Aromatization of 4-Carboxybenzene Oxide

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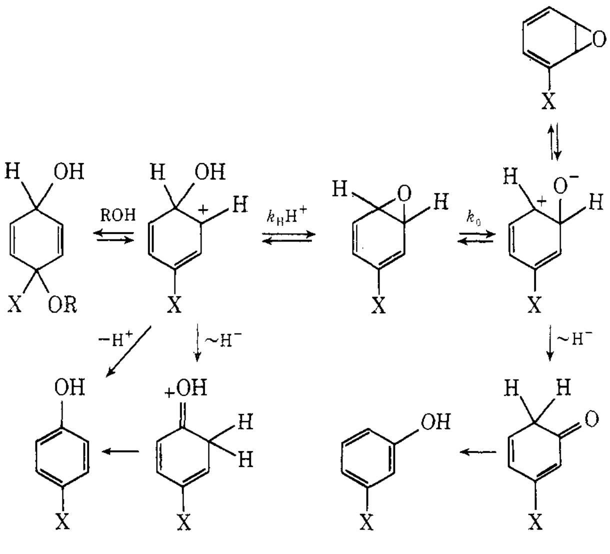
4-Carboxybenzene oxide (I) has been synthesized and the kinetics of its aromatization studied in the pH range of 0-10 (H_2O, 30°, μ = 0.2 KCl). General catalysis was found to be unimportant in both the acidic and basic regions of pH. The pH-log k_{obsd} profile dictates three competitive pathways leading to phenols: specific acid-catalyzed aromatization of undissociated I (Ia) and its anion (Ib) as well as uncatalyzed aromatization of the anion. The lack of spontaneous aromatization of undissociated I is as predicted on the basis of a previous investigation of substituent effects upon the rate constants of both specific acid catalyzed and uncatalyzed aromatization of benzene oxides. The products of reaction were found to be *m*- and *p*-hydroxybenzoic acid (no ortho isomer). The ratio of meta:para isomers was found to be ~1:1 for both the acid-catalyzed and noncatalyzed reactions with Ib, while acid-catalyzed aromatization of Ia yields predominantly the meta isomer. The product analysis as well as the lack of importance of spontaneous aromatization of undissociated I is in accord with a previous suggestion of formation of resonance-stabilized carbonium ions as being rate determining in the aromatization of benzene oxides.

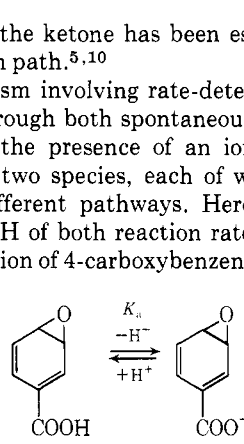
Arene oxides have been proposed as metabolic intermediates involved in necrosis,[1] mutagenesis,[2] and carcinogenesis.[3] Detailed studies of the kinetics for the aromatization of these intermediates indicate that the reaction proceeds *via* both specific acid catalyzed (k_H) and spontaneous (k_0) pathways.[4] Both pathways involve oxirane ring opening to form carbonium ions in the rate-determining step. In the spontaneous path, the carbonium ion may undergo intramolecular hydride transfer to give a ketone, which then enolizes to form the phenol (NIH shift). In competition with the NIH shift the carbonium ion may collapse to form isomeric arene oxides.[5] In the acid-catalyzed path, the intermediate carbonium ion may undergo intramolecular hydride transfer to give the protonated ketone, simply lose a proton to give the phenol directly, or reversibly trap solvent to give a diol.[6] The overall reaction is shown in Scheme I.

Scheme I



Support for the rate-determining formation of the carbonium ion lies in the observation of strong substituent effects ($\rho \cong -7$) on the aromatization of several substituted benzene oxides.[7] The intermediacy of a ketone was proposed to account for the NIH shift[8] which has been observed to occur during the aromatization of these compounds. In certain instances the ketone may be observed.[9] For indan oxide the ketone has been established to reside along the reaction path.[5,10]

If the mechanism involving rate-determining carbonium ion formation through both spontaneous and acid catalysis is correct, then the presence of an ionizable substituent should result in two species, each of which may react by either of two different pathways. Herein is reported the dependence on pH of both reaction rate and product ratio in the aromatization of 4-carboxybenzene oxide (I).



Ia Ib

Experimental Section

Materials. Reagent grade potassium chloride, ferric chloride, and potassium hydroxide were used without further purification. The *o*- and *p*-hydroxybenzoic acids were purchased from Eastman, the *m*-hydroxybenzoic acid from Aldrich, and the 2,4-dihydroxybenzoic acid from Matheson Coleman and Bell. These compounds were also used without further purification. The former acid buffer was prepared from formic acid (Matheson Coleman and Bell) and sodium formate (B and A grade, Specialty Chemicals Division, Allied Chemical Co.) while the acetic acid buffer was prepared from glacial acetic acid (B and A grade, General Chemical Division, Allied Chemical Co.) and sodium acetate trihydrate (Analytical Reagent, Mallinckrodt Chemical Works). Dioxane was refluxed over and distilled from sodium prior to use.

3,4-Oxo-2,5-dihydrobenzoic Acid (2). To a suspension of 84.2 g (0.68 mol) of 2,5-dihydrobenzoic acid[11] and 10 g of anhydrous NaOAc in 1250 ml of $CHCl_3$ was added dropwise 168 g (0.88 mol) of 40% peracetic acid. The mixture was stirred overnight at room temperature, extracted with two 300-ml portions of saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated to give off-white crystals that were recrystallized from $CHCl_3$ to give 65.5 g (69%) of **2**: mp 149-150°; ir ($CHCl_3$) 3600-2300 (broad), 1700, 1655, 1425, 1305, 1275, 950, 885 cm^{-1}; nmr ($CDCl_3$, DMSO-d_6) δ 9.16 (broad s, 1 H), 6.80 (m, 1 H), 3.30 (m, 2 H), and 2.70 ppm (m, 4, H).

Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.82; H, 5.55.

Trimethylsilyl 3,4-Oxo-2,5-dihydrobenzoate (3). A mixture of 59.0 g (0.42 mol) of **2** and 55.0 g (0.42 mol) of *N*-(trimethylsilyl)-acetamide in 450 ml of CCl_4 was heated under reflux for 1 hr. The mixture was cooled, the acetamide was filtered, the solvent was evaporated, and the residual oil was distilled to give 72.1 g (81%) of **3**: bp 77-82° (0.15 mm); ir (CCl_4) 2990, 2955, 2895, 2800, 1695, 1660, 1440, 1420, 1410, 1395, 1365, 1345, 1300, 1265, 1250, 1210, 1080, 1050, 1005, 950, 850 cm^{-1}; nmr ($CDCl_3$) δ 6.83 (m, 1 H), 3.38 (m, 2 H), 2.73 (m, 4 H), and 0.33 ppm (s, 9 H).

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4-Carboxyoxepin-4-Carboxybenzene Oxide (1). To a solution of 5.43 g (25.5 mmol) of 3 in 50 ml of CCl_4 was added 4.54 g (25.5 mmol) of *N*-bromosuccinimide and the mixture was heated under reflux and irradiated for 0.5 hr. The mixture was cooled, the succinimide was filtered, and the solvent was evaporated to give a bromide mixture which was used without further purification. The bromide mixture was dissolved in 50 ml of ether, 3.34 g (33 mmol) of triethylamine was added, and the mixture was stirred overnight at room temperature. The precipitated triethylamine hydrobromide was removed by filtration and the ether was evaporated to give a red-brown oil that was triturated with hexane. The hexane solution was decanted and evaporated under reduced pressure to give a red-orange oil that was distilled under reduced pressure to give 1.65 g (31%) of **4**: bp 85-90° (0.1 mm); ir (CCl_4) 3030, 2950, 2885, 1695, 1635, 1575, 1450, 1320, 1280, 1255, 1235, 1100, 1075, 990, 950, 850 cm^{-1}; nmr (CCl_4) δ 7.07 (d, 1 H, J = 6 Hz), 6.18 (d, 1 H, J = 6 Hz), 5.63 (m, 3 H), and 0.33 ppm (s, 9 H).

To a solution of 0.4 g (2 mmol) of **4** in 1 ml of CCl_4 was added 40 μl of water and 60 μl of CH_3OH. The mixture was kept at room temperature for 45 min with occasional shaking and the solvents and trimethylsilyl alcohol were evaporated under vacuum to give 0.28 g (100%) of **1** that was recrystallized from hexane as light orange needles: mp 94-98°; uv max (hexane) 306 nm (ϵ 2010); ir (CCl_4) 3350-2400 (broad), 1695, 1640, 1610, 1580, 1430, 1400, 1280, 1240, 1105, 1080, 950 cm^{-1}; nmr (CCl_4) δ 11.10 (broad s, 1 H), 7.05 (d, 1 H, J = 6 Hz), 5.95 (d, 1 H, J = 6 Hz) and 5.42 ppm (m, 3 H).

Anal. Calcd for $C_7H_6O_3$: C, 60.86; H, 4.38. Found: C, 61.06; H, 4.15.

Kinetic Measurements. The kinetic reactions were run in either deionized and glass-distilled water or in 50% aqueous dioxane. In both solvents the temperature was held at 30.0 ± 0.1° and the ionic strength was maintained at μ = 0.2 with potassium chloride. With the exception of the buffer dilutions, all reactions were carried out in a thermostated pH-stat cell designed for use in a Cary 15 spectrophotometer.[12]

The reactions run in water were followed by monitoring the appearance of products at 233 nm below pH 6, and at 235 nm at higher pH values. Those run in 50% aqueous dioxane were followed by monitoring both product formation at 260 nm and arene oxide disappearance at 330 nm. These wavelengths were chosen because they represent the wavelengths at which the maximum change in absorbance occurs. Each reaction was initiated by the addition of a small amount of solid 4-carboxybenzene oxide to give a concentration of 10^{-5}-10^{-6} M.

The reactions were clearly first order without the intervention of any detectable intermediates. When the reactions were followed by repetitive scanning, tight isosbestic points were established. In water, the isosbestic points appeared at 280 nm at pH 4.0 and at 299 nm at pH 8.6. In 50% aqueous dioxane they appeared at 307 nm at pH 2.9 and at 300 nm at pH 10.3. Pseudo-first order rate constants for all reactions were calculated by least-squares analysis of plots of ln $(A_\infty - A_0)/A_\infty - A_t)$ *vs.* time on a Hewlett-Packard 9820A calculator. The plots were all linear over at least 2 half-lives.

For the buffer dilutions the reactions were run in cuvettes. At each pH, the reaction was run at five different buffer concentrations. The reactions were carried out in a Cary 16 spectrophotometer so that all five reactions could be run simultaneously. As before, the reactions were followed by monitoring the change in absorbance at 233 nm. Pseudo-first order rate constants were calculated for each reaction as described above.

Product Analysis. Product analysis was carried out spectrophotometrically. At the end of each reaction the pH was adjusted to 7.0 and the spectrum was recorded. The following simultaneous equations were then solved for the concentrations of *p*-hydroxybenzoic (C^p) and *m*-hydroxybenzoic acid (C^m) in solution. In

$$A_{235} = a^p{}_{235}bC^p + a^m{}_{235}bC^m$$

$$A_{245} = a^p{}_{245}bC^p + a^m{}_{245}bC^m$$

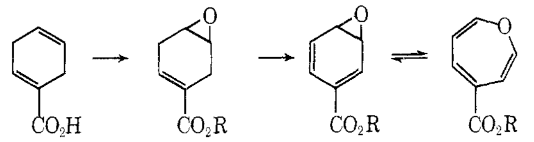
these equations, A_{235} and A_{245} are the absorbances at 235 and 245 nm, respectively, b is the path length of the cell in centimeters, and a^p and a^m are the absorptivities of *p*- and *m*-hydroxybenzoic acids at the respective wavelengths. The products $a^p{}_{235}b$, $a^m{}_{235}b$, $a^p{}_{245}b$, and $a^m{}_{245}b$ were determined from the spectra of a set of standard solutions containing the same total concentration but different ratios of the isomeric *m*- and *p*-hydroxybenzoic acids. These particular wavelengths were chosen because calculations using the parameters determined at these wavelengths resulted in the best agreement when solutions of known concentrations were analyzed. The accuracy of this method is limited to ±5%.

The presence of *o*-hydroxybenzoic acid was analyzed for by mixing an aliquot of the reaction products with a 20% solution of ferric chloride in 0.1 N HCl.[13] Control runs using both salicylic acid and 2,4-dihydroxybenzoic acid resulted in the formation of a dark brown complex which absorbs strongly in the region 550-530 nm. When this test was applied to the products of the hydrolysis of 4-carboxybenzene oxide, no absorbance was detected in the specified region.

Results

The synthesis of 1 was accomplished as indicated in Scheme II. Epoxidation of 2,5-dihydrobenzoic acid with peracetic acid afforded **2**, that was converted to **3** by reaction with *N*-trimethylsilyl acetamide. Allylic bromination of **3** with *N*-bromosuccinimide gave a mixture of monobromides which afforded **4** on treatment with triethylamine in ether. Ester **4** was hydrolyzed to the carboxylic acid **1** by treatment of a carbon tetrachloride solution with a small amount of aqueous methanol.

Scheme II



2, R = H
3, R = Me₃Si

4, R = Me₃Si
1, R = H

The rate of aromatization of 4-carboxybenzene oxide was measured over the pH range 0-10.5. The reactions were carried out in water at 30°, with μ = 0.2. The resulting log k_{obsd} *vs.* pH profile is shown in Figure 1. The solid line which best fits the experimental data was generated by computer from eq 1, where a_H = hydrogen ion activity

$$k_{obsd} = \frac{k_H a_H{}^2 + k'_H a_H K_a + k'_0 K_a}{K_a + a_H} \tag{1}$$

as determined with the glass electrode and $k_H = 8.50 \times 10^{-2}\ M^{-1}\ sec^{-1}$, $k'_H = 4.25\ M^{-1}\ sec^{-1}$, $k'_o = 3.50 \times 10^{-4}\ sec^{-1}$, and $pK_a = 3.70$. The dotted line in Figure 1 was generated from eq 2 assuming $k_o = 3.50 \times 10^{-4}\ sec^{-1}$ and $k_H = 8.50 \times 10^{-2}\ M^{-1}\ sec^{-1}$. The inability of eq 2 to fit the experimental data is evidence for observable, aromatization rates for both Ia and Ib.

$$k_{obsd} = k_0 + k_H a_H \tag{2}$$

The products of the aromatization of 4-carboxybenzene oxide are *m*- and *p*-hydroxybenzoic acid. The absence of *o*-hydroxybenzoic acid was shown by mixing aliquots of the reacton products with a 20% solution of ferric chloride in 0.1 N HCl. The lack of absorbance by the solutions in

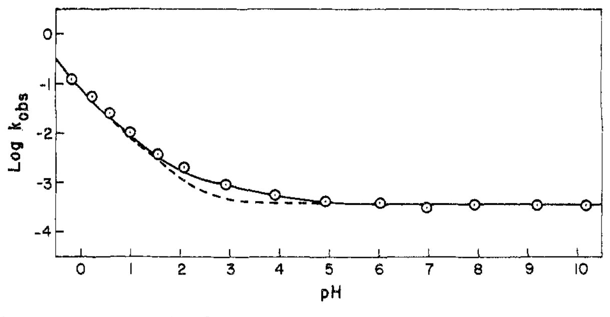


Figure 1. Plots of log k_{obsd} *vs.* pH at 30°. The solid line was generated by computer from eq 1. The dashed line was generated by computer from eq 2.

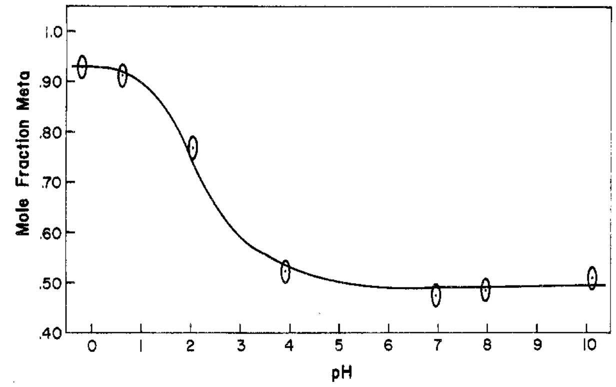


Figure 2. Plot of mole fraction meta *vs.* pH. The line was generated by computer from eq 3.

the region 530-550 nm is proof that *o*-hydroxybenzoic acid was not present in the products. The product ratio (*i.e.*, meta/para) was found to be pH dependent. A plot of mole fraction meta *vs.* pH is shown in Figure 2. The line which best fits the experimental data was generated from eq 3.

$$\text{Mole fraction meta} = \frac{Ak_\text{H}a_\text{H}^2 + Bk'_\text{H}a_\text{H}K_\text{a} + Ck'_0K_\text{a}}{k_\text{H}a_\text{H}^2 + k'_\text{H}a_\text{H}K_\text{a} + k'_0K_\text{a}} \qquad (3)$$

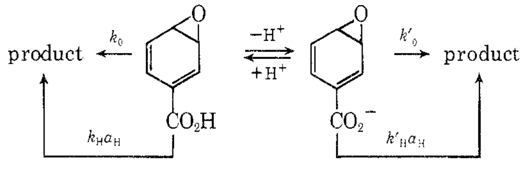
In this equation, A is the mole fraction of meta isomer produced *via* k_H, B is the mole fraction of meta produced *via* k_H', and C is the mole fraction of meta *via* k'_0. The values calculated for these constants are $A = 0.93$, $B = 0.56$, and $C = 0.49$.

The effect of total buffer concentration on the rate of aromatization is shown in Table I. The buffer at pH 4.41 was prepared from a mixture of acetic acid and sodium acetate, while the buffer at pH 3.42 consisted of formic acid and sodium formate. The lack of any significant concentration dependence is evidence that general acid catalysis is not operative with either acetic or formic acids.

Discussion

The kinetics of the aromatization of 4-carboxybenzene oxide are essentially the same as those observed for the aromatization of benzene oxide. The only difference lies in the number of rate terms needed to describe the pH dependence of the reaction. Owing to the presence of an ionizable carboxyl group, 4-carboxybenzene oxide can exist in solution as either a neutral molecule (Ia) or as a negatively charged carboxylate anion (Ib). Since each of these species can react by both a spontaneous and an acid-catalyzed path, the overall reaction would be as shown in Scheme III. Thus, the rate expression used to describe this reaction should incorporate all four rate constants, plus the equilibrium constant, K_a, for the acid dissociation. The equation derived for this reaction is eq 4. In this

Scheme III



$$k_\text{obsd} = \frac{k_\text{H}a_\text{H}^2 + k_0a_\text{H} + k'_\text{H}a_\text{H}K_\text{a} + k'_0K_\text{a}}{K_\text{a} + a_\text{H}} \qquad (4)$$

equation k_H and k_0 represent the acid-catalyzed and spontaneous aromatization of Ia, while k'_H and k'_0 denote the corresponding rates for Ib.

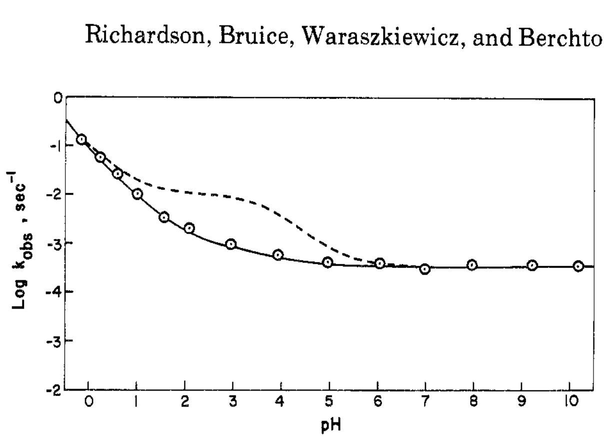


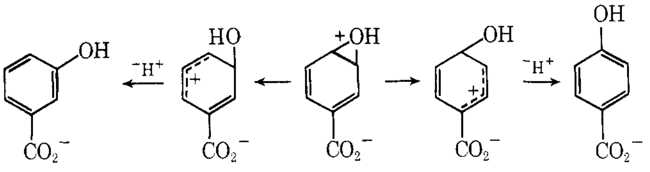
Figure 3. Plots of log k_obsd *vs.* pH. The dashed line was generated from eq 4, where $k_\text{H} = 8.50 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$, $k_0 = 9.00 \times 10^{-3}\ \text{sec}^{-1}$, $k'_\text{H} = 4.25\ M^{-1}\ \text{sec}^{-1}$, $k'_0 = 3.50 \times 10^{-4}\ \text{sec}^{-1}$, and p$K_\text{a}$ = 3.70. The solid line is the same as that shown in Figure 1.

Table I
Effect of Total Buffer Concentration on the Rate of Aromatization of 4-Carboxybenzene Oxide

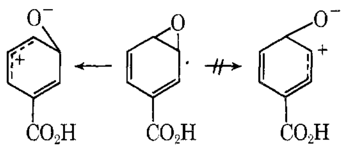
Total buffer concn, M	$k_\text{obsd} \times 10^4$, sec^{-1} pH 3.42	 pH 4.41
0.01	5.84	4.01
0.0075	6.56	4.32
0.0050	6.37	4.30
0.0025	6.87	4.49
0.0010	6.67	4.58

If all four rate processes included in Scheme III (eq 4) are competitive with each other, then the log k_obsd *vs.* pH profile predicted for I would be as shown in Figure 3, where $k_\text{H} = 8.50 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$, $k_0 = 9.0 \times 10^{-3}\ \text{sec}^{-1}$, $k'_\text{H} = 4.25\ M^{-1}\ \text{sec}^{-1}$, and $k'_0 = 3.50 \times 10^{-4}\ \text{sec}^{-1}$. This profile contains plateau regions for both k_0 and k'_0, plus acid-catalyzed regions for k_H and k'_H. The experimentally observed log k_obsd *vs.* pH profile is shown in Figure 1. The only difference between the predicted and observed profiles occurs in the pH range 1.5-5.0. Although the observed profile does include an inflection in this region, a distinct plateau is not observed. The rate expression which best fits the experimental eq 1 differs from eq 4 in that the rate constant (k_0) for the spontaneous aromatization of Ia is absent. The omission of this rate constant may be justified if one considers the effect substituents have on the reaction rate. The ρ for the aromatization of a series of substituted arene oxides has been determined to be ~ -7.6 in 50% dioxane-water. The value of σ^+ for the carboxyl group is $+0.42$, while the corresponding value for the carboxylate anion is -0.02. If $\rho = -7.6$, then k'_0 should be greater than k_0 by a factor of $\sim$1200. Since $k'_0 = 3.50 \times 10^{-4}\ \text{sec}^{-1}$, the value for k_0 would be $\sim 4.2 \times 10^{-7}\ \text{sec}^{-1}$. A reaction associated with such a small rate constant would not be competitive with the other processes. Further justification for this treatment can be obtained by comparing the difference between k_H and k'_H. Even if this 50-fold difference is all that applies to the spontaneous rates, that would still correspond to a k_0 of $\sim 7 \times 10^{-6}\ \text{sec}^{-1}$. It is unlikely that a reaction this slow would be observable under our conditions.

As shown in Figure 2, the product ratio is different for various reaction paths. While the ratio of *m*- to *p*-hydroxybenzoic acid is essentially 1:1 for both the acid-catalyzed and spontaneous aromatization of Ib, the meta isomer is the major product for the aromatization of Ia. Again, possible justification can be found in the electronic effects of the substituents. Since the carboxylate anion has a very small substituent constant ($\sigma^+ = -0.02$), its presence should have little influence on the π-electron system of the ring. Therefore, regardless of whether the oxirane ring opens to form an incipient carbonium ion at the 1 or 2 position, both would be allylically stabilized by the adjacent double bond (eq 5). On the other hand, the protonated carboxyl is strongly electron withdrawing ($\sigma^+ = +0.42$). This effect should be particularly significant on the π electrons of the double bond between carbons 3 and 4. As a result, these electrons would not be as available for stabilization of a positive charge as would the electrons in the π bond between carbons 5 and 6. Consequently, the opening which leads to formation of the meta isomer would be of lower energy than the opening which leads to the *p*-hydroxybenzoic acid, as shown in eq 6.

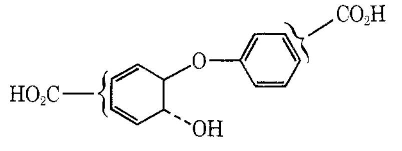


(5)



(6)

In an effort to correlate the reaction of I with the reaction of previously studied arene oxides, the rate of aromatization of I was measured in 50% dioxane–water. At high pH the reaction was first order. Although the observed rate constant was smaller than that predicted from the $\sigma^+\rho$ plot, the agreement was not unreasonable. At pH 0.5, the reaction exhibited biphasic kinetics. This was possibly due to some type of nucleophilic participation by the dioxane oxygens. In conjunction with this, it was found that I also undergoes some sort of transformation on standing in THF. The reaction probably involves rearrangement of 1 to a mixture of *m*- and *p*-hydroxybenzoic acid that undergoes nucleophilic addition to 1 to afford a mixture of products (5). The transformation is analogous to the formation of *trans*-6-phenoxycyclohexa-2,4-dien-1-ol from oxepin-benzene oxide.[14]



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Registry No.—1, 51380-68-8; 2, 51380-69-9; 3, 51380-70-2; 4, 51380-71-3; 2,5-dihydroxybenzoic acid, 490-79-9.

References and Notes

(1) B. B. Brodie, W. D. Reid, A. K. Cho, G. Sipes, G. Krishna, and J. R. Gillette, *Proc. Nat. Acad. Sci. U. S.*, **68**, 160 (1971).
(2) B. N. Ames, P. Sims, and P. L. Grover, *Science*, **176**, 47 (1972).
(3) P. L. Grover, P. Sims, E. Huberman, H. Marquardt, T. Kuroki, and C. Heidelberger, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1098 (1971).
(4) G. J. Kasperek and T. C. Bruice, *J. Amer. Chem. Soc.*, **94**, 198 (1972).
(5) G. J. Kasperek, P. Y. Bruice, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Amer. Chem. Soc.*, **95**, 1673 (1973).
(6) G. J. Kasperek, T. C. Bruice, H. Yagi, N. Kaubisch, and D. M. Jerina, *J. Amer. Chem. Soc.*, **94**, 7876 (1972).
(7) G. J. Kasperek, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Chem. Soc., Chem. Commun.*, 784 (1972).
(8) G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science*, **157**, 1524 (1967).
(9) E. Vogel and H. Günther, *Angew. Chem., Int. Ed. Engl.*, **6** (5), 385 (1967).
(10) G. J. Kasperek, P. Y. Bruice, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Amer. Chem. Soc.*, **95**, 6041 (1973).
(11) R. Grewe and I. Hindrichs, *Chem. Ber.*, **97**, 443 (1964).
(12) J. R. Maley and T. C. Bruice, *Anal. Biochem.*, **34**, 275 (1970).
(13) T. Maugh, II, and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 3237 (1971).
(14) A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. DeMarinis, C. H. Foster, D. E. Piccolo, and G. A. Berchtold, *J. Amer. Chem. Soc.*, submitted.

Electron Spin Resonance Studies of Hydrogen Transfer to Alkoxy Radicals from the Hydroxyl Group of Alcohols

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The esr spectra of *tert*-butyl radicals are observed during the reactions of various alkoxy radicals with tertiary alcohols containing one or more *tert*-butyl groups. The homolytic fragmentation of the alcohol is attributed to hydrogen transfer from the hydroxylic function to the alkoxy radical. Structural factors pertinent to the alcohol and alkoxy radical are explored in hydrogen transfer reactions of the hydroxyl group. Hydrogen bonding of alcohols to HF strongly inhibits the transfer of hydrogen from a hydroxylic function.

In solution, the majority of alcohols are preferentially attacked by free radicals at the α-CH bond, with the exception of tertiary alcohols, of course. The resulting α-hydroxyalkyl radicals have been trapped by olefins and their electron spin resonance spectra examined.[1-4]

Abstraction of the hydroxylic proton has been less commonly observed. For example, deuterium-labeling studies indicate that methanol reacts with methyl radicals in solution at the carbon–hydrogen bond 15 times faster than at the hydroxylic position at 30°.[5-7] The activation energy for hydrogen abstraction by methyl radical has been estimated to be 8.4 kcal/mol, which is approximately 3 kcal/mol higher than that of the corresponding reaction with methoxy radical.[8] Thermodynamic factors also favor abstraction from the α-CH bond by 5–10 kcal/mol.[9,10]

$$CH_3\cdot + CH_3OH \longrightarrow \dot{C}H_2OH + CH_4 \qquad (1)$$

$$CH_3\cdot + CH_3OH \longrightarrow CH_3O\cdot + CH_4 \qquad (2)$$

In the gas phase, however, the relative rates of reactions 1 and 2 are reversed, and the O–H bond is preferentially broken. Solvent effects on the reactions of hydroxyl groups and free radicals could be partly accounted for by the dif-