a factor of about 10. However, since the rate constant itself is so small, this estimate may be subject to considerable error, and the catalytic efficiency of the cation may be even less than that here estimated.

The hydrolysis of methyl ethylene phosphate is subject to steric hindrance of moderate size; the effects are comparable to those for mutarotation and for the inversion of menthone. Furthermore, the solvent isotope effect is about 2. Although the latter is somewhat small for general base catalysis, the application of the two criteria—steric effects and solvent isotope effects—combine to indicate that the hydrolysis is subject to general base rather than to nucleophilic catalysis.

The three reactions here studied show steric hindrance, determined kinetically, which exceeds that in the corresponding ionizations.[20] Presumably the ionization constant reflects hindrance which accompanies addition of the proton and solvation of the cation, BH^+, whereas the catalytic constant k_B or k_{BH^+} reflects the interaction of the base with a large organic molecule at the moment when a proton is transferred from one to another. It is not astonishing that these two steric effects are different.

One may tentatively conclude that steric effects for general acid and general base catalysis are of moderate size (perhaps an order of magnitude for 2,6-lutidine), whereas those for nucleophilic attack at carbon[2] or phosphorus[5] are large. Probably the sharpest contrast (and best criterion) rests on the behavior of 2,4-lutidine, which (in the few examples cited) is nearly as active in general acid or general base catalysis as predicted from its pK, but practically without effect as a nucleophilic catalyst.

In addition to the contribution of these kinetic effects to an understanding of general base catalysis, the strong catalytic effect of imidazole in the hydrolysis of methyl ethylene phosphate suggests the role of this base (in histidine residues) in the action of ribonuclease. This aspect of our findings has already been discussed elsewhere.[21,22]

Acknowledgment.—The authors wish to thank the National Science Foundation for their support of this work.

(20) H. C. Brown, D. H. McDaniel and O. Hafliger, "Determination of Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, Inc., New York, N. Y., 1953, p. 634 ff.

(21) F. H. Westheimer, "Proceedings of the 5th International Congress of Biochemistry," 4th Symposium, Moscow, 1961, in press.

(22) F. H. Westheimer, *Advan. Enzymol.*, **25**, 441 (1961).

[CONTRIBUTION FROM THE CENTRAL BASIC RESEARCH LABORATORIES OF ESSO RESEARCH AND ENGINEERING CO., LINDEN, N. J.]

Catalysis by Catechol Monoanion

BY E. J. FULLER

RECEIVED JANUARY 16, 1963

Hydrolysis of phenyl chloroacetate has been shown to be strongly catalyzed by the monoanion of catechol. Rate measurements were taken by titrating the acid formed at constant pH, in ~2% dioxane–0.2 M aqueous sodium perchlorate, over a pH range of 6.5 to 9.0 and from 25 to 45°. The catalysis is postulated to proceed by formation of the intermediate ester catechol monochloroacetate, which was shown to hydrolyze about 800 times as fast as phenyl chloroacetate. Participation of the neighboring phenolic hydroxyl group of the catechol anion was indicated by the failure of phenol, guaiacol, resorcinol and hydroquinone to exhibit positive catalysis. The energy of activation for the catalysis by catechol ion is 5.37 ± 0.07 kcal./mole; the entropy of activation −36.3 ± 6 e.u. This is apparently the first reported instance of a difunctional acid–base catalyst for carboxylic ester hydrolysis exclusive of an enzyme system. The similarities to the action of α-chymotrypsin are discussed. The demonstration of catalytic action involving a general acid of $pK_a \geq 12.3$ suggests a similar phenomenon in the enzymatic-active site.

Introduction

Catalysis of ester hydrolysis by nucleophiles has been studied by several workers. Interest in such catalytic species as imidazole[1,2] and *o*-mercaptobenzoic acid[3] has been stimulated by evidence that their functional groups may be responsible for the behavior of enzymatic-active sites.

One reason for the high efficiency of enzyme action may be the participation of more than one functional group on the catalytic site. This investigation concerns the catalysis of ester hydrolysis by non-enzymatic substances which are also polyfunctional. Such a substance is the monoanion of catechol, which has previously been shown to be effective as a nucleophilic agent toward Sarin (isopropyl methylphosphonofluoridate) and toward acid anhydrides and chlorides.[4] Phenyl chloroacetate, with an easily observable hydrolysis rate, was chosen as a substrate.

Experimental

Materials.[5]—Inorganic substances were of reagent grade purity and were not further purified. Imidazole (m.p. 86.6–87.9°) was Eastman Kodak Co. White Label grade. Reagent grade hydroquinone (m.p. 169.8–171.3°) was obtained from Matheson, Coleman, and Bell. Resorcinol and phenol were ACS reagent grade. Catechol and phenyl chloroacetate were recrystallized from commercial products. Commercial guaiacol was redistilled, b.p. 97–99° at 18.9 mm. 1,4-Dioxane was purified by Fieser's[6] procedure. Its purity was checked by vapor-phase chromatography and was better than 99.9%. Catechol monochloroacetate (m.p. 78.5–81.0°; lit.[7] m.p. 81°) was prepared from catechol and chloroacetic anhydride. It was recrystallized from hexane.

Kinetics.—The hydrolysis rates were followed by titrating the acid produced, using a Radiometer pH-Stat apparatus, which included a titrator, titrigraph recorder and a scale expander. Reactions were run in a Teflon-lined stainless-steel vessel of approximately 100-ml. capacity with a water jacket. Temperature of the vessel was maintained within ±0.02° of the desired value by a water-bath. A current of prehumidified nitrogen was passed through the cell during runs.

The reaction medium was 50.0 ml. of 0.2 M sodium perchlorate, with 1.0 ml. of dioxane solution of ester. Where more than one water-insoluble reactant was present, the total amount of dioxane was kept to 1.0 ml. The titrant was 0.2 N sodium hydroxide, delivered from a 0.5-ml. syringe by the titrator through a capillary glass tube (to minimize leakage) to the reaction cell. When it was desirable to introduce an excess of one reactant, the necessary amount was weighed into a polyethylene cup, which fit into the vessel mentioned earlier. Water was put into the space between the cup and the cell wall to allow for rapid temperature equilibration.

pH was measured with a G202B glass electrode and a K401 calomel electrode, manufactured by Radiometer. The calomel

(1) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652 (1957).

(2) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).

(3) G. R. Schonbaum and M. L. Bender, *ibid.*, **82**, 1900 (1960).

(4) J. Epstein, D. H. Rosenblatt and M. Demek, *ibid.*, **78**, 341 (1956); J. W. Churchill, J. M. Lapkin, F. Martinez and J. A. Zaslowsky, *ibid.*, **80**, 1944 (1958).

(5) Melting points are not corrected.

(6) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 368.

(7) E. Ott, *Ber.*, **59**, 1070 (1926).

electrode was kept at room temperature outside the cell and was connected to it by a salt bridge of 2 M sodium nitrate, to keep chloride ions out of the reaction system. The liquid junction potential between the hydrolysis solution and the salt bridge was established with a glass sleeve made from a standard-taper connection.

Before each run, the apparatus was adjusted to read the correct pH of an appropriate buffer solution, prepared from packaged buffer kits (Beckman, Inc.). The pH during the run was maintained within ± 0.02 pH unit of the value desired. Results were discarded if the buffer reading after the run was more than 0.02 pH unit from the correct value, after a 5-minute interval allowed for temperature equilibration.

Most of the kinetics were run at 35° to reduce the likelihood of exceeding the solubility limits of any of the reactants. Values of K_w for the various temperatures were taken from the work of Harned and Fallon.[8] Dissociation constants for substances under the conditions of these experiments were estimated by reading the pH values of their solutions when approximately half-titrated by standard perchloric acid or sodium hydroxide. A weighed amount of electrolyte, dissolved in the reaction medium, was flushed with nitrogen and thermally equilibrated for at least 5 minutes. Then acid or base was added by calibrated pipet, and the pH was read on the scale expander after another 5-minute equilibration period. The apparent pK_a values were calculated from the relation $pK_a = p\text{H} + \log (\text{HA})/(\text{A}^-)$.

TABLE I

APPARENT DISSOCIATION CONSTANTS OF PHENOLS AND IMIDAZOLE[a]

Substance	Temp., °C.	Apparent pK_a
Catechol	25	9.287, 9.258
	30	9.220, 9.225
	35	9.112, 9.131
	40	9.062, 9.059
	45	8.985, 8.996
Phenol	35	9.703, 9.698
Resorcinol	35	9.123, 9.117
Hydroquinone	35	9.765, 9.775
Guaiacol	35	9.780, 9.785
Imidazole	35	6.877, 6.857

[a] Solutions were approximately 0.17 M in $NaClO_4$ and contained 1 ml. of dioxane in a total volume of 55 ml.

The titrigraph recorded the amount of base added as a function of time, at constant pH. This information, taken for each run over at least three half-times, was used to construct Guggenheim plots from which the specific rate constants were obtained.[9] Each rate constant reported was checked by at least one independent run, taken on a different day, with at least one other run intervening. The average deviation from the mean value was usually less than 4%.

The products of the reaction of phenyl chloroacetate with catechol were determined by vapor-phase chromatography and by ultraviolet spectrophotometry. Comparison of vapor-phase chromatograms and ultraviolet spectrograms of the solution after reaction and of solutions of known composition indicated the presence of phenol and catechol, with no derivatives of either. The end-point of the titration corresponded to the release of one mole of acid for each mole of phenyl chloroacetate added, whether catechol was present or not. Finally, the reaction of equimolar quantities of phenyl chloroacetate and catechol was followed to completion; then a second quantity of ester was added. The initial rate was essentially the same as it was for the first ester addition, which is consistent with the presence of an unchanged amount of catechol. The rate with catechol absent under the conditions of this test was shown to be much slower than that observed in the presence of catechol, as will be discussed later.

Results

The pseudo-first-order rate constants for the release of acid from the reaction of phenyl chloroacetate in water solution are listed in Table II.

No change in rate constant was observed when the ester concentration was changed by a factor of two. The data fit the expression

$$k_{obs} = k_0 + k_{OH}(OH^-) \qquad (I)$$

Here k_0 is the rate constant for the water reaction, k_{OH} is that for hydroxide ion attack and (OH^-) is the hydroxide ion activity. In Table III, eq. I was used to obtain k_0 and k_{OH} from k_{obs} at two different pH values. Then the values of k_0 and k_{OH} were put into eq. I to predict k at a third pH, which may be compared with k_{obs} in the column on the far right.

(8) H. S. Harned and L. D. Fallon, *J. Am. Chem. Soc.*, **61**, 2374 (1939).
(9) E. A. Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

TABLE II

PHENYL CHLOROACETATE HYDROLYSIS[a]

Temp., °C.	pH	$k_{obs} \times 10^4$, sec.$^{-1}$	Temp., °C.	pH	$k_{obs} \times 10^4$, sec.$^{-1}$
25	8.0	8.12	30	8.0	14.7
25	8.0	7.92	30	8.0	15.3
25	8.5	25.0	30	8.5	45.5
25	8.5	24.8	30	8.5	46.7
25	9.0	78.3	35	7.5	10.1
25	9.0	78.0	35	7.5	9.95
30	7.5	4.92	40	7.5	15.4
30	7.5	5.13	40	7.5	15.8
30	8.0	15.4	45	7.5	31.8
30	8.0	15.2	45	7.5	31.7

[a] 1.5×10^{-3} M ester. Total dioxane was 1.0 ml. added to 50.0 ml. of 0.2 M sodium perchlorate.

TABLE III

pH DEPENDENCE OF PHENYL CHLOROACETATE HYDROLYTIC RATE CONSTANT

Temp., °C.	$k_0 \times 10^5$, sec.$^{-1}$	k_{OH}, l. mole^{-1} sec.$^{-1}$	pH	$k \times 10^4$, sec.$^{-1}$ Calcd.[a]	Obsd.
25	1.7[b]	785[b]	9.0	78.7	78.2
30	2.7[c]	1023[c]	8.5	47.8	46.2

[a] From values of k_0 and k_{OH} at the stated temperature. [b] Calculated from averages of rate constants observed at pH values 8.0 and 8.5. [c] Calculated from averages of rate constants observed at pH values 7.5 and 8.0.

For the reaction in the presence of catechol, a rate increase was observed which was dependent on the amount of catechol monoanion present. The data in Table IV demonstrate the effect on the hydrolysis rate of catechol, as well as other substances tested.

TABLE IV

HYDROLYSIS OF PHENYL CHLOROACETATE IN THE PRESENCE OF PHENOLS AND IMIDAZOLE[a]

Temp., °C.	pH	$k_0 + k_{OH}(OH^-) \times 10^4$, sec.$^{-1}$	Substance added	Total phenol or base, M	$k_{obs} \times 10^4$, sec.$^{-1}$	k_c, l. mole[b] sec.$^{-1}$
25	6.5	0.25	Catechol	0.0147	5.11	19.6
25	6.5	.25	Catechol	.0147	4.95	19.0
30	6.5	.50	Catechol	.0147	8.38	28.3
30	6.5	.50	Catechol	.0148	8.57	28.8
35	6.0	.32	Catechol	.0148	3.85	31.5
35	6.0	.32	Catechol	.0148	4.10	33.8
35	6.5	1.00	Catechol	.0147	12.58	33.1
35	6.5	1.00	Catechol	.0149	12.72	33.0
35	7.0	3.16	Catechol	.0148	36.5	30.0
35	7.0	3.16	Catechol	.0147	34.6	28.5
35	7.5	10.0	Catechol	.0147	109.7	29.1
35	7.5	10.0	Catechol	.0147	110.1	29.2
40	6.5	1.6	Catechol	.0146	17.5	39.8
40	6.5	1.6	Catechol	.0147	16.9	38.0
45	6.5	3.2	Catechol	.0148	24.0	43.7
45	6.5	3.2	Catechol	.0148	23.8	43.3
35	7.5	10.0	Phenol	.0159	7.98	
35	7.5	10.0	Phenol	.0160	7.96	
35	7.5	10.0	Guaiacol	.0148	8.21	
35	7.5	10.0	Guaiacol	.0146	7.88	
35	7.5	10.0	Resorcinol	.0148	9.03	
35	7.5	10.0	Resorcinol	.0148	8.86	
35	7.5	10.0	Hydroquinone	.0146	6.72	
35	7.5	10.0	Hydroquinone	.0147	6.79	
35	8.0	31.6	Imidazole	.00735	26.8	
35	8.0	31.6	Imidazole	.00735	27.0	

[a] 1.5×10^{-3} M ester. [b] $k_c = [k_{obs} - k_0 - k_{OH}(OH^-)]/(\text{anion})$.

The value of k_c, the catalytic constant for the catechol anion, is shown in Table IV to be reasonably invariant with pH. This demonstrates the effect of varying the amount of catalytic species by a factor of thirty. The slower rates observed for the other phenols and for imidazole are consistent with attack by a nucleophilic species to yield an intermediate which is hydrolyzed no more rapidly than the original ester. The negative catalytic constants are not reported here since the rate differences observed were in some cases not greatly in excess of experimental error.

The energy and entropy of activation for the catechol anion-catalyzed hydrolysis of phenyl chloroacetate were calculated from the data of Table IV. The slope and intercept of a plot of ln k_c/T *vs.* $1/T$ were obtained by the method of least squares. E_a was 5.37 ± 0.07 kcal./mole; $\Delta S^{\ddagger}$ was −36.3 ± 6 e.u., calculated from the intercept according to the Eyring equation.[10]

The high rate observed for hydrolysis in the presence of catechol anion was suspected to be due to the formation of an intermediate capable of faster hydrolysis than the parent ester. As a likely possibility, catechol monochloroacetate was synthesized and its rate of hydrolysis studied.

The figures shown in Table V demonstrate a dependence of the rate of ester hydrolysis on the concentration of hydroxide ion. The end-point of the run indicated one mole of acid formed per mole of ester added. No estimate was made of the water rate, which is presumably relatively slow, since the values for k_{OH} obtained by neglecting it are in good agreement over half a pH unit. The rate constant for hydroxide ion attack on this ester is therefore about eight hundred times as large as k_{OH} for phenyl chloroacetate hydrolysis.

TABLE V

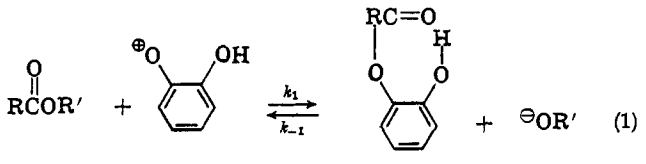
HYDROLYSIS OF CATECHOL MONOCHLOROACETATE (35°)[a]

pH	$k_{obs} \times 10^4$, sec.$^{-1}$	$k_{OH} \times 10^{-5}$, l. mole sec.$^{-1}$[b]
5.0	16.9	8.09
5.0	17.5	8.38
5.0	18.1	8.66
5.5	56.4	8.53
5.5	57.3	8.67

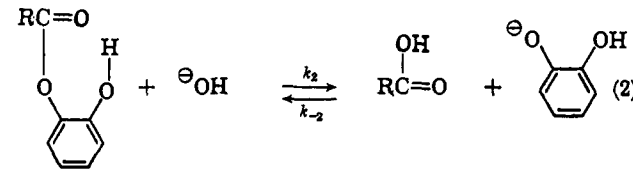
[a] 1.5×10^{-3} M ester. [b] Values obtained from $k_{obs}/(OH^-)$, neglecting the water rate.

Discussion

The monoanion of catechol is implicated as the reactive species by the kinetic data of Table IV. Phenyl esters are sensitive to nucleophilic attack,[11] and phenolate anions have been shown to be effective as nucleophilic agents toward Sarin[4] and p-nitrophenyl acetate.[12] The postulate of displacement of the phenolate group of phenyl chloroacetate by catechol monoanion to form catechol monochloroacetate in a rate-limiting step, followed by rapid hydrolysis of the monoester of catechol, is illustrated by the mechanism



(1)



(2)

The steady-state approximation, when applied to the monoester as an intermediate yields

$$d(acid)/dt = k_2(monoester)(OH^-) - k_{-2}(acid)(C^-) = k_1(ester)(C^-) - k_{-1}(monoester)(OR'^-) \quad (3)$$

where C^- = catechol anion. If $k_1(ester)(C^-) \gg k_{-1}(monoester)(OR'^-)$, then

$$d(acid)/dt = k_1(ester)(C^-) = k_c(ester)(C^-) \quad (4)$$

If 1 represents a slower reaction than 2, the mechanism described fits the experimental results, although it is by no means proved.

The nature of the effect of a neighboring hydroxyl group on the rate of hydroxide ion attack in ester solvolysis has been investigated by Bruice and Fife.[13] Solvation of the transition state for hydroxide ion attack by the neighboring hydroxyl group, considered by them to be the most reasonable explanation, would account for the high rate of hydrolysis of catechol monochloroacetate. The neighboring hydroxyl might also affect the rate of formation of catechol monoester. In the reaction of Sarin with catechol, which is similar to eq. 1, the high rate was shown to depend on the presence of the neighboring hydroxyl group.[4] Either the initial attack of the catechol anion on the ester molecule involves both the phenolate ion and the acidic phenol group in a "difunctional"[14] manner or a sequential action takes place. A decision as to which mechanism is followed cannot be made from the present results.

That the effect is not an inductive one is indicated by the failure of guaiacol to demonstrate effective catalysis. The presence of a phenolic hydroxyl group in the position *ortho* to the nucleophilic phenolate ion is required for efficient catalysis, as inferred from the results with the other phenols. The hydrolysis in the presence of imidazole is in sharp contrast to the efficient catalysis of hydrolysis of phenyl and substituted phenyl acetates observed by Bender and Turnquest[1] and by Bruice and Schmir.[2] Undoubtedly, this is a result of: (1) the high rate of hydrolysis of phenyl chloroacetate, which is about five times that reported for N-acetylimidazole at 25° and pH[1] 7; and (2) the extremely high rate of hydrolysis of catechol monochloroacetate. A study of acetate ester hydrolysis, now in progress, should allow direct comparison between imidazole and catechol anion as catalysts under conditions where both are effective.[15] Comparison of the rate constants k_{OH} and k_c from Table III and IV shows that hydroxide ion is about forty times as efficient as catechol anion for phenyl chloroacetate hydrolysis at 25°.

Apparently, this is the first observation of catalysis of carboxylic ester hydrolysis by a difunctional acid–base molecule in a non-enzymatic system. The action of catechol anion has some points of similarity to that of an enzyme, in that more than one active group is involved in catalysis and an acyl intermediate is postulated. Also, the involvement of the phenolic hydroxyl is of interest. The second pK_a of catechol should be at least as high as 12.3, by analogy with oxalic acid ($pK_{a_2} - pK_{a_2} \sim 3$).[16] Bender, *et al.*, have reviewed the results of the deuterium oxide isotope effect

(10) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 199.

(11) M. L. Bender and B. L. Turnquest, *J. Am. Chem. Soc.*, **79**, 1656 (1957).

(12) T. C. Bruice and R. Lapinski, *ibid.*, **80**, 2265 (1958).

(13) T. C. Bruice and T. H. Fife, *ibid.*, **84**, 1973 (1962).

(14) C. G. Swain and J. F. Brown, *ibid.*, **74**, 2534 (1952).

(15) E. J. Fuller, to be published.

(16) "Handbook of Chemistry and Physics," 41st ed., C. D. Hudgman, ed. in chief, Chemical Rubber Publishing Co., Cleveland, O., 1960, p. 1745.

studies on the rates of acylation and deacylation reactions of α-chymotrypsin and find them consistent with possible participation of a general acid species of pK_a above 13.9.[17] While no claim is intended here for the presence of a catechol group in the active site of any enzyme, these observations do suggest the involvement of a general acid species.

No catalysis of ethyl acetate hydrolysis by catechol anion was observed under the conditions of this work. This may indicate that the action of the catalyst is essentially nucleophilic, since ethyl acetate is not sensitive to nucleophilic agents.[18] It does mean that catechol anion cannot compare favorably with chymotropsin for increasing the rate of an "unactivated" ester hydrolysis reaction.

Acknowledgment.—The author gratefully acknowledges valuable discussions with Dr. J. L. Kurz.

(17) M. L. Bender, *J. Am. Chem. Soc.*, **84**, 2582 (1962).

(18) W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

Proximity Effects. XXXIII. Solvolysis of *trans*-Bicyclo[6.1.0]nonane[1,2]

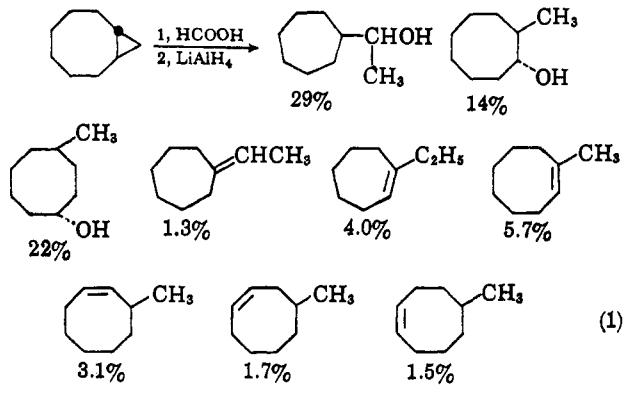
BY ARTHUR C. COPE AND JEFFREY K. HECHT[3]

RECEIVED JANUARY 26, 1963

trans-Bicyclo[6.1.0]nonane has been synthesized stereospecifically from *trans*-cycloöctene. Its solvolysis in formic acid resulted in several transannular reactions.

The stereospecific formation of *trans*-cycloöctene oxide from *trans*-cycloöctene has led us to investigate the possibility of preparing *trans*-bicyclo[6.1.0]nonane, which has the interesting structural feature of a *trans*-fused cyclopropane ring. The method of choice was irradiation of the pyrazoline formed by reaction of *trans*-cycloöctene with diazomethane. The over-all yield of *trans*-bicyclo[6.1.0]nonane was 23%.[4] The structure was proved by elemental analysis and by spectral evidence.

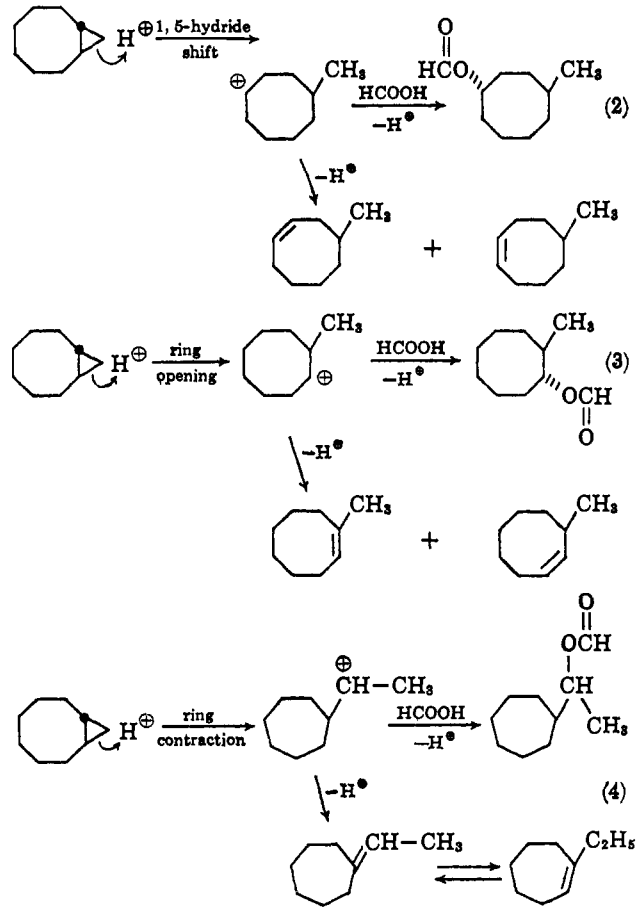
The cyclopropane ring was cleaved by shaking *trans*-bicyclo[6.1.0.]nonane with formic acid at room temperature for one week. Lithium aluminum hydride reduction of the product mixture gave a mixture of alcohols and olefins in 85% yield. The products, identified by comparison of their infrared spectra and gas chromatographic retention times with those of authentic samples, are shown in eq. 1. A small portion (2–3%) of the products was unidentified.



(1)

α-Methylcycloheptanemethanol was synthesized by lithium aluminum hydride reduction of cycloheptyl methyl ketone, formed by the reaction of cycloheptanecarboxylic acid with methyllithium. Ethylidenecycloheptane was synthesized from cycloheptanone and triphenylphosphinethylidene. 1-Ethylcycloheptene was the major product of dehydration of the 1-ethylcycloheptanol formed from cycloheptanone and ethylmagnesium iodide. The remaining products will be described in the next paper of this series.[5]

Initial cleavage of the cyclopropane ring followed by ring contraction or hydride shifts could lead to the observed products as shown in eq. 2, 3 and 4.



The formates of *trans*-2-methylcycloöctanol and *trans*-4-methylcycloöctanol could most likely arise from attack by formic acid concerted with a 1,3- or 1,5-hydride shift, respectively.

Experimental[6]

***trans*-Bicyclo[6.1.0]nonane.**—A solution of diazomethane in ether was prepared by addition of a solution of 70 g. of sodium

(1) Supported by a research grant (NSF-G5055) of the National Science Foundation.

(2) Paper XXXII: A. C. Cope and J. K. Hecht, *J. Am. Chem. Soc.*, **84**, 4872 (1962).

(3) Procter and Gamble Fellow, 1961–1962; National Science Foundation Summer Fellow, 1962.

(4) Reaction of *trans*-cycloöctene with methylene iodide–zinc–copper couple gave 80% of *cis*-bicyclo[6.1.0]nonane and 20% of the *trans* isomer.

(5) A. C. Cope and G. L. Woo, *J. Am. Chem. Soc.*, in press.