

encounter-controlled rates,<sup>30</sup> but studies of the radical-induced deiodination of aryl iodides in alkaline methanol<sup>29</sup> indicate that NH is a considerably better electron acceptor than iodobenzene. NI should be better yet. It therefore is conceivable that electron transfer and ensuing events may convert some NI to NH, and this complication is likely to be manifest particularly at higher NaOCH<sub>3</sub> concentrations, but we are unable to assess how serious it may be.

A third conceivable complication is arylation of iodobenzene, NH, or NI by nitrophenyl or phenyl radicals. However, arylation is much slower than iodine atom abstraction<sup>12</sup> and is unlikely to make much difference in this system.

### Experimental Section

**Materials.** Anhydrous reagent grade methanol was distilled from magnesium methoxide, and then saturated with dry oxygen-free nitrogen. Oxygen was removed by passing commercial high-purity nitrogen over BASF catalyst R-3-11 (BASF Colors & Chemicals, Inc.). Sodium methoxide solutions were prepared by dissolving clean metallic sodium in methanol under nitrogen, and then filtering through a fine sintered-glass filter under nitrogen; stock solutions were standardized against standard hydrochloric acid solutions (Titrisol).

Iodobenzene was prepared according to the method of Lucas and Kennedy<sup>31</sup> via the diazotization of aniline, followed by treatment with aqueous potassium iodide. Commercial samples have, in the past,<sup>12a</sup> proved too impure for use. The synthetic material was pure by glpc analysis.

Neopentyl iodide was prepared according to the procedure of Beringer and Schultz.<sup>32</sup> Neopentyl tosylate, from the alcohol and

*p*-toluenesulfonyl chloride in pyridine, was treated with 2 equiv of sodium iodide in refluxing 2-methoxyethanol. Distillation of the product, bp 70° (100 mm), afforded the iodide, which was pure by glpc and nmr analysis.

*p*-Nitrophenylazo methyl ether was synthesized as described previously by Bunnett and Takayama.<sup>10a</sup>

**Product Analysis.** The product yield data reported in the tables were determined as follows: 1 ml of a stock solution of iodobenzene or neopentyl iodide was pipetted into a 10-ml volumetric flask. An appropriate volume of *ca.* 2 *M* NaOCH<sub>3</sub> solution was added and the flask filled to the mark with methanol. After equilibration at 30.0°, a 0.1-mmol sample of *p*-nitrophenylazo methyl ether was added and the flask shaken vigorously to dissolve the ether. The solutions were maintained at 30.0° for 16–20 hr, then poured into 50 ml of 0.5 *N* HCl; 1 ml of a standard solution of *p*-nitrochlorobenzene in methanol was added and the mixture was extracted with 3 × 20 ml methylene chloride. The extracts were washed with water (25 ml), saturated NaHCO<sub>3</sub> solution (25 ml), and water (25 ml), then dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent evaporated. The residue was dissolved in 1.0 ml of methylene chloride and analyzed by glpc. By subjecting known mixtures to this extraction procedure it was shown that there is no selective loss of material.

Glpc analysis of the products was carried out on a Hewlett-Packard Model 5750 gas chromatograph equipped with flame detectors and temperature programming capability. A 1/8 in. × 3 ft column of 4% Carbowax 20M on Chromosorb G AW/DMCS was used to separate the products with an air flow of 30 ml/min. A temperature program over the range of 138–168° provided excellent separation and peak shapes. The Hewlett-Packard Model 7123A strip-chart recorder was equipped with an electronic integrator from which areas were determined. Standard solutions of nitrobenzene, *p*-nitroanisole, *p*-nitrochlorobenzene, and *p*-nitroiodobenzene were used to determine relative response factors for each compound. Two or three runs were made for each sample and reproducibility of areas was usually within 2%.

**Calculation of Slope and Intercept.** The fit of the data to eq 4 was evaluated by linear least-squares analysis on an Olivetti-Underwood Programma 101 calculator.

(30) M. Anbar and E. J. Hart, *J. Amer. Chem. Soc.*, **86**, 5633 (1964); A. Szutka, J. K. Thomas, S. Gordon, and E. J. Hart, *J. Phys. Chem.*, **69**, 289 (1965).

(31) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 251.

(32) F. M. Beringer and H. S. Schultz, *J. Amer. Chem. Soc.*, **77**, 5533 (1955).

## Ring-Closure Reactions. II.<sup>1</sup> Kinetics of Six- to Ten-Membered Ring Formation from *o*- $\omega$ -Bromoalkoxyphenoxides

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**Abstract:** First-order rate constants and activation parameters have been determined for the formation of six- to ten-membered catechol polymethylene ethers from *o*- $\omega$ -bromoalkoxyphenoxides in 75% ethanol solution at reactant concentrations as low as 2 × 10<sup>-4</sup> *M* or less. No higher order kinetics terms due to polymerization were detected. The expected cyclic ethers formed in essentially quantitative yields under the conditions of the rate measurements, except for the eight- and nine-membered rings. In the latter cases, significant amounts of the isomeric open-chained alkenylphenols were found as by-products, as a result of a competing intramolecular  $\beta$ -elimination reaction. The ring-closure reactivity did not show any minimum in agreement with Ziegler's work. However, the structural effects responsible for a reactivity minimum in other series are shown to give a contribution to the enthalpy of activation. Perhaps the most important result is the observed probability relationship between entropy of activation and chain length of the ring to be formed, which provided the first test for Ruzicka's theory on ring formation.

The strong dependence of intramolecular reactivity on chain length is well recognized. However, quantitative studies on ring-closure reactivity are scanty for

seven-membered and higher ring formation. What is available from the earlier literature is a correlation of ring size with yields and, in a few cases, with only approximate rate studies.<sup>2</sup> No significant progress has

(1) Part I: C. Galli, G. Illuminati, and L. Mandolini, *J. Amer. Chem. Soc.*, **95**, 8374 (1973).

(2) See references cited in ref 1.

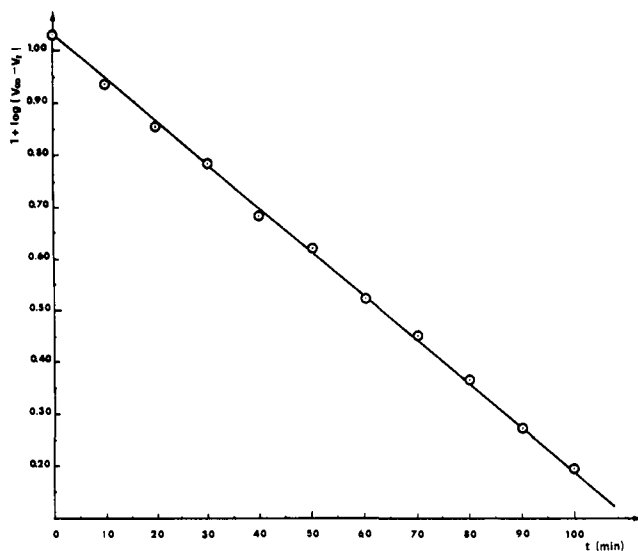
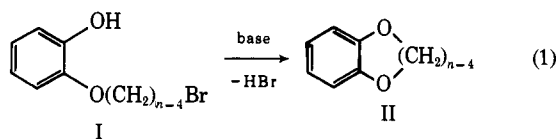


Figure 1. First-order plot for the cyclization reaction of compound I,  $n = 9$  (size of the ring to be formed), in 75% aqueous ethanol and 0.01  $M$   $K_2CO_3$  at 60.0°.

been recorded in the more recent literature, despite the fact that many new methods for the synthesis of macrocyclic compounds have been devised.<sup>3</sup> Obviously, no reliable activation parameters have ever been reported, despite their importance in order to separate probability factors from strain factors as involved in ring-closure reactions. Medium rings (8- to 11-membered) are known to be seriously affected by strains such as bond angle deformations, bond opposition forces, and transannular interactions.<sup>4</sup> These factors play an essential role in determining a region of reactivity minimum for certain ring-closure reactions. Kinetic data confirming this phenomenon have been provided by us for lactone formation.<sup>1</sup> In contrast, the above factors appear to be essentially unimportant in other reactions. Thus, no definite yield minimum was observed by Ziegler, Lüttringhaus, and Wohlgemuth<sup>5</sup> for the cyclization of catechol  $\omega$ -bromoalkyl ethers (I,  $n = 6-14$ ) to catechol polymethylene ethers (II) in the presence of  $K_2CO_3$ .



Half-lives were also estimated in ethanolic sodium ethoxide solution and showed a steady decrease in cyclization rate with increasing ring size. However, clean first-order kinetics could not be obtained due to the varying dissociation of phenols (I) in that medium. Also, polymerization was found to compete significantly with cyclization for the highest terms of the series because of the relatively high initial concentration used (0.01  $M$ ) in the kinetic runs. A further complication arose from some side reactions which were assumed to occur according to (2), although compounds III and IV

(3) For comprehensive reviews see: (a) L. I. Belen'kii, *Russ. Chem. Rev.*, **33**, 551 (1964); (b) P. R. Story and P. Brisch, *Advan. Org. Chem.*, **8**, 67 (1972).

(4) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, Chapter 7; J. Sicher, *Progr. Stereochem.*, **3**, 202 (1962).

(5) K. Ziegler, A. Lüttringhaus, and K. Wohlgemuth, *Justus Liebig's Ann. Chem.*, **528**, 162 (1937).

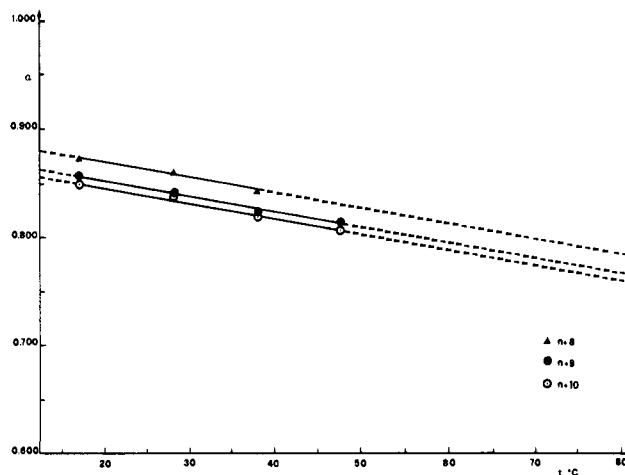
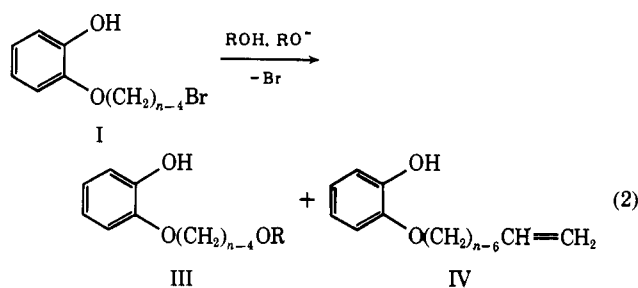


Figure 2. Degrees of dissociation for some catechol  $\omega$ -bromoalkyl ethers I,  $n = 8, 9$ , and 10, in 75% aqueous ethanol and 0.01  $M$   $K_2CO_3$ , as a function of temperature.



were not isolated. Despite the above complications, the substantial simplicity of the system drove us to a reinvestigation, with the aim of obtaining reliable quantitative data for ring closure.

In the present paper we wish to report our results for the ring closure of compounds I,  $n = 6-10$ , under conditions preventing the above complications to a large extent. Product analysis, rate constants, and activation parameters were obtained.

## Results

**Titrimetric Rate Measurements.** The rate measurements for compounds I ( $n = 6-10$ ) were carried out in 75% aqueous ethanol (v/v) by monitoring the bromide ion release by a highly sensitive potentiometric method, so that the kinetic runs could be performed at very low initial concentrations,  $2 \times 10^{-4} M$  or even less. For the least reactive compounds (I,  $n = 8, 9$ , and 10) the cyclizations were run in the presence of a large excess of  $K_2CO_3$  (0.01  $M$ ). Under such conditions the reaction medium is substantially buffered and complications due to the varying extents of dissociation of the phenols are avoided. First-order plots were found to be linear up to 70–90% conversion. A typical example is represented in Figure 1. However, in the reaction medium, compounds I are not completely dissociated. The degree of dissociation  $\alpha$  was determined spectrophotometrically at 293 nm as the ratio of the apparent molar extinction coefficient in the  $K_2CO_3$  solution to the value obtained in a solution of concentrated NaOH and assumed for the complete dissociation. The  $\alpha$  values were found to be slightly dependent on both structure and temperature. The results are plotted in Figure 2. The relatively high cyclization rate of compound I,  $n = 8$ , prevented precise determinations above 40°.

Table I. Kinetic Data for the Ring-Closure Reaction of  $o$ - $\text{OC}_6\text{H}_4\text{O}(\text{CH}_2)_n\text{-Br}$  in 75% Aqueous Ethanol (v/v) at 0.03 M Ionic Strength

$n^a$	Temp, °C	$k_R^{\text{obsd}}$ , $\text{sec}^{-1}$ <sup>d</sup>	$\alpha$	$k_R$ , $\text{sec}^{-1}$	$k_R$ (at 50°), $\text{sec}^{-1}$	$k_{\text{rel}}$ (at 50°)	$n k_R / (n+1) k_R$ (at 50°)	$\Delta H^\ddagger$ , kcal/mol <sup>f</sup>	$\Delta S^\ddagger$ , eu <sup>f</sup>
6 <sup>b</sup>	-10.0	$8.31 \pm 0.06 \times 10^{-4}$	1.00	$8.31 \times 10^{-4}$					
	0.0	$3.78 \pm 0.11 \times 10^{-3}$	1.00	$3.78 \times 10^{-3}$	1.55 <sup>e</sup>	$2.55 \times 10^4$	107	20.6	+6.2
	10.0	$1.40 \pm 0.02 \times 10^{-2}$	1.00	$1.40 \times 10^{-2}$					
7 <sup>b</sup>	20.0	$5.38 \pm 0.21 \times 10^{-2}$	1.00	$5.38 \times 10^{-2}$					
	10.0	$9.83 \pm 0.02 \times 10^{-5}$	1.00	$9.83 \times 10^{-5}$					
	20.0	$3.99 \pm 0.07 \times 10^{-4}$	1.00	$3.99 \times 10^{-4}$	$1.45 \times 10^{-2}$ <sup>e</sup>	$2.39 \times 10^2$	21.9	22.0	+1.2
8 <sup>c</sup>	30.0	$1.48 \pm 0.04 \times 10^{-3}$	1.00	$1.48 \times 10^{-3}$					
	40.0	$4.55 \pm 0.01 \times 10^{-3}$	1.00	$4.55 \times 10^{-3}$					
	20.0	$1.27 \pm 0.07 \times 10^{-5}$	0.869	$1.46 \times 10^{-5}$					
9 <sup>c</sup>	30.5	$5.79 \pm 0.07 \times 10^{-5}$	0.854	$6.77 \times 10^{-5}$	$6.61 \times 10^{-4}$	10.9	5.37	23.1	-1.3
	40.0	$1.70 \pm 0.01 \times 10^{-4}$	0.840	$2.02 \times 10^{-4}$					
	50.0	$5.46 \pm 0.14 \times 10^{-4}$	0.826	$6.61 \times 10^{-4}$					
10 <sup>c</sup>	40.0	$3.21 \pm 0.01 \times 10^{-5}$	0.823	$3.90 \times 10^{-5}$					
	50.0	$9.91 \pm 0.49 \times 10^{-5}$	0.808	$1.23 \times 10^{-4}$	$1.23 \times 10^{-4}$	2.03	2.03	23.1	-4.9
	60.0	$3.06 \pm 0.10 \times 10^{-4}$	0.793	$3.86 \times 10^{-4}$					
10 <sup>c</sup>	70.0	$8.36 \pm 0.05 \times 10^{-4}$	0.778	$1.07 \times 10^{-3}$					
	50.0	$4.86 \pm 0.09 \times 10^{-5}$	0.801	$6.07 \times 10^{-5}$					
	60.0	$1.38 \pm 0.01 \times 10^{-4}$	0.787	$1.75 \times 10^{-4}$	$6.07 \times 10^{-5}$	1.00		21.5	-11.1
	70.0	$3.89 \pm 0.05 \times 10^{-4}$	0.773	$5.03 \times 10^{-4}$					
	80.0	$8.40 \pm 0.00 \times 10^{-4}$	0.758	$1.11 \times 10^{-3}$					

<sup>a</sup> Number of members (ring size) in the ring to be formed. <sup>b</sup> Kinetics carried out in 0.03 M NaOH solution, where the dissociation of phenols is assumed to be complete. <sup>c</sup> Kinetics carried out in 0.01 M  $\text{K}_2\text{CO}_3$ . The degree of dissociation ( $\alpha$ ) is estimated from the plots reported in Figure 2. <sup>d</sup> Runs in duplicate or triplicate. <sup>e</sup> Extrapolated from Arrhenius plots. <sup>f</sup> At 50°.  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  are probably accurate within  $\pm 0.3$  kcal/mol and  $\pm 1$  eu, respectively.

For each compound a linear dependence of  $\alpha$  on temperature was assumed, the three lines being parallel to each other. Corrected rate constants for the ring-closure reactions were obtained at each temperature from the observed rate constants  $k_R^{\text{obsd}}$  by means of the equation  $k_R = k_R^{\text{obsd}}/\alpha$ , where  $\alpha$  was estimated from the appropriate plot (Figure 2) at any given temperature. For the very reactive compounds I,  $n = 6$  and 7, the determination of  $\alpha$  in the  $\text{K}_2\text{CO}_3$  solution was either unreliable or impracticable. The ring-closure rates for the latter compounds were conveniently measured in the presence of 0.03 M NaOH, where the dissociation is complete ( $\alpha = 1$ ) and  $k_R^{\text{obsd}} = k_R$ . For each compound rate constants were obtained at four different temperatures over a 30° range. Arrhenius plots gave excellent straight lines, with correlation coefficients very close to unity. The rate constants and the activation parameters are collected in Table I.

**Spectrophotometric Study and Product Analysis.** In some cases the kinetics could be followed spectrophotometrically by recording the phenoxide absorption decrease at either 243 or 293 nm. The spectrophotometric first-order rate coefficients were found to be remarkably independent of a tenfold initial concentration change ( $2 \times 10^{-4}$  to  $2 \times 10^{-5}$  M). These rate data were also found to be in good agreement with the titrimetric data in all tested cases. However, because of the relatively poor thermostating ability of the instruments, particularly above 40°, the spectrophotometric rate constants were only used as occasional independent checks and were not used for the compilation of Table I. Infinite time spectra from the kinetic runs were found to be in substantial agreement with those predicted on the basis of the known absorption spectra of the expected cyclic products. However, in every case a small residual phenoxide absorption was observed which disappeared on adding a drop of concentrated hydrochloric acid. The yields in cyclic products were calculated from the expression  $100(1 - \text{OD}/$

$\text{OD}_0)$ , where  $\text{OD}_0$  is the optical density at zero time and OD is the amount of absorption that disappeared on acidification at infinite time. Both quantities were measured at 293 nm, where the absorption of the phenols (I) was negligible. The extent of the side reaction was largely independent of temperature. The yields were also determined by gas chromatography for compounds I,  $n = 8, 9$ , and 10, and found to be in reasonable agreement with the above data. The yields are summarized in Table II. The presence of phenolic mate-

Table II. Yields of Cyclic Products Obtained from I,  $n = 6-10$ , in the Kinetic Runs

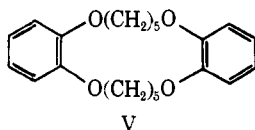
$n$	6	7	8	9	10
% <sup>a</sup>	>96	>96	85	95	95
% <sup>b</sup>			87.5	91	101

<sup>a</sup> Spectrophotometric data at 293 nm. <sup>b</sup> Data from vpc analyses.

rials in the reaction products cannot be accounted for as being due to polymerization or such side reactions as (2), which should compete more effectively with the slowest cyclization reactions. In fact the largest amounts of by-products were found to accompany the cyclization of I,  $n = 8$  and 9, to the eight- and nine-membered rings, respectively, which are formed faster than the ten-membered homolog. Moreover, the amount of by-products is similar for  $n = 8$  and 9, while the corresponding cyclization rates differ by a factor of 5. The rate of bromide ion release from hexyl bromide in 75% ethanol in the presence of 0.01 M  $\text{K}_2\text{CO}_3$  was measured. The kinetic data are as follows:  $k$ ,  $4.47 \times 10^{-6}$   $\text{sec}^{-1}$  at 60.0° and  $7.48 \times 10^{-5}$   $\text{sec}^{-1}$  at 90.0°. Thus, provided that hexyl bromide is a sufficiently close model compound for the solvolysis reaction, it would appear that side reactions 2 could account for no more than 3% of the lowest cyclization rate (ten-membered ring formation). From such

evidence, the side reaction accompanying the eight- and nine-membered ring formation was likely to be an intramolecular  $\beta$ -elimination reaction, leading to *o*-hydroxyphenyl 3-butenyl ether (IV,  $n = 8$ ) and *o*-hydroxyphenyl 4-pentenyl ether (IV,  $n = 9$ ), respectively. The latter compounds were indeed isolated (see Experimental Section) together with the expected macrocyclic diethers from compounds I,  $n = 8$  and 9, respectively, under conditions similar to those used for the kinetic runs.

In the case of compound I,  $n = 9$ , a small amount (3.4%) of the cyclic dimer V was also obtained. Thus



at the initial concentration  $C_0 = 1.36 \times 10^{-2} M$ , the second-order polymerization began to compete appreciably with the cyclization process. This means that condition  $C_0 \ll k_R/2k_P$ , where  $k_P$  is the second-order rate constant for the dimerization reaction, no longer holds (see ref 1). From the data above, an approximate value for the rate ratio  $k_R/k_P$ , 0.3 M at ca. 80°, is estimated for the anion derived from compound I,  $n = 9$ . A similar value,  $k_R/k_P = 0.21 M$  at 70°, is calculated assuming  $k_P = 2k_2$ , where  $k_2 = 2.5 \times 10^{-3} M^{-1} \text{sec}^{-1}$  is the bimolecular rate constant for the reaction between sodium guaiacolate and butyl bromide under the same conditions,<sup>6</sup> and 2 is the statistical factor. It is worth noting that although in the early stages of this work the time-consuming Ziegler's high dilution procedure<sup>5</sup> (see Experimental Section) was followed for the preparation of the cyclic ethers, more convenient conditions were used later on, in accordance with the very favorable  $k_R/k_P$  values. In other words, the kinetic results for the cyclization reactions turn out to be a valuable guide to adjusting more appropriate conditions for the syntheses of macrocyclic compounds. This point will be the object of further work in this laboratory.

## Discussion

Both the kinetic data and the product analysis show that under the stated conditions undesired side reactions such as the second-order polymerization and the pseudo-first-order reactions with either the solvent ROH or its conjugate base RO<sup>-</sup> (2) do not appreciably compete with the cyclization process. In the cyclization of I,  $n = 8$  and 9, where the lowest yields are obtained, the competing side reaction appears to be essentially an interesting case of intramolecular  $\beta$ -elimination reaction involving medium-sized cyclic transition states. Competition between intramolecular nucleophilic substitution and elimination has been given some attention by Stirling *et al.*<sup>7</sup> Although  $\beta$ -elimination usually fails to accompany cyclization, it was claimed<sup>8</sup> that some evidence for intramolecular proton transfer was obtained. However, so far no further report has appeared. Among intramolecular reactions other than eliminations, related cases do exist. For example, some intramolecular general base and/or acid catal-

ysis of proton transfer<sup>9,10</sup> as well as radical hydrogen transfers<sup>11</sup> have been assumed to involve eight- and/or ten-membered cyclic transition states.

The data in Table I show the remarkable influence of the chain length on intramolecular reactivity. Thus at 50° the six-membered cyclic diether is formed about 25,000 times as fast as the ten-membered one. The rate regularly decreases as the chain length increases, the retarding effect caused by each additional methylene group being smaller the larger the ring to be formed, as shown by the  ${}_n k_R/{}_{n+1} k_R$  values. According to an early Ruzicka suggestion,<sup>12</sup> the ease of ring formation results from a combination of independent factors. Whereas the activation energy might be expected to reflect the stability of the ring to some extent, the probability factor would also be important because the encounters between chain terminals should become less likely the longer the chain. A steady decrease of the entropy of activation with increasing ring size was then assumed. The concepts underlining this view are now widely accepted and have become material for basic organic chemistry textbooks.<sup>13</sup> However, to the best of our knowledge, no experimental support for them is available in the literature. This is provided for the first time by the present data showing that the  $\Delta S^\ddagger$  values gradually decrease with increasing  $n$ . Comparison of the  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values shows the relative importance of both strain and probability factors in determining the overall kinetic picture. On going from the six-membered ring to the eight-membered ring, both effects operate in the same direction, *i.e.*, slow down the reaction rate, the relative contribution of each to the free energy of activation being of the same order of magnitude. It is of interest to note that a rise in  $\Delta H^\ddagger$  is observed for the eight- and nine-membered rings, which appear to suffer from a greater ring strain effect than the neighboring rings on either side. The observed drop in reactivity on going from the eight- to the nine-membered ring is a purely entropy effect, as the activation enthalpies happen to be identical. Although this cyclization series does not show the familiar minimum in reactivity in the medium-ring region, the nine-membered ring approaches quite closely to it. Indeed with the ten-membered ring, the unfavorable entropy effect ( $-T\Delta\Delta S^\ddagger = +2.0 \text{ kcal/mol}$ ) is partially compensated by a substantial relief of strain ( $\Delta\Delta H^\ddagger = -1.6 \text{ kcal/mol}$ ). As a consequence, the ten-membered ring is formed at a rate only twice as slow as the nine-membered one. Reactivity inversion between these neighboring homologs to produce a minimum would have required a greater difference in  $\Delta H^\ddagger$  by no more than an extra 0.5 kcal/mol or so.

It is worth noting that the appreciable extent of elimination accompanying formation of the strained eight- and nine-membered rings could be accounted for by the operation of a steric effect increasing the E/S<sub>x</sub> ratio, as is found to be the case for the intramolecular reactions.

The general reactivity pattern as found by us is in

(9) M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8818 (1972).

(10) J. Hine, M. S. Cholod, and J. H. Jensen, *J. Amer. Chem. Soc.*, **93**, 2321 (1971).

(11) M. Katoh and C. Djerassi, *Chem. Commun.*, 1385 (1969).

(12) L. Ruzicka, *Chem. Ind. (London)*, **54**, 2 (1935).

(13) See, for example, R. O. C. Norman, "Principles of Organic Synthesis," Methuen, London, 1968, p 238.

(6) Preliminary data from this laboratory.

(7) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 67 (1968).

(8) J. Crosby and C. J. M. Stirling, unpublished results.

good agreement with Ziegler's data<sup>5</sup> in all tested compounds (six- to ten-ring formation) and confirms the reliability of Ziegler's semiquantitative work, according to which no minimum in rate of ring closure was found up to the 14-membered ring. As an explanation for the diminished tendency for the catechol system to display a minimum in comparison with other series, it has been suggested<sup>5,4,14</sup> that the presence of two "bare" oxygen atoms and two trigonal carbon atoms in a given ring should reduce a great deal or even suppress the strains due to bond opposition forces and transannular interactions that are usually considered to especially affect the medium rings (8- to 11-membered).

As to the factors affecting the rate of intramolecular displacement of bromide ions, besides steric and conformational effects, the electron-attractive inductive effect of the remote bromo substituent on the reactivity of the nucleophilic site at the anionic oxygen must be taken into account. Knipe and Stirling<sup>15</sup> found that the inductive effect of remote substituents could still be appreciable at very high degrees of separation, such as a chain of 6 carbon atoms or even more. They concluded that in these cases the overall inductive effect was mainly due to the field component, whose magnitude was assumed to be much less dependent upon the length of the chain than the through-chain transmitted component. Accordingly, for compounds I,  $n = 8, 9$ , and  $10$ , we found  $\alpha$  values (Figure 2) decreasing on increasing  $n$ . Thus the remote  $\omega$ -bromo group appears to depress the basicity of the phenoxide ions appreciably even when  $n$  is large. Since the basicity and the nucleophilicity of phenoxides are related to each other, a diminishing nucleophilicity as the chain length decreases is expected. However, the importance of this effect in the overall cyclization rate should be small. For example, the reaction between a series of substituted phenoxides and a primary alkyl bromide in water was found<sup>16</sup> to be only slightly sensitive to the basicity of the former compounds; a value as low as 0.22 was reported for the Brønsted coefficient ( $\log k$  vs.  $pK$  relationship).

### Experimental Section

Vpc analyses were carried out on a Carlo Erba Fractovap Model G.1. Pmr spectra were recorded on a Varian A-60 spectrometer, using TMS as internal standard and  $CCl_4$  as solvent unless otherwise stated. Uv spectra were measured either on a Beckman DB GT or Perkin-Elmer 402. Ir spectra were obtained on a Perkin-Elmer 257 from 2% solutions in  $CCl_4$ . Automatic microtitrations of bromide ions were performed with Radiometer Ag P401 and  $Hg_2SO_4$  K601 electrodes on a SbR2c-AbUlb-TTTL apparatus, fitted with a 2.500-ml microburet. Mass spectra were performed on a AEI MS 12 spectrometer.

**Materials.** Hexyl bromide (Schuchardt), 1,3-dibromopropane (Merck), 1,4-dibromobutane (Fluka), 1,5-dibromopentane (Fluka), and catechol (Erba RP) were all commercial samples and used as received. 1,6-Dibromohexane (Merck) and 3,4-dihydro-2H-pyran (Merck) were redistilled before use. Catechol mono-2-tetrahydropyranyl ether (bp 116–119°, (17 mm),  $n_D^{20}$  1.5406; lit.<sup>11</sup>  $n_D^{20}$  1.5369) was prepared as described.<sup>17</sup>

**$\omega$ -Hydroxyphenyl  $\omega$ -Bromoalkyl Ethers.** In the original method by Ziegler, *et al.*,<sup>5</sup> compounds I,  $n = 7-10$ , were obtained by treating catechol (3 mol) with an excess of the appropriate  $\alpha,\omega$ -dibromo-

alkane (9 mol) and sodium ethoxide (1 mol) in boiling ethanol. We have somewhat modified the procedure by using a much smaller excess of dibromoalkane. To a boiling heterogeneous mixture of the appropriate  $\alpha,\omega$ -dibromoalkane (0.13 mol) and catechol (0.30 mol) dissolved in water (50 ml), a solution of NaOH (4.0 g, 0.10 mol) in water (15 ml) was added in *ca.* 1 hr under vigorous stirring. The reaction was carried out in a nitrogen atmosphere in order to prevent the oxidation of catechol in the alkaline reaction medium. The mixture was refluxed under stirring for an additional hour, and then cooled and transferred into a separatory funnel. The lower dark brown organic phase was separated from the aqueous upper phase with the aid of  $CCl_4$  (50 ml), washed several times with water in order to remove the excess of catechol (negative test with  $FeCl_3$  in the aqueous washings), and dried overnight ( $Na_2SO_4$  anhydrous). Then the solvent was distilled off and the residue was fractionated under vacuum to give the pure *o*-hydroxyphenyl  $\omega$ -bromoalkyl ether after a forerun of the unreacted dibromoalkane. On attempted preparation of I,  $n = 6$ , from 1,2-dibromoethane, benzo-dioxane (II,  $n = 6$ ) was the sole product (66% yield). A small amount of cyclic ether (II,  $n = 7$ ) was also obtained from 1,3-dibromopropane, together with the desired I,  $n = 7$ . With the remaining dibromoalkanes no trace of cyclic product was ever found. In these cases from the tetrachloride solution of the crude reaction product, white crystalline solids would separate on standing. The solids were collected by filtration and showed strong hydroxyl absorption ( $3560\text{ cm}^{-1}$ ) in the ir spectra. These compounds were tentatively assigned a diether structure, *o*- $HOC_6H_4O(CH_2)_nOC_6H_4OH$ -*o*, on the basis of their pmr spectra in  $CDCl_3$ . *o*-Hydroxyphenyl 2-bromoethyl ether (I,  $n = 6$ ) was prepared by the following procedure. Catechol mono-2-tetrahydropyranyl ether (17.9 g, 0.092 mol) in 50 ml of dry xylene was added dropwise to a well stirred suspension of finely dispersed sodium (2.1 g, 0.092 mol) in 100 ml of the same solvent. After the evolution of hydrogen was over, 1,2-dibromoethane (32 ml, 0.37 mol) was added to the deeply green mixture that was then refluxed for 5 hr, cooled, and filtered. On removal of the solvent a dark oil (23.9 g) was obtained that was treated with 15% hydrobromic acid in order to remove the protecting group. The organic material was then extracted with  $CCl_4$ , washed several times with water, and dried ( $Na_2SO_4$  anhydrous). Removal of the solvent left a residue (13.7 g) that was fractionated to give I,  $n = 6$  (4.7 g, 0.022 mol), as a pale yellow liquid.

All phenols showed strong hydroxyl absorption in the ir spectra ( $3560\text{ cm}^{-1}$ ) and gave the expected pmr spectra with no detectable impurities. Yields and physical constants are reported in Table III. On storage, in some cases the compounds showed a tendency

Table III. Physical Constants of *o*-Hydroxyphenyl  $\omega$ -Bromoalkyl Ethers I,  $n = 6-10$

$n$	Yield, %	Bp, °C (mm)	Lit. <sup>5</sup> bp, °C (mm)	$n_D^{20}$
6	24	97 (1)		1.5718
7	18	130 (2)	101 (0.25)	<i>a</i>
8	27	157 (3.7)	117 (0.25)	1.5572
9	31	170 (3.7)	132 (0.25)	1.5501
10	36	179 (2)	150 (0.25)	1.5436

<sup>a</sup> Mp 57–58.5° from methanol–water 1:1, lit.<sup>5</sup> mp 59°. <sup>b</sup> Anal. Calcd: C, 49.00; H, 5.34. Found: C, 49.04; H, 5.41. Ziegler, *et al.*,<sup>5</sup> obtained a very poor elemental analysis for this compound.

to turn reddish. For kinetic purposes only colorless freshly purified (by chromatography on silica gel and/or redistillation) materials were used.

**Catechol Polymethylene Ethers.** Compounds II,  $n = 7-10$ , were prepared from the corresponding  $\omega$ -bromoalkylphenols by the high dilution method of Ziegler, *et al.*,<sup>5</sup> with the sole difference that the slow addition was accomplished with a Hershberg dropping funnel rather than by slow displacement of mercury. Physical constants are collected in Table IV, together with those of compound II,  $n = 6$ , obtained as described in the preceding section. All ethers gave the expected pmr spectra and showed only one peak in vpc using different stationary phases.

**Rate Measurements.** The base-containing mixed solvent was prepared in a 1-l. volumetric flask at 20° by diluting 250 ml of aqueous stock solutions of base (NaOH or  $K_2CO_3$  in bidistilled water) with anhydrous ethanol (Erba RS, water content less than 0.1% by K.F. titration) up to the mark. After the quenching of 3- to 5 ml-

(14) E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1965, p 117.

(15) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 808 (1967).

(16) R. F. Hudson and G. Loveday, *J. Chem. Soc.*, 1068 (1962).

(17) W. E. Parham and E. L. Anderson, *J. Amer. Chem. Soc.*, 70, 4187 (1948).

**Table IV.** Physical Constants of Catechol Polymethylene Ethers II,  $n = 6-10$ 

$n$	Yield, %	Bp, °C (mm)	Lit. <sup>5</sup> bp, °C (mm)	$n_{20D}$
6	66	94 (20)		1.5514
7	60	120 (20)	103 (10)	1.5396
8	45	93 (5)	112 (10)	1.5370
9	47	95 (2)	122 (10)	1.5346
10	70	104 (1)	140 (10)	<i>a</i>

<sup>a</sup> Mp 34–36° from methanol, lit.<sup>5</sup> 36°.

samples from kinetic runs in 10 ml of acetate buffer (0.2 *M* in bi-distilled water), microtitration of the bromide ion was performed potentiometrically.<sup>1</sup> Depending on the reactivity of the substrates, the procedures adopted varied somewhat from each other. The reactions for the formation of seven- to ten-membered rings below 50° were run in a 100-ml volumetric flask, while those above 50° were run in sealed ampoules. Temperatures were controlled to  $\pm 0.05^\circ$ . The reactions were followed up to 70–90% conversion. For each run two or three samples were spared for infinite time determinations and titrated after at least ten half-lives. Data from a representative run are reported in Table V. With the most reac-

**Table V.** Typical Kinetic Run for the Cyclization of I,  $n = 9$ , in 75% Aqueous Ethanol (v/v) in the Presence of 0.01 *M*  $K_2CO_3$  at 60.0°

Time, min	AgNO <sub>3</sub> , $V_t^a$	$1 + \log(V_\infty - V_t)^b$
0	0.100	1.030
10	0.310	0.936
20	0.460	0.853
30	0.565	0.783
40	0.690	0.683
50	0.760	0.615
60	0.840	0.521
70	0.890	0.450
80	0.940	0.366
90	0.985	0.272
100	1.015	0.196
$\infty$	1.172 (mean)	

<sup>a</sup> Volumes (in ml) of  $4.5 \times 10^{-4}$  *N* AgNO<sub>3</sub> necessary for the titration of the released bromide ion at time  $t$  in 3.96-ml samples, quenched in 0.2 *M* acetate buffer (10 ml). <sup>b</sup> A plot of  $1 + \log(V_\infty - V_t)$  vs. time yielded a straight line (Figure 1) from which  $k_R^{\text{obsd}} = 4.11 \times 10^{-4} \text{ sec}^{-1}$  was calculated.

tive *o*-hydroxyphenyl 2-bromoethyl ether (six-membered ring formation), a batchwise procedure and low temperatures were employed. The apparatus and techniques are as before.<sup>18</sup>

**Product Analyses.** These were carried out by vpc for the formation of the eight-, nine-, and ten-membered rings using the method of the internal standard on scaled-up kinetic experiments (usually 300 ml of  $ca. 2 \times 10^{-4}$  *M* solutions). After the reaction was complete, a known amount of the proper standard was added, and about 150 ml of the solvent was distilled off through a 20-cm Vigreux column. The residue was diluted with water and extracted with hexane, and the organic phase washed several times with water. After drying ( $Na_2SO_4$  anhydrous) the solution was carefully concentrated to a small volume and then analyzed by vpc on a FFAP column. In each case the chromatogram consisted of only two peaks, *i.e.*, the ones of the standard and of the expected cyclic ether. The correctness of the entire procedure was checked by blank experiments. The *o*-alkenylphenols that were subsequently found to accompany the eight- and nine-membered ring formation (see below) were not detected in the chromatograms, because the solutions containing the crude reaction products were not made acid prior to extraction with hexane.

Further product analysis for compounds I,  $n = 8$  and 9, was carried out as follows. A  $2.33 \times 10^{-2}$  *M* solution of I,  $n = 8$ , in 75% aqueous ethanol (700 ml) was treated with an equivalent amount of NaOH and 3.3 g of  $K_2CO_3$ . The mixture was heated at 60° for 1 hr, and then most of the solvent was distilled off. The residue was made strongly alkaline by adding concentrated NaOH and extracted with hexane. From the latter, catechol tetramethylene ether (II,  $n = 8$ ) was recovered in 78% yield. The alkaline solution was then made acid and extracted with  $CHCl_3$ . Usual work-up procedure afforded *o*-hydroxyphenyl-3-butenyl ether (IV,  $n = 8$ ) in 5.6% yield: ir, bands at 3550, 1640, 990, and 925  $cm^{-1}$ ; mass,  $M^+$  164; pmr  $\delta$  6.75 (m, 4 H, ArH), 4.85–6.2 (m, 4 H, vinyl protons plus OH), 4.05 (t, 2 H,  $CH_2O$ ), 2.3–2.7 (m, 2 H, allylic protons).

A similar procedure was adopted for I,  $n = 9$ , starting from a  $1.36 \times 10^{-2}$  *M* solution (370 ml). The neutral fraction, after removal of hexane, gave a mixture of a liquid and a white crystalline solid that was treated with a few milliliters of hexane and filtered. The structure of the solid, mp 185.5–187.5°, was found to be consistent with V on the basis of pmr and mass spectra ( $M^+$  356). The yield was 30 mg (3.4%). After removal of the solvent from the filtrate, catechol pentamethylene ether (II,  $n = 9$ ) was obtained in 58.6% yield. Treatment as above of the alkaline solution afforded *o*-hydroxyphenyl 4-pentenyl ether (IV,  $n = 9$ ) in 6.8% yield. Ir and pmr spectra were analogous to those of compound I,  $n = 8$ ; mass,  $M^+$  178.

(18) E. Baciocchi and L. Mandolini, *J. Chem. Soc. B*, 1361 (1967).