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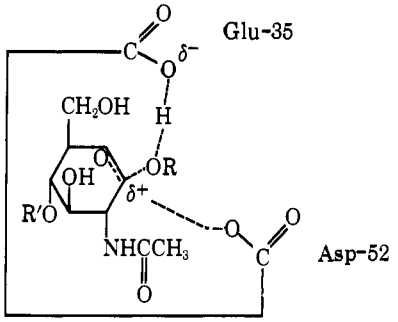
# Carboxylate Anion Stabilization of a Developing Carbonium Ion in Acetal Hydrolysis. Hydrolysis of Phthalaldehydic Acid Acetals

**Thomas H. Fife* and Theodore J. Przystas**

*Contribution from the Department of Biochemistry, University of Southern California, Los Angeles, California 90033.* *Received January 28, 1977*

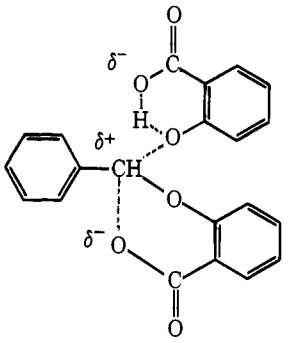
**Abstract:** The rates of phenol release from a series of 2- and 4-carboxybenzaldehyde methyl substituted phenyl acetals and their corresponding methyl esters have been measured in 50% dioxane-$H_2O$ (v/v) at 30 °C ($\mu$ = 0.5 M). With the ester acetals, the second-order rate constant for hydronium ion catalysis decreases as electron withdrawal in the leaving group increases ($\rho$ = −0.5), and general acid catalysis is observed. The corresponding carboxylic acid acetals give pH-rate constant profiles showing hydronium ion catalysis of the reaction of the un-ionized species and a faster reaction which is either hydronium ion catalyzed reaction of the anionic species or the kinetically equivalent intramolecular general acid catalysis. The latter possibility is supported by a positive $\rho$ value (+0.3) and by the absence of buffer acid catalysis in the reactions of any of the 2-carboxyl substituted acetals. Rate enhancements for carboxyl group participation are of the order of $10^2$-$10^3$ in comparison with the respective methyl esters. A pH-independent reaction is observed at high pH with the 3,5-dichlorophenyl acetals. This reaction is a unimolecular decomposition to a stabilized carbonium ion, and proceeds 100 times faster with the ortho carboxyl substituted acetal than with the para carboxyl substituted compound. Thus, carboxylate anion stabilization of a developing carbonium ion has been unambiguously demonstrated and shown to be capable of generating significant rate enhancements, but only in reactions where there is a relatively large amount of C-O bond breaking in the transition state. The implications of these results for lysozyme-catalyzed reactions are discussed.

The complete amino acid sequence of the glycosidic enzyme lysozyme has been determined.[1,2] Also, the three-dimensional structure of the enzyme has been elucidated by x-ray crystallographic analysis at 2 Å resolution.[3,4] Carboxyl groups from glutamic acid-35 and aspartic acid-52 are located at the active site. A number of mechanisms have been suggested for lysozyme, all of which involve general acid catalysis by glutamic acid-35.[5] The mechanism which has received the most attention and support utilizes general acid catalysis by Glu-35 and electrostatic stabilization of the developing glycosyl carbonium ion by the Asp-52 carboxylate anion (I).[4,5]




I

General acid catalysis by buffer acids has been observed in the hydrolysis of a number of simple acetals,[6-10] and the structural features in the acetal that will facilitate such catalysis have been determined.[11,12] Intramolecular general acid catalysis by a neighboring carboxyl group will give rise to rate enhancements of $10^5$-$10^6$ in hydrolysis of salicylic acid acetals.[13] Benzaldehyde disalicyl acetal, in which there are two properly positioned carboxyl groups, has a bell-shaped pH-rate constant profile for release of salicylic acid and displays a rate enhancement of $3 \times 10^9$ in comparison with hydrolysis of the corresponding dimethyl ester.[14] Thus, the mechanism for the reactive monoanionic species (II) could be formally analogous

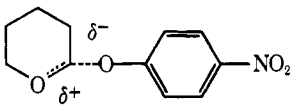



II

to that suggested for lysozyme. The product of the reaction is the stable acylal. However, it was shown by placing one of the carboxyl groups in the para position that the maximum contribution of the second carboxyl to the rate enhancement could be no more than a factor of 50. Intramolecular general acid catalysis by a carboxyl group has also been suggested in hydrolysis of 2,3-(phenylmethylenedioxy)benzoic acid,[15] 2-carboxyphenyl $\beta$-D-glucoside,[16] and 2-methoxymethoxybenzoic acid,[16] although the mechanism for hydrolysis of the latter compound is in dispute,[17,18] No evidence was found for electrostatic participation by a second carboxyl in hydrolysis of

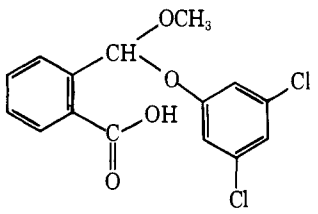
methoxymethoxyisophthalic acid.[19] Thus, while evidence for the occurrence of intramolecular general acid catalysis in acetal hydrolysis is strong, there is little support from model studies for a significant role for Asp-52 in lysozyme as an electrostatic or nucleophilic catalyst.

Acetals having a good leaving group (a phenol with electron-withdrawing substituents) hydrolyze in a pH-independent reaction which has been shown to be a unimolecular decomposition (III).[6-8] Such reactions should provide the maximum

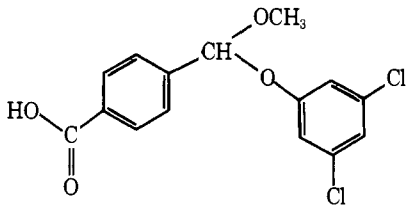


III

opportunity for quantitatively assessing the rate-facilitating effect of electrostatic stabilization of a developing carbonium ion by a neighboring carboxylate anion because (1) extensive bond breaking must occur to attain the transition state, and (2) the complicating effects of acid catalysis are absent. We have therefore determined the rates of phenol release from phthalaldehydic acid methyl 3,5-dichlorophenyl acetal (IV) and the corresponding para carboxyl derivative (V) for comparison purposes. It would not be expected that the carboxyl group of IV would be an efficient intramolecular general acid because of the steric situation (seven-membered ring) and the fact that the carboxyl is in the aldehyde portion of the molecule rather than in the leaving group.[16] In fact, we have found that IV does have a pH-independent region in the pH–rate constant profile for phenol release at high pH which is markedly enhanced in comparison with V.



IV



V

## Experimental Section

**Materials.** The acetals of phthalaldehydic acid (2-carboxybenzaldehyde) were prepared in a manner similar to the procedure outlined by Fife and Anderson.[13] 2-Carboxybenzaldehyde (Aldrich) was converted to its methyl ester (bp 80–82 °C (0.03 mm)) by refluxing in dry acetone with methyl iodide following the procedure of Brown and Sargent.[20] This ester was reacted with trimethyl orthoformate in acidic methanol to give the corresponding dimethyl acetal. Conversion to the α-chloro ether was accomplished by refluxing the dimethyl acetal in excess acetyl chloride with a catalytic amount of thionyl chloride for 1 h and allowing the mixture to stand overnight. Unreacted acetyl chloride and acetal were removed by distillation, and the freshly distilled α-chloro ether (bp 95–96 °C (0.05 mm)) was frozen in a dry ice–acetone bath and used immediately in the next step. The sodium salt of the appropriate phenol was prepared by slowly adding a solution of the phenol in DMF to an equivalent amount of sodium hydride in DMF at 0 °C and stirring until the evolution of hydrogen ceased. The phenolic salt solution was then added to the frozen α-chloro ether, and the mixture was allowed to warm to room temperature and stand for 20 min. This solution was then diluted fivefold with benzene, washed with water containing potassium carbonate, and dried over sodium sulfate. The benzene was removed on a rotary evaporator, and the product acetal was purified by distillation. In general, yields for the reaction varied with the p$K$ of the phenol, ranging from a 60% yield for *p*-methoxyphenol (calculated on the basis of starting dimethyl acetal) to a 15–20% yield for the 3,5-dichlorophenol. In addition, the *m*-nitro derivative was synthesized. However, this acetal could not be made in large enough quantities to be completely separated from unreacted phenol. Nevertheless, hydrolysis reactions of this sample were first order and the good fit of the data on Hammett $\sigma\rho$ plots seems to justify inclusion of this compound. It should be noted that with the exception of the *p*-methoxyphenyl acetals, the acetals cannot be stored in the pure state. It was found that storing the acetals in dry benzene greatly improved their stability.

The acetals of terephthalaldehydic acid (4-carboxybenzaldehyde) were prepared as follows. 4-Carboxybenzaldehyde (Aldrich) was converted to its methyl ester by refluxing with methanol for 3 days with *p*-toluenesulfonic acid as a catalyst. After cooling, an equivalent amount of trimethyl orthoformate was added to form the dimethyl acetal. Conversion of the dimethyl acetal (bp 90–92 °C (0.03 mm), lit.[21] bp 90 °C (0.01 mm)) to the α-chloro ether (bp 96–98 °C (0.03 mm)) was accomplished with acetyl chloride as in the synthesis of the phthalaldehydic acid acetals. The α-chloro ether was reacted with the sodium salt of the desired phenol as previously described to yield the mixed acetal.

**2-Carbomethoxybenzaldehyde methyl 3,5-dichlorophenyl acetal** (iv′) had bp 125 °C (0.02 mm), $n^{24}_D$ 1.5620. Anal. Calcd for $C_{16}H_{14}Cl_2O_4$: C, 56.34; H, 4.10. Found: C, 56.53; H, 4.32.

**4-Carbomethoxybenzaldehyde methyl 3,5-dichlorophenyl acetal** (V′) had bp 100 °C (0.005 mm), $n^{22}_D$ 1.5670. Anal. Calcd for $C_{16}H_{14}Cl_2O_4$: C, 56.34; H, 4.10; Cl, 20.82. Found: C, 56.00; H, 4.48; Cl, 20.07.

**2-Carbomethoxybenzaldehyde methyl *p*-methoxyphenyl acetal (VI′)** had bp 155 °C (0.03 mm), $n^{23}_D$ 1.5534. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 5.96. Found: C, 67.61; H, 6.12.

**4-Carbomethoxybenzaldehyde methyl *p*-methoxyphenyl acetal (VII′)** had mp 50–51 °C. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 5.96. Found: C, 68.30; H, 5.92.

**2-Carbomethoxybenzaldehyde methyl *p*-methylphenyl acetal (VIII′)** had bp 150 °C (0.4 mm), $n^{23}_D$ 1.5371. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.32; H, 6.32. Found: C, 71.97; H, 6.79.

**2-Carbomethoxybenzaldehyde methyl *m*-methylphenyl acetal (IX′)** had bp 160 °C (0.3 mm), $n^{25}_D$ 1.5362. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.32; H, 6.32. Found: C, 71.58; H, 6.75.

**2-Carbomethoxybenzaldehyde methyl *m*-methoxyphenyl acetal (X′)** had bp 155 °C (0.10 mm), $n^{24}_D$ 1.5503. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 5.96. Found: C, 67.93; H, 6.15.

**2-Carbomethoxybenzaldehyde methyl *p*-chlorophenyl acetal (XI′)** had bp 160 °C (0.35 mm), $n^{24}_D$ 1.5564. Anal. Calcd for $C_{16}H_{15}ClO_4$: C, 62.66; H, 4.90; Cl, 11.43. Found: C, 63.11; H, 5.28; Cl, 10.93.

**2-Carbomethoxybenzaldehyde methyl *m*-fluorophenyl acetal (XII′)** had bp 125 °C (0.20 mm), $n^{24}_D$ 1.5336. Anal. Calcd for $C_{16}H_{15}FO_4$: C, 66.21; H, 5.17. Found: C, 65.73; H, 5.57.

**2-Carbomethoxybenzaldehyde methyl *m*-acetylphenyl acetal (XIII′)** had bp 200 °C (0.10 mm), $n^{24}_D$ 1.5598. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.73. Found: C, 68.01; H, 5.86.

The acetal esters were converted to their respective carboxylate salts by hydrolysis in NaOH–EtOH solution. Both *p*-methoxyphenyl acetal salts were obtained by evaporation of the solvent; their infrared spectra showed no traces of unhydrolyzed ester. In general, the acetal salts were not isolated but were used in situ. Typically, 1 mL of a solution that was $2 \times 10^{-2}$ M in acetal ester and 0.2–0.4 M NaOH in 90/10 EtOH/$H_2O$ was allowed to stand for at least 6 h before use. These stock solutions were stable for a day or longer, except that of the 3,5-dichlorophenyl acetal of phthalaldehydic acid. With this acetal, a stock solution was prepared by adding 0.1 mL of 0.2 M acetal ester in etOH to 0.1 mL of 2 M NaOH in 95% EtOH. This solution was allowed to stand for 3 h; it was then diluted with 0.8 mL of EtOH and used for kinetic studies. Such a stock solution would last about 90 min before noticeably decomposing.

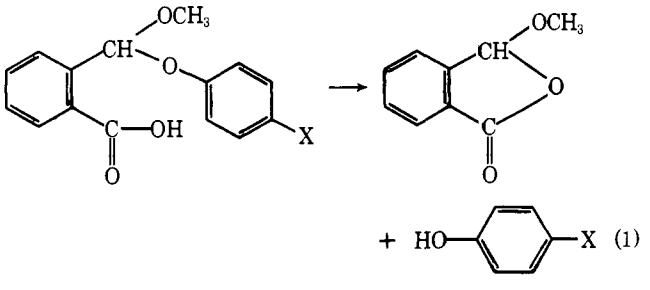
The $D_2O$ (99.8%) employed in these studies was obtained from Bio-Rad. The dioxane was spectral grade (Mallinckrodt) and was refluxed over sodium borohydride for 6 h and freshly distilled prior to use.

**Kinetic Measurements.** The rates of hydrolysis of all the acetal esters in 50% dioxane–$H_2O$ (v/v) at 30 °C were measured on a Gilford Model 2000 or a Beckman Model 25 recording spectrophotometer

by following the appearance of aldehyde at 295 nm. Kinetic runs with the *m*-nitrophenyl (335 nm) or the *m*-acetylphenyl (330 nm) acetals showed that the rate of phenol release was the same as that for appearance of aldehyde. The hydrolysis rates of the terephthalaldehydic acid acetal salts were also measured at 295 nm. However, because of the lack of aldehyde absorption due to acylal formation, the hydrolysis rates of the phthalaldehydic acid acetal salts in 50% dioxane-$H_2O$ had to be measured at wavelengths where phenol release could be observed. The wavelengths used were 288, 300, 283, and 293 nm for the 3,5-dichlorophenyl, *p*-methoxyphenyl, *m*-methylphenyl, and p-chlorophenyl acetals, respectively.

In typical kinetic experiments, 10-20 $\mu$L of the acetal ester or acetal salt stock solution was injected into 2 or 3 mL of reactant solution maintained at the desired temperature. The reaction followed pseudo-first-order kinetics for at least 4 half-lives. Pseudo-first-order rate constants and subsequent kinetic parameters were evaluated using a nonlinear least-squares computer program. Typical standard deviations for individual kinetic runs were about 2-3%. Reaction solution pH values were measured with a Beckman Model 3500 digital pH meter standardized with Mallinckrodt standard buffer solutions.

**Product Analysis.** Spectral analysis of the products from the phthalaldehydic acid acetals in the kinetic runs failed to reveal the presence of free aldehyde at all pH values, indicating that acylal formation is occurring. Nevertheless, an attempt was made to more fully characterize the products of the reaction. The *p*-methoxy (0.3 g) and the 3,5-dichloro (0.5-1.0 g) acetal esters VI′ and IV′ were placed in 10 mL of the EtOH-NaOH solutions previously described to hydrolyze the ester linkage. The freshly prepared acetal acid salts were then placed in 100 mL of 50% dioxane-water solutions containing either 0.2 M formate (pH 4.9) or 0.2 M cacodylate (pH 8.0). After 8-9 half-lives was allowed for acetal hydrolysis, the solutions were extracted with hexane, and the extracts were dried with sodium sulfate and concentrated by rotary evaporation. An infrared spectrum of the residue from the hexane extract when the *p*-methoxy acetal was reacted at pH 4.9 was very similar to the infrared spectrum of 3-methoxyphthalide prepared independently by the method of Bender et al.[22] (mp 45-46 °C, lit.[22] 42-44 °C), except that it showed slight contamination by *p*-methoxyphenol. The spectra of the products from the 3,5-dichlorophenol derivative at pH 4.9 and 8.0 also showed evidence for the presence of 3-methoxyphthalide, but contamination by 3,5-dichlorophenol was more pronounced. When the pH was raised from 8.0 to 9.6 after reaction to ionize the phenolic product, the hexane residue from this basified solution still contained phenol, but less phthalide, presumably due to hydrolytic ring cleavage. The ultraviolet spectra of the isolated products did not show any absorption due to free aldehyde, only that due to phenol and phthalide. Thus, it is likely that the product at all pH values is 3-methoxyphthalide and the appropriate phenol (eq 1).




(1)

A 0.6-g sample of VI′ had the ester linkage hydrolyzed in the usual manner. It was then placed in 100 mL of 0.2 M acetate buffer in water (pH 5.1) and was allowed to stand for 45 min at room temperature. The solution was extracted with hexane, dried with sodium sulfate, and concentrated on a rotary evaporator. The residue was recrystallized from hexane three times. A white solid resulted which melted at 43-44 °C and which had an infrared spectrum identical with that of 3-methoxyphthalide. A mixture melting point with an authentic sample of 3-methoxyphthalide revealed no depression.

## Results

Reactions in 50% dioxane-$H_2O$ (v/v) of all of the phthalaldehydic acid acetals in the series with para or meta substituents in the phenol leaving group follow eq 2 or the kinetically equivalent eq 3

$$k_{obsd} = [k_1 a_H + k_0]\left[\frac{a_H}{K_a' + a_H}\right] \quad (2)$$

$$k_{obsd} = k_1 a_H\left[\frac{a_H}{K_a' + a_H}\right] + k_2 a_H\left[\frac{K_a'}{K_a' + a_H}\right] \quad (3)$$

where $k_{obsd}$ is the observed pseudo-first-order rate constant for phenol release, $k_0$ is the rate constant for intramolecular general acid catalysis by the neighboring carboxyl group, $k_1$ is the second-order rate constant for hydronium ion catalyzed reaction of the un-ionized species, $k_2$ is the second-order rate constant for hydronium ion catalyzed reaction of the ionized species, and $K_a'$ is the apparent dissociation constant of the carboxyl group. Values of these constants at 30 °C are given in Table I. In Figure 1 plots are presented of log $k_{obsd}$ vs. pH for reaction of the ortho and para carboxyl substituted *p*-methoxyphenyl derivatives (from VI′ and VII′). The rate constant $k_0$ (or $k_2$) is significantly larger with the ortho carboxy derivative. Buffer catalysis was not detected in chloroacetate or acetate buffer (0-1.0 M) in the reactions of any of the ortho carboxyl substituted acetals. Plots of log $k_1$ and log $k_2$ vs. $\sigma$, the Hammett substituent constant, are presented in Figure 2. The values of $\rho$ are −0.6 and +0.3, respectively.

The corresponding methyl esters give plots of log $k_{obsd}$ vs. pH that are linear with slopes of −1.0. The second-order rate constants for hydronium ion catalysis ($k_H$) are given in Table II. The plot of log $k_H$ vs. $\sigma$ in Figure 3 is linear with $\rho = -0.5$. Buffer catalysis is not observed with the methyl ester VI′, but

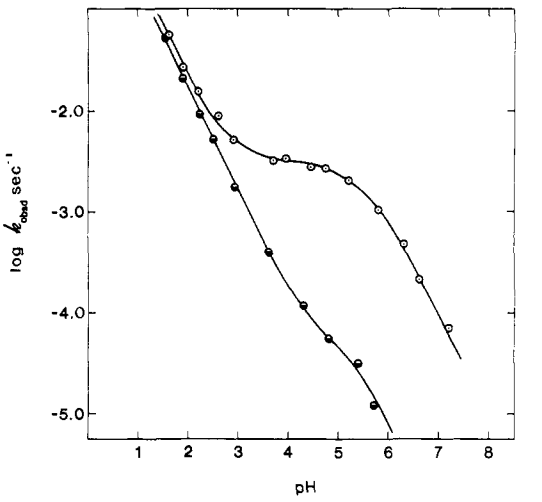



**Figure 1.** Plots of log $k_{obsd}$ vs. pH for phenol release from phthalaldehydic acid methyl *p*-methoxyphenyl acetal (⊙) and terephthalaldehydic acid methyl *p*-methoxyphenyl acetal (⊖) in 50% dioxane-$H_2O$ (v/v) at 30 °C ($\mu$ = 0.5 M with KCl).

**Table I.** Rate Constants[a] for Phenol Release from Phthalaldehydic and Terephthalaldehydic Acid Acetals at 30 °C in 50% Dioxane-$H_2O$ (v/v) with $\mu$ = 0.5 M

| Compd[b] | $k_1$, $M^{-1}$ $s^{-1}$ | $k_2 \times 10^{-2}$, $M^{-1}$ $s^{-1}$ | $k_0 \times 10^3$, $s^{-1}$ | $k_3 \times 10^4$, $s^{-1}$ | p$K_a'$[c] |
|---|---|---|---|---|---|
| *p*-$OCH_3$ (VI) | 1.99 | 9.33 | 3.07 | | 5.48 |
| *p*-$OCH_3$ (VII) | 1.63 | 0.10 | 0.05 | | 5.33 |
| *m*-$CH_3$ (IX) | 1.05 | 11.5 | 3.01 | | 5.57 |
| *p*-Cl (XI) | 0.66 | 13.1 | 4.18 | | 5.50 |
| 3,5-Di-Cl (IV) | 0.38 | 20.4 | 6.31 | 6.61 | 5.56 |
| 3,5-Di-Cl (V) | 0.34 | | | 0.067 | 5.20 |

[a] Rate constants are those from eq 2-5. [b] Acid acetals are numbered IV-XIII in correspondence with the respective esters. [c] p$K_a'$ values were obtained by computer fitting of the data.

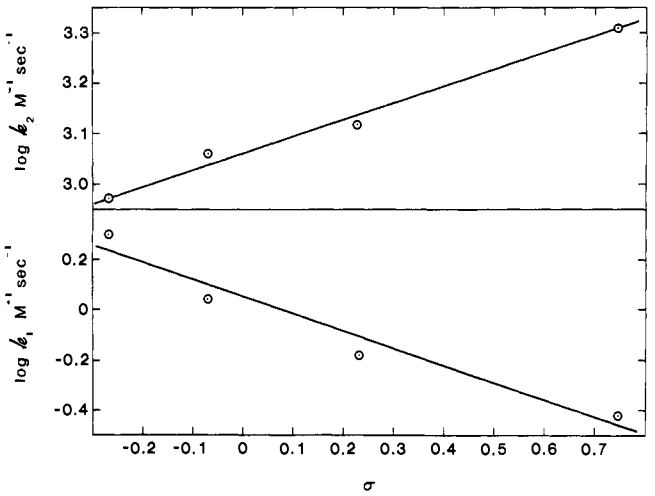



**Figure 2.** Plots of log $k_1$ and log $k_2$ vs. $\sigma$ for phenol release from phthalaldehydic acid methyl substituted phenyl acetals in 50% dioxane-$H_2O$ (v/v) at 30 °C ($\mu$ = 0.5 M with KCl).

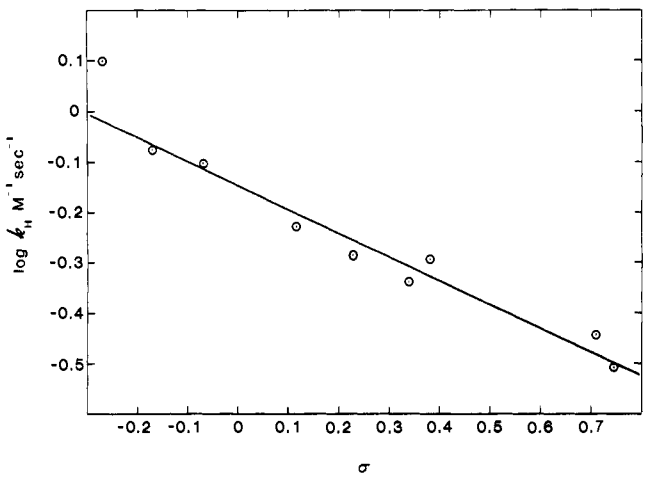



**Figure 3.** A plot of log $k_H$ vs. $\sigma$ for hydronium ion catalyzed hydrolysis of 2-carbomethoxybenzaldehyde methyl substituted phenyl acetals in 50% dioxane-$H_2O$ (v/v) at 30 °C ($\mu$ = 0.5 M with KCl).

as electron withdrawal is increased in the leaving group, catalysis by chloroacetic acid becomes more pronounced. Rate constants for chloroacetic acid catalysis are also given in Table II. A plot of log $k_{ClAC}$ vs. $\sigma$ has a slope of +1.0.

In Figure 4 are presented plots of log $k_{obsd}$ vs. pH for reaction of phthalaldehydic acid methyl 3,5-dichlorophenyl acetal (IV) and the corresponding compound with the carboxyl group in the para position (V). The profiles are similar to those for the other compounds in the series except that at high pH the reactions become pH independent. Thus, an additional term for this reaction ($k_3$) is required in the equation for $k_{obsd}$ (eq 4 and 5).

$$k_{obsd} = [k_1 a_H + k_0]\left[\frac{a_H}{K_a' + a_H}\right] + k_3\left[\frac{K_a'}{K_a' + a_H}\right] \quad (4)$$

$$k_{obsd} = k_1 a_H\left[\frac{a_H}{K_a' + a_H}\right] + [k_2 a_H + k_3]\left[\frac{K_a'}{K_a' + a_H}\right] \quad (5)$$

In the case of V the $k_0$ or equivalent $k_2K_a'$ term is not sufficiently large to be detected in the plot of Figure 4. The value of $k_3$ for IV is the same in $D_2O$ as in $H_2O$ ($k_3(H_2O)/k_3(D_2O)$ = 1.0), whereas $k_0$ is 1.8-fold less in $D_2O$ than in $H_2O$. The value of $k_{obsd}$ at pH 5.0 is $10^3$ greater for IV than V, and $k_3$ is 100-fold greater.

Pronounced buffer acid catalysis is observed in the hydrolysis of terephthalaldehydic acid methyl 3,5-dichlorophenyl

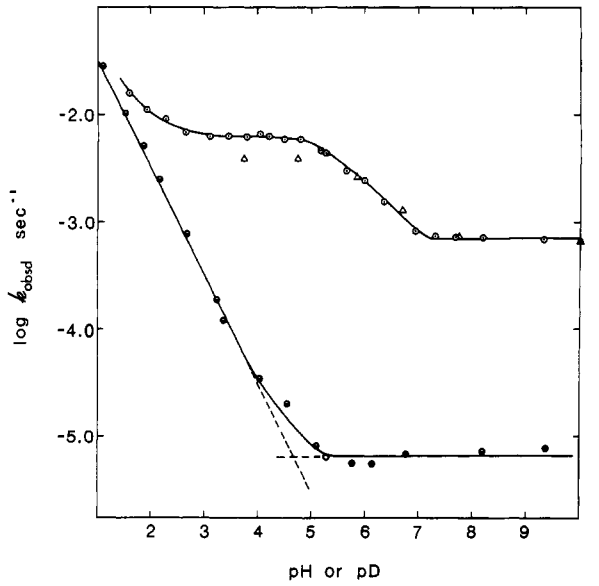



**Figure 4.** Plots of log $k_{obsd}$ vs. pH for phenol release from terephthalaldehydic acid methyl 3,5-dichlorophenyl acetal (V) (◒) and phthalaldehydic acid methyl 3,5-dichlorophenyl acetal (IV) (⊙) in 50% dioxane-$H_2O$ (v/v) or in 50% dioxane-$D_2O$ (△) at 30 °C ($\mu$ = 0.5 M with KCl).

**Table II.** Rate Constants for Hydrolysis of 2- and 4-Carbomethoxybenzaldehyde Methyl Substituted Phenyl Acetals at 30 °C in 50% Dioxane-$H_2O$ (v/v) with $\mu$ = 0.5 M

| Compd | $k_H$,[a] $M^{-1}s^{-1}$ | $k_{ClAC}$[b] × $10^4$, $M^{-1}s^{-1}$ | $k_{HF}$[c] × $10^4$, $M^{-1}s^{-1}$ | $k_{HAC}$[d] × $10^5$, $M^{-1}s^{-1}$ |
|---|---|---|---|---|
| 3,5-Di-Cl (IV′) | 0.31 | 14.6 | 4.77 | 6.31 |
| 3,5-Di-Cl (V′) | 0.28 | 17.2 | 4.77 | |
| *p*-$OCH_3$ (VI′) | 1.26 | | | |
| *p*-$OCH_3$ (VII′) | 1.22 | | | |
| *p*-$CH_3$ (VIII′) | 0.84 | | | |
| *m*-$CH_3$ (IX′) | 0.79 | | | |
| *m*-$OCH_3$ (X′) | 0.59 | | | |
| *p*-Cl (XI′) | 0.52 | 4.35 | 1.22 | |
| *m*-F (XII′) | 0.46 | 5.11 | | |
| *m*-$COCH_3$ (XIII′) | 0.51 | 5.54 | | |
| *m*-$NO_2$ | 0.36 | 11.3 | | |

[a] Second-order rate constants for hydronium ion catalysis. [b] Second-order rate constants for chloroacetic acid catalysis. [c] Second-order rate constants for formic acid catalysis. [d] Second-order rate constants for acetic acid catalysis.

acetal (V). The rate constants for acetic acid catalysis were determined at five pH values and were found to increase with increasing pH. Thus, catalysis is greater when the carboxyl group of the substrate is ionized. Utilizing

$$k_{HAC} = k_{HAC}^{COOH}\left[\frac{a_H}{K_a' + a_H}\right] + k_{HAC}^{COO^-}\left[\frac{K_a'}{K_a' + a_H}\right] \quad (6)$$

second-order rate constants for the ionized and un-ionized species were determined. Computer analysis of these data showed that the best fit was provided by $k_{HAC}^{COOH} = 0.7 \times 10^{-4}\ M^{-1}\ s^{-1}$, $k_{HAC}^{COO^-} = 6.0 \times 10^{-4}\ M^{-1}\ s^{-1}$, and $pK_a' = 5.2$.

## Discussion

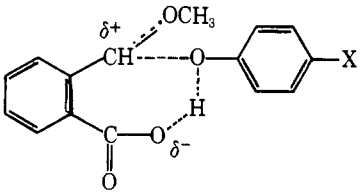
Phthalaldehydic acid methyl *p*-methoxyphenyl acetal has a pH–rate constant profile for release of *p*-methoxyphenol

which shows that ionization of the neighboring carboxyl group is producing an increase in the second-order rate constant for hydronium ion catalysis. The value of $k_2$ from eq 3 is 470-fold greater than $k_1$. The difference in $k_1$ and $k_2$ for the corresponding acetal with a carboxyl group in the para position is only a factor of 6.3, which must be the consequence of the changing electronic effect due to carboxyl ionization. Thus a factor of 75 in $k_2$ cannot be accounted for on the basis of electronic effects, suggesting that the ortho carboxyl group is participating in the reaction. General acid catalysis by buffer acids is not detectable in reactions of the ortho carboxyl substituted compound or in hydrolysis of the corresponding methyl ester. Therefore, *p*-methoxyphenol is not a sufficiently good leaving group for bimolecular general acid catalysis to be observable even though the carbonium ion intermediate that is formed is a relatively stable benzyl carbonium ion.

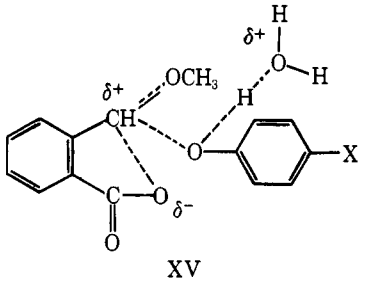
As electron withdrawal in the leaving group of the phthalaldehydic acid acetals becomes greater, the difference between $k_1$ and $k_2$ becomes more pronounced. The difference in these rate constants is a factor of 2000 with the *p*-chlorophenyl derivative and 5400 with the 3,5-dichlorophenyl derivative. The increasing magnitude of $k_2$ relative to $k_1$ is reflected in the Hammett $\rho$ values for these reactions; $\rho$ for the $k_1$ step is $-0.6$ whereas $\rho$ for the $k_2$ step is $+0.3$. The $\rho$ for hydronium ion catalyzed hydrolysis of the corresponding methyl esters is $-0.5$. Buffer acid catalysis is observed in hydrolysis of the methyl esters when the leaving group has an electron-withdrawing substituent, and $\rho$ is $+1.0$ for chloroacetic acid catalysis, which is in accord with previous studies of the hydrolysis of phenyl acetals.[7,10,23] However, buffer acid catalysis does not occur in the reactions of any of the *o*-carboxyl substituted acetals.

Capon and Nimmo[23] have made a thorough investigation of substituent effects in both the leaving group and the benzaldehyde portion of the molecule in the hydrolysis of benzaldehyde methyl phenyl acetals. As electron withdrawal in the benzaldehyde portion increases, the rate decreases in both hydronium ion and general-acid-catalyzed reactions ($\rho = -2.26$ for hydronium ion catalysis). The $\rho$ value for hydronium ion catalyzed hydrolysis of benzaldehyde methyl substituted phenyl acetals is $-0.6$. Thus, the more negative $\rho$ for the $k_1$ step (un-ionized carboxyl) than for $k_2$ (carboxylate anion) with the present series of compounds could be due in part to the greater electron-withdrawing ability of an un-ionized carboxyl group as compared to a carboxylate anion. however, the large difference in magnitude of the $\rho$ values and the positive $\rho$ for the $k_2$ step would not be expected on this basis. These features suggest carboxyl group participation in the reaction governed by $k_2$ or the kinetically equivalent $k_0/K_a'$.

Kinetically equivalent possibilities exist for carboxyl group participation in the cyclization of the phthalaldehydic acid acetals in which there is an electron-withdrawing substituent in the leaving group. These possibilities are intramolecular general acid catalysis (XIV) and electrostatic catalysis by the carboxylate anion (XV). 3-Methoxyphthalide is the product



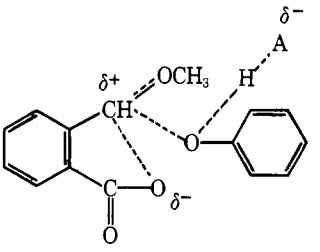

XIV




XV

of the reaction at all pH values, but this fact does not give information in regard to the mechanism of the reaction.[24] The rate enhancements in the cyclization of the anionic species ($k_2$ step), and the large $D_2O$ solvent isotope effects ($k_0^{H_2O}/k_0^{D_2O} = 1.8$) are in accord with either mechanism. It would not be expected that the neighboring carboxyl group would be an efficient intramolecular general acid because of the steric situation; a seven-membered ring would be required for intramolecular proton transfer. Nevertheless, in view of the large rate enhancements of $10^5$–$10^9$ found for intramolecular general acid catalysis in acetal hydrolysis,[11-13] even relatively unfavorable intramolecular catalysis of that type might provide a detectable enhancement in the rate. Hence, the magnitude of $k_2$, or the kinetically equivalent $k_0/K_a'$, either provides a measure of electrostatic stabilization (XV) in these reactions or is an upper limit for such stabilization. If XIV is the mechanism, it is apparent that electrostatic stabilization is not sufficiently favorable to be competitive.

The difference between $k_1$ and $k_2$ becomes larger as electron withdrawal increases in the leaving group. The largest enhancement in $k_2$ ($k_0/K_a'$) that occurs in the series is with the dichlorophenyl derivative (IV) where there is a maximum difference of $10^3$ in $k_{obsd}$ in comparison with the para carboxyl substituted compound V. The fact that $k_2$ ($k_0/K_a'$) becomes larger as the leaving group becomes better ($\rho = +0.3$) supports XIV as the mechanism of the reaction.[7,11,12] The lack of buffer catalysis in reactions of the phthalaldehydic acid acetals also supports XIV since external catalysis by general acids should be facilitated by electrostatic stabilization of the carbonium ion intermediate (XV), i.e., the Brönsted coefficient for general acid catalysis should be lowered. As carbonium ion stability is increased or as leaving group ability is facilitated by electron withdrawal the transition state will be reached sooner, with less C–O bond breaking and less need for complete proton transfer to the leaving group. General acid catalysis of acetal hydrolysis has been found to be promoted by electron withdrawal in the leaving group and $\rho$ values are positive.[7,23] On the other hand, it would be expected that the importance of electrostatic stabilization (XV) would increase as the leaving group was made worse so there would be greater carbonium ion character in the transition state. Electrostatic stabilization should be most important with the *p*-methoxyphenyl acetal which has the poorest leaving group in the series, but the difference between $k_1$ and $k_2$ is only 470-fold in that case. Thus, carboxylate anion stabilization of the developing carbonium ion does not provide sufficient advantage for the bimolecular reaction XVI so that

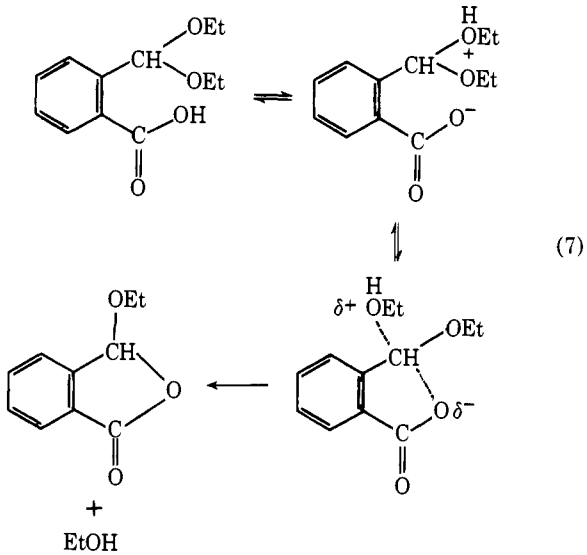



XVI

it will occur in preference to intramolecular general acid catalysis even though the latter mechanism should be quite unfavorable from a steric standpoint. Pronounced buffer acid catalysis is detected in hydrolysis of the methyl esters and the 3,5-dichlorophenyl acetal with the carboxyl group in the para position, showing that buffer acid catalysis is feasible in reactions of these compounds.

The cyclization of phthalaldehydic acid diethyl acetal to 3-ethoxyphthalide in $H_2O$ is only about three-fold faster than hydrolysis of terephthalaldehydic acid diethyl acetal,[25] indicating that the ortho carboxyl group is not participating. In 82% w/w aqueous dioxane the pH-rate constant profile for

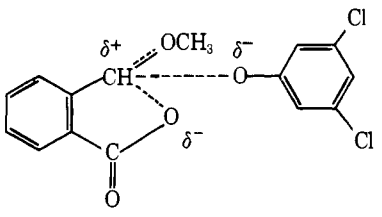
cyclization of phthalaldehydic acid diethyl acetal at 60 °C is sigmoid, and at pH 9.46 the reaction is 3000 times faster than hydrolysis of terephthalaldehydic acid diethyl acetal. Therefore, it appears that in the less aqueous solvent the carboxyl group does participate in the reaction. It was suggested that the carboxylate anion acts as a nucleophile toward the protonated acetal (eq 7); however, the kinetically equivalent



(7)

possibilities were not eliminated. In 82% dioxane a carbonium ion intermediate would be poorly solvated. Furthermore, the carboxylate anion must be quite basic in that solvent ($pK_a$ = 10–11). Therefore, if a large amount of bond breaking is required to attain the transition state, there could be considerable driving force for nucleophilic participation. Whether bond breaking and nucleophilic attack are synchronous or whether some bond breaking precedes nucleophilic attack (incipient carbonium ion stabilization) was not considered.[25]

The pH-independent reactions of IV and V at high pH demonstrate unambiguously the ability of a neighboring carboxylate anion to stabilize a developing carbonium ion. The lack of a $D_2O$ solvent isotope effect ($k_3(H_2O)/k_3(D_2O)$ = 1.0) indicates that the reaction is a unimolecular decomposition, as was found in the pH-independent hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran.[7] The unimolecular reaction is brought about by the good leaving group and the reasonably stable carbonium ion intermediate, which make bond breaking a facile process. The pH-independent reaction of IV, which has an ortho carboxylate anion, takes place at a rate 100 times faster than the corresponding reaction of V where the carboxylate anion is in the para position where it cannot directly participate in the reaction. Since electronic effects should be roughly the same in the ortho and para positions, the rate difference of $10^2$ shows that electrostatic participation is taking place.[24] The amount of C–O bond breaking required to attain



XVII

the transition state in this unimolecular reaction must be greater than in the corresponding reaction involving proton transfer to the leaving group. The observed rate enhancement ($10^2$) therefore represents the maximum enhancement possible by electrostatic stabilization of the developing carbonium ion in reactions of this compound.

**Lysozyme.** The mechanism for lysozyme catalyzed reactions which has received the most support involves general acid catalysis by glutamic acid-35 and electrostatic stabilization of a developing carbonium ion by the carboxylate anion of aspartic acid-52 (see I). A nucleophilic role for Asp-52 has been looked upon with disfavor because of the 3.0-Å distance between the aspartyl oxygen and the reaction center.[26] Also there is no evidence, kinetic or otherwise, for the existence of an acylal intermediate in the lysozyme reaction. It would be expected that if such an intermediate were being formed it would have sufficient stability to allow its detection.[27] The present study of IV demonstrates unambiguously that carboxylate anion stabilization of a carbonium ion can facilitate the rate of acetal hydrolysis, in this case by 100-fold. A rate enhancement of that magnitude in the enzyme reaction would be significant, and in combination with other mechanistic features could lead to a large total rate enhancement. Also, such electrostatic stabilization of the developing carbonium ion would help to provide the ease of bond breaking necessary for general acid catalysis by glutamic acid-35.[11]

The neighboring carboxylate anion facilitation of the pH-independent unimolecular reaction of IV illustrates the fact that the more bond breaking that occurs in the critical transition state, the more effective will be electrostatic stabilization. As a consequence, in the enzymatic reaction, where the glycosyl carbonium ion intermediate is less stable than the benzyl ion from IV, electrostatic effects could be much more important. Balanced against this is the fact that Asp-52 is apparently not within bonding distance of the glycosyl carbon of the substrate; electrostatic effects would fall off markedly with distance. Solvent polarity is also a factor of importance. If the active site of the enzyme is less polar than 50% dioxane-$H_2O$, then electrostatic effects should be correspondingly more important. However, the $pK_a$ of Asp-52 has been reported as 4.5,[28] which indicates that in the free enzyme it is in an aqueous environment.

For electrostatic stabilization effects to be important in acetal hydrolysis there must be considerable C–O bond breaking in the transition state. On the other hand, for general acid catalysis to occur, C–O bond breaking must be a facile process resulting in a transition state with relatively little C–O bond breaking.[11,12] Thus, the structural features that will give rise to and facilitate these mechanisms are in opposition. For involvement of both features there must be a precise balancing of effects which is reflected in the amount of bond breaking in the transition state. The structural features of the enzyme substrates (a relatively unstable carbonium ion and a poor leaving group) are those which should make effects enhancing the ease of bond breaking (electrostatic and relief of steric strain) of great importance.

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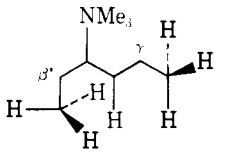
# Mechanism of Elimination Reactions. 28. Stereochemistry of Elimination Reactions of 2- and 3-Hexyl Tosylates[1]

**Wen-Bin Chiao[2] and William H. Saunders, Jr.***

*Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627.* *Received April 4, 1977*

**Abstract:** The rate of reaction of 3-hexyl tosylate with *tert*-butoxide in *tert*-butyl alcohol depends on the cation in the order K > Na ≫ Li. The stereochemistry of elimination with 3-hexyl-*4-d* tosylate and sodium *tert*-butoxide in *tert*-butyl alcohol containing dimethyl sulfoxide runs (percent syn → trans, percent dimethyl sulfoxide) 28.4, 0; 19.9, 5; 9.3, 10; and 6.4, 90. Potassium *tert*-butoxide gives 20.3% syn → trans elimination. These results further confirm the favorable effect of base ion pairing on syn elimination from tosylates. 3-Hexyl-*4-d*, 3-hexyl-*2-d*, and 2-hexyl-*3-d* tosylates give 28.4, 16.6 and 12.3% syn → trans elimination, respectively. Examination of partial rates shows that the higher proportion of syn elimination from 3-hexyl-*4-d* tosylate arises essentially entirely from a decrease in the rate of the anti → trans path. These results are compared with those reported for structurally similar quaternary ammonium salts. While both can be explained by the steric theory of structural effects on the stereochemistry of elimination in acyclic systems, important questions remain.

Some time ago, we advanced a steric explanation[3,4] of the syn-anti dichotomy[5-8] (trans olefin partly or mainly by syn elimination, but cis olefin almost entirely by anti elimination) in E2 reactions of acyclic quaternary ammonium salts. According to this explanation, the bulky leaving group forced alkyl groups in the $\beta'$ and $\gamma$ positions (**1**) into a conformation




**1**

such that they interfered with the approach of base to the anti-$\beta$ hydrogen, and did so to a greater extent for the anti → trans than for the anti → cis path. A modification of this picture by Felkin, reported by Sicher,[9] allows for changes in dihedral angles due to steric congestion, but leaves the essential idea unchanged. The theory accounted very well for the effect of alkyl substitution at the $\beta'$ and $\gamma$ positions on the propensity for syn elimination.[4,10]

Subsequent reports made it clear, however, that the steric theory in its original form could not be correct. Alkyl fluorides, which have a much smaller leaving group than quaternary ammonium salts, nonetheless give major amounts of syn elimination.[11,12] In addition, partial rates of the various paths of elimination from acyclic quaternary ammonium salts show that the increase in syn elimination with increased steric requirements of the $\beta'$ substituent arises mainly from increases in the rate of syn elimination, rather than the decreases in rate of anti elimination predicted by the steric theory.[13]

In order to gain further information on the effects of alkyl structure on stereochemistry of elimination in open-chain systems, we decided to examine the 2- and 3-hexyl systems[4] with a neutral leaving group of relatively modest steric requirements. While alkyl fluorides give substantial syn elimination, they react so sluggishly that some interconversion of the olefinic products occurs under the elimination conditions.[11,12] Consequently, we chose the tosylates, which give fairly small but significant amounts of syn elimination.[12,14,15]

Our first experiments used 3-hexyl-*4-d* tosylate and were aimed at finding conditions giving sufficient syn elimination that changes when the structure was changed would be readily observable. Prior evidence suggested that *tert*-butoxide[14,15] and strong ion pairing of the base with the metal ion[12] should be most favorable for syn elimination. The overall rate of reaction (Table I) was found to decrease sharply as the metal ion was changed from potassium to sodium to lithium, as expected for increasing ion pairing. In fact, the first two entries of Table I show that lithium *tert*-butoxide reacts so slowly that solvolysis constitutes a significant side reaction even at base concentrations as high as 1.0 M. Sodium *tert*-butoxide, however, gives <2% solvolysis at 0.5 M, and Table III shows that syn elimination accounts for nearly 30% of the *trans*-3-hexene. The smaller proportions of syn elimination with potassium *tert*-butoxide, and with sodium *tert*-butoxide in *tert*-butyl alcohol containing dimethyl sulfoxide, confirm the importance of ion pairing.

The erythro and threo stereoisomers of 3-hexyl-*4-d* (**2**), 3-hexyl-*2-d* (**3**), and 2-hexyl-*3-d* (**4**) tosylates were prepared as described in the Experimental Section and treated with sodium *tert*-butoxide in *tert*-butyl alcohol at 80 °C. The olefin proportions (Table II) and the deuterium analyses of the olefins (Table III) were combined as previously described[4] to give values for the percentages of syn elimination which would be observed in the absence of an isotope effect. The average values for percent syn → trans run **2**, 28.4; **3**, 16.6; and **4**, 12.3.

When the structures of **2**–**4** are written as shown, it becomes apparent that the most syn elimination is found when both the $\beta'$ and $\gamma$ positions contain alkyl substituents, while much less