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You should be able to quickly draw cyclohexane rings in which the axial and equatorial bonds are readily identifiable and distinguishable.. Up to now we have not described in detail the rotational path of cyclohexane and what is the end result. We understand that the best path (the lowest energy path) available proceeds via the half chair and requires an energy input of 10 kcal/mol. This transition state proceeds to a twist boat energy minimum, but this is not highly populated and generally plays little or no role in cyclohexane's structure or chemistry.

Cyclohexane Conformational Analysis
<http://research.cm.utexas.edu/ibuild/teach/cyclohex.html>

Cyclohexane Conformational Analysis

Cyclohexane Conformations and Energies

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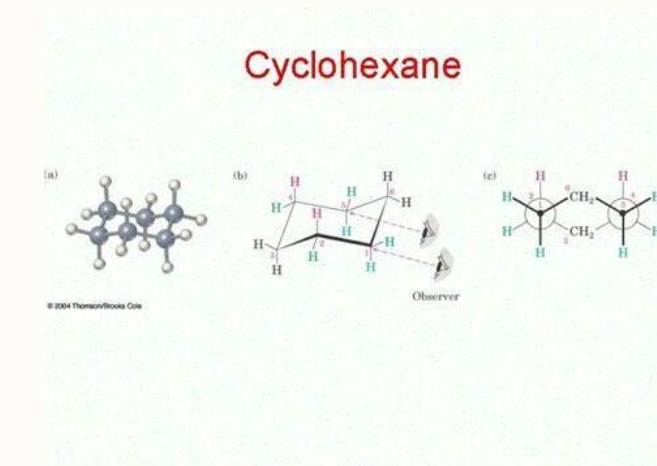
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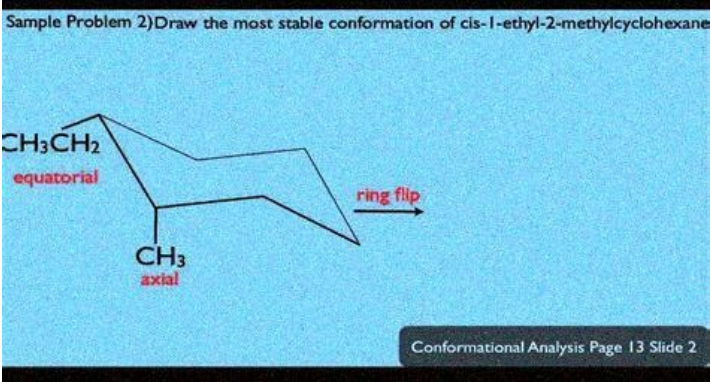
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CYCLOHEXANE CONFORMATIONS

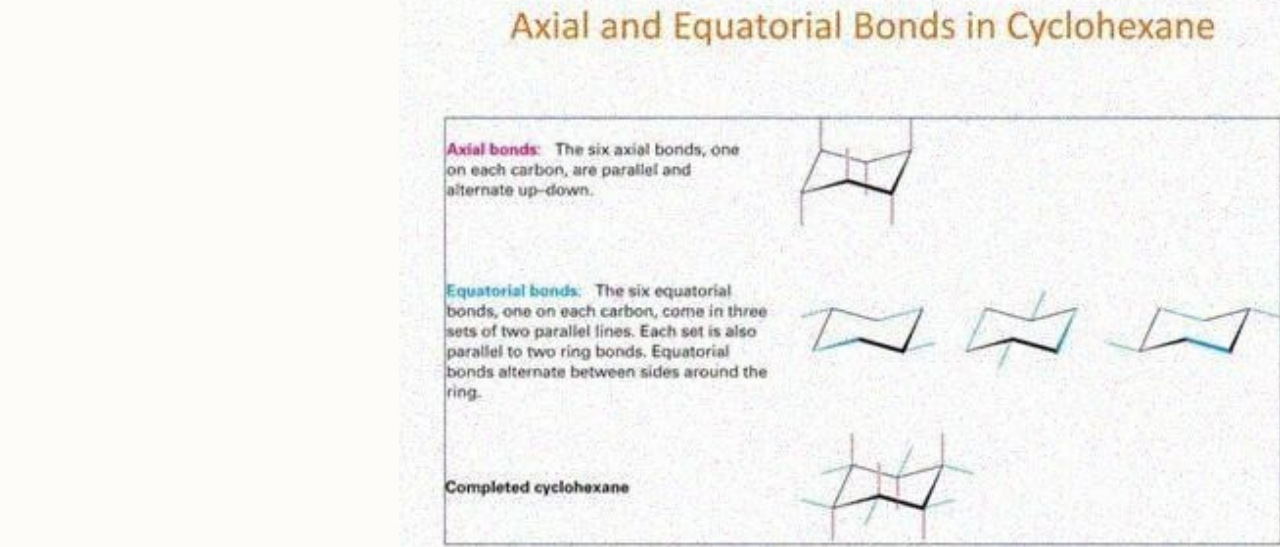
We use the simple methyl group as an example, but the same concept applies to any substituent. Equatorial methyl cyclohexane is the more stable conformation. When the ring flip occurs, however, it converts to axial methylcyclohexane. These two conformations are in rapid equilibrium at room temperature, but can be frozen out as distinct compounds at -78degrees. The equatorial conofrmation is favored in the equilibrium by a modest amount because the axial isomer has about 1.8 kcal/mol of steric strain.



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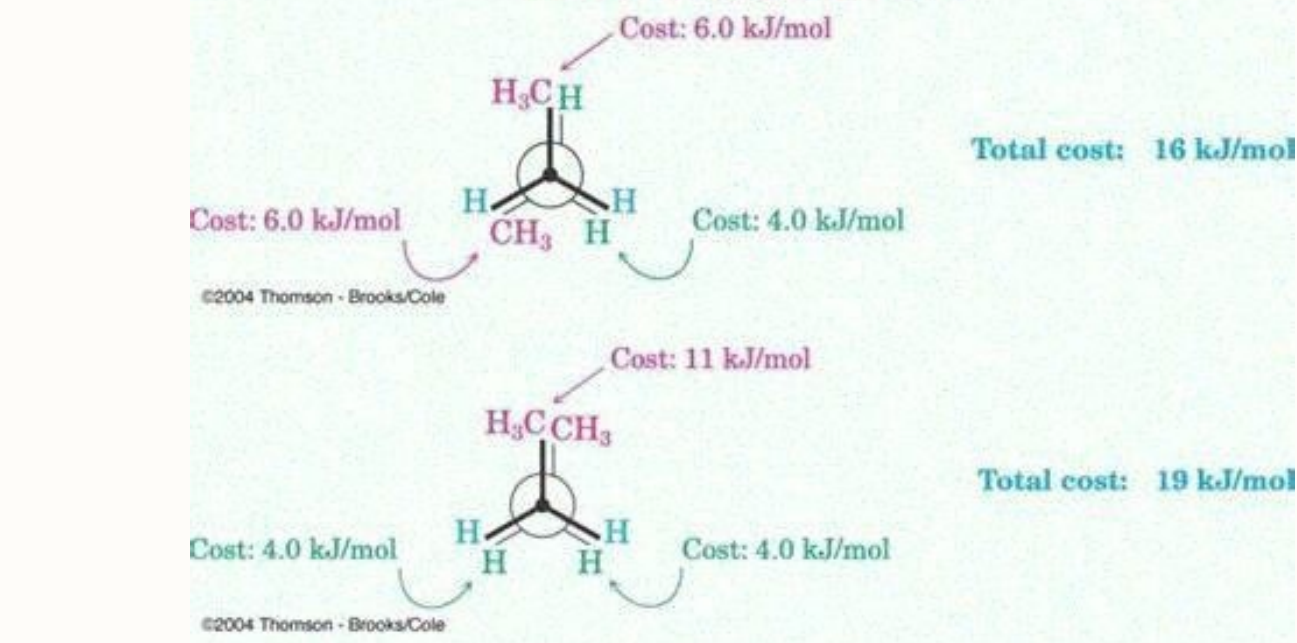


Since axial and equatorial bonds are non-equivalent, there are two non-equivalent positions in which to place any substituent. We use the simple methyl group as an example, but the same concept applies to any substituent. Equatorial methyl cyclohexane is the more stable conformation. When the ring flip occurs, however, it converts to axial methylcyclohexane. These two conformations are in rapid equilibrium at room temperature, but can be frozen out as distinct compounds at -78degrees. The equatorial conformation is favored in the equilibrium by a modest amount because the axial isomer has about 1.8 kcal/mol of steric strain. This strain arises from the interaction of one of the hydrogens of the axial methyl group with each of the two other axial hydrogens on the same side of the ring, as illustrated above. Each of these steric interactions is approximately equivalent to one gauche butane interaction of 0.9 kcal/mole, so the total is 1.8 kcal/mol. The point of the gauche butane comparison is that the H/H distance of the sterically hindered hydrogens is almost exactly the same in gauche butane as with axial methyl cyclohexane, except that there are two such H/H interactions in the latter case. The steric interactions in axial methylcyclohexane are referred to as "1,3-diaxial interactions", because the interactions involve two axial atoms or groups (one H and one CH3 and the carbons bearing these atoms or groups are 1,3 related. Ring flipping gives a conformation in which the methyl substituents are anti (dihedral angle of 180) to each other, but this is still trans, and this conformation is less stable because it has two axial substituents.



You should be able to quickly draw cyclohexane rings in which the axial and equatorial bonds are readily identifiable and distinguishable.. Up to now we have not described in detail the rotational path of cyclohexane and what is the end result. We understand that the best path (the lowest energy path) available proceeds via the half chair and requires an energy input of 10 kcal/mol. This transition state proceeds to a twist boat energy minimum, but this is not highly populated and generally plays little or no role in cyclohexane's structure or chemistry. However, the twist boat can interconvert with another equivalent twist boat (via the true boat conformation as a transition state) to give another chair structure, in which the sense of the ring puckering is reversed. This is significant in cyclohexane itself, because in this process the axial and equatorial hydrogens are interconverted. Since this interconversion or ring flip occurs rapidly at room temperature, all hydrogens spend 50% of their time as axial hydrogens and 50% of their time as equatorial hydrogens, so that on the time average all C-H bonds of cyclohexane are equivalent. However, at any given instant, there are always two types of hydrogen. Since axial and equatorial bonds are non-equivalent, there are two non-equivalent positions in which to place any substituent. We use the simple methyl group as an example, but the same concept applies to any substituent. Equatorial methyl cyclohexane is the more stable conformation. When the ring flip occurs, however, it converts to axial methylcyclohexane. These two conformations are in rapid equilibrium at room temperature, but can be frozen out as distinct compounds at -78degrees. The equatorial conformation is favored in the equilibrium by a modest amount because the axial isomer has about 1.8 kcal/mol of steric strain. This strain arises from the interaction of one of the hydrogens of the axial methyl group with each of the two other axial hydrogens on the same side of the ring, as illustrated above. Each of these steric interactions is approximately equivalent to one gauche butane interaction of 0.9 kcal/mole, so the total is 1.8 kcal/mol. The point of the gauche butane comparison is that the H/H distance of the sterically hindered hydrogens is almost exactly the same in gauche butane as with axial methyl cyclohexane, except that there are two such H/H interactions in the latter case. The steric interactions in axial methylcyclohexane are referred to as "1,3-diaxial interactions", because the interactions involve two axial atoms or groups (one H and one CH3 and the carbons bearing these atoms or groups are 1,3 related. THE "EQUATORIALITY PRINCIPLE" PROVIDES THAT ANY SUBSTITUENT PREFERS TO OCCUPY THE LESS STERICALLY HINDERED EQUATORIAL POSITION, IF AT ALL POSSIBLE. IN THE CASE OF DI- OR POLY-SUBSTITUTED CYCLOHEXANES NOT ALL SUBSTITUENTS CAN OCCUPY ALL EQUATORIAL POSITIONS IN EVERY ISOMER, BUT THAT ISOMER WILL BE THE MOST STABLE IN WHICH ALL OF THE SUBSTITUENTS OCCUPY EQUATORIAL POSITIONS (see examples below). Note that with the 1,4-disubstitution pattern, the diequatorial (mosts stable) arrangement is what we call the "trans" isomer. In it, one substituent is "slant up" and one "slant down". Ring flipping gives a conformation in which the methyl substituents are anti (dihedral angle of 180) to each other, but this is still trans, and this conformation is less stable because it has two axial substituents.

2 Different Eclipsed Conformations



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Recall that cis and trans isomers are diastereoisomers, they are not different conformations of the same isomer and cannot be readily interconverted by a simple rotational process (a bond would have to be broken). In the cis isomer, here, one methyl group is equatorial and one axial, and ring flipping simply gives and other equivalent conformation. Since one methyl is axial, this costs 1.8 kcal of steric strain. Consequently, the cis isomer is less thermodynamically stable than the trans, which has no steric strain in the more stable conformation. The energy difference is again, 1.8 kcal/mol. In the cis isomer, one substituent is vertically up (or down) and the other slant up (or down). So they both point, in a general sense, in the same direction, i.e., both up or both down. 1,3-Dimethylcyclohexane In the 1,3-disubstitution pattern (whether it is dimethyl or any other 1,3-disubstitution), both groups can only be equatorial when they are both cis. So the cis isomer is the more stable isomer in this case. Ring flipping gives a conformation of the cis isomer which has both methyls axial. Worse than that, they are both on the same side of the ring, so it is not an axial methyl/axial hydrogen interaction any longer, it is an axial methyl/axial methyl interaction, which is sterically much worse. Consequently this ring flip is too energetically difficult, and this conformer can be neglected in the conformational analysis. The trans-1,3-dimethylcyclohexane isomer, on the other hand, has one methyl axial in both ring-flip conformers, so that it is less stable than the cis isomer by 1.8 kcal/mol. Both trans-1,4-dimethylcyclohexane and cis-1,3-dimethylcyclohexane have essentially the same energy, since neither one of them has any strain at all. The 1,2-disubstitution pattern is very much like the 1,4 pattern, in that the two groups can only be equatorial if they are trans, so the trans isomer is more stable than the cis. The diaxial trans conformer has 3.6 kcal of steric strain, of course and is much less favored than the diequatorial conformer. The cis isomer is less stable than the trans because in it, one methyl must be axial. The cis isomer is therefore less stable than the trans by 1.8 kcal. The key difference between the 1,2 and 1,4 patterns, is that in the diequatorial 1,2 conformation, the methyl groups are gauche as in gauche butane (remember that gauche essentially implies a 60 degree dihedral angle). Consequently, this diequatorial conformation no longer is strain free, as was the 1,4-trans diequatorial conformation, where the methyls are very far apart. The 1,2-diequatorial isomer is 0.9 kcal/mol less stable than the 1,4-diequatorial isomer, because of this gauche butane-like interaction (recall that the gauche isomer in butane is destabilized by exactly this amount). BACK TO THE TOP OF THE PAGE ON TO THE NEXT PAGE BACK TO THE BAULD HOME PAGE Chair conformation of cyclohexane Cyclohexane is the most stable cycloalkane. It is strain-free, meaning neither angle strains nor torsional strains apply, and it shows the same stability as chain alkanes. This special stability is due to a unique conformation it adopts. The most stable conformation of cyclohexane is called the "chair" conformation, since it somewhat resembles a chair. In the chair conformation of cyclohexane, all the carbons are at 109.5° bond angles, so no angle strain applies. The hydrogens on adjacent carbons are also arranged in a perfect staggered conformation that makes the ring free of torsional strain as well. This will be illustrated more clearly later when we learn about the Newman projection of the chair conformation. Properties of the chair conformation In the chair conformation of cyclohexane, the twelve C-H bonds can be divided into two categories based on the orientations, which are axial ("a") and equatorial ("e"). In the structure below, the six red-coloured bonds are axial, and the six blue-coloured bonds are equatorial. Axial bonds are vertical and perpendicular to the average plane of the ring, while the equatorial bonds are more "flat" and extend from the perimeter of the ring. For both "a" and "e", they can either point up (above the ring), or point down (below the ring). The trending of "a" and "e" bonds in the chair conformation can be summarized as: Each carbon has one "a" bond and one "e" bond; if one bond points up (above the ring), the other has to point down (below the ring) For the same type of bonds, the orientation up (above the ring) and down (below the ring) alternates from one carbon to the adjacent carbon, meaning if a certain carbon has a (up), then the adjacent carbon must have a (down) For the twelve C-H bonds: 3a (up), 3a (down), 3e (up), and 3e (down). How to draw the chair conformation It is important to understand and recognize all the bonds in the chair conformation, and you are also expected to be able to draw the conformation correctly and quickly. The procedure is: Draw two parallel lines of the same length that both point slightly down (if connected, they would form a parallelogram with an internal angle of about 60°/120°). Connect the right ending points of the two lines with a "V" shape so that the vertex of the V points to the upper right. Connect the left starting points of the two lines with another "V" shape so that the vertex of the V points to the bottom left. Add up all of the "a" bonds on each carbon as the vertical lines, and follow the alternating trend on adjacent carbons. Add all of the "e" bonds by following the trend in which on a certain carbon, if an "a" bond points up, then an "e" bond must point down, and vice versa. Also notice that the "e" bond is parallel to the C-C bond which is one bond away, as shown below. The "green e" is parallel to the "green C-C bond", and the "blue e" is parallel to the "blue C-C bond". (It is more challenging to draw "e" bonds, and following the above trend makes it easier). It is highly recommended that a molecular model set is used as a study tool in this section. Assemble a cyclohexane ring with the model and become familiar with all the bonds in the chair conformation. Practice makes perfect! A lot of practice is required to become skilled in drawing and understanding the chair conformation. Ring flipping When a cyclohexane ring undergoes a chair-chair conformation conversion, this is known as ring flipping. Ring flipping comes from C-C bond rotation, but since all of the bonds are limited within the ring, the rotation can only partially occur, which leads to the ring "flipping". Cyclohexane rapidly interconverts between two stable chair conformations because of the ease of bond rotation.

The energy barrier is about 45 kJ/mol, and the thermal energies of the molecules at room temperature are high enough to cause about 1 million interconversions to occur per second. For cyclohexane, the ring after flipping still appears almost identical to the original ring, but some changes happen on the C-H bonds. Specifically, all the "a" bonds become "e" bonds, and all the "e" bonds become "a" bonds. In cyclic compounds, each carbon atom is not bonded to four identical substituents and hence, bond lengths and angles do not exactly correspond to the ideal tetrahedral values. You will notice that the red a (up) converted to a red e (down) and the blue e (up) converted to a blue a (down) after ring flipping. Summary of ring flipping for chair conformation: This is NOT rotation, but ring flipping. The two structures are conformation isomers (or conformers). All "a" bonds become "e" bonds and all "e" bonds become "a" bonds. These two conformations are equivalent for the cyclohexane ring itself (without any substituents), with the same energy level. A molecular model is very useful for understanding ring flipping. Newman projection of the chair conformation The chair conformation is strain-free, with all the C-H bonds in a staggered position. However, it is not easy to see the staggered conformation in the drawings we have so far, and a Newman projection helps for this purpose. To draw Newman projections for the chair conformation of cyclohexane, we also need to pick up the C-C bonds to view along, just as we did for alkanes. Since there are a total of six C-C bonds, we will pick two of them, and these two need to be parallel to each other. For the chair conformation example here, the two blue parallel C-C bonds, C1-C2 and C5-C4, are chosen for viewing. (There are 3 pairs of parallel bonds in the chair conformation, and any pair can be chosen with the resulting Newman projection looking the same). For the C1-C2 bond, C1 is the "front" carbon and C2 is the "rear" carbon. For the C5-C4 bond, C5 is the "front" carbon and C4 is the "rear" carbon. These two bonds will be represented by two "Newman projections" we are familiar with (two circle things), and each represents two carbons, as shown below: Keep in mind that there are a total of six carbons in the ring, and the drawing above only shows four of them with C3 and C6 being left out. Additionally, the two "separated" Newman projections above are actually connected to both C3 and C6, so the overall Newman projection of the chair conformation of cyclohexane looks like this: The staggered conformation of cyclohexane is clearly shown in the Newman projection here! Notes for Newman projections of the chair conformation (refer to the drawing below): The "a" or "e" bonds on four carbons (C1, C2, C4 and C5) are shown explicitly, while the bonds on C3 and C6 are just shown as CH2. The vertical red C-H bonds are the "a" bonds, and the "flat" blue C-H bonds are the "e" bonds. The dashed line in the drawing below can be regarded as the average plane of the ring. Those above the line are the bonds that point up (up), and those below the line are the bonds that point down (down). Other conformation of cyclohexane The chair conformation is the most stable one with the lowest energy, but it is not the only conformation for cyclohexane. During the ring flipping from one chair conformation to another, the ring goes through several other conformations, and we will only briefly discuss the boat conformation here. Figure 4.3a Boat conformation of cyclohexane The boat conformation comes from partial C-C bond rotations (only flipping one carbon up to convert the chair to a boat) of the chair conformation, and all the carbons still have 109.5° bond angles, so there are no angle strains. However, the hydrogens on the base of the boat are all in eclipsed positions, so there are torsional strains. This can be illustrated by the Newman projection below. The Newman projection is drawn by viewing along C6-C5 and C2-C3 bonds of the above boat conformation. Figure 4.3b Newman projection of boat conformation Other than that, the two hydrogen atoms on C1 and C4 are very close to each other and cause steric strain. This is also called the "flagpole" interaction of the boat conformation. The two types of strains make the boat conformation have considerably higher energy (about 30 kJ/mol) than the chair conformation. Diamond is an allotropic modification of carbon composed of sp³-hybridized carbon atoms. In a diamond, carbon atoms assume arrangement described as a diamond lattice (Fig. 44). In a diamond lattice each carbon atom is bonded to four identical substituents—four other carbon atoms. Therefore, all the bond angles are ideal tetrahedral angles and all the bond lengths are 1.54 Å. Furthermore, all of the dihedral angles are either gauche (60°) or anti (180°). Thus, one can consider, to a first approximation, that any cyclic structure that can be superimposed to a diamond lattice is going to be a strain-free conformation [21]. In reality, that is the case with only a few rings. In cyclic compounds, each carbon atom is not bonded to four identical substituents and hence, bond lengths and angles do not exactly correspond to the ideal tetrahedral values. Additional factors, such as transannular strain, which is not present in a diamond lattice, also play a role. However, diamond lattice method still has importance. Fig. 44 a Diamond lattice, b Examples of six-membered rings superimposed on the diamond lattice The diamond lattice method can be applied to six-membered and larger rings as the smallest ring that can be superimposed on the diamond lattice is cyclohexane (Fig. 44b). Therefore, any smaller ring must exhibit angle strain. Furthermore, only rings with an even number of carbon atoms can form a closed path on a diamond lattice. As a result, all odd-membered rings must exhibit some torsional strain. We already encountered such situation with cyclopentane. Even-membered rings can be classified into two types: those with 4n and those with 4n + 2 carbon atoms. Only rings with 4n + 2 carbon atoms can have a completely strain-free conformation. An example is cyclohexane (n = 1). Cyclodecane (n = 2) is an exception. As a medium-sized ring, it exhibits steric (transannular) strain. Cyclotetradecane and larger n + 2 rings are essentially strain free. Other rings with even number of carbon atoms (4n) exhibit some strain and for them the diamond lattice conformation is not always optimal. Among the large rings, those with odd number of carbon atoms exhibit the most strain. While diamond lattice approach may represent a good starting point in conformational analysis of medium and large rings, nowadays its importance has decreased and we rely more on experimental (IR and Raman spectroscopies, X-ray diffraction, electron diffraction, low-temperature 1H and 13C NMR) and theoretical approaches such as molecular mechanics (MM), molecular orbital (MO) and molecular dynamics (MD) methods. Medium rings: common features of medium rings Compounds with 8-11 atoms in a ring are classified as medium rings. Conformational analysis of medium rings is complex. They are not simply intermediate between common and large rings. They have some specific features that are characteristic of them. Common and large rings generally differ little in chemical behavior compared to their open-chain counterparts. Perhaps the most distinguishing feature of medium-sized rings is the difficulty in synthesizing them. Due to the both unfavorable enthalpy and entropy of activation ring closure reactions that result in formation of medium rings are difficult to carry out. Furthermore, medium-sized rings are characterized by a relatively high strain. The strain per CH2 group in cyclooctane, cyclononane, cyclodecane and cycloundecane is rather high (Table 1; Fig. 45) [22]. Therefore, medium rings always exhibit strain.

In most cyclic compounds, the strain is a compromise between minimizing angle and torsional strain. In medium rings, angle and torsional strain are relatively low. However, they exhibit a unique type of steric strain. It is a consequence of conformations in which some of the bonds are directed into the ring. Such bonds and substituents are called intraannular bonds or substituents. Typically the substituent is a hydrogen atom since any substituent larger than hydrogen cannot occupy an intraannular position. Intraannular hydrogens "bump" into each other and exhibit steric hindrance called transannular strain. The substituents arranged outside the ring are called extraannular or peripheral substituents. Therefore, the overall strain is a result of a combination of bond angle distortion, partial eclipsing of hydrogens and transannular steric repulsions. It is not possible for medium-sized rings to relieve all of these strain-producing interactions in a single conformation. Thus, medium rings do not have a single low-energy conformation. Instead, there is an equilibrium among the several conformations that are close in energy to each other and are separated by low energy barriers.

As ring gets larger, the strain decreases. There is a considerable reduction in strain in cyclodecane. This is an indication that it belongs to the category of large rings, which are characterized by low strain. Essentially strain-free conformations are attainable only for large-sized cycloalkanes, such as cyclotetradecane. In such rings, the carbon chain adopts a structure very similar to that of the straight-chain alkanes, having staggered hydrogens and an all-anti configuration. One can notice that the value for strain for cycloheptadecane is negative. Strain of a cycloalkane is not determined experimentally. Rather it is a comparison of experimentally determined values of heats of formation compared to hypothetical "unstrained" molecule [23]. Table 1 Ring strain of cycloalkanes Fig. 45 Ring strain of cycloalkanes Finally, there is a specific type of transannular reactions (reactions across the ring) that only medium-sized rings undergo. Such reactions are a consequence of conformations of medium rings. Their intraannular hydrogen substituents readily undergo 1,3- and 1,5-hydride shift resulting in rearranged products. In summary, medium rings are characterized by three principal phenomena: low formation tendency, high strain and transannular reactions. Cycloheptane exhibits strain energy close to that of the medium rings. However, compared to eight- to eleven-membered rings, it is easy to prepare. Thus, it is classified as a common ring. On the other hand, cyclodecane, while difficult to prepare, has low strain energy. Therefore, it is a large ring. Both from the names and from the actual conformations, one can infer that the elements of cyclohexane conformations are present in medium and larger rings. As the number of atoms in the ring increases, the number of conformations sharply increases. There is no formula or an algorithm to determine the number of conformations from the number of ring atoms. While in small and common rings there was an attempt to identify and study all the conformations regardless of their energies, in medium and large rings an effort is made to clearly distinguish between a conformation, which is a local minimum on an energy diagram, and a transition state, which is a local maximum. While most efforts were placed in identification of all of the conformations of individual rings, study of transition states is also important. They represent pathways for interconversion of individual conformations, allowing one to identify the nature of the conformational "flip" (such as pseudorotation or inversion), the energies involved and hence how likely is that a particular conformation will be interconverted into another. Study of the transition states is also important when considering their reactivity and biomedical properties (such as interactions with enzymes and receptors). Cyclooctane Cyclooctane is the smallest member of the class of medium rings. It exhibits all of the typical properties of a medium ring: difficulty in cyclizing, transannular strain, transannular reactions and lack of single lowest energy structure. A total of 10 different conformations have been identified [24, 25]. In fact, an additional conformation was reported [26], but it was apparently identical to the one already known [27]. Complexities of conformational analysis of cyclooctane are a very good illustration of the challenges encountered when dealing with medium and large rings. On the diamond lattice there is a cyclic path involving eight carbon atoms (Fig. 46a). However, the resulting ring exhibits a high degree of strain.

The two pairs of hydrogen atoms (indicated as Ha and Hb) must point "inwards" (Fig. 46b), and are competing for the same positions in the diamond lattice, shown as red dots (Fig. 46c). Even though the carbon-hydrogen bond is shorter (1.10 Å) compared to the carbon-carbon bond (1.54 Å), still there is steric hindrance since the two hydrogen atoms should occupy the same space that a single carbon atom occupied in the diamond lattice. This is an example of transannular strain. Therefore, the conformation of cyclooctane derived from a diamond lattice, called boat-boat, is unstable. An alternative name for this conformation is "saddle".

Figure 46 a Conformation of cyclooctane obtained by following a closed path of eight carbon atoms on the diamond lattice, b Steric strain is a result of two pairs of hydrogen atoms competing for the same positions (shown as red dots) in the lattice, c A more common representation of the same conformation The twist-boat conformation is obtained by a slight twist of the boat-boat to get interacting hydrogen atoms away from each other (Fig. 47). That relieves transannular strain, but increases torsional strain. Fig. 47 Boat-boat and twist-boat are high energy conformations of cyclooctane By analogy with the chair of cyclohexane, crown conformation of cyclooctane may appear to be of a low energy. However, symmetrical crown conformation has high torsional strain because of the high degree of eclipsing in all of the pseudo-equatorial bonds (Fig. 48). Unlike the chair of cyclohexane, where neighboring equatorial bonds are gauche to each other, in the crown of cyclooctane they are eclipsing. Alternatively, one can slightly distort the crown conformation to obtain almost ideal torsion angles and bond angles. However, the resulting conformation has intraannular hydrogens on each side of the ring approaching very closely to each other resulting in a high steric strain. Fig. 48 Side-on perspective view (left) and view from the top (right) of a chair of cyclohexane, and b crown of cyclooctane Stretching the crown conformation between the opposite atoms results in a "chair-chair" conformation. Alternatively, stretching of the opposite bonds results in a "twist-chair-chair". The latter is slightly favored (Fig. 49). Fig. 49 Chair-chair and twist-chair-chair conformations of cyclooctane In summary, there are ten conformations of cyclooctane, which are divided into four families (Fig. 50) [24]. Interconversions within each family are by pseudorotation (a low energy barrier), while interconversions between different families are by inversion (a high energy barrier). Fig. 50 There are four families of conformations of cyclooctane A hybrid between boat-boat and chair-chair conformations, the so-called boat-chair, has the lowest energy. Starting with diamond lattice-derived boat-boat conformation, the flip (Fig. 51), removes one of the transannular interactions directly as the two interacting hydrogens (Ha pair) are moved away from each other. The second transannular interaction (Hb pair) is also removed as the "flip" causes the remaining ring atoms to rotate and that moves the second pair of interacting hydrogens away from each other. However, as a result of change of dihedral angles, the angle strain increases. Fig. 51 Starting with diamond lattice-derived boat-boat conformation one can obtain the most stable conformation of cyclooctane After the boat-chair, the next lowest energy conformation of cyclooctane is the twist-boat-chair followed by the twist-chair-chair. Crown and boat-boat are rather high in energy. At room temperature, boat-boat conformation is present only in trace amounts. Conformations such as boat or chair represent high-energy transition states.

Therefore, as is the case with other medium rings, there is an equilibrium among the several conformations that are close in energy to each other and are separated by low energy barriers (Fig. 52) [27]. Fig. 52 Conformations of cyclooctane with the amount of each present in the gas phase at 298 K. The amounts were determined based on calculated free energies of the conformers [27]. As a medium ring, cyclooctane also undergoes transannular reactions (reactions across the ring), which are covered later. Cyclooctane Odd-membered medium and large rings have been studied somewhat less extensively compared to even-membered rings. Cyclooctane has the highest strain of all medium ring cycloalkanes. Dale wrote that "On the basis of thermochemical strain cyclooctane can be considered the most typical medium-sized ring. It can also be considered the smallest macrocyclic alkane inasmuch as torsion angles larger than 120° start to play a role, and since the greater mobility of the ring permits conformational conversions to take place in a more localized step processes rather than as synchronous changes of the whole ring" [28]. Eight conformations that are cyclooctane energy minima have been identified [29]. However, some conformations have relatively high energies and are separated from the lower energy conformations by extremely low energy barriers. Such conformations have relatively little thermodynamic significance. Cyclooctane is the first case of a cycloalkane that does not have a lowest energy conformation. Rather it has several conformations of approximately equal energies that are separated by low energy barriers. Conformations of cyclooctane are combinations of various chair and boat forms as named by Hendrickson [19, 30]. He identified boat-chair, chair-boat and chair-chair forms as high-energy conformations [30]. Twisting of each gives the corresponding low-energy conformations of cyclooctane (Fig. 53). Calculations show that a twist-boat-chair (TBC) is the lowest energy form. It is a symmetric "triangular" conformation and is also designated as [333] conformation. Two other forms, twist-chair-boat (TCB) and twist-chair-chair (TCC), are relatively close in energy. Dale identified an additional, somewhat higher energy conformation as [234] or skew-chair-boat (SCB) [31]. Dale's representations and nomenclature is explained next. Corner carbon atoms are indicated as white circles and side atoms as black dots. Fig. 53 Conformations of cyclooctane In the case of cyclooctane the role of entropy is important. Usually when considering energy of a particular conformation, we consider only its enthalpy even though we should consider free energy. In most cases, particularly when determining only the relative stabilities of different conformations, the role of entropy is minor and can be neglected. That is not the case with cyclooctane.

The lowest energy conformation, TBC, has high symmetry and, thus, a low entropy. On the other hand a higher enthalpy conformation TCB also has considerably higher entropy as it is less symmetrical. As the contribution of entropy to the overall free energy increases with temperature (ΔG = ΔH – TΔS), at the higher temperatures TCB becomes the major conformation. TCC conformation is undetectable by low-temperature 13C NMR at –173 °C, barely detectable at –95 °C (estimated to be present in the amount of ca. 1 %) and present in significant amount at room temperature (Table 2) [32]. Table 2 Variation in abundance of conformations of cyclooctane with temperature Dale ("Wedge") representations of medium and large rings With cyclooctane both the perspective drawings and the nomenclature of various conformations get somewhat confusing. Side-on perspective views suitable for representation of smaller rings make it difficult to visualize and analyze a larger ring conformation. There is also an issue with nomenclature. Naming is now less descriptive as it is rather difficult to draw conformation from a given name, or assign a unique unambiguous name to a conformation. Furthermore, there is considerable possibility for confusion as in the case of TCB, TBC and SCB. Dale made an attempt to address these issues by introducing new conventions to represent and to name individual conformations [31]. In small and common rings each bond represents one "side" of the corresponding polygon (Fig. 54).

In medium and large rings, bonds are aligned in such a way that two, or more bonds, are roughly linear and represent a side of a polygon. Dale represented the ring as viewed from the top and the individual bonds as wedges. Signs +, – (gauche) or a (anti) are sometimes included to indicate conformation of the ring bonds. As mentioned earlier, hydrogen substituents in medium rings can be intraannular (pointing to the inside of the ring), or extraannular (pointing to the outside). Most carbon atoms in medium rings have one intraannular and one extraannular hydrogen. Such carbon atoms are on the "sides" of a polygon. A corner carbon atom has both extraannular hydrogen substituents

(pointing "outward") and they are isoclnal.Fig. 54Corner atoms in medium rings with both substituents pointing "outward," while side atoms have pointing "inward" and the other one "outward". A Molecular model and Dale's representation There are numerous variations in Dale's representation of rings. In one form, open wedge bonds are used (Fig. 55a). They can be combined with filled circles to indicate corner atoms (Fig. 55b). Alternatively, all of the atoms can be indicated and one distinguishes side atoms from corner atoms by knowing that both carbon-carbon bonds on a corner atom must be gauche. That is sometimes a problem as in medium and large rings angles frequently enlarge to accommodate steric strain. That in turn, results in change in torsional angles and they frequently deviate from ideal gauche (60°) and anti (180°) angles. A more convenient definition of a corner atom is that it is the one with two extraannular isoclnal bonds.

One can infer positions of hydrogens from the indicated carbon-carbon bonds. In a more complete representation, carbon-hydrogen bonds are indicated. Either filled (Fig. 55c) or open wedge bonds (Fig. 55d) can be used. Open circles are used to represent carbon atoms. C-H bonds are indicated as wedges (above the plane) or solid lines (below the plane). While that provides a more complete picture of stereochemistry, sometimes the drawing is cluttered and extraannular bonds are not always clear.Fig. 55Various forms of Dale's convention From the indicated stereochemistry of ring carbons one can infer stereochemistry of the carbon-hydrogen bonds (Fig. 56).

When there are two anti bonds on a carbon atom, it is a side carbon with one C-H bond extraannular and the other one intraannular. Ring carbon atom with a gauche bond is a corner carbon with both C-H bonds extraannular. From this representation it may not be clear that these bonds are also isoclnal. Note that, when carbon-hydrogen bonds are represented, ring carbons should be indicated with an open circle.Fig. 56Stereochemistry as indicated by Dale's convention: a anti bonds, b gauche bonds, c anti bonds with substituents, and d gauche bonds with substituents in most representations in this text hydrogen atoms have been omitted and open wedges are used to indicate carbon-carbon bonds. Corner atoms are indicated as open circles (Fig. 57a). When needed a top-view perspective formula of the carbon skeleton, with hydrogen atoms omitted, was also included (Fig. 57b).Fig. 57Examples of representations used in this text: a [333] and [225] conformers of cyclononane, b [3333] conformation of cyclododecane represented as a Dale's formula (left) and a perspective drawing (right) Each conformation is designated by a series of numbers within square brackets. Each number gives the number of bonds in one side, starting with the shortest and the direction of the ring is chosen so that the following number is the smallest possible [31]. For example, each "side" of TBC conformation has three bonds and the Dale notation is [333].

In SCB conformation the shortest side has two bonds, the shortest next to it three and the last one four. Hence, the notation is [234].

The sum of the numbers gives the ring size.According to Dale convention, based on the number of sides, conformations of medium and large rings can be classified as triangular, quadrangular and quinquangular. All of the cyclononane conformations we examined are triangular. Quadrangular conformations are commonly encountered in even-membered large rings while quinquangular in odd-membered large rings.CyclodecaneThe most studied and perhaps the most interesting medium-sized ring is that of cyclodecane. It is a very good illustration of the uniqueness of medium rings.

For example, it is the only ring that has 4n + 2 carbon atoms that exhibit significant strain.Since cyclodecane has an even number of ring atoms, there is one closed diamond lattice path for the carbon skeleton. The result is a conformation designated as boat-chair-boat (BCB) or [2323] (Fig. 58a). However, as was the case with cyclooctane, the two pairs of hydrogen atoms (pairs 1,5 and 6,10) are competing for the same positions (represented as red dots) in the diamond lattice. Thus, there is steric hindrance. To accommodate hydrogen atoms and reduce steric strain, bond angles become larger (on average 116°) and some bonds rotate out of the ideal staggered conformation. Therefore, steric strain is relieved at the expense of increased angle and torsional strain [33]. While that gets the two hydrogen atoms of each pair further apart, it also brings them closer to the third intraannular hydrogen on the same side of the ring (hydrogen 3 or 8 depending on the pair). As a result, on each side of the ring there are three hydrogen atoms cramped into a small space, which causes considerable steric (transannular) strain. In this conformation, a substituent larger than hydrogen cannot occupy an intraannular position. An alternative representation of the same conformation shows transannular interactions more clearly (Fig. 58b).Fig. 58Diamond lattice conformation and transannular strain in cyclodecane An alternative way to a diamond lattice approach to arrive at this conformation is to start with two fused cyclohexanes of trans-decalin in boat conformations (Fig. 59). Rotation of the two carbons "out" as indicated, causes change in bond and torsional angles resulting in the lowest energy, BCB, conformation.Fig. 59Derivation of the lowest energy conformation of cyclodecane starting with trans-decalin Cyclodecane in its lowest energy conformation has six different types of hydrogen atoms and three types of carbon atoms. For comparison, in the chair conformation of cyclohexane there is only one type of carbon atom and two types of hydrogens (axial and equatorial). As the most stable structure is based on a diamond lattice, substituents can be classified as axial and equatorial. Definition of axial and equatorial bonds in rings other than cyclohexane was provided by Anet [34]. There are 6 axial and 14 equatorial hydrogens (Fig. 60). Also, there are 6 intraannular and 14 peripheral hydrogens. Intraannular hydrogens are of two types--two are axial (labeled as 1) and four are equatorial (substituents 2). Of the 14 peripheral hydrogen atoms, four are axial (substituents 3). The remaining 10 belong to three types: (1) four are attached to a carbon that contains a peripheral axial hydrogen (substituents 4), (2) four are attached to the carbon that contains an intraannular equatorial hydrogen (substituents 5), and (3) two are attached to the carbon that contains an intraannular axial hydrogen (substituents 6). Therefore, four carbon atoms have both hydrogens in peripheral positions (a), two have one is peripheral and the other one is intraannular axial (b) and four have one is peripheral and the other one is intraannular equatorial (c).Fig. 60Different types of hydrogen and carbon atoms in BCB conformation of cyclodecane There may be a temptation to represent cyclodecane as a trans-decalin (two fused cyclohexanes in chair conformations) with the "middle" bond (C1-C6) missing (Fig. 61). That is not a reasonable conformation as the steric hindrance between hydrogens 1 and 6 would be prohibitively large.

As the C1-C6 bond of trans-decalin is broken in its place there would have to be a hydrogen atom on each carbon. However, the carbons 1 and 6 are separated by only 1.54 Å and there is no space for hydrogen substituents. Obviously such structure is not reasonable. However, this conformation is a good starting point in search of a low-energy one. As was the case with the diamond lattice-type conformation, by change in bond and torsional angles the two hydrogens are moved further apart. The resulting conformation, CCC (Fig. 62), is only slightly less stable compared to the diamond lattice-derived conformation.Fig. 61An alternative conformation of cyclodecane Fig. 62The six lowest energy conformations of cyclodecane There are 18 conformations of cyclodecane [29]. 13C NMR studies have shown that at a low-temperature BCB is the principal conformer [35]. At room temperature, cyclodecane exists as a mixture of a rather large number of conformations. The six lowest energy conformations are shown in Fig. 62 [27, 36].CycloundecaneCycloundecane is the least studied medium ring and only a few studies of its conformations are available. There are 41 conformations of cycloundecane identified by MM2 method and 32 identified by MM3 [29]. The most stable conformations of cycloundecane are either triangular or quinquangular [31]. 13C NMR studies have

shown that at a low temperature there is an equilibrium of two forms (Fig. 63) [37]. As the temperature increases other forms appear and, at a room temperature, cycloundecane is a mixture of several forms as indicated by its low melting point. Cycloundecane conformers cannot be described by the chair and boat nomenclature used for smaller rings and one has to use Dale nomenclature.Fig. 63Equilibrium of conformations of cycloundecane at a low temperature as determined by 13C NMR Since there is no closed path on the diamond lattice for an odd-membered ring, the diamond lattice method cannot be used directly. However, one still can start with the nearest even-membered ring and either add or truncate one carbon atom to arrive at the desired odd-membered ring [31]. Thus, in the case of cycloundecane one can start with the diamond lattice-derived [2323] conformation of cyclodecane and add one carbon atom (shown in red) to arrive at the cycloundecane conformation [12323] (Fig. 64a), or start with diamond lattice-derived conformation [3333] of cyclododecane and remove one carbon atom (shown in red) to arrive at the cycloundecane conformation [335] (Fig. 64b).

Among the numerous other conformations of cycloundecane the four represented in Fig. 65 are closest in energy to the lowest energy [12323] and [335] conformations [37]. An eleven-member ring is the largest one that exhibits transannular reactions. Larger rings do not and that is one reason why rings larger than eleven-member are classified as large rings.Fig. 64Generation of low energy conformations of cycloundecane starting with the diamond lattice-derived conformation of a cyclodecane and b cyclododecane Fig. 65Some additional low energy conformations of cycloundecane Transannular reactionsThe most interesting features of medium-sized rings are the phenomena of transannular interactions and the transannular reactions.

Transannular interactions have been covered when dealing with each individual cycloalkane. In medium-sized rings, transannular reactions take place between atoms on opposite sides of the ring.A transannular reaction is any reaction that occurs across a ring. All cyclic compounds, except of course a three-membered ring, can undergo transannular reactions. Thus, even cyclobutane undergoes a transannular reaction (Fig. 66) [38]. Transannular reactions on larger rings are common and are frequently exploited in synthesis. An example is the transannular aldol reaction (Fig. 67) [39]. Asymmetric transannular reactions have been recently reviewed [40].Fig. 66A transannular reaction of cyclobutane ester to give the corresponding bicyclo[1.1.0]butane ester Fig. 67Some examples of transannular reactions There is a specific type of transannular reactions that occur only in medium rings [41]. Such reactions do not occur in open-chain compounds or other rings. Most of them involve 1,5-hydrogen shift. An example is bromination of cyclooctene with N-bromoacetamide (NBA) in methanol (Fig. 68) [42]. Minor product, 1-bromo-2-methoxycyclooctene, was the result of the expected 1,2-addition to the double bond. Major products were the result of 1,5-hydride shift. Only in medium rings there is an intraannular hydrogen that is positioned for 1,5-hydride shift. Common rings underwent only the 1,2-addition reaction.Fig. 68Transannular reactions of cyclooctene Large ringsLarge rings are highly flexible. Properties of large rings resemble those of the corresponding open-chain compounds. As the rings get sufficiently large, they assume conformations of extended rectangles composed of two long parallel chains linked by two bridges of minimum length [43]. Disubstituted derivatives do not exhibit cis-trans isomerism since the rotation about carbon-carbon bonds in larger rings is free and the individual carbon atoms can rotate without affecting the rest of the ring. The number of conformations increases rapidly with the increasing ring size. For even-membered rings the number of possible diamond lattice conformations also increases and all large rings have more than one diamond lattice conformation.Cyclododecane is considered to be the first large ring cycloalkane. It lends itself to some interesting line formulas (Fig. 69). Line formula a is almost never used as the size of the ring is not clear. Formula b is the one that is most commonly used. It clearly indicates the number of carbon atoms in the ring and it can represent both cis and trans double bonds in a ring. Formulas c and d are sometimes encountered.Fig. 69Various line formulas of cyclododecane Weinberg and Saul found 97 conformations of cyclododecane utilizing MM3 and 121 utilizing MM2 method [29]. Even though there is a large number of different conformations, there is an agreement that cyclododecane exists as a single low-energy conformation, designated as [3333] (Fig. 70), with other conformations being considerably higher in energy. That is supported by both experimental results [44] and theoretical calculations [18, 45]. Thus, considering cycloalkanes in the order of increasing ring size, this is the first case since cyclohexane that a single low-energy conformation can be assigned to a cycloalkane.Fig. 70[3333] conformation of cyclododecane The lowest energy conformation of cyclododecane is not of diamond lattice type. There are four diamond lattice conformations (Fig. 71) [21]. All of the diamond lattice-type conformations have "overlap" interactions (interactions where hydrogen substituents compete for the same position in the diamond lattice indicated as a red dot), which renders them high in energy. For example, conformation a has two hydrogen-hydrogen interactions, conformation b three, while each of the conformations c and d has one serious "triple hydrogen" interaction.Fig. 71The diamond-lattice conformations of cyclododecane: a the conformation that exhibits two pairs of hydrogen-hydrogen interactions, b the conformation that exhibits three pairs of hydrogen-hydrogen interactions, and c, d two conformations that exhibit a "triple hydrogen" interaction CyclotridecaneThe conformational analysis of cyclotridecane is complex, as is common for odd-membered rings. Only a few theoretical and experimental studies were carried out so far and relatively little is known.

Low-temperature NMR studies have been one of the best methods to study conformational equilibria of cycloalkanes. Cyclotridecane undergoes a fast pseudorotation and low-temperature NMR studies did not yield any useful results [46]. According to the strain energy calculations, there are five low-energy conformations, which are separated by low energy barriers (Fig. 72) [31, 47]. Two quinquangular conformations are of the lower energy, while three triangular are of somewhat higher. Based on the calculations [48] and the studies of related systems [46, 49], some authors have proposed conformation [12433] [29, 31, 48] while others [13333] [46, 47] to be the lowest energy conformation.Fig. 72Low energy conformations of cyclotridecane Recently a [337] was proposed as the lowest energy conformation [49].

It is a variation of [13333] conformation with corner atoms 2 and 3 now being now a part of one long seven-carbon side (Fig. 73). One should note that the study was based on a ring in which carbon 1 was sp 2 hybridized. Thus, a distinction between a triangular [337] and quinquangular [13333] conformation may not be clear. About 35 years earlier, Dale himself predicted such a possibility: "Sometimes there is even a problem of classification, since a definition based on whether the ring projection "looks" triangular or quinquangular, and a definition based on whether the relevant dihedral angles are above or below 120°, may lead to different results" [31].

However, it should be noted that in the same paper Dale identified [337] as a high-energy conformation of cyclotridecane.Fig. 73 a [13333] and [337] conformations of cyclotridecane with hydrogens omitted, corner carbon atoms are shown in blue and the sp 2-hybridized carbon atom is shown in green. b [337] conformation is based on the X-ray structure of 2,4-dinitrophenylhydrazone of cyclotridecanone [49] As in the case of cycloundecane, two lowest energy conformations can be derived from the diamond lattice conformations of the nearest even-membered rings (Fig. 74). Conformation [12433] may be derived by ring contraction from the diamond lattice conformation [3434] of cyclotetradecane. Conformation [13333] can be derived from the [3333] conformation of cyclododecane by ring expansion.Fig. 74Generation of low energy conformations of cyclotridecane starting with the diamond lattice-derived conformation of a cyclotetradecane and b cyclodecane. Carbon atom indicated by an arrow and shown in red is a removed or b added CyclotetradecaneCyclotetradecane is the smallest saturated ring (in addition to cyclohexane) that is strain free. It has a diamond lattice-type conformation [3434] (Fig. 75a), with enough space for all interior hydrogen atoms (Fig. 75b,c) [31]. The substituents, however, can only occupy exterior positions, and geminal substituents only the corner positions. A non-diamond-lattice conformation [3344] (Fig. 75d) is the next-best candidate and has been calculated to be about 2.6 kcal mol^{−1} higher in energy.Fig. 75 a The lowest energy [3434] conformation of cyclotetradecane generated from the diamond lattice. b [3434] Conformation showing internal hydrogen atoms. c [3434] conformation.

d [3344] conformation CyclopentadecaneThere are five low-energy conformations of cyclopentadecane according to the strain energy calculations [31, 47]. All of the low-energy conformations are quinquangular (Fig. 76). The highly symmetrical [33333] conformation has the lowest strain energy. However, it also has low entropy. When entropy is taken into account, at room temperature, conformations [13443] and [14334] have about the same free energy as [33333] and the remaining two, [13434] and [13353], only slightly higher. Therefore, at room temperature cyclopentadecane is a mixture of the five low-energy conformations shown in Fig. 76.Fig. 76Low energy conformations of cyclopentadecane Larger ringsAs expected, complexity of conformational situation increases with the ring size. Conformational analysis becomes more complex and there are fewer studies available. However, one can still draw some general conclusions. With the increase in ring size the number of possible conformations sharply increases and finding all reasonable conformations becomes a problem [29].

Larger rings are likely to exist as mixtures of several conformations. Even-membered rings exhibit low strain and tend to be mixtures of various quadrangular conformations. Odd-membered rings are more strained and are usually more complex mixtures of a larger number of various, mainly quadrangular and quinquangular, conformations.The most stable conformation of cyclohexadecane is the diamond lattice [4444] conformation [31] (Fig. 77a). It is 1.9 kcal mol^{−1} more stable compared to the next most stable conformation [3535] [50]. More recent molecular dynamics structures indicate that, at higher temperatures, cyclohexadecane is a mixture of a large number of different conformations with [4444] still being the most abundant, but the second most populated conformer is [3445] [51].Fig. 77Conformations of a cyclohexadecane and b cycloheptadecane Cycloheptadecane presents an interesting problem for conformational analysis. Since it is a large odd-membered ring, there is no obvious low-energy conformation. Cycloheptadecane is a challenging target and search for all of its conformations has been used as a test for validity of a particular search method [29, 52, 53]. There is an extremely large number of conformational minima and 264 conformations in the range of 0-3 kcal mol^{−1} have been identified [52].

Conformation shown in Fig. 77b has been identified as the preferred conformation of cycloheptadecane [53, 54].Conformations of even larger rings become even more interesting as the increased conformational flexibility and attractive van der Waals interaction begin to play a role. With the increase in ring size long and thin rectangular conformations become preferred over the square ones. The lowest energy conformation of cyclooctadecane is [3636] while [4545] has a slightly higher energy (Fig. 78) [55]. While in medium rings, molecules underwent valence angle and torsion angle distortion to move the intraannular hydrogens further apart, large rings, such as cyclooctadecane, assume conformations that bring them closer together and maximize attractive van der Waals interactions (a more accurate though less commonly used term is London forces). In the [4545] conformer intraannular hydrogens are further apart resulting in a decreased van der Waals stabilization. By flipping inwards two carbons on the opposite "long" sides of the conformation [4545] one obtains the next most stable conformation, which can be designated as [234234] (Fig. 78c). Note that in it the intraannular hydrogens are closer to other intraannular hydrogens compared to [4545] conformation. Cyclooctadecane is the smallest ring in which such conformation is possible without causing transannular strain. In cyclooctacosane (C28H56) and larger cycloalkanes the attractive van der Waals forces can actually cause the ring to be distorted inwards (Fig. 79) [55].Fig. 78Conformations of cyclooctadecane in the order of increasing strain energy a [3636], b [4545], and c [234234] Fig. 79In cyclotriacontane (C30H60) the attractive van der Waals interactions cause the ring to be distorted inwards The lowest energy conformations of cyclononadecane and cycloicosane are analogous to those of cyclooctadecane (Fig. 80).Fig. 80The lowest energy conformations in the order of increasing strain energy of a cyclononadecane and b cycloicosane Page 2Formulas of ethane. In each case, staggered conformation is on the left and eclipsing conformation is on the right. a Perspective formulas. b Newman Projections. c Sawhorse formulas