Subsequent articles will describe the phenylation of additional aromatic and heterocyclic compounds by nitrobenzene at elevated temperatures.

Acknowledgment. The authors acknowledge with thanks the assistance of D. K. Albert of the American Oil Company in gas chromatographic analyses.

The Participation of Solvent and General Acids in Acetal Hydrolysis. The Hydrolysis of 2-(*para*-Substituted Phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes

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Abstract: The hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane in 0.100 *M* HCl is characterized by a ΔS^* of -14.2 eu and a D_2O solvent isotope effect of $k_D/k_H = 2.4$. The value of ρ for hydrolysis of a series of 2-(*para*-substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in 0.100 *M* HCl at 30° was found to be -2.0. The values of ΔS^* and k_D/k_H are considerably less than normally found in acetal hydrolysis while the ρ value is much more positive than found previously for hydrolysis of the diethyl acetals of *meta*- and *para*-substituted benzaldehydes. The rate constants for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in moderately concentrated HCl solutions are proportional to the stoichiometric acid concentration while a plot of log k_{obsd} *vs.* $-H_0$ shows a pronounced downward curvature. The slope *w* of a plot of log $k_{obsd} + H_0$ *vs.* the logarithms of the activity of water is $+1.9$. Thus the evidence supports the incursion of an A2 mechanism involving attack of water on the protonated substrate. The rate of hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane is subject to catalysis by increasing concentrations of formic acid at constant pH and ionic strength.

The generally accepted mechanism for the acid-catalyzed hydrolysis of acetals involves a fast pre-equilibrium protonation of the substrate followed by a unimolecular rate-determining decomposition to an alcohol and a resonance-stabilized carbonium ion.[1] The hydrolysis of fully protonated 2-(substituted phenyl)-3-ethyloxazolidines, carbonyl derivatives similar to acetals (1,3-dioxolanes) in which an oxygen has been replaced by an N-ethyl group, is marked however by solvent participation and general catalysis in the ring-opening step.[2]

It was thought that similar mechanisms might be observable in the hydrolysis of acetals if the A1 transition state could be made sterically unfavorable. Intramolecular participation by various functional groups in acetal hydrolysis has been postulated in several instances.[3-6] The mechanism of such participation, however, has not been established. The clearly unambiguous finding of buffer catalysis and solvent participation in an acetal hydrolysis could lead to insight into the mechanistic possibilities by which glycosidic enzymes effect catalysis since it is likely that functional groups at the active sites of these enzymes are involved in the bond-breaking process.

In preliminary work it was found that the hydronium ion catalyzed hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane proceeded in water at 30° with a second-order rate constant approximately 1030-fold less than that of the corresponding ethylene glycol derivative. There is little doubt that this large observed effect is steric in origin resulting from substitution at the 4 and 5 positions in the 1,3-dioxolane ring system. While this rate effect could be reflecting differences in the dissociation constants for the conjugate acids it is also quite likely that the bond-breaking process is strongly hindered with the tetramethylethylene glycol derivative due to greater steric interactions in the A1 transition state than in the ground state. Since the 1,3-dioxolane ring is normally puckered by carbon–oxygen bond angles of less than 109°,[7] a substantial dihedral angle should exist between the methyl groups on adjoining carbons so that ground-state interactions would not be unusually large. A detailed study of the hydrolysis of a series of 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes has therefore been made. It has indeed been found that the hydrolysis reactions of these acetals proceed by an A2 mechanism with general acid catalysis by formic acid being detectable.

Experimental Section

Materials. 2-(*para*-Substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes were prepared by refluxing in benzene or toluene equivalent amounts of the appropriately substituted benzaldehyde and tetramethylethylene glycol. A trace of *p*-toluenesulfonic acid was added as a catalyst. Water was continuously removed from the reaction by azeotropic distillation with the solvent. After collection of a theoretical amount of water the reaction mixture was washed with 1 *M* KOH solution. The benzene or toluene extract was then dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation, and the residue was either distilled or recrystallized from an ether–hexane mixture.

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(1) For the evidence which has led to this mechanism and the pertinent references see T. H. Fife and L. K. Jao, *J. Org. Chem.*, 30, 1492 (1965).

(2) T. H. Fife and L. Hagopian, unpublished data.

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(4) B. Capon and M. C. Smith, *Chem. Commun.*, 523 (1965).

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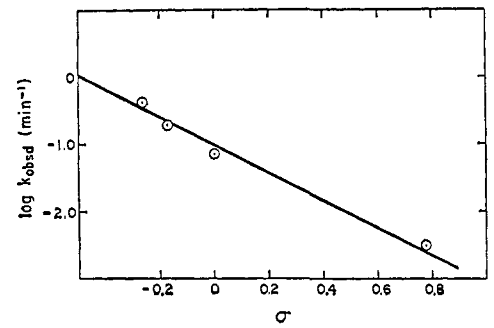

Figure 1. Plot of log k_{obsd} for hydrolysis of 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in 0.100 *M* HCl at 30° *vs.* σ.

2-(*p*-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane had bp 112–115° (1.2 mm), n^{21}D 1.5090. *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 70.90; H, 8.37. 2-(*p*-Methylphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane had bp 99° (1.8 mm), n^{21}D 1.4998. *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.48; H, 9.01. 2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane had bp 82–83° (1.4 mm), n^{25}D 1.4975. *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.47; H, 8.99. 2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane had mp 85–87°. *Anal.* Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.39; H, 6.98; N, 5.87. Dioxane was purified by the method of Fieser[8] and was stored frozen.

Kinetic Measurements. The rates of appearance of the aldehyde products in water as the solvent were measured spectrophotometrically with a Zeiss PMQ 11 spectrophotometer. The dioxolane, dissolved in dioxane, was added to the aqueous solution in a thermostated cuvette in the cell compartment of the spectrophotometer by means of a calibrated dropping pipet. The solution was then stirred vigorously. The rates were generally followed to 75–90% of completion, and infinity points were taken at 10–20 half-lives and were stable. Pseudo-first-order rate constants (k_{obsd}) were obtained from the slopes of plots of log $(OD_\infty - OD_t)/(OD_\infty - OD_t)$ *vs.* time. Constant temperature (± 0.1°) was maintained in the kinetic runs by circulating water from a Haake Model F constant-temperature circulating bath through a Zeiss constant-temperature cell holder. All pH measurements were made with a Radiometer pHM 22 pH meter.

In work utilizing 99.8% D_2O as the solvent, the glass electrode correction formula of Fife and Bruice[9] was employed in the determination of a_{D^+}.

In the determination of activation parameters for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane in 0.100 *M* HCl points were obtained at four temperatures (20, 30, 40, and 50°) ± 0.1°. The rates were measured in triplicate at each temperature with an average deviation of less than 2% in the rate constants in all cases.

Results

The rate constants for hydrolysis of the series of 2-(*para*-substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in 0.100 *M* HCl at 30° are presented in Table I.

Table I. Rate Constants for Hydrolysis of 2-(*para*-Substituted Phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in 0.100 *M* HCl at 30°

Substit	k_{obsd}, min^{-1}	l. mole^{-1} min^{-1} k_H[a]	l. mole^{-1} min^{-1} k_D[b]
p-OCH$_3$	0.400		
p-CH$_3$	0.199		
H	0.0739	0.739	1.80
p-NO$_2$	0.00324		

[a] $k_{obsd}^{H_2O}/C_{H_3O^+}$. [b] $k_{obsd}^{D_2O}/C_{D_3O^+}$.

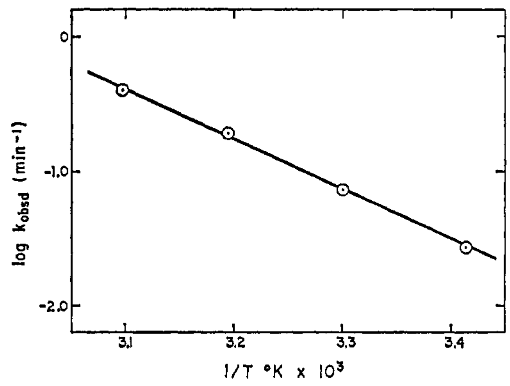

Figure 2. Plot of log k_{obsd} for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane in 0.100 *M* HCl *vs.* 1/*T*° K.

The logarithms of these rate constants are plotted in Figure 1 *vs.* σ, the Hammett substituent constant.[10] A straight line relationship is obtained with a ρ of −2.0. Also reported in Table I is the rate constant determined in D_2O as the solvent. The ratio k_D/k_H is 2.4 for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane.

The rate constants for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane were determined as a function of temperature and are given in Table II. In Figure 2 is shown a plot of the logarithms of these rate constants *vs.* 1/*T*°K. The value obtained for ΔH^* is 16.1 ± 0.5 kcal/mole and ΔS^* has the value −14.2 ± 1.7 eu calculated at 30° with the rate constant having the units l. mole^{-1} sec^{-1}. The errors reported in ΔH^* and ΔS^* were calculated from the standard error of the regression coefficient of a plot of ln k_{obsd} *vs.* 1/*T*°K.

Table II. Rate Constants for Hydrolysis of 2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane at Various Temperatures in 0.100 *M* HCl

Temp, °C	k_{obsd}, min^{-1}
20	0.0275
30	0.0739
40	0.197
50	0.384

The hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane was studied as a function of increasing concentrations of HCl. The rate constants are reported in Table III. It can be seen in Figure 3

Table III. Rate Constants for Hydrolysis of 2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in HCl Solutions at 30°

HCl concn, *M*	k_{obsd}, min^{-1}
1.0	0.0429
1.22	0.0586
1.84	0.121
2.45	0.226
3.65	0.525
4.90	1.11
5.51	1.41

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(8) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston Mass., 1955, p 284.

(9) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

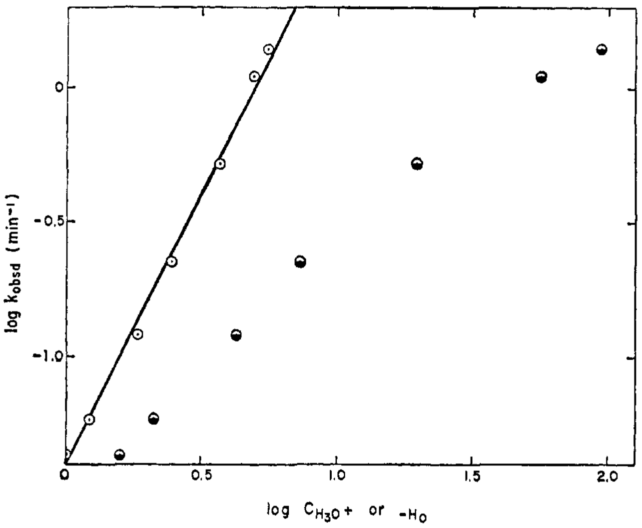

Figure 3. Plot of log k_{obsd} for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane at 30° *vs.* the logarithms of HCl concentration (log $C_{H_3O^+}$), ⊙, or $-H_0$, ◒.

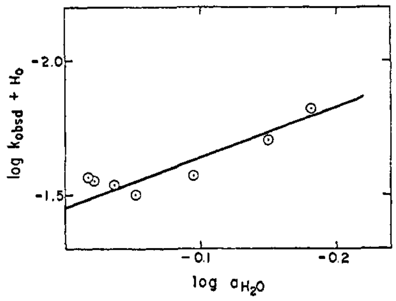

Figure 4. Plot of log k_{obsd} + H_0 for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane at 30° *vs.* the logarithms of the activity of water.

that the logarithms of the rate constants are proportional to the logarithms of the stoichiometric acid concentration while curvature is obtained in a plot *vs.* $-H_0$. It will be noted, however, that the slope of the plot of log k_{obsd} *vs.* log $C_{H_3O^+}$ is 2.0 rather than 1.0 as might be expected. In Figure 4 is presented a plot of log k_{obsd} + H_0 *vs.* the logarithms of the activity of water in these solutions.[11] A straight line through these points has a slope, *w*,[11] of +1.9.

The rate of hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane was found to be catalyzed by increasing concentrations of formate buffer at 40°. The observed catalysis is weak, but it is well outside the range of possible experimental error. The observed rate constants obtained at two pH values are plotted in Figure 5 *vs.* total formate concentration ($HCOOH + HCOO^-$). The slopes of the lines increase as pH is decreased showing a kinetic dependence upon the concentration of the acid species. The rate constant for the general acid catalyzed reaction is 0.0026 l. mole^{-1} min^{-1}.

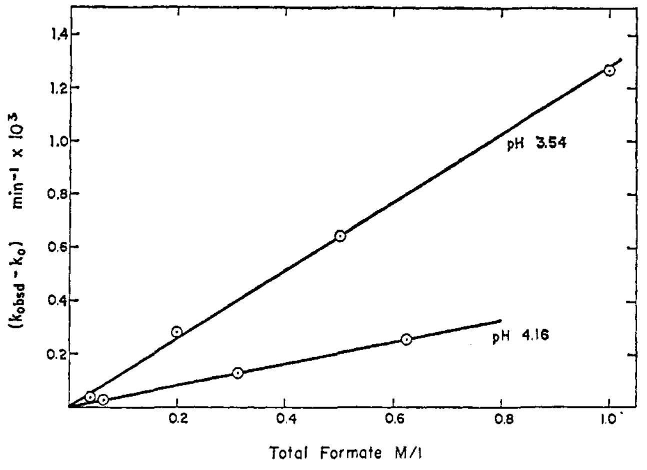

Figure 5. Plot of ($k_{obsd} - k_0$) for hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane *vs.* total formate concentration ($HCOOH + HCOO^-$) at 40° and μ = 0.5 *M*. The values of the intercept rate constants, k_0, are 0.00407 min^{-1} at pH 3.54 and 0.0010 min^{-1} at pH 4.16.

Discussion

Mechanisms designated A2 involving attack of solvent on the protonated substrate have been postulated in the hydrolysis of several different types of acetals.[5,12,13] In none of these cases, however, was more than one criteria of mechanism applied, and in each case some doubt exists as to the correctness of the assigned mechanism. Thus Kreevoy and Taft[14] have pointed out that the data of Kaeding and Andrews[12] on the hydrolysis of the diethyl ketal of *p*-nitrobenzophenone in ethanol–water mixtures is also compatible with an A1 mechanism. Kwart and Price[13] suggested that the hydrolysis of 2,2-diphenyl-1,3-dioxolane was A1, and a series of similar 2,2-disubstituted 1,3-dioxolanes all have D_2O solvent isotope effects characteristic of an A1 mechanism.[15] Capon and Thacker[5] postulated on the basis of slightly negative values of ΔS^* that furanoside hydrolysis has an A2 mechanism, but it has been found that the hydrolysis of 2-ethoxytetrahydrofuran, a model furanoside, is characterized by a ΔS^* of +3.3 eu[16] which although considerably more negative than that for hydrolysis of 2-ethoxytetrahydropyran is still in the range normally associated with an A1 mechanism.[17] In addition, a D_2O solvent isotope effect characteristic of an A1 reaction was found.[16]

In the present study several mechanistic criteria have been applied to the hydrolysis of 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes and some point strongly to incursion of an A2 mechanism in the hydrolysis of these compounds. A ratio of k_D/k_H of 2.4 was found for the hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane. Ratios of k_D/k_H in the range 1.3–1.7 are normally associated with A2 reactions while ratios greater than this can be considered as indicative of an A1 mechanism.[18] The D_2O solvent isotope effects found in A1 acetal hydrolysis reactions vary generally from approximately 2.7 to 3.0.[1,15] Thus the value of k_D/k_H of 2.4 found in the present study is considerably less than is usually found for A1 acetal hydrolysis.

The value of ΔS^* for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane, −14.2 eu, is not as highly

[11] J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4978 (1961).

[12] W. W. Kaeding and L. J. Andrews, *ibid.*, **74**, 6189 (1952).

[13] H. Kwart and M. B. Price, *ibid.*, **82**, 5123 (1960).

[14] M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, **77**, 3146 (1955).

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[16] T. H. Fife, unpublished data.

[17] F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).

[18] F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

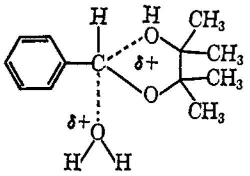
negative as one might expect to find in an A2 reaction where values in excess of −15 eu are commonly observed[17] but is still more in accord with a mechanism involving solvent participation than with a unimolecular mechanism. The A1 cleavage of the 1,3-dioxolane ring system is characterized by ΔS^* values 8–10 eu more negative than for hydrolysis of the analogous open-chain diethyl acetals,[1,15] but the ΔS^* for hydrolysis of 2-phenyl-1,3-dioxolane in 50% dioxane–H_2O is still only −8.9 eu,[1] so the value observed in the case of tetramethylethylene glycol acetal is much more negative.

The logarithms of the rate constants for hydrolysis of the series of 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes are a linear function of σ with a ρ of −2.0 in contrast to the upward curvature obtained in the plot of log k_H for hydrolysis of the diethyl acetals and ethylene glycol acetals of substituted benzaldehydes *vs.* σ.[1] Employing *meta*-substituted benzaldehyde diethyl acetals ρ was found to be −3.35,[1] so the value obtained in the present study is much more positive. Electron withdrawal should hinder protonation, make departure of the leaving group more difficult, and destabilize a carbonium ion intermediate in an A1 reaction. Nucleophilic attack by solvent, however, should be facilitated by electron withdrawal. Solvent participation therefore should result in a less negative value of ρ. The linear relationship with σ shows there to be much less carbonium ion character in the transition state for hydrolysis of the tetramethylethylene glycol acetals than in the case of the diethyl acetals or ethylene glycol acetals since it is undoubtedly resonance interaction of the *p*-methoxy group with the incipient carbonium ion in the transition state that causes positive deviation in the latter series of compounds.

A classic method for distinguishing between A1 and A2 mechanisms has been to determine whether the observed rate constants are proportional to the stoichiometric acid concentration or to h_0.[19] Bearing in mind the criticisms that have been made of this method and the possible exceptions that have been found,[20] the linear relationship between log k_{obsd} and log acid concentration $C_{H_3O^+}$ would strongly suggest an A2 mechanism for the hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane. The w value of +1.9 is also in the range associated with solvent participation in the Bunnett classification,[11] water acting as a nucleophile. This w value is, of course, only approximate because of the scatter of points about the line in Figure 4, but there is no question that the slope is quite positive for hydrolysis in the more concentrated acid solutions. The positive value of w can be contrasted with the highly negative values that are generally observed for acetal hydrolysis.[11]

A complication in the interpretation of the data obtained in moderately concentrated HCl is the high slope of 2.0 found in the plot of log k_{obsd} *vs.* log $C_{H_3O^+}$. Slopes considerably greater than unity have been observed in plots of log k *vs.* $-H_0$ for acetal hydrolysis in HCl solutions although such plots are linear.[14,21] Possible explanations for this behavior are salt effects on the activity coefficients[19,22] or nucleophilic participation by chloride ion.[11] The best straight line through the present H_0 plot has a slope of 0.84.

Each piece of evidence cited in the present study contains some ambiguity, but taken together a consistent picture is presented of a reaction in which water is participating as a nucleophile but in which either the bond being formed in the transition state is not well developed or in which an A1 mechanism is still making some contribution to the observed rate.



If water can participate in the reaction it is reasonable that buffer catalysis might also be observed. The catalysis observed in formate buffer (Figure 5) is small but certainly real. This then is the first reported example of buffer participation in acetal hydrolysis. No rate enhancements were observed for hydrolysis of benzaldehyde diethyl acetal in the same series of buffers at 25°. Thus the observed catalysis is very likely not due to medium effects caused by increasing buffer concentrations.

The different mechanisms observed in the present study can be seen because the normally favored A1 mechanism has been made unfavorable by the increased steric bulk. The rates of hydrolysis of the tetramethylethylene glycol acetals are many times slower than those of the corresponding ethylene glycol acetals even though solvent and buffer are involved. It would appear, however, that glycosidic enzymes probably function by extremely facile general acid–general base mechanisms in which the participating groups catalyze the reactions near neutrality at rates much greater than can be observed in simple acid-catalyzed reactions at the same pH values. Before mechanisms of this type can be understood it must, of course, be demonstrated that they are indeed chemically feasible, and the structural features which promote their utilization must be determined. A step in that direction has now been taken.

Acknowledgment. This work was supported by the National Institutes of Health Research Grant GM-10316-04. The author also acknowledges the able technical assistance of Miss Lily Hagopian.

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