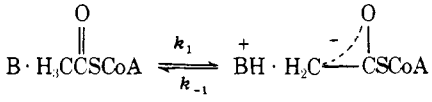
Unstable Carbanions. General Acid Catalysis of the Cleavage of 1-Phenylcyclopropanol and 1-Phenyl-2-arylcyclopropanol Anions[1]

Alf Thibblin and William P. Jencks*

Contribution No. 1265 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. *Received February 8, 1979*

Abstract: Cleavage of the anion of 1-phenylcylopropanol to 1-phenylpropanone in aqueous solution, a reverse aldol-type reaction, is subject to general acid catalysis by protonated tertiary amines with $\alpha = 0.25$, a primary deuterium (discrimination) isotope effect of $k_H/k_D = 1.9 \pm 0.2$ for quinuclidine-H^+ and water as proton donors to carbon, and a kinetic isotope effect of $k_{OH}/k_{OD} = 1.22 \pm 0.05$. 1-Phenyl-2-arylcyclopropanols cleave 10^5 times faster and show general acid catalysis with $\alpha \ll 0.1$ and an inverse kinetic isotope effect of $k_{OH}/k_{OD} = 0.7 \pm 0.1$ that indicate less proton transfer in the transition state. The Hammett ρ values for a small series of the cis and trans compounds are 5.0 and 4.0, respectively. It is concluded that these S_E2 displacements and some related reactions proceed through preassociation and concerted mechanisms that are determined by the short lifetimes of carbanion "intermediates".

We have been interested in the mechanisms that are available for reactions involving unstable carbanions for two reasons. First, it appears that the carbanion "intermediates" that have been implicated in a number of enzymic reactions are so unstable as to have, at best, a borderline existence. For example, the turnover number of 100 s^{-1} for citrate synthase[2] requires $k_1 \geq 100\ s^{-1}$ at the active site in eq 1 if the reaction

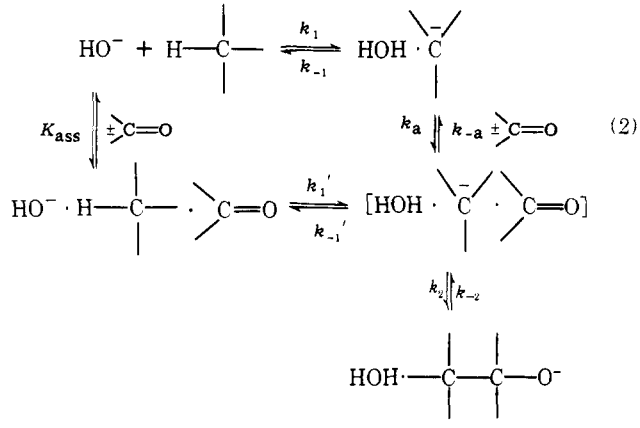


(1)

proceeds through an intermediate carbanion. A limiting value of $k_{-1} \ll 10^{13}\ s^{-1}$, on the order of a vibration frequency, gives $K_{eq} \gg 10^{-11}$. For a catalytic group of $pK = 7$ at the active site the pK_a for the dissociation of acetyl-CoA to a carbanion must then be $\ll 18 = 7 + \ll 11$. Analogous calculations give $pK_a \ll 15$ for the formation of a carbanion intermediate in the Δ^5-keto steroid isomerase reaction[3] and $pK_a \ll 17$ for such an intermediate at the active site of mandelate racemase.[4] If the pK_a values are higher than these, the values of k_{-1} will be larger than a vibration frequency so that the carbanion will have too short a lifetime to exist as an intermediate species. The pK_a values of these carbon acids in aqueous solution are not accurately known, but these limiting pK_a values are sufficiently low as to suggest that the enzymic reactions proceed through some mechanism that avoids or stabilizes such unstable species and that the carbanions have an extremely short lifetime if they do exist as intermediates.

Second, we would like to know the extent to which the mechanisms of reactions involving carbanions are determined by the lifetime of the carbanion "intermediate". It is known from the work of Cram and others that the behavior of carbon acids is determined in large part by the relative rates at which a carbanion undergoes reprotonation, racemization, rearrangement, or other reactions.[5] The mechanisms of general acid–base catalysis of many carbonyl additions and related reactions are determined in a simple way by the lifetimes of addition intermediates and follow a sequence of solvent-catalyzed, trapping, preassociation, hydrogen-bonding and concerted mechanisms as the intermediate becomes progressively less stable.[6-9] An analogous sequence has been suggested for reactions involving oxocarbonium ion "intermediates"[10] and may determine the mechanisms of reactions of phosphate compounds that are thought to generate metaphosphate-like species.

Consider the pathways for an aldol condensation shown in eq 2. When the carbanion is moderately stable the reaction will



(2)

occur through the stepwise mechanism involving proton abstraction (k_1), encounter with the carbonyl compound (k_a), and addition (k_2). However, when the carbanion becomes so unstable that it is reprotonated faster than the carbonyl compound can diffuse away from the species [HOH·$\gtrless$C$^-$·>C=O], so that $k_{-1}' > k_{-a}$, the reaction will proceed through the preassociation pathway along the bottom of eq 2. This mechanism involves an initial association of the reactants into an encounter complex (K_{ass}), followed by proton abstraction within the complex (k_1'). The reason for this is apparent from inspection of Figure 1, with B = HO^- and BH^+ = HOH. When reprotonation is faster than diffusion away of the carbonyl compound, so that the barrier for k_{-1}' is less than that for k_{-a}, the lowest energy path for reversion of the [HOH·>C$^-$·>C=O] complex to reactants is via k_{-1}'. The same path is then the lowest energy path for formation of the complex as well. Application of the same argument to the second part of the reaction leads to the conclusion that, when the carbanion adds to the carbonyl compound faster than water diffuses away, the water molecule will remain in place during the addition reaction and will serve as the proton donor for protonation of the carbanion in the reverse reaction of aldol cleavage.

The same situation applies for other bases, B, when the reaction proceeds through a ternary complex [BH^+·>C$^-$·>C=O] that undergoes reprotonation and C–C bond formation faster than diffusional separation.[11] If the carbanion becomes still less stable, so that the barriers for reprotonation and C–C bond formation disappear, the intermediate will not exist, a stepwise mechanism is not possible, and the reaction must proceed through a one-step, concerted mechanism.

The requirement for a preassociation mechanism may be

0002-7863/79/1501-4963$01.00/0

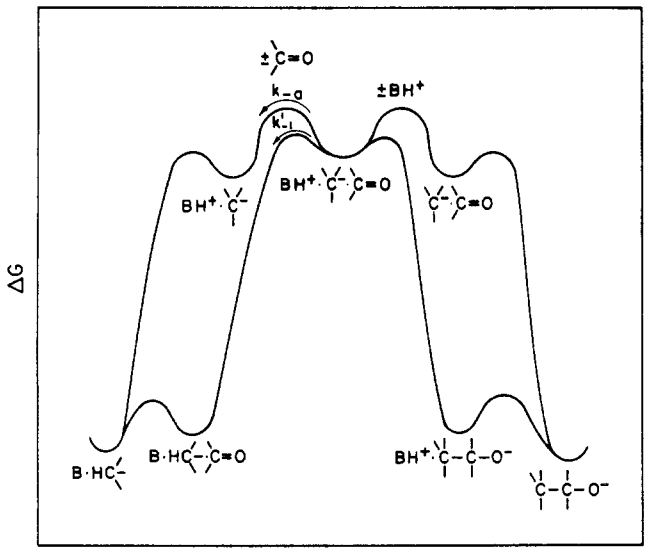


Figure 1. Gibbs free energy–reaction coordinate diagram to illustrate how a preassociation mechanism (lower lines) provides the lowest energy pathway for a reversible aldol condensation when the carbanion intermediate reacts sufficiently fast with water and with a carbonyl compound.

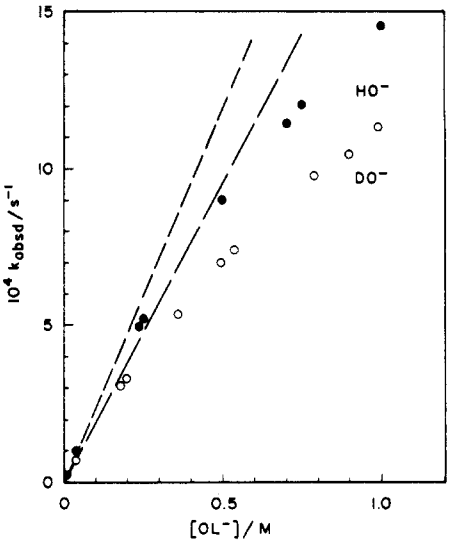


Figure 2. Dependence of the pseudo-first-order rate constants for the cleavage of 1-phenylcyclopropanol on the concentration of hydroxide ion (in H_2O) and deuteroxide ion (in D_2O) at 25 °C and ionic strength 1.0 M, maintained with potassium chloride. The dashed lines show the rate increase that would be expected if there were no ionization of the cyclopropanol.

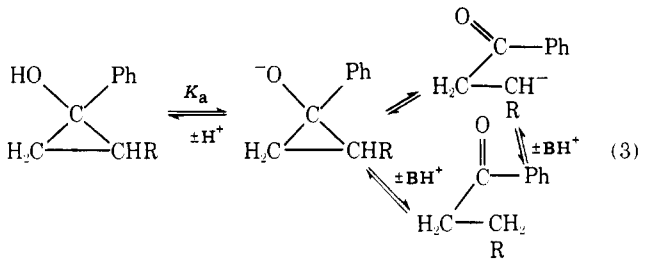
Table I. Rate Constants for the Base-Catalyzed Cleavage of 1-Phenylcyclopropanol to 1-Phenylpropanone at 25.0 ± 0.1 °C, Ionic Strength 1.0 M[a]

solvent	[KOL], M	10^3k_{OH}, M^{-1} s^{-1}	10^3k_2, s^{-1}
H_2O	0.0010	2.38	
H_2O	0.010	2.37	
H_2O	0.0375	2.32	
H_2O	0.24–1.00[b]	2.4[c]	3.7
H_2O	0.23–0.97[d]	2.5[c,d]	3.7
H_2O	0.040[d]	2.46	
H_2O	pH 12.00	2.80[e]	
H_2O	pH 12.00[f]	2.84[e,f]	
D_2O	0.358	1.90	
D_2O	0.18–0.99[b]	1.9[c]	2.7

[a] Maintained with KCl if not otherwise stated. [b] See Figure 2. [c] From the slope of a double reciprocal plot (eq 5). [d] Ionic strength 2.0 M. [e] Calculated using $[OH^-] = 10^{pH-14}$. [f] 75% Me_4NCl + 25% KCl.

generalized as follows. *The lowest energy pathway for a reaction that proceeds through an unstable intermediate complex containing the elements of three molecules involves a preassociation of the reactants prior to the first covalent step when the intermediate reverts to reactants (k_{-1}') faster than the final reactant can diffuse away (k_{-a}).*[12] The mechanism will involve general acid–base catalysis (a) when the catalyst provides significant stabilization of the transition state for the rate-limiting step, relative to the solvent, or (b) when one step is an addition, as in carbonyl addition reactions, and proton transfer with the solvent in the second step is slower than with a buffer acid or base (this situation does not require stabilization of the rate-limiting transition state by the catalyst, because the primary role of the catalyst is to bypass a different transition state that would be rate limiting in the absence of catalyst).

In order to obtain experimental evidence relevant to these considerations we have examined an aldol-type reaction in the cleavage direction by utilizing the strain energy of cyclopropanols to permit the generation of unstable carbanions at a convenient rate.[13] The base-catalyzed cleavage reactions of 1-phenylcyclopropanol and 1,2-diphenylcyclopropanol should generate the carbanions $R'CH_2^-$ and $R'PhCH^-$, which we expected would have a sufficiently short lifetime to give rise to an enforced preassociation or concerted mechanism with the proton donor already present in the transition state for C–C cleavage (lower pathway, eq 3). Our attention was directed to

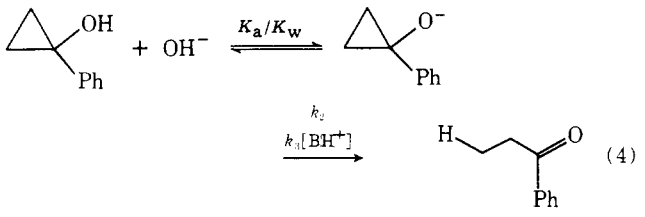


(3)

this reaction by the observation that the alkaline cleavage of 1,2,2-trimethylcyclopropanol exhibits a significant discrimination between protium and deuterium in heterogeneous H_2O–D_2O mixtures and the suggestion that the reaction is initiated by electrophilic attack of water on the alkoxide ion.[14]

Results

The observed pseudo-first-order rate constants for the base-catalyzed cleavage of 1-phenylcyclopropanol to 1-phenylpropanone (eq 3, R = H) increase linearly with increasing hydroxide ion concentration in dilute solution at ionic strength 1.0 M and give a second-order rate constant of k_{OH} = 2.4×10^{-3} M^{-1} s^{-1} (Table I). In more concentrated solutions of hydroxide ion the rate constants show a negative deviation from linearity that is attributed to conversion of a significant fraction of the cyclopropanol to the cyclopropoxide anion with the dissociation constant K_a (Figure 2).



(4)

Table II. General Acid Catalysis of 1-Phenylpropanone Formation in Water at 25.0 ± 0.1 °C, Ionic Strength 1.0 M[a]

acid	pK_a'	total buffer concn range, M	fraction as acid	k_{cat}/k_0, M^{-1} uncor	k_{cat}/k_0, M^{-1} cor	$10^3 k_{BH}$,[b] $M^{-2}\,s^{-1}$
water	15.74		1.00			0.043[c]
quinuclidine hydrochloride (QH^+)	11.55[d]	0.01-0.81	0.75	1.9	2.4 (2.1)[e]	5.7
		0.04-0.81	0.51	1.3	2.3 (1.8)[e]	5.5
in D_2O (QD^+)		0.04-0.84	0.76		1.9	3.7[f]
trimethylamine hydrochloride (TH^+)	10.16[g]	0.10-0.99	0.80	4.5	5.2	12
3-quinuclidinol hydrochloride (QLH^+)	10.13[d]	0.04-0.81	0.52	3.2	4.7	11
diazabicyclo[2.2.2]octane hydrochloride (DAH^+)	9.22[d]	0.03-0.63	0.25	6.5	11	26
piperidine hydrochloride (PIH^+)	11.42[g]	0.16-0.80	0.75	1.1	1.3	3.1
		0.02-0.80	0.72	1.0	1.3	3.1
dimethylamine hydrochloride (DMH^+)	11.11[h]	0.10-1.00	0.80	1.4	1.5	3.6
piperazine hydrochloride (PZH^+)	10.12[h]	0.10-1.00	0.40	1.9	3.2	7.7
propylamine hydrochloride (PRH^+)	10.89[g]	0.10-1.00	0.80	0.9	1.0	2.4
2,2,2-trifluoroethanol	12.4[i]	0.08-1.02	0.49	0[j]		0

[a] Maintained with Me_4NCl plus KCl (see Experimental Section). [b] Calculated using $k_{BH} = 2.37 \times 10^{-3} \times (k_{cat}/k_0)_{cor}$. [c] $k_{BH} = 2.37 \times 10^{-3}/55.3$ for BH = H_2O. [d] J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 6353-6361 (1969). [e] Corrected values using eq 8. [f] Calculated using $k_{BH} = 1.90 \times 10^{-3} \times (k_{cat}/k_0)_{cor}$. [g] W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622-2637 (1968). [h] Determined by titration. [i] Reference 18. [j] A rate decrease was observed when increasing the buffer concentration ($k_i/k_0 = -0.5\ M^{-1}$), probably due to a medium effect of the acid. Ethanol was found to inhibit the rate ($k_i/k_0 = -0.2\ M^{-1}$).

A plot of $1/k_{obsd}$ against $1/[OH^-]$ according to

$$1/k_{obsd} = \frac{1}{k_2}\frac{1 + (K_a/K_w)[OH^-]}{K_a/K_w}\frac{1}{[OH^-]} \qquad (5)$$

gives the first-order rate constant for breakdown of the cyclopropoxide anion, $k_2 = 3.7 \times 10^{-3}\ s^{-1}$, as the ordinate intercept and $K_w/K_a k_2 = 1/k_{OH}$ as the slope, which gives $pK_a = 14.2$ based on $K_w = 10^{-14}$. The same treatment of the data obtained in deuterium oxide solution (lower curve, Figure 2, Table I) gives $k_{OD} = 1.9 \times 10^{-3}\ M^{-1}\,s^{-1}$, $k_2 = 2.7 \times 10^{-3}\ s^{-1}$, and $pK_a = 15.0$.[15]

The difference between the pK_a value of 14.2 and an estimated pK_a of 16.1 for 2-phenylpropan-2-ol[16] indicates that the cyclic structure of 1-phenylcyclopropanol stabilizes the alcoholate anion by ~2 pK units. This difference is larger than would be expected from the small polar electron-withdrawing effect of the cyclopropyl group;[19] it is consistent with a conjugative stabilization of the anion that involves a significant resonance contribution of the homoenolate ion structure.[13]

The pK_a value of 14.2 is consistent with the rate constants of 0.18 and 0.065 for the alkaline hydrolysis of cyclopropyl acetate and *n*-butyl acetate, respectively.[20] These rate constants give a value of $\beta_{lg} = -0.26$, based on $pK_a = 15.9$ for 1-butanol,[17] which is in reasonable agreement with the value of $\beta_{lg} = -0.32$ for the hydrolysis of acetate esters.[21]

The cleavage reaction is catalyzed by amine buffers and follows the rate law

$$v = k_2[RO^-] + k_3[BH^+][RO^-] = k_{OH}[HO^-][ROH] + k_{BH}[BH^+][HO^-][ROH] \qquad (6)$$

in which ROH is 1-phenylcyclopropanol. Representative data are shown in Figure 3, for catalysis by quinuclidine buffers, and rate constants for a series of different catalysts are given in Table II. The rate constants are reported as k_{cat}/k_0, the slope/intercept ratio of a plot of k_{obsd} against $[BH^+]$, and as $k_{BH} = k_{OH}(k_{cat}/k_0)$. Use of k_{cat}/k_0 in this way serves to minimize errors due to errors in pH measurements. Protonated secondary amines and primary amines are less effective catalysts and no catalysis was observed with trifluoroethanol, which causes a small rate decrease (Table II).

Rate measurements at high concentrations of hydroxide ion, at which buffer catalysis is not significant, show that the cleavage reaction is inhibited by the basic form of most amine buffers (Table III; it is also inhibited by ethanol as well as trifluoroethanol, as indicated in Table II). The observed rate constants were corrected for inhibition by the base component of the amine buffers according to

$$k_{cor} = k_{obsd} \Big/ \left(1 + \frac{k_i}{k_0}[\text{amine}]\right) \qquad (7)$$

in which k_i is the slope of a plot of k_{obsd} against amine concentration (Table III). This correction is based on the assumption that the inhibition is caused by a decreased dissociation of 1-phenylcyclopropanol to the anion upon the addition of organic compounds to water, so that the observed rate

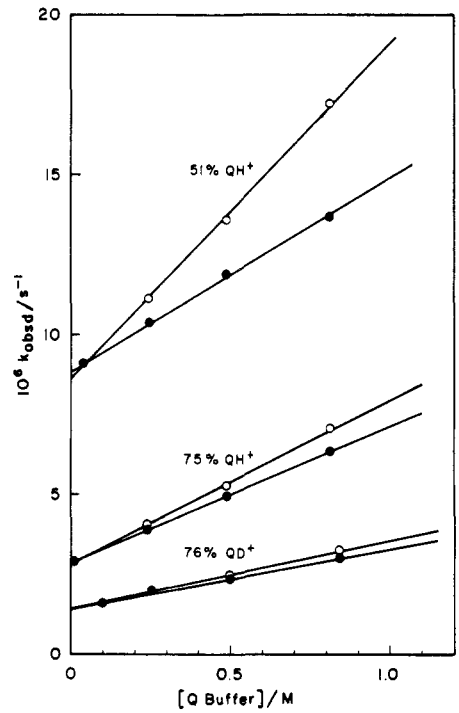


Figure 3. Uncorrected (●) and corrected (○) rate constants for the cleavage of 1-phenylcyclopropanol in quinuclidine buffers of the indicated compositions in water and deuterium oxide at ionic strength 1.0 M (Me_4NCl + KCl). Corrections were made according to eq 7.

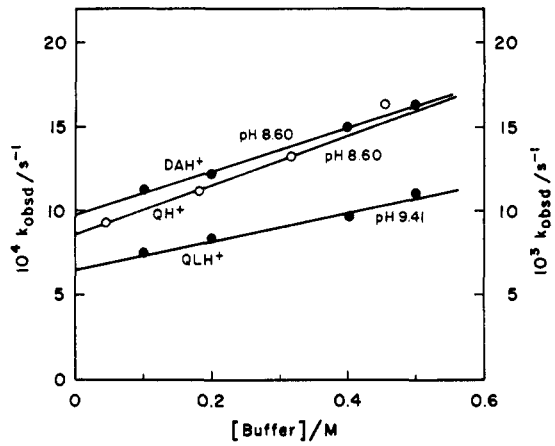


Figure 4. Corrected rate constants for the cleavage of *trans*-1,2-diphenylcyclopropanol in diazabicyclooctane and quinuclidine buffers (left ordinate) and 3-quinuclidinol buffers (right ordinate) at ionic strength 1.0 M (Me_4NCl).

Table III. Free Amine Inhibition of the Hydroxide-Catalyzed Cleavage of 1-Phenylcyclopropanol at 25.0 ± 0.1 °C, Ionic Strength 1.0 M[a]

amine	pH (pD)	$-k_i$, 10^{-5} M^{-1} s^{-1}	$-k_i/k_0$, M^{-1}
quinuclidine	12.81	9.8	0.53
in D_2O	12.90	8.1	0.37
trimethylamine	12.93	10.7	0.40
3-quinuclidinol	12.71	5.4	0.44
diazabicyclo[2.2.2]octane	12.94	9.4	0.47
piperidine	12.91	10.5	0.39
dimethylamine	12.86	3.6	0.16
piperazine	12.86	8.8	0.40
propylamine	12.84	5.5	0.21

[a] $[Me_4NCl]/[KCl] = 1.5$.

constants for the reactions involving both water and BH^+ as proton donors are inhibited. The corrected catalytic constants are given in Table II and were used to calculate k_{BH}. An alternative correction is based on the assumption that only the buffer-independent reaction is inhibited by free amine, according to

$$k_{cor} = k_{obsd} + k_i 10^{\Delta pH}[amine] \quad (8)$$

in which ΔpH is the difference between the pH of the kinetics and the inhibition experiments. This correction gave less satisfactory agreement between the catalytic constants obtained at different buffer ratios of quinuclidine-quinuclidine hydrochloride (Table II). The rate constants are not sensitive to variations in the nature or concentration of the salts used to maintain ionic strength = 1.0 M; there is no significant change upon increasing the ionic strength from 1.0 to 2.0 M with potassium chloride nor upon substituting 0.75 M tetramethylammonium chloride for potassium chloride (Table I).

Isotope discrimination experiments in water-deuterium oxide mixtures show that protium is incorporated preferentially into the product with $k_H/k_D = 1.9 \pm 0.2$ for both water and quinuclidine hydrochloride as the proton donor (Table IV). The data with <20% deuterium in the product are less accurate and are not included in the average. These values and the smaller solvent deuterium isotope effects on the rate constants are summarized in Table V. The kinetic solvent deuterium isotope effects are reported in terms of the hydroxide-catalyzed reactions with water or quinuclidine-H^+ as proton donors, k_{BH}, and in terms of the alcoholate anion reaction, k_2.

The cleavage of *trans*-1,2-diphenylcyclopropanol is also

Table IV. Isotope Discrimination Experiments with 1-Phenylcyclopropanol at 25.0 ± 0.1 °C

general acid	solvent composition D/H	product composition CH_3/CH_2D	isotope effect[a] k_H/k_D
H_2O[b]	1.489	1.30	1.94 ± 0.17
H_2O[b]	2.54	0.752	1.91 ± 0.15
H_2O[b]	3.67	0.524	1.92 ± 0.15
H_2O[b]	6.77	0.287	1.94 ± 0.19
H_2O[b]	11.30	0.152	1.71 ± 0.24
$H_2O + QH^+$[c]	5.94	0.327	1.94 ± 0.18
$H_2O + QH^+$[c]	8.67	0.192	1.66 ± 0.19

[a] Calculated using the relation $k_H/k_D = (CH_3/CH_2D)(D/H)$. [b] Base concentration 0.10 M. [c] 1.0 M quinuclidine buffer, buffer ratio $QH^+/Q = 3.4$, 2×10^{-4} M EDTA, ca. 60% buffer-catalyzed reaction and 40% water reaction.

Table V. Kinetic and Discrimination Deuterium Isotope Effects for the Cleavage of 1-Phenylcyclopropanol at 25.0 ± 0.1 °C

base	$k_{BH}^{H_2O}/k_{BD}^{D_2O}$	$k_2^{H_2O}/k_2^{D_2O}$	$(k_H/k_D)_{discr}$
KOH (D)	1.22 ± 0.05[a]	1.4 ± 0.2[a]	1.93 ± 0.15[d]
QH^+ (D)[b]	1.5 ± 0.3[c]		1.9 ± 0.2[d]

[a] Ionic strength 1.0 M (KCl). [b] Quinuclidine hydrochloride. [c] Ionic strength 1.0 M (Me_4NCl + KCl, see Experimental Section). [d] See Table IV.

catalyzed by hydroxide ion and by buffers according to the rate law of eq 6; the rate constants are summarized in Table VI. The catalysis by amine buffers is smaller than for the cleavage of 1-phenylcyclopropanol (Figure 4), but appears to represent true catalysis rather than a medium effect. The ionic strength was maintained constant at 1.0 M with tetramethylammonium chloride so that the total concentration of cationic nitrogen remained constant with increasing buffer concentration, in order to minimize possible specific salt effects and salting out of the diphenylcyclopropanol. A small correction was made for inhibition by the base component of amine buffers, as in the reactions of 1-phenylcyclopropanol (Table VI); no correction was necessary for catalysis by quinuclidine-H^+ because this catalyst was examined in carbonate or tris(hydroxymethyl)aminomethane buffers in which the amount of the basic species is negligible. Variation of the ionic strength from 0.46 to 1.41 M at four concentrations of tetramethylammonium chloride in the presence of 0.02 M tris(hydroxymethyl)-aminomethane buffers was found to change the observed rate constants by ⩽2%, and a similar rate constant for catalysis by quinuclidine hydrochloride was found when the ionic strength was not maintained constant by the addition of salts. The kinetic solvent deuterium isotope effect was found to be $k_{OH}/k_{OD} = 0.7 \pm 0.1$.

Rate constants for the base-catalyzed cleavage of a series of *cis*- or *trans*-1-phenyl-2-arylcyclopropanols, substituted in the 4 position of the 2-phenyl group, are given in Table VII. The experiments were carried out in 35% (by weight) acetonitrile in water, because of the low solubility of the substituted compounds in water. The rate constants increase with electron-withdrawing substituents on the 2-phenyl group and give values of $\rho \sim 4.0$ and ~ 5.0 for the trans and cis series, respectively, in correlations with σ^n (Figure 5).

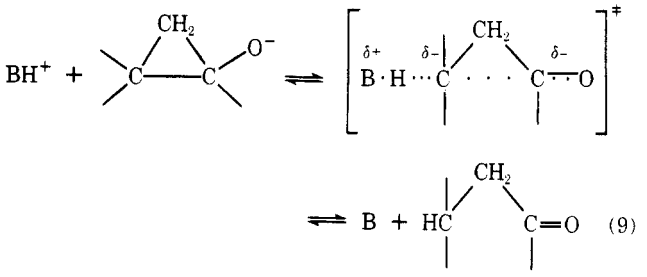
Discussion

The data are consistent with an S_E2 mechanism for the alkaline cleavage of cyclopropanols (eq 9) in which a general acid assists carbon-carbon bond cleavage by transferring a proton to the leaving carbanion. The reverse reaction involves the removal of a proton from the attacking carbon atom by the conjugate base of the catalyst, as it attacks the carbonyl group

Table VI. General Acid Catalysis of 1,3-Diphenylpropanone Formation in Water at 25.0 ± 0.1 °C, Ionic Strength 1.0 M[a]

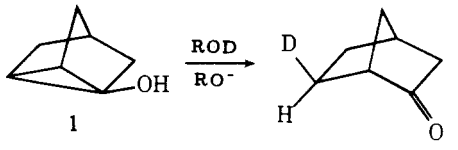
acid	pK_a'	total buffer concn range, M	fraction as acid	k_{cat}/k_0, M^{-1} uncor	k_{cat}/k_0, M^{-1} cor	$10^{-2}k_{BH}$,[b] $M^{-2}\ s^{-1}$
water	15.74		1.00			0.044[c]
quinuclidine hydrochloride (QH^+)	11.55[d]	0.10–0.48	1.00[e]	1.8[f]		4.4
		0.05–0.46	1.00[g]	1.7[f]		4.2
		0.08–0.41	1.00[e]	1.5[f,h]		3.7
3-quinuclidinol hydrochloride (QLH^+)	10.13[d]	0.10–0.50	0.82	1.4	1.6[i]	3.9
		0.10–0.50	0.95	1.5	1.6[i]	3.9
diazabicyclo[2.2.2]octane hydrochloride (DAH^+)	9.22[d]	0.10–0.50	0.76	1.5	1.7[i]	4.2
2-cyanoethylamine hydrochloride	8.17[j]	0.05–0.50	0.60	0		0
potassium bicarbonate	9.9[d]	0.10–0.50	0.95	0		0

[a] Maintained with Me_4NCl. [b] Calculated using $k_{cat} = 245(k_{cat}/k_0)_{cor}$. [c] 245/55.3. [d] J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 6353–6361 (1969). [e] Buffered with 0.05 M carbonate buffer. [f] Correction not necessary. [g] Buffered with 0.02 M tris(hydroxymethyl)-aminomethane buffer. [h] Not constant ionic strength. [i] Corrected using eq 7 and the values in Table III. [j] M. I. Page and W. P. Jencks, *J. Am. Chem. Soc.*, **94**, 8818–8827 (1972).



(9)

in an aldol-type condensation. The reaction can be formulated as a proton transfer to the backside of an orbital that is involved in the C–C bond that undergoes cleavage. This mechanism is consistent with the observed inversion of configuration in the base-catalyzed cleavage of *trans*-1-methyl-2-phenylcyclopropanol in aqueous dioxane[22] and provides an alternative to the complex rotation mechanism suggested by Hoffman and Cram to account for this stereochemical result.[23] It is also in agreement with the predominant inversion found in the ring opening of **1**,[24] which cannot be accounted for by a rotation mechanism.



1

The observed structure–reactivity behavior and deuterium isotope effects indicate an open transition state with a large amount of carbanionic character and relatively little proton transfer to the central carbon atom. This carbon atom is pentavalent in the transition state, as in S_N2 displacement reactions, and is presumably connected to the proton and the carbonyl carbon atom by a long, three-center two-electron bond. Most nucleophilic displacement reactions have weak bonding to the nucleophile (β_{nuc} ~0.1–0.3)[25] and a large amount of bond cleavage to the leaving group in the transition state (β_{lg} ~−0.7 to −0.9),[26] as expected for bonding to a pentacoordinate carbon atom. The small amount of proton transfer in the cleavage of 1-phenylcyclopropanol is manifested in the Brønsted α value of 0.25 for catalysis by unhindered tertiary ammonium ions and the less reliable value of $\alpha = 0.31$ for protonated secondary amines (Figure 6). There is even less proton transfer in the transition state for cleavage of *trans*-1,2-diphenylcyclopropanol, which exhibits no detectable dependence on the acidity of the limited number of catalysts examined (Table VI); the estimated upper limit of the Brønsted slope for this reaction is ≤ 0.1.

The order of catalytic activity in the series of protonated amines is tertiary > secondary > primary (Figure 6) and no

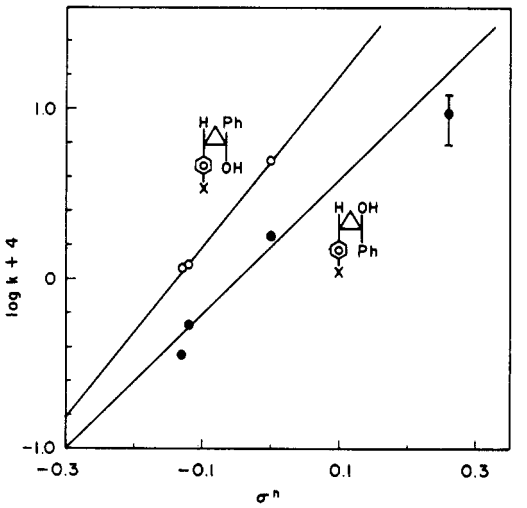


Figure 5. Hammett plots for the base-catalyzed cleavage of *cis*- (○) and *trans*- (●) 1-phenyl-2-(4-X-phenyl)cyclopropanols in 35 wt % acetonitrile in water.

Table VII. Observed Rate Constants for the Cleavage of *cis*- and *trans*-1-Phenyl-2-arylcyclopropanols to 1-Phenyl-2-(4-X-phenyl)-propanone (*c*-X and *t*-X) in Water–CH_3CN[a]

substrate	10^4k_{obsd}, s^{-1}	σ^n [b]
t-Cl	9.2 ± 3.0	0.26
t-H	1.80 ± 0.13	0
t-Me	0.530 ± 0.037	−0.12
t-OMe	0.348 ± 0.035	−0.13
c-H	4.93 ± 0.35	0
c-Me	1.21 ± 0.08	−0.12
c-OMe	1.17 ± 0.08	−0.13

[a] 35 wt % acetonitrile buffered with 0.025 M tris(hydroxymethyl)aminomethane, buffer ratio 1.0. [b] J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley-Interscience, New York, 1975, p 72.

catalysis was detected with trifluoroethanol. There is precedent for this order of catalytic activity in the amine series for proton transfer to or from carbon.[27] The catalytic constant for water falls below the Brønsted line for protonated tertiary amines by a factor of 20 for 1-phenylcyclopropanol cleavage and by a factor of 180 for 1,2-diphenylcyclopropanol cleavage. The reaction involving water as the proton donor in the cleavage direction represents proton removal by hydroxide ion in the reverse direction. Negative deviations of the catalytic constants for HOH and HO^- are well-known for proton transfers to or

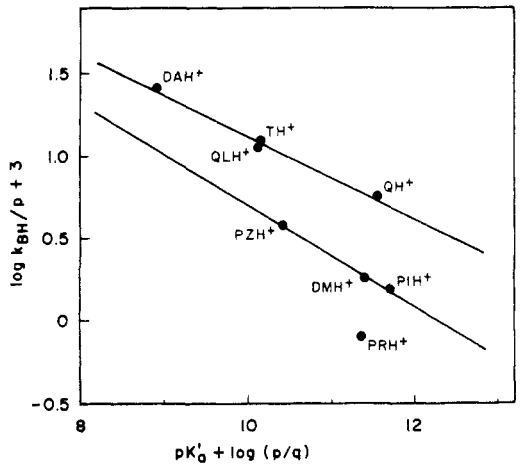


Figure 6. Brønsted plots for general acid catalysis of the cleavage of 1-phenylcyclopropanol anion by protonated amines. The upper and lower lines are drawn through the points for catalysis by protonated tertiary and secondary amines, respectively.

from carbon; similar deviations are found for aliphatic alcohols.[28] The low catalytic activity of water and trifluoroethanol probably reflects some kind of solvation effect and the absence of a favorable electrostatic interaction between protonated amines and the developing negative charge of the carbanion in the transition state.[29] This electrostatic interaction is not present in the reference, dissociation reaction.

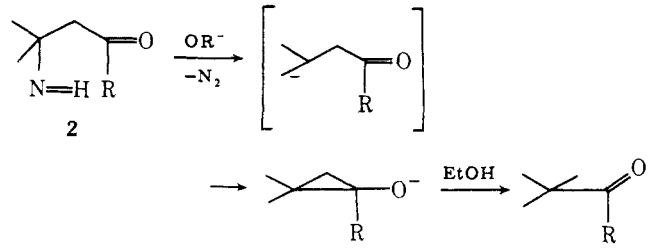
The isotope discrimination of $k_H/k_D = 1.9$ in H_2O–D_2O mixtures is a measure of the primary isotope effect for proton transfer in the cleavage of *trans*-1-phenylcyclopropanol anion catalyzed by water and by quinuclidine-H^+. This small isotope effect is consistent with an open, asymmetric transition state that involves only a small amount of proton transfer; it may also reflect coupling between motions of the proton and heavy atoms.[30] The kinetic isotope effects on the observed rate constants of $k_{BH}/k_{BD} = 1.22$ for water and 1.5 for quinuclidine-H^+ as proton donors (Table V) include both primary and secondary effects; the former value gives an inverse secondary solvent isotope effect of $k_{DOD}/k_{HOH} = 1.9/1.22 = 1.6$. The secondary isotope effect may be ascribed to loss of the solvation of lyoxide or alkoxide ions by three solvent molecules and has a maximum value of 2.0 in water.[31,32] The observed value of 1.6 suggests that the reaction has proceeded more than halfway to products in the transition state, with loss of most of the negative charge on the oxygen atom that is donating a proton to the developing carbanion. The relationship $k_{DOD}/k_{HOH} = 2.0^{\beta}$ for the secondary isotope effect[32] gives $\beta = 0.68$. This value of β is consistent with the observed small value of $\alpha = 1 - \beta = 0.25$ and with loss of most of the anionic character of the oxygen atom of the developing carbonyl group in the transition state of eq 9.

The discrimination isotope effect was not determined for the unstable and insoluble 1,2-diphenylcyclopropanol, for technical reasons. However the observed inverse kinetic isotope effect of $k_{OH}/k_{OD} = 0.7$ for this compound means that the primary isotope effect must be very small and the secondary isotope effect must be inverse and large. This is consistent with the conclusion that there is less proton transfer in the transition state for cleavage of the diphenyl compound.

The Hammett ρ values of 5.0 and 4.0 for cleavage of the *cis*- and *trans*-1-phenyl-2-arylcyclopropanols are not of high precision but do indicate that there is a large amount of negative charge development on the leaving carbon atom in the transition state. DePuy et al. have shown that polar substituents on the benzene ring of 1-arylcyclopropanols have only a small effect on the observed rate constants for base-catalyzed cleavage.[33] This is consistent with a considerable amount of carbon–carbon bond cleavage in the transition state. The initial ionization of the cyclopropanol is aided by electron withdrawal ($\rho = 1.1$ for the ionization of trifluoroacetophenone hydrates[34]) and this is largely compensated by carbon–carbon cleavage, which is aided by electron donation.[35]

Preassociation Mechanisms. The results suggest that these reactions proceed through a preassociation or concerted mechanism that is enforced by the short or negligible lifetime of the carbanion intermediate, as described in the introductory section. The pK_a for the ionization of toluene to the benzyl anion has been estimated to be 41 in cyclohexylamine and 42 in dimethyl sulfoxide, and is probably even higher in water.[37] The benzyl anion–sodium ion pair reacts with water in tetrahydrofuran with a rate constant of 5.5×10^9 M^{-1} s^{-1}, close to the diffusion-controlled limit, and exhibits a small isotope effect of $k_H/k_D = 1.2$–1.7 for the free anion and ion pair reacting with ethanol.[38] The ionization of toluene may occur either with or without a significant primary isotope effect, depending on the reaction conditions.[39] The basicity of the aliphatic carbanion $PhCOCH_2CH_2^-$ that would be formed in the unassisted cleavage of 1-phenylcyclopropanol is higher than this by at least 6 pK units, the difference in the pK of PhOH and EtOH, which gives a pK_a of $\geqslant 48$; the pK_a of isobutane has been estimated to be 71.[40] Thus, a free carbanion with this structure would certainly react at a diffusion-controlled rate with BH^+ or HOH and would have little or no barrier for the proton-transfer step within the encounter complex.

There is also evidence from several reactions that there is little or no barrier for addition of the carbanion (or potential carbanion) to the carbonyl group in the reverse, ring-closure reaction.[13] For example, the "carbanion" that is generated upon the decomposition of **2** adds to the carbonyl group, to give



a rearranged product, faster than it is protonated by the solvent ethanol.[41] Since there is little or no barrier for protonation, there must be little, if any, barrier for C–C bond formation.

We conclude, for the reasons given in the introductory section, that the lowest energy pathway for the decomposition of the anion of 1-phenylcyclopropanol involves movement of the proton donor into position for reaction before C–C cleavage takes place. The reaction is certainly concerted in the sense that both proton transfer and carbon–carbon cleavage have occurred to a significant extent in the transition state. The barriers for the two possible reactions of the carbanion may well be so small that the carbanion cannot exist as an intermediate with a significant lifetime, so that the reaction must proceed in one step by a fully concerted mechanism (we will not comment at this time on the nature of any coupling of the motions of the proton and heavy atoms in the transition state). Such a mechanism is consistent with the observed general acid catalysis, detuerium isotope effects, structure–reactivity parameters, and stereochemistry of the reaction, as discussed above.

Figure 7 shows a Gibbs free energy profile based on a rough estimation of the equilibrium constants for the steps of the reaction. The value of K_{ov} is on the order of 3×10^{13}, based on $K_{eq} = 400$ M^{-1} for the aldol condensation of acetaldehyde,[42] 27 kcal of strain energy in cyclopropane,[43] a factor of 10^4 for stabilization of the carbonyl group by conjugation with the

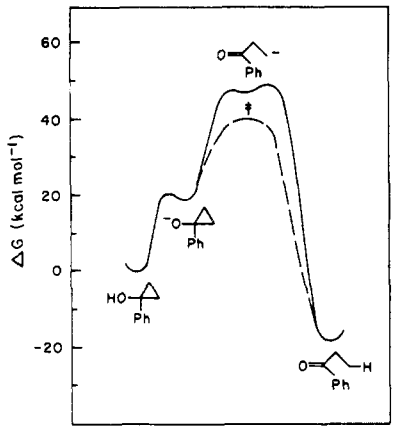
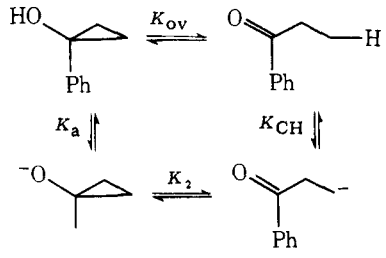


Figure 7. Diagram to illustrate the approximate Gibbs free energy profile for the alkaline cleavage of 1-phenylcyclopropanol. The diagram is drawn with small barriers for the two reactions of the carbanion, but these may not exist if the reacting atoms are in a suitable position for reaction. The dashed line shows the observed Gibbs activation energy barrier for the overall reaction.



(10)

1-phenyl group,[44] and a factor of $\sim 10^8$ M corresponding to the difference in the entropy loss for an intramolecular and an intermolecular reaction.[45] Values of $pK_a = 14.2$ and $pK_{CH} \geqslant 48$ then give $K_2 \leqslant 10^{-20.4}$. The value of ΔG_2 for the formation of the carbanion at equilibrium is $\geqslant 27.8$ kcal mol^{-1}, which is larger than the observed value of $\Delta G^{\ddagger} = 20.8$ kcal/mol for cleavage of the cyclopropanol anion. Since pK_{CH} is almost certainly larger than 48 (because conjugation with a phenyl group is expected to provide more stabilization to a carbanion than to phenolate ion), this comparison suggests that the transition state for the overall reaction is more stable than the free carbanion (Figure 7), in spite of the crudity of the calculations. This supports the conclusion that the carbanion is not a free intermediate and that the reaction proceeds through a more-or-less concerted mechanism.

We cannot say whether C–C or C–H bond formation and cleavage represents the "dominant" or "important" process for aldol-type reactions of this kind. Although one might conclude that proton transfer is relatively unimportant from the small amount of proton transfer in the transition state for the cleavage reaction, the reverse, addition reaction involves a large amount of proton abstraction and little or no additional barrier once the proton is removed. Figure 7 shows that proton removal from the carbon acid is thermodynamically more difficult than cleavage of the C–C bond of cyclopropanol and that it is the large change in free energy of the proton-transfer process that drives the reaction toward the ring-opened form in the cleavage direction and provides the large barrier for the reaction in the addition direction. It is notable that a carbanion that is generated from another reaction follows the kinetically controlled, intramolecular pathway of addition to the carbonyl group in preference to the intermolecular, thermodynamically favored path of protonation.[41] Thus, the proton transfer is, in a sense, the more difficult process for the reaction in both the addition and the cleavage directions.

Cleavage of the 1-phenyl-2-arylcyclopropanols appears to proceed through a preassociation mechanism with assistance

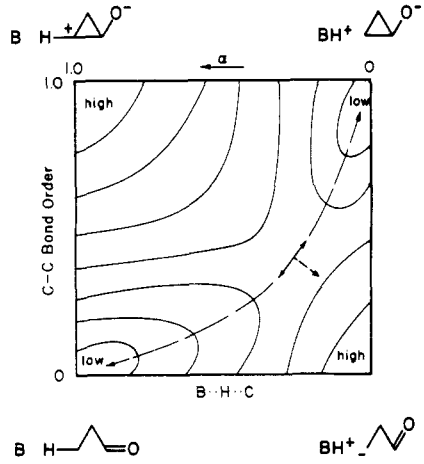
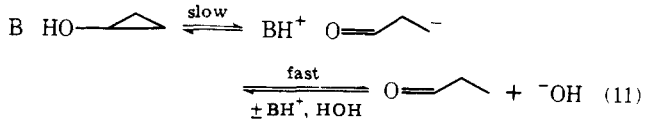


Figure 8. Reaction coordinate–energy diagram with proton transfer on the horizonal axis and C–C cleavage on the vertical axis to illustrate the effect of increasing carbanion stability on the position of the transition state for cleavage of cyclopropanol anions. The position of the transition state at the saddle point is indicated by the double-headed arrow. The reactants and products are in potential wells. The species at the other two corners may be too unstable to exist in potential wells.

to the reaction by weak hydrogen bonding of the proton donor to the developing carbanion in the transition state. This assignment is consistent with the 10^5 times faster cleavage of the 1,2-diphenyl compound to the more stable benzyl carbanion, the observed general acid catalysis with $\alpha < 0.1$, and the small or absent primary deuterium isotope effect. The primary driving force for this reaction arises from the anionic oxygen atom and strain of the cyclopropane ring; buffer catalysis would not be detectable if it were not for the poor ability of water to protonate carbanions and electrostatic stabilization of the transition state by cationic catalysts.

This behavior agrees with that expected from a three-dimensional reaction coordinate–energy diagram with separate axes for C–C and C–H bond formation or cleavage (Figure 8). Stabilization of the carbanion by a benzene ring will lower the energy of the carbanion in the lower right corner of the diagram so that the transition state will tend to slide downhill toward the carbanion, perpendicular to the reaction coordinate, in an "anti-Hammond" direction.[46] The movement of the transition state toward the right corresponds to a decrease in the amount of proton transfer and α, as observed. The same behavior has been observed previously for the general-acid-catalyzed expulsion of water and alcohols from carbonyl and related addition compounds.[9]

An alternative, kinetically equivalent mechanism for the buffer-catalyzed reactions involves proton transfer between the catalyst and the oxygen atom, rather than the carbon atom, in the transition state. This mechanism is excluded because (1) addition–elimination reactions of the carbonyl group and strongly basic nucleophiles are not subject to general acid–base

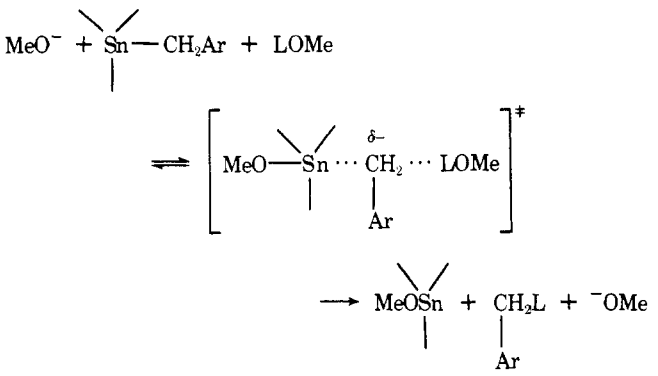


(11)

catalysis at the carbonyl oxygen atom,[47] (2) there is no thermodynamic advantage or driving force for such catalysis with $BH^+ = HOH$,[48] (3) the observed isotope discrimination in the cleavage of 1-phenylcyclopropanol shows that there is proton transfer to carbon in the transition state (a free carbanion would not be expected to discriminate between protium and deuterium, as indicated above), (4) the decrease in α with increasing leaving ability of the carbanion, in the cleavage of 1,2-diphenylcyclopropanol compared with 1-phenylcyclo-

propanol, is in the opposite direction from that expected for this mechanism,[9] and (5) this mechanism does not explain the change from a normal kinetic solvent deuterium isotope effect for the cleavage of 1-phenylcyclopropanol to an inverse effect for the 1,2-diphenyl compound. Furthermore, it is reasonable that catalysis should occur in such a manner as to avoid the most unstable intermediate, as in the mechanism of eq 9, and it is probable that proton transfer to the leaving carbanion is enforced by the high basicity of this carbanion in the transition state, as discussed above.

Comparison with Related Reactions. The cleavage of a series of substituted benzyltrimethylstannanes by methoxide ion exhibits an almost constant primary deuterium isotope effect (based on isotope discrimination in MeOH–MeOD mixtures)



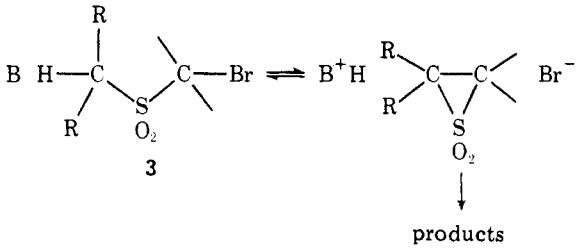
of k_H/k_D = 2.1–2.45.[49] The solvent isotope effect on the observed rate constants is k_{MeOH}/k_{MeOD} = 0.95, which gives a secondary isotope effect of $k_{ROD}/k_{ROH} \simeq 2.4$ that suggests virtually complete addition of methoxide ion in the transition state. The Hammett ρ value of 4.2 suggests a large amount of bond cleavage and negative charge development on the leaving benzyl group in the transition state.[50] A series of the corresponding silicon compounds exhibits a smaller primary (discrimination) isotope effect of k^H/k^D = 1.1–1.3 and an inverse kinetic isotope effect of k_{MeOH}/k_{MeOD} = 0.42–0.49, giving a secondary isotope effect of k_{ROD}/k_{ROH} = 2.6 that is essentially the same as that for the tin compounds.[51] However, *p*-nitrobenzyltrimethylsilane and other compounds with strongly electron-withdrawing substituents on the leaving benzyl group exhibit a sharp rise in the discrimination isotope effect to $k_H/k_D \simeq 10$.[51]

Eaborn and co-workers have concluded, principally because of the significant primary deuterium isotope effect, that cleavage of the benzyltrimethylstannanes proceeds by a synchronous mechanism in which there is significant electrophilic assistance by proton transfer to the benzyl group as it is expelled from the metal.[49] Although assistance to carbanion expulsion by solvent is not excluded, they conclude that cleavage of the benzyltrimethylsilanes proceeds by a different mechanism in which a free carbanion is formed and protonated by the solvent in a subsequent fast step.[51] The very small primary isotope effect for the basic benzyl carbanions and the increase to a large isotope effect for the more stable carbanions were ascribed to a "Westheimer effect" resulting from an asymmetric transition state that becomes less asymmetric as ΔpK between the proton donor and acceptor becomes smaller.[51]

We suggest that these reactions proceed through a preassociation mechanism, similar to that proposed for the alkaline cleavage of cyclopropanols, when the leaving carbanion is unstable and through a free carbanion intermediate only when the carbanion has a sufficient lifetime to diffuse and discriminate among solvent molecules before it is protonated by solvent. If the leaving carbanion is sufficiently unstable a preassociation mechanism will provide the lowest energy reaction path and, if the transition state is sufficiently basic, it will be stabilized by partial proton donation from the solvent or a general acid in the transition state. The leaving benzyl groups behave similarly to the leaving groups in 1-phenyl-2-arylcyclopropanols; the larger primary isotope effects and smaller ρ value[50,52] suggest that there is more proton transfer to the leaving group in the benzyltrimethylstannanes than in the benzyltrimethylsilanes. When electron-withdrawing substituents are added to the leaving group and the carbanion becomes more stable, a fully stepwise reaction mechanism provides the lowest energy reaction path and the free carbanion exhibits a large isotope discrimination between MeOH and MeOD.

Very similar behavior is observed for the hydroxide ion induced cleavage of cumyltriphenylphosphonium ion, which exhibits an isotope discrimination effect of k_H/k_D = 1.21, and for benzyltriphenylphosphonium ion, which has an inverse kinetic solvent isotope effect of k_{ROH}/k_{ROD} = 0.6 (in 75% ethanol).[53]

The Ramberg–Bäcklund reaction involves the same kind of processes in the reverse direction, with proton removal from carbon by a base and nucleophilic attack of the fully or partially formed carbanion to form a new carbon–carbon bond.[54]



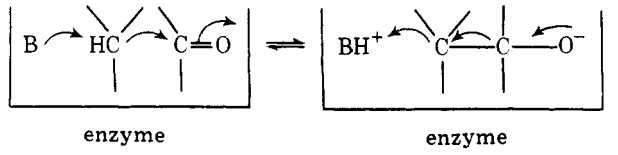
The unsubstituted compound (**3**, R = H) forms a carbanion reversibly and exhibits proton exchange from solvent (40% aqueous dioxane) into the starting material, but the addition of methyl groups (**3**, R = CH_3) gives a reaction that occurs faster than the exchange reaction by a factor of $\sim 10^2$.[55] This shows that nucleophilic attack occurs faster than protonation of the carbanion for the methyl-substituted compound. The observed inversion of configuration at the attacking carbon atom in this class of reactions shows that attack also occurs faster than rotation of the carbanion.[54] It is not definitely known whether some degree of carbon–carbon bond formation accompanies the proton removal in these reactions.

Kirby has recently shown that the intramolecular addition of an amine to an unactivated double bond (the reverse of a Hoffman elimination) is subject to general acid catalysis with a Brønsted α value of 0.15 and a solvent deuterium kinetic isotope effect of k_{H_2O}/k_{D_2O} = 1.70 in 20% dioxane–water.[56] The carbanion that would be generated in the absence of proton transfer in this reaction is sufficiently unstable that an enforced preassociation or concerted mechanism appears to be virtually certain. The same type of mechanism must, of course, hold for the reverse, elimination reaction when the β carbon atom is not activated by carbanion-stabilizing substituents.

The isotope effects for the incorporation of protium or deuterium into the product in this group of reactions exhibit a characteristic pattern that depends on the lifetime of the carbanion and the degree of proton transfer in the transition state, with a minimum isotope effect for carbanions of intermediate stability (Figure 9). When the carbanion is too unstable to exist the reaction must proceed through a concerted mechanism, which can have a large component of proton transfer and a large isotope effect. This isotope effect will decrease with increasing coupling to other processes in the transition state and with an asymmetric transition state.[30,57] A reaction that gives a carbanion of intermediate stability will proceed through a preassociation mechanism with only a small amount of proton transfer in the hydrogen-bonded transition

state; the isotope effects in the examples noted here are in the range 1.0–2.5. A still more stable carbanion will have a lifetime sufficient to diffuse through the solution and discriminate among proton donors ($k_{-a} > k_{-1}'$) so that it will show a large isotope effect, as illustrated dramatically by the substituted benzyltrimethylsilanes examined by Eaborn et al.[51]

Enzyme-Catalyzed Reactions. These results suggest that one of the several mechanisms that are utilized by enzymes to catalyze aldol-type reactions may involve assistance to proton removal by interaction with an electrophile in the transition state, and assistance to carbon-carbon bond formation and cleavage by a significant amount of associated proton transfer in the transition state. This is illustrated for addition to a carbonyl group by eq 12. Such mechanisms would serve to avoid



(12)

the formation of highly unstable free carbanion intermediates and the transition states leading to their formation. Hydrogen exchange with the solvent in the presence of substrate analogues, but in the absence of the carbonyl substrate, may involve formation of the uncharged enol or other stabilization mechanisms. Enzymes may facilitate stabilization of the carbanion or the transition state of a concerted S_E2 mechanism by compressing the reacting groups together and thereby decreasing the barriers for the individual steps. Calculations have suggested that bringing together the proton donor and acceptor significantly decreases the barrier for simple proton transfer reactions and may occur to a significant extent even in an uncatalyzed, bimolecular reaction.[58] It is of interest that enzyme-catalyzed addition reactions of acetyl-coenzyme A proceed with inversion of configuration, consistent with the mechanism of eq 12, whereas aldol-type reactions that involve more stable carbanions proceed with retention of configuration.[59]

Experimental Section

Materials. Amine hydrochlorides were purchased (Aldrich) or prepared from the amine and were purified by recrystallization. Amine buffers were prepared by neutralizing solutions of the hydrochlorides with aqueous potassium hydroxide. Reagent grade inorganic salts and acetonitrile were used without further purification. Water and deuterium oxide were glass distilled and were deoxygenated by bubbling with argon for >5 min before use for kinetic experiments.

1-Phenylcyclopropanol was prepared from 1,3-dichloroacetone, purified by recrystallization, and shown to be of high purity by NMR and high-performance liquid chromatography (LC).[60] **1-Phenyl-2-arylcyclopropyl acetates**[33] were received as a gift from Charles DePuy. The cis and trans isomers of the 4-methyl and 4-methoxy compounds were separated by recrystallization from hexane, which gave the cis isomers, and LC (60%, by weight, methanol in water) followed by two recrystallizations from hexane to give the trans isomers. The identity and high purity were established by NMR and LC analyses and by melting points.[33] *trans*-1,2-Diphenylcyclopropyl acetate gave mp 68.5–69 °C, higher than the previously reported value of 53–54 °C.[33]

1-Phenyl-2-arylcyclopropanols were prepared from the acetates by cleavage with methyllithium.[33,61] The product was usually used directly for kinetic experiments after changing the solvent from ether to acetonitrile. No difference in kinetic behavior was obtained with *trans*-1,2-diphenylcyclopropanol which had been purified by recrystallization from hexane–ether (mp 102–106 °C, reported[61] mp 96.5–99 °C) and shown to be free of detectable impurities by NMR analysis. The cyclopropanols were stored in a freezer as the solid or in acetonitrile solution.

LC separations were carried out with a Waters 6000A solvent delivery system, absorbance detector (Model 440), and differential refractive index detector (Model R401). μBondapak C18 or μPorasil columns (4 × 300 mm) were used for analytic separations and a μBondapak C18 column (7 × 300 mm) was used for preparative separations.

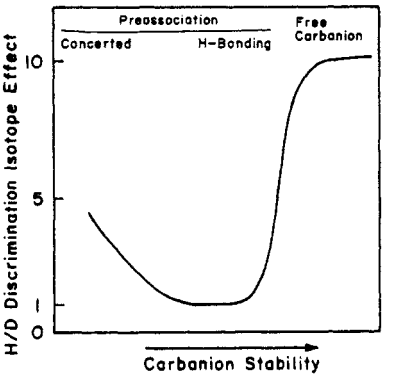


Figure 9. Schematic diagram to illustrate the change in the primary discrimination solvent isotope effect for the incorporation of protium or deuterium into the product in reactions that generate carbanions of varying stability.

Kinetic Measurements. Rate constants were determined using a Zeiss PM6 spectrophotometer with a thermostated cell compartment at 25.0 ± 0.1 °C. The absorbance change was followed at 280 nm using tightly stoppered 1-cm cuvettes for 1-phenylcyclopropanol and 4-cm semimicro cells for the less soluble 1-phenyl-2-arylcyclopropanols.

The rate of the base-catalyzed cleavage of 1-phenylcyclopropanol was followed by measuring the change in absorbance after the addition of 2–4 μL of 0.6 M substrate in methanol to 3 mL of thermostated base solution. Pseudo-first-order rate constants, k_{obsd}, were evaluated from plots against time of ln $(A_\infty - A)$, in which A_∞ is the final absorbance of the reaction mixture. The slower reactions in buffer solutions were followed by measurements of the initial rate of reaction (~2% reaction, $\Delta A \geqslant 0.1$) after the addition of 5 μL of 2.6 M 1-phenylcyclopropanol with a microsyringe. The infinity absorbance, A_∞, was determined from aliquots of parallel runs in potassium hydroxide solutions and the rate constants were obtained from the relationship $k_{obsd} = (\Delta A/\Delta t)/(A_\infty - \Delta A/2)$. Kinetic runs with quinuclidine at buffer ratio 1.0 were carried out using both initial rate and complete first-order rate constant measurements and were found to give the same rate constants within experimental error. Kinetic runs were done at least twice. The ionic strength was maintained constant with potassium chloride in most reactions catalyzed by potassium hydroxide and with tetramethylammonium chloride and potassium chloride in the buffer-catalyzed reactions, using a solution with a ratio $[Me_4NCl]/[KCl]$ the same as the ratio $[BH^+]/[KCl]$ in the stock solution of amine buffer. All reaction mixtures contained 2×10^{-3} M ethylenediaminetetraacetate to inhibit oxidation catalyzed by trace metals.

Kinetic experiments with the relatively unstable and insoluble 1,2-diphenylcyclopropanol were initiated by adding 2 mL of 2×10^{-4} M substrate in water to 2 mL of buffer. The diphenylcyclopropanol solution was prepared by shaking 50 μL of an acetonitrile stock solution with 13 mL of 1.0 M tetramethylammonium chloride containing 4×10^{-3} M disodium ethylenediaminetetraacetate. Ionic strength was maintained with tetramethylammonium chloride (potassium chloride was found to salt out the diphenylcyclopropanol). The reactions of 1-phenyl-2-arylcyclopropanols were initiated by the addition of 10 μL of a stock solution of substrate in acetonitrile to 4 mL of buffer containing 2×10^{-3} M ethylenediaminetetraacetate in acetonitrile–water. The reactions followed satisfactory pseudo-first-order kinetics with a total absorbance change of ~0.4 except for *trans*-1-phenyl-2-(4-chlorophenyl)cyclopropanol, which was linear to only 40–50% reaction and therefore gave only an approximate value of k_{OH} (Table VII).

The pH was measured directly after a kinetic run using a Radiometer Model 26 pH meter with a GK 2321C glass electrode standardized at pH 7.0 and 10.0. The observed rate constants were corrected for small variations in pH with changing buffer concentration. The pD of deuterium oxide solutions was obtained by adding 0.40 to

the observed pH meter readings.[62] The deuterium oxide content of the reaction solutions was larger than 99%. Quinuclidine hydrochloride was exchanged prior to use by dissolving in deuterium oxide and removing most of the solvent by distillation under dry nitrogen. The solvent deuterium isotope effect on the catalytic constant for the quinuclidine-catalyzed reaction was calculated from

$$k_{QH}/k_{QD} = [(k_{cat}/k_0)_{H_2O}(k_{OH}/k_{OD})]/(k_{cat}k_0)_{D_2O}$$

The kinetic isotope effect for 1,2-diphenylcyclopropanol was measured in 0.012 M tris(hydroxymethane)aminomethane buffer, 50% Tris-H^+.

Rate constants, derived rate constants, and correlations of rate constants were calculated by the method of least squares, except for the Hammett plot for *trans*-1-phenyl-2-arylcyclopropanols. Estimated errors are based on the maximum errors derived from maximum systematic errors and random errors. The maximum errors of the directly measured rate constants were thus allowed to propagate as maximum errors into derived quantities.

Product Analysis. Cleavage of 1-phenylcyclopropanol in the presence of hdyroxide ion was found to produce a single product with UV and ^1H NMR spectra and LC mobility identical with that of authentic 1-phenylpropanone. Cleavage of 1,3-diphenylcyclopropanol gave a single product that was identified by NMR ($CDCl_3$) as 1,3-diphenylpropanone: δ 3.25 (4 H, m), 7.59 and 8.01 (10 H, m). The UV spectra of the products from the cleavage of the other 1-phenyl-2-arylcyclopropanols exhibited a band similar to that of the conjugated carbonyl group of 1-phenylpropanone.

Isotope discrimination in water-deuterium oxide mixtures was determined by NMR analysis of the products. A solution of 1-phenylcyclopropanol in methanol (200 μL) was added to 25 mL of an H_2O-D_2O mixture at 25 °C containing 0.1 M KOH or quinuclidine buffer, to give a final concentration of 0.03 M. After 10 half-lives the cleavage product was extracted from the homogeneous solution with carbon tetrachloride and transferred to another flask containing KOD in D_2O. The heterogeneous mixture was stirred overnight to obtain complete exchange of the α protons. The CCl_4 phase was separated and 30% (v/v) of $CDCl_3$ was added. The solutions were then analyzed on a 270-MHz NMR instrument with gated deuterium decoupling, which gave a clean separation of the monodeuterated and nondeuterated methyl singlets. The isotope effects were calculated from the peak areas and the H/D ratios of the reaction solutions (Table IV).

Acknowledgments. We are greatly indebted to Dr. Charles DePuy, who made this work possible by informing one of us about the unpublished observation in his laboratory of protium-deuterium discrimination in the alkaline cleavage of 1,2,2-trimethylcyclopropanol, and by generously donating to us a series of 1-phenyl-2-arylcyclopropyl acetates, and to Dr. Alfred Redfield for his help with the analysis of protium-deuterium discrimination by a new NMR technique.

References and Notes

(1) Supported by grants from the National Science Foundation (BG-31740) and the National Institutes of Health (GM20888 and GM20168).
(2) Srere, P. A. *Adv. Enzymol.* **1975,** *43,* 57–101.
(3) Malhotra, S. K.; Ringold, H. J. *J. Am. Chem. Soc.* **1965,** *87,* 3228–3236.
(4) Maggio, E. T.; Kenyon, G. L.; Mildvan, A. S.; Hegeman, G. D. *Biochemistry* **1975,** *14,* 1131–1139.
(5) Cram, D. J. "Fundamentals of Carbanion Chemistry", Academic Press: New York, 1965; Chapter 3.
(6) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973,** *95,* 5637–5649.
(7) Jencks, W. P. *Acc. Chem. Res.* **1976,** *9,* 425–432.
(8) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 7931–7947.
(9) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978,** *100,* 5444–5459, and references cited therein.
(10) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 8238–8248.
(11) Alternative pathways that do not involve a ternary complex are available and will be favored when the carbanion is stable. However, if the carbanion is sufficiently unstable the direct interconversion of $BH^+ \cdot\!>\!C^-$ and $HOH \cdot\!>\!C^-$ will be too slow to compete with other steps and both of these species will react independently through preassociation mechanisms.
(12) If there is a large barrier for the second step, the intermediate species will be formed in a rapid equilibrium step through a preassociation mechanism. However, when the first step is proton transfer the transition state for the second, rate-limiting step will contain a water molecule, rather than BH^+, unless BH^+ provides stabilization to this transition state.
(13) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974,** *74,* 605–623.
(14) DePuy, C. H. *Trans. N.Y. Acad. Sci., Ser. 2,* **1966,** *28,* 561–568. Arney, W. C. Ph.D. Dissertation, University of Colorado, 1967.
(15) Using $K_w^{D_2O}$ = 14.869: Covington, A. K.; Robinson, R. A.; Bates, R. G. *J. Phys. Chem.* **1966,** *70,* 3820–3824.
(16) Calculated using pK_a = 15.44 for benzyl alcohol (Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971,** *36,* 1205–1209) and the pK_a difference of 0.7 between isopropyl alcohol[17] and methanol.[18]
(17) Sauers, C. K.; Jencks, W. P.; Groh, S. *J. Am. Chem. Soc.* **1975,** *97,* 5546–5553.
(18) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959,** *81,* 1050–1053. **1960,** *82,* 795–798.
(19) Rhodes, Y. E.; Vargas, L. *J. Org. Chem.* **1973,** *38,* 4077–4078. Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *Ibid.* **1978,** *43,* 3095–3101.
(20) DePuy, C. H.; Mahoney, L. R. *J. Am. Chem. Soc.* **1964,** *86,* 2653–2657.
(21) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964,** *86,* 837–846.
(22) DePuy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966,** *88,* 3347–3354.
(23) Hoffman, T. D.; Cram, D. J. *J. Am. Chem. Soc.* **1969,** *91,* 1009–1020.
(24) Nickon, A.; Lambert, J. L.; Williams, R. O.; Werstiuk, N. H. *J. Am. Chem. Soc.* **1966,** *88,* 3354–3358.
(25) Hudson, R. F.; Klopman, G. *J. Chem. Soc.* **1962,** 1062–1067. Hudson, R. F.; Loveday, G. *Ibid.* **1962,** 1068–1075. Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1976,** *15,* 569–575.
(26) Hammett, L. P.; Pfluger, H. L. *J. Am. Chem. Soc.* **1933,** *55,* 4079–4089.
(27) Spencer, T. A.; Kendall, M. C. R.; Reingold, I. D. *J. Am. Chem. Soc.* **1972,** *94,* 1250–1254.
(28) Hupe, D. J.; Wu, D. *J. Am. Chem. Soc.* **1977,** *99,* 7653–7659.
(29) Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973,** *95,* 803–806.
(30) Melander, L. C. "Isotope Effects on Reaction Rates", Ronald Press: New York, 1960. Westheimer, F. H. *Chem. Rev.* **1961,** *61,* 265–273. Bell, R. P. "The Proton in Chemistry", 2nd ed.; Chapman and Hall: London, 1973; p 250. More O'Ferrall, R. A. In "Proton Transfer Reactions", Caldin, E. F., Gold, V., Eds.; Wiley: New York, 1975; pp 201–261. Kalder, S. B.; Saunders, W. H., Jr. *J. Chem. Phys.* **1978,** *68,* 2509–2510.
(31) Gold, V.; Grist, S. *J. Chem. Soc. B* **1971,** 2282–2285.
(32) Winey, D. A.; Thornton, E. R. *J. Am. Chem. Soc.* **1975,** *97,* 3102–3108.
(33) DePuy, C. H.; Klein, R. A.; Clark, J. P. *J. Org. Chem.* **1974,** *39,* 483–486.
(34) Stewart, R.; Van der Linden, R. *Can. J. Chem.* **1960,** *38,* 399–406.
(35) The rate constants follow a shallow, U-shaped Hammett curve that reflects a faster rate with substituents that donate electrons by resonance and that withdraw electrons by a polar effect, compared with the unsubstituted compound. This behavior can be attributed to facilitation of the initial ionization step by electron withdrawal (but not by resonance) and facilitation of C–C cleavage by electron donation that stabilizes the developing carbonyl group by both polar and resonance effects. It can be described approximately by a modified Yukawa-Tsuno equation[10,36]

$$\log (k/k_0) = \rho\sigma^n + \rho^r(\sigma^+ - \sigma^n)$$

with values of ρ = 0.6 and ρ^r = −0.4. A value of ρ = 1.1 for ionization of the alcohol[34] gives values of ρ = −0.5 and ρ^r = −0.4 for the C–C bond cleavage step. These values are similar to the values of ρ = −0.5 and ρ^r = −0.45 for the corresponding step in the base-catalyzed expulsion of sulfite from addition compounds of substituted acetophenones, which suggest a transition state that is roughly midway to products.[36]
(36) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.,* **1979,** *101,* 3288–3294.
(37) Streitwieser, A., Jr.; Granger, M. R.; Mares, F.; Wolf, R. A. *J. Am. Chem. Soc.* **1973,** *95,* 4257–4261. Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975,** *97,* 7006–7014. Bordwell, F. G.; Algrim, D.; Vanier, N. R. *J. Org. Chem.* **1977,** *42,* 1817–1819.
(38) Bockrath, B.; Dorfman, L. M. *J. Am. Chem. Soc.* **1974,** *96,* 5708–5715. The free benzyl carbanion reacts with water with a smaller rate constant of 5.3×10^7 M^{-1} s^{-1}. This difference may reflect the difficulty for forming a free hydroxide ion in this aprotic solvent; the hydroxide ion and the transition state for its formation can presumably be stabilized by a sodium ion or by a hydroxylic solvent.
(39) Streitwieser, A., Jr.; Langworthy, W. C.; Van Sickle, D. E. *J. Am. Chem. Soc.* **1962,** *84,* 251–254. Streitwieser, A., Jr.; Van Sickle, D. E.; Reif, L. *Ibid.* **1962,** *84,* 258–260. Hofmann, J. E.; Schriesheim, A.; Nickols, R. E. *Tetrahedron Lett.* **1965,** *22,* 1745–1747.
(40) Breslow, R.; Goodin, R. *J. Am. Chem. Soc.* **1976,** *98,* 6076–6077.
(41) Freeman, J. P.; Plonka, J. H. *J. Am. Chem. Soc.* **1966,** *88,* 3662–3663.
(42) Guthrie, J. P. *Can. J. Chem.* **1974,** *52,* 2037–2040.
(43) Bernett, W. A. *J. Chem. Educ.* **1967,** *44,* 17–24.
(44) Based on the difference in the equilibrium constants for the addition of bisulfite to acetophenone[10] and to acetaldehyde (Green, L. R.; Hine, J. *J. Org. Chem.* **1974,** *39,* 3896–3901).
(45) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971,** *68,* 1678–1683.
(46) Thornton, E. R. *J. Am. Chem. Soc.* **1967,** *89,* 2915–2927. More O'Ferrall, R. A. *J. Chem. Soc. B* **1970,** 274–277. Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 7948–7960.
(47) do Amaral, L.; Sandstrom, W. A.; Cordes, E. H. *J. Am. Chem. Soc.* **1966,** *88,* 2225–2233. Jencks, W. P. "Catalysis in Chemistry and Enzymology", McGraw-Hill: New York, 1969; p 198.
(48) Jencks, W. P. *J. Am. Chem. Soc.* **1972,** *94,* 4731–4732.
(49) Alexander, R.; Asomaning, W. A.; Eaborn, C.; Jenkins, I. D.; Walton, D. R. M. *J. Chem. Soc., Perkin Trans. 2* **1974,** 490–494.
(50) Bott, R. W.; Eaborn, C.; Swaddle, T. W. *J. Chem. Soc.* **1963,** 2342–2350.
(51) Eaborn, C.; Walton, D. R. M. *J. Chem. Soc., Perkins Trans. 2* **1976,** 1857–1861. Macciantelli, D.; Seconi, G.; Eaborn, C. *Ibid.* **1978,** 834–838, and references cited therein.
(52) Eaborn, C.; Parker, S. H. *J. Chem. Soc.* **1955,** 126–131.

(53) Corfield, J. R.; Trippett, S. *Chem. Commun.* **1970**, 1267.
(54) Bordwell, F. G., *Acc. Chem. Res.* **1970**, *3*, 281–290.
(55) Bordwell, F. G.; Wolfinger, M. D. *J. Am. Chem. Soc.* **1971**, *93*, 6303–6304.
(56) Kirby, A. J.; Logan, C. J. *J. Chem. Soc., Perkins Trans. 2* **1978**, 642–648.
(57) Katz, A. M.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 4469–4472.
(58) Delpuech, J. J.; Serratrice, G.; Trich, A.; Veillard, A. *J. Chem. Soc., Chem. Commun.* **1972**, 817–819. Merlet, P.; Peyerimhoff, S. D.; Buenker, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8301–8308.
(59) Hanson, K. R.; Rose, I. A. *Acc. Chem. Res.* **1975**, *8*, 1–10.
(60) DePuy, C. H.; Dappen, G. M.; Eilers, K. L.; Klein, R. A. *J. Org. Chem.* **1964**, *29*, 2813–2815.
(61) DePuy, C. H.; Van Lanen, R. J. *J. Org. Chem.* **1974**, *39*, 3360–3365.
(62) Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188–190.

Structures of $[C_4H_4O]^{+\cdot}$ Ions Produced from 2- and 4-Pyrone

John L. Holmes*[1a] and Johan K. Terlouw[1b]

Contribution from the Chemistry Department, University of Ottawa, Ottawa, Ontario, Canada, K1N 9B4, and the Analytical Chemistry Laboratory, University of Utrecht, Croesestraat 77A, Utrecht, The Netherlands.
Received June 22, 1978

Abstract: Contrary to earlier conclusions, the nonfragmenting $[C_4H_4O]^{+\cdot}$ ions generated by loss of CO from 2- and 4-pyrone mainly have the $[furan]^{+\cdot}$ structure; some $[vinylketene]^{+\cdot}$ ions are also generated. This conclusion was drawn from examination of the collisional activation spectra of $[C_4H_4O]^{+\cdot}$ ions of known structure and from measurements of the heats of formation of the molecular ions of 11 isomeric $[C_4H_4O]^{+\cdot}$ species. It was further concluded that no firm structural assignment can be made for the $[C_4H_4O]^{+\cdot}$ ions having sufficient internal energy to fragment on the microsecond time scale.

Introduction

The elucidation of molecular and ionic structures by mass spectrometry has greatly benefitted from simple rationalizations derived from organic chemistry. However, an intriguing and longstanding exception concerns the loss of CO from 2- and 4-pyrone molecular ions.[2a] The proposed generation of $[furan]^{+\cdot}$ as a stable daughter ion seems a priori very reasonable. McLafferty and Pike[2b] cautiously concluded, from a study of relative metastable peak abundances for the fragmenting $[C_4H_4O]^{+\cdot}$ ions derived from furan and 2- and 4-pyrones, that a substantial fraction of the decomposing ions cannot have the furan structure.

Shortly thereafter, Pirkle and Dines,[3] in their second detailed study, concluded that the majority of further decomposing $[C_4H_4O]^{+\cdot}$ ions could confidently be excluded from having the structure of $[furan]^{+\cdot}$.

We here present evidence that, for the nondecomposing (lifetimes > 5 μs) $[C_4H_4O]^{+\cdot}$ ions from both pyrones, the $[furan]^{+\cdot}$ structure is the *predominant* species and that no firm deductions concerning the structures of either the reacting or the nonreacting ions can be made from metastable peak characteristics.

Results and Discussion

The heats of formation, ΔH_f, of the m/z 68, $[C_4H_4O]^{+\cdot}$ daughter ions from 2- and 4-pyrones were estimated to be $+217$ and $+222$ kcal mol^{-1}, respectively. (From appearance energy (AE), m/z 68, for 2-pyrone AE = 10.34 ± 0.05 eV, and for 4-pyrone AE = 10.64 ± 0.05 eV, both measured with energy selected electrons;[4] ΔH_f(2-pyrone) = −43 ± 2 kcal mol^{-1} and ΔH_f(4-pyrone) = −34 ± 2 kcal mol^{-1} from group additivity,[5] whence $\Delta H_f([C_4H_4O]^{+\cdot})$ from 2-pyrone = 222 ± 2 kcal mol^{-1} and $\Delta H_f([C_4H_4O]^{+\cdot})$ from 4-pyrone = 237 ± 2 kcal mol^{-1}. However, both fragmentations are associated with appreciable reverse activation energies (E_{rev}) whose *minimum* values, calculated from the widths of the dish-topped metastable peaks across their maxima,[6,7] were E_{rev}(2-pyrone) ≥ 4.5 kcal mol^{-1} and E_{rev}(4-pyrone) ≥ 14.5 kcal mol^{-1}.[8]) Thus, the above ΔH_f values represent *upper limits* for the $[C_4H_4O]^{+\cdot}$ daughter ions. Comparing these values with representative thermochemical data (Table I) permits the elimination of all structures proposed earlier[3] and leaves but three feasible structures for *threshold* $[C_4H_4O]^{+\cdot}$ (i.e., ions having *insufficient energy* to fragment further), $[vinylketene]^{+\cdot}$, $[furan]^{+\cdot}$, and $[buta\text{-}1,2\text{-}dienone]^{+\cdot}$.

Structural information for nondecomposing ions can also be obtained from their collisional activation (CA) mass spectra. These spectra represent the intensity distribution of the ionic products of decomposition from the fast dissociations which a mass selected stable ion is forced to undergo upon collision with an inert gas in the field free region between the magnetic and electric sector of the mass spectrometer. The high energy imparted to the ion by the collision precludes extensive isomerization before fragmentation and so fast reactions characteristic of ion structure are normally observed.[13]

The $[C_4H_4O]^{+\cdot}$ ions from the pyrones display only three important peaks in their collisional activation (CA) mass spectra, m/z 39, 40, and 42. The complete spectra are shown in Table II. The CA mass spectrum of 4-pyrone is closely similar to that of furan but significantly different from that of vinylketene. We conclude that loss of CO from $[4\text{-pyrone}]^{+\cdot}$ indeed produces $[furan]^{+\cdot}$ as the nonfragmenting daughter ion. We propose that loss of CO from $[2\text{-pyrone}]^{+\cdot}$ generates mainly $[furan]^{+\cdot}$ ions together with $[vinylketene]^{+\cdot}$.

The generation of $[vinylketene]^{+\cdot}$ from 2-pyrone can be rationalized by invoking a 1,4- or a 1,2-hydrogen shift prior to the loss of CO from a molecular ion which has undergone a ring-opening analogous to the photochemical behavior of the neutral molecule.[14–16] Isomerization of $[2\text{-pyrone}]^{+\cdot}$ into the molecular ion of bicyclo[2.2.0]pyran-2-one can be ruled out on the basis of their mass spectra.[17]

We suggest that the possible third isomer, $[buta\text{-}1,2\text{-}dienone]^{+\cdot}$ is an unlikely $[C_4H_4O]^{+\cdot}$ daughter ion because its CA mass spectrum would be expected to display appreciable loss

0002-7863/79/1501-4973$01.00/0