

Hydrolysis of Acetaldehyde Diethyl Acetal and Ethyl Vinyl Ether: Secondary Kinetic Isotope Effects in Water and Aqueous Dioxane and the Stability of the Ethoxyethyl Cation

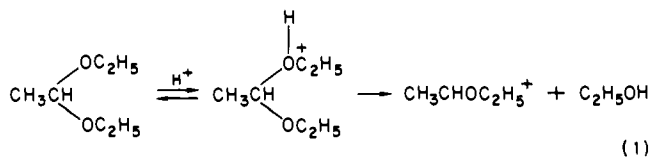
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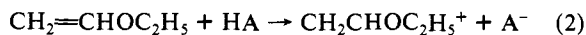
Revised Manuscript Received July 9, 1984

Abstract: Secondary deuterium isotope effects on the hydronium ion catalyzed hydrolysis of acetaldehyde diethyl acetal and ethyl vinyl ether were determined in wholly aqueous and aqueous dioxane solutions by comparing rates of reaction of the normal substrates with those of CD₃CH(OC₂H₅) and CH₃CD(OC₂H₅) and of CD₂=CHOC₂H₅ and CH₂=CDOC₂H₅. All of the isotope effects observed are consistent with the values expected on the basis of the changes in hyperconjugation, bond hybridization, and inductive effect which occur during the course of these reactions. The solvent dependence of the isotope effects, however, suggests that the ethoxyethyl cation intermediate generated in these reactions becomes sufficiently unstable in aqueous dioxane to require the conventional mechanisms for these reactions to give way to concerted pathways.

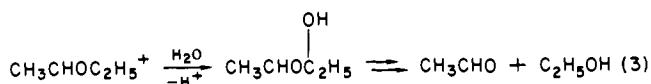
It is generally accepted that the acid-catalyzed hydrolysis of acetaldehyde diethyl acetal in aqueous solution occurs through rate-determining carbon-oxygen bond cleavage of the oxygen-protonated acetal to give the ethoxyethyl cation as an unstable reaction intermediate, eq 1.² This cation is also formed in the



acid-catalyzed hydrolysis of ethyl vinyl ether, this time by rate-determining protonation of a carbon-carbon double bond, eq 2.³



In both cases the ethoxyethyl cation is then rapidly hydrated, and further reaction of the hemiacetal thus produced leads to acetaldehyde and ethanol as the ultimate reaction products, eq 3.



In order to gain further insight into the mechanistic details of these processes, and into the chemistry of this simple alkoxy cation, we have measured α - and β -secondary deuterium isotope effects on these two hydrolyses. Such isotope effects have served well as informative probes of the cationic nature of transition states in nucleophilic displacement reactions⁴ and in the hydrolysis of other acetals,^{2b,5} as well as in the hydrolysis of ketals⁶ and ortho

esters;^{5a} their use in reactions which involve protonation of carbon-carbon double bonds has been more limited.⁷

In the present study we measured isotope effects both in wholly aqueous solution and in water-dioxane mixtures. The solvent dependence of these isotope effects suggests that the ethoxyethyl cation becomes sufficiently unstable in aqueous dioxane to require the conventional mechanisms of eqs 1 and 2 to be replaced by concerted pathways.⁸

Experimental Section

Materials. Acetaldehyde-2,2,2-*d*₃ diethyl acetal was prepared in 60% yield by allowing 0.069 mol of methyl-*d*₃-magnesium iodide made from methyl-*d*₃ iodide (Merck, 99.5 atm % D) to react with an equivalent amount of triethyl orthoformate in ether at reflux for 22 h. The reaction of Grignard reagents with orthoformate esters customarily gives 60-80% of acetal products,⁹ but methylmagnesium iodide is reported to be an exception giving very poor yields.^{9a} We found that substantial improvement could be effected by carefully distilling off the ether solvent, but not allowing the temperature to rise above 50 °C, before using the workup procedure recommended by McElvain.^{9c}

Acetaldehyde-1-*d*₁ diethyl acetal was prepared in 65% yield by prolonged (2.5 days) reaction of 0.062 mol of triethyl orthoacetate with 0.016 mol of lithium aluminum deuteride (Aldrich, 98 atm % D) in very dry ether at reflux.¹⁰

Ethyl vinyl-2,2-*d*₂ and ethyl vinyl-1-*d*₁ ethers were prepared by passing the correspondingly deuterated acetals, in a stream of dry nitrogen gas, through a 22-cm column filled with pumice stone (4-8 mesh) at 300-320 °C according to the method of Sagatys.¹¹ The crude products, which contained ethanol and unreacted starting material in addition to the desired vinyl ethers, were purified by preparative gas chromatography.

All other substances were best available commercial grades. Substrates for rate determinations were purified by gas chromatography and were stored in the cold over anhydrous potassium carbonate; they had spectral and physical properties consistent with their structures. The NMR spectra (T-60) of deuterated substrates showed no detectable protium at the labeled positions. Semicarbazide hydrochloride was recrystallized from 50% aqueous ethanol and dried under vacuum. Sem-

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Table I. Rate Constants for Hydrolysis Reactions at 25 °C^a

| substrate | $k,^b \text{ M}^{-1} \text{ s}^{-1}$ |
|---|--------------------------------------|
| 100% Water | |
| $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 1.634 ± 0.018 |
| $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 1.603 ± 0.013^c |
| $\text{CD}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 1.426 ± 0.017 |
| $\text{CD}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 1.419 ± 0.012^c |
| $\text{CH}_3\text{CD}(\text{OC}_2\text{H}_5)_2$ | 1.390 ± 0.017 |
| $\text{CH}_2=\text{CHOC}_2\text{H}_5$ | 1.941 ± 0.004 |
| $\text{CD}_2=\text{CHOC}_2\text{H}_5$ | 1.937 ± 0.006 |
| $\text{CH}_2=\text{CDOC}_2\text{H}_5$ | 2.012 ± 0.009 |
| 50% Water:50% Dioxane (w/w) | |
| $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 0.2416 ± 0.0025 |
| $\text{CD}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 0.2122 ± 0.0016 |
| $\text{CH}_3\text{CD}(\text{OC}_2\text{H}_5)_2$ | 0.2099 ± 0.0012 |
| 10% Water:90% Dioxane (w/w) | |
| $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 0.09011 ± 0.00031 |
| $\text{CD}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 0.08212 ± 0.00060 |
| $\text{CH}_3\text{CD}(\text{OC}_2\text{H}_5)_2$ | 0.08127 ± 0.00028 |
| $\text{CH}_2=\text{CHOC}_2\text{H}_5$ | 0.2522 ± 0.0016 |
| $\text{CD}_2=\text{CHOC}_2\text{H}_5$ | 0.2510 ± 0.0010 |
| $\text{CH}_2=\text{CDOC}_2\text{H}_5$ | 0.2698 ± 0.0037 |

^aIn HCl solution, ionic strength = 0.10 M (NaCl), except as indicated. ^bError limits are standard deviations of the mean. ^cIn semicarbazide buffer, $[\text{BH}^+] = 0.090 \text{ M}$, $[\text{B}] = 0.021 \text{ M}$.

icarbazide buffer solutions, as well as all solutions containing dioxane, were prepared just prior to use; spectral grade dioxane, distilled from cuprous chloride and then from sodium and stored under argon (for no more than 4 days), was used. Aqueous solutions were prepared from deionized water which was purified further by distillation.

Kinetics. Rate measurements were made spectroscopically with a Cary Model 118C spectrometer with cell compartment thermostated at $25.0 \pm 0.02 \text{ }^\circ\text{C}$. For ethyl vinyl ether hydrolysis the disappearance of substrate absorbance was followed, at 210 nm in wholly aqueous solutions and, because of solvent interference, at 220 nm in aqueous dioxane. The hydrolysis of acetaldehyde diethyl acetal was monitored by following the appearance of aldehyde absorbance at 275 nm and also by semicarbazide scavenging¹² using the absorbance of acetaldehyde semicarbazone at 222 nm. In the latter case, semicarbazide also served as a buffer, and it was established in separate experiments that the scavenging reaction was complete in these solutions in times very much shorter ($<10 \text{ s}$) than the acetal hydrolysis. Because the acetaldehyde absorbance band at 275 nm is weak, the first of these methods required initial substrate concentrations of the order of 10^{-2} M ; this, nevertheless, is sufficiently low to make the hydrolysis reaction essentially nonreversible.¹³ The semicarbazone absorption at 222 nm, on the other hand, is strong, and much lower substrate concentrations, ca. $2 \times 10^{-5} \text{ M}$, were therefore used when this method was employed. Similarly low substrate concentrations were also used in the vinyl ether hydrolysis reactions.

When the trapping method was employed in dioxane solutions, slowly upward-drifting end points were observed. We were unable to eliminate this feature of these reactions, and we attribute it to a carbonyl compound producing decomposition of dioxane. End-point absorbances were not used in the data analysis for these cases, and absorbances were rather fitted to the exponential expression $A = (A_\infty - A_0)e^{-kt}$ by a least-squares method which optimized A_∞ in addition to A_0 and k . The drift in A produced by the disturbing reaction was negligible over the period of time measurements were made (at least 2 half-lives), and the fit of the data to the exponential function was always very good. Both this method of data analysis and a linear least-squares fitting to a logarithmic form of the first-order rate expression were used for the other runs with stable end points. Agreement between the two methods was always better than the statistical error limits (standard deviations in k).

Results

Acetaldehyde Diethyl Acetal. Observed first-order rate constants for the hydrolysis of this substance in wholly aqueous HCl solutions (0.002–0.010 M), measured by monitoring the appearance of acetaldehyde product (Table S1),¹⁴ were accurately proportional

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Table II. Kinetic Isotope Effects

| substrate ^a | medium | $k_{\text{H}}/k_{\text{D}}^b$ |
|---|-----------------------|-------------------------------|
| $\text{CL}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 100% water | 1.134 ± 0.011 |
| $\text{CL}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 50% water:50% dioxane | 1.114 ± 0.007 |
| $\text{CL}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ | 10% water:90% dioxane | 1.097 ± 0.009 |
| $\text{CH}_3\text{CL}(\text{OC}_2\text{H}_5)_2$ | 100% water | 1.176 ± 0.019 |
| $\text{CH}_3\text{CL}(\text{OC}_2\text{H}_5)_2$ | 50% water:50% dioxane | 1.151 ± 0.014 |
| $\text{CH}_3\text{CL}(\text{OC}_2\text{H}_5)_2$ | 10% water:90% dioxane | 1.109 ± 0.005 |
| $\text{CL}_2=\text{CHOC}_2\text{H}_5$ | 100% water | 1.002 ± 0.004 |
| $\text{CL}_2=\text{CHOC}_2\text{H}_5$ | 10% water:90% dioxane | 1.005 ± 0.008 |
| $\text{CH}_2=\text{CLOC}_2\text{H}_5$ | 100% water | 0.965 ± 0.004 |
| $\text{CH}_2=\text{CLOC}_2\text{H}_5$ | 10% water:90% dioxane | 0.935 ± 0.014 |

^aL = H or D. ^bError limits are standard deviations of the mean.

to acid concentration. Linear least-squares analysis of these data gave the second-order rate constants listed in Table I and showed no spontaneous (water catalyzed) reaction for either normal or deuterated substrates. Rates of hydrolysis were also measured for this substance by this method in aqueous dioxane solutions (50 and 90% dioxane) at a single HCl concentration (0.010 M) (Table S2),¹⁴ the second-order rate constants obtained in these media are listed in Table I.

Rates of hydrolysis of acetaldehyde diethyl acetal were also measured by the semicarbazide trapping method at a single concentration of semicarbazide buffer in wholly aqueous and 50% aqueous dioxane solutions (Table S3).¹⁴ The hydrogen ion concentration of the wholly aqueous buffer solution was calculated using $\text{p}K_{\text{a}} = 3.65$ for the acidity constant of protonated semicarbazide¹⁵ and activity coefficients estimated by the Debye-Hückel equation with an ion-size parameter of 9 Å for H_3O^+ ¹⁶ and 6 Å for BH^+ ,¹⁷ the activity coefficient of the uncharged base was taken to be unity. Second-order rate constants obtained in this way are listed in Table I. The hydrogen ion concentration of the aqueous dioxane buffer solution could not be determined by a similar calculation because the required acidity constant is not available for this medium.

Second-order rate constants obtained by the two methods are in good agreement with one another, e.g., for $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2$ in wholly aqueous solution, $k_{\text{H}}^+ = 1.634 \pm 0.018 \text{ M}^{-1} \text{ s}^{-1}$ by monitoring acetaldehyde appearance and $k_{\text{H}}^+ = 1.603 \pm 0.013 \text{ M}^{-1} \text{ s}^{-1}$ by semicarbazide trapping. Both of these values, however, are somewhat greater than $k_{\text{H}}^+ = 1.45 \text{ M}^{-1} \text{ s}^{-1}$ determined before,¹⁸ but the latter was measured by the dilatometric method which has recently been shown to be subject to systematic errors that produce low values.^{13b} The result obtained here for $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)$ in 50% aqueous dioxane, $k_{\text{H}}^+ = 0.2416 \pm 0.0025 \text{ M}^{-1} \text{ s}^{-1}$, agrees well with a previously published value for this medium, $k_{\text{H}}^+ = 0.248 \text{ M}^{-1} \text{ s}^{-1}$.¹⁹

The kinetic isotope effects produced by these rate measurements are listed in Table II. The values given for $\text{CL}_3\text{CH}(\text{OC}_2\text{H}_5)$ in wholly aqueous and 50% aqueous dioxane solutions are weighted averages of results obtained by the aldehyde appearance and semicarbazide trapping methods of monitoring this reaction.

Ethyl Vinyl Ether. Rates of hydrolysis of this substance were measured in wholly aqueous and 90% aqueous dioxane solutions at a single HCl concentration in both cases. The data are summarized in Table S4,¹⁴ and the second-order rate constants derived therefrom are listed in Table I. The result obtained here for $\text{CH}_2=\text{CHOC}_2\text{H}_5$, $k_{\text{H}}^+ = 1.941 \pm 0.004 \text{ M}^{-1} \text{ s}^{-1}$, is slightly greater

(14) Tables S1–S4 are available as supplementary material; see paragraph at the end of this paper.

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than values measured before, $k_H^+ = 1.89^{3a}$ and $1.75^{3b} \text{ M}^{-1} \text{ s}^{-1}$. The latter, however, were determined at lower ionic strengths than that used here, and it is known that reactions such as this are subject to small positive salt effects.²⁰

Kinetic isotope effects derived from these measurements are given in Table 2.

Discussion

Aqueous Solution. The isotope effects determined here in wholly aqueous solution for both of the reactions investigated are wholly consistent with the conventional mechanisms for these processes, eq 1 and 2, and currently accepted isotope effect theory. For example, it is generally agreed that β -deuterium isotope effects on carbocation-forming processes are primarily hyperconjugative in origin: hyperconjugative interaction of the positive center with carbon-hydrogen bonds in β -positions weakens these bonds, and that diminishes the difference in zero-point energy between C-H and C-D and produces isotope effects in the direction $k_H/k_D > 1$.⁴⁶ The β -deuterium isotope effect observed here on acetaldehyde diethyl acetal hydrolysis, $k_H/k_D = 1.134 \pm 0.011$, is consistent with this. The present value is somewhat stronger than the isotope effects determined for aliphatic ketal hydrolysis, e.g., $k_H/k_D = 1.05 - 1.06$ per methyl group for acetone diethyl ketal,⁶ but the dialkylalkoxy cations formed in those reactions are more stable than the monoalkylalkoxy cation formed here; the hyperconjugative interaction per methyl group will therefore be weaker in ketal than in acetal hydrolyses, and the isotope effect will consequently be weaker as well.

The present results show no β -deuterium isotope effect on the hydrolysis of ethyl vinyl ether, $k_H/k_D = 1.002 \pm 0.004$, despite the fact that this is a carbocation-forming reaction as well. However, there is another source of secondary deuterium isotope effects in operation here. The orbitals at carbon used to form carbon-hydrogen bonds at the β -position of ethyl vinyl ether undergo a change in hybridization from sp^2 to sp^3 as the ethoxyethyl cation is formed; this raises the frequency of the out-of-plane bending vibrations of these bonds, and that increases the zero-point energy difference between C-H and C-D and gives an isotope effect in the direction $k_H/k_D < 1$.⁴²¹ This opposes the hyperconjugative contribution to this isotope effect; in the only other reported examples of isotope effects of this kind, there apparently was a close balance between these two opposing contributions and overall isotope effects of unity were observed.^{7a}

A hybridization change is also responsible for the α -deuterium isotope effect on the acetaldehyde acetal hydrolysis reaction. This time the change is from sp^3 to sp^2 , and k_H/k_D will therefore be greater than unity. The value observed here, $k_H/k_D = 1.176 \pm 0.019$, is similar to $k_H/k_D = 1.17$ found for the hydrolysis of propionaldehyde diethyl acetal.^{5a}

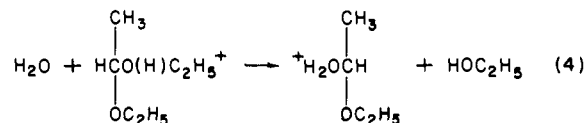
There is no change in hybridization at the α -carbon atom in the rate-determining step of the hydrolysis of ethyl vinyl ether, and hyperconjugation is not possible from this position. However, the weak inverse isotope effect observed here, $k_H/k_D = 0.965 \pm 0.004$, can be attributed to still another cause. The anharmonicity of a carbon-hydrogen bond vibration makes the time-average internuclear distance for C-D slightly shorter than that for C-H, and that makes the electron density in these bonds somewhat closer to carbon for C-D than for C-H.^{4b} This is the so-called "inductive" isotope effect.²² The value observed here is in the correct direction and of the right magnitude.

Aqueous Dioxane Solutions. As the data of Table I show, the hydrolysis of acetaldehyde diethyl acetal is retarded appreciably by the replacement of water with dioxane as its reaction medium. This slowing down should move the rate-determining transition state of this reaction in a product-like direction, giving it more carbocationic character. The demand for hyperconjugative stabilization at the transition state will therefore be increased, and the $sp^3 \rightarrow sp^2$ hybridization change will also be advanced. These

changes should be reflected in stronger isotope effects at both the α - and the β -positions. Such solvent-induced changes in β -deuterium isotope effects have in fact been observed in the hydrolysis of aliphatic ketals⁶ and similar changes in α -deuterium isotope effects have been found in the hydrolysis of benzaldehyde dimethyl acetal.^{5c}

The isotope effects on the hydrolysis of acetaldehyde acetal determined here, however, change in a direction opposite to this prediction: as the data of Table II show, both α - and β -effects become weaker with increasing dioxane content of the reaction medium. In the case of the β -deuterium isotope effect, this change is small and barely outside the experimental uncertainty. The change in the α -isotope effect, however, is greater and is significant to the 99% confidence level.

This difference in behavior between acetaldehyde acetal and the aliphatic ketals and benzaldehyde acetal may be due to a difference in stability of the alkoxylation intermediates involved in these hydrolysis reactions. Rates of reaction of a number of alkoxy-substituted carbocations with water in aqueous solution have been determined recently.²³ The results suggest that the dialkylalkoxy cations derived from aliphatic ketals and the phenylalkoxy cation derived from benzaldehyde acetal are more stable than the monoalkylalkoxy cation related to acetaldehyde acetal. All of these ions, however, are very short lived in aqueous solution and probably have lifetimes approaching the limit beyond which a substance can no longer be a reaction intermediate.⁸ These ions will be still less stable in aqueous dioxane solution, and it is possible that the least stable of them, the ethoxyethyl cation, will cease to exist as a reaction intermediate in some sufficiently water-poor medium. The acetaldehyde acetal hydrolysis reaction will then become a concerted process involving nucleophilic displacement by solvent of a protonated alkoxy leaving group, eq 4. This



mechanistic change will reduce the cationic character of the rate-determining transition state, and that will lower the hyperconjugative interaction and weaken the β -deuterium isotope effect. This nucleophilic involvement will also stiffen the out-of-plane bending vibration of the α -carbon-hydrogen bond, which will weaken the α -deuterium isotope effect as well.

Instability of the ethoxyethyl cation should also enforce a change in the ethyl vinyl ether hydrolysis reaction from the stepwise mechanism of eq 2 and 3 to a concerted pathway in which proton transfer to the β -carbon atom is accompanied by nucleophilic attack of a water molecule on the α -carbon. This prediction is consistent with the slight strengthening of the α -deuterium isotope effect on this reaction observed in going from water to an aqueous dioxane solvent, as shown by the last set of entries in Table II. The β -deuterium isotope effect on this reaction, on the other hand, remains constant over the same solvent change, and that implies that the hyperconjugative and hybridization change contributions to this isotope effect remain in exact cancellation. Since the hyperconjugative contribution should have diminished upon incursion of a concerted mechanism, the contribution from the hybridization change must have decreased as well, and that means that proton transfer to the β -carbon atom must be less advanced at the rate-determining transition state in the concerted mechanism than in the stepwise scheme. It would be interesting to see whether this hypothesis is supported by a decrease in the Brønsted exponent for this reaction upon going from water to an aqueous dioxane medium.

Acknowledgment. We are grateful to Professor James R. Keefe for much useful discussion and to the Natural Sciences and Engineering Research Council of Canada for generous financial support of this work.

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Registry No. acetaldehyde diethyl acetal, 105-57-7; ethyl vinyl ether, 109-92-2; ethoxyethyl cation, 87676-39-9; deuterium, 7782-39-0; acetaldehyde-2,2,2- d_3 diethyl acetal, 92144-49-5; acetaldehyde-1- d_1 diethyl acetal, 92184-46-8; ethyl vinyl-2,2- d_2 ether, 92144-50-8; ethyl vinyl-1- d_1 ether, 75213-98-8; methyl- d_3 iodide, 865-50-9; triethyl orthoformate,

122-51-0; triethyl orthoacetate, 78-39-7.

Supplementary Material Available: Tables of rate constants (4 pages). Ordering information is given on any current masthead page.

Robotic Orchestration of Organic Reactions: Yield Optimization via an Automated System with Operator-Specified Reaction Sequences¹

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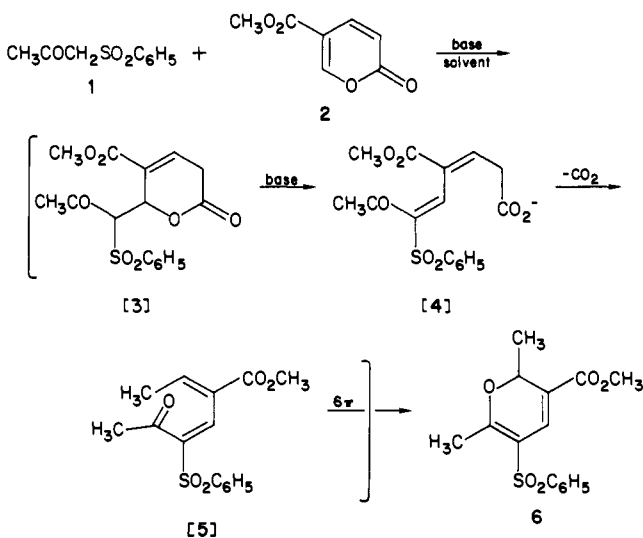
Abstract: A microcomputer-driven reaction protocol has been developed that allows a researcher to initiate a series of experiments which are performed automatically by a robot. The current system is capable of carrying out as many as nine simultaneous, operator-specified reactions complete with automated workup (aliquot quenching, extraction, and plug filtration) combined with automated HPLC yield analysis. Automated reactor cleaning allows multiple runs to be made without operator intervention. Application of this system to the yield optimization of a highly functionalized vinyl sulfone is described.

In our synthetic program we required access to substantial quantities of the trifunctional vinyl sulfone **6**.² Initial investigations revealed that this compound could be prepared in a one-pot sequence from the readily available keto-sulfone **1** and methyl coumalate **2**. The reaction apparently involves the base-catalyzed 1,6-addition³ of the keto-sulfone anion to **2** thereby generating intermediate **[3]**, which undergoes proton transfer, β -elimination (to produce **[4]**), decarboxylation (to yield **[5]**), and finally cyclization⁴ to afford the desired adduct **6**. Unfortunately this reaction appears to be highly sensitive to the exact nature of the basic catalyst as well as the solvent employed. Initial product yields varied widely between 5 and 30%. It appeared that a detailed experimental study would be required to delineate optimal reaction conditions for this synthesis.

Production of a desired target molecule, whether a natural product, drug, or industrial chemical, requires a substantial experimental effort on the part of the practicing chemist. The problem presented by an inefficient chemical reaction is a familiar one in the organic laboratory; a choice must be made as to whether to "push ahead" with an inefficient synthesis (where additional time and effort is required in "going back to prepare more starting material") or to expend the resources necessary to optimize the offending reaction step. It seems clear that *given sufficient resources*, the most practical solution would be to immediately optimize each "bad" reaction as it is encountered along a synthetic sequence.

Computer-driven technology already has had a profound impact upon organic synthesis on the macro (2000 gallon) scale.⁵ A

Scheme I



number of pharmaceutical companies have recently implemented extensive computer-controlled modifications in their pilot plants. Synthesis automation on a more moderate scale (1–12 L) has been pioneered largely by French researchers.^{6–9} Early efforts by these groups have dealt with automation of physical processes (material transfer, temperature, and pH control),^{6,7} and more recently some of the control functions in their systems have been done with a microprocessor-based system.^{8,9}

Single-reactor, closed-loop reaction systems have been developed on a scale (50–100 mL) which begins to approach that needed

(1) Laboratory Automation 1: Syntheses via Vinyl Sulfones. 14. For the previous paper in the latter series, see: P. R. Hamann, J. E. Toth, P. L. Fuchs, *J. Org. Chem.* in press.

(2) M. H. Nantz, unpublished results.

(3) While the 1,6-addition of "soft" nucleophiles to methyl coumalate is well-known,^{3a-c} the synthesis of **6** apparently involves the first example of the formation of a carbon-carbon bond by this process. (a) L. Tsai, J. V. Silverton, and H. T. Linghi, *J. Org. Chem.* **43**, 4415 (1978). (b) N. P. Shusharina, V. L. Lapteva, and O. V. Khrushcheva, *Zh. Org. Khim., Engl. Transl.*, **13**, 1790 (1977). (c) K. Yamada, *Bull. Chem. Soc. Jpn.*, **35**, 1329 (1962).

(4) (a) R. G. Salomon, J. R. Burns, and W. J. Dominic, *J. Org. Chem.*, **41**, 2918 (1976). (b) A. deGroot, B. J. M. Jansen, *Tetrahedron Lett.*, 3407 (1975). (c) T. A. Goslink, *J. Org. Chem.*, **39**, 1942 (1974). (d) E. Marvell, G. Caple, T. A. Goslink, G. Zimmer, *J. Am. Chem. Soc.*, **88**, 619 (1966), and references cited therein.

(5) Pilot plant automation in the petroleum industry continues to be a rapidly evolving area. See preprints of "Division of Petroleum Chemistry, American Chemical Society" Vol. 24, abstracts of papers for the August 1983 Washington D.C. ACS meeting, No. 4.

(6) M. Legrand and A. Foucard, *J. Chem. Educ.*, **12**, 767 (1978).

(7) A. Delacroix, J. N. Veltz, and A. LeBerre, *Bull. Soc. Chem. Fr.*, **2**, 481 (1978).

(8) G. Lonchambon, A. Delacroix, J. Petit, and P. Lecomte, *Bull. Soc. Chem. Fr.*, **1**, 71 (1981).

(9) C. Porte, R. Borrin, S. Bouma, and A. Delacroix, *Bull. Soc. Chem. Fr.*, **1**, 90 (1982).