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STRAIN AND REACTIVITY IN MONOCYCLIC SYSTEMS

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INTRODUCTION

The idea of strain in cyclic molecules, as a measure of their stability and, in certain respect, their reactivity, was introduced into organic chemistry by A. Baeyer in 1885. Subsequently, Baeyer's original conceptions underwent considerable modification as a result, primarily of the new theoretical ideas, developed by Sachse and Mohr and appearing in the twenties and thirties in the work of Ružicka, Hückel, etc.

The last 10–15 years have witnessed a new stage in the development of the strain theory. A vast quantity of experimental material has accumulated by the widespread use of modern methods in organic chemistry, which provide thermochemical values to a hitherto unattainable degree of accuracy, and reliable spectral and kinetic data. These data are now of paramount importance in interpreting the physical properties and chemical behaviour of cyclic molecules. Strain cannot now be regarded as a function only of the deformation of the valence angle; other types of strain can be distinguished, which are sometimes of greater importance in determining the properties of cyclic compounds. A characteristic feature of many recent chemical investigations of ring strain is that they reflect the influence of strain on chemical properties not related to the rupture or

formation of rings. This permitted a fresh approach to the evaluation and explanation of the phenomenon of strain.

It is not possible in this paper to encompass the whole mass of physical, thermochemical and chemical data connected with the history and the present state of the strain theory. For this reason, the authors, while appreciating the possibility of serious omissions, have decided to confine themselves to a consideration of what they believe to be the more interesting recent work, with only a short preface reviewing the development of the fundamental tenets of the strain theory up to the 1940's*. More comprehensive reviews of the evolution of the theory may be found in the works of Hückel[1] and Domnin[2,3].

In the first of his works devoted to strain in cyclic compounds[4], Adolf Baeyer formulated the following proposition:

"The four valencies of a carbon atom act in directions connecting the centre to the apices of a tetrahedron and form angles of 109°28' with each other. The direction of attraction can deviate, which results, however, in strain that grows with the magnitude of the deviation". Baeyer considered half the change in the angle between two bonds to be a measure of the strain.

From the outset, Baeyer realised that the theory could be verified by thermal measurements, since strain involved an increase in energy content. "Thus, for example, the heat of combustion of hexahydrobenzene should, on the earlier view, have been twice as great as that of cyclopropane; owing to the greater strain in the latter, however, it (i.e. the difference in the heats of combustion of the two compounds) should be appreciably less"[4]. Baeyer's ideas were justified by experiment (see, for example, Zubov's well-known work[5,6]), and accurate measurement of heat of combustion remains to this day the most important criterion in the study of strain in rings.

The higher energy content of a ring should, naturally, reduce its stability. Assuming that in cyclic compounds the carbon atoms lie in one plane, Baeyer concluded that a five-membered ring was the least strained (according to Baeyer, its strain was measured by the deviation of the valency bonds, equal to 0°44'). In planar six-membered and larger rings, in which the valency angle must be greater than the tetrahedral angle, the deviation of the valency bonds becomes negative**. Thus the strain in a ring increases with ring size (for a six-membered ring, the deviation is -5°16', while for a 17-membered ring the absolute value of this deviation is equal to that for cyclopropane). When Baeyer's theory was formulated, compounds containing more than seven atoms in a ring were unknown and it was considered that they could not, in general, exist, owing to the great strain involved. At the same time, as Baeyer himself indicated, there was sufficient evidence to show that, in spite of its greater strain, a six-membered ring was about as stable as a five-membered ring. In 1890, Sachse[7] showed that Baeyer's conception of a planar structure for all rings was not in any way a consequence of the tetrahedral model for a carbon atom. Furthermore, if one considered that a tetrahedral arrangement of bonds was the most advantageous, a model for any ring could be constructed, with a minimum deviation from the tetrahedral angles. Such a model would not, in general, be planar. In this way Sachse showed that Bayer's conception of a planar structure was valid only for three-, four-, and five-membered rings but not for larger rings. According to Sachse, a five-membered ring was more strained than a six-membered one, for which two "normal" (i.e. unstrained) forms were possible; he called these symmetrical and unsymmetrical (corresponding to the so-called "chair" and "boat" forms). The form in which a cyclohexane derivative existed depended, according to Sachse, on the origin and nature of the substituent. In particular, Sachse considered that the most probable form of cyclohexane itself was the symmetrical (chair) one, in which he distinguished between two types of hydrogen atom (axial and equatorial, in modern terminology). From this, Sachse concluded that it was possible for isomers of monosubstituted cyclohexanes to exist. Since his predictions of the number of isomers, based on a rigid model, were not confirmed, Sachse's work did not receive the attention that it undoubtedly merited.

It was only after Mohr[8] suggested that mutual transitions from "chair" to "boat" and from "chair" to its mirror image occurred easily that it became possible to explain the discrepancy between Sachse's predictions and the experimental data. Mohr examined in detail unstrained and non-planar models of larger rings as well as of cyclohexane (the idea of the non-planarity of larger rings was stated by Sachse only in general terms). After Mohr's work[8,9], which soon received experimental support, the idea of a non-planar structure and the absence of strain for cyclohexane and larger rings became generally accepted. The work of Böeseken on the stereochemistry of cyclic 1,2-diols[10] demonstrated that six- and seven-membered rings had such a structure; likewise, that of Hückel, who prepared *trans*-decahydronaphthalene[11], the existence of which had been predicted by Mohr. After Ružicka had shown that the natural perfumes — muscone and civetone — were macrocyclic ketones[12,13] and had synthesised a number of similar ketones[14], the question of whether many-membered rings could exist was finally settled. Macrocyclic compounds appeared to be perfectly stable[15], although in Baeyer's view they should have possessed about the same amount of strain as three- and four-membered rings. There was thus no doubt about the lack of strain and hence the non-planar structure of the largest rings. As the number of links increase, a many-membered ring compound approximates to a three-dimensional kind of linear "twofold" straight-chain macromolecule, the ends of which are connected by "half" of a six- or five-membered ring[16].

The Baeyer strain theory, supplemented by Sachse and Mohr provided the explanation of a large number of phenomena. However, new facts began to emerge quite soon, which could not be explained by this theory alone.

In 1930, Stoll and Stoll–Comte published a paper[17] in which they discussed the relation between ring-size and density of cyclic hydrocarbons. They noticed that hydrocarbons of intermediate ring-size had anomalously high densities and that their preparation by Ružicka's method gave very poor yields. From a consideration of models of cyclic hydrocarbons, made up of spheres (the diameter of the van der Waals sphere for C was taken as 1.55 Å and that for H as 2.3 Å), the authors concluded that in intermediate-sized rings a compression of the van der Waals spheres for the hydrogen atoms occurred. Somewhat later, Carothers[18] developed in detail the idea that interaction between atoms attached to the carbon chain (generally hydrogen atoms)

* In this review, we have intentionally confined ourselves to monocyclic systems and have excluded polycyclic compounds. We intended in this way to simplify the presentation as far as possible and to clarify the new ideas developed in recent years.

** Occasionally, the term "negative strain" is used in connection with six-membered and larger rings.

was the cause of interference in ring closure and of strain in already formed rings. The effective volume of the hydrogen atom used by Stoll was clearly too high, so that the idea of compression cannot be considered as substantiated. Nevertheless, the idea that interaction between atoms not directly bonded is responsible for strain, has proved extremely fruitful.

In a cyclic system, two types of interaction between atoms not directly bonded are possible: (1) transannular (across the ring, i.e. 1,3-, 1,4-, 1,5-, and 1,6-interactions); (2) vicinal, i.e. between substituents on neighbouring atoms of the ring. Those peculiarities in properties that depend on a transannular effect are more clearly manifested in compounds with an intermediate-sized ring (8–12 members), a fact that is connected with the peculiar geometry of these compounds (for greater detail, see the review by Gol'dfarb and Belen'kii[19]).

We shall consider here certain cases of the second type of interaction which depends mainly on the volume of the substituents, i.e. on purely steric factors, similar to those responsible for restricted rotation about single bonds.

Let us briefly consider the internal rotation* of a molecule of n-butane about the single C–C bond between the second and third carbon atoms. During such rotation, the butane molecule is continuously changing, forming an innumerable number of conformations**. Of these, we shall select six extreme ones. The curve in Fig. 1 shows the relation between potential energy and angle of rotation; the six conformations correspond to the maxima (eclipsed forms) and minima (staggered forms).

The difference of energy between the most favourable conformation, *d*, and the unfavourable conformations, *a* and *c* is 4 and ~3.5 kcal/mole respectively (approximate data[25]). The *gauche*-conformation *b* differs from the *trans*-conformation by only 0.8 kcal/mole.[25] From this, it is understandable why an actual molecule of n-butane (and other n-alkanes) exists almost exclusively in the staggered (*trans*- and *gauche*-) conformations.

Consideration of models of cyclic compounds, in particular cycloalkanes, shows that only for cyclohexane and for macrocyclic compounds containing more than 12 atoms in a ring is it possible to construct a molecule without energetically unfavourable eclipsed conformations[26,27]. In planar, four- and five-membered rings, as was assumed in classical stereochemistry, the carbon chain must be made up of unfavourable *cis*-conformations *a*. Just this explains why 4- and 5-membered rings are not, in fact, planar. In the "chair" form of a cyclohexane molecule, all six C–C

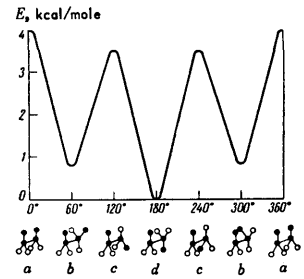


Fig. 1. Change in potential energy during the internal rotation of a n-butane molecule: *a*) cisoid conformation; *b*) skew-staggered or *gauche*-conformation; *c*) eclipsed skew conformation; *d*) transoid conformation.

bonds are in favourable, staggered conformations (the hydrogen atoms on neighbouring carbons do not face each other); in the "boat" form on the other hand, two of the six bonds are in the unfavourable conformation *a*. It is thus clear why the "chair" form of cyclohexane predominates over the "boat" form.

Seven-membered and intermediate-sized rings are energetically less favoured than six-membered ones. In the "chair" form of a cyclohexane molecule, six C–H bonds are parallel to the axis of the molecule (axial bonds), which results in a minimum interaction of axial hydrogen atoms. As the number of atoms in the ring is increased, while preserving the zig-zag form of the chain, made up of *b*-conformations, the "quasi-axial" hydrogen atoms must be displaced more and more towards the centre of the ring. However, study of models which take both covalent and van der Waal's radii into account, e.g. Stuart models, shows that only with large rings (13 links and greater) is the space inside the ring large enough to accommodate the hydrogen atoms freely, in such a way that the polymethylene chain does not contain energetically unfavourable eclipsed conformations. In this respect, macrocyclic molecules remind one of the corresponding acyclic molecules referred to earlier. In intermediate-sized rings the internal space is insufficient to accommodate all the quasi-axial hydrogen atoms while preserving the most favourable conformation of the chain. The result can be either a compression of the van der Waals radii of the hydrogen atoms and a retention of the zig-zag chain made up of *gauche*-conformations, or an alteration in the form of the chain, with the appearance of unfavourable eclipsed *c*-conformations. It is difficult to say, at present, which of these alternatives in fact happens. It is extremely probable that both can occur simultaneously. For the sake of simplicity, we shall later confine ourselves to a consideration of chain conformation as the fundamental cause of peculiarities* in chemical and physical properties

* The internal rotation of molecules has been discussed in detail in a number of reviews[20,21] and monographs[22,23] and also in the second volume of the fifth edition of A. E. Chichibabin's "Fundamental Principles of Organic Chemistry". We shall deal with this question for the sake of completeness and also to define more precisely the terms used, since, unfortunately, there is so far no generally accepted terminology in this field.

** The term "conformations" denotes those different spatial arrangements of atoms in a simple classical organic structure (configuration) that are produced by rotation or bending (but not breaking) of bonds. This definition, taken from Klyne[24], seems to us to be quite satisfactory. To avoid misunderstanding it should be emphasised that one can speak not only of a conformation of a whole molecule (e.g. the "chair" and "boat" forms of cyclohexane) but of a conformation of part of a molecule (usually, two atoms in the main chain, linked by a single bond, and their substituents).

* In particular, unfavourable conformations result in a decrease of molecular volume, which shows itself in intermediate-sized rings by an increase of density and a lowering of molar refraction. These phenomena have been particularly carefully and clearly studied for those cycloalkyl acetates which are liquid at ordinary temperatures[27].

of intermediate-sized rings. It should be noted that, apart from the compression of the van der Waals radii, the mutual approach of the quasi-axial hydrogen atoms must strengthen their interaction and therefore increase the energy content of the molecule. Consequently, one can say that both factors (interaction of the quasi-axial hydrogen atoms, i.e. transannular interaction, on the one hand and unfavourable chain conformation, i.e. vicinal 1,2-interaction, on the other) bring about an increased energy content in the intermediate-sized rings — in other words, "non-classical", conformational strain** [26,28]. What has been said above is well illustrated by the Stuart models of cyclopentane, cyclohexane, and cyclodecane (Fig. 2).

Thus, on the basis of information obtained in recent years, one can state that in addition to classical angular or Baeyer strain ("the energy increment of a compound due to deformation of the optimal valency angles" [30]), a so-called conformational strain ("that part of the energy of a compound connected with the presence of an energetically unfavourable conformation" [30]) can also be detected in cyclic systems. It should be borne in mind that, as a rule, both types of strain are present simultaneously in an actual molecule, in a state of close interaction. Thus, a cyclopentane molecule, which on the classical view is almost unstrained, proves, owing to conformational strain, to be non-planar and the non-planarity in turn results in (more accurately, it increases) angular strain.

If one assumes that the strain energy (U_{str}) of a molecule is equal to the sum of the energy of deformation of the valency angles (U_{ang}) and the energy of repulsion of the unbonded atoms (U_{rep}), it can be said that for a strained molecule, neither of the terms on the right-hand side of the equation

$$U_{str} = U_{ang} + U_{rep}$$

is equal to zero. Obviously, a real molecule will exist principally in the conformation that corresponds to the least strain energy. Physical and chemical methods, by means of which strain in rings can be detected, only give an idea of the total strain. It can only be supposed that Baeyer angular strain predominates in small rings, and conformational strain in five-membered and intermediate-sized rings.

1. PHYSICAL PROPERTIES OF CYCLIC MOLECULES AS A MEASURE OF THEIR STRAIN

Strain in rings is frequently detected by a study of certain physical properties. The determination of thermodynamic quantities, particularly enthalpy and entropy, gives valuable information, and direct determination of the geometry of a molecule by electron diffraction is also of importance. Accurate measurement of heats of combustion (Table 1) shows the presence of strain particularly clearly.

Cyclopentane and cyclohexane have been the most fully investigated, by a variety of methods. We shall therefore begin our account with these two cycloalkanes.

Electron diffraction has shown that cyclohexane normally exists in the "chair" form [41], in which the carbon chain is made up of *gauche*-conformations *b*; this is therefore more favourable than the "boat" form*. The values of the entropy and heat capacity (at constant volume) and the infra-red and Raman-spectral frequencies calculated for a "chair" model (symmetry group D_{3d}) agree well with the experimental values [42]. The heat of combustion of cyclohexane also points to the absence of strain in this compound. When calculated per CH_2 group, it is the same as that for saturated acyclic hydrocarbons. In discussing the various properties of cyclic systems related to strain, cyclohexane derivatives are used for comparison, as compounds known to be unstrained.

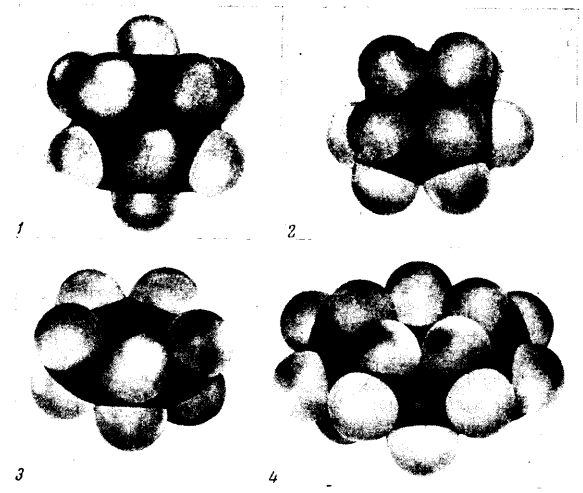


Fig. 2. 1) "Chair" form of cyclohexane; 6 axial C-H bonds parallel to the axis of the molecule, 6 equatorial hydrogen atoms arranged around the periphery; the chain is constructed of *gauche*-conformations (*b* in Fig. 1). 2) "Boat" form of cyclohexane, the chain contains 4 gauche conformations and 2 eclipsed cisoid conformations (*a*, in Fig. 1). 3) Cyclopentane (planar model); all ten hydrogen atoms are turned outwards; the chain consists of eclipsed cisoid conformations (*a*, in Fig. 1). 4) Cyclodecane (the carbon atoms lie in different planes; some of the 20 hydrogen atoms are concentrated inside the ring; the chain contains eclipsed skew conformation (*c*, in Fig. 1).

On the subject of cyclohexane stereochemistry we shall, in this review, limit ourselves to what has been said above. More detailed information may be found in numerous reviews (see, for example, ref. 43).

Cyclopentane, as has already been indicated, was for a long time thought to be unstrained. However, about 20 years ago, data emerged that entailed a reconsideration of this question. Measurements of the heats of hydrogenation of cyclopentene and cyclohexene appeared, at first sight, to be contradictory [44,45]. It might have been supposed that the

** Conformational strain is sometimes called Pitzer strain since Pitzer first compared cyclohexane and cyclopentane from this point of view [29]. In essence we are dealing here with a manifestation of steric hindrance, so that Pitzer strain can be discussed in terms relevant to this latter concept.

* The "boat" belongs to the family of so-called flexible cyclohexane conformations, which also includes the skewed or half-rotated form, discussed in recent publications (see Allinger [186] and Stolow [187] and the literature cited there).

TABLE 1. Heats of combustion of cycloparaffins.

Hydrocarbon, and the number of atoms in the ring (n)	$-\Delta H_c$ (l)	$\frac{-\Delta H_c\ (l)}{n}$	$+\Delta H_{vap}$	$-\Delta H_c$ (g)	$\frac{-\Delta H_c\ (g)}{n}$	Δ_n	$n\cdot\Delta_n$	Reference
Cyclopropane, $n=3$	—	—	—	499.85±0.13	166.6	9.2	27.6	32
Cyclobutane, $n=4$	650.22±0,10	162.5	5.56	655.78±0.16	163.9	6.5	26.0	33, 34
Cyclopentane, $n=5$	786.67±0,15	157.3	6.91	793.58±0.17	158.7	1.3	6.5	34, 35, 36
Cyclohexane, $n=6$	936.58±0,17	156.1	8.01	944.69±0.17	157.4	0	0	34, 35, 36
Cycloheptane, $n=7$	1098.9±0,15	157.0	9.42	1108.3±0.27	158.3	0.9	6.3	34, 35
Cyclooctane, $n=8$	1258.6±0,22	157.3	10.68	1269.3±0.35	158.6	1.2	9.6	34, 35
Cyclononane, $n=9$	1417.7±0,22	157.5	11.88	1429.5±0.39	158.8	1.4	12.6	34
Cyclodecane, $n=10$					158.6	1.2	12.4	37
Cycloundecane, $n=11$					158.4	1.0	10.8	37
Cyclododecane, $n=12$					157.8	0.3	3.4	37
Cyclotridecane, $n=13$					157.7	0.4	4.6	37
Cyclotetradecane, $n=14$					157.4	0.04	0.6	37
Cyclopentadecane, $n=15$					157.5	0.1	1.8	37
Cyclohexadecane, $n=16$					157.5	0.1	1.8	57

Note: $-\Delta H_c$ (l) and $-\Delta H_c$ (g) are the heats of combustion (kcal mole^{-1}) in liquid and gaseous states respectively, at 25° and constant pressure. Gaseous CO_2 and liquid H_2O are assumed to be reaction products; ΔH_{vap} is the heat of evaporation. $-\Delta H_c$ (l)/n and $-\Delta H_c$ (g)/n are the heats of combustion per CH_2 group of n-alkanes, equal to 156.26 and 157.44 kcal mole^{-1} respectively[38]. Δn is difference in the heat of combustion (in gaseous state) per CH_2 group of a given hydrocarbon and of cyclohexane (assumed to be unstrained); $n\Delta n$ is the so-called "strain", i.e. the difference between the experimental and calculated (additive) heats of combustion, assuming the increment per CH_2 group to be 157.4 kcal mole^{-1}, Old, and apparently insufficiently accurate, data on the heats of combustion of higher cycloalkanes at constant value [39,40] have not been given in the Table. However, if they are used to calculate the heats of combustion of constant pressure, good agreement with new data is obtained in a number of cases (for n = 10, 15, and 17).

conversion of a strained cyclopentene molecule to an unstrained cyclopentane molecule would be accompanied by the release of a larger amount of energy than the conversion of unstrained cyclohexene, which has a non-planar structure (for the structure of cyclohexene, see later date[46]), to cyclohexane, known to be unstrained. However, the heat of hydrogenation of cyclopentene proved, in fact, to be about 1.7 kcal/mole lower than that for cyclohexane. The explanation was found to be that cyclopentane was not unstrained[47]. Its increased energy content was attributed to the interaction of the hydrogen atoms, which, in a flat cyclopentane molecule, are in mutually eclipsing positions (conformation *a*, Figs. 1 and 2). Cohn, Kistiakowsky, and Smith[47] estimated the excess energy of cyclopentane compared to that of cyclohexane to be about 2.75 kcal per C–C bond; if one accepts the data of Dauben and Pitzer[25], this figure could be increased approximately twofold. This energy change must affect the heats of combustion, as in fact, does happen (Table 1), but it is considerably less than the values indicated for a planar model (1.3 kcal per CH_2 group, which, naturally also expresses the excess energy per C–C bond).

Aston and his colleagues obtained important data on this topic by comparing the entropy of cyclopentane, as determined by thermochemical measurements, with values calculated for various cyclopentane models: a planar model (symmetry group D_{5h}), a non-planar model with one atom outside the plane (C_s), and a non-planar model with two atoms outside the plane (C_2). The second model was found to agree best with the experimental data. The authors attributed the non-planarity of the cyclopentane molecule to mutual repulsion of the hydrogen atoms. A Raman-spectral investigation[50] also led to the conclusion that the cyclopentane molecule was probably non-planar.

After Pitzer and his colleagues[29,51] had summarised the data on electron diffraction, infra-red* and Raman spectra, and the thermodynamic functions of cyclopentane, its non-planar structure became generally accepted. The maximum deviation from planarity (referred to in the English literature as "puckering") is, in Pitzer's opinion, 0.3 Å; its

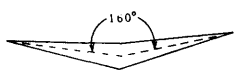
* The frequency of the infra-red absorption maximum of the carbonyl group in 5-membered cyclic ketones and lactones is appreciably higher than that in the corresponding 6-membered ring compounds. The usual explanation is that, because of the diminution of the CCC valence angle of the carbonyl group in a strained five-membered ring, the character of the hybridisation of the valence orbitals changes and causes a shift of the carbonyl absorption maximum[52]. In a recent publication[53], Hall and Zbinden tried to show that this shift depends only on a change in the character of the hybridisation, since it is also manifested by 5-membered ring compounds that, in their opinion, are unstrained; in other words, spectral data cannot indicate strain. It should be pointed out that it is not logical to consider in isolation two such closely connected factors as a change in the character of hybridisation and a diminution of the valence angle, i.e. angular strain. Hall's conclusions concerning the strain-free nature of certain 5-membered ring compounds are in error, since they are based on the inability of these compounds to polymerise. It will be shown later that no direct relation exists between strain in a ring and its tendency to polymerisation.

position is not fixed, but shifts among the five corners of the molecule. Such a shift is known as pseudo-rotation*.

Accurate measurements of heats of combustion (Table 1), have firmly established that seven-membered rings and intermediate-sized rings (8–12-membered) are strained. Similar data for macrocyclic hydrocarbons, however, clearly indicate that these are unstrained.

Further information about the presence of conformational strain in compounds containing 7-membered and intermediate-sized rings has been obtained from the heats of hydrogenation of cycloolefins in the gas phase, extrapolated to 82° (for cycloheptene and *cis*-cyclooctene)[47], and in the liquid phase at 25° (for cycloheptene[54] and the *cis*- and *trans*-isomers of cyclooctene, cyclononene, and cyclodecene[55]). All the *cis*-cycloolefins, starting from cyclohexene, and the cycloparaffins obtained from them by hydrogenation are unstrained according to the Baeyer–Sachse–Mohr conception of strain. From the point of view of classical stereochemistry, therefore, one would expect the heats of hydrogenation of *cis*-cycloolefins to be the same as those of normal *cis*-alkenes. However, this is found only for cyclohexene, whose heat of hydrogenation (28.59 kcal/mole)[47] is practically the same as that of *cis*-but-2-ene (28.57 kcal/mole)[56], and as the average value of the heat of hydrogenation of normal *cis*-olefins (28.40 ± ± 0.50 kcal/mole)**[57]. The heat of hydrogenation of cycloheptene and the other higher *cis*-cycloalkenes is lower than that of cyclohexene, which indicates that the energy content of cycloparaffins containing intermediate-sized rings is higher than that of cyclohexene and the alkenes, i.e. that the cycloparaffins are strained in the non-classical sense[55] (see the similar discussion for cyclopentane). Table 2 presents the heats of hydrogenation of *cis*-cycloolefins at 25° in acetic-acid solution with a platinum oxide catalyst[54,55].

The concept of strain in small rings has been developed somewhat in recent years. In particular, an electron-diffraction study of cyclobutane[58] showed that the four-membered ring is not quite planar, but is dihedral, with an angle of about 160° (D_{2d} symmetry). Alternatively, it could be a planar ring with low rigidity (D_{4h} symmetry) leading to large-amplitude out-of-plane bending.



This structure for cyclobutane was confirmed by comparing values of entropy obtained from experimental heat capacities and heats of transition with values calculated statistically for a planar model[59]. The observed divergence was attributed to non-planarity of the cyclobutane molecule (see the similar discussion for cyclopentane, above).

* Doubts were later expressed, based on spectroscopic studies, as to the necessity of invoking the concept of pseudo-rotation in order to explain the various properties of cyclohexane. However, new thermodynamic data indicate the validity of the original concept (see recently published work by McCullough et al[188] and the literature cited therein).

** It should be noted that the first two figures were obtained in the same experimental conditions (gas phase, 82°) while the last is for 25°. Nevertheless, it may be used for comparison, since the change with temperature of the heat of hydrogenation is less than the deviation of the calculated figures from the experimental ones (0.5 kcal/mole).

The fact that the C–C bond length in cyclobutane (1.56 Å) is somewhat greater than the normal C–C bond length, has been attributed to the mutual repulsion of unbonded carbon atoms (across the ring)[58]. It can be shown that a non-planar structure must lead to an increase of Baeyer-type strain, which is evidently compensated by a diminution of conformational strain.

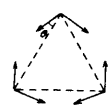
The structure of cyclopropane has been studied repeatedly, by a variety of methods. Attempts have been made to explain its high reactivity, expecially its ready isomerisation to olefins, by special features of the chemical bonds in cyclopropane compounds, as well as by the large strain of a three-membered ring.

Walsh[60] proposed the formula $CH_2{=}CH_2$ with a bond from the CH_2 group to the CH_2 group, but it did not receive recognition. Both electron-diffraction data[61] and comparison of entropy values from thermal measurements and from a statistical method[62], lead to the conclusion that all the bonds in cyclopropane are equivalent and that the carbon atoms lie at the apices of an equilateral triangle. The vibration frequencies calculated for such a model[63] agree well with the observed values.

TABLE 2. Heats of hydrogenation of *cis*-cycloolefins.

Compound	$-\Delta H_{hydrog}$ kcal mole^{-1} at 25°
Cyclohexane	27.10±0.08
Cycloheptene	25.85±0.09
cis-Cyclooctane	22.98±0.10
cis-Cyclononene	23.62±0.07
cis-Cyclodecene	20.67±0.08

Some interesting views on the nature of the chemical bonds in cyclopropane were expressed by Coulson and Moffit[64], who proceeded from the fact that in the hybridisation of valency electrons a condition of orthogonality must be observed, i.e. the angle between the hybridised orbitals cannot be less than 90°. Since, in cyclopropane, this angle should be 60°, they proposed a special system of bent valencies ("banana" bonds). Calculation showed that the most favourable angle of deviation (θ) of orbitals from the straight line joining the carbon atoms is 22°, i.e. the angle



between the directions of the valency orbitals should be $2 \times \times 22 + 60 = 104°$. Such a concept of unusual hybridisation is, in essence, a modernised expression of the Baeyer strain theory; it enables one to explain qualitatively the high reactivity of cyclopropane compounds in reactions involving ring cleavage and also the observed shortening of the C–C bonds in cyclopropane (1.53 Å[61] instead of the usual 1.54 Å).

Dyatkina and Syrkin[66] suggested that so-called three--centred orbitals exist in cyclopropane and similar compounds. Closely similar views had been expressed earlier by Walsh[66]. Byt this means it is possible to explain both the easy rupture of a three-membered ring and the conjugation of the cyclopropane group with a double bond.

A new theory of the bonds in cyclopropane and cyclobutane has recently been proposed, involving non-orthogonal orbitals[67], which shows that it is possible for a type of hybridisation to exist, in which the angle between the orbitals remains 60°. Thus the question of the special nature of the bonds in cyclopropane cannot be considered as settled.

What has been said above applied, in the main, to the simplest heterocyclic compounds. A particular feature here is that the strain in a heterocyclic compound containing oxygen or sulphur in the ring is always less than the strain in a cycloalkane with the same ring size. This is well illustrated by the thiacyclanes, for which there are fairly complete data on heats of combustion[68,69,70] (Table 3). The smaller strain in thiacyclanes is explained by the fact that the divalent sulphur atom is devoid of substituents, so that the number of interactions between non-bonded atoms is less[34]. The decrease in the conformational strain when a CH_2 group in a ring is replaced by a divalent hetero-atom can also explain the fact that the four-membered ring, trimethylene sulphide, is apparently flat[71] (C_{2v} symmetry). A five-membered ring is still non-planar in the case of the thiacyclanes, but in contrast to cyclopentane, "pseudo--rotation" is difficult in thiophane (i.e. movement of the position of greatest deviation from the plane, among the atoms)[72].

The heats of combustion of the simplest oxygen heterocycles are given in Table 4 and do not require special explanation. Unfortunately, no calorimetric figures are available for trimethylene oxide but, as far as one can judge from micro-wave[75] and vibrational spectra[76], the four-membered oxygen-containing ring has a flat structure like its sulphur analogue.

TABLE 3. Heats of combustion of thiacyclanes.

No. of atoms in ring n	Heat of combustion $-\Delta H_c$ (g), kcal mole^{-1}		Strain, kcal mole^{-1}	
	cyclanes (see Table 1)	thiacyclanes[68]	cyclanes (see Table 1)	thiacyclanes (see Note)
3	499.8	344.4	27.6	19.6
4	655.8	502.0	26.0	19.8
5	793.6	643.0	6.5	3.4
6	944.6	797.0	0	0
7	1108.3	958 5	6.3	3.9

Note. The values of the heats of combustion of the thiacyclanes are given for combustion to CO_2 (g), H_2O (l), and S (rhombic). The strain of the thiacyclanes, relative to thiacyclohexane, the strain of which is assumed to be zero, can be expressed as the difference between the observed heat of combustion and that calculated for the same, hypothetical, unstrained ring:

$$-\Delta H_{c,\text{excess}} = -\Delta H_{c_n} + \Delta H_{c_6} + (n-6)\,\Delta H_{c_{CH_2}},$$

where $\Delta H_{c,\text{excess}}$ is the strain, ΔH_{c_n} is the heat of combustion of an n-membered ring compound, ΔH_{c_6} the heat of combustion of a 6-membered ring compound and $\Delta H_{c_{CH_2}}$ the normal increment for CH_2 in cyclohexane and n-alkanes, equal to 157.4 kcal/mole (for the calculation of strain, see Skuratov et al.[73]).

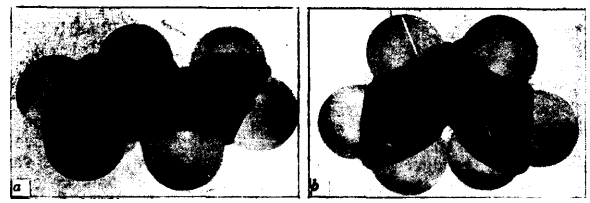


Fig. 3. Conformations of a butadiene molecule: *a*) transoid; *b*) cisoid.

TABLE 4. Heats of combustion of oxacyclanes.

No. of atoms in ring n	Heat of combustion $-\Delta H_c$ (g), kcal mole^{-1}	Strain, kcal mole^{-1}	Reference
3	312.6	26.2	74
5	605.8	4.6	73
6	758.6	0	73

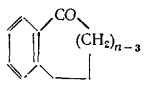
As far as the heats of combustion of the saturated nitrogen heterocycles are concerned, that of ethyleneimine is the only one that has been determined recently*[77]. Apart from this, there are some old data for piperidine[78]. If one reckons piperidine to be unstrained and takes $-\Delta H_c$ (g) for ethyleneimine and piperidine as 384.9 and 834.1 kcal/mole respectively, one can estimate the strain in ethyleneimine to be about 23 kcal/mole, a figure that is little different from those for other three-membered rings (Tables 3 and 4). Conformational strain in cyclic compounds possessing a conjugated system of double bonds takes an unusual form. It is well known that the preferred conformation of a conjugated system is a coplanar one in which the single bonds are transoid to each other. For example, Fig. 3*a* depicts such a conformation for butadiene. A *cis*-conformation for conjugated dienes is less favourable, as is clearly shown by their ultra-violet spectra (the intensity of the absorption maxima of *cis*-dienes is about half that of *trans*-dienes).

In cyclic compounds, coplanarity of the diene system is possible in only a few cases. Non-coplanarity results in an increased energy content and in partial or, with large interplanar angles, complete disappearance of the properties of a conjugated system. This variety of conformational strain is known as "steric hindrance of the delocalisation of valency electrons"[28] or "steric hindrance of mesomerism"[79]. It

* After this paper had been despatched for printing, some data on the heats of combustion of pyrrolidine have been published[189]: $-\Delta H_c$ (l) = 673.80 ± 0.1 kcal/mole; ΔH_{vap} = 8.98 ± 0.015 kcal/mole and consequently $-\Delta H_c$ (g) = 682.8 ± 0.1 kcal/mole, which agrees well with the existing data for 3- and 6-membered saturated nitrogen-containing rings.

can easily be detected with the help of ultra-violet absorption spectra, and also manifests itself in a number of chemical properties. For example, the absorption coefficient of the *cis–cis*-cycloalka-1,3-dienes decreases progressively from cyclohexadiene to cyclooctadiene[80]. In the case of *cis–cis*-cyclodeca-1,3-diene,[81] conjugation of the double bonds is not manifested at all — the ultra-violet spectrum does not contain a maximum in the 215–230 mμ region, characteristic of conjugated dienes. It is interesting to note that *cis–cis*-cyclodeca-1,3-diene[81] and *cis–cis*-cycloocta-1,3-diene[82] do not form adducts with maleic anhydride.

A similar effect is observed in a number of 1,2-benzocycl-1-ene-3-ones[83,84], 1,2-benzolactams[85] and other similar condensed compounds[79]. Thus, for the 1,2-benzocycl-1-ene-3-ones there is a decrease in the intensity of the



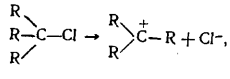
absorption maximum at 240–250 mμ, characteristic of aliphatic-aromatic ketones, as the ring size increases from 5- to 10-membered. This is explained by the increasing deviation of the plane of the carbonyl group from the plane of the benzene ring, as the ring size increases.

2. TYPES OF STRAIN. THE EFFECT OF STRAIN ON THE REACTIVITY OF CYCLIC COMPOUNDS

It has been known for a long time that ring-strain materially affects the reactivity of organic compounds. For instance, three- and four-membered ring compounds, in contrast to their higher cyclic homologues, readily take part in reactions accompanied by ring fission. This is understandable, since such reactions are accompanied by the evolution of heat (e.g. the free energy of isomerisation of cyclopropane and cyclobutane to olefins is -9.99 and -11.73 kcal/mole respectively[59], while that of cyclopentane is +5.04 kcal/mole[59]).

There are, however, much finer distinctions between the reactivities of cyclic compounds, which are found in substitution reactions and do not involve ring fission. For example, nucleophilic substitution reactions are very difficult in three-, four- and six-membered rings, and considerably easier in five- and seven-membered rings. At first glance, these differences are quite inexplicable. Neither a polar effect nor a steric effect, in its usual sense ("steric hindrance"), can explain peculiarities of this sort in the reactivity of cyclic compounds.

Some interesting and unusual ideas have been developed recently by Brown[86,87], who considers that steric factors can assist a reaction (steric assistance) as well as hinder it*. This viewpoint is reflected in his interpretation of the results of studies of cyclic systems (see below); it may be illustrated here by some data obtained by Brown and Fletcher[88] in an investigation of the effect of structure on the ease of hydrolysis of tertiary aliphatic halides. According to Brown and Fletcher this reaction, which proceeds by the



carbonium-ion mechanism, is facilitated by the decrease in strain occurring when the original strained molecule is converted to a flat, unstrained ion. It is well known that the ready hydrolysis of tertiary halides can be explained either by the total inductive effect of the three alkyl groups, which facilitates ionisation, or by stabilisation of the carbonium ion due to hyperconjugation. However, examination of the two series $(CH_3)_{3-x}(C_2H_5)_xCCl$ and $(CH_3)_{3-x}(\text{iso-}C_3H_7)_xCCl$ does not reveal the regular behaviour that would be expected on the above considerations. While, in the first series, an increase in the hydrolysis rate occurs each time an ethyl group is introduced, in the second series, exchange of one CH_3 group by an isopropyl group leads to a decrease of hydrolysis rate, while the second and third exchanges result in an increase. Whatever the nature of the effect evoked by the first isopropyl group it should have been maintained when the second and third groups were introduced. In the opinion of Brown and Fletcher[88] a steric effect is the only simple explanation of the influence on hydrolysis rate of the accumulation of isopropyl groups. Two such groups result in a crowding at the reaction centre, which facilitates ionisation.

On the basis of a great deal of experimental material, relating mainly to acyclic compounds, Brown originally introduced the idea of two types (*F* and *B*) of steric strain that became evident in a study of chemical reactivity. One of these, the so-called *F*-strain, "is an enhancement of steric strain, due to the spatial interference between groups attached to two atoms, which arises during the formation of a bond between these atoms".[86] It is usually detected in cases where the product of interaction of two molecules contains bulky substituents in the vicinity of the atoms, forming the bond between the molecules.

This may be illustrated by examples from Brown's work[86]. The basic strength of the pyridine bases increases in the order

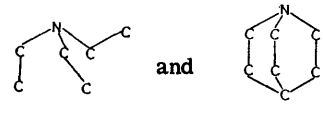
$$\text{pyridine} < \text{2-picoline} < \text{2,6-lutidine}$$

due, in the author's view, to the inductive effect of the methyl groups. This order of basicity is found in a study of the heats of reaction with a proton acid (methanesulphonic acid). However, with Lewis acids, e.g. boron trifluoride, which naturally have a larger volume than a proton, the ability to form salts increases in the reverse order. This can be explained by the repulsive forces acting between the nuclear substituents and the fluorine atoms. It is interesting that the particularly bulky trimethylboron does not react with 2,6-lutidine, or with 2-t-butylpyridine.

As a second example, triethylamine and quinuclidine may be cited. The basic strengths of these (towards a proton) are about the same, but their molecular compounds with trimethylboron differ markedly in stability:

$$(C_2H_5)_3N + B(CH_3)_3 \rightleftarrows (C_2H_5)_3N:B(CH_3)_3 + 10 \text{ kcal},$$
$$C_7H_{13}N + B(CH_3)_3 \rightleftarrows C_7H_{13}N:B(CH_3)_3 + 20 \text{ kcal},$$

i.e. the second is the more stable. The difference is due to the different spatial relationships of the substituents in the two bases:



i.e. in the first, the three ethyl groups are free to rotate about the C–N bonds, so that by their interaction with the

* It should be noted that such an idea is not new and was previously developed using hexaphenylethane derivatives as examples.

methyl groups of the trimethylboron, repulsive forces can be set up. In the second base, the substituents on the nitrogen atom are held fixed so that this sort of steric interaction is impossible.

Thus *F*-strain manifests itself as a force which hinders the formation of an addition compound or tends to separate the two parts of an existing adduct. It does not act within a molecule but in the plane between two components of a molecule ("in front") and was called *F*-strain for this reason. A characteristic of this type of strain is its dependence on the volume of both components.

Brown contrasted the concept of *F*-strain with that of *B*-strain, in connection, however, with acyclic systems. It is useful, nevertheless, to understand these concepts since they are related to other of Brown's views, discussed below. An example, quoted by Brown and his coworkers [89] will be considered. It is well known that the methylamines form a series in order of basic strength:

$$(CH_3)_2NH > CH_3NH_2 > (CH_3)_3N > NH_3.$$

The stabilities of their trimethylboron addition compounds, characterised by the dissociation pressures, are in the same order. The authors conclude that the affinity of these bases for $B(CH_3)_3$ is, on the whole, the same as their affinity for a proton, i.e. that their relative basic strengths do not depend on the nature of the acid component and hence on its steric features. Thus the degree of stability of these addition compounds must be related to the steric relationship of the groups attached to the nitrogen atom. The angle between the bonds of tetravalent nitrogen is equal to the tetrahedral angle, whereas in amines it is somewhat greater. According to Brown, the change to the ionic state here involves a diminution of the angle. This is the cause of the strain, called by the authors "*B*-strain"*. It is localised behind (hence *B*) the reactive centre, in this case the nitrogen atom and, as already stated, does not depend on the steric nature of the second component. Essentially, *B*-strain is brought about by deformation of valency angles and interaction of non-bonded atoms, i.e. by the causes responsible for the whole phenomenon of strain.

In a study of the reactivity of cyclic compounds, Brown introduced the concept of so-called *I*-strain (from "internal") [93,94]. This enables on to explain many features of the chemical behaviour of cyclic compounds and to classify much varied material.

In order to clarify what Brown meant by "*I*-strain", we shall quote some data obtained in an examination [93] of the properties of addition compounds of trimethylboron with several organic bases, and the authors' interpretation. Table 5 shows the extent of thermal dissociation of these compounds, which is a measure of their stability. The authors consider that the lower stability of the diethylamine

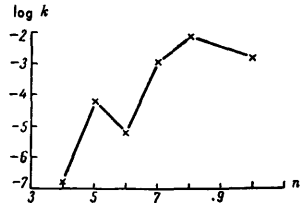


Fig. 4. Relation between the decomposition rate of azodinitriles and ring size (n).

TABLE 5. Thermal dissociation of trimethylboron complexes of amines.

Base	ΔH_{diss}	K_{diss} at 100°
Dimethylamine	19.26	0.0214
Diethylamine	16.31	1.22
Ethyleneimine	17.59	0.0284
Trimethyleneimine	22.48	0.000322
Pyrrolidine	20.43	0.00350
Piperidine	19.65	0.0210

complex compared to the trimethylamine complex can be ascribed to the greater volume of the ethyl groups. The increase of stability on passing to the piperidine complex, manifested by a fall in the rate constant and a rise in the heat of dissociation, is related to the fact that the methylene groups in a piperidine molecule are not free to rotate and cannot interact with the methyl groups of trimethylboron. Comparision of the data for the piperidine and pyrrolidine complexes shows that the second is the more stable. Since in aqueous solution piperidine and pyrrolidine have equal basic strengths, one may conclude that *F*-strain is present in these two compounds as well. In pyrrolidine its magnitude is less, because the two α-CH_2 groups are "pulled away" from the $B(CH_3)_3$ molecule to a greater extent than in piperidine — in other words, because of the smaller steric effect of two CH_2 groups in pyrrolidine. The trimethyleneimine complex with trimethylboron is even more stable, a fact that can again be explained by the geometry of the ring. However, with ethyleneimine-trimethylboron there is an unexpected decrease of stability. This points to the operation, in the three-membered ring, of another effect which becomes more important than the *F*-strain. The relative stabilities of the cyclic complexes mentioned may be expressed as the series $6 < 6 < 4 \gg 3$. The heat of dissociation of trimethyleneimine-trimethylboron is some 5 kcal greater than that of ethyleneimine-trimethylboron. *F*-strain should be less in ethyleneimine. Consequently, the 5 kcal must be ascribed to some other form of destabilisation. The authors of the work quoted consider that this is caused by the so-called internal strain of the ring, brought about by the change in the valency angle when the free cyclic imine is converted to a compound containing a tetravalent

* There are comparatively few data, in the literature, concerning the magnitude of the valency angle of nitrogen in amines, and these are insufficiently accurate and frequently contradictory. For example, two values are quoted [90] for the CNC angle in dimethylamine: 108° ± 4° and 111° ± 3°. It may be said that in the case of the methylamines, the observed deviation from the tetrahedral angle is within the experimental error. There are therefore good grounds for the view that β-strain is negligible in the methylamines and that the anomalies referred to cannot be ascribed to its influence [91,92]. At the same time, in highly branched tertiary amines, *B*-strain may exert an appreciable influence on reactivity; however, this has not yet been confirmed experimentally.

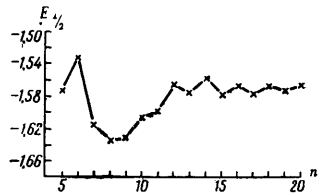
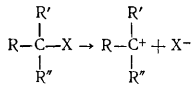


Fig. 5. Dependence on ring size (n) of the half-wave potential ($E_{1/2}$) for the polarographic reduction of the products of reaction between cyclic ketones and Girard's reagent T.

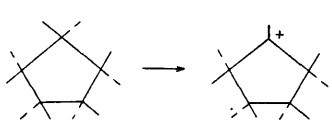
nitrogen atom. For such an atom, the tetrahedral disposition of valencies will be the most stable. Thus the strain in ethyleneimine-trimethylboron is measured by 109°28'–60°, exceeding the strain in free ethyleneimine, which, from a quantum-mechanical picture of a nitrogen atom, was estimated to be 90°–60°. All that has been said throws some light on the following definition:

"I-strain is the increase of internal strain of a cyclic structure, brought about by the disturbance of valency angles and conformations that accompany a change in the coordination number of an atom in the ring during reaction"[86].

Several examples from the carbocyclic field will serve as further examples. The monomolecular reaction of nucleophilic substitution (S_N1) proceeds via the formation of a carbonium ion:



There is thus a change in the coordination number of carbon from 4 to 3. What effect does this have on the strain of a cyclic compound, if the carbon atom affected forms part of a ring? An atom with a coordination number of 4 is tetrahedral with an optimal valency angle of 109°28'; for a coordination number of 3, planar symmetry with a valency angle of 120° is the most favourable. In small rings (three- and four-membered), where Baeyer strain plays an important part, such a change of valency angle must lead to increased strain. In fact, with the optimal angle of 109°28', the change of valency angle in a three-membered ring is 109°28'–60° = 49°28'; with an angle of 120°, this change is greater, viz. 120°–60° = 60°. In 5-, 7-membered, and intermediate rings, the chief source of strain is interaction between non-bonded atoms. For example, the idealised planar structure of cyclopentane contains 5 unfavourable eclipsed conformations, or, in Brown's terminology, there are in such a ring 10 interactions brought about by C–H bond oppositions; this gives rise to the strain in a five-membered ring. When one hydrogen atom is removed, the number of C–H bonds is 9, while the "number of interactions" between neighbouring, mutually eclipsed hydrogen atoms, is 6. As a result there is a considerable decrease of conformational strain.

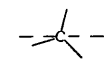


Brown's opinion concerning a six-membered ring is that a change of coordination number from 4 to 3 is in this case unfavourable as it leads to a less symmetrical system, in which "bonds of positions" make their appearance.

The reverse process, i.e. increase of coordination number from 3 to 4, e.g. by addition to a C=O group, is facilitated in six-membered and small rings since it is associated with a decrease of strain, while in 5-membered, 7-membered, and intermediate-sized rings it is less favourable.

It is natural to suppose that, if the change of coordination number occurs at the rate-determining stage of a reaction the associated change of internal strain of the ring will affect the reaction kinetics. There are, in fact, many examples in which the ratio of reaction rates for different rings is in good agreement with predictions of the I-strain theory. This applies not only to addition to carbonyl groups and S_N1 reactions but also to radical reactions and S_N2 reactions.

In the case of radical reactions, the above discussion of S_N1 reactions also applies. In S_N2 reactions, the transition complex has a coordination number of 5. For small rings, the effect of changing the coordination number from 4 to 5 is the same as changing it from 4 to 3, since the three groups not participating in the substitution process are arranged



in one plane with a central atom, while the valency angle is 120°. For rings in which conformational strain is predominant, this picture may be somewhat distorted owing to interaction of the fifth ligand with non-bonded atoms, i.e. the acceleration of a reaction, in comparison with a six-membered ring, is appreciably less than in an S_N1 reaction.

TABLE 6.

Type of reaction	Rings						
	small		normal		intermediate		large
	3-	4-	5-	6-	7-	8- to 12-	13- and larger
S_N1, S_N2, and free radical	very slow	slow	fast	slow	fast	fast	medium rate
Addition to carbonyl group	very fast	fast	slow	fast	slow	slow	medium rate

Thus, the size of the ring can affect reaction rate in different ways, depending on the type of reaction[86] (Table 6).

A number of examples illustrating the effect of I-strain on reaction rate will now be considered. It has been known for some time that many nucleophilic substitution reactions proceed slowly with cyclopropyl, cyclobutyl, and cyclohexyl derivatives and considerably faster with derivatives of other rings. Thus Gustavson[95] in 1891 found that chlorocyclopropane reacted with great difficulty with alcoholic caustic potash; according to his estimate, the reactivity of chlorocyclopropane in this reaction was even lower than that of 1-chloroprop-1-ene, which contains a vinyl chlorine atom. At about the same time, Perkin[96] drew attention to

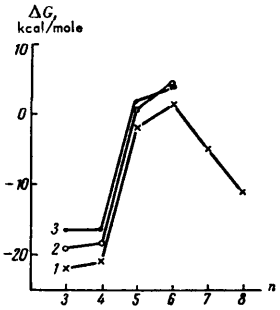


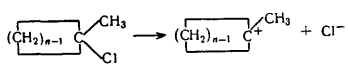
Fig. 6. Semi-empirical values of the free-energy change for the hypothetical polymerisation of cycloalkanes: 1) unsubstituted cyclanes; 2) methyl-substituted cyclanes; 3) 1, 1-dimethyl--substituted cyclanes.

the low rate of reaction between chlorocyclobutane and potassium iodide. Chlorocyclohexane also exhibits an anomalously low reactivity towards potassium iodide[97]; the rate constant of this reaction is more than 150 times smaller than in the case of isopropylchloride, chosen as an example of a secondary aliphatic chloride. Cyclohexyl halides react appreciably more slowly with pyridine and piperidine than do secondary aliphatic halides[98]. A comparison of the reactivity of cyclopentyl, cyclohexyl, and cycloheptyl bromides with various bases[99] showed that cyclohexyl bromide was the least reactive in these reactions and cyclopentyl bromide the most reactive.

The kinetics of S_N1 reactions of various rings have been studied in detail for the solvolysis (with acetic acid) of 1-chloro-1-methylcycloalkanes (Table 7) and cycloalkyl-*p*--toluenesulphonates (Table 8).

The kinetics of S_N2 reactions have been studied in comparatively few cases. In the literature, there are data for the reaction of cyclic bromides with potassium iodide in acetone[101,104,105] and the exchange of iodine in cyclic iodides, using labelled iodine[106] (Tables 9 and 10)*.

TABLE 7.



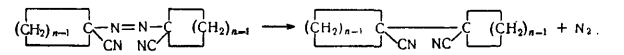
(from data of Brown and Borkowski[100]).

n	k_1, h^{-1}, at 25 °C	Relative rate
4	0.00224	0.211
5	1.32	124
6	0.0106	1.00
7	1.15	108
8	3.03	286
9	0.465	43.9
10	0.188	17.7
11	0.127	12.0
13	0.0302	2.85
15	0.0192	1.81
17	0.0201	1.90
$(CH_3)_3$ CCl	0.0302	2.85

* After this paper had been despatched for printing, some new work appeared[190] which substantially supplemented the existing data on the kinetics of S_N2 reactions for cyclic compounds and confirmed the earlier conclusions about the reactivity of compounds with rings of different size in this type of reaction.

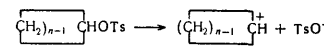
Radical reactions of cyclic compounds, involving a change in the coordination number of an atom in the ring, have been comparatively little studied. However, such data as exist are apparently not inconsistent with the *I*-strain concept. Thus an investigation of the kinetics of hydrogen removal by a methyl radical from cycloalkane molecules[107,108] showed that reactivity varied with the size of the ring, in the order $C_5 > C_6 > C_4 \gg C_3$.

Some very interesting results were obtained by Overberger and coworkers from a study of the kinetics of the decomposition of azodinitriles, containing cyclic groups[109]:



It had been shown earlier that this radical reaction was

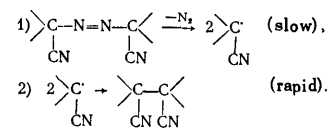
TABLE 8.



n	Relative rate at 70°C	Reference
3	$2 \cdot 10^{-5}$ (at 60°C)	101
4	11.3	102
5	14.0	102
6	1.00*	102
7	25.3	102
8	191	102
9	172	102
10	380	103
11	48.9	102
12	3.25	102
13	3.50	102
14	1.32	102
15	2.19	102
17	2.17	102
20	1.80	103

* $k_1 = 2.37 \cdot 10^{-5}$ sec^{-1}; for $(n\text{-}C_3H_7)_2$ CHOTs the relative rate was found to be 1.33.

of first order:



It is easy to see that the slow step, which determines the reaction rate, involves a change in the coordination number of the carbon atom from 4 to 3. It is not surprising that the rate of this reaction depends substantially on the size of the ring. The results obtained[109] are in good agreement with the concept of *I*-strain (see Table 11 and the curve in Fig. 4).

It is particularly important that the rate of decomposition of the azodinitriles does not depend on the solvent[111], so that a solvent effect, which can affect reaction rate to such a great extent, is in this case absent. According to Overberger[109], the rate of decomposition of azodinitriles

TABLE 9.

$$(CH_2)_{n-1}CHBr + I^- \rightleftharpoons (CH_2)_{n-1}CHI + Br^-$$

n	$k_2 \times 10^5$, litres mole^{-1} sec^{-1}, at 25°C	Reference
3	no reaction even at 100°	101
4	0.00980	104
5	2.08	104
6	0.0129	104
7	1.27	104
8	0.69	105

is an accurate measure of the differences in the strain of rings.

Reactions involving addition to a carbonyl group proceed at noticeably different rates for rings of different size. For example, the formation of phenylhydrazones[112], oximes[113], and semicarbazones[114], which can be represented as additions to a carbonyl group followed by elimination of water,

$$R_2C{=}O + H_2N{-}X \rightleftarrows R_2C(O^-)(\overset{+}{N}H_2{-}X) \xrightarrow{-H_2O} R_2C{=}N{-}X,$$

and the formation of bisulphite derivatives[113], proceed fastest with cyclohexanone, slower with cyclopentanone, and slower still with cycloheptanone. The same order of reactivity, i.e. $C_6 > C_5 > C_7$, is found in the reaction of perbenzoic acid with cycloalkanones[115] (Table 12).

This reaction proceeds according to the scheme:

$$1)\ >C{=}O + C_6H_5COOOH \rightarrow >C(OH)(OOCOC_6H_5) \quad \text{(slow)},$$

$$2)\ >C(OH)(OOCOC_6H_5) \rightarrow >C(OH)(O^-) + C_6H_5COO^- \quad \text{(rapid)},$$

$$3)\ >C(OH)(O^-) \rightarrow >C{=}O + H^+ \quad \text{(rapid)}.$$

Thus, additions to a carbonyl group also proceed fastest with cyclohexanone.

Naturally, for the reverse reaction (dissociation to form a carbonyl group) the order is reversed. For example, the dissociation constants of the hemiketals of cyclic ketones[116] clearly indicate that the hemiketals of cyclobutanone and cyclohexanone are much more stable than those of other cyclic ketones or of aliphatic ketones (Table 13).

We may note that the dissociation constant of the hemiketal of di-n-propyl ketone was found by Wheeler[116] to be 89.0. Also, cyclopropanone is quite unknown in the free state and exists only as the hydrate and the hemiketal. Attempts to prepare the semicarbazone lead to rupture of the three-membered ring[117].

The addition of hydrogen (hydrogenation with sodium borohydride[118], see Table 14) and hydrogen cyanide (for dissociation constants of cyanhydrins[119], see Table 15) to carbonyl groups have been studied in great detail.

The latter data are particularly interesting since they refer to an equilibrium and hence characterise the relative stabilities of the components. The Table shows that with intermediate rings, the keto-form is the most stable; this conforms to the ideas of *I*-strain.

Results consistent with the idea of *I*-strain were also obtained by the polarographic reduction of the products of the reaction between Girard's reagent T and cyclic ketones[120] (Fig. 5). The mechanism of this reaction may be represented as follows:

$$1)\ >C{=}NNHCOCH_2\overset{+}{N}(CH_3)_3 + H^+ + e^- \underset{\text{reversible}}{\rightleftarrows} >\dot{C}{-}NHNHCOCH_2\overset{+}{N}(CH_3)_3,$$

$$2)\ >\dot{C}{-}NHNHCOCH_2\overset{+}{N}(CH_3)_3 + H^+ + e^- \xrightarrow[\text{irreversible}]{} >CHNHNHCOCH_2\overset{+}{N}(CH_3)_3.$$

In this case, the half-wave potential (i.e. the energy used for reduction and hence for changing the coordination number of carbon from 3 to 4) is least for a six-membered ring and greatest for intermediate-sized rings.

I-strain is only one of the factors that determine relative reaction rates of cyclic compounds. Remarking on this, Brown[100] pointed out that such factors as *F*-strain, solvation, the influence of neighbouring groups, etc., can play an important and sometimes predominant part. Accurate accounting for all these factors is extremely difficult, so that it is not surprising that the nature of the relation between reactivity and ring size is different for different reactions and different types of cyclic compound. For instance, the rate of solvolysis of 1-chloro-1-methylcyclobutane in acetic acid[100] is considerably less than the rate of solvolysis of the five-membered 1-chloro-1-methylcyclopentane and less than that of the six-membered ring; at the same time, for solvolysis of chlorocycloalkanes in 50% ethanol[101], the reaction rate for the four-membered ring is three times as fast as that for the five-membered ring and forty times as fast as that for the six-membered ring.

TABLE 10.

$$(CH_2)_{n-1}CHI + I^{*-} \rightleftarrows (CH_2)_{n-1}\dot{C}HI + I^-$$

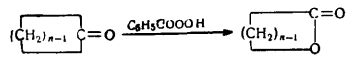
(from data by Van Stratenetal.[106])

n	5	6	7	8	15
k_2, litres mole^{-1} sec^{-1} at 25°C	0.88	0.0084	1.2	0.28	0.099

TABLE 11. Kinetics of decomposition of azodinitriles[109].

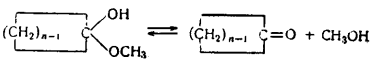
n	$k_1 \times 10^4$, sec^{-1}, at 80°C	$\Delta E_{act.}$, kcal mole^{-1}
4	0.00173	32.1±1.0
5	0.726	33.8±0.9
6	0.063	35.4±0.6
7	12.22	27.5±0.9
8	83.5	25.9±0.9
10	18.42	28.0±0.7

TABLE 12.



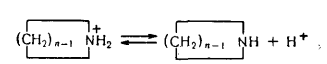
n	5	6	7
$k_2 \times 10^5$, litres mole^{-1} sec^{-1}, at 27°C	17.3	106	1.69

TABLE 13.



n	4	5	6	7	8
k_{diss} at 25°C	1.11	15.1	2.16	53.5	268

The relation between the basicities of the cyclic imines, determined by the equilibrium constant of the reaction*



can be explained fairly easily on the basis of *I*-strain, for $6 \leqslant n \leqslant 20$.[121] Piperidine is the most basic in this series; this corresponds to the greater stability of a tetrahedral nitrogen atom in a six-membered ring, compared to one in other rings. The intermediate-sized rings are the least basic, i.e. nitrogen with a coordination number of 3 is here relatively more stable. At the same time, examination of the basic strengths of the cyclic imines having $3 \leqslant n \leqslant 6$ [122] shows that they are similar for n = 4, 5, 6 while for ethyleneimine K_b is anomalously low (Table 16).

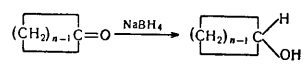
Brown attempted to explain the different basic strengths of the imines (in their reaction with trimethylboron, see Table 5) [95] by the competing influences of *I*- and *F*-strain. Searles et al.[122] consider that these differences are determined by the nature of the electron-density distribution in the cyclic-imine molecules. In this case, it would appear that both steric and polar factors play an important part. The importance of steric factors is evident, if only from the fact that the relation between ring size and basic strength determined by the dissociation constants of the trimethylboron complexes, differs from that for proton-addition.

In some cases, the influence of polar factors can be taken into account. For example, the data on the rates of alkaline hydrolysis of lactones[123,124] (Table 17) clearly fall into two groups. Lactones with a ring-size of up to 8 members hydrolyse relatively quickly. Those with 10–16-membered rings hydrolyse at rates some hundred of times slower. This phenomenon was explained by the fact that the ester group has different conformation, depending on the ring size[79,124]. In rings of the usual size, the energetically more favourable planar transoid conformation, inherent in esters, cannot exist since it would involve considerable



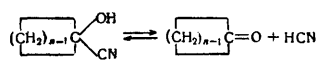
deformation of the valence angles. The cisoid ester conformation has an excess of free energy of about 3.6 kcal/mole over the transoid. The greater reactivity of lactones with usual-size rings compared to aliphatic esters is thus understandable. In lactones with intermediate-sized and large rings, the transoid ester conformation can exist. Their hydrolysis rates are closely similar to those of acyclic esters. A comparison of the dipole moments and boiling points of lactones shows that the change from a cisoid to a transoid conformation occurs between an eight- and nine-membered ring. An eight-membered lactone is mainly in the *cis*-form with a small amount of the *trans*-form present, while with a nine-membered lactone, the *trans*-form predominates. We may note that the relation between rate of

TABLE 14.



n	$k_2 \times 10^4$ litres mole^{-1} sec^{-1}, at 0°C	ΔE_{act}, kcal mole^{-1}
4	264	8.6
5	7.01	9.8
6	161	5.8
7	1.02	10.2
8	0.0781	11.9
9	0.0316	12.2
10	0.0132	13.1
11	0.0235	12.0
12	0.182	11.3
13	0.194	11.8
15	0.420	11.5
17	0.593	10.7
di-n-hexyl ketone	0.454	11.5

TABLE 15



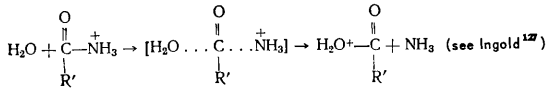
n	$K_{diss} \times 10^2$ at 22°-23°C	ΔG, kcal mole^{-1}
5	2.1	−2.4
6	0.1	−4.2
7	13	−1.3
8	86	−0.1
9	170	+0.3
10*		
11	112	+0.1
12	31	−0.7
13	26	−0.8
14	6	−1.7
15	11	−1.4
16	9	−1.5
17	12	−1.3
18	10	−1.4
19	10	−1.4
20	7	−1.6
di-n-octyl ketone	7	−1.6

* The constant for this reaction characterises the acid dissociation constant of the corresponding cation, i.e. it is smaller the more basic the amine. The constants in Table 16 appear to be true basic dissociation constants, i.e. they correspond to the reaction $RNH + H_2O \rightleftharpoons RNH_2^+ + OH$ (Ed. of Translation).

* K_{diss} for the cyanhydrin of cyclohexanone is very large. Its value could not be accurately determined because the equilibrium mixture contains practically no cyanhydrin.

hydrolysis and ring size for cisoid lactones confirms the idea of *I*-strain (a maximum for six-membered and small rings).

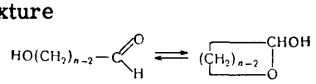
The rates of alkaline hydrolysis of five-, six-, and seven--membered lactams bear the following relation to ring size[125]: $6 > 5 > 7$. This can be explained from the point of view of *I*-strain, in a similar way to the alkaline hydrolysis of lactones. Similar results were obtained from a study of the kinetics of acid hydrolysis of lactams with rings of from 5 to 8 members. The rates of hydrolysis for the eight-, five-, seven-, and six-membered lactams were in the ratio 1.1 : : 2.1 : 4.75 : 17.5 respectively. If the acid hydrolysis of amides proceeds via proton addition to the nitrogen atom (rapid stage), while the slow, rate-determining step involves the formation of a complex in which the carbonyl carbon has a coordination number of 4



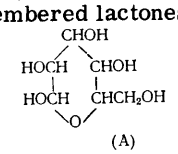
it is possible to explain the observed relative reaction rates from the point of view of *I*-strain.

The conception of *I*-strain arose following the analysis of a large quantity of material concerning the reactivity of various cyclic systems. Naturally, the most detailed data available were those for five- and six-membered rings. Consideration of these data led Brown to a further generalisation[128] concerning the relative stability of five- and six--membered rings. "An exocyclic double bond in a five--membered ring is less reactive and more stable than a corresponding exocyclic double bond in a six-membered ring. Reactions which involve the formation or retention of an exocyclic double bond in a five-membered cyclic derivative will be facilitated relative to the corresponding reactions which involve formation or retention of an exocyclic double bond in a six-membered cyclic derivative. Reactions which involve loss of an exocyclic double bond will be more favoured in a six-membered ring compound than in the corresponding five-membered ring compound"[129]. This conclusion is evidently supported by the data quoted above, concerning the reactivity of cyclic ketones in reactions involving the keto group.

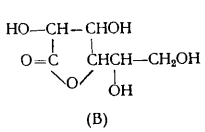
It is interesting to compare the data concerning ring--fission in five- and six-membered heterocycles containing an exocyclic double bond and in saturated compounds. It has already been noted that five-membered lactones are more stable to hydrolysis than six-membered ones. However, the internal cyclic hemiacetals of ω-hydroxyaldehydes which contain a six-membered ring are more stable than those which contain a five-membered ring[130]. The equilibrium mixture



contains 11.4% free aldehyde when $n = 5$ and 6.1% when $n = 6$. Thus, in the absence of an exocyclic double bond a six--membered ring is more stable, otherwise, a five-membered ring. Brown thus explains the fact that sugars (hydroxyaldehydes) prefer to form six-membered pyranose (A) rings, while the saccharic acids (hydroxyacids) prefer five-membered lactones (B):



(A)



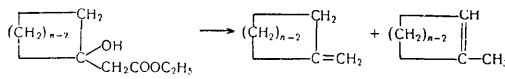
(B)

TABLE 16. Basic dissociation constants of cyclic imines.

n	$K_b \times 10^4$, at 25°C
3	0.011
4	20
5	18
6	16.6

It must not be concluded that five-membered ring compounds with an exocyclic double bond are generally more stable than their isomers with an endocyclic double bond, or that for six-membered rings, the *exo*-form is always less stable than the *endo*-form*.

It should be pointed out that, even in its strictest sense, Brown's generalisation does not always prove to be correct. Thus, the mixture of olefins, obtained by heating the esters of cycloalkanolacetic acids[133]:

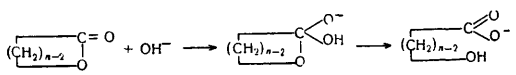


contains less of the *exo*-isomer with a five-membered ring than with a six-membered ring, not more, as should be the case according to Brown (39% for $n = 5$ and 62% for $n = 6$). The ease of isomerisation of the exocyclic isomer to the endocyclic isomer is about the same in both cases.

A study of the heat of hydrogenation of exo- and endocyclic olefins[134] (Table 18), showed that the *exo*-form is relatively less destabilised with a six-membered ring than with a five-membered ring. As Table 18 shows, the difference between the heats of hydrogenation of *exo*- and *endo*-isomers, brought about by the greater energy content of the *exo*-form (or, its lower stability), is greater for

* Similar incorrect interpretations of Brown's views have been repeatedly met with in the literature (see, for example, Fleck[131]). This can largely be attributed to lack of clarity in their formulation and to an insufficiently critical selection of material in the paper by Brown and collaborators[128], which generalised the properties of 5- and 6-membered rings. In the principal works devoted to *I*-strain, Brown links kinetic data inseparably to reaction mechanism, which enabled him to create an extremely orderly system of ideas. On the other hand, in the paper referred to[128], a large number of facts are presented, relating to various classes of compounds and concerning the relative stability of 5- and 6-membered rings, without a detailed discussion of the corresponding reaction mechanism. It is not surprising that such a one-sided approach should occasionally lead to contradictions. For example, Brown[128] points to the tendency of δ-valerolactone to polymerise and to the absence of a similar tendency in γ-butyrolactone as facts confirming the relatively greater stability of five-membered rings with an exocyclic double bond compared to six-membered ones. It would seem that a similar relationship should exist for the lactams. In fact, however, α-pyrrolidone polymerises much easier than α-piperidone[132]. Polymerisation processes are extremely complex and, without a thorough study of their mechanism, it is not permissible to make any broad generalisations about different classes of chemical compounds.

TABLE 17.



(hydrolysis by NaOH in water-dioxane medium according to data of Huisgen and Ott[124]).

n	$k_2 \times 10^4$, litres mole^{-1} sec^{-1}, at 0°C	Dipole moment in benzene D	$B.p.$, at 10–11 mm Hg, °C
4	350 000 (at 20°C) [123]	3.8	51
5	1 480	4.09	79–80
6	55000	4.22	97–98
7	2 550	4.45	104–106
8	3 530	3.70	80–82
9	116	2.25	72–73
10	0.22	2.01	86–87
11	0.55	1.88	100
12	3.3	1.86	116
13	6.0	1.86	130
14	3.0	1.86	143
16	6.5	1.86	169
n-butyl ester of caproic acid	8.4	1.79	83°

TABLE 18. Heats of hydrogenation of *exo*- and *endo*-isomers.

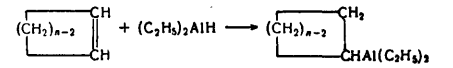
Olefin					
	exo-	$CH_2=$	$CH_2=$	$CH_3CH=$	$CH_3CH=$
	endo-	CH_3-	CH_3-	CH_3CH_2-	CH_3CH_2-
$\Delta H_{hydrog.}$, kcal mole^{-1}, at 25°C		−26.9 −23.0	−27.8 −25.4	−24.9 −23.6	−26.3 −25.1

five-membered rings than for six-membered rings; this clearly contradicts Brown's views.

It should be borne in mind that not all reactions that involve a change of coordination number can be fitted into the scheme of *I*-strain. The reaction mechanism, which is frequently not known, evidently plays an important part. We have seen that addition to carbonyl groups proceeds according to predictions based on the concept of *I*-strain. It would seem that reactions involving addition to various reagents to C=C double bonds should also proceed faster with six-membered rings than with others (at least for the *cis*-cycloolefins free from Baeyer strain). In fact, just the reverse is observed. If the rate constants for the addition of diethyl aluminium hydride to *cis*-cycloolefins[135] are examined (Table 19), it turns out that the reaction is slowest with six-, ten-, and eleven-membered rings. The same relationship holds for the addition of hexachlorocyclopentadiene to *cis*-cycloolefins[135] (Table 20); in this reaction, the cycloolefin acts as the dienophile.

Similar correlations are encountered in the addition of silver nitrate to *cis*-cycloolefins[136]. Even if the greater reactivity of cyclobutene and cyclopentene can be ascribed to Baeyer strain, the reason for the reactivity of *cis*-cycloolefins with 7–9 atoms in the ring remains obscure.

TABLE 19.



n	4	5	6	7	8	9	10	11
$k_{1,-1} \times 10^4$, min^{-1} at 78°C	180	35	4	65	80	25	3	5

TABLE 20. Addition of hexachlorocyclopentadiene to *cis*-cycloolefins.

n	5	6	7	8	9	10
$k_1 \times 10^4$, min^{-1} at 78°C	90	4	120	300	60	3.7

To sum up, it can be said that the present concept of *I*-strain is not universally applicable and requires a more precise definition. However, it is extremely useful for the systematisation of the various reactions of cyclic compounds and, when other factors (both steric and polar) are taken into account, makes possible successful explanation of certain peculiarities in the chemical behaviour of various cyclic compounds.

3. RING FORMATION AND CLEAVAGE; THEIR RELATION TO STRAIN*

It is well known that ever since the formulation of the Baeyer theory, the idea has taken root of a direct relation between the ease of formation and cleavage of rings, on the one hand, and their strain, on the other. It was supposed that the probability of forming a ring from an acyclic compound and its stability to ring-cleavage reactions were less the greater the strain of the ring. It should be pointed out that at the time when the strain theory was formulated macrocyclic compounds were quite unknown, while the few compounds with three-, four-, and seven-membered rings that had been obtained appeared to be exceptions which only lent support to the general rule that such rings were unstable and tended not to be formed. However, the development of alicyclic chemistry towards the end of the last century and the beginning of the present one revealed the inadequacy of these ideas.

Advances in the synthesis of three- and four-membered rings (the work of G. G. Gustavson and W. Perkin, Jr. should be particularly mentioned) and the work of V. V. Markovnikov in the field of seven-membered rings, made these compounds available, and N. Ya. Dem'yanov's investigations of the isomerisation of cyclic compounds showed that there was no impassable gulf between rings of different size. In spite of the fact that large rings were still unknown, doubts arose in view of the fairly stable nature of seven-membered rings, of the existence of Baeyer "negative strain" in all rings containing more than five atoms.

* Ring formation under the conditions of gas-phase heterogeneous catalysis is beyond the scope of this paper and requires special consideration.

It was mentioned earlier that conformational strain is inherent in seven-membered and intermediate-sized rings, which according to Sachse and Mohr are free of angular strain, and in five-membered rings; this results in an increase of energy content (Table 1). It would be natural to suppose that, like angular strain, conformational strain should exert a definite influence on the stability of rings in various chemical reactions. However, since the rupture of a C–C bond requires an extremely vigorous attack on a molecule, small differences of energy can remain undetected. At the same time, ring cleavage in a number of heterocyclic compounds is generally much easier, and the relation between ease of cleavage and ring size shows more clearly. It must be borne in mind that a direct variation of ease of ring cleavage with strain can only be expected when the ring-cleavage step is the slowest. In general, data about the stability of rings, based on the rates of cleavage, give no indication of the amount of strain. For example, hydrolysis of six-membered lactones and lactams, as was mentioned earlier, is considerably faster than that of the five- and seven-membered compounds. However, it would be wrong to assert in this connection that six-membered rings are more strained than five- or seven-membered rings. The observed relation between rate of hydrolysis and ring size can be explained by the concept of *I*-strain, inasmuch as a change in the coordination number of an atom in the ring occurs in the rate-determining stage of the reaction, while the subsequent ring cleavage proceeds at a faster rate. In certain cases, apparently, there is a direct relationship between the stability and the strain of a ring. This was observed, for example, in an investigation of the thermal dissociation of cyclic polymethyleneureas[137] and of the stability of cyclic disulphides[138]. In general there are no grounds for a connection between the stability and strain of rings. The nature of the relationship between these two factors is, in each instance, determined by the reaction mechanism.

With regard to a relation between tendency to ring formation and ring strain, the regular connection suggested by Baeyer, does not exist. Mohr[8], referring to the unstrained models of higher rings, tried to explain why these unstrained than eight members were unknown). In order to form a ring from an acyclic molecule, the latter must adopt a form suitable for cyclisation, i.e. one in which the reacting groups will be close together. The longer the chain of an aliphatic compound, the more various forms can its molecule adopt by internal rotation (these forms are now called conformations). We cannot, at will, impart to a molecule the necessary form or prevent the presence of forms unfavourable to cyclisation, so that the required form becomes rarer the longer and more mobile the chain between the two end-groups; in other words, the laws of statistics apply. Furthermore, Mohr pointed out that the ease of cyclisation may be affected by the mutual attraction or repulsion of atoms and by the presence or absence of substituents, but he did not deal in detail with this subject. These statements retain their significance to this day.

Making use of modern ideas, one can say that the tendency to ring formation is a complex function of the distance between the reacting groups and the loss of entropy involved in their fixation, of Baeyer strain, Pitzer strain, and the compression of van der Waals radii.

In cyclisation, two reactions are competing: intramolecular–ring formation, and intermolecular–polycondensation or polymerisation. As a rule, the latter reaction is thermodynamically more favourable. Calculation of the change of Gibb's free energy for the hypothetical polymerisation of cycloalkanes to linear polymethylenes, shows that such a process must be accompanied by a diminution of free energy with all rings except five- and six-membered rings (cyclohexane, alkylcyclohexanes, and alkylcyclopentanes)[139]. The same conclusions also apply to heterocyclic compounds[140]. Here, the general nature of the relation between ΔG and ring size is similar to that worked out for the cycloalkanes, particularly if the hetero-atom is not very different from carbon in volume and in the angles between the bonds (e.g. oxygen or nitrogen but not sulphur). Consequently, it may be supposed that the formation of rings, except five- and six-membered ones, involves a smaller gain of free energy than polycondensation and, in the case of reversible reactions, the products of intermolecular condensation should predominate over cyclic compounds in the equilibrium mixture. However, the possibility of cyclisation is not determined only by thermodynamic factors. If the processes are practically irreversible, the nature of the products depends only on the ratio of the rates of the monomolecular cyclisation reaction and the bimolecular reaction of linear dimerisation, which is the first stage of polycondensation, and not on the ratio of the values of ΔG for the two competing reactions. Thus, the greater rate of cyclisation compared to that of dimerisation corresponds to the fact that even the strained three- and four-membered rings are formed fairly easily. At the same time, the unstrained large rings and particularly the little-strained (as far as this can be judged from heats of combustion) intermediate-sized rings were first obtained in very low yields[14]. Apparently for reasons first discussed by Mohr (see above), the rate constant for the formation of macrocyclic compounds is appreciably lower than the rate constant for polycondensation. It is well known that macrocyclic compounds can now be obtained in fairly high yield (see the review by Ziegler[141]); this is accomplished primarily by using high dilution during cyclisation. The principle of high dilution, proposed by Ruggli, was first applied by Ziegler[142]. In conditions of high dilution, the possibility of intermolecular reaction is limited and intramolecular cyclisation becomes more probable. Naturally, the rate of both reactions is reduced, but that of the intermolecular reaction is reduced more than that of the intramolecular. The point is that the rate of the monomolecular reaction is proportional to the concentration of the starting material ($v_1 = k_1 c$) while the rate of the bimolecular reaction is proportional to the square of this concentration ($v_2 = k_2 c^2$). Thus if the rate of the first reaction is decreased 10 times by dilution, that of the second will decrease 100 times*.

The effect achieved by using high dilutions does not generally depend on whether the reaction is reversible or irreversible. In the case of an irreversible reaction, the composition of the products already formed is not changed by extending its duration. In a reversible reaction, thermodynamic equilibrium can, in principle, be achieved, although in practice, because of the retardation of the reaction by the high dilution, a very long time is required for the establishment of equilibrium.

Inasmuch as the height of the activation barrier of any chemical reaction is determined by the change of the free

* In order not to increase the volume of the reaction mixture unduly, cyclisation reactions are conducted using a special technique of high dilution[141]. In some cases, when the solubility of the substance being cyclised is small and the reaction proceeds in a heterogeneous medium, macrocyclic compounds can be obtained in a small volume of solvent, without using the high dilution technique (see, for example, work by Gol'dfarb and Kondakova[143]).

energy of activation $\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$ ($\Delta H^{\#}$ corresponds to the activation energy in the Arrhenius equation, while $\Delta S^{\#}$ — — the entropy of activation — represents the probability of attaining the transition state), one can refer to the enthalpy ($\Delta H^{\#}$) and entropy ($-T\Delta S^{\#}$) barriers of the cyclisation reaction[28].

In the synthesis of unstrained large rings (13 members and greater), the entropy barrier is of prime importance, while in the synthesis of strained small rings, it is the enthalpy barrier. The enthalpy factor is essentially *energetic* in nature: it represents that part of the energy of the transition state that is associated with distortion of valence angles and unfavourable conformations. The entropy factor is associated with the probability of occurrence of the "kinked" form of the chain, favourable to cyclisation, with the functional groups adjacent. The influence of both these factors is clearly manifested in the synthesis of intermediate-sized rings (8–12 atoms in the ring). These rings are the most difficult to obtain by cyclisation, which can be explained by both the small probability of an encounter between the spatially remote end-groups and the non-classical strain of the completed ring.

Although there is no regular relationship between strain and the rate of formation of rings (p. 229), cyclisation is generally easier from certain more favourable types of chain or when an unstrained ring is being formed. For example, exchanging a methylene group in the bifunctional compound for oxygen is generally accompanied by an increase in the yield of cyclic compound (the "oxygen effect"[28,141]); this is due to the diminution of conformational strain when a tetravalent atom is exchanged for a divalent atom. The presence of rigid groups (double bonds, aromatic rings) in the chain of the compound being cyclised, causes a decrease of mobility of the chain and hence of the number of possible conformations. As a result, favourable conformations become more probable and the yield of cyclic compound increases (the "rigid-group principle"[141]*).

The probability of formation of a favourable configuration of the chain also depends on the mechanism of cyclisation. Thus, in the acyloin condensation of esters of dicarboxylic acids, which is carried out in a heterogeneous medium, the probability of approach of the alkoxycarbonyl groups is increased on account of chemisorption on the surface of the molten metallic sodium[26,28].

The probability of cyclisation can be increased by the presence in a bifunctional compound of even quite small side-groups, which limit internal rotation[144]. As a result, the chain can more often adopt a "kinked" conformation with a favourable disposition of the functional groups. As the ratio of the first and second dissociation constants of alkyl-substituted dicarboxylic acids shows, the carboxyl groups are closer together than in the unsubstituted acids[145,146]. In this connection, the very easy formation of the anhydrides of alkyl-substituted glutaric and succinnic acids, which has been known for a long time, can be understood, The presence of substituents in the higher dicarboxylic acids similarly facilitates cyclisation. Thus $\alpha,\alpha,\alpha',\alpha'$-tetramethyladipic acid forms a monomeric anhydride with a seven-membered ring, while under the same conditions, adipic acid gives a polymeric anhydride[147]. Higher $\alpha,\alpha,\alpha',\alpha$-tetramethyl-substituted dicarboxylic acids give dimeric as well as polymeric anhydrides, whereas the corresponding unsubstituted acids give only the latter[148].

The effect of substituents on the ease of cyclisation is due primarily to their volume. This can be clearly seen from the kinetic data on the cyclisation of substituted ω-bromobutylamines[149] (Table 21). Aryl and alkyl groups have opposite inductive effects. Nevertheless, the rates of cyclisation of the diphenyl- and diisopropyl-substituted compounds are not very different.

In general, one can say that the increase in the rate of cyclisation when substituents are introduced, is due primarily to a conformational effect[149]. The substituents promote an increase in the content of the *gauche*-form at the expense of the transoid form; as a result, the reactive groups find themselves in a position where cyclisation is possible.

Bulky substituents, situated near the reactive groups, can increase the probability of cyclisation not only by virtue of their effect on the conformation of the chain, but also because they create steric hindrance to intermolecular reaction. The use of bifunctional compounds with large substituents has made it possible, in a number of cases, to obtain macrocyclic compounds without having to use high dilutions[150,151,152].

The presence of substituents also plays an important part in the production of small rings. There is even a view[153] that, in general, "the presence of substituents and their nature are of greater importance to the ease of closure and the stability of a ring, than the number of atoms making up the ring".

The relative tendencies to cyclisation of bifunctional compounds referred to above can be extremely helpful in considering the processes of polycondensation of bifunctional compounds and polymerisation of heterocyclic compounds important in practical applications.

A vast amount of literature has been devoted to problems connected with the production of high-molecular-weight compounds. Much of this has been generalised in a number of reviews and monographs (see the monograph by Korshak[154] and the literature cited therein). We are at present interested only in the comparative polymerisability of rings of different size and its relation to the probability of formation of ring compounds in polymerisation and polycondensation processes. Certain questions, relating to the thermodynamics and kinetics of polymerisation of cyclic compounds, are dealt with in a recently published review by Dainton and Ivin[155]. The values quoted there, and already referred to, of the change in free energy for the hypothetical polymerisation of cycloalkanes (Fig. 6, see p.224) are of particular interest. From these values, it is possible to conclude, for example, that the polymerisation of cyclohexane and, similarly, methyl- and 1,1-dimethylcyclohexane at 25°, is impossible. It should be emphasised, however, that the fact that a process is thermodynamically possible is no guarantee that it can be realised in practice. At present, there is no known method of polymerising cyclopropane and cyclobutane. 1,1-Dimethylcyclopropane is the only simple cycloalkane that will polymerise comparatively easily, in the presence of aluminium bromide[156]. Polymers can also be obtained from 1,2-dimethyl-, ethyl-, and propylcyclopropanes and from methyl- and ethylcyclobutane, but with these the reaction is much slower. The small tendency of cycloalkanes to polymerise in the presence of a reagent such as aluminium bromide, can probably be explained by the fact that in such conditions other reactions proceed at a fast rate. Turova–Polyak and coworkers[157] (see also the literature

* What has been said concerning the influence of rigid groups, naturally relates to macrocyclic systems and does not apply to compounds with rings of the usual size.

cited by Turova–Polyak[157]) showed that in the presence of aluminium chloride four-, seven-, and eight-membered rings are converted to cyclohexane derivatives. Homologues of cyclopentane, except for methylcyclopentane, are similarly converted to cyclohexane derivatives, while methylcyclopentane forms an equilibrium mixture, containing from 78 to 88% cyclohexane, depending on the temperature. Clearly, if the formation of cyclohexane derivatives proceeds at an appreciable rate, there is little hope of obtaining polymerisation products, since the formation of these from cyclohexane derivatives is thermodynamically impossible.

The polymerisation of many heterocyclic compounds, e.g. lactams, lactones, and anhydrides, can be regarded as an equilibrium process. In a number of cases, it proceeds via a stage in which the corresponding open-chain bifunctional compound is formed[158]. In particular, the polymerisation of caprolactam only takes place in the presence of catalysts, e.g. water, which convert the lactam to ϵ-aminocaproic acid[159,160], which then reacts with another molecule of lactam. The hydrolysis stage is the slowest and determines the rate of polymerisation[161]*. Such processess can be considered together with polycondensation of bifunctional compounds, since the equilibrium mixture can contain the linear monomer (bifunctional compound), the cyclic monomer, and the linear polymer.

The products formed in equilibrium polymerisation reactions depend on the reaction conditions. This statement can be illustrated by a few examples. As early as 1929, Carothers[164] formulated a rule according to which condensation reactions proceed intramolecularly if five- or six-membered rings can be produced thereby; reactions that can lead to seven-membered and larger rings generally proceed intermolecularly and result in polycondensation products. Although seven-membered rings may sometimes be obtained, eight-membered and larger rings are hardly ever found. This rule does not always hold, but it is supported by observations on the polymerisation of lactams in the presence of traces of water: the five-membered γ-butyrolactam and the six-membered δ-valerolactam do not polymerise under these conditions, the seven-membered ϵ-caprolactam partially polymerises (the equilibrium mixture always contains a small amount of monomer), the eight-membered ξ-enantholactam polymerises practically completely[158], while the nine-membered η-caprylolactam and the amino-acids that form 10-, 11-, 12-, and 18-membered lactams all polymerise completely[165].

TABLE 21. Rate of cyclisation of substituted ω-bromobutylamines.

Starting material	Relative cyclisation rate
4-Bromobutylamine	1.00
1,1-Dimethyl-4-bromobutylamine	2.19
2,2-Dimethyl-4-bromobutylamine	158
2,2-Diethyl-4-bromobutylamine	594
2,2-Diisopropyl-4-bromobutylamine	9190
2,2-Diphenyl-4-bromobutylamine	5250
3,3-Dimethyl-4-bromobutylamine	0.158

It might appear that the examples quoted prove the existence of a parallel between strain in rings and their ability to polymerise, although there is, in general, no such relationship. Not infrequently, unstrained rings undergo polymerisation, for example, six-membered* (see the review by Strepikheev[158]), 16-membered[173], and also five-membered rings[173,174,175]. It is interesting to note that α-pyrrolidone, which does not polymerise in the presence of water, polymerises under the influence of alkaline reagents[175]. The seven-membered ϵ-caprolactam[158] and tetramethyleneformal[174], which polymerise to the extent of 80–90% without a solvent, do not polymerise at all in 5–10% solution. Evidently, even a relatively small dilution (compared to that used in the synthesis of macrocycles), is sufficient for the preferential formation of the seven-membered ring, as against the polymer.

The equilibrium

cyclic monomer $\rightleftharpoons$ linear monomer $\rightleftharpoons$ linear polymer

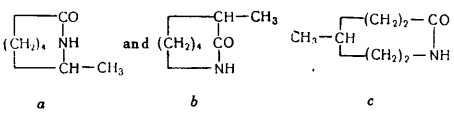
can also be shifted, without the use of dilution, towards formation of the cyclic monomer, if this is removed from the equilibrium mixture. In this way one can obtain the monomeric and dimeric cyclic anhydrides of the higher dicarboxylic acids[176], cyclic esters of glycols and dicarboxylic acids[177,178], and the higher lactones[179]. It has been suggested that the pyrolysis (after Ružicka) of the salts of di-

* However, one cannot conclude from this that the polymerisability of a ring is greater, the faster the hydrolysis rate. The formation of an amino-acid from a lactam may proceed easily, but if the amino-acid does not subsequently react with a molecule of lactam or with another molecule of amino-acid, polymerisation products of the lactam cannot be formed at all. Carothers[162] once suggested a parallel between polymerisability and hydrolysis rate of cyclic monomers. In recently published work[163], Hall, Brandt, and Mason showed that this was rarely justified and could not be called a general rule. It may be noted that, while the rate of hydrolysis of α-piperidone is greater than that of α-pyrrolidone, the polymerisabilities are in the reverse order; similarly, propiolactone polymerise readily, while γ-butyrolactone does not polymerise, although they hydrolyse at comparable rates.

* From the heats of combustion (in the liquid state) of 5- to 8-membered lactams, determined in the Thermal Laboratory at the University of Moscow[166], the authors concluded that even the 6-membered α-piperidone is strained, and to a greater extent than the 5-membered α-pyrrolidone. This conclusion clearly contradicts all the data on the strain of cyclic compounds. If the possibility of experimental error is excluded, it may be that in piperidone, compared to other lactams, the tautomeric lactim-lactam equilibrium is displaced in the direction of the endocyclic lactim form, and that the experimental value of the heat of combustion should not be compared with the value calculated for the lactam form, but with that for the lactim form (or with a mixture of the two). However, an infra-red spectroscopic study shows that the lactim form is not present in the lactams that have a ring containing from the 5-membered α-pyrrolidone. This conclusion clearly contradicts molecular interaction, which, as spectral data[168] and dipole-moment measurements[169] show, is extremely powerful in lactams. To exclude the influence of molecular interaction, it would be of very great interest to determine heats of combustion of lactams in the gaseous, instead of the liquid, state. The heats of combustion of alkyl-substituted lactams[170] and *N*-methyllactams[171], determined in the same laboratory of the University of Moscow, clearly indicate the lack of strain in a 6-membered ring. The heats of combustion of cyclic ketones[172], which are steric analogues of lactams, show that, in this case too, the 6-membered ring is unstrained.

carboxylic acids, is also a reversible reaction and that the formation of macrocyclic ketones is due to removal of one of the components of the equilibrium mixture[18].

As would be expected, when substituents are present in a molecule of cyclic monomer polymerisation is hindered[132,144,162,180]; the proximity of a substituent to the reaction centre is of the greatest importance. Thus, of the isomeric methylcaprolactams that have been studied[144], the slowest to polymerise is the mixture of ϵ-methyl-ϵ-caprolactam (*a*) and α-methyl-ϵ-caprolactam (*b*), obtained by the Beckmann rearrangement of the oxime of *o*-methylcyclohexanone, while the fastest is the γ-methyl-ϵ-caprolactam (*c*):



a *b* *c*

N-methylcaprolactam, and also a number of other *N*--substituted caprolactams, do not polymerise at all[181,182]; neither do dialkyl-substituted caprolactams[182,183]. At the same time, no difficulties are encountered in the polycondensation of 10-aminoundecanoic[184] and *N*-methyl-11--aminoundecanoic[185] acids. Apparently, the formation of 11- and 12-membered rings is so improbable that it need not be considered, even when the bifunctional molecule is branched; a seven-membered lactam is formed readily, without dilution, when the molecule of ϵ-aminocaproic acid contains one alkyl substituent on the nitrogen atom or two on carbon atoms[182].

For all the above reasons, one cannot agree with the statement by Hall and his collaborators[163]: "Polymerisability of a cyclic derivative is an indication of strain in the ring." They refer, in particular to the work of Dainton and Ivin[155], although it contains data which contradict their thesis. It seems to us, that the material that has been discussed enables one to conclude that, in general, the ability of a cyclic compound to polymerise is no indication of its strain. In particular, the example of the equilibrium polymerisation of heterocyclic compounds shows that in such reactions certain general rules, discussed above, play an important part, determining both the course of polymerisation and the processes of cyclisation.

CONCLUSION

Introduction of electronic concepts into chemistry led to the widespread use of polar effects in the interpretation of the reactivity of organic compounds. It is hardly necessary to stress the importance of these ideas, which played a prominent part in the development of the modern structure of organic chemistry. At the same time it should be noted that excessive enthusiasm for polar effects and attempts to ascribe every occurrence to the interaction of charges arising or existing in a molecule, led to the neglect or underestimation of several other factors that frequently play a decisive part in the development of a chemical reaction. This applies particularly to the spatial "shape" of a molecule, which is usually considered in connection with so--called steric hindrance. The influence of this factor on chemical behaviour was noted by Kehrmann, V. Meyer, N. A. Menshutkin, and others before the end of the last century, and for many years served as one of the means of interpreting the reactivity of organic compounds. However, around the 1940's, owing to the efforts to fit everything into the frame of one electronic concept, an extraordinary scepticism became widespread, concerning the role of the steric effect in chemical behaviour. The well-known books by Hammett and Remick hardly consider the steric effect. Moreover, as Brown[87] remarks, the steric effect is sometimes regarded as a meaningless concept: "Steric hindrance.... has become the last refuge of the puzzled organic chemist" states Ray in his textbook of organic chemistry (quoted from Brown[87]). Such a statement does not need to be refuted, but the importance of steric factors in a fairly wide range of chemical reactions still requires to be evaluated. At the present time, there is no generalised theoretical basis for this purpose, but several valuable facts and opinions may be gleaned from the book "Steric Effects in Organic Chemistry" (see Dauben and Pitzer[25] and other chapters in this book). To a certain extent, the present review may serve as a similar source of data in the limited field of cyclic compounds. In fact, ideas about strain, both as developed by Baeyer and also the very latest, are concerned primarily with the relative disposition in space of separate parts of a molecule, and enable one to clarify the bearing of these purely steric factors on the reactivity of a chemical compound. As we have seen already, peculiarities in those reactions of cyclic compounds not involving ring cleavage, which are best described in terms of the steric effect, have been increasingly studied in recent years. Of course, the steric effect cannot explain all the diverse reactions of cyclic systems. In this connection, we should like to emphasise again that in considering specific chemical problems it is essential to take various effects into account (polar, steric, solvation, etc.), each of which may, in one case or another, be of decisive importance. Although an accurate appraisal of the influence of all the factors is not possible at present, methods exist which make it possible, by analogy and by consideration of molecular models, to make an approximate estimate of their importance*.

The steric effect is caused by interaction of the outer electron shells of non-bonded atoms and, consequently, it is based, as is the polar effect also, on forces that are electrical in nature. However, steric interaction decays exponentially with distance; its nature is far from clear and this is one reason why the importance and the role of steric factors are still largely unknown. At the same time, it is evident enough that further study of their role in chemical reactions, linked with new advances in the modern electronic theory is a necessary condition for the progress of organic chemistry.

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Organic Chemistry

THE RADIATION CHEMISTRY OF AQUEOUS SOLUTIONS OF INORGANIC NITROGEN COMPOUNDS

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The radiolysis of solutions of inorganic nitrogen compounds is an extremely complex and important problem in radiochemistry owing to the multiplicity of the valency states of nitrogen and the comparative ease of their mutual interconversion. Although a great deal of work has been done on the mechanism of the radiolytic reactions of nitrogen compounds in solution, much remains obscure.

1. NITROGEN FIXATION INDUCED BY IONISING RADIATION IN THE PRESENCE OF WATER

Orekhov et al.[1-3] found that on irradiating a KOH solution with Co^{60} γ-rays in the presence of oxygen, the nitrite formed and the equivalent quantity of nitrate increased linearly with the dose. The G value* for the nitrogen entering into combination was about 0.2 atoms. Increasing the air pressure on the solution (up to 25 atm) had no appreciable effect on G. They considered that this reaction depends on the reaction of free OH radicals, formed by the radiolysis of water, with free molecules of nitrogen, simultaneously with atomic hydrogen or the radical HO_2:

$$OH + N - N + HO_2 \rightarrow NOH + HNO_2. \quad (1)$$

This reaction of nitrogen was not observed in acid solutions.

Primak and Fuchs irradiated a mixture of nitrogen and oxygen with a nuclear reactor in the presence of nickel or other metals in a quartz ampoule. No products were formed with dry gases. A significant quantity of $Ni(NO_3)_2 \cdot 6H_2O$ was produced when air at 1 atm was saturated with water at 28°. The yield of bound nitrogen, G, was about 3 atoms, but the accuracy of the determinations was not high.

Wright et al.[5] studied the formation of HNO_3 from air and nitrogen irradiated over water in a nuclear reactor. G (HNO_3) was about 1 molecule (calculated from the energy absorbed by the gases).

Dmitriev and Pshezhetskii[6,7] found that G was 0.2 atoms for the oxidation of nitrogen at atmospheric pressure over water by 200 keV electrons. The reaction proceeded essentially at the expense of the energy absorbed in the gaseous phase.

Jones[8] found that nitric acid and nitrous oxide were formed by a beam of fast electrons (1 MeV) acting on a nitrogen–oxygen–water system. With high integral doses (using up all the water vapour present in the mixture) the HNO_3

* In this and all subsequent cases, G is the amount of radiolytic reaction (in molecules, atoms, ions, etc.,) per 100 eV of energy absorbed.