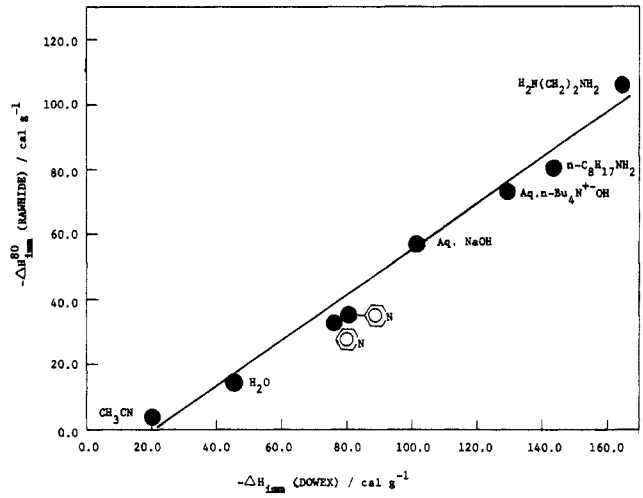

Figure 7. Heats of immersion of Dowex MP-50 at 80 °C in eight solvents vs. corresponding values for Wyoming Rawhide subbituminous coal at 80 °C.

ΔH_{rxn} vs. ΔH_{imm} for Dowex MP-50. Titration calorimetry experiments in acetonitrile and corresponding heats of immersion have been conducted with Dowex MP-50, and the results appear in Table V for the direct immersion of dry resin samples into a large excess of the various neat bases in contrast to the ΔH_{rxn} values from thermometric titrations of the bases into acetonitrile solutions or slurries of the excess acids.

A heat of immersion experiment was attempted for the interaction of microporous Dowex 50W-X8 with pyridine but gave such slow heat evolution that the reaction was incomplete even after several hours, presumably because the majority of acid sites were not accessible without prior preswelling of the polymer.

Comparison with Other Heterogeneous Systems. The heats of immersion for the sulfonic acid resin in these bases are directly relevant to the use of such measurements for comparing the distribution and types of acid sites in various kinds of solid acids. Figure 6 and Table V compares the response of Nafion, perfluorosulfonic acid resin, to that of Dowex. A clear parallel is seen between the acidic behavior of the two resins with these bases. The aqueous systems are significantly differentiated from nonaqueous ones although the slopes of the two lines are roughly parallel. Nonetheless, taking these thermochemical results at face value, Nafion is significantly stronger than Dowex as has been proposed on the basis of its catalytic behavior.

Finally, Figure 7 correlates the heats of immersion of Dowex at 80 °C in a series of bases with corresponding values for the complex natural heteropolymer, Wyoming Rawhide subbituminous coal with use of data from a previous report from this laboratory.[36] A remarkably good correlation is seen and, in contrast to Figure 6, the aqueous systems fall on the same line as the nonaqueous ones. We conclude that this sample of coal is modeled well by the purely Brönsted acid sites of Dowex sulfonic acid resin. The poor correlation between heats of immersion of Rawhide coal with Illinois No. 6 bituminous reported previously[36] suggests a different distribution of types of acid sites which we intend to discuss in future articles.

Acknowledgment. This work was initiated under NSF Grant CHE-8006202 and continued with generous support from DOE Grant DE-FG22-82PC50807 for which we are most appreciative. We are glad to acknowledge the help of Karen Cassidy, Carole Fetzer, and Robert Beckler.

Registry No. 3,5-Dichloropyridine, 2457-47-8; 4-cyanopyridine, 100-48-1; 3-bromopyridine, 626-55-1; 4-carbomethoxypyridine, 2459-09-8; pyridine, 110-86-1; 2-methylpyridine, 109-06-8; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; 2,6-dimethylpyridine, 108-48-5; 2,4-dimethylpyridine, 108-47-4; 2,4,6-trimethylpyridine, 108-75-8; 2,6-diethylpyridine, 935-28-4; 2,6-di-*tert*-butylpyridine, 585-48-8; 3-nitroaniline, 99-09-2; 2,6-dimethylaniline, 87-62-7; 2,4,6-trimethylaniline, 88-05-1; aniline, 62-53-3; 3,4-dimethylaniline, 95-64-7; *N,N*-dimethyl-3-nitroaniline, 619-31-8; *N,N*-dimethylaniline, 121-69-7; *N,N*-diethylaniline, 91-66-7; triethylamine, 121-44-8; *tert*-octylamine, 107-45-9; octylamine, 111-86-4; 1-(*N,N*-dimethylamino)naphthalene, 86-56-6; isopropylamine, 75-31-0; pyrrolidine, 123-75-1; quinuclidine, 100-76-5; *tert*-butylamine, 75-64-9; *p*-toluenesulfonic acid, 104-15-4; dowex 50W X8, 11119-67-8; hexylamine, 111-26-2; ethylenediamine, 107-15-3; dowex MP 50, 102807-64-7; 3-chloropyridine, 626-60-8; 2-*tert*-butylpyridine, 5944-41-2; 4-*tert*-butylpyridine, 3978-81-2.

Solvent Dependence of the Carbon Kinetic Isotope Effect on the Decarboxylation of 4-Pyridylacetic Acid. A Model for Enzymatic Decarboxylations

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Abstract: Carbon kinetic isotope effects have been measured for the decarboxylation of 4-pyridylacetic acid in pure water and in water–dioxane mixtures at 25 °C. The isotope effects are $k^{12}/k^{13} = 1.064$ in 75% dioxane, 1.060 in 50% dioxane, 1.056 in 25% dioxane, and 1.057 in pure water. This decrease in kinetic isotope effect parallels a more dramatic 4000-fold decrease in the observed first-order rate constant on going from 75% dioxane to pure water. No solvent isotope effect is observed in 50% water/dioxane, and as expected, the carbon isotope effect is the same in 50% D_2O/dioxane as in 50% H_2O/dioxane. The reaction appears to occur in a single step, without appreciable proton movement. The variation in rate is attributed to variations in the degree of transition-state solvation with only very small changes in ground-state effects and in the degree of carbon–carbon bond breaking in the transition state. These results indicate that the magnitudes of isotope effects observed in model reactions in H_2O are an appropriate model for magnitudes of isotope effects in enzymatic decarboxylations.

Charge neutralization is a common feature of mechanisms of enzyme-catalyzed decarboxylations.[1] In many cases, the intermediate that undergoes decarboxylation is a zwitterion involving a carboxylate connected by a conjugated system to an ammonium ion or oxonium ion. The two charges are neutralized in the decarboxylation step (eq 1). Examples include reactions de-

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$$A^+—(C{=}C)_n—C—CO_2^- \rightarrow CO_2 + A{=}C—(C{=}C)_n \quad (1)$$

pendent on pyridoxal 5′-phosphate (amino acid decarboxylases), thiamine pyrophosphate (pyruvate decarboxylase), covalently bound pyruvate (histidine decarboxylase), and lysine amino groups (acetoacetate decarboxylase). Rates of these reactions exceed those of the corresponding model reactions by several orders of magnitude.

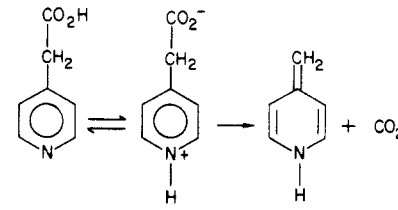
Model studies indicate that the decarboxylation rate is strongly affected by the medium.[2-5] Thus, environmental control may be an important source of catalytic power of these enzymes. This environmental effect appears to have two components. First, medium polarity is an important factor. Enzymes may provide a nonpolar environment to destabilize the ground-state zwitterion relative to the charge-dissipated transition state.[2-4] Model studies for thiamine pyrophosphate catalyzed decarboxylations have demonstrated that rates of decarboxylation of such zwitterions are very sensitive to medium polarity, with factors of several thousand observed on going from pure water to water–organic solvent mixtures.[4] The rate of decarboxylation of 4-pyridylacetic acid (which decarboxylates through a zwitterion, see below) is greatly enchanced in the presence of nonpolar cosolvents, despite a low relative concentration of zwitterion in such nonpolar media.[2,3]

The second component appears to be solvation or ion-pairing of the carboxylate ion. A carboxyl group, being polar and ionic, is highly solvated in aqueous solution. The product, carbon dioxide, being nonpolar, is less solvated. The transition state is somewhere in between—certainly less solvated than the starting state but more solvated than the final product. Studies of the decarboxylation of benzisoxazole-3-carboxylic acids[5] have demonstrated that desolvation can contribute quite substantially to catalysis of decarboxylation.

Less detailed information is available for enzyme-catalyzed decarboxylations, but it has frequently been suggested[1] that similar solvation factors may be responsible for catalytic power in enzymatic decarboxylations. A medium effect is observed for the enzymatic decarboxylation of arginine.[6] In this case, the carbon kinetic isotope effect on decarboxylation decreased with decreasing polarity of the medium, indicating that the rate of the decarboxylation step was increased relative to rates of other steps.

Carbon isotope effects are an important tool in studies of both nonenzymatic[7] and enzymatic[1,6,8-10] decarboxylations. In the case of nonenzymatic reactions, isotope effects are often large (k^{12}/k^{13} = 1.03 to 1.07), reflecting extensive carbon–carbon bond cleavage in the transition state. In the case of enzymatic decarboxylations, the isotope effects observed are usually smaller, presumably because decarboxylation and a prior step (generally formation of the zwitterionic intermediate) are jointly rate-determining. However, this conclusion is based on the partially untested assumption that the isotope effect on the decarboxylation step is the same as would be observed for the corresponding nonenzymatic reaction in aqueous solution. That is, neither the medium nor the enzyme seriously affect the magnitude of the isotope effect on the decarboxylation step. Although a variety of lines of evidence suggest that this is so, direct proof has been lacking.

Pyridylacetic acids undergo thermal and photochemical decarboxylations.[2,3] These reactions occur through zwitterionic intermediates (eq 2) and give rise to neutral decarboxylation products, which then undergo tautomerization. This mechanism



(2)

is supported by the observation that only 2- and 4-pyridylacetic acids readily undergo thermal decarboxylation, whereas 3-pyridylacetic acid is stable (**3**). Thus, these reactions are an excellent model for enzyme-catalyzed decarboxylations (**1**, **2**).

In this paper, we present the medium dependence of rates and isotope effects on the decarboxylation of 4-pyridylacetic acid. These results enable us to estimate the magnitudes of environmental effects on the intrinsic isotope effects[11] in enzymatic decarboxylation.

Experimental Section

The HCl salt of 4-pyridylacetic acid, Gold Label D_2O, and spectrophotometric grade 1,4-dioxane were obtained from Aldrich Chemical Co. Water was purified by a Millipore Super-Q water purification system.

Isotope ratios were measured on a Finnigan Delta-E isotope ratio mass spectrometer. Isotope ratios have been corrected for the presence of ^{17}O and for instrumental effects. Isotope effects were calculated from mass spectrometer data by published procedures.[12]

Kinetics. Rates of decarboxylation were measured spectrophotometrically at 257 nm on a Cary 118 spectrophotometer or else manometrically. A modification of the UV assay reported by Taylor[2] was used for systems containing 50% or 75% dioxane. The HCl salt of 4-pyridylacetic acid was dissolved in H_2O (or D_2O) and the pH (pD) brought to 4.0 by addition of 1.0 M KOH (KOD). In the absence of cosolvent, decarboxylation is extremely slow. The reaction was initiated by addition of cosolvent; all solutions were 0.10 M in 4-pyridylacetic acid. At appropriate times, a 20.0-μL aliquot was withdrawn and added to 3.10 mL of 0.032 M KOH. This solution was extracted with 4 mL of $CHCl_3$, the layers were separated, and the absorbance of the aqueous solution at 257 nm was determined. The molar extinction coefficient for 4-pyridylacetic acid at this wavelength is 2590 M^{-1} cm^{-1} at 25 °C. The product, 4-methylpyridine, was completely extracted into the $CHCl_3$ layer under these conditions. First-order kinetics was observed for several half-lives in 75% and 62% dioxane and for at least 1 half-life in 50% dioxane. D_2O solvent isotope effects were also measured by this assay.

Reactions in 25% dioxane–H_2O and in pure H_2O were followed by manometric measurement of the amount of CO_2 produced. These reactions were too slow to follow beyond several percent reaction, so it is assumed that first-order kinetics would also be observed, as has been reported by others at higher temperatures.[2,3]

Carbon Isotope Effects. The HCl salt of 4-pyridylacetic acid was dissolved in H_2O and brought to pH 4.0 with 1.0 M KOH. In separate reaction vessels, the aqueous solution of substrate and the cosolvent were freed of dissolved CO_2 by purging for 4 h with N_2 gas which had been passed through an Ascarite trap. The reaction was initiated by addition of cosolvent; the final concentration of substrate was 0.10 M (at all cosolvent concentrations) in a total volume of 25.0 mL. An aliquot was withdrawn immediately and placed in a separate reaction vessel, and enough dioxane was added to bring the cosolvent concentration to 75% (v/v). This aliquot was incubated at 35 °C for 2 days and served as the 100% conversion sample. Taking this end point aliquot immediately after purging the solution with CO_2-free N_2 ensured that the isotope effect would not be dependent on the small amount of decarboxylation that occurred during purging with CO_2-free N_2 in water. The low conversion samples were quenched with concentrated H_2SO_4, which was added through a sidearm of a reaction vessel equipped with a stopcock and a septum. The CO_2 was collected and analyzed as described previously.[12]

The 100% conversion sample was worked up in an identical manner. For isotope effects carried out in D_2O, the CO_2 produced was equilibrated with H_2O to normalize the oxygen isotopes prior to isotope ratio measurement.

Control Experiments. To ensure that the CO_2 analyzed originated only from decarboxylation of 4-pyridylacetic acid, the following controls were

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(10) O'Leary, M. H.; Yamada, H.; Yapp, C. J. *Biochemistry* **1981**, *20*, 1476.
(11) The intrinsic isotope effect in an enzyme-catalyzed reaction is the isotope effect for the single isotope-sensitive step, in the absence of kinetic contributions from any other steps.
(12) O'Leary, M. H. *Methods Enzymol.* **1980**, *64*, 83.

Table I. Observed First-Order Rate Constants for the Thermal Decarboxylation of 4-Pyridylacetic Acid in Various Dioxane–Water Mixtures at 25 °C

% dioxane (v/v)	mol fraction of dioxane	k_{obsd} (s^{-1})
0	0	$1.0 \pm 0.2 \times 10^{-8}$
25	0.063	$1.8 \pm 0.2 \times 10^{-7}$
50	0.17	$5.43 \pm 0.09 \times 10^{-6}$
50[a]	0.18	$5.47 \pm 0.05 \times 10^{-6}$
62	0.25	$1.74 \pm 0.03 \times 10^{-5}$
75	0.38	$3.83 \pm 0.08 \times 10^{-5}$

[a] Dioxane–D_2O mixture.

Table II. Carbon Isotope Effects on the Thermal Decarboxylation of 4-Pyridylacetic Acid in Various Dioxane–Water Mixtures at 25 °C

% dioxane (v/v)	k^{12}/k^{13}	no. of determinations
0	1.0573 ± 0.0008	7
25	1.0555 ± 0.0009	5
50	1.0598 ± 0.0011	5
50[a]	1.0605 ± 0.0009	5
75	1.0636 ± 0.0010	7

[a] Dioxane–D_2O mixtures.

performed: First, H_2O, and dioxane were freed from dissolved CO_2 by the N_2 purging method, and any volatile impurities that might be present were collected by the same vacuum procedure used to collect the CO_2. This sample was scanned on the mass spectrometer, and no impurities were detected. A small sample of tank CO_2 of known isotopic composition was then added to this sample, and its isotopic composition was reanalyzed and found to be unchanged. Second, a sample of 0.10 M 4-pyridylacetic acid was freed of dissolved CO_2 by purging. The solution was then quenched with H_2SO_4, and any CO_2 or impurities produced were collected and analyzed. Only a small amount of CO_2 (<1 μmol) was collected, and the isotopic composition of this CO_2 was found to be nearly the same as that of the CO_2 collected in low conversion samples for the reaction in pure H_2O. Since this isotopic composition is quite different from atmospheric CO_2, it is apparent that this small amount of CO_2 originated from the slow aqueous decarboxylation of 4-pyridylacetic acid. For the isotope effect runs, CO_2 samples of 100 μmol or more were always generated for both low- and high-conversion samples to eliminate any contribution due to the presence of this CO_2.

Results

Rate constants for the decarboxylation of 4-pyridylacetic acid in various dioxane–water mixtures are summarized in Table I. These values are in good agreement with those reported previously.[2,3] In 50% dioxane–H_2O, the solvent isotope effect $k(H_2O)/k(D_2O)$ is 1.00 ± 0.02 at 25 °C.

Carbon isotope effects on the decarboxylation of 4-pyridylacetic acid in various dioxane–water mixtures at 25 °C are summarized in Table II. Isotopic compositions for all measurements at 100% reaction were in good agreement, as expected. The reaction shows a small but significant variation in carbon isotope effect with solvent composition. In 50% dioxane–water, the carbon isotope effect is the same in dioxane–H_2O as in dioxane–D_2O.

Discussion

The rate of decarboxylation of 4-pyridylacetic acid increases by a factor of 500 on going from water to 50% dioxane and by a factor of 4000 on going from water to 75% dioxane. This is similar to the factor of 330 seen for the same reaction by Button and Taylor[3] for changing the solvent from 20% isopropyl alcohol to 80% isopropyl alcohol. It is also similar to the factor of 5400 change in rate on going from water to dioxane in the decarboxylation of 3-carboxy-5-nitrobenzisoxazole seen by Kemp and Paul[5] as well as the factor of 9000 seen in the decarboxylation of the thiamine model 2-(1-carboxy-1-hydroxyethyl)-3,4-dimethylthiazolium chloride for transferring from water to ethanol.[4] Qualitatively, this rate effect is attributed to changing solvation of the transition state with changing medium polarity.

The decarboxylation of 4-pyridylacetic acid occurs by a single-step decomposition of the zwitterion (eq 2). The zwitterion is an essential intermediate, but there is no evidence for any other intermediate. The solvent isotope effect on the reaction is unity, making it unlikely that any proton transfer steps are concerted with the decarboxylation step. The large carbon isotope effect is consistent with the decarboxylation step being entirely rate-determining.

The effect of D_2O solvent on the carbon isotope effect is a useful test for single-step and multistep mechanisms of decarboxylation.[10] For a two-step mechanism, the carbon isotope effect will be different in H_2O from that in D_2O unless the solvent isotope effects on both steps are the same. In the present case, the fact that the carbon isotope effect is the same in H_2O as in D_2O is consistent with a single-step mechanism. This observation also confirms our previous expectation[10] that carbon isotope effects on decarboxylation steps should be the same in D_2O as in H_2O.

Carbon isotope effects have been measured for a variety of enzymatic and nonenzymatic decarboxylations.[7] The isotope effects reported here are among the larger isotope effects which have been reported for decarboxylations in which the decarboxylation step is entirely rate-determining. However, it should be noted that most of these reactions have been studied at higher temperatures (50–200 °C) than used in the present study. Little information is available on intrinsic isotope effects for decarboxylations at 25 °C. Qualitatively, these isotope effects usually increase with decreasing temperature,[7] and the values observed here are probably typical of isotope effects at 25 °C.

Medium Effects. The isotope effects reported in this study change slightly with medium polarity. Isotope effects reflect the difference in bonding between ground state and transition state,[13] and changes in either ground state or transition state may give rise to a change in the observed isotope effect. We would like to know the origin of the changes we observe. We examine ground-state effects first.

The zwitterion which is written as the starting state for the decarboxylation (eq 2) is in equilibrium with the neutral form. In pure water, the zwitterion is the predominant form. As the solvent becomes less polar, the proportion of zwitterion decreases. In the least polar solvents used here, the neutral substrate predominates.[3] If there is a carbon isotope effect on the pK_a of the substrate, the transformation from zwitterion to neutral form can produce a change in observed isotope effect. The carbon isotope effect on the pK_a of benzoic acid has been reported to be 1.0014, with ^{13}C concentrating in the carboxylic acid.[14] If a similar factor applies to 4-pyridylacetic acid, then we would expect the isotope effect to increase by a factor of about 1.0014 on going from a more polar solvent to a less polar solvent. The observed change is in the correct direction, but it is about four times larger than predicted. Thus, we conclude that protonation of the carboxyl group is not the principal contributor to the change in isotope effect.

The other possible change in the ground state is a change in solvation. Solvation is an important factor in decarboxylations,[5] and it is likely that there are small changes in the solvation of the carboxyl group on going from pure water to 75% dioxane. However, even 75% dioxane contains adequate water to solvate the carboxylate ion extensively, and we believe that differences in solvation are not a significant contributor to the change in isotope effects.

Thus, we believe that ground-state contributions to the change in isotope effect with solvent are small. Instead, the observed change in carbon isotope effect primarily reflects changes in transition-state structure or solvation. Calculations with the BEBOVIB-IV program[15] (P. Paneth, unpublished) indicate that a small change in the order of the breaking carbon–carbon bond—for example, from 0.45 to 0.50—would account for the observed increase in isotope effect. This small change in transition-state structure is particularly striking, given the large change

(13) For purpose of understanding isotope effects, the "ground state" must be recognized to be the *principal form* of the starting material in solution. If changes in solvent cause the substrate to change from zwitterion to neutral species, then this should be reflected in a change in rate and potentially in a change in isotope effect.

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in rate which occurs in the same interval. These data do not enable us to determine whether changes in solvation are also important, although changes in transition-state solvation could possibly be of a magnitude to produce the observed change in isotope effect.

Relation to Studies of Enzymes. The decarboxylation of 4-pyridylacetic acid is a good model reaction for the decarboxylation step of pyridoxal 5′-phosphate dependent decarboxylases and other decarboxylations involving zwitterionic starting states. We have suggested[1] that decarboxylases work by providing a nonpolar active site for decarboxylation. Our analysis of isotope effects on enzymatic decarboxylations has always been predicated on the assumption that the intrinsic carbon isotope effect on the decarboxylation step in such a nonpolar environment would be about the same as that observed in aqueous solution. This study provides confirmation of that assumption.

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Registry No. 4-Pyridylacetic acid, 28356-58-3; carbon-13, 14762-74-4.

Product Ratio Variation in Reactions of *o*-(3-Butenyl)halobenzenes and 6-Bromo-1-hexene with Alkali Metals in Ammonia/*tert*-Butyl Alcohol Solution. Indications of Reaction-during-Mixing Effects

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Abstract: The four *o*-(3-butenyl)halobenzenes, on reaction with K, Na, or Li in 67% ammonia/33% *tert*-butyl alcohol medium, afford mainly 1-methylindan, considerable 3-butenylbenzene, and some 1,2-bis(1-indanyl)ethane. The first and third of these products are believed to result from cyclization of intermediate *o*-(3-butenyl)phenyl radical. The variation of product ratio with the identity of the halogen is inconsistent with a conventional assumption of reaction with the solvated electron in homogeneous solution and seems better accounted for by a model of reaction in local surroundings of steep concentration gradients during mixing of species through diffusion. 6-Bromo-1-hexene affords very little methylcyclopentane during reaction with potassium in this medium.

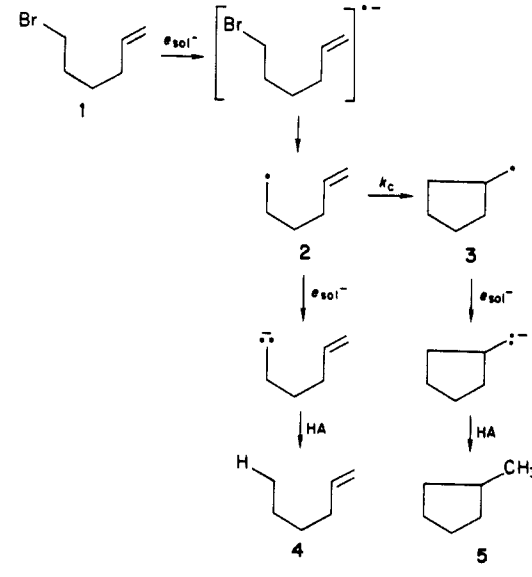
The four familiar halobenzenes behave quite differently in their $S_{RN}1$ reactions with acetone enolate ion in ammonia, provoked by dissolved potassium metal.[1] All four give the same three principal products, phenylacetone, 1-phenyl-2-propanol, and benzene, but the ketone/alcohol ratio decreases sharply as the halogen changes from iodine to fluorine, and the percent of benzene increases steeply as the same change of halogen occurs. It has been suggested[1] that these trends are consequences of the occurrence of reaction during mixing; in that case, strong concentration gradients exist and relatively small changes in the timing of chemical events can affect the environment in which ensuing intermediates must react, and therefore the stable products eventually formed.

We desired to explore some further system in which aryl halides would react with solvated electrons to form aryl radicals, via $ArX^{\bullet-}$ intermediates, and in which the aryl radicals would be able to partition between different modes of reaction. For this purpose we chose to study the action of alkali metals on the four *o*-(3-butenyl)halobenzenes; the solvent chosen was 67% ammonia/33% *tert*-butyl alcohol.[2] Work by Beckwith and associates[5,6] has demonstrated that the *o*-(3-butenyl)phenyl radical cyclizes readily to the 1-indanylmethyl radical. The alterntive mode of reaction of the aryl radical would be to accept a further electron to form the aryl anion which on being hydronated[7] would afford 3-butenylbenzene.

Results

Reactions of 6-Bromo-1-hexene (1). Actually we first investigated an allied system, namely, one involving the thoroughly investigated[8,9] 5-hexenyl radical cyclization. The anticipated events, upon reaction of 6-bromo-1-hexene with solvated electrons

Scheme I



* University of California.

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