

## Cyclic Esters of Inorganic Acids. I.

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The mechanisms of reaction of carboxylic esters have received great attention for many years. However, only within the past few years have systematic investigations been made of the mechanisms of reactions of other types of esters. Phosphate esters are of great interest because of their biochemical importance in metabolic processes involving ribonucleic acids, sugars and other hydroxylic compounds. Sulfate esters are rather common in living organisms, the most important esters being those of the mucopolysaccharides. Phenol detoxication in animal tissues is performed by sulfate esterification followed by urinary excretion.

The role of five-membered cyclic phosphate esters as intermediates in the hydrolysis of ribonucleic acids has recently been demonstrated.<sup>5</sup> The cyclic esters are readily hydrolyzed to the open-chain monoesters of phosphoric acid.<sup>6,7</sup> However, most diesters of phosphoric acid are relatively resistant to hydrolytic cleavage.<sup>10</sup>

The examination of the hydrolysis of potassium ethylene phosphate has been made by Westheimer.<sup>17</sup> The rate equation was first order in ester and first order in hydroxide ion. A positive salt effect was found and is expected for a reaction between two negatively charged ions. It was found that the five-membered ring ester is about  $10^7$  times more reactive than potassium dimethyl phosphate (Table I). This corresponds to difference in free energies of activation of about 9 kcal. The heat of alkaline saponification ( $\Delta H$ ) of the cyclic ester methyl ethylene phosphate<sup>13</sup> is  $-29.5$  kcal/mole at  $30^\circ\text{C}$ . The open chain dimethyl  $\beta$ -hydroxyethyl phosphate has a  $\Delta H$  of  $-21.9$  kcal. Thus closure of the ring introduces kinetic acceleration of 8-9 kcal/mole and results in a thermodynamic strain of  $7.6 \pm 1.2$  kcal (Table I).

The sulfate esters have been studied by Westheimer and coworkers.<sup>15</sup> In basic solution there is little kinetic acceleration upon closing the five-membered ring. However, the heat of hydrolysis increases by  $7.7 \pm 1.0$  kcal. In base, the cleavages are usually C-O except for 15% of S-O cleavage in ethylene sulfate. In acidic solution only S-O cleavage is observed and the rates are nearly independent of the ring size.

The sulfite esters have been studied both by Bunton and coworkers<sup>8,9,10</sup> and by the present author. The present investigation has measured the very rapid rates of alkaline hydrolysis of ethylene sulfite and obtained more accurate data on dimethyl sulfite. The heats of solution and heats of hydrolysis have also been measured. The position of bond cleavage is in each case S-O.<sup>8,9,10</sup> The data have been presented in Tables I, II, and III.

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1. The author wishes to thank Robert Wall and Thomas Kaiser for the calorimetric determinations. The invaluable discussions of this material with Prof. Frank Westheimer of Harvard is also gratefully appreciated. The initial phases of this work were begun under financial support from the National Institute of Health. The conclusion of the present study was made with support from The Walter Reed Army Institute of Research. The financial support of these organizations is gratefully appreciated.

TABLE I  
 Basic Hydrolysis of Esters

A. Phosphates		$T^{\circ}C$	$k_2 \text{ } l m^{-1} \text{ } sec^{-1}$	$\Delta H^{\ddagger}$ a	$\Delta S^{\ddagger}$ b	$\Delta H$ c
ethylene phosphate	d	25	$4.6 \times 10^{-4}$			
dimethyl phosphate	d	25	$3.0 \times 10^{-11}$			
		115	$2.2 \times 10^{-6}$	27.5	-14	
		125	$6.1 \times 10^{-6}$			
trimethyl phosphate	e	0.4	$1.24 \times 10^{-5}$	15.2	-26	$-20 \pm 2$
		35	$3.39 \times 10^{-4}$			
dimethyl $\beta$ -hydroxyethyl phosphate	f	30				$-21.9 \pm 0.4$
methyl ethylene phosphate		30				$-29.5 \pm 0.6$
B. Sulfates g		$T^{\circ}C$	$k_2 \text{ } l m^{-1} \text{ } sec^{-1}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H$
ethylene		0.4	$1.44 \times 10^{-2}$	16	-9	
		9.97	$4.03 \times 10^{-2}$			
		30				$-35.9 \pm 0.7$
trimethylene		30	$2.73 \times 10^{-3}$			
		40	$6.23 \times 10^{-3}$	15	-21	
dimethyl		9.97	$2.14 \times 10^{-3}$	18	-8.5	
		30	$1.60 \times 10^{-2}$			$-28.2 \pm 0.3$
C. Sulfites						
ethylene		0	28			
		25	104	7.9	-23	$-33.5 \pm 0.5$
trimethylene	h	0	$8.0 \times 10^{-2}$			
		25	$5.0 \times 10^{-1}$	11.3	-8	
dimethyl		0	$2.33 \times 10^{-2}$			
		25	$1.68 \times 10^{-1}$	12.2	-21	$-32.8 \pm 0.6$

a—kcal/mole b—cal/mole degree c—kcal/mole d—Ref. 17 e—Ref. 3 f—Ref. 13 g—Ref. 15 h—Ref. 8, 9, 10

The problem can be stated by comparing the open chain derivative to the five-membered ring compound of both acid and basic solutions. The phosphates show tremendous kinetic acceleration and large thermodynamic strain. The sulfites show kinetic acceleration in basic solution but absolutely no thermodynamic strain. In acidic solution the reactivity pattern is reversed and the open chain compound is now reacting twenty times faster but there is still no thermodynamic strain.

The data have been interpreted in several manners. Westheimer has suggested the possible importance of 1,3-nonbonded interaction between the ring oxygen atoms.<sup>10</sup> This has been further developed by Bunton.<sup>9</sup> Westheimer also suggested the possible importance of the C-O-P dihedral

TABLE II  
Acidic Hydrolysis

<i>B. Sulfates</i> <sup>d</sup>	<i>T</i> <sup>o</sup> <i>C</i>	<i>k</i>	$\Delta H^{\ddagger}$ <sup>a</sup>	$\Delta S^{\ddagger}$ <sup>b</sup>	$\Delta H$ <sup>c</sup>
ethylene	0.4	$1.75 \times 10^{-5}$ <sup>e</sup>			
	9.97	$7.24 \times 10^{-5}$ <sup>e</sup>	20.3	-5.4	
	30.0	$7.6 \times 10^{-4}$ <sup>e</sup>			
trimethylene	30.0	$6.28 \times 10^{-5}$ <sup>e</sup>			
	40.0	$1.86 \times 10^{-4}$ <sup>e</sup>	20	-12	
dimethyl	9.97	$2.2 \times 10^{-5}$ <sup>e</sup>			
	30	$1.86 \times 10^{-4}$ <sup>e</sup>	23	1.3	
<i>C. Sulfites</i>					
ethylene	0	$4.1 \times 10^{-7}$ <sup>f</sup>			
	25	$1.01 \times 10^{-5}$ <sup>f</sup>	20.2	-16	
	45 <sup>g</sup>	$7.5 \times 10^{-5}$ <sup>f</sup>			
	75 <sup>g</sup>	$1.27 \times 10^{-4}$ <sup>f</sup>			
trimethylene <sup>g</sup>	35	$1.41 \times 10^{-5}$			
	60	$1.57 \times 10^{-4}$ <sup>f</sup>	20.2	-13	
diethyl <sup>g</sup>	0	$1.98 \times 10^{-3}$	20.3	-8.2	
	25	$3.36 \times 10^{-3}$			

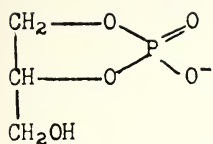
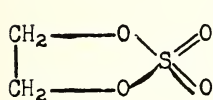
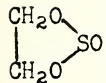
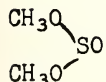
a—kcal/mole b—cal/mole degree c—kcal/mole, calculated from basic reaction with heat of neutralization added d—Ref. 15 e—First order rate constant, independent of  $[H^+]$ , units  $sec^{-1}$  f—Second order rate constant, rate =  $k_2 [Ester] [H^+]$ , units  $lm^{-1} sec^{-1}$ . g—Ref. 8, 9, 10.

angle.<sup>17</sup> The first of these considerations has been examined in detail using the methods of molecular quantum mechanics. The model chosen for study is a two electron atom approaching another two electron atom. Slater nodeless AO orbitals have been used for this homopolar LCAO MO diatomic molecule. The screening factor has been kept constant. The energy difference between the ( $\Psi_a - \Psi_b$ ) state and the ( $\Psi_a + \Psi_b$ ) state has been used as an estimate of the repulsion forces. The data have been presented in Figs. 1 and 2.

Unfortunately, the bond angles and distances of these molecules are not known. It is known that ethylene sulfite is not planar. The NMR spectrum demonstrates that two of the four hydrogens are not equivalent with the others. At least one heavy atom is out of the plane of the ring. Indeed this is to be expected from sulfites as three-bonded sulfur forms a shallow pyramid.<sup>1</sup>

The calculations indicate that 1,3-nonbonded interactions may be of the order of magnitude to give rise to the effects observed. However, the effect is *not due entirely* to interaction between the two oxygen in the ring. Otherwise analogous reactivity patterns ought to be observed in the phosphates, phosphites, sulfates, sulfites, and carbonates. Most likely these interactions determine the dihedral angle. It is suggested that the presence of another oxygen atom about the sulfur or phosphorus atom gives rise to the thermodynamic strain while the kinetic acceleration is

TABLE III  
Position of Bond Cleavage in Base

	P-O	Ref. 3	
$(\text{CH}_3\text{O})_3\text{PO}$	P-O	$(\text{S}_{\text{N}}2(\text{P}))$	Ref. 3
	C-O	85%	Ref. 15
	S-O	15%	
$(\text{CH}_3\text{O})_2\text{SO}_2$	C-O	100%	Ref. 15
	S-O	Ref. 8	
	S-O	Ref. 19	

only observed if the nucleophilic attack is on the sulfur or phosphorus rather than on the carbon atom.

Detailed kinetic, thermodynamic and  $\text{O}^{18}$  experiments are currently in progress on phosphite esters. The results will be reported elsewhere.

### Experimental

#### Materials.

*Ethylene sulfite* was prepared in high yield from ethylene glycol and thionyl chloride in the manner described by Carlson and Cretcher.<sup>11</sup> The material was purified by repeated vacuum distillations, b. p. 85.0 – 85.6° at 50 mm, reported b. p. 86 – 88° at 52 mm.

*Methyl sulfite* was prepared from methanol and thionyl chloride, b. p. 126° at 758 mm.

The buffer solutions<sup>12</sup> were prepared from reagent grade salts. Conductivity water was used to prepare the solutions which were protected from atmospheric contamination.

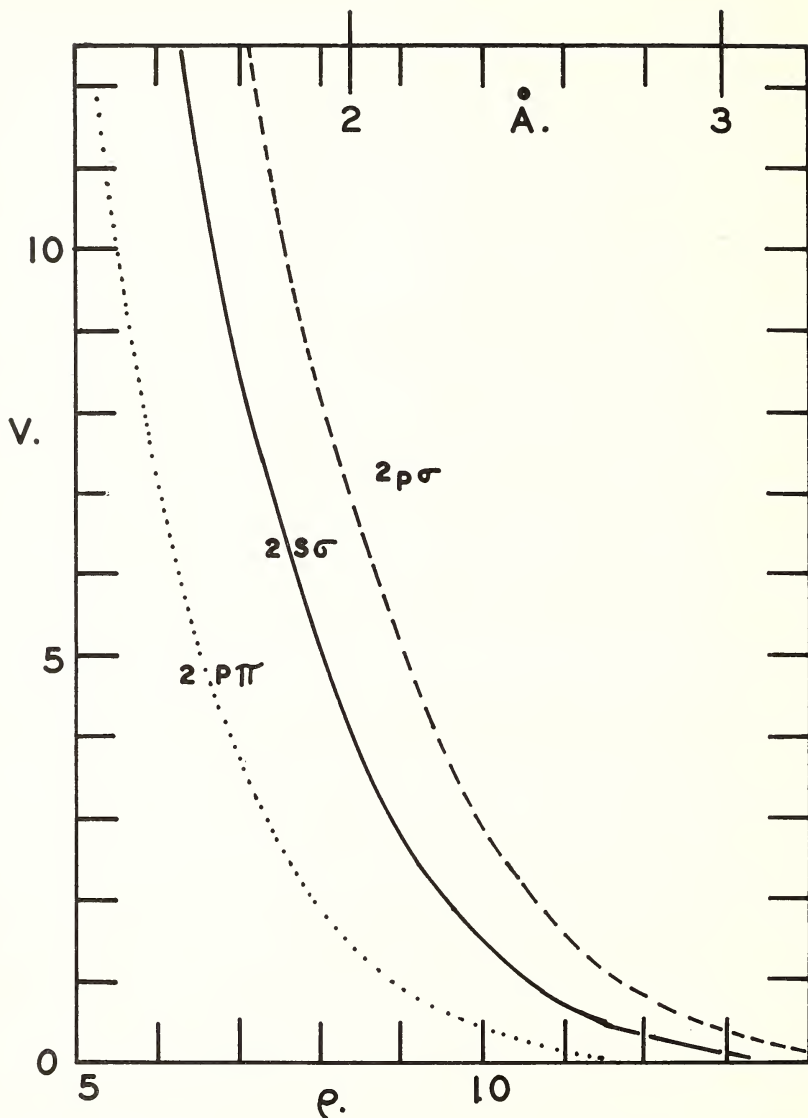


Fig. 1. Non bonded repulsion  $V$ , in kcal/mole versus distance between centers in Å for a four electron homopolar diatomic system. Calculated by the LCAO MO method.

#### Kinetic Methods.

During the basic hydrolysis of I or II, hydroxide ion is consumed and sulfite or bisulfite ion produced. Therefore, several methods have been used to study the reaction. All solutions were oxygen free and protected by pure nitrogen.

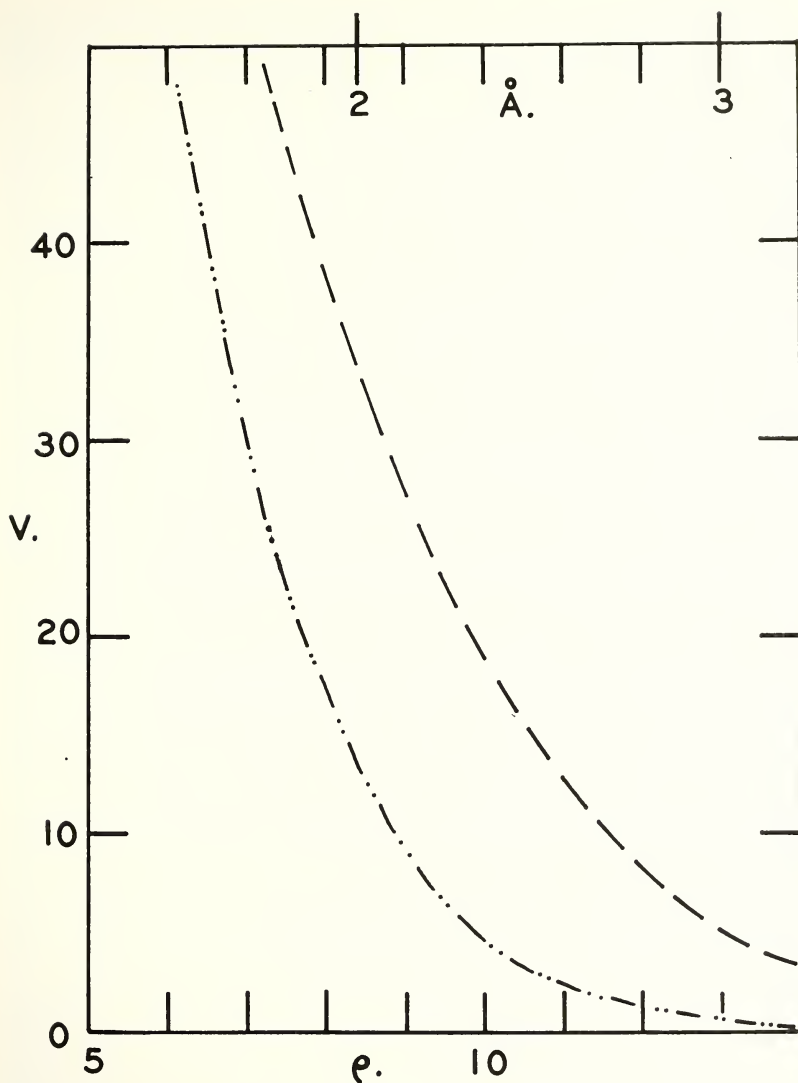


Fig. 2. Average potential energy  $V$  kcal/mole between two oxygen molecules. Dashed line represents the experimental curve of Amdur. The lower dash-dot line has been calculated using the data of Fig. 1 by a simple LCAO MO method.

The *amperometric method* (Method A) is based upon the electrolytic generation of hydroxide ion at an electrode and then measuring the steady-state hydroxide ion concentration with a pH meter.<sup>18</sup> A measured volume of an oxygen-free solution of ethylene sulfite (about 1 to  $5 \times 10^{-2}$  molar) in aqueous 0.1 molar potassium chloride is placed in a jacketed beaker. Through a large, tight-fitting rubber stopper is passed a centrally located

glass tube allowing nitrogen to be bubbled through the solution. The glass electrode and calomel electrode of a Beckman model G pH meter are placed near one side of the beaker. The generating electrode assembly is placed on the opposite side. The platinum cathode is placed directly into the solution. The anode compartment is constructed from a 10 x 1.5 cm. glass tube covered on one end by a Nepton CR-61 cation exchange membrane<sup>14</sup> cut in a circle. The membrane is slanted slightly to prevent gas bubbles from collecting under the anode and changing the electrode resistance. The glass tube is then filled with a slurry of Dowex 50, 50-100 mesh in 0.10 molar potassium chloride. A platinum wire inserted into this slurry forms the complete anode. The generating electrodes are very firmly mounted as this detail and a slanting membrane give good electrode stability. The cation ion resin and membrane thus prevent the diffusion of hydrogen ions into the solution. After each electrolysis the resins are reconverted into the potassium salt form. A voltage of one to sixteen volts D.C. is applied across the generating electrodes. An accurate D.C. milliammeter in series with the cell measures the current which is between 2 and 40 ma. By adjusting the voltage slightly during electrolysis, a steady state is soon reached where both the pH and current remain constant. When a new voltage is selected a new pair of steady state values are recorded, yielding another estimate of the rate of reaction. The apparatus was checked at 25° by measuring the rate of ionization of nitroethane:<sup>5,18,20</sup>  $k_2$  reported.

The *titrametric method* at static pH (method TS) for studying the reaction has been performed in the same jacketed beaker. The solution of ester (about  $10^{-2}$  molar) is prepared in dilute buffer solution of a specific pH. The pH is then maintained constant by the addition of hydroxide from a micro buret driven by a "pH Stat." Two equivalents of base per mole of ester are consumed in a strictly first order reaction.

The *spectrophotometric-iodometric method* (method SI) involves the addition of a very dilute  $KI_3$  ( $10^{-5}$  molar) to buffer solutions (pH 5.8-7.4) containing the ester. Only sulfite or bisulfite ion react with iodine and this reaction is very fast. Therefore, the rate of disappearance of the  $I_3^-$  color measured at 353  $m\mu$  in a Beckman DU spectrophotometer equals the rate of production of sulfur dioxide. As the ester concentration is  $10^{-3}$  to  $10^{-1}$  molar and the solution buffered, the disappearance of iodine occurs in a zero order reaction. The extinction coefficient of  $KI_3$  has been found to be  $2.60 \pm 0.06 \times 10^4$ , in agreement with the value of  $2.64 \times 10^4$  reported by Autrey and Connick<sup>2</sup> at 353  $m\mu$  in water. In neutral or mildly acidic solution,  $I_3^-$  is very stable. However, as the pH is raised about 9, hypoiodite is formed, with a decrease in the optical density of the solution.

The *indicator method* (method I) involves the addition of a pH indicator which changes color as a function of pH. Dilute solutions of ester ( $10^{-2}$  to  $10^{-3}$  molar) and sodium hydroxide ( $10^{-3}$  molar) are rapidly mixed and the time of the color change of the indicator is measured visually with a stop watch. This time then gives a two-point kinetic curve: the initial time,  $t = 0$ , with known concentrations of reactants and the time,  $t$ , of the color change which occurs at a known pH. Indicators which are useful for this type of kinetic experiments are phenolphthalein ( $pK = 9.7$ ),

*m*-cresol purple ( $pK = 8.3$ ) and cresol red ( $pK = 8.1$ ). If a rapid mixer is used and if a spectrophotometer is fitted to rapidly record the color change, the method becomes much more general and a useful tool to study rapid reactions with a pH change.

The more conventional technique was a *titrametric method* (method *T*) in deoxygenated aqueous buffer solutions based on the rate of appearance of sulfite ion. Aliquots of the solution were run into excess acidic  $KI_3$  and back titrated with standard thiosulfate. This method has been used to study the alkaline hydrolysis of trimethylene sulfite.

#### Product Study.

The products of the basis hydrolysis of ethylene sulfite in sodium hydroxide are ethylene glycol and sodium sulfite. These compounds were determined to be the only products within 1-2% uncertainties of the analytical procedures of titration, spectral analysis and isolation. The pH profiles of solutions only partly hydrolyzed as determined by electrometric titration with dilute perchloric acid showed breaks for neutralization of the hydroxide ion, the sulfite and then the bisulfite ion. Derivative curves showed no other component present to within 1-2% uncertainty. Thus no evidence has been obtained for the accumulation of mono esters,  $ROSO_2H$  or  $ROSO_2^-$ .

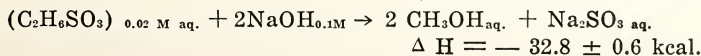
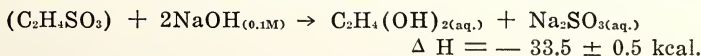
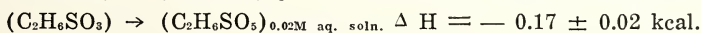
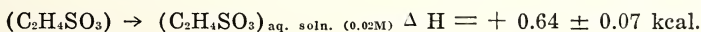
Likewise the sole products of hydrolysis of dimethyl sulfite are methanol and sodium sulfite.

#### Temperature Control.

For methods *A* and *TS* water from a constant temperature bath ( $\pm 0.01^\circ$ ) was circulated rapidly through the jacketed beaker. For method *SI* a Westheimer brass jacket<sup>4</sup> was used as the cell compartment of the DU spectrophotometer. Circulating water maintained the temperature to  $\pm 0.02$ . All temperatures were referred to NBS certified thermometers. Method *I* was studied in an ice bath at  $\pm 0.005^\circ$ . Method *T* was studied in Pyrex volumetric flasks, thermostated under  $N_2$  in water baths  $\pm 0.01^\circ$ .

#### Thermochemistry.

The heats of hydrolysis were determined in a calorimeter constructed from a small Dewar flask and Beckman thermometer within a submergable copper can. The calorimeter had a thermal leak coefficient of  $0.0043^\circ/\text{min}$ . Calibration was performed using the heat of dilution of sulfuric acid and electrical measurements. The reproducibility was  $\pm 1.5\%$ . An ampule of about 0.1 gram of the ester was crushed under 50.00 ml of 0.1 N sodium hydroxide at  $30.00^\circ$ . The heat of solution of each ester was measured in pH 7 phosphate buffer (0.1 M) at  $30.0^\circ$ . The results were averaged over several runs.





### Equilibria Studies.

The equilibrium between ethylene sulfite, methanol, dimethyl sulfite and ethylene glycol has been measured using VPC analysis of the materials on a Perkin-Elmer 2 meter, R column at 100°.

### Literature Cited

1. ABRAHAMSON, S. C. 1956. The Stereochemistry of Sub-Group VI B of the Periodic Table. *Quart. Rev.* **10**: 424.
2. AUTREY, A. D., and R. CONNICK. 1951. The Absorption Spectra of  $I_3^-$ ,  $I_3^-$ ,  $I^-$ ,  $IO_3^-$ ,  $S_4O_6^{2-}$  and  $S_2O_3^{2-}$ . Heat of the Reaction  $I_3^- = I_2 + I^-$ . *J. Am. Chem. Soc.* **73**: 1842.
3. BARNARD, P. W. C., *et al.* 1955. The Hydrolysis of Organic Phosphates. *Chem. and Ind.* **1955**: 760.
4. BARTLETT, P. D., and R. E. DAVIS. 1958. Reactions of Element Sulfur. II. The Reaction of Alkali Cyanides with Sulfur, and Some Single-Sulfur Transfer Reactions. *J. Am. Chem. Soc.* **80**: 2513.
5. BELL, R. P., and J. C. CLURIE 1952. *Proc. Roy. Soc. London.* **A212**: 16.
6. BROWN, D. M., and A. R. TODD. 1952. Nucleotides. Part X. Some Observations on the Structure and Chemical Behavior of the Nucleic Acids. *J. Chem. Soc.* **1952**: 52.
7. BROWN, D. M., D. I. MAGRATH, and A. R. TODD. 1952. Nucleotides. Part XII. The Preparation of Cyclic 2' 3' - Phosphates of Adenosine, Cytidine, and Uridine. *J. Chem. Soc.* **1952**: 2708.
8. BUNTON, C. A., *et al.*, 1956. The Mechanisms of Hydrolysis of Cyclic Sulphites. *Chem. and Ind.* **1956**: 490.
9. BUNTON, C. A., *et al.*, 1958. Nucleophilic Displacements in Organic Sulfitcs. Parts I, II, III, and IV. *J. Chem. Soc.* **1958**: 4751, 4754, 4761, 4766.
10. BUNTON, C. A., *et al.*, 1950. Nucleophilic Displacements in Organic Sulfitcs. Part VI. *J. Chem. Soc.* **1960**: 37.
11. CARLSON, W. W., and L. H. CRETCHER. 1947. Hydroxyalkylatrons with Cyclic Alkylene Esters. I. Synthesis of Hydroxyethylapocupreine. *J. Am. Chem. Soc.* **69**: 1953.
12. CLARK, W. M. 1928. The Determination of Hydrogen Ions. 3rd. Edition, Williams and Wilkins. Baltimore.
13. COX, J. R., R. E. WALL, and F. H. WESTHEIMER. 1959. Thermochemical Demonstration of Strain in a Cyclic Phosphate. *Chem. and Ind.* **1959**: 929.
14. IONICS, INC. 152 Sixth Street. Cambridge, Mass.
15. KAISER, T. 1959. Thesis. Harvard.
16. KOSOLAPOFF, G. M. 1950. Organo phosphorous compounds. John Wiley and Sons. New York. Chapter 9.
17. KUMAMOTO, J., J. R. COX, and F. H. WESTHEIMER. 1956. Barium Ethylene Phosphate. *J. Am. Chem. Soc.* **78**: 4858.
18. PEARSON, R. G., and L. H. PIETTE. 1954. A Simple Steady State Method for Obtaining Rates of Rapid Reactions. *J. Am. Chem. Soc.* **76**: 3087.
19. WESTHEIMER, F. H. 1957. Studies of the Solvolysis of Some Phosphate Esters. *Chem. Soc. Special Publ. No. 8*, p. 1.
20. YOUNG, J. A., and R. J. ZETA. 1958. An Amperometric-Kinetic Experiment Emphasizing the Importance of Enor Treatment. *J. Chem. Ed.* **35**: 146.