It should be noted that general acid catalysis was not detected in the hydrolysis of *p*-nitrophenyl β-D-glucopyranoside.[7] With glycosides, the hydroxyl groups will, of course, exert an electron-withdrawing inductive effect on basicity in opposition to that of electron-withdrawing substituents in the *para* position of the phenoxy group.

Only one other example of buffer catalysis in acetal hydrolysis reactions has been previously reported;[2] the hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane was found to be weakly catalyzed by formic acid.[2] Several examples of possible intramolecular catalysis of acetal hydrolysis by various functional groups have been found,[3-7] but for purposes of determining the factors that will facilitate general acid catalysis of acetal hydrolysis, the finding of reactions subject to buffer catalysis is an essential step since the presence of buffer catalysis can be determined in an unambiguous manner. It is of interest that Bruice and Piszkiewicz[9] could not find intramolecular catalysis in the hydrolysis of carboxyl-substituted ketals. The reasons for the lack of catalysis with these compounds are now clear; since the leaving groups are poor, partial proton transfer is unlikely, and alkyl substitution at the reaction center would inhibit any possible nucleophilic attack.

It was found in this laboratory that the acid-catalyzed hydrolysis of 2-(*para*-substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in water proceeds in a manner markedly different from that of simple acetals.[2] The application of various mechanistic criteria gave evidence which pointed consistently to a mechanism involving solvent participation in the hydrolysis of these acetals not having an electron-withdrawing substituent in the leaving group. This mechanism difference must be produced by steric inhibition of the A1 reaction due to the presence of methyl groups at the 4 and 5 positions of the 1,3-dioxolane ring since similar 2-(substituted phenyl)-1,3-dioxolanes hydrolyze normally with an A1 mechanism.[17,18] Of the possible mechanisms, including partially rate-determining protonation by hydronium ion or nucleophilic assistance by water in an A2 type of reaction, the A2 mechanism was preferred[2] in view of the extreme slowness of the reactions in comparison to analogous diethyl and ethylene glycol acetals of substituted benzaldehydes, the D_2O solvent isotope effect ($k_D/k_H = 2.4$) which indicated that proton transfer was essentially complete, and the magnitude of the slope (+1.9) of a plot of log $k_{obsd} + H_0$ *vs.* log a_{H_2O}. It has also been found that replacement of hydrogen at the acetal carbon by a methyl group in 2-phenyl-2-methyl-4,4,5,5-tetramethyl-1,3-dioxolane reduces the rate 540 times compared to the corresponding benzaldehyde derivative.[28] Thus, examples have now been found of acetal hydrolysis reactions in which either electronic effects or steric effects can give rise to a mechanism change from the normal A1 mechanism, and it is likely that partially rate-determining protonation will be observed when an electron-withdrawing substituent in the leaving group has substantially reduced basicity.

Acknowledgment. This work was supported by the National Institutes of Health Research Grant GM 10613.

(28) T. H. Fife, unpublished data.

A Base-Catalyzed and a Base-Invariant Mechanism in the Rearrangement of Cyclohexenyl to Cyclopentenyl Cations

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Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received January 4, 1968*

Abstract: Two independent mechanisms have been found for the rearrangement of cyclohexenyl to cyclopentenyl cations. One is base catalyzed and the other is base invariant. The ratio of the two paths, and the two products, can be varied by varying the acidity.

With the discovery that many simple allyl cations are stable in aqueous mineral acids,[1] opportunity was provided for directly observing interconversions between such ions. Four general types of such rearrangements have emerged so far. They are (1) the conversion of bicycloalkyl cations to cyclohexenyl cations,[2] (2) the cyclization of linear dienyl cations to cyclopentenyl cations,[3,4] (3) alkyl migrations within cyclopentenyl cations,[5,6] and the contraction of cyclohexenyl cations to cyclopentenyl cations.[2] The purpose of the work reported herein was to examine the effect of structural changes on the last of these four rearrangements.

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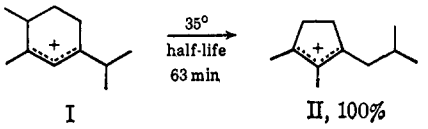
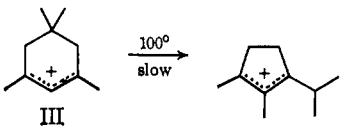
It had been found that I rearranges to II in 96% sulfuric acid, whereas III is indefinitely stable at 35°,

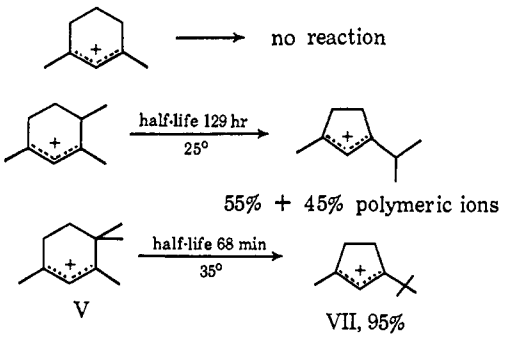


I II, 100% (1)



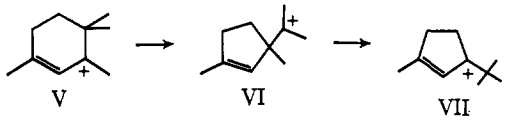
III IV (2)

though it does slowly rearrange to IV at 100°.[7] The contrast in rates between reactions 1 and 2 suggested that alkyl groups on C-4 of the cyclohexenyl cation would facilitate rearrangement. This was found to be true as shown by the following results, all conducted in 96% sulfuric acid.



V VII, 95%

These results suggest that an intermediate cation is formed which has the positive charge on C-4 and which is stabilized by increasing methyl substitution on C-4. This mechanism would be



V VI VII (3)

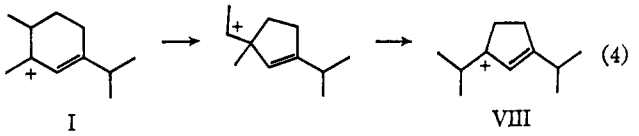
Support for this mechanism was achieved by conducting the reaction in deuterated 96% sulfuric acid and by examining the effect of basicity (activity of water) on the rate. Since hydrogens at C-2 of cycloalkenyl cations do not exchange deuterium,[5] and since the C-2 hydrogen of V becomes the C-2 hydrogen of VII, the sum of these two areas (7.50 and 7.70 bands, Table II) should be constant throughout the rearrangement. This was found to be true (Table II).

Further, the *gem*-dimethyl of V becomes two-thirds of the *t*-butyl group of VII. The other third arises from the C-3 methyl of V. Since the latter largely exchanges before rearrangement, Table II, and the conversion of VI to VII should be very fast, the sum of the areas of the *gem*-dimethyl in V and the *t*-butyl (1.37 and 1.43 bands, Table II) should remain constant. In other words, the *t*-butyl group in VII should have six hydrogens and three deuteriums. This was found to be so.

Equation 3 indicates that the reaction rate would be invariant with activity of water, and this was essentially correct. The half-life at 96 and 80% sulfuric acids at 35° were comparable, 63 and 15 min. The difference in log *k* is 0.62, which is far less than the difference in log a_{H_2O}, 2.36.[8]

At this point an anomaly was evident. Although mechanism 3 appears established for the conversion of V to VII, this mechanism cannot account for the formation of II from I. Specifically, mechanism 3 predicts the formation of VIII from I.

Base-Invariant Path

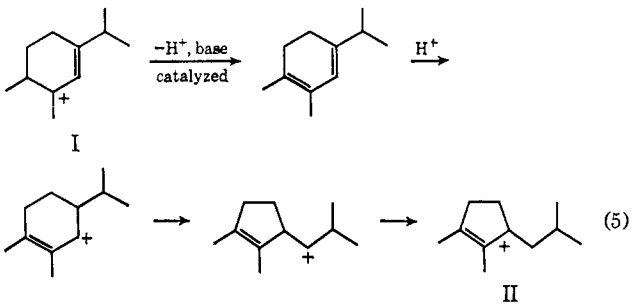


I VIII (4)

A search was made for this path, and it was found. Addition of 2-methylfenchol to HO_3SF produces I, and in this medium it rearranges to form 25% of VIII and 75% of II as determined by nmr band areas.

The discovery of reaction 4 in a medium, HO_3SF, more acidic (and lower water activity) than 80 or 96% sulfuric acid was not unexpected. The base invariant mechanism should be favored at higher acidities in view of the evidence that the alternate path, eq 1, is at least, in part, base catalyzed. This evidence arose from the half-lives at 95 and 82% sulfuric acid at 35°. These were 63 and 6.5 min leading to a log *k* difference of 0.99. Although this falls short of the difference in log a_{H_2O}, 1.86,[8] the magnitude and direction indicate that water activity is a major factor leading to the rate decrease. A reasonable speculation for this base-catalyzed path is shown below.

Base-Catalyzed Path



I II (5)

Log *k* for reaction 1 is not up to first order in water activity and log *k* for reaction 3 is not completely invariant with water activity. Thus, the categorization of reaction 1 as base catalyzed and reaction 3 as base invariant rests heavily on the nature of the products and the deuterium experiment.

Experimental Section

Nmr Spectra. All spectra were recorded on a Varian A-60 spectrometer. Field homogeneity was adjusted with a degassed sample of bromoethane until resolution was better than 0.5 cps. All band positions are given in ppm downfield from tetramethylsilane (δ). Tetramethylammonium ion (3.10 ppm) was used as a secondary standard.

Identification of Cations. These were identified entirely from their nmr spectra for which there is much precedent.[1-6] The nmr spectra of the six new cycloalkenyl cations are summarized in Table I.

(7) Communication from Dr. J. J. Houser, University of Akron, Akron, Ohio.

(8) Log a_{H_2O} is −4.62 and −2.26 at 97 and 80% sulfuric acids at 25° (see J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961), and N. C. Deno and R. W. Taft, Jr., *ibid.*, **76**, 244 (1954), for compilations of values). It is probable that the difference is little changed at 35° (E. M. Arnett and R. D. Bushick, *ibid.*, **86**, 1564 (1964)).

Table I. Nmr Spectra of Cycloalkenyl Cations

Cations	Position, ppm	Assignment	Rel areas Found	Rel areas Calcd
Cyclohexenyl	7.58	H on C-2	1	1
1,3-Dimethyl	3.15[a]	H on C-4 and C-6	4	4
	2.07[a]	H on C-5	2.2	2
	2.82	CH_3 on C-1 and C-3	6	6
1,3,4-Trimethyl	7.55	H on C-2	0.94	1
	3.22[a]	H on C-6	2	2
	2.82	CH_3 on C-1 and C-3	6	6
	2.20[a]	H on C-5	*b*	2
	1.40[c]	CH_3 on C-4	3	3
1,3,4,4-Tetramethyl (V)	7.50	H on C-2	0.86	1
	3.16[a]	H on C-6	*b*	2
	2.82	CH_3 on C-1 and C-3	6	6
	1.98[d]	H on C-5	2.3	2
	1.37	CH_3 on C-4	6	6
Cyclopentenyl				
1-Isopropyl-3-methyl	7.68	H on C-2	1.1	1
	3.53	H on C-4 and C-5	3.8	4
	3.00	CH_3 on C-3	3	3
	1.42[c]	CH_3 of isopropyl	6.1	6
1-*t*-Butyl-3-methyl (VII)	7.70	H on C-2	1	1
	3.54	H on C-4 and C-5	4	4
	2.99	CH_3 on C-3	3.1	3
	1.43	*t*-Butyl	9.3	9
1,3-Diisopropyl (VIII)	7.73	H on C-2	*b*	1
	3.52	H on C-4 and C-5	3.5	4
	1.45	CH_3 of isopropyl	12	12

[a] Partially resolved multiplets. [b] The area could not be reliably measured. [c] Doublet, J = 6.6 cps. [d] Triplet, J = 6.6 cps.

Rearrangement in D_2SO_4. The rearrangement of V to VII was conducted in 96% D_2SO_4. Table II shows the relative areas in per cent at the start and the areas at various times as per cent of the original area. An internal standard was used to ensure a constant instrument response.

Table II. Nmr Band Areas in the Rearrangement of V to VII in 96% D_2SO_4 at 35°

Band, ppm	Area (% of initial) at time (min) listed					
Cation V	4	12	19	64	104	297
7.50, H on C-2	8	5.8	5.2	3.5	2.4	0.5
2.82, CH_3 on C-1 and C-3	32	20	10.4	. .	...	...
1.98, H on C-5	14	13	10.4	7.1	4.7	...
1.37, CH_3 on C-4	46	33	26	...	...	...
	100%					
Cation VII						
7.70, H on C-2	...	2.4	2.8	5.2	5.9	7.6
3.54, H on C-4 and C-5	...	5.8	9.5	13.7	12.8	13.3
2.99, CH_3 on C-3	...	...	7.6	9.5	7.6	7.6
1.43, *t*-butyl	...	13	19	45	43	38

1,3-Dimethylcyclohexenyl Cation. 3-Methyl-2-cyclohexen-1-one was prepared as described[9] by condensing 2 mol of ethyl 3-oxobutanoate and 1 mol of formaldehyde and cyclizing the diethyl 2,4-diacetylglutarate with 10% sulfuric acid at reflux. The over-all yield from the ethyl 3-oxobutanoate was 48%. The 3-methyl-2-cyclohexen-1-one was treated with excess methyllithium at 4° in ether under nitrogen. The mixture was hydrolyzed and the ether extract dried over sodium sulfate. Removal of the ether below 25° left 1,3-dimethyl-2-cyclohexen-1-ol. The infrared spectrum contained an OH band at 2.95 μ and no C=O band. The nmr spectrum consisted of singlets at 5.30 (H on C-2), 3.43 (OH), 1.60 (CH_3 on C-3), and 1.17 (CH_3 on C-1), and a complex multiplet at 1.5–2.0 in the anticipated ratios of 1:1:3:3:6. This cyclohexenol had been prepared in a similar way using methylmagnesium bromide in place of methyllithium.[10]

The cation was obtained by addition of the cyclohexenol to sulfuric acid. The nmr spectrum of the cation supports the structure assigned to the cyclohexenol.

1,3,4-Trimethylcyclohexenyl Cation. Diethyl oxalate was condensed with 3-methylcyclohexanone.[11] The crude glyoxalate was decarbonylated over powdered soft glass to produce ethyl 4-methyl-2-oxocyclohexanecarboxylate[11,12] in 79% yield from the methylcyclohexanone. This was methylated with iodomethane in 80% yield as described.[12] Bromination in CCl_4 produced ethyl 3-bromo-1,4-dimethyl-2-oxocyclohexanecarboxylate in 86% yield.[12] The elimination of HBr was conducted in collidine at 150° to produce ethyl 1,4-dimethyl-2-oxo-3-cyclohexenecarboxylate in 82% yield.[12] The carbethoxy group was removed by saponification and acidification[12] to produce 3,6-dimethyl-2-cyclohexen-1-one in 79% yield.

The infrared spectrum of this ketone contained a C=O band at 6.02 μ. The nmr spectrum consisted of singlets at 5.70 (H on C-2), 1.93 (CH_3 at C-3), and 1.05 (CH_3 at C-6) and a multiplet from 1.8–2.5 due to the hydrogens on C-4 and C-5.

Excess methyllithium in ether converted the ketone to 1,3,6-trimethyl-2-cyclohexen-1-ol, which was isolated in a manner analogous to that used 1,3-dimethyl-2-cyclohexen-1-ol.

The infrared spectrum of 1,3,6-trimethyl-2-cyclohexen-1-ol had an OH band at 2.95 μ and no C=O band. The nmr spectrum consisted of singlets at 5.30 (H on C-2), 1.66 (CH_3 on C-3), and 1.18 (CH_3 on C-1) and multiplets at 1.35–2.0 (OH and ring hydrogens) and 1.00 (CH_3 on C-6) in the ratios 1:3:3:6:3.

The cation was produced by adding the cyclohexenol to sulfuric acid and the nmr spectrum of the cation supports the structure assigned to the cyclohexenol.

1,3,4,4-Tetramethylcyclohexenyl Cation. 2,2-Dimethylglutaric acid was prepared by nitric acid oxidation and hydrolysis[13,14] of 4-cyano-2,2-dimethylbutanol, prepared from isobutyraldehyde and acrylonitrile.[13,15] The esterification to the diethyl ester[13,16] hydrolysis to the monoester,[13] and conversion to the monoester mono acid chloride[13] were conducted as described.

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The ester acid chloride was treated with dimethylcadmium to form the methyl ketone,[13] and this was cyclized with potassium *t*-butoxide to produce 4,4-dimethylcyclohexan-1,3-dione,[13] mp 104.5–106° (lit.[13] 106°).

This dione was produced by an alternate path patterned after a method used to prepare 6-pentacyclohexane-1,3-dione.[17] A suspension of sodium ethoxide in xylene was prepared from 17.4 g of ethanol, 6.90 g of sodium, and 200 ml of xylene. To this suspension was added 40 g of ethyl acrylate. While maintaining the temperature at 4°, 13.0 g of 3-methyl-2-butanone was added over a period of 2 hr. After 30 min, the temperature was allowed to rise to 30°, and it was held there until heat evolution subsided. After a further 20 hr at 25°, 100 ml of water was added and the mixture acidified with acetic acid. Ether was added and the ether extract washed with water. The ether extracts from three separate runs were combined, and the solvent was evaporated. Recrystallization of the crude solid from ethyl acetate gave 24.3 g (37%), mp 105–107°. The infrared and nmr spectra were identical with 4,4-dimethylcyclohexane-1,3-dione prepared by the first method, and a mixture melting point showed no depression.

4,4-Dimethylcyclohexane-1,3-dione was converted to the monoisobutyl enol ether with isobutyl alcohol and *p*-toluenesulfonic acid as catalyst,[13] yield 66%. Addition of methylmagnesium iodide in ether produced 3,4,4-trimethyl-2-cyclohexen-1-one[13] in 24% yield.

This ketone was treated with methyllithium in ether. The crude product was a mixture of about 75% 1,3,4,4-tetramethyl-2-cyclohexen-1-ol and 25% of the two dienes formed by dehydration. These percentages were based on a reasonably satisfactory analysis of the nmr spectrum.[18] However, what is of importance is that addition of the mixture to sulfuric acid produced only cation V.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Also acknowledged is support from the National Science Foundation, particularly for the purchase of a Varian A-60 pmr instrument.

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Rearrangement Accompanying the Photolysis of Diazoacyl Esters[1]

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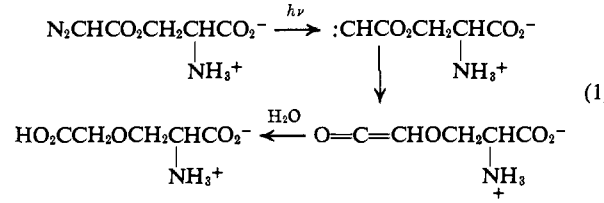
Abstract: Ethyl diazoacetate, phenyl diazoacetate, and N-methyldiazoacetamide were photolyzed in aqueous or methanolic solution and the products identified. In all cases, two major products were formed: one by the insertion of the expected carbene into water or the OH bond of methanol, the other by a rearrangement analogous to the photochemical Wolff rearrangement of diazo ketones. A minor product (ethyl β-hydroxypropionate) from the photolysis of ethyl diazoacetate in methanol is formed by C–H insertion. Methyl phenoxyacetate, formed by photochemical rearrangement of phenyl diazoacetate, undergoes further photochemical reaction to yield methyl esters of *o*- and *p*-hydroxyphenylacetic acids.

Diazo compounds may be used to probe the nature of the active sites of enzymes. These compounds (in the presence[3–5] or absence[5–7] of cupric ion) react stoichiometrically with proteins, presumably at a carboxyl group. In a second type of investigation, illustrated by the preparation of diazoacetyl chymotrypsin,[8–10] a diazo ester is attached at the active site of the enzyme and then subsequently the diazo group is forced to react with neighboring amino acid residues. In particular, photolysis of diazoacetyl chymotrypsin presumably generates a carbene that reacts by a molecular rearrangement analogous to the δ rearrangement of diazo ketones, by insertion into water, or by insertion into amino acid residues, where a histidine and a tyrosine residue have so far been identified as objects of attack.

The rearrangement encountered in these investigations was also illustrated[10] with azaserine, which reacts in part as shown in eq 1.



(1)

The photolysis of diazo esters extends the range of the Wolff rearrangement;[11,12] before these examples, no rearrangement of a diazo ester was known, although a rearrangement of an alkoxy group in a diazo acetal[13] was discovered independently and published simultaneously with our preliminary[9] announcement. Re-

(1) This research was supported by Grant GM-04712 of the Institute of General Medical Sciences of the National Institutes of Health.

(2) (a) Holder of Rockefeller Foundation Scholarship, 1966–1967; (b) National Science Foundation Fellow, 1965–1968.

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