Protolytic Cleavage of Cyclopropanes. The Two Mechanisms for the Acid-Catalyzed Cleavage of 1-Phenylcyclopropylmethyl Ether[1]

Michael A. McKinney* and Elisa C. So

Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53233

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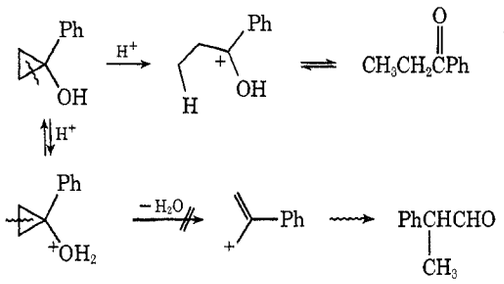
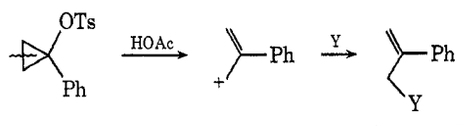
The kinetics of cleavage of 1-phenylcyclopropylmethyl ether (1) in acid solution has been measured as a function of sulfuric acid concentration in 64–75 wt % acid. The ether was found to cleave by two mechanisms: a normal rate-determining protonation of the carbon–carbon bent bond of the cyclopropyl ring leading to propiophenone (2) and a reversible protonation of the ether oxygen followed by the loss of methanol leading to 2-phenylpropionaldehyde (5). It was shown that 2-phenylallyl alcohol (4) is a reasonable intermediate in the reaction which produces 5. The percentages of 2 and 5 formed were a function of acid concentration. A kinetic scheme has been outlined to allow calculation of the rates of formation of 2 and 5 over the acid range studied. The "pK_a" of protonated 1 is estimated from the data to be −5.06. The reactivity of 1 is compared to those of other 1-substituted phenylcyclopropanes and the reactivities are discussed in terms of initial-state inductive effects.

Recently there has been a good deal of interest in the chemistry of cyclopropanols both in terms of mechanism of reaction[2] and as intermediates in organochemical synthesis.[3] Cyclopropanols are cleaved in acid solution by a rate-determining protonation at carbon with retention of configuration.[4] The sole product of cleavage of 1-phenylcyclopropanol in acid solution is propiophenone.[4] Thus, proton attack occurs at C_2 or C_3 and the carbon–carbon bond adjacent to the hydroxyl group is cleaved. Proton attack at oxygen followed by loss of water leading to cleavage of the C_2–C_3 bond is not observed. Cyclopropyl tosylates[5,6]



undergo solvolytic ring cleavage in acetic acid, producing allyl acetates. The bond cleaved in this case is across the ring from the leaving tosylate group.



Y = OAc and OTs

Although the acid cleavage of cyclopropyl methyl ethers has been used synthetically to prepare quaternary α-methyl compounds,[3] the mechanism of cyclopropyl ether cleavages in general has not been extensively studied. The only mechanistic study reported involves the cleavage of cyclopropyl methyl ethers with mercuric acetate.[7] The cleavage was found by DePuy to be a bimolecular process with the mercury(II) attacking the least substituted ring carbon. The reaction proceeds with inversion of configuration at the site of electrophilic attack.

We have examined the acid-catalyzed cleavage of 1-phenylcyclopropyl methyl ether (1) and we find, in marked contrast to the cleavage of 1-phenylcyclopropanol,[4] that the cyclopropyl ether cleaves by way of two competitive pathways. The first is that operative in the acid-catalyzed ring opening of cyclopropanols[4] and arylcyclopropanes,[8] namely, a rate-determining protonation on carbon. The second involves reversible protonation on oxygen followed by loss of methanol. The acidity of the medium determines which mechanistic pathway predominates.

Experimental Section[9]

Preparation of Materials. 1-Phenylcyclopropylmethyl Ether (1).—This ether was synthesized through Simmons–Smith[10] methylene addition to α-methoxystyrene, which was prepared by elimination of hydrogen iodide from 2-methoxy-2-phenylethyl iodide.[11] Distillation at reduced pressure gave 1: bp 75–77° (12 mm) [lit.[7] bp 50° (2 mm)]; nmr (CCl_4) δ 0.92 (m, 2, cyclopropyl), 1.12 (m, 2, cyclopropyl), 3.25 (s, 3, $-OCH_3$), and 7.5 (s, 5, $-C_6H_5$). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.54; H, 8.30.

2-Phenyl Allyl Alcohol (4).—This alcohol was prepared by the oxidation of α-methylstyrene with selenium dioxide[12] in acetic acid–acetic anhydride. The acetate ester obtained was reduced with lithium aluminum hydride and the crude product was distilled, bp 73° (0.25 mm) [lit.[12] bp 116–118° (11 mm)].

2-Phenylpropionaldehyde (5) and propiophenone (2) were purchased from Aldrich Chemical Co., Milwaukee, Wis. Both were distilled at reduced pressure before use.

Product Study.—To determine the products obtained from the reaction of 1 or 4 with aqueous sulfuric acid, 100–200 mg of the substrate was dissolved in 5 ml of absolute ethanol and the solu-

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(2) For a recent review, see C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

(3) (a) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Amer. Chem. Soc.*, **92**, 7428 (1970); (b) E. Wenkert and D. A. Berges, *ibid.*, **89**, 2507 (1967); (c) R. E. Ireland, D. R. Marshall, and J. W. Tilley, *ibid.*, **92**, 4754 (1970).

(4) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *ibid.*, **88**, 3347 (1966).

(5) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *ibid.*, **87**, 4006 (1965).

(6) C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966).

(7) A. DeBoer and C. H. DePuy, *ibid.*, **92**, 4008 (1970).

(8) M. A. McKinney, S. H. Smith, S. Hempelman, M. M. Gearen, B. V. M., and L. Pearson, *Tetrahedron Lett.*, 3657 (1971).

(9) Boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratory, Skokie, Ill. The nuclear magnetic resonance spectra were recorded at 60 Mc with a Varian A-60A spectrometer.

(10) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(11) S. Winstein and L. L. Ingraham, *ibid.*, **77**, 1738 (1955).

(12) L. Hatch and T. Patton, *ibid.*, **76**, 2705 (1954).

tion was injected by means of a syringe into 1 l. of sulfuric acid of known concentration. The reaction mixture was stirred for 5–7 half-lives reaction and poured into 2 l. of ice–water, and the resulting solution was extracted with three portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution to neutrality, dried over sodium sulfate, and concentrated. The concentrated product mixture was analyzed by glc.[13] The concentrated reaction mixture obtained from 1 in sulfuric acid showed two peaks in the chromatogram. These were identified as 2 and 5 by comparison of the retention time and nmr spectra of collected samples with those of authentic samples.

Only a single product was obtained in the analysis of the concentrated reaction mixture from 4 in sulfuric acid. It was identified as 5 by comparison of retention time and nmr spectra with those of an authentic sample.

Kinetic Procedure.—For the ring opening of 1 in sulfuric acid, the rates of the reaction were determined by observing the increase in optical density at the absorption maximum of 2 or protonated 2 at 255 or 285 nm, respectively. The ultraviolet spectrophotometer[14] was set at a fixed wavelength and optical density *vs.* time curves were recorded. For the rearrangement of 4 in sulfuric acid, the disappearance of 4 was followed at 238 nm.

The kinetic runs were initiated by injecting 50 μl of a stock solution (*ca.* 1×10^{-3} *M*) of substrate in absolute ethanol into 30 ml of acid solution contained in a 10-cm spectrophotometric cell. Prior to injection, the acid solution was allowed to equilibrate to the constant temperature maintained in the cell compartment. The rate of increase or decrease in optical density was recorded for at least ten half-lives reaction, after which a product spectrum was taken from 400 to 210 nm. From the product spectrum at different acid concentrations, the extent of reaction was calculated. Pseudo-first-order rate constants were obtained as the slope of a plot of ln $(A_\infty - A)$ *vs.* time.

The acid solutions used were prepared from reagent grade concentrated sulfuric acid and distilled water. The weight per cent sulfuric acid was determined by titration of a weighed sample of acid solution with standard sodium hydroxide solution.

Results

In terms of acid catalysis there are two mechanisms by which a cyclopropyl ether can react. The first is the mechanism by which cyclopropanols cleave,[2] namely, a rate-determining protonation of the carbon–carbon bent bond of the cyclopropane ring. Such a mechanism of cleavage for 1-phenylcyclopropylmethyl ether is shown below (eq 1–4).

The second mechanism involves the reversible protonation of the ether oxygen followed by a rate determining loss of methanol leading to products (eq 5–9).

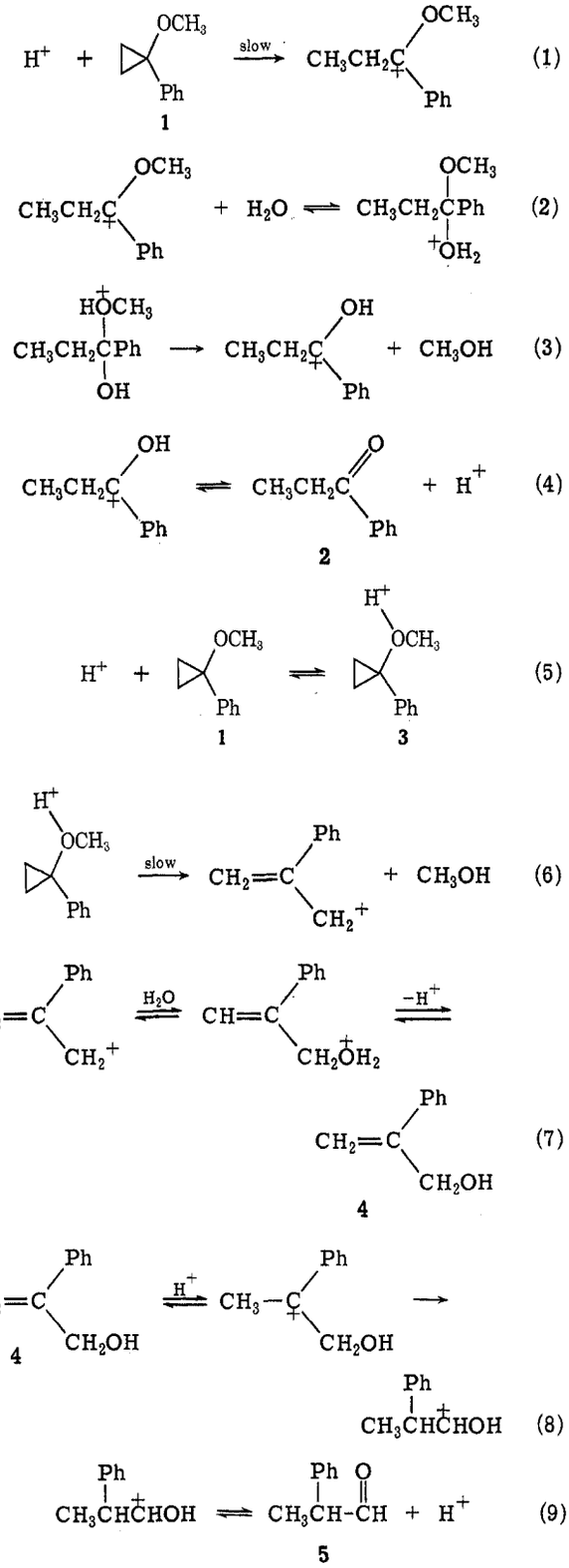
The two mechanistic pathways are distinguishable because each leads to a different product.

The cyclopropyl ether 1 was found to cleave in 65–75 wt % sulfuric acid, yielding propiophenone (2) and 2-phenylpropionaldehyde (5). The rate of appearance of 2 was followed spectrophotometrically and the relative composition of the product mixtures was determined from the relation

$$\frac{[2]}{[5]} = \frac{\epsilon_{\text{mixture}} - \epsilon_5}{\epsilon_2 - \epsilon_{\text{mixture}}}$$

where $\epsilon_{\text{mixture}}$ is the molar extinction coefficient of the product mixture, and ϵ_2 and ϵ_5 are the molar extinction coefficients for the pure compounds in the appropriate acid at a fixed wavelength. The reaction product composition was also determined by glc analysis of the product mixtures isolated from the appropriate acid. The product compositions and the observed pseudo-first-order rate constants for the appearance of 2, as a function of acid concentration, are given in Table I.

The proposed intermediate in the formation of 5, 2-phenylallyl alcohol (4), was found to be converted to 5 at a conveniently measurable rate in 37–50 wt % sulfuric acid. The rate of disappearance of 4 as a func-



(13) Vapor phase analyses were made with a Hewlett-Packard F & M Scientific 700 laboratory chromatograph equipped with a thermal conductivity detector and a Leeds and Northrup nonintegrating recorder. A 6 ft × 0.25 in. aluminum column packed with 20% SE-30 on 80–100 mesh Chromosorb W was used.

(14) Ultraviolet spectra were recorded on a Cary Model 14 recording spectrophotometer equipped with a constant-temperature cell compartment regulated by a Precision Scientific Co. constant temperature and circulating bath with a Philadelphia microset thermoregulator.

Table I

Product Composition and Observed Rate of Cleavage of 1-Phenylcyclopropylmethyl Ether (1) in Sulfuric Acid at 25°

Wt % H_2SO_4	$-H_0$	% Ketone Uv[a]	% Ketone Glc[a]	$10^4 k_{obsd}$, sec^{-1}[b]
64.19	4.96	92.0	96.5	1.31
67.16	5.37	89.0		2.11
70.86	5.93	87.0	90.0	3.83
73.45	6.32	75.4	79.0	6.86
74.00	6.40	72.0	73.0	8.31
75.95	6.70	60.0	63.0	11.3

[a] The percentage listed is for propiophenone. The balance of product is 2-phenylpropionaldehyde. [b] The rate constants given are the average of at least two determinations; the initial concentration of 1 in all the kinetic runs was 8.5×10^{-6} M.

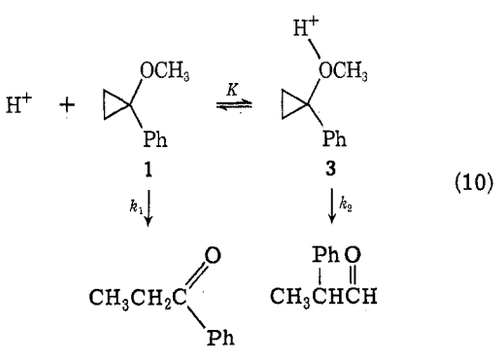
tion of acid concentration was measured spectrophotometrically and the data are given in Table II. Extrapolation of the linear log k *vs.* $-H_0$ plot[15] for reaction of **4** to higher acid concentrations allows a calculation of the expected half-life for reaction of **4** in 64.19% sulfuric acid. At this acid concentration, the weakest acid used in the cleavage of **1**, the half-life for the rearrangement of **4** to **5** would be 8.4×10^{-4} sec. Thus, **4** is a reasonable intermediate in the formation of **5** from **3**.

Table II

Rates of Rearrangement of 2-Phenylallyl Alcohol (4) in Sulfuric Acid at 25°

Wt % H_2SO_4	$-H_0$	$10^3 k_{obsd}$, sec^{-1}
36.97	2.21	0.383
38.50	2.32	0.472
41.90	2.56	1.00
45.28	2.88	1.94
47.81	3.14	3.48
48.74	3.24	4.10
50.46	3.42	6.29

The acid cleavage of 1-phenylcyclopropylmethyl ether (**1**) therefore proceeds according to the scheme shown in eq 10.



(10)

Here k_1 is the pseudo-first-order rate constant for SE2 cleavage of **1**, k_2 is the first-order rate constant for the solvolytic cleavage of **3**, and K is the ratio of **3**:**1** at a given acid concentration. The three differential equations which can be written for the scheme with their solutions are given in ref 16. Using the data of Table I and the equations given below,[16] the following relationships must hold for the cleavage of **1** in 64.19% sulfuric acid. The independent knowledge of k_1 or K

$$\frac{k_1}{k_2K} = \frac{[2]_\infty}{[5]_\infty} = 16.3 \qquad \frac{k_1}{K+1} = k_{obsd}[2]_\infty = 1.23 \times 10^{-4}\ sec^{-1}$$

would allow calculation of the other two variables. Although k_1 and K cannot be measured independently, k_1 can be estimated. The lower limit for k_1 is 1.2×10^{-4} sec^{-1}. A value smaller than this would make K negative. It has been observed by DePuy[7] that cyclopropanols are cleaved by mercuric acetate 10–20 times faster than their methyl ether derivatives when an SE2 mechanism of cleavage is operative. If a rate ratio of 10 is assumed for the relative rate of cleavage of 1-phenylcyclopropanol[17] to **1** in 64.19% sulfuric acid, a value of 2.3×10^{-4} sec^{-1} is obtained for k_1. At this acid concentration the cyclopropyl ether is cleaved in an SE2 fashion to the extent of 94% (see Table I). The values of K and k_2 thus obtained are 0.84 and 1.64×10^{-5} sec^{-1}, respectively. If the acidity dependence of protonation of **1** is assumed to be similar to the methyl ethers studied by Arnett,[18] a value of -5.06 is obtained for the "pK_a" of **3**. The pK_a's of the methyl ethers studied by Arnett correlated with Taft's substituent parameters,[19] σ^*, indicating that inductive effects are of major importance in determining the acidity of these oxonium ions. If the correlation is used to calculate the "pK_a" of **3**, a value of -5.89 is obtained.[20] The knowledge of the "pK_a" of **3** allows a calculation of k_1, k_2, and K for all the acid concentrations studied. These values are compiled in Table III.

Table III

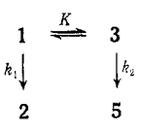
Calculated Values of k_1, k_2, and K

Wt % H_2SO_4	K[a]	$10^4 k_1$, sec^{-1}	$10^4 k_2$, sec^{-1}
64.19	0.84	2.26	0.164
67.16	1.80	5.26	0.340
70.86	5.20	20.9	0.525
73.45	10.76	62.1	1.71
74.00	12.6	82.2	2.89
75.95	21.9	152.0	4.35

[a] A plot of log K *vs.* $-H_0$ was used to calculate K. A slope of 0.83 was assumed. This slope is the average of the slopes observed for the seven methyl ethers studied by Arnett, ref 18.

(15) The rate data fit the relation $\log k = -1.00H_0 - 5.62$.

(16) The three differential equations which can be written for the scheme



are $d[2]/dt = k_1[1]$, $d[5]/dt = k_2[3]$, and $-d[E]/dt = d[2]/dt + d[5]/dt$, where $[E] = [1] + [3]$. These equations may be solved to give $[2]_\infty = \frac{k_1[E]_0}{k_1 + Kk_2}$, $[5]_\infty = \frac{Kk_2[E]_0}{k_1 + Kk_2}$, and $k_{obsd} = \frac{k_1 + k_2K}{K+1}$, where $[2]_\infty$ and $[5]_\infty$ are the concentrations of **2** and **5**, respectively, after 10 half-lives reaction, $[E]_0$ is the initial concentration of **1** (assuming that there is no **3** present at $t = 0$), and k_{obsd} is the pseudo-first-order rate constant for the appearance of **2**.

(17) M. A. McKinney, Ph.D. Thesis, Illinois Institute of Technology, 1967.

(18) E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, **84**, 1680 (1962).

(19) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 619.

(20) The correlation equation for the methyl ethers is "pK_a" $= -3.90 - 3.33\Sigma\sigma^*$. A σ^* of 0.60 was used for Ph and a σ^* of 0.0 for cyclopropyl.

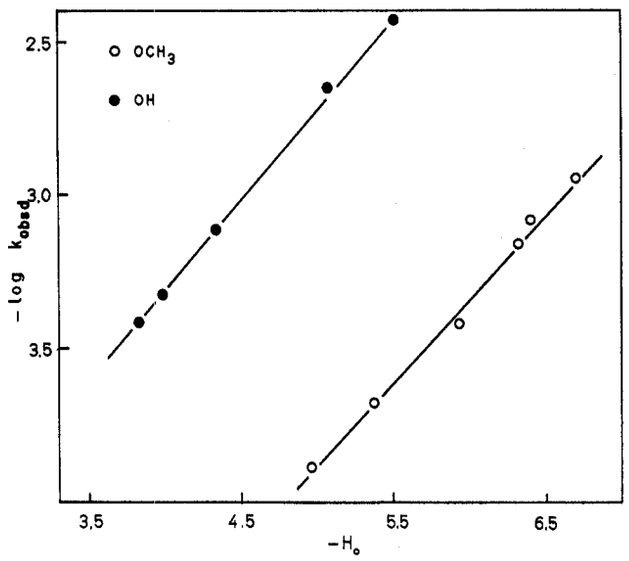
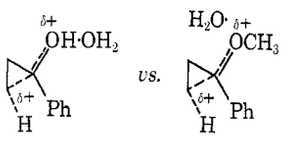


Figure 1.—The relationship between H_0 and log k_{obsd} for 1-phenylcyclopropylmethyl ether and 1-phenylcyclopropanol.

Discussion

Acidity Dependence.—The data of Tables II and III allow a comparison of the kinetic acidity dependence of the cleavage rates of 1-phenylcyclopropylmethyl ether (**1**) and 1-phenylcyclopropanol (**6**)[17] in sulfuric acid solution. The comparisons are shown graphically in Figures 1 and 2. The observed rate of cleavage of **1** shows a linear relationship between log k_{obsd} and $-H_0$ with a slope of 0.58 and the rates of cleavage of **6** exhibit a similar linear relationship with a slope of 0.59 (Figure 1). However, when account is made of the two distinct paths of cleavage of **1**, and the relationship between log k_1 and $-H_0$ is determined, a linear relationship with a slope of 1.11 is obtained (Figure 2).

This diverse acidity dependence behavior is nevertheless consistent with a single reaction mechanism when account is made of the solvation interactions present in the transition states for the two reactions. The transition state for cleavage of **6** can form a hydrogen bond with the solvent, whereas the corresponding transition state for the normal cleavage of **1** can only interact with the solvent electrostatically. These interactions are shown below.



As the water activity of sulfuric acid solutions decreases with increasing acid concentration, the water available for solvation is decreased. The transition state for the cleavage of **6** is destabilized to a greater extent than the transition state for cleavage of **1** by the water loss and, thus, the cleavage rates for **6** show a less steep acidity dependence than those of **1**. These effects are similar to those proposed to account for differences in protonation behavior between primary, secondary, and tertiary anilines[21] as well as the protonation behavior of phenols and phenol ethers.[22]

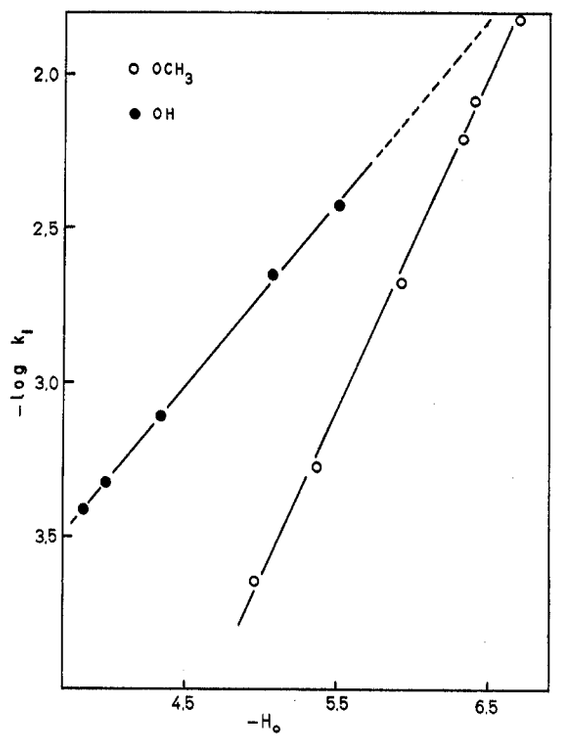


Figure 2.—The relationsnship between H_0 and log k_1 for 1-phenylcyclopropylmethyl ether and 1-phenylcyclopropanol.

Structure–Reactivity.—The data of Table III shows that the normal C_1–C_2 bond cleavage of **1** proceeds 14 to 40 times faster than the solvolytic C_2–C_3 bond cleavage of **3**, its protonated form. The solvolysis reaction can effectively compete with the normal cleavage, however, because the protonation equilibrium is shifted toward the oxonium ion in the acid range studied. The proposed dual mechanism of cleavage of **1** is not observed for 1-phenylcyclopropanol, owing to the greater C_1–C_2 bond cleavage reactivity of the cyclopropanol as well as to its lower basicity.

The cyclopropanol is more reactive than the cyclopropyl ether at relatively dilute sulfuric acid concentrations because of the hydroxyl group's ability to stabilize a carbonium ion center relative to a methoxyl group. Thus, phenol is brominated in acetic acid 90 times faster than anisole.[23] As seen in Figure 2, the reactivity order is reversed in more concentrated acid owing to the solvation effects noted above.

The kinetic data reported herein, and the data for cyclopropane[24] and the substituted phenylcyclopropanes reported previously,[8] allow a quantitative evaluation of the effect of substituents on the rate of ring cleavage. The pertinent data are summarized in Table IV. The data show that substitution of phenyl on a cyclopropane ring results in an almost eightfold rate *deceleration*. This is in contrast to the analogous hydration of olefins, where the substitution of phenyl at the 2 position of propene leads to a rate acceleration of 5000.[25] It therefore appears that the electron-with-

(21) R. W. Taft Jr., *J. Amer. Chem. Soc.*, **82**, 2965 (1960); E. M. Arnett and G. W. Mack, *ibid.*, **86**, 2671 (1964); **88**, 1177 (1966).

(22) A. J. Kresge, H. J. Chen, L. E. Hakka, and J. E. Kouba, *ibid.*, **93**, 6174 (1971), and references cited therein.

(23) P. B. D. de la Mare, *Tetrahedron*, **5**, 112 (1959).

(24) R. L. Baird and A. A. Aboderin, *J. Amer. Chem. Soc.*, **86**, 252 (1964).

(25) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, New York, N. Y., 1965, p 26.

Table IV

Rate Constants for the Reaction of Cyclopropane and Its Derivatives in Sulfuric Acid ($-H_0$ = 4.1) at 25°

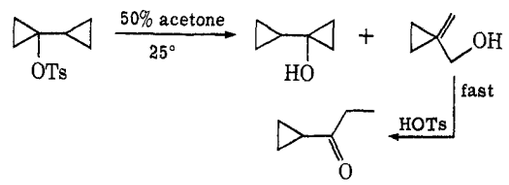
	$10^3 k_1$, sec^{-1}	k_{rel}	$-d \log k/dH_0$
 7	5.07[a]	113[d]	~1.0
 8	5.95[b]	133	1.18
 9	0.645[b]	14.5	1.25
 6	0.551[c]	12.3	0.59
 1	0.0447	1	1.11

[a] Calculated from the data in ref 24. [b] See ref 8. [c] This value is taken from ref 17. [d] Corrected for three equivalent sites of cleavage.

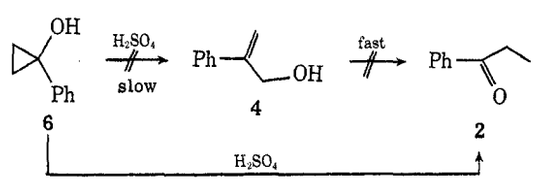
drawing inductive effect of the phenyl group is stabilizing the initial state to a greater extent than the resonance stabilization of the transition state. In the series of phenylcyclopropanes which have a 1 substituent, initial state inductive effects again play a predominant role in controlling reactivity. Thus, 1-methylphenylcyclopropane (**8**) is cleaved 9.2 times faster than phenylcyclopropane (**9**). The introduction of a hydroxyl group or a methoxyl group at C-1 of **9** caused a rate retardation relative to **9** of 0.85 and 0.07, respectively. The effect of substitution on the rate of ring cleavage is relatively independent of acid concentration except for **6**. At a sulfuric acid concentration of 20 wt % ($-H_0$ = 1.0), **6** is 10^3 times more reactive than **9**. This rate acceleration is similar to the 10^4 effect observed by DePuy[7] in the mercury(II) acetate cleavage of **6** relative to the similar cleavage of **9** studied by Ouellette.[26] However, 1-phenylcyclopropyl methyl ether does not exhibit such a reversal of reactivity relative to **9** and, thus, remains less reactive than **9** over a wide acid concentration range.

On the basis of the substituent effects discussed above on the reactivity of 1-substituted phenylcyclopropanes and the results reported earlier[8] on the reactivity and site of cleavage of C-1 and C-2 methyl-substituted phenylcyclopropanes, it appears that both initial- and transition-state electronic effects are important in controlling these reactions. The reactivity of the cyclopropane bent bonds toward a proton is determined by initial-state inductive effects of the substituents on the cyclopropane ring. Thus, phenyl, hydroxyl (in relatively concentrated acid), and methoxyl substitution cause a rate retardation while methyl substitution produces a modest rate acceleration. However, the site of cleavage appears to be controlled, at least in part, by the ability of the substituents to stabilize the carbon-bridged intermediates and/or transition states which are produced in these cleavages.[8]

Finally, it was recently found by Jewett[27] that 1-cyclopropylcyclopropyl tosylate hydrolyzes in aqueous acetone to unrearranged alcohol and ethyl cyclopropyl ketone. The latter product was found to arise from a rearrangement of 2-cyclopropylallyl alcohol and not a normal acid-catalyzed cleavage of 1-cyclopropylcyclopropanol as outlined below.



These results suggested that in other homoketonizations of cyclopropanols allylic alcohols may have been undetected intermediates which gave rise to the ketone products observed. Thus, 1-phenylcyclopropanol (**6**)



may cleave, in part, in acid solution by a solvolytic pathway giving 2-phenylallyl alcohol (**4**) as an initial product which then, in a fast step, rearranges to propiophenone (**2**).

That this is not the case if borne out by our results, which show that **4** rearranges to 2-phenylpropionaldehyde (**5**) in the acid range where **6** is cleaved to give **2**. It would therefore appear that the results of Jewett only pertain to the system he was studying and they do not necessitate a revision of the generally accepted mechanism for the homoketonization of cyclopropanols.[2]

Registry No.—**1**, 29526-97-4; **4**, 6006-81-1; **6**, 29526-96-3.

(26) R. J. Ouellette, R. D. Robins, and A. South, Jr., *J. Amer. Chem. Soc.*, **90**, 1619 (1968).

(27) B. A. Howell and J. G. Jewett, *ibid.*, **93**, 798 (1971).