Thinking in Blue #8 - in our introduction to conformational analysis, we look at two processes: bond rotations as depicted by Newman projections, and the conformational drawings of small rings (4- and 6-membered as exemplars), using Questions 6.09 and 6.15.

6.09 The ubiquitin/proteasome system (UPS) is a major protein degradation pathway in eukaryotes. Molecules that can inhibit unwanted degradation are attractive targets for autoimmune disorders. In one such study, an inhibitor molecule is proposed to make the following conformational change in the UPS.

![Newman projections for UPS conformation change](image)

(a) Draw the two Newman projections for these conformations. Use the point of view where the carbon a is the front atom and carbon b is the back atom (see above for labels).

(b) As drawn in (a), what is the value of the $\Delta G^\circ$ for this conformational change? kcal/mol

6.15 Menthol is a naturally occurring compound found in the oils of the mint tree *Mentha arvensis*. Menthol is well known for its cooling effects and its mint flavor and odor, which are the basis of the majority of its uses. The single largest use for menthol is probably in cigarettes. A survey of pharmaceutical products indicates that menthol is formulated in over-the-counter rubs and liniments (2–10% concentrations), antipruritic lotions, nasal sprays, expectorants, mouthwashes and sprays, cough drops, and foot powders.

(a) Draw the two chair conformations of menthol.

![Menthol chair conformations](image)

(b) The experimentally determined conformational energy difference between the two chair forms of menthol is quite consistent with the value estimated from the A-Values of the three substituent groups. What is the estimated $\Delta G^\circ$ for the equilibrium, as shown above?

(c) Both of the chair conformations have additional interactions beyond those accounted for by the A-Values. What are these interactions, and what is the conclusion about the relative magnitude of these interactions, based on the fact that the energy difference based on the A-Values alone does a good job reproducing the experimental result for the energy difference?
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Two of the topics from this point in CHEM 210 are among the easiest to identify: questions that deal with purely conformational analysis and those that deal with stereochemistry. These are finite topics with well-defined rules and boundaries. This question identifies itself as being “conformational” in the text, and so that generally means one of two types of analysis: (1) using Newman projections (drawings) to assess the relative stability of up to three staggered conformers of any given bond, or (2) using chair cyclohexane drawings to assess the relative stability of a pair of ring conformers. The understanding of these topics, and how to correctly represent molecules, and what these drawings mean, is all that needs to be carried into the question. Once you are trying to answer it, you are only interested in applying the ideas… not trying to learn them!

Newman projections and chair cyclohexane drawings were designed to make it as easy as possible to visualize and assess, on paper, the non-covalent (non-bonded) interactions that influence stability in these three-dimensional structures. There is no question whatsoever that a person’s ability to read and use these drawings is critically linked to relating them to a set of three-dimensional models.

The non-covalent (non-bonded) interactions that influence stability are:

(a) steric (size) repulsion by large groups - as they bend out of each other’s way, they cause torsional (twisting) strain on the bonds; this interaction always leads to instability

(b) charge/charge attraction and repulsion - electrostatic attraction of positive and negative charges, including partial charges, is favorable, while the electrostatic repulsion of like charges (positive/positive; negative/negative), including partial charges, is unfavorable

(c) intramolecular hydrogen bonding - when a hydrogen bond donor and an acceptor can be close to one another, hydrogen bonding gives the assessment of relative stability; in general, the front-back relationship, called “staggered”: one of them is 180˚ away (“anti”) and the other two are 60˚ away (“gauche”)

Newman projections - visualizing bond rotations by looking down the bond axis (rather than at its side) allows you to see and assess the non-covalent (non-bonded) interactions that influence stability

- you are looking directly down the carbon-carbon bond, with the carbon in front (C₀) sitting directly ahead of the one in the rear (C₁); the carbon in the front, from your point of view, has three other groups on it: Fₗ which is on top, pointed straight up, Fᵣ which is down to your right, and Fᵢ which is down to your right; these three bonds, in your field of vision, from this perspective, are all 120˚ apart

- the carbon in the rear (C₁), from your point of view, has three other groups on it: Rᵢ which is up to your left, and Rᵣ which is up to your right; these three bonds, in your field of vision, from this perspective, are all 120˚ apart; in the Newman projection, the atom in the back is represented by the circle onto which the 3 back groups are attached, while the front remains the same as before; these three are also 120˚ apart, meaning that every group on the front carbon has a well-defined relationship to the groups on the back, called “staggered”: one of them is 180˚ away (“anti”) and the other two are 60˚ away (“gauche”)

- analysis of the sum of front-to-back relationships according to steric, electrostatics, and hydrogen bonding gives the assessment of relative stability; in general, the front-to-back interactions with hydrogen atom groups is ignored (H/H and group/H)

- a +120˚ bond rotation, turning the back carbon, removes a gauche steric interaction by placing the methyl groups anti to each other, K_EQ > 1

- a -120˚ bond rotation, turning the front carbon, removes a gauche steric interaction AND the repulsion of two partially negative atoms, by placing the groups anti to each other, K_EQ > 1

- a +120˚ bond rotation, turning the front carbon, adds a gauche steric interaction, adds a partial negative charge repulsion, and adds a hydrogen bond attraction; you need the experimental results to know that the hydrogen bonding dominates in this case, so K_EQ > 1
Chair conformational drawings - visualizing the three-dimensional, all-staggered form of the favored cyclohexane conformation

(1) three-dimension cues (such as lines, dashes and wedges) are not used, but rather a form of perspective that relies on understanding how a circle looks like an oval when viewed from an edge.

This was an x-axis spin; now take each of these and perform a z-axis spin of +90°.

And now take each of these and perform a y-axis spin of -90°.

This visualization skill is absolutely critical! Now imagine a planar 6 membered ring (benzene is, in fact, planar); the double bonds provide a nice reference for which atoms are located where, but a few of the hydrogens are also marked for added reference.

Now take a look at that image on the far right in the line above this... the cyclohexane ring is NOT planar; instead, the bonds can partially rotate and it creates an alternating up-down relationship between all of the ring carbons (only the top surface is being modified here, not the lower surface).

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![Diagram of cyclohexane chair conformation](image1)

- viewed as a side-on perspective, the correspondence of the vertices is shown by the 3 types of circles; on the left, the two shaded circles are in the writing surface, while the string of atoms with the open circle is projected above the page, towards the viewer (and the other is below the surface)
- the same two rings, as viewed from directly above (or, a +90° rotation along the x-axis)
- the up-down zig-zag is not observable, but a darker tone on the circle is used to indicate the vertex is closer to the viewer, while a lighter tone indicates that the vertex is farther away from the viewer

(2) in the cyclohexane chair conformation, all of the carbons are perfectly tetrahedral and each pair of adjacent atoms is perfectly staggered; this creates a highly regular and predictable bonding pattern, not only for the 6 bonds shown within the ring, but also for the 12 bonding sites that are not shown in the drawings above (2 at each vertex); these relationships are not obvious when the ring is drawn using the top-down hexagon view; from this perspective, there is always one bonding site at each vertex pointed towards you, and one pointed away (which is true, but their spatial relationships with one another is hidden - this relationship is nonetheless useful, because when two groups are “cis” to each other (same side of the ring) then they are always cis to each other, regardless of the form that the ring takes)

![Diagram of cyclohexane chair conformation](image2)

- in the cyclohexane chair conformation, there are 6 bonding sites that alternate straight up and straight down, parallel to the y-axis running through the cavity of the ring, and in the “vertical up” or “vertical down” direction according to the way the vertex is pointing; these 6 bonding sites are pointed in the axial orientation with respect to the ring
- three alternating “up” vertices with the 3 bonding sites oriented axially up, parallel to ring cavity y-axis
- three alternating “down” vertices with the 3 bonding sites oriented axially down, parallel to ring cavity y-axis
- six axial sites, alternating according to vertex, all mutually parallel to ring cavity axis

![Diagram of cyclohexane chair conformation](image3)

- in the cyclohexane chair conformation, there is a non-axial bonding site at each vertex that moves out perpendicularly from the y-axis, more or less in the direction of the x-z plane; these 6 equatorial (along the equator) sites can be groups in 2 sets of 3 when you draw them, also: the 3 sites on the right hand half of the ring point to the right, and the 3 on the left point left, each one is exactly parallel to the 2 ring C-C bonds that are one carbon away in each direction
- the ring cavity y-axis
- three equatorial sites on the right hand half of the ring point right
- three equatorial sites on the right hand half of the ring point left
- three equatorial sites on the far right vertex: (a) points right, (b) parallel to 2 rings bonds one carbon away
- six equatorial sites

![Diagram of cyclohexane chair conformation](image4)
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you need to keep track of which vertices are which, and which bonding sites are which, during this conformational change:

summary of relationships seen here:
(a) the chair-chair interconversion is a partial bond rotation in which groups that were axially oriented become equatorially oriented and vice versa
(b) relative positions (up/down with respect to the ring; cis/trans with respect to each other) are unchanged
(c) the line/dash/wedge representation (right side, above) cannot distinguish between the two chair forms (yes, indeed, those two drawings are identical); thus, a line/dash/wedge drawing does not communicate information about axial and equatorial orientations, but instead always implies the pair of conformational (chair) drawings
(d) the specific placement of the substituents when you translate back and forth needs to be internally consistent, but unless you are intentionally showing a molecular rotation around an axis, there are many correct drawings for any given molecule — keeping a correspondence between the drawings is a good idea, however, because there are also many incorrect drawings

(3) assessment of conformational stability is the same, regardless of the system you are analyzing; the factors to consider are: steric effects, charge/charge effects, and hydrogen bonding

In cyclohexane rings, the bonds are all in perfectly staggered arrangements, so for considering sterics, the following is true: a group in the axial position experiences two gauche (60˚) interactions with the ring atoms on the other two vertices pointed in the same direction as it is, while a group in the equatorial position is anti (180˚) with respect to those same atoms, and so the steric repulsion is higher for groups in the axial position.

While it is possible to view this bond by redrawing it as a Newman projection, it is arguably better to be able to visualize the two relationships that MUST exist for a staggered bond conformation while looking directly at the chair drawing itself. Notice that any two adjacent axial bonds (such as A and F) are necessarily 180˚ apart (one straight up, the other straight down), and that alone is enough to define the staggered arrangement. With respect to A, then, if F is 180˚ away and the bond is staggered, then A is 60˚ away (gauche) with respect to both D₁ and E. And there it is! The axial group (A) is gauche with respect to the ring atom (D₁) that is pointed in the same direction as the vertex on which A sits. And by exactly the same analysis, A would also be gauche to D₂.

Moreover, when you analyze the other chair conformation, where the A group is in the equatorial position, it is now 180˚ (anti) from the D group, and so is not experiencing steric interaction with the ring, and so represents a position where the ring is more stable.

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**Chair conformational drawings** - visualizing the three-dimensional, all-staggered form of the favored cyclohexane conformation

1. Three-dimension cues (such as lines, dashes and wedges) are not used, but rather a form of perspective that relies on understanding how a circle looks like an oval when viewed from an edge.
2. In the cyclohexane chair conformation, all of the carbons are perfectly tetrahedral and each pair of adjacent atoms is perfectly staggered; this creates a highly regular and predictable bonding pattern, not only for the 6 bonds shown within the ring, but also for the 12 bonding sites that are not shown above (2 at each vertex: one axial, one equatorial).
3. Assessment of conformational stability is the same, regardless of the system you are analyzing; the factors to consider are: steric effects, charge/charge effects, and hydrogen bonding.

This moment is a great time to remind you that those four previous pages were all just “thinking in blue,” that is, inspired by the single word “conformational” in the text of the question. This is fundamentally what the word is communicating, and basically one half of what you need to be carrying as understanding when you try to answer a question.

The other half of what you need to be able to do is apply the ideas spurred by the word “conformational” to the specific example provided on the page — and you have not even gotten to that part, yet!

This moment is the reason this series of Thinking in Blue documents have been created: if you are trying to do exam problems and you have not learned what you need to learn from the chapters to be able to answer the question, then working on those questions is not yet the most effective use of your time. You can try them, but your fast conclusion ought to be: I am not ready to work on these yet… I should go back to the basics of where these topics were the focus - in the practice questions. You are obviously perfectly free to seek out, listen to, copy down, and try to focus on the answer itself, but how will that lead to an understanding of the concepts… and particularly where you might have been incorrect in your understanding?

This is another good time to remind you that, in CHEM 210, an exam question is not going to ask you to recall a specific factoid or structure or answer to a previously solved problem. That is not what you need to be worried about remembering. You need to be remembering what “conformational” means, as an idea, in two ways: (1) as a general understanding, represented on these previous 4 pages; but just committing a bunch of stuff to memory is not the same as understanding, because you are never going to be asked to recite it back, instead, you need to treat it as (2) knowledge that can now be used and applied to any appropriate example, to the degree that you see it is “only just another example”!

These “thinking in blue” pages are designed to help you understand how well you are actually learning the concepts. These are not intended as review sheets. These are not intended as instructional summaries. If you find that you do not have the “blue knowledge” needed to answer the question, then you should be going back to the chapters, notes, and lectures and learn it before proceeding, because the only thing you are learning is that you are not yet ready to work on these questions. “Blue knowledge” is the prerequisite understanding about these ideas. The answers cannot truly be understood without it.

Now we can work on the questions.
6.09 The ubiquitin/proteasome system (UPS) is a major protein degradation pathway in eukaryotes. Molecules that can inhibit unwanted degradation are attractive targets for autoimmune disorders. In one such study, an inhibitor molecule is proposed to make the following conformational change in the UPS.

(a) Draw the two Newman projections for these conformations. Use the point of view where the carbon a is the front atom and carbon b is the back atom (see above for labels).

As drawn, conformations L1 and L2 are both staggered. The 180° relationship between the hydrogen atoms drawn on carbons a and b as being in the plane of the page is the most compelling point for making this important assessment, because you need to know whether to draw a staggered or an eclipsed form. The point of view for the Newman projections needs to be as specified in part (a):

(b) As drawn in (a), what is the value of the ΔG° for this conformational change?

-0.6 kcal/mol

The term “conformational” in the text of the question means (at least for CHEM 210) that you are anticipating drawing and/or analyzing Newman projections or chair cyclohexanes, or something that would use those concepts for creating an analogy. The directions in part (a) are extremely prescriptive:

1. Newman projections are needed
2. Carbon a is in the front
3. Carbon b is in the back

From L1 to L2, the front atom is fixed, and the back atom has turned +120°, moving the -CH₂SCH₃ group from the back upper left to the back upper right position, with the corresponding changes in the hydrogen atoms.

In L1, the -CH₂SCH₃ group is gauche to the P₂ unit, and the value of that gauche interaction is given as 1.1 kcal/mol¹; while in L2, the gauche interaction with the P₁ unit, also from that boxed information on the page, is given as 0.5 kcal/mol¹.

As drawn, L1 (the less stable one) is on the left and L2 (the more stable one) is on the right, so the ΔG° needs to be negative. Going away from L1 is -1.1, while going towards L2 is +0.5, so the net difference is -0.6 kcal/mol¹.
6.15 Menthol is a naturally occurring compound found in the oils of the mint tree *Mentha arvensis*. Menthol is well known for its cooling effects and its mint flavor and odor, which are the basis of the majority of its uses. The single largest use for menthol is probably in cigarettes. A survey of pharmaceutical products indicates that menthol is formulated in over-the-counter rubs and liniments (2–10% concentrations), antipruritic lotions, nasal sprays, expectorants, mouthwashes and sprays, cough drops, and foot powders.

(a) Draw the two chair conformations of menthol.

Drawing good chair forms and getting the groups correct does not depend on the particular example. It is a general skill that can be applied to any example once you get the idea (outline on previous pages in some detail).

If you elect to relate the "planar" drawing to the "chair perspective" drawing, you can treat the drawing as a rotation of the molecule by 90° - even then, the single "planar" form does NOT imply either of the chair forms, but rather it implies BOTH of them.

Following through with this method, the placement of the groups would be implied by the molecular rotation:

Continuing with this method, the orientation of the groups would be implied by the selected chair form, and what was "up" versus "down" at that particular vertex. The placement of the bonding directions would be fixed by the chair form itself:

And finally, the A group is "up" and the B and C groups are "down" (as seen in the planar form), and so this some relative "up" and "down" needs to be translated as the more upwardly (u) or downwardly (d) pointed bonding site.
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(a) Draw the two chair conformations of menthol.

Using the rotation method (which simply defines the atoms):

-90° rotation

place the bonding sites:

add the atoms:

assess the relative stability:
all 3 groups are axial: less stable form
all 3 groups are equatorial: more stable form

one last cross-check is possible here, because you know that the ring interconversion takes axial groups and makes them equatorial, and vice versa, so the fact that all 3 axial groups on the left are equatorial on the right is (at least) consistent.

less stable chair form

more stable chair form

as demonstrated in the second method, there are going to be numerous correct representations for exactly these two conformations, so even comparing answers with others means that you need to understand that there is a degree of flexible thinking required (and this is true with numerical solutions, too; after all, an answer of "2" can be represented by "4/2" or "log(100)" or "d/dx[2x]" or …)
The experimentally determined conformational energy difference between the two chair forms of menthol is quite consistent with the value estimated from the A-Values of the three substituent groups. What is the estimated $\Delta G^*$ for the equilibrium, as shown above?

![Diagram showing less stable chair form and more stable chair form]

The A-Value contributions will all be negative (left to right) because all three groups are heading from the axial to the equatorial positions.

- $\text{CH}_3$ (axial to equatorial) : -1.7
- $\text{OH}$ (axial to equatorial) : -0.87
- $\text{CH(\text{CH}_3)_2}$ (axial to equatorial) : -2.15

$\Delta G^*$ (est.) = -4.72 kcal/mol

(c) Both of the chair conformations have additional interactions beyond those accounted for by the A-Values. What are these interactions, and what is the conclusion about the relative magnitude of these interactions, based on the fact that the energy difference based on the A-Values alone does a good job reproducing the experimental result for the energy difference?

![Diagram showing less stable chair form and more stable chair form]

1,3-diaxial $\text{CH}_3$/OH a destabilizing effect

Both effects are destabilizing, and so the inference is that they offset each other and the $\Delta G^*$ determined from the A-values remains relatively unchanged.