Aromatization of Arene 1,2-Oxides. 1-Carboxy- and 1-Carboalkoxybenzene Oxides

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Abstract: The mechanisms for aromatization of arene 1,2-oxides are discussed. The reaction course for aromatization of 1-carboxy- and 1-carboalkoxybenzene oxides is established, and the importance of the 1,2-oxides of benzoic acids as intermediates in biological hydroxylations is considered in view of the observed results. Acid-catalyzed rearrangement of 1-carbomethoxybenzene oxide (**4a**) and the corresponding 2-^{2}H, 2-CH_3, 4-CH_3, and 2-CH_3O_2C derivatives of **4a** occurs exclusively by an NIH shift involving migration of the carbomethoxy group. Aromatization of 1-carboxybenzene oxide (**13**) affords a mixture of salicylic acid and phenol, the ratio of which is pH dependent. The 2-CH_3 and 4-CH_3 derivatives of **13** decarboxylate to *o*- and *p*-cresol, respectively, on attempted isolation.

A common pathway for the oxidative metabolism of aromatic substrates involves monooxygenase-catalyzed formation of arene oxides that subsequently rearrange to phenolic metabolites.[2-4] Although few cases exist where the arene oxide has been trapped as a metabolic intermediate (arene oxides of chlorobenzene,[5] and several polycyclic aromatic hydrocarbons[6]), other evidence supporting the intermediacy of arene oxides over a wide range of substrates, while not obligatory in most cases, is compelling. The evidence includes observations of substituent migration and retention (H, D, T, halogen, alkyl) consistent with the established pathway for aromatization of arene oxides via the NIH shift and formation of other metabolites (nonphenolic) consistent with ring-opening reactions of an arene oxide intermediate.[2-4]

The para position of a substituted benzene is the most common position for hydroxylation in animal metabolism. By contrast, ortho hydroxylation is more common in microbial and plant metabolism, and mechanistic studies to date have been largely neglected. On the assumption that arene oxide intermediates are also involved in ortho hydroxylation, a wider range of mechanistic possibilities exists than in para hydroxylation.

Ortho hydroxylation of monosubstituted benzenes by a metabolic pathway involving initially the arene oxide could proceed via the 1,2- or the 2,3-oxide, and factors that determine the regioselectivity of epoxidation of benzene derivatives in monooxygenase-catalyzed reactions are not understood. Hydroxylations involving arene oxide intermediates that occur with loss of the substituent at the site of hydroxylation ought to proceed via the 1,2-oxide. The direction of oxirane ring opening for such arene oxides and the relative ease of migration of the substituent or hydrogen atom in the subsequent cationic intermediate should be determined by the electronic character of the substituent.

Arene oxides have been suggested as intermediates in the ortho hydroxylation and the oxidative decarboxylation of aromatic carboxylic acids. Salicylic acid biosynthesis from benzoic acid (or cinnamic acid via benzoic acid) in *Gaultheria procumbens* occurs with no migration of the carboxyl group and with migration and retention (16–35%) of ortho tritium labeling.[7] The latter observation, while of lower retention of tritium than expected, is consistent with a significant contribution by the NIH shift pathway, and presumably would involve the 1,2- or 2,3-oxide of benzoic acid. Haslam has suggested an alternative biosynthetic route to salicylic acid from the 1,2-oxide of benzoic acid.[8] Aromatic hydroxylation of *p*-hydroxybenzoic acid to gentisic acid by a strain of *Bacillus stearothermophilus* occurs by intramolecular ortho migration of the carboxyl group.[9]

The 1,6-oxide of salicylic acid has been suggested as an intermediate in the salicylate hydroxylase-catalyzed oxidative decarboxylation to catechol;[10] similar arene oxide intermediates may be involved in the oxidative decarboxylation of substrates such as *p*-methoxybenzoic acid,[11] vanillic acid,[12] phenazine-1-carboxylic acid,[13] and *p*-aminobenzoic acid[14,15] in microorganisms.

In spite of the growing number of proposals and body of evidence in favor of the in vivo formation of 1,2-arene oxides, few 1-substituted benzene oxides are known; to date the only examples where their aromatization pathway has been studied are those in which the substituent is H, D, T, and alkyl. No studies from other laboratories on the aromatization of 1-substituted 2-deuteriobenzene oxides have been reported. In view of the importance of the substituent on the pathway of aromatization, a general study of the synthesis and aromatization of 1-substituted benzene oxides is under investigation. Emphasis is being placed on such arene oxides that are potential biological intermediates in order to compare the nature of their aromatization reactions with evidence suggesting their intermediacy in biological oxidation reactions. Described herein are the preparation and aromatization studies of 1-carboalkoxy- and 1-carboxybenzene oxides.[16]

Synthesis of the carboalkoxyarene oxides (**4a–e**) was accomplished from dienes **1a–e** by bromination to **2a–e**, epoxidation to **3a–e**, and elimination of HBr with diazabicyclo[4.3.0]non-5-ene (DBN) (Scheme I). Arene oxides **4a,c–e** are yellow liquids, and **4b** is a yellow, crystalline solid. The long-wavelength absorption in the UV spectrum of each (Scheme I) indicates that they exist predominantly as the oxepin valence isomer.[17] The shoulder at 260 nm may be due to the benzene oxide valence isomer. The similarity in chemical shift in the ^{1}H NMR spectra for each ring proton among the different arene oxides suggests that the relative amounts of oxepin and arene oxide valence isomer do not differ significantly. The low-field position of proton H_3, 6.7–6.9 ppm (oxepin numbering), also supports the contention that **4a–e** exist predominantly as the oxepin valence isomer, but the high-field position of proton H_7 (5.9 ppm) suggests some contribution due to the arene oxide valence isomer in which the proton is on an epoxide ring carbon atom rather than an olefinic carbon atom.

Arene oxides **4a–e** and 2,7-dicarbomethoxyoxepin (**4f**, $R^1 = CH_3$; $R^2 = CO_2CH_3$; $R^3 = H$), previously prepared by Vogel and co-workers,[18] underwent acid-catalyzed rearrangement in neat CF_3CO_2H or in $CHCl_3$ containing a trace of CF_3CO_2H. Products and yields are listed in Scheme II. Except for **4f**, the reactions were complete within a few minutes at room temperature. The sole product from rearrangement of **4a** was methyl salicylate (**8a**) and from **4b** was salicylic acid (**8b**) due to cleavage of the *tert*-butyl ester under the acidic

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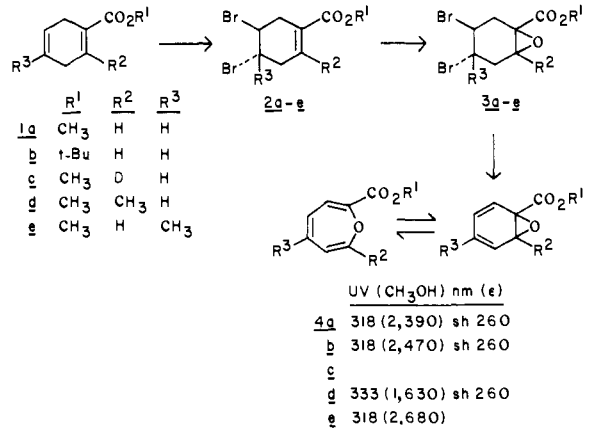
Scheme I



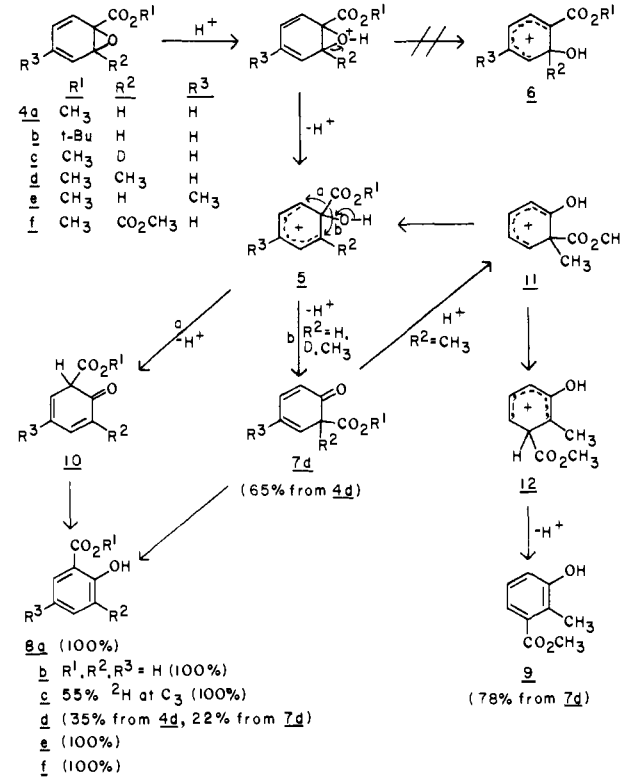
conditions. The electron-withdrawing carbomethoxy substituent in **4a** should favor ring opening of the protonated oxirane to the more stable cation **5** rather than **6**, and subsequent migration of the carbomethoxy group (paths a and b) and enolization affords **8a.**

Migration of carboalkoxy groups to a carbocation center β to the migrating group is well documented.[19-21] Bach and co-workers[19] have established that acid-catalyzed isomerization of glycidic esters involves migration of the carbethoxy group with inversion of configuration at the migration terminus. Marx and co-workers[20] have shown that 4-substituted 4-carbethoxy-2,5-cyclohexadienones rearrange in CF_3CO_2H with migration of the carbethoxy group, and the relative rates ($4\text{-}C_6H_5 \gg 4\text{-}CH_3 > 4\text{-}C_2H_5$) are a reflection of stability of the carbocation formed on migration of the carbethoxy substituent.

That the course of the reaction for aromatization of **4a** occurs exclusively via cation **5** (Scheme II) is established from the acid-catalyzed aromatization of **4c** and **4e.** Rearrangement of **4c** affords **8c** with ~55% retention of deuterium, and the deuterium is at the ortho position to the hydroxyl group (^1H NMR). Within experimental error (±5%) the results are consistent with formation of **5** and subsequent migration of the carbomethoxy group by path a and b to afford **8c** with ~50% loss of deuterium to solvent on enolization. Although it might be argued that reaction could occur by the energetically less favorable cation **6** to give the observed deuterium retention, formation of **8e** as the sole product from aromatization of **4e** is consistent only with the pathway involving migration of the carbomethoxy group. Any reaction of **4e** via cation **6** would yield methyl 4-methylsalicylate instead of **8e.**

Acid-catalyzed rearrangement of **4d** also occurs exclusively by initial formation of cation **5.** As indicated in Scheme II, the products, **8d** (35%) and **7d** (65%), result from the two possible modes of carbomethoxy migration in **5** (temperature maintained at 10 °C, reaction time <5 min), but without temperature control (reaction time <5 min), **9** (10%) is formed in addition to **8d** (45%) and **7d** (45%). While formation of **9** superficially appears to be an example of a 1,3-migration of a carbomethoxy group, it occurs from further acid-catalyzed reaction of **7d.** Keto ester **7d,** in fact, reacts slowly ($t_{1/2} \sim 12$ h) in CF_3CO_2H at ambient temperature to afford **9** (78%) and **8d** (22%). The complete sequence of events is summarized in Scheme II. Phenol **8d** is derived from the initially formed carbocation **5** by carbomethoxy migration to the unsubstituted ortho position to afford **10** that enolizes to **8d.** Carbomethoxy migration to the methyl-substituted ortho position yields dienone **7d.** The fact that **7d** (or **7d** + **9**) is formed in higher yield than **8d** provides further evidence that substituent migration in the NIH shift pathway is favored in the direction of the ortho position that is the site of higher charge stabilization. Formation of **9** occurs by the sequence **7d** → **11** → **12** → **9,** and

Scheme II

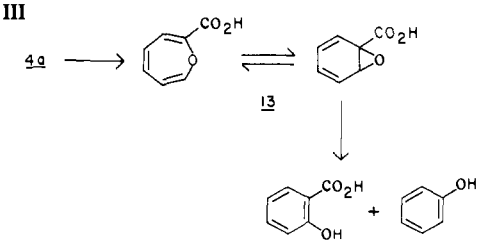


it is the major pathway for aromatization of **7d.** Formation of **8d** in 22% yield from **7d** indicates that carbomethoxy migration in **11** must also occur to the ortho position bearing the hydroxyl group to regenerate **5** and, subsequently, **8d.** Formation of **9** rather than **8d** as the major product from **7d** does not conflict with the suggestion that substituent migration is favored in the direction of the ortho position that is the site of higher charge stabilization (position bearing the hydroxyl group in **11**) since **5** formed from **11** favors return to **7d** over formation of **10.** Consequently, although **11** → **5** may well be favored over **11** → **12,** the effect is hidden by the rearrangement **5** → **7d** being favored over **5** → **10,** and the relative yields of **8d** and **9** are not a reflection of the preferred direction of carbomethoxy migration in **11.**

Acid-catalyzed rearrangement of **4f** affords **8f** as the only product observed. Carbomethoxy migration to the ortho position bearing a carbomethoxy substituent does not occur. Whereas **4a–e** rearrange quantitatively within minutes at ambient temperature, **4f** requies 1 month in CF_3CO_2H at this temperature for 95% reaction. Acid-catalyzed ring opening in **4f** undoubtedly is slower than in **4a–e** owing to the lower electron density on the epoxy oxygen atom and less favorable carbocation formation, but the exceedingly slow rate of reaction of **4f** probably is due in large part to the fact that **4f** exists almost entirely as the oxepin valence isomer and formation of the arene oxide valence isomer is unfavorable.

Since the 1,2-oxides of benzoic acids are of interest as possible intermediates in the ortho hydroxylation or oxidative decarboxylation of aromatic acids as described earlier, the 1,2-oxide of benzoic acid (**13**) has been prepared to investigate its stability and aromatization. Hydrolysis of **4a** with aqueous hydroxide at ambient temperature for 30 min, acidification with NaH_2PO_4. and immediate extraction with ether and concentration afforded **13** as yellow crystals in 94% yield (Scheme III). The UV spectrum of **13** in CH_3OH [315 nm (ϵ 2308), sh 260 (1723)] establishes that **13** exists predominantly as the oxepin valence isomer. Although prepared in a state of high purity, **13** in the crystalline state or in solution undergoes decomposition to a mixture of salicylic acid and phenol over a period of several hours. The product ratio from decomposi-

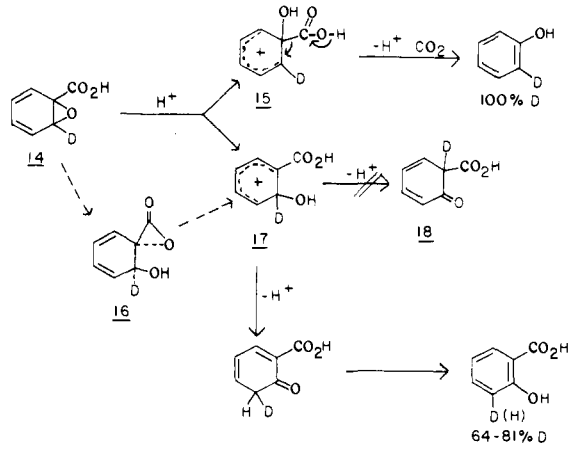
Scheme III



Pure CF_3CO_2H	64	36
pH 1 in 9:1 CH_3OH/H_2O	40	60
pH 2.5 in 9:1 $HOAc/H_2O$	32	68
pH 5 in 9:1 CH_3OH/H_2O[a]	21	79
Neat, crystalline state	20	80
pH 12 in 9:1 CH_3OH/H_2O[a]	14	86

a Conversion of 13 to phenolic products <50%

Scheme IV

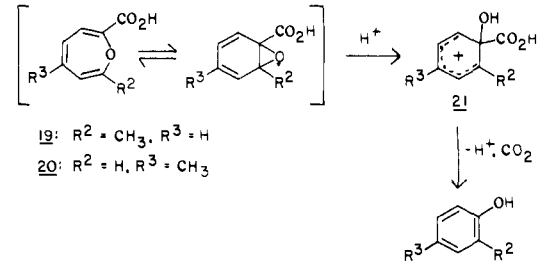


tion of **13** in solution is pH dependent as indicated in Scheme III.

Deuterium-labeled acid **14**, prepared from **4c** by the same procedure for the preparation of **13**, decomposed in the crystalline state to afford phenol with complete retention of deuterium and salicylic acid with 72% retention of deuterium on the carbocyclic ring that was shown by ^1H NMR to be at the ortho position to the hydroxyl group (Scheme IV). Deuterium retention in the salicylic acid from reaction of **14** in CF_3CO_2H and in aqueous solution at pH 7.4 (phosphate buffer) was 64 and 81%, respectively. The data are consistent with a pathway mainly involving ring opening of the oxirane, either prior to or after protonation, to afford **15** and **17** (Scheme IV) or the corresponding carboxylates depending on the pH of the reaction medium. Cation **15** (or the corresponding zwitterionic carboxylate) undergoes decarboxylation to phenol with complete retention of deuterium. Cation **17** undergoes migration of deuterium to the unsubstituted ortho position and subsequent enolization with observed deuterium retention consistent with that expected due to the isotope effect.[2,22] The high deuterium retention indicates that little, if any, reaction occurs to form **18** by migration of deuterium to the ortho position bearing the carboxyl substituent since enolization of **18** would result in complete loss of deuterium on exchange with solvent. Here again migration by the NIH shift pathway appears to occur to the site of optimal cationic stabilization.

It has been established that the NIH shift pathway for phenol formation from benzene oxide in aqueous solution may occur by initial protonation of the oxirane and subsequent C–O bond cleavage or by C–O bond cleavage of the unprotonated oxirane followed by protonation of the zwitterion so formed.[23] By either mechanism for oxirane ring opening, if Scheme IV does indeed represent the pathway of reaction of **14** and if the electron-withdrawing character of the substituent determines

Scheme V



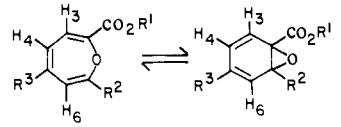
the direction of oxirane ring opening, then at lower pH (carboxyl group un-ionized) formation of **15** and, consequently, phenol should be favored since the electron-withdrawing character of $-CO_2H$ is similar to that of $-CO_2CH_3$.[24] Correspondingly at higher pH, in which case the carboxyl group exists as the less electron-withdrawing carboxylate anion, formation of **17** and, consequently, salicylic acid should be equally favorable. In fact, the reverse is observed: phenol is favored at higher pH and salicylic acid is the major product at lower pH (Scheme III). Intramolecular carboxyl participation in ring opening of the protonated oxirane to afford α-lactone **16** would provide one explanation for the increase in salicylic acid/phenol as the pH of the reaction medium is decreased. It would appear, however, that the observed deuterium migration and retention in salicylic acid formation would require that **16** undergo acid-catalyzed ring opening of the α-lactone to **17** that subsequently forms salicylic acid. A dihydrodiol intermediate could be formed by hydrolysis of α-lactone **16** in aqueous solution, but such a reaction probably does not occur since it would be expected to be sufficiently stable to be isolated at pH 7 or higher. Intramolecular carboxyl participation to afford a β-lactone in principle could be involved in phenol formation, but the data available do not provide evidence to support such participation. Structurally related β-lactones have, however, been shown to decarboxylate readily under mild conditions to afford aromatic products.[25]

Acids **19** and **20**, prepared from **4d** and **4e** by the same procedure for preparation of **13**, were too unstable to isolate. They underwent quantitative decarboxylation to *o*- and *p*-cresol, respectively (Scheme V). Acid **19** could be detected spectroscopically in solution to the extent of 30–60% in the ether extract of the acidified hydrolysis reaction, but decarboxylation was occurring rapidly. As expected, methyl substitution at the 2 or 4 position of **13** increases the rate of oxirane ring opening and favors formation of cation **21** to the total exclusion of oxirane ring opening in the other direction to afford a methyl-substituted salicylic acid. The greater stability of **19** (relative to **20**) may be a result of a decrease in the proportion of arene oxide tautomer in **19** and supports the conclusion[3] that methyl substitution on the oxirane ring leads to enhanced stability over methyl substitution at another position.

Oxepin-2,7-dicarboxylic acid (**22**) failed to undergo any observable reaction on standing in CF_3CO_2H at room temperature for 10 days. Whereas diester **4f** must have some benzene oxide valence isomer present, acid **22** would appear to exist only as the oxepin valence isomer as suggested by Vogel.[18]

Although the results from aromatization of deuterium-labeled acid **14** do not exclude rigorously the possibility that salicylic acid formation occurs via carboxyl migration, the quantitative formation of *o*- and *p*-cresol from **19** and **20** indicates that carboxyl migration does not occur in cation **21** (or **15**). It would appear that the intramolecular carboxyl migration in the biological hydroxylation of *p*-hydroxybenzoic acid to gentisic acid[9] does not occur by **21** (R^2 = H; R^3 = OH), derived from oxirane ring opening of the arene oxide or by direct addition of HO^+ (or HO· and subsequent oxidation) to

Table I. 270-MHz ^{1}H NMR Spectral Data of Arene Oxides **4a,d,e** and **13** in $CDCl_3$



benzene oxide-oxepin	R^1	H_3	H_4	R^3	H_6	R^2
4a (R^1 = CH_3; R^3 = H_5; R^2 = H_7)	3.82 (s, 3 H)	6.85 (d, 1 H, $J_{3,4}$ = 5.9)	6.35 (dd, 1 H, $J_{3,4}$ = 5.9, $J_{4,5}$ = 10.6)	6.47 (dd, 1 H, $J_{4,5}$ = 10.6, $J_{5,6}$ = 5.9)	5.78 (dd, 1 H, $J_{5,6}$ = 5.9, $J_{6,7}$ = 5.2)	5.94 (d, 1 H, $J_{6,7}$ = 5.2)
4d (R^1 = R^2 = CH_3; R^3 = H_5)	3.81 (s, 3 H)	6.86 (d, 1 H, $J_{3,4}$ = 5.9)	6.21 (dd, 1 H, $J_{3,4}$ = 5.9, $J_{4,5}$ = 10.7)	6.39 (dd, 1 H, $J_{4,5}$ = 10.7, $J_{5,6}$ = 5.9)	5.61 (d, 1 H, $J_{5,6}$ = 5.9)	2.01 (s, 3 H)
4e (R^1 = R^3 = CH_3; R^2 = H_7)	3.79 (s, 3 H)	6.75 (d, 1 H, $J_{3,4}$ = 5.9)	6.09 (d, 1 H, $J_{3,4}$ = 5.9)	1.97 (s, 3 H)	5.57 (d, 1 H, $J_{6,7}$ = 5.0)	5.87 (d, 1 H, $J_{6,7}$ = 5.0)
13 (R^1 = H_1; R^3 = H_5; R^2 = H_7	9.00 (s, 1 H)	6.91 (d, 1 H, $J_{3,4}$ = 5.9)	6.32 (dd, 1 H, $J_{3,4}$ = 5.9, $J_{4,5}$ = 10.6)	6.46 (dd, 1 H, $J_{4,5}$ = 10.6, $J_{5,6}$ = 5.9)	5.75 (dd, 1 H, $J_{5,6}$ = 5.9, $J_{6,7}$ = 5.1)	5.96 (d, 1 H, $J_{6,7}$ = 5.1)

the aromatic substrate, but the migration may involve a cation analogous to **21** in which the carboxyl group is present as an ester, thiol ester, or carboxamide derivative.[27]

Phenol formation from the monocarboxylic acids described above supports the suggestion that 1,2-oxides of aromatic carboxylic acids may be intermediates in biological oxidative decarboxylation reactions. The formation of salicylic acid from **13** and the deuterium migration and retention observed in the conversion of **14** to salicylic acid are in agreement with the suggestion that **13** is an intermediate in the ortho hydroxylation of benzoic acid in higher plants,[7] but a priori the 2,3-oxide is an equally attractive intermediate.[26]

The present work provides for the first time unequivocal evidence for arene 1,2-oxide aromatization reactions proceeding by all the possible general routes to ortho-substituted phenols and phenol with substituent loss.

Experimental Section

Melting points were determined using a Thomas-Hoover Uni-melt apparatus and are corrected. ^{1}H NMR spectra were obtained at 60 or 270 MHz with Hitachi Perkin-Elmer R-24B and Brüker FT spectrometers,[30] respectively (Table I). Deuteriochloroform solvent was used unless otherwise stated. Chemical shift values (δ) are reported in parts per million downfield from tetramethylsilane. The degree of incorporation of deuterium in labeled molecules was estimated by mass spectrometry using a Varian MAT 44 instrument operating at an ionizing potential of 70 eV and from ^{1}H NMR spectra. High-pressure liquid chromatography (LC) was carried out using a Waters Model 204 equipped with 660 Model programmer and US-K injector.[31] Phenol and salicylic acid were separated using this LC equipment and a micro Bondapak (μC_{18}) column in the reverse phase mode. Elution with 27% MeOH containing 0.1 M ammonium formate (pH 4.3 to suppress ionization) at a rate of 1.0 mL/min and 1000 psi gave peaks with retention times of 7.2 (salicylic acid) and 11.6 min (phenol) which were estimated with the aid of a Waters Model 440 UV detector at 254 nm using reference samples.

Phenolic products which were identified by comparison with commercial samples (or derived methyl esters) include phenol, salicylic acid, and 3- and 5-methylsalicylic acid. A sample of 3-hydroxy-2-methylbenzoic acid was kindly provided by Professor M. V. Sargent.[32] Ultraviolet spectra were measured with a Cary Model 14 recording spectrophotometer using methanol as solvent. Deuterated compounds **1c**, **2c**, **3c**, **4c**, and **14** were prepared by the same procedure for the undeuterated compounds and showed identical physical properties of the nondeuterated forms; the ^{1}H NMR and mass spectral data were consistent with >95% D incorporation at the indicated positions in all cases. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-Carboxy[2-^{2}H]cyclohexa-1,4-diene. The diene was prepared in 33% yield from [3-^{2}H]propiolic acid[33] (>95% ^{2}H) and butadiene by heating in a sealed tube at an oil-bath temperature of 54 °C for 4 days.[34] If the cycloaddition reaction was carried out a temperature of ca. 120 °C, some scrambling of deuterium occurred.

1-Carboalkoxycyclohexa-1,4-dienes 1a-e. Esters **1a,c-e** were prepared by reaction of the corresponding acids with CH_2N_2 or CH_3OH/HCl.

1-Carbomethoxycyclohexa-1,4-diene (1a): from 1-carboxycyclohexa-1,4-diene[34] (87%), bp 100 °C (6 mm) [lit.[35] bp 94-96 °C (20 mm)].

1-Carbo-*tert*-butoxycyclohexa-1,4-diene (1b): bp 50-60 °C (0.6 mm) [lit.[36] bp 49-51 °C (0.2-0.3 mm)].

1-Carbomethoxy-2-methylcyclohexa-1,4-diene (1d): from 1-carboxy-2-methylcyclohexa-1,4-diene[37] (68%): bp 50-55 °C (0.1 mm); ^{1}H NMR δ 2.03 (s, 3 H, CCH_3), 2.86 (m, 4 H, allylic H), 3.82 (s, 3 H, $-OCH_3$), 5.70 (m, 2 H, vinyl H). Anal. ($C_9H_{12}O_2$) C, H.

1-Carbomethoxy-4-methylcyclohexa-1,4-diene: from 1-carboxy-4-methylcyclohexa-1,4-diene[35] (87%), bp 65-75 °C (0.2 mm) [lit.[35] bp 110.5-11.5 °C (20 mm)].

1-Carboalkoxy-*trans*-4,5-dibromocyclohex-1-enes 2a-e. Diene ester **1a-e** (67 mmol) in CH_2Cl_2 (100 mL) was stirred at ~ 5 °C while bromine in the same solvent was added dropwise until a slight excess of bromine was present in the reaction vessel. The solution was washed with water and with saturated sodium thiosulfate solution. The dried ($MgSO_4$) solution was concentrated and on distillation yielded the product (**2a-e**) as a colorless oil.

1-Carbomethoxy-*trans*-4,5-dibromocyclohex-1-ene (2a): 98%; bp 105 °C (0.05 mm); ^{1}H NMR δ 2.50-3.70 (m, 4 H, allylic H), 3.71 (s, 3 H, $-OCH_3$), 4.50 (m, 2 H, CHBr), 6.85 (m, 1 H, vinyl H). Anal. ($C_8H_{10}Br_2O_2$) C, H.

1-Carbo-*tert*-butoxy-*trans*-4,5-dibromocyclohex-1-ene (2b): 91%; bp 143 °C (0.25 mm); ^{1}H NMR δ 1.48 (s, 9 H, CMe_3), 2.5-3.7 (m, 4 H, allylic H), 4.52 (m, 2 H, CHBr), 6.79 (m, 1 H, vinyl H). Anal. ($C_{11}H_{16}Br_2O_2$) C, H.

1-Carbomethoxy-2-methyl-*trans*-4,5-dibromocyclohex-1-ene (2d): 90%; bp 80-90 °C (0.05 mm); ^{1}H NMR δ 2.10 (s, 3 H, CCH_3), 2.34-3.40 (m, 4 H, allylic H), 3.72 (s, 3 H, OCH_3), 4.52 (m, 2 H, CHBr). Anal. ($C_9H_{12}Br_2O_2$) C, H.

1-Carbomethoxy-4-methyl-*trans*-4,5-dibromocyclohex-1-ene (2e): 95%; bp 89-91 °C (0.02 mm); ^{1}H NMR δ 1.90 (s, 3 H, CCH_3), 2.6-3.5 (m, 4 H, allylic H), 3.70 (s, 3 H, OCH_3), 4.49 (m, 1 H, CHBr), 6.84 (m, 1 H, vinyl H). Anal. ($C_9H_{12}Br_2O_2$) C, H.

1-Carboalkoxy-1,2-oxido-*trans*-4,5-dibromocyclohexanes 3a-e. An excess of peroxytrifluoroacetic acid[38] prepared from 90% H_2O_2 (10.8 mL, 0.4 mol) and trifluoroacetic anhydride (68 mL, 0.48 mol) in CH_2Cl_2 (70 mL) was added dropwise to a vigorously stirred solution of dibromide **8a-e** (67 mmol) and 170 g of Na_2HPO_4 in CH_2Cl_2 (300 mL) at room temperature. The resulting suspension was refluxed for 20 h and filtered, and the filtrate was washed with sodium sulfite (2 N) and sodium carbonate (2 N). The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to afford crude **3a-e** that was sufficiently pure for conversion to the arene oxides. Purification by molecular distillation gave product as a viscous oil.

1-Carbomethoxy-1,2-oxido-*trans*-4,5-dibromocyclohexane (3a): 86%; bp 130 °C (0.04 mm); ^{1}H NMR δ 2.2-3.25 (m, 4 H, CH_2), 3.55 (m, 1 H, epoxy H), 3.75 (s, 3 H, OCH_3), 4.25 (m, 2 H, CHBr). Anal. ($C_8H_{10}Br_2O_3$) C, H.

1-Carbo-*tert*-butoxy-1,2-oxido-*trans*-4,5-dibromocyclohexane (3b): 88%; bp 130 °C (0.01 mm); ^{1}H NMR δ 1.46 (s, 9 H, CMe_3), 2.26-3.23 (m, 4 H, CH_2), 3.23-3.60 (m, 1 H, epoxy H), 4.05-4.52 (m, 2 H, CHBr). Anal. ($C_{11}H_{16}Br_2O_3$) C, H.

1-Carbomethoxy-2-methyl-1,2-oxido-*trans*-4,5-dibromocyclohexane (3d): 86%; bp 100 °C (0.02 mm); ^{1}H NMR δ 1.35 (s, 3 H, CCH_3), 2.08-3.35 (m, 4 H, CH_2), 3.77 (s, 3 H, OCH_3), 4.25 (m, 2 H, CHBr). Anal. ($C_9H_{12}Br_2O_3$) C, H.

1-Carbomethoxy-4-methyl-1,2-oxido-*trans*-4,5-dibromocyclohexane (3e): 86%; bp 110-112 °C (0.05 mm); ^{1}H NMR δ 1.90 (s, 3 H, CCH_3), 2.5-3.3 (m, 4 H, CH_2), 3.51 (m, 1 H, epoxy H), 3.72 (s, 3 H, OCH_3), 4.3-4.7 (m, 1 H, CHBr). Anal. ($C_9H_{12}Br_2O_3$) C, H.

1-Carboalkoxyarene Oxides 4a-e. A solution of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 8.0 g, 66 mmol) in dry THF (30 mL) was added dropwise to a stirred solution of epoxide **3a-e** (22 mmol) in THF (30 mL) at 0-5 °C under N_2. Stirring was continued for 4 h before filtration to remove DBN·HBr. The solution was concentrated under vacuum at room temperature, diluted with CH_2Cl_2 (75 mL), and washed with saturated NaCl solution. The CH_2Cl_2 solution was dried ($MgSO_4$) and concentrated under vacuum to yield a brown oil that was purified by a chromatography on a silica gel column.[39] Elution with ether-pentane (1:9) gave arene oxide **4a-e** as a yellow oil that was distilled under reduced pressure.

1-Carbomethoxybenzene Oxide-Oxepin (4a): 46%; bp 48-50 °C (0.02 mm). Anal. ($C_8H_8O_3$) C, H.

1-Carbo-*tert*-butoxybenzene Oxide-Oxepin (4b): 52%; bp 75-77 °C (0.025 mm); mp 40-42 °C (pentane). Anal. ($C_{11}H_{14}O_3$) C, H.

1-Carbomethoxy-2-methylbenzene Oxide-Oxepin (4d): 65%; bp 70-75 °C (0.1 mm). Anal. ($C_9H_{10}O_3$) C, H.

1-Carbomethoxy-4-methylbenzene Oxide-Oxepin (4e): 68%; bp 54-61 °C (0.04 mm). Anal. ($C_9H_{10}O_3$) C, H.

1-Carboxybenzene Oxide-Oxepin (13). Arene oxide **4a** (0.41 g, 2.7 mmol) was stirred with 5% aqueous NaOH at room temperature until a homogeneous, yellow solution was obtained (ca. 30 min). The aqueous solution was washed with ether, acidified by addition of solid NaH_2PO_4 until the solution was saturated (pH ~4-5), and extracted immediately with ether. The ether extracts were dried (Na_2SO_4) and concentrated under vacuum at 0-5 °C to afford a yellow oil that crystallized (94%). Recrystallization of **13**, mp 68-72 °C with decomposition and evolution of CO_2, was effected from pentane. Pure **13** decomposed slowly in the crystalline state at ambient temperature.

Preparation and Aromatization of 19 and 20. When ester **4d** was hydrolyzed under identical experimental and workup conditions for the preparation of **13**, evaporation of the ether afforded a yellow, crystalline solid that was shown by ^{1}H NMR analysis to be a mixture of **19** and *o*-cresol (30:70). Neat arene oxide **19** was extremely unstable at room temperature, and purification attempts under optimal conditions gave only the same mixture with an enrichment of **19** relative to *o*-cresol (60:40).

Attempts to prepare **20** from **4e** by the above method yielded only *p*-cresol.

Acid-Catalyzed Aromatization of Arene Oxides 4a-c, 4e,f, and 22. The arene oxides were dissolved in neat CF_3CO_2H or in $CDCl_3$ containing a few drops of CF_3CO_2H and the reaction was followed by ^{1}H NMR. The reaction of **4a-c** and **4e** was complete within a few minutes. Arene oxide **4f** in CF_3CO_2H required 1 month at room temperature for 95% reaction, and **22** showed no sign of reaction after 10 days. Each reaction afforded a single product in quantitative yield as indicated in Scheme II. The products were characterized by isolation and comparison (IR, ^{1}H NMR, melting point) with authentic samples.

Acid-Catalyzed Rearrangement of 4d. Preparation and Rearrangement of 7d. Arene oxide **10d** was dissolved in CF_3CO_2H maintaining the temperature at 10 °C and also without temperature control. In each case the reaction was complete within 5 min and afforded the products indicated in Scheme II. The products were separated by column chromatography on silica gel. Phenols **8d** and **9** were characterized by comparison (IR, ^{1}H NMR) with authentic samples. Product **7d** was characterized as 6-carbomethoxy-6-methylcyclohexa-2,4-dienone: bp 35-40 °C (0.02 mm); IR ($CHCl_3$) 1745, 1670, 1633, 1558 cm^{-1}; UV (CH_3OH) 302 nm (ε 4030); mass spectrum (70 eV) *m/e* (rel intensity) 166 (17, M^+); ^{1}H NMR δ 1.51 (s, 3 H, CCH_3), 3.69 (s, 3 H, OCH_3), 6.11 (d, 1 H, J = 9.9 Hz, H_2), 6.30 (m, 2 H, H_4 and H_5), 7.10 (m, 1 H, H_3). Anal. ($C_9H_{10}O_3$) C, H.

Dienone **7d** was dissolved in CF_3CO_2H and kept at room temperature for 4 days. The products were **8d** (22%) and **9** (78%) that were characterized as described above.

Aromatization of Arene Oxides 13 and 14. Arene oxide **13** decomposed to a mixture of salicylic acid and phenol in the neat state (1 day) or in solution as indicated in Scheme III. The ratio of products was determined by LC as described earlier.

In similar fashion the reaction of **14** was affected in the crystalline state, in CF_3CO_2H, and in aqueous solution at pH 7.4 (phosphate buffer), and the deuterium content in each product was established by ^{1}H NMR and mass spectrometry.

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References and Notes

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