TABLE IX

RATE OF EVOLUTION OF AMMONIA FROM ABA IN DMSO AT 70°

Reaction time, hr.[a]	Δt, min.	Equiv. acid added $\times 10^5$	$dNH_3/dt \times 10^5$ $(R \times 10^5)$, equiv./hr.
103.56	28.5	1.94	4.08
104.13	38.3	2.90	4.55
104.66	26.7	1.94	4.35
122.50	30.1	1.94	3.86
123.03	29.7	1.94	3.91
123.57	30.6	1.94	3.80
125.58	31.7	1.94	3.66
126.21	47.1	2.90	3.70
126.88	31.0	1.94	3.75
147.00	35.2	1.94	3.30
147.58	35.0	1.94	3.32
148.18	36.1	1.94	3.22
148.82	35.7	1.94	3.25
195.18	47.8	1.94	2.43
196.37	94.8	3.87	2.45

[a] The reaction time refers to the total time of reaction corresponding to the rate of ammonia evolution listed in the fourth column. It is an average value of the reaction times at the beginning and end of a given neutralization. Data prior to the 103-hour reaction time have been obtained but there is extremely large scatter due to poor experimental technique.

then simultaneously placed in a constant temperature bath regulated at 69.8°. An initial drop in temperature of 0.4° was noted. The bath re-equilibrated in less than 7 minutes. After a predetermined length of time the tubes were removed from the bath and immediately quenched by cooling with ice-water, and then immersed in a slurry of carbon dioxide in isopropyl alcohol.

The total length of time (to the nearest minute) from initial immersion of the tubes in the constant temperature bath, to quenching in ice-water, was taken to be the reaction time. The tubes were stored in solid carbon dioxide in the dark until analysis was performed. Analyses were carried out within 2 days of the kinetic run.

A typical analysis for polymer content will be described. The tube was warmed to room temperature and carefully broken open. Previously, a Waring blender had been filled with approximately 500 ml. of absolute methyl alcohol. The speed of the blender was controlled by a Variac. The alcohol solution was stirred at a moderate speed and the contents of the tube were rapidly, but carefully, poured into the blender. The tube was washed with several small portions of benzene and the washings were transferred to the blender. When all of the reaction mixture had been transferred, the blender speed was increased and the heterogeneous mixture was stirred for 4–5 minutes. The supernatant liquid and solid flocculent polymer were rapidly transferred to a 1-liter erlenmeyer flask with the aid of a large powder funnel taking care to avoid loss of polymer due to seepage of liquid down the side of the blender container. The sides of the blender container were scraped with a spatula while a stream of methanol was directed on them to remove a small amount of residual polymer. These washings were transferred to the 1-liter erlenmeyer flask. The funnel was also carefully washed. The heterogeneous mixture in the flask was then filtered through two dry and preweighed sintered glass crucibles with the aid of an aspirator vacuum. The flask was rinsed with several washings of methyl alcohol and these were passed equally through the two crucibles. The crucibles were covered with filter paper and allowed to stand at room temperature for several hours. The crucibles were then dried in an oven at 70° for 45 minutes, allowed to cool and weighed.

Mechanisms of Acid-catalyzed Reaction. IV.[1] The Kinetics of Ring Opening of Styrene Episulfide

BY HAROLD KWART AND JOST A. HERBIG

The kinetics of styrene episulfide ring opening have been studied in various solvent media and over a wide range of acid strengths. Similar studies on styrene epoxide appear to fail because of a competing rearrangement reaction. The rate data from runs in water–alcohol solutions have been correlated with the S.–C. criterion,[1a] providing a basis for concluding that an A1 mechanism does not prevail under these conditions. The corresponding data in purely aqueous solutions, however, when correlated by means of the w and Z.–H. criteria[5] appear to suggest to the contrary. Some attempt has been made to reconcile these contradictions and to unify the conclusions which are obtainable when the S.–C. and w criteria are concurrently applied.

Introduction

One of the general objectives of our program of study is to establish the nature and extent of differences in reactivity introduced by substitution of a sulfur for an oxygen atom in analogous structures. The results we are reporting here were obtained in the effort to characterize the acid-catalyzed episulfide ring opening reaction for comparison with the corresponding epoxide reaction.

Pritchard and Long have studied the kinetics of solvolysis of ten epoxides in aqueous perchloric acid.[2a] On the basis of these and related studies[2b–e] these authors have concluded that an A1 mechanism (rate-determining unimolecular ring opening of the conjugate substrate acid) prevails. The keystone in their argument is their finding[2a] that log k is proportional to $-H_0$ in every case, consistent with the Zucker–Hammett (Z.–H.) criterion.[3] However, this conclusion has been disputed

in several cases on the basis of other criteria which suggest that the reaction of the conjugate substrate acid with hydroxylic solvent is rate determining.[4] Recently, also, Bunnett has developed an empirical criterion for acid-catalyzed mechanism in aqueous solution[5] which, when applied to the data of Pritchard and Long,[2a] appears to support the nucleophilic participation of water in the slow step of epoxide hydrolysis.[5d]

In our approach to the study of the analogous episulfide ring opening reaction we have also sought to compare deductions reached by means of several mechanistic criteria with the purpose of determining, if possible, where the limitations may lie in the application of each. Thus, it was necessary to examine reaction rates over a range of ethanol–water and acid concentrations in order to apply the solvent composition criterion.[1a] Data obtained for the reaction rates in aqueous solutions as a function of concentrations varying

(1) For previous papers in this series see: (a) H. Kwart and L. B. Weisfeld, *J. Am. Chem. Soc.*, **80**, 4670 (1958); (b) H. Kwart and A. L. Goodman, *ibid.*, **82**, 1947 (1960); (c) H. Kwart and M. B. Price, *ibid.*, **82**, 5123 (1960); (d) H. Kwart and J. A. Herbig, *ibid.*, **85**, 226 (1963).

(2) (a) J. G. Pritchard and F. A. Long, *ibid.*, **78**, 2667 (1956); (b) **78**, 6008 (1956); (c) **79**, 2365 (1957); (d) **80**, 4162 (1958); (e) F. A. Long, J. G. Pritchard and F. E. Stafford, *ibid.*, **79**, 2362 (1957).

(3) L. Zucker and L. P. Hammett, *ibid.*, **61**, 2791 (1939).

(4) See ref. 1b and J. Koskikallio and E. Whalley, *Trans. Faraday Soc.*, **55**, 815 (1959), for the detailed treatments which dispute the A1 mechanism proposed.[2a]

(5) (a) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961); (b) **83**, 4968 (1961); (c) **83**, 4973 (1961); (d) **83**, 4978 (1961).
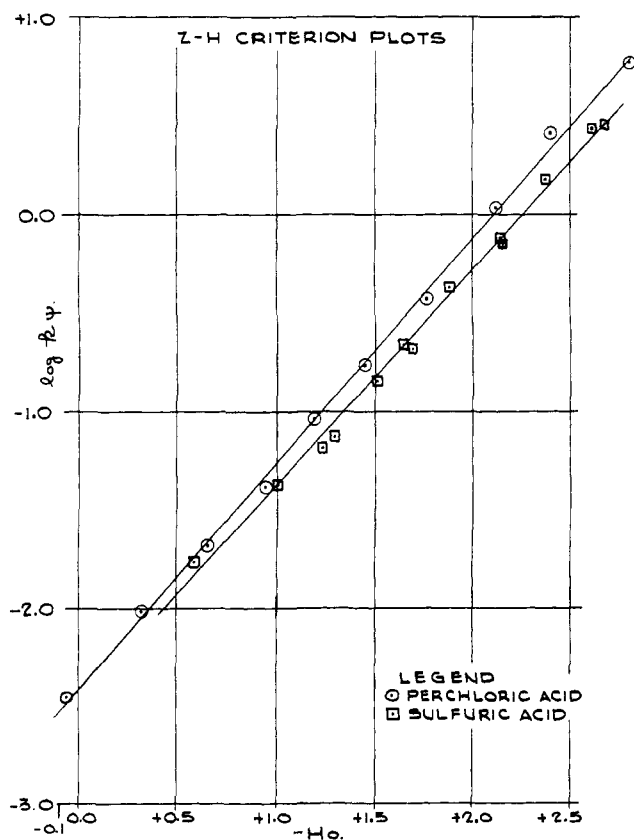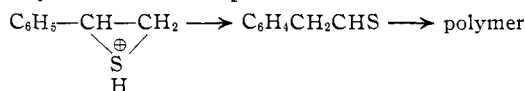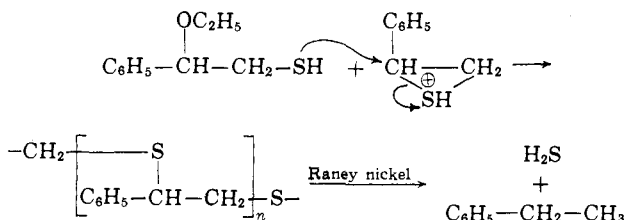
approximately from 0.5–6 M in sulfuric as well as perchloric acids were analyzed in the manner customary for the Zucker–Hammett[3] and Bunnett[5] treatments.

Experimental

Materials. Absolute ethanol was prepared according to the method of Lund and Bjerrum.[6] Styrene episulfide was prepared according to the directions of Guss[7] and after purification (b.p. 59° at 0.2 mm., $n^{20}D$ = 1.6018) was stored under refrigeration in dry ethanol solution until just prior to use in a kinetic run.

Kinetic Procedure.—The course of ring opening was pursued spectrophotometrically at 227 mμ by means of an instrumental arrangement and analytical procedure previously described.[1c] The temperature of the reaction cell could be maintained at 25.1 ± 0.05° for runs of less than 30 min. duration and 25.1 ± 0.1° for longer runs. The pseudo-first-order characteristics of the ring opening reaction, under all the various experimental conditions employed, were established in several cases by means of the linear relationships that resulted when the rate of change of optical density (O.D.) with time was plotted against O.D. for nearly the entire course of reaction. Thereafter, the first-order rate constants, $k\psi$, were computed by means of the Guggenheim[8] procedure.

Product Analysis. (A) In Concentrated Substrate Solution. —A solution of 12 g. of styrene episulfide in 500 ml. of dry ethanol was rapidly saturated with dry HCl under sufficient cooling so that the temperature remained near ambient. After 48 hours of standing, the white precipitate (8.3 g.) which formed was filtered off and washed with ethanol until the washings were neutral. Recrystallization from benzene and from carbon disulfide proved to be difficult because of the apparently amorphous, polymeric nature of the product. Element tests confirmed the presence of major amounts of sulfur and only traces of chlorine. A sample of 4 g. (m.p. 53–55°) was refluxed with Raney nickel in benzene according to the Mozingo desulfurization method.[9] When the solvent was carefully removed by distillation through a helix-packed column, the residual liquid was established to be pure ethylbenzene by vapor phase chromatography.

(B) In Dilute Substrate Solution.—A solution of 15 g. of styrene episulfide in 500 ml. of dry ethanol was added very slowly (during ca. 10 hours) to a vigorously stirred solution of 300 g. of H_2SO_4 in 2 l. of ethanol. After stirring for an additional 40 hr., concentrated ammonia was slowly added until neutrality. The precipitated ammonium sulfate was filtered off and washed with ether. The combined filtrate and ether extracts were dried over sodium sulfate and the volume reduced by evaporation to a total of 1.5 l. This residue was then treated (as in A above) by the Mozingo method.[9] Upon stripping off the solvent from the filtered, desulfurized product there remained 12 g. of liquid. This was shown to contain only one component, 1-phenylethyl ethyl ether—$C_6H_5CH(OC_2H_5)CH_3$.

(C) Identification of Products.—A mixture prepared from authentic samples of ethyl benzene, 1- and 2-phenylethyl ethyl ether could be readily separated with an Aerograph–Master A-100 (Wilkens Instrument and Research, Inc.), equipped with a 10-foot silicone 210 on firebrick column, helium flow set at 51 ml./min. and column temp. 145°. The unknown samples, described in sections A and B above, were analyzed by enhancing the observed peaks with additions of the authentic components. These results were readily confirmed also by superposition of infrared spectra since each of the products proved to consist of a single component.

Results and Discussion

The Dependence of Rate on Solvent Composition.—The data obtained on measurement of the reaction rates in acidic aqueous alcohol solutions of varying compositions are arranged in Table I for plotting the parameters of the mechanistic criterion[1] expressed by eq. 1; (the significance of the various terms have been discussed previously[1a,d]).

$$\log k\psi - \log I = A' + \Delta m Y_0 \qquad (1)$$

The plot displayed in Fig. 1 shows a decidedly nonlinear relationship suggesting that the acid-catalyzed ring opening of episulfides under these conditions involves nucleophilic participation of hydroxylic solvent molecules in the reaction transition state.

It seems appropriate at this point to consider the products obtained under solvolytic conditions which are

(6) H. Lund and J. Bjerrum, Ber., **64**, 210 (1931).

(7) C. O. Guss and D. L. Chamberlain, Jr., J. Am. Chem. Soc., **74**, 1342 (1952).

(8) E. A. Guggenheim, Phil. Mag., **2**, 538 (1926).

(9) R. Mozingo, J. Am. Chem. Soc., **65**, 1013 (1943).

Fig. 1.—S.-C. criterion plot.

similar to those examined in the rate studies in Table I. Thus, the single product obtained when the substrate is hydrolyzed at low concentrations in a strong acid solution in ethanol is the consequence of hydroxylic solvent attack at the secondary carbon center. This is clearly what would be expected in either a ring-opening process

TABLE I

SOLVOLYSIS OF STYRENE EPISULFIDE IN AQUEOUS ETHANOL SOLUTIONS OF VARYING SOLVENT COMPOSITION AND ACIDITY AT 25°, 10^{-4} MOLE/L.

Wt. % EtOH	Mole/l. H_2SO_4	log I	k_4 × 10^{-4}, min.$^{-1}$	log I — log $k\psi$	— Y_0
17.4	2.965	1.213	65.2	3.40	0.048
27.7	2.932	0.960	29.9	3.48	.090
36.4	2.963	.744	19.5	3.45	.140
54.6	2.867	.513	9.21	3.55	.275
64.2	2.883	.570	8.94	3.62	.365
72.6	2.520	.471	6.35	3.67	.465
84.7	1.892	.660	9.28	3.69	.650
91.4	1.112	.790	14.5	3.63	.790
91.4	0.950	.542	8.51	3.61	.790

in which the conjugate substrate acid underwent unimolecular ionization of the carbon–sulfur bond (path a) or in the event that the ionization was assisted by rearward nucleophilic attack at the benzilic carbon (path b), as in the SN2 type process discussed previously.[10]

$$C_6H_4—CH—CH_2 \xrightarrow[\text{path a}]{\text{Ionization}} C_6H_5—\overset{+}{CH}—CH_2$$

The response of rate to solvent composition and medium acidity as tested by the criterion of eq. 1 would suggest that path b is the more likely.

The nature of the product formed during solvolysis at high concentration in ethanol and which is converted to ethylbenzene on desulfurization is open to some speculation. We have considered the possible occurrence of a rearrangement similar to that which has been identified for oxides in general[10] and in styrene oxides, in par-

(10) See R. E. Parker and N. S. Isaacs, Chem. Rev., **59**, 772 (1959), for references and discussion.

Figure 2.

ticular, in the presence of strong acid catalysts[11] as illustrated by the reaction sequence

$$C_6H_5—CH—CH_2 \longrightarrow C_6H_4CH_2CHS \longrightarrow polymer$$
$$\underset{\underset{H}{S}}{\overset{\oplus}{\diagdown \diagup}}$$

The failure to observe strong coloration and/or fluorescence in the reaction solution is a prominent weakness of this proposal, since thiocarbonyl compounds are deeply colored and readily distinguished even in small concentrations.

A second possibility considered is plainly in keeping with the requirement of nucleophilic bonding to the reaction center in the transition state, as deduced above *via* the solvent composition–acidity function (S.–C.) test. This assumes that the thiol product of ring opening of one molecule competes with solvent ethanol in nucleophilicity when present in sufficiently high concentration.

$$\underset{}{\overset{OC_2H_5}{C_6H_5—CH—CH_2—SH}} + \overset{C_6H_5}{\overset{}{CH}\underset{\underset{SH}{\oplus}}{—}CH_2} \longrightarrow$$

$$-CH_2\left[\begin{array}{c} S \\ | \\ C_6H_5—CH—CH_2 \end{array}S-\right]_n \xrightarrow{\text{Raney nickel}} \begin{array}{c} H_2S \\ + \\ C_6H_5—CH_2—CH_3 \end{array}$$

The attempt to obtain the analogous rate data for the corresponding solvolysis of styrene oxide failed because of serious deviation from first-order kinetics at even moderate acid concentrations. The indications were that two reactions were proceeding independently and with different kinetic controls leading to two kinds of products—phenylethylene glycol derivatives and phen-

(11) S. Winstein and R. B. Henderson in "Heterocyclic Compounds," edited by R. C. Elderfield, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 1. See also S. Winstein and L. L. Ingraham, J. Am. Chem. Soc., 77, 1738 (1955).

ylacetaldehyde derivatives, respectively. These results stand in sharp contrast to the episulfide solvolysis where under the actual conditions of rate measurement only a single ring opening product is obtained with a simple kinetic order observed essentially throughout the course of reaction. It would almost seem as if the incidence of a competing carbonium ion rearrangement in the case of the styrene oxide conjugate acid might be correlated with a greater degree of unimolecular ionization of the carbon–oxygen bond than occurs in the carbon–sulfur bond of the episulfide conjugate acid.

The Dependence of Rate on Medium Acidity.

(A) According to the Zucker–Hammett Treatment.—The data obtained on the rates of solvolysis over a range of essentially pure (a very small amount of ethanol was used to assure substrate and product solubility) aqueous acid solutions have been arranged in Tables II and III. Various parameters have been computed

TABLE II

SOLVOLYSIS OF STYRENE EPISULFIDE IN SULFURIC ACID–H_2O CONTAINING 1.64 VOL. % ETHANOL, 25°, $[10^{-4} \text{ MOLE/L.}]_0$

Mole/1. H_2SO_4	$-H_0$	$k\psi \times 10^2$, min.$^{-1}$	$\log k\psi$	$-(\log k\psi + H_0)$	$-\log a_{H_2O}$
1.497	0.585	17.0	−1.770	2.355	0.029
2.211	0.992	42.1	−1.375	2.367	.051
2.703	1.232	64.3	−1.192	2.424	.070
2.807	1.283	75.1	−1.124	2.407	.075
3.260	1.505	140	−0.854	2.359	.098
3.538	1.636	215	− .668	2.304	.113
3.657	1.690	203	− .692	2.382	.120
4.072	1.877	423	− .374	2.251	.146
4.664	2.134	755	− .122	2.256	.190
4.705	2.156	725	+ .134	2.290	.192
5.180	2.360	1500	+ .177	2.183	.236
5.689	2.600	2700	+ .431	2.169	.288
5.835	2.665	2830	+ .452	2.213	.302

Summary:

(A) Zucker–Hammett plot, $\log k\psi$ vs. $-H_0$ in Fig. 2
least squares slope = 1.11, intercept = −2.50, r = 0.998, σ = 0.045

(B) Bunnett plot, $(\log k\psi + H_0)$ vs. $\log a_{H_2O}$ in Fig. 3
least squares slope w = −0.85, intercept = 2.43, r = 0.885, σ = 0.041

and listed therein which permit us to apply the graphical tests of the Z.–H. criterion (among others). Thus, plots of $\log k\psi$ vs. $-H_0$ for reactions (respectively) with perchloric and sulfuric acid catalyst are displayed in Fig. 2. The high quality of the fit to a straight line relationship can be evaluated with reference to the correlation coefficients (r) and the standard deviation of the slope (σ), bearing in mind that both plots represent a considerable number of measurements over a relatively large range of acid concentrations.

For the hydrolysis of a number of epoxide structures the Z.–H. slopes have been reported[2a] to vary over what must be regarded as a very considerable range of values; epibromhydrin and epichlorhydrin, 0.86; glycidol, β-methylglycidol and β-methylepichlorhydrin, 0.89; and ethylene and propylene oxide, 1.06. The significantly greater slope that characterizes styrene episulfide ring opening in perchloric acid (1.15) may be due to the aromatic substituent, for it is obvious that substituent effects do regulate the magnitude of the Z.–H. slopes. Bunnett[5] has provided considerable data to support the view that such substituent influences on the value of the slope are a manifestation of change in the role of and/or degree of participation of water molecules in the transition state.

Table III

Solvolysis of Styrene Episulfide in Perchloric Acid–H_2O Containing 1.64 Vol. % Ethanol, 25°, $[10^{-4}$ mole/l.$]_0$

Mole/l. $HClO_4$	$-H_0$	$k\psi$ $\times 10^3$, min.$^{-1}$	$\log k\psi$	$-(\log k\psi + H_0)$	$-\log$ a_{H_2O}
0.548	−0.06	3.49	−2.457	2.397	0.009
1.150	.315	9.42	−2.026	2.341	.021
1.727	.650	20.6	−1.686	2.336	.036
2.342	.942	42.4	−1.390	2.333	.054
2.890	1.190	89.2	−1.050	2.240	.076
3.452	1.446	170	−0.770	2.216	.102
4.085	1.760	370	− .432	2.192	.141
4.766	2.110	1070	+ .029	2.081	.194
5.262	2.385	2550	+ .407	1.978	.243
5.921	2.795	5870	+ .769	2.026	.320

Summary:

(A) Zucker–Hammett plot, $\log k\psi$ *vs.* $-H_0$ in Fig. 2
    least squares slope = 1.15, intercept = −2.42, r = 0.999,
    σ = 0.041

(B) Bunnett plot, $(\log k\psi + H_0)$ *vs.* $\log a_{H_2O}$ in Fig. 3
    least squares slope = −1.33, intercept = 2.37, r = 0.955,
    σ = 0.045

(B) According to the Bunnett Treatment.[5]—Following the recommended procedures for classifying the reaction under study in the several categories discussed by Bunnett, we were able to demonstrate the following characteristics of the kinetic data in Tables II and III: (1) plots of $\log k\psi$ *vs.* $\log a_{H_2O}$ for both sulfuric and perchloric acid reactions give smooth curves (Fig. 2 and 3) which cannot be said to be truly linear over any extended portion of the acid range studied; (2) plots of $(\log k\psi - \log (HX))$ *vs.* $\log a_{H_2O}$ gave only non-linear relationships independently of the acid nature (sulfuric or perchloric) and curving smoothly and continuously (see Fig. 2 and 3); (3) plots of $(\log k\psi + H_0)$ *vs.* $\log a_{H_2O}$ gave no clear indications of curvature with all points falling randomly about a line as illustrated in Fig. 3. The quality of fit to the straight line in the latter case is quite within the limits of acceptability, reckoning by comparison with the statistical parameters listed for more than 100 reactions analyzed by Bunnett.[5] From these considerations, also, we recognize that styrene episulfide is not a substrate of any considerable basicity (in agreement with experience) and that classification according to the alternative ω^*-values of Bunnett is not permissible. These facts at once delimit the kinds of acid-catalyzed mechanism with which the episulfide ring opening reaction can be compared.[5]

Interpretation.—The most recent empirical criterion of acid-catalyzed mechanism, w, would appear to indicate that in aqueous solution water possesses no nucleophilic function in the rate-determining step of episulfide ring opening, thereby confirming the A1 mechanism inferred from the Z.–H. criterion. These inferences are obviously at odds with the result we have obtained (*vide supra*) by application of the solvent composition–acidity function (S.–C.) criterion. We have attempted to reconcile these apparently diametrically opposite conclusions by considering the possible factors that could lead to a contradiction of this nature.

The first explanation to be considered stems from the fact that both the Z.–H. and w criteria are applied to the reaction taking place in purely aqueous solutions, whereas the S.–C. criterion studies the rate variation in media of continuously varying polarity. In the latter case, the identification of an A1 mechanism is restricted only to substrates in which (for instance) the generation of a carbonium ion center from SH^+ in the transition state requires no nucleophilic assistance from solvent for its
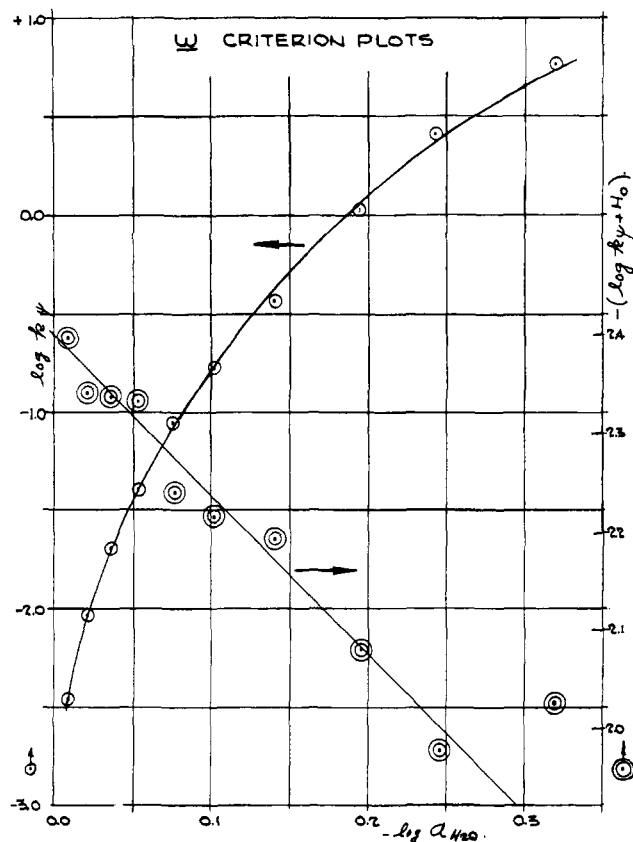

Figure 3.

development even as the ion-solvating power of the solvent decreases to that of pure ethanol. In other words, it may be possible to have a borderline mechanism which is more strongly dependent on the ion-solvating power of the medium. In mostly aqueous media it manifests itself as A1 and in media of somewhat lesser ionizing power it degenerates to the A2 process and assumes some dependence on the nucleophilic properties or nucleophilic agents in the medium, the latter being the case when acid polymerizes the episulfide.

Indications exist in the literature, too, that some epoxides may even undergo ring opening with a similarly equivocal dependence on medium composition. For instance, the ethylene and propylene oxide ring opening reactions have been characterized[2a] with a Z.–H. slope = 1.06 (corresponding to a small, negative w-value) in apparent agreement with an A1 mechanism. Stewart and VanderWerf,[12] however, have shown that with the use of aqueous halogen acids, up to 88% of the product formed arises from bonding of the most nucleophilic (iodide) anion at the least substituted carbon in propylene oxide. When the solvent is made less polar (ether) as much as 89% of the product can result from chloride ion attack. These facts tend to dispute the conclusion arrived at by applying mechanistic criteria to the reaction in purely aqueous media containing the least nucleophilic anions, perchlorate.[2a]

An alternative explanation for the discrepancy is one that has been advanced by Bunnett[5,13] for various other cases which he has examined. He has postulated that the w-value is a measure of the difference in degree of hydration between ground and transition states and has anticipated the possibility that unusually high hydration of the ground state may obscure a small degree of nucleophilic participation by solvent in the transition

(12) C. A. Stewart and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1257 (1954).

(13) See also ref. 1d for a similar discussion.

state. Reasoning from the fact that the valence shell orbitals of sulfur are quite extended and pursuant upon the idea advanced by Pauling[14a] that high hydration properties accompany only relatively contracted orbitals, the very contrary could have been expected. However, the most recent studies on hydrogen bonding in analogous sulfur and oxygen models[15] strongly suggest that sulfur is a much better proton acceptor than oxygen. When this is taken in conjunction with the well recognized fact that sulfur tolerates positive charge much better than oxygen in comparable onium ion substrates, a plausible explanation for the high negative w-values for acid-catalyzed ring opening of episulfides becomes evident. That is to say, the greater degree of onium ion character must be associated with a greater extent of hydration of the protonated episulfide reagent as compared to thiol product. The attainment of the transition state and consequent loss of onium ion character could correspond to the stripping away of water molecules of hydration in greater number than are participating as nucleophiles on the (opposite) back side of the rupturing carbon–sulfur bond.

On the other hand, we may also be encountering "hydration theory" deviations[5c] that can arise in cases where the substrate is exceedingly different in chemical nature from the indicator bases used in determining the H_0 scale. Under such circumstances, where there may

(14) L. Pauling, "The Nature of the Chemical Bond," 3rd Ed., Cornell Univ. Press, Ithaca, N. Y., Chap. 12, 1960.

(15) P. von R. Schleyer and R. West, *J. Am. Chem. Soc.*, **81**, 3164 (1959); and private communication from P. von R. Schleyer, Dec. 27, 1962.

be experienced considerable dislocation in comparing the hydration properties of the indicator base and conjugate acid with those of the corresponding substrate species, negative w-values are not unexpected.[5c] Indeed, the acid–base centers of the indicators are usually (second row) nitrogen atoms, whereas the corresponding functional center in our substrate is a (third row) sulfur atom with attendant differences in hydration properties to be anticipated.[14] Despite the occurrence of linear relationships (Fig. 2 and 3) in applying both the Zucker–Hammett and Bunnett criteria, some residual uncertainty may still exist concerning the validity of this application until it can be demonstrated by an independent method that the degree of protonation of the sulfur atom of our substrate correlates with H_0.

Whatever may prove to be the correct explanation for the apparent disparity in the results obtained, we believe that the simultaneous application of both (S.–C. and w) criteria as tests of mechanism can be recommended. The S.–C. criterion at this writing appears to be a sensitive (but negative) test[1a] by use of which one may learn whether there is any solvent involvement in the transition state. The w criterion, on the other hand, appears to possess the potential, thus far lacking in the S.–C. criterion, of identifying the extent and the role of H_2O participation in the transition state, where unusual hydration properties of the substrate, medium sensitivity of the reaction mechanism or other factors do not obfuscate the result. When used concurrently, as in the present instance, interpretations can be ventured with somewhat greater confidence.

The Synthesis of Substituted Aldosterone[1]

BY M. AKHTAR, D. H. R. BARTON, J. M. BEATON AND A. G. HORTMANN

A number of substituted aldosterones have been synthesized. In each case the angular 18-aldehyde grouping has been inserted by nitrite photolysis. The best procedure for the synthesis of 17α-hydroxyaldosterones involves protection of the side chain as the 17,20;20,21-bismethylenedioxy grouping. One of the methylenedioxy groups is hydrolyzed when an 18-oxime is treated with nitrous acid. The other has been removed under acidic hydrolytic conditions which afford, in general, 18,21-anhydro compounds. By special acid-catalyzed acetylation procedures the 18,21-anhydro ring has been opened to give 17,18-triacetates which on mild alkaline hydrolysis afford the desired 17α-hydroxyaldosterones.

In recent papers from this Institute[2] we have described convenient syntheses of aldosterone and 19-noraldosterone acetates. In spite of the potential biological interest of substituted aldosterones, especially those bearing 17α-hydroxyl groups, very few compounds of this type have hitherto been described. Racemic 16α-methyl- and 17α-hydroxyaldosterone have been obtained recently by total synthesis.[3] The present paper records the synthesis of a number of substituted aldosterones. The success of the work was made possible by the photolytic rearrangement of nitrites discovered earlier in this Institute.[4]

Dehydrogenation of aldosterone acetate (II) with selenium dioxide[5] gave 1-dehydroaldosterone acetate

(1) This paper is Communication No. 22 from the Research Institute for Medicine and Chemistry. For No. 21 see M. M. Pechet, Fifth Pan-American Congress of Endocrinology, in press.

(2) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, (a) **82**, 2641 (1960); **83**, 4083 (1961); (b) **83**, 750 (1961); **84**, 199 (1962).

(3) P. Wieland, K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **43**, 617 (1960); **43**, 2066 (1960).

(4) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet. *J. Am. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961); A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962).

(5) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. A. Szpilfogel, T. A. P. Posthumus, M. S. de Winter and D. A. van Dorp, *Rec. trav. chim.*, **75**, 475 (1956); H. Ringold and G. Rosenkranz, U. S. Patent 2,957,895.

(IIa).[6] This compound was, however, more conveniently prepared by photolysis of the 11-nitrite (Ia) of 1-dehydrocorticosterone acetate (Ib) followed by treatment with nitrous acid as detailed earlier.[2,4] 1-Dehydroaldosterone acetate was supplied to Dr. Marcel Gut of the Worcester Foundation and used by him in a synthesis of tritium labeled aldosterone acetate.[7]

In similar experiments, corticosterone acetate (I) was dehydrogenated with chloranil[8] to the 6-dehydro compound Ic which was converted to the nitrite Id, photolyzed and further processed with nitrous acid to furnish 6-dehydroaldosterone acetate (IIb). Addition of thiolacetate ion to the latter gave the interesting[9] 7α-thiolacetoxy derivative IIc. We also examined the addition of thiolacetic acid to 6-dehydrocorticosterone acetate (Ic) and thus obtained the 7α-thiolacetoxy derivative Ie. Conversion of the latter to its nitrite and

(6) E. Vischer, J. Schmidlin and A. Wettstein, *Experientia*, **12**, 50 (1956), record a m.p. (182-185°) for this compound which was prepared microbiologically from a racemic intermediate.

(7) K. R. Laumus and M. Gut, *J. Org. Chem.*, **27**, 314 (1962).

(8) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).

(9) R. M. Dodson and R. C. Tweit, *ibid.*, **81**, 1224 (1959); J. A. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959); R. C. Tweit. *ibid.*, **27**, 2693 (1962); R. C. Tweit, F. B. Colton, N. L. McNiven and W. Klyne, *ibid.*, **27**, 3325 (1962).