correct in theory, there exists, to our knowledge, no example of a negative salt effect of this magnitude on solvolysis of *any* substrate in *any* solvent by *any* salt; and in fact there exists but one authenticated example (NaCl in 50 wt % aqueous dioxane with neophyl tosylate) of a relevant negative salt effect of *any* magnitude ($b = -0.22$ to -0.37).[45] We conclude that the available evidence is overwhelmingly opposed to an SN2 interpretation of the 2-octyl mesylate data.

Finally, it should be recognized that the 2-octyl system, our first published example of the operation of the ion-pair mechanism, is now but one of several "borderline" systems which have been shown to conform to the predictions of the ion-pair mechanism. Among them are *p*-methoxybenzyl chloride (NaN_3 in 70% acetone),[4,12] benzoyl chloride[4,11] (*o*-nitroaniline in 50 wt % aqueous acetone), two of the substrates considered in this manuscript (α-phenylethyl bromide and α-*p*-tolylethyl chloride with N_3^- and SCN^- in ethanol), and α,γ-dimethylallyl chloride (N_3^- and SCN^- in ethanol and 90% ethanol).[13] The evidence in each case against mechanistic alternatives has been presented and argued. While the case for the operation of the ion-pair mechanism with any one of these substrates singly might not be completely convincing as an isolated example to all observers it is difficult for us to see how the cumulative weight of all of these studies can be denied.

Solvolytic Chemistry of 1,4-Dimethylbenzene Oxide. A New and Novel Mechanism for the NIH Shift

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Abstract: The kinetics of the aromatization of 1,4-dimethylbenzene oxide (I) into 2,5-dimethylphenol (II) and 2,4-dimethylphenol (III), the latter arising *via* the NIH shift of a methyl group, were measured over the pH range of 1–12, in 50% aqueous dioxane, $\mu = 0.1$ (KCl), and follow the equation $-d[I]/dt = [I][k_0 + (k_H{}^1 + k_H{}^2)a_H]$ (where $k_0 = 4.8 \times 10^{-3}$ sec^{-1}; $k_H{}^1 = 7.3 \times 10^2$ M^{-1} sec^{-1}; and $k_H{}^2 = 5.3 \times 10^2$ M^{-1} sec^{-1}). In this equation, k_0 is a spontaneous rate giving rise to a 13:87 ratio of II:III and $k_H{}^1$ and $k_H{}^2$ are acid-catalyzed terms giving rise to a 54:46 ratio of II:III. The reaction proceeding through the $k_H{}^1$ path does not involve detectable intermediates, whereas that through the $k_H{}^2$ path proceeds *via* the intermediate 1,4-dimethyl-2,5-cyclohexadiene-2,4-diol (IV). The $k_H{}^2$ path represents a new mechanism for the NIH shift. The mechanistic details of these reactions are discussed.

With the recent demonstration that arene oxides function as the initial intermediates in the enzymatic formation of phenols and other metabolites of the aromatic nucleus,[3] considerable interest has developed in the chemical and biological fate of these labile compounds. In particular, arene oxides have been implicated as agents in the toxicity,[4] mutagenicity,[5] and carcinogenicity[3,6] of mono- and polycyclic aromatics. These adverse reactions have been speculated to be the consequence of covalent binding of arene oxides to cellular nucleophiles. Thus, an understanding of the mechanisms by which arene oxides isomerize to phenols and react with nucleophiles acquires considerable significance.

A characteristic of the mixed function oxidase-catalyzed formation of phenols is the migration and subsequent retention of ring substituents originally present at the position of hydroxylation, the NIH shift.[7] Evidence that arene oxides are intermediates compatible with the NIH shift is found in the isomerizations of 1-^2H-4-methylbenzene oxide[8] and 1-^2H-naphthalene oxide[9] to the corresponding phenols. The magnitude of deuterium retention was found to be a function of pH in each case. Kinetics of the isomerization of benzene and naphthalene 1,2-oxide[10] have shown that different mechanisms are operative at high and low pH. In the neutral to basic region, an un-

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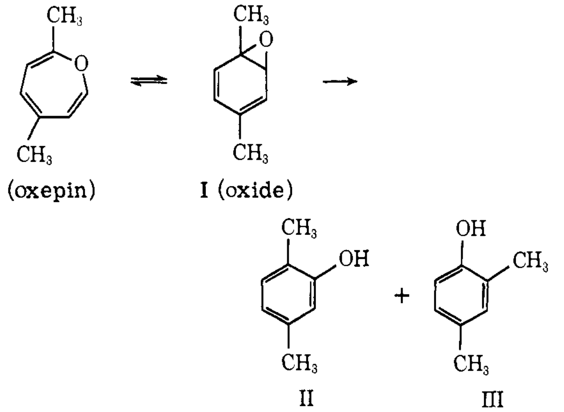
catalyzed, spontaneous rearrangement occurs while at low pH (<6), acid catalysis predominates. Concerted rearrangement to the keto form of the phenol (high pH) and acid-catalyzed rearrangement to the protonated ketophenol tautomer (low pH) are thought to be the rate-controlling steps. Variation in deuterium retention with pH is consistent with these mechanisms.[9]

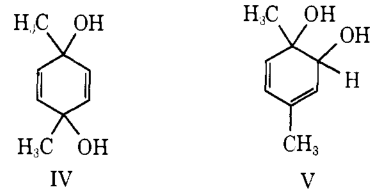
Isomerization of 1,4-dimethylbenzene oxide (I) is known to proceed with varying degrees of methyl migration, dependent on pH.[11] That is, both 2,5-dimethylphenol (II) and 2,4-dimethylphenol (III) are formed (eq 1). The rearrangement products are thought to arise from the oxide form of I since oxepins typically undergo ring cleavage to dialdehydes.[12] Study of this rearrangement has led to proof for a remarkable new mechanism for arene oxide isomerization in which 1,4-dimethyl-2,5-cyclohexadiene-1,4-diol (IV) and possibly 1,4-dimethyl-3,5-cyclohexadiene-1,2-diol (V) are involved.



I (oxepin) I (oxide)

II III

(1)



IV V

Experimental Section

Materials. 1,4-Dimethylbenzene oxide (I) was prepared and purified as previously described.[11b] Reagent grade potassium chloride, potassium acetate, potassium hydroxide, methanol, and trifluoroacetic acid were used without further purification. Reagent grade dioxane was refluxed with and then distilled from sodium prior to use. The ^{18}O content of $H_2{}^{18}O$ (Bio-Rad, enriched in deuterium) was determined by reacting 50 mg of p-toluenesulfonyl chloride with 100 μl of $H_2{}^{18}O$ in 1 ml of dry pyridine for 1 hr at room temperature. The solution was then concentrated to a solid, dissolved in 1 ml of dry methanol, and reconcentrated. The methanol evaporation was repeated, and the mass spectrum of the toluenesulfonic acid was obtained on a LKB 9000 mass spectrometer at 70 eV. The toluenesulfonic acid contained 39.7% ^{18}O in excess of natural abundance (m/e 174) indicating the $H_2{}^{18}O$ contained 39.7% ^{18}O.

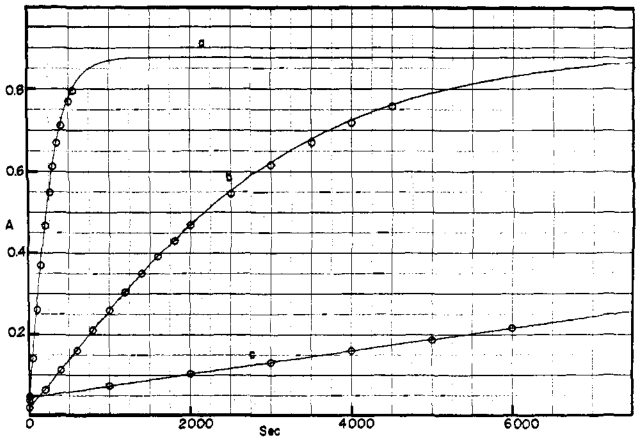
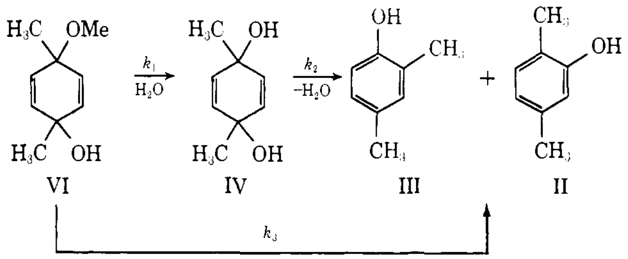


Figure 1. Plots of absorbance *vs.* time for the formation of II and III from VIa. The points are experimental and the lines are computer generated. a, b, and c are reactions at pH 2, 3, and 4, respectively.

Scheme I



VI IV III II

Kinetic Measurements. Kinetic studies were carried out either in deionized and then glass distilled water or aqueous dioxane (50% v/v). The ionic strength was held at 1.0 with KCl for the kinetic studies in water and 0.1 for the studies in aqueous dioxane. The kinetic measurements were carried out spectrophotometrically and without buffers in a Radiometer pH-stat assembly specifically designed for a Cary-15 spectrophotometer[13] thermostated at 30.0 ± 0.1°. The change in absorbance *vs.* time was followed at 310 nm (decreasing) due to the disappearance of I or 278 nm (increasing) due to formation of II and III. The disappearance of I was followed at 310 nm because at this wavelength none of the products absorbed, while the formation of II and III was followed at 278 nm because at this wavelength the change in absorbance was maximal. Reactions were initiated in all cases by the addition of 10–20 μl of a solution of the oxepin–arene oxide mixture in tetrahydrofuran to give a final concentration between 10^{-4} and 10^{-5} M. The kinetic measurements carried out at pH's >3.5 and monitored at 278 nm were made by adding the oxepin–arene oxide mixture at pH 3.5, waiting 30 sec, and then adjusting to the desired pH. The kinetics of the aromatization of 4-methoxy-1,4-dimethyl-2,5-cyclohexadienol (VI) were followed in a similar manner. The rate of aromatization of the crystalline isomer VIa and the oily isomer VIb (20% VIa) was determined by monitoring the increase in absorbance at 278 nm due to the formation of II and III. The kinetics for the reactions of I, decreasing absorbance at 310 nm and increasing absorbance at 278 nm after the decrease at 310 nm was complete, were pseudo-first order and the rate constants (k_{obsd}) were calculated by least-squares analysis of plots of ln $(A_\infty - A_0)/(A_\infty - A_t)$ *vs.* t on an Olivetti-Underwood Programma 101. The plots of ln $(A_\infty - A_0)/(A_\infty - A_t)$ *vs.* t for the aromatization of VI showed considerable curvature so the rate constants could not be obtained in the usual manner. The absorbance *vs.* t plots could be fitted nicely by assuming a mechanism as shown in Scheme I. Figure 1 shows plots of absorbance *vs.* time for the formation of II and III from VIa at various pH's. The lines were generated by an EAI TR-20 analog computer program as shown in Figure 2. The product ratios for the reactions of I were determined by carrying out the reactions under exactly the same conditions as the kinetic studies except the reactions were initiated by adding 19.5 μl of I to give a final concentration of about 3 × 10^{-3} M. After completion of the reaction, the

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[11] (a) D. M. Jerina, N. Kaubisch, and J. W. Daly, *Proc. Nat. Acad. Sci. U. S.*, **68**, 2545 (1971); (b) N. Kaubisch, J. W. Daly, and D. Jerina, *Biochemistry*, **11**, 3080 (1972); (c) Edward A. Fehnel, *J. Amer. Chem. Soc.*, **94**, 3961 (1972).

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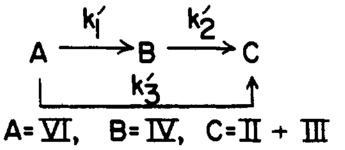


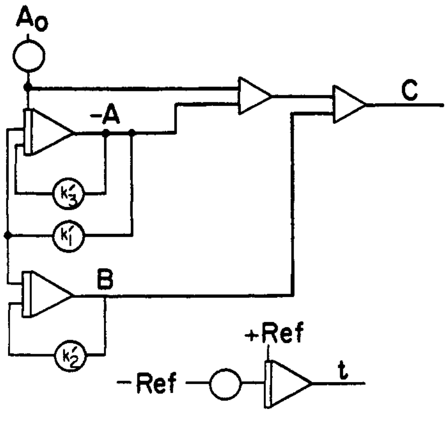


Figure 2. Wiring diagram for the analog computer which generated the lines in Figure 1.

basic solutions were acidified and all samples were concentrated to approximately half their original volume under reduced pressure. The resulting solutions were extracted with ethyl acetate, dried (Na_2SO_4), and evaporated to leave an oil which was silanized prior to gas chromatography (3% OV-17, 6 ft × 0.25 in. o.d., 120°) for determination of the ratio of II and III by peak height.

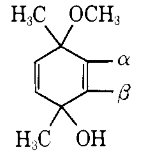
The product ratio was also determined spectrophotometrically. The following simultaneous equations were solved for C^{II} and C^{III}, the concentrations of II and III, respectively

$$A_{290} = a_{290}{}^{II}bc^{II} + a_{290}{}^{III}bc^{III}$$

$$A_{285} = a_{285}{}^{II}bc^{II} + a_{285}{}^{III}bc^{III}$$

In the above equations A_{290} and A_{285} are the absorbance at 290 and 285 nm, respectively, $b = 3.5$ the path length of the cell in centimeters, and a is the absorptivity of II or III indicated by superscripts at the wavelength indicated in the subscript. The values of $a_{290}{}^{II}$, $a_{290}{}^{III}$, $a_{285}{}^{II}$, and $a_{285}{}^{III}$ are 2.93×10^2, 1.10×10^3, 1.30×10^3, and 1.77×10^3. The wavelengths 290 and 285 nm were chosen for these calculations because they are in the region where the difference in absorptivity of II and III is greatest. This procedure is not as accurate as the direct determinations of the products by gas chromatography because the uv spectra and absorptivity of II and III are very similar. For example, at pH 8 gas chromatography shows 87% III while spectrophotometrically 82% III is detected. Since direct determination of the phenol ratio in these solutions containing IV is not possible due to decomposition of IV to II and III during attempted isolation of the phenols, the spectrophotometric method was used to calculate the percentages of II and III at pH 3.2, a pH where two reactions are occurring (see Discussion). The disappearance of I was followed at 310 nm at pH 3.2. When this is complete the reaction is stopped by rapidly adjusting the pH to 7. At this point all the I has disappeared and the concentrations of II and III are determined by recording the absorbance at 290 and 285 nm and solving the above simultaneous equations. The pH is readjusted to 3.2 and held there until a much slower reaction producing additional II and III is complete (increasing absorption at 278 nm stops). The concentrations of II and III are then determined as above. Now the amounts of II and III produced by this slower reaction can be calculated by subtracting the concentrations of II and III produced in the initial reaction (while I is disappearing) from the total amount of II and III produced in both reactions. In this way the percentages of II and III produced by each reaction can be calculated.

Preparation of 4-Methoxy-1,4-dimethyl-2,5-cyclohexadienol (VI). A solution of 1.2 g of I in absolute methanol (20 ml) was added to a stirred solution of 2 drops of trifluoroacetic acid in anhydrous methanol (20 ml) at −78°. During the course of 20 min the temperature was raised to 0° and held there for 10 min. The mixture was then made basic by the addition of 4 drops of triethylamine. The methanol was evaporated and the residue was dissolved in chloroform. After washing with 4% sodium hydroxide solution and then water, the chloroform was dried with anhydrous potassium carbonate. Evaporation of the solvent gave a colorless oil which was separated by tlc on silica gel F254 (0.5 mm, Merck) with chloroform. A mixture (540 mg) of the cis and trans stereoisomers (~1 : 1) of VI was isolated from the band with an R_f value



VI

of 0.13. Crystallization of this oil from petroleum ether (bp 30–60°) gave stereoisomerically pure VIa as colorless feathers: mp 94–95°; ir $\lambda_{max}^{CHCl_3}$ 3600 cm^{-1} (OH); nmr (220 MHz, $CDCl_3$) δ 1.30 (s, 3 H, $-C-CH_3$), 1.34 (s, 3 H, $-C-CH_3$), 1.67 (s, 1 H, OH), 3.03 (s, 3 H, OCH_3), 5.54 (d with fine structure, $J = 10$ Hz, 2 H, olefinic protons β), 6.02 (d with fine structure, $J = 10$ Hz, 2 H, olefinic protons α); uv ν_{max}^{MeOH} end absorption; mass spectrum (70 eV) main peaks *m/e* 139, 136, 123; chemical ionization mass spectrum (70 eV, reactant gas isobutane) *m/e* 155 $(M + H)^+$, 153, 152. Although a molecular ion (*m/e* 154) could not be observed for this crystalline isomer on electron impact, the protonated molecular ion (*m/e* 155) was readily detected on chemical ionization.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.80; H, 9.14.

The mother liquor of the above recrystallization was evaporated to give the other isomer VIb as an oil. An nmr spectrum showed the oil to contain about 20% VIa. This mixture showed ir $\lambda_{max}^{CHCl_3}$ 3600 cm^{-1} (OH); nmr (220 MHz, $CDCl_3$) δ 1.23 (s, 3 H, $-C-CH_3$), 1.32 (s, 3 H, $-C-CH_3$), 2.04 (s, 1 H, OH), 3.09 (s, 3 H, OCH_3), 5.61 (d with fine structure, $J = 10$ Hz, 2 H, olefinic proton β), 5.97 (d with fine structure, $J = 10$ Hz, 2 H, olefinic proton α); uv ν_{max}^{MeOH} end absorption; mass spectrum (70 eV) main peaks *m/e* 139, 136, 123. The relative stereochemistry in VIa and VIb was not assigned.

Reactions of VIa and VIb in Aqueous Acetone and in Methanol. A sample of 17 mg of VIa or VIb was dissolved in a mixture of 0.4 ml of deuterioacetone and 0.15 ml of D_2O and acidified gradually by the addition of a DCl-D_2O solution. The change in the nmr spectrum was monitored with time. In the neutral pH range (*ca.* 7), no change was observed; however, in the acid pH range (*ca.* 3.4) a slow change was observed that gave clear evidence of the formation of IV in a ~1 : 1 ratio for cis : trans as a minor component during formation of II and III.

The compounds VIa and VIb are particularly prone to methanolysis. When either was treated with acidified perdeuteriomethanol in an nmr tube, the spectrum showed almost complete conversion to a ~1 : 1 mixture of the dimethoxy analog along with minor amounts of II and III. Attempted isolation of the dimethoxy analog free of II and III led to solvolysis.

Incorporation of ^{18}O into II and III. The pH of a solution of 14.8 mg of potassium chloride in 0.5 ml of dioxane and 1 ml of ^{18}O enriched water (39.7%) was adjusted to 3.2 with 6 *N* hydrochloric acid. To this solution 10 mg of arene oxide I in 0.5 ml of dioxane was added and the resulting mixture was stirred at room temperature for 1.5 hr. The products II and III were isolated and analyzed by combined gas chromatography–mass spectrometry of the silyl ethers as described above. Incorporation of ^{18}O was measured on an LKB-9000 mass spectrometer–gas chromatograph at 70 eV using a column (6 ft × 0.25 in. o.d.) of 3% OV-17 operated at 120°. Found was 59% II (43% ^{18}O incorporation) and 41% III (47% ^{18}O incorporation). A similar experiment was performed in the basic region. In this case the pH was adjusted to 11.2 with sodium hydroxide. The pH measured at the end of the reaction was 10.0. No incorporation of ^{18}O was found in the products. The same experiment was performed using 4.3 mg of VI instead of I at pH 3.2. In this case 35% II (100% ^{18}O incorporation) and 65% III (70% ^{18}O incorporation) were found.

The amounts of II and III produced from I *via* the direct ($k_H{}^1$) and the diol ($k_H{}^2$) pathway (see Discussion) are calculated by the product ratio ^{18}O method according to the following equations

$$II_{dir} + II_{diol} = II_{total}$$

$$\frac{II_{diol}}{II_{dir} + II_{diol}} = \text{fraction } ^{18}O \text{ incorporation}$$

Similar equations can be written for III. This method assumes that all the II and III arising *via* the diol path incorporate 100% ^{18}O.

Results

At slightly acidic to basic pH, the disappearance of I (decrease in absorption at 310 nm) is pseudo-first order, proceeding without detectable intermediates to the phenols II and III whose concentrations were determined spectrophotometrically and by gas chromatography. In contrast, the disappearance of I at pH $\lesssim$ 3.5 (310 nm) is not stoichiometric with the production of II and III. A spectrophotometrically undetectable intermediate forms whose subsequent disappearance then gives rise to additional quantities of II and III. The appearance of II and III from the intermediate may be followed by recording the increase in absorbance at 278 nm, a wavelength at which II and III have similar absorptivities. This intermediate will subsequently be shown to be IV as a mixture of cis and trans isomers.

The log of the observed pseudo-first-order rate constants (k_{obsd}) *vs.* pH for the reactions of arene oxide I is shown in Figure 3. Plot a pertains to the pH dependence for the disappearance of I (310 nm) in aqueous dioxane (50% v/v), μ = 0.1 with KCl. The theoretical line of plot a has been generated from eq 2

$$k_{obsd} = k_0 + k_H a_H \quad (2)$$

where a_H is the hydrogen ion activity determined at the glass electrode, $k_0 = 4.8 \times 10^{-3}$ sec^{-1}, and $k_H = 1.26 \times 10^3 M^{-1}$ sec^{-1}. The rate constants for profiles b and c were determined at 278 nm in aqueous dioxane and water (μ = 1.0), respectively, and relate to the appearance of II and III from the intermediate derived from I at acidic pH values. The solid lines which best fit the experimental points were generated from eq 3.

$$k_{obsd} = 0.78 a_H \text{ sec}^{-1} \text{ (aqueous dioxane)} = 3.16 a_H \text{ sec}^{-1} \text{ (H}_2\text{O)} \quad (3)$$

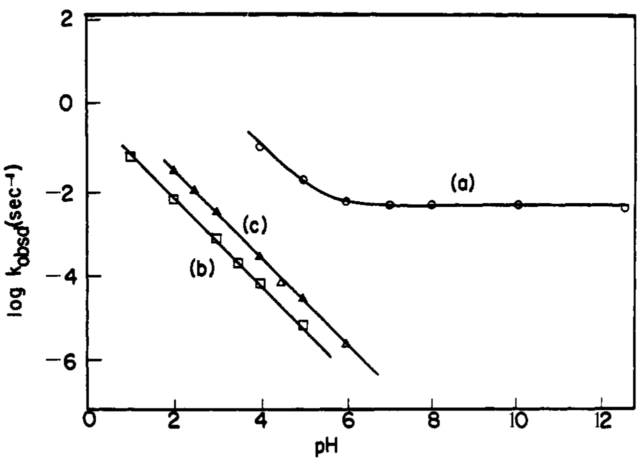


Figure 3. Plots of log k_{obsd} *vs.* pH at 30°: (a) disappearance of I in aqueous dioxane (50% v/v); (b) formation of II and III from IV in aqueous dioxane (50% v/v); (c) formation of II and III from IV in water. The points are experimental and the lines are theoretical fits.

The product distribution of II and III was found to be pH dependent. At low pH, II and III are formed in approximately equal proportions, and at moderately acidic to high pH, III, which results from methyl migration, is the predominant product. When the reaction was allowed to proceed at pH 3.5 for 30 sec and the pH then adjusted to 5 (Table I), the product distribution was the same as at low pH. This experiment demonstrates that I is converted to an intermediate *via* acid catalysis which then yields II and III in a ratio that is not influenced by pH. In an additional experiment the reaction was followed (pH 3.2) until I had disappeared (no further decrease in absorbance at 310 nm), the pH was then adjusted to 7, and the uv spectrum was recorded. This showed that 32% II and 28% III (based on total II and III produced at end of reaction) were formed directly from I. The pH was then adjusted to pH 3.2 and a much slower increase at 278 nm was observed. When this was complete, the uv spectrum was again recorded and 52% II and 48% III were found. Thus, 20% II and 20% III arose from the intermediate. The total yield of II determined spectrophotometrically was found to compare quite favorably with the 54% II found in the acid region by gas chromatography. At high acid concentrations (Table II) the ratio of II and III changes from that noted in the acidic pH range. This is apparently due to a change in the activity of H_2O, as can be seen by the effect of Li^+ on the product ratio of II and III. The activity of H_2O is known to be similarly influenced by Li^+ and H^+ ion.[14] The results in Table II show that increasing the LiCl concentration affects the product distribution arising through the k_H path (though not that through the k_0 path) and that this effect is similar to that obtained on increase in HCl concentration above 0.1 *N*.

Table I. Product Distribution Determined by Gas Chromatography from the Rearrangement of I in Dioxane–H_2O (50% v/v) at 30° (μ = 0.1 with KCl)

pH	% II	% III
1	54	46
3	54	46
3.5 → 5[a]	53	47
5	39	61
7	14	86
10	13	87
12.5	13	87

[a] The reaction was initiated at pH 3.5 and then adjusted to pH 5 when all I had disappeared and run to completion.

Table II. Effect of Ionic Strength on the Product Distribution from the Rearrangement of I (Solvent H_2O, 30°)

NaOH, *N*	HCl, *N*	LiCl, *N*	II	III
6			17	83
1		5	18	82
0.01			10	90
	0.1		64	33
	1	5	44	56
	6		45	55

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(14) R. A. Robinson and R. H. Stokes, "Electrolytic Solutions," Butterworths, London, 1959, p 483.

The effect of acetic acid on the reaction rates was determined to see if k_H represented general acid rather than specific acid catalysis. Table III shows that although acetic acid–potassium acetate buffer does have a slight effect on the rate of decrease in absorbance at 310 nm, there is no general acid catalysis of the reactions of I because at pH 4, when all the buffer is in the acid form (solution 50% dioxane–H_2O v/v), there is no catalysis on increase of [CH_3COOH]. This result is reminiscent of that obtained in certain instances of acetal hydrolysis (also in mixed solvents) and is most likely attributed to exchange of Cl^- for AcO^- at the lower pH values.[15] Extreme care must be taken in interpreting small changes in rate on increase of buffer concentration, especially in mixed solvents.

Table III. Effect of Acetate Buffer on the Reaction Rates of the Rearrangement of I [Solvent Dioxane–H_2O (50% v/v), 30°, $\mu = 0.1$ with KCl]

[AcOH + AcO⁻]	$k_{obsd} \times 10^3$ sec⁻¹ pH 6.1	pH 5.4	pH 4.0
0.10	6.43	10.06	100
0.06		9.02	94
0.04	5.80		
0.02	5.66	8.38	104
0.00	5.58	8.20	105

The rate constants for the aromatization of I in 50% dioxane–H_2O as a function of temperature at pH 12.5 are presented in Table IV. The value of E_a is 13.0 ± 0.1 kcal/mol, and $\Delta S^{\ddagger}$ has a value of -28.2 ± 0.3 eu at 30°. The reported uncertainties were calculated from the standard error of a plot of ln k_{obsd} *vs.* $1/T$. The solvent deuterium kinetic isotope effect was determined to be $k_{obsd}^{H_2O}/k_{obsd}^{D_2O} = 1.34$ at pH 9 and 1.07 at pH 3.

Table IV. Effect of Temperature on the Aromatization of I [at pH 12.5, $\mu = 0.1$ in 50% Dioxane–H_2O (v/v)]

T, °C	$k_{obsd} \times 10^3$ sec⁻¹
25	3.37
30	4.69
40	9.90
50	18.0

The introduction of ^{18}O into II and III was determined in both the acidic and basic pH range by reacting I in 50% dioxane–$H_2$$^{18}O$ (v/v). In the basic pH range (plateau in Figure 3), no ^{18}O was detected in II or III showing conclusively that the oxygen in the products originates from I and not the solvent. In the experiment in the acidic region (pH 3.2) 59% II and 41% III were found. The introduction of ^{18}O into II and III was 43 and 47%, respectively. Thus, a substantial quantity of the products in the acid range derive their oxygen from solvent H_2O.

When I is added to acidic methanol, a mixture of the cis and trans stereoisomers of 4-methoxy-1,4-dimethyl-2,5-cyclohexadienol (VI) can be isolated. These can be separated into a pure crystalline isomer VIa and a mixture of 20% VIa and the other isomer (VIb). Relative stereochemistry has not been assigned. The kinetics of the formation of II and III from both VIa and the mixture of VIa and VIb were determined in aqueous dioxane under the same conditions as used in determining the kinetics of the reactions of I. Appearance of II and III could be fit to a process as depicted in Scheme I. Dimethylanisoles are not formed in this reaction. The analog computer fit (Figure 1) was generated by assuming k_2' to be equal to k_{obsd} for the formation of II and III from the intermediate produced in the acid-catalyzed aromatization of I. This assumption is compatible with the aromatization VI and the proposed intermediate IV; *e.g.*, solvolysis (*vide* nmr) with methanol or water is very rapid. The calculated rate constants for the reaction of IV are found in Table V.

Table V. Calculated[a] Rate Constants for the Formation of II and III from VI in Aqueous Dioxane at 30°

	VIa		VIb[b]	
pH	k_1'	k_3'	k_1'	k_3'
2	3.3×10^{-3}	2.6×10^{-3}	2.9×10^{-3}	2.3×10^{-3}
3	3.1×10^{-4}	2.6×10^{-4}	2.6×10^{-4}	2.7×10^{-4}
4	2.8×10^{-5}	3.6×10^{-5}	2.5×10^{-5}	3.4×10^{-5}

[a] Calculated on an analog computer according to Scheme assuming $k_2' = 0.78a_H$. [b] 20% VIa.

The introduction of ^{18}O into II and III derived *via* IV was determined in 50% aqueous dioxane (50% v/v) in which the water was ^{18}O enriched. At pH 3.2 35% of II and 65% of III were found. The ^{18}O incorporation into II and III was 100 and 70%, respectively.

The solvolysis of VI was also monitored by nmr in a mixture of acetone-d_6 and D_2O and clear evidence was obtained for the formation of IV as a 1:1 ratio of cis:trans in the acidic pH range.

Discussion

The kinetics for the rearrangement of I into II and III, like the rearrangement of other arene oxides in aqueous solution,[10] exhibit two distinct rate terms: one spontaneous (k_0) and the other hydrogen ion dependent ($k_H a_H$). The reaction paths through k_0 and k_H are principally characterized by different ratios of the products II and III. The striking feature of the aromatization of I is that two distinct reaction paths were detected in the acid-catalyzed region ($k_H = k_H^1 + k_H^2$). The mechanism of the acid-catalyzed and pH-independent aromatization of I will be discussed separately.

pH-Independent Region. In the pH-independent region, III, which results from methyl migration, is the predominant product.[11] A high percentage of deuterium migration has previously been reported for the isomerizations of 1-^2H-4-methylbenzene oxide[8] and 1-^2H-naphthalene oxide[9] to the corresponding phenols. This migration has provided evidence for arene oxides as intermediates in the production of phenols catalyzed by mixed function oxidases, since migration of ring substituents at the position of hydroxylation (NIH shift[7]) is observed in these reactions.

There are two possible mechanisms for the formation of II and III from I in the pH-independent region. The first of these is one of concerted migration and

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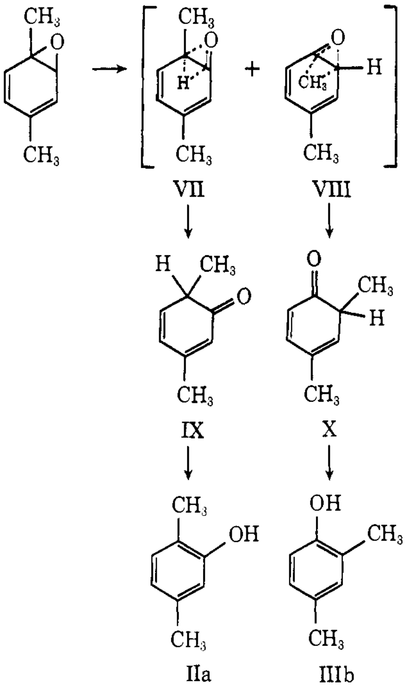
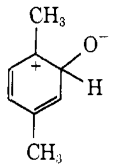
(15) M. Lahti and A. Kankaanpera, *Acta Chem. Scand.*, 24, 706 (1970).

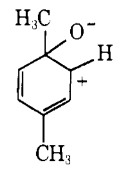
Scheme II



oxide ring opening (Scheme II) while the second is stepwise going through the intermediacy of zwitterions XI and XII in which XI and XII rearrange to IX and X, respectively, and then enolize to products as in Scheme II. While the entropy of activation ($\Delta S^{\ne}$ = −28.2 eu) is indicative of an ordered transition state such as VII or VIII, definitive mechanistic interpretations cannot be made on entropy values alone. The two mechanisms are very similar, differing only in the timing of the methyl or hydride migration, and cannot be distinguished by the data.



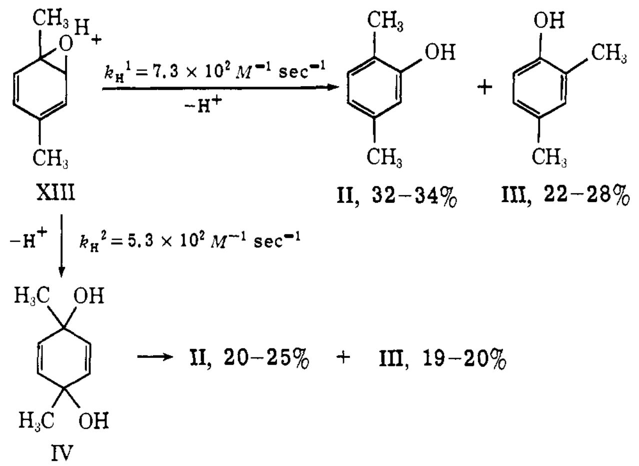
XI



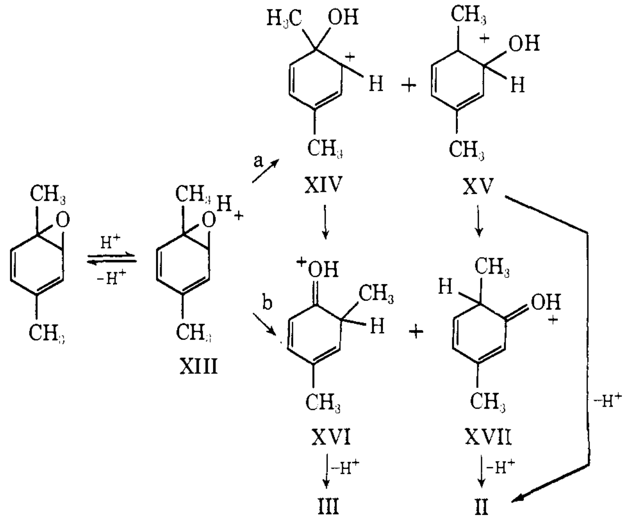
XII

Acid-Catalyzed Region. The formation of II and III from I is subject to specific acid catalysis. The acid-catalyzed isomerization differs from the pH-independent isomerization in that two distinct reactions are observed. Acid catalysis yields II and III directly from I but when all of I has disappeared an additional 40–44% of II plus III is formed from an intermediate produced in an acid-catalyzed reaction of I. This is shown in Scheme III in which $k_H{}^1$ is the rate of formation of II and III by the direct path and $k_H{}^2$ is the rate of formation of IV. Although it could not be isolated, IV is proposed as the intermediate for the following reasons. (1) In the acid region in acetone-d_6–D_2O the formation and disappearance of IV from either I or VI can be followed and its structure deduced *via* nmr spectroscopy. (2) When I is placed in acid methanol the methoxy analog of IV, 4-methoxy-1,4-dimethyl-2,5-cyclohexadienol (VI), can be isolated. (3) The kinetics of the formation of II and III from VI can be fit to a scheme (Scheme I) that involves IV as an intermediate which provides II and III at a rate identical with the rate of formation of II and III from the intermediate derived from I (Scheme III). The values of $k_H{}^1$ and $k_H{}^2$ can be obtained by determining the relative amounts of products that are formed *via* each pathway and a knowledge of k_H. The relative amounts of II and III that appear *via* each pathway were calculated by both spectral and product ratio–^{18}O methods. The best agreement between the two methods is obtained if 100% ^{18}O incorporation in the II and III produced *via* the $k_H{}^2$ path is assumed. *This means IV produced by I exchanges –OH groups with the solvent* $H_2{}^{18}O$ *faster than it aromatizes.* This assumption is warranted since VI, the analogous methyl ether of IV, aromatizes with a high percentage of ^{18}O incorporation. Furthermore, dimethylanisoles are not formed. The spectral method gives 32% II and 28% III *via* the $k_H{}^1$ path and 20% II and 20% III *via* the $k_H{}^2$ path, while the product ratio–^{18}O method gives 34% II and 22% III *via* the $k_H{}^1$ and 25% II and 19% III *via* the $k_H{}^2$ path. Thus, the values of $k_1{}^H$ and $k_2{}^H$ are 7.3 ± 0.3 × 10^2 and 5.3 ± 0.3 × 10^2 M^{-1} sec^{-1}, respectively. The detailed mechanism for the direct path ($k_H{}^1$) is similar to that suggested for other arene oxides in the acid region[9,10] and is depicted in Scheme IV. The protonated arene oxide XIII can either open (path a) to form carbonium ions XIV and XV which rearrange to intermediate protonated ketones XVI and XVII,

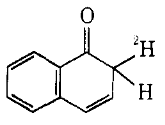
Scheme III

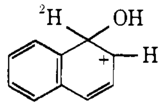


Scheme IV

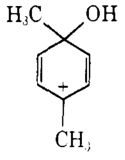


or XIII can proceed directly to XVI and XVII *via* a concerted mechanism (path b); it is also possible to envision direct formation of II from XV by loss of a proton. Whether the reaction proceeds through path a or b or both cannot be determined from the data; however, the involvement of both pathways must be considered. The rearrangement of 1-^2H- and 2-^2H-naphthalene 1,2-oxides is known to provide 1-naphthol containing different amounts of deuterium which indicate mechanistic pathways through both XVIII (retains deuterium) and XIX (loses deuterium).

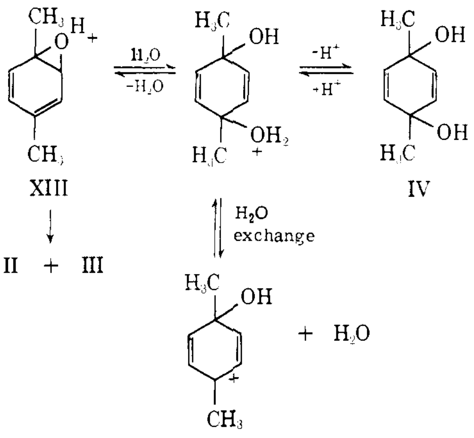

XVIII


XIX

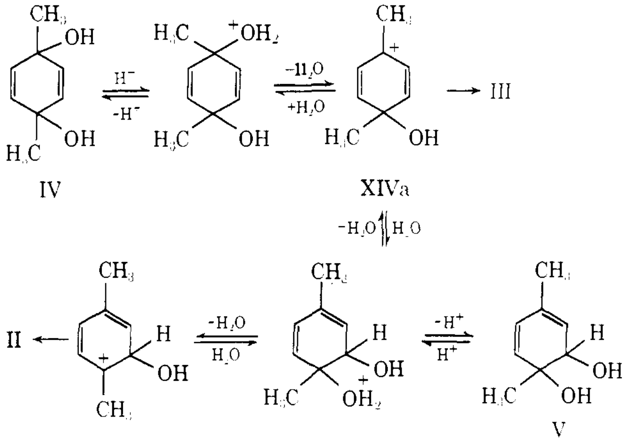
The portion of the acid-catalyzed reaction going through the diol path ($k_{H}{}^2$), Scheme III, may involve either reaction of the protonated arene oxide XIII or carbonium ion XIV with water to produce diol IV. The fact that carbonium ion XIV is unusually stabilized (positive charge stabilized by two allylic and one methyl group XIVa) accounts for its exchanging OH groups with solvent H_2O faster than it aromatizes. There are two possible mechanisms for the formation of II and III from IV. In the first (Scheme V), II and III are produced *via* a steady-state concentration of protonated arene oxide XIII in a mechanism identical with that in the direct route. The second mechanistic possibility (Scheme VI) is more complicated and involves a 1,2-diol V as an intermediate in the pathway to II while III is produced *via* the same route as in the direct mechanism. Although an unequivocal choice cannot be made between these two mechanisms, the one depicted in Scheme V is "preferred" because it predicts the II/III ratio to be the same in the direct path and the diol path because both pathways involve the same product-determining intermediate XIII. Examination of this ratio as calculated by the more accurate product ratio ^{18}O method yields 1.55 for the direct path and 1.32 for the diol path in good agreement with the mechanism of Scheme V.[16]


XIVa

Scheme V



Scheme VI



Acknowledgment. This work was supported in part by a grant to T. C. Bruice from the National Institutes of Health.

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[16] Since submitting this study, conclusive proof that aromatization of arene oxides occurs *via* rate-determining carbonium ion formation has appeared [see G. J. Kasperek, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Chem. Soc., Chem. Commun.*, 784 (1972)].