The Role of Ring Strain on the Ease of Ring Closure of Bifunctional Chain Molecules

Carlo Galli*[a] and Luigi Mandolini*[a]

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The role of ring strain on the ease of ring formation over a wide range of ring sizes is discussed on the basis of a comparison of transition state versus product-ring strain energies. A general procedure is illustrated for the assessment of transition-state strain energies, based on experimental effective molarities (*EM*s) and an extra-thermodynamic treatment of entropy data for ring closure. It is found that the ring product is a good model of the transition state of cyclisation for all but the shortest chains. Our earlier interpretation of this remarkable lack of correspondence between transition state and product-ring strain energies in intramolecular nucleophilic substitutions of the very short chains, is compared with the results of recent theoretical calculations.

Introduction

It is over a quarter of a century since we co-authored, with the late Gabriello Illuminati, the first of a long series of papers on ring-closure reactions.[1a] This series included studies of the kinetics of formation of lactones,[1] carbocyclic diethyl malonates,[2] cyclic ethers,[3] cyclic *N*-tosylamines,[4] and cyclic aromatic ketones.[5] Results from these early investigations have been thoroughly reviewed.[6,7]

Our work developed along the lines traced by many pioneers in the field, notably Freundlich, Ziegler, Stoll, and Salomon,[8] and was particularly inspired by a seminal paper by Ruzicka.[9] According to Ruzicka's hypothesis, (*i*) the probability of end-to-end reactions in a bifunctional linear precursor and (*ii*) ring strain are independent factors in determining the ease of cyclisation. Whereas the activation energy for ring closure is thought to reflect the ring strain of the cyclic product, there is a diminishing probability for chain ends meeting as the chain grows longer.

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Carlo Galli (right), born in Rome in 1949, studied chemistry at the University "La Sapienza" of Rome, where he obtained a Laurea degree in 1972 with a thesis on the kinetics of lactonization of ω-bromoalkanoate ions, under the guidance of Gabriello Illuminati and Luigi Mandolini. He was a postdoctoral fellow with Joseph F. Bunnett at the University of California, Santa Cruz, USA (1978−1979). After 12 years as a Research Fellow of the National Council of Research of Italy (CNR), he became Associate Professor of Organic Reaction Mechanisms in 1988 and then Professor of Organic Chemistry in 1990 at the University "La Sapienza", Rome. Recently, he has been a visiting scientist at the University of Colorado, Boulder, USA (in 1995 and in 1998). He has received the CNR Prize for productivity in 1987, and the Ciamician Medal of the Italian Chemical Society in 1985. His research interests are in ring-closure reactions, and in radical and electron-transfer processes.

Luigi Mandolini (left), born in Pesaro in 1943, was educated in Chemistry in Rome under Gabriello Illuminati. He began his academic career as an assistant and lecturer in Organic Reaction Mechanisms (1970−1980) at the University "La Sapienza", Rome, where he has been Professor of Organic Chemistry since 1980, and Director of the "Centro di Studio sui Meccanismi di Reazione" of CNR since 1987. He was awarded the 1979 Ciamician Medal of the Organic Chemistry Division of the Italian Chemical Society for his contributions to the field of macrocyclisation reactions. He was a visiting scientist at the University of Canterbury, UK, in 1975. He is at present chairman of the Management Committee of COST action D11, Supramolecular Chemistry. His principal research interests lie in physical and mechanistic organic chemistry and supramolecular science, with particular emphasis on reactivity and catalysis in supramolecular systems.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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Activation parameters obtained by us and others[7] for a number of cyclisation reaction series, provided a sound experimental basis for testing the validity of Ruzicka's hypothesis. The entropy of activation data fully confirmed that the probability of end-to-end interaction decreases regularly on increasing the length of the chain connecting the reacting groups. On the other hand, the enthalpy of activation data clearly suggested that in a number of cases the relationship between $\Delta H^{\neq}$ and strain energy of the ring being formed is far from simple. No doubt, a severe limitation in such a comparison arose from the fact that the cycloalkanes were the only series of ring compounds for which strain energy data were available over a wide range of ring sizes.[10]

The publication of the strain energies of the lactones, due to the thermochemical work of Wiberg and others,[11–13] as well as the sizeable number of experimental and theoretical studies published in the past decade and addressing the formation and properties of ring compounds, have revived our old interest in the field. This has prompted us to offer comments on the still open question of whether, and to what an extent, the ring product is a good model of the transition state in ring-closure reactions.

The Effective Molarity (*EM*)

The *EM* parameter has been extensively used over the past two decades as a quantitative measure of the ease of ring closure.[6,7,14] If reaction rates are considered, the *EM* is defined by Equation (1a), where k_{intra} and k_{inter} are the specific rates of analogous intra- and intermolecular reactions run under identical conditions. Consistently, for equilibrium studies, the equilibrium *EM* is defined by Equation (1b).[7]

$$EM = k_{intra}/k_{inter} \quad (1a)$$

$$EM = K_{intra}/K_{inter} \quad (1b)$$

The *EM* is of great significance in physical-organic studies of cyclisation reactions. It represents an intramolecular reactivity that is corrected for the inherent reactivity of the end groups. By applying either transition state theory or thermodynamics to Equation (1), Equation (2) is obtained where ΔH and ΔS are to be read as $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for the rate case, or ΔH° and ΔS° for the equilibrium case.

$$EM = \exp[-(\Delta H_{intra} - \Delta H_{inter})/RT]\cdot\exp[(\Delta S_{intra} - \Delta S_{inter})/R] \quad (2)$$

Equation (2) is conveniently written in the compact form of Equation (3), where EM_H and EM_S, defined in the given order by the two exponential terms of Equation 2, represent the enthalpic and entropic components of the *EM*.

$$EM = EM_H \times EM_S \quad (3)$$

In the equilibrium case, the quantity $(\Delta H^{\circ}_{intra} - \Delta H^{\circ}_{inter})$ has the obvious meaning of the strain energy of the ring. In the rate case, $(\Delta H^{\neq}_{intra} - \Delta H^{\neq}_{inter})$ may reasonably be called the strain energy of the ring-shaped transition state. When strainless rings are formed, $EM_H = 1$, and the *EM* is solely determined by its entropic component EM_S.

Examination of entropy changes for a number of cyclisation reaction series, and for the corresponding intermolecular counterparts, revealed that to a useful approximation, the quantity $(\Delta S_{intra} - \Delta S_{inter})$ is independent of factors such as nature of the reacting groups, solvent, or reaction mechanism, but depends solely on the number (r) of skeletal bonds in the bifunctional precursor undergoing cyclisation (Equation 4).

$$\Delta S_{intra} - \Delta S_{inter} = f(r) \quad (4)$$

A fairly large number (ca. 60) of experimental $(\Delta S_{intra} - \Delta S_{inter})$ data related to several cyclisation series, and including the formation of rings from 3- to 23-membered, were averaged in order to estimate $f(r)$; these data are given in Table 1. Extension to the cyclisation of chains with up to 100 skeletal bonds was essentially based on the Jacobson-Stockmayer theory,[15] as applied to the formation of strainless rings.

Table 1. Entropy changes accompanying cyclisation of bifunctional chains as a function of the number of skeletal single bonds (r)

r	$\Delta S_{intra} - \Delta S_{inter}$ [eu][a]	EM_S[b]
0	30	3.6×10^6
1	26	4.8×10^5
2	22	6.4×10^4
3	18	8.6×10^3
4	14	1.1×10^3
5	10	1.5×10^2
6	6	2.0×10
7	2	2.7
8	0	1.0
9	−0.8	6.7×10^{-1}
10	−1.5	4.7×10^{-1}
12	−2.7	2.6×10^{-1}
14	−3.7	1.6×10^{-1}
16	−4.3	1.1×10^{-1}
20	−5.3	6.9×10^{-2}
25	−6.0	4.9×10^{-2}
30	−6.5	3.8×10^{-2}
40	−7.3	2.5×10^{-2}
50	−8.0	1.8×10^{-2}

[a] From ref.[7]; 1 eu = 4.184 J K^{-1} mol^{-1}. – [b] Calculated as $\exp[(\Delta S_{intra} - \Delta S_{inter})/R]$.

The behaviour of the short chains with up to about 7 single bonds, is well described by the simple Equation (5),[16] with S given in eu (1 eu = 4.184 J K^{-1} mol^{-1}). The drop of 4.0 eu per added single bond corresponds to a drop of $\exp(4.0/R)$ or 7.3-fold in cyclisation rate or equilibrium constant.

$$\Delta S_{intra} - \Delta S_{inter} = 30 - 4.0\ r \quad (5)$$

Since the torsional entropy contribution of one C−C internal rotor has been estimated as 4.4−4.8 eu,[17,18] Equation (5) shows that cyclisation of short chains occurs with loss of most of the torsional entropy. Conversely, the entropy data for the longer chains exhibit a much smaller dependence on chain length (Table 1) because the incremental increase in torsional entropy brought about by an additional single bond in a long chain reactant is largely retained in the corresponding cyclic transition state or product.

Ring Strain and Ease of Closure to Cycloalkanes and Lactones

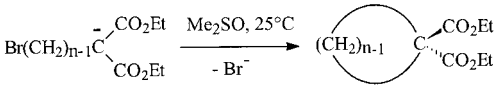
A general discussion of the role of ring strain on the ease of ring closure as a function of size and nature of the ring being formed, calls for a comparison of strain energies of transition states and ring products. The cycloalkanes[10] and the lactones[11−13] are the only classes of ring compounds for which strain energies are available over a large ring-size range, including small (3- and 4-membered), common (5- to 7-membered), medium (8- to 11-membered), and a number of large rings (12-membered and higher) (Table 2).

Table 2. Strain-energies of cycloalkanes and lactones [kcal/mol]

Ring size *n*	Cycloalkanes[a]	Lactones[b]
3	27.5	40.4[c]
4	26.1	23.3[d]
5	6.2	7.7[d]
6	0.1	9.5[d]
7	6.0	10.7
8	9.4	12.4
9	12.2	11.6
10	12.2	8.2
11	11.1	7.3
12	4.0[e]	7.1
13	5.0[e]]	6.7
14	3.2[e]]	4.5
15	1.7	
16	1.8	

From ref.[10] — [b] From refs.[11−13] — [c] See refs.[11c−13] — [d] From ref.[11b] — [e] From ref.[10c]

To illustrate how the extra-thermodynamic treatment of entropy data serves to the purpose of extracting transition state strain energies from *EM* data, we will consider two cyclisation reaction series, namely, the cyclisation of ω-bromoalkylmalonates to 1,1-bis(ethoxycarbonyl)cycloalkanes,[2] Equation (6), and the lactonization of ω-bromoalkylcarboxylates,[1] Equation (7).



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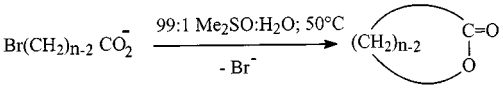


(7)

The corresponding log *EM* versus ring size profiles are shown in Figure 1 and Figure 2 together with the idealised log EM_S profile based on data from Table 1. As shown by Equation (3), the difference between the log EM_S and the experimental log *EM* profiles provides a direct measure of the enthalpic component (log EM_H) for each ring size. In other words, the log EM_S profile can be viewed as an entropic baseline common to all cyclisation reactions, and the difference between the log EM_S value and the experimental log *EM* value for any ring size provides the strain energy of the ring-shaped transition state [Equation (8)].

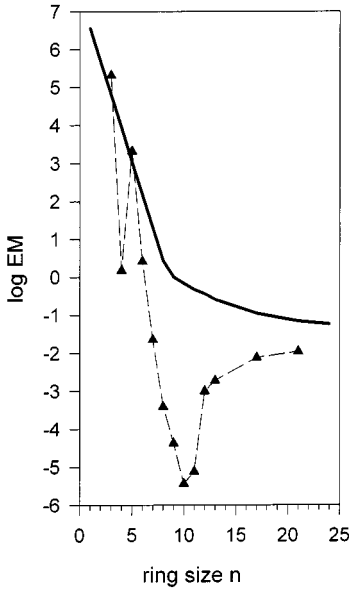


Figure 1. Plot of the experimental *EM* for the malonate cyclisation (Equation 6); the EM_s profile (Table 1) is also shown as a thick line

$$(\Delta H^{\neq}_{intra} - \Delta H^{\neq}_{inter}) = 2.303\ RT\ (\log EM_S - \log EM) \quad (8)$$

When applied to the cyclisation of ω-bromoalkylmalonates [Equation (6)], this treatment leads to the transition-state strain energies plotted in Figure 3 together with the cycloalkanes strain energies as a function of ring size. A glance at Figure 3 shows that the two profiles are structured in much the same way, with the exception of the smallest ring region, which will be discussed in detail in a following section. Both profiles exhibit pronounced maxima around ring size 10, followed by a more or less regular drop in strain energy on increasing ring size. There seems to be little doubt that the stereochemical features which resist medium-ring formation are of the same nature as those responsible for the high strain energies of medium-ring cycloalkanes, namely, bond angle deformations, forced adoption of eclipsed conformations, and transannular interactions.[19] There is a definite tendency for the strain energies of transition states to be lower than those of the cycloalkanes, which leads to the important observation that only a fraction of the product-ring strain shows up in the transition state. This observation is not weakened by the fact that the two profiles do not strictly refer to the same ring compounds. In fact, the 1,1-bis(ethoxycarbonyl)cycloalkanes,

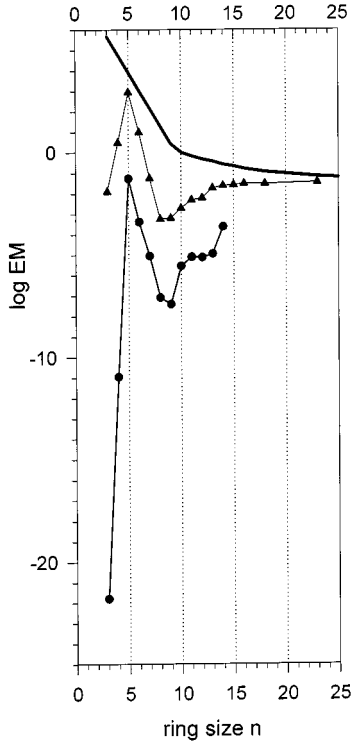


Figure 2. Lactonization reaction: experimental kinetic *EM*s (▲; Equation 7), and equilibrium *EM*s (●), calculated from Equation 2 and the strain energies of the lactones (Table 2); the EM_s profile is also shown as a thick line

for which strain-energy data are not available, are expected to exhibit a more pronounced medium-ring effect than the parent cycloalkanes, on account of increased eclipsing and transannular interactions of the bulky ethoxycarbonyl groups.

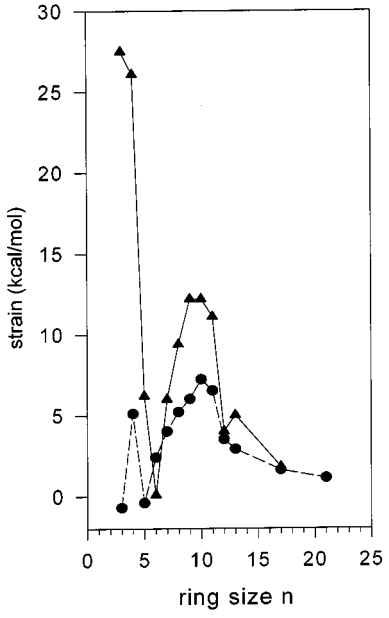


Figure 3. Comparison of the transition-state strain energies for the malonate cyclisation (●; Equation 6) with the strain energies of the cycloalkanes (▲; from Table 2)

Figure 2 plots the corresponding profiles for the lactonization of ω-bromoalkanoates [Equation (7)]. In the same figure, the equilibrium *EM* values, calculated from Equation (3) and the lactone strain energies (Table 2), are plotted for comparison. Lactones with ring size $n \leq 8$ are forced to adopt the less stable *E* ester conformation, whereas the larger ring lactones adopt the *Z* conformation.[11a,20] In the case of methyl acetate, the *E* conformation is 8.5 kcal/mol higher in energy than the *Z* conformation.[21] As a consequence, an extra enthalpic penalty is imposed on the smallest lactones, which explains, inter alia, the high strain energy of the 6-membered lactone,[11a] and causes the lactones' strain-maximum to shift away from the ring sizes 9 and 10 of the cycloalkanes to ring size 8[1a] (Figure 4).

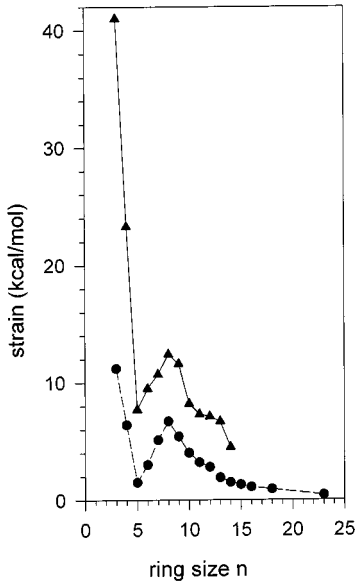


Figure 4. Comparison of the transition state strain energies for the lactonization reaction (●; Equation 7) with the strain energies of the lactones (▲; from Table 2).

Whereas a discussion of the smallest rings is again postponed, it is remarkable to see how closely the transition states reproduce the strain energy pattern of the lactones (Figure 4).[22,23] Once more, transition-state strain energies are much smaller than product-ring strain energies. This suggests that the mere stretching of a covalent bond in a strained ring, up to the length of the bond being formed in the transition state, is responsible for a substantial strain relief. Although no simple functional relationship appears to exist between transition state and product-ring strain energies, there is an undeniable tendency for the strain relief at the transition state to be sizeable when the strain of the ring being formed is large. This implies that, whenever highly strained rings are formed, the kinetic *EM*s turn out to be much higher than the corresponding thermodynamic *EM*s, as nicely shown by a direct comparison of kinetic and thermodynamic data for lactone formation (Figure 2).

From a synthetic point of view this is a fortunate situation, since the dilution required to successfully run an irreversible cyclisation reaction is higher the lower the kinetic *EM*.[7] It also explains why highly strained rings can hardly

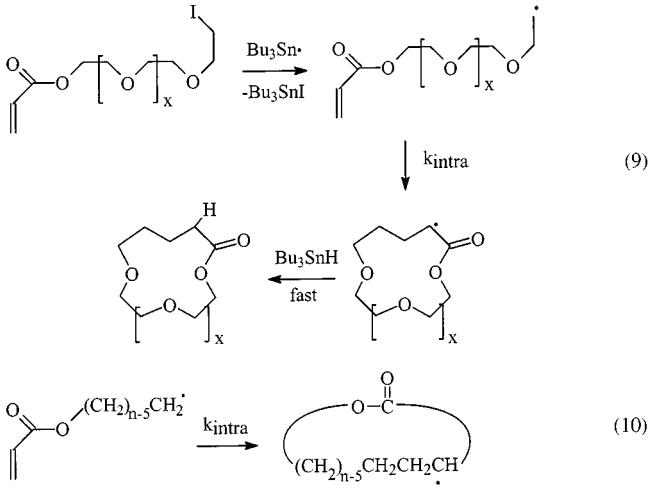
be prepared using reversible cyclisation reactions. The case of β-propiolactone (ring size 4) illustrates this point rather well. The irreversible lactonization of 3-bromopropanoate (*EM* = 3.0 M) can be run almost *quantitatively* at an initial concentration of about 0.3 M, where the competing polymerisation is almost suppressed. Conversely, the extremely low thermodynamic *EM* value of 1.1×10^{-11} M would require an initial concentration as low as 10^{-12} M to obtain a comparable yield under equilibrium conditions.

More on Macrolactonization and Related Reactions

The destabilising interactions that notably affect the energy of the medium rings,[19] are significantly relieved when the ring becomes larger. Unfortunately, ring-strain energies are not available for very large ring compounds. Morawetz and Goodman have suggested that even large-ring cycloalkanes would be affected by a ring strain energy of about 2 kcal/mol because of the presence of a larger proportion of *gauche* conformations than in linear alkanes.[24] Indirect evidence has been obtained to show that the ring strain of polymethylene compounds is still significant for ring sizes below 20, and becomes vanishingly small in the neighbourhood of ring size 30.[3b,25]

During the past decade, there has been a substantial accumulation of data in the form of kinetic or equilibrium measurements of cyclisation reactions leading to large and very large rings. It is of interest to discuss those data in the light of our general treatment, because they bear directly on the question of the role of strain in large-ring formation. All of the reported systems involve either macrolactonization or closely related reactions, but the chemistry involved is in all cases quite different from the simple S_N2 process of Equation (7).

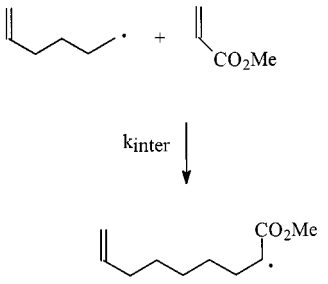
A free-radical C−C bond formation is the ring-closing step in the formation of 12-, 15-, 18-, 21-, and 24-membered polyoxalactones [Equation (9); $x = 1-5$), for which the kinetics have been measured in benzene at 80 °C.[26] The same source also reported the rate constants of cyclisation to 11-, 12-, 15-, 16-, and 20-membered polymethylene lactones [Equation (10)] under the same conditions.[26]



(9)

(10)

We have converted the reported k_{intra} values into the *EM*s using the second-order rate constant ($k_{inter} = 6.9 \times 10^5$ M^{-1} s^{-1}) for the intermolecular model reaction of 5-hexen-1-yl radical with methyl acrylate [Equation (11)], extrapolated to 80 °C from data obtained at lower temperatures in CH_3CN/AcOH (6:4, v/v).[27]



(11)

These *EM* data are plotted in Figure 5, along with the *EM* data for lactonization of ω-bromoalkanoates [Equation (7)]. The *EM* data of the polymethylene lactones [Equation (10)] appear almost indistinguishable from those of the reaction of Equation (7), in spite of the markedly different chemistry involved in the two series. This again emphasises the use of the *EM* as an absolute measure of intramolecular reactivity, as it represents a cyclisation efficiency "corrected" for the inherent reactivity of the end groups, including medium effects. In line with the well-known strain relief exerted by oxygen atoms and trigonal groups,[6,7] substantially higher *EM* values are seen for the polyoxalactones of Equation (9), whose representative points closely adhere to the idealised EM_S profile. It appears, therefore, that within the precision on which log EM_S is defined,[28] the transition states leading to the polyoxalactones, and consequently the polyoxalactones themselves, are to be viewed as virtually strainless.

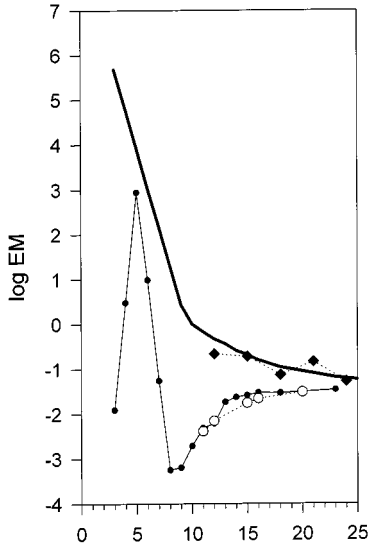
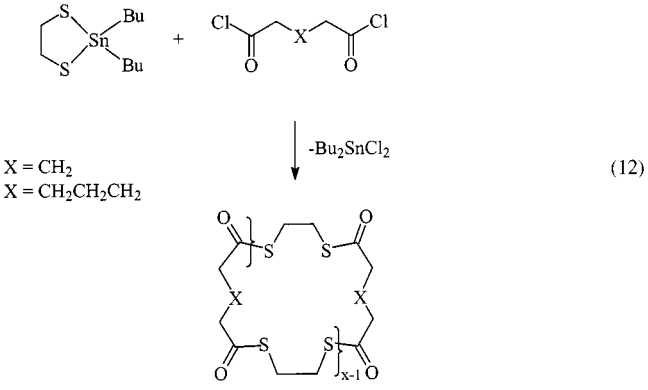


Figure 5. Plot of the *EM*s for the lactonization of ω-bromoalkanoates, Equation 7 (●), and for the radical lactonization reactions, Equations 9 (◆) and 10 (○); the EM_s profile is also shown as a thick line

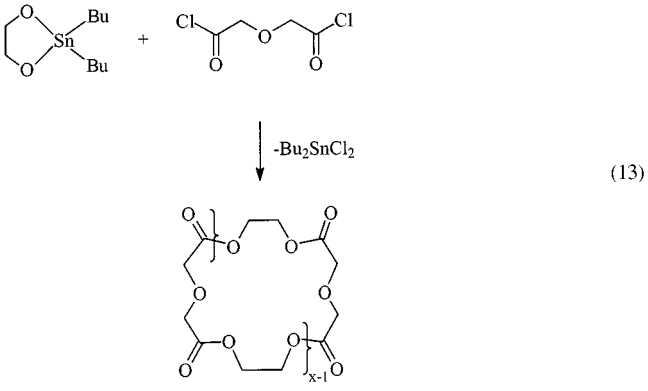
Theoretical models of macrocyclisations occurring either under kinetic[29] or thermodynamic[30] control have been developed. Based on these models, *EM* data have been extracted from the distribution of cyclic oligomers in a number of cyclo-oligomerization reactions. These reactions are:

1) The kinetically controlled formation of macrocyclic poly(thiolactones) by reaction of 2,2-dibutyl-1,3,2-dithiastannolane with glutaryl chloride (X = CH_2) and pimeloyl chloride (X = $CH_2CH_2CH_2$) in refluxing $CHCl_3$ [Equation (12)].[29] The *EM* data refer to the formation of the cyclic monomer, dimer, trimer, and tetramer in both series, corresponding to ring sizes 9, 18, 27, and 36 for the glutarates, and 11, 22, 33, and 44 for the pimelates.



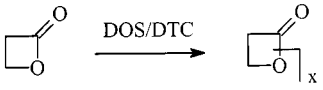
(12)

2) The thermodynamically controlled formation of macrocyclic polylactones by reaction of 2,2-dibutyl-1,3,2-dioxastannolane with diglycolyl chloride in $CHCl_3$ at room temperature [Equation (13)].[30] The *EM*s are equilibrium *EM*s,[31] and refer to the formation of the dimer (18-membered ring), trimer (27-membered ring), and tetramer (36-membered ring).



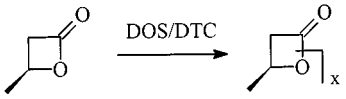
(13)

3) The reversible cyclo-oligomerization of β-propiolactone, catalysed by a mixture of 2,2-dibutyl-1,3,2-dioxastannolane (DOS) and dibutyltin dichloride (DTC) in $CHCl_3$ at 70 °C [Equation (14)].[32] Equilibrium *EM*s were reported for the formation of the cyclic trimer (x = 3, 12-membered ring) through octamer (x = 8, 32-membered ring).[31]



(15)

4) The reversible cyclo-oligomerization of (*S*)-β-butyrolactone, catalysed by DOS/DTC in $CHCl_3$ at 70 °C [Equation (15)].[33] Equilibrium *EM*s were reported for the formation of the cyclic tetramer (x = 4, 16-membered ring) through the undecamer (x = 11, 44-membered ring).[31]



(14)

All of the above *EM* values are compared in Figure 6, with the idealised EM_S profile. Marked downward deviations are seen for the 9-membered thioglutarate and 11-membered thiopimelate [Equation (12)], whose *EM*s are 500 and 28.5 times smaller than predicted for strainless rings. The latter values correspond to transition-state strain energies of 4.2 and 2.3 kcal/mol, respectively. The remaining

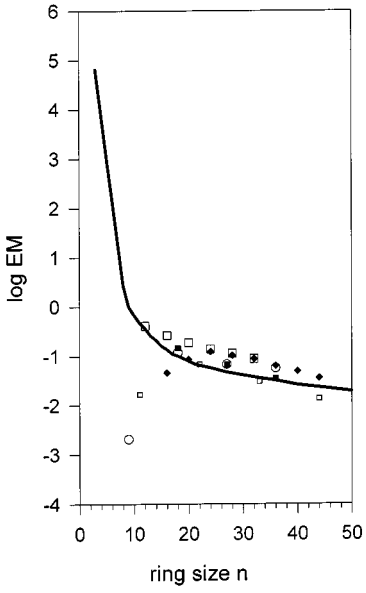


Figure 6. *EM*s for cyclo-oligomerization reactions: ○ = Equation 12, X = CH_2; □ = Equation 12, X = $CH_2CH_2CH_2$; ■ = Equation 13; □ = Equation 14; ◆ Equation 15; the EM_s profile is also shown as a thick line

data points in Figure 6, with the possible exception of the 16-membered tetra[(*S*)-β-butyrolactone], for which a ring strain of 0.7 kcal/mol was calculated from Equation (8), show a very good adherence[28] to the behaviour predicted for strainless rings. It is worth stressing that both kinetic and thermodynamic *EM* values, related to the formation of strainless rings, can be predicted with remarkably high accuracy[28] on the basis of the ($\Delta S_{intra} - \Delta S_{inter}$) values listed in Table 1.

Cyclisation of the Shortest Chains

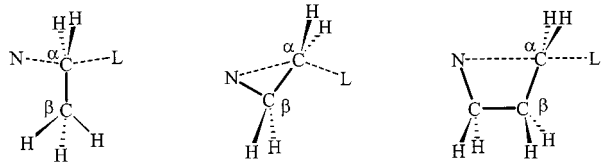
Cyclisation of short chains has attracted much attention, not only because they are important in their own right, but also because they are involved in neighbouring-group participation and intramolecular catalysis phenomena, which are believed to mimic the extraordinary reactivity displayed by enzyme-substrate complexes.[14,34]

Three- and four-membered rings, in spite of being much more strained than their larger homologues, are nevertheless very easily formed in intramolecular nucleophilic reactions. The entropic advantage due to the close proximity of end groups in the very short bifunctional precursors is responsible, but to a minor extent, for their high ease of formation. As shown in Figure 3 and Figure 4, much more important is the enthalpic factor, in that the large strain energies of the ring products do not show up, or show up only to a very small extent, in the transition states. For example, a comparison of the experimental *EM* values for closure of the 3- and 4-membered lactones with the corresponding equilibrium *EM* values, Figure 2, illustrates quite well the puzzling behaviour experienced by rates of closure to small rings.

We further note that in intramolecular S_N2 reactions, the ease of formation of 5-membered rings is always higher than that of the usually less strained 6-membered homologues,[35] by extents that exceed the entropic advantage of 5- versus 6-membered ring formation. Thus, the anomalous behaviour is not confined to closure of 3- and 4-membered rings, but to a certain degree also involves closure of 5-membered rings.

These intriguing features of closure to the smallest rings have been remarked on for some time. For example, DeTar and Brooks have pointed out[36] that comparison of cyclisation rates with thermodynamic data led to a wrong estimate of the 5- versus 6-membered ring formation by a factor of 10^4, and by a factor of 10^{12} for 4- versus 7-membered rings! Benedetti and Stirling have suggested that formation of the highly strained small rings involves very open transition states, with a consequently limited development of ring strain.[37,38] However, based on the determination of the leaving-group effect (k_{Br}/k_{Cl}) in typical S_N2 cyclisation reactions in the ring-size range of 3−6, the degree of cleavage of the bond to the leaving group, and hence the degree of ring formation in the transition state, was found to be significant for the small rings.[39] In fact, these k_{Br}/k_{Cl} values were found to be more pronounced than in the acyclic analogues.

We have put forward[39] a qualitative explanation for the lack of correspondence between transition state and product strain energies in nucleophilic cyclisations of very short chains. It is based on the classical interpretation of steric retardation in bimolecular S_N2 reactions,[40] where a major contribution to the activation barrier arises from compression of atoms not directly bonded together. In primary alkyl substrates such compressions derive from the interaction of both the entering (N) and leaving (L) groups, with substituents attached to the α- and β-carbon atoms (as in **I**). It is clear that in **II** such compressions with the β-hydrogen atoms are not present, and the α-hydrogen atoms are quite far away from the bent trajectory of the N group. It also seems likely that the leaving group L would take advantage of this geometrical situation, in that it can follow a favourable bent trajectory away from the β-hydrogen atoms. The picture of the 4-membered transition state (**III**) shows that interactions of N with the β-hydrogen atoms are absent as well.

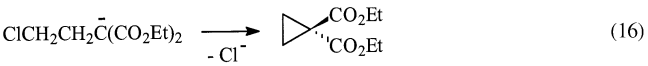


We have suggested that such a reduction of nonbonded interactions is very important for forming 3-membered rings, decreases in the order 3 > 4 > 5, and becomes negligibly small for the 6-membered rings. This is equivalent to saying that steric hindrance to the attack of the nucleophile is much less pronounced for closure of the shortest chains than for closure of the longer ones and for the intermolecular reactions. As a consequence, enthalpies of activation for closure of the small rings will reflect very poorly the large strain energies of the ring being formed, even though bond making is significant in the transition state.[39]

Largely consistent with the above hypothesis are the ab initio calculations reported by Gronert and Lee on the (hypothetical) ring closures of $HS(CH_2)_2S^-$, $HS(CH_2)_3S^-$, and $HS(CH_2)_4S^-$ to give thiirane, thiethane, and tetrahydrothiophene, and on the reference intermolecular reaction of CH_3S^- with CH_3CH_2SH.[41] Calculations have disclosed a much later transition state for closure to thiirane than to tetrahydrothiophene, with an intermediate behaviour being found for the 4-membered ring formation. The calculated activation barriers were 19.2, 29.4, and 23.1 kcal/mol for the formation of the 3-, 4-, and 5-membered rings, respectively, and 25.0 kcal/mol for the acyclic analogue. Two factors have been held responsible for the surprisingly small barrier to the formation of thiirane,[41] as well as of other 3-membered rings.[42] First, there is little development of angular strain because of the nature of the bonding in S_N2 transition states. The second factor is the close proximity of the nucleophilic atom to the electrophilic site, which causes part of the typical S_N2 barrier to be already built into the substrate undergoing cyclisation. In other words, short bifunctional chains leading to 3-membered rings start closer to the transition state because a part of the reaction path is already provided by a destabilisation of the reactant state. Such an effect, referred to by the Authors as a "proximity effect", is purely enthalpic in nature.[41,42] This term is somewhat unfortunate because it might be confused with the identical terminology used for a long time to express the entropic advantage of intra- versus intermolecular reactions.[43] Nevertheless, and

without giving too much emphasis to the exact numbers obtained from such calculations carried out in the gas phase, there is little doubt that the above ab initio studies provide valuable insights into the intriguing peculiarities involved in the formation of small rings.

Another issue was raised by Stirling many years ago.[44] It concerns the finding that 3-membered rings are sometimes formed very much more slowly than 5-membered rings, but in other cases very much more rapidly. Cyclisations involving nitrogen and oxygen nucleophiles have higher rate constants for forming 5-membered rings than for 3-membered rings,[35,44] but when the nucleophile is a stabilised carbanion the opposite reactivity order is observed.[44] A typical example is provided by the high ease of formation of bis(ethoxycarbonyl)cyclopropane [Equation (16)] compared with bis(ethoxycarbonyl)cyclopentane, by cyclisation of the corresponding chloromalonates, for which a k_3/k_5 ratio of 100 has been estimated.[45]



(16)

In view of the well-documented ability of the strongly distorted σ-bonds of cyclopropane to interact with electron-withdrawing substituents,[46] Knipe and Stirling suggested that the high ease of formation of bis(ethoxycarbonyl)cyclopropane could be due to a substantial reduction of the strain of the 3-membered ring brought about by the two geminal electron-withdrawing substituents.[45]

This hypothesis appeared rather sound, but no thermochemical data were provided to support it. We have decided to investigate this point, and provide thermochemical data for mono- and gem-dialkoxycarbonyl-substituted cycloalkanes in the ring-size range of 3−5.[47] A weak stabilising effect of 1.9 kcal/mol was found for *(methoxycarbonyl)*cyclopropane,[47] which finds a counterpart in the weak stabilising effect of 2.0 kcal/mol reported for *acetyl*cyclopropane,[48] of 1.7 kcal/mol for *phenyl*cyclopropane,[48] and of less than 0.7 kcal/mol for *cyano*cyclopropane.[49] However, in contrast to the above suggestion,[45] no stabilisation of 1,1-bis(ethoxycarbonyl)cyclopropane with respect to cyclopropane could be brought into evidence.[47] This investigation also allowed us to clarify that a previous literature claim,[50] concerning a stabilisation of 7 kcal/mol for (methoxycarbonyl)cyclobutane with respect to cyclobutane, was based on an erroneous determination of the enthalpy of combustion. In conclusion, any strain-relieving effect by electron-withdrawing substituents for the 3- and 4-membered cycloalkanes appears to be very small, and certainly cannot be taken as responsible for the high rate of formation of 1,1-bis(ethoxycarbonyl)cyclopropane,[45] or of other cyclopropane derivatives substituted with electron-withdrawing groups.

A satisfactory rationalisation of the relationship between the type of the nucleophile undergoing ring closure and ring-size preference has been provided by Gronert et al. in terms of the "proximity effect" mentioned above.[42] Their computational data nicely show that, with bulky delocalized carbanions as nucleophiles, the formation of the 3-membered ring is easier than that of the 5-membered homologue. Conversely, with small and localised nucleophiles, such as oxygen and nitrogen, the incoming group N needs to approach the electrophilic centre more closely, thereby imposing a more severe angular strain to the transition state and making the formation of a 3-membered ring to be more difficult than that of the 5-membered homologue.

Conclusion

An extra-thermodynamic treatment of entropy changes in ring closure reactions and their acyclic analogues has been extensively used to extract transition-state strain energies from experimental kinetic *EM* data, and to calculate equilibrium *EM* values from ring-strain energies.

Whenever large, strainless rings are formed, no strain energy shows up in the transition states. As a result, kinetic and thermodynamic *EM*s become indistinguishable from one another, and are practically coincident with the tabulated EM_S values. Thus, the ease of ring closure of very long chains is independent of the chemical nature of end groups, as well as of the nature of the ring being formed, but solely depends on the loss of torsional entropy suffered by the chain undergoing cyclisation.

In the medium-ring region, a fraction of the significant strain energy of the ring product develops in the transition state, and the resulting unfavourable enthalpic contribution adds to the entropy loss upon ring closure. This leads to kinetic *EM* values usually much lower than those of the large rings, albeit significantly higher than the corresponding thermodynamic *EM* values, and explains why the choice of appropriate high-dilution conditions[51] is critical to obtain satisfactory yields of medium-sized rings in synthetic procedures.

In the reversible cyclisation of the shortest chains, the entropic advantage compensates only to a minor extent for the severe enthalpic disadvantage due to the extremely large strain energies of the small rings. The thermodynamic *EM* values are so low as to prevent the significant formation of small rings in reversible reactions at any reactant concentration of practical interest. It is fortunate that the transition state for closure of the small rings enjoys a spectacular discount of the enthalpic toll required to cross the activation barrier. This phenomenon is most pronounced in closures of 3-membered rings, for which kinetic *EM* values as high as several powers of ten are known.[7,14] The lack of correspondence between transition-state and ring-strain energy is understood on the basis of a substantial reduction of the nonbonded interactions in the small ring transition states.

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[22] We have reported activation parameters for lactonization over the whole ring-size range.[1] Not surprisingly, the experimental ($\Delta H^{\neq}_{intra} - \Delta H^{\neq}_{inter}$) values compare well with the values calculated from Equation (8), because the related experimental ($\Delta S^{\neq}_{intra} - \Delta S^{\neq}_{inter}$) values were included in the set of data used to estimate the numerical values of $f(r)$ listed in Table 1. In this paper we have used the extra-thermodynamically derived ($\Delta H^{\neq}_{intra} - \Delta H^{\neq}_{inter}$) values, in place of the experimental values, with the aim of illustrating and emphasising the general use of Equation (8).

[23] Strain and entropy effects on lactone formation have been recently re-evaluated, see: F. C. Lightstone, T. C. Bruice, *Bioorg. Chem*. **1998**, *26*, 193−199. Using our $\Delta H^{\neq}_{intra}$ and $\Delta S^{\neq}_{intra}$ data, and comparing the $\Delta H^{\neq}_{intra}$ and $T\Delta S^{\neq}_{intra}$ contributions for each ring size, the above authors concluded that the lactonization is enthalpy-driven for ring sizes 3−6, whereas is entropy-driven for ring sizes 8 and larger. It is worth stressing that $\Delta H^{\neq}$ and $\Delta S^{\neq}$ data for ring closure contain contributions from chemical changes and solvent reorganisation, which are generally unknown and presumably very large. Therefore, conclusions based on the relative magnitude of $\Delta H^{\neq}_{intra}$ and $T\Delta S^{\neq}_{intra}$ values are of limited significance. Enthalpy and entropy effects on ring closure are more correctly discussed in terms of *EM*s and their enthalpic and entropic components [Equation (3)], since the EM_S data listed in Table 1 provide an "entropic baseline" common to all cyclisation reactions.

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