenoxy stabilization energies are of the same magnitude in anions and free radicals. On the other hand, the actual mechanism of H transfer to quinones is not well established.[37]

V. Summary

(1) The primary decomposition step in all dissociation reactions of anisoles is O–methyl bond homolysis. The decomposition rate is very sensitive to the nature and position of the substituent.

(2) The *o*-hydroxy substituent has large effect, weakening the phenoxy–CH_3 and phenoxy–CH_2CH_3 bonds by about 7 kcal mol^{-1}. The presence of a strong hydrogen bond in the radical seems to be the best explanation for this effect.

(3) Relative dissociation rates of anisole, *o*-bromoanisole, and *o*-chloroanisole show that a 1,3-methyl shift is not a significant reaction pathway in their decomposition reactions.

(4) Rate parameters from the present experiments reproduce rates of decomposition in condensed-phase thermolysis reactions. This suggests that even in the complex reaction environments of lignin and coal thermolysis simple bond homolysis is an important, perhaps rate-controlling, step in the decomposition of alkyl aryl ethers.

(5) A comparison of the present bond strengths and H-abstraction rate constants from phenols suggests that substantial polar effects are operative in the H-abstraction reactions.

(6) In agreement with Linstead et al.,[37] the present results suggest that the higher reactivity of *o*-quinones than *p*-quinones may be largely due to the exceptional stability of the *o*-hydroxyphenoxy radical (or anion) formed by H transfer to the former molecules.

Acknowledgment. This work was supported by a grant from the Gas Research Institute.

Registry No. *o*-Bromoanisole, 578-57-4; *o*-chloroanisole, 766-51-8; *o*-hydroxyanisole, 90-05-1; *m*-hydroxyanisole, 150-19-6; *p*-hydroxyanisole, 150-76-5; phenetole, 103-73-1; *o*-hydroxyphenetole, 94-71-3; *m*-methoxyanisole, 151-10-0; anisole, 100-66-3; *m*-chloroanisole, 2845-89-8; *p*-chloroanisole, 623-12-1; *m*-bromoanisole, 2398-37-0; *p*-bromoanisole, 104-92-7; *o*-hydroxyphenoxy radical, 5593-75-9; *o*-methoxyphenoxy radical, 41115-74-6; *o*-chlorophenoxy radical, 63125-12-2; *o*-bromophenoxy radical, 63125-15-5; *m*-hydroxyphenoxy radical, 24856-47-1; *m*-methoxyphenoxy radical, 28504-31-6; *m*-chlorophenoxy radical, 54560-44-0; *m*-bromophenoxy radical, 63125-14-4; *p*-hydroxyphenoxy radical, 3225-30-7; *p*-methoxyphenoxy radical, 6119-32-0; *p*-chlorophenoxy radical, 3148-13-8; *p*-bromophenoxy radical, 63125-13-3; *p*-methoxyanisole, 150-78-7; *o*-methoxyanisole, 91-16-7.

Carbanionic Rearrangements of (Halomethylene)cycloalkanes

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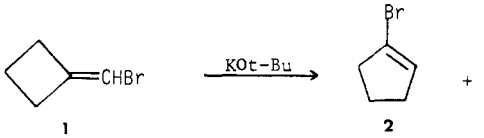
Abstract: The mechanism for the unusual base-induced ring-enlargement reaction of (halomethylene)cyclobutanes to 1-halocyclopentenes was examined by C-13 labeling studies with (bromomethylene)cyclobutane (**1**), *cis*- and *trans*-1-(bromomethylene)-3-ethoxy-2,2-dimethylcyclobutane (**15** and **16**), and 1-(bromomethylene)-2,2,4,4-tetramethylcyclobutane (**22**). Two competing processes were found to lead from the vinyl anion to rearranged products: (1) rehybridization of the vinyl anion to a 1,2-carbene–anion, which subsequently undergoes rearrangement, and (2) a Beckmann-like simultaneous migration of bromide and ring carbon. Both processes subtly bypass the "forbidden" alkyl-to-carbanion shift.

In 1968 the unusual rearrangement reaction of (bromomethylene)cyclobutane (**1**) to 1-bromocyclopentene (**2**) in the presence of potassium *tert*-butoxide was reported (eq 1).[1] The



(1)

rearranged bromide was accompanied by small amounts (2–4%) of the ring-enlarged enol ether 1-*tert*-butoxycyclopentene (**3**). It was shown that **3** arises from carbene and cyclopentyne intermediates, in analogy to larger ring homologues,[2] but 1-bromocyclopentene (**2**) does not. Thus, Diels–Alder trapping of the cyclopentyne intermediate has no effect on the yield of **2** while that of **3** drops to zero (Scheme I).[1,3]

Evidence for the intermediacy of cyclopentyne in ring enlargements of methylenecycloalkanes generated from (diazomethylene)cyclobutanes[4] and (dibromomethylene)cyclobutanes[5] has also been reported, so the rearrangement of **1** to **3** cannot be considered unusual. However, the rearrangement of **1** to **2** is totally unexpected and mechanistically of great interest.

Several mechanisms for the **1** to **2** conversion may be written and are depicted in Scheme II. All involve the vinyl carbanion **4**, whose presence in the reaction medium has been amply demonstrated by deuterium-exchange studies.[3,6] The above-cited trapping experiments and stereochemical studies[7] (vide infra) have

(1) Erickson, K. L.; Vanderwaart, B. E.; Wolinsky, J. *J. Chem. Soc., Chem. Commun.* **1968**, 1031.
(2) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1142.
(3) Erickson, K. L.; Markstein, J.; Kim, K. *J. Org. Chem.* **1971**, *36*, 1024.
(4) Gilbert, J. C.; Baze, M. E. *J. Am. Chem. Soc.* **1983**, *105*, 664.
(5) Fitjer, L.; Kliebisch, R.; Wehle, D.; Modaressi, S. *Tetrahedron Lett.* **1982**, *23*, 1661. Fitzer, L.; Modaressi, S. *Ibid.* **1983**, *24*, 5495.
(6) Erickson, K. L. *J. Org. Chem.* **1973**, *38*, 1463.
(7) Erickson, K. L. *J. Org. Chem.* **1971**, *36*, 1031.

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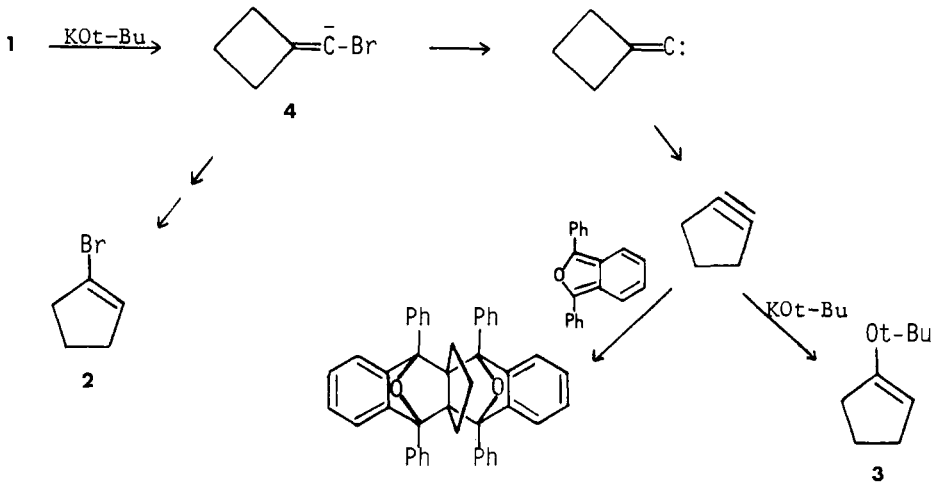
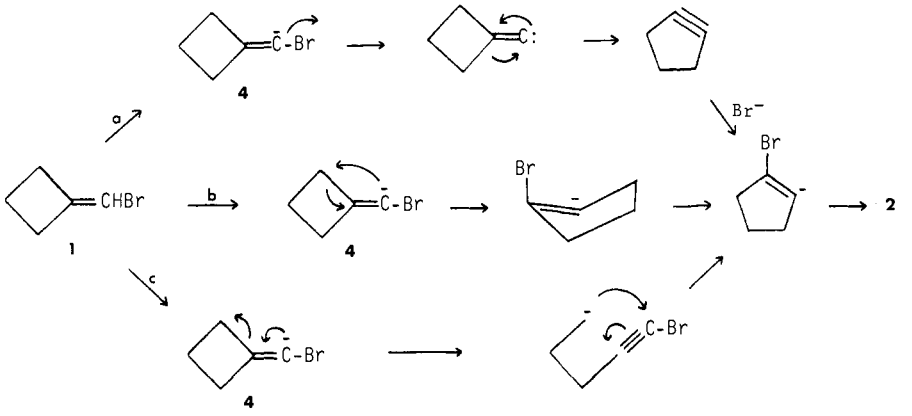
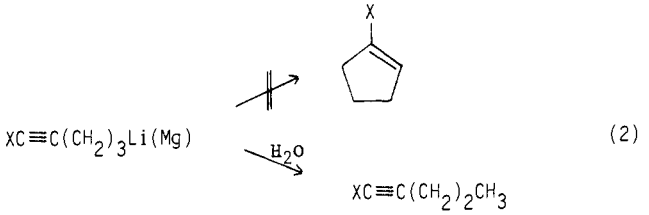
Scheme I



Scheme II

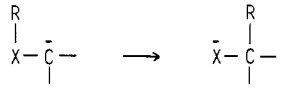


ruled out the carbene–cyclopentyne route (mechanism a, Scheme II). Similarly, mechanism c (cleavage–recombination) is unlikely as no acyclic products are formed in this reaction and acyclic (1-halopentynyl)lithium and Grignard reagents corresponding to the ring-opened anion do not cyclize (eq 2).[6]

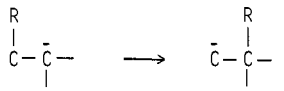


(2)

The carbanionic rearrangement of mechanism b (Scheme II) is also unattractive. Apart from the unlikely formation of a highly strained *trans*-cyclopentenyl anion, electronic considerations argue against such a process. While [1,2]-sigmatropic shifts of carbanions are known in systems where the migration origin is a heteroatom (Wittig and Stevens rearrangements, eq 3)[8] and where the migrating group is sp^2- or sp-hybridized (eq 4),[9] a 1,2-shift



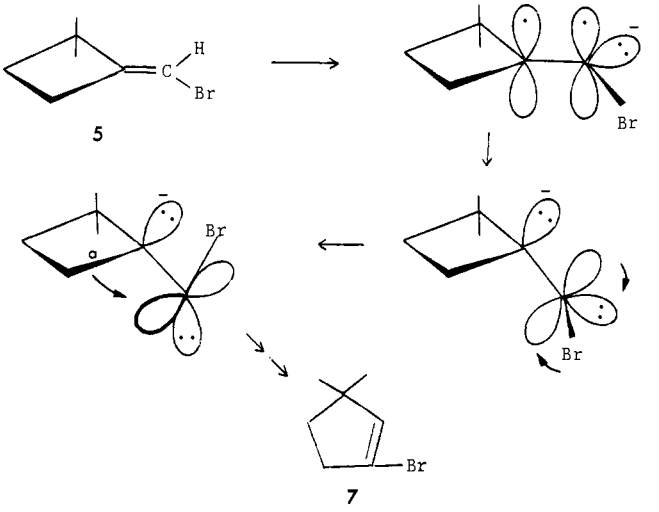
(3)



(4)

R = Aryl, Vinyl, Alkynyl

Scheme III



of an alkyl group to a carbanionic center has no precedent, and orbital symmetry theory predicts that it will not occur concertedly.[9a,10]

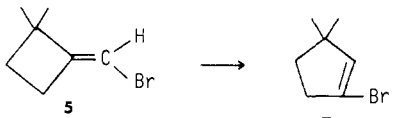
Although the direct alkyl-to-carbanion shift depicted in mechanism b (Scheme II) is unlikely, the fact that the rearranging

(8) (a) Schollkopf, U. *Angew. Chem., Int. Ed., Engl.* **1970**, *9*, 763. (b) Ollis, D. O.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009.

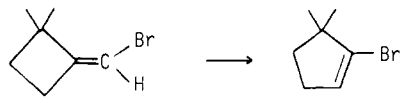
(9) (a) Grovenstein, E., Jr. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 313. (b) Grovenstein, E., Jr.; Chiu, K. W.; Patil, B. B. *J. Am. Chem. Soc.* **1980**, *102*, 5848. (c) Grovenstein, E., Jr.; Lu, P. C. *J. Org. Chem.* **1982**, *47*, 2928.

(10) Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic Press: New York, 180; Vol. I, Chapter 6.

species is a vinyl, rather than an alkyl carbanion, makes it possible to write other carbanionic-rearrangement mechanisms. Two such mechanisms[6] are outlined in Schemes III and IV and are based, in part, on the following well-established characteristics of the rearrangement reaction: (1) (Chloro-, bromo-, and iodomethylene)cyclobutanes all rearrange to the corresponding ring-enlarged vinyl halides,[3] while their saturated analogues do not.[6] (2) Vinyl ethers, amines, and sulfides do not react.[3,6] (3) A number of strong bases (*n*-BuLi, $NaNH_2$, molten KOH) effect the rearrangement.[3] (4) The rate is slowed considerably in polar and especially protic solvents.[1] Alternate reactions become predominant in aprotic solvents.[6] (5) Unsymmetrically substituted (halomethylene)cyclobutanes rearrange to give ring-enlarged halides whose structures reflect the stereochemistry of the starting material.[7] Thus:



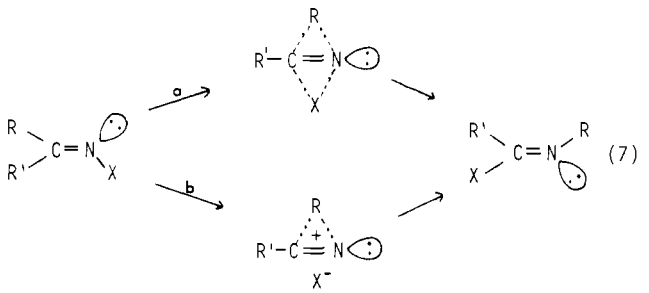
(5)



(6)

This last-named characteristic is especially intriguing and any proposed mechanism must account for it, as do the mechanisms presented in Schemes III and IV.[6] In Scheme III, rehybridization of the vinyl anion occurs, which then permits rotation about the exocyclic bond. The direction of rotation is such that eclipsing of the two unshared electron pairs is avoided and their separation is maximized. Bond a becomes parallel to the empty p orbital of the exocyclic carbon and an alkyl shift occurs from an electron-rich site (carbanion) to an electron-poor site (carbene). Rehybridization and protonation gives the final product.

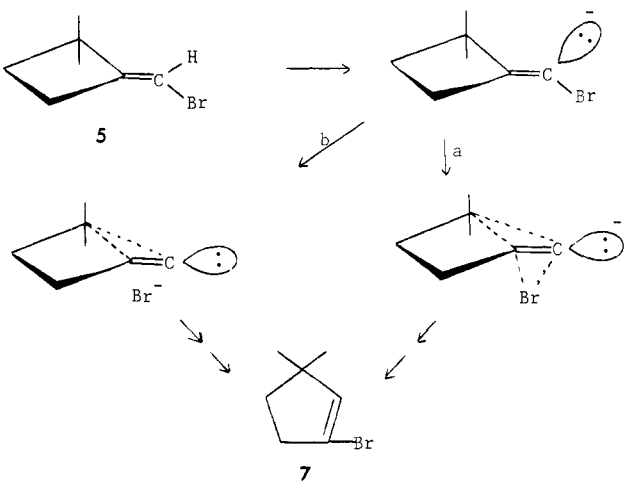
In Scheme IV, a simultaneous trans migration of two groups occurs in the carbanion (route a) or via a bromide–carbene complex (route b). The bromide dissociates but remains partially bonded or closely associated with the cyclobutyl moiety. In this double migration, the bromide exchanges positions with the ring carbon trans to it on the vinyl site. This mechanism is analogous to the Beckmann rearrangement of oximes (eq 7);[11] indeed, the latter compounds are isoelectronic with the vinyl carbanion.[4]



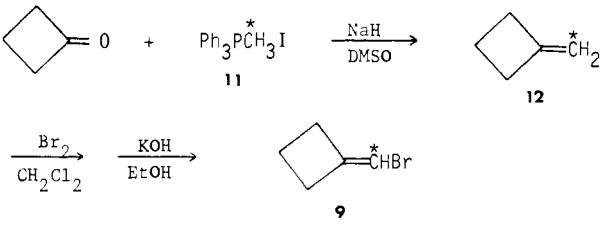
(7)

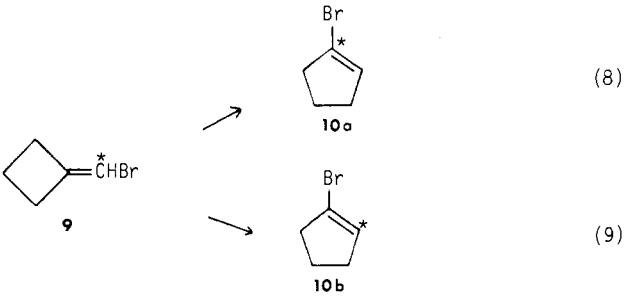
In order to distinguish between the rehybridization and the Beckmann mechanisms, labeling experiments are required. In the rehybridization mechanism, the bromide remains attached to the same carbon throughout; the ring bond cis to the bromide migrates. In the Beckmann mechanism, the bromide migrates to the adjacent vinyl carbon, and the ring bond trans to the bromide migrates. If (bromomethylene-^{13}C)cyclobutane (**9**) was used as the substrate, the rehybridization process would yield 1-bromocyclopentene-*1*-^{13}C (**10a**) (eq 8) while the Beckmann process would yield 1-bromocyclopentene-*2*-^{13}C (**10b**) (eq 9). This paper describes the results of studies with **9**, its symmetrically substituted tetramethyl, and its unsymmetrically substituted dimethyl analogues.

Scheme IV



Scheme V





(8)

(9)

Synthesis of Labeled Compounds

A series of ^{13}C-labeled (bromomethylene)cyclobutanes were prepared for the rearrangement studies (Schemes V–VIII). Various modifications of the Wittig reaction were employed to convert the appropriate cyclobutanones to the methylene compounds, the immediate precursors of the vinyl bromides. ^{13}C NMR spectra of these compounds confirmed the fact that only the exocyclic vinyl carbon atom was labeled.

Corey's method[12] involving the methylsulfinyl anion to generate the ylide from labeled methyl-^{13}C-triphenylphosphonium iodide (**11**) was employed in the preparation of methylene-^{13}C-cyclobutane (**12**). Bromination–dehydrobromination[3] afforded the desired (bromomethylene-^{13}C)cyclobutane (**9**) (Scheme V).

3-Ethoxy-2,2-dimethylcyclobutanone (**13**) was prepared by a cycloaddition reaction between dimethylketene and ethoxyethylene following the procedure of Hasek and co-workers.[13] Better yields and shorter reaction times resulted when acetonitrile was used as the solvent and the ethoxyethylene was used in excess. With **13**, Bestmann's method[14] of employing sodium bis(trimethylsilyl)amide in hexamethylphosphoramide for the Wittig reaction gave the best yields of 3-ethoxy-2,2-dimethyl-1-(methylene-

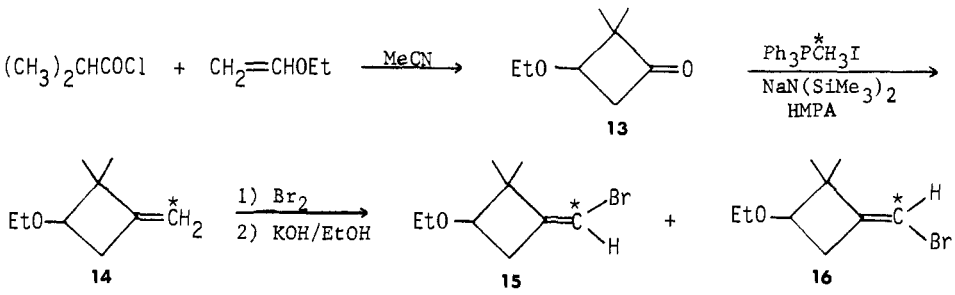
(11) Conley, R. T.; Ghosh, S. *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1971; Vol. 4, p 197.

(12) Grunwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

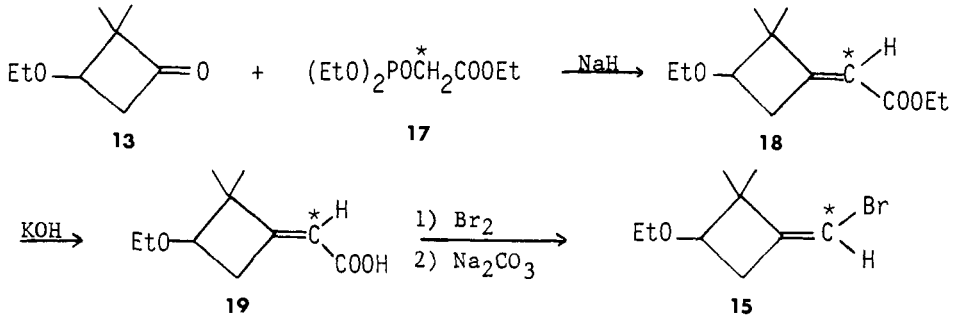
(13) Hasek, R. H.; Gott, P. G.; Martin, J. C. *J. Org. Chem.* **1964**, *29*, 1239.

(14) Bestmann, H. J.; Stansky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694.

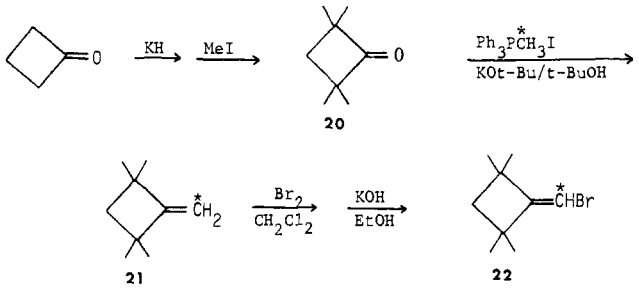
Scheme VI



Scheme VII



Scheme VIII



^{13}C)cyclobutane (**14**). Bromination–dehydrobromination afforded a mixture of **15** and **16** in ratios averaging 30/70–35/65 (Scheme VI). Assignment of stereochemistry to the two isomers was made by comparison of their ^1H NMR spectra with spectra of their analogues, **5** and **6**, whose structures were previously established.[7] In particular, the vinyl hydrogen in the cis isomer absorbs at higher field than that of the trans isomer (δ 5.75 for **15** vs δ 5.90 for **16** compared to δ 5.62 for **6** vs δ 5.77 for **5**). These isomers were not readily separable and were generally rearranged as a mixture.

cis-1-(Bromomethylene-^{13}C)-3-ethoxy-2,2-dimethylcyclobutane (**15**) was prepared essentially free of the trans isomer (**16**) via the stereocontrolled synthesis shown in Scheme VII.[7,15] The Wadsworth–Emmons version[16] of the Wittig reaction afforded ethyl *trans*-(3-ethoxy-2,2-dimethylcyclobutylidene)acetate-2-^{13}C (**18**). Hydrolysis to the acid (**19**) followed by bromination and decarboxylative debromination[7] afforded the labeled cis isomer **15**. On standing in the cold, **15** slowly isomerized to the trans isomer **16** (see the Experimental Section).[17]

Scheme VIII illustrates the syntheses in the tetramethyl series. Cyclobutanone was permethylated with potassium hydride and methyl iodide to give 2,2,4,4-tetramethylcyclobutanone (**20**).[18] In this case, potassium *tert*-butoxide/*tert*-butyl alcohol[19,20] was the system of choice to effect the Wittig reaction. 1-(Bromomethylene-^{13}C)-2,2,4,4-tetramethylcyclobutane (**22**) was obtained by bromination–dehydrobromination of the Wittig product (**21**).

Table I. Product Ratios from **15** and **16** at 36 °C

initial **15**/**16** ratio	product ratio (**23**/**24**)
94/6	82/14
86/14	75/25
77/23	73/27
23/77	33/67

Results

The substrates were rearranged with potassium *tert*-butoxide under two different sets of reaction conditions: at 36 °C in refluxing pentane (3 h) and at 100 °C in the absence of solvent (10 min). In all cases a minimum of two separate runs were made under both sets of reaction conditions. Chromatographically pure samples were used. All products were distilled and isolated by vapor-phase chromatography. Products were identified by their spectral and analytical data. ^{13}C NMR assignments were made on the basis of chemical shifts and multiplicities (from APT[21] spectra). The aqueous phase of the product mixture from **9** was analyzed for bromide by standard gravimetric techniques (precipitation with $AgNO_3$). The balance of the bromine was invariably found in ionic form.

Compounds **15** and **16** were rearranged as a mixture to easily separable products **23** and **24**. Pure cis isomer **15** gave rearranged bromide **23** together with small amounts of **24**. The latter compound arises from the isomerization of **15** under the reaction conditions. To establish the extent of isomerization, the cis compound (**15**) was subjected to low-temperature reaction conditions for varying lengths of time. The unreacted starting material was recovered and its cis/trans ratio was measured by integration of the gas-chromatograph peak areas and/or the vinyl hydrogen absorptions in the ^1H NMR spectrum (δ 5.75 vs δ 5.90, respectively). Compound **15**, when stirred for 1 h in a pentane suspension of potassium *tert*-butoxide at 25 °C, underwent less than 10% isomerization; at 36 °C, 13–18% isomerization was observed after 1 h, during which time the rearrangement reaction was 60–98% complete (dependent upon the amount of potassium *tert*-butoxide present). This isomerization under the reaction conditions complicates the situation; nevertheless, it is clear that the products obtained are a function of the stereochemistry of the starting

(15) Walborsky, H. M.; Banks, R. B. *Bull. Soc. Chim. Belg.* **1980**, *89*, 849.
(16) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
(17) This type of isomerization of exocyclic vinyl bromides has been previously reported: Suzuki, M.; Kurosawa, E. *Tetrahedron Lett.* **1978**, 4805.
(18) Millard, A. A.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 1834.
(19) Schlosser, M.; Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 636.
(20) Morton, D. R.; Turro, N. J. *J. Am. Chem. Soc.* **1973**, *95*, 3947.
(21) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.

Table II. Reaction of **9**, **15**, **16**, and **22** with KO-*t*-Bu

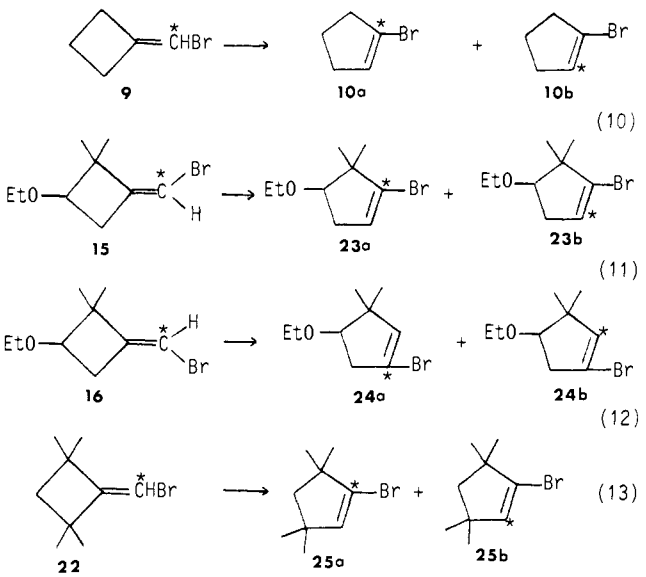
compd	reaction conditions	% yield of **10**, **23**–**25**[a]	ratio of **b**/**a**
9	36 °C, pentane	60	1.1/1.0
15[b]	36 °C, pentane	62	0.5/1.0
16[b]	36 °C, pentane	62	2.6/1.0
22	36 °C, pentane	84	3.4/1.0
9	100 °C, neat	24	1.3/1.0
15[b]	100 °C, neat	23	1.0/1.0
16[b]	100 °C, neat	23	1.7/1.0
22	100 °C, neat	74	3.5/1.0

[a] Isolated yields. [b] As a 94/6 mixture of **15**/**16**.

material as was observed for the dimethyl compounds **5** and **6**.[7] Table I illustrates this point.

Isomers **23** and **24** was distinguished by ^1H and ^{13}C NMR. The allylic protons in **24** are further downfield than those of **23** (δ 2.70 vs δ 2.35). The same holds true for the carbon bearing these allylic protons (δ 44.55 vs δ 36.23). The bromine atom adjacent to the allylic carbon in **24** accounts for this deshielding effect. In addition, the proton $J_{\text{vinylic-allylic}}$ value is expected to be smaller for **24** than for **23**,[22] and this is found to be the case (1.8 vs 2.6 Hz).

The C-13 enrichments at the labeled carbons were determined by NMR on samples with added $Cr(AcAc)_3$ and inverse gated broad-band ^1H decoupling (see the Experimental Section). The results are summarized in eq 10–13 and Table II.



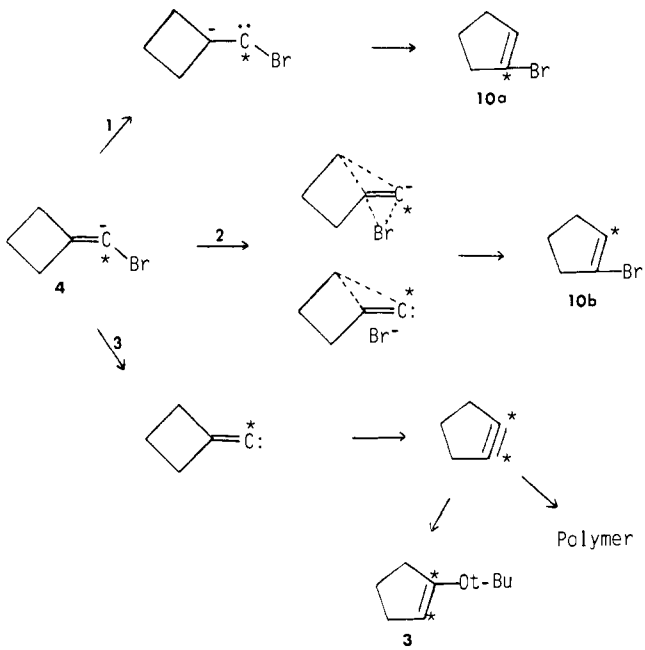
Control experiments have established that the label is not scrambled before nor after the rearrangement. Subjecting **9** to the reaction conditions and quenching the reaction prior to completion affords recovered **9** with the label intact at C-1. Similarly, subjecting **25** to the two sets of reaction conditions leads to a 72–76% recovery (isolated yield) of **25** with the label ratio unchanged.

Discussion

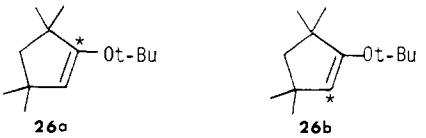
The labeling studies show that, in all cases, the label is found in the rearranged product at both vinyl carbons. The relative amount of label at each vinyl carbon, however, is a function of substrate structure and the reaction temperature. These results support the involvement of more than one mechanism. Scheme IX summarizes three mechanisms which differ only in the degree to which the bromide is allowed to dissociate. Route 1 (Scheme IX) is the rehybridization pathway of Scheme III, where the bromide remains attached to C-1 throughout the reaction; route 2 (Scheme IX) is the Beckmann pathway of Scheme IV, where the bromide dissociates but remains partially bonded or closely associated with the cyclobutyl moiety. Both of these paths lead

(22) Smith, G. V.; Kriloff, H. *J. Am. Chem. Soc.* **1963**, *85*, 2016.

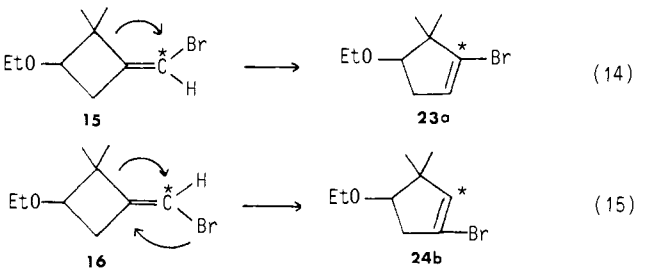
Scheme IX



to rearranged bromides which differ only in the position of the label. Route 3 (Scheme IX) is the familiar carbene–cycloalkyne mechanism of Scheme II, wherein the bromide becomes completely detached and remains so. The cyclopentyne produced from the carbene polymerizes, but it can be trapped with 1,3-diphenylisobenzofuran (vide ante) or in small amounts with the excess potassium *tert*-butoxide. In the present studies, only the 100 °C reaction of **22** afforded isolable yields of ring-enlarged *tert*-butyl enol ether **26** (8%). Significantly, in this compound the label was equally distributed between the two vinyl carbons, revealing its cyclopentyne origin.



The Beckmann pathway (route 2, Scheme IX) gives the b product series (eq 10–13 and Table II) arising from migration of the ring carbon trans to the bromide. It is the preferred process for all compounds studied with the exception of **15**, which at low temperature favors the rehybridization pathway by a 2:1 margin. This may be explained on the grounds that with **15** the more electron-rich ring carbon migrates in the rehybridization process (eq 14) while for **16** the more electron-rich ring carbon migrates in the Beckmann process (eq 15). The effect of adjacent methyl



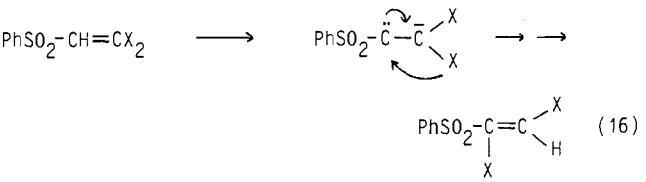
substitution is more clearly seen when comparing **9** with **22**. The Beckmann mechanism is 3 times more favored than the rehybridization mechanism when the migrating carbon bears two methyl groups.

In general, increased reaction temperatures lead to increased bromide dissociation as evidenced by increased Beckmann products relative to rehybridization products and increased carbene–cycloalkyne products relative to bromide products at 100 °C. The one exception here is compound **16**, which shows a decreased

Beckmann/rehybridization ratio at increased temperatures. This may simply reflect an increased dissociation of the carbene–bromide complex of route 2 (Scheme IX) to the free carbene of route 3 (without an equivalent shift in the route 1 vs route 2 pathways).

The combination of processes depicted in Scheme IX accommodates all of the experimental characteristics of the base-induced rearrangement reaction of (halomethylene)cyclobutanes. The carbene–cycloalkyne pathway, long known to be operative in these systems,[2] is irrevelant in discussing the origin of the halocyclopentene products; these apparently arise by routes 1 and 2 instead.

In the intervening years since the rehybridization and Beckmann mechanisms were first postulated,[6] a few scattered reports have appeared dealing with carbene–anions, the species involved in the rehybridizations process. Cohen and co-workers[23] have generated carbene–anions from dianions where the carbene site is two or more atoms removed from the carbanion site. More pertinent to the present case is a recent report[24] which postulates the intermediacy of a 1,2-carbene–anion in the fluoride-induced rearrangement of β,β-dihalovinyl sulfones (eq 16). The substantial



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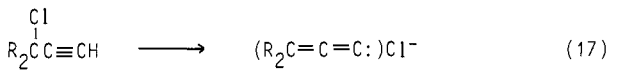
contribution of the carbene–anion resonance form is ascribed to the anion-stabilizing effect of the two halogen substituents. The carbene–anion form of **4** lacks such stabilizing groups. However, the rehybridization of the vinyl ring carbon from sp^2 to sp^3 with its attendant relief of strain may well provide sufficient driving force.

With respect to carbene–anion complexes, possible intermediates in the Beckmann mechanism, le Nobel and co-workers[25] have provided evidence for an allenic carbene–chloride complex generated from a propargyl halide (eq 17). Thus, the rehybridization



(17)

and Beckmann mechanisms of Schemes III and IV (and Scheme IX) may not be as rare as one would have initially supposed, although both are unprecedented in carbocyclic systems. These are technically carbanionic rearrangements, but the vinylic nature of the carbanion allows the reaction to proceed via a carbene–carbanion or a carbene–halide complex. Perhaps this is as close as one can come to the illusive alkyl-to-carbanion shift.

Experimental Section

General Procedures. Commercial chemicals were used without purification unless noted otherwise. Reaction solvents were dried and distilled before use: ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl in an inert atmosphere. Monoglyme was predried over KOH, stirred with 0.4% $NaBH_4$, and distilled successively from CaH_2 and K under an inert atmosphere. Benzene was dried by azeotropic distillation, rejecting the first 10% of the distillate. Dimethyl sulfoxide (DMSO) was distilled from CaH_2 in vacuo. *tert*-Butyl alcohol and triethylamine were distilled from CaH_2. Acetonitrile was predried over $MgSO_4$ and K_2CO_3 and was then distilled successively from CaH_2 and P_2O_5; it was stored over 3A molecular sieves.

All melting and boiling points were uncorrected. Analytical thin-layer chromatography (TLC) was done on commercial BakerFlex (silica gel IB_2F), and preparative TLC was done on Brinkmann HF 254 + 366 type 60 silica gel. Vapor-phase chromatography (VPC) was carried out with a Varian-Aerograph A90-P3 instrument with 10% Carbowax 20M columns (10 ft × $^1/_8$ in. or 10 ft × $^1/_4$ in.) on Anakrom Q, 80/100. Infrared spectra (IR) were recorded on Perkin-Elmer Models 137, 710B, and 1330 spectrophotometers. Nuclear magnetic resonance (NMR) spectra were obtained on Perkin-Elmer R-24B (60 MHz) and Brucker WP-250 spectrometers in $CDCl_3$ unless otherwise noted. Elemental analyses were performed by Desert Analytics, Tucson, AZ, and Galbraith Laboratories, Inc., Knoxville, TN.

NMR Analyses on ^{13}C-Labeled Compounds. Samples were dissolved in $CDCl_3$ with 0.05–0.10 M chromium(III) acetoacetonate [$Cr(AcAc)_3$]. The typical operating conditions were as follows: 30° pulse, repetition time = 1.2 s, 16 or 32K data set, 1.0 Hz line broadening, inverse gated broad-band ^{1}H decoupling. Spectra of natural abundance samples with added $Cr(AcAc)_3$ showed that the integrals of all the signals were equal within ±5.9%.

Relative ^{13}C-enrichment values were obtained by comparison of the enriched with the natural abundance samples: The average of the integrals over the vinyl carbon signals was assigned a value of 1, and all other signal integrals were standardized to this scale. The same was done for the labeled samples with $Cr(AcAc)_3$. Relative enrichments were calculated as the ratios of the standardized integrals for the labeled sample vs the integrals for the natural abundance sample.

Methyl-^{13}*C*-triphenylphosphonium Iodide (11). Iodomethane-^{13}*C* (10% enriched, 50.0 g, 0.353 mol) was added dropwise to 101 g (0.384 mol) of triphenylphosphine in 300 mL of anhydrous benzene cooled in an ice bath. Precipitation began immediately. The mixture was stirred at 25 °C for 2 h and the precipitate was collected by filtration. It was then dissolved in 150 mL of hot methylene chloride and was diluted with a mixture of 150 mL of methylene chloride and 150 mL of THF. The solution was concentrated on a steam bath to ~200 mL and was then cooled to 25 °C to give 130.0 g (0.322 mol, 91%) of **11**, mp = 182–184 °C (lit.[26] mp = 184–186 °C).

Methylene-^{13}*C*-cyclobutane (12). Sodium hydride (1.55 g, 0.032 mol), 50% oil dispersion, was placed in a three-necked flask under Ar. The NaH was washed several times with pentane by decantation. The flask was then fitted with a condenser, a drying tube, and a dropping funnel equipped with an Ar inlet tube. Anhydrous DMSO (17 mL) was added dropwise, and then the mixture was heated at a bath temperature of 75 °C for 1 h. The mixture was cooled in ice, and a solution of methyl-^{13}*C*-triphenylphosphonium iodide (**11**) (10% enriched) (13.3 g, 0.033 mol) in 30 mL of warm DMSO was added dropwise. The solution was then stirred at 25 °C for 15 min and cyclobutanone (2.25 g, 0.032 mol) in 5 mL of DMSO was added dropwise. After stirring of the mixture for 1 h, a bulb-to-bulb distillation at 20 mm was carried out while the bath temperature was maintained at <75 °C. The distillate, collected in a dry ice cooled receiver, afforded 1.94 g (0.029 mol, 89.5%) of **12** (10% enriched) contaminated with small amounts of benzene. The distillate was used directly in the next step.

1-(Bromomethylene-^{13}*C*)cyclobutane (9). Methylene-^{13}*C*-cyclobutane (**10**) (10% enriched) (1.95 g, 0.029 mol) was dissolved in 25 mL of methylene chloride containing 1.3 mL of anhydrous pyridine, and the mixture was cooled in an ice bath. Bromine (~2 mL) was added dropwise until the color persisted. Stirring was continued at 0 °C for 15 min after addition of the bromine. The reaction mixture was washed successively with aqueous $NaHSO_3$, 6 M HCl (until the washings were acidic), and finally water. The organic layer was dried over $MgSO_4$, and after filtration, the solvent was removed in vacuo to give crude dibromide (3.56 g, 0.016 mol, 55%).

The dibromide was dissolved in a solution of 3 g of KOH in 30 mL of 95% ethanol, and the resulting solution was refluxed for 3 h. Water was added, and the aqueous mixture was extracted with pentane. The pentane extracts were washed with water and were dried over $MgSO_4$. The pentane was removed by fractional distillation. Distillation of the residue under reduced pressure gave 2.50 g (0.011 mol, 71%) of (bromomethylene-^{13}*C*)cyclobutane (**9**) (10% enriched), bp_{60} = 62 °C (lit.[27] bp = 61–63 °C). The IR and ^{1}H NMR were identical with those reported earlier.[3] ^{13}C NMR δ 146.17 (C-1), 95.93 (CHBr), 31.3 (C-2 or C-4), 30.71 (C-2 or C-4), 15.78 (C-3).

Triethyl Phosphonoacetate-*2*-^{13}*C* (17). Freshly distilled triethylphosphite (10.04 g, 0.061 mol) was placed in a 50-mL three-necked flask equipped with a dropping funnel, a magnetic stirrer, and a distillation head attached to a condenser, an adapter, and a receiver. Stirring was begun as 20.0 g (0.060 mol) of ethyl bromoacetate-*2*-^{13}*C* (10% enriched) was added dropwise over 1 h. The temperature was increased to 100 °C, and the ethyl bromide began to distill. The reaction mixture was maintained at 170 °C for 7 h and was then subjected to distillation under reduced pressure. The fraction boiling at 90–93 °C (0.35 mm) was collected to give 12.8 g (0.057 mol, 95%) of triethyl phosphonoacetate-*2*-^{13}*C* (**17**) (10% enriched); lit.[27] $bp_{0.8}$ = 109–109.5 °C.

(23) Cohen, T.; Ritter, R. H.; Ouellette, D. *J. Am. Chem. Soc.* **1982**, *104*, 7142. Cohen, T.; Yu, L. C. *Ibid.* **1983**, *105*, 2811.
(24) Shainyan, B. A.; Mirskova, A. N.; Vitkovskii, V. Yu. *J. Org. Chem. USSR (Engl. Transl.)* **1985**, *21*, 877.
(25) le Noble, W. J.; Chiou, D. M.; Okaya, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3244.
(26) Wittig, G.; Geissler, A. *Liebigs Ann. Chem.* **1953**, *580*, 44.
(27) Wolinsky, J.; Erickson, K. L. *J. Org. Chem.* **1965**, *30*, 2208.

3-Ethoxy-2,2-dimethylcyclobutanone (13). A stirred solution of triethylamine (13.6 g, 0.135 mol), freshly distilled ethoxyethylene (14.4 g, 0.200 mol), and anhydrous acetonitrile (30 mL) was treated dropwise over 30 min with a solution of 12.8 g (0.118 mol) of isobutyryl chloride in 15 mL of acetonitrile. The amine salt began to precipitate immediately. The reaction mixture was heated to 90 °C (oil bath) for 4 h. After cooling, the mixture was filtered and was evaporated in vacuo to remove the solvent. The crude ketone was distilled under reduced pressure to give 12.0 g (67%) of **13**, bp_{13} = 62–64 °C (lit.[13] bp_{38} = 82–83 °C).

Dimerization of the ketene intermediate can be minimized in this reaction if vigorous stirring is maintained and excess ethoxyethylene is used.

3-Ethoxy-2,2-dimethyl-1-(methylene-^{13}C)cyclobutane (14). Methyl-^{13}C-triphenylphosphonium iodide (10% enriched, 4.04 g, 0.010 mol) was added to a solution of sodium bis(trimethylsilyl)amide[28] (1.83 g, 0.010 mol) in 25 mL of hexamethylphosphoramide. The solution turned yellow. The mixture was stirred for 2 h at 25 °C, and then ketone **13** (1.42 g, 0.010 mol) was added dropwise; the solution immediately turned red. Stirring was continued overnight at 25 °C and then the solution was flash distilled under reduced pressure. The distillate was collected in a dry ice cooled receiver to give 1.30 g (93%) of **14** (10% enriched) contaminated with small amounts of benzene and hexamethyldisilazane, which did not interfere with the next step and hence were not removed. Preparative gas chromatography afforded pure product: IR (neat) 2940, 2860, 1665, 1470, 1450, 1335, 1125, 875 cm^{-1}, ^1H NMR (60 MHz) δ 4.80 (2 H, m), 3.55 (3 H, m), 2.6–2.8 (2 H, m), 1.15 (6 H, s), 1.15 (3 H, t).

1-(Bromomethylene-^{13}C)-3-ethoxy-2,2-dimethylcyclobutanes (15 and 16). A solution of **14** (10% enriched) (0.720 g, 0.005 mol) and pyridine (0.500 g, 0.005 mol) in 15 mL of methylene chloride was cooled in an ice bath. Bromine (1.50 g, 0.009 mol) was added dropwise. Stirring was continued at 0 °C for 15 min after the addition was complete. The solution was then washed successively with aqueous $NaHSO_3$, 6 M HCl (until the washings were acidic), water, and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was refluxed with a solution of 1.00 g of KOH in 10 mL of 95% ethanol for 3 h, and then water was added and the mixture was extracted with pentane. The pentane extracts were washed with water and were dried over $MgSO_4$. The pentane was removed by fractional distillation, and the residue was flash distilled to give 0.65 g (59%) of a 70/30 mixture of **16**/**15**: IR (neat) 2940, 2860, 1665, 1450, 1335, 1230, 1190, 1125 cm^{-1}; ^1H NMR (60 MHz) δ 5.90 (1 H, t), 5.74 (1 H, t), 3.50 (6 H, m), 2.65 (4 H, dddd), 1.40 (6 H, s), 1.30 (6 H, s), 1.20 (6 H, t); ^{13}C NMR δ 149.24, 146.09, 96.72, 95.44, 77.02, 76.62, 64.97, 64.89, 50.76, 50.26, 36.33, 36.21, 25.87, 24.67, 20.75, 17.88, 15.16 (2 carbons). Anal. Calcd for $C_9H_{15}BrO$ (unlabeled sample): C, 49.32; H, 6.85. Found: C, 49.32; H, 7.03.

Ethyl (3-Ethoxy-2,2-dimethylcyclobutylidene)acetate-2-^{13}C (18). Sodium hydride (1.63 g, 0.032 mol), 50% oil dispersion, was put into a three-necked flask under Ar and was washed several times with pentane by decantation. Anhydrous monoglyme (20 mL) was added to the NaH followed by dropwise addition of a solution of 7.15 g (0.032 mol) of **17** (10% enriched) in 15 mL of monoglyme. The solution was stirred at 25 °C for 30 min and then 4.47 g (0.035 mol) of ketone **13** was added dropwise. After one additional hour of stirring, water was added and the mixture was extracted with ether. The combined ether layers were washed with water and were dried over $MgSO_4$. The ether was removed in vacuo, and the residue was distilled to give 4.61 g (0.024 mol, 66%) of colorless ester **18** (10% enriched): $bp_{0.08}$ = 55–60 °C; IR (neat) 2890, 2870, 2830, 1720, 1680, 1370, 1340, 1270, 1180, 1120, 1100, 1060, 1040, 980, 860 cm^{-1}; ^1H NMR (60 MHz) δ 5.65 (1 H, m), 4.15 (2 H, q), 3.2–3.8 (3 H, m), 2.8–3.1 (2 H, m), 1.20 (12 H, s). Anal. Calcd for $C_{12}H_{20}O_3$ (unlabeled): C, 67.92; H, 9.43. Found: C, 67.62; H, 9.43.

(3-Ethoxy-2,2-dimethylcyclobutylidene)acetic Acid-2-^{13}C (19). Ester **18** (10% enriched) (4.61 g, 0.024 mol) was dissolved in 40 mL of 95% ethanol containing 2.00 g (0.036 mol) of KOH. The solution was refluxed for 4 h and then cooled and poured into cold water. The aqueous solution was extracted with ether, and the aqueous layer was acidified. The yellow oil which formed was separated from the water by ether extraction. The combined ether extracts were dried over $MgSO_4$ and the ether was removed in vacuo to give 3.16 g (0.019 mol, 80%) of crude **19**. The crude acid was dissolved in a minimum amount of 50% aqueous ethanol at 55 °C. Cooling afforded 2.49 g (0.015 mol, 63%) of purified **19** (10% enriched): mp = 61–62 °C; IR ($CHCl_3$) 2940, 2855, 1695, 1640, 1410, 1335, 1280, 1110, 860 cm^{-1}; ^1H NMR (60 MHz) δ 11.7 (1 H, s), 5.68 (1 H, m), 3.0–3.9 (5 H, m), 1.20 (3 H, t), 1.20 (6 H, = s).

***cis*-1-(Bromomethylene-^{13}C)-3-ethoxy-2,2-dimethylcyclobutane (15).** Acid **19** (10% enriched) (2.49 g, 0.015 mol) was dissolved in 15 mL of methylene chloride, and the solution was cooled in an ice bath. Bromine (3.10 g, 0.019 mol) was added dropwise with stirring; after complete addition, stirring was continued at 25 °C for 6 h. The solution was washed successively with aqueous $NaHSO_3$ and water, and then the organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The residue was suspended in 70 mL of 10% aqueous Na_2CO_3, and the mixture was subjected to steam distillation. The distillate was extracted with pentane; the pentane extracts were dried over $MgSO_4$, and the solvent was removed in vacuo. The residue afforded 1.41 g (0.007 mol, 47%) of **15** (10% enriched). A sample of **15** purified by VPC displayed the following spectral characteristics: IR (neat) 3090, 2980, 2940, 2880, 1665, 1460, 1340, 1200, 1130, 1060, 770 cm^{-1}; ^1H NMR (60 MHz) δ 5.75 (1 H, t), 3.51 (3 H, m), 2.70 (2 H, dddd), 1.40 (3 H, s), 1.30 (3 H, s), 1.20 (3 H, t); ^{13}C NMR δ 145.99 (C-1), 95.34 (CHBr), 77.08 (C-3), 64.97 (CH_2O), 50.76 (C-2), 36.36 (C-4), 24.67 (CH_3), 17.89 (CH_3), 15.19 (CH_3).

On standing at 0 °C for 2 weeks, **15** isomerized to a 75/25 mixture of **15**/**16**. After 10 weeks, the ratio of **15**/**16** was 63/37 and after 1.5 years, the ratio had reached **24**/**76**.[17]

2,2,4,4-Tetramethylcyclobutanone (20).[18] Potassium hydride (35% oil dispersion, 35.0 g, 0.306 mol) was placed in a 500-mL three-necked flask under Ar and was washed several times with pentane by decantation. Anhydrous THF (250 mL) was added. At 25 °C, 5.00 g (0.071 mol) of cyclobutanone was added dropwise. After complete addition, stirring was continued for 5 min and then iodomethane (28.3 mL, 0.458 mol) was added dropwise over 15 min. The mixture was then stirred for an additional 15 min before water (25 mL) was carefully added. The mixture was filtered to remove solids, and the filtrate was extracted with pentane. The pentane layers were washed with water and dried over $MgSO_4$, and the solvent was removed by fractional distillation. The residue was purified by bulb-to-bulb transfer in vacuo (30 mm). The distillate froze in the dry ice cooled receiver. The yield of **20** averaged 38%.

2,2,4,4-Tetramethyl-1-(methylene-^{13}C)cyclobutane (21). Potassium *tert*-butoxide (freshly sublimed, 5.60 g, 0.050 mol) was dissolved in a mixture of 30 mL of anhydrous *tert*-butyl alcohol and 120 mL of anhydrous ether in a flask fitted with a dropping funnel, a condenser, a drying tube, an Ar inlet tube, and a dry ice trap. After dissolution of the butoxide, 15.2 g (0.038 mole) of methyl-^{13}C-triphenylphosphonium iodide (**11**) (10% enriched) was added. Stirring was continued at 25 °C for 2 h, during which time the color became yellow. 2,2,4,4-Tetramethylcyclobutanone (3.15 g, 0.025 mol) was added dropwise, and the reaction mixture was stirred for an additional 21 h at 25 °C under Ar. Vacuum filtration removed the solids, and the filtrate was distilled to remove the ether. The residue was extracted with pentane; the pentane layer was washed with 50% aqueous methanol and was dried over $MgSO_4$. The solvents were removed by fractional distillation, and the residue was distilled under reduced pressure to give 52% of **21** (10% enriched) in the 45–50 °C boiling fraction (90 mm). This sample contained small amounts of benzene and recovered ketone, neither of which was removed before the next step.

A VPC-pure sample displayed the following: IR (CCl_4) 3050, 2950, 2920, 2850, 1660, 1460, 1440, 1360, 880 cm^{-1}; ^1H NMR (60 MHz) δ 4.60 (2 H, s), 1.65 (2 H, s), 1.15 (12 H, s).

1-(Bromomethylene-^{13}C)-2,2,4,4-tetramethylcyclobutane (22). A mixture of **21** (1.68 g, 0.013 mol, 10% enriched) and pyridine (1.03 g, 0.013 mol) was cooled in an ice bath with stirring. Bromine was added dropwise until the red color persisted. The mixture was then stirred for 30 min at 25 °C. It was washed successively with aqueous $NaHSO_3$, 6 M HCl, aqueous $NaHCO_3$, and water. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo to give the crude dibromide (2.37 g, 0.008 mol, 64%).

The dibromide (4.48 g, 0.016 mol) was treated with a solution of 8.00 g of KOH in 70 mL of 95% ethanol at rflux for 3 h. The mixture was cooled, diluted with water, and extracted with pentane. The pentane layers were dried over $MgSO_4$, and the pentane was removed by fractional distillation. The residue was distilled under reduced pressure to give 2.28 g (0.011 mol, 71%) of **22** (10% enriched), bp_7 = 43 °C. A VPC-pure sample displayed the following: IR (CCl_4) 3050, 2950, 1640, 1360, 1275, 1180 cm^{-1}; ^1H NMR (60 MHz) δ 5.70 (1 H, s), 1.68 (2 H, s), 1.32 (6 H, s), 1.16 (6 H, s); ^{13}C NMR δ 162.40 (C-1), 94.65 (CHBr), 47.42 (C-3) 39.95 (C-2 or C-4), 39.37 (C-2 or C-4), 29.36 (CH_3), 26.35 (CH_3). Anal. Calcd for $C_9H_{15}Br$ (unlabeled): C, 53.22; H, 7.44. Found: C, 53.41; H, 7.62.

Potassium *tert*-Butoxide Induced Rearrangements of Vinyl Halides. General Procedure. In Pentane Solvent. Freshly sublimed potassium *tert*-butoxide (10% excess) was suspended in pentane in a flask equipped with a reflux condenser, a drying tube, a magnetic stirrer, an Ar inlet, and a septum cap. The system was heated to reflux and the labeled vinyl bromide was injected by syringe. After 3 h at reflux, water was added and the reaction mixture was extracted with pentane. The combined pentane layers were washed with water and dried over $MgSO_4$, and the

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pentane was removed by fractional distillation. The residue was subjected to flash distillation under reduced pressure; all volatiles were collected in a dry ice cooled receiver. The volatile products were purified by preparative gas chromatography. All yields reported are isolated yields of purified products.

Without Solvent. Freshly sublimed potassium *tert*-butoxide (100% excess) was placed in a flask equipped with a condenser, a drying tube, an Ar inlet tube, and a septum cap. The butoxide was heated to an oil-bath temperature of 100 °C and then the labeled vinyl bromide was injected beneath the surface of the base via a syringe. The mixture was maintained at 100 °C for 10 min, cooled, and water was added to it. The water was extracted with pentane, and the pentane layers were washed with water and dried over $MgSO_4$. The pentane was removed by fractional distillation, and the residue was flash distilled under reduced pressure; all volatiles were collected in a dry ice cooled receiver and were purified by preparative gas chromatography. All reported yields are isolated yields of purified products.

Rearrangement Products. 1-Bromocyclopentene (10):[27] IR ($CHCl_3$) 2270, 2855, 1620, 1440, 1315, 1040, 1010, 945, 900 cm^{-1}; ^1H NMR (250 MHz) δ 5.84 (1 H, m), 2.57 (2 H, m), 2.30 (2 H, m), 1.98 (2 H, m); ^{13}C NMR δ 130.94 (C-2), 120.74 (C-1), 39.51 (C-5), 32.29 (C-3), 23.18 (C-4).

1-Bromo-4-ethoxy-5,5-dimethylcyclopentene (23): IR (neat) 2940, 2860, 1610, 1450, 1335, 1125, 1040, 990, 880, 815 cm^{-1}; ^1H NMR (60 MHz) δ 5.75 (1 H, t), 3.60 (3 H, m), 2.35 (2 H, dddd), 1.20 (3 H, t), 1.12 (3 H, s), 1.00 (3 H, s); ^{13}C NMR δ 132.20 (C-1), 125.39 (C-2), 85.44 (C-4), 65.48 (CH_2O), 49.58 (C-5), 36.23 (C-3), 26.09 (CH_3), 19.10 (CH_3), 15.40 (CH_3). Anal. Calcd for $C_9H_{15}BrO$: C, 49.32; H, 6.85. Found: C, 49.21; H, 6.95.

1-Bromo-4-ethoxy-3,3-dimethylcyclopentene (24): IR (neat) 2985, 2900, 1612, 1470, 1350, 1125, 1030, 845, 795 cm^{-1}; ^1H NMR (60 MHz) δ 5.75 (1 H, t), 3.58 (3 H, m), 2.70 (2 H, dddd), 1.20 (3 H, t), 1.10 (3 H, s), 1.00 (3 H, s); ^{13}C NMR δ 140.29 (C-2), 116.42 (C-1), 86.28 (C-4), 65.76 (CH_2O), 48.21 (C-3), 44.56 (C-5), 27.20 (CH_3), 20.66 (CH_3), 15.41 (CH_3). Anal. Calcd for $C_9H_{15}BrO$: C, 49.32; H, 6.85. Found: C, 49.21; H, 6.95.

1-Bromo-3,3,5,5-tetramethylcyclopentene (25): $bp_{2.5}$ = 31 °C; IR (neat) 3050, 2960, 1620, 1365, 1320, 850 cm^{-1}; ^1H NMR (60 MHz) δ 5.55 (1 H, s), 1.75 (2 H, s), 1.11 (6 H, s), 1.10 (6 H, s); ^{13}C NMR δ 138.75 (C-2), 131.29 (C-1), 52.65 (C-4), 48.19 (C-5), 43.54 (C-3), 30.25 (CH_3), 29.07 (CH_3); Anal. Calcd for $C_9H_{15}Br$: C, 53.22; H, 7.44. Found: C, 53.37; H, 7.65.

1-*tert*-Butoxy-3,3,5,5-tetramethylcyclopentene (26): IR 3100, 3000-2900, 1655, 1380, 1200, 1160; ^1H NMR (250 MHz) δ 4.28 (1 H, s), 1.50 (2 H, s), 1.31 (9 H, s), 1.06 (6 H, s), 1.03 (6 H, s); ^{13}C NMR δ 157.58 (C-1), 106.94 (C-2), 52.00, 44.89, 39.68, 32.13, 28.61, 27.93.

Treatment with 2,4-dinitrophenylhydrazine in ethanolic H_2SO_4 gave the 2,4-dinitrophenylhydrazone derivative of 2,2,4,4-tetramethylcyclopentanone, purified by TLC (4% ether/petroleum ether), mp = 146-148 °C; lit.[29] mp = 145-146 °C.

Incomplete Reaction of 1-(Bromomethylene-^{13}C)cyclobutane (9) with Potassium *tert*-Butoxide. A 200-mg sample of **9** (10% enriched) was subjected to the rearrangement reaction conditions at 36 °C in pentane. After 30 min, 35% rearrangement had occurred. The reaction mixture was worked up and unreacted **9** was recovered and was analyzed by ^{13}C NMR. All of the label was located on the bromomethylene carbon; no scrambling had occurred.

Reaction of 1-Bromo-3,3,5,5-tetramethylcyclopentene (25) with Potassium *tert*-Butoxide. A. In Pentane Solvent. A 150-mg sample of a 3.4/1.0 mixture of **25b**/**25a** was subjected to the rearrangement conditions for 3 h. Workup afforded a 72% recovery of **25** and no other volatile products. ^{13}C NMR analysis showed the ratio of **25b**/**25a** to be unchanged (3.4/1.0).

B. Without Solvent. A 460-mg sample of a 3.5/1.0 mixture of **25b**/**25a** was subjected to the rearrangement conditions for 10 min. Workup gave 76% recovered **25** as the only volatile product with the **25b**/**25a** ratio unchanged (3.5/1.00).

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Stereochemical Studies in Crystal Nucleation. Oriented Crystal Growth of Glycine at Interfaces Covered with Langmuir and Langmuir-Blodgett Films of Resolved α-Amino Acids[§]

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Abstract: In a stereochemical approach aimed at the understanding of crystal nucleation on a molecular level, the oriented crystallization of glycine at air-solution interfaces covered with monolayers **1-12** of resolved α-amino acids has been studied. Three types of monolayers with different packing motifs of the polar head groups have been used. Coverage of a supersaturated aqueous glycine solution with monolayers **1** and **2** did not lead to crystallization at the interface; on the other hand, coverage with monolayers **3-8** yielded a fast crystallization with only partial orientation. Finally, monolayers **9-12** yielded a fast nucleation of glycine with complete orientation of the crystals. These results imply that the packing of the polar head groups determines the nucleation rate and the degree of orientation of the attached growing crystals. This conclusion is strongly substantiated by the assignment of the structures of monolayers **3** and **9** using grazing-angle X-ray diffraction and reflectivity measurements from a synchrotron light source. Crystallization experiments were performed on solid hydrophobic glass supports coated with Langmuir-Blodgett films of monolayers of **1**, **3**, **4**, **6**, **9**, and **11**; in all cases the results were similar to those observed with the corresponding Langmuir monolayers.

I. Introduction

Although crystal nucleation is central to many processes in the living and inanimate world, its understanding and control on a molecular level is still at a rudimentary stage. Fundamental questions, such as the number of molecules needed for the nucleus to cross the critical size and the role played by surfaces and the solvent or foreign additives present in solution in the promotion or inhibition of primary or secondary nucleation, require clarification.

Studies of crystal nucleation that are based on thermodynamic

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