

cloptane is difficult to refute on the basis of work done only with 6-chloro-1-phenyl-1-hexyne. However, our recent studies of the reductions of 6-bromo- and 6-iodo-1-phenyl-1-hexyne, for which **10** is generated at potentials near -1.75 V, indicate that 1-phenyl-1-hexyne is the major product; therefore, it is quite unlikely that conversion of **10** to **3** takes place to any appreciable extent.

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 (25) An alternate pathway can be suggested for the formation of **4** and **14** from **12** which is mechanistically similar to that mentioned in ref 16 for the conversion of **10** to **3**. Thus, **12** could yield the species $C_6H_5CH=C=CH(CH_2)_3$ that cyclizes intramolecularly to give **13** which leads to **4** and **14**. If this process did occur, one should obtain more $C_6H_5CH=C=CH(CH_2)_2CH_3$ and its reduction products as the concentration of starting material increases; however, the yield of these reduction products definitely decreases with increasing involvement of the allene at higher starting-material concentrations, indicating that this alternate pathway is unimportant.

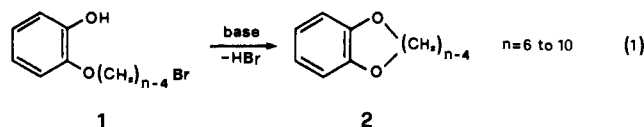
Ring-Closure Reactions. V.¹ Kinetics of Five- to Ten-Membered Ring Formation from *o*- ω -Bromoalkylphenoxides. The Influence of the O-Heteroatom

Gabriello Illuminati,* Luigi Mandolini, and Bernardo Masci

Contribution from the Centro di Studio sui Meccanismi di Reazione del Consiglio Nazionale delle Ricerche, Istituto Chimico dell'Università, 00185 Rome, Italy.
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Abstract: Rates and activation parameters have been determined for the intramolecular Williamson synthesis of coumaran, chroman, and their higher homologs up to ring size ten, starting from the corresponding *o*- ω -bromoalkylphenoxides in 75% ethanol solution. Interestingly, the entropy of activation was found to decrease linearly with increasing chain length, with an average drop of 4 eu per added methylene group. Eight- and nine-membered ring closures are accompanied by significant amounts of the isomeric open-chained alkenylphenols, which are believed to result from a peculiar intramolecular β -elimination reaction of the E2 type. Enthalpy of activation data indicate that strain in the cyclic transition states is highest for ring sizes eight and nine. Therefore, the side reaction becomes favored as a consequence of a steric factor responsible for the increase in the elimination/substitution ratio. Comparison of the present data with those previously established for a closely related system, i.e., the formation of catechol polymethylene ethers from *o*- ω -bromoalkoxyphenoxides has allowed an assessment of the influence of the oxygen atom on ease of ring closure. Replacement of a methylene group by an oxygen atom causes a rate enhancement which is largest for the most strained eight- and nine-membered rings. This effect is discussed in terms of strain and other factors.

It is well known that medium ring compounds (8- to 11-membered) exhibit special features when compared with rings of either smaller or greater ring size. The structural effects responsible for a special behavior are angular distortions, eclipsing interactions, and van der Waals repulsions of atoms across the rings.² A dissection into the different contributions has been recently effected on a theoretical basis by Allinger et al. for the series of cycloalkanes.³ It was shown that angle deformation and van der Waals interaction are particularly severe for the medium rings and are responsible for most of the total strain energy. When the variation of both physical and chemical properties of ring compounds as a function of ring size are considered, extrema are often found in the medium ring region. In particular, one of such extrema, namely a deep minimum in ring-closure tendency, was apparent in the early history of the many-membered rings on attempted medium ring formation by Ruzicka's cyclization reaction of dicarboxylic acids salts^{2,4} and is generally regarded as the most characteristic feature of the medium rings. However, the rates of cyclization of conjugate bases of *o*- ω -bromoalkoxyphenols **1** to the corresponding catechol polymethylene ethers **2** were found by us⁵ to display no minimum but, rather, to decrease con-



tinuously with increasing chain length, in agreement with Ziegler's early semiquantitative work.⁶ In macro ring chemistry, the presence of rigid groups and/or oxygen atoms in place of one or more methylene groups has long been known to enhance ring-closure tendency.² More recently, calculations by Allinger et al.⁷ showed that medium ring ketones and *cis*-alkenes are significantly less strained (by 2.5–5.4 kcal/mol) than the corresponding cycloalkanes. Accordingly, the presence of the O—C=C—O moiety in the cyclic ethers **2** was held responsible for the lack of a minimum in ring-closure reactivity.⁶ In order to assess the relative contributions of the double bond and oxygen atoms, rate data for the formation of the homocyclic rings **3** would

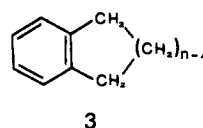
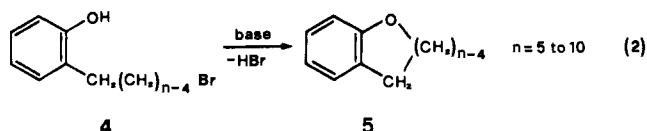


Table I. Yield Data (%) for the Cyclization Reactions of Compounds 4, for $n = 5$ to 10 in the Kinetic Runs

Product	$n = 5$	6	7	8	9	10
Cyclic ether 5 ^a	>96	>96	>96	64	78	85
Cyclic ether 5 ^b				60.5	76	81.5
Alkenyl phenol 6 ^b				35	11	None

^a Data from spectrophotometric analysis at 293 nm. The results are independent of temperature in the 30° range used in the kinetic runs. ^b Data from VPC analysis.

be required, as suggested by Eliel.⁸ Since a reaction of this kind is not experimentally accessible at present, we have turned our attention to the closely related cyclization reaction $4 \rightarrow 5$, in which only one oxygen atom has been re-



placed by a methylene group. A quantitative study of this reaction for $n = 5$ to 10 is reported in the present paper.

Results

Rate Measurements and Product Analysis. The cyclization reactions were run in 75% aqueous ethanol (v/v) in the presence of excess base at sufficiently low substrate concentrations, i.e., $2 \times 10^{-4} M$ or lower, to prevent any appreciable competition of the second-order polymerization reaction, as shown by kinetics and product analysis.

The kinetics were followed in most cases by the argentometric determination of the released bromide ions and found to be strictly first order up to 2 or 3 half-lives. De-

pending on substrate reactivity, different techniques were adopted as previously described for the cyclization of compounds 1.⁵ For the most reactive compounds 4, $n = 5, 6,$ and 7, 0.03 M NaOH was used as reagent. Under these conditions, the dissociation of the phenols was complete, and practically quantitative yields in cyclic product were obtained (Table I). The extremely fast five-membered ring formation was followed in the earlier part of this work by the batchwise procedure⁵ in the temperature range of -28 to -8° . A spectrophotometric stopped-flow technique was used later on in the range of 20.1 – 50.1° . The two methods gave results in excellent agreement with each other (Table II, footnote *c*).

The reactions with the least reactive compounds 4, $n = 8, 9,$ and 10, were run in the presence of 0.01 M K_2CO_3 , where the dissociation is not complete. The degrees of dissociation (α) for these members and for *o*-ethylphenol and guaiacol were determined spectrophotometrically⁵ in the accessible temperature ranges and plotted vs. temperature (Figure 1). The α values for the lower terms of the series (4, $n = 5, 6,$ and 7) were not directly measured. However, comparison of the kinetic data, as obtained in K_2CO_3 solution, with those obtained in the presence of NaOH indicates that α values increase as n decreases, up to a limiting value of $\alpha \approx 1$ for the term with $n = 5$. This phenomenon can be explained in terms of the remote inductive effect, which has been previously discussed in some detail.⁵ Steric inhibition to solvation may also be a factor in determining the observed acidity pattern.

A spectrophotometric analysis⁵ showed that medium-sized (eight-, nine-, and ten-membered) cyclic ethers did not form in quantitative yields and were accompanied by significant amounts of phenolic materials. As previously found⁵ for the cyclization reaction of compounds 1, $n = 8$

Table II. Kinetic Data for the Ring-Closure Reaction of *o*- $OC_6H_4CH_2(CH_2)_{n-4}Br$ in 75% Aqueous Ethanol (v/v) at 0.03 M Ionic Strength

n^a	Temp, °C	k_R (obsd), sec ⁻¹ ^e	α	k_R , sec ⁻¹	k_R (at 50°), sec ⁻¹	k_{rel} (at 50°)	$\frac{n k_R}{n+1 k_R}$ (at 50°)	ΔH^\ddagger , kcal/mol ^g	ΔS^\ddagger , eu ^g
5 ^{b,c}	20.1	2.05	1.00	2.05					
	30.2	5.63	1.00	5.63					
	39.8	14.6	1.00	14.6	38.4 ^f	2.63×10^6	20.0	18.0	+4.1
	50.1	39.8	1.00	39.8					
6 ^b	-10.0	$1.13 \pm 0.03 \times 10^{-3}$	1.00	1.13×10^{-3}					
	0.0	$4.95 \pm 0.14 \times 10^{-3}$	1.00	4.95×10^{-3}					
	10.0	$2.01 \pm 0.08 \times 10^{-2}$	1.00	2.01×10^{-2}	1.92 ^f	1.32×10^5	55.7	20.3	+5.3
	20.0	$6.60 \pm 0.23 \times 10^{-2}$	1.00	6.60×10^{-2}					
7 ^b	0.0	$9.45 \pm 0.07 \times 10^{-5}$	1.00	9.45×10^{-5}					
	10.0	$3.51 \pm 0.06 \times 10^{-4}$	1.00	3.51×10^{-4}					
	20.0	$1.29 \pm 0.01 \times 10^{-3}$	1.00	1.29×10^{-3}	3.45×10^{-2f}	2.36×10^3	335	20.1	-3.2
	30.0	$4.08 \pm 0.01 \times 10^{-3}$	1.00	4.08×10^{-3}					
8 ^d	40.0	$3.17 \pm 0.03 \times 10^{-5}$	0.62 ₇	3.05×10^{-5}					
	50.0	$1.06 \pm 0.03 \times 10^{-4}$	0.61 ₉	1.03×10^{-4}					
	60.0	$3.12 \pm 0.02 \times 10^{-4}$	0.61 ₂	3.08×10^{-4}	1.03×10^{-4}	7.05	6.32	23.3	-4.8
	70.0	$8.83 \pm 0.10 \times 10^{-4}$	0.60 ₄	8.83×10^{-4}					
9 ^d	60.0	$3.81 \pm 0.04 \times 10^{-5}$	0.58 ₇	4.93×10^{-5}					
	70.0	$1.11 \pm 0.00 \times 10^{-4}$	0.57 ₉	1.46×10^{-4}					
	80.0	$2.99 \pm 0.08 \times 10^{-4}$	0.57 ₁	3.97×10^{-4}	1.63×10^{-5f}	1.12	1.12	23.3	-8.5
	89.9	$7.17 \pm 0.10 \times 10^{-4}$	0.56 ₄	9.65×10^{-4}					
10 ^d	60.0	$2.94 \pm 0.00 \times 10^{-5}$	0.56 ₅	4.24×10^{-5}					
	70.0	$8.16 \pm 0.01 \times 10^{-5}$	0.55 ₇	1.19×10^{-4}					
	80.0	$2.06 \pm 0.00 \times 10^{-4}$	0.55 ₀	3.05×10^{-4}	1.46×10^{-5f}	1.00		22.3	-11.7
	90.0	$4.99 \pm 0.03 \times 10^{-4}$	0.54 ₂	7.49×10^{-4}					

^a Ring size of the ring to be formed. ^b Kinetics carried out in 0.03 M NaOH solution, where the dissociation of phenols is assumed to be complete. ^c Kinetics carried out by stopped flow. The oscilloscope traces from two independent runs were found to be perfectly superposable; errors are probably in the order of $\pm 2\%$. The earlier batchwise procedure at low temperatures gave $\Delta H^\ddagger = 17.8$ kcal/mol ($r = 0.99742$), $\Delta S^\ddagger = +3.5$ eu, k_R (at 50°) = 37.3 sec⁻¹. ^d Kinetics carried out in 0.01 M K_2CO_3 . The degree of dissociation (α) is estimated from the plots reported in Figure 1. ^e Runs in duplicate or triplicate. ^f Extrapolated from Arrhenius plots. ^g ΔH^\ddagger values calculated as $\Delta H^\ddagger = E_a - RT$ (at 50°). E_a was obtained by the least-squares method from the Arrhenius plots, which had the following correlation coefficients (ring size in parentheses): 0.99970 (5); 0.99955 (6); 0.99988 (7); 0.99980 (8); 0.99975 (9); 0.99995 (10). The entropies of activation were obtained by the formula $\Delta S^\ddagger = 4.576 (\log k - 10.753 - \log T) + E_a/T$ (at 50°). ΔH^\ddagger and ΔS^\ddagger are probably accurate within ± 0.3 kcal/mol and ± 1 eu, respectively.

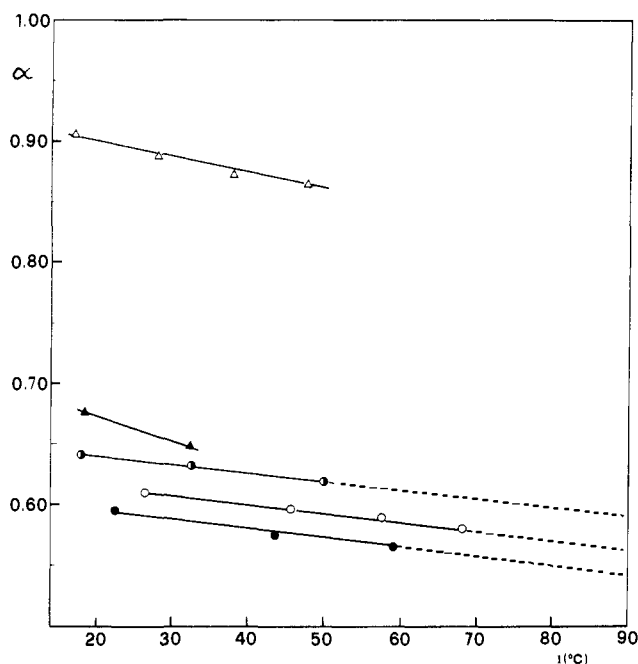
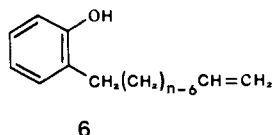


Figure 1. Degree of dissociation in 75% ethanol and 0.01 *M* K_2CO_3 as a function of temperature for the following *o*-substituted phenols: (Δ) guaiacol; (\blacktriangle) *o*-ethylphenol; (\bullet) 4, $n = 8$; (\circ) 4, $n = 9$; (\bullet) 4, $n = 10$.

and 9, a considerable part of the side reaction was due to a competing β -elimination reaction, leading to the open-chained isomeric alkenylphenols 6. Varying amounts of the



latter compounds were shown to be formed by VPC for $n = 8$ and 9 (Table I). Considering that the competing "spontaneous" solvolytic reaction, as estimated from the rate of bromide ion release from hexyl bromide in the water-ethanol K_2CO_3 solution,⁵ amounts to 1.4, 10.8, and 14.7% of $k_R(\text{obsd})$ for the eight, nine, and ten rings, respectively, it appears that more than 96% of the starting material was ac-

counted for in all cases. Yield data and α values were used to obtain cyclization rate constants (k_R) from the observed first-order rate constants [$k_R(\text{obsd})$] by means of the expression $k_R = f k_R(\text{obsd})/\alpha$, where f is the fraction of cyclic product formed in a given cyclization reaction. It was based on VPC data for the eight-, nine-, and ten-membered rings (Table I) and was assumed to be unity for ring sizes five, six, and seven. The results are collected in Table II.

The alkylations with butyl bromide of the anions derived from both guaiacol and *o*-ethylphenol were studied in the same solvent, as the intermolecular counterparts of the cyclization reactions 1 and 2, respectively. In order to force the equilibrium $ArOH + OH^- \rightleftharpoons ArO^- + H_2O$ to the right and to avoid any excess of base, the phenol to hydroxide ion ratio was never less than 2. Pseudo-first-order kinetics were obtained by keeping the initial concentration of butyl bromide quite low (2.5 to 3.5×10^{-4} *M*). Second-order rate constants (k_2) were then calculated by means of the equation $k_2 = k(\text{obsd})/[ArO^-]$, where $[ArO^-]$ was assumed to be equal to the stoichiometric concentration of NaOH. In agreement with this assumption, the k_2 values were found to be independent of the $[ArOH]_{\text{added}}/[NaOH]_{\text{added}}$ ratio. The measurements were carried out at three different temperatures over a 30° range for both phenols. Rate data and activation parameters are reported in Table III.

In order to compare intra- with intermolecular reactivity, the so-called effective molarities,^{9,10} as defined by the ratio between the first-order intramolecular rate constants and the second-order rate constants of the intermolecular counterparts, were calculated and reported in Table IV, together with the $k_R(\text{diether})/k_R(\text{monoether})$ ratios. Since the rates of the intermolecular reactions are very similar, these ratios are practically coincident with the ratios between the corresponding effective molarities and provide a quantitative measure of the oxygen atom effect on the ease of ring closure.

Discussion

The Effect of Chain Length. Reactivity data, enthalpies, and entropies of activation of monoether formation (reaction 2) and, for comparison, similar data for diether formation (reaction 1) are plotted as functions of ring size in Figures 2, 3, and 4, respectively. Figure 2 shows the marked ef-

Table III. Kinetic Data for the Intermolecular Alkylation of the Anions Derived from Both Guaiacol and *o*-Ethylphenol with Butyl Bromide^a in EtOH-H₂O 3:1 (v/v) at 0.03 *M* Ionic Strength

Parent phenol	Temp. °C	[ArOH] ^b	[NaOH] ^b	$k(\text{obsd}), \text{sec}^{-1}$	$k_{\text{inter}}, M^{-1} \text{sec}^{-1}$ ^b	$\Delta H^\ddagger, \text{kcal/mol}^d$	$\Delta S^\ddagger, \text{eu}^d$
Guaiacol	50.0	0.060	0.030	1.14×10^{-5}	3.91×10^{-4}	19.0	-15.4
	50.0	0.060	0.030	1.19×10^{-5}	4.06×10^{-4}		
	65.0	0.060	0.030	4.43×10^{-5}	1.54×10^{-3}		
	65.0	0.060	0.030	4.49×10^{-5}	1.56×10^{-3}		
	80.0	0.060	0.015 ^c	7.55×10^{-5}	5.29×10^{-3}		
	80.0	0.120	0.030	1.58×10^{-4}	5.54×10^{-3}		
	80.0	0.120	0.015 ^c	7.73×10^{-5}	5.41×10^{-3}		
	80.0	0.060	0.030	1.53×10^{-4}	5.34×10^{-3}		
<i>o</i> -Ethylphenol	50.0	0.060	0.030	8.71×10^{-6}	2.97×10^{-4}	20.3	-12.2
	50.0	0.060	0.030	8.47×10^{-6}	2.89×10^{-4}		
	65.0	0.060	0.030	3.50×10^{-5}	1.21×10^{-3}		
	65.0	0.060	0.030	3.69×10^{-5}	1.28×10^{-3}		
	80.0	0.060	0.030	1.31×10^{-4}	4.59×10^{-3}		
	80.0	0.120	0.030	1.30×10^{-4}	4.55×10^{-3}		
	80.0	0.120	0.015 ^c	6.87×10^{-5}	4.81×10^{-3}		
	80.0	0.060	0.015 ^c	6.87×10^{-5}	4.81×10^{-3}		

^a The initial concentration of butyl bromide was in the range 2.5 – 3.5×10^{-4} *M*. ^b The initial concentrations are calculated at room temperature. The k_{inter} values are corrected for the expansion of solvent with temperature. ^c $NaClO_4$, 0.015 *M*, was added in order to buffer the ionic strength. ^d See footnote *g* of Table II. The Arrhenius plots had correlation coefficients 0.99989 and 0.99986 for guaiacol and *o*-ethylphenol, respectively.

Table IV. Comparison of Ring-Closure Tendencies of the Anions Derived from Both *o*- ω -Bromoalkoxyphenols 1 and *o*- ω -Bromoalkylphenols 4 for Different Ring Sizes^a

Ring size <i>n</i>	Effective molarity, <i>M</i> (diethers) ^{b,c}	Effective molarity, <i>M</i> (monoethers) ^{b,d}	$k_R(\text{diether})/k_R(\text{monoether})$ ^{c,d}
5		131000	
6	3880	6560	0.81
7	36.3	118	0.42
8	1.66	0.352	6.54
9	0.308	0.0557	7.55
10	0.152	0.0499	4.16

^a All rate constants at 50.0°. ^b Calculated as k_R/k_2 , where k_2 is the corresponding intermolecular counterpart (from Table III). ^c k_R 's for diethers from ref 5. ^d k_R 's for monoethers from Table II.

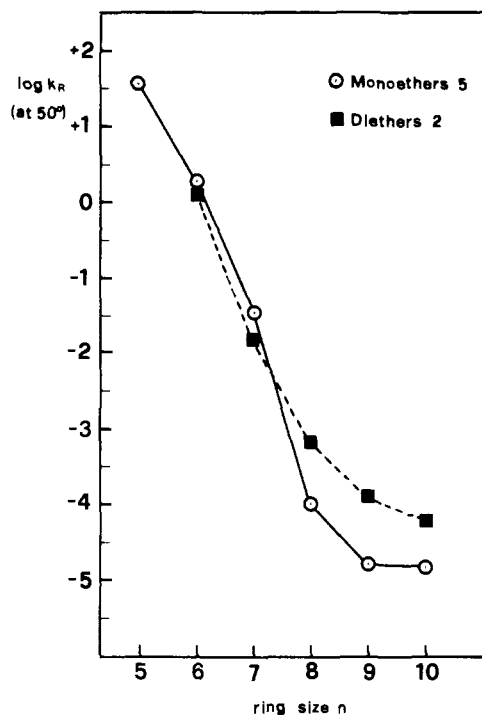


Figure 2. Dependence of $\log k_R$ on ring size for the formation of cyclic mono- and diethers from the parent open-chained *o*-substituted phenoxides in 75% ethanol at 50°.

fect of chain length on the rate of ring closure, the five-membered monoether being formed over six powers of ten as fast as the nine- and ten-membered rings. The retarding effect caused by each additional methylene group is expressed by the ${}_n k_R/{}_{n+1} k_R$ ratio (Table II). A factor of 20 is found for $n = 5$. The reactivity order ${}_5 k_R > {}_6 k_R$ is quite common in ring-closure reactions of the S_N2 type.¹¹ The largest reactivity drop is found on going from the seven- to the eight-membered ring, where a factor of 335 is observed. A substantial leveling off results for greater ring sizes, the nine- and ten-membered monoethers being formed at practically the same rate. Preliminary data for the 16-membered ring seem to suggest that a minimum in the ease of ring closure is probably little pronounced, if it exists at all. Thus, the mono- and diether series behave similarly, as a clean-cut reactivity minimum does not appear in either case.

If we now consider the enthalpies of activation (Figure 3), we find that the structural effects responsible for a maximum in free energy of activation in other series^{12,13} still give an appreciable contribution to the enthalpy of activation of the medium ring ethers, where a maximum lying at

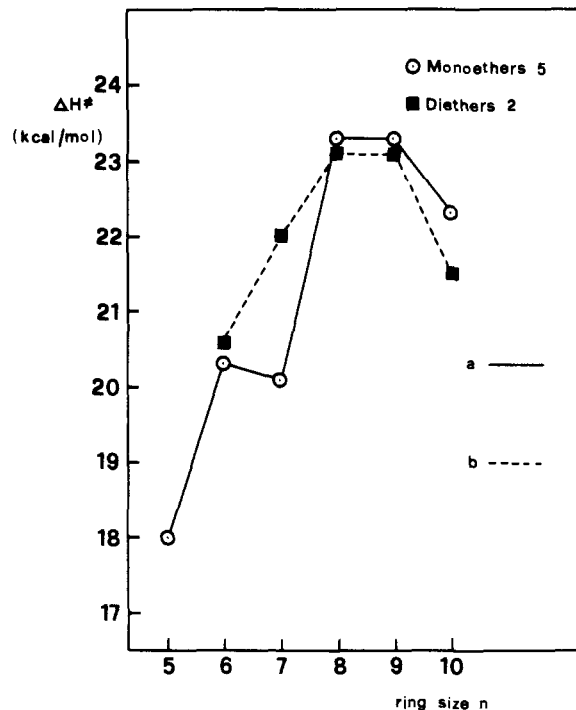


Figure 3. Enthalpies of activation vs. ring size for the formation of cyclic mono- and diethers. ΔH^\ddagger values for the relative intermolecular counterparts are also shown, i.e., for the reaction of guaiacololate ion with butyl bromide (a) and for the reaction of *o*-ethylphenolate ion with butyl bromide (b).

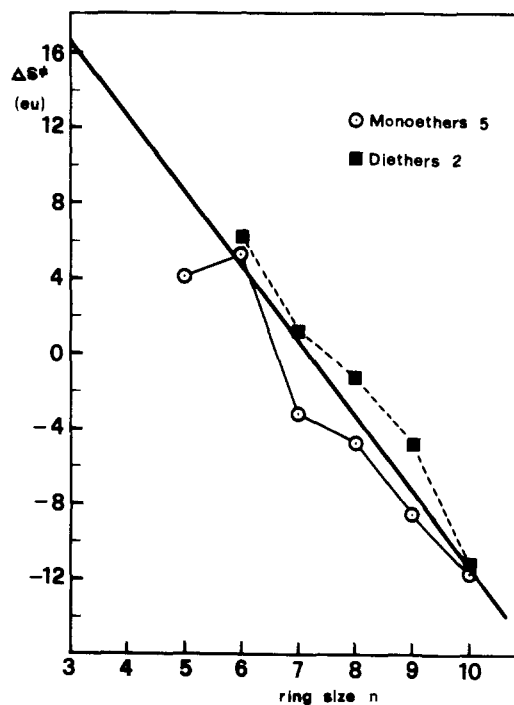


Figure 4. Entropy of activation vs. ring size for the formation of cyclic mono- and diethers. The heavy line, as obtained by a least-squares treatment of data for ring sizes 6 to 10 in both series, corresponds to the equation, $\Delta S^\ddagger = 28.7 - 4.0n$.

the eight- and nine-membered rings is observed. Hence, the latter rings (or, rather, the transition states leading to them) appear to be the most strained terms in both mono- and diether series. A strain energy in the order of 3 to 4 kcal/mol can be estimated by comparison with the ΔH^\ddagger values of the corresponding strain-free intermolecular coun-

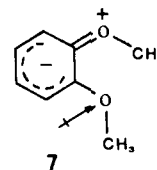
terparts. Accordingly, ring closure to the six-membered ring is seen to be essentially unaffected by strain, although it has been suggested that a 90° bond angle should produce an unfavorable geometry in a six-membered cyclic transition state.¹⁰

The entropies of activation are plotted in Figure 4. The present data substantially confirm previous findings,⁵ namely a general decrease as n increases from 6 to 10, in agreement with the well-known Ruzicka's hypothesis⁴ on the diminishing probability of encounter between chain terminals as the chain length increases. The heavy line, resulting from a linear least-squares treatment of data for ring size 6 to 10 of both series, follows the equation $\Delta S^\ddagger = 28.7 - 4.0n$, with correlation coefficient $r = 0.954$. The slope, -4.0 eu, represents the coarse average decrease in entropy of activation per added methylene group. This value is in surprisingly good agreement with the representative value of ca. 4.5 eu that has been estimated for the maximum entropy loss resulting from freezing an internal rotation as taking place upon the cyclization process.^{10,14} Following Benson and O'Neal's ideas,¹⁴ compensating factors due to the different degree of "looseness" in the out-of-plane bending motions of the various rings can greatly decrease the entropy loss upon cyclization. Our experimental results suggest a substantially similar "tightness" for the transition states leading to both series of cyclic ethers in the investigated range, despite the fact that larger rings are expected to be considerably "looser" than the smaller ones.¹⁴ If, in the linear correlation above, we extrapolate ΔS^\ddagger down to ring size $n = 3$, the value of +16.7 eu thus obtained may be taken as representative of hypothetical ring closure reactions essentially free from any entropy loss contribution because of freezing internal rotations in both series. This highly positive value reflects a substantial desolvation of the nucleophilic oxide anion for any member of the series undergoing change to the corresponding transition state. Also, assuming a similar extent of desolvation for the intermolecular reactions, "corrected" values of -32 and -29 eu are obtained for the bimolecular alkylation reactions of guaiacol and *o*-ethylphenol, respectively. The latter can be viewed as "normal" entropies of activation for bimolecular reactions in solution,¹⁰ devoid of specific solvation entropy effects, and represent losses of translational plus (overall) rotational entropy. Following Page and Jencks,¹⁰ these values provide the entropic driving force for maximum intramolecular rate acceleration. Accordingly, maximum "effective concentrations" of 10^7 and $10^{6.3}$ *M* are obtained as $\exp(32/R)$ and $\exp(29/R)$ for the intramolecular alkylation reactions of *o*-alkoxy- and *o*-alkylphenols, respectively, which can be compared with the value of ca. 10^8 *M* estimated by Page and Jencks. Considerably lower values were actually observed even with the smallest ring sizes (Table IV). This is to be ascribed mainly to entropy losses because of freezing internal rotations.

The five-membered ring formation requires a further comment. A reduced extent of solvation of the least basic phenoxide precursor could be held responsible for the low ΔS^\ddagger observed. Assuming that the difference in solvation free energy is negligible as a result of a compensation effect,¹⁵ i.e., $\delta\Delta G^\ddagger_{\text{solv}} = \delta\Delta H^\ddagger_{\text{solv}} - T\delta\Delta S^\ddagger_{\text{solv}} \approx 0$, and that $\delta\Delta S^\ddagger_{\text{solv}}$ may be estimated as the difference between the observed value and the extrapolated one, i.e., $\delta\Delta S^\ddagger_{\text{solv}} = +4.1 - 8.7 = -4.6$ eu, it follows that the reduced extent of initial state solvation lowers the enthalpy of activation by ca. 1.5 kcal/mol. The "corrected" enthalpy of activation of 19.5 kcal/mol compares well with those of both the six- and seven-membered homologs, as well as with that of the intermolecular counterpart, and suggests that the five-membered cyclic monoether formation is not characterized by a

reduced strain, although a low enthalpy of activation is observed. However, since the slope (4.0) of the line in Figure 4 is very close to the maximum expected value (4.5), $\Delta S^\ddagger_{\text{solv}}$ for the terms with $n > 5$ is likely to be constant or nearly so. In other words, our data suggest that, although the remote ω -bromo substituent is capable of exhibiting an acidity enhancing effect even when n is large, the basicity differences of the corresponding phenoxides are not so large (when $n > 5$) as to determine a substantial difference in either initial state solvation and nucleophilic ability. This is further substantiated by the fact that the more basic sodium *o*-ethylphenolate reacts with butyl bromide at about the same rate, and with similar activation parameters, as does sodium guaiacolate. As a consequence, the activation parameters ΔH^\ddagger and ΔS^\ddagger can be regarded with some confidence as substantially reflecting internal factors, with the possible exception of the values found for ring size $n = 5$.

The Oxygen Atom Effect. The $k_{\text{R}(\text{diether})}/k_{\text{R}(\text{monoether})}$ ratios at 50° for different ring sizes are reported in Table IV. This is the first report of a quantitative determination of the oxygen atom effect on the ease of ring closure. In the medium ring region, the ratios are significantly greater than the value of 1.3 observed for the intermolecular reactions (Table III), with a maximum lying at ring sizes eight and nine. Therefore, it appears that substitution of the benzylic methylene group of **5** with an oxygen atom lowers the free energy of activation of the cyclization reaction by 1.2, 1.3, and 0.9 kcal/mol for ring sizes eight, nine, and ten, respectively. Since it has been estimated^{7b} that substitution of a $-\text{CH}_2\text{CH}_2-$ grouping by a *cis* double bond reduces the strain energy of cyclooctane and cyclodecane by 2.7 and 5.4 kcal/mol, respectively, it is concluded that the presence of two sp^2 carbon atoms is the main factor in determining the peculiar behavior of both mono- and diethers, i.e., the substantial lack of a minimum in ease of formation, the oxygen atom(s) having a somewhat smaller effect. The fact that the magnitude of the oxygen atom effect as expressed by the $k_{\text{R}(\text{diether})}/k_{\text{R}(\text{monoether})}$ ratio substantially parallels the behavior of the enthalpies of activation strongly supports the view that strain in the cyclic transition states is the dominating factor, i.e., the greater the strain, the greater the relief of transannular interactions and bond opposition forces associated with the replacement of the benzylic methylene group by a "bare" oxygen atom. However, comparison of reactivity data for the two given series requires additional factors to be considered. These are (i) intramolecular dipole-dipole repulsion of the oxygen- C_α bond moments of the diethers and (ii) steric hindrance to conjugation. Molecular models clearly show that the cyclic diethers cannot assume, even when $n = 10$, the planar conformation that has been proposed¹⁶ for veratrole (**7**) for optimum electrostatic



interactions but, rather, nonplanar conformations resulting in varying degrees of opposition of the $\text{O}-\text{C}_{\text{aliph}}$ bond moments, depending on ring size. As to the conjugation effect, literature uv data,^{16,17} together with data from this laboratory,¹⁸ clearly indicate that, in seven, eight, and nine-membered mono- and diethers, conjugative interactions of the alkoxy chromophores with the benzene ring are severely hindered, as compared with the open-chained counterparts, *o*-methylanisole and veratrole, respectively. However, while the ten-membered diether still shows a substantial hypochromic effect, comparable to those of the lower homologs,

the corresponding monoether has both λ_{\max} and ϵ_{\max} practically coincident with those of *o*-methylanisole. This is in agreement with the view that optimum conjugative interaction has greater steric requirements in the diethers than in the monoethers, because of the presence of two conjugative substituents in the former compounds. To sum up, electrostatic and resonance effects are expected to lower the rate of formation of the cyclic diethers. Since what is observed is just the opposite in the medium ring region, it appears that these effects play but a minor role in determining the oxygen atom effect. They could be responsible, at best, for the slight reversed effect observed for ring size seven (Table IV).

The Competing Intramolecular β -Elimination Reaction. Yield data from Table I show that cyclization to the eight- and nine-membered rings is accompanied by extensive formation of the isomeric alkenylphenols **6**, $n = 8$ and 9 , respectively. Even greater yields of the latter compounds were isolated when the cyclizations were carried out on a preparative scale in Me_2SO solution at 55° .¹⁹ Furthermore, alkenylphenols were already found to accompany eight- and nine-membered diether formation,⁵ although yields were smaller than those found in this work. The same arguments used previously to show that olefin formation derives from an intramolecular β -elimination reaction of the E2 type, in which the neighboring oxygen anion acts as the base, can also apply to the present case.

Intramolecular hydrogen transfer via medium-sized cyclic transition states in reactions other than eliminations has received increasing attention in the last few years, particularly in connection with the problem of intramolecular acid-base catalysis.²⁰⁻²² In the dedeuteration of $(\text{CD}_3)\text{CO}$ catalyzed by ω -dimethylaminoamines Hine et al.²¹ found that optimum ring size for internal proton transfer is eight atoms. As an explanation, it was suggested that an eight-membered transition state should be highly preferred over a smaller one, particularly when a double bond is present in the ring, essentially because the greater ring can better accommodate a linear (or quasilinear) arrangement of donor-proton acceptor. According to these ideas in a recent paper, Gandour²² stated as a general rule that optimum ring size for intramolecular proton transfer is eight atoms. This rule would seem to offer an explanation to our findings, i.e., that the olefin forming side-reaction most easily occurs for ring sizes eight and nine. Although there is no doubt that both weak and strong hydrogen bonds tend to be linear,²³ no quantitative information is available so far with regard to the bending force constants. However, the latter should not be very large as shown by the fact that the strain energy of the proton-bound cyclic 1,3-diaminopropane (ring size six), whose strong hydrogen bond is severely bent, is very similar to those of the eight- and ten-membered homologs.²⁴ Hence, we believe that additional data are required for a proper understanding of the general problem of optimum ring size for intramolecular proton transfer. Therefore, the consistency of our data with Gandour's suggestion is likely to be fortuitous. The facts that, in our systems, the side reaction accompanies only the most strained rings in both series, and that the extent of elimination increases on going from the diether to the monoether series, as well as from aqueous ethanol to Me_2SO , where an enhanced basicity of the phenoxide ions is expected, lead to the conclusion that both the operation of a steric congestion at the cyclic transition states and an increase in base strength facilitate intramolecular elimination at the expense of intramolecular substitution. The similarity between these factors and those affecting the E2/SN2 ratio in the case of the intermolecular reactions²⁵ is evident, if one considers that the special strain features in the cyclic transition states render the carbon

atom bearing the leaving group less prone to nucleophilic attack as branching at the α or β position does in the intermolecular reactions.

Experimental Section

Most techniques and apparatuses were as previously described.⁵ Stopped-flow kinetics were performed by following the phenoxide ion absorption at either 243 or 293 nm on a Durrum-Gibson stopped-flow spectrophotometer Model D-110, matched with a Hewlett-Packard storage oscilloscope Model 1207 B.

Materials. Guaiacol (Merck) and *o*-ethylphenol (Merck-Schuchardt) were commercial samples and distilled before use. *o*- ω -Bromoalkylphenols **4**, $n = 8, 9, 10$, the corresponding cyclic ethers **5**, $n = 8, 9, 10$, and alkenylphenols **6**, $n = 8$ and 9 , were available from a previous investigation.¹⁹ Chroman²⁶ (**5**, $n = 6$) [bp $99-102^\circ$ (16 mm); $n^{19.5}_D$ 1.5496 [lit.²⁶ bp $96-100^\circ$ (17 mm); n^{17}_D 1.5505]] and homochroman²⁷ (**5**, $n = 7$) [bp $114-115^\circ$ (27 mm); n^{20}_D 1.5407 [lit.²⁸ bp 102° (13 mm); $n^{20.5}_D$ 1.5412; mp 28° 17]] were prepared by literature methods.

Coumaran (**5**, $n = 5$) and *o*-2-bromoethylphenol (**4**, $n = 5$) were prepared by refluxing (8 hr) a solution of 6.3 g (0.041 mol) of β -*o*-anisylethanol²⁹ [bp $146-150^\circ$ (25 mm); n^{20}_D 1.5412 [lit.³⁰ bp $140-148^\circ$ (18 mm); n^{25}_D 1.5361]] in 60 ml of an acetic acid-concentrated hydrobromic acid mixture (2:1 v/v). Fractional distillation of the crude reaction product obtained after standard work-up afforded **5**, $n = 5$ [1.90 g, 0.016 mol, 39% yield; bp $50-55^\circ$ (2.5 mm); n^{21}_D 1.5506 [lit.¹⁷ bp $77-80^\circ$ (8 mm); $n^{15.5}_D$ 1.5528]; ¹H NMR δ 6.5-7.2 (m, 4 H, aromatic protons), 4.45 (t, 2 H, CH_2O), 3.1 (t, 2 H, benzylic protons), and **4**, $n = 5$ [1.35 g, 6.7 mmol, 16% yield; bp $107-115^\circ$ (2.5 mm); mp $41-42.5^\circ$] after sublimation under vacuum at 30° . Structure assignment to the latter compound was effected on the basis of spectral data and elemental analysis: ir 3610 cm^{-1} (OH); ¹H NMR δ 6.5-7.2 (m, 4 H, aromatic protons), 4.8 (s, 1 H, OH), 2.9-3.7 (symmetric m, 4 H, CH_2CH_2 protons).

Anal. Calcd for $\text{C}_8\text{H}_9\text{BrO}$: C, 47.79; H, 4.51; Br, 39.74. Found: C, 47.79; H, 4.52; Br, 39.96.

o-3-Bromopropylphenol (**4**, $n = 6$) and *o*-4-bromobutylphenol (**4**, $n = 7$) were obtained in 66 and 59% yield by treatment of the corresponding cyclic ethers chroman and homochroman, respectively, with BBr_3 in dry CH_2Cl_2 .³¹ The products were purified by distillation. Compound **4**, $n = 6$: bp 105° (1 mm), n^{22}_D 1.5696; ir 3605 cm^{-1} (OH); ¹H NMR δ 6.5-7.2 (m, 4 H, aromatic protons), 4.75 (s, broad, 1 H, OH), 3.35 (t, 2 H, CH_2Br), 2.75 (t, distorted, 2 H, benzylic protons), 1.9-2.35 (m, 2 H, "central" methylene protons).

Anal. Calcd for $\text{C}_9\text{H}_{11}\text{BrO}$: C, 50.26; H, 5.15. Found: C, 50.41; H, 5.14.

Compound **4**, $n = 7$: bp $140-141^\circ$ (6 mm); n^{21}_D 1.5623; ir 3605 cm^{-1} (OH); ¹H NMR δ 6.5-7.2 (m, 4 H, aromatic protons), 4.8 (s, 1 H, OH), 3.35 (t, 2 H, CH_2Br), 2.55 (t, distorted, 2 H, benzylic protons), 1.5-2.1 (m, 4 H, "central" methylene protons).

Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{BrO}$: C, 52.42; H, 5.72; Br, 34.88. Found: C, 52.14; H, 5.55; Br, 35.07.

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