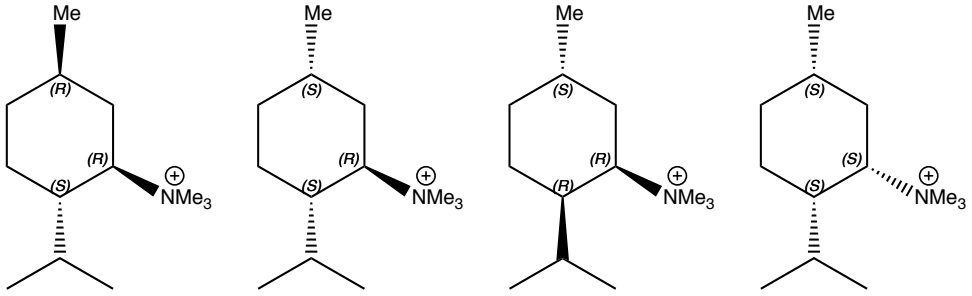
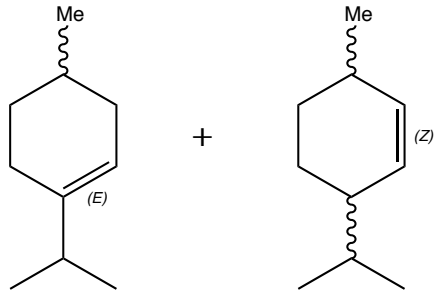
Conformational Analysis. Tutorial Problem 1.

The compounds A-D represent four diastereomeric ammonium salts in the naturally occurring configurations (or their four un-natural enantiomers). When treated with base they undergo an E2 elimination to give either alkene E or F, or a mixture of both. Your tasks are to use the principles of conformational analysis to predict:

1. Whether the product of each elimination is E, or F, or both, and what the stereochemistry of the methyl and iso-propyl group is in each case
2. To try to rank the four molecules A-D in terms of their predicted reaction rates, from the fastest to the slowest (assuming the initial concentration of each is the same).



A Menthyl | B Isomenthyl | C Neomenthyl | D Neoisomenthyl



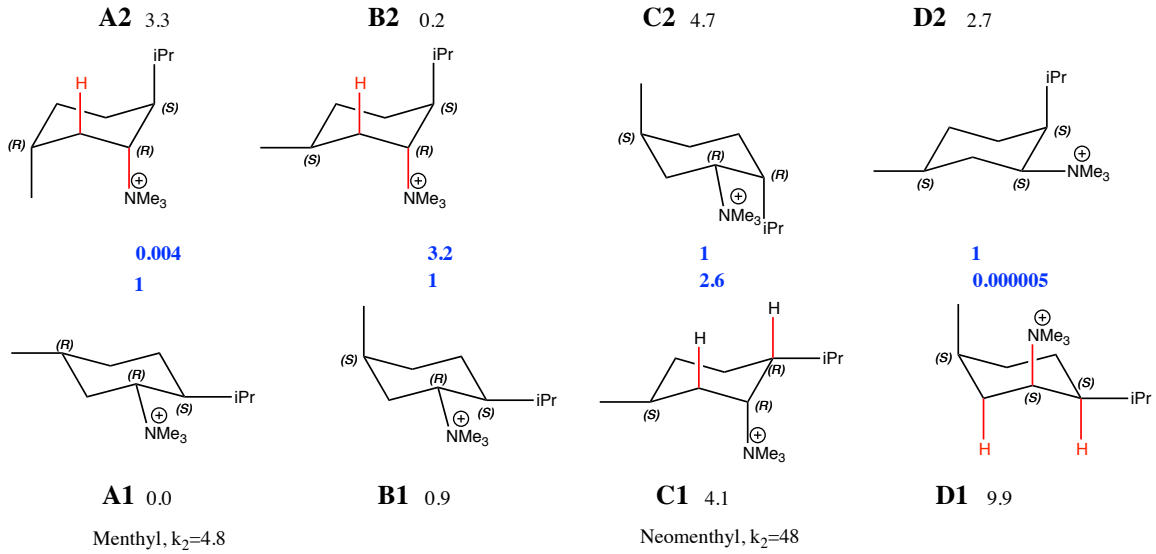
E F

Hint 1: Each of the reactants has two possible chair conformations (ignore the twist boat), which can equilibrate by flipping all the axial and equatorial substituents. Try to decide which of these two has the higher concentration (lower free energy), and for each conformation, label all the substituents as either axial or equatorial.

Hint 2: An E2 elimination requires a specific orientation between the NMe_3^+group and a β-hydrogen. The rate of this elimination will be largely determined by the concentration of the requisite conformer, determined by the position of the equilibrium between the two chair conformations.

Answer

The problem really amounts to looking at the eight chair conformations of these four diastereomers. Using a tool such as ChemDraw to assign the R, S configurations to the centres makes it really easy. Thus:



Menthyl, k_2=4.8

Neomenthyl, k_2=48

For each pair of conformations (A1, A2, etc.), one must now decide which one is capable of E2 elimination. Only those with the Me_3N^+ in an axial position and which also has an appropriate hydrogen anti-periplanar to it can eliminate to form an alkene. Only conformations A2 and B2 can give just alkene F, whilst C1 and D1 can give potentially both E or F (show with red bonds above). The ratio of E/F might be predicted using the Saytzeff rule (in which the more substituted alkene forms in preference to the less substituted[1]) if the reaction is thermodynamically controlled, or by the nature of the transition state if kinetically controlled.

In order to estimate the relative rate of reaction, one has to decide the position of the equilibrium between the two alternative chair conformations for each of A-D. This is potentially trickier; since there are three groups of different size (NMe_3 > i-Pr > Me). One could develop a set of simple rules:

1. An equatorial methyl will be lower in energy than an axial methyl. Thus means that A1, C1, B2 and D2 are respectively more stable than B1, D1, A2 or C2.
2. 1,3 diaxial bumps between the methyl and NMe_3 groups are unfavourable. This means that A2 and D1 would be less stable than respectively B2 or C1.
3. The relationship between two adjacent groups that are both quite large (Me_3N^+ and i-Pr) is more complex. Having both axial (being as far apart as possible from each other, B2) turns out to be energetically quite similar to having both equatorial (bumping into each-other, but then also avoiding other ring substituents, A1). Having the larger Me_3N^+ axial (C1) may less favourable than having the smaller iPr axial (D2).

By combining the various rules above, one might conclude for each of the pairs above, that:

1. A1 is more stable than A2 (1,3-diaxial bumps and methyl equatorial more stable than methyl axial)
2. B1 and B2 are similar (methyl equatorial might be a little more stable than methyl axial)
3. C1 and C2 are similar (methyl equatorial might be a little more stable than methyl axial)
4. D2 is more stable than D1 (1,3-diaxial bumps and methyl equatorial more stable than methyl axial)

From the above, it follows that conformations **B2** and **C1** can both react anti-periplanar to give alkene and also have a high concentration, therefore they will be fastest to react. Likewise **A2** and **D1**, both with appropriate anti-periplanar alignments, would be minor components (low concentrations) and so will react more slowly than either B2 or C1.[2] So, summarizing **B ≈ C > A ≈ D**

One can be a little more precise by adopting a molecular modeling procedure to estimate the relative energies of all eight conformations. A method that includes a proper treatment of "steric bumps" (*aka* van der Waals dispersion interactions) and orbital alignments is needed (effects 1-3 in lecture notes). The first is handled well by methods known as molecular mechanics (MM2 in the Chembio3D program). Quoted in the diagram above next to each label however are the relative energies obtained using a quantum mechanical based method, which incorporates all the effects 1-3 (if you care, ωB97XD/6-311G(d,p) with solvation correction for methanol was used), in kcal/mol. You can look at any pair of conformations above and judge whether their relative energies conform to the simple rules set out above or not. These more quantitative energies can be inserted into the equation $\Delta\Delta G = -RT\ Ln\ K_{eq}$ to obtain the equilibrium constant for any pair. This can be expressed as a relative concentration, and these numbers are shown in blue in the chart above. The resulting number associated with each of the four conformations which have an H anti-periplanar to the leaving group Me_3N^+ should give an indication of the relative rate of each species (assuming there is no difference in the transition states, which may be a big assumption). These numbers indicate a rate order of **B ≈ C > A > D.** The big looser is D1. It seems in this conformation, the 1,3-diaxial bump is larger than expected. If you tried your own modeling, how do your energies compare to the ones above?

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[1] See M. J. Webber and A. C. Spivey, *Nature Chemistry* **1**, 2009, 435 – 436. DOI: http://dx.doi.org/10.1038/nchem.348

[2] This prediction is verified by the experiments reported by E. D. Hughes and J. Wilby ***J. Chem. Soc.***, 1960, 4094-4101, DOI: http://dx.doi.org/10.1039/JR9600004094