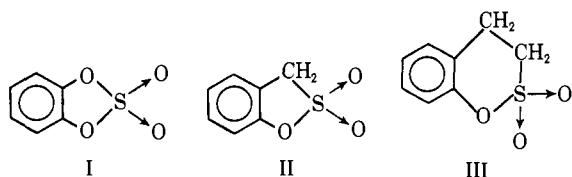# Hydrolysis and Methanolysis of Cyclic Sulfate and Sulfonate Esters in Strongly Basic Media. Correlations of Rate Data with $H_-$ and $H_M$

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Contribution from the Department of Chemistry, University of Chicago, Chicago, Illinois 60637. Received July 26, 1971
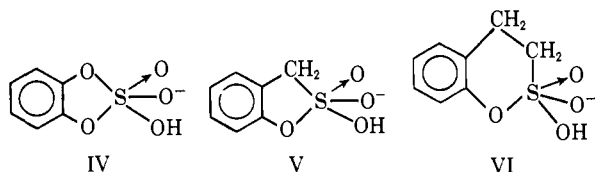
**Abstract:** The hydrolysis and methanolysis of $\beta$-$o$-hydroxyphenylethanesulfonic acid sultone (III), $\gamma$-$o$-hydroxyphenylpropanesulfonic acid sultone (VIII), and biphenylene cyclic sulfate (IX) have been studied in strongly basic media. The observed hydrolysis and methanolysis rate constants showed a first-order dependence on the functions $a_w 10^{H_-}$ and $a_M 10^{H_M}$, respectively. Salt effects were briefly examined for the alkaline hydrolysis of VIII, and added $NaClO_4$ was found to decrease the rate of reaction whereas $Na_2SO_4$ increased it. While the present results certainly do not rule out the possibility that pentacoordinate intermediates in which the attacking nucleophiles are covalently bound to sulfur are formed in the hydrolysis and methanolysis of III, VIII, and IX under basic conditions, they do not require the postulation of such species.

Considerable attention has been focused recently on the hydrolysis of cyclic sulfate and sulfonate esters.[3] The rate constants for the alkaline reactions of the aromatic five-membered cyclic esters catechol cyclic sulfate (I) and $o$-hydroxy-$\alpha$-toluenesulfonic acid sultone (II) are approximately $10^6$–$10^7$ times greater than those for the hydrolysis of their acyclic analogs.[4] These rate enhancements appear to be primarily a result of angle strain in the five-membered rings of I and II; the internal O–S–O bond angle is only 97.1° in I[5] and the corresponding C–S–O bond angle in II is 96.1°.[6] Thus, the alkaline hydrolysis of the aromatic six-membered sultone $\beta$-$o$-hydroxyphenylethanesulfonic acid sultone (III) which has a much larger internal C–S–



O bond angle than does II (101.4°)[6] shows a rate enhancement of only a factor of 10 over that of the open-chain ester phenyl $\alpha$-toluenesulfonate.[7]

The question concerning whether or not pentacoordinate intermediates like IV, V, and VI lie along the



reaction pathway in the alkaline hydrolysis of I, II, and III remains unanswered. No significant exchange into the recovered starting esters was observed when they were isolated after the incomplete hydrolysis of I, II, and III in alkaline solutions containing excess oxygen-18.[8] This does not rule out the possibility that pentacoordinate species are formed irreversibly in these reactions or that such intermediates are formed reversibly but the oxygens external to the ring do not become equilibrated to a significant extent. The Hammett $\rho$ value of 1.23 for the alkaline hydrolysis of 5-substituted 2-hydroxy-$\alpha$-toluenesulfonic acid sultones likewise does not distinguish between mechanisms involving direct displacement by the attacking hydroxide ion and those postulating the formation of reactive intermediates.[9]

A kinetic term second order in hydroxide ion concentration has been found for the alkaline hydrolysis of anilides,[10] and this has been interpreted in terms of the ionization of the tetrahedral intermediates produced by the addition of the hydroxide ions to the carbonyl carbons. Similarly, a pentacoordinate intermediate such as VI might be expected to ionize in basic media to give the labile species VII, and if this occurred the rate
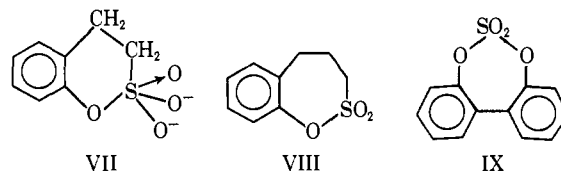


law for the alkaline hydrolysis of III could contain a kinetic term second order in hydroxide ion concentration. However, to the best of our knowledge the observation of a rate law term second order in hydroxide ion has not been recorded yet in the alkaline hydrolysis of sulfate or sulfonate esters. Since this might be due to the low base concentrations used in the previous kinetic studies, we have extended the range of hydroxide

(1) Postdoctoral Fellow of the National Institute of General Medical Sciences.

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(3) E. T. Kaiser, Accounts Chem. Res., 3, 145 (1970).

(4) (a) E. T. Kaiser, I. R. Katz, and T. F. Wulfers, J. Amer. Chem. Soc., 87, 3781 (1965); (b) O. R. Zaborsky and E. T. Kaiser, ibid., 88, 3084 (1966).

(5) F. P. Boer, J. J. Flynn, E. T. Kaiser, O. R. Zaborsky, D. A. Tomalia, A. E. Young, and Y. C. Tong, ibid., 90, 2970 (1968).

(6) E. B. Fleischer, E. T. Kaiser, P. Langford, S. Hawkinson, A. Stone, and R. Dewar, Chem. Commun., 197 (1967).

(7) E. T. Kaiser, K. Kudo, and O. R. Zaborsky, J. Amer. Chem. Soc, 89, 1393 (1967).

(8) E. T. Kaiser and O. R. Zaborsky, ibid., 90, 4626 (1968).

(9) O. R. Zaborsky and E. T. Kaiser, ibid., 92, 860 (1970).

(10) (a) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, and references cited therein; (b) R. M. Pollack and M. L. Bender, J. Amer. Chem. Soc., 92, 7190 (1970); (c) L. D. Kershner and R. L. Schowen, ibid., 93, 2014 (1971).

ion concentrations employed in the hydrolysis of such esters to include strongly basic media.

The rate laws observed for a number of reactions in strongly basic solution have been correlated with the acidity function $H_-$.[11] Although detailed mechanistic interpretations based on acidity functions may be questionable, it appears that their use in determining the order of a reaction with respect to hydroxide ion is valid.[12] In the present paper we report a kinetic study of the hydrolysis of the aromatic six- and seven-membered sultones, III and VIII, and the aromatic seven-membered cyclic sulfate, IX, in strongly basic solutions. Their methanolysis in anhydrous methanol was also examined.

## Experimental Section

**Syntheses.** β-o-Hydroxyphenylethanesulfonic acid sultone (III) was prepared in connection with an earlier study.[7]

γ-o-Hydroxyphenylpropanesulfonic acid sultone (VIII) was prepared by the cyclization of sodium γ-o-hydroxyphenylpropanesulfonate. The latter sodium salt was synthesized according to the literature procedure.[13] To 35.0 g of sodium γ-o-hydroxyphenylpropanesulfonate was added 260 g of phosphorus oxychloride. A slightly exothermic reaction occurred, and then the reaction mixture was heated slowly to 125°. HCl fumes started to evolve at 110°. The mixture was refluxed at 125° for 2 hr, and the excess POCl₃ was removed by distillation. The cream-colored residue was allowed to cool, ground, and then transferred slowly into ice-water. The white material resulting was left in contact with the water for 4 hr, suction-filtered, thoroughly washed with cold water, and finally air-dried.[4b] Crystallization from ethanol gave 21.1 g (72.4% yield) of pure, white crystals, mp 132–133° (lit.[13] 132°). The nmr (CDCl₃), infrared, and mass spectra observed for this compound were all consistent with the sultone structure.

*Anal.* Calcd for C₉H₁₀O₃S: C, 54.54; H, 5.05; S, 16.15. Found: C, 54.41; H, 5.10; S, 15.97.

**Biphenyl ne cyclic sulfate (IX)** was prepared in low yield from the reaction of sulfuryl chloride with o,o'-biphenol. An ether solution of o,o'-diphenol (9.3 g) was added in a dropwise manner simultaneously with an ether solution of sulfuryl chloride (4 ml) to a flask containing 150 ml of ether and 11 ml of pyridine which was mechanically stirred at room temperature. After a few hours, the ether portion of the reaction mixture was extracted with dilute HCl. The aqueous layer was used to dissolve the solid remaining in the reaction flask and then extracted with ether. The combined ether portions were dried with MgSO₄ and the ether was removed by rotary evaporation. The liquid residue was distilled, giving a large fraction of o,o'-biphenol, bp 115–140° (0.03 mm), and a small amount of material which had bp 145–155° (0.03 mm). The higher boiling fraction was chromatographed on alumina (15% Et₂O–petroleum ether) giving a white material, mp 122–123°. Infrared and mass spectra were consistent with the assigned structure.

*Anal.* Calcd for C₁₂H₈O₄S: C, 58.06; H, 3.25; S, 12.91. Found: C, 57.67; H, 3.11; S, 13.05.

**Solvents.** Methanol was distilled from Mg prior to use.[14] Dimethyl sulfoxide was distilled from CaH₂ under reduced pressure.

**Kinetics.** The wavelengths at which hydrolysis was followed were 290 nm for III and VIII and 306 nm for IX. For the methanolysis reactions, the corresponding wavelengths were 290, 291, and 305 nm. These are the λ_max values for the uv absorption due to the hydrolysis products. A thermostated Gilford instrument was employed. In the case of the slower runs the reaction mixtures were thermostated in an external bath; aliquots were taken periodically and their optical densities determined. The substrate concentrations ranged between $1.5 \times 10^{-4}$ and $2.6 \times 10^{-4}$ M. Base was always present in large excess in the reaction solutions assuring pseudo-first-order conditions. The reactions of the sulfonates were initiated by introducing with microliter pipets small amounts of a DMSO stock solution of substrate into the thermostated basic solutions, re-

sulting in a solution containing about 1% DMSO. However, because of the low aqueous solubility of the aromatic seven-membered cyclic sulfate, IX, the basic solutions employed for its hydrolysis contained 20% DMSO.

Hydrolysis of the six-membered sultone, III, was shown previously to give β-o-hydroxyphenylethanesulfonate as the product.[7,8] Hydrolysis of the seven-membered sultone, VIII, was demonstrated to result in formation of γ-o-hydroxyphenylpropanesulfonate by the comparison of the uv spectrum at the end of the reaction with that for an authentic sample of sodium γ-o-hydroxyphenylpropanesulfonate in basic solution. By analogy to the hydrolysis of catechol cyclic sulfate, whose half-ester is stable to 5 M NaOH at 90° for 12 hr,[8] hydrolysis of the seven-membered cyclic sulfate, IX, is assumed to give its corresponding half-ester product.

## Results and Discussion

For hydroxide ion concentrations less than 3 M the observed rate constants for the alkaline hydrolysis of the cyclic esters III, VIII, and IX fit the expression given in eq 1. This equation is closely related to that found in the alkaline hydrolysis of anilides,[10] a reaction which appears to involve the production of transient tetrahedral intermediates. Our results then in alkaline solutions containing less than 3 M hydroxide ion would at first glance seem to be consistent with mechanisms for the reactions of the cyclic esters involving the intermediacy of ionizable pentacoordinate species like VI, produced by the addition of hydroxide ion to the sulfonyl sulfur atoms. A reasonable mechanism according to this hypothesis for the hydrolysis of III, for instance, is illustrated in eq 2.

$$k_{obsd} = k_1[OH^-] + k_2[OH^-]^2 \qquad (1)$$

$$(2)$$
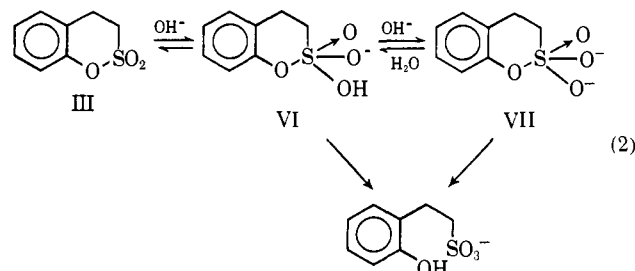
In Figures 1 and 2 the observed rate constants for the basic hydrolysis of III and VIII divided by the hydroxide ion concentration are plotted against hydroxide ion concentration. Clearly, when the hydroxide ion concentration is greater than 3 M, the observed rate constants are larger than would be predicted from eq 1. These results indicate that either the hydroxide ion concentration is not the appropriate parameter to use in analyzing our rate data or that the explanation for our findings is more complicated than would be implied by a mechanism such as that of eq 2.

As discussed earlier in this paper, acidity functions have been employed in a number of studies[11] to determine the orders of reactions with respect to hydroxide ion. For example, the rates of an aromatic nucleophilic substitution reaction, the displacement by hydroxide ion of a nitro group in 2,4-dinitroanisole, have been correlated with the $J_-$ acidity function of the very basic media used.[12] The relationship between the pseudo-first-order rate constants observed, $k_{obsd}$, and the acidity function $J_-$ was postulated to be given by eq 3.[12] Because suitable measurements of the $J_-$ function were not available, the approximate eq 4[15] was substituted

(11) C. H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970.

(12) C. H. Rochester, *Trans. Faraday Soc.*, **59**, 2826 (1963).

(13) Henkel & Cie, G.m.b.H. (by K. J. Gardenier), German Patent 1,197,447; *Chem. Abstr.*, **63**, 14766e (1965).

(14) F. Reverdin, "Organic Synthesis, Collect. Vol. I," Wiley, New York, N. Y., 1932, p 220.
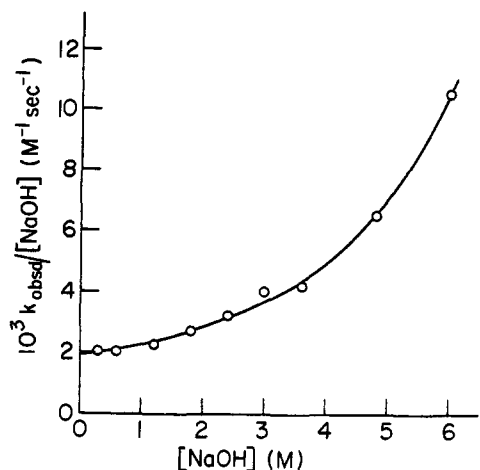
(15) R. Stewart and J. R. O'Donnell, *J. Amer. Chem. Soc.*, **84**, 493 (1962).

Figure 1. Rate constants observed at 25° for the alkaline hydrolysis of $\beta$-o-hydroxyphenylethanesulfonic acid sultone (III) (2.15 × $10^{-4}$ M, 1% DMSO), plotted in terms of hydroxide ion concentrations.



Figure 3. Dependence on $H_-$ of the observed rate constants in the alkaline hydrolysis of $\beta$-o-hydroxyphenylethanesulfonic acid sultone (III) (2.15 × $10^{-4}$ M, 1% DMSO) at 25°.
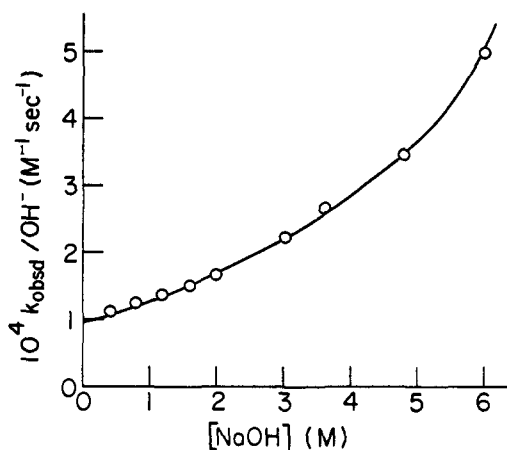


Figure 2. Rate constants observed at 50° for the alkaline hydrolysis of $\gamma$-o-hydroxyphenylpropanesulfonic acid sultone (VIII) (2.14 or 1.94 × $10^{-4}$ M, 1% DMSO), plotted in terms of hydroxide ion concentrations.



Figure 4. Dependence on $H_-$ of the observed rate constants in the alkaline hydrolysis of $\gamma$-o-hydroxyphenylpropanesulfonic acid sultone (VIII) (2.14 or 1.94 × $10^{-4}$ M, 1% DMSO) at 50°.

in eq 3 to give eq 5 which fitted the data very satisfactorily.[16]

$$\log k_{obsd} = \log (kK_w) + J_- \qquad (3)$$

$$J_- = H_- + \log a_w \qquad (4)$$

$$\log k_{obsd} = \log (kK_w) + H_- + \log a_w \qquad (5)$$

In view of the lack of any results in the earlier literature[8] requiring the postulation of reactive intermediates in the alkaline hydrolysis of cyclic sulfate and sulfonate esters, despite the *apparent* high-order dependence on hydroxide ion concentrations of the rates of reactions as discussed above, it seemed reasonable to us to test the possibility that the pseudo-first-order rate constants for the hydrolysis of III, VIII, and IX might be correlated with $H_-$ employing eq 5. If the rates of reactions of these compounds do in fact have a first-order dependence on hydroxide ion, it follows from eq 5 that a plot of $k_{obsd}$ vs. $a_w 10^{H_-}$ should be linear. However, if

(16) As discussed in ref 12, $k$ in eq 3 and 5 may refer either simply to the rate constant for the rate-determining attack of hydroxide ion on 2,4-dinitroanisole or it may be a more complex constant. The subscript w in these equations denotes water.
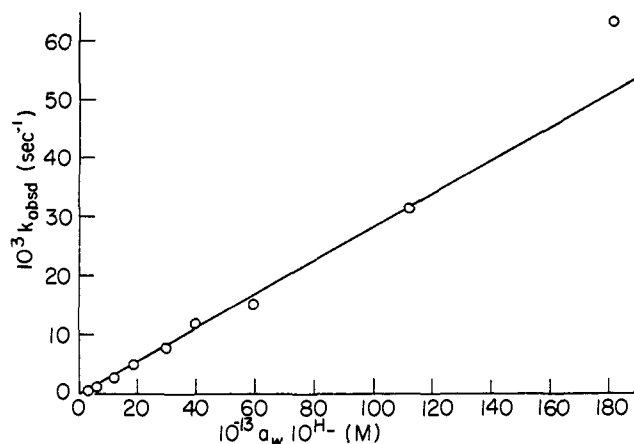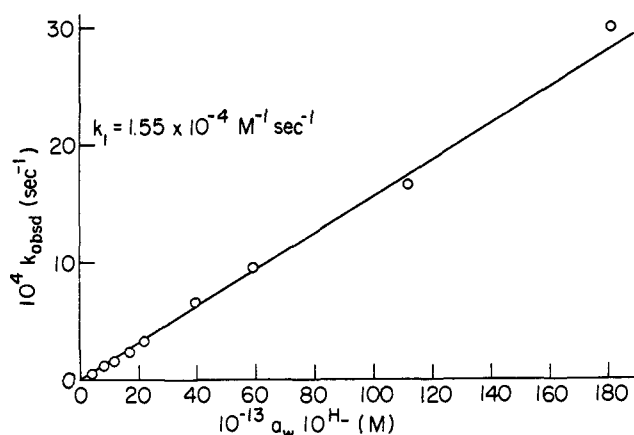
reactive intermediates like VII are formed, then a higher order dependence of $k_{obsd}$ on $a_w 10^{H_-}$ should be found. In our determination of the dependence of the rates of the hydrolysis reactions on hydroxide ion, literature values of $H_-$[17] and $a_w$[18] were employed.

For the methanolysis of the cyclic esters, eq 6, which

$$\log k_{obsd} = \log (kK_M) + H_M + \log a_M \qquad (6)$$

is analogous to eq 5, was tested. Plots of $k_{obsd}$ vs. $a_M 10^{H_M}$ were drawn, where $a_M$ represents the activity of methanol[19] and $H_M$ is the acidity function for the methanol solutions.[20]

The temperatures at which the hydrolysis and methanolysis reactions were carried out in this study often differed from the temperatures at which the acidity functions had been determined. However, since the acidity function dependence of several reactions has been shown to be independent of temperature,[21] the conclusions we draw about the hydroxide ion or

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(18) (a) R. H. Stokes, *J. Amer. Chem. Soc.*, 67, 1689 (1945); (b) G. Akerlof and G. Kegeles, *ibid.*, 62, 620 (1940).
(19) M. F. Terrier, *C. R. Acad. Sci., Ser. C*, 265, 1433 (1967).
(20) Reference 11, p 247.
(21) (a) J. Barband, C. Georgoulis, and R. Schaal, *ibid.*, 260, 2533 (1965); (b) C. H. Rochester, *J. Chem. Soc., B*, 1076 (1967).
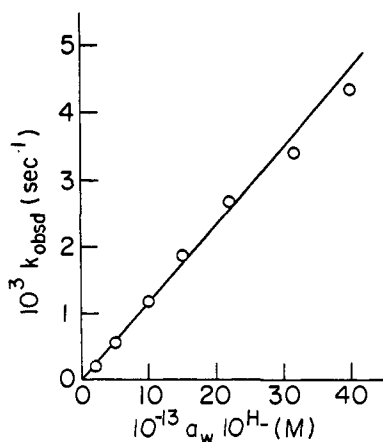
Figure 5. Dependence on $H_-$ of the observed rate constants in the alkaline hydrolysis of biphenylene cyclic sulfate (IX) (1.50 × 10⁻⁴ $M$, 21% DMSO) at 50°.



Figure 6. Effects of added salts on the alkaline hydrolysis of $\gamma$-$o$-hydroxyphenylpropanesulfonic acid sultone (VIII) (2.14 × 10⁻⁴ $M$, 1% DMSO) at 50°: ionic strength maintained at 3.0 with $Na_2SO_4$ (□); ionic strength maintained at 3.0 with $NaClO_4$ (○); ionic strength equals [NaOH] (●).



Figure 7. Dependence on $H_M$ of the observed rate constants in the basic methanolysis of $\gamma$-$o$-hydroxyphenylpropanesulfonic acid sultone (VIII) (1.94 × 10⁻⁴ $M$, 1% DMSO) at 25°.

methoxide dependence of the solvolysis reactions should not be affected by the temperature variations.

As shown in Figures 3–5, plots of $k_{obsd}$ vs. $a_w10^{H-}$ for the alkaline hydrolysis of the cyclic esters III, VIII, and IX were linear, indicating that these reactions are indeed first order in hydroxide ion. A higher order term in hydroxide ion would cause an upward curvature in the plots in the very basic region. Thus, we have shown that if the appropriate acidity function is used, it is not necessary to postulate the intermediacy of pentacoordinate species to account for kinetic measurements on the hydrolysis of cyclic sulfonate and sulfate esters in very alkaline solutions.

When salts were added to maintain a constant ionic strength in the alkaline hydrolysis of VIII, the results obtained varied with the nature of the salt. As shown in Figure 6, $NaClO_4$ decreased the rates of reaction while $Na_2SO_4$ increased them. Similar effects have been observed previously in other systems,[22] although the cause of such effects is uncertain. It seems unlikely in our case that changes in the $ClO_4^-$ and $SO_4^{2-}$ concentrations are affecting the acidity functions since $Br^-$ and $Cl^-$ are known to have little effect on the basicity of alkaline solutions.[23]

The pentacoordinate intermediates which might be formed in the methanolysis of the cyclic esters III, VIII, and IX would not be able to undergo an ionization corresponding to the transformation of VI to VII. Therefore, a high-order dependence of the solvolysis rates on methoxide ion would not be expected. We have found that plots of $k_{obsd}$ for the methanolysis of

III, VIII, and IX vs. methoxide ion concentration show strong curvature but, as exemplified by Figure 7, plots of $k_{obsd}$ vs. $a_M10^{H_M}$ are linear, indicating that the reactions do have a first-order dependence on methoxide ion.

The second-order constants calculated for the basic hydrolysis and methanolysis of III, VIII, and IX, using the acidity functions, are summarized in Table I. The present results demonstrate that the $H_-$ and $H_M$ functions are useful mechanistic tools in the study of displacement reactions at sulfonyl sulfur even though the structures of the indicators employed in establishing these acidity functions are very different[17,20] from those of the sulfonate and sulfate esters we investigated.[24]

Table I

| Compd | Nucleophile | Temp, °C | Second-order rate constant, $M^{-1}$ sec⁻¹ |
|-------|-------------|----------|---------------------------------------------|
| III | OH⁻ | 25 | 2.8 × 10⁻³ |
| VIII | OH⁻ | 50 | 1.6 × 10⁻⁴ |
| IX | OH⁻ | 50 | 1.2 × 10⁻³ |
| III | OMe⁻ | 25 | 1.3 × 10⁻³ |
| VIII | OMe⁻ | 25 | 8.6 × 10⁻⁶ |
| IX | OMe⁻ | 25 | 4.3 × 10⁻⁵ |

(22) (a) S. Marburg and W. P. Jencks, J. Amer. Chem. Soc., 84, 232 (1962); (b) E. J. Fendler and J. H. Fendler, J. Org. Chem., 33, 3852 (1968).

(23) G. Yagil, J. Phys. Chem., 71, 1045 (1967).

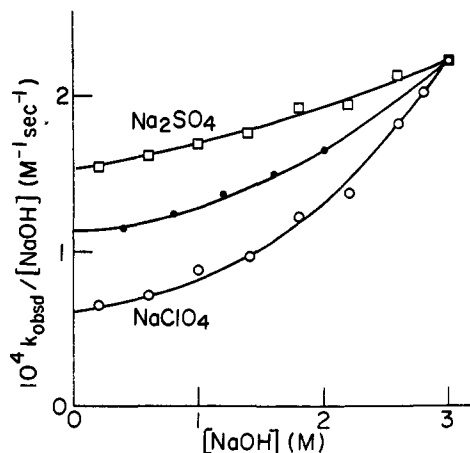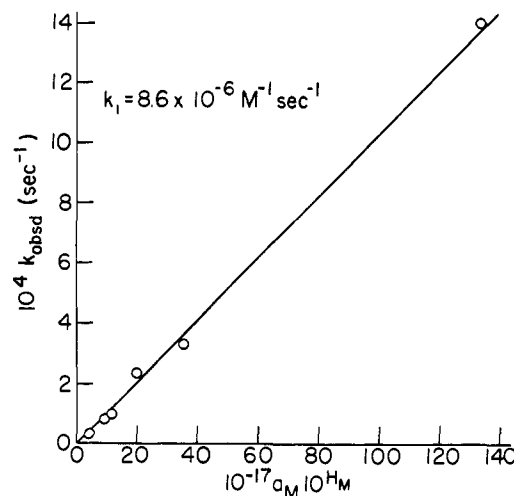(24) It appears that the $H_-$ function can be used to establish the molecularity in hydroxide ion displacement at phosphoryl phosphorus also. For example, a plot similar to those in Figures 1 and 2 has been published by E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaaks, J. Org. Chem., 35, 3063 (1970), for the alkaline hydrolysis of phenylmethylphosphonic acid and $p$-nitrophenylmethylphosphonic acid. Despite the apparent second-order dependence on hydroxide ion concentration of the latter reactions, the authors postulated that there really was no second-order term in base and that the probable explanation for their observations was that a salt effect was operative. We have found that the rate constants observed for these reactions are correlated

Further studies along these lines of displacement reactions at heteroatoms in very basic solutions are in progress in our laboratory.

by $H_-$, indicating, as the authors had suggested, that the reactions are in fact first order in hydroxide ion. The second-order rate constants we have calculated using eq 5 are $3.3 \times 10^{-3}$ $M^{-1}$ min$^{-1}$ for the alkaline hydrolysis of phenylmethylphosphonic acid at 78° and $4.0 \times 10^{-3}$ $M^{-1}$ min$^{-1}$ for that of p-nitrophenylmethylphosphonic acid at 30°. By

extrapolation of their data to low hydroxide ion concentration, Behrman, et al., obtained a value of $3.0 \times 10^{-3}$ $M^{-1}$ min$^{-1}$ for the second-order rate constant in the case of the unsubstituted phosphonate at 78° and the same value for the nitro-substituted compound at 30°, in reasonable correspondence with our calculation.

# Carboxyl-Catalyzed Intramolecular Aminolysis. A Side Reaction in Solid-Phase Peptide Synthesis

**B. F. Gisin\* and R. B. Merrifield**

*Contribution from The Rockefeller University, New York, New York 10021, and Department of Physiology, Duke University Medical Center, Durham, North Carolina 27706. Received October 2, 1971*

**Abstract:** The polymer-supported peptide ester, D-valyl-L-prolyl-resin, was found to undergo intramolecular aminolysis which was catalyzed by carboxylic acids. The resulting loss of the dipeptide from the resin, which amounted to 70% during a regular coupling with N,N'-dicyclohexylcarbodiimide, was repressed by adding the carbodiimide reagent prior to the carboxyl component. The diketopiperazine of D-valyl-L-proline, the only detectable product of this side reaction, was isolated and characterized. The rate of the intramolecular aminolysis was dependent on the composition and configuration of the dipeptide. None of the other reagents tested were as efficient catalysts as the carboxylic acids.

In the course of the synthesis of the peptide sequence D-Pro-D-Val-L-Pro[1] by the solid-phase method,[2] we observed a considerable loss of peptide from the resin.[3] Although the yield of the protected dipeptide was nearly quantitative, only about 30% of the expected amount of tripeptide was found. A step-by-step monitoring of the synthesis indicated that the loss did not occur during deprotection or neutralization of the dipeptide-resin[4] but during the coupling with Boc-D-proline and DCC. This unexpected finding called for a closer investigation, some aspects of which are presented here.

The methods and procedures employed were essentially the established techniques of solid-phase peptide synthesis.[5] Polystyrene-co-1% divinylbenzene resin was chloromethylated with chloromethyl methyl ether and stannic chloride[2,6] which was converted, first, to acetoxymethyl resin[7,8] and then aminolyzed with diethylamine[8] to yield hydroxymethyl resin. Boc-L-proline was esterified to the resin by the N,N'-carbonyldiimidazole method[7,9] and the remaining hydroxy

groups were blocked by esterification with acetic anhydride. This procedure was chosen in order to avoid the introduction of any quaternary ammonium groups into the polymer[10] which can interfere with the quantitative determination of amino groups as described below. The dipeptide-resins were prepared using two DCC couplings[11] with a twofold excess of Boc-amino acid and DCC reagent each time.

In order to monitor the loss of dipeptide from the resin, a procedure for the determination of amino groups on an insoluble polymer with picric acid[12] was adopted. The amine-containing resins were treated with a solution of picric acid to form the polymer supported amine picrate. After thorough washings to remove nonionically bound picric acid, the resins were treated with an excess of diisopropylethylamine which quantitatively released the picrate from the polymer into solution. The concentration of picrate in this solution, which was determined spectrophotometrically, reflected the amine content and therefore the amount of dipeptide on the resin. These values were used to compute apparent first-order rate constants for the decrease in amine content of dipeptide resins (Tables I and II[13]) as described in the Experimental Section.

Since diketopiperazines can be quantitatively determined by gas–liquid chromatography,[14] this method was used to measure the release of D-Val-L-Pro diketopiperazine[15] from the solid support. These experi-

(1) The abbreviations recommended by the IUPAC–IUB Commission on Biochemical Nomenclature (*J. Biol. Chem.*, **241**, 2491 (1966); **242**, 555 (1967) have been used throughout. In addition, TFA = trifluoroacetic acid, DMF = dimethylformamide, DCC = N,N'-dicyclohexylcarbodiimide.

(2) R. B. Merrifield, *J. Amer. Chem. Soc.*, **85**, 2149 (1963).

(3) B. F. Gisin and R. B. Merrifield, in preparation.

(4) The expression "peptide-resin" denotes a peptide, the C-terminal carboxyl group of which is esterified to a polymeric benzyl alcohol.

(5) R. B. Merrifield, *Advan. Enzymol.*, **32**, 221 (1969).

(6) K. W. Pepper, H. M. Paisley, and M. A. Young, *J. Chem. Soc.*, 4097 (1953).

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(9) H. A. Staab, *Angew. Chem.*, **71**, 194 (1959).

(10) R. B. Merrifield, 1966, unpublished.

(11) J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, **77**, 1067 (1955).

(12) B. F. Gisin, *Anal. Chim. Acta*, **58**, 248 (1972).

(13) C. E. Moore and R. Peck, *J. Org. Chem.*, **20**, 673 (1955).

(14) A. B. Mauger, *J. Chromatogr.* **37**, 315 (1968).