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Ring-Closure Reactions. 9.[1] Kinetics of Ring Formation from *o*-ω-Bromoalkoxy Phenoxides and *o*-ω-Bromoalkyl Phenoxides in the Range of 11- to 24-Membered Rings. A Comparison with Related Cyclization Series[2]

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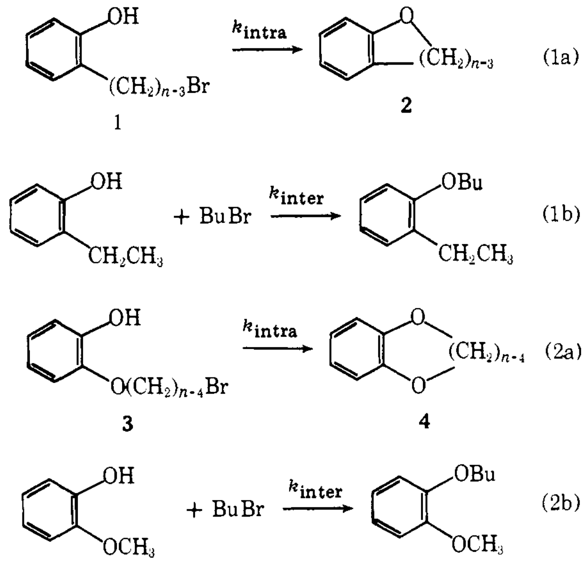
Abstract: Our quantitative investigations of the formation of aromatic mono- and diethers via intramolecular Williamson synthesis have been considerably extended. Kinetic data are now available for the 11-, 14-, and 16-membered monoethers and for the 11-, 12-, 13-, 14-, 16-, and 24-membered diethers. When combined with previous results, the present data provide a good insight into intramolecular reactivity, which spans seven powers of ten in the monoether series. Ring-closure reactivity is found to be remarkably insensitive to ring size in the large ring series, as a result of a substantial leveling off in both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values. The influence of the oxygen atom on ease of ring closure has been shown to display a general decrease on decreasing the strain energy of the transition states. A striking feature emerges from a comparison of the reactivity data related to different cyclization reaction series, when brought out in terms of effective molarities (EM). Even though marked and significant structure-dependent differences are observed in the common- and medium-ring regions for several of the series considered, EM values converge to a rather narrow range of values between 0.1 and 0.01 M. This remarkable result suggests that the ease of formation of large rings is substantially independent of the nature of the functional groups, the length of the chain, and the presence of structural moieties other than methylene groups.

In the last few years a considerable interest has been devoted to intramolecular interactions of remote groups in long-chain compounds. A wealth of new information has been collected on chain length dependent phenomena also in fields other than mechanistic organic chemistry.[3-11]

Our studies[1] on ring-closure reactions of long-chain bifunctional substrates include the physical and mechanistic aspects of intra- vs. intermolecular reactivity and are intended to establish the relationship between structure and reactivity on a quantitative basis. A significant body of data is needed to allow an assessment of the ease of ring closure in terms of structure and size of the ring to be formed. Rate data and activation parameters in 75% aqueous ethanol have been reported for the formation of cyclic mono- and diethers, **2** and **4**,[12,13] up to ring size ten. We now report an extension of our kinetic studies to the formation of higher homologues in both series. Rate data have been obtained for the formation of the 11-, 14-, and 16-membered monoethers **2**, and of the 11-, 12-, 13-, 14-, 16-, and 24-membered diethers **4**. The activation parameters for representative terms in the diether series have also been determined.

When the results from the present work are compared with available quantitative data on large rings in related systems from this and other laboratories, a uniform pattern is revealed, which will be shown to be an inherent feature of large ring formation in general.

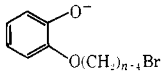
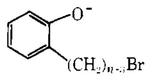


1 (1a) 2
(1b)
3 (2a) 4
(2b)

Experimental Section

Rate measurements and product analyses were carried out as previously described.[12,13] The preparation of the compounds used in this work has been reported elsewhere.[1]

Table I. Kinetic Data for the Ring-Closure Reaction of $o\text{-}^{-}OC_6H_4O(CH_2)_{n-4}Br$ and $o\text{-}^{-}OC_6H_4(CH_2)_{n-3}Br$ in 75% Aqueous Ethanol at 0.03 M Ionic Strength

Compd	n[a]	Temp, °C	k_{obsd}, s^{-1}	α[b]	Yield, %[c]	k_{intra}, s^{-1}	k_{intra} (at 50 °C), s^{-1}	$\Delta H^{\neq}$, kcal/mol[e]	$\Delta S^{\neq}$, eu[e]
	11	59.8	$4.64 \pm 0.04 \times 10^{-5}$	0.78_7	90.4	5.33×10^{-5}			
		69.7	$1.18 \pm 0.01 \times 10^{-4}$	0.77_3	90.1	1.37×10^{-4}			
		79.6	$3.00 \pm 0.01 \times 10^{-4}$	0.75_9	90.1	3.56×10^{-4}	1.85×10^{-5}[d]	22.0	−12.3
		89.5	$7.22 \pm 0.00 \times 10^{-4}$	0.74_4	90.1	8.74×10^{-4}			
	12	50.0	$1.97 \pm 0.04 \times 10^{-5}$	0.80_1	92.1	2.27×10^{-5}	2.27×10^{-5}		
	13	50.0	$1.36 \pm 0.01 \times 10^{-5}$	0.80_1	88.5	1.50×10^{-5}	1.50×10^{-5}		
	14	59.8	$2.36 \pm 0.02 \times 10^{-5}$	0.78_7	81.1	2.43×10^{-5}			
		69.7	$6.17 \pm 0.05 \times 10^{-5}$	0.77_3	81.0	6.47×10^{-5}			
		79.6	$1.52 \pm 0.00 \times 10^{-4}$	0.75_9	80.5	1.61×10^{-4}	8.89×10^{-6}[d]	21.4	−15.5
		89.5	$3.50 \pm 0.00 \times 10^{-4}$	0.74_4	79.6	3.74×10^{-4}			
	16	59.8	$2.28 \pm 0.01 \times 10^{-5}$	0.78_7	80.5	2.33×10^{-5}			
		69.7	$5.77 \pm 0.02 \times 10^{-5}$	0.77_3	79.7	5.95×10^{-5}			
		79.6	$1.38 \pm 0.01 \times 10^{-4}$	0.75_9	78.5	1.43×10^{-4}	9.07×10^{-6}[d]	20.1	−19.6
		89.5	$2.93 \pm 0.07 \times 10^{-4}$	0.74_4	75.7	2.98×10^{-4}			
	24	50.0	$2.20 \pm 0.03 \times 10^{-5}$	0.80_1	92.9	2.56×10^{-5}			
		59.8	$5.06 \pm 0.06 \times 10^{-5}$	0.78_7	91.2	5.86×10^{-5}			
		79.6	$2.57 \pm 0.04 \times 10^{-4}$	0.75_9	88.4	2.99×10^{-4}	2.56×10^{-5}[d]	18.2	−23.4
		89.5	$5.30 \pm 0.11 \times 10^{-4}$	0.74_4	86.5	6.16×10^{-4}			
	11	50.0	$3.71 \pm 0.07 \times 10^{-6}$	0.54_3	58.0	3.96×10^{-6}	3.96×10^{-6}		
	14	50.0	$3.38 \pm 0.08 \times 10^{-6}$	0.54_3	53.8	3.35×10^{-6}	3.35×10^{-6}		
	16	50.0	$4.14 \pm 0.06 \times 10^{-6}$	0.54_3	62.3	4.75×10^{-6}	4.75×10^{-6}		

[a] Size of ring to be formed. [b] Degree of dissociation of the parent phenols in the reaction medium. [c] Calculated from eq 3. [d] Extrapolated from Arrhenius plots. [e] Calculated as previously reported.[13] The Arrhenius plots had the following correlation coefficients (ring size in parentheses): 0.99982 (11); 0.99996 (14); 0.99953 (16); 0.99987 (24). $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are probably accurate within ±0.3 kcal/mol and ±1 eu, respectively.

Results

The kinetics of cyclization were run in 75% aqueous ethanol (v/v) in the presence of a large excess of K_2CO_3 (0.01 M) at very low substrate concentration, in the order of $1\text{-}2 \times 10^{-4}$ M. Bromide ion release was found to follow strictly first-order kinetics up to 3 half-lives, the reaction being free from any appreciable contribution of higher order kinetics terms. As previously found,[12,13] under the given conditions the observed first-order rate coefficient k_{obsd} is given by the sum of two independent terms, as shown in eq 3, where k_{intra} refers to ring closure and k_{solv} represents the "spontaneous" solvolytic reaction of the CH_2Br end in the reaction medium.

$$k_{obsd} = \alpha k_{intra} + k_{solv} \qquad (3)$$

The incomplete dissociation of the starting phenols under the reaction conditions is accounted for by the degree of dissociation α, which was determined spectrophotometrically[12] and found to be independent of chain length within the limits of experimental error. Equation 3 does not contain any term related to the intramolecularly assisted β-elimination reaction, which has been reported to accompany ring closure in the case of the eight- and nine-membered ring formation.[12-14] This side reaction did not appreciably compete with the ring-closure reactions studied in the present work, as was found to be the case for the ten-membered ring formation in either series.[12-14]

In order to correct the observed rate constants k_{obsd} and to obtain the cyclization rate constants k_{intra} by means of eq 3, k_{solv} values at the proper temperatures were required. The latter were estimated on the basis of a model reaction, namely, the solvolysis of hexyl bromide in the reaction medium, for which quantitative data were available from previous work.[12] The correctness of the above procedure was checked in the following way. The yield of cyclic product to be obtained in a given cyclization reaction can be predicted according to

$$\text{yield} = 100(k_{obsd} - k_{solv})/k_{obsd} \qquad (4)$$

which is derived from eq 3. VPC product analysis of the kinetic solutions at the end of the reactions was effected at 78 °C in two typical cases. The following results were obtained: cyclization of compound **1**, $n = 16$, 77.7% yield (predicted 78.5%); compound **2**, $n = 14$, 56.5% yield (predicted 53.8%). The agreement between actually found and predicted yields is quite satisfactory, the observed difference being probably less than the experimental uncertainty.

No attempt was made to detect the solvolysis products by VPC. The results of the kinetic experiments are collected in Table I. Table I shows that no less than 75% yield can be predicted by means of eq 4 for all cyclization reactions in the diether series. Moreover, since the activation enthalpy of the solvolytic reaction ($\Delta H^{\neq}_{solv} = 21.9$ kcal/mol)[12] is very close to those of the cyclization reactions, a nearly temperature-independent correction was needed. It is therefore assumed that the precision of the activation parameters, which were determined for selected terms of the given series, is not greatly affected by the above corrections. In the monoether series, however, the extent of the solvolytic side reaction is larger. The inherent precision of the "corrected" cyclization rate constants was not considered such as to allow the determination of reliable values for the activation parameters. Hence, the study of the temperature dependence of ring-closure rates was not undertaken in the latter series.

Discussion

Effect of Chain Length on Reactivity. The kinetic data from the present work, when combined with our previous data for the common and medium ring regions,[12,13] offer a wide intramolecular reactivity picture. Figure 1 shows a plot of log k_{intra} (at 50 °C) as a function of ring size for both mono- and diether formation. The absence of a well-defined minimum in ease of ring closure for the medium-ring region and beyond is conclusively confirmed in each series. As previously found for the lactonization reaction,[15] ring-closure reactivity experiences a substantial leveling off in the large-ring region. For example, in the diether series k_{intra} values in the ring size range 11 to 24 lie well within a factor of 3. This behavior results from the fact that both enthalpies and entropies of activation (Figures 2 and 3, respectively) are relatively insensitive to chain length in the

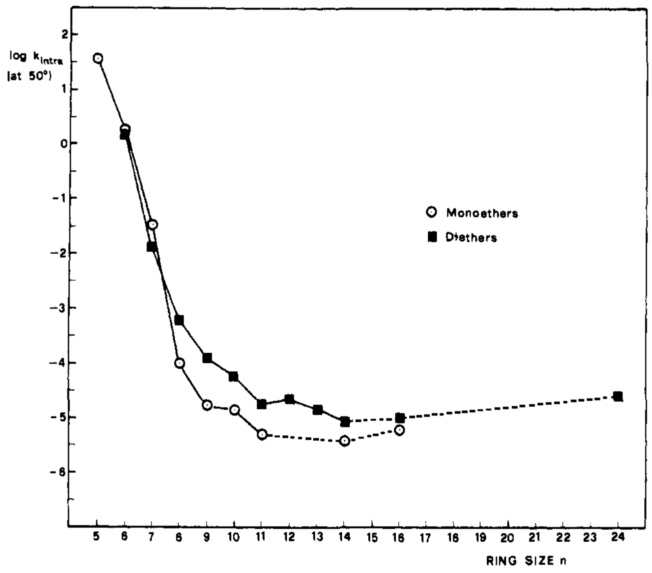


Figure 1. Rate profiles vs. ring size for the formation of cyclic mono- and diethers in 75% ethanol at 50 °C. Data from the present work and from ref 12 and 13.

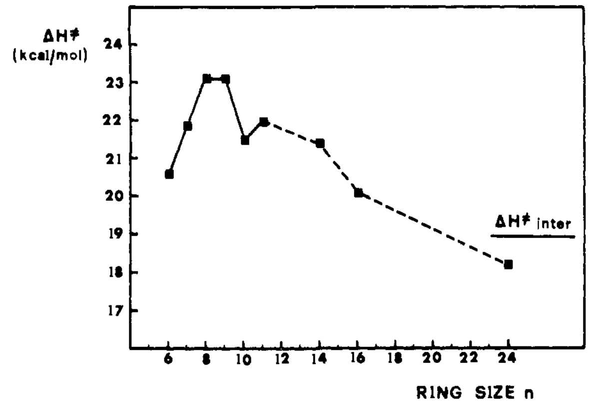


Figure 2. Enthalpy of activation for the formation of cyclic diethers in 75% ethanol as a function of ring size. The value for the intermolecular model reaction (2b) is also shown. Data from the present work and from ref 12 and 13.

large-ring region, when compared with corresponding changes for smaller ring sizes. Moreover, besides being small, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ changes are mutually divergent and lead to essential compensation in the resulting $\Delta G^{\ddagger}$ values.

The activation parameters for diether formation qualitatively bear striking analogies to those observed for the lactonization of ω-bromoalkanoate ions.[15] A clean-cut maximum in the 8- to 11-membered ring region is displayed by the enthalpies of activation, as a result of an overall medium-ring effect, due to a combination of bond angle deformations, bond opposition forces, and transannular interactions.[16] On increasing ring size, $\Delta H^{\ddagger}$ values decrease regularly, except for a small inversion involving the 10- and the 11-membered rings. At ring size 24 $\Delta H^{\ddagger}$ attains a value in the same order of magnitude as that for the intermolecular model reaction, in fact lower by an amount that is close to the sum of the experimental errors (Figure 2). A small, but still appreciable, strain energy, as estimated by the difference $\Delta H^{\ddagger}_{\text{intra}} - \Delta H^{\ddagger}_{\text{inter}}$, is present for ring size 14 and, possibly, also for ring size 16, in agreement with the view that even relatively large rings should be affected by a larger number of gauche conformations than the corresponding open-chained compounds.[17] It is of interest that theoretical calculations by Sisido[18] on the conformational energies of activation for ring-closure in the ring size range of 6–16 are in qualitative agreement with our data. In particular, conformational energies of activation of the order of 1.5 and 1.2 kcal/mol were reported for ring size 14 and 16, respectively.[19] It is unfortunate that theoretical calculations for larger rings are not available. Morawetz and Goodman[17] estimated the limiting value of large-ring strain energy as 2 kcal/mol. In contrast, $\Delta H^{\ddagger}_{\text{intra}}$ values for the formation of the 23-membered lactone[15] and 24-membered diether indicate that for these large ring sizes the strain energy, if any, is certainly not higher than the experimental uncertainty in determining the corresponding $\Delta H^{\ddagger}$ values.

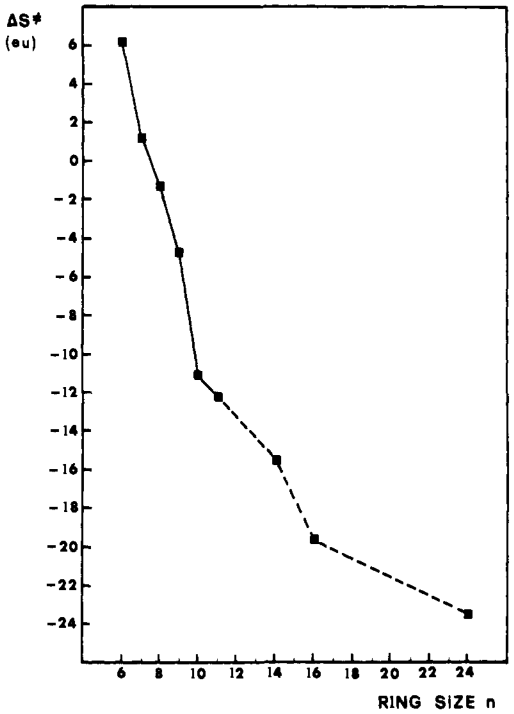


Figure 3. Entropy of activation for the formation of cyclic diethers in 75% ethanol as a function of ring size. Data from the present work and from ref 12.

A general decrease with increase of chain length is displayed by the entropies of activation. While a very steep drop of about 4 eu per added methylene group is observed for the lower terms up to $n = 10$, the higher rings exhibit a much less pronounced dependence on chain length, in agreement with the suggestion that looseness due to out-of-plane bending motions in the larger rings[20] tends to substantially offset the entropy loss due to freezing internal rotations upon cyclization.

The Oxygen Atom Effect. An extended sequence of $k_{\text{intra}}^{\text{diether}}/k_{\text{intra}}^{\text{monoether}}$ ratios, at 50 °C, which provides a measure of the oxygen atom effect arising from the replacement of a methylene group with an oxygen atom,[13] is reported in Table II. As suggested in a previous paper,[13] the greater the strain in the ring to be formed, the greater the oxygen atom effect, as a consequence of the relief in transannular interactions and bond opposition forces experienced by the diethers as compared to the monoethers. The oxygen atom effect closely parallels the behavior of the enthalpies of activation (Figure 2), even in the slight inversion which is found on going from the 10- to the 11-membered ring. Thus, such an inversion is likely to be real, and not merely an experimental artifact. The $k_{\text{intra}}^{\text{diether}}/k_{\text{intra}}^{\text{monoether}}$ ratios for either ring sizes 14 and 16 are still significantly larger than 1.36, i.e., the corresponding ratio for the analogous intermolecular reactions.[13] The latter observation provides further evidence that the investigated large rings are still affected by appreciable strain.

A Comparison with Related Cyclization Series. The Effective

Table II. The Oxygen Atom Effect as a Function of Ring Size

n^a	6^b	7^b	8^b	9^b	10^b	11	14	16	Inter^b
$\dfrac{k_{\text{intra}}^{\text{diether}}}{k_{\text{intra}}^{\text{monoether}}}$	0.807	0.420	6.42	7.55	4.16	4.67	2.65	1.91	1.36

[a] Ring size. [b] Data from ref 12 and 13.

Table III. Effective Molarity Data for Different Cyclization Reactions in the Ring-Size Range n = 3–24

n^a	Lactones^b	Monoethers^c	Diethers^c	Cyclic ammonium ions^d	Szwarc reaction^e
3	1.23×10^{-2}				
4	1.35×10				
5	1.60×10^{3}	1.31×10^{5}			
6	1.45×10	6.56×10^{3}	3.88×10^{3}	1.0×10^{2}	
7	5.51×10^{-2}	1.18×10^{2}	3.63×10	1.7	1.9×10
8	5.66×10^{-4}	3.52×10^{-1}	1.66		4.5
9	6.33×10^{-4}	5.57×10^{-2}	3.08×10^{-1}		2.6×10^{-1}
10	1.90×10^{-3}	4.99×10^{-2}	1.52×10^{-1}		1.1×10^{-1}
11	4.82×10^{-3}	1.35×10^{-2}	4.64×10^{-2}		
12	6.02×10^{-3}		5.69×10^{-2}	2.0×10^{-2}	7.0×10^{-2}
13	1.82×10^{-2}		3.76×10^{-2}		
14	2.37×10^{-2}	1.14×10^{-2}	2.23×10^{-2}	3.5×10^{-2}	5.7×10^{-2}
15	2.56×10^{-2}			4.0×10^{-2}	
16	2.94×10^{-2}	1.62×10^{-2}	2.28×10^{-2}		4.5×10^{-2}
17				7.5×10^{-2}	
18	2.90×10^{-2}				
20					
23	3.42×10^{-2}				2.4×10^{-2}
24			6.42×10^{-2}		1.1×10^{-2}

[a] Ring size. [b] ω-Bromoalkanoate ions in 99% Me_2SO at 50°C, from ref 15. [c] Data at 50°C from the present work and from ref 13. [d] ω-Bromoalkylamines in 30% 2-propanol at 73°C. Data of H. Freundlich and co-workers, and G. Salomon, quoted by G. Salomon, *Trans. Faraday Soc.*, **32**, 153 (1936). The reported values are cyclization constants C (see text) rather than effective molarities EM, since they have been calculated employing the available dimerization rate constants. The latter were obtained only with moderate accuracy. Hence the reported C values are to be regarded as affected by substantial errors. [e] Intramolecular electron exchange in $N(CH_2)_mN^{-\cdot}$ (N denoting an α-naphthyl moiety) in HMPA at 45°C, from ref 11b. Szwarc and co-workers have also reported EM data for the same same series in DME,[11b] and for a closely related series (phthalimide groups in place of α-naphthyls) in five different solvents.[11c] In all cases EM values are closely akin to those cited in this table.

Molarity. A correct comparison of the reactivity data from different reaction series for a proper understanding of the factors involved in intramolecular reactivity can be obtained in terms of the $k_{\text{intra}}/k_{\text{inter}}$ ratio, where k_{inter} is the second-order rate coefficient for a properly chosen intermolecular model reaction. Such a ratio defines the effective molarity (EM) of one reactive end relative to the other in the bifunctional compound and is expressed in M units. It is conceptually analogous to the "cyclization constant", C, first introduced by Stoll and Rouvé,[21] which was defined as $k_{\text{intra}}/k_{\text{dim}}$, where k_{dim} is the dimerization rate coefficient of the bifunctional monomer. C is the fundamental parameter for the interpretation of the kinetic behavior of a system in which cyclization is accompanied by polymerization,[21,22] and for predicting yield of cyclic product to be obtained in a given cyclization reaction as a function of reactant concentration.[17,21,23] For example, a virtually quantitative yield of cyclic product is expected when the initial concentration of the bifunctional monomer is much less than C. To this end, EM can be set equal to C as a first approximation, even though they may differ to some extent.[24]

The EM parameter has increasingly been used in recent years by many chemists working in different fields. Reports on the configurational statistics and on the dynamic properties of chain molecules[10,11,17,18,25] regard the $k_{\text{intra}}/k_{\text{inter}}$ ratio as a physically real "effective concentration" of one chain end in the neighborhood of the other. As Kuhn has pointed out,[26] such a concentration is given in the limit of $h \rightarrow 0$ by $W(h)/4\pi h^2$, $W(h)$ being the appropriate probability distribution function of the displacement h of the chain ends from one another. Strong rate accelerations observed for intramolecular reactions proceeding via five- and six-membered rings correspond to concentration values which exceed physically conceivable maximum values by several powers of ten.[27] In problems related to intramolecular catalysis and neighboring group participation,[27] which usually involve the above common rings, large effective molarities clearly do not represent real concentrations and may be accounted for by well-known chemical principles without the introduction of new chemical concepts.[27a,28] For a most general definition, the effective molarity is to be regarded as a "reduced" intramolecular reactivity, i.e., a reactivity of a bifunctional compound that is corrected for the characteristic reactivity of the two functional groups as if they were not connected by the intervening chain. The EM parameter provides a measure of the ease of ring closure and, depending on ring size, may involve acceleration as well as deceleration relative to the nonconnected 1 M functional groups.

EM data obtained from this and from our previous studies[12,13,15] are reported in Table III, together with the available literature data for which a quantitative comparison is possible.[29] It may incidentally be noted that the fact that EM data for both mono- and diethers are in all cases greater than 1×10^{-2} M is consistent with the finding that the contribution of the bimolecular polymerization reaction is negligible at the concentrations used in the kinetic runs, which are in the order of 10^{-4} M. While most of the data refer to ring-closure reactions in which a stable, covalently bonded ring compound is formed, the last column in Table III refers to a degenerate, reversible reaction, i.e., the intramolecular electron transfer in α-naphthyl-$(CH_2)_m$-α-naphthyl radical anions,[11b] which will be referred to as the Szwarc reaction. It has been argued

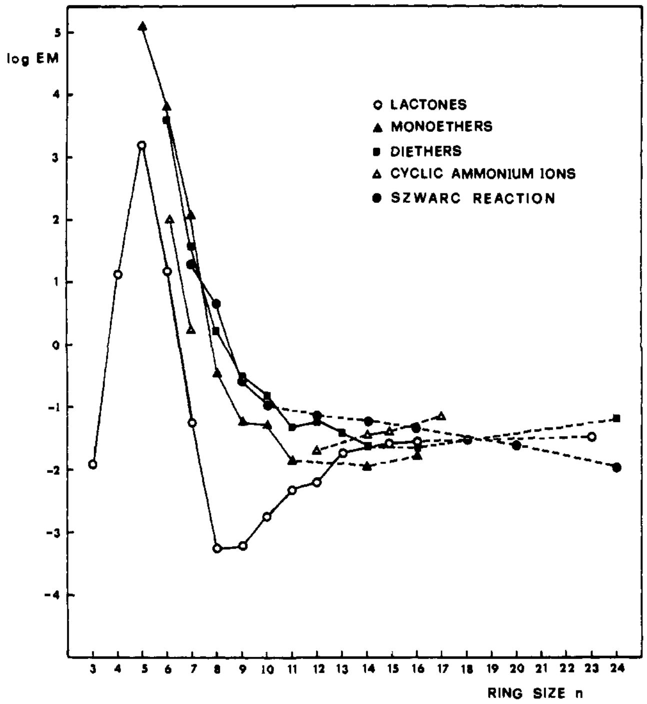


Figure 4. EM profiles vs. ring size for different cyclization reaction series. Data from different sources (see Table III).

that electron exchange between the two α-naphthyl moieties occurs at an approach distance of about 7-9 Å, the interacting groups being separated by two (or three) solvent molecules during electron exchange.[11b] For the sake of comparison, we have set the ring size for the latter system equal to $m + 4$, where m is the number of methylene groups linking the two α-naphthyl moieties, and 4 is an arbitrary number of "ring members" accounting for the intervening α-naphthyl moieties and solvent molecules.

A plot of log EM vs. ring size for the different systems is reported in Figure 4. A major feature in this comparison is that in spite of the structurally different type of the series considered, a generally uniform pattern is noted. Nevertheless, interesting structure-dependent differences are also observed in the common and medium ring region. In the case of mono- and diether formation, where the reactivity minimum expected for the medium ring region is missing, a major role is played by the incorporation in the ring of the two sp^2 carbon atoms and, to a lesser extent, of the oxygen atom(s).[13] This results in a substantial relief of strain. As a consequence high EM values are observed as compared to the lactones, where a definite reactivity minimum is obtained. In the lactone series ease of ring closure is lower also in the common ring region, because of the destabilizing factor due to the imposed "cis" conformation of the ester function in the rings with less than nine members.[22] It is worth noting that the behavior of the diethers approaches that of the Szwarc reaction, the latter representing an essentially strainless intramolecular process, as shown by the fact that the values of the energy of activation are practically coincident with those of the corresponding intermolecular model reaction.[11b] The monoethers exhibit intermediate behavior; i.e., the increased strain due to the presence of the benzylic methylene group in place of an oxygen atom appreciably decreases the ease of formation of the medium and lower large rings, thereby shifting the curve downwards, though not quite to the point that any real minimum appears.

In the large-ring region the vertical differences between the different series tend to vanish. Log EM values converge to a rather narrow range of values lying between −1 and −2 log units. This is a remarkable result, indicating that the ease of formation of large rings from a bifunctional precursor is essentially independent of the nature of the functional groups, the length of the chain, and the presence of structural moieties other than methylene groups. Moreover, since the different reactions have been studied in different solvents, the ring-closure tendency in the large-ring region also appears to be little sensitive to the nature of the solvent system. It has been shown[11b] that in the Szwarc reaction electron exchange between the two α-naphthyl groups occurs virtually at every intramolecular "collision", the rate of conformational changes being the limiting term, while this is certainly not the case for the other series reported in Table III. It is perhaps a little surprising that, in spite of this substantial difference, the EM values for the large rings of this reaction are quite close to those of the slower reactions.

In this paper we have emphasized the importance of the EM parameter and the related profiles vs. ring size for use in the comparison of data from different reactions as the correct approach to the quantitative study of intramolecular processes in general. Relations of the present experimental evidence with theoretical predictions based on the statistical treatment of chain molecules,[10,18,25] and with static and dynamic models of intramolecular reactions as proposed by Szwarc,[11b,c] deserve careful attention in further work.

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