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CHAPTER 3

The Concept of Molecular Strain: Basic Principles, Utility, and Limitations

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CONTENTS

To know a lot does not teach reason.
Heraclitus

1. INTRODUCTION

The continuous improvement of both experimental and theoretical methods in the past decades has swamped chemistry with a tremendous amount of data about molecules and their properties. A systematization and rationalization of the myriad of established facts is of paramount importance for progress in chemistry. The human mind can best comprehend and interpret molecular properties in terms of conceptual models. Of course, models always differ from the object being modeled. If we are using models of molecules, we relinquish accuracy but gain generality, simplicity, and feasibility. Such a compromise is acceptable provided one is always aware that models are just temporary aids, always to be revised, and eventually to be discarded as better models are developed. Also one has to bear in mind that a model may be suitable for one purpose but inadequate for other needs. Models always have to be adjusted to reflect and to cope with improved insights into nature.

A useful model for the description of molecular properties should fulfill three basic requirements. First, it should be simple and easy to memorize. Second, it should possess a sound physical basis and provide a consistent description of its objects. Finally, it should be flexible and applicable over as wide a range as possible. Insofar as these requirements are partially contradictory, each and every model is open to criticism. For example, increased simplicity of a model usually entails more insight and clarity, but also, a decrease in flexibility and applicability. A rigorous theoretical approach very often discloses inconsistencies in a model and, as a consequence, can lead to its revision.

Many models in chemistry have been inspired by classical mechanics. They describe molecules with the properties of macroscopic quantities such as balls, sticks, and springs. A typical example is the concept of molecular strain introduced into chemistry a century ago by Adolf von Baeyer to explain the relative stabilities of cycloalkanes.[1] Despite its simplicity, this model has been of astonishing value for chemistry with regard to both the rationalization of known molecular properties and the prediction of unknown properties. For example, in nearly all modern textbooks the essence of von Baeyer's strain concept is described and then used to rationalize the stability of small cycloalkanes and other strained compounds. Without exception, chemical textbooks impart to the reader the impression that the relative stabilities of ring compounds are well understood in the light of the concept of molecular strain.

This view has been challenged recently by various authors[2-9] who have pointed out that the structure and stability properties of cyclopropane and possibly other three-membered rings evade classical descriptions of chemical bonding and, thereby, also classical strain theory. Analyzing the chemical and physical properties of small cycloalkanes, Dewar[2] came to the conclusion that cyclopropane possesses a sextet of delocalized σ electrons and, therefore, is isoconjugate with benzene, an idea that can already be found in an early PPP-type description of cyclopropane by Brown and Krishna.[3] In the same way that benzene may be considered a π-aromatic system, cyclopropane may be considered to be σ-aromatic.[10] Delocalization of σ electrons adds to the stability of cyclopropane, thus compensating for part of its ring strain.

Cremer and Kraka[4,5] added support to the idea of σ-delocalization by analyzing the properties of the electron density distribution of three-membered rings. They estimated the extra stablization of cyclopropane due to σ-delocalization. This work was extended by Cremer and Gauss,[6] who compared cyclopropane and cyclobutane on the basis of ab initio calculations. These authors confirmed the idea of σ-electron delocalization and assigned energies to the various effects acting in cyclopropane.

Schleyer[11] reviewed the question of the stability of small cycloalkanes and, on the basis of his analysis, challenged the idea of σ-aromaticity. He argued that the energetics of small cycloalkanes can safely be explained within an extended concept of strain.

These controversial views indicate that contrary to what is written in chemical textbooks, the use of the concept of strain to rationalize the energetics of small cycloalkanes is questionable. Furthermore, the controversy that has recently flared up concerning strain in cyclopropane and other three-membered rings probably will not be settled in the near future. A critical review of the notion of strain is needed at this time to properly evaluate the various arguments. We attempt to present such a review in this chapter, not by listing in an encyclopedic way the many investigations that have been devoted to the subject, but by searching for the roots of the notion of strain and exploring its facets in modern chemistry. In particular, we will investigate the extent to which von Baeyer's classical strain concept can be confirmed within the realm of quantum chemistry. Is there a way of placing the concept of strain on a sound quantum mechanical basis, hopefully improving the self-consistency, flexibility, and applicability of the model but at the same time retaining its simplicity?

We will deal with this question by reviewing briefly the origin of the concept of strain and the various types of strain discussed in chemistry (Section 2). Then, we will discuss ways of quantitatively assessing molecular strain and its energetic consequences (Section 3), also pointing out the chemical consequences of strain (Section 4). In Section 5, we will focus on the strain energies determined for small cycloalkanes, giving special emphasis to the puzzling similarity of the strain energies of cyclopropane and cyclobutane. The sections that follow will be devoted to a quantum chemical approach to molecular strain, first on the basis of the molecular orbitals (MO) (Section 6), then within the realm of electron density theory (Section 7) and, finally, by considering the Laplace distribution of electrons in strained molecules (Section 8). Ways of assessing the strain energy from quantum chemical calculations will be put forward in Sections 9, 10, and 11, either on the basis of in situ bond energies (Section 10) or by a dissection of the molecular strain energy according to Westheimer (Section 11). In Section 12, we will focus on cyclopropane and will display the results of quantum chemical calculations under the heading of pros and cons of σ-aromaticity. Then we will establish the limitations of the concept of molecular strain (Section 13), by concentrating on the relationship between three-membered rings and π complexes. Section 14 contains concluding remarks. We hope that our account will sharpen the reader's eye with respect to the utility and the limitations of the concept of molecular strain.

2. THE CONCEPT OF STRAIN

A. Strain in Classical Mechanics

If forces act on an elastic body, the body is deformed. It becomes *strained*. Quantitatively, this deformation, called *strain*, is given by the relative displacements $\Delta x/x$ of the parts of the elastic body.[12] Thus, strain is a dimensionless quantity. One distinguishes dilatation (compression) strain, shearing strain, and torsional strain.

There are forces in a strained body that act to restore its original form. The restoring force per unit area is called *stress*. According to Hooke, the stress set up within an elastic body is proportional to the strain to which the body is subjected:

$$\text{stress} = k \times \text{strain} \qquad \text{(Hooke's law)}$$

where k, the modulus of elasticity, is a proportionality constant that possesses the same dimension as the stress, namely force per unit area.

The potential energy per unit volume stored up in the body is called the strain energy function.[12]

B. Strain in Chemistry

The notion of "strain" was introduced into chemistry by Adolf von Baeyer in 1885,[1] at a time when the tetravalency of the carbon atom, the tetrahedral arrangement of carbon bonds, and the connection between molecular structure and bonding had been established by Kekulé, Couper, van't Hoff, Le Bel, and others. Von Baeyer postulated that the valencies (bonds) of a carbon atom may deviate from the tetrahedral directions. These deviations lead to *strain* that increases with the magnitude of the deviation.[13] According to von Baeyer, strain should be largest in small cycloalkanes such as cyclopropane and cyclobutane that possess CCC bond angles that deviate by 49° and 19°, respectively, from a tetrahedral angle of 109.5°.

Von Baeyer drew the connection to the notion of strain in classical mechanics by considering the carbon bonds as elastic springs or sticks, deformation of which can be described by Hooke's law. Thus, the "elastic body" considered in chemical strain theory is the chemical bond. *Obviously, the concept of strain is intimately connected with the concept of the chemical bond.* Any weakness, oversimplification, or inconsistency in the latter inevitably shows up in the concept of molecular strain. Clearly, both chemical bonding and molecular strain are model-bound quantities. In other words, *the strain energy of a molecule is (contrary to the strain energy of an elastic body) nonobservable* (as are the bond properties bond energy, bond polarity, etc). This has to be borne in mind when applying the concept of strain in chemistry.

C. Types of Molecular Strain

Von Baeyer defined what is termed "bond angle strain" (Table 3-1). Its equivalent in classical mechanics is the shearing strain. Since von Baeyer's work, the strain concept has been extended in chemistry and other strain types have been taken from classical mechanics.

For example, the stretching or dilatation (compression) of a bond from an idealized value leads to stretching strain. Torsion of a bond causes torsional strain. The latter type of strain was first identified by Pitzer when investigating the conformational behavior of ethane.[14] In the equilibrium form, all CH bonds of ethane are staggered (torsion angle $\tau = 60°$). CH bond eclipsing ($\tau = 0°$) leads to an increase in the energy of ethane, the reason for which is considered to be torsional strain. This type of strain has also been termed "bond opposition strain"[15] or "Pitzer strain."

The shape of a molecule is determined by internal coordinates such as bond lengths, bond angles, and torsional angles. As an alternative to bond angles and torsional angles, one can use nonbonded distances when describing molecular shape. Similarly, as in the case of internal coordinates, ideal-

TABLE 3-1. Types of Strain Used in Chemistry

Strain	*Description and alternative names*	*Ref.*
1. Baeyer strain	Bond angle strain	1
2. Pitzer strain	Torsional strain	14
	Bond opposition strain	
	Bond eclipsing strain	
3. Stretching strain	Bond length strain	19
4. Dunitz–Schomaker strain	Nonbonded strain	18
	Compression of van der Waals radii (van der Waals strain)	16
	Transannular strain or Stoll pressure (better: Stoll strain)	17
5. Steric strain	Sum of 1–4	19
6. I strain	Internal strain comprising 1–4	15
7. F strain	Front strain leading to a retardation of chemical reactions	15
8. B strain	Back strain leading to an acceleration of chemical reactions	15
9. Electrostatic strain	Actually electrostatic stress caused by more than one charge within a molecule	20
10. Superstrain	Difference between the total strain and the sum of the strain of the fused rings in polycyclic molecules	22

ized values can be defined for nonbonded distances utilizing the van der Waals radii of the atoms. If the molecular structure entails nonbonded distances that are smaller than the sum of the van der Waals radii, the molecule is compressed, an idea first proposed by F. Kehrmann in 1889.[16] In this case one speaks of steric strain, nonbonded strain, transannular strain, or Stoll pressure (in the case of ring compounds).[17] Dunitz and Schomaker[18] investigated nonbonded C,C repulsion in cyclobutane and showed it to be an important factor influencing the stability of this molecule. Therefore, nonbonded interactions are often listed under "Dunitz–Schomaker strain" (Table 3-1).

The four types of strain are usually subsumed under the term "steric strain."[19] Brown has coined the term I- (internal) strain[15] for the total molecular strain in ring systems and uses this when discussing strain in connection with molecular reactivity. Other types of strain have been introduced in connection with the concepts of steric hindrance and steric assistance: for example, F- (front) strain, leading to retardation of chemical reactions, or B- (back) strain, causing acceleration of chemical reactions.[15] Other types of strain are listed in Table 3-1.[20–22]

D. Colloquial Use of the Term "Strain"

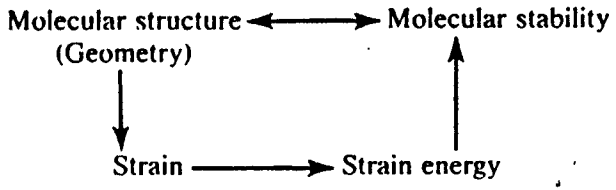
A description of the concept of strain is most often found in textbooks of organic chemistry.[23] In all cases, the strain in cycloalkanes is discussed in terms of Baeyer strain, which is considered to dominate the relative stabilities of the ring compounds. Therefore, it is not surprising that "strain" and "Baeyer strain" often are used synonymously. For example, in encyclopedic books on chemistry a description of bond angle strain is given under the key word "strain theory."[24]

There are only a few general textbooks,[23b,23d,25] that present a clear distinction between the various types of strain. More information can be obtained from books that deal with such special topics as conformational analysis, stereochemistry, and force field calculations.[26–29] Elaborate discussions of the various types of strain can be found in a number of review articles that have appeared over the years.[30–35]

Some authors use "stress" and "strain" interchangeably; that is, they use terms like "steric pressure" or "steric forces" as substitutes for the notion of strain. Of course, this may sometimes happen because chemists are in general more interested in the energetic consequences of strain than in strain itself. Also, the terms "stress" and "strain" are differently used in other languages.[13]

3. QUANTITATIVE ASSESSMENT OF STRAIN AND STRAIN ENERGY

In a deformed elastic body, potential energy is stored in the form of strain energy. Similarly, a strained molecule possesses a strain energy (SE) that increases its potential energy in relation to a hypothetical strain-free molecule. Chemists are interested in the SE of a molecule in order to rationalize its stability and reactivity. Thus strain and strain energy provide a basis that links the structure, stability, and reactivity of molecules (Scheme I).



Scheme I

In contrast to classical mechanics, which defines the SE of an elastic body as a macroscopic property, the SE of a molecule is determined by the individual SEs of all the "elastic" subunits making up the molecule, namely atoms, atomic groups, and bonds. In a classical sense these can be consid-

ered as elastic balls, connected by elastic sticks or springs. To obtain the individual parts of the total molecular SE, each elastic subunit of a molecule must be defined in a hypothetical strain-free state.

There exist countless ways of defining the strain-free subunits. Each of these ways establishes a specific model of molecular strain. The value of these models can be determined only by examining the extent to which chemical properties of molecules can be rationalized. A model of strain can be considered useful if the structure and stability of a large set of molecules can be rationalized in a consistent way.

There are both theoretical and experimental ways of defining strain-free subunits and their SEs. We will briefly describe those used for the evaluation of strain and SE in saturated hydrocarbons.

A. Establishment of "Strain-free" Reference States

In classical mechanics strain is determined by the relative displacements of the parts of an elastic body, that is, by the deformation of the body.[12] Von Baeyer introduced strain into chemistry by considering tetravalent carbon as an elastic body that can be deformed by forcing the four valencies out of the tetrahedral directions.[1] Such deformations become necessary when forming a strained hydrocarbon molecule from unstrained CH_n (n = 0, 1, 2, 3) subunits. (It is stressed that these subunits are just model building blocks and should not be confused with atomic carbon, methylidyne, carbene, or the methyl radical.) Angle strain is relieved as soon as tetravalent carbon is extricated from the strained molecule. For sp^3-hybridized carbon, the ideal CCC, CCH, and HCH angles in hydrocarbons should be 109.5°. Other choices of ideal angles have been advocated on the grounds that the preferred angles in small hydrocarbons differ from 109.5°.[37–40] However, these choices were made with the intention of reproducing experimental ΔH_f° values or other molecular properties using the molecular mechanics approach. Thus, the molecules possessing these angles are strain-free in an operational but not absolute sense.

Von Baeyer's idea of an elastic chemical "body" has to be extended when assessing stretching and torsional strain of a molecule. In this case, unstrained reference molecules must be defined. For hydrocarbons, molecules such as methane, ethane, propane, n-butane, or isobutane are considered to possess unstrained CH and CC bonds.[37–40] Deviation of measured CC and CH bond lengths from the reference bond length is indicative of stretching strain. Similarly, ideal HCCH, CCCH, and CCCC torsional angles (60°) are taken from the staggered forms of ethane, propane, and n-butane and are used to detect torsional strain.[37–40]

The van der Waals radii of C (1.85 Å) and H (1.20 Å) have been determined from the intermolecular distances in crystalline hydrocarbons.[29,41] If the nonbonded distances of a molecule fall short of the sum of the corresponding van der Waals radii, the molecule will be considered to suffer from nonbonded strain.

Chemists are primarily interested in the energetic consequences of strain, that is, the strain energy. Therefore, the choice of the reference molecule is often guided by the intention to determine the SE of a molecule. For this purpose, molecules have been selected that lead to ideal CC or CH bond energies or, alternatively, to ideal group increments $\Delta H_f^\circ(CH_n)$ with n = 0, 1, 2, 3. It would be beyond the scope of this chapter to list all the possible choices suggested in the literature during the past decades. (Some of these are listed in References 37, 38, and 42–45.) Instead, we have summarized some basically different possibilities of selecting appropriate reference groups CH_n in Table 3-2. For example, one can select CH_4 as a reference molecule and subject it to angle deformations typical of strained hydrocarbons. The corresponding increase in the energy of CH_4 can be used to determine the bond angle SE.[46,47]

Hydrocarbons are made up from the four subunits CH_n, n = 0, 1, 2, and 3, namely)C(,)CH—,)CH_2, and —CH_3. Accordingly, one needs the ΔH_f° value of just four appropriate reference molecules, each containing at least one of these groups. Solving four equations with four unknowns, the $\Delta H_f^\circ(CH_n)$ (n = 0, 1, 2, 3) values lead to the definition of strainless CH_n subunits to be used when assessing strain and SE in hydrocarbons. This approach has been employed in several cases. Investigators have used as reference molecules the smallest alkanes that possess the respective subunit,[48] or hydrocarbons that consist uniquely of one and the same subunit ('diagonal' reference states,[45] see Table 3-2).

Alternatively, one can set up an overdetermined system of linear equations for the four unknowns by utilizing known ΔH_f° values of a series of

Table 3-2. Possible Reference Molecules for Analyzing Strain and Calculating Strain Energies in Hydrocarbons

Reference molecules	*Remark*	*Source*	*Ref.*
1. CH_4	HCH angles are distorted to values of CCC angles in strained molecules; distortion energies are calculated	Wiberg et al. Schleyer	46 47
2. CH_3CH_3, $(CH_3)_2CH_2$, $(CH_3)_3CH$, $(CH_3)_4C$	Definition of homodesmotic references	George et al.	48
3. Ethane, cyclohexane, cubane, adamantane, diamond	Definition of "diagonal" reference states	Liebman and Van Vechten	45
4. Acyclic and cyclic hydrocarbons	Definition of averaged groups	Franklin Benson et al. Boyd Schleyer et al. Allinger et al.	42 43, 44 36 38, 39 29a, 37

acyclic and cyclic hydrocarbons. This approach has been employed by several authors.[37-39,42-44] In case of substituted hydrocarbons, especially when electronegativity differences become pronounced, non-next-nearest-neighbor interactions (unanticipated within the Benson scheme[44b]) may play a dominant role; hence strain energies may depend strongly on uncertainties in the decision of the model group increment as pointed out by Liebman and co-workers[134] for fluorocycloalkanes.

In the case of compounds with nonclassical structures (e.g., π complexes, H-bridged structures, structures with penta- or hexacoordinate C), the definition of appropriate reference groups or reference molecules becomes problematic, if not meaningless. This, of course, has to do with the fact that von Baeyer's idea of a bond as an elastic spring is no longer useful, for example, in the case of two-electron, multicenter bonds.

B. Definition of the Molecular Strain Energy (SE)

Within the concept of strain, the SE is used to rationalize the thermodynamic stability of a strained molecule. Once the strain-free subunits of the molecule have been defined, the SE can be calculated using the Westheimer equation[19]:

$$\Delta E = \Delta E_r + \Delta E_\alpha + \Delta E_\tau + \Delta E_{nb} \tag{3-1}$$

where ΔE_r and ΔE_α are the SEs arising from total bond length and bond angle strain, respectively. They are calculated for all bond lengths r_i and bond angles α_j using Hooke's law:

$$\Delta E_r = \sum_i \frac{k_{ri}}{2} (r_i - r_i^\circ)^2 \tag{3-2}$$

$$\Delta E_\alpha = \sum_j \frac{k_{\alpha j}}{2} (\alpha_j - \alpha_j^\circ)^2 \tag{3-3}$$

The torsional SE is assessed by:

$$\Delta E_\tau = \sum_k \frac{V_{3k}}{2} (1 + \cos 3\tau_k) \tag{3-4}$$

for saturated hydrocarbons (with torsional angles τ_k) and more elaborate Fourier series for other compounds.[29]

The expression for nonbonded interactions is generally of the form of a Buckingham potential[29]:

$$\Delta E_{nb} = \sum a_{mn} \exp\{-b_{mn} l_{mn}\} + c_{mn} l_{mn}^{-6} \tag{3-5a}$$

or a Lennard–Jones potential[29]:

$$\Delta E_{nb} = \sum_{mn} a'_{mn} l_{mn}^{-12} + b'_{mn} l_{mn}^{-6} \tag{3-5b}$$

where constants a_{mn}, b_{mn}, c_{mn}, or a'_{mn}, b'_{mn} depend on the pair of atoms m and n separated by a distance l_{mn}. Both functions work comparably well, and the preference for one or the other may be considered as a matter of convenience.[29]

Contrary to spectroscopic force fields, in which only the $3N - 6$ degrees of freedom of a molecule are considered, the summations in Equations 3-2 through 3-5 lead to considerably more terms including all possible internal coordinates. For example, for each bonded tetravalent carbon there are four bond lengths and six bond angles in addition to all possible torsional angles and nonbonded distances. For all internal coordinates, the constants of Equations 3-2 through 3-5 (k_{ri}, r_i°, $k_{\alpha j}$, α_j°, V_{3k}, τ_k; a_{mn}, b_{mn}, c_{mn}, or a'_{mn}, b'_{mn}) must be known for the strain-free reference states in order to determine SE by Equation 3-1. One could consider determining these constants from the structural spectroscopic properties of the reference compounds listed in Table 3-2. Indeed, complete sets of these constants are known, and one might consider the calculation of SE to be straightforward. However, two basic problems impede the immediate use of Equation 3-1.

1. The bending force constants of the strain-free CH_n subunits should be determined in the absence of any 1,3-nonbonded repulsion. Any $k_{\alpha j}$ taken from small hydrocarbons contains effects from nonbonded repulsions. Accordingly, ΔE_α and ΔE_{nb} are interdependent and must be adjusted to avoid counting the corresponding energetic contributions to the SE twice. The same holds for all other terms in Equation 3-1. Therefore, the choice of the correct constants for the determination of SE becomes a difficult enterprise. This is why Equation 3-1 and more sophisticated equations derived from it are used to calculate the *steric energy* rather than the SE of a molecule.[19] The steric energy obtained from molecular mechanics calculations is not (!) equal to SE. Even for a strainless molecule like ethane, the steric energy is nonzero because Equation 3-1 is used to reproduce or to predict the heat of formation ΔH_f° of a molecule rather than its SE. The value of ΔH_f° is obtained by adding appropriate enthalpy increments for bonds and atomic groups to the steric energy. Different force fields distribute energy contributions needed for the calculation of ΔH_f° differently between steric energy and enthalpy increments. Therefore, the steric energy is of little significance and differs in magnitude considerably from force field to force field.[29] As a consequence, the SE can be obtained from ΔH_f° only by introducing another set of enthalpy increments applicable for the calculation of ΔH_f° of strainless reference molecules.[29,36,37,39]

For reasons of simplicity, we will not follow the molecular mechanics procedure to obtain SE. Instead, we will stick to the original assumption that the steric energy is equal to the SE. But even with this assumption

another serious problem remains when attempting to calculate SE from Equation 3-1.

2. The observed geometrical data r_i, α_j, τ_k, and I_{mn} of a molecule are affected not only by strain but also by other stabilizing or destabilizing effects such as π conjugation, hyper- or homoconjugation, aromaticity, antiaromaticity, and steric attraction. Hence, Equation 3-1 can be solved only if each energy term is corrected for all other effects also active in the molecule and influencing either r_i, α_j, τ_k, or I_{mn}. This means that a new set of geometrical parameters must be inserted in Equations 3-2 through 3-5 to yield energies $\Delta E'$, which add up to the actual SE:

$$SE = \Delta E'_r + \Delta E'_\alpha + \Delta E'_\tau + E'_{nb} \qquad (3\text{-}6)$$

To solve Equation 3-6 it is necessary to specify exactly the geometrical consequences of other energetic effects such as aromaticity or antiaromaticity, quantities that in turn are defined only within a specific model.

For the reasons just enumerated, an application of Equation 3-1 or 3-6 to calculate the SE has been attempted only in simple cases using various approximations. More often, thermochemical data, either from experiment or theory, have been used to define molecular SEs in one of the following ways (compare with Figure 3-1).[43–45,48–57]

1. *From heats of atomization (ΔH_a) and bond enthalpies (BE).* This approach implies a definition of appropriate bond enthalpies taken from strain-free molecules. Various procedures have been suggested to obtain normal, averaged, or intrinsic BEs.[49–51]

2. *From heats of formation (ΔH_f°) and group enthalpies [ΔH_f° (group)].*[38,42–45] Different ways of deriving $\Delta H_f^\circ(CH_n)$ are discussed in Subsection A of Section 3 and are listed in Table 3-2.

3. *From in situ bond energies (be) of the molecule in question and appropriate reference molecules.* The in situ (or instantaneous) bond energy[52] is the energy needed to homolytically break the bond in question while maintaining in the fission products all molecular features such as hybridization of atoms and bond lengths. The sum of the in situ bond energies is (per definition) equal to the atomization energy of a molecule. In situ bond energies can be calculated from overlap[53] or overlap populations, from shared electron numbers,[54] from resonance integral contributions to semiempirical energies,[55] or from the total electron density distribution $\rho(\mathbf{r})$ in the bond regions of a molecule.[56]

4. *From in situ atomic (or atomic group) energies (ae) of the molecule in question and of appropriate reference molecules.* In analogy to the in situ bond energy, the in situ atomic energy is defined as the energy of an atom within its molecular environment. The sum of the in situ atomic energies is equal to the molecular energy. However, this approach requires a clear

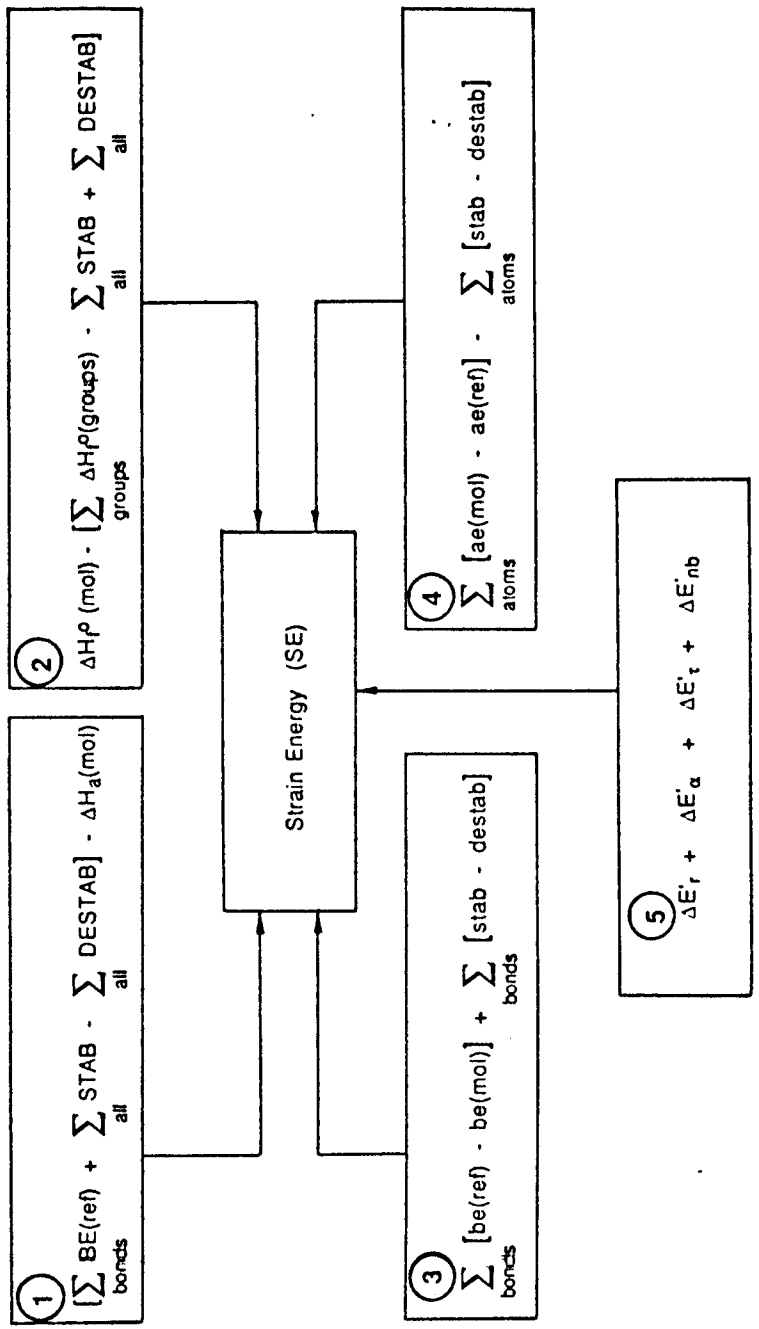


Figure 3-1. Methods of defining the strain energy (SE) of a molecule: mol = strained molecule, ref = reference, group = reference group. BE = bond enthalpy, ΔH_a = heat of atomization, ΔH_f° = heat of formation, be = in situ bond energy, ae = in situ atomic energy, STAB (DESTAB) = stabilization (destabilization) energy per bond or per atom (not arising from strain), $\Delta E'_r$, $\Delta E'_\alpha$, $\Delta E'_\tau$, $\Delta E'_{nb}$ = strain energies arising from bond length, bond angle, torsional strain, and nonbonded strain. For explanation of primed ΔE terms, see text.

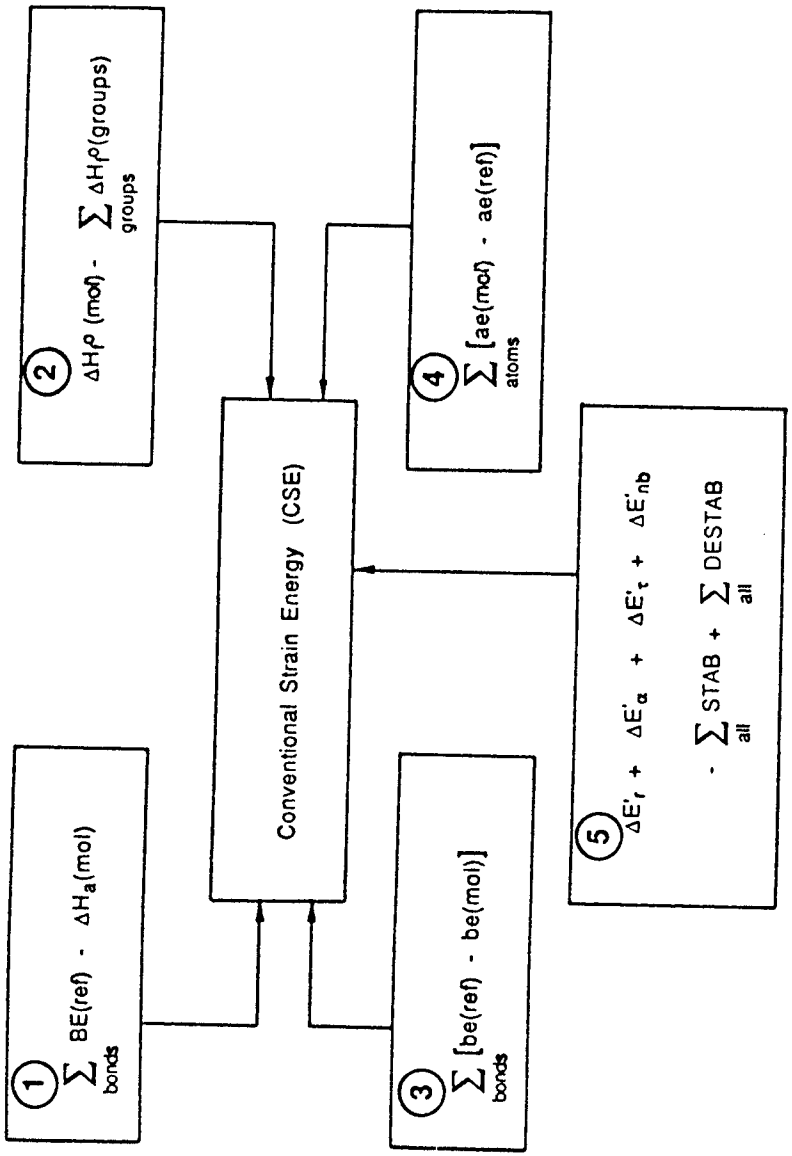


Figure 3-2. Methods of defining the conventional strain energy (CSE) of a molecule. Compare with Figure 3-1.

definition both of what is meant by an atom (or atomic group) in a molecule and of a method for evaluating the energies of atoms (or atomic groups) in their molecular environment. This can be done by the virial partitioning method of Bader,[57] which is based on a quantum mechanical dissection of $\rho(\mathbf{r})$.

When the SE is derived from enthalpies, it is advisable to speak of a strain enthalpy, SH. For a similar reason one could distinguish between SE at finite temperature and at 0 K, with and without zero-point energy corrections. However, compared to the uncertainties in determining the energetic consequences of strain, differences between SE(0), SE(T), SH, and so on are relatively small, justifying the somewhat inaccurate use of the term "strain energy."

Methods 1 through 4 are based on *model quantities* such as the bond enthalpy, group enthalpies, and in situ bond energies or atomic energies. In methods 1 and 2, model quantities are compared with observed (or calculated) enthalpies to obtain SE, while methods 3 and 4 are based on a comparison of two sets of theoretical energies defined within a given model for bonds or atoms.

In all methods, the energetic consequences of stabilizing and destabilizing effects (apart from strain) have to be determined to obtain the proper SE. For methods 1 and 2, this can be done in a cumulative way, but for methods 3 and 4 appropriate corrections have to be evaluated for each bond or each atom. Since this may be problematic for the reasons mentioned above, the term "conventional strain energy" (CSE) has been introduced.[49]

The CSE contains all stabilization and destabilization energies. This makes its evaluation far easier than that of SE, as is shown in Figure 3-2. If, however, the CSE is to be evaluated by means of Equation 3-6, stabilization or destabilization energies must be added to the SE (Figure 3-2).

Although CSE and SE values are similar in saturated hydrocarbons, it is important to note that *in general, a small CSE does not necessarily imply that the molecule is unstrained.* Stabilization and destabilization effects may just cancel each other out. Also, if two CSEs are similar, the corresponding molecules will not necessarily be equally strained. We will come back to this point when discussing the CSEs of cyclopropane and cyclobutane.

4. CHEMICAL CONSEQUENCES OF STRAIN

The molecular properties of strained molecules differ distinctly from those of unstrained molecules. This has been amply demonstrated in the case of cycloalkanes with regard to molecular geometry, thermodynamic stability (as discussed), and various spectroscopic properties.[58–60] The main achieve-

ment of the concept of strain has been the rationalization of known properties and the prediction of yet unknown properties as well.

Another objective of the concept of strain has been the prediction of molecular reactivity. A highly strained molecule should try to rearrange, decompose, or react with another molecule to adopt a less strained form. Thus, it is reasonable to expect that an increase in strain would lead to an increase in molecular reactivity and that a strained molecule would react faster than its unstrained counterpart. However, an analysis of this expectation in terms of barriers to reaction casts some doubts on whether or not strain and reactivity are related in a simple way.

Figure 3-3 shows qualitative reaction profiles of two possible extremes. One and the same reaction is considered for both the strain-free reference molecule M1 and the strained molecule M2. In Figure 3-3*a*, the same transition state is traversed by both M1 and M2. This implies that the activation energy $\Delta E_2^{\ddagger}$ ($\Delta G_2^{\ddagger}$) is smaller than $\Delta E_1^{\ddagger}$ ($\Delta G_1^{\ddagger}$) by the amount SE; hence the reaction involving M2 should be faster. In Figure 3-3*b*, the transition state traversed by M2 is energetically higher than that traversed by M1, namely by the amount SE [ie, $\Delta E_1^{\ddagger} = \Delta E_2^{\ddagger}$ ($\Delta G_1^{\ddagger} = \Delta G_2^{\ddagger}$)]. Thus, M1 and M2 should react equally fast. For both cases, the difference in the reaction energies $\Delta_R E_2 - \Delta_R E_1$ ($\Delta_R G_2 - \Delta_R G_1$) is assumed to be equal to SE.

Clearly, actual reactions will mostly fall between these two extremes, thus leading to $k_2 \geq k_1$. This inequality may be a useful relationship when rationalizing kinetic data. However, a caveat is appropriate when using these qualitative relations between the strain energy (thermodynamical stability) of a molecule and its kinetic stability; no quantitative connection between these molecular properties can be expected (see also Section 13). This will be possible only if the TS energy is known—that is, only if the predictive value of the concept of strain actually is no longer needed.

Even qualitative predictions concerning the reactivity of a strained molecule will no longer be possible if the rate determining step does not lead to strain relief.[61] Also, a strained molecule may not react at all if (a) the strain-relieving reaction is endothermic or (b) the barrier to reaction is too high (e.g., since the reaction in question is symmetry forbidden). In the latter case the paradoxical situation is encountered that a highly strained (thermodynamically labile) molecule is kinetically stable.[62] One example of this situation is the "perfluoroalkyl (R_f) effect."[62c] The R_f effect is a combination of stabilizing effects that perfluoroalkyl groups confer upon highly strained hydrocarbon rings. Although perfluoroalkylation generally thermodynamically destabilizes strained organic rings by enhancing nonbonded repulsion, perfluoroalkylated compounds are more resistant to both catalyzed and unimolecular destruction than their parent compounds. As such, their striking thermal stability has been identified as being purely kinetic in nature.[62d]

Finally, it must be noted that rate constants depend on the free energy of activation, $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, rather than simply on $\Delta E^{\ddagger}$. Also, measure-

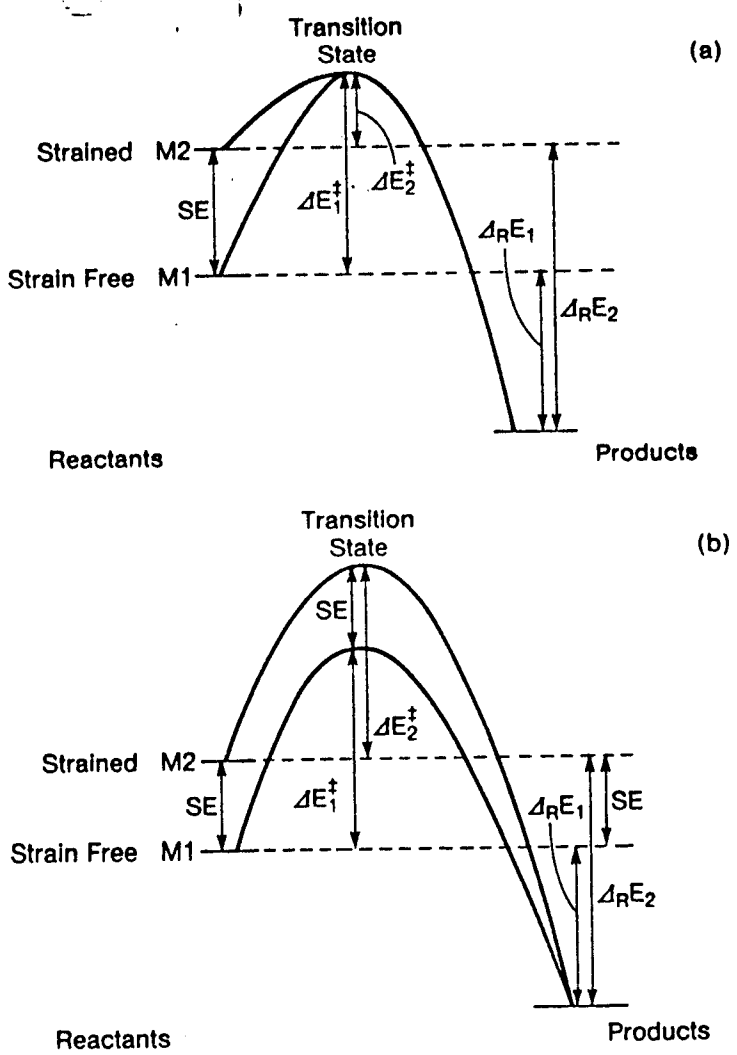


Figure 3-3. Schematic representation of the energy profiles of the reaction of a strained molecule M2 and its strain-free counterpart M1; $\Delta E^{\ddagger}$ and $\Delta_R E$ denote activation and reaction energies, respectively. (*a*) M1 and M2 traverse the same transition state (i.e., the whole SE of M2 is relieved when the transition state is reached. (*b*) M1 and M2 traverse different transition states separated by the energy SE (i.e., the SE of M2 is set free after traversing the transition state.

ments of reaction energetics lead to $\Delta_R G = \Delta_R H - T\Delta_R S$. Hence, changes in entropy may disguise effects resulting from strain.[27b,63]

Despite all the difficulties mentioned above, the concept of strain has been successfully applied when discussing reactions of strained molecules. Many

examples can be found in the literature in which rate constants of strained molecules are rationalized utilizing the relation between strain and reactivity.[33,64,65] (The interested reader may also refer to the forthcoming chapter "Intramolecularity: Proximity and Strain,"[66] in which the relationship between rate constants and strain energy will be discussed in more detail.)

Also, the kinetic data for the formation of ring compounds have been successfully rationalized by considering the strain of the molecules formed.[7,136]

5. COMPARISON OF THE STRAIN ENERGIES IN SMALL CYCLOALKANES

A. Evaluation of Strain Energies from Thermochemical and ab initio Data

Table 3-3 summarizes heats of formation (ΔH_f°), heats of atomization (ΔH_a),[49] and various sets of CSEs reported in the literature.[37,38,42,44,51] CSE values that have been derived from either averaged BEs or group increments (Table 3-2) vary by less than 1 kcal/mol, a variance that results from the choice of the "strain-free" reference molecules. It is noteworthy that Schleyer[38] and Allinger[37] consider cyclohexane to be slightly strained, contrary to the general belief that this molecule is strain-free. However, these authors make use of a definition of strain in an operational sense, not necessarily in terms of absolute strain. As a consequence, all CSEs of cycloalkanes given by Schleyer and Allinger are somewhat higher than those of other authors (see Table 3-3).

If group increments are determined from the enthalpies of single molecules rather than by averaging over the enthalpies of many molecules, CSE values will differ considerably from the average CSEs given in Table 3-3. As an example, CSEs derived from homodesmotic reaction enthalpies suggested by George and co-workers[48] are listed in Table 3-4. The homodesmotic CH_2 group increment is taken from ΔH_f° of propane by subtracting from the latter the ΔH_f° value of ethane (i.e., twice the enthalpy of the CH_3 group increment). This can be expressed in terms of a formal reaction, the homodesmotic reaction[48]:

$$(CH_2)_n \rightarrow n[CH_3CH_2CH_3 - C_2H_6] \qquad 1$$

the reaction enthalpy of which is equal to the CSE. To distinguish the CSE thus obtained from those based on averaged group increments, we will speak of homodesmotic SEs (HSE).

In the same way, the "diagonal" reference states (cyclohexane in the case

TABLE 3-3. Heats of Formation (ΔH_f°), Heats of Atomization (ΔH_a), and Conventional Strain Energies (CSE) of Cycloalkanes[a]

	Cox and Pilcher (1970)		*Conventional strain energies*						
	$\Delta H_f^\circ(T)$	$\Delta H_a(T)$	*Franklin (1949)*	*Cox and Pilcher (1970)*	*Schleyer et al. (1970)*	*Allinger et al. (1971)*	*Benson et al. (1976)*	*Leroy (1985)*	*Average*
Cycloalkane	*Ref.: 49*	*49*	*42*	*49*	*38*	*37*	*44*	*51*	
C_3H_6	12.74	812.57	27.2	27.5	28.1	—[b]	27.6	27.6	27.6
C_4H_8	6.38	1093.62	26.1	26.5	26.9	27.2	26.2	26.9	26.6
C_5H_{10}	−18.46	1393.94	5.7	6.2	7.2	7.5	6.3	6.0	6.5
C_6H_{12}	−29.43	1680.10	−0.6	0	1.3	1.7	0	0.2	0.4
C_7H_{14}	−28.34	1953.91	6.1	6.2	7.6	8.0	6.4	6.4	6.8
$\Delta H_f^\circ(CH_2)$	—	—	−4.9	−4.9	−5.2	−5.2[b]	−4.9	−4.9[c]	−4.9

[a] All enthalpies in kcal/mole. Some authors have used slightly different ΔH_f° values.
[b] The CSE of cyclopropane could not be calculated within the molecular mechanics approach using the same parameters as for other cycloalkanes.[37]
[c] From averaged bond enthalpies.

Table 3-4. Experimental and Theoretical Strain Energies

(a) Homodesmotic and diagonal strain energies obtained at 298 and 0 K with and without ZPE corrections

Cycloalkane $(CH_2)_n$	$\Delta H_f^\circ(298)$		$\Delta H_f^\circ(0)$[b]			ZPE correction		$E(THEO)$,[c]
	HSE	DSE	HSE	DSE	ZPE[b]	HSE	DSE	HSE = DSE
$n = 3$	26.5	27.5	25.5	26.7	49.6	3.4	2.2	28.9
4	25.1	26.0	24.4	26.0	67.1	3.6	2.0	28.0
5	4.5	6.1	4.3	6.3	85.5	2.8	0.8	7.1
6	0.4	0	−2.4	0	103.6	2.4	0	0
CH_2 group	−4.6	−4.9	−2.9	−3.3				

(b) Strain energies obtained with various basis sets at the HF level[a]

n	STO-3G	4-31G	6-31G(d)	6-31G(d, p)
3	46.8[d]	30.4	28.8	28.0
4	29.5	27.0	26.6	27.3
5	6.4		6.8	
6	0.8		0.9	

[a] All enthalpies and energies in kilocalories per mole. The ΔH_f° values of Table 3-3 have been used to calculate CSEs.
[b] ZPE values and vibrational corrections are obtained from frequencies given in Reference 102.
[c] For the definition of E(THEO) see text and Reference 67.
[d] Value from Lathan et al.[72]

of the CH_2 group), suggested by Van Vechten and Liebman[45] lead to the formal reaction:

$$a\,(CH_2)_n \rightarrow b\,(CH_2)_6 \qquad (a \cdot n = 6 \cdot b) \qquad 2$$

that can be used to determine CSE = $-\Delta_R H/a$. In this case we will speak of diagonal SEs (DSE).

Reactions 1 and 2 are useful for a theoretical calculation of CSEs. Table 3-4 gives experimental and theoretical HSEs and DSEs for some cycloalkanes. The HSEs are 1–2 kcal/mol smaller than the CSE values obtained from an averaged $\Delta H_f^\circ(CH_2)$. *Obviously, the CH_2 group in propane is slightly strained.* DSE values, on the other hand, are similar to those given in Table 3-3, which means that a CH_2 group in cyclohexane comes closer to the ideal strain-free CH_2 group than that in propane.

Correcting ΔH_f° values from 298 to 0 K leads to a slight decrease of CSEs. This decrease is compensated when zero-point energy (ZPE) corrections are taken into account and the CSEs are calculated for the motionless molecules at 0 K. These values are listed in Table 3-4 under the heading E(THEO).[67] Two interesting observations can be made.

1. *The energies E(THEO) for the homodesmotic and the diagonal reference state CH_2 are identical (i.e., HSE and DSE are the same for all cycloalkanes).*
2. In the case of small cycloalkanes, the CSEs at 0 K for the motionless molecules are 1–3 kcal/mol larger than the CSE values normally used in chemistry (Table 3-3).

These trends can be explained in the following way. The SEs derived from E(THEO) represent the *electronic consequences* of strain. These will be changed by molecular vibrations where the changes depend on the reference state chosen. The ZPE per CH_2 group is higher for propane-ethane (17.7 kcal/mol) than that for cyclohexane (17.3 kcal/mol). It seems that this has to do with the fact that in the following homodesmotic reaction:

$$(CH_2)_6 \rightarrow 6\,(CH_3CH_2CH_3 - C_2H_6) \qquad 3$$

there are 6 degrees of vibrational freedom fewer (6 degrees of translational/rotational freedom more) on the side of the cyclohexane molecule [total number: $(3 \times 18) - 6 + 6 = 48$ on both sides]. That is, per CH_2 group there are formally just 8 degrees of vibrational freedom on the left but 9 on the right-hand side of reaction 3. Since translational/rotational degrees of freedom do not contribute at 0 K, the ZPE correction per CH_2 group is higher in the case of a homodesmotic definition of CH_2 than in the case of a diagonal definition (based on cyclohexane).

Since ZPE values have to be added to energies E(THEO),[67] the *electronic* SE derived for motionless molecules will be reduced and HSE and DSE values are no longer identical. When the temperature is raised from 0 to 298 K, the difference between HSE and DSE is essentially maintained since $\Delta H_f^\circ(CH_2$, homodesmotic) and $\Delta H_f^\circ(CH_2$, diagonal) change only slightly. This is schematically shown in Figure 3-4.

The definition of HSE and DSE is advantageous when determining the CSE by theoretical means. Calculation of the reaction energies $\Delta_R E$ of reactions 1 and 2 can be performed at the Hartree–Fock (HF) level of theory, since correlation effects play a minor role if number and types of bonds are conserved in a reaction.[48,68] In addition, one can take advantage of the fact that HSE = DSE for theoretical energies E(THEO) and confine the evaluation of CSE to just one reaction.[69] In the following, we will use homodesmotic reaction energies to obtain the CSE = HSE of a cycloalkane. In Table 3-4, HF values of CSEs are given for the STO-3G, 4-31G, 6-31G(d), and 6-31G(d, p) basis set developed in the Pople group.[71] Apart from the STO-3G value for cyclopropane, useful HF CSE values can already be obtained with minimal or split-valence basis sets. The failure of the STO-3G basis in the case of the three-membered ring is well known and has to do with an inadequate description of the strained CC bonds in cyclopropane.[72]

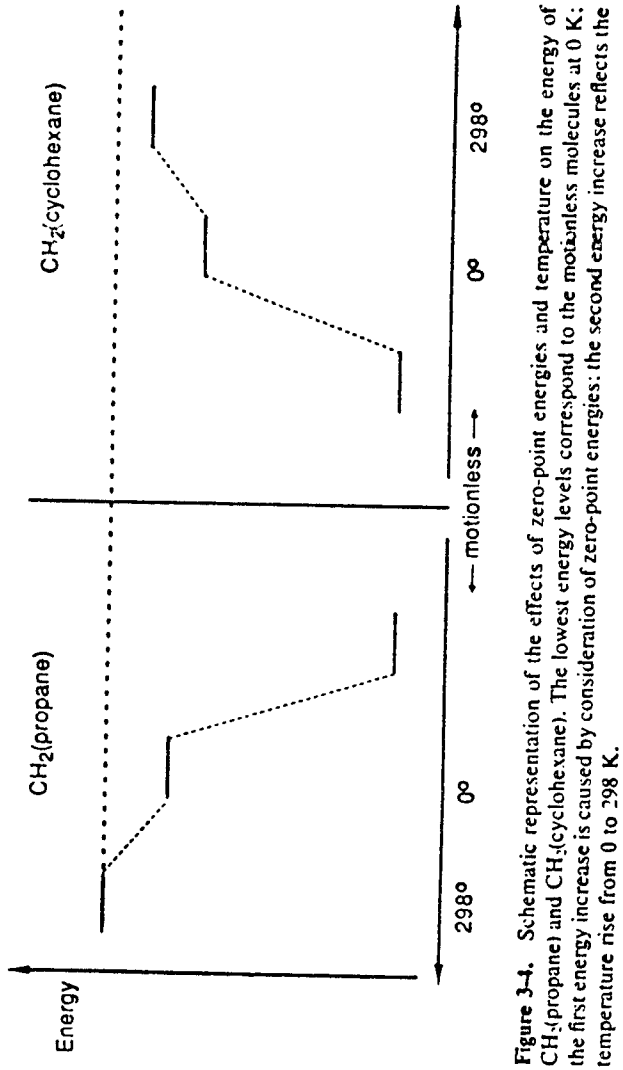


Figure 3-4. Schematic representation of the effects of zero-point energies and temperature on the energy of CH_2(propane) and CH_2(cyclohexane). The lowest energy levels correspond to the motionless molecules at 0 K; the first energy increase is caused by consideration of zero-point energies; the second energy increase reflects the temperature rise from 0 to 298 K.

These are reasonably described when polarization functions are included in the C basis (see, eg, 6-31G(d) results in Table 3-4). At this level of theory, SEs are already close to values derived from E(THEO), that is, values one would obtain if an infinitely large basis set were used and correlation, relativistic, and other corrections were incorporated.[67] However, an HF/6-31G(d) description of strained rings is still somewhat unbalanced, which becomes obvious when analyzing the properties of the H atoms in these molecules. A more reliable account is obtained when moving to a 6-31G(d,p) basis with polarization functions both in the C and the H basis (Table 3-4).[6]

B. The Puzzling Similarity of the Strain Energies of Cyclopropane and Cyclobutane

The energy and enthalpy data of Tables 3-3 and 3-4 reveal that for decreasing ring size, the SE values increase almost exponentially. If one assumes that this increase will be dominated by the increase in Baeyer strain caused by an increasing reduction in the CCC angle, then the SE should be parallel to SE(Baeyer) given in Equation 3-7 (for reasons of simplification, cyclopentane and cyclobutane are taken to be planar):

$$\text{SE(Baeyer)} = n\frac{k_\alpha}{2}\left[109.5° - \frac{180°(n-2)}{n}\right]^2 \qquad (3\text{-}7)$$

An analysis of this equation reveals that the Baeyer SE for (CH_2) increases with $1/n$ for n = 5, 4, 3. This implies a *monotonic* increase of the total SE when going from cyclohexane to cyclopropane. As a matter of fact, a monotonic function CSE = CSE(n) has been found for example in the case of cyclosilanes by Schleyer and co-workers.[11,47] This, however, is only partially true in the case of cycloalkanes. While CSE values increase for n = 6, 5, and 4, *the CSEs of cyclopropane and cyclobutane are almost the same* (see Tables 3-3 and 3-4, and Figure 3-5). This puzzling fact has been disguised for a long time by discussing CSEs per CH_2 group ("normalized CSEs"[32]) rather than total CSE values. If, however, both sets of CSEs are plotted as a function of the ring size n (Figures 3-5 and 3-6), it becomes immediately clear that the CSE of cyclopropane, whether normalized or not, should be considerably larger than the one observed.

In principle, there are three explanations possible for the striking anomaly in the CSEs of cyclopropane and cyclobutane. First, the CSE of cyclopropane could signal a stabilizing effect that reduces its Baeyer strain. This would mean that the CSE of cyclobutane is normal (see curves I in Figures 3-5 and 3-6). Second, the CSE of cyclobutane could be abnormally high while that of cyclopropane is normal (curves II in Figures 3-5 and 3-6). Finally, both CSEs may contain effects not arising from ring strain (curve III in Figure 3-5).

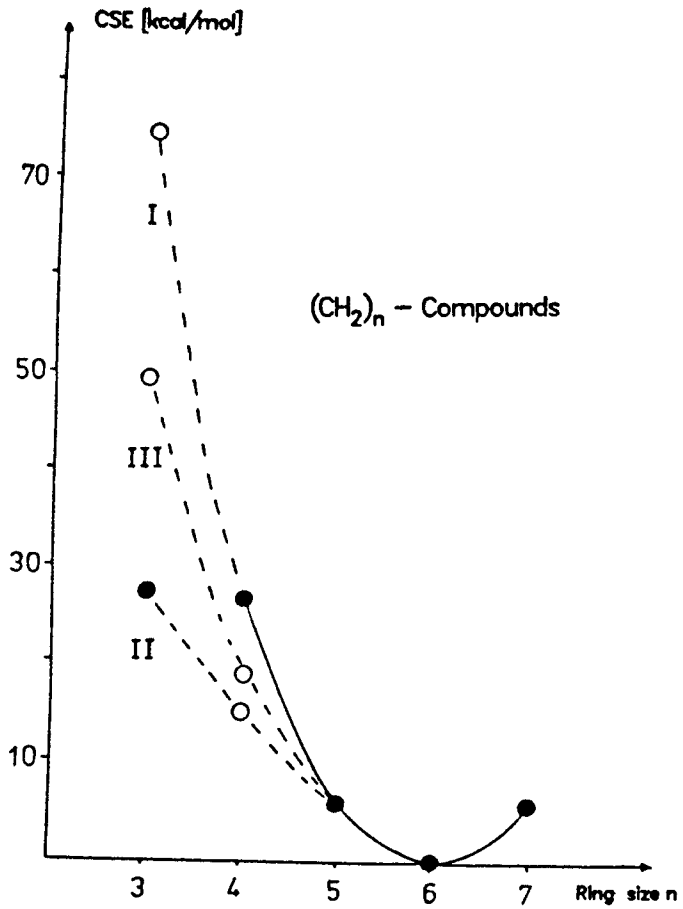


Figure 3-5. Dependence of the conventional strain energies CSEs (solid circles) of cycloalkanes on the ring size n. Curve I: extrapolated to CSE(3) utilizing CSE values for n = 4, 5, 6. The extrapolated value for n = 3 is denoted by the open circle. Curve II: based on the CSE values for n = 3, 5, 6. The interpolated CSE for n = 4 is denoted by the open circle. Curve III: based on the CSE values for n = 5 and 6 and the calculated SEs (Baeyer plus Pitzer SEs) for n = 3 and n = 4 given in Table 3-12.

To find out which of these three explanations is correct, one needs a better understanding of the bonding situation in cyclopropane and cyclobutane. As mentioned in Section 2, the concept of strain is inseparably connected to the concept of bonding. Therefore, one has to examine whether the bonding in cyclopropane and cyclobutane is correctly described in terms of a classical (two-center) electron pair bonding scheme on which the concept of strain is based. This implies an analysis of the electronic structure of the two ring compounds. We will do this by first discussing the wave function (and molecular orbitals) of cyclopropane and cyclobutane and then analyzing the total electron density distribution $\rho(\mathbf{r})$ of these molecules.

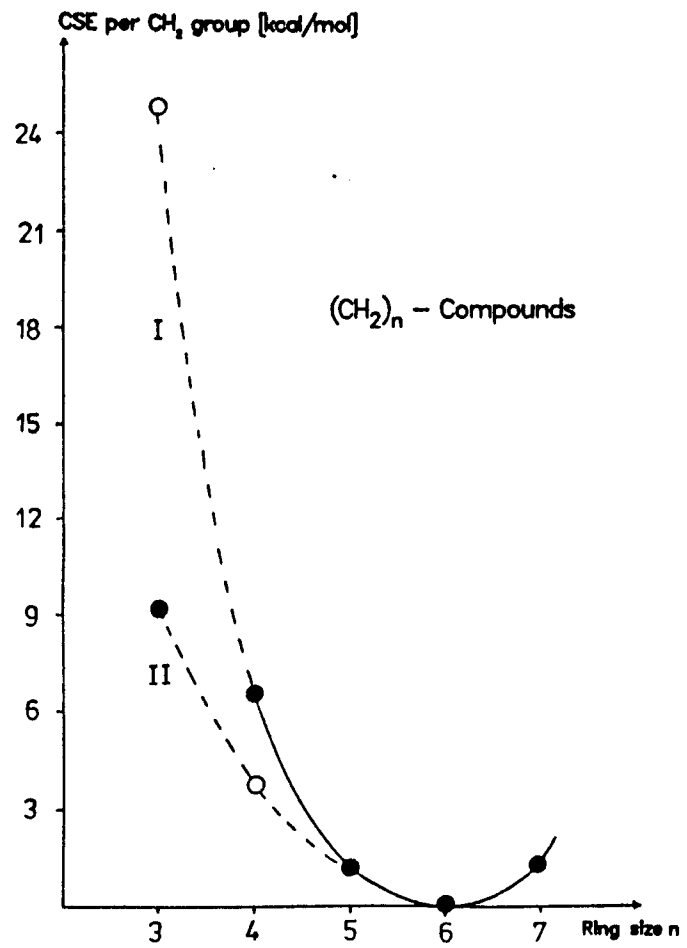


Figure 3-6. Dependence of the strain energy per CH_2 group on the ring size n. Curves I and II have the same meaning as in Figure 3-5.

6. MOLECULAR ORBITAL APPROACH TO STRAIN

In general, the bonding σ MOs of an alkane are symmetric about the interatomic connection line. This can be nicely demonstrated by using localized rather than delocalized MOs. Upon bending of a CC bond, the bond orbital is no longer symmetric with regard to the interatomic connection line. In a strained molecule the hybrid orbitals of an atom try to maintain the tetrahedral directions at the costs of bonding overlap. *Thus strain is closely related to hybrid orbital bending and the concomitant defect in bonding overlap.*

This can be seen when analyzing the localized MOs of cyclopropane ob-

tained from self-consistent field (SCF) MOs by a Boys localization, in which localized orbitals are constructed from the delocalized SCF MOs under the constraint that the distances between the centroids of charge, determined for all occupied orbitals, become maximal. The CC bonding hybrid orbitals are directed outward, by 28° relative to the CC connection line; that is, they enclose an interorbital angle of 116°.[31] Using the Müller–Pritchard equation,[73] hybrid orbitals and interorbital angles can also be derived from ^1J(CH) NMR coupling constants. Lüttke and co-workers[74] have obtained a CCC interorbital angle for cyclopropane somewhat smaller than the ab initio value (102.6°, see Table 3-5), but still substantially larger than the geometrical angle α of cyclopropane. Most important, the hybridization degree n of sp^n hybrid orbitals is considerably larger than 3 (Table 3-5) while that of the CH hybrid orbitals of cyclopropane is essentially 2.

This result was first anticipated by Coulson and Moffitt,[75] who established the bent bond model of cyclopropane by elaborating ideas first proposed by Förster.[76] These authors used two types of sp^n hybrid orbital to describe CC and CH bonding in small cycloalkanes. They minimized the energy of a molecule with respect to the hybridization ratios using different constraints. For cyclopropane they obtained sp^4(CC) and sp^2(CH) hybrid orbitals enclosing angles of 104° (CCC) and 116° (HCH) (Table 3-5). Bonding and antibonding CC bent bond orbitals of cyclopropane are shown in Figure 3-7.

There are various other ways of ascertaining the hybridization ratio n. Randić and Maksić[53] have applied the criterion of maximum overlap connected with a proper weighting of CC and CH bond energies. They obtained sp^5, sp^2 hybrid orbitals for cyclopropane (Table 3-5).

Taking all these clues from the bent bond orbital picture, three important results emerge:

1. Strain is reflected by the nature of the bond orbitals. Bending of the orbitals and a concomitant decrease of bonding overlap is indicative of strained bonds.[75]
2. The hybridization ratios of the bent bond orbitals reveal that the CC bonds in cyclopropane are severely strained while those of cyclobutane are already close to normal.
3. Most important, the CH bond orbitals of cyclopropane differ markedly from those in cyclobutane. They are made up from sp^2 hybrids, which suggests that the CH bonds of cyclopropane are definitely stronger than those in the higher cycloalkanes $(CH_2)_n$ with $n = 4, 5, 6$.

Result 3 suggests that the exceptional similarity in the CSEs of three- and four-membered ring may result from extra-stabilizing effects in the case of cyclopropane. However, before investigating the energetic consequences of these effects, we will consider the Walsh model[77] of cyclopropane and cyclobutane. Since Walsh MOs have been discussed extensively in the literature,[78] we will confine ourselves to pointing out only some essential

TABLE 3-5. Hybridization and Interorbital Angles in Cycloalkanes

		C_3H_6				C_4H_8			C_5H_{10}	C_6H_{12}	
Parameter	Bond	Coulson and Moffitt, 1949 Ref.: 75	Randić and Maksić, 1965 53	Newton, 1977 31	Honegger et al., 1982 80a	Wardeiner et al., 1982 74	Coulson and Moffitt, 1949 75	Newton, 1977 31	Coulson and Moffitt, 1949 75	Wardeiner et al., 1982 74
n in sp^n	CC	4.12	4.91	3.38	3.21	4.58	3.24	2.44	3.0	2.99
	CH	2.28	2.02	1.86	1.94	2.12	2.79	2.54 ax 2.35 eq	3.0	3.01
Interorbital angle	CCC	104	101.7	115	117.4	102.6	108	111.4	108	109.6
	HCH	116	119.6	117.1	115.9	118.2	111	113.3	109.5	109.4

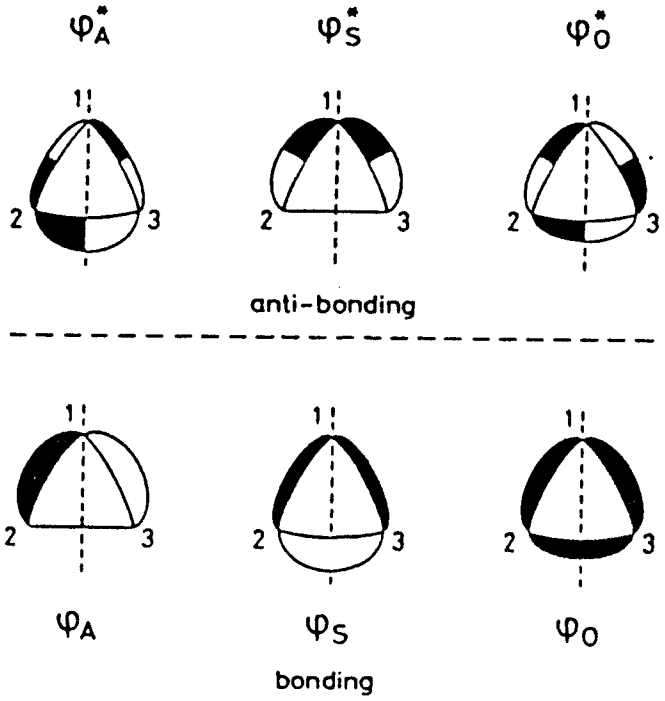


Figure 3-7. The Förster–Coulson–Moffitt bent bond MOs of cyclopropane. (Reproduced with permission from Reference 80b. Copyright © 1986 from *Nouveau Journal de Chimie*.)

features of the MOs of the three- and four-membered ring (compare with Figure 3-8).

There are two distinct sets of Walsh MOs, the *r* set, which consists of linear combinations of radially (toward the ring center) oriented sp^2 hybrid orbitals, and the *t* set, which consists of linear combinations of tangentially (with respect to the ring parameter) oriented p orbitals. The *r* orbitals always form a Hückel system while the *t* orbitals lead to a Möbius system for cyclopropane (*n* odd) and a Hückel system for cyclobutane (*n* even). As shown in Figure 3-8, the final orbitals are obtained by combining *r* and *t* orbitals of appropriate symmetry. There exists always a totally symmetric, doubly occupied, low-lying *r* MO (a_1' and a_{1g} in Figure 3-8) resulting from an in-phase overlap of all sp^2 orbitals inside the ring. The nature of this orbital changes dramatically with the size of the ring (Figure 3-9): For cyclopropane, it is a *surface orbital* covering the ring surface due to effective overlap of the sp^2 hybrid orbitals inside the ring. Increase of the ring size leads to an exponential decrease of orbital overlap. The surface orbital changes to a *ribbon orbital*, which facilitates electron delocalization along the carbon skeleton of cycloalkane similar to a π orbital in cyclopolyenes (Figure 3-9). For rings with $n > 4$, the ribbon MO is topologically equivalent to a π orbital while the *t*-set orbitals correspond to σ orbitals.

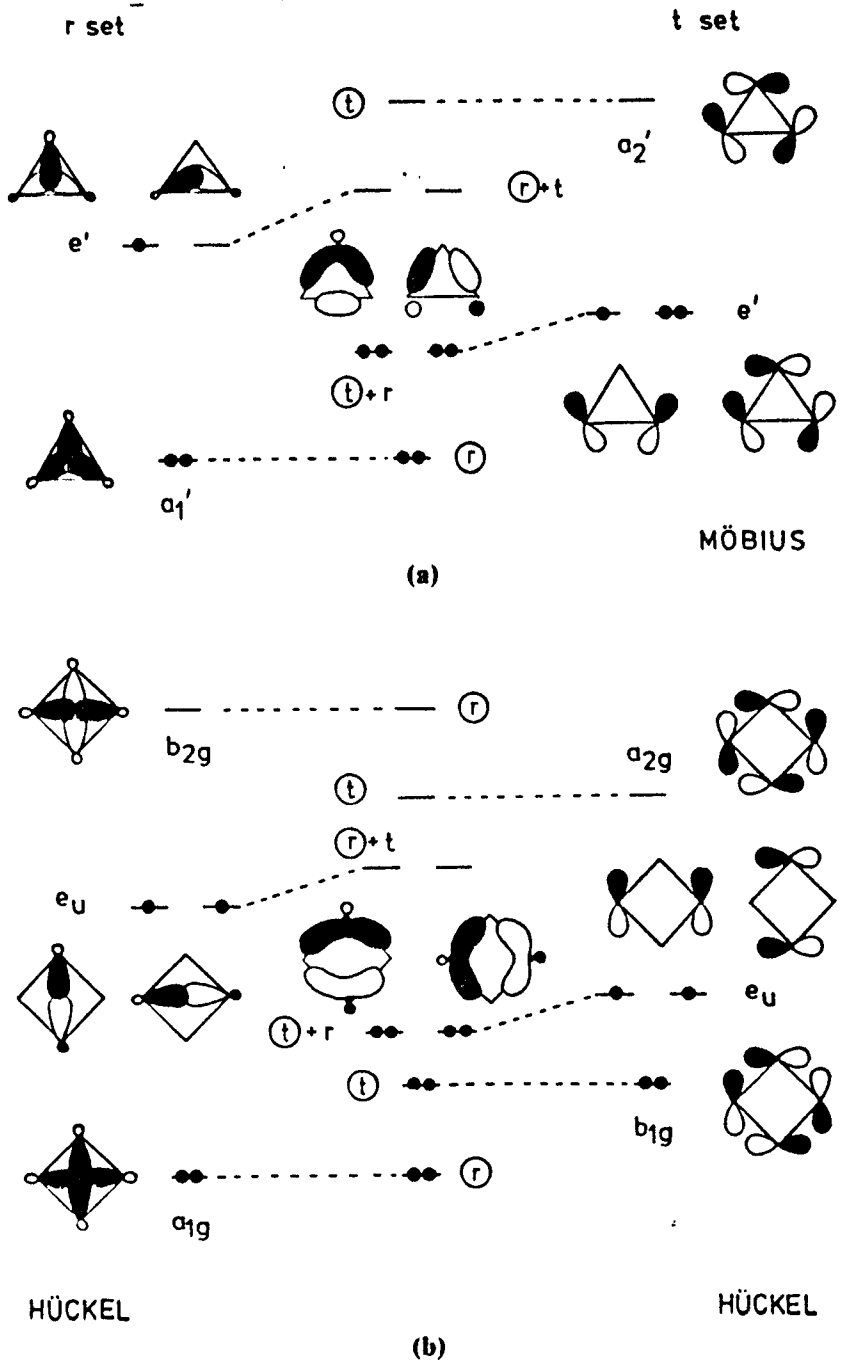


Figure 3-8. The Walsh MOs of cyclopropane (*a*) and cyclobutane (*b*). The predominant nature of the final MOs is indicated by a circled *r* or *t*, respectively. (Reproduced with permission from Reference 6. Copyright © 1986 from the American Chemical Society.)

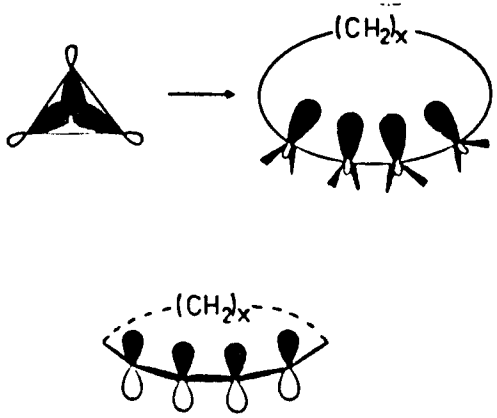


Figure 3-9. Equivalence of the r MOs in a large n-membered ring and the p_π MOs of a cyclopolyene. (Reproduced with permission from Reference 6. Copyright © 1986 from the American Chemical Society.)

For cyclopropane, this correspondence is reversed. Now, the r and t orbitals can be classified as σ and π orbitals as becomes immediately clear by comparison with the MOs of ethylene. For cyclobutane, a classification of r and t orbitals is no longer possible, since both enclose angles of 45° with the CC connection lines.[6]

From the Walsh MOs of cycloalkanes one can draw some important conclusions:

1. *Due to its topology, cyclopropane differs from all other cycloalkanes by possessing a surface orbital. Occupation of this MO leads to a two-electron, three-center bond* similar to that in H_3^+, B_2H_6, or other electron-deficient compounds. Hence, CC bonding in cyclopropane may be much stronger than one would expect in view of the poor overlap of the t orbitals (Figure 3-8).

2. Since the t orbitals of cyclopropane resemble the π MOs of ethylene, the former should possess properties typical of alkenes.[79]

3. Mixing of r and t orbitals for $n > 3$, apart from improving 1, 2-bonding interactions in the ring (see Figure 3-8), leads to antibonding interactions across the ring. They are strongest in cyclobutane, causing relatively large 1,3-CC nonbonded repulsion.

The Walsh MOs provide further clues for the electronic effects operating in cycloalkanes and, possibly, affecting their thermodynamic stability. It is evident from the discussion that nonbonded repulsion plays an important role in cyclobutane by enhancing total strain. In the case of cyclopropane, a two-electron, three-center bond may reduce ring strain effectively.[6]

The Walsh and the Coulson–Moffitt bent bond models provide complementary pictures of small rings employing two different sets of basis orbitals. As has been demonstrated by Heilbronner and co-workers,[80] they are equivalent provided complete orbital sets, including bonding and antibonding MOs, are considered. It seems that the Coulson–Moffitt model easily offers a possibility of estimating the energetic consequences of strain in cycloalkanes, while the Walsh model provides a basis of drawing a connection between strain and reactivity. Of course, neither of the two orbital models leads to a direct assessment of the SE or of the energetic effects increasing or decreasing it. Even if the existence of a two-electron, three-center bond is established for cyclopropane, its energetic consequences cannot be readily established through an orbital analysis. This has to do with the present lack of a rigorous solution to the problem of obtaining a unique definition of the chemical bond based on orbital theory. Since any conceptual approach to molecular strain is inevitably connected to a unique description of chemical bonding, one must spend some time establishing a physically reasonable definition of the chemical bond before assessing the energetic effects of CH bond strengthening or three-center bonding in cyclopropane. We will tackle this objective by investigating the electron density distribution in cycloalkanes before returning to the energetic consequences of strain.

7. ELECTRON DENSITY APPROACH TO STRAIN

Contrary to the nonobservable molecular orbitals, the total electron density distribution $\rho(\mathbf{r})$ of a molecule is an observable quantity that can be determined both experimentally and theoretically.[81] As shown by Hohenberg and Kohn,[82] the energy of a molecule in a nondegenerate ground state is a functional of $\rho(\mathbf{r})$. All physical and chemical properties of a molecule depend in some way on the electron density distribution. Therefore, it may be possible to derive useful information about molecular strain from $\rho(\mathbf{r})$.

Figure 3-10 depicts the calculated electron density distribution of cyclopropane in the form of a perspective drawing with regard to the plane of the three C nuclei. The distribution $\rho(\mathbf{r})$ is maximal at the positions of the nuclei and decreases exponentially in off-nucleus directions. It seems that the exponential decay of $\rho(\mathbf{r})$ obscures all details of the density distribution that relate to the peculiar bonding situation or to the effects of strain in cyclopropane. Hence, the main problem in analyzing $\rho(\mathbf{r})$ is to find the right tool to uncover bonding features like the bent bond character of a strained CC bond.

A. Description of Bent Bonds with Difference Densities

A popular way of eliminating the dominant exponential decay in the off-nucleus direction and unearthing the details of $\rho(\mathbf{r})$ in the bonding region is based on the difference density distribution[83]:

$$\Delta\rho(\mathbf{r}) = \rho[\text{molecule}] - \rho[\text{promolecule}] \qquad (3\text{-}8)$$

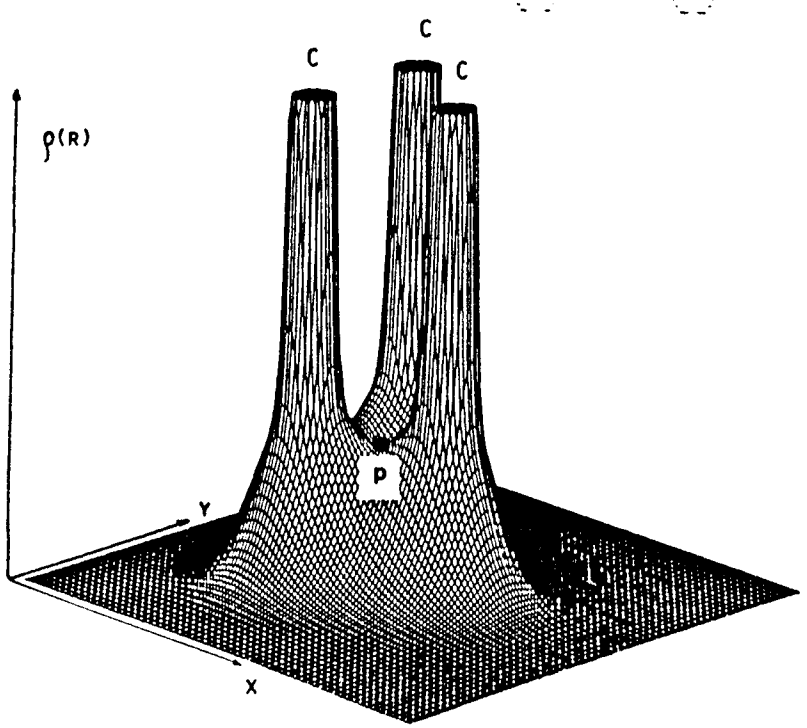


Figure 3-10. Perspective drawing of the calculated [HF/6-31G(d, p)] electron density distribution $\rho(\mathbf{r})$ in the ring plane of cyclopropane; p denotes the position of the bond critical point between two neighboring carbon atoms. (For better presentation, values above 14 e/Å^3 are cut off.)

The promolecular density is conventionally constructed by summing over spherically averaged atomic densities, with the atoms kept in the positions that they adopt in the molecule. A positive difference density in the internuclear region is generally considered to be indicative of bonding.

X-ray diffraction studies of various compounds containing strained three-membered rings have led to difference electron density maps which reveal $\Delta\rho(\mathbf{r})$ maxima displaced up to 0.3 Å from the internuclear axes[84] (see Figure 3-11). These maxima are generally interpreted as arising from the bent character of the strained bonds. Connecting their location with the nuclei, the resulting CCC angles are 104–108°,[84] which is reminiscent of the interorbital angles of the bent bond orbitals (see above: Table 3-5). However, it must be stressed that interorbital angles and angles derived from difference electron densities are not comparable quantities. Also, these angles are *not* related to the true interbond angles needed for a description of strained bonds.

The use of $\Delta\rho(\mathbf{r})$, although convenient from the point of view of the crystallographer, implies some serious problems insofar as it depends on a hypothetical reference state, the promolecule. For example, negative rather than positive difference electron densities have been found for several bonds.[85] A new method for deriving suitable difference electron densities from "oriented" rather than spherically averaged atomic densities proposed by Schwarz and co-workers[86] may alleviate these problems. Nevertheless, it would be far better to analyze the observable quantity itself rather than a model-dependent quantity, derived from the observable quantity. A physically meaningful description of the chemical bond is more likely to be developed from an analysis of $\rho(\mathbf{r})$ rather than any arbitrarily defined $\Delta\rho(\mathbf{r})$. Therefore, we will briefly describe the topological analysis of $\rho(\mathbf{r})$, a method that is quantum mechanically justified,[57] and does not suffer from the difficulty of choosing a proper reference state.

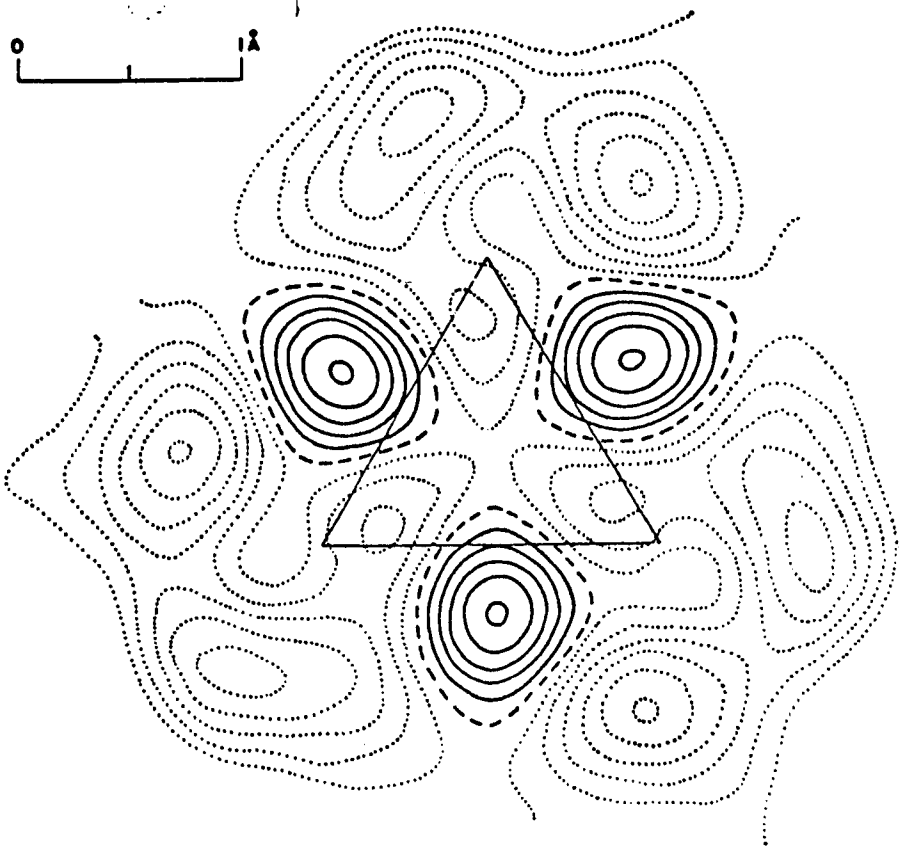


Figure 3-11. Contour line diagram of the difference density in the ring plane of *cis,cis*-,1,2,3-tricyanocyclopropane (X-ray diffractometric study). Solid lines are in regions with positive difference density, dotted lines are in regions with negative difference density. Dashed lines correspond to zero values. (Reproduced with permission from Reference 84a. Copyright © 1986 from *Acta Crystallographica*.)

B. The Topological Analysis of the Electron Density Distribution

The topological analysis of $\rho(\mathbf{r})$, developed by Bader and co-workers,[57] is based on the investigation of the critical (stationary) point $\mathbf{p}_s$ of $\rho(\mathbf{r})$. These are the sources and sinks of the gradient paths (trajectories) of the gradient vector field $\nabla\rho(\mathbf{r})$. The gradient vector always points into the direction of a maximum increase in $\rho(\mathbf{r})$.

An analysis of the gradient vector field $\nabla\rho(\mathbf{r})$ is more than just a way of describing the distribution $\rho(\mathbf{r})$ with appropriate mathematical tools. It directly leads to a *quantum mechanically* based definition of molecular subspaces, which in turn can be used to define an *atom in a molecule*, a *chemical bond*, and the *molecular structure*—that is the network of bonds connecting the atoms in a molecule. These definitions are of general chemical importance, but they become particularly important when trying to determine the SE of a molecule from in situ bond energies or in situ atomic energies (see Subsection B of Section 3).

To facilitate a brief discussion of the essence of the topological analysis, the gradient vector field $\nabla\rho(\mathbf{r})$ corresponding to the distribution $\rho(\mathbf{r})$ of Figure 3-10 is shown in Figure 3-12. Three types of trajectory of the vector field $\nabla\rho(\mathbf{r})$ can be distinguished. First, there are those that end at one of the three nuclei starting either at infinity or at the center of the ring (type I). Second, there are trajectories that start at a point $\mathbf{p}$ between the C nuclei and terminate at one of the nuclei in question (type II). The point $\mathbf{p}$ is shown in Figure 3-10 for the CC bond in front. The electron density assumes a minimal value at $\mathbf{p}$ in the internuclear direction but a maximal value at $\mathbf{p}$ in all directions perpendicular to that direction; that is, $\mathbf{p}$ is a saddle point in three dimensions. Exactly, three saddle points $\mathbf{p}$ can be found in the $\nabla\rho(\mathbf{r})$ field of the carbon ring, each being located in one of the three CC bond regions (Figure 3-12). There are just two type II trajectories per saddle point $\mathbf{p}$. They connect the neighboring C nuclei and describe a *path of maximum electron density (MED path)*. Any lateral displacement from the MED path leads to a decrease in $\rho(\mathbf{r})$. Finally, there are trajectories that originate at infinity and terminate at the saddle point $\mathbf{p}$ (type III). In three dimensions, these trajectories form a surface S separating the two nuclei that are linked by the MED path. The flux of $\nabla\rho(\mathbf{r})$ vanishes for all surface points:

$$\nabla\rho(\mathbf{r}) \cdot \mathbf{n}(\mathbf{r}) = 0 \qquad \mathbf{r} \in S \tag{3-9}$$

where $\mathbf{n}$ is the unit vector normal to the surface S. The surfaces S have been named *zero-flux surfaces*.[57]

As shown in Figure 3-12, the zero-flux surfaces partition the molecular space into subspaces, each containing one and only one atomic nucleus. This observation has been made for many molecules and, therefore, it is reasonable to consider the subspaces derived from zero-flux surfaces as atomic subspaces.[57] All type I trajectories terminating at a given nucleus define its basin. The nucleus and its associated basin define the atom in the molecule.[57] Hence, the zero-flux surfaces correspond to *interatomic* surfaces.

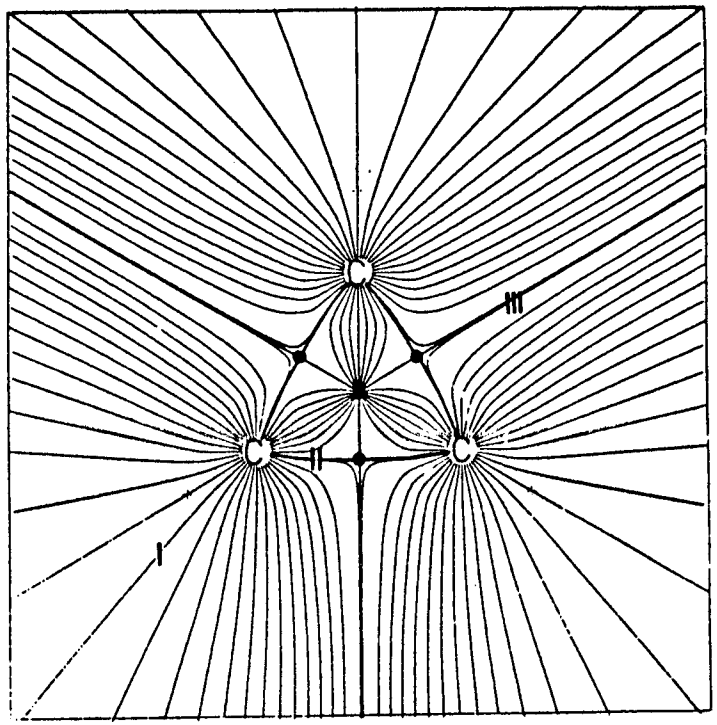


Figure 3-12. Gradient vector field of the [HF/6-31G(d, p)] electron density distribution $\rho(\mathbf{r})$ calculated for the plane of the cyclopropane ring. Bond critical points are denoted by dots. Type I trajectories start at infinity or the center of the ring and end at a carbon nucleus; type II trajectories (heavy lines) define the bond path linking two neighboring carbon atoms; type III trajectories form the three zero-flux surfaces between the C atoms (in the two-dimensional display, only their traces can be seen). They terminate at the bond critical points.

C. The Definition of a Chemical Bond

Investigation of the ring opening of cyclopropane has revealed that the MED path vanishes upon bond rupture and reappears when the bond is formed again.[87] These observations have led Cremer and Kraka[88] to consider the existence of a saddle point $\mathbf{p}$ and hence a MED path linking the two nuclei of the adjoining atomic subspaces as a necessary condition for the existence of a chemical bond.

However, MED paths are also found for any ensemble of weakly or noninteracting atoms and molecules or for the dissociation products of a molecule.[88] To distinguish between covalent chemical bonds and closed-shell interactions as found in the case of van der Waals molecules, hydrogen

bonding, or electrostatic (ionic) interactions, it has been suggested that the properties of the energy density[88]:

$$H(\mathbf{r}) = G(\mathbf{r}) + V(\mathbf{r}) \tag{3-10}$$

are analyzed.[57] Here, $G(\mathbf{r})$ and $V(\mathbf{r})$ correspond to *a* local kinetic energy density and to *the* local potential energy density, respectively. Since $G(\mathbf{r})$ is always positive and $V(\mathbf{r})$ is always negative, the sign of the energy density $H(\mathbf{r})$ reveals whether accumulation of electron density at a point $\mathbf{r}$ is stabilizing [$H(\mathbf{r}) < 0$] or destabilizing [$H(\mathbf{r}) > 0$]. Analysis of a variety of different bonds[88,89] suggests that covalent bonding is characterized by a predominance of the local potential energy density $V(\mathbf{r})$ at $\mathbf{p}$, hence $H(\mathbf{p}) < 0$. In contrast, closed-shell interactions lead to $H(\mathbf{p}) \geq 0$. Therefore, Cremer and Kraka[88] suggested that a negative local energy density $H(\mathbf{r})$ at the minimum $\mathbf{p}$ of the MED path be considered as *sufficient* condition for covalent bonding (Table 3-6). In this case, the MED path provides an image of the covalent chemical bond and, therefore, may be called a "bond path." Accordingly, the saddle point $\mathbf{p}$ corresponds to a "bond critical point."

A clear definition of the (covalent) chemical bond is of paramount importance when describing strained bonds. In this connection, two further definitions are useful, namely those of the bond length and the bond angle. The former is equal to the bond path length r_b. It is not necessarily identical with

Table 3-6. Description of Atoms in Molecules and Chemical Bonds in Terms of the Properties of $\rho(\mathbf{r})$

Chemical term	*Terms used in density analysis*	*Comment*
Atom	Nucleus + basin	Basin defined by virial partitioning[57]
Interatomic surface	Zero-flux surface	Using zero-flux surfaces defined by Equation 3-9
Covalent bond	Bond path	Necessary condition: Existence of MED path linking the bonded atoms
		Sufficient condition: Negative energy density $H(\mathbf{p})$ at the minimum of the MED path
	Bond critical point $\mathbf{p}$	Saddle point of ρ, identical with the minimum of the MED path
Bond length	Bond path length r_b	r_b is larger than the geometrical distance r_e for bent bonds
Bond angle	Interpath angle β	β is (normally) larger than the geometrical angle α in strained rings
Bent bond character		Deviation d of bond path from the interatomic connection line
Bond order		Evaluated from ρ at $\mathbf{p}$ according to Equation 3-11
π Character	Bond ellipticity ε	Defined by the curvatures of ρ at $\mathbf{p}$ perpendicular to the bond (see Equation 3-12)

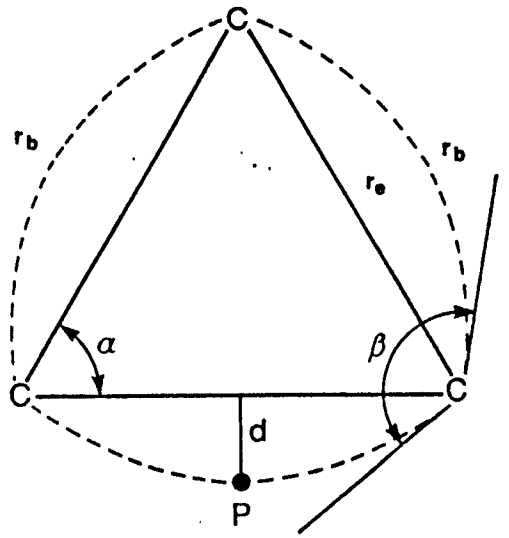


Figure 3-13. Geometrical and bond parameters of cyclopropane. Bond paths are indicated by dashed lines and α is the geometrical angle, β the interpath angle, r_e the geometrical distance, and r_b the bond path length; d denotes the perpendicular distance between the bond critical point $\mathbf{p}$ and the internuclear connection line.

the geometrical distance r_e between two bonded atoms. As a matter of fact r_b is larger than r_e in the case of bent bonds (Table 3-6; see also Reference 75). The bond angle is equal to the interpath angle β, which also can differ considerably from the geometrical angle α for strained molecules. Thus the curvature of a bond is described by both the ratio r_b/r_e and the interpath angle β. Another useful quantitative measure of bond bending is the perpendicular distance d between the bond critical point $\mathbf{p}$ and the internuclear connection line (see Figure 3-13).

Other useful bond features (e.g., the bond order n and the π character) can be extracted from the properties of $\rho(\mathbf{r})$ at the bond critical point.[87,88] For hydrocarbons, the bond order is determined with the relationship:

$$n(\mathrm{CC}) = \exp\{a\,[\rho(\mathbf{p}) - b]\} \tag{3-11}$$

where $b = \rho(\mathbf{p}, \text{ethane})$ and a is adjusted to lead to $n \approx 2$ (3) for ethylene (acetylene). The bond order thus defined depends on a local property of $\rho(\mathbf{r})$; hence, care must be taken when discussing the bond strength, which actually depends on both the total electron density in the internuclear region and the forces exerted on this density.

The π character of a bond can be related to the anisotropy of $\rho(\mathbf{r})$ at the bond critical point. It is measured with the aid of the three curvatures of $\rho(\mathbf{r})$ along the principal axes at $\mathbf{p}$ corresponding to the eigenvalues λ_i ($\lambda_1 \leq \lambda_2 \leq \lambda_3$) and the eigenvectors $\mathbf{v}_i$ of the matrix of second derivatives $\partial^2\rho/\partial x_i \partial x_j$ (i,

$j = 1, 2, 3$).[87] For the standard CC bond in ethane, the charge distribution at **p** is isotropic, yielding $\lambda_1 = \lambda_2 < 0$. In the case of ethylene, however, the density falls off less rapidly in the π direction ($\mathbf{v}_2$) and $\lambda_1 < \lambda_2 < 0$. The density distribution at the bond critical point of the CC double bond (or other double bonds) is *anisotropic*. The degree of anisotropy is measured by the bond *ellipticity* ε[87]:

$$\varepsilon = \frac{\lambda_1}{\lambda_2} - 1 \tag{3-12}$$

Since values of ε larger than zero are found for bonds with (partial) π character, it is useful to define the π character of a bond by its ellipticity ε at **p**. The bond properties defined with the aid of $\rho(\mathbf{r})$ are summarized in Table 3-6.

D. Bonding in Cyclopropane and Cyclobutane

In Table 3-7, bond parameters of some strained rings are compared with the corresponding geometrical parameters. For three-membered rings the bond lengths r_b are up to 0.02 Å longer than the r_e values, while $r_b \approx r_e$ for cyclobutane. The shift parameters d, however, range from 0.04 to 0.08 Å with the smaller values for the four-membered ring. Even more pronounced are the differences between the angles α and β (Table 3-7), being roughly 19° for cyclopropane and 6–7° for cyclobutane.[4,6]

The importance of this result can be highlighted by inserting β and α values in the Hooke equation (3-3, above). Assuming a force constant of unity, a Baeyer strain energy of 58 kcal/mol is evaluated from β(CCC) of cyclopropane while an SE of 161 kcal/mol results from the geometrical angle.

TABLE 3-7. Description of Strained Rings in Terms of the Properties[a] of $\rho(\mathbf{r})$

Molecule	*Bond*	r_e	r_b[b]	d[c]	ε[d]	*Angle*	α	β[b]
Cyclopropane	CC	1.497	1.506	0.060	0.49	CCC	60	78.8
Aziridine	CC	1.470	1.486	0.080	0.39	CCN	59.5	77.3
	CN	1.449	1.455	0.043	0.50	CNC	60.9	76.4
Oxirane	CC	1.453	1.476	0.094	0.31	CCO	58.8	72.8
	CO	1.401	1.404	0.004	0.88	COC	62.4	75.8
Bicyclobutane	CC[e]	1.484	1.502	0.089	0.36	CCC[e]	58.8	73.6
	CC	1.513	1.522	0.056	0.49	CCC	60.6	77.4
Cyclobutane	CC	1.544	1.547	0.038	0.02	CCC	88.6	95.6

[a] Distances in angstrom units, angles in degrees. All values from HF/6-31G(d, p) calculations[4,6] and unpublished results of the authors.
[b] Compare with Figure 3-13 and Table 3-6.
[c] Bent bond character: see Table 3-6.
[d] Bond ellipticity (π character) defined in Equation 3-12.
[e] Central bond and angle opposite to central bond, respectively.

Clearly, *the latter value is meaningless because it is derived from a value that depends on the topology of the ring but bears no resemblence to the actual deformation of the CC bonds.*

Another interesting feature emerges from the density analysis. The calculated CC bond orders are literally identical with that of ethane ($n \approx 1$).[4] It must be remembered, of course, that the bond order is derived from a local property, the value of $\rho(\mathbf{r})$ at **p**. It is unlikely that any local quantity is a useful means of assessing a global property of a molecule. This also applies to the interorbital angle, but not to the orbital overlap and the interpath angles. Hence, the latter quantities will lead to a useful description of strain (see Table 3-8).

TABLE 3-8. Descriptors of Strain

Property	*MO Approach*	*ρ Approach*	*Assessment of strain*
Local	Interorbital angle	Bond order (density at **p**)	No
Global	Overlap	Interpath angle	Yes

For cyclopropane, CC bond ellipticities (0.49) comparable to those of ethylene (0.45) have been calculated (Table 3-7[4,87]). Not surprisingly, the soft curvature of $\rho(\mathbf{r})$ is *in* the plane of the C_3 ring, indicating that the density extends from the bond critical point toward the ring center. Hence, the π character of the cyclopropane bonds, which has been substantiated in many experimental investigations,[79] is confirmed and quantified by the analysis of the electron density distribution. In addition, an important conclusion can be drawn from the density parameters that describe the bent bonds in cyclopropane: *bending of a formal CC σ bond leads to an admixture of π character.*[90]

The π character of the CC bonds of cyclopropane is connected with the extension of the density into the center of the ring. At the ring center, the value of $\rho(\mathbf{r})$ is more than 80% that at the CC bond critical points.[4–6] Obviously, electron density is smeared out over the whole ring surface, a phenomenon that has been termed *surface delocalization*.[4–6] For cyclobutane, the density at the center of the ring is just 30% of that found at the CC bond critical points. Also, the bond ellipticity is vanishingly small (0.02), revealing that both π character and surface delocalization are of no relevance for the four-membered ring.[4–6]

It is appealing to draw a connection between the surface delocalization of electrons revealed by the analysis of $\rho(\mathbf{r})$ and the existence of a surface orbital within the Walsh MO description of the three-membered ring. Obviously, the properties of $\rho(\mathbf{r})$ add further support to the existence of a two-electron, three-center bond in cyclopropane. On the other hand, there are remarkable differences between the MO and the ρ description of the three-membered ring. Interorbital and interpath angles (Tables 3-5 and 3-7) differ greatly. The value of $\rho(\mathbf{p})$ in the CH bonds of cyclopropane is not very different from that found for the CH bonds of cyclobutane (although a slight

increase of the former value is found). A weakening of the CC bonds in cyclopropane is not reflected by the bond order.

A priori, one should expect any information about bonding and strain gained from an analysis of the MOs to be "hidden" also in the electron density. The only question is, How can this information be displayed? We tackle this problem next, by analyzing the Laplacian of $\rho(\mathbf{r})$.

8. A STEP TOWARD A UNIFIED DESCRIPTION OF STRAIN: THE LAPLACIAN OF THE ELECTRON DENSITY

The Laplacian of any scalar field $f(\mathbf{r})$, $\nabla^2 f(\mathbf{r})$, is given by the second derivatives of $f(\mathbf{r})$ with regard to $\mathbf{r}$. It can be obtained as the sum of the eigenvalues of the Hessian matrix [matrix of the second derivatives of $f(\mathbf{r})$ with regard to the three components of the vector $\mathbf{r}$, namely x, y, and z]. The Laplacian is negative where the scalar field concentrates.[91] It adopts a minimum where $f(\mathbf{r})$ possesses a maximum.[92] The Laplacian of the electron density distribution $\nabla^2\rho(\mathbf{r})$ has been used to detect locations in molecular space at which electronic charge is concentrated ($\nabla^2\rho(\mathbf{r}) < 0$) or is depleted ($\nabla^2\rho(\mathbf{r}) > 0$).[89,93] This can be done *without* defining an arbitrary reference density.

Bader has shown that the Laplacian $\nabla^2\rho(\mathbf{r})$ plays a key role in the quantum mechanical equations governing the behavior of $\rho(\mathbf{r})$.[57] For example, $\nabla^2\rho(\mathbf{r})$ provides the link between electron density and energy density via a local virial theorem:

$$\frac{\hbar^2}{4m}\nabla^2\rho(\mathbf{r}) = 2G(\mathbf{r}) + V(\mathbf{r}) \qquad (3\text{-}13)$$

where the sum of the kinetic energy density $G(\mathbf{r})$ and the potential energy density $V(\mathbf{r})$ equals the energy density $H(\mathbf{r})$ (Equation 3-10).[88]

An increase of $|V(\mathbf{r})|$ leads to enhanced concentration of electronic charge at $\mathbf{r}$, an increase of $G(\mathbf{r})$ to its depletion. Integrated over an atomic subspace defined by the zero-flux surfaces (Equation 3-9), or integrated over total molecular space, the Laplacian of $\rho(\mathbf{r})$ vanishes; that is, the fluctuations in $\nabla^2\rho(\mathbf{r})$ are such that local depletion or concentration of electronic charge cancel each other, both for an atom in a molecule and for the molecule itself.

For an isolated atom with spherically averaged electron density, negative charge is concentrated in spheres, which in turn are separated by spheres of charge depletion.[93] [One must keep in mind that charge concentration and electron density are two different quantities and, as such, this finding does not contradict the exponential decay of $\rho(\mathbf{r})$, described above.] It is appealing to associate the spheres of the Laplacian with quantum shells. Then, for a first-row element, the inner concentration sphere is assigned to the 1s shell, the outer sphere to the valence shell. This is shown in Figure 3-14*a* for

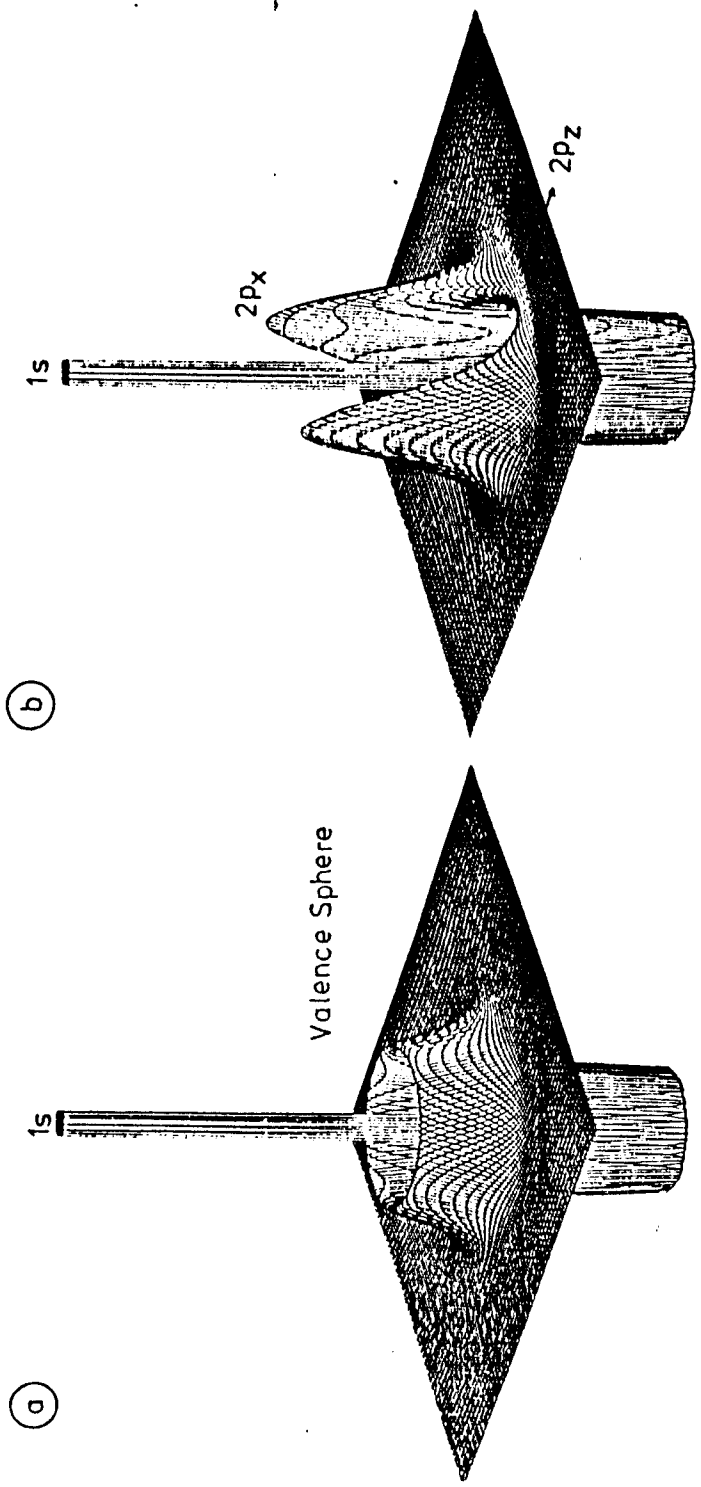


Figure 3-14. Perspective drawing of the calculated [UHF/6-31G(d)] Laplace concentration $-\nabla^2\rho(\mathbf{r})$ of the carbon atom. (*a*) C atom with spherically averaged electron density. (*b*) C atom in the ^3P ($1s^2\,2s^2\,2p_x\,2p_y$) ground state, depicted in the xz plane. The concentration peak at the position of the C nucleus is assigned to the 1s electrons, the outer concentration sphere to valence shell electrons. In (*b*), the lumps and holes in the valence sphere correspond to the occupied $2p_x$ and the empty $2p_z$ AO, respectively. (For a better presentation, values above 48 $e/Å^5$ and below -24 $e/Å^5$ are cut off.)

TABLE 3-9. Information Available from $\rho(\mathbf{r})$

Analysis of $\rho(\mathbf{r})$ via	*Calculation of*	*Leads to*	*Chemical information about*
Gradient vector field $\nabla\rho(\mathbf{r})$	First derivatives of $\rho(\mathbf{r})$	Critical points and electron density paths	Atoms in molecules, chemical bonds, molecular structure
(Scalar) Laplace field $\nabla^2\rho(\mathbf{r})$	Second derivatives of $\rho(\mathbf{r})$	Concentration lumps and holes	Reactive sites in a molecule

If the charge distribution of the isolated atom possesses isotropic and anisotropic components as in the case of the C atom in the ^3P ($1s^2 2s^2 p^2$) ground state, then the Laplacian of $\rho(\mathbf{r})$ is no longer spherical. Local maxima (lumps) and minima (holes) develop in the valence shell, while the inner concentration shell remains unchanged. The lumps are in the direction of the occupied p orbitals, the holes in the direction of the empty p orbital. Hence, the lumps and holes of the Laplacian of $\rho(\mathbf{r})$ reflect the shape of the "frontier orbitals" of C(^3P).

The Laplacian bridges the gap between the orbital and density descriptions of electronic structure. Information extracted from the analysis of the orbitals is also obtained in $\rho(\mathbf{r})$ and can be revealed by the analysis of the Laplacian of ρ.

In the same way that sites of nucleophilic or electrophilic attack in a molecule can be predicted by analyzing the form of the frontier orbitals, an investigation of the Laplace concentration of $\rho(\mathbf{r})$ helps to identify the active sites of the molecule: sites with distinct electron concentration lumps are prone to an electrophilic attack, while deep concentration holes in the valence shell are prone to a nucleophilic attack.

The chemically relevant information extracted from $\rho(\mathbf{r})$ by analyzing either $\nabla\rho(\mathbf{r})$ or $\nabla^2\rho(\mathbf{r})$ is summarized in Table 3-9. It is important to keep in mind that only $\rho(\mathbf{r})$ is observable and that $\nabla\rho(\mathbf{r})$ and $\nabla^2\rho(\mathbf{r})$ must not be mixed up with $\rho(\mathbf{r})$ itself.

Figure 3-15 presents a perspective drawing of $\nabla^2\rho(\mathbf{r})$ for cyclopropane with respect to the plane of the carbon nuclei. The positions of the carbon atoms can be easily recognized by the 1s concentration peaks. The valence shells are distorted so that each carbon possesses four concentration lumps in the direction of the four carbon valences, two of which are hidden in Figure 3-15 because they are perpendicular to the reference plane. The distinct concentration lumps at the C atoms suggest that corner protonation is more likely than edge or face protonation of cyclopropane.[4]

At first sight, the concentration lumps in the CC bonding regions seem to disclose the location of the CC bond paths. A quantitative analysis, however, reveals that the concentration maxima in the valence region of C are

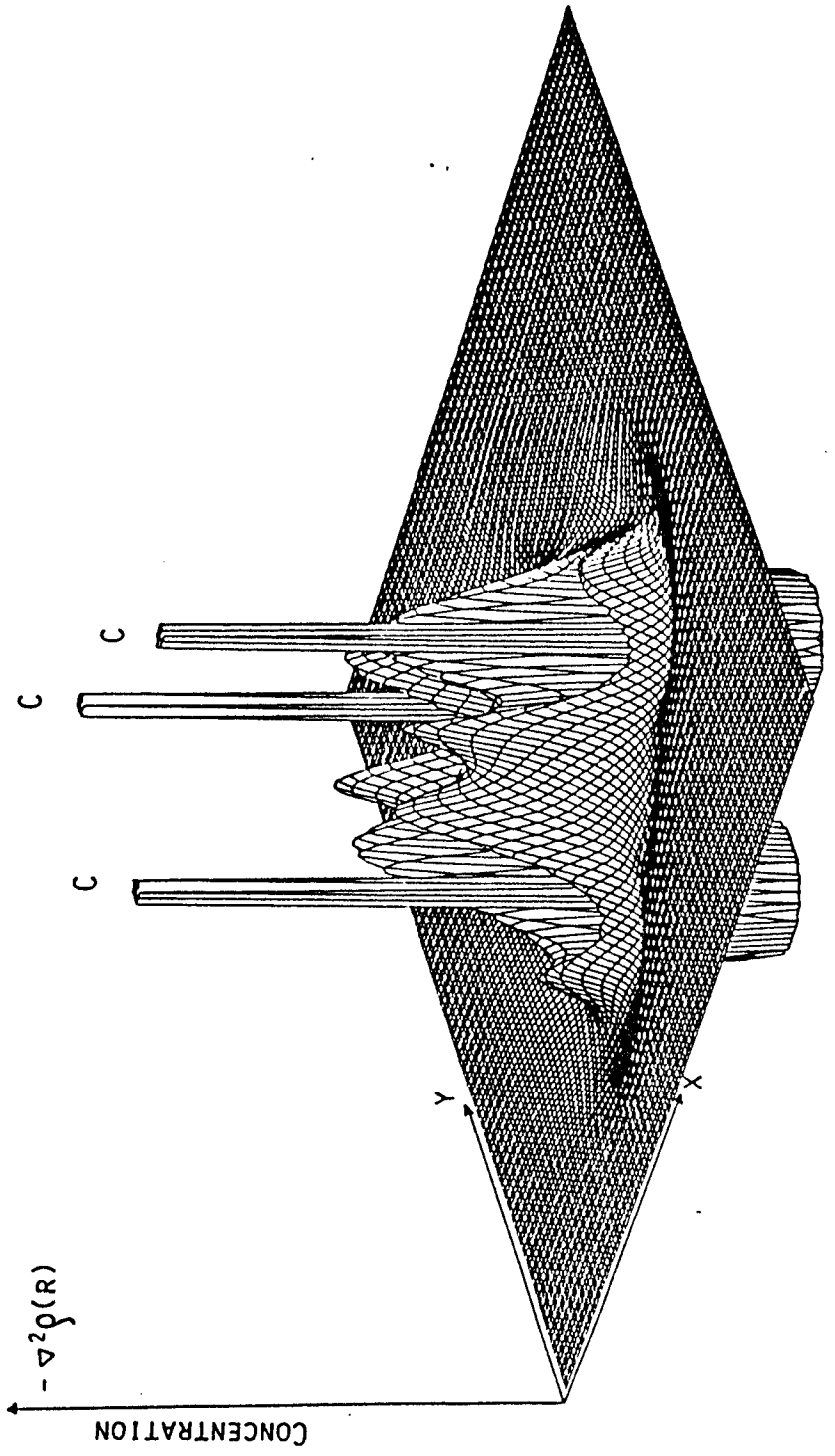


Figure 3-15. Perspective drawing of the calculated [HF/6-31G(d, p)] Laplace concentration $-\nabla^2\rho(\mathbf{r})$ of cyclopropane, depicted in the ring plane. (For a better presentation, values above 48 e/Å^5 and below -24 e/Å^5 are cut off.)

significantly displaced away from the bond paths (compare with Figure 3-16). They enclose angles of 92° that are closer to the interorbital angles (102°) than the interpath angles (79°).[4] In the same way, as found for C(^{3}P), the lumps can be associated with the highest occupied molecular orbital (HOMO) of cyclopropane. Maximal concentration of negative charge is found where the e' MOs of cyclopropane (compare with Figure 3-8) possess their largest amplitude. Similarly, the holes at the C atoms (Figures 3-15 and 3-16) can be linked to the a_2' lowest unoccupied MO (LUMO) of cyclopropane (Figure 3-8).

Inspection of the contour line diagram of $\nabla^2\rho(\mathbf{r})$ shown in Figure 3-16*a* reveals that the σ electrons of the three-membered ring concentrate not only in the bonding region but also in the ring interior (contour lines with $\nabla^2\rho(\mathbf{r}) < 0$ are dashed in Figure 3-16). Hence the Laplacian of $\rho(\mathbf{r})$ also reflects the surface delocalization of electrons.[4] We attribute this to the occupation of the a_1' MO of cyclopropane, which is identified as a surface orbital (Section 6).[6]

Surface delocalization of σ electrons implies that the absolute value of the potential energy density is large inside the ring. Electrons "stay" longer in the ring center (relatively low kinetic energy), since they experience the stabilizing attraction of the three carbon nuclei. The electrostatic potential due to the nuclei is homomorphic with $\rho(\mathbf{r})$,[94,95] which indicates that nucleus–

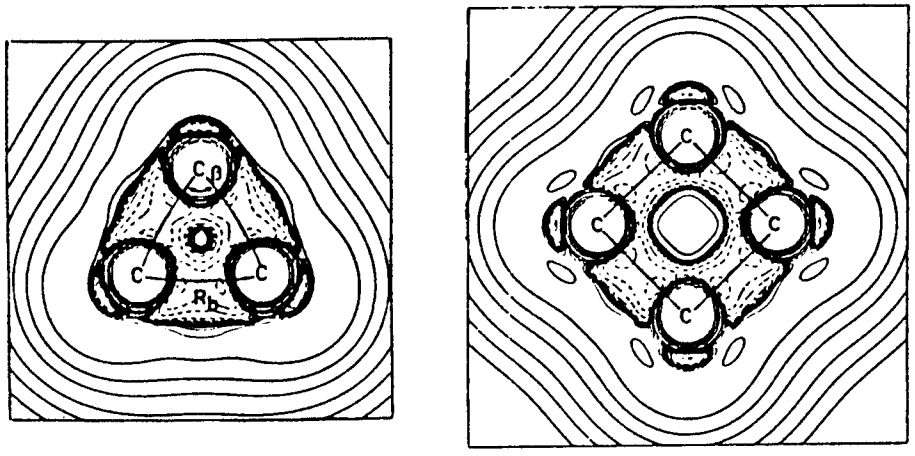


Figure 3-16. Contour line diagrams of the calculated [HF/6-31G(d, p)] Laplace concentrations $-\nabla^2\rho(\mathbf{r})$ of cyclopropane (*a*) and cyclobutane (*b*). Bond paths are indicated by heavy solid lines; R_b denotes the bond path length and β the interpath angle. Dashed and solid lines are in regions in which electronic charge is concentrated and depleted, respectively. Inner shell concentrations are not shown. (Reproduced with permission from Reference 6. Copyright © 1986 from the American Chemical Society.)

electron attraction is the dominant physical factor supporting σ-electron delocalization in cyclopropane.

There are some significant differences in Laplacian distribution for three-membered and four-membered rings. As can be seen from the contour line diagram of $\nabla^2\rho(\mathbf{r})$ for cyclobutane (Figure 3-16*b*), the CC concentration maxima are much closer to the CC bond paths, indicating that orbital overlap within the HOMO can follow the bond paths. The CC bonds are less strained. Contrary to cyclopropane, electronic charge is depleted from the interior of the four-membered ring (Figure 3-16*b*). Surface delocalization no longer plays any role in cyclobutane.[6]

Another feature of $\nabla^2\rho(\mathbf{r})$ provides information that is not easily obtained from $\rho(\mathbf{r})$ itself. A quantitative analysis of the carbon concentration lumps in the direction of the CH bonds reveals that these are larger for cyclopropane than for cyclobutane, which is consistent with the higher s character of the CH hybrid orbitals in the former case.

We conclude that a unified analysis of the electron density distribution and its associated Laplacian reveals all critical characteristics of strained cycloalkanes. The next step will be to attach energies to the various effects described and, in this way, to give a detailed accounting of the strain energy and the possible factors comprising it.

9. WAYS OF ASSESSING THE STRAIN ENERGY FROM QUANTUM CHEMICAL CALCULATIONS

The major advantage of the electron density analysis is that it leads to a precise and physically meaningful definition of *atoms in molecules, chemical bonds, molecular geometry, and molecular structure* (Section 7; see also Section 13). As a consequence, a calculation of CSEs or SEs becomes feasible starting either from in situ atomic energies, in situ bond energies, or deformation energies evaluated with Hooke's law and inserted into the Westheimer equation (compare Figures 3-1, 3-2, and 3-17). The last method, actually, should lead to a value close to the true SE.

If there are other effects acting in the molecule, their energetic consequences will become obvious in the difference CSE − SE. By applying a second or a third method for the calculation of CSE and SE, there is a good chance of unraveling the various effects contributing to the stability of the molecule. For example, there may be two electronic effects reducing the ring SE of cyclopropane, namely CH bond strengthening due to hybridization effects and σ-electron delocalization. The joint contribution of these effects to the molecular stability will show up in the difference CSE − SE. Using a method other than method 5 in Figure 3-17 leads to the energy change due to CH bond strengthening or σ-electron delocalization, allowing one to determine all energies contributing to the stability of cyclopropane. Obviously,

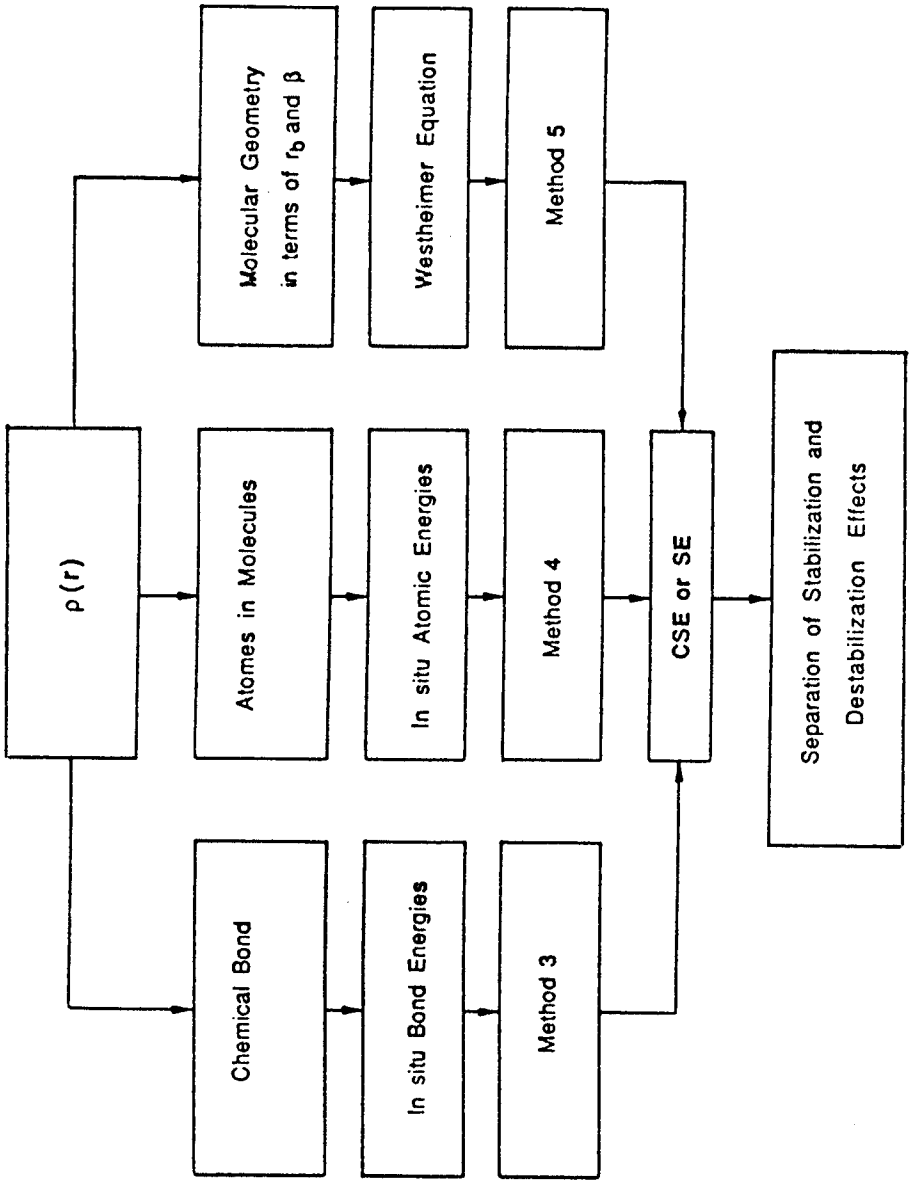


Figure 3-17. Schematic survey of possible ways to access conventional strain energies (CSE) or strain energies (SE) from the properties of the electron density distribution $\rho(\mathbf{r})$. (For explanation of methods, see Figures 3-1 and 3-2.)

method 3, which is based on in situ bond energies, is the best method for separating the energy contribution resulting from CH bond strengthening.

One could also think of calculating in situ bond energies from orbitals by relating their overlap to bond strength and bond energy.[96,97] Such a procedure, although operationally satisfactory for some bond types, suffers from the problem that atoms in molecules, chemical bonds, and molecular geometry cannot be defined in terms of orbitals in a rigorous way. Orbitals are nonobservables and change their form if subjected to an appropriate unitary transformation.

In the sections that follow, we will describe two of the three possible ways of determining CSE or SE of cycloalkanes from properties of the electron density distribution. The third method, based on the calculation of in situ atomic energies, has been discussed by Cremer and Gauss.[6] It shows that due to the higher s character of the CH hybrid orbitals in cyclopropane, there is a buildup of negative charge on the carbon atoms, which therefore possess lower atomic energies than in cyclobutane or in an alkane such as propane. The hydrogen atoms of cyclopropane, on the other hand, are destabilized relative to those in cyclobutane or in an alkane, since they have lost part of their negative charge to the C atoms. Their atomic energies entail CH_2 group energies of E(cyclopropane) > E(cyclobutane) > E(alkane) and SEs of 27.9 and 26.4 kcal/mol for cyclopropane and cyclobutane, respectively, in close agreement with experimentally based SE values.[6] Hence, the relative stabilities of small cycloalkanes appear to be a consequence of a destabilization of their H atoms. This is a novel description,[6] which, however, adds little to a conceptual understanding of ring strain and, therefore, is not discussed further.

10. CALCULATION OF THE STRAIN ENERGY FROM IN SITU BOND ENERGIES

As mentioned in Section 3, one way of calculating SEs or CSEs is based on the determination of in situ bond energies (see Figures 3-1 and 3-2). If these are known for cyclopropane, then the energetic consequences of CC bond bending can be directly determined with the aid of appropriate reference bond energies. Also, the importance of CH bond strengthening due to C(sp^2)—H bonding in cyclopropane should become obvious from in situ bond energies.

A. In Situ Bond Energies from Hybrid Orbitals

More than 50 years ago, Pauling[98] pointed out that larger overlap between two hybrid orbitals will give rise to a stronger bond. If the bond strength is in turn taken to be proportional to the bond energy, it will be possible to

determine the latter from calculated orbital overlaps (S), provided a linear dependence on S can be assumed and an appropriate conversion factor can be found:

$$be = k\,S \tag{3-14}$$

Kilpatrick and Spitzer[99] used this approach to evaluate the CC bond energy of cyclopropane. By assuming that C(sp^2)—H bonds possess the same bond strength as C(sp^3)—H bonds, i.e. that the stability of cyclopropane is solely determined by the strain in the CC bonds, these authors estimated the CC bond energy to be 70.1 kcal/mol, which is 8.7 kcal/mol smaller than the CC bond energy of ethane. This difference implies an SE of 26 kcal/mol, close to the experimental CSE of cyclopropane.

However, this approach did not consider CH bond strengthening. Randić and Maksić,[53] in a similar calculation, explicitly took the CH bond strengthening for cyclopropane into account, using as standard CC and CH bond energies 79.2 (from ethane) and 99.5 kcal/mol (from methane). With scaling factors k(CC) = 121.37 kcal/mol and k(CH) = 142.67 kcal/mol and calculated S values for cyclopropane, they obtained be(CC) = 69.9 and be(CH) = 102.5 kcal/mol. Hence, CC bond bending was estimated to cause an SE of 27.8 kcal/mol, while CH bond strengthening reduces this value by 6 × 3.1 kcal/mol, leading to a CSE of just 9.7 kcal/mol, one-third of the experimental CSE of cyclobutane. Obviously, this approach either underestimates CC bond weakening or overestimates CH bond strengthening.

In this connection we note that bond energies for strained molecules have also been obtained from quantum chemically computed valencies.[133] According to these calculations, the CC bonds of cyclopropane are weakened by just 3 × 6.4 = 19.2 kcal/mol; another 8.4 kcal/mol of strain is attributed to a weakening of the CH bonds. This, however, is contrary to all other descriptions of the CH bonds in cyclopropane and, therefore, casts doubts on the usefulness of the theoretical model employed.

B. Estimation of CH Bond Energies from Experimental Data

The CH bond dissociation enthalpy DH of cyclopropane (106.3 kcal/mol) is 11.2 kcal/mol higher than the one for the secondary CH bond of propane (95.1 kcal/mol).[100] It has been suggested that this difference be used to estimate the CH bond energy of cyclopropane.[10] However, DH values do not necessarily reflect the magnitude of bond energies (enthalpies), since they depend on both the stability of the reactant *and* the stability of the fission products. The large DH(CH) value of cyclopropane simply reflects the significant increase in ring strain when the cyclopropyl radical is formed.

The CH stretching frequency of cyclopropane (3056 cm^{-1}) is almost identical with that of ethylene (3055 cm^{-1}) but about 100 cm^{-1} higher than that of alkanes (ethane: 2950 cm^{-1}; s-CH of propane 2920 cm^{-1}).[102,103] By relating the CH stretching frequency to the strength of the CH bond, a bond energy (102 kcal/mol) 3 kcal/mol higher than that of a normal alkane has been predicted for the CH bonds of cyclopropane.[104] This is in line with estimates derived from orbital overlap[53] and a comparison of CH bond lengths.[35,79] Roberts and Caserio[105] used the similarity of the CH bonds in cyclopropane and ethylene to predict an overall stabilization of 18 kcal/mol for the former molecule. Hence, the actual SE of the three-membered ring could be decreased by this amount to yield the CSE.

Although this estimate of the energetic consequences of hybridization effects appears to be reasonable, a caveat is appropriate. CH force constants and stretching frequencies reflect the curvature of the potential hypersurface at the minimum. The curvature, however, depends to some extent on the stability (lability) of the fission products: the higher their energy, the steeper the potential curve and the higher the force constants and stretching frequencies. This is reflected by the fact that experimental CH stretching frequencies correlate with dissociation enthalpies DH(CH), as demonstrated by McKean.[103,106] Therefore, bond energies cannot be unambiguously derived from spectroscopic data.

C. In Situ Bond Energies from Electron Density Analysis

The number of electrons in the bonding region provides a measure of the bond strength. This number can be assessed by integrating the total electron density distribution $\rho(\mathbf{r})$ over the zero-flux surface (see Equation 3-9) and relating the value thus obtained to the thermochemical bond energies of appropriate reference compounds.[56] Cremer and Gauss[6] have used this approach to evaluate in situ bond energies at 0 K from HF/6-31G(d,p) calculations using the atomization energies of CH_4 and C_2H_6 at 0 K (ZPE corrected) to derive suitable conversion factors. Their values are summarized in Table 3-10. Comparison with the appropriate bond energies of propane leads to ring strain energies of 34 and 29 kcal/mol for cyclopropane and cyclobutane, respectively. These energies, however, are reduced by 6.6 and 3.2 kcal/mol (Table 3-10) resulting from CH bond strengthening in both the three- *and* four-membered rings as was first predicted by Coulson and Moffitt.[75]

The approach by Cremer and Gauss[6] represents a successful attempt to derive the SE of small cycloalkanes with method 3, shown in Figure 3-1 above. It resolves part of the problem of assessing the SE in small molecules but not the whole. In Sections 6 and 7, it was pointed out that CC bonding in cyclopropane may be improved by delocalization of two electrons in the ring surface. Clearly, any stabilization resulting from σ-electron delocalization will be absorbed in the CC bond energies. Thus, the SE values given in Table 3-10 may be still too small. Other ways (Figure 3-17) must be used to examine SEs obtained from in situ bond energies.

Table 3-10. Bond Energies and Strain Energies (kcal/mol) from Hartree–Fock Calculations with a 6-31G(d,p) Basis Set

Molecule	*Bond*	*Bond energy*	*SE(CC)*[a]	*STAB(CH)*[b]	*CSE*[c]
Propane[d]	*sec*-C—H	105.5			
	C—C	81.9			
Cyclopropane[e]	C—H	106.6	34	6.6	27.5
	C—C	71.0			
Cyclobutane	C—H	105.9	29	3.2	26
	C—C	73.9			

[a] Strain energy derived from the difference in the CC bond energies and corrected for errors in the theoretical atomization energies (see Reference 6).
[b] Stabilization due to hybridization effects in CH bonding.
[c] Conventional strain energy.
[d] The CH_3 group of propane is used as a reference (see Section 3).
[e] To be compared with 69.9 and 102.5 kcal/mol found in Reference 53.
Source: Cremer and Gauss.[6]

11. QUANTUM CHEMICAL EVALUATION OF THE MOLECULAR STRAIN ENERGY USING THE WESTHEIMER APPROACH

As described in Section 7, the analysis of the electron density distribution $\rho(\mathbf{r})$ leads to a definition of the chemical bond and, thereby, a characterization of bonds in terms of π character, bent bond character, and so on. In addition, it leads to clear definitions of bond length and bond angle. In this way, it becomes possible not only to evaluate in situ bond energies for strained molecules but also to evaluate the Westheimer equation using quantum chemical methods (Equations 3-1 and 3-6; see also method 5 in Figure 3-1). For this purpose, one must define a set of suitable reference compounds that can be used to derive all constants needed for the various terms in the Westheimer equation.

Such a set is shown in Table 3-11.[6] It is based on ab initio calculations on molecules such as ethane, propane, cyclopropane, and cyclobutane complemented by known spectroscopic constants.[107] *The determination of a CCC bending constant k that does not lead to energy contributions actually arising from 1,3-CC nonbonded repulsion* is essential for the evaluation of the Baeyer SE. In molecular mechanics, this problem is solved by considering k as an adjustable parameter that is chosen to reproduce experimentally known molecular properties. Values between 0.45 and 0.8 mdyn-Å/rad^2 have been used[29,36,37,39] (i.e., values considerably smaller than the CCC bending force constant of propane: 1.071 mdyn-Å/rad^2).[107]

Cremer and Gauss[6] solved the problem of determining an appropriate k(CCC) by setting the Baeyer SE of cyclobutane in relation to its 1,3-CC

Table 3-11. Constants for an ab initio Evaluation of the Westheimer Equation for Cyclopropane and Cyclobutane[6]

Strain	*Energy term*	*Constants*	*Reference value*	*Reference molecule*	*Comment*
Stretching	ΔE_r	k_r(CC) = 4.57 mdyn/Å k_r(CH) = 4.88 mdyn/Å	$r(CC)^0$ = 1.5268 Å $r(CH)^0$ = 1.0858 Å	Ethane	k_r from experiment[107] r^0 from HF/6-31G(d,p)[6] *Note:* Bond path lengths r_b are used for bent bonds
Baeyer	ΔE_α	k_β(CCC) = 0.583 mdyn-Å/rad^2 k_α(CCH) = 0.656 mdyn-Å/rad^2 k_α(HCH) = 0.550 mdyn-Å/rad^2	α° = 109.5°	Propane	k_β calculated for the absence of 1,3-CC repulsion[6]; k_α from experiment[107] *Note:* Bond path angles β are used for bent bonds
Pitzer	ΔE_τ	V_3 = 3.0/3 kcal/mol	τ_3 = 60°	Ethane	V_3 from HF/6-31G(p,d)[6]
Dunitz–Schomaker	ΔE_{ab}	Directly evaluated for cyclobutane	l_{CC} = 3.7 Å	Propane	From CNDO/2 calculations[108] *Note:* Results scaled in dependence of k_β(CCC) to reproduce CSE and inversion barrier of cyclobutane[6]

nonbonded repulsion energy. For the latter they utilized appropriately scaled CNDO/2 energy differences calculated for cyclobutane with and without C,C-nonbonded repulsion.[108] Bending force constant and scaling factor were chosen to reproduce the CSE and the inversion barrier of cyclobutane. In this way, they obtained a k(CCC) value (k^* in Reference 6) of 0.58 mdyn-Å/rad², applicable in the absence of 1,3-CC nonbonded repulsion and a Dunitz–Schomaker SE of 12 kcal/mol for cyclobutane.[6]

To describe the strain in cycloalkanes, Cremer and Gauss[6] chose the bond path length r_b and the interpath angle β rather than the geometrical distance r_e and the geometrical angle α. Clearly, the geometrical parameters are not of direct relevance when assessing the bending of the bond (i.e., the elastic spring in Baeyer's strain model).[1] As discussed in Section 7, the geometrical angle may be 60° in cyclopropane, but the CC bonds are bent by an angle β of only 79°.[4] Similarly, the actual bond path length is larger by a factor of 1.006 than the geometrical distance [HF/6-31G(d,p): r_e = 1.497 Å, r_b = 1.506 Å[4-6]]. This, of course, is of utmost importance when assessing the Baeyer SE of a small ring.

Baeyer and nonbonded SEs obtained by the procedure suggested in Reference 6 cannot be compared with energies used in molecular mechanics calculations. In molecular mechanics a physically meaningful definition of the chemical bond cannot be given and, therefore, information about bond bending, bending angles, and so on is not accessible in principle. By using geometrical distances and angles *without* defining the chemical bond, a consistent description of the factors contributing to molecular strain is impossible. *The various energy terms leading to the steric energy calculated in molecular mechanics cannot be related to the various strain energies of Equation 3-1 in a consistent and physically meaningful way*. They are only of operational value, namely to add up to a quantity that finally leads to the molecular enthalpy.

Table 3-12 lists the various strain energies calculated for cyclopropane and cyclobutane with the constants of Table 3-11.[6] The Baeyer SE of cyclopropane is 46 kcal/mol, including an estimated 5 kcal/mol from anharmonicity effects,[37] while the Baeyer strain of cyclobutane is just 13 kcal/mol. However, in the latter case, 12 kcal/mol is due to Dunitz–Schomaker strain, destabilizing the four-membered ring considerably. Pitzer strain adds in both cases just 4 kcal/mol.[6] The total SE of cyclopropane is 51 kcal/mol (ie, 21 kcal/mol larger than that of cyclobutane). We note that these values fit reasonably into the expected increase in the ring SE with decreasing ring size (Figure 3-5).

As noted in earlier Sections 3 and 9 (Figures 3-1 and 3-17), the calculated SEs must be corrected for stabilization or destabilization effects other than ring strain to get CSE values. From Figure 3-17 we see that this is possible only when determining the strain energy in a different way (e.g., from in situ bond energies). Calculated bond energies (see above: Table 3-10) show that both cycloalkanes are stabilized due to CH bond strengthening. Taking these

Table 3-12. Ab initio Strain Energies and Stabilization Energies of Cyclopropane and Cyclobutane

	Strain energy (kcal/mol)	
Strain	*Cyclopropane*	*Cyclobutane*
Stretching	0.5	1.0
Baeyer[a]	46.3	13.0
Pitzer	4.0	3.9
Dunitz–Schomaker	0	12.0
Total	50.8	29.9
	– Stabilization energies (kcal/mol)	
CH strengthening	6.4	2.8
σ Delocalization	x = 16.4	0
CSE	28.0 = 44.4 + x	27.1

[a] Baeyer strain energy of cyclopropane calculated with Hooke's law (41.3 kcal/mol)[6] plus energy increase from anharmonicity effects calculated from a bending function with and without a cubic term[37] for β = 79° (5 kcal/mol). [Note that the strain energy of propane (Reference 6, Table IX) has been set erronously to 5.1 kcal/mol. This energy, however, is compensated by the increase in the CC bond energy relative to that of ethane, Table V, Reference 6.]

kcal/mol result. The latter value is in good agreement with both experimental and other theoretical CSE values for cyclobutane.

In the case of cyclopropane, however, there remains an energy difference of about 16 kcal/mol (x in Table 3-12), which can be attributed to another stabilizing effect, namely the delocalization of σ electrons in the ring surface[4-6] as indicated by both the Walsh MOs (Section 6) and the properties of $\rho(\mathbf{r})$.

12. PROS AND CONS OF σ AROMATICITY

According to Hückel theory, planar annulenes with (4q + 2) (q = 0, 1, 2, . . .) π electrons are aromatic.[109-111] The accepted empirical tests for aromatic character involve (among others) a determination of the molecular geometry and an NMR investigation of the compound in question. The shortening of formal CC single bonds leading to bond equalization[111] and the proton shifts arising from a diamagnetic ring current are considered to be indicative of aromatic character.[109] To assess the aromatic stabilization energy, a reference compound is defined that possesses the same number of π electrons in a localized form (suppression of π conjugation).[110]

1. The CC bonds of cycloalkanes such as cyclopropane or cyclobutane are all equivalent. As discussed in Section 6, all cycloalkanes possess "aromatic" subshells of electrons (compare with Figure 3-8) and, therefore, it seems to be trivial and of no particular advantage to term them σ aromatic. Comparing on the other hand, the CC bond lengths in cyclopropane and cyclobutane, it should be noted that both r_e and r_b (Table 3-7) are considerably shorter in the smaller ring. It seems that a particular force contracts the three-membered ring, thus enhancing the stabilizing electronic interactions.

2. Due to the C(sp^2)—H bond nature, one would expect the proton NMR signal for cyclopropane to appear downfield relative to the signals of the methylene protons in alkanes. In fact, it appears upfield by 1 ppm (δ = 0.22 ppm).[112] Zilm and co-workers[113] have investigated the ^{13}C NMR spectrum of cyclopropane. They note that circulation of electrons in the ring plane leads to a most unusual upfield shift (~20 ppm) of the ^{13}C NMR signal of cyclopropane.

3. The analysis presented in Section 11 suggests that the cyclopropane ring is stabilized by at least 16 kcal/mol relative to a hypothetical three-membered ring in which surface delocalization of electrons is impeded.

Seeing points 1 through 3 in one context, it is appealing to consider cyclopropane as being σ aromatic.[2-6]

The description of cyclopropane as a system with six delocalized σ electrons dates back to the 1960s. For example, Brown and Krishna[3] calculated the excited electronic states of C_3H_6 by treating its σ electrons in the same way as the π electrons of benzene in a PPP description. These authors explicitly pointed out that there is a striking resemblance between the σ electrons of cyclopropane and the π electrons of benzene.[3]

Dewar[2] was probably the first to elaborate the idea of σ-electron delocalization. He stressed that the overlap, hence the resonance integrals between different hybrid orbitals of a given atom, will not vanish, even if the constituting atomic orbitals are orthogonal. The value of a resonance integral between sp^n hybrids in hydrocarbons is considerably larger than that of the π-resonance integral between adjacent 2p AOs in a polyene.[2,3] Taking this into account, Dewar concluded that the relative stabilities of alkanes can be rationalized only by considering σ-conjugative interactions. The latter should be even more important for small cycloalkanes. It is well known that in conjugated polyenes the 2pπ AOs overlap with one another and the two-center MOs coalesce into a resonating system in which the π electrons can delocalize. Taking into account that the hybrid AOs of a given atom also overlap (an often neglected fact), then each two-orbital CH_2 unit in a parafin will play the same role as a two-orbital =CH—CH= unit in a conjugated polyene or cyclopolyene. Hence, cyclopropane can be considered to be isoconjugate with benzene (see Figure 3-18), hence σ aromatic, since both systems possess a six-electron ensemble that is delocalized along the ring framework.[2,3]

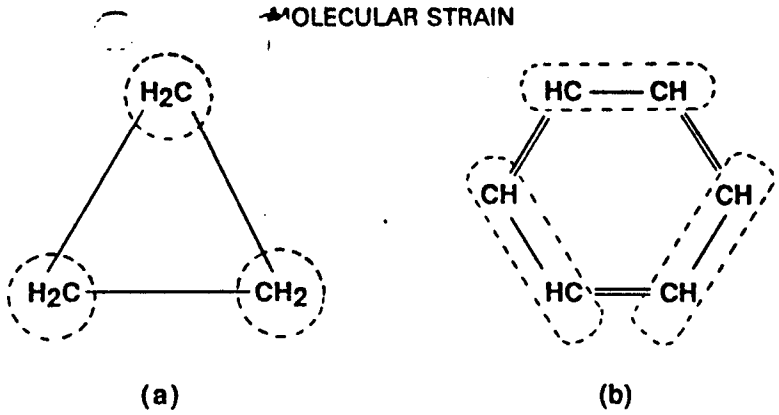


Figure 3-18. Analogy between cyclopropane (*a*) and benzene (*b*). Groups that interact in a σ-conjugated and in a π-conjugated system are circled.

Clearly, this description is based on a model, the model of hybrid orbitals. Within the Walsh model, the picture of a surface orbital with two delocalized electrons emerges (Section 6). Both descriptions are essentially equivalent within the limitations pointed out by Heilbronner.[80]

One might criticize the term "σ aromaticity," since aromaticity is connected strongly to the idea of π conjugation in cyclopolyenes. Comparison with an acyclic system consisting of the same number of conjugated π bonds is an inherent part of the definition of aromaticity. Such a comparison, of course, cannot be readily made in the case of cyclopropane. Certainly neither propene nor the trimethylene biradical constitutes an appropriate reference system. In addition, "aromatic" character usually implies a breakdown in a localized bonding picture—that is, the existence of more than one resonance structure with alternating single and double bonds for a given molecule, which is not true in case of cyclopropane. For these reasons, the present authors prefer the term *surface* or *σ-electron delocalization* and speak of a "*σ-delocalization energy*"[4-6] rather than an aromatic stabilization energy.

σ-Electron delocalization causes or, at least, influences a number of properties of cyclopropane, including the following:

1. The relatively low CSE
2. The relatively high electron density in the interior of the ring as reflected by both $\rho(\mathbf{r})$ and $\nabla^2\rho(\mathbf{r})$
3. The relatively short CC distances
4. The upfield shifts of its proton and ^{13}C NMR signals
5. The similarity of the activation energies needed to break a CC bond in cyclopropane (61 kcal/mol) and in cyclobutane (62.5 kcal/mol).[114]

Furthermore, σ-electron delocalization may play an important role in the interaction of cyclopropane with substituents.[5,115,117] This has been stressed

by Cremer and Kraka.[5] Also, the incorporation of the three-membered ring in conjugated systems and the possibility of homoaromatic interactions has been discussed utilizing the idea of σ-electron delocalization.[4-6,8,7b]

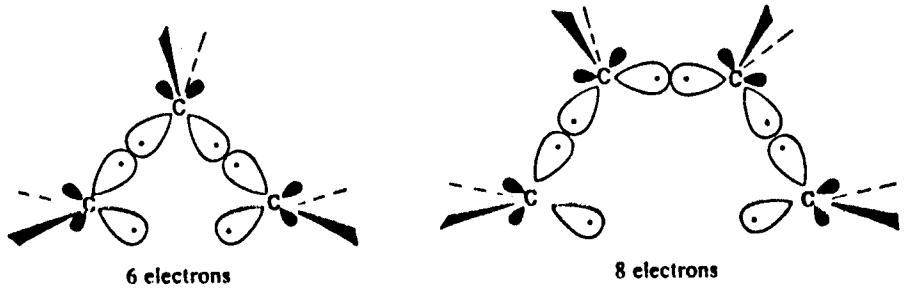
Various authors have added support to this concept. For example, Coulson and Moffitt[75] were the first to note that there is a plateau of relatively high negative charge inside the C_3 ring. Over the years other authors have also pointed to the special role of the a_1' MO of cyclopropane and terms like "internal σ orbital"[59b] were coined. Recently, Schwarz and co-workers[8] have investigated MO composition and AO reorganization in cyclopropane and propane. They note that the total electron density is increased by 0.16 e/Å^3 in the center of the cyclopropane ring as compared to superimposed spherical free atoms. The topology of the ring supports favorable interference of three overlapping contragradient 2s or 2p, orbitals, which is constructive over the whole ring surface and increases the total electron density in the ring center. The response of the AOs to the strongly reduced kinetic energy density in the a_1' (surface) orbital is enhanced AO contraction, which restores the virial relation and lowers the total energy significantly.[8] This AO contraction is essential for the stabilization of the C_3 ring and, also, causes a CC bond length reduction. Contrary to their behavior in the central "super-σ bond," the AOs expand in the Walsh e' MOs, which is typical of π orbitals and supports the π character of the cyclopropane ring bonds.[8]

Ahlrichs and Ehrhardt[9] have calculated shared electron numbers for alkanes. While bonding is reflected in these compounds by two-center contributions and negligible contributions from three- and four-center terms, a CCC shared electron number of 0.3 is calculated for cyclopropane, which is indicative of three-center bonding.

Experimental observations indicative of special electronic effects active in the three-membered ring have been published by a number of authors.[7,136] For example, Verhoeven and co-workers[7] have found kinetic anomalies for the formation of small cycloalkanes that cannot be explained by the Ruzicka hypothesis.[130] In the latter approach, two competing effects are considered, namely increasing ring strain for decreasing ring size and an opposing entropy factor that favors ring closure for small rings. Contrary to these explanations, the closure of a four-membered ring is exceptionally slow when compared with that of a five- or three-membered ring. Verhoeven[7] has shown that this is due to irregularities in the activation enthalpies; that is, anomalies in the kinetics are due not only to a decrease of $\Delta S^{\ddagger}$ with decreasing n but have also an electronic reason. The latter can be elucidated when utilizing the Dewar–Zimmermann rules[131] for transition states of pericyclic reactions: a thermal pericyclic reaction is allowed (forbidden) for an aromatic (antiaromatic) transition state. Aromatic character requires the involvement of 4q + 2 electrons for a Hückel system and 4q electrons for a Möbius system.

If a cyclopropane ring is formed, a Hückel aromatic transition state with six electrons will be traversed. However, in case of the formation of a

cyclobutane ring, a Hückel antiaromatic transition state with eight electrons results. This is schematically shown in Scheme II. As a consequence, the activation enthalpy for the closure of a cyclobutane ring is markedly higher than that for a cyclopropane (cyclopentane) ring. This has been found for carbanion cyclizations and other reactions.[7] (For a different opinion, see References 136).



Scheme II. Cyclic transition rotates with Hückel aromatic (left) and Hückel antiaromatic electron ensembles (right).

In this connection, it is interesting to note that a description of the CC and CH MOs of cyclopropane in terms of Hückel and Möbius arrays has been given by Epiotis.[132] He describes bonding in cyclopropane as due to a "superaromatic" interaction between Hückel/Möbius-aromatic C_3 and $(CH_2)_3$ cycles.

The idea of σ-electron delocalization has not met with unanimous approval. For example, Schleyer[11,47] has questioned whether a delocalization of σ electrons in cyclopropane, if existing, entails any energetic consequences. Analyzing the various contributions to the CSE of cyclopropane and cyclobutane, he concludes that there is no need to invoke σ aromaticity to explain the relative stabilities of small cycloalkanes.[11] He suggests that the low CSE of cyclopropane is due to CH bond strengthening and assumes a stabilizing contribution of 10 kcal/mol from this source.

Certainly, if CH bond strengthening is not correctly described by the bond energies given in Table 3-10, the delocalization energy (x in Table 3-12) will change. This is shown in Figure 3-19. Assuming for example, values given by Schleyer[11] or Roberts and Caserio,[105] σ-delocalization energies of 13 and 5 kcal/mol, respectively, result from CSE and the strain-energies listed in Table 3-12. A delocalization energy even smaller than zero would be obtained if the total effect of CH bond strengthening were larger than 23 kcal/mol. However, this is unlikely in view of the similarity of the *sec*-CH bonds in cyclopropane and propane.[6]

The σ-delocalization energy of cyclopropane also depends critically on the calculated Baeyer SE, which in turn depends on the value of the CCC bending force constant. If one uses the spectroscopic force constant of pro-

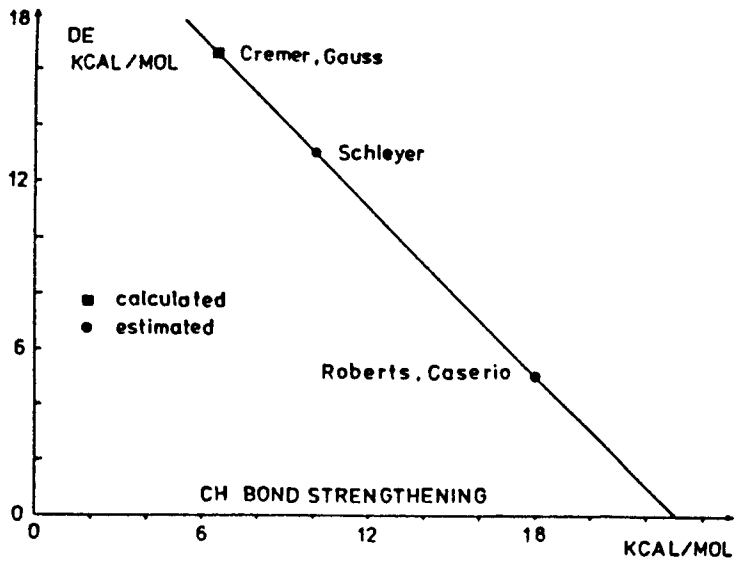


Figure 3-19. Dependence of the σ-delocalization energy DE on the CH bond strengthening (hybridization effect) in cyclopropane. Values of the latter have been taken from References 6, 11, and 23f, respectively. (Reproduced with permission from Reference 6. Copyright © 1986 from the American Chemical Society.)

pane, a delocalization energy of about 50 kcal/mol will be found[2,4] (see Figure 3-20). This value can be considered only as an upper bound to the σ-delocalization energy, since $k(CCC)_{propane}$ corresponds to CCC bending in the presence of strong H,H- and C,C-nonbonded repulsion.

The force constant determined in Reference 6 describes CCC bending in the absence of nonbonded repulsion and, therefore, is appropriate to evaluate the Baeyer SE of cyclopropane. Similar values of k are used in molecular mechanics. They will lead to comparable σ-delocalization energies as can be seen from Figure 3-20.

Schleyer[11] adjusts the Baeyer SE to 33 kcal/mol to reproduce the CSE of cyclopropane. According to Hooke's law, this implies a CCC bending force constant of 0.20 mdyn-Å/rad², which is probably far too low. By applying the same method to determine the Baeyer SE of cyclobutane, Schleyer obtains a value of 10 kcal/mol, which corresponds to $k(CCC) = 0.27$ mdyn-Å/rad². If the latter force constant is used for cyclopropane, a Baeyer SE of 43 kcal/mol will be obtained, entailing a σ-delocalization energy of 10 kcal/mol. Hence, the estimate of various contributions to the CSEs of cyclopropane and cyclobutane given by Schleyer[11] makes it difficult to draw *any* conclusions about the energetic consequences of σ-electron delocalization.

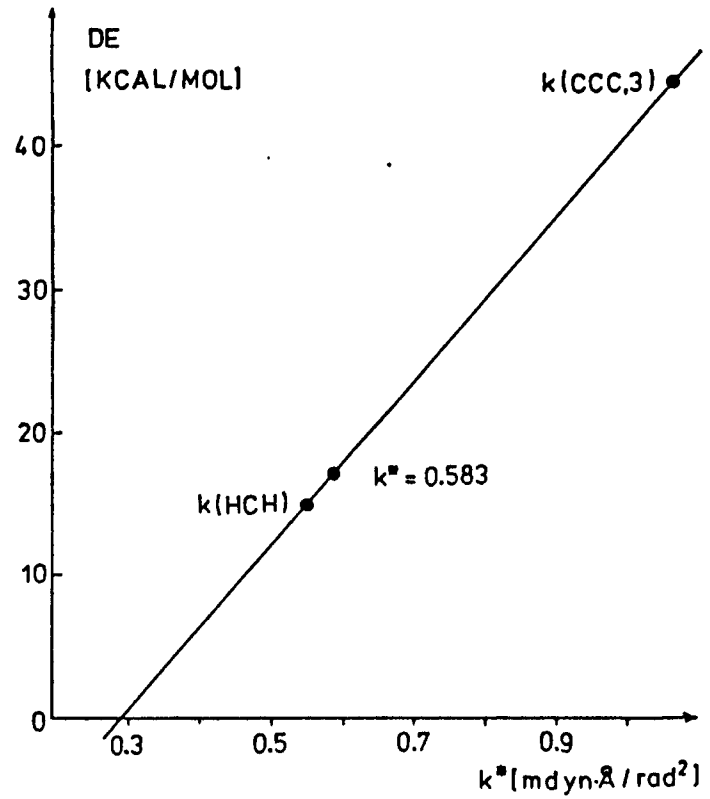


Figure 3-20. Dependence of the σ-delocalization energy DE on the value of the CCC bending force constant k^* in cyclopropane: $k(CCC)$ and $k(HCH)$ are from propane. k^* has been calculated for CCC bending in the absence of 1,3-CC-nonbonded repulsion. (Reproduced with permission from Reference 6. Copyright © 1986 from the American Chemical Society.)

13. LIMITATIONS OF THE CONCEPT OF STRAIN

The concept of strain is applied to molecules with covalent bonds. It looses its usefulness when discussing, for example, ionic bonding. The strength of the ionic bond is best determined by Coulomb's law. A description of deformed ionic bonds in terms of stress and strain appears superfluous. Of course, this applies also to those bonds that possess strong ionic character. The transition from covalent to ionic bonding is continuous, and the pure covalent (ionic) bond is more the exception than the rule. One might also ask whether a description of molecular stability in terms of strain could also be done from an electrostatic point of view.[118] This question, of course, can be rephrased in a more fundamental form: Will the concept of strain still be useful if one

describes strained molecules strictly with the tools and aids of quantum chemistry, abolishing the model taken from classical mechanics?

A quantum chemical assessment of molecular strain implies the calculation of the stress tensor $\overleftrightarrow{\sigma}(\mathbf{r})$ that determines in a stationary state the force density $\mathbf{F}(\mathbf{r})$[57]:

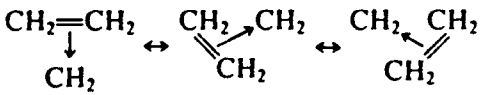
$$\mathbf{F}(\mathbf{r}) = -\nabla \cdot \overleftrightarrow{\sigma}(\mathbf{r}) \tag{3-15}$$

Analysis of the force density in strained bonds probably will lead to a quantum mechanical definition of what is exceptional in these bonds. However, it remains to be seen whether such a definition can be expressed in terms of a simple physical model. Much work remains to be done to clarify this point.

The concept of strain becomes questionable also when considering nonclassical bonding. It makes little sense to discuss the strain of a penta- or hexavalent carbon atom. But even in the case of tetravalent carbon, one may doubt the validity of applying the concept of strain in all situations. We will exemplify this for three-membered rings.

A. The Relationship Between Three-membered Rings and π Complexes

Following ideas first proposed by Dewar,[119] Walsh[120] suggested in 1947 a π-complex formula for three-membered rings:



Later he renounced this description because the molecular properties of cyclopropane were difficult to describe with the π-complex model.

Dewar[121] revived the π-complex description by showing that two kinds of interaction must be considered in three-membered rings. First, an electron donation from the ethylene π orbital (basal group) to a vacant orbital of the apical group X (CH_2, NH, O, etc). Second, back-donation of electrons from a filled p orbital of X into an antibonding π^* MO of the ethylene double bond. The apical group X and the basal group C_2H_4 are doubly linked by two opposed dative bonds. Depending on which interaction is stronger, three situations are possible.

1. Donation and back-donation are of comparable magnitude. A stable three-membered ring is formed.
2. Donation prevails over back-donation. A three-membered ring results, which possesses partial π-complex character.
3. There is just donation to the apical group. A π complex is formed.

Dewar and Ford[122] have suggested geometry- or orbital-based parameters that describe the degree of π-complex character. They have shown that a change in the electronegativity difference between the apical and basal groups leads to a continuous transition from the classical ring structure (small electronegativity difference) to a π complex (large electronegativity difference).

Cremer and Kraka[4] have approached the problem of distinguishing between a three-membered ring and a π complex by analyzing the electron density distribution $\rho(\mathbf{r})$ (see Section 7). As schematically shown in Figure 3-21*a*(*b*), donation from (to) the basal group via an a_1 MO leads to a buildup of electron charge along the C_2 axis of a system A_2X (A_2: CH_2CH_2, HCCH, CC, etc) with C_{2v} symmetry. The resulting bond path[123] (Section 7) connects the apical group X with the midpoint of A_2. The T-structure of a π complex is formed (Figures 3-21*a* and 3-21*b*).

As soon as back-donation, e.g., from an occupied b_2 MO of X occurs, electron density builds up along the lines A, X. Together with the accumulation of density along the C_2 axis, a plateau of relatively high negative charge is formed between A_2 and X. Depending on the electronic nature of A_2 and X, or more specifically on the energy gap between the b_2 MOs and, hence, the amount of electronic charge back-donated, bond paths are formed between A and X. Strong back-donation leads to outwardly curved (*convex*) AX bond paths (Figure 3-21*c*), while relatively weak back-donation yields inwardly curved (*concave*) AX bond paths (Figure 3-21*d*). Concave bond paths are indicative of partial π-complex character of A_2X. Hence, *an analysis of the electron density reveals in a quantitative way the extent to which a given molecule should be classified as either a three-membered ring or a π complex.*[4]

Figure 3-22 shows the calculated bond paths by means of heavy lines (bond critical points are indicated by dots), as well as the Laplace concentrations (dashed contour lines indicate charge concentration) of six molecules: cyclopropane, oxirane, protonated oxirane, F-bridged fluoroethyl cation, beryllocyclopropane, and beryllocyclopropyne.[4] As can be seen, the CX bond paths gradually change with increasing electronegativity of group X, that is, in the series:

$$\mathrm{X = Be,\ CH_2,\ NH(not\ shown),\ O,\ NH_2^+(not\ shown),\ OH^+,\ F^+}$$

from convex to concave bending. In the extreme case, the two CX bond paths coincide largely ($X = F^+$) or completely as in BeC_2 (Figure 3-22*f*; see References 4 and 124 for a detailed discussion). These molecules are π complexes and, therefore, possess a T structure.

Figure 3-22 reveals the very dubious nature of the concept of strain when applied to three-membered rings other than cyclopropane. Certainly, no chemist would ever think of discussing the "strain of a π complex." But on the other hand, it appears to be completely legitimate to most chemists to

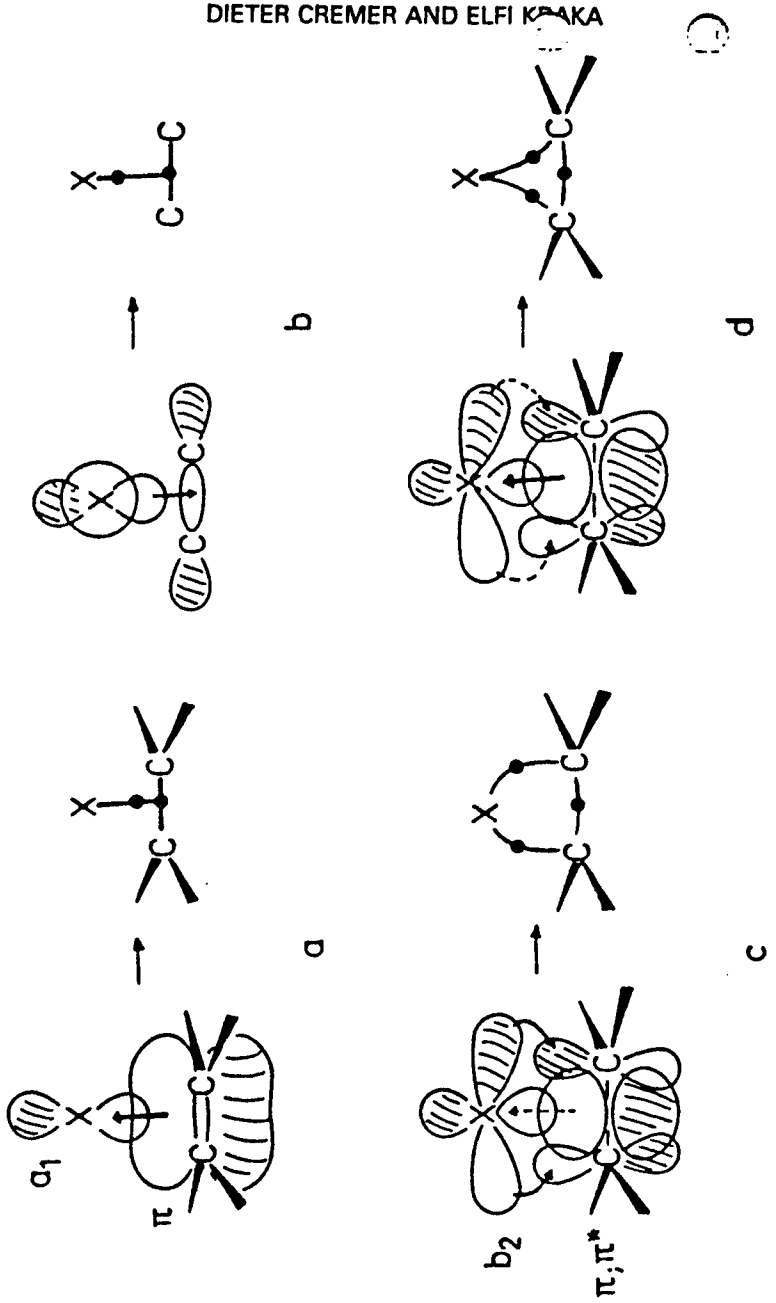


Figure 3-21. Donor–acceptor interactions between A_2 (C_2H_4 or C_2) and X, showing relevant orbitals (a_1 or b_2 symmetry) on the left and the corresponding molecular graphs on the right. (*a*) T structure of an ethylene π complex. (*b*) T structure of BeC_2. (*c*) Convex-shaped three-membered ring. (*d*) Concave-shaped three-membered ring. The direction of the charge transfer is indicated by arrows (reduced charge transfer by dashed arrows); dots denote bond critical points. (Reproduced with permission from Reference 4. Copyright © 1986 from the American Chemical Society.)

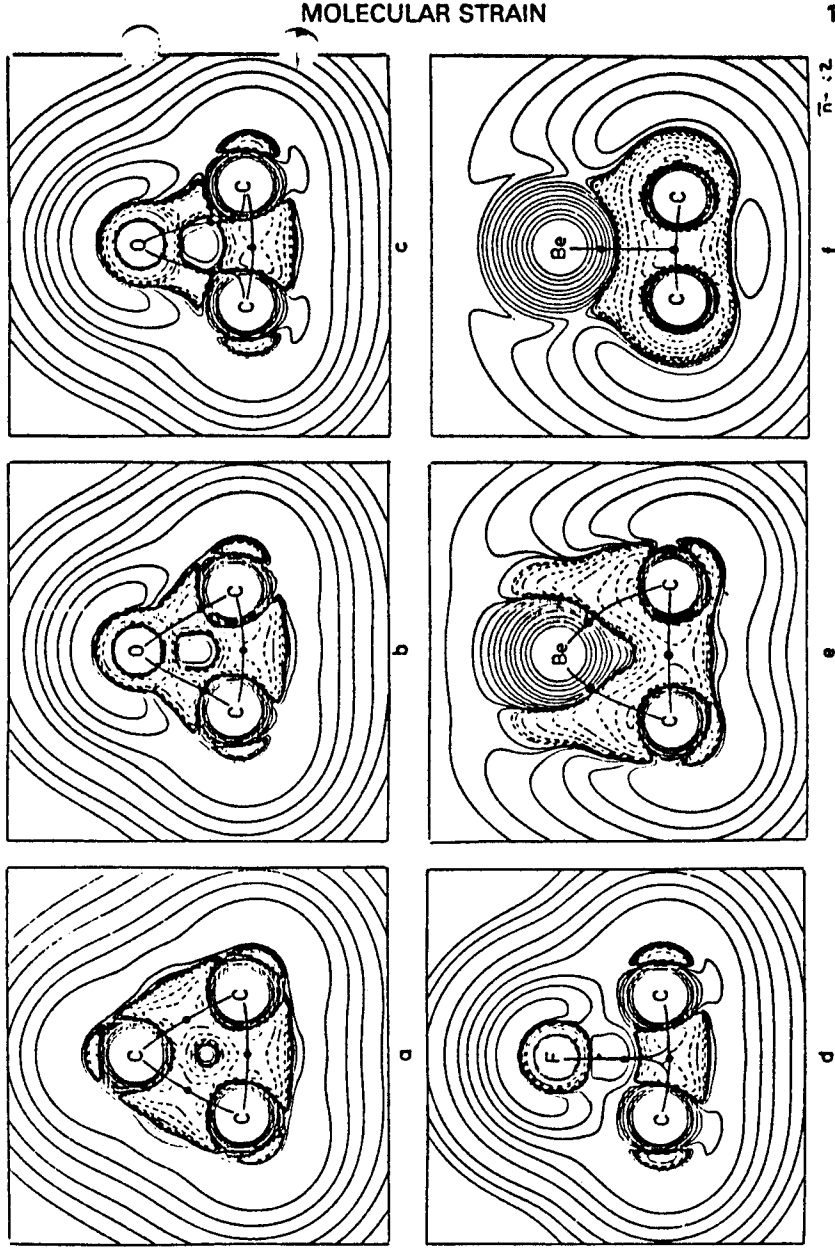


Figure 3-22. Molecular graphs and Laplace concentrations $-\nabla^2\rho(\mathbf{r})$ [HF/6-31G(d) calculations] of cyclopropane (*a*), oxirane (*b*), protonated oxirane (*c*), F-bridged fluoroethyl cation (*d*), beryllocyclopropane (*e*), and beryllocyclopropine (*f*). Bond paths are indicated by heavy lines and bond critical points by dots. Dashed and solid contour lines of $\nabla^2\rho(\mathbf{r})$ are in regions in which electronic charge is concentrated and depleted, respectively. Inner shell concentrations are not shown. (Reproduced with permission from Reference 4. Copyright © 1986 from the American Chemical Society.)

tron density, it should be close to the transition state in energy space. We note that at this point A_2X is far from possessing the classical ring structure with fully developed (convex) bent bonds. Hence, a discussion of the transition state structure in terms of strain (bond angle strain, stretching strain, etc) again is useless. The same is true for structural changes of A_2X when moving along region Va or Vb (Figure 3-23*a*).

On the other hand, the concept of strain may be useful when describing the structural changes of A_2X from region I to either II or III. This, however, implies that the three-membered-ring region I is large enough to encompass classic ring geometries. As indicated by Cremer and Kraka,[4] region I will become smaller as the electronegativity difference between A_2 and X increases (Figure 3-23*b*). In this way, the concept of strain becomes useless to describe the ring structure of A_2X; it is all the more useless for describing any structural changes of the ring.

Taking all aspects together, we conclude that the application of the concept of strain to other than normal hydrocarbons in the ground state requires considerable care and additional information about bonding in the molecule in question.

14. CONCLUSIONS

Investigation of the strain energies of small cycloalkanes has led to an improved understanding of the factors contributing to the relative stabilities of these molecules. *Due to its topology, cyclopropane differs from all other cycloalkanes.* Surface delocalization of σ electrons leads to enhanced stability of the three-membered ring, compensating in part the destabilizing effect of Baeyer strain. Cyclobutane is also exceptional, as it is the cycloalkane with the largest Dunitz–Schomaker strain (Table 3-12).

These observations entail a number of chemically important conclusions for molecules containing three- or four-membered rings (Figure 3-24).

1. Substituents with σ-electron acceptor capacity withdraw electrons from the surface orbital of cyclopropane, thus destabilizing the ring. For cyclobutane, however, a σ-electron acceptor withdraws charge from the 1,3-antibonding MO (Figure 3-8), thus leading to a stabilization of the molecule. As an example, the strain energy of hexafluorocyclopropane is found to be remarkably high relative to that of the parent cyclopropane. In contrast, the strain energy of octafluorocyclobutane is likewise low when compared to that of cyclobutane[134] (see also discussion in Reference 6).

2. When replacing the C atoms of cyclopropane by Si or Ge atoms, the threefold overlap inside the ring is reduced by (a) an increase of the ring dimensions and (b) a decreasing tendency of the atoms to form sp^2-hybrid orbitals. Also, H has to be considered as a relatively strong σ-electron

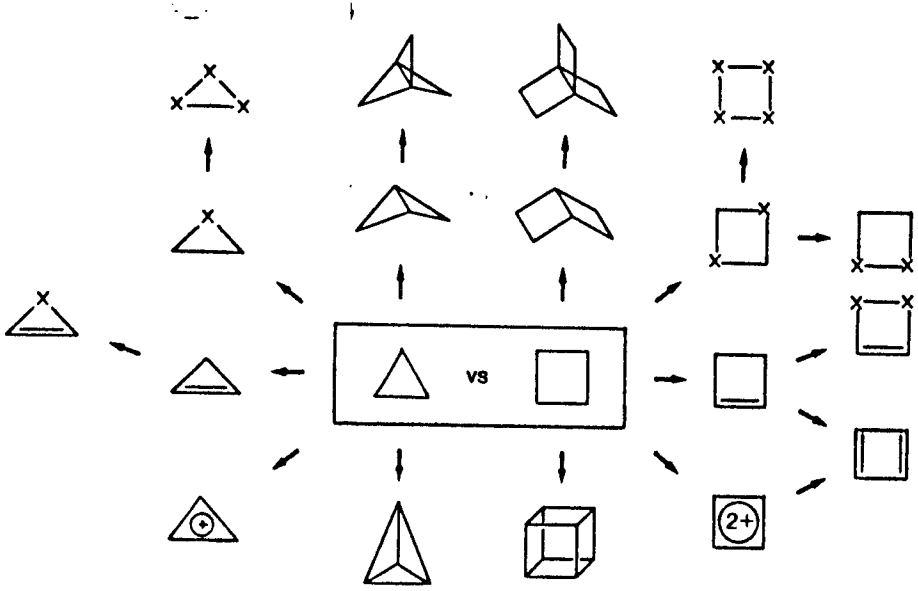


Figure 3-24. Schematic representation of compounds for which the electronic effects influencing structure and stability of cyclopropane and cyclobutane may be of importance.

acceptor if bound to Si or Ge. As a consequence, σ-electron delocalization is of little importance in $(SiH_2)_3$ or $(GeH_2)_3$. Thus, the CSE should be larger in trisilacyclopropane than in cyclopropane. For similar reasons, 1,3-repulsion should be lower in the Si, Ge, etc analogues of cyclobutane; hence the CSE (SE) should be smaller in these systems. Work by Schleyer and co-workers[129] confirms these predictions as illustrated in Figure 3-25. Calculated CSEs of cyclosilanes $(SiH_2)_n$ show the expected increase with decreasing n ($n \leq 6$) as originally expected for $(CH_2)_n$ (compare with Figures 3-5 and 3-6).

3. Although in some cases the SEs of bicyclic and tricyclic compounds containing cyclopropane and cyclobutane as subunits equal the sum of the SEs of its subunits, this cannot be expected to be true in general. Interactions between the subunits may either enlarge or reduce the SE arising from the subunits. For example, the SE of bicyclobutane is about 8 kcal/mol larger than twice the SE of cyclopropane.[49]

4. Electron delocalization may occur not only in one dimension (ribbon delocalization of π electrons) or in two dimensions (surface delocalization of σ electrons) but also in three dimensions (volume delocalization of σ electrons).[6] In a cage compound like tetrahedrane, there is a totally symmetrical a_1 MO that leads, when occupied, to a two-electron, four-center bond. This can improve CC bonding in tetrahedrane and, as a consequence, reduce destabilizing effects caused by strain. Two-electron, four-center bonding is also invoked to describe the structure of the neutral *closo*-boron compounds B_4R_4 (R = Cl, *t*-Bu, etc).[135]

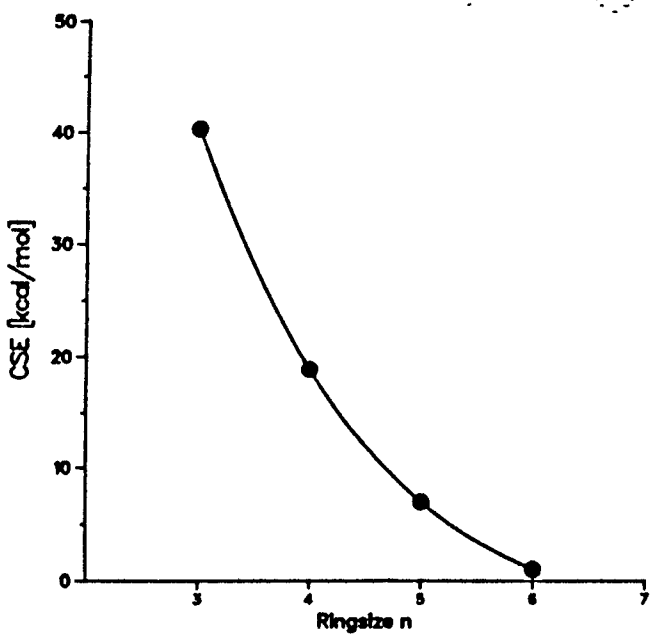


Figure 3-25. Homodesmotic SEs of cyclosilanes $(SiH_2)_n$ in dependence of the ring size n. (Unpublished [HF/3-21G//HF/3-21G] results of P. v. R. Schleyer[29a].)

5. Discussion of a compound like [1.1.1]propellane in terms of strain should be postponed until the nature of the central CC bond has been clarified.

Further investigations are needed to show the energetic consequences of strain and σ-electron delocalization in detail. Theory has advanced in understanding the strain in small rings. Nevertheless, there is still a long way to go to assess all facets and aspects of the chemical behavior of strained molecules. Certainly, textbooks claiming that the strain in small rings is nowadays well understood ought to have their sections on strain revised.

ACKNOWLEDGMENTS

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13. We note that in German, von Baeyer's mother tongue, the word *Spannung* (English: strain) is often used for stress rather than for the deformations. This, however, does not comply with the original formulation of Hooke's law: *Ut tensio sic vis*. Thus, von Baeyer speaks in his seventh sentence about the *stress* (and not the strain) that is proportional to the relative deviation (strain) from the tetrahedral angle. See Reference 1a.
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$$\lim_{\Delta x \to 0} \{f(x) - \frac{1}{2}[f(x - \Delta x) + f(x + \Delta x)]\} = -\frac{1}{2} \lim_{\Delta x \to 0} \{\frac{1}{2}[f(x + \Delta x) - f(x) - [f(x) - f(x - \Delta x)]\} = -\frac{1}{2}\frac{d^2f}{(dx)^2}(dx)^2$$

If the second derivative, hence, the curvature of f, is negative at x, then f at x is larger than the average of f at all neighboring points. See Morse, P. M.; Feshbach, H. "Methods of Theoretical Physics," Vol. 1; McGraw Hill: New York, 1953, p. 6.
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CHAPTER 4

Twisted Bridgehead Bicyclic Lactams

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CONTENTS

1. INTRODUCTION

Among the bicyclic (*l*, *m*, *n*) bridgehead lactams (**BBL**), those containing a zero bridge ($m = 0$) have been extensively investigated because they include many unstrained molecules as well as penicillins, cephalosporins, and a variety of other bioactive compounds. These compounds appear to derive most of their activity from the strain in the β-lactam ring, although devia-