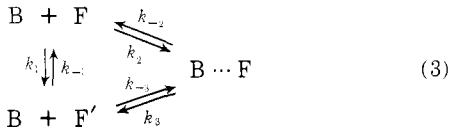
constants, detailed balancing requires that $k_1/k_{-1} \approx k_2/k_{-2}$.

The relaxation time is substantially shortened by the presence of basic species such as imidazole, citrate, glycine, and acetate. The shortening is a linear function of the amount of unprotonated basic species added. A simple scheme that explains the data is given in eq 3, where B stands for base and



(3)

B···F is a transient complex present in vanishingly small concentrations. By applying the steady-state assumption to (B···F), we obtain for the reciprocal relaxation time τ_b^{-1} in the presence of base

$$\tau_b^{-1} = k_{ss}(B) + (k_1 + k_{-1}) \quad (4)$$

where the steady-state constant k_{ss} is given by

$$k_{ss} = \frac{k_2k_3 + k_{-2}k_{-3}}{k_{-2} + k_3} \quad (5)$$

For imidazole (B = unprotonated form) we obtain $k_{ss} \approx 10^8$ M^{-1} s^{-1}.

Since the rate is shortened in a linear fashion with increasing (B), the rate-determining step in tautomerization is undoubtedly the abstraction by B of a proton from N(1) (or N(2)); the resulting transient intermediate then quickly adds back a proton from the solvent or species BH. In the absence of buffer species such as imidazole, the faster tautomerization of the protonated form ($k_2 + k_{-2} \gg k_1 + k_{-1}$; see eq 1 and 2 ff) presumably occurs because the positive charge helps to stabilize the transient anion generated in the pyrazole part of the ring during the rate-determining step.

The pyrazole ring nitrogen has a pK of ~9.5.[9] For a proton-transfer reaction in which $pK_{acceptor} < pK_{donor}$, the rate of transfer is reduced below that of the diffusion controlled rate (because the acceptor binds the proton more weakly than the donor).[10,11] Consistent with this expectation is the value of $\sim 10^8$ M^{-1} s^{-1} for k_{ss} for imidazole, a value which is below the diffusion controlled limit.[10]

The rapid rate ($1/\tau > 10^3$ s^{-1}) of formycin tautomerization demonstrated here is faster than the turnover rates for many enzymes. This means that, even though the 1-H tautomer is predominate, the quick tautomerization to the 2-H form occurs sufficiently fast so as not to limit the rate of an enzymatic process that is specific for the 2-H species.

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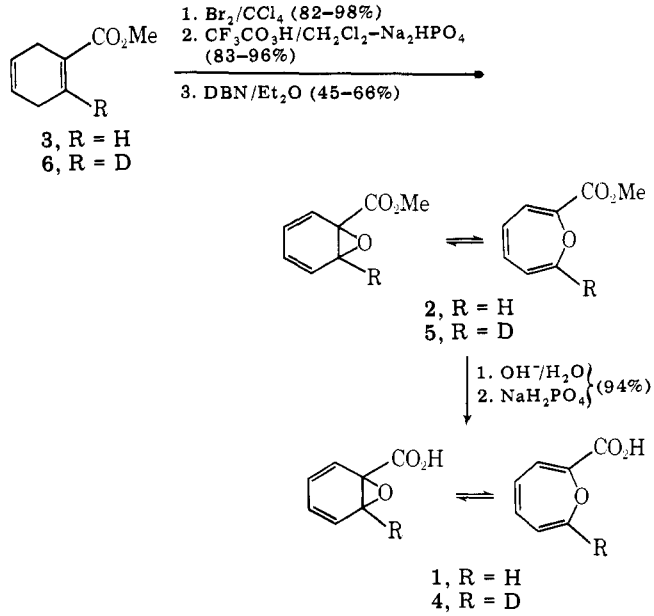
Synthesis and Aromatization of 2-Carboxy- and 2-Carbomethoxyoxepin–Benzene Oxide

Sir:

The metabolism of aromatic substrates in mammals, microorganisms, and higher plants by initial formation of arene oxides and subsequent aromatization to phenols via the NIH shift pathway is well documented.[1] Many of the monooxygenase-catalyzed ortho hydroxylations of substituted benzenes[1a,b,f,g,2] probably proceed by such a pathway involving the arene 1,2-oxide, but, with the exception of 2-methyloxepin–benzene oxides,[1a,b,d,e] few 2-substituted arene oxides have been available for aromatization studies to establish whether the fate of substituents is consistent with the observed biological reaction.

In various studies 2-carboxyoxepin–benzene oxide (**1**) and some of its derivatives have been postulated as biological intermediates in ortho hydroxylation or oxidative decarboxylation reactions. 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.[2b] The latter observation, while of lower retention of tritium than expected, is nevertheless 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 unusual biosynthesis of salicylic acid from **1**.[3] The 1,6-oxide of salicylic acid has been suggested as an intermediate in the salicylate hydroxylase catalyzed oxidative decarboxylation to catechol,[4] and similar arene oxide intermediates may be involved in the biological oxidative decarboxylations of substrates such as phenazine-1-carboxylic acid[5] and *p*-aminobenzoic acid.[1h,6]

In view of the interest in **1** as a biosynthetic intermediate, we have prepared **1** by hydrolysis of methyl ester **2** and investigated the aromatization reactions of **1** and **2**.[7] Bromination of **3**[8] at the C_4–C_5 double bond, epoxidation at the C_1–C_2 double bond, and dehydrobromination afforded **2** as stable yellow liquid. Hydrolysis of **2** in aqueous base, acidification with NaH_2PO_4, and rapid extraction gave pure **1** as yellow crystals (mp 68–72 °C dec). Although prepared in a state of high purity, **1** suffers decomposition to a mixture of phenol and salicylic acid in the crystalline state or in solution over a period of several hours. Phenol formation is favored with increasing pH (salicylic acid:phenol[9]) as follows: pure CF_3CO_2H (64:36),



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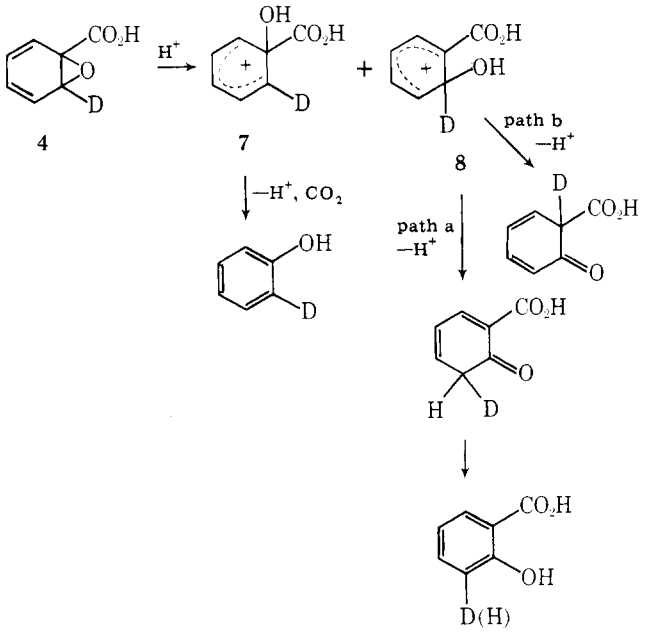
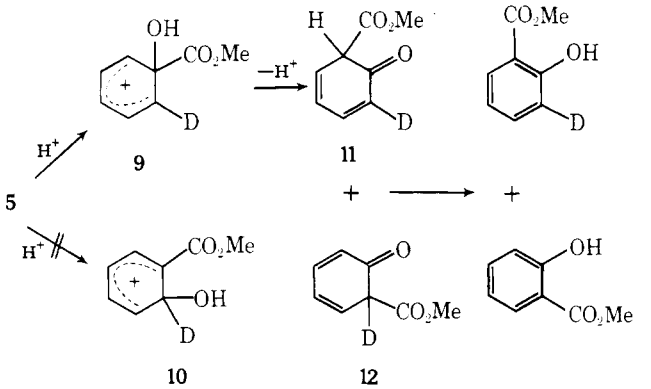
pH 1 in 9:1 MeOH-H_2O (40:60), pH 2.5 in 9:1 HOAc-H_2O (32:68), neat, crystalline state (20:80).

Deuterium-labeled acid **4**, prepared by hydrolysis of **5**,[10] decomposed neat to afford phenol with complete retention of deuterium and salicylic acid with 72% retention of deuterium.[11] Deuterium retention in the salicylic acid from reaction of **4** in CF_3CO_2H and in aqueous solution at pH 7.4 (phosphate buffer) was 64 and 81%, respectively. The data are consistent with oxirane ring opening to **7** and **8**, the former of which



undergoes decarboxylation to phenol, and the latter undergoes migration of deuterium via path a and subsequent enolization to salicylic acid with observed deuterium retention consistent with that expected because of the isotope effect.[12] The NIH shift via path b would result in complete loss of deuterium and appears not to be significant. The possiblity of pathways involving carboxyl participation to form α- or β-lactone intermediates in the reactions described above can not be ruled out.

Ester **2** in CF_3CO_2H rearranges to methyl salicylate in quantitative yield. Under similar conditions deuterium-labeled ester **5** affords methyl salicylate with 55% retention of deuterium,[11] consistent with the established mechanism for the NIH pathway in which protonated **5** undergoes cleavage of the oxirane ring with exclusive formation of the more stable cation **9** rather than **10.** Proton loss from **9** with migration of the



carbomethoxy group affords **11** and **12** (about equivalent amounts) that isomerize to the observed product.[11,13,14]

The results described above support the suggestion that 1,2-oxide of benzoic acids may be intermediates in biological oxidative decarboxylation reactions and that **1** may be an intermediate in the ortho hydroxylation of benzoic acid. The aromatization of **2** provides the first case of carboalkoxy migration in the aromatization of arene oxides.

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Interpretation of the Microwave Dielectric Relaxation of Iron Pentacarbonyl in Terms of the Molecule's Fluxional Nature

Sir:

We have recently obtained results which show that iron pentacarbonyl, $Fe(CO)_5$, exhibits significant microwave dielectric absorption in the range of 0.3-5 cm^{-1}. This observation appears to be quite meaningful particularly in terms of the dynamic aspect of this molecule's structure since rotational absorption involving its "ground" vibrational state is forbidden by symmetry. The equilibrium configuration of $Fe(CO)_5$ is the

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