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Ring Closure Reactions of Bifunctional Chain Molecules

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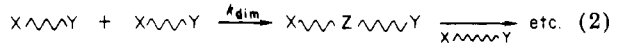
The foundations to our present knowledge of macrocyclization reactions were laid in the twenties and thirties by the pioneering work of Ruzicka[1] and Ziegler.[2] A major motivation in Ruzicka's work was the occurrence of ring compounds in nature and the discovery that 15- and 17-membered rings occur in muscone and civetone. The search for synthetic methods to make rings of all sizes soon became a major objective of investigation. This obliged consideration of physical aspects of the cyclization reactions.

Ring formation by an intramolecular reaction implies the use of a bifunctional substrate as the starting material. This is shown schematically in eq 1 where X and

(1)

Y are reactive functional groups at the ends of a chain undergoing ring closure and forming functional group Z. The cyclization reaction suffers from the competition of a polymerization reaction through head-to-tail condensation (eq 2). If the latter process is bimolecular,



(2)

the intermolecular reaction is second order whereas cyclization is first order. Hence was derived the principle that high substrate concentrations favor polymerization and that cyclization can occur without competition only at low concentrations.[3] Ziegler was the first to apply this principle to the synthesis of many-membered rings by the so-called high dilution method.[4] The formation of medium size rings (8- to 11-membered) is in many instances the most difficult to effect, even under Ziegler high dilution conditions.

In order to understand the structural and energetic factors controlling the formation of rings, kinetic information is required. From this point of view, until a few years ago little progress had been made since the early studies,[5] except that reactions forming five- and six-membered rings and, to a lesser extent, small rings received considerable attention. Kinetic studies were made[6] mainly in connection with neighboring group participation and intramolecular catalysis phenomena.[7,8] Most of the available evidence with regard to the larger rings and, notably, to the extreme difficulty of formation of the medium rings comes from preparative studies.[4,9] Our objective was to expand our knowledge of cyclization by a comprehensive kinetic investigation over a wide spectrum of ring sizes.

It should be stressed that the structure of the ring to be formed has an important influence on the cyclization rate. In terms of transition-state theory, cyclization rates depend on the structure of the open chain initial state and on that of a transition state resembling the cyclic product. Reactivity in cyclization reactions may be interpreted in terms of activation energy and the probability of end-to-end encounters. The activation energy is thought to reflect the strain energy of the ring to be formed, which is markedly dependent on ring size as shown by strain energy data concerning the cycloalkanes.[10] Ring strain arises from a combination of (1) bond opposition forces due to imperfect staggering (Pitzer strain), (2) deformation of ring bond angles (Baeyer strain), and (3) transannular strains due to repulsive interactions between atoms across the ring

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(1) L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, **9**, 249 (1926).
(2) K. Ziegler, H. Eberle, and H. Ohlinger, *Liebigs Ann. Chem.*, **504**, 94 (1933).
(3) P. Ruggli, *Liebigs Ann. Chem.*, **392**, 92 (1912); **399**, 174 (1913); **412**, 1 (1916).
(4) K. Ziegler in "Methoden der Organischen Chemie" (Houben-Weyl), Vol.4/2, E. Müller, Ed., georg Thieme Verlag, Stuttgart, 1955.
(5) G. Salomon, *Trans. Faraday Soc.*, **32**, 153 (1936).
(6) (a) R. Bird, A. C. Knipe, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1215 (1973); (b) R. Bird and C. J. M. Stirling, *ibid.*, 1221 (1973).
(7) M. I. Page, *Chem. Soc. Rev.*, **2**, 295 (1973).
(8) B. Capon and S. P. McManus, "Neighboring Group Participation", Vol. 1, Plenum Press, New York, 1976.
(9) J. Sicher, *Progr. Stereochem.*, **3**, 202 (1962).
(10) J. F. Liebman and A. Greenberg, *Chem. Rev.*, **76**, 311 (1976).

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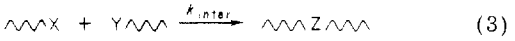
when they are forced close to each other. The magnitudes of such strains have been evaluated by Allinger et al.[11] on the basis of force-field calculations. Strains (1) and (3) are especially severe for medium-ring cycloalkanes. Unfortunately, extensive strain energy data for ring compounds other than cycloalkanes are not available.

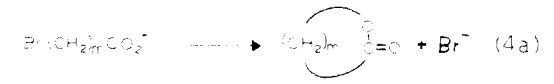
According to Ruzicka's intuition,[12] the probability of the chain terminals coming close enough to each other for the reaction to occur should decrease as the chain gets longer. In terms of entropy, this implies negative $\Delta S^{\ddagger}$ contributions owing to reduction of freedom of internal rotation around the single bonds of the molecular backbone when the disordered open-chain precursor is converted into the ring-shaped transition state.

When studying an intramolecular reaction, we need a reference intermolecular reaction for comparison. Knowledge of the inherent reactivity of the reacting functional groups is of practical as well as theoretical significance. An obvious intermolecular model reaction is dimerization of the bifunctional substrate itself (eq 2). However, an experimentally more accessible model is the reaction between monofunctional chains (eq 3)



(3)

whose nonreacting moieties resemble the nonreacting chemical environment of the bifunctional chain that cyclizes. Model reactions involving low molecular weight monofunctional reactants have proved to be suitable.[13] Reaction 3 is more generally applicable than reaction 2 for purposes of comparing intra- to intermolecular reactivity. A specific example is our use of intermolecular model reaction 4b in our studies of lactone formation from ω-bromoalkane-carboxylate ions (eq 4a).



(4a)

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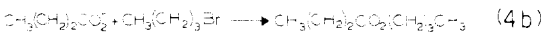

(4b)

Comparison is expressed by the k_{intra}/k_{inter} ratio, which has units of moles per liter and is called *effective molarity* (EM). This name may be misleading because it suggests that the ratio k_{intra}/k_{inter} be taken as a physically real "effective concentration" of one chain end relative to the other, that is, that the first-order rate constant for ring closure is the product of such "effective concentration" times the second-order rate constant for the reaction between the chain ends as if they were not connected by the intervening chain. That this is actually not the case is shown, for instance, by the finding[7,8] that experimental EM values for rings 5 and 6 often exceed physically conceivable concentrations by several powers of ten. The EM concept has been discussed at length elsewhere[14] and will be applied later on.

(11) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Am. Chem. Soc.*, **93**, 1637 (1971).
(12) (a) L. Ruzicka, W. Brugger, M. Pfeiffer, H. Shinz, and M. Stoll, *Helv. Chim. Acta*, **9**, 499 (1926); (b) L. Ruzicka, *Chem. Ind. (London)*, **54**, 2 (1935).
(13) C. Galli and L. Mandolini, *J. Chem. Soc., Perkin. Trans. 2*, 443 (1977).
(14) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **99**, 6308 (1977).

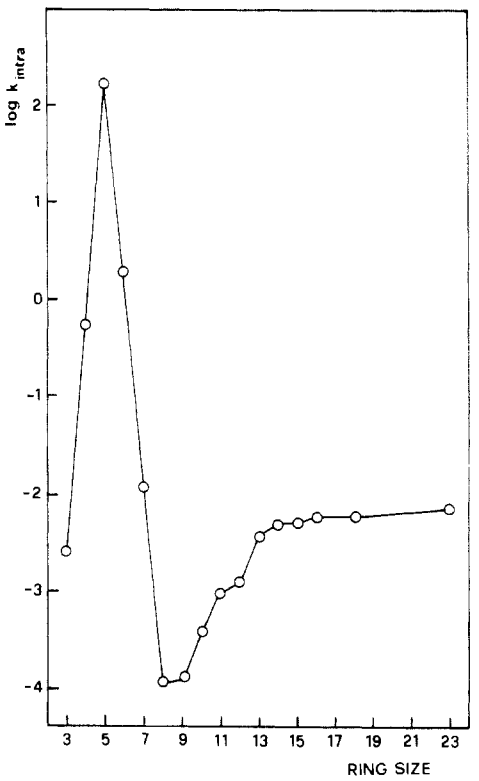


Figure 1. Reactivity profile for lactone formation (eq 4a).

A useful corollary of the definition of effective molarity is that ring formation from a bifunctional substrate predominates over polymerization whenever the substrate concentration is markedly lower than the EM value. Since the EM values may strongly depend on ring size, the EM parameter enables prediction of the conditions under which a given ring can be synthesized free from competing polymerization reactions.[15]

The Reactivity Profile

Lactone-Forming Reactions. The ease of ring formation for lactones[16-18] in 99% (v/v) aqueous Me_2SO (eq 4a) as a function of ring size is illustrated in Figure 1. On going from the three- to the five-membered lactone the rate constant increases by 5 powers of ten, but then the rate decreases rapidly to a nadir at the eight-membered ring; the overall decrease is a millionfold. The drop in rate in this region is approximately 2 powers of 10 per added methylene group. The reactivity of lactone formation up to the eight-membered ring is somewhat lowered by the requirements of the ring size to force the ester function into the cis conformation.[16] Cyclization to the nine-membered ring is almost as slow as to the eight-membered, but from the ten-membered ring on the ease of ring closure increases again until it eventually levels off with the largest rings. The rate constants for the region of 13–23 lie well within a factor of 2. The substantial lack of sensitivity of rate to ring size in this region is in agreement with previous studies which were based on semiquantitative or preparative work.[5,9] Noteworthy

(15) C. Galli and L. Mandolini, *Gazz. Chim. Ital.*, **105**, 367 (1975).
(16) C. Galli, G. Illuminati, and L. Mandolini, *J. Am. Chem. Soc.*, **95**, 8374 (1973).
(17) C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *J. Am. Chem. Soc.*, **99**, 2591 (1977).
(18) L. Mandolini, *J. Am. Chem. Soc.*, **100**, 550 (1978).

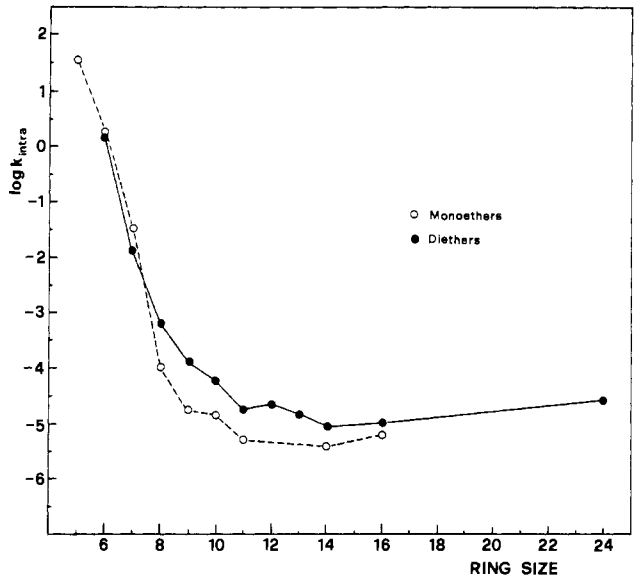
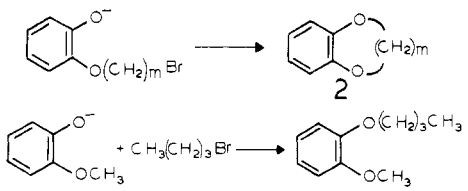


Figure 2. Reactivity profile for the formation of **2** (eq 5a).

is the disappearance of the zigzag, alternating variation of yields with ring size that was reported in preparative studies.[19]

Cyclic Diether-Forming Reactions. The reactivity pattern for the formation of diethers of type **2** (eq 5a)



in 75% (v/v) aqueous EtOH[14,20] is illustrated in Figure 2. Reactivity decreases markedly as the ring size increases from 6 to 9, by an overall rate factor greater than 10^4. Unlike the formation of lactones, there is no definite minimum in the medium-ring region, but then the rate levels off as ring size increases. Reaction 5b serves as an intermolecular model.

A closely similar reactivity profile is obtained for the same reactions in 99% (v/v) aqueous Me_2SO,[21] in spite of the fact that in this solvent the reactions are some 10^4 times faster than in 75% EtOH. Use of 99% Me_2SO as the solvent allows determination of the rate of formation of the 32-membered ring, which was prevented in 75% EtOH by solubility problems. This considerably extends the investigated ring size range and serves further to illustrate how insensitive to chain length is the ease of formation of quite large rings.

The general reactivity pattern that emerges from the kinetics is in good agreement with Ziegler's data,[22] particularly as to the lack of a minimum. The latter feature has been explained[20] as due to the presence of two "bare" oxygen atoms and two trigonal carbon atoms which should reduce the strain due to bond oppositions and transannular interactions that is usually considered to be severe in medium rings. It has been estimated[23]

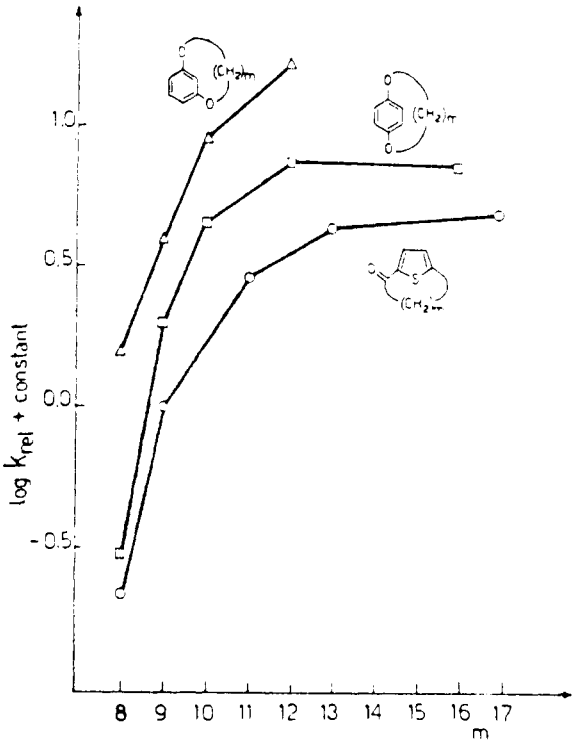
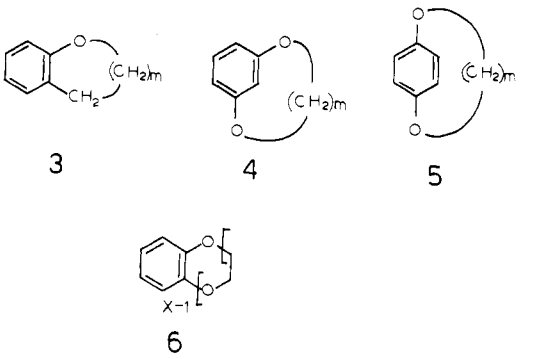


Figure 3. Reactivity profiles for the formation of some bridged aromatic compounds. Reproduced from ref 27.

that substitution of a $-CH_2CH_2-$ grouping by a cis double bond reduces the strain energy of cyclooctane and cyclodecane by 2.7 and 5.4 kcal/mol, respectively. Clearly the presence of two sp^2 carbon atoms is an important factor in determining the characteristic behavior of this series.

Cyclic Monoether-Forming Reactions. The rate profile for the monoether series **3** in 75% (v/v) aqueous EtOH[14,24] is much the same as for the diether series **2** (Figure 2). Significant differences do, however, exist, as discussed below (oxygen atom effect).

Reactions Forming Ansa-Bridged Products. When the junction between the rigid unit and the polymethylene bridge moves to the meta and para positions to give diethers **4** and **5**, respectively, the rate

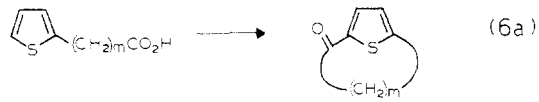


profile is profoundly modified. The pertinent data as obtained in 99% Me_2SO[25,26] are plotted in Figure 3.

(19) As an example, see Figure 2 in ref 17.
(20) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **96**, 1422 (1974).
(21) A. Dalla Cort, G. Illuminati, L. Mandolini, and B. Masci, J. Chem. Soc., *Perkin Trans. 2*, 1774 (1980).
(22) K. Ziegler, A. Lüttringhaus, and K. Wohlgemuth, *Liebigs Ann. Chem.*, **528**, 162 (1937).
(23) N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, **94**, 5734 (1972).
(24) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **97**, 4960 (1975).
(25) L. Mandolini, B. Masci, and S. Roelens, *J. Org. Chem.*, **42**, 3733 (1977).
(26) A. Dalla Cort, L. Mandolini, and B. Masci, *J. Org. Chem.*, **45**, 3923 (1980).

The reactivity drop observed when the chain length of the cyclophane products decreases is presumably the result of increasingly greater strain in the lower homologues. No such drop is observed for series **2**.

Another example of highly strained ring closure resulting from a reduced length of the connecting chain is the formation of thiophenophan-1-ones (**7**).[27] (See eq 6a and intermolecular model reaction 6b.) Here the



(6a)

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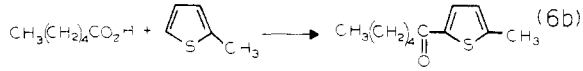


(6b)

rigid moiety incorporated in the cyclization product is a thiophene ring connected with the rest of the structure through two α carbons. The resulting rate profile (Figure 3) is similar to those described for the meta and para diether series, in spite of the difference in reaction type. It follows, therefore, that the major factor in determining the shape of the reactivity profile is a geometrical one, i.e., incorporation into the cyclic structures of rigid structural moieties by means of nonadjacent points of attachment.

The *gem*-Dimethyl Effect

Substituting two methyl groups for hydrogens at a methylene carbon has long been known to enhance the rate of formation of small and common rings.[8] This is known as the *gem*-dimethyl effect. It has been interpreted by Allinger and Zalkow,[28] who considered the formation of six-membered rings in terms of enthalpy and entropy effects. They concluded that, insofar as enthalpy effects are concerned, ring closure is favored by *gem*-dimethyl substitution owing to a change in the number of gauche interactions in going from the open-chain reactant to the cyclic transition state or product. However, for the formation of medium rings, less favorable or unfavorable enthalpy factors are conceivable because ring strain and transannular compressions may increase as a result of methyl substitution. There is also a favorable entropy factor, stemming from reduction of the rotational motion in the open-chain precursor. However, as the length of the chain increases, the torsional motions of both the open-chain reactant and the cyclic product increase and eventually make any entropy change due to alkyl substitution relatively unimportant. As a result, the rate enhancement due to the entropy factor is expected to die out in the larger rings.

Data for lactone formation[29] provide the first consistent set of rate data covering a broad spectrum of ring sizes, i.e., from 6 to 16, concerning the *gem*-dimethyl effect (Table I). Although no activation parameters are available, the reactivity picture is in qualitative agreement with the stated enthalpy and entropy considerations. As expected, the effect is largest with ring size 6, still appreciable with ring size 9, but becomes negligible in the next homologue. It is even slightly inverted with ring size 11, presumably as a result of an adverse enthalpy factor in the latter rings. The effect is also negligible with the 16-membered ring, where enthalpy and entropy effects have probably disappeared.

Table I
Gem-Dimethyl Effect on the Rate of Lactone Formation[a]

gem-substituted substrate	ring size	$k_{intra}^{gem}/k_{intra}$
$Br(CH_2)_2C(CH_3)_2CH_2CO_2^-$	6	38.5
$Br(CH_2)_5C(CH_3)_2CH_2CO_2^-$	9	6.62
$Br(CH_2)_6C(CH_3)_2CH_2CO_2^-$	10	1.13
$Br(CH_2)_7C(CH_3)_2CH_2CO_2^-$	11	0.61
$Br(CH_2)_6C(CH_3)_2(CH_2)_7CO_2^-$	16	1.22

[a] In 99% Me_2SO at 50.0 °C (from ref 29).

Thus the *gem*-dimethyl effect appears to be an important rate-enhancing effect only for relatively short reacting chains.

The Oxygen Atom Effect

We now inquire what influence on the ease of ring closure is exerted by replacing methylene groups by heteroatoms, specifically by oxygen atoms. We gain insight by comparing behavior in the diether and monoether series **2** and **3**, respectively. In Table II the $k_{intra}^{diether}/k_{intra}^{monoether}$ ratios at varying ring sizes display a definite medium ring effect and closely parallel the behavior of the enthalpies of activation (vide infra). The greater the strain in the cyclic transition states, the greater the oxygen atom effect, which is believed to arise from a reduction of bond opposition forces and transannular interactions upon the substitution of oxygen for the benzylic methylene group of the monoethers **3**. This is consistent with the view of Dale[30] that 1,4- and 1,5-CH···O interactions are less unfavorable than the corresponding CH···HC interactions. Furthermore, the ease formation of the benzo-3x-crown-x ethers **6**, x = 4, 5, and 6, in 99% Me_2SO is some three times greater than that of the polymethylene compounds **2** with similar ring size.[31] Again, the effect tends to disappear when the chain becomes longer. The EM value of 0.036 M for the formation of the 30-membered benzo crown ether **6**, x = 10, is very close to that of 0.041 M for the 32-membered polymethylene compound **2**, m = 28.

Thus, in the absence of such a highly specific interaction as coordination with a metal ion (template effect[32]), a polyoxyethylene chain behaves much in the

(27) C. Galli, G. Illuminati, and L. Mandolini, *J. Org. Chem.*, **45**, 311 (1980).
(28) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).
(29) C. Galli, G. Giovannelli, G. Illuminati, and L. Mandolini, *J. Org. Chem.*, **44**, 1258 (1979).
(30) J. Dale, *Tetrahedron*, **30**, 1683 (1974).
(31) B. Masci et al., manuscript in preparation.

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

ring size	6	7	8	9	10	11	14	16	inter
$k_{intra}^{diether}$ / $k_{intra}^{monoether}$	0.81	0.42	6.42	7.55	4.16	4.67	2.65	1.91	1.36

[a] Data in 75% EtOH at 50.0 °C (from ref 14).

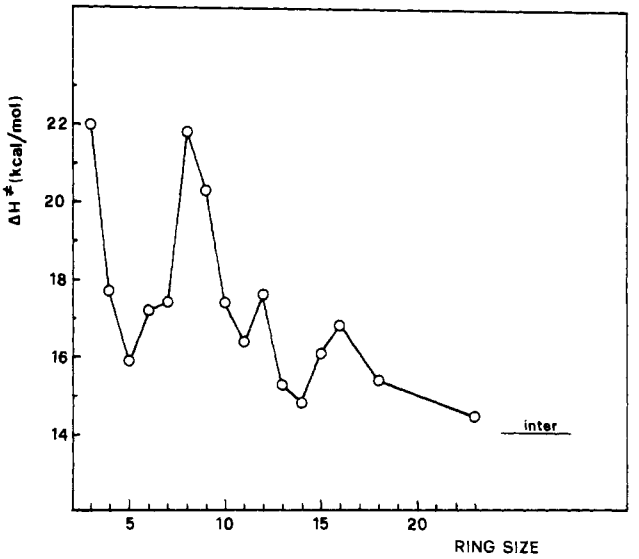


Figure 4. $\Delta H^{\ddagger}$ profile for the formation of lactones (eq 4).

same way as a polymethylene one when large rings are formed.

Strain Effects

Enthalpy of activation data are available for a few cyclization series. The general shapes of the $\Delta H^{\ddagger}_{intra}$ vs. ring size profiles (Figures 4 and 5), as well as comparisons with the related values for the intermolecular model reaction ($\Delta H^{\ddagger}_{inter}$), suggest that the difference $\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}$ provides a measure of the strain energies involved in the formation of the ring-shaped transition states.

In large ring formation (lactones[18]) there is a general trend for $\Delta H^{\ddagger}$ to decrease as the chain length of the bifunctional substrate increases (Figure 4). The formation of rings as large as 18- and 23-membered is accompanied by $\Delta H^{\ddagger}_{intra}$ values which are quite close to $\Delta H^{\ddagger}_{inter}$, showing that in the large ring region the intramolecular reaction is nearly strainless. However, in the 3–16 region the $\Delta H^{\ddagger}_{intra}$ profile is markedly structured. By far the highest strains are experienced with the three- and eight-membered rings. In both cases $\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}$ is about 8 kcal/mol. The cis conformation of the ring to be formed still predominates for ring size 8. No doubt this imposes an extra enthalpic penalty which causes the maximum to shift away from ring size 10 which experiences the maximum strain in cycloalkanes.[10]

In a discussion of the main conformations of medium- and large-ring compounds, Dale[33] has proposed different sets of similar conformational situations. Two such sets are the series $4n$ and $4n + 2$, where n is the number of ring atoms. It is of interest that the structuredness of the $\Delta H^{\ddagger}$ profile in lactone formation displays some

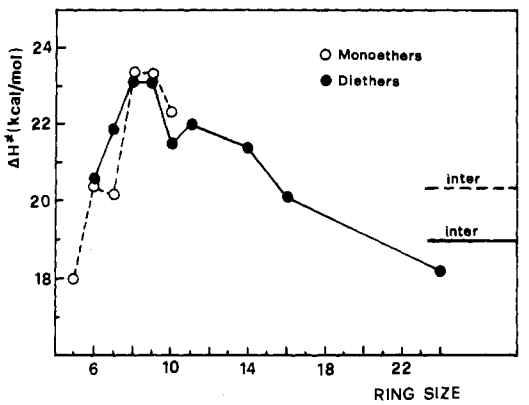


Figure 5. $\Delta H^{\ddagger}$ profile for the formation of 2 and 3 and for the related intermolecular model reactions.

peculiar behavior that is hardly fortuitous and appears to be related to Dale's sets. Of special note are a sequence of three maxima at n = 8, 12, and 16 ($4n$ set) and two minima at 14 and in the surroudings of 10 ($4n + 2$ set).

In going to the formation of cyclic ethers **2**[14] where no minimum appears in the reactivity profile, the $\Delta H^{\ddagger}$ pattern (Figure 5) displays a maximum in the medium-ring region which is on the order of 3–4 kcal/mol relative to $\Delta H^{\ddagger}_{inter}$. In the largest ring region a general decrease of the $\Delta H^{\ddagger}$ values is evident. At ring size 24, $\Delta H^{\ddagger}_{intra}$ is of the same order of magnitude as $\Delta H^{\ddagger}_{inter}$. The residual ring strain in the 14- and 16-membered large rings can be explained in terms of a larger number of gauche conformations for these rings as compared to the corresponding open-chain compounds.[34] The monoethers **3** display a similar pattern.[24] This series includes the five-membered ring whose $\Delta H^{\ddagger}$ is appreciably lower than that of the seemingly nonstrained six-membered ring. This is attributed to a reduced solvation in the shorter reacting chain (vide infra).

Entropy Effects

The $\Delta S^{\ddagger}$ values for the cyclization of bifunctional chains cleanly demonstrate one of the basic reactivity postulates, that the probability of end-to-end encounters decreases as the chain length increases. This postulate was proposed by Ruzicka in 1935[12] and has been accepted by chemists ever since, although previously without direct experimental proof.

The $\Delta S^{\ddagger}$ profile for lactone formation[18] (Figure 6) shows an irregular pattern, with a general decrease as the chain length increases. The $\Delta S^{\ddagger}$ values eventually tend to level off for the large rings owing to an increase in looseness of the rings due to low-frequency out-of-plane bending motions.[35] This results in partial compensation of the entropy loss caused by freezing of in-

(32) L. Mandolini and B. Masci, *J. Am. Chem. Soc.*, **99**, 7709 (1977).
(33) J. Dale, *J. Chem. Soc.*, **93** (1963).
(34) H. Morawetz and N. Goodman, *Macromolelcules*, **3**, 699 (1970).
(35) H. E. O'Neal and S. W. Benson, *J. Chem. Eng. Data*, **15**, 266 (1970).

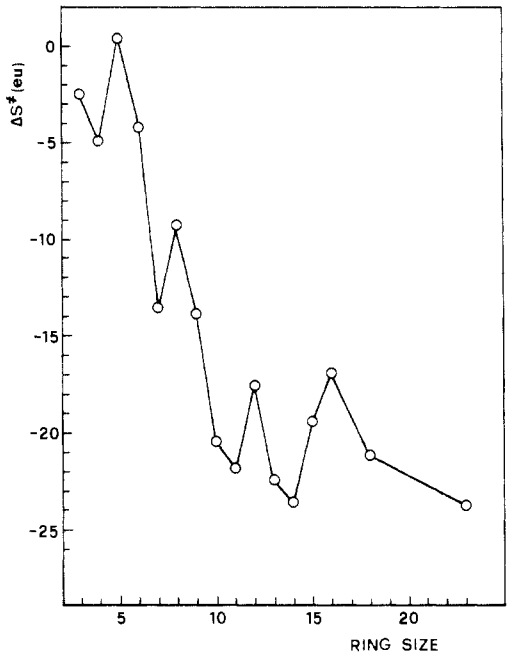


Figure 6. $\Delta S^{\ddagger}$ profile for lactone formation (eq 4).

ternal rotations upon ring closure. The irregularities of the pattern as in the medium- and large-ring region, up to ring size 16, indicate that conformational features may vary in individual rings in a rather specific way so that they display a periodic character to some extent. Maxima at 8, 12, and 16 are also observed here (as in the $\Delta H^{\ddagger}$ profile).

In the three- to six-ring region, the $\Delta S^{\ddagger}$ values are surprisingly insensitive to ring size and seem to reflect the expected losses of internal rotations very poorly. The $\Delta S^{\ddagger}$ for forming the smallest rings are unexpectedly much too low. This phenomenon seems to be rather general; it is also observed in other series.[18] A reasonable explanation is reduced initial-state solvation in the shortest bifunctional chains. For sufficiently long chains, e.g., of more than 5 carbon atoms, it is likely that the two solvation shells around the chain ends are independent of each other and constant throughout. However, for shorter chains the mutual (polar) interactions of the end groups may suffer from significant changes in initial-state solvation. If we keep in mind that the transition state for the lactone formation should be less solvated than the initial state and, therefore, that the solvation contribution to $\Delta S^{\ddagger}$ ($\Delta S^{\ddagger}_{solv}$) is positive, reduction of this term should lower the overall $\Delta S^{\ddagger}$ in the small-ring region.

In the diether **2** the entropy of activation decreases regularly as the ring size increases[14] (Figure 7). The $\Delta S^{\ddagger}$ profile displays the same basic features as those observed for the lactonization reaction, namely, a steep drop among the lower members of the series and a much less pronounced dependence on chain length among the larger rings. Although the entropy effect on reactivity is depressive throughout the investigated series, reactivity tends to rise in the larger ring region because the decrease in enthalpy of activation due to residual strain relief more than offsets the entropy effect. The monoether series **3**, for which $\Delta S^{\ddagger}$ data up to ring size 10 are available[24] (Figure 7), behaves similarly. If we consider all the $\Delta S^{\ddagger}$ data up to ring size 10 for the diether and monoether series together, we

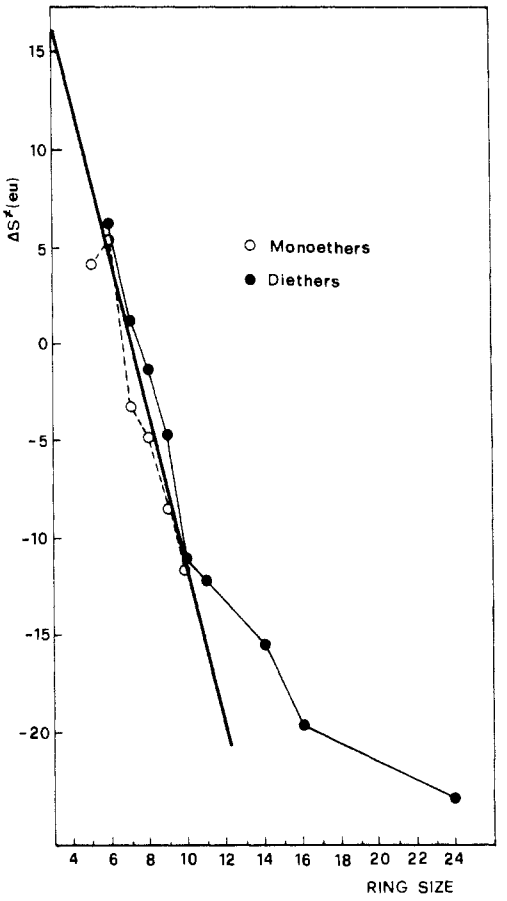


Figure 7. $\Delta S^{\ddagger}$ profiles for the formation of **2** and **3**.

note that they grossly describe a common line whose slope is −4 eu/CH_2, which is in surprisingly good agreement with the value of 4.5 eu estimated[35,36] for the maximum entropy loss associated with the freezing of internal rotation around a single bond.

The deviation observed for the five-membered monoether may be interpreted in terms of reduced solvation of the reactant, as already noted for lactone formation. In contrast, the longer chains in the 6–10 region may be assumed to be solvated more or less uniformly as the essentially nonhindered polar ends require. By extrapolation, an entropy of activation for n = 3 of +16.7 eu is obtained; this would pertain to a hypothetic cyclization of a regularly solvated chain in which no entropy of internal rotation is lost. Thus, the extrapolated value of +16.7 eu can be taken as a measure of the entropy of desolvation suffered by *any* member of the series on going from the open-chain bifunctional reactant to the transition state. In our intermolecular model (eq 5b) for the diether series[24] we found an activation entropy of −15.4 eu. This value must be corrected for the contribution of solvation by subtracting 16.7 eu. We obtain −32 eu as the amount of entropy of activation which stands for the loss of translational and rotational entropy. A similar value, −29 eu, is obtained from the monoether series.[24]

These values are then estimates for these reaction series of the "entropy driving force" for the highest possible intramolecular or proximity effect. They are equivalent to maximum EM values of $\exp(32/R)$ and $\exp(29/R)$, or ca. 10^7 and $10^{6.5}$ M, which compare fairly well to the limiting value of 10^8 M theoretically estimated by Page and Jencks.[7,36] Observed accelerations

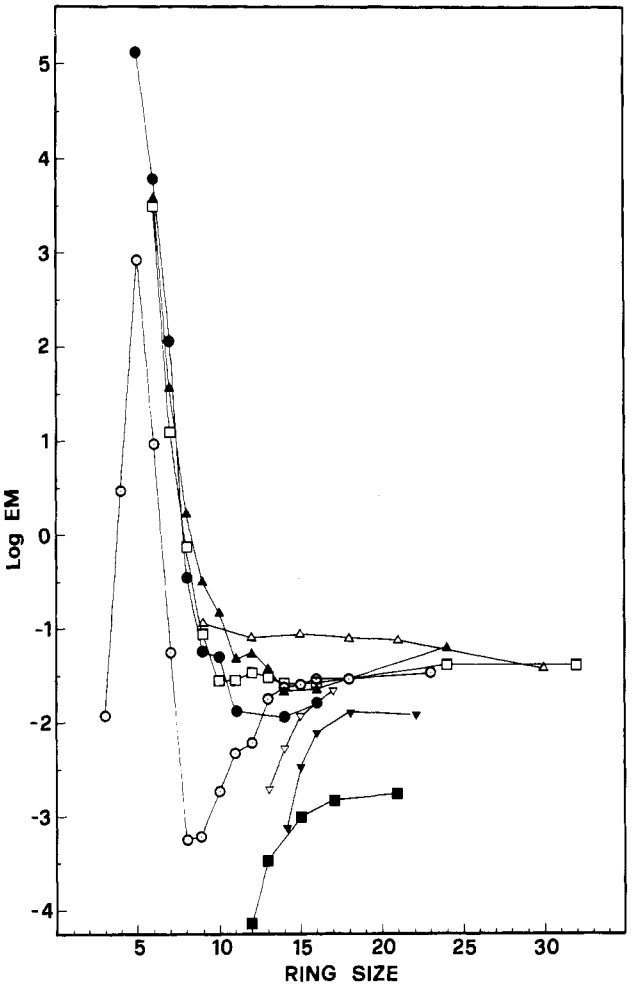


Figure 8. EM profiles for the formation of (○) lactones 1, (▲) diethers 2 in 75% EtOH, (□) diethers 2 in 99% Me_2SO; (●) monoethers 3, (▽) dioxametacyclophanes 4, (▼) dioxaparacyclophanes 5; (△) benzo crown ethers 6, (■) (2,5)-thiophenophan-1-ones 7.

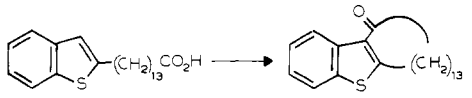
in the absence of initial-state strain relief are less than the maximum limit because, even in the shortest chains, a few internal rotations must still be frozen out on going to the transition state.

The Effective Molarity

By definition, the EM profile for each individual series has the same shape as the log k_{intra} profile. Furthermore, since the EM parameter is "corrected" for the reactivity between end groups as separate entities, it provides a measure of the tendency of the bifunctional chain to cyclize and a common scale for comparing ring closures in diverse reaction series. These features are well illustrated in the diagram presented as Figure 8. The EM differences reflect structural effects inherent to ring closure, which are especially strong for the small and medium rings. In the large ring region, where strain energy effects are small or negligible, even large rate differences turn out to be due to the nature of the end groups of the reacting chains and largely disappear in the EM values. In this region the EM parameter tends to reach values lying in the fairly limited range of about 0.01 to 0.05 M.

Besides the cyclization reactions described above, there are several examples showing that this EM behavior applies quite generally to a large variety of reactions and conditions. One early example is the formation of large-ring cyclic ammonium ions from ω-bromoalkylamines.[37] For intramolecular hydrogen abstraction in the excited triplet state of long-chain *p*-(carboxyalkyl)benzophenones, Winnik et al.[38] reported kinetic data from which average EM values per methylene group of 0.04 to 0.08 M can be estimated.[39] EM data for the intramolecular encounter-controlled electron transfer in $N(CH_2)_mN^{-}\cdot$, where *N* denotes α-naphthyl or *N*-phthalimide groups, have been recently reported by Szwarc et al.[40] to lie in the neighborhood of 0.02–0.04 M when *m* is in the range 10–20. A final example is intramolecular excimer formation in $Me_2N(CH_2)_mNMe_2$,[41] for which EM values close to 10^{-2} M are observed when *m* is in the neighborhood of 12. Thus, in long-chain bifunctional compounds of up to 20–30 atoms the reactivity appears to differ from that of the nonconnected 1M end groups by a factor common to all the intramolecular reactions, which can be related to the flexible long chain connecting the reacting ends. That is, the common EM level reflects similar losses in conformational entropy in the formation of large rings, irrespective of the chemistry involved at the ends of the chains and of the chain length in the investigated region.

Departure from the general behavior may be diagnostic for special effects. Thus the finding that the EM values for the formation of the large-ring thiophenophan-1-ones 7 lie below the usually observed range by about one order of magnitude (Figure 8) can be attributed to desolvation in the cyclic transition states.[27] Solvent molecules may be prevented from solvating the ring especially in the vicinity of the sulfur atom by the chain crossing over the thiophene ring plane, as required by the geometry of the σ adduct to be formed. This view is consistent with the fact[27] that the α-to-β intramolecular acylation of the 2-substituted benzothiophene 8 leading to the 16-ring ketone 9, for



8 9

which extensive desolvation is not expected, shows a "normal" value of 1.1×10^{-2} M for the EM, which is 10 times as high as that observed in the same ring size region for the α-to-α′ intramolecular acylation of the thiophene compounds.

Cyclization of Very Long Chains

Interactions of functional groups attached to the same polymer chain have stimulated a great deal of experimental and theoretical investigation.[42,43] A major

(36) M. I. Page and W. P. Jencks, *Proc. Natl. Acad. Sci. U.S.A.*, 68, 1678 (1971).

(37) Work by H. Freundlich and co-workers and G. Salomon, quoted in ref 5.

(38) (a) M. A. Winnik, S. N. Basu, C. K. Lee, and D. S. Saunders, *J. Am. Chem. Soc.*, 98, 2928 (1976); (b) M. A. Winnik, *Acc. Chem. Res.*, 10, 173 (1977).

(39) The EM values have been estimated multiplying by 4 the slopes of the straight lines reported in Figure 2 of ref 38b. The multiplying factor accounts for the presence of four methylenes in hexane, which is the compound chosen to model the bimolecular quenching of the benzophenone derivative phosphorence by alkane chains.

(40) (a) K. Shimada and M. Szwarc, *J. Am. Chem. Soc.*, 97, 3313 (1975); (b) K. Shimada, Y. Shimozato, and M. Szwarc, *ibid.*, 97, 5834 (1975).

(41) A. M. Halpern, M. W. Lagenza, and B. R. Ramachandran, *J. Am. Chem. Soc.*, 101, 5736 (1979).

motivation in these studies was to relate intrachain reactivity to the conformational and/or dynamic properties of the chain connecting the functional groups, thus providing a probe for the shape and flexibility of polymer chains in solution. While the matter is outside the scope of this Account, attention is called to recent studies by Sisido and his group[43] on the kinetics and equilibria of intramolecular interactions of end groups attached to polysarcosine and polyoxyethylene chains with a number of atoms up to about 50–100. The ease of ring closure was found to decrease but moderately as the chain length increased, the EM values for the cyclization of very long chains being in the order of 1×10^{-2} M or slightly less. Thus, only within chain lengths of about 10 atoms does a dramatic reactivity drop occur. Sisido's data indicate that the reactivity level we have determined for large rings up to about 30-membered decreases only slightly for chains whose length is as high as 100 members.

(42) See, for example, (a) H. Morawetz, *Pure App. Chem.*, **38**, 267 (1974); (b) A. Perico and C. Cuniberti, *J. Polym. Sci.*, **15**, 1435 (1977); (c) M. Sisido and K. Shimada, *J. Am. Chem. Soc.*, **99**, 7785 (1977); (d) M. Sisido and K. Shimada, *Macromolecules*, **12**, 790, 792 (1979); (e) D. S. Saunders and M. A. Winnik, *ibid.*, **11**, 18, 25 (1978); (f) G. Wilemski and M. Fixman, *J. Chem. Phys.*, **60**, 866, 878 (1974).

(43) (a) M. Sisido, T. Mitamura, Y. Imanishi, and T. Higashimura, *Macromolecules*, **9**, 316 (1976); (b) M. Sisido, H. Takagi, Y. Imanishi, and T. Higashimura, *ibid.*, **10**, 125 (1977); (c) *Bull. Chem. Soc. Jpn.*, **50**, 1807 (1977); (d) M. Sisido, E. Yoshikawa, Y. Imanishi, and T. Higashimura, *ibid.*, **51**, 1464 (1978).

Concluding Remarks

We have gained new insights into the factors controlling the formation of ring molecules by quantitative investigation of ring-closure reactions over a wide spectrum of ring sizes. The determination of effective molarities (EM) has stimulated accurate collateral analysis of intermolecular model reactions.

One of the most spectacular results of these studies is the observation that EM values tend to become similar to each other whatever the nature of the reaction, the structural series and the experimental conditions, as the ring size increases slightly beyond the medium ring region. The effect has been ascertained as far as ring size 32.

The data obtained and the principles revealed by this approach provide a general basis for the interpretation of ring closure reactivity. Among other applications, this basis will enable recognition and assist interpretation of unusual effects encountered in special cases.

Synthetic Model Compounds for Hemoproteins

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Hemoproteins are biomolecules which employ iron porphyrins in their active sites. They accomplish dioxygen transport, electron transport, hydrogen peroxide destruction, oxygen reduction, and several kinds of oxidation including alkane hydroxylation.[1,2] Except for electron-transporting proteins, all of these molecules employ a five-coordinated iron in order to leave the sixth position open for ligand binding or catalytic activity. The dioxygen-transporting hemoproteins further require that the iron be maintained in the ferrous state.[1] This is not the thermodynamically stable state in the presence of dioxygen, and thus the protein somehow retards oxidation to the Fe^{III} state.

We began our present work with the idea of removing the active site from these dioxygen-transporting proteins and studying the effects of structure and environment upon its reversible oxygenation. To do this we needed to obtain a "model compound" which would resemble the protein and resist oxidation long enough for measurements to be made. This can be accomplished by either slowing down oxidation or speeding up the measurements.

Following Wang's seminal discovery that a heme–imidazole mixture in a polymer matrix could be reversibly oxygenated,[3] we conceived the idea that a model compound should have one side protected with a hydrophobic structure and should have on the opposite side a covalently attached imidazole to maintain five-coordination,[4] the "chelated heme" approach. We reported the synthesis of a protected porphyrin, porphyrin cyclophane, in 1971, at which time we planned to combine the "protected heme" and "chelated heme" approach into a single molecule. However, alternative ways to observe reversible oxygenation were discovered,[5-8] and we temporarily abandoned the protected

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(1) Antonini, F.; Brunori, M. "Hemoglobin and Myoglobin and Their Reactions with Ligands"; North-Holland Publishing Co.: Amsterdam, 1971: (a) p 50; (b) p 221; (c) p 93; (d) p 225; (e) p 227.

(2) Gunsalus, I. C.; Meek, J. R.; Lipscomb, J. D.; Debrunner, P.; Munck, E. "Mechanisms of Oxygen Activation"; Hayaishi, O., Ed.; Academic Press: New York, 1974; pp 559–613.

(3) Wang, J. H. In "Oxygenases"; Hayaishi, O., Ed.; Academic Press: New York, 1962; pp 502–511.

(4) (a) Diekmann, H.; Chang, C. K.; Traylor, T. G. *J. Am. Chem. Soc.* 1971, *93*, 4068–4070. (b) This cyclophane was not tested for dioxygen binding. However, we have recently prepared an anthracene-7,7-heme cyclophane which forms a stable oxygen complex in solution, thus demonstrating the viability of the original cyclophane approach to heme protection (S. Tsuchiya, unpublished). See also ref 13b for another example.

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