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Cyclization and the Conformation of Hydrocarbon Chains

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I. Introduction

The polymethylene chain is the structurally simplest known polymer. It is also one of the most important. Its oligomers play a key structural role in micelles, microemulsions, and biological membranes, where the hydrophobic interactions between the CH_2 groups couple with the intrinsic flexibility of the chain to provide these systems with their unique properties. The *n*-alkanes, as a homologous series, have played an important role in the elucidation of the physical and chemical properties of nonpolar molecules. Polyethylene is a polymer of vast commercial importance. It has also been a convenient testing ground for theories of the structure and dynamics of polymer molecules.

Mitchell A. Winnik was born in Milwaukee, WI, in 1943. At the age of 7, his father bought him his first chemistry book. It remained unread for several years. He entered high school the year the first Sputnik was launched, when excellence in science and science teaching became a major objective all over North America. He spent 1 year at the University of Wisconsin, then transferred to Yale University, completing the B.A. degree in Chemistry in 1965. He returned to Wisconsin for the summer of 1962, where he had the privilege of working as a research assistant in the laboratory of Professor H. E. Zimmerman. This was his first exposure to organic photochemistry. He did his graduate studies at Columbia University in New York. His Ph.D. research, under the supervision of Professor Ronald Breslow, involved the initial studies leading to the development of the "remote oxidation" technique for oxidizing unactivated CH bonds. In 1970, after a year of postdoctoral work with Professor George Hammond at the California Institute of Technology and a summer teaching chemistry in what is now Bangladesh, Professor Winnik accepted a position at the University of Toronto, where he is now Professor of Chemistry. His interest in polymer chemistry is recent, and his experimental work in the area began in 1978 during a sabbatical year in France. His current research interests are in the application of organic photochemistry and luminescence spectroscopy of the study of the shapes and motions of flexible molecules, in hydrocarbon chains and polymers, as well as in more complex systems such as lipid bilayers and colloids.

Interest in the conformational properties of hydrocarbon chains began in the early part of this century with the work of Langmuir[1] on monolayers of fatty acids and Ruzicka and his colleagues[2] to understand cyclization phenomena. Even earlier interest in the connection between cyclization and chain flexibility can be traced to the experiments of Freundlich[3] and Rüggli.[4] Thus in the history of stereochemistry, the recognition that hydrocarbon chains were flexible led immediately to the idea that they could cyclize. Cyclization was understood to be one expression of chain conformation: Ring closure reactions and their kinetics were studied from the beginning as one of the first experimental approaches to this difficult question.

It has been nearly 12 years since the subject of polymethylene chain conformation has been thoroughly reviewed.[5] During those years new techniques have been applied to the problem (e.g., neutron diffraction[6]). The advent of lasers has vastly improved Raman

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spectroscopy.[7] New magnet and Fourier transform technology has revolutionized the application of ^1H and ^{13}C NMR to problems in chain conformation and chain dynamics.[8] The last 12 years have also borne witness to enormous advances in the quantitative study of cyclization reactions. It is the impact of these studies on the subject of hydrocarbon chain conformation and hydrocarbon chain dynamics that is the subject matter of this review.

There have been a number of previous reviews which have treated aspects of chain cyclization phenomena. Semylen[9] has published a thorough and critical review of ring–chain polymerization reactions, including a discussion of the applications of the rotational isomeric state (RIS) model to calculate cyclization probabilities in those reactions. Winnik[10] has published a short account reviewing his photochemical approach to determining cyclization kinetics and his variant of the RIS model to simulate those results. Cycloalkane stereochemistry and conformational dynamics have been reviewed by Dale,[11] who stresses the impact of molecular mechanics calculations on the development of this field. It should be clear from these citations that many of the most important advances in understanding conformational problems come from the concerted development of new experiments and new theoretical models. An older review by Dunitz[12] examined the conformation of cycloalkanes in the solid state.

This review is divided into six parts. It begins by giving a general background to the field, discussing early experiments on cyclization and the development of contemporary theory of chain conformation and dynamics. The next section develops important concepts and classifications of cyclization reactions. Cycloalkane stereochemistry is reviewed, followed by a discussion of results on end-to-end cyclization equilibria. Finally the relationship between intramolecular reaction kinetics and cyclization conformation and dynamics are examined and many examples are discussed.

II. General Background

A. Early Experiments

There are many known examples of chemical reactions occurring between substituents attached to the ends of a flexible chain molecule. When these reactions occur intramolecularly, as in ring-closure reactions where molecules of the form $A(CH_2)_nB$ cyclize to form ring compounds $(CH_2)_nD$, their study can provide information on the conformational properties of the intervening chain. One of the first careful and quantitative studies of ring-closure reactions was carried out by Freundlich and his co-workers beginning in 1911.[3] They examined the kinetics of cyclization of $Br(CH_2)_mNH_2$ in basic aqueous media to give $(CH_2)_mNH$ and demonstrated that the reaction was irreversible. One of the conclusions of their work was the now well-recognized fact that in kinetically controlled reactions three-, five-, and six-membered rings form with particular ease.

The discovery that the naturally occurring musks, civetone and muscone, contained larger rings stimulated much effort in the synthesis of macrocyclic compounds. Ruzicka[2] discovered that the pyrolysis of the thorium salts of dibasic acids leads to the formation of cyclic ketones. This method works for rings of 8 members as well as for those larger than 12. Ziegler[14] developed an approach involving the treatment of a dinitrile with base. Neither method works well for rings of 9 to 12 atoms. These rings were not readily accessible until the development of acyloin synthesis, the reaction of a diester with sodium to give an α-hydroxy ketone.[15]

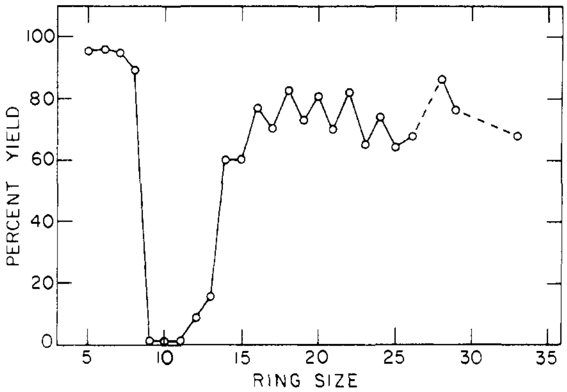
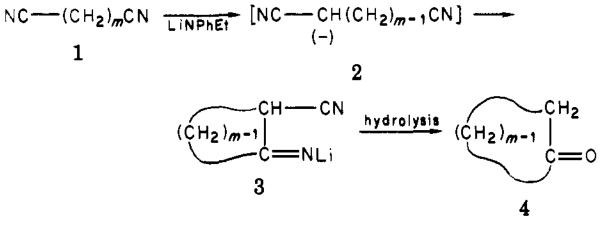


Figure 1. Percent yield of cyclic ketone formation reported by Ziegler in the Thorpe reaction of $NC\text{-}(CH_2)_m\text{-}CN$. Data are taken from ref 14c.

The kinetic principles governing macrocycle formation were elucidated through the contributions of Ruzicka,[2,13] Ziegler,[14] Carothers,[16] Salomon,[17] Stoll,[18] and their co-workers. Ring-closure reactions are always in competition with the corresponding bimolecular reactions. Since the rate of the latter depends upon concentration while the former does not, the yield of intramolecular cyclization product can be enhanced by dilution of the reaction media. This point was raised explicitly by Rüggli[4] in 1912, but for various reasons his work attracted little attention until some 15 years later. Bennett[19] has written an excellent review of the early work in this area.

Ziegler pioneered the dilution method for the synthesis of macrocyclic compounds.[3] He also recognized that for irreversible reactions, high dilution need not imply large volumes of solvent: slow addition of a bifunctional reagent to a solution containing a promoter serves to maintain a continuous low concentration of the reactive species. One of his most famous examples[3a] is the intramolecular Thorpe reaction (eq 1). His data



(1)

are pictured in Figure 1. The key aspects of these data, which were widely appreciated at the time, were (i) the difficulty in synthesizing rings of 9 to 16 members and (ii) the apparent differences in the ease of formation of even- and odd-membered rings, persisting to long chain lengths.

An alternative approach to the synthesis of ring compounds was developed by Carothers and his group.[16] Here condensation polymers of a dibasic acid with a diol, or of an ω-hydroxy carboxylic acid, were depolymerized in the melt with the aid of a catalyst. The reaction vessel was heated under vacuum and the volatile

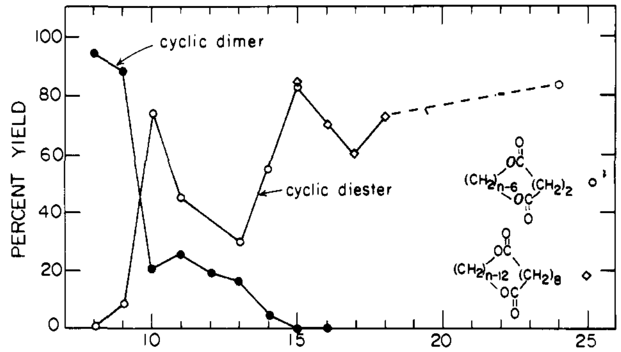


Figure 2. Percent yield of cyclic diester (diolide) and cyclic dimeric tetraester (tetrolide) formation reported by Spanagel and Carothers in the depolymerization of polymethylene succinates (○) and polymethylene sebacates (□). Data are taken from ref 16b.

components, cyclic monomers and dimers, were collected and analyzed. The yields of these lactones as a function of ring size are shown in Figure 2. The curve in Figure 2 is similar in form but different in detail to that in Figure 1. Again it is apparent that rings of medium size form with difficulty while those of larger size form with greater ease, with significant odd–even alternation effects in the yield of cyclic products.

Another important principle to emerge at this time was the recognition that the data in Figure 1 and 2 were not amenable to quantitative interpretation. Ziegler's reactions were run in such a way as to maximize yield. Since the reaction conditions were not exactly comparable for each chain length and the secondary reaction products not characterized and quantified, these data could not be transformed into relative reaction rates. In Carothers' experiments, the original ring–chain equilibrium was disrupted by distillation of the volatile components, again to produce a maximum yield of cyclics. That the yields of cyclics in these experiments parallel the rate constants for ring closure obtained by Salomon[17] and the equilibrium constants of Stoll and Rouvé[18] is a tribute to the magnitude of the effects opposing cyclization for medium-size rings.

Salomon's[17] results on the kinetics of cyclization in $Br(CH_2)_mNH_2$, for large m, were important particularly for later developments in understanding reaction mechanisms of organic molecules. They were not sufficiently extensive to serve as the basis for testing statistical models of chain conformation (see next section) which were beginning to be developed. His experiments, and those of Freundlich, have recently been critically reviewed and reinterpreted by De Tar.[20a]

The classic quantitative studies of the prewar era were those of Stoll and Rouvé,[18] who examined ring–chain polymerization of ω-hydroxy-n-alkyl carboxylic acids in benzene at reflux in the presence of an acid catalyst. From their data, the equilibrium constant for cyclization, K_{cy}, as a function of chain length could be calculated. Their results, which will be presented in more detail in a subsequent section, stood for nearly 40 years as the sole quantitative data pertinent to the question of end-to-end cyclization of polymethylene chains. They were discussed for their conformational implications by Flory[21] in his first book, and subsequent to a slight modification of the data analysis[22] were used by Sisido[23] as the comparison data for his computer simulation of hydrocarbon chain cyclization.

In summary, considerable understanding of ring-closure processes was developed during the years 1920–1940. Hydrocarbon chains were perceived to be flexible. Ruzicka[2] pointed out that the probability of the chain ends meeting should diminish with increasing chain length, although in retrospect this aspect of flexible chains played a minor role in the reactions studied by his contemporaries. Molecular models were employed, and these pointed to steric crowding between hydrogens in the ring interior as a major factor in inhibiting formation of medium-size rings. This idea was tested by synthesizing ring compounds containing oxygens and planar aromatic rings.[24] Here transannular repulsions were minimized and ring formation was enhanced. It was also noticed that models of rings of 20–30 atoms contained parallel zigzag segments.[19] In modern terms, this suggests that such rings might be rich in trans rotamers. The existence of barriers to rotation about carbon–carbon bonds was unknown at that time. In consequence, the one aspect of cyclization not appreciated by these research groups was that medium-ring formation is also disfavored because of torsional strain in the molecules.

B. Early Theory

In the early 1930s, Kuhn[25] developed his now classic treatment of polymer configuration in terms of the random walk model. For such a model, the distribution function $W(r)$ of the end-to-end chain displacement r, in the limit of a large number of links, has a Gaussian form. Kuhn showed that in the limit of $r \rightarrow 0$, $W(r)$ exists and has the value

$$W(0) = 4\pi r^2[3/(2\pi\langle r_0^2\rangle)]^{3/2} \qquad (2)$$

In this expression, $W(0)$ is the cyclization probability of the chain. It is seen to be related in a simple way to $\langle r_0^2\rangle$, the mean-squared end-to-end length, which in turn for Gaussian chains is simply related to $\langle s_0^2\rangle$, the mean-squared radius of gyration of the chain. The term $W(0)/4\pi r^2$, in the limit of $r \rightarrow 0$, can be thought of as the effective or local concentration C_{eff} of one chain end in the vicinity of the other.

The relationship between $W(0)$ and the equilibrium constant for cyclization, K_{cy}, was made more explicit in the work of Jacobson and Stockmayer.[26] Since the freely jointed chain has no internal energy, $W(0)$ is related to K_{cy} only through the entropy of cyclization. For a polymeric macrocycle made up of N monomer units, the dependence of the cyclization probability on N is sensitive to one feature of the cyclization process. If cyclization is reversible at a unique bond in the macrocycle, then

$$K_{cy} \sim N^{-3/2} \text{ (one site of ring opening)} \qquad (3)$$

If, however, any of the monomer–monomer bonds can reopen, then ring opening is N-fold degenerate and

$$K_{cy} \sim N^{-5/2} \text{ (N sites of ring opening)} \qquad (4)$$

For hydrocarbon chains, this theory has never properly been tested. There have been attempts to account for polycyclics in nylon in terms of an updated modification of this theory.[9,27] The single most important test of these conclusions has been carried out for polysiloxane polymers,[28a] based upon the discovery by Brown and Slusarczuk[28b] that in poly(dimethylsiloxane)

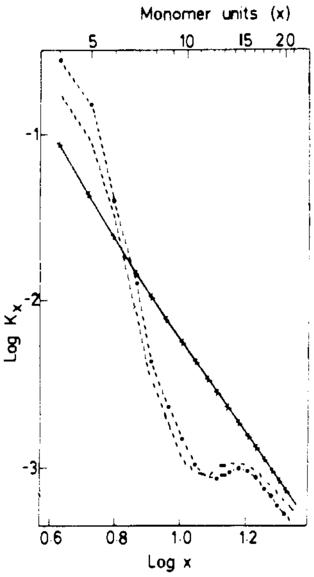


Figure 3. Molar cyclization equilibrium constants of dimethylsiloxanes at 110 °C. Values calculated from the rotational isomeric state model assuming a Gaussian end-to-end distribution (×) are compared with values measured by Semlyen[9] for equilibration in bulk (○) and values measured by Brown and Slusarczuk[28b] for equilibration in toluene solution (●). Reproduced with permission from J. A. Semlyen and P. V. Wright, *Polymer*, 10, 543 (1969). Copyright 1969, IPC Business Press Ltd.

(PDMS) synthesis the cyclics could be quantitatively isolated and K_{cy} determined.

To describe these results, Flory and Semlyen[28a] recast the theory of Jacobson and Stockmayer in terms of the rotational isomeric state model, assuming that for sufficiently long chains in a Θ solvent, the distribution of the end-to-end length is Gaussian. For both the theory and experiment, long chains showed a dependence of K_{cy} on $N^{-5/2}$ (see Figure 3). For shorter chains, theory and experiment are in poor agreement. These differences may be due to the non-Gaussian nature of short chains, bond angle correlations associated with the details of the cyclization process,[29] or transannular steric effects (an excluded volume effect). Semlyen has continued both the theoretical and experimental aspects of this work and recently reviewed the subject of ring-chain polymerization.[9]

Recent results on the kinetics of polysiloxane ring formation by Chojnowski's group in Poland[30] suggest that in these reactions, where a conformational equilibrium precedes irreversible cyclization, $K_{cy} \sim N^{-3/2}$. Photochemical studies of the cyclization of polystyrene[51] of $\bar{M}_n$ = 3000–10 000 also indicates that $K_{cy} \sim N^{-3/2}$.

C. Contemporary Models of Chain Conformation and Chain Dynamics

Mathematical models play an important role in understanding chain conformation and chain dynamics. These models serve several functions. They provide a means of interpreting experimental results. They serve as a vehicle for exploring the fundamental physics contributing to the conformation and dynamics of polymers. In addition they make predictions which lead to new experiments.

There are many kinds of models which have been applied to conformational and dynamic questions in polymer science. These range from simple models, which are applied in a more or less general way to properties of all flexible chain molecules, to very realistic models, in which structural aspects of the polymer are taken explicitly into account. The simple models include the freely jointed chain, in which rigid segments are connected by universal joints,[5,25] the harmonic spring model,[32] which treats the polymer as two beads attached to the ends of an infinitely flexible harmonic spring, and the Rouse–Zimm model,[33] in which the polymer is viewed as a sequence of beads connected by harmonic springs, with any hydrodynamic interactions acting only upon the beads. These are continuous models in that the chain ends and individual segments have distribution functions that are continuous in space. Their predictions frequently take the form of a chain-length-dependent property being proportional to the chain length raised to a power described by a critical exponent. This exponent is then considered to be a universal property of all polymers in the limit of infinite chain length.

It is important to note two aspects of continuous models. First, the probability of finding the polymer at any point in space is zero, but finite in a volume element. Second, in order to evaluate properties associated with these models, the form of the appropriate distribution function must be known.

In discrete models, individual polymer chains are confined to discrete points in space. At such points, the probability of finding the polymer is finite, but zero elsewhere. The probability is not continuous in space. Average properties associated with the polymer are calculated by summing over all possible configurations of the chains

$$\langle P \rangle = \frac{\sum_j P_j \exp(-E_j/RT)}{\sum_j \exp(-E_j/RT)} \qquad (5)$$

where P_j is the magnitude of the property P associated with the jth chain in the sample, and E_j is the energy associated with that chain. The denominator in eq 5 represents the conformational partition function for the polymer

$$Z_{cf} = \sum_j \exp(-E_j/RT) \qquad (6)$$

Various techniques exist for evaluating the sums in eq 5. These fall into two general classes, enumeration methods for evaluating the sums exactly and Monte Carlo methods for estimating them.[5,34] Among the former is Flory's matrix multiplication method, based originally upon the eigenvalue techniques developed by Volkenstein,[35a] Lifson,[35b] and Nagai.[35c] These methods have been applied extensively to the calculation of a wide variety of properties of alkane chains.

Although the number of chains over which the sums taken in eq 5 are finite, for very long chains this number is very large. The distribution associated with some chain property such as the end-to-end distance r is represented by a series of points. For sufficiently long chains, the distribution can be approximated by a continuum constructed by drawing a smoothed curve through these points.[6] Discrete models of long chains in which excluded volume is neglected generate distribution functions of r which have Gaussian shapes. In this respect, properties of long chains are, where calculable, the same for discrete and continuous models.[37,38]

1. Realistic Models of Hydrocarbon Chains

The fundamental idea associated with realistic models of polymers is that one constructs the details of the repeat unit using information obtained from small molecule analogues. The repeat units are attached to one another by a scheme which is in keeping with our knowledge of bond lengths, bond angles, and rotational angles in the analogous small molecule. After each chain is constructed, its energy is evaluated according to the same scheme plus other terms to describe interactions between groups with larger separations along the chain contour. Partition functions are evaluated from eq 6 and properties of the polymer from eq 5.

While the repeat unit of polymethylene chains is the CH_2 group, local interactions between neighboring methylenes make it necessary to formulate models on the basis of butane and pentane, where these interactions first appear. Models exist of varying degrees of complexity. Most sophisticated are molecular force field models which consider the entire rotational surface about each bond as well as harmonic (or even anharmonic) vibrations of the molecule.[39] Near the other extreme are models involving random walks on a diamond lattice. Carbons are seen as confined to the vertexes of the lattice, with the distance between them taken as the C–C bond length.

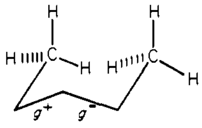
Ideally one would like a model simple enough to be tractable for long chains, yet sophisticated enough to allow a wide variety of properties of hydrocarbon chains to be calculated. In addition, the model should be sufficiently detailed to allow insights into how chain properties derive from local geometries, local potentials, and interactions between groups separated along the chain contour without being so complex as to obscure which contributors to these properties are the most important.

Many of these features are contained within the 3-fold rotational isomeric state model (RIS model).[5] According to this model, one views a hydrocarbon chain as a molecule with fixed bond lengths and bond angles. The rotational potential about each bond is accommodated into the model as a series of discrete rotational states associated with the energy minima of the rotation. For hydrocarbons, these minima correspond to the trans and two gauche rotational states.

Such a model could not be expected to simulate strained ring formation or other phenomena which depend upon conformations in which bond angles or rotational angles are distorted from their normal minima. On the other hand, such a model offers a tremendous breadth for describing a wide variety of conformationally dependent properties of hydrocarbon chains within limitations that have yet to be fully explored. Different research groups often use different parameters in connection with the RIS model.[39] In addition, several variants exist, depending upon how the CCC bond angle and nonbonded interactions between remote CH_2 groups are treated.

The RIS model of hydrocarbon chains is based primarily upon pentane. Bond lengths and bond angles are taken from X-ray crystallographic studies of pentane and higher alkanes.[41] These are known with high precision. Rotational angles of gauche conformations have been inferred from electron diffraction studies of gaseous pentane[42] and have been calculated by means of molecular force field models. The former place the rotational angle at 121 ± 3° while calculations predict a value of 117°.[14] These values are larger than the corresponding gauche rotational angle of ~112° inferred for butane.[43]

In pentane, the rotational energies are not independent; the energy of bond 3 being in the gauche state depends upon the rotational state of bond 2. When a gauche conformation of one sense is followed by a gauche conformation of the other sense, there is a prohibitive steric interaction between the methyl groups. First recognized by Taylor,[44] this "pentane effect" makes it necessary to consider pairs of adjacent bonds when evaluating the energy of hydrocarbon chains.



In fact, the $g^{\pm}g^{\mp}$ sequence is not completely prohibited, since a small rotation about either gauche bond relieves much of the repulsion. In force-field calculations, the $g^{\pm}g^{\mp}$ geometry appears at a saddle point on the energy surface, flanked by a pair of minima destabilized by 2000 to 3000 cal/mol relative to the *gt* state of the molecule.[43,45]

These features are incorporated into the RIS model in the following way: First, bond lengths and bond angles are specified. Second, the rotational angles corresponding to gauche and trans minima are introduced. For simplicity, one usually takes the gauche minima to be at ±120° rather than the 117° inferred experimentally. Flory[5] has commented that this is not a serious distortion of reality and can, in any case, be compensated for by small changes in the gauche/trans energy difference E_σ. Third, one introduces values for E_σ and also for the additional destabilization E_ω associated with $g^{\pm}g^{\mp}$ sequences.

Until recently, E_σ has not been known with great precision. Experimental values between 400 and 1000 cal/mol were reported.[46] Now it seems established that in the liquid state and in solution, E_σ takes a value close to 600 cal/mol. Supporting evidence comes from Raman spectroscopy,[7,47] low-temperature ^{1}H NMR studies,[48] and neutron diffraction analysis[49] of low molecular weight *n*-alkanes. Furthermore, and rather surprisingly, E_σ for *n*-butane is clearly different in the gas phase and in the neat liquid. In the gas phase E_σ = 950 kcal/mol[7,47] and in the liquid phase E_σ = 600 cal/mol.[47–49] Such a difference has also been predicted by Chandler's theoretical analysis of butane.[50] In the RIS model, interactions between methylenes separated by more than four C–C bonds are treated in a variety of ways which reflect either the limitations of the model or the choice of the person carrying out the calculations. Where excluded volume is neglected, these interactions are not considered. Where excluded volume is considered, these interactions are introduced in the form of hard-sphere repulsions, nearest-neighbor pair potentials, Lennard-Jones potentials, etc.

This somewhat arbitrary choice of separating the treatment of interactions between neighboring atoms up to and including the pentane effect (local interactions) from the treatment of interactions of groups further removed is dictated by the requirements of most realistic models. Local interactions enter into calculations in the form of energy and geometry parameters obtained experimentally or from consideration of very detailed models. Nonlocal interactions are treated in a less detailed manner, in part because over these separations along the chain backbone low-frequency vibrations smooth out the interactions. In addition, for hydrocarbon chains of less than 50 carbons, these interactions make only small contributions to their solution properties. Experimentally, for appropriate choices of solvents [Θ conditions], these interactions for any chain length can be suppressed entirely.

In his book in 1969, Flory[5] stressed that the RIS model was sufficiently realistic to account for all conformationally dependent properties of sufficiently long alkyl chains. Experiments over the past 12 years have served to reinforce this point of view. Notable among these, which have been simulated successfully in terms of the RIS model, are experiments on chain cyclization by Winnik[10] and by Shimada and Szwarc,[51,52] experiments on depolarized Rayleigh light scattering from *n*-alkanes carried out by Bothorel and his group,[53a,b] as well as by Flory and Patterson,[53c] and neutron scattering studies on *n*-alkanes by Dettenmaier.[49]

2. Molecular Mechanics Calculations

Empirical force-field calculations use simple models of bonding and nonbonded interactions in molecules to compute energies as a function of geometry. The idea behind this class of models is to parameterize a set of potential functions to reproduce many experimentally determinable quantities and then to use the model to compute similar but experimentally inaccessible quantities.[39] There are many such models of varying degrees of complexity. Those with a large number of input parameters must succeed in reproducing far larger numbers of experimental geometries and energies.

In the molecular mechanics approach outlined by Westheimer,[55] a molecule is viewed as a collection of particles held together by simple elastic forces. Such forces are defined in terms of potential energy functions of the internal coordinates of the molecule and make up what is termed the molecular force field. Early calculations in the area were carried out by Westheimer. More recently a number of critical reviews have appeared, and the reader is referred in particular to recent papers by Allinger,[3] Schleyer,[56] and Bartell.[57]

The total energy of a molecule is seen to be composed of various factors defined in terms of the potential energy functions associated with bond length l, bond angles θ, torsional angles ϕ and nonbonded terms nb (eq 7). In many chemical problems, all four terms contribute.

$$E_{\text{total}} = E(l) + E(\theta) + E(\phi) + E_{\text{nb}} \qquad (7)$$

In the RIS model of hydrocarbon chains, attention is focused on the torsional and nonbonded energy terms, with the latter being of crucial importance when excluded volume is considered.

3. Reference States for Conformational Calculations

In order to compare the results of a calculation with an experimental result, the model from which the theoretical result was obtained must contain an appropriate description of the milieu in which the experiment was carried out. It is at present far too difficult to include in conformational calculations detailed account of solvent–solute and solvent–solvent interactions. Conformational calculations of polymers are almost always carried out on the isolated molecule, yet experiments are usually carried out in solution, in the melt or in the amorphous solid.

The way around the problem involves a judicious choice of reference states for carrying out experiments and a corresponding choice of nonbonded interaction potentials to simulate that reference state. For hydrocarbon chains, there are three obvious choices for experimental reference states: the gas phase, Flory's Θ conditions,[21] and the athermal solution.[58] There are correspondingly three choices of remote nonbonded potentials which one can introduce into an RIS model calculation to simulate chain behavior in each of these three reference states.

All realistic models of hydrocarbon chains take account of local interactions. These include bond lengths, bond angles, rotational angles, and rotational energies. Various models take different accounts of nonlocal interactions. The most obvious of such interactions are the steric repulsions that keep two atoms from occupying the same space. The net effect of these (excluded volume) interactions is to increase the dimensions of the chain compared to the dimensions calculated when these interactions are ignored. This effect increases with the length of the chain. It affects the magnitudes of $\langle r^2 \rangle$ and $\langle s^2 \rangle$ by about 6% for a chain of 50 carbon atoms and 12% for a 100-carbon chain.[40]

In polymers, the Θ state is defined as the solvent and temperature conditions such that solute–solvent repulsions compress the mean dimensions of the polymer to compensate exactly for the expansion caused by nonlocal steric interactions.[5] Values of $\langle r^2 \rangle$ and $\langle s^2 \rangle$ inferred from measurements in Θ solvents for polyethylene can be compared with corresponding values obtained from models which neglect nonlocal interactions.

In a number of calculations, nonlocal interactions have been accommodated by means of a hard-sphere potential.[10,40,52,53a,b,59] This effectively keeps two atoms out of the same region of space but neglects dispersive attractions between them. Such calculations for hydrocarbon chains are applicable to experiments carried out in athermal solutions,[58] or regular solutions,[58] where the pair potential between CH_2 groups and solvent molecules can be thought of as compensating for the attractive pair potential between CH_2 groups positioned remotely along the hydrocarbon chain.

To simulate the gas phase, a calculation must take account of both attractive and repulsive contributions to the nonbonded interactions between remote groups. These can take the form of appropriate Lennard-Jones or Buckingham potentials between CH_2 groups or their individual atoms. A requirement of appropriate nonbonded potentials is that they should be able to reproduce the sublimation enthalpy of crystalline alkanes.[61]

4. Theories of Cyclization Probability, W(O)

A number of approaches have been taken to develop general theories of cyclization probability. An important parameter in these models is the value of the critical exponent for cyclization in the limit of infinitely long chains. In Θ solvents, the distribution function $W(r)$ of the chain ends is Gaussian. Consequently, $W(0)$ decreases as $N^{-3/2}$. In good solvents, $\langle s^2 \rangle$ increases approximately as $N^{6/5}$. If one guesses that $W(0)$ decreases as $\langle s^2 \rangle^{-3/2}$, then one predicts that $W(0)$ decreases as $N^{-9/5}$.

Scaling theory[62] indicates that $\langle s^2 \rangle$ is proportional to N^{ν}, with $\nu = 0.588$. Although it assumes that a single scaling length suffices to describe the mean-squared end-to-end length $\langle r^2 \rangle$ and, consequently, $\langle s^2 \rangle$, of a polymer chain, one finds that a second exponent enters into the chain length dependence of $W(0)$. In the presence of excluded volume, $W(0)$ is predicted to depend upon $N^{-1.83}$ whereas $\langle s^2 \rangle^{-3/2}$ is proportional to $N^{-1.76}$.

Series analysis, which involves extrapolations based upon exact enumeration of lattice walks, leads to the conclusion that $W(0)$ decreases as $N^{-23/12}$, i.e., $N^{-1.92}$.[63]

Realistic models treat finite chains. In the approach of Flory and Semlyen,[28a] the RIS model without excluded volume was used to parameterize a Gaussian distribution function for the end-to-end distance in poly(dimethylsiloxane). This necessarily predicts that $W(0)$ and K_{cy} decreases as $N^{-3/2}$ for chains in a θ solvent. The data in Figure 3 indicate that for sufficiently long chains the predicted and calculated values of K_{cy} are comparable. For shorter chains, another approach developed by Flory approximates $W(r)$ in terms of various moments of the distribution of $\langle r^2 \rangle$, calculated from the RIS model.[29] A more direct approach, first attempted by Fluendy[64] and later developed by Sisido[23] and by Winnik,[65] uses a computer to generate individual chains of various conformations and exact enumeration or Monte Carlo methods to calculate the partition functions for cyclized and total chains. $W(0)$ is equal to their ratio. In these approaches, the success of the model does not depend upon evaluating a critical exponent, but rather simulating specific experimental results.

5. Theories of Cyclization Dynamics

The field of polymer dynamics is much more complicated than that of polymer conformation. To appreciate the difficulty of developing proper theories of polymer dynamics, one need only realize that a polymer of M atoms has $(3M - 6)$ normal modes. Each of these represents a different dynamic mode of the polymer, and these differ in their mean relaxation times, for ordinary polymers, by factors of 10^8 or larger.

For short chains and for polymer motions localized over relatively few atoms, jump-diffusion models have been developed, where the chain or segment jumps from one configuration to another in some arbitrary jump time. More realistic, RIS model-like simulations of small alkane dynamics, involving trajectories over realistic rotational barriers, have been carried out. These are very expensive in their consumption of computer time. At the present time, these models are limited to molecules of no more than six or seven carbons. For molecules larger than heptane and smaller than polyethylene, there are no really satisfying yet convenient models for calculating chain dynamics.[160]

For long polymers, the Rouse–Zimm bead-and-spring model[33] has found wide applicability.[66] It gives essentially a normal mode picture of chain dynamics. The real polymer is represented as a linear sequence of dynamic segments (harmonic springs) whose segment length scans several or many monomer units, depending upon the dynamic stiffness of the chain. Hydrodynamic forces operate at the beads, which are point masses located at the intersection of each pair of segments. This model is remarkably successful in describing low-frequency, large amplitude motions of polymer chains in terms of two adjustable parameters: the length of the dynamic segment and the strength of the hydrodynamic interaction.[66,67a]

For the specific question of cyclization dynamics, appropriate theories must take account of at least three aspects of the problem: the motion of the chain ends, the connectivity of the chain, and the chemical reaction between the chain ends when the chain ends achieve a reactive configuration. In order for such theories to be tractable, simplifying assumptions need to be made. Various models of cyclization dynamics at various levels of sophistication have been examined.

The simplest of these models is the free particle model of Brereton and Rusli.[68] These authors treat the motion of the chain ends as that of independent particles which, at equilibrium, satisfy the same Gaussian distance distribution that they would obey if they were connected by a chain of N segments. The authors consider the Brownian motion of the particles and examine the frequency with which one approaches to within some reactive distance a of the other. They find that k_{cy} can be expressed as a product of three terms: an effective cross section $4\pi a^2$ for the reaction, the probability density $W(r)$ of the end-to-end distance, and the mean speed dr/dt with which the ends approach. According to these authors, the average speed term in their model does not depend upon N. Consequently k_{cy} shows the same dependence on N as does $W(r)$; namely it depends upon $N^{-3/2}$ in Θ solvents and $N^{-9/5}$ in good solvents.

Wilemski and Fixman[69] presented the first theoretical analysis of polymer cyclization dynamics. In an important series of papers, these authors developed a formalism for diffusion-controlled reactions and showed how a polymer chain connecting two reactive groups could be incorporated into this formalism. Two simplified models of the polymer chain were considered. Their first model, a harmonic spring (HS) model, treats the polymer as a simple harmonic spring connecting the two reactive groups. A "sink term" describes the reaction probability as the groups approach, and the motion of the chain ends satisfies Smoluchowski boundary conditions. For a critical reactive radius a about one of the groups, the rate constant for diffusion controlled reaction for this model, k_{cy}^{HS}, is related to the slowest relaxation time τ_m^{HS} of the chain according to

$$k_{cy}^{HS} \propto \frac{a\tau_m^{HS-1}}{\langle r^2 \rangle^{1/2}}$$

In commenting on this model, Doi[32] has pointed out that for harmonic springs, $\tau_m^{HS} \propto \langle r^2 \rangle$. Since $\langle r^2 \rangle$ is proportional to N in the absence of excluded volume, one concludes that $k_{cy}^{HS} \propto N^{-3/2}$.

In the second model of Wilemski and Fixman,[69] the polymer is treated as a Rouse chain of N segments of length b connected by harmonic springs. Wilemski and Fixman calculated values of k_{cy} for both the free draining limit (k_{cy}^{FD}) and the nondraining limit (k_{cy}^{ND}) of hydrodynamic interaction. Their results indicate that for small values of $a/\langle r^2\rangle^{1/2} << 1$, k_{cy}^{FD} is independent of a and is close in magnitude to the slowest relaxation time τ_m^{FD} of the free draining Rouse chain. Since τ_m^{FD} is proportional to N^2, k_{cy} is expected to be strongly dependent upon the degree of polymerization according to

$$k_{cy}^{FD} \propto (\tau_m^{FD})^{-1} \propto N^{-2}$$

Doi[32] has commented extensively on the differences in cyclization behavior between the harmonic spring model and the free-draining Rouse chain. He has examined a number of assumptions in the Wilemski and Fixman approach and discusses at some length the origin of the $a/\langle r^2\rangle$ dependence of k_{cy}^{HS} and its absence for k_{cy}^{FD}.

Doi[70] has also carried out a computer simulation of end-to-end cyclization dynamics using an off-lattice model similar in conception to that first developed by Verdier and Stockmayer.[19] This model has features in common with the free-draining Rouse chain. Values of k_{cy} calculated from this model for various values of $(a/\langle r^2\rangle$ are seen to approach a dependence upon N^{-2}, although for the chain lengths examined [$N \leq 70$] this asymptotic behavior was not yet reached.

Wilemski and Fixman[69] also extended their treatment to include both excluded volume effects and also nondraining hydrodynamic interactions in the Rouse chain. Calculations of k_{cy}^{ND} were carried out for the nondraining Rouse chain in the absence of excluded volume, with the result that

$$k_{cy}^{ND}/k_{cy}^{FD} \propto N^{1/2} \qquad (8)$$

and k_{cy}^{ND} will always be larger than k_{cy}^{FD} except at very short chain lengths. Equation 8 leads to the prediction that in the absence of excluded volume, $k_{cy}^{ND} \propto N^{-3/2}$.

Perico and Cuniberti[67] have become deeply involved in the question of end-to-end cyclization dynamics. These authors developed a method for calculating the exact eigenvalues of the hydrodynamic equation of a Rouse chain of finite length. By comparing these calculations with intrinsic viscosity measurements of various polymers in Θ solvents, they were able to describe each polymer in terms of two parameters—an effective scaling length related to chain flexibility and a hydrodynamic interaction parameter. Introducing these values into the Wilemski–Fixman theory permitted Perico and Cuniberti to calculate values of k_{cy} for polystyrene and poly(dimethylsiloxane) for reasonable values of solvent viscosity and temperature. A plot of their calculated k_{cy} values for polystyrene as log k_{cy} vs. log N shows a slope of −1.43.

III. Important Concepts

A. Ring Size

The experimental results on ring closure reactions of $HO(CH_2)_mCO_2H$ and PDMS point to the fact that short chains are often sensitive to different factors than are long chains. It is convenient in discussing cyclization phenomena to distinguish various domains of chain length according to the types of factors influencing cyclization. The boundaries between these domains may not be sharp, but even in these boundary regions, it can be helpful to recognize the interplay of contributions whose effects are more obviously manifest for longer and shorter chains. Our classification follows, with minor modifications, the proposal of Brown and Prelog.[71]

Large Rings

For any polymer no matter how stiff, there will be some chain length above which the chain ends will be free to encounter without the need for bond angle distortions or intramolecular steric effects. DNA, particularly double-helical DNA, is a very stiff polymer. Yet macrocyclic DNA is well-documented,[72] and plays an important role in gene replication. For large rings, the accessible number of conformations is sufficiently large that the molecule can relax to avoid steric interactions between nonadjacent substituents. Cyclization probability is determined only by chain statistics, which is in turn governed by entropic factors, internal energies associated with rotational states of the various bonds in the polymer, and solvent effects.

Medium Rings

The term "medium rings" will be used to distinguish those ring sizes for which certain features of the chemical structure of the polymer inhibit cyclization. The features which characterize medium rings are primarily rotational angle distortion and transannular steric effects. In medium rings the number of available conformations is small. Severe steric repulsions can be minimized only at the expense of distorting rotational angles and even perturbation of bond angles. Experimentally, the details of these interactions are only beginning to be understood through conformational analysis of the corresponding cycloalkanes and their derivatives (vide infra).

Small Rings and Common Rings

The term "small rings" will be used to describe those ring sizes for which cyclization can be achieved only at the expense of severe bond angle distortions. Consequently the ring strain so generated is considerable. It often happens that there exist ring sizes which are nearly strain free (e.g., cyclohexane) and because of their small size require comparatively little loss in entropy for ring closure to occur. These ring sizes serve as a suitable boundary between small and medium rings. Brown and Prelog[71] refer to carbon containing rings of five and six members as "common rings". The focus of this section will be on medium- and large-ring formation.

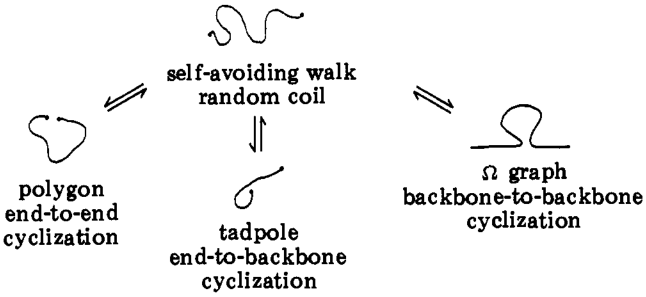
B. Cyclization and Ring Formation

A "ring closure" reaction is one in which a new covalent bond is formed in the cyclization process. The stereochemical demands on an equilibrium ring closure reaction can be more severe than simple proximity of the reactants attached to the chain termini. The angular relationship between the reactants must correspond to the bond angle of the appropriate atoms in the product or reaction transition state. Thus it is necessary to distinguish this term from the more general term "cyclization" reaction. A cyclization reaction can be considered to be any observable process which occurs when the ends of a polymer chain, or substituents attached to those ends, are in proximity.

In the definition above, the word "proximity" was left ill-defined. This was intentional because in an experiment proximity is determined by the details of the chemical reaction. For example, electron transfer or electronic energy transfer by a Förster mechanism[73] can occur over substantial distances. In the first example, the process might occur whenever the chain ends labeled by D and A approach to within 6 to 10 Å of one another. Förster energy transfer can occur over distances in excess of 50 Å,[73] depending upon the choice of D and A, and the radius a of the reactive volume can serve as an important variable in cyclization phenomena. In other reactions, a may be of the order of a bond length, and the reactive volume may depend sensitively on the orientation of D and A. One must remain aware of these aspects in any comparison of cyclization data with theory.

C. Classification of Cyclization

One can consider three distinct topologies for cyclization of an open-chain compound. (i) "End-to-end cyclization" describes a process which occurs when its two chain termini are in proximity. In the language of graph theory,[74] graphs which contain a single intersection at the chain ends are called "polygon graphs", and graphs without intersections are called "self-avoiding walks". Penczek[75] has referred to such reactions as "tail-biting" reactions. (ii) The reaction of a chain terminus with the interior of the chain may be called an "end-to-backbone" cyclization, for which Penczek has coined the phrase "back-biting" reaction. Corresponding graphs with single intersections are called "tadpole graphs". (iii) "Backbone-to-backbone" cyclizations involve reactions of functional groups attached to the interior of a polymer chain. The name applied to graphs with one such intersection is "twin-tailed tadpoles", but the term Ω graph may be more appropriate.



Molecules which have each of the topologies described above and chemical reactions whose transition states resemble these topologies are important probes of the probability and energetics associated with each type of cyclization. Many pertinent examples are known, and some have been studied in sufficient detail to provide conformational information about polymer chains.

TABLE I. Entropy Changes Accompanying Cyclization[a, b]

no. of carbons	$S°$ n-alkane	$S°$ cyclo-alkane	$-\Delta S°_{cy}$	$-\Delta S°_{cy}$ per int rot	$-\Delta S°_{cy,cor}$ per int rot[c]
3	64.51	56.75	7.7	3.85	3.85
4	74.12	63.43	10.9	3.63	4.90
5	83.40	70.00	13.3	3.32	4.77
6	92.82	71.28	21.2	4.25	4.25
7	102.27	81.82	19.8	3.30	3.72
8	111.55	87.66	19.0	2.71	3.91

[a] 298 K, gas phase. Data are from ref 77. [b] Units of S in cal mol^{-1} deg^{-1}. [c] Corrected for low-frequency modes in the cycloalkanes following M. I. Page and W. P. Jencks.[78a]

IV. The Cycloalkanes

Many of the factors that influence the cyclization of hydrocarbon chain can be seen in a comparison of normal alkanes and cycloalkanes. This comparison is normally carried out by examining the internal energies or heats of formation ($\Delta E_f°$ or $\Delta H_f°$) and entropies of formation ($\Delta S_f°$) of appropriate pairs of compounds and estimating the changes in energy and entropy which occur upon cyclization. One approaches the problem by recognizing that in the hypothetical reaction[76]

$$CH_3(CH_2)_{n-2}CH_3 \rightarrow \boxed{(CH_2)_n} + H_2 \qquad (9)$$

the accompanying changes in $\Delta H(9)$, $\Delta S(9)$, and $\Delta G(9)$ contain information about the cyclization entropy (ΔS_{cy}) and the strain energy (ΔH_{strain}) of the ring.

A. Cyclization Entropy

There are two contributions to $\Delta S(9)$ for reaction 9: the entropy of cyclization and the entropy of formation of H_2. Consequently

$$\Delta S_{cy} = \Delta S(9) - \Delta S_f°(H_2) = \Delta S_f°(\text{cycloalkane}) - \Delta S_f°(n\text{-alkane}) \qquad (10)$$

Entropies of formation are available for the n-alkanes up to eicosane,[77] but entropy data for the cycloalkanes are sparse. Values of $\Delta S_f°$ have been obtained for cyclopropane through cyclooctane.[77] Using these in conjunction with eq 10, one can compute values for ΔS_{cy}. These are presented in Table I. The entropy loss per internal rotation for saturated hydrocarbons of up to eight carbons is 2.7–4.3 cal mol^{-1} deg^{-1}. Some of the entropy associated with internal rotations in the n-alkane is transformed into low-frequency vibrations (pseudorotation, bending modes) in the cycloalkanes.[76,78] After correction for these motions in the C_4, C_5, C_7, and C_8 rings, one can take ca. 4 cal mol^{-1} deg^{-1} as a representative value for freezing an internal rotation in a short alkyl chain.

Two factors have not been considered in calculating the ΔS_{cy} in Table I: the change in symmetry number (σ) and statistical mechanical considerations associated with the presence of multiple conformations. Symmetry changes occur upon cyclization. For all unsubstituted cycloalkanes of n carbons, there are n equivalent carbons in each discrete conformation. When there are very low barriers separating conformations that cause the hydrogens of the cycloalkane to become equivalent, Benson chooses $\sigma = 2n$. This choice is made for the C_4,

C_5, C_7, and C_8 cycloalkanes.[76] For cyclohexane and for very large rings the potential wells associated with individual conformations are sufficiently deep that the motions interconvening them make little contribution to the molecular partition function, and hence to their entropy.

For the *n*-alkanes, Benson assigns $\sigma = 18$, since there are three identical rotamers of each methyl group, and for the all-trans conformation, an additional twofold axis or plane of symmetry ($3 \times 3 \times 2 = 18$).[76] The *n*-alkanes longer than propane, at 298 K, are mixtures of rotational isomers. Butane at ordinary temperatures is composed of two gauche rotamers and one trans rotamer. The gauche forms in the gas phase are higher in energy by 950 cal/mol. They have lower symmetry ($\sigma = 9$) than the trans rotamer, and comprise 29% of the molecules at 298 K. The presence of conformational isomers is rarely taken explicitly into account in discussions of the entropy of cyclization for small- and medium-ring formation.

For large-ring formation, polymer chemists consider the conformational contribution to the entropy of cyclization to be dominant. To understand this point of view, it is necessary to examine cyclization in terms of statistical mechanics: the entropy of a species is related to its molecular canonical partition function Z according to

$$S° = R \ln Z + RT(\partial \ln Z/\partial T)$$

One can write an identical equation for the cyclized species:

$$S°_{cy} = R \ln Z_{cy} + RT(\partial \ln Z_{cy}/\partial T)$$

Hence the entropy change on cyclization is

$$\Delta S_{cy} = R \ln (Z_{cy}/Z) + RT(\partial \ln Z_{cy}/\partial T - \partial \ln Z/\partial T) \qquad (11)$$

The molecular partition function can be calculated from its translational, rotational, and vibrational components. For each conformation i of a flexible molecule one can write

$$Z_i = Z_{tr,i}Z_{rot,i}Z_{vib,i}$$

An ensemble of molecules is made up of a Boltzmann distribution of the various conformations: thus at finite temperatures

$$Z = \sum_{\text{all conf}} n_i Z_i \exp(-\Delta E_i/RT) \qquad (12)$$

Here Z_i is the partition function of the ith conformation, ΔE_i is its energy relative to that of the lowest energy conformation, and n_i is the number of such conformations. The summation is carried out over all conformations accessible to the molecule. To understand cyclization entropy in terms of these equations, one must look at the individual components of Z_i and their changes upon cyclization.

Translational entropy changes very little upon cyclization. The multitude of conformations of the acyclic molecule have the same mass, which is identical or virtually identical with that of the cyclized form. Hence their translational partition functions are equal. Changes in rotational entropy upon cyclization are quantitatively unimportant. While the cyclized molecule has a smaller radius of gyration than most of the conformations of the open form of the molecule, these changes are not large. In solution, where most cyclization reactions of long-chain molecules are studied, the distinction between overall rotation and translation becomes blurred, and moment of inertia changes contributing to ΔS_{cy} are negligible.

Changes in the vibrational contribution to the molecular partition function upon cyclization are thought to be minimal for large ring formation. It is known that the normal modes of the *n*-alkanes differ with conformation.[79] Discrete vibrational bands associated with various gauche–trans sequences have been identified. These frequency differences are not large, and their contributions to the vibrational component of the molecular partition function may be expected to be similar. Cyclization to form strained rings might cause important changes in Z_{vib}, since as indicated above, low-frequency vibrations associated with pseudorotation and bending modes make important contributions to $\Delta S_f°$(cycloalkane). For large-ring formation, little is known about the vibrational changes occurring upon cyclization, particularly for the lowest frequency modes which make the most important contribution to Z_{vib}. This aspect merits further investigation.

If the translational, rotational, and vibrational components of Z_i do not change significantly for the various accessible conformations of a molecule, they can be factored out of eq 12. Setting $Z_{cf} = \sum n_i \exp(-\Delta E_i/RT)$, we can write that

$$Z = Z_{tr}Z_{rot}Z_{vib}Z_{cf}$$

The conformational contributions to the entropy of cyclization can be large and important. The origin of these effects is the decrease in the number of accessible conformations at ordinary temperatures when an open-chain molecule cyclizes. For long chains, the number of conformations, each of slightly different energy, is enormous. Similarly, large rings have many different conformations. The number of conformations of each increase with the number of atoms in the chain or ring.

Simulations of hydrocarbon chain cyclization in terms of the RIS model indicate that $(Z_{cf,cy}/Z_{cf,total}) \sim 10^{-3}$ for 30 carbon chains.[80] This represents, from the first term on the right-hand side of eq 11 a contribution of −14 cal deg^{-1} mol^{-1} to the cyclization entropy. These simulations also indicate that for unstrained rings, the fraction of bonds in the gauche and trans rotational states is very similar to that in the acyclic molecule.[52,80,81] Consequently, $(\partial \ln Z_{cf,cy}/\partial T) \approx (\partial \ln Z_{cf,total}/\partial T)$, and eq 11 simplifies, for large-ring formation, to

$$\Delta S_{cy} = R \ln W(0) = R \ln (Z_{cf,cy}/Z_{cf,total})$$

where $W(0)$ is the cyclization probability of the chain.

In cyclization to form strained rings, changes in Z_{vib} can be anticipated. These will depend upon the detailed structure of the cycloalkane or its derivatives. One would not a priori anticipate monotonic changes in ΔS_{cy} in a homologous series of strained rings.

B. Ring Strain

The strain energy of a molecule can be defined in many ways. Qualitatively one recognizes features of a molecule which are distorted beyond the normal, customary limits of structural theory. For example, cyclopropane and cyclobutane are clearly more strained than propane or cyclohexane. Quantitatively one can estimate the strain energy in terms of two standard models: the conventional ring strain energy (CRSE) used by Cox and Pilcher[82] and the single conformation strain energy (SCSE) described by Schleyer et al.[83]

In the CRSE approach, the strain energy is defined as the difference between the estimated and observed heats of formation of the cycloalkane at 298 K

$$\Delta H_{\mathrm{strain}} = \Delta H_f^\circ(\text{estimated}) - \Delta H_f^\circ(\text{observed})$$

where ΔH_f°(estimated) is obtained from a bond-energy or group-equivalent scheme. It represents the energy of a reference "strain-free" ring.

Schleyer[83] has pointed out that strain energy defined in this way is misleading because ΔH_f°(*n*-alkane) contains the "strain energy" of gauche interactions contributed by that fraction of the conformational population at 298 K possessing gauche bonds. It makes more sense, Schleyer agrues, to use as the reference state the lowest energy conformation of the *n*-alkane and to compare its heat of formation with that of the cycloalkane. This comparison defines the single conformation strain energy.

These models are formalized in a very clever way by Clark and McKervey.[84] These authors begin by recognizing that $\Delta H_{\mathrm{cy}}(9)$ for reaction 9 reflects the strain energy present in the cycloalkane. They translate the enthalpy of cyclization into group increments, so that for a strain-free C_{n+2} ring

$$\begin{aligned}\Delta H^\circ_{\mathrm{cy}} &= -[n(\mathrm{CH_2}) + 2(\mathrm{CH_3})] + (n+2)(\mathrm{CH_2}) \\ &= 2[(\mathrm{CH_2}) - (\mathrm{CH_3})]\end{aligned}$$

where $(\mathrm{CH_2})$ and $(\mathrm{CH_3})$ are the appropriate group increments. For a ring with strain energy $\Delta H_{\mathrm{strain}}$

$$\Delta H^\circ_{\mathrm{cy}} = 2[(\mathrm{CH_2}) - (\mathrm{CH_3})] + \Delta H_{\mathrm{strain}}$$

Since the heat of formation of the cycloalkane is given by

$$\Delta H_f^\circ(\text{cycloalkane}) = n(\mathrm{CH_2}) + \Delta H_{\mathrm{strain}}$$

The strain energy can be defined as

$$\Delta H_{\mathrm{strain}} = \Delta H_f^\circ(\text{cycloalkane}) - n(\mathrm{CH_2})$$

This derivation is useful for two reasons: (i) it is applicable to any group increment method, and (ii) it avoids the necessity of introducing the so-called "strain-free" isomer as a point of reference.[84] If one calculates the group increment directly from the heats of formations of the *n*-alkanes in the gas phase, one obtains the appropriate value of $(\mathrm{CH_2})$ to yield the conventional ring strain energy. The CRSE values in Table II were calculated by using Benson's value of $[(\mathrm{CH_2}) = 4.95$ kcal/mol]. On the other hand, the heats of formation of the *n*-alkanes at 298 K can be corrected for the presence of a Boltzmann distribution of higher energy conformations. These yield Schleyer's value[83] $[(\mathrm{CH_2}) = 5.13$ kcal/mol] from which the SCSE data in Table II are calculated. It is worth noting that these data are not corrected for the presence of higher energy cycloalkane conformations which may be present in the gas phase at 298 K.

The large values of the strain energy for cyclopropane and cyclobutane are largely angular in origin, with additional contributions from H/H eclipsing interactions whose effects are minimized at the expense of additional angle distortions by ring puckering. The small strain energy in the C_5 and C_7 rings is due primarily to torsional strain due to enforced eclipsing interactions between vicinal hydrogens.

TABLE II. Enthalpy Changes Accompanying Cyclization[a,b]

no. of carbons	ΔH_f° *n*-alkane	ΔH_f° cycloalkanes	$\Delta H_{\mathrm{cy}}^\circ$	$\Delta H_{\mathrm{strain}}$ CRSE	$\Delta H_{\mathrm{strain}}$ SCSE
3	−24.83	+12.78	37.6	27.6	28.2
4	−30.36	+6.78	37.1	26.6	27.3
5	−35.10	−18.44	16.7	6.3	7.2
6	−37.40	−29.50	7.9	0.2	1.3
7	−44.85	−28.21	16.6	6.4	7.7
8	−49.86	−29.73	20.1	9.9	11.3
9	−54.66	−31.73[c]	17.8	12.8	14.4
10	−59.67	−36.88[c]	22.8	12.6	14.4
11	−64.75	−42.87[c]	21.9	11.6	13.6
12	−69.34	−55.03[c]	14.3	4.4	6.5
13	−74.45[d]	−58.88[c]	15.6	5.5	7.8
14	−78.38[d]	−47.13	22.3	12.2	14.7
15	−84.31[d]	−72.04	12.3	2.2	4.9
16	−89.80	−76.88	12.9	2.3	5.2
17	−94.15[d]	−87.07	7.1	−2.9	0.1

[a] 298 K, gas phase. Data from Cox and Pilcher[82] except where noted. [b] ΔH values are in kcal/mol. [c] ΔH_f° values for these cycloalkanes were calculated by using estimated heats of vaporization. [d] Taken from Stull, Westrum, and Sinke.[77]

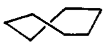
In the CRSE description, cyclohexane is strain free. In the SCSE description, it has a small but real strain energy. The possible origins of this strain are discussed in detail by Schleyer,[83] who concludes that repulsions occur between parallel C–C bonds in the chair form of cyclohexane.

The C_8, C_9, C_{10}, and C_{11} rings suffer from strong H/H repulsions for $\mathrm{CH_2}$ groups across the ring. These transannular interactions are sufficiently severe to enlarge the CCC bond angles in the crystalline C_9 and C_{10} rings.[35]

For rings larger than cyclotridecane, the strain energies are small, although the value for the C_{14} compound seems curiously high. Cox and Pilcher[82] comment that a detailed discussion of these values seems unwarranted, because the error in the ΔH_f° of the cycloalkanes are significant in relation to the magnitude of the strain energies.

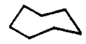
C. Conformation of Rings Larger Than Cyclohexane

While the conformations of rings of six or fewer carbons are quite well understood, those of larger rings are considerably more complex. As the rings get larger, there are many more conformations. These are often comparable in energy, and for medium-size rings are often separated by very small barriers. Hendrickson has used molecular mechanics calculations to identify the low-energy conformations of cycloheptane and to estimate their relative energies.[85] These calculations suggest four particularly stable conformations (drawn below, following Clark and McKervey): the twist-chair, chair, boat, and twist-boat. NMR measurements[86] on



twist-chair

boat



chair

twist-boat

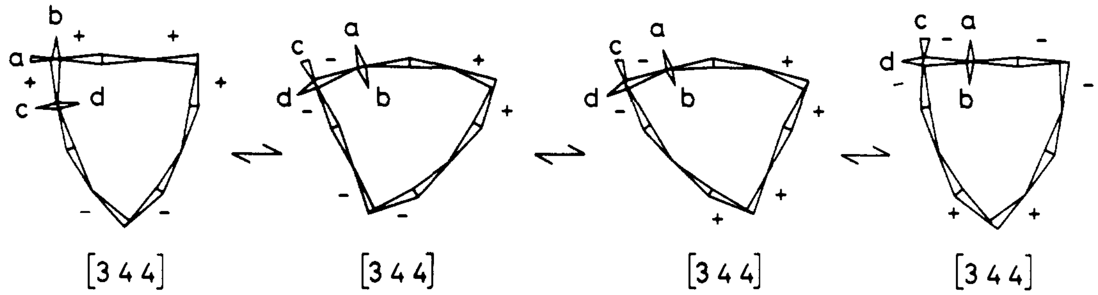
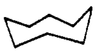


Figure 4. The projection perspective used by Dale[11] to depict the conformations of cycloalkanes. The numbers [344] refer to the number of carbons between each apex in the projection.

the dimethyl derivatives suggest that the twist-boat is the most stable and the boat, the least stable. The energy differences are small. At ordinary temperatures there is rapid interconversion by pseudorotation among the various twist-boat forms.

Cyclooctane is quite complicated. Hendrickson identified 11 conformations representing energy minima by molecular mechanics calculations.[85b] He suggested the boat-chair conformation to be most stable. More recent calculations disagree about which form is lowest in energy. Allinger's calculations (MM1)[87a] suggest that the boat-chair conformation is lowest in energy, while Schleyer's calculations (EAS)[88b] find that the boat-chair is comparable in energy to the crown and twist-chair-chair conformations. Both the boat-chair and crown conformations have been found in X-ray crystallographic studies on cyclooctyl derivatives.[12] ^{19}F NMR measurements on fluorinated derivatives of cyclooctane support the boat-chair conformation as most stable at low temperatures.[82] On the other hand, electron diffraction studies on cyclooctane vapor at 40 °C are consistent only with a mixture of conformations.[89] Dale comments in detail in his recent review[11,90] on the conformations of cyclooctane and the dynamics of their inverconversion.


boat-chair


crown

The cyclononane conformation calculated to be the most stable, and the major one observed,[91] is the "triangular" conformation, which in the nomenclature of Dale[11] is called [333]. (For an explanation, see Figure 4.) The barrier for the interconversion of these conformations, which involves passage through two unsymmetric minima, is calculated to be 6.9 kcal/mol. This is in reasonable agreement with the 6.0 kcal/mol barrier observed by Anet in dynamic ^{1}H NMR experiments.[91] Two minor conformers, a pentagonal or quinquangular form of the type [12222] and an asymmetric triangular form of the type [144], are calculated to 1.7 and 1.2 kcal/mol higher in energy. These both are found in room temperature solutions of cyclononane, and the former is found in the crystal structure of cyclononane derivatives.[12]

Hendrickson identified 12 different conformations of cyclodecane.[85c] Both experiments and molecular mechanics calculations establish the rectangular [2323] conformation of the diamond lattice type as the lowest in energy.[11] In the X-ray crystallographic structure of cyclodecane, this conformation, also called the boat-chair-boat form, has six pairs of hydrogens across the ring approach within 1.8 Å.[12] This must contribute substantially to strain energy of the ring.

Cycloundecane, cyclotridecane, and cyclopentadecane have been examined very recently by Anet and Rawdah using molecular mechanics calculations.[92] For the C-11 compound, six low-energy conformations were identified and their paths of interconversion mapped out. Two of these forms, [335] and [12323], were found to be of virtually identical energy. These conformations are depicted in terms of Dale's wedge system in Figure 4. Anet's calculations are in accord with those of Dale,[93] but differ significantly from earlier calculations by Schleyer.[87b] Both ^{13}C and ^{1}H NMR measurements at low temperature are in accord with two different conformational populations, differing in energy by less than 0.5 kcal/mol, which interconvert only at higher temperatures.[94]

These calculations suggest five low energy conformations for cyclotridecane and five low energy conformations for cyclopentadecane. For the C-13 molecule, at least three of the conformations would be populated at room temperature, and cyclopentadecane should be a mixture of all five conformations.

The lowest energy form of cyclododecane has the [3333] "square" conformation.[95] The X-ray crystal structure indicates small distortions of the CCC bond angle and all CH$_2$ groups in the staggered configuration.[12] There are eight pairs of transannular H/H repulsions, but the crowding is less severe than in cyclodecane. Two other conformations, higher in energy by ca. 1.5 and 3 kcal/mol, are predicted by molecular mechanics calculations.[11,95]

Cyclotetradecane is the smallest cycloalkane that can be fit on a diamond lattice[158] and still avoid unstable g^+g^- sequences. This conformation, which is called the "rectangular" or [3434] conformation by Dale;[93,96b] is found experimentally to be the lowest energy form of the molecule, both in the solid state[11] and in solution.[94] This form is also calculated to be the most stable by molecular mechanics calculations, and these calculations identify two additional conformations of slightly higher energy. The lowest pathway for interconversion of carbons in the [3434] conformation is thought to involve a $tg^+g^+ \rightarrow g^-g^-t$ process, which leads to the pseudorotated [3434] conformer after a sequence of four steps.[11]

Cyclohexadecane is a member of the family of large rings and is essentially free of ring strain caused by nonbonded transannular interactions. Both low-temperature ^{13}C NMR measurements and molecular mechanics calculations point to the "square" [4444] conformation, which fits onto a diamond lattice, to be the most stable.[96] This form is thought to be quite flexible,

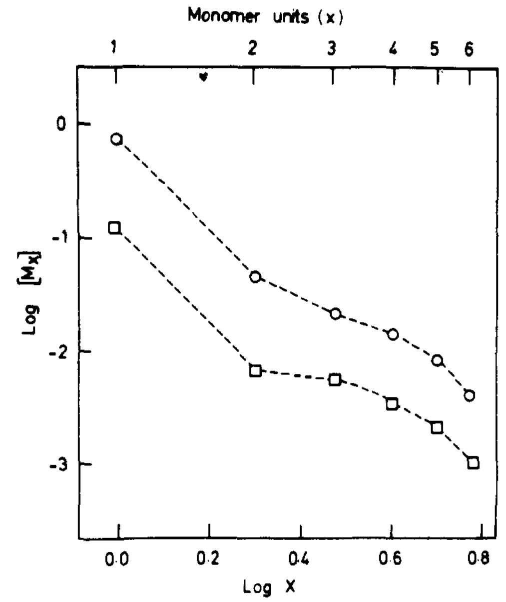


Figure 5. Concentration of cyclics M_x (in mol kg^{-1}) in a sample of nylon-6 prepared by polymerizing ε-caprolactam at 459 K and heating for a total of 36 days (□). These values are compared with cyclic concentrations in a polymer prepared by ring-chain equilibration in the melt at 525 K. See ref 9.

with low-frequency large amplitude librations contributing to the substantial entropy of fusion for cyclohexadecane. These motions also explain the broadening of the infrared bands in going from the low-temperature solid to solutions of cyclohexadecane or to the solid at room temperature.[97] A second conformation is thought to lie ca. 1 kcal/mol above that of [4444] conformation and may comprise up to 30% of the population of cyclohexadecane at room temperature.

V. End-to-End Cyclization Equilibria

The theory of Jacobson and Stockmayer[26] provides a connection between the equilibrium constant for intramolecular cyclization K_{cy} and the end-to-end cyclization probability $W(0)$ of the chain. Experimentally this connection is made by comparing K_{cy} to a corresponding bimolecular equilibrium reaction ($K^{(2)}$), which for ring–chain polymerization reactions is taken to be the chain elongation reaction. The ratio $[K_{cy}/K^{(2)}]$ has units of moles per liter and is often referred to as the effective concentration, C_{eff}. For long chains in which $C_{eff} << 1$, it can be taken as equal to the mean local concentration of one chain end in the vicinity of the other. For Gaussian chains,

$$C_{eff} = \frac{1000}{N_A}\left(\frac{3}{2\pi\langle r_0^2\rangle}\right)^{3/2}$$

where N_A is Avagadro's number.

Nylons are polyamides in which the amide groups are separated by polymethylene chains. In their synthesis, some cyclics are produced which tend to be detrimental to the desired commercial properties of the nylons. K_{cy} has been determined for nylon-6 ($-[NH(CH_2)_5CO]_x-$) in the high-temperature melt for a relatively small number of values of x.[9,27] These results are shown in Figure 5. K_{cy} decreases markedly with the degree of polymerization. Recent attempts to calculate K_{cy} by Flory et al.,[29] using new theoretical methods which avoid assuming a distribution function for the chain ends, were reasonably successful for all but the shortest chain lengths. For these chains, transannular steric effects, not considered in the model, may be important.

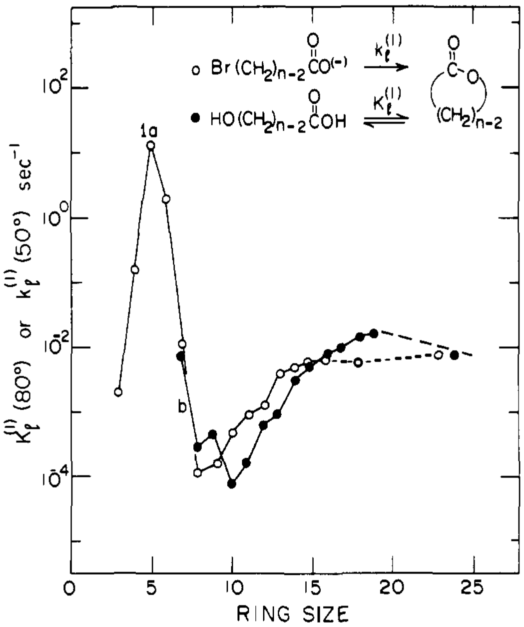


Figure 6. Molar equilibrium constants $K_e^{(1)}$ for cyclization of $HO(CH_2)_{n-2}CO_2H$ at 80 °C (●) determined from ring–chain polymerization studies by Stoll and Rouvé.[18,22] First-order rate constants $k_e^{(1)}$ for cyclization of $Br(CH_2)_{n-2}CO_2^-$ at 50 °C (○) studied by Mandolini, Illuminati, and their co-workers.[101]

For hydrocarbon chains, the most complete data available are those of Stoll and Rouvé[18] for the reaction

$$\text{polyester} + H_2O \underset{K^{(2)}}{\rightleftharpoons} H^+ +$$

$$\underset{5}{HO(CH_2)_nCOOH} \underset{K_{cy}}{\rightleftharpoons} \underset{6}{\overline{(CH_2)_nCOO}} + H_2O$$

Their data, as reinterpreted by Morawetz and Goodman,[22] are presented in Figure 6. Many of the features of the more qualitative experiments of Ziegler[14] and Carothers[15] are seen, with a minimum for rings of 9 atoms, a maximum for the 18-membered ring, and a very weak dependence of K_{cy} on ring size for somewhat longer chains. These data should be compared to those of Mandolini and Illuminati (also Figure 6) on the kinetics of intramolecular lactone formation, which is discussed in the next section.

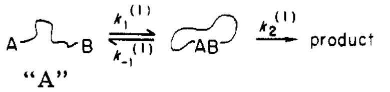
VI. Cyclization and Reaction Kinetics

Many of the studies of cyclization phenomena involve kinetic studies of the rate of ring formation. Since the interpretation of these results in terms of chain conformation or chain dynamics requires many assumptions, some of which are subtle, this relationship merits a detailed examination.

The fundamental hypothesis underlying the use of kinetic studies to obtain information about the probability or dynamics of chain cyclization is that for a reaction to occur, the reactive groups must be in proximity. The nature of this proximity (distance, mutual orientation) depends upon the individual reactions. It is usually assumed that proximity is such that significant overlap of molecular orbitals occurs. To overcome this rather vague definition of proximity, intramolecular cyclization reactions are never studied in isolation.

They are always compared to an "equivalent" bimolecular reaction which serves as a model reaction for all quantitative interpretations. It must be emphasized that the model reaction must be chosen with some care.

The general mechanism for intramolecular cyclization can be expressed as



(13)

For this reaction, the phenomenological rate coefficient $k_{\text{obsd}}^{(1)}$ can be defined according to

$$\frac{-\mathrm{d}[\text{``A''}]}{\mathrm{d}t} = k_{\text{obsd}}^{(1)}[\text{``A''}]$$

where the superscripts 1 and 2 will serve as reminders of which processes are first order and which are second order. The power and most of the conceptual difficulties of the method arise from the comparison of first- and second-order rate constants.

In principle, there exists a corresponding bimolecular reaction

$$\sim\!\!\sim\!A + B\!\sim\!\!\sim \underset{k_{-3}^{(1)}}{\overset{k_3^{(2)}}{\rightleftharpoons}} \underset{\substack{\text{encounter}\\ \text{pair}}}{[\sim\!\!\sim\!AB\!\sim\!\!\sim]} \xrightarrow{k_4^{(1)}} \text{products} \tag{13a}$$

whose phenomenological second-order rate coefficient is defined by

$$\frac{-\mathrm{d}[A\!\sim\!\!\sim]}{\mathrm{d}t} = k_{\text{obsd}}^{(2)}[A\!\sim\!\!\sim][B\!\sim\!\!\sim]$$

In this reaction, the encounter pair is assumed to be formed at the diffusion-controlled rate. A critical assumption for comparing the two reactions is that both involve the same kind of encounter complex and the same reaction transition state. Hence for $k_{\text{obsd}}^{(1)}$ and $k_{\text{obsd}}^{(2)}$ to be compared meaningfully in terms of a conformational preequilibrium of the chain, $k_2^{(1)}$ must equal $k_4^{(1)}$. One often has little information on this point.

For bimolecular reactions, $k_{\text{obsd}}^{(2)}$ can be expressed in terms of the reaction mechanism by

$$k_{\text{obsd}}^{(2)} = \frac{k_3^{(2)}k_4^{(1)}}{k_{-3}^{(1)} + k_4^{(1)}} \tag{13b}$$

For reactions occurring on every collision, $k_4^{(1)} >> k_{-3}^{(1)}$ and $k_{\text{obsd}}^{(2)} = k_3^{(2)}$. Such a reaction is said to be diffusion controlled, i.e., $k_{\text{obsd}}^{(2)} = k_{\text{diff}}$, the diffusion-limited rate constant. There are a number of methods for determining the value of k_{diff}.[98] When $k_{\text{obsd}}^{(2)}$ is less than k_{diff}, but still sufficiently large that it is sensitive to changes in solvent viscosity, $k_{-3}^{(1)}$ and $k_4^{(1)}$ are of comparable value, and the reaction is said to be "partially diffusion controlled".[99] As a practical matter, if $k_{\text{obsd}}^{(2)}$ is smaller than $10^{-2}k_{\text{diff}}$, the reaction involves a preequilibrium.

Similar formulas can be developed for the intramolecular reaction. A reaction which occurs on every encounter between A and B is said to be dynamically controlled or encounter controlled. Inefficient reactions between A and B are said to be conformationally controlled. For $k_{\text{obsd}}^{(1)} = k_1^{(1)}$, this rate constant measures the dynamics of end-to-end cyclization. For $k_{\text{obsd}}^{(1)} = (k_1^{(1)}/k_{-1}^{(1)})k_2^{(1)}$, the ratio in parentheses represents the equilibrium constant, $K_{\text{cy}}^{(1)}$, for intramolecular encounter pair formation and is proportional to the cyclization probability of the chains.

A. Criteria for Diffusion-Controlled and Conformationally Controlled Intramolecular Reactions

It is often assumed that if the corresponding bimolecular reaction is much slower than diffusion controlled, a preequilibrium will occur in the intramolecular reaction, and this reaction will be conformationally controlled. This assumption is valid. It is also frequently assumed that if the bimolecular reaction is so fast as to be diffusion controlled, so too will be the corresponding intramolecular reaction—i.e., that it will be encounter controlled. Unfortunately *this assumption is not always valid.* An encounter-controlled reaction rate depends not only on the relative rates of processes described by $k_{-1}^{(1)}$ and $k_2^{(1)}$ but, in non-steady-state kinetics, also on the magnitude of $k_1^{(1)}$! An example of this complex interplay of rate constants is presented in Appendix I.

In conformationally controlled reactions, information comes from the ratio $(k_{\text{obsd}}^{(1)}/k_{\text{obsd}}^{(2)}$. This ratio has units of concentration and is often called the effective concentration, C_{eff}.[100] By definition, it represents the concentration of $B\!\sim\!\!\sim$ (or $A\!\sim\!\!\sim$) in the presence of $A\!\sim\!\!\sim\!B$ which gives 50% bimolecular reaction.

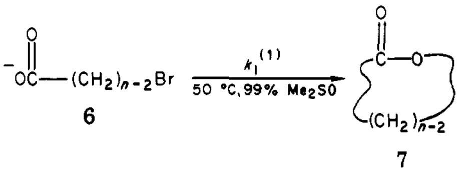
Small ring formation is often characterized by C_{eff} values of 100 to 10^8 M. These "unrealistic" concentrations come about because of the way entropic factors enter into the reaction and from the arbitrary (but universal) choice of 1 M solution as the standard state for solution thermodynamics. Page has written an excellent review on the subject.[78] In a bimolecular reaction such as (13), three translational and three rotational degrees of freedom are lost in going to the transition state. These are replaced by six new internal modes, which, if they are of relatively high frequency, make little contribution to the total partition function. Tight transition states should be formed with $\Delta S^{\ddagger}$ values of ca. -40 cal K^{-1} mol^{-1}. Loose transition states have lower frequency normal modes and consequently much less negative $\Delta S^{\ddagger}$ values.[78]

In the corresponding intramolecular reaction, there are no rotational or translational degrees of freedom to be lost. Small rings are formed by converting relatively few low frequency internal rotations into higher frequency torsional oscillations. The corresponding change in entropy upon cyclization is relatively small. The entropic contribution to $(k_{\text{obsd}}^{(1)}/k_{\text{obsd}}^{(2)}$ can be as large as $\Delta S^{\ddagger} = 30$ to 40 cal K^{-1} mol^{-1} for reactions with tight transition states, which corresponds to C_{eff} values of 3×10^6 M to 4×10^8 M.

For medium- and large-ring formation C_{eff} values are often much smaller than 1 M and $\Delta\Delta S^{\ddagger} < 0$. This comes about because in the formation of large rings, conformational entropy is lost, and in addition, very low frequency vibrational and internal rotational modes are replaced by new normal modes. Some of these, particularly the ones associated with new bond formation in the product or transition state, are of higher frequency and make smaller contributions to the partition function of the cyclized form. The low frequency and conformational contributions to the partition function which are lost upon cyclization correspond to the loss of translational and rotational degrees of freedom in bimolecular reactions. Even when the entropy of cyclization is more negative than that of the corresponding bimolecular reactions and $C_{eff} << 1$ M, the intramolecular reaction will always predominate in sufficiently dilute solution, since both the rate and entropy of bimolecular reactions are concentration dependent.

B. Kinetic Studies of End-to-End Cyclization Reactions Operating under Conformational Control

One of the most thorough studies of ring closure kinetics has been carried out by Mandolini and Illuminati and their co-workers.[101,102] Using a bromide-sensitive electrode, these authors carried out detailed kinetic studies of intramolecular nucleophilic substitution reactions. In lactone formation the rate constant $k_l^{(1)}$ is a strong function of chain length. It changes by nearly 5 orders of magnitude for values of n between 3 and 23. As in Stoll and Rouvé's data for the equilibrium constant $K_l^{(1)}$ for lactone formation,[7] cyclization to form rings of 7 to 12 atoms is inhibited. Figure 6 contains plots of both log $k_l^{(1)}$ and $K_l^{(1)}$ as a function of ring size. Since the geometry of the transition state for lactone formation by an S_N2 mechanism is not the same as the geometry of the lactone itself, it would not be surprising if the two plots showed differences. Nonetheless they are surprisingly similar. It appears that the transition state and product are similarly sensitive to the strain of medium-size ring formation. If the small differences between the curves are to be trusted as real, one might conclude that the S_N2 reaction is somewhat less sensitive than product to formation of 11- to 14-membered rings.



Arrhenius parameters have been obtained for reaction 14. Values of E_a and $\Delta S^{\ddagger}$ for this reaction are plotted in Figure 7. Several features of these plots are of interest. First of all the activation energy E_a is large for $n = 3$ and decreases substantially for $n = 4$–6. This pattern does not follow that of the strain energy of small- and common-ring formation in the cycloalkanes. There $\Delta H_{strain}(4) > \Delta H_{strain}(3)$ and $\Delta H_{strain}(7) > \Delta H_{strain}(6) < \Delta H_{strain}(5)$ (Table II). The reaction geometry for these chain lengths must be significantly different from those of the corresponding cycloalkanes. Second, there is a strong destabilization energy associated with 8- and 9-membered-ring formation. The oscillations in the E_a plot for $n = 10$–14 may reflect a change in the reaction pathway, since chains shorter than 9 are known to produce only the higher energy *cis*-lactone whereas those longer than 12 give only the *trans*-lactone.[103] Only the 24-membered ring is formed via a transition state that is virtually strain free.

Little entropy is lost upon cyclization to the transition state for formation of 3- to 6-membered rings. $\Delta S^{\ddagger}$ drops precipitously for $n = 7$ and then oscillates with E_a in a compensatory manner, so that reactions with particularly unfavorable activation energies have less negative entropies of activation. The contribution of solvent entropy to these reactions is of course not known. The variation in E_a suggests the possibility of differences in transition-state geometry and its solvation for different chain lengths. Such a factor might also account for the enthalpy–entropy compensation seen in Figure 7.

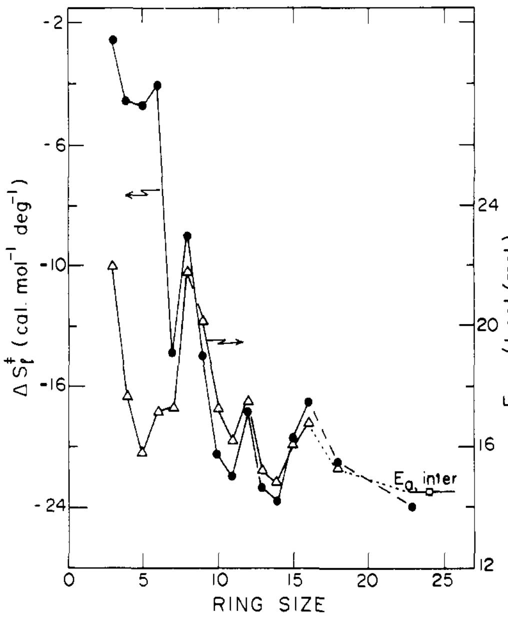
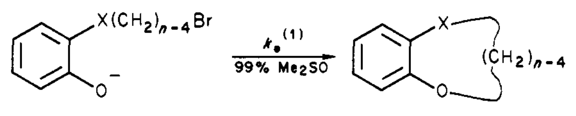


Figure 7. Activation energy $E_{a,l}$ (right ordinate) and activation entropy $\Delta S^{\ddagger}_l$ (left ordinate) for the kinetics of lactone formation from $Br(CH_2)_{n-2}CO_2^-$ as a function of ring size. Note the compensation effects for $E_{a,l}$ and $\Delta S^{\ddagger}_l$ with different chain lengths. Data from ref 101 and 102. The point (□) refers to the activation energy for the intermolecular reaction of RCO_2^- with RCH_2Br.

Mandolini, Illuminati, and their co-workers have studied the kinetics of ether formation in the molecules **8a** and **8b**.[102] In these reactions, the rings formed contain two sp^2 carbons and one or two oxygens, respectively. Here the rate constants $k_e^{(1)}$ show a nearly monotonic decrease as the product ring sizes increase. These results confirm in a quantitative way the suggestion of Carothers[16] and Ziegler[14] that introduction of oxygens and aromatic substituents into a medium-size ring relieves much of the strain associated with ring closure. The data, including the Arrhenius parameters, are plotted in Figures 8 and 9.

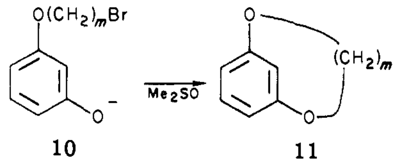


8a, X = CH$_2$
8b, X = O

9

More recently the group of Mandolini and Illuminati[104] has reported on the kinetics of cyclization for reactions 14–16. Reaction 14 was studied for values of $m = 8$–10 and 12; reaction 15 for $m = 8$–10, 12, and 16; reaction 16 for $m = (n - 4) = 8, 9, 11, 13,$ and 17. These reactions share in common the fact that the site of reaction is remote from the point of origin of the chain. Hence the chain must achieve a critical length before the intramolecular reaction can occur. The rate constants for these reactions are plotted as $k^{(1)}/k^{(2)} = C_{eff}$ in Figure 9 where $k^{(2)}$ is the second-order rate constant for an appropriate model intermolecular reaction.[104]

A surprising feature of the data in Figure 9 is that for reactions 14–16, C_{eff} *increases* substantially as the chain



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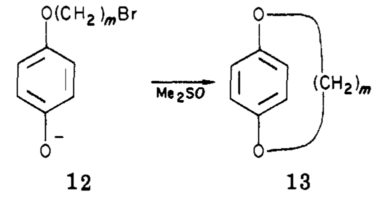

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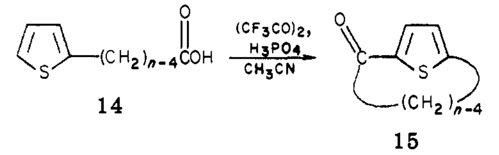

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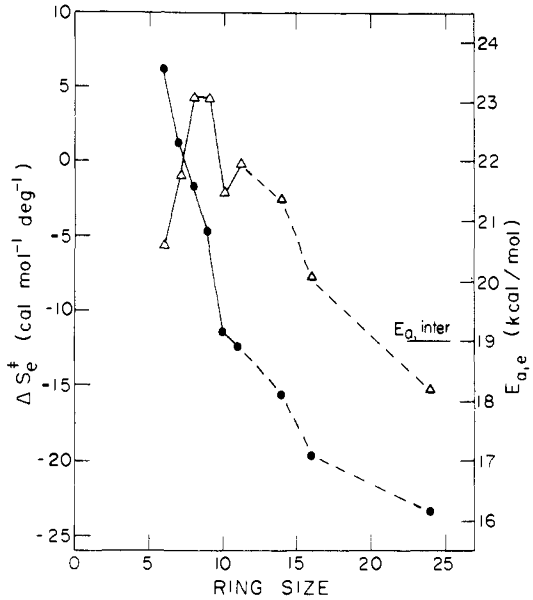


Figure 8. Activation energy $E_{a,e}$ (right ordinate) and activation enthalpy $\Delta S^{\ddagger}_{e}$ (left ordinate) for intramolecular catechol diether formation in o-$^{-}OC_6H_4O(CH_2)_{n-4}Br$ as a function of ring size. The line Ea, inter refers to the activation energy of a corresponding bimolecular reaction. Data from ref 102.

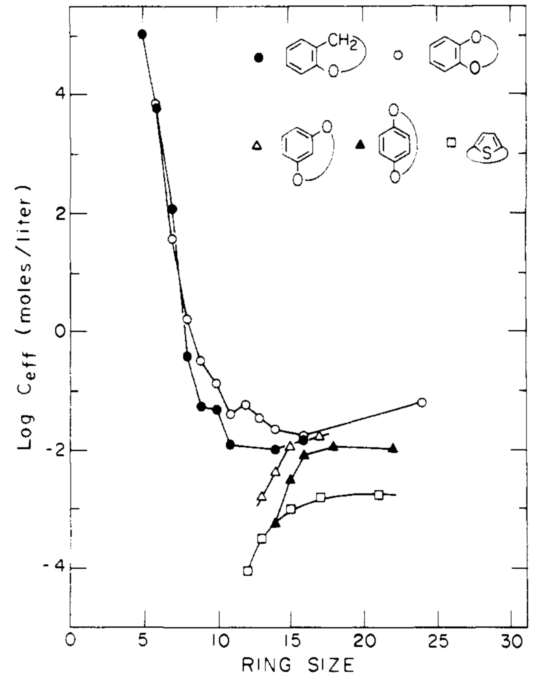


Figure 9. Effective concentration C_{eff} (moles/liter) plotted semilogarithmically vs. chain length for a variety of cyclization reactions whose kinetics were studied by Mandolini, Illuminati, and their co-workers.[104]

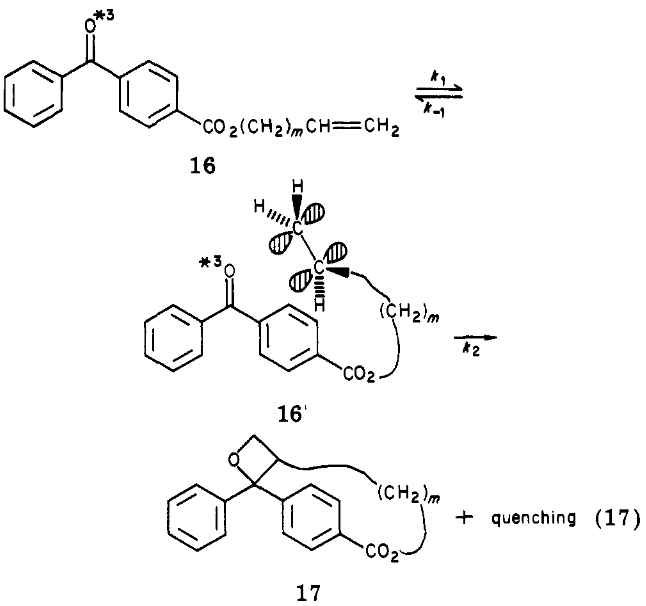
length increases. One anticipates, on the basis of Jacobson–Stockmayer theory, that C_{eff} would decrease with n for sufficiently long chains. Computer simulations of this kind of reaction by Fraser and Winnik[81] suggest that one important factor contributing to this increase is the steric effect of the aromatic ring acting in conjunction with the remoteness of the reaction site. For chains that can just reach the reaction site, the conformational component of the partition function (Z_{cy}) is small; i.e., there are very few reactive (cyclized) chain conformations. Longer chains are increasingly more able to circumvent the intervening ring so that the number of conformations of cyclized chains increases faster with n than the total number of chain conformations. Z_{cy} increases faster than Z_{total}, and the cyclization probability (Z_{cy}/Z_{total}) increases with chain length until the chains are sufficiently long that the steric effects of the ring become relatively unimportant in limiting the accessibility of the chain end to the reaction site.

In this sense, the behavior of C_{eff} with chain length for reactions of **8a,b** are more "normal" in that C_{eff} decreases with chain length. For longer chains $k^{(1)}$ goes through a minimum (Figure 9). As the Arrhenius data in Figure 8 indicate, these decreases in $k_l^{(1)}$ are not purely entropic in origin. E_a varies with chain length, and for $n = 24$, E_a is actually less than that of the bimolecular model reaction. Solvation effects may be important here. Mandolini[101b] has argued that the unusually low values of C_{eff} for medium-ring formation in reaction 16 may be due to differences in solvation in the intramolecular and model bimolecular reactions.

DeTar has begun a reinvestigation of ω-bromoalkylamine cyclization.[20] This work has taken the form of some new experiments,[20b] a critical evaluation of data obtained in the early experiments by Freundlich[3] and Salomon,[17] and the application of molecular mechanics calculations to the problem of amine cyclization.[105a] The dilemma upon which DeTar and his group have focused is the traditional use of cycloalkanes as models for the factor influencing cyclization reactions. In other words, in the ring closure reaction of ω-bromoalkylamines to form cyclic ammonium salts, is it valid to invoke the product as a model for comprehending the factors affecting the transition state?

For example, five-membered rings form faster than six-membered rings, yet the former are more strained. Seven- and four-membered rings close at about the same rate. On the basis of $\Delta G_f°$ for the corresponding cycloalkanes, one predicts that the former should be faster by a factor of 10^{12}. DeTar has been able to account for these differences by recognizing that the transition state for the S_N2 reaction has a trigonal-bipyramid geometry. Simulating these transition-state geometries by molecular mechanics methods permits the corresponding strain energies to be estimated. These are significantly different from those of the product rings and account for the reactivity pattern reported in the literature. DeTar takes a unique approach to estimating entropies of cyclization, obtaining values different from those presented in Table I. Inasmuch as the reactions he has examined are dominated by enthalpy effects, these entropies play little role in the explanations he develops.

Winnik and his co-workers have examined end-to-end cyclization in the intramolecular phosphorescence quenching reaction of ω-alkenyl esters of benzophenone-4-carboxylic acid.[105] In these molecules, the quenching group, a monosubstituted alkene, quenches the ketone triplet state with a bimolecular rate constant, $k_q^{(2)}$, 100 to 1000 times less than k_{diff}. Consequently the intramolecular reaction is preceded by a conformational equilibrium.



The phosphorescence lifetime τ_m of 16 is concentration dependent. This arises from the ability of the alkene group on one molecule to quench the excited state of the aromatic ketone in another molecule of 16. In these experiments a Stern–Volmer analysis of these exponential decay times, as a function of the concentration of 16, was used to obtain $\tau_m°$, the triplet state lifetime extrapolated to infinite dilution. The rate constants for intramolecular quenching were obtained from

$$k_{iq}^{(1)} = \frac{1}{\tau_m^{\circ}} - \frac{1}{\tau_{Me}^{\circ}} = (k_1/k_{-1})k_2 \qquad (18)$$

where $\tau_{Me}°$ is the phosphorescence lifetime of the corresponding methyl ester, the model compound, where intramolecular quenching cannot occur. These values are presented in Figure 10, and for chains of $m > 10$ are corrected for the relatively small amount of intramolecular hydrogen abstraction by the ketone within the chain. In terms of mechanism 17, $k_{iq}^{(1)}$ is given by the term on the far right hand side of eq 18.

The steep rise and sharp maximum at $m = 12$ in the curve of Figure 10 are indicative of the stereochemical demands of the quenching reaction: Chains shorter than eight CH_2 groups cannot achieve conformations where the π electrons of the double bond overlap the half-filled n orbital on the ketone oxygen without causing serious increases in the torsional energy of the chain. For chains of $m > 8$, the activation energy is independent of chain length; hence the changes in k_{iq}, particularly its decrease for $n > 11$, are sensitive only to entropic factors associated with achieving a reactive configuration.

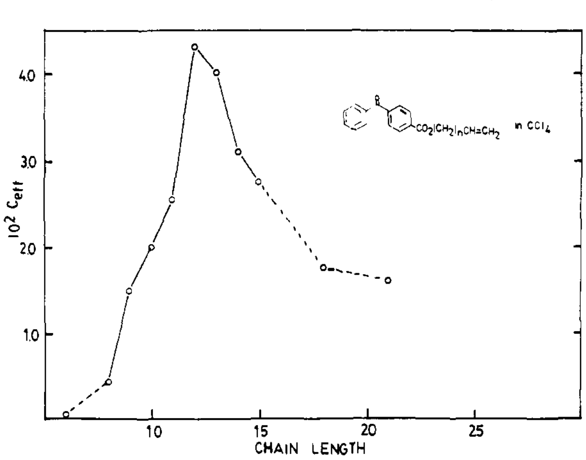
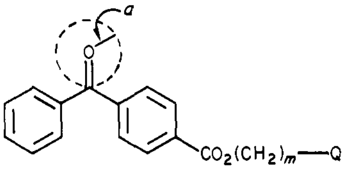


Figure 10. The rate constant for intramolecular phosphorescence quenching, $k_{o,n}$, by the terminal alkene group in the molecules benzophenone-4CO_2-$(CH_2)_m$-$CH{=}CH_2$, expressed as $C_{eff} = k_{o,n}/k_q^{(2)}$, as a function of chain length. The data were obtained from measurements in CCl_4 solution at 5×10^{-4} M at 22 °C. See ref 105c.

For $m = 8$, the activation energy is nearly 40% larger than that for $m \geq 9$ [$E_a(8) = 3.2$ kcal/mol; $E_a(9) = 2.4$ kcal/mol]. Here an interplay between chain distortion and a less than ideal reaction geometry conspires to permit the reaction to occur, albeit with an increased energy of activation. For $m \geq 9$, the E_a's are approximately 1 kcal/mol larger than those of corresponding bimolecular reactions [$E_a^{(2)} = 1.6$ kcal/mol]. This difference may be associated with the conformational energy of the chain. In terms of the RIS model, it can be due either to an increased fraction of gauche bonds, or an important contribution to cyclization from a very small fraction of $g^{\pm}g^{\mp}$ sequences. These become more important at higher temperatures and could easily contribute to $E_a^{(1)}$.

It is interesting to compare these data with the results of a computer simulation of the reaction.[81] In the simulation the steric requirements of the benzophenone were modeled on a diamond lattice. We examined cyclization of molecule 18 in which the quencher Q on the chain end was taken to be an NH_2 group.[81b] The reactive volume was taken as that of a sphere ($a = 3.1$ Å) centered on the ketone oxygen. Cyclization was detected and counted when the amine nitrogen was inside the sphere with its nonbonding electron pair pointing toward the oxygen atom. In the tetrahedral lattice model, the chain bonds are maintained in the gauche or trans rotational states, with the former taken to be 600 cal/mol higher in energy. Steric effects were accommodated by hard sphere repulsions. Because of the second-neighbor avoiding nature of the random walk, $g^{\pm}g^{\mp}$ sequences were completely prohibited at all temperatures. A plot of cyclization probability, W_{cy}, and the entropy of cyclization, calculated from [$\Delta S_{cy} = -R$



18

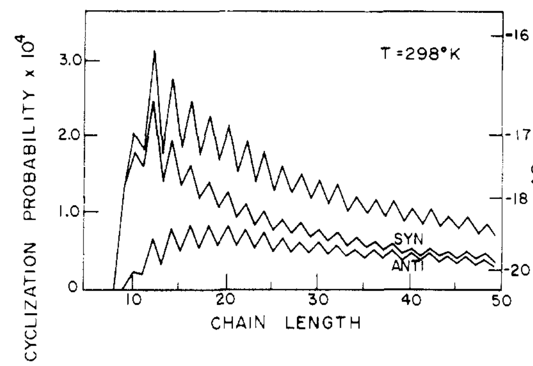
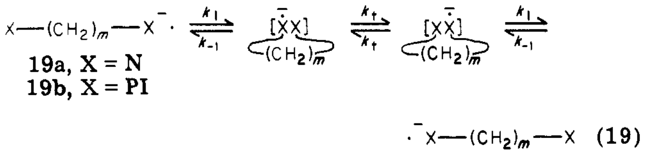


Figure 11. End-to-end cyclization probability $W(0)$ for the molecules benzophenone-$4CO_2(CH_2)_mNH_2$, as a function of chain length. The data were obtained from a lattice-based RIS model employing Monte Carlo calculations. See ref 105e.

ln W_{cy}], vs. chain length is shown in Figure 11. The odd–even oscillations are artifacts associated with the parity of lattice sites which designate the reactive volume.

The key features to be appreciated from a comparison of Figures 10 and 11 is that the steep rise in W_{cy} and k_{iq} as well as the detailed shape of the curve near the maximum are dependent primarily on the details of the chemical reaction: proximity and orientation of the reactive species, the tightness of the transition state, and the distance of the site of chemical reaction from the point of origin of the chains. For longer chains, the decrease in these values reflects the decrease in cyclization probability with increasing chain length—i.e., the statistical aspects of chain configuration. Comparison of ΔS_{cy} from the simulation with ΔS^* from the reaction shows that the latter is ca. 10 cal mol^{-1} deg^{-1} more negative. If the former value is correct, this difference can be associated with the entropy changes on the chemical quenching step (k_2; ΔS_2^*).

Shimada and Szwarc[51,106,107] have published an important series of papers reporting on the kinetics of intramolecular electron exchange in the molecules 1-naphthalene-$(CH_2)_m$-1-naphthalene$^{-}\cdot$ [N-$(CH_2)_m$-N$^{-}\cdot$], phthalimide-$(CH_2)_m$-phthalimide$^{-}\cdot$ [PI-$(CH_2)_m$-PI$^{-}\cdot$], and phthalimide-$(CH_2CH_2O)_xCH_2CH_2$-phthalimide$^{-}\cdot$. These have been widely cited as the first quantitative measurements of dynamically controlled end-to-end cyclization reactions. Two theoretical papers[52,68] have appeared which simulated the cyclization dynamics in these systems. These authors' conclusion that the reactions operated under dynamic control was based upon an oversimplified model of cyclization reactions (eq 19 and 20). It is important to realize that *these reactions are not sensitive to chain diffusion. These reactions operate under conformational control.*[108]



19a, X = N
19b, X = PI

$$X\text{—}(CH_2)_m\text{—}X^{-}\cdot \rightleftharpoons \ldots \rightleftharpoons \cdot^{-}X\text{—}(CH_2)_m\text{—}X \quad (19)$$

$$k_{ex}^{(1)} = k_1k_t/(2k_t + k_{-1}) \quad (20)$$

In these experiments, electron spin resonance measurements were used to obtain values of $k_{ex}^{(1)}$ for different chain lengths and for different temperatures.

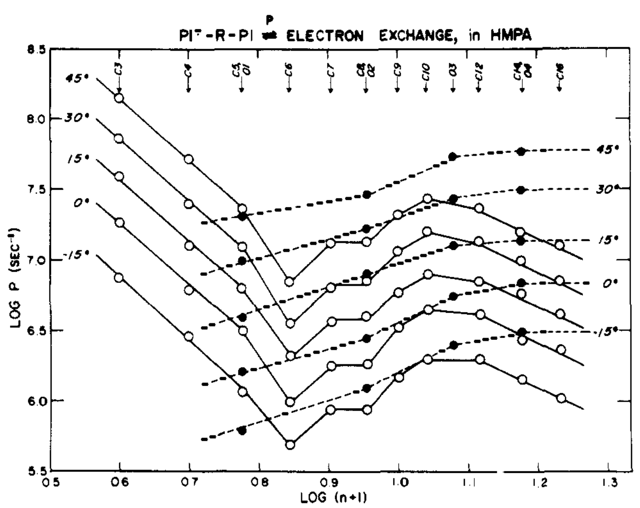


Figure 12. Dependence of the frequency P (s^{-1}) for intramolecular electron exchange upon the number of atoms separating the two substituents on the chain ends, in HMPA at the temperature indicated. (○) PI-$(CH_2)_n$-PI$^{-}\cdot$; (●) PI-$(CH_2CH_2O)_mCH_2CH_2$PI$^{-}\cdot$; PI is the N-phthalimide group. From ref 107b.

These measurements were based upon the idea that if the unpaired electron were localized on only one naphthalene, it would have its spin coupled by hyperfine interactions to those of seven protons. In the rapid exchange limit, it would be coupled to the 14 proton spins of two naphthalenes. In the intermediate domain, $k_{ex}^{(1)}$ could be determined from the actual ESR spectra. These values were comparable with values of $k_{ex}^{(2)}$, the second-order rate constants for bimolecular electron exchange between the appropriate model compounds (eq 21, 22).

$$N\text{-}C_2H_5 + \cdot^{-}N\text{-}C_2H_5 \xrightarrow{k_{ex}^{(2)}} \cdot^{-}N\text{-}C_2H_5 + N\text{-}C_2H_5 \quad (21)$$

$$n\text{-}C_4H_9\text{-PI} + n\text{-}C_4H_9\text{-PI}^{-}\cdot \xrightarrow{k_{ex}^{(2)}} n\text{-}C_4H_9\text{-PI}^{-}\cdot + n\text{-}C_4H_9\text{-PI} \quad (22)$$

The data from these experiments are plotted in Figures 12 and 13. One notices immediately an important difference between the reactions involving naphthalene ion radicals and those involving PI$^{-}\cdot$. It would seem that the stereochemical requirements for electron transfer are much more relaxed for the N$^{-}\cdot$ → N reaction than for the PI$^{-}\cdot$ → PI reaction.

Shimada and Szwarc[51] support this conclusion by additional experiments on the monoanion radical of molecules in which N- or PI- are attached via equatorial CH_2 groups, to the 1,4-positions of a cyclohexane ring. In the former example, electron exchange is observed, which implies that for the N$^{-}\cdot$ → N reaction, electron transfer can occur over distances of 8 to 10 Å. In the latter example, no electron exchange is observed. For electron exchange among PI units, a closer approach is necessary.

The curve shapes in Figures 12 and 13 can be explained by the contribution of the chain to the intramolecular electron exchange reaction. Where close approach of the end groups is necessary, the stereochemical features which oppose medium ring formation play a role, and a minimum in the log $k_{ex}^{(1)}$ vs. m plot is observed. In the naphthalene electron exchange, the end groups remain sufficiently separated that these destabilizing interactions are avoided. In these reac-

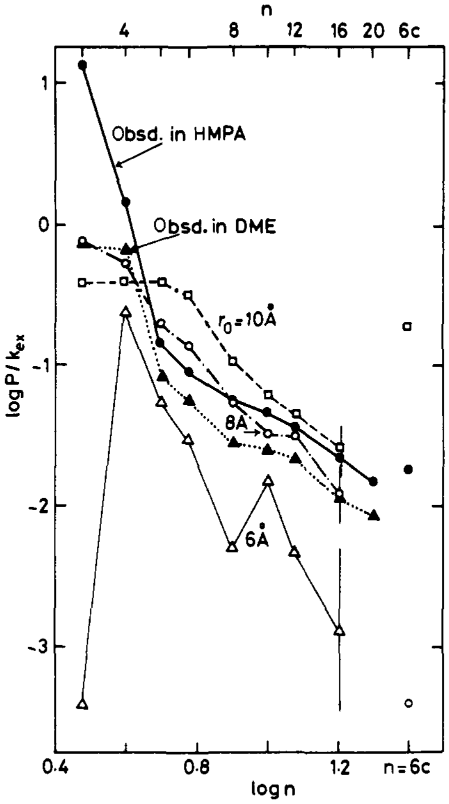


Figure 13. Dependence of the frequency P (s^{-1}) for intramolecular electron exchange divided by the corresponding bimolecular rate constant k_{ex} (M^{-1} s^{-1}) as a function of chain length for the molecules N-(CH$_2$)-N$^{-}\cdot$ (N is the 1-naphthyl group). Experimental values from Shimada and Szwarc.[51] In HMPA solvent (●); in DME solvent (▲). (○, □, △) Calculated values based upon the RIS model using 6, 8, and 10 Å, respectively, as the reactive distance for electron transfer. Theoretical values from Sisido and Shimada.[52]

tions cyclization occurs not at the chain origin but at some distance from the origin determined by the spacial requirements of the electron transfer reaction.

The key outstanding question remaining for the interpretation of these data is whether the reactions are dynamically or conformationally controlled. Is k_t in reaction 19 so fast that $k_{ex}^{(1)}$ is dominated by k_1, or is it so slow that a preequilibrium is established before electron exchange occurs?

Electron-transfer reactions are accompanied by both solvent and counterion reorganization. As the authors point out, Marcus theory[98,110] predicts this effect and explains the large preexponential factors in the bimolecular reactions 21 and 22. The barriers to these reactions are significant, but they are also comparable in magnitude to the activation energy for diffusion. Consequently the E_a values for these reactions do not help settle the question of whether these reactions are encounter controlled. For the PI$^{-}\cdot$ → PI exchange, $k_{ex}^{(2)}$ is substantially smaller than k_{diff}, estimated from the Debye equation (η is the solution viscosity):[73a]

$$k_{diff} = \frac{8RT}{3000\eta} \tag{23}$$

These values are collected in Table III. Furthermore these $k_{ex}^{(2)}$ values are identical in five solvents of very different viscosities. There seems little doubt that these reactions are sufficiently slow that one would anticipate conformational control in the intramolecular reaction.

TABLE III. Second-Order Rate Constants $k_{ex}^{(2)}$ for Electron Exchange in the Ion Radicals 1-$C_2H_5N^{-}\cdot$ and n-C_4H_9-PI[a,b]

1-$C_2H_5N^{-}\cdot$ in DME–2% HMPA				1-$C_2H_5N^{-}\cdot$ in HMPA			
T, °C	η	10^{-8}-$k_{ex}^{(2)}$	10^{-8}-k_{diff}[c]	T, °C	η	10^{-8}-$k_{ex}^{(2)}$	10^{-8}-k_{diff}
−60	1.69	0.88	24	30	3.03	7.1	22
−30	0.93	2.3	58	15	4.24	5.0	15
0	0.61	4.2	100	0	6.23	3.0	10
E_a = 3.0 kcal/mol				E_a = 4.0 kcal/mol			
n-$C_4H_9PI^{-}\cdot$ in in DME–2% HMPA				n-C_4H_9PI in HMPA			
0	0.61	1.2	100	0	6.23	1.8	10
20	0.48	1.8	130	15	4.24	2.7	15
40	0.39	2.9	180	30	3.03	4.2	22
E_a = 3.6 kcal/mol				E_a = 5.3 kcal/mol			
$E_{a,diff}$ = 2.7 kcal/mol				$E_{a,diff}$ = 4.5 kcal/mol			

[a] 1-Ethylnaphthalene; N-butylphthalimide. Data from ref 51, 106, and 107. [b] Appropriate units are $k_{ex}^{(2)}$, M^{-1} s^{-1}; η, solvent viscosity, cP. [c] k_{diff}, M^{-1} s^{-1}, calculated from eq 23.

In the N$^{-}\cdot$ → N reaction, $k_{ex}^{(2)}$ is only a factor of 3 smaller than k_{diff} calculated from eq 23. This equation underestimates k_{diff} for the N reaction because here the reactive cross section is much larger than the diffusion cross section. Actual values of k_{diff} here may be an order of magnitude larger than those in Table III.

Shimada and Szwarc were aware of these problems, but they invoked dynamic control in the intramolecular reactions because they found their values of C_{eff} (= $k_{ex}^{(1)}/k_{ex}^{(2)}$) were smaller than what they believed a reasonable minimum value C_{min} should be. This minimum concentration was taken as that of two molecules in a sphere whose radius r_{max} was that of the fully extended chain connecting the chromophores. Since $\langle r \rangle$ is always less than r_{max}, C_{eff}, they conclude, must always be larger than C_{min}. When $C_{min} > C_{eff}$, dynamic factors must retard chain cyclization.

This argument fails because it implicitly assumes that the chain connecting the chromophores is freely jointed, so that the positions of the chromophores are uncorrelated.[111] Real chains have essentially fixed bond angles and a limited number of rotational conformations. C_{eff} is dependent upon the ratio of partition functions (Z_{cy}/Z). It is found experimentally for medium- and large-ring formation to be almost always smaller than C_{min}, even when $k^{(2)}$ is 10 orders of magnitude less than k_{diff} (Figure 9).[101,104]

The deciding factor, however, is the sensitivity of the reaction to solvent viscosity. Dynamic processes are always sensitive to the viscosity of their environment.[111-114] Both k_1 and k_{-1} in reaction 19 should be similarly sensitive to solvent viscosity, but their ratio, which is an equilibrium constant, should be unaffected by changes in η. Shimada and Szwarc[51,106,107] carried out careful studies in both HMPA and DME–2% HMPA (1,2-dimethoxyethane–2% hexamethylphosphoramide), with the former, at identical temperatures, being 10 times more viscous. Since $k_{ex}^{(1)}$ values (Table IV) are slightly larger in the more viscous solvent, the reaction must operate under conformational control.

It should be pointed out that the authors raised the points in the preceding paragraph about viscosity effects and rejected them because they believed that localized

TABLE IV. **First-Order Rate Constants $k_{ex}^{(1)}$ for Electron Exchange in the Ion Radicals $N\cdot(CH_2)_m\cdot N^{-}$.**[a]

	M						
	6	8	10	12	16	20	η
$10^{-7}k_{ex}^{(1)}$(DME)[b]	2.5	1.3	1.1	0.88	0.56	0.42	0.61
$10^{-7}k_{ex}^{(1)}$(HMPA)	2.3	1.8	1.6	1.1	0.70	0.55	6.23
$10^{-7}k_{ex}^{(1)}$(DME)[b]	3.3	1.7	1.5	1.3	0.70	0.52	0.51
$10^{-7}k_{ex}^{(1)}$(HMPA)	4.4	2.8	2.3	1.8	1.1	0.74	4.24

[a] $k_{ex}^{(1)}$ in s^{-1}; viscosity η in cP; data from ref 51, 106, and 107. [b] DME-2% HMPA.

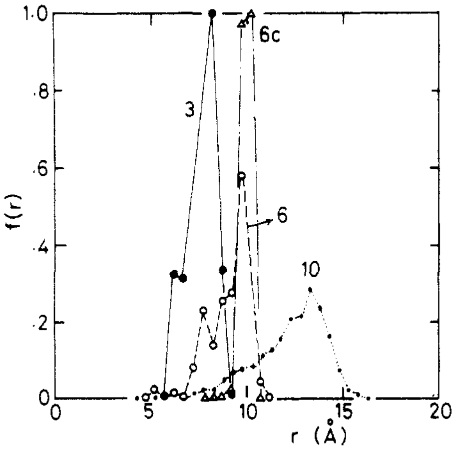


Figure 14. Distribution of the end-to-end distance r of $N-(CH_2)_n-N$ from calculations based upon the RIS model. The numbers in the figure indicate the number of CH_2 groups n in the molecule. 6c = *trans*-1,4-bis(1-naphthylmethyl)cyclohexane. From ref 52.

conformational changes in alkanes could be so retarded by internal barriers as to make them insensitive to solvent viscosity. Subsequent studies by NMR by the group of Reynolds and Winnik[113] as well as the detailed fluorescence studies by Morawetz and his co-workers[114] demonstrate that these motions are indeed sensitive to the viscosity of the surrounding medium.

Sisido and Shimada have attempted to simulate the results on electron exchange in $N-(CH_2)_m-N^{-}\cdot$ employing calculations based upon a RIS model.[52,115] Molecular mechanics calculations were used to map out the conformational space accessible to the terminal naphthalenes, and off-lattice exact enumeration or Monte Carlo methods were used to calculate the distribution of end-to-end distances in these molecules. This distance was taken as that between the centers of the respective naphthalene rings. Their results are plotted in Figure 14. In this figure, 6c refers to 1,4-bis(α-naphthylmethyl)cyclohexane.

One interesting feature of this plot is the limited distribution of the chain ends for $m = 3$ and for the cyclohexyl derivative. Since $k_{ex}^{(1)}$ is 6.7×10^9 s^{-1} for the former and 0.9×10^7 s^{-1} for the latter in HMPA, it would seem that the frequency of electron transfer decreases by a factor of ca. 10^3 when the separation of the naphthyl groups increases from 7 to 10 Å.

Another important result from the work of Sisido and Shimada is that the cyclization probability is only very weakly sensitive to changes in temperature. Since they believed that the intrinsic electron-exchange reaction would have a very low activation energy (ca. 1 kcal/mol),[52] they concluded that conformational control would imply an E_a for electron exchange comparable to that of $W(0)$. Consequently they too inferred that reaction 19 is dynamically controlled and developed a jump-diffusion model to describe chain dynamics in these reactions. As pointed out previously,[98,109] an electron-transfer reaction between identical chromophores can have a substantial activation barrier associated with the solvent reorganization energy. Thus this conclusion of Sisido and Shimada[52] is not warranted by the data, and there is little doubt that reaction 19 is under conformational control.

The reader is also directed to an important series of papers by Sisido and his co-workers[116] on end-to-end cyclization phenomena in terminally substituted poly(ethylene oxide) and poly(*N*-methylglycine) ("polysarcosine") chains. This group has examined in a very careful and thorough manner both intramolecularly catalyzed ester hydrolysis and intramolecular donor–acceptor complex formation between groups attached to the ends of these chains. One of the surprising findings in these experiments was that the decrease in cyclization with increase in chain length was associated with a change of enthalpy of cyclization. Computer simulations[116] based upon the rotational isomeric state model predicted an entropic origin to this decrease. This rather important discrepancy may in fact arise from specific solvent–polymer interactions associated with a polar polymer in a polar solvent. It is not unreasonable to imagine that these interactions might undergo changes when the chains cyclize.

C. Kinetic Studies of Cyclization Reactions Operating under Diffusion Control

Many bimolecular fluorescence quenching reactions are diffusion controlled.[98] These processes, which can also give rise to photoproducts, energy transfer, ions, or new emissions (excimers and exciplexes), have been studied in great detail over the past decade. From this work has emerged a certain fundamental understanding about what factors lead to diffusion-limited reaction rates. Thus it is not surprising that the intramolecular analogues of these reactions, with the luminescent chromophore and quenchers at opposite ends of a flexible chain, have been chosen for study in order to obtain measures of chain dynamics.

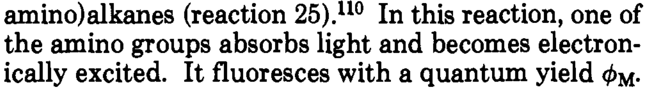
There have been many studies of the properties of polymers containing fluorescent and quenching chromophores randomly distributed along the backbone. These results have proved extremely difficult to interpret quantitatively. The first such study is normally attributed to Kabanov[117] and his group, although excimer formation in polystyrene, studied earlier, is conceptually similar. The first experiments specifically geared to studying cyclization dynamics of long chains were those of Cuniberti and Perico[118] who looked at pyrene excimer formation between pyrenes covalently attached to the ends of poly(ethylene oxide) chains. Their results, unfortunately, can only be considered to be qualitative, since they were unable to measure fluorescence lifetimes in their system.

During the past 10 years many research groups have examined intramolecular interactions between chromophores connected by attachment to the ends of a short chain.[119] Frequently, these studies involved intramolecular excimer formation in molecules of the form $A^{*}-CH_2-X-CH_2-A$ (X = CH_2, O, NAc), in which the excimer to locally excited-state fluorescence intensity ratio, I_E/I_M, was measured. In virtually all these systems, at sufficiently low temperatures, I_E/I_M increased with decreasing solvent viscosity.[120] In this low-temperature limit cyclization dynamics is rate limiting. At the extreme of high temperature, however, I_E/I_M often shows a positive Arrhenius slope, implying that a preequilibrium precedes excimer emission. These experiments have the potential for measuring both the rate constant for dynamic cyclization and the corresponding equilibrium constant. To date very few such reactions have been studied in sufficient kinetic detail for these important values to be obtained.

Two notable exceptions are the recent experiments of DeSchryver et al. and the group of N. C. Yang. DeSchryver and his co-workers[121a] looked at intramolecular exciplex formation in the molecules $C_6H_5(CH_2)_mNMe_2$ for m = 2, 3, 5, and 11 over a wide range of solvents and temperatures. In these experiments, the time scale of cyclization was on the order of nanoseconds and very sensitive to chain length. For short chains, the kinetics were quite complicated, since, apparently, rotation about the CH_2–NMe_2 bond was slow on the time scale of the cyclization. In Yang's experiments[121b] on intramolecular exciplex formation in 9-anthracene-$(CH_2)_3$-$NMeC_6H_5$, two important points emerge: First he found that k_1, the rate constant for dynamic cyclization, varied inversely with solvent viscosity. Second, he found that k_{-1}, the rate constant for dissociation of the exciplex to the open, electronically excited molecule, had the same viscosity sensitivity. Hence k_1/k_{-1} $(=K_{cy})$ was independent of the viscosity of the medium.

Simple tertiary alkyl amines fluoresce when their solutions in alkane solvents are appropriately excited.[122] Furthermore, these excited states undergo concentration quenching (self-quenching) when they encounter a ground-state amine. This process is reasonably efficient. About one collision in five results in deactivation $[k_{sq}^{(2)} \sim (k_{diff}/5)$ in hexane at 23 °C].[117]

$$Me_3N^* + Me_3N \xrightarrow{k_{sq}^{(2)}} 2Me_3N \qquad (24)$$



$$\underset{\mathbf{20}}{Me_2N^*(CH_2)_mNMe_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Me_2N\cdots NMe_2]^* \xrightarrow{k_2} Me_2N(CH_2)_mNMe_2 \qquad (25)$$

$$k_{iq}^{(1)} = \frac{k_1k_2}{k_{-1} + k_2}$$

Halpern has recently examined the kinetics of intramolecular fluorescence quenching in bis(dimethylamino)alkanes (reaction 25).[110] In this reaction, one of the amino groups absorbs light and becomes electronically excited. It fluoresces with a quantum yield ϕ_M. (M = "monomer" is the photochemist's jargon for a locally excited state in an excimer of exciplex forming reaction.) After excitation with a short pulse of light, the fluorescence of trialkylamines decay exponentially with a lifetime τ_M typically 25 ns in out-gassed alkane solvents at room temperature. In a molecule such as **20**, intramolecular cyclization both decreases ϕ_M and shortens the decay time of the excited state. In addition, for m = 2, 3, and 4 a new emission appears to the red of the amine fluorescence. The factors which lead to this excimer emission in amines are still not very clear. The detailed kinetics can become quite complex, especially for short chains where local barriers due to the chain make it possible that molecules in different rotational conformations react at different rates.[121a]

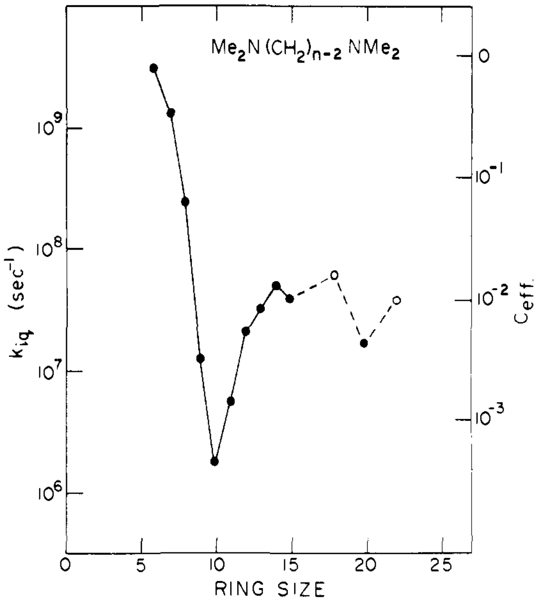


Figure 15. Estimated rate constant k_{iq} (s^{-1}) for intramolecular fluorescence quenching in the molecules $Me_2N(CH_2)_{n-2}NMe_2$ studied by Halpern et al.[110a] as a function of chain length. C_{eff} values are calculated from the ratio ($k_{iq}/k_q^{(2)}$, where $k_q^{(2)} = 3.9 \times 10^9$ M^{-1} s^{-1} is the bimolecular rate constant for self-quenching in $Me_2N(CH_2)_8NMe_2$.

In Halpern's experiments, the cyclization kinetics were found to be quite complicated for some chain lengths (m = 3, 4, 16, and 20) and apparently simple for others.[110] For example, m = 3 showed double exponential kinetics, with the first decay time too fast to measure. In m = 4, the *excimer* decayed as a sum of two exponentials, and its rise time could not be measured. This behavior is not predicted by mechanism 25. Amine fluorescence decays were found to be exponential for m = 6–13 and 18. A curious feature of the data is that for m = 16 and 20, the fluorescence decay curves were nonexponential. They could be fit to a sum of two exponential decays with the long-time component identical with that of simple tertiary amines. This result, the authors note, implies either a small fraction of monosubstituted chains in their samples as impurities that they could not detect by other means or that some of the chain conformations could not cyclize on the time scale of the experiment (several lifetimes, e.g., ca. 100 ns).

For chain lengths in which exponential decays were observed, Halpern obtained $k_{iq}^{(1)}$ values from the expression $[k_{iq}^{(1)} = 1/\tau_n - 1/25$ ns]. In order to obtain estimates of $k_{iq}^{(1)}$ when the fluorescence decays of the "monomer" were sums of exponentials, the short-time component of the decay λ_{short} was treated as though it were the appropriate decay rate: $[k_{iq}^{(1)} \approx \lambda_{short} - 1/25$ ns]. This gives a correct value for $k_{iq}^{(1)}$ for m = 16, 20 if their long-time components are indeed due to trace impurities. For m = 4, 5, it gives a numerical value which is neither $k_{iq}^{(1)}$ nor k_1 and is thus difficult to interpret.

Values of $k_{iq}^{(1)}$ from Halpern's data are plotted in Figure 15. Self-quenching is very sensitive to chain

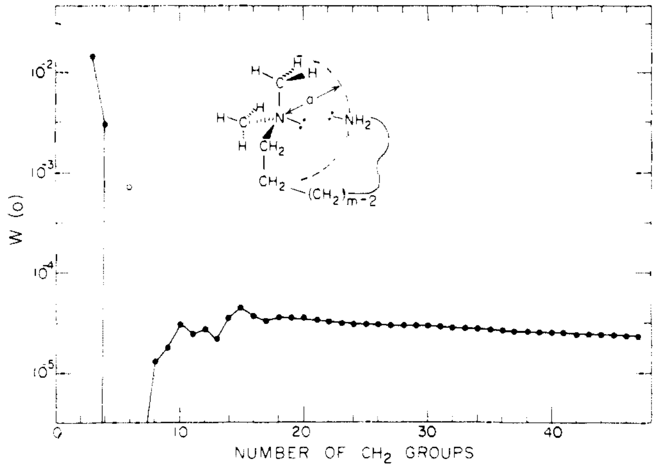
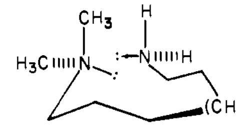


Figure 16. Calculated end-to-end cyclization probability $W(O)$ for the molecules $Me_2N(CH_2)_{n-2}NH_2$ as a function of chain length, using a lattice-based RIS model.[110b]

length, and $k_{iq}^{(1)}$ changes by over three orders of magnitude for rings of 6–10 atoms. The shape of the plot near the minimum at $m = 10$ is quite narrow, substantially more so than that for lactone formation (Figure 6). There is some evidence to suggest that in amine excimers, both nitrogens have nearly tetrahedral configurations.[123] Consequently, the molecular geometry in the transition state for intramolecular quenching may well resemble that of a cycloalkane. The wider minimum observed in intramolecular lactone formation would be a consequence of energetic features associated with the cis and trans conformation of the lactone.



Fraser and Winnik[124] have attempted to simulate the configurational contributions to amine self-quenching using a diamond lattice model (with second neighbor exclusions) for the polymethylene chain. Chains were grown at random originating from the dimethylamino nitrogen. After each step in chain elongation an amino group was temporarily affixed to the growing chain end. If its nitrogen was located within an arbitrarily specified reactive volume—within three lattice steps of Me_2N, ca. 3 Å—*and* if its nonbonded pair of electrons pointed toward the Me_2N group, that chain was counted as cyclized (reactive). Monte Carlo methods were used to estimate the partition functions for cyclized and total chains, and their ratio gives the cyclization probability of the chain.

The results of these calculations are shown in Figure 16. Cyclization occurs readily for $m = 2$, 3, and 4. It becomes prohibitive for $m = 5$ and 7, though the model permits chains of six CH_2 groups to cyclize. For longer chains, cyclization becomes increasingly important and then decreases gradually for chains of more than 12 CH_2 groups. The decrease in $W(O)$ is much less pronounced than the $m^{-3/2}$ dependence predicted by simple theories of cyclization probability.

It is important to recognize that this model, with its rigidly gauche and trans rotational states and its all-or-nothing (hard sphere) incorporation of steric effects, can account for only the gross features of the experimental data for short- and medium-ring formation. The model is more reliable for long chains where there are unfortunately few experimental data. It would be very interesting to see what kind of behavior would be predicted by more sophisticated models of the molecular mechanics type.

Zachariasse[125] has examined intramolecular excimer formation in the molecules pyrene-$(CH_2)_m$-pyrene. These molecules, when electronically excited, give the

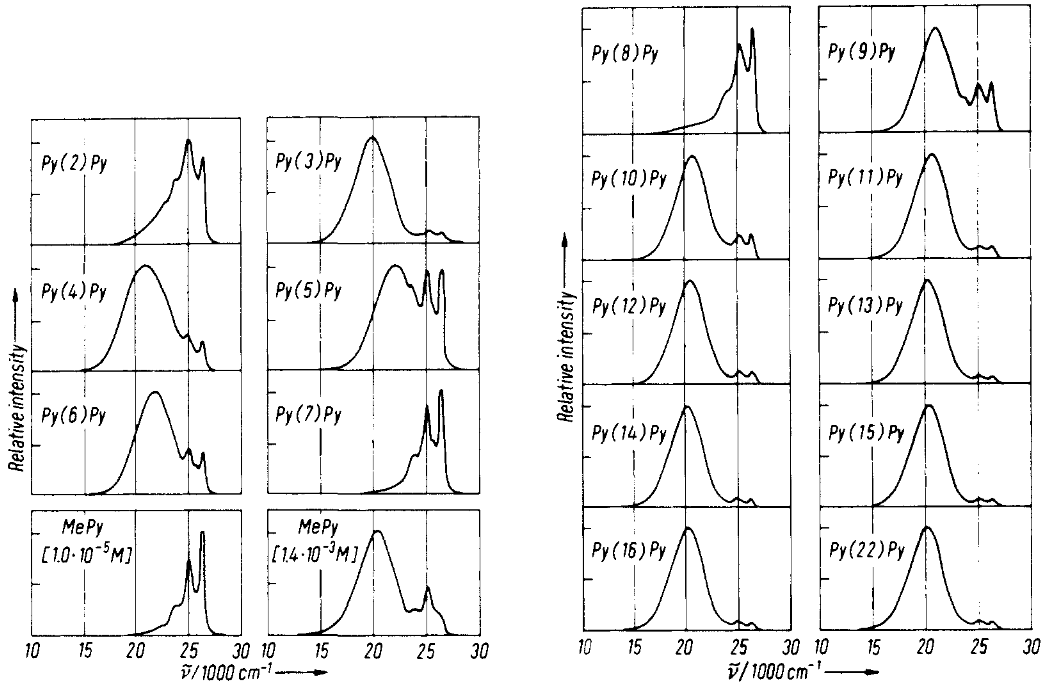


Figure 17. Fluorescence spectra at room temperature of di(1-pyrenyl)alkanes Py-$(CH_2)_n$-Py, 1×10^{-5} M solutions in methylcyclohexane. In the lower left-hand part of the figure, fluorescence spectra of solutions of 1-methylpyrene are shown. The structured emission above 25 000 cm^{-1} (below 400 nm) originates from the locally excited pyrene ("monomer" fluorescence). The structureless emission at ca. 21 000 cm^{-1} (480 nm) comes from the excimer. Taken from Zachariasse and Kuhnle.[125]

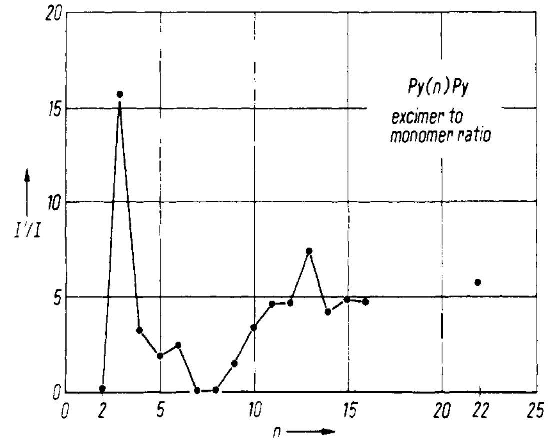
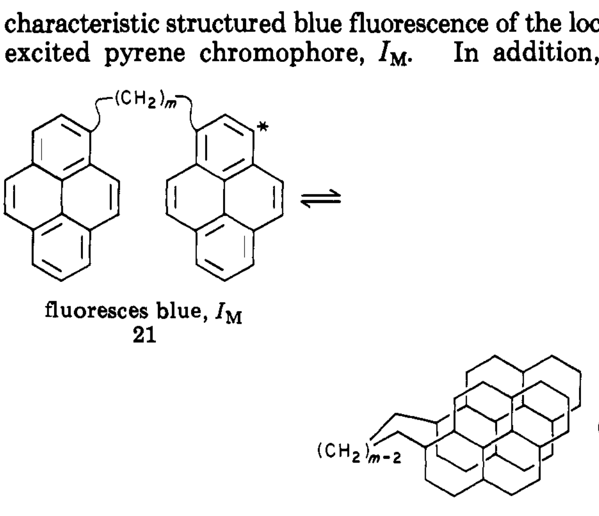


Figure 18. Dependence of the excimer to monomer emission intensity ratio (I_e/I_m) upon chain length in the molecules Py-$(CH_2)_n$-Py. Taken from ref 125.

characteristic structured blue fluorescence of the locally excited pyrene chromophore, I_M. In addition, by



fluoresces blue, I_M
21

(26)

fluorescences green, I_E
21

end-to-end cyclization, they show the broad green structureless emission of the pyrene excimer, I_E (see Figure 17). In the lowest energy configuration of the pyrene excimer, the two pyrene rings lie face-to-face in parallel planes. Distortion from this geometry destabilizes the excimer and results in a hyposochromic shift of the excimer emission.

In pyrene itself, intermolecular excimer formation is diffusion controlled, and at ordinary temperatures is essentially irreversible. In the absence of a full kinetic analysis of reaction 26, one cannot establish whether or not intramolecular excimer formation is partially reversible.

Zachariasse has reported the excimer to locally excited state fluorescence intensities (I_E/I_M) as a function of chain length for many hydrocarbon chain lengths connecting the two pyrenes (Figure 18). This ratio is very sensitive to the number of CH_2 groups separating the terminal chromophores. For n = 2, 4, 5, 6, 8, and 9, not only is excimer formation inhibited, but the excimer fluorescence spectrum is blue shifted relative to that of methyl pyrene, the model compound. Only in the case of m = 3 for short chains (the Hirayama rule[126]) is excimer fluorescence normal and intense. Excimer emission is again normal for chains of more than $12CH_2$ groups. I_E/I_M passes through a maximum at m = 12 and slowly declines thereafter, showing some hint of the odd–even alternating effects observed earlier by Ziegler[14] and Carothers.[16]

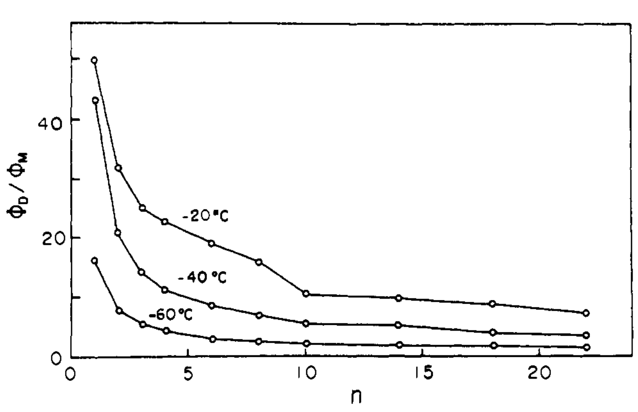
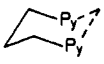


Figure 19. Dependence of the excimer to monomer fluorescence intensity ratio (I_e/I_m) upon chain length in the molecules $PyCH_2O_2C(CH_2)_nCO_2CH_2Py$ at various temperatures. Taken from ref 127.

Zachariasse argues that to compare his data with those of ring closure reactions, one should consider the ring size to be $n = m + 3$. This reasoning follows from the Hirayama $m = 3$ rule for maximum efficiency in excimer formation: the two chromophores, in cyclizing, serve to complete the chair form of cyclohexane.



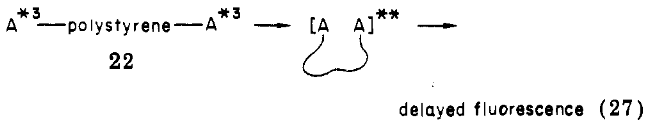
It should be noted that the data in Figure 18 are not in the proper form to be compared to models of chain conformation or dynamics. For these, rate constants are needed.

Nishijima has examined excimer formation in 1-pyrenylmethyl esters of dibasic acids [pyrene-CH_2O_2C-$(CH_2)_mCO_2CH_2$-pyrene].[127] Ratios of excimer to locally excited-state emission intensities (I_E/I_M) were measured at various temperatures. These data are shown in Figure 19. By assuming that at −60 °C excimer formation is rate limiting (i.e., irreversible), that the radiative rate constants for both excimer and pyrene locally excited emission are temperature independent, and that a simple reaction scheme (cf. reaction 25) suffices to describe the reaction mechanism, these I_E/I_M values are proportional to the rate constants for encounter-controlled chain cyclization. If, following Zachariasse,[125] one considers that pyrene excimer formation is equivalent to adding three carbons to the chain length, the ring sizes for Nishijima's molecules may be considered to be $m = m + 9$. The minimum Zachariasse observed for n = 9 and 10 is not apparent in these I_E/I_M values. Rather, they decay monotonically. The two ester groups must relax the steric constraints to cyclization. According to Mita,[128] the data in Figure 19 can be fit to the form log $(I_E/I_M) \sim m^{-1.5}$.

Winnik and his co-workers have applied the technique of pyrene excimer formation to the study of end-to-end cyclization dynamics in polystyrene.[31,129] Since the chains involved are not hydrocarbon chains, a detailed discussion is outside the scope of this review. These authors found that in a Θ solvent both the equilibrium constant for cyclization, K_{cy}, and the dynamic rate constant, k_{cy}, decreased as $N^{-1.6\pm0.1}$, in accord with theory of Wilemski and Fixman.[69] One of the limitations of this approach is that for long chains the fluorescence lifetime of pyrene is not sufficient to allow k_{cy} to be obtained with good precision.

This technique has been applied as well to other polymers, but the data are not as complete. Early experiments on poly(ethylene oxide) were carried out by Cuniberti and Perico.[118] Subsequent experiments by Cheung and Winnik[130] demonstrated that for this polymer k_{cy} is inversely proportional to solvent viscosity, as required by the theory of diffusion-controlled kinetics. Winnik and his co-workers have demonstrated that poly(ethylene oxide) chains and poly(dimethylsiloxane) chains, comparable in length to those of polystyrene, cyclize faster. This again emphasizes that k_{cy} measures the *dynamic* flexibility of polymer chains.

Mita[128] has used the observation of delayed fluorescence resulting from triplet–triplet annihilation between anthracene chromophores to infer the magnitude of k_{cy} for polystyrene (eq 27). These polymers were substituted at both ends with anthracene groups and irradiated with an intense pulse from a nitrogen laser. This very attractive technique, which lends itself to the study of cyclization of very long polymer chains, currently suffers from certain technological limitations. One cannot yet work at sufficient dilution or produce a large fraction of polymers with both ends in the triplet state. Mita's results give values of k_{cy} within an order of magnitude of those obtained by Winnik et al.[31] and predicted by Perico and Cuniberti,[67] but problems in separating intramolecular from bimolecular contributions to the delayed fluorescence have led Mita to conclude that k_{cy} depends only weakly upon chain length.[118]



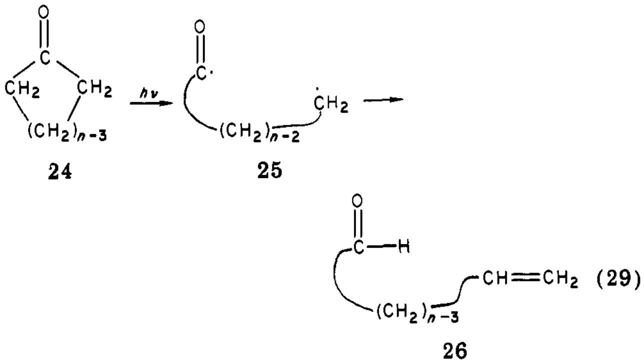
Katzir and his co-workers have applied Förster energy transfer between two chromophores attached to the ends of polypeptide oligomers to the problem of measuring chain dynamics[132] (eq 28). Selective excitation of a naphthalene chromophore in his system [D*] in reaction 28 led to naphthalene fluorescence and (in competition with that emission) through-space energy transfer to a dansyl chromophore [A] at the other end of the chain. Spectroscopic studies indicated that energy transfer between these chromophores occurs with a critical distance, R_0, of 22 Å.

$$\underset{23}{\text{D*-polypeptide-A}} \xrightarrow{\text{energy transfer}} \text{D-polypeptide-A*} \tag{28}$$

For experiments carried out in a very viscous solvent,[132a] glycerine, these authors were able to infer a distribution function for the chain ends, $W(r)$, that successfully accounted for the nonexponential form of the fluorescence decay of the naphthalene in 22. In less viscous media, dynamic factors shorten the naphthalene decay time. Making certain simplifying assumptions, Katzir et al.[132b] were able to obtain the diffusion constants of the chain ends for the various chain lengths of polypeptide they examined. These diffusion constants varied inversely with solvent viscosity.

Sisido[133] has reported preliminary results on similar experiments with poly(*N*-methylglycine). He has established that energy transfer in his system has a dynamic component, but the data are as yet insufficient for him to interpret them quantitatively.

In each of the preceding experiments, a molecule in its conformationally relaxed random configuration was irradiated in such a way that, in some of the molecules, groups at one or both ends became electronically excited. The experiments measured the cyclization of that subset of the total ensemble of molecules. One can conceive of a different kind of approach to measuring the cyclization dynamics of a flexible chain. One could begin with cyclic polymer, induce scission at a bond in the ring, and observe the recyclization of the species generated by bond rupture (eq 29).



Reaction 29 is an example of this process. Irradiation of a cyclic aliphatic ketone (24) by an α-cleavage reaction generates a biradical species, **25**. Since **25** is initially formed in a triplet state, geminate reclosure to 24 is inhibited. As the chain ends separate, the singlet–triplet splitting decreases. After a spin flip, the singlet biradical undergoes cyclization to form **26** or re-form 24. Both processes are thought to be encounter controlled.

If this reaction is carried out in a magnetic field and observed by NMR spectroscopy, CIDNP signals are observed.[134] These occur because the electron spins in the biradical never have a chance to become completely uncorrelated. In the biradical, the electron and proton spins interact, resulting in non-Boltzmann populations of proton spins in the products. Strong CIDNP signals (here, emission) result. Furthermore, and more important, Closs and Doubleday have discovered that the intensity of these signals is sensitive to the strength of the magnetic field applied during the irradiation and also varies with the ring size of the cyclic ketone.[134] These results are presented in Figures 20 and 21.

There is no way that one can simply take these results and extract rate constants for dynamic cyclization. In this respect, there are parallels between these experiments and the intramolecular Förster energy-transfer studies of Katzir et al. In order to appreciate the dynamic contribution to the CIDNP effect, one must assume or calculate a distribution function of the chain ends in the biradical, treat the electron spin–spin interaction for each conformation, and include in the calculation a model for the mutual diffusion of the chain ends which leads to product formation. In this way one can hope to obtain a reasonable simulation of the data presented by Closs and Doubleday.

Such an approach has been taken, and with good success, by the combined efforts of Kaptein and der Hollander and their research groups.[135] Beginning with the off-lattice model of Lal and Spencer[136] for hydro-

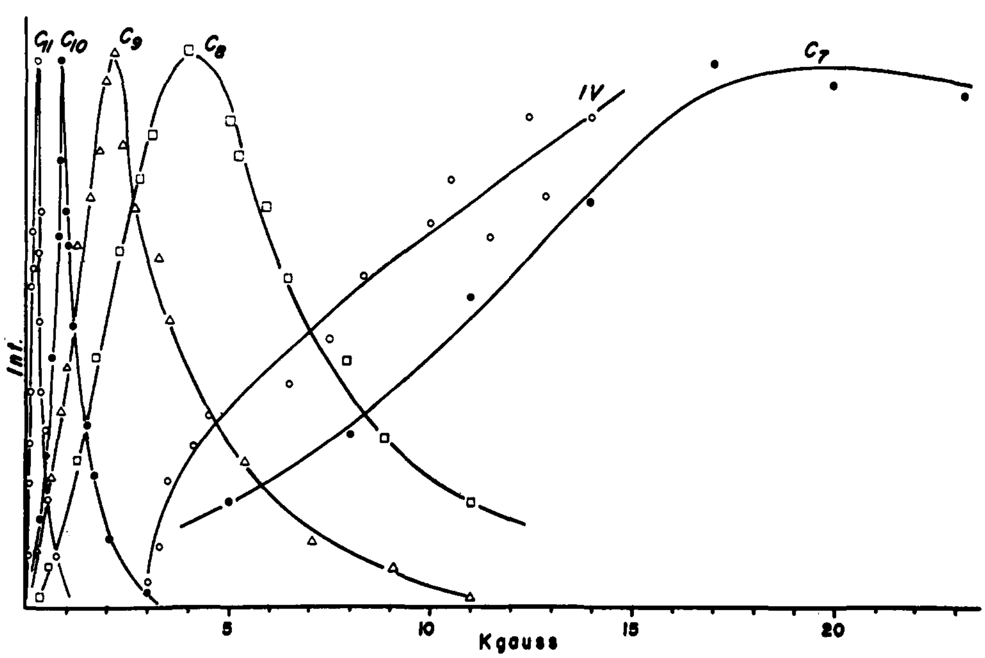


Figure 20. Intensities of the aldehyde proton emission from the photoproducts $HCO(CH_2)_{n-3}CH{=}CH_2$ in photo-CIDNP studies of the irradiation of cyclic alkyl ketones as a function of field strength. The numbers C_{11}, C_{10}, etc., refer to *n*, the number of carbons in the cycloalkanone. The intensities are in arbitrary units. From Closs and Doubleday.[134] IV refers to bicyclo[3.2.1]octan-2-one.

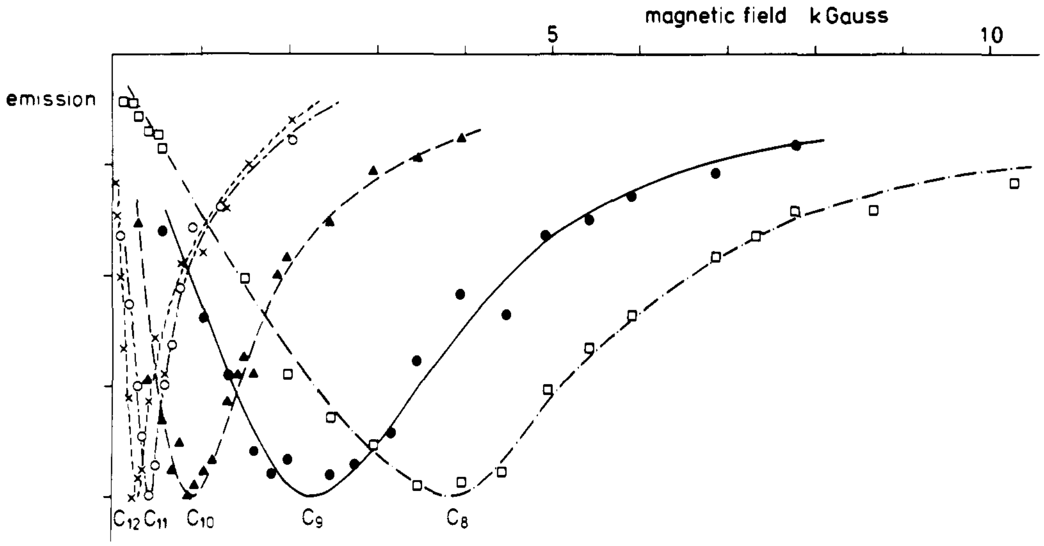


Figure 21. Experimental ^{13}C CIDNP emission intensity of the carbonyl carbon of the same series of cyclic ketones described for Figure 20 as a function of the magnetic field strength. From ref 137.

carbon chains, which allows for a modest amount of rotational angle distortion, these authors calculated the end-to-end distribution functions $W(r)$ for alkanes of 6–12 carbons. They assumed that these alkanes and the biradicals **25** of the same number of carbons had the same distribution of their chain ends. Plots of $W(r)$ vs. r are presented in Figure 22. It is interesting to note that even with the realistic off-lattice model of Lal and Spencer, these distribution functions are highly structured.[135b]

As can be seen in Figure 22, the authors divided these plots into segments of equal area (equal population). A restricted jump-diffusion model was invoked, where the chain ends, driven by Brownian motion, jump to adjacent segments with a transition rate taken as

$$W_{kl} = D'/(r_l - r_k)^2 \qquad \text{for } k = l + 1$$

where W_{kl} is the jump rate between the kth and lth segment, of mean distances r_k and r_l, respectively, from the other end (the C=O group) of the biradical. Here D' is the effective diffusion constant of the chain ends; it is assumed to be independent of r and of chain length.

In fitting the model calculations to the data, the authors had to optimize three parameters: D', and two parameters associated with the distance dependence of the electron–electron interaction. In addition, the intrinsic rate constant for bond formation from adjacent pairs, k_p, plays an important role. Good agreement between experimental and calculated magnetic field dependence curves were obtained for values of these parameters chosen to be the same for all chain lengths. This does not necessarily mean that end-of-chain diffusion is independent of separation and chain length, but it may mean that a value of $D' = 5 \times 10^{-5}$ cm^2 s^{-1} is a reasonable approximation to these effective diffusion constants.

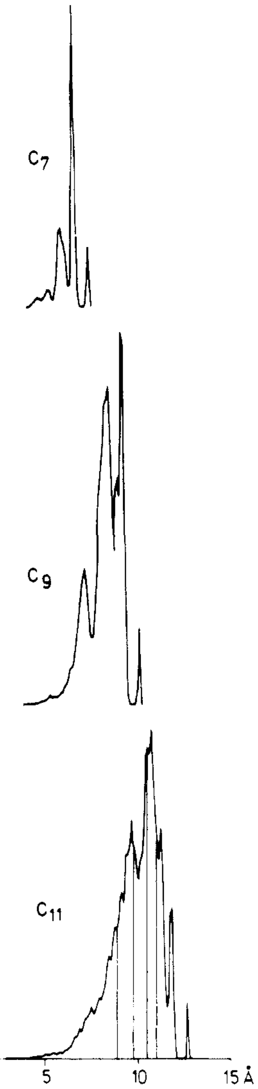


Figure 22. Normalized end-to-end distribution functions for polymethylene chains, derived from the model of Lal and Spencer. This model is more sophisticated than usual forms of the RIS model in that it allows for torsion angles different from those associated from gauche and trans minima. Monte Carlo methods were used; 50000 configurations were examined for (CH_2)-, 75000 for $(CH_2)_9$, and 110000 for $(CH_2)_{11}$. From ref 135b.

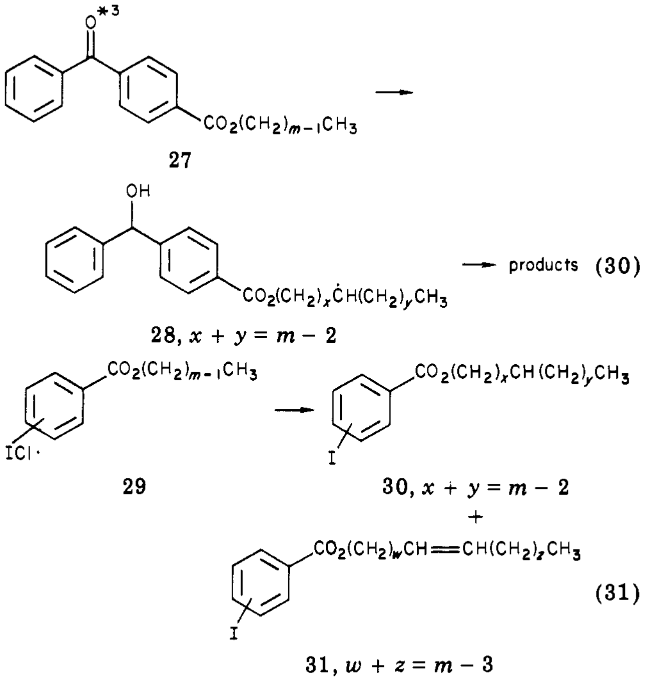
A more important conclusion is that k_p must be chosen to be sufficiently fast ($\sim 10^{11}\ s^{-1}$) that the reaction is effectively dynamically controlled. When k_p was chosen to be small, the calculated emission intensity vs. magnetic field strength curves no longer resembled those in Figure 21. Rather they acquired peaks corresponding to the peaks in the end-to-end distribution. Hence one can assert with some confidence that the CIDNP effects observed by Closs and Doubleday are indeed measures of chain dynamics.

In more recent work,[137] DeKanter and Kaptein have examined the role of hyperfine interactions in determining the magnitude of the ^1H and ^{13}C CIDNP effects. In addition they have succeeded in trapping the biradical **25** with 2-methyl-2-propanethiol. This shortens the lifetime of the biradical and changes its CIDNP behavior.

D. Cyclization into the Chain Interior

Many reactions are known which occur between groups attached to the interior of a polymer chain. These include excimer formation between nonadjecent monomer units in a wide variety of polymers [poly(acenaphthene), poly(naphthyl methacrylate)],[138] energy transfer in polymers,[139] and intramolecular catalysis of ester hydrolysis in copolymers carrying small numbers of randomly distributed ester groups and nucleophiles catalyzing ester solvolysis.[140] Since the probability of interaction between the ester and catalytic group depends on their spacing along the polymer chain, a dispersion of the rate constant is observed. This was interpreted by assuming that rings smaller than a critical size cannot form and that the probability of forming larger rings decays as a negative power of the ring size. Using this model, the dispersion of the rate constant was consistent with a "ring closure exponent" which increased with the solvent power of the medium. However, the dispersion of the rate constant involving the interaction of groups distributed at random along a polymer chain does obviously not lend itself to a unique interpretation. Unfortunately, the preparation of polymers in which interacting groups are separated by well-defined numbers of monomer residues constitutes a formidable synthetic problem.

In end-to-backbone cyclization reactions, the situation becomes more tractable if the terminal substituent is capable of reacting with each monomer unit. In a kinetics experiment one still observes a sum of reactions occurring at each site. If the reaction leads to the formation of chemical products, a product analysis can in principle indicate the fraction of reactions occurring at each site (eq 30, 31).



27

28, $x + y = m - 2$ (30)

29 **30**, $x + y = m - 2$ (31)

31, $w + z = m - 3$

In hydrocarbon chain chemistry, a number of such reactions have been studied by Breslow,[141] Winnik,[10,142] Money,[143] and Schäfer.[144] The inspiration behind these experiments was to design systems that would impose stereochemical constraints on an intramolecular chemical reaction and permit selectivity in the functionalization of sites of identical intrinsic chemical reactivity. This approach, which Breslow calls "remote oxidation", examines ways of limiting the number of sites in the molecule which would intramolecularly come into con-

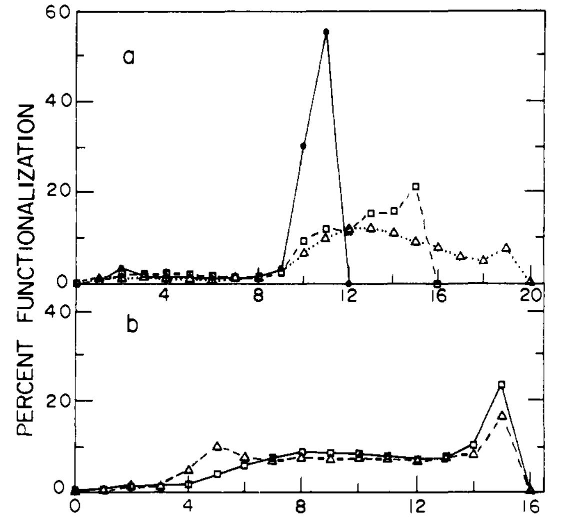


Figure 23. Percent reaction at each of the CH_2 groups, via intramolecular remote oxidation in the molecules. (a) Benzophenone-4-CO_2-$(CH_2)_{n-1}CH_3$ (△) *n*-eicosyl ester; (□) *n*-hexadecyl ester; (●) *n*-dodecyl ester. Product distribution from photolysis in CCl_4 at 0.001 M. (b) (□) *n*-hexadecyl *p*-(dichloroiodo)benzoate; (□) *n*-hexadecyl *m*-(dichloroiodo)benzoate. Product distribution from intramolecular chlorination in CCl_4 at 0.001 M. Data from ref 141b.

tact with the reactive functionality.[141]

In **27** the reactive functionality is the ketone carbonyl oxygen of the electronically excited molecule. Intramolecular hydrogen abstraction can occur only at those CH_2 groups which the oxygen atom can reach. The need for the chain to cyclize essentially excludes reaction of the first nine CH_2 groups in the chain. A product analysis (Figure 23a) indicates that all other CH_2 groups can react and that a distribution of oxidation sites is observed. The reaction is not particularly selective, except for chains whose chains can just reach the reactive C=O group. The distribution of oxidation sites along the chain is not uniform. It reflects the relative cyclization probability of each individual CH_2 group in the chain.

In **29**, the aromatic iodide group serves to deliver Cl· to the chain, where a hydrogen abstraction reaction occurs.[141] A broader distribution of reaction sites is observed for both the meta and para isomers (Figure 23b). This suggests that the iodobenzoate-bound Cl· reacts with fewer stereochemical constraints than the ketone C=O in **27**.

Increasing the synthetic utility of these reactions requires that access to the reactive functionality be further restricted. This can be done in several ways. Breslow has successfully employed the remote oxidation technique in steroid functionalization.[145] The rigid steroid framework permits only certain sites to encounter the reactive group. Another approach applicable to flexible chain molecules would be to tie these molecules down at more than one site, limiting the number of reactive configurations.

Winnik and his group, using flash photolysis techniques,[10,142] have studied reaction 30. These techniques permit one to obtain the rate constant for intramolecular hydrogen abstraction in **27**. This rate constant, k_n, represents the sum of rate constants for hydrogen abstraction at each of the CH_2 groups in the chain in **27**; k_n, in turn is proportional to the sum of cyclization probabilities of each of these CH_2 groups. Consequently, these experiments allow the factors affecting chain-to-backbone cyclization probability to be examined.

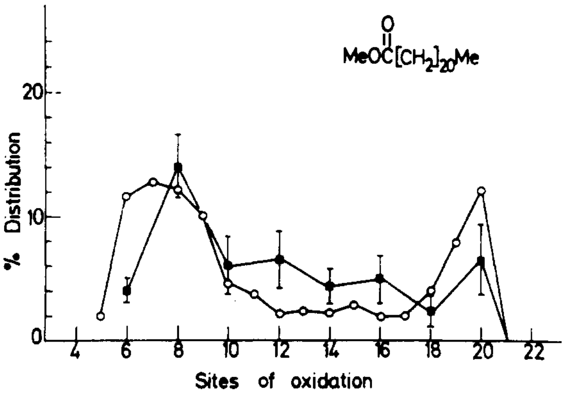
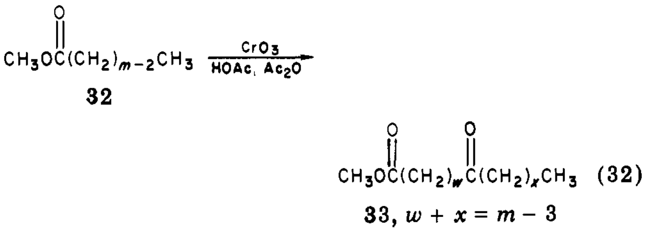


Figure 24. Percent reaction at each of the CH_2 groups in the CrO_3 oxidation of methyl docosanoate as a function of carbon number. Experimental data (○) from ref 143. Relative cyclization probability for each of the CH_2 groups to occupy lattice sites adjacent to the Cr=O oxygens in an RIS model of the complex between $CrO_2(OAc)_2$ and methyl docosanoate. Simulated values from ref 146.

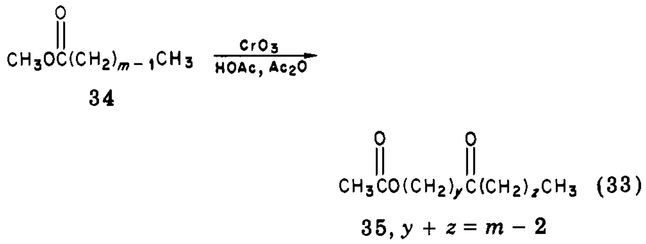
These results and the product distribution analyses by Breslow have been examined in the context of RIS model calculations.[65,81] Many of the details of this chemistry and the associated calculations have been reviewed.[10] The key features to be reiterated here are the following: (i) In all solvents, k_n is a monotonically increasing function of *n*. Each additional CH_2 group on the chain causes an incremental addition to both the cyclization probability and k_n. (ii) In nonpolar solvents the chain behaves entirely in accord with the predictions of the RIS model. (iii) In aqueous media, there are small but real increases in the cyclization probability of the chain (eq 32, 33).



$$CH_3O\overset{O}{\overset{\|}{C}}(CH_2)_{m-2}CH_3 \xrightarrow[HOAc,\ Ac_2O]{CrO_3} CH_3O\overset{O}{\overset{\|}{C}}(CH_2)_w\overset{O}{\overset{\|}{C}}(CH_2)_xCH_3 \quad (32)$$

32

33, $w + x = m - 3$



$$CH_3O\overset{O}{\overset{\|}{C}}(CH_2)_{m-1}CH_3 \xrightarrow[HOAc,\ Ac_2O]{CrO_3} CH_3\overset{O}{\overset{\|}{C}}O(CH_2)_y\overset{O}{\overset{\|}{C}}(CH_2)_zCH_3 \quad (33)$$

34

35, $y + z = m - 2$

The reaction of CrO_3 with esters of fatty acids and with acetates of long-chain alcohols gives monoketo esters in reasonable yields.[143a] The distribution of oxidation sites in these reactions (Figure 24) is incompatible with a random attack of the CrO_3 in a bimolecular fashion. Saunders and Winnik[146] have postulated that $O_2Cr(OAc)_2$, the species formed from CrO_3 in this medium, binds to the ester group. In this complex, oxidation occurs intramolecularly by cyclization of the chain to a reactive site adjacent to either of the Cr=O oxygens. Monte Carlo calculations, incorporating this

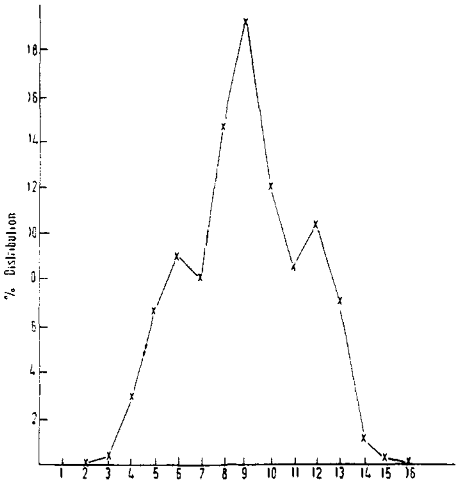
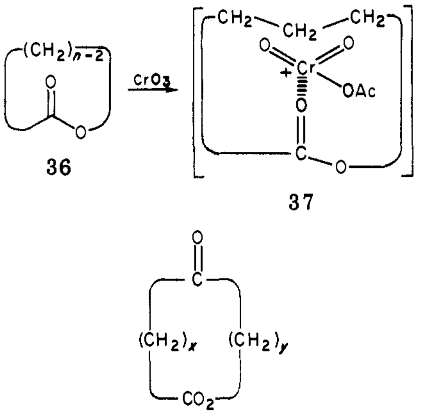


Figure 25. Percent oxidation of each of the CH_2 groups as a function of carbon number in the reaction of CrO_3 with hexadecanolide. From Eigendorf, Ma, and Money.[143]

hypothesis into the RIS model, are effective at simulating the experimental results. The experimental and simulated results are shown in Figure 24.

Money and his co-workers have recently examined CrO_3 oxidation of macrolides.[143b] These give keto-macrolide products 38 in high yield (eq 34). Product



36

37

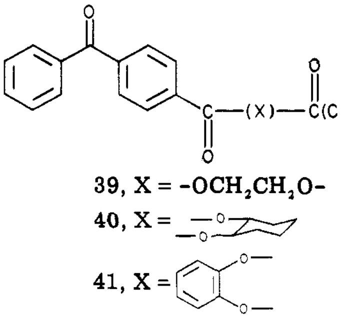
(34)

38, $x + y = n - 3$

analyses shown in Figure 25 indicate a narrower distribution of oxidation sites than in reaction 32 and 33.

A complex such as 37 may be involved as the reactive species. If this argument is correct, it indicates the implications of tying down both ends of a flexible chain molecule in a remote oxidation experiment.

Schäfer and his co-workers[144] have examined the synthetic utility of incorporating a "kink" into the hydrocarbon chain in remote oxidation experiments. Upon irradiation, the molecules 39, 40, and 41 undergo



39, X = $-OCH_2CH_2O-$

40, X =

41, X =

an intramolecular hydrogen abstraction reaction as in reaction 30. The oxygens and ester group in 39 permit additional flexibility in the chains. In the molecules 40 and 41, attachment of the reactants to the 1,2-positions of the cyclohexane or benzene rings serves to cause the chain to double back toward the reactive site. These substituents affect not only the site of maximum reaction but also the distribution of oxidation sites in the chain. Solvent effects, especially in aqueous acetonitrile, cause large enhancements in C_{eff} and small changes in the distribution of reaction sites within the chain.[144]

E. Cyclization and the Gas-Phase Conformation of Hydrocarbon Chains

The question of the conformation of hydrocarbon chains in the gas phase has generated considerable controversy. In the early 1920s Langmuir[1] proposed that because of attractive dispersion forces between the CH_2 groups, such chains would "coil up" into a tight ball in the gas phase. This suggestion was made before the existence of gauche and trans rotational isomers and rotational energy barriers were known.[147] Subsequently, a number of nondefinitive experiments led to a great deal of speculation.[148] While the question has never been fully resolved, a better understanding of the important contributions has emerged. The reader is referred to an article by Meyer and Stec[149] for a particularly lucid summary of the history of this controversy.

The problem has an importance beyond the question of chain conformation in the gas phase. Aspects of the problem bear on the question of chain folding in poor solvents and the question of adjacent reentry in polymer crystals.

In a regular solution, the dispersive attractions between chain segments is nearly balanced by interactions with solvent molecules.[58] In very poor solvents or in the gas phase one can imagine that chain folding can occur, even at the expense of configurational entropy, if the net enthalpic changes are favorable. The appropriate thermodynamics have been discussed by Liu and Ullman.[150] The question then becomes for what chain lengths can the cooperative dispersive interactions between CH_2 groups be sufficient to overcome the entropy loss on folding.

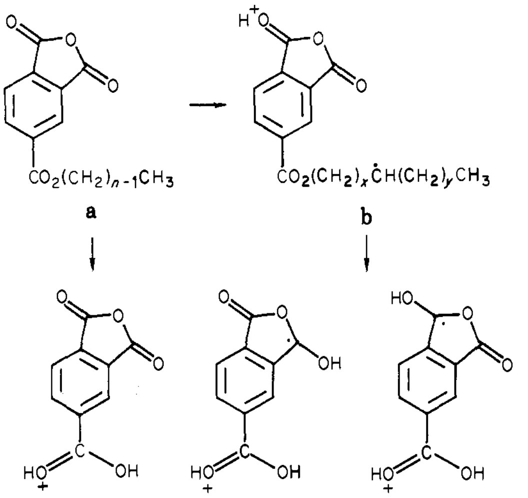
It is not widely recognized that in the absence of $g^{\pm}g^{\mp}$ sequences, *it takes 11 C–C bonds or 12 CH_2 groups for a polymethylene chain to double back 180° upon itself.* There is no particular stabilization energy associated with the 12 carbons in the loop. Consequently, for chain folding to be energetically favorable, it must involve polymethylene chains substantially longer than 12 carbons.

Lal and Spencer[136] have used a sophisticated variant of the RIS model to look at the mean shape of alkanes. Since these calculations include both the attractive and repulsive terms of a Lennard-Jones potential, they effectively simulate the gas-phase behavior of isolated chains. In their calculations, chains of 20 carbons are not seen to fold at ordinary temperatures. For hydrocarbon chains of 30 and 50 carbons, there are critical temperatures (near 100 °C for the former), at which pronounced changes in mean shape occur. Below this critical temperature, the molecule is in the form of an elongated ellipse. This cigar-like mean shape is what one would anticipate for a folded molecule. One can think of the molecule above the critical temperature undergoing internal "melting". Above this temperature $T\Delta S_{cf}$ becomes more important than the energy of interaction between the CH_2 groups. Molecular beam techniques[151] make it in principle possible to prepare samples of large molecules in the gas phase at low vibrational temperatures. It would be fascinating to see if one could use such techniques to observe this "critical phenomenon".

The mass spectrometer also provides a technique for studying large molecules in the gas phase. Until recently, it has also had the concomitant disadvantage that one could not control the internal energy of the molecular ions.[151] Thus the observed processes were convolutions of relative reaction kinetics and the distribution of internal energies in the ions. These two factors are very difficult to separate.

The mass spectrometer has been an important tool for studying cyclization reactions in the gas phase. For reactions which appear to go through medium and large rings, important papers have been published by Djerassi,[152] McCloskey,[153] Meyerson,[154] and Winnik.[155] A review has been published which suggests that such cyclizations are far more frequent and important for proton-transfer reactions in the mass spectrometer than one might otherwise have thought.[156]

Among the molecules which have been studied in the greatest detail are the *n*-alkyl esters of trimellitic anhydride,[152,154] (eq 35). Its molecular ion, a, like that of all alkyl esters, undergoes a rearrangement-fragmentation reaction to produce ions of *m*/*e* 192 and 193 whose structure has been assigned that of the protonated carboxylic acid d. In competition with this, for chains of a sufficient length, a new ion of *m*/*e* 194 appears in the mass spectrum. Its structure has been assigned as e or e′. It is thought to arise in a, where, for sufficiently long chains, cyclization and hydrogen abstraction to form b compete with fragmentation to form d. If this reaction were conformationally controlled, the ratio of ion intensities [*m*/*e* 194/(193 + 192)] would be proportional to the summed cyclization probabilities of the individual CH_2 groups in the reactive volume about the anhydride group. In accord with this picture, the ion at *m*/*e* 194 first appears in chains sufficiently long to reach the remote C=O groups, and the *m*/*e* 194/193 ratio increases monotonically with increasing chain length (Figure 26c).



a

b

d, *m*/*e* 193 e, *m*/*e* 194 e′, *m*/*e* 194 (35)

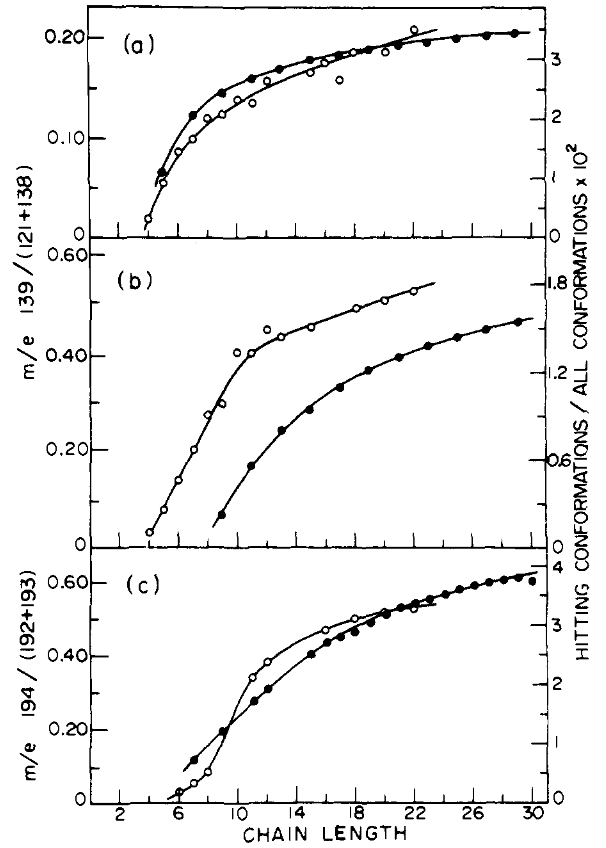
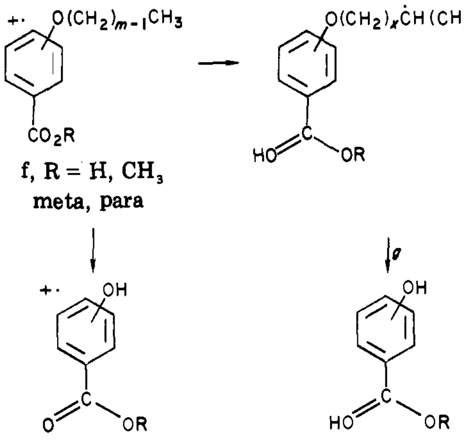


Figure 26. Comparison of the calculated summed cyclization probability ("hitting" conformations/all conformations (○)) with observed ion intensity ratios as a function of chain length in the 70-eV electron impact mass spectra of (a) *m*-alkoxybenzoic acids, (b) *p*-alkoxybenzoic acids, (c) trimellitic anhydride esters. Experimental data from ref 154 and 155. Simulations from ref 157.

Winnik, Lee and Kwong[153] have studied very similar transformations in *n*-alkyl ethers of *m*- and *p*-hydroxybenzoic acid and also in the corresponding methyl esters (eq 36). Similar kinds of observations were made. For the short-chain ethers of these species (methyl, ethyl, propyl, butyl) the ions *m*/*e* 138 (R = H) and *m*/*e* 152 (R = CH_3) are prominent in the mass spectra. These ions were assigned the respective structures h and i. For longer chains, new ions appear in the mass spectra at *m*/*e* 139 and 15, respectively. The scheme depicted for these transformations (eq 36)



f, R = H, CH_3
meta, para

h, R = H, *m*/*e* 138
i, R = CH_3, *m*/*e* 152

j, *m*/*e* 139
k, *m*/*e* 153

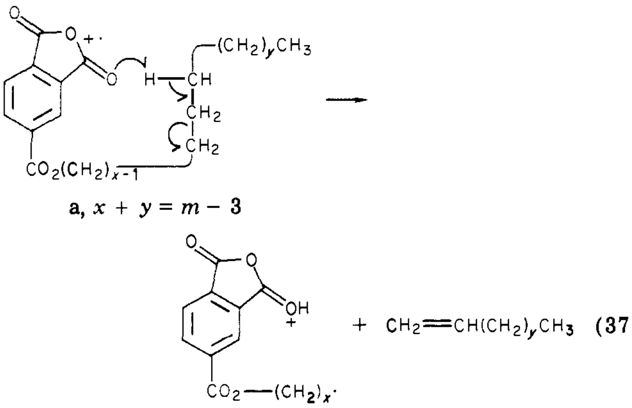
(36)

involves cyclization and intramolecular hydrogen abstraction in the molecular ions f to give the isomeric ions g in competition with rearrangement of f to form h or i. The ion intensity ratios *m/e* 139/138 and 153/152 increase with increasing chain length (Figure 26a,b), and the shapes of these plots are different for the meta- and para-substituted molecules.[156,154]

Beginning with the assumption that these chain-length-sensitive ion ratios reflected chain conformation, Winnik et al.[157] applied Monte Carlo calculations based upon the RIS model to the simulation of reactions 35 and 36. The stereochemistry of the aromatic chromophore was included into the model, and regions within 2.6 Å (two tiers of lattice sites) of the reactive carbonyl oxygen were chosen to represent the reactive volume. A cyclized configuration was counted if it had a hydrogen from a CH_2 group within the reactive volume. Partition functions were calculated for cyclized chains and for the total ensemble of chains. Their ratio gave the cyclization probability.

Good agreement was observed (Figure 26) between the chain length dependence of the total cyclization probability P_n and the chain length dependence of the $[m/(m + 1)]$ ion ratios, as long as one key feature of the reaction was included into the simulation. For this agreement to be observed, one had to assume that the molecular ions a and f, produced upon electron impact, had sufficient internal energy that the ester groups could rotate out of planarity with the aromatic ring. Such an assumption is probably justified in light of the energy distribution in the molecular ions. It would be interesting to repeat these experiments using energy-transfer techniques so that the internal energies of the initially produced molecular ions could be known with some confidence.

The preceding experiments give insights into the sum of cyclization events from all of the CH_2 groups from the chain. The reactivity of individual CH_2 groups may be inferred from an additional pathway for fragmentation of a described Meyerson, Puskas, and Fields.[154] These authors reported the observation of a series of peaks at *m/e* $[M - C_jH_{2j}]$ in the mass spectra of *n*-alkyl esters of trimellitic anhydride. They attributed these peaks to the fragmentation reaction 37, which implies that the relative intensity of each ion from a given molecule is related to the factors affecting the proximity of a CH_2 group to the anhydride function. These data and simulations of these data based upon the RIS model[157] are shown in Figure 27. These plots emphasize the relationship between the ion fragment pattern observed and the relative cyclization probabilities of individual CH_2 groups in the molecule.



(37)

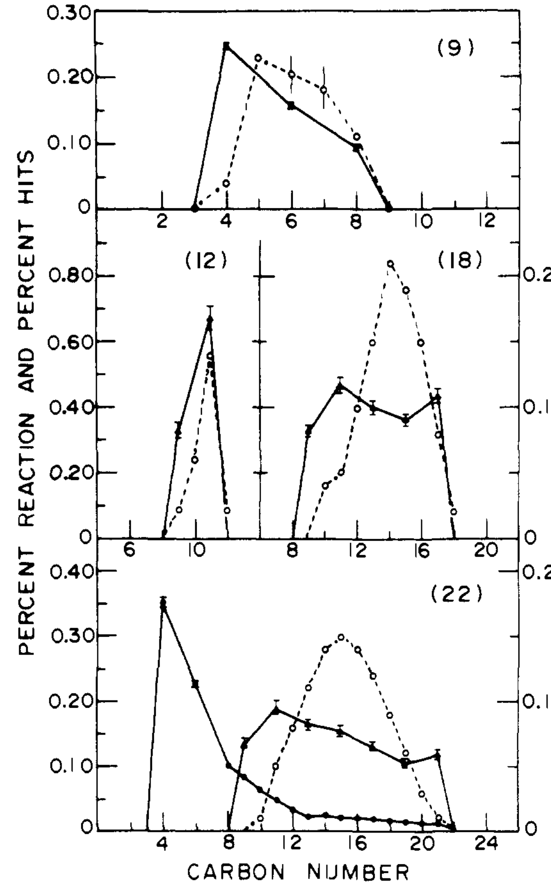


Figure 27. Percent reaction and relative cyclization probability (percent "hits") as a function of carbon number for *n*-alkyl esters of trimellitic anhydride: (○) experimental data; (●) simulated cyclization probability based upon the RIS model. For $n = 22$ the points (▲) derive from the assumption that only one of the anhydride carbonyl oxygens is reactive toward remote hydrogen abstraction. Taken from ref 157.

There is as yet no evidence on the question of whether these reactions are conformationally or dynamically controlled. At the time these reactions were studied, one did not have the necessary tools to study these reactions in the same kind of detail that one can elaborate for cyclization reactions in solution. If such techniques become available, one can imagine that the mass spectrometer will prove to be a powerful tool for the study of chain conformation and chain dynamics in the gas phase.

VII. Summary

The concepts of cyclization and chain flexibility have been linked since the earliest days of concern about conformation in chemistry. Many of the fundamental ideas were developed in the 1920s and 1930s. Although these concepts coincided with the publication of many related experiments, the experiments were simply not up to the task of evaluating the ideas critically.

The real turning point in the application of modern experimental technology to the interrelationship between chain conformation and cyclization began in 1965 with the quantitative analysis of cyclics in poly(dimethylsiloxane).[29] It was only in the 1970s that substantial advances were made in developing a quantitative understanding of the factors affecting chain cyclization. These took the form of accurate measures of ring closure reaction kinetics by Sisido[116] and by Mandolini and Illuminati,[101,102,104] application of photochemical and luminescent techniques by Winnik,[10] careful analysis of ring–chain polymerization equilibria by Semlyen,[9] and ESR studies by Shimada and Szwarc.[51,106,107]

At the same time, refinements in the RIS model by Sisido,[52] Winnik and Whittington,[65] Semlyen,[9] and Flory[29] permitted calculations based upon this model to be employed effectively in the analysis of cyclization reactions. Conformational analysis of medium- and large-ring cycloalkanes was developed, particularly through the NMR studies of Anet[90–96] and the molecular mechanics calculations of Dale.[11] There are still many unanswered questions, particularly in the relationship between cyclization kinetics and the details of the chemical reaction leading to cyclization.

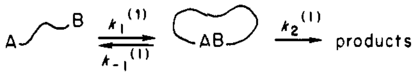
The 1970s saw the origin of the field of cyclization dynamics, with the now classic papers by Wilemski and Fixman.[69] In spite of considerable activity in the theory of cyclization dynamics, relatively few experimental studies have been published. The most promising of these involve fluorescence quenching techniques. The use of pyrene excimer formation to study end-to-end cyclization in polymers and terminally substituted alkanes was first developed by Zachariasse[125] and by Cuniberti and Perico.[118] Its application to cyclization dynamics in polystyrene was recently published by Winnik, Redpath, and Richards.[31,129] Katchalski-Katzir[132] has shown how Förster energy transfer between groups attached to the termini can be used to measure cyclization dynamics in polypeptide oligomers. An NMR technique, a CIDNP study of photochemically generated biradical cyclization by Closs,[134] and its subsequent analysis by der Hollander and Kaptein[135] provided important information on cyclization dynamics of hydrocarbon chains.

Obviously the field of cyclization dynamics is still in its infancy. One looks forward in the next 10 years to the development of new techniques and a large body of quantitative data relating cyclization dynamics to molecular structure, chain length, and solvent properties. Hopefully these experiments will be accompanied by a new generation of theoretical models—realistic models for finite chains—which will permit theory and experiment to grow together.

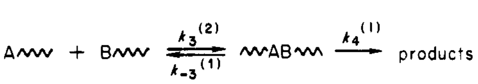
Acknowledgments. I thank my co-workers, cited in the references, for their efforts. They deserve the credit for the experiments from our research group which have contributed to the field of chain cyclization. NSERC Canada, the Research Corporation, the Atkinson Foundation, and the Petroleum Reaserch Fund, administered by the American Chemical Society, have provided generous financial support. I thank Dr. David Holden and Professors S. G. Whittington and J. E. Guillet at Toronto for their comments. Special thanks are due to Professor Herbert Morawetz of the Polytechnic Institute of New York for his constant encouragement and critical comments. This manuscript was begun at the Centre des Rescherces Paul Pascal in Talence, France, while I was on sabbatical leave in 1978. I wish to express my appreciation to Professor P. Bothorel for his kind hospitality and very helpful discussions in the entire area of hydrocarbon chain conformation.

VIII. Appendix. Diffusion-Controlled Intramolecular Reactions

A bimolecular reaction is said to be diffusion controlled if every encounter pair leads to a chemical reaction. This situation obtains for reaction 13a if $k_{-3}^{(1)} << k_4^{(1)}$ and for reaction 13 if $k_{-1}^{(1)} << k_2^{(1)}$. Typically,



(13a)



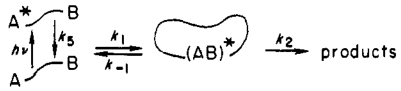
(13)

however, $k_{-3}^{(1)}$ and $k_4^{(1)}$ or $k_{-1}^{(1)}$ and $k_2^{(1)}$ differ only by one to two orders of magnitude. In a steady-state experiment, $k_{\text{obsd}}^{(1,2)}$ is still dominated by $k_1^{(1)}$ or $k_3^{(2)}$, since only the relative magnitudes of $k_{-3}^{(1)}$ and $k_4^{(1)}$ or $k_{-1}^{(1)}$ and $k_2^{(1)}$ appear in eq 13b and 13c.

$$k_{\text{obsd}}^{(2)} = \frac{k_3^{(2)}k_4^{(1)}}{k_{-3}^{(1)} + k_4^{(1)}} \tag{13b}$$

$$k_{\text{obsd}}^{(1)} = \frac{k_1^{(1)}k_2^{(1)}}{k_{-1}^{(1)} + k_2^{(1)}} \tag{13c}$$

In a time-resolved experiment the kinetics are more involved. For example, in the flash photolysis experiment analogous to reaction 13a. The excited state



(A1)

species (A*⁓B) decays as the sum of two exponentials with decay constants λ_1 and λ_2 when $k_{-1}^{(1)}$ and $k_2^{(1)}$ are comparable in magnitude. The λ's are in turn complicated functions of the rate constants. If for convenience we define $X = (k_1 + k_5)$ and $Y = (k_{-1} + k_2)$, with k_5 being the sum of first-order rate constants for decay of A* via pathways that do not involve cyclization, we can write

$$\lambda_1, \lambda_2 = \tfrac{1}{2}\{(X + Y) \mp [(Y - X)^2 - 4k_1k_{-1}]^{1/2}\} \tag{A2}$$

The reaction is diffusion controlled when $4k_1k_{-1}$ is much smaller than $(Y - X)^2$. This occurs when k_{-1} is zero. When k_{-1} is finite and within a factor of 10^2 of k_2, the extent of feedback from the cyclized form via k_{-1} contributing to the measured reaction kinetics will depend upon the magnitude of k_1. In other words, when k_1 is large, the molecules rapidly cyclize, and the fraction of excited species in the open form is very small. Even if only a small fraction of the cyclized molecules reopen to form (A*⁓B), these contribute to the time dependence of the concentration of the open form. A treatment of the data which overlooked this contribution, presuming exponential decays and diffusion-controlled cyclization, would generate k_1 values that would be too small.

In principle the same problem would occur for bimolecular reactions. One can write an equation analogous to eq A2 where the rate of reaction of A* with B is described by the product of the second order rate constant $k_3^{(2)}$ times the concentration of B present in the solution (eq A3). Here the important criteria are

$$\lambda_1, \lambda_2 = \tfrac{1}{2}\{(X + Y) \mp [(Y - X)^2 - 4k_3^{(2)}[\mathrm{B}]k_{-3}]^{1/2}\} \tag{A3}$$

the relative magnitudes of $(Y - X)^2$ and $4k_3^{(2)}[\mathrm{B}]k_{-3}$. For diffusion-controlled reactions, $k_3^{(2)}$ is always large; one accommodates this fact by working with dilute solutions of B. In bimolecular reactions, one can use the concentration of B as a variable to perform experiments under the optimum conditions for data analysis. When such experiments lead to the conclusion that the rate of a bimolecular reaction is diffusion controlled, one cannot simply assume, under the same conditions, that feedback from the cyclized form of the corresponding intramolecular reaction is unimportant.

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