Multiple Pathways for Aromatization of 8,9-Indan Oxide

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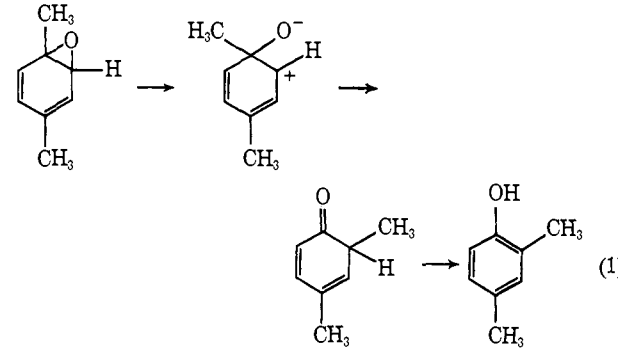
Abstract: The pH dependence of both rates and ratios of product distribution for the aromatization of 8,9-indan oxide (**1**) to 4- and 5-indanol (**4** and **5**) has led to the reaction sequences of Scheme I. The pH–rate profile for the disappearance of **1** establishes acid-catalyzed and spontaneous pathways which are suggested to proceed from carbonium ions **6** and **2**, respectively. This suggestion is based on our previous demonstration that arene oxide aromatizations occur *via* initial carbonium ion formation. *In base*, **2** yields a spiroketone (**3**) which has been isolated and, when reintroduced into base, yields >97% of **4**. The isolation of **3** marks the first instance of the preparative identity of a ketonic intermediate in the NIH shift. However, for the rearrangment of **1** in base, it has been shown kinetically that the sequences **1** → **2** → **3** cannot account for more than ~30% of the **4** which forms. To account for the remaining ~70% of **4**, a second intermediate must be produced from **2** at a rate more than twice that for the formation of **3**. This second intermediate never accumulates and no structure other than **8** is apparent. The formation of **8** and subsequent arguments for the existence of **10** amount to an "oxygen walk" involving arene oxide opening to carbonium ion, ring closure to an isomeric arene oxide, carbonium ion formation, arene oxide formation, etc. *In acid*, **1** yields in the main **5** (93–98%) and very little **4** (2–7%). Since the rate of disappearance of **1** in acid is much greater than that for the appearance of **4** + **5**, a long-lived intermediate generated from **6** is required. Since solvolysis of **1** in acidic methanol yields 5-methoxy-8-hydroxy-5,8-dihydroindan, the required intermediate is logically assigned the dihydroxydiene structure **7**. Instability of **7** precluded its isolation. Nonetheless, acid-catalyzed dehydration of **7** can reasonably be assumed to produce exclusively **5**. The 2–7% of **4** formed at acidic pH is accountable from the formation of small amounts of **3** formed *via* partitioning of carbonium ion **6** between **7** and **3**. In acid, pure **3** was shown to yield 68% **4** and 32% **5**.

The demonstration of the intermediacy of naphthalene 1,2-oxide in the metabolism of naphthalene[2] and the subsequent implications that arene oxides are involved in necrosis,[3] mutagenesis,[4] and carcinogenesis[5] have led to considerable interest in the chemistry of these labile compounds.

The aromatization of arene oxides involves specific acid catalyzed (k_H) and pH-independent (k_0) pathways.[6] The phenolic products may vary for the k_H and k_0 paths. For example, the relative amounts of 2,5-dimethylphenol and 2,4-dimethylphenol formed in the aromatization of 1,4-dimethylbenzene oxide are pH dependent.[7] Thus, both reaction rates and product distributions are influenced by pH. The mechanisms associated with k_H and k_0 involve rate determining carbonium ion formation. Thus, for the formation of 2,4-dimethylphenol from 1,4-dimethylbenzene oxide in the pH-independent region, the mechanism of eq 1 pertains.[8] Alternate mechanisms such as epoxide ring opening concerted



(1)

with group migration have been eliminated. Thus, for both the spontaneous and specific acid catalyzed reactions, no primary kinetic isotope effect was found in the case of either perdeuteriobenzene oxide or [1-^{2}H]-naphthalene 1,2-oxide, and pronounced substituent effects for the aromatization of variously substituted benzene oxides were detected ($\rho \cong -7$ for spontaneous and acid-catalyzed paths). These observations are only in accord with a stepwise mechanism involving rate determining carbonium ion formation followed by hydride migration (eq 1).[9] If conjugated carbonium ion formation is rate determining, then it should be anticipated that solvent trapping should produce diols which would provide alternate paths to phenolic compounds. Indeed, a detailed study of the aromatization of 1,4-dimethylbenzene oxide to 2,4-dimethylphenol and 2,5-dimethylphenol has revealed an intermediate diol.[8] Since carbonium ion formation is rate limiting, cases might exist in which the rate of collapse of carbonium

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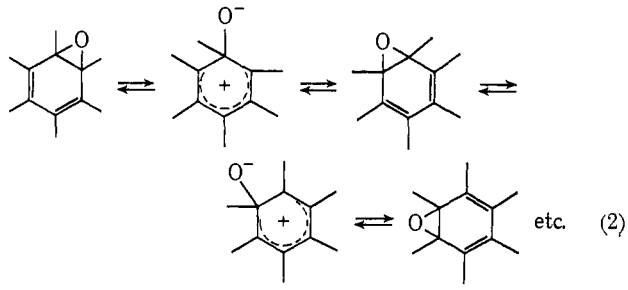
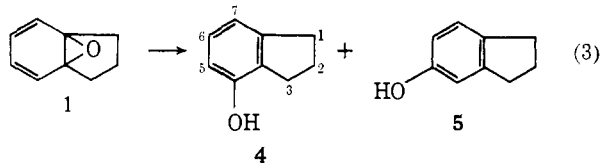
ion to the same or a new arene oxide exceeds that of group migration or solvent trapping. When collapse to a new arene oxide predominates, isomerization of the arene oxide results. We should like to term this process *the oxygen walk* (eq 2).



oxygen walk (2)

In order to ascertain the generality of our mechanism for the rearrangement of arene oxides, we have undertaken a detailed investigation of the aromatization of 8,9-indan oxide (**1**) to 4- and 5-indanol. Our objective in employing this more rigid system has been specifically: (1) to see if the formation of a diol as in 1,4-dimethylbenzene oxide can be detected; (2) to see if a ketone analogous to that of eq 1 can be detected; and (3) to see if an oxygen-walk mechanism is operating. The phenols 4-hydroxyindan (**4**) and 5-hydroxyindan (**5**) have previously been shown to arise from **1** (eq 3) and



(3)

the ratio of **4**:**5** was shown to be a function of acidity yielding mainly **5** in the acid region[10] and **4** in the neutral region,[11] indicating multiple pathways and making 8,9-indan oxide an excellent model for the studies alluded to above.

Experimental Section

8,9-Indan Oxide (1). The procedure described here is essentially that of Wiesel.[12] Bicyclo[4.3.0]nona-3,6(1)-diene (Aldrich) was epoxidized in methylene chloride to give the 8,9-oxide as an oil (bp 78–83° (12 mm)) in 75% yield. Bromination of the oxide in methylene chloride at −78° gave the desired 5,6-dibromo-8,9-oxide as colorless prisms (mp 87–88° from *n*-hexane, 41% yield). Although the mother liquor from the above crystallization still contained substantial amounts of the desired compound, it could not readily be isolated in high purity. The dibromoepoxide was mixed with 4 equiv of potassium *tert*-butoxide in ether at 0°. The mixture was stored at room temperature for 5 hr and then refluxed 15 min. Work-up provided **1** as a pale yellow oil (bp 30° (0.4 mm)) in 90% yield. When the precursor for **1** was not completely pure, substantial contaminants were present after the distillation.

Several attempts to generate and isolate **8** from **1** were without success. In the kinetic medium, **8** never accumulates. However, solutions of **1** in methanol turn intensely yellow on standing at room temperature. The nmr spectra of these solutions indicated the yellow material *was not* **3** and was extremely sensitive to acid. Conditions were not found which caused accumulation of the yellow species. Photolysis of **1** in acetone also generated small amounts of yellow compound. The bright yellow color of the compound is compatible with structure **8** since a substantial contribution of its oxepin tautomer is expected.

Spiro[3.5]nona-6,8-dien-5-one (3). To a solution of 94 g (0.6 mol) of Na_2HPO_4 and 252 g (0.67 mol) of $Na_3PO_4 \cdot 12H_2O$ in 4 l. of water at 25° was added 1.0 g of 8,9-indan oxide. The heterogeneous mixture was agitated 18 min and then extracted (4 × 100 ml) with CS_2; total extraction time was 22 min. The combined extracts were dried (K_2CO_3) and concentrated (*in vacuo*, <20°) to 10.0 ml. The 220-MHz nmr spectrum of this solution (line positions in δ relative to internal TMS and coupling constants in hertz: six methylene cyclobutane hydrogens 1.70–3.10, 5.87 (1, H_6), 6.86 (1, H_7), 6.10 (1, H_8), and 6.72 (1, H_9) with $^3J_{6,7} = {}^3J_{8,9} = 9.5$ Hz, $^3J_{7,8} = 6.0$ Hz, $^4J_{6,8} = 1.0$ Hz, $^4J_{7,9} = 1.75$ Hz, and $^5J_{8,9} = 0.71$ Hz) showed the desired spiroketone to be free of any detectable contaminants. Careful concentration of 0.50 ml of the solution produced 11.2 mg of a Diels–Alder dimer whose melting point and ir, nmr, and mass spectra were identical with the dimer previously identified[12] among the rearrangement products of **1**. Based on the weight of dimer produced above, **3** had $\lambda_{25°}^{max}$ 318 nm (ϵ 4305, 50% dioxane–H_2O). The related stable spiro[4.5]deca-7,9-dien-6-one shows a λ^{max} 305 nm (ϵ 4301, cyclohexane). Treatment of pure **3** or **3** generated from **1** in the kinetic medium with $NaBH_4$ results in loss of the 320-nm absorption; subsequent acidification results in an indan spectrum. Rearrangement of 112 mg of **3** in the kinetic medium at pH 11.4 resulted in 98% **4** and 2% **5**; at pH 2, 68% **4** and 32% **5**.

5-Methoxy-8-hydroxy-5,8-dihydroindan. To a solution of 2 drops of trifluoroacetic acid in 10 ml of absolute methanol at −30° was added 1 g of **1**. The solution was maintained at −30° for 15 min and then at +15° for 5 min before being made basic with 5 drops of triethylamine. The solvent was removed *in vacuo* below 10° to leave 1.2 g of colorless oil which was purified by distillation (bp 110–115° (0.1 mm)). The 60-MHz nmr spectrum of the distillate (line positions in δ relative to TMS; 6 methylene and 1 hydroxy proton 1.0–3.0, 3 methoxy protons as two sharp singlets at 3.17 and 3.23, one methine proton at C-5 4.0–4.50, and three olefinic protons at 5.50–6.35) indicated the sample consisted of a 1:1 mixture of the cis and trans isomers since the pattern of coupling could not be analyzed and since the methyl group appeared as two sharp lines of equal intensity. Microanalyses for carbon and hydrogen were within 0.16% of theory. The 70-eV mass spectrum showed a weak signal at *m/e* 166 and a base peak at *m/e* 148 which correspond to the molecular ion and the loss of water.

Attempted separation of the two stereoisomers by chromatography on silica gel provided a quantitative yield of 5-methoxyindan.[13] Storing the material at room temperature for 2 months or heating at 130° for 2 hr gave the same result. In a preparative run, 0.5 g of the material was dehydrated in the kinetic medium to produce 5-methoxyindan (mp 109–110° (13 mm)) in 80% yield after distillation. Neither **4** nor **5**, nor 4-methoxyindan, could be detected in this last experiment. Several attempts to isolate **7** generated from **1** were without success, and only phenols could be obtained.

Kinetic studies were carried out in aqueous dioxane (50% v/v). The dioxane was purified by distillation from sodium prior to use and the water was deionized and glass distilled. The ionic strength was held at 0.1 with KCl. The kinetic measurements were carried out spectrophotometrically and without buffers in a Radiometer pH-stat assembly specifically designed for a Cary 15 spectrophotometer[14] thermostated at 30.0 ± 0.1°. Reactions were initiated in all cases by addition of 10–20 μl of a solution of **1** in tetrahydrofuran to give a final concentration between 10^{-4} and 10^{-5} *M*. The disappearance of **1** with time was followed at 250 nm, a wavelength where **1** has an appreciable absorptivity. An increase in absorption at 320 nm due to the formation of what will later be shown to be spiroketone **3** can be observed and its subsequent disappearance as function of time was monitored. When the pH is less than 7 the amount of **3** produced is small, so for convenience the reaction was run at pH 8 until the maximum amount of **3** was produced (all **1** had disappeared), then the pH was adjusted to the desired value and the disappearance of **3** followed at 320 nm. The kinetics for all the reactions studied 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.

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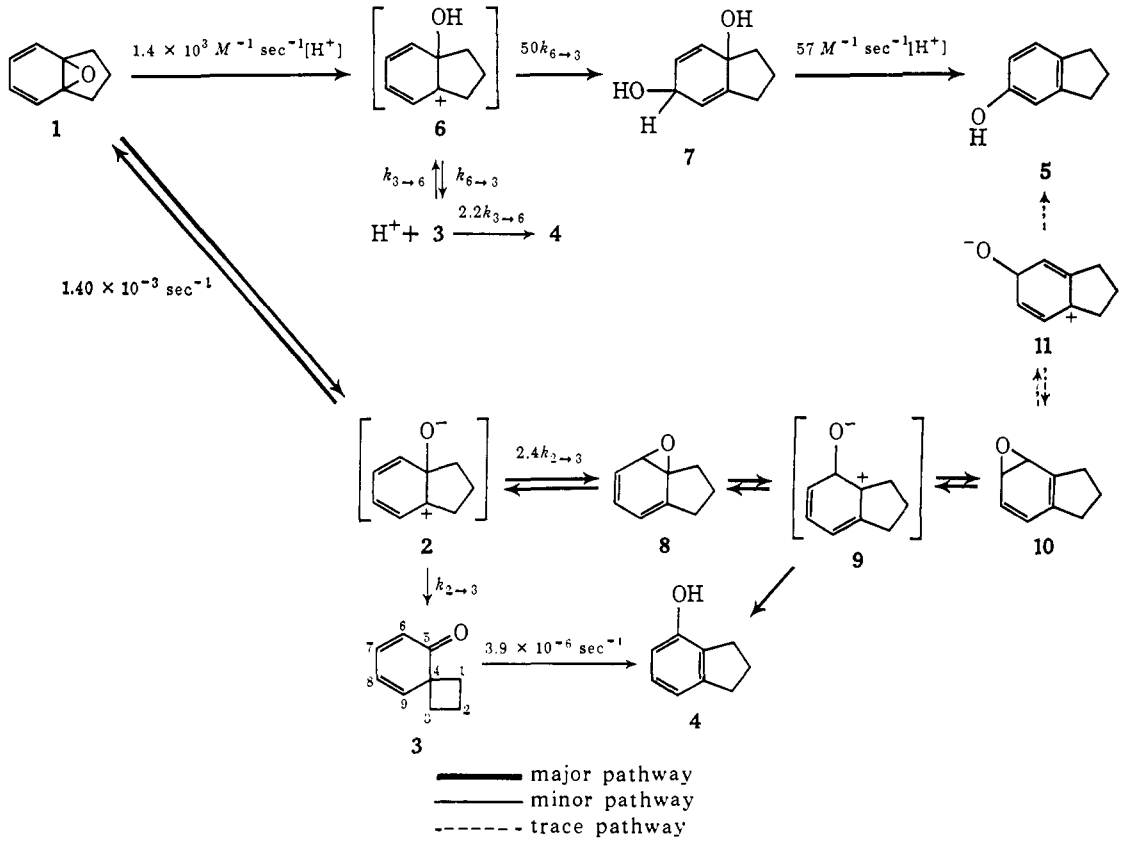
Scheme I



The product ratios obtained from the reaction of **1** were determined by carrying out reactions under exactly the same condition as the kinetic studies except the reactions were initiated by adding 5 μl of **1** to give a final concentration of about 3×10^{-3} *M*. These products were isolated from the acidified kinetic medium by concentration of the medium to half-volume *in vacuo* to remove dioxane, saturation of the resulting solution with salt, and extraction into ether. The extracts were dried (Na_2SO_4) and concentrated prior to analysis of phenol ratios by glc. Samples were injected onto a 6 ft × 0.25 in. column of 15% Hi-Eff 2BP on gas Chromosorb Q at 150°. As soon as the solvent cleared the detector, the temperature was manually raised to 200°. By this method, base line separation of the two phenols was effected in a flat region of the glc trace. Ratios were calculated from peak areas. The product ratios were also determined spectrophotometrically at the lower concentrations of **1** employed for kinetic studies by determining the absorbance of the final solutions at 285 and 275 nm where the absorptivity of **4** and **5** are different. This procedure has been described previously.[8] The molar absorptivities of **4** at 285 and 275 nm are 3.42 × 10 and 6.19×10^2 M^{-1} cm^{-1}, and that of **5** are 2.73×10^3 and 2.09×10^3 M^{-1} cm^{-1}, respectively.

Results

In acidic solutions (pH <6) the disappearance of **1** follows first-order kinetics. After all of **1** has disappeared, a scan of the spectrum indicates that no or very little **4** or **5** has been produced. If the absorbance at 280 nm, a wavelength at which both **4** and **5** have appreciable absorbtivity, is then monitored with time, a pseudo-first-order increase in absorption is observed indicating the production of **4** and/or **5** from some spectroscopically undetectable intermediate generated from **1**. Product analysis established **5** (Experimental Section) to be formed from the intermediate in *ca.* 98% yield. The latter has been assigned structure **7** (Scheme I) on the basis that replacement of acidic H_2O by acidic CH_3OH allowed isolation of 5-methoxy-8-hydroxy-5,8-dihydroindan. Further support for structure **7** is found by analogy to the production of 1,4-dimethyl-2,5-cyclohexadiene-1,4-diol from 1,4-dimethylbenzene oxide in water at acidic pH.[8]

In the basic pH range, as under acid conditions, the disappearance of **1** is first order. At pH 12, repetitive scanning several days in the uv reveals the formation of **4** as the only product. [At pH 12, 5-hydroxyindan (**5**) has an extinction coefficient of 1.23×10^3 M^{-1} cm^{-1} at 300 nm, a wavelength at which no other species has any significant absorption; thus, if it were produced, it should be spectrophotometrically detectable.] The continued appearance of **4** occurs long after all **1** has disappeared. Further, the rate of disappearance of **1** was found to be equal to the rate of appearance of an intermediate absorbing at 320 nm which has been assigned the spiroketone structure **3** on the basis of its isolation and characterization (nmr) from basic aqueous solution. When all **1** had disappeared, the slower rate of disappearance of the spiroketone (**3**) was measured at 320 nm. This rate agreed with the rate of formation of **4** from an authentic sample of **3**. When a sample of the spiroketone is put in 50% dioxane–water at pH 11 and the products of the reaction are analyzed by gas chromatography, 4-hydroxyindan is found to be essentially the only product. [A very small peak (<3%) is also obtained at the point expected for 5-hydroxyindan but this peak is too small to be definitely characterized.] In the acidic pH region, **1** yields a small amount of **3** and its rate of formation was followed. Since at pH 2 the ratio of **5**:**4** obtained is 50 (see Table I), the rate of formation of **7** from the carbonium ion (**6**) must be 50 times greater than the rate of formation of **3** from **6**. The products obtained from a sample of spiroketone placed in 50% dioxane–water at pH 2 were analyzed by gas chromatography. Unlike its reaction in base where it gives only 4-hydroxyindan, the spiroketone in

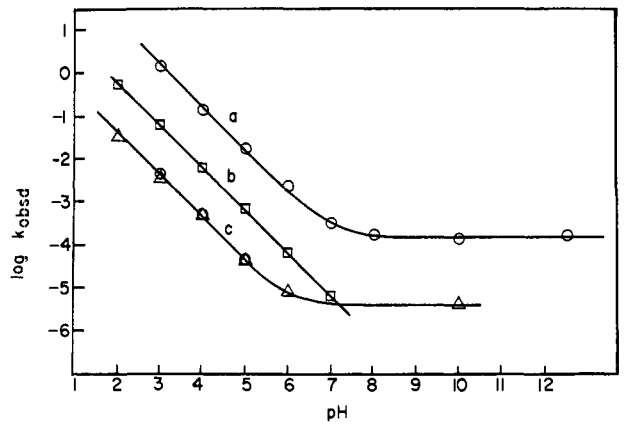


Figure 1. Plots of log k_{obsd} *vs.* pH at 30°, μ = 0.1, in aqueous dioxane (50% v/v): (a) disappearance of **1** or in the spontaneous region, formation of **3**; (b) formation of **5** from **7**; (c) Δ represents disappearance of **3** generated from **1**, O represents disappearance of authentic ketone. The points are experimental and the lines theoretical, being derived from eq 4, 5, and 6.

Table I. Product Distribution from the Rearrangement of **1** in Dioxane–H_2O (50% v/v) at 30° (μ = 0.1 with KCl)

pH	% **4**	% **5**
2[a]	2	98
3[a]	3	97
5[a]	7	93
8[b]	≥97	*d*
11[a,b]	≥97	*d*
11 → 2[a–c]	91	9
5 → 7[a–c]	8	92

[a] Determined by gas chromatography. [b] Determined spectrophotometrically. [c] The reaction was initiated at the pH indicated by the first number, then adjusted to the pHi ndicated by the second number when all **1** had disappeared and then run to completion. [d] Trace amounts (2–3%) of a glc peak corresponding to **5** are detectable. However, the identity of this material could not be established by tlc since authentic **5** does not form a colored compound with Gibbs reagent.

acid reacts to give 68% **4** and 32% **5**. Thus, the rate of formation of **4** from **3** is 2.2 times faster than the rate of formation of **6** from **3**.

An intermediate other than **3** is also obtained in basic solution: if an aliquot of **1** is added to 50% dioxane–water at pH 12, **4** (237 nm) arises after an induction period of about 10 min. That the species being formed is indeed **4** is evident from spectral scans which show it to be identical with the product produced from **3**. That it is being produced from an intermediate other than **3** is evident from the observation that a considerable amount is produced before a significant amount of **3** has formed and its rate of production is considerably greater than the rate of **3** → **4**. This second intermediate can only be **8** (see Discussion). The percentage of **1** → **4** going *via* intermediates **3** and **8** can be calculated to be 29 and 71%, respectively. This was determined at pH 8 by measuring the absorbance at 261 nm when all the 8,9-indan oxide has disappeared (at this point absorption at 320 nm is maximal) and designating it as *A*. When all the spiroketone has disappeared (absorption at 320 nm has disappeared), the absorbance at 261 nm is again measured and is designated as *B*. The percentage of the reaction that goes *via* the spiroketone **3** is $(B - A)/B$.

Plots of the log of the observed pseudo-first-order rate constant (k_{obsd}) *vs.* pH for the various reactions in aqueous dioxane are provided in Figure 1. Plot a of Figure 1 pertains to the pH dependence for the disappearance of **1** (250 nm) and, in the spontaneous region, to the formation of **3** (320 nm). The theoretical line of plot a has been generated from eq 4 where a_H

$$k_{obsd} = 1.40 \times 10^{-3}\ \text{sec}^{-1} + 1.41 \times 10^{3} a_H\ \text{sec}^{-1} \quad (4)$$

is the hydrogen ion activity determined at the glass electrode. Plot b in Figure 1 pertains to the pH dependence of the formation of **5** (280 nm) from **7** which was generated *in situ* from **1**. The theoretical line of plot b was generated by eq 5. The pH dependence of

$$k_{obsd} = 57 a_H\ \text{sec}^{-1} \quad (5)$$

the disappearance of **3** (320 nm) generated from **1** is shown in plot c of the figure. The solid line which best fits the experimental points is generated by eq 6. The

$$k_{obsd} = 3.9 \times 10^{-6}\ \text{sec}^{-1} + 3.9 a_H\ \text{sec}^{-1} \quad (6)$$

rates of the disappearance of an authentic sample of **3** were measured at pH 3, 4, and 5 and are represented by the circles on plot c.

The product distribution of **4** and **5** was found to be a function of pH. At low pH, **5** is the predominant product, while at high pH, **4** appears to be essentially the sole product (<3% of **5** can be detected by glc). The product distribution as a function of pH is shown in Table I.

Discussion

The kinetics of the rearrangement of **1** into **4** and **5** are similar to those observed for the rearrangement of other arene oxides in aqueous solution[6,8,9] in that two distinct rate terms are exhibited, one spontaneous (k_0) and the other hydrogen ion dependent ($k_{II}a_{II}$).[15] As in the case of the aromatization of 1,4-dimethylbenzene oxide, the phenolic products of **1** vary for the k_H and k_0 pathways.

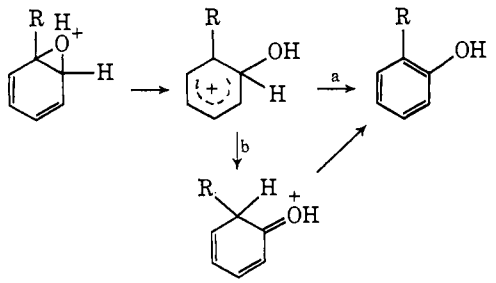
Acid-Catalyzed Reaction. In the acid-catalyzed region, 5-hydroxyindan (**5**) is the predominant product. Its formation involves, overall, the addition of H_2O to **1**, to form a diol (**7**), followed by subsequent elimination of the oxygen originally present as the epoxide oxygen. The mechanism of this reaction is shown in Scheme I. The diol **7** is postulated as the intermediate for the following reasons: (i) dehydration of **7** produces the observed indanol **5**; (ii) the analogous 1,4-diol is produced in the acid pH region in the aromatization of 1,4-dimethylbenzene oxide;[8] (iii) 5-methoxy-8-hydroxy-5,8-dihydroindan can be isolated from acidic methanol. A mechanism involving direct formation of **7** from protonated **1** *via* nucleophilic attack of H_2O as originally proposed[10] can be dismissed on the basis that the rate-determining step in the formation of products from arene oxide involves carbonium ion formation.[9] The

(15) Other arene oxides that have been studied to date are benzene oxide, a series of 4-substituted benzene oxides, 1,4-dimethylbenzene oxide, 1,2-naphthalene oxide, and 9,10-phenanthrene oxide (ref 6, 8, and 9). Of these, only the latter was found to aromatize just *via* specific acid catalysis (the reaction was followed only to pH 5.5; a feeble spontaneous reaction present at higher pH values is possible). This has been attributed to the fact that the 9,10 position in phenanthrene acts as an isolated double bond. Other K-region and non-K-region arene oxides of polycyclic hydrocarbons are under study to determine if this phenomena is general to the K-region and if it accounts for the markedly greater stability of the K-region oxides.

small amount of **4** produced in acid arises from **3** by a route which becomes a more predominant pathway in the pH-independent region and will be disscussed in that section.

The question as to the importance of hydrogen migration in the aromatization of arene oxides in the low pH region has been raised.[7c] That is, does path b of Scheme II, which involves hydride migration, compete with

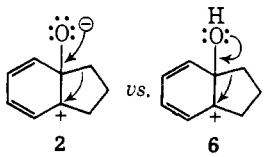
Scheme II



path a which proceeds by direct proton loss. It is impossible to distinguish between the two possibilities, unless deuterated species are used. In the rearrangement of 4-methyl[1-^2H]benzene oxide to 4-hydroxytoluene[16] and in the rearrangement of 1- or [2-^{2}H]-naphthalene oxide to 1-naphthol,[17] the amount of deuterium in the products is a measure of the minimal amount of migration (path b). When the above rearrangements were carried out at low pH, the 4-hydroxytoluene and 1-naphthol produced retained 37 and 59% deuterium, respectively, proving that path b must be involved. These values are necessarily minimal since subsequent enolization can only reduce the amount of deuterium retained.

In the present case, very little migration of the methylene group of **1** is involved in the low pH region because the carbonium ion formed (Scheme I) is trapped by water before significant migration can occur. (From the product ratio of **5**:**4** at low pH, it is evident that trapping of **6** by solvent occurs 50 times more readily than methylene group migration.) As might be anticipated, the amount of migration occurring in any given case depends on both the group that is migrating and the structure of the molecule undergoing rearrangement.

pH-Independent Region. At pH 11 where 100% of the reaction goes through zwitterion **2**, essentially the only product obtained is 4-hydroxyindan (**4**). This product arises from two different intermediates that are formed from **2**, a spiroketone (**3**) and an isomeric arene oxide (**8**). In basic solution, migration to give the spiroketone or isomeric oxide through the oxygen walk competes favorably with solvent trapping of **2**. This cannot be attributed to the greater rate of solvent trapping of **6** *vs.* **2** but to the greater driving force for rearrangement of **2** *vs.* **6** to spiroketone or isomeric



2 **6**

oxide. The spiroketone was actually isolated from aqueous solution. When placed in basic solution, **3** produced only **4**, while in acidic solution the dienone–phenol rearrangement can occur either *via* a spontaneous pathway which leads to **4** or *via* an acid-catalyzed pathway which leads to **5** (*via* **6** and **7**, see Results) in addition to **4**. Although the intermediacy of a dienone has been previously postulated as a requisite species in producing the NIH shift,[6–9,16] the actual isolation and demonstration of such a species as a kinetic intermediate on the pathway to phenols has not been proven until now. In an earlier study,[10] isolation of the Diels–Alder dimer of **3** from **1** prompted the suggestion that dienone–phenol rearrangement was the sole source of **4**; that **3** is not the principal source of **4** is shown in what follows.

Since a considerable amount of 4-hydroxyindan (**4**) is produced before a significant amount of spiroketone (**3**) is formed, **4** must be formed not only from **3** but also from another intermediate. The only intermediate that could logically lead to **4** is the arene oxide **8** which is formed from reclosing of the zwitterion **2**, an oxygen walk. This intermediate opens to give **9** which aromatizes to the expected product (**4**). If the oxygen of zwitterion **2** can walk to give **8**, there is no reason that the oxygen of zwitterion **9** cannot walk to give **10** (Scheme I). This second isomerization could account for a portion of the 5-indanol that is formed during the aromatization of **1** in base. The realization of an oxygen walk in the present kinetic scheme may at first seem somewhat surprising. However, such a mechanism should have been anticipated. Closure of a carbonium ion to a protonated arene oxide which isomerizes to an oxepin,[18] closure of a diradical generated photochemically from one arene oxide to form a new arene oxide,[19] and the thermal isomerization of 15,16-pyrene oxide[20] to 1-pyrenol provide an ample base on which to draw analogy.

The validity of Scheme I was checked by generating intermediates at one pH, allowing them to rearrange at a second pH, and determining product ratios (Table I). For example, in basic solution 71% of **4** derives from intermediate **8** and 29% *via* intermediate **3**. It is known that **8** should yield essentially[7b] only **4** and that in base **3** yields only **4** while in acid **3** yields 68% **4** and 32% **5**. Thus, if **1** is allowed to rearrange at pH 11, the product is >97% 4-hydroxyindan. However, if **1** is placed in a solution of pH 11 and the pH changed to 2 when the maximum amount of spiroketone has formed, the expected product ratios can be calculated to be 71 + (0.29 × 68) = 91% 4-hydroxyindan and (0.29 × 32) = 9% 5-hydroxyindan (see Table I).

In conclusion, in the aromatization of **1** and arene oxides in general, the initial step is the formation of a carbonium ion *via* an acid-catalyzed pathway or a zwitterion *via* an uncatalyzed (spontaneous) pathway.[9] The intermediates formed from these two pathways for ring opening may or may not be different. In the present study, a diol is formed from the carbonium ion

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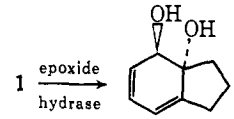
(20) V. Boekelheide, Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research XII Chemical Synthesis, W. O. Milligan, Ed., Houston, Texas, 1969, p 83.

and a spiroketone as well as an isomeric arene oxide(s) from the zwitterion. The products obtained from the intermediates may or may not depend on pH. For example, the diol results only in the formation of 5-hydroxyindan, the intermediate arene oxide(s) essentially only in the formation of 4-hydroxyindan but the spiroketone gives both products in acid and only 4-hydroxyindan in base. Thus, the ultimate products formed from the aromatization of **1** depend on the pH at which the intermediates form as well as the pH at which they react to give products. Three key points emerge which are of considerable significance to the biochemist and biologist studying the metabolic fate of aromatic hydrocarbons: (i) an enzymatically formed arene oxide may rearrange to a new arene oxide prior to undergoing subsequent reactions in the cell, (ii) a phenol can form by a solvolysis pathway without incorporation of molecular oxygen,[8a] and (iii) a number of pathways other than direct nucleophilic opening of an arene oxide are available for the covalent binding of drugs and other xenobiotic substances to cellular constituents—pathways which result from prior chemical reactions of the arene oxide.

The present study may well bear on the mechanism by which the enzyme epoxide hydrase converts **1** into a dihydrodiol (eq 7). The structure of the diol suggested



(7)

homoallylic addition of water[11] to the diene system had occurred. In view of the present results which demonstrate an oxygen walk to form **8** from **1** in aqueous media, an alternate and equally attractive mechanism for the above enzyme-catalyzed reaction emerges; isomerization of **1** to **8**, possibly enzyme catalyzed, followed by normal 1,2-trans opening of **8**. Trisubstituted oxiranes such as **8** are known to be better substrates for the enzyme than tetrasubstituted oxiranes such as **1**.[21]

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Lanthanide Induced Nuclear Magnetic Resonance Shifts. A Structural and Computational Study

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Abstract: The preparation and X-ray crystal structure of the 1 : 1 complex between 3,3-dimethylthietane 1-oxide (**1**) and tris(dipivalomethanato)europium(III), $Eu(dpm)_3$, are described. The $Eu(dpm)_3$ induced shifts for a group of 13 organic compounds were analyzed using the McConnell–Robertson equation (1) and the C_2 shift equation (8). In a number of cases it was found to be advantageous to average the calculated shifts over the molecular conformations. Such averaging is shown to give additional conformational information. For sulfoxide **1** it is shown that neglecting to average the calculated shifts results in an incorrectly assigned pmr spectrum. The structure of the complex is a near perfect wedged octahedron with the Lewis base **1** occupying one of the four equivalent positions of lowest symmetry. The Eu–O bond lengths were 2.33(2) Å to the dpm ligands and 2.40(1) Å to the sulfoxide oxygen. Four formula units of the adduct were distributed in a monoclinic cell ($P2_1/c$) of dimensions a = 14.412(6) Å, b = 20.23(1) Å, c = 15.660(8) Å, and β = 98.55(3)°. The structure's disagreement factor for 2890 diffractometer collected reflections is 0.064 based on F.

Simplification of nmr spectra by the addition of lanthanide shift reagents has proven to be a most significant extension to the usefulness of nmr spectroscopy.[2] The lanthanide induced shifts (LIS) are generally accounted for in terms of pseudocontact interactions, and their magnitudes have been correlated with substrate stereochemistries. Initially the LIS were used in a qualitative sense; however, increasing effort is being directed toward a more quantitative treatment of the data.[3] The spatial dependence of the shifts (S_i^c) for axially symmetric complexes is given by the McConnell–Robertson equation[4a] (eq 1), where ΔH_i

$$S_i^c = \frac{\Delta H_i}{H} = \left\langle \sum\left(\chi_{\parallel}, \chi_{\perp}, K, \frac{1}{T}\right) \frac{(3\cos^2\theta_i - 1)}{r_i^3} \right\rangle_{av} \quad (1)$$

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