CHEMISTRY 650-25584        EXAM II        ANSWERS

I.  1.  This is essentially identical to the reactions of
basketene (discussed in lecture).
Compounds 1 and 3 can each be described as
a homobasketene; each has one extra
CH2 group.

It's intriguing that the NPMI trapping is fast
enough to compete effectively with retro
Diels-Alder reaction to cyclopentadiene and
an aromatic compound.  It's clear that the
rate-limiting step is the initial retro Diels-Alder
process; thus, \( d[2]/dt = k \) [1] and is independent of [NPMI].  Note that the trapping of the cyclohexadiene
moiety comes on the more exposed bottom face and proceeds with endo stereochemistry, as expected.

2.  Compound 1 had two identical cyclohexene units that could break
down in retro Diels-Alder fashion.  Compound 3, in contrast, has only
one cyclohexene.  Retro Diels-Alder reaction gives 4 which cannot
undergo a second cleavage because its diene is in a seven-membered
(not a six-membered) ring.

B.  Yes, yes, I know!  A very similar reaction was featured on Exam I from the 1990 course.  I put it here for two
reasons: (1) I wanted to see if you remembered having studied such a reaction during your preparation for your
own Exam I and (2) this question is based on new data published by Huisgen and his co-workers just this year.

1.  We cannot label the reaction of the 1,3-dipole with E-CH=CH-E as stereospecific, as maleate gives
measurable losses of stereochromaticity.  It would be possible to explain these results by claiming a
concerted \( [H^2 \pi + H^2 \sigma] \) process for the fumarate
reaction and either a stepwise or a combined
concerted plus stepwise process for maleate.  The
most economical explanation is to suggest a stepwise
process for both.  In the fumarate reaction, if \( k_{close} \) >> \( k_{rotate} \), exclusive formation of trans adduct would
result; in the maleate reaction, some \( k_{rotate} \) competes with \( k_{close} \), perhaps to escape some steric
effect of adjacent ester groups in zwitterionic
intermediate B.  The stepwise process arbitrarily
uses CH2 to form the initial bond, but initial attack by
the R2C end of the 1,3-dipole can also be imagined.

2.  With the dicyano diesters, the zwitterion formed in a
stepwise reaction is much more stable, as the negative charge can be stabilized by two groups.  The
lifetimes of the zwitterions that are analogous to A
and B are greater, thus allowing substantial rotation
before closure occurs.  This is not a case of \( k_{rotate} \) >> \( k_{close} \) or of \( k_{close} \) >> \( k_{rotate} \), because each
reaction still gives more retention than inversion.

Why is the loss of stereochemistry greater
for the fumarate than the maleate?  [It would have been
easier to make a case for the opposite outcome, but
we are not so blessed.  Nevertheless, as practicing
organic chemists, we can fashion explanations for
any result.]  When an ester group stabilizes a
carbanion through resonance, the entire ester moiety must be coplanar with the carbanion sp2-plane; when
a cyano group stabilizes it, it occupies much less space as it is linear.  It is possible that the steric repulsion
twixt ester and cyano on both sides of the zwitterion
is greater than the steric repulsion between one pair of esters on the same side of a zwitterion
like B.  In other words, it's possible that \( k_{rotate} \) > \( k_{rotate} \).

3.  As shown to the right, ring closure can occur via the nitrogen
end of the resonance stabilized anion.

C.  1.  This case is taken directly from
lecture.  For compound 5 the
two boat conformations are of
equal energy.  When N2 loss
occurs (by a retro Diels-Alder
reaction), one double bond is
formed with \( E \) stereochemistry,
the other with \( Z \).  (The easiest
way to see this is to note that
intermediate A has the close
methyl eclipsed with the vinylic
H to its left, an \( E \) alkene is the
inevitable result.)

For compound 6 the boat
conformations are of very different energies. Not only is D more stable than C but also, for steric reasons, the transition state leading to the E,E diene is much more stable than the other.

2. This case was not discussed in lecture, although the analogous compounds with cyclopropane rings were a major focus of attention. Conformations E and F are not of equal energy; I would guess that F is more stable because it avoids steric interaction of a methyl and the small ring. In any event, loss of N\textsubscript{2} from either conformation (as was the case with A and B) gives one E and one Z double bond. [Based on the analysis of 8, however, it seems certain that all reaction is occurring via E.]

![Diagram of conformations E and F]

The interesting (and important) case is that of 8. There can be no doubt that conformation H has much lower steric hindrance than does G. Furthermore, the product from H would be more stable than that from G. Nevertheless, all reaction occurs from the less populated conformation and gives the less stable diene, a superb illustration of Curtin-Hammett ideas. The conclusion is that the transition state for G \( \rightarrow \) Z,Z is considerably lower in free energy than the other.

One way to account for this is to invoke an explanation similar to that used for the cyclopropane compounds in lecture. Although the cyclobutanes react much more slowly (note the much higher temperature required), one can still make the case that the strained four-membered ring has some bent bond character for its \( \sigma \)-bonds. (It is estimated that cyclobutane has about 1/3 of the bent bond character of a three-membered ring.) And, one can make the case, that the breaking of one \( \sigma \)-sigma bond, along with two C-N bonds in a concerted fashion, occurs best when the N\textsubscript{2} is being eliminated anti to the four-membered ring. Because the incipient p-orbitals are nearly parallel on each side of the molecule, partial \( \pi \)-bonding in the TS lowers its energy.

3. The calculated (or measured) \( E_\text{a} \) is the difference in energy between the more stable conformation and the transition state for the reaction. If one assumes that the transition states for the cyclobutane-participation reactions are about the same, then one can attribute the higher \( E_\text{a} \) for 8 to the fact that it is largely in the much more stable conformation H. [The calculations alluded to on the exam were performed by someone whom most of you know (or know of), as can be seen from the list of references. Her calculations suggest that the transition state for 7's reaction is 1.8 kcal/mol more stable than for 8's. Therefore, the remaining 1.8 kcal/mol difference in \( E_\text{a} \) must be the result of the substantially greater population of conformation H.]

II.

A. 1. According to the Woodward-Hoffmann method of analysis of sigmatropic reactions, one imagines a homolytic cleavage of the migrating bond, in this case, it produces a H atom and an ethene radical-anion. The latter has, as its HOMO, \( n^\sigma \) of ethene [the total configuration is \( \pi^2(\sigma^\pi)^0 \)] which means that the concerted process cannot be suprafacial across the carbon face. The symmetry-allowed process \( [1^\sigma_2,2^\sigma_1] \) is geometrically impossible.

2. The intramolecular [1,2] H-shift, already made unlikely because of orbital symmetry ideas, is now ruled out experimentally. This is an interesting case, because the potential A \( \rightarrow \) B reaction is very highly exothermic with a very early transition state. The experiments with the heavy isotopes of H require that the aldehyde H come from the solvent, not from another site in the molecule.
3. A better mechanism than $S_{N2}$ displacement of Cl is the addition/elimination sequence on the next page.

When the trimethyl phenoxide reacts with $:CCl_2$, the intermediate analogous to A on the exam is shown to the right. This anion can pick up a proton from solvent, but because there is no adjacent H there is no opportunity for an elimination reaction, such as that shown above. This, the CHCl$_2$ group survives, and is not transformed into an aldehyde.

B. This reaction is a [1,7] sigmatropic shift of H from the allylic position in the five-membered ring to the carbon that bears the methyl in the six-membered ring. The symmetry-allowed process is $[1\sigma,7\sigma]$ which means that H should move from one face of the system at C$_1$ to the opposite face at C$_7$ (see the numbering in the drawing). This is possible, as we noted for similar cases in lecture, because the triene has enough flexibility at its C-C single bonds to coil. One such coil (shown here) allows H to move from the bottom of C$_1$ to the top at C$_7$; coiled in the opposite sense, H moves from the top of C$_1$ to the bottom of C$_7$. Structures 2 and 3 reveal that H can end up on either side of C$_7$ but they do not establish the overall antarafacial nature of the reaction. This is the role of labeled compound 1d: H moves from the top of C$_1$ to the bottom of C$_7$, producing 2d or D moves from the bottom of C$_1$ to the top of C$_7$, producing 3d.

C. 1. Considering substituents that are attached to the carbons of the diene, the reactant has a phenyl and an alkyl, whereas the product has phenyl and methyl at one terminus, methyl and R at the other. Furthermore, phenyl in the stereoismeric products allows extended conjugation for the entire diene, instead of at just one double bond. There is no doubt but that these products are much more stable than the reactant.

2. Arbitrarily shown here is one enantiomer of the reactant. (The same analysis holds if the other enantiomer were shown.) Transfer of H in conformation A in symmetry-allowed $[1\sigma,5\sigma]$ fashion results in the formation of the E,E diene; transfer of H in conformation B gives the E,Z product. The transition state for the latter is much more crowded, as the larger R group is close to the terminal CH$_2$. The larger R is, the greater this repulsion, and the more that E,E product is favored.

3. $[1\sigma,5\sigma]$ sigmatropic transfer of H from a conformation like A gives not only the E,E diene but also a new asymmetric carbon at the terminus. (Any transfer of H from a conformation like B would give the opposite configuration at the asymmetric carbon, but we know that the amount of this will be very low.)

4. Ozonolysis cleaves all of the C=C bonds. Trifluoroperacetic acid leads to Baeyer-Villiger rearrangement in which O is effectively inserted into the Ph-C bond. Saponification converts this ester into phenol and "acetate ion" in which the "methyl" carbon is asymmetric by virtue of having H and its two heavier isotopes. It is produced, according to the analysis in Part 3, 100% with S configuration. [Such a compound has played a major role in elucidating the mechanism and stereochemistry of various enzymic methyl transfers, most notably from S-adenosylmethionine, which has been dubbed "Nature's methylating agent" (see, for example, the undergraduate text by Loudon, p. 517).]
1. As we discovered several times in lecture (e.g., in the Favorskii-like [1,4] shifts of the oxallyl system), a given stereochemistry can be the result of one symmetry-allowed reaction or another, even a series of two or more other symmetry-allowed reactions. Such is the case here. Both [1s,5s] and [1a,3s] lead to the same product, which happens to be the minor product found in the reaction. In the former, cleavage of C1-C9 is accompanied by rotation of C9 about its remaining bond to C8 so that its positive lobe can overlap with both C1 and C5; the HOMO shown is of a pentadienyl radical (C1 to C5) by the pretended homolytic cleavage of C1-C9; the HOMO is \( \psi_3 \) which has nodes at C2 and C4 and this results in retention of configuration at C9.

For the [1a,3s], cleavage of C1-C9 and rotation of C9 such that its plus lobe maintains overlap with C1 at the same time that its negative lobe is bonded to C3; shown in figure is \( \psi_2 \) of the allyl system involving C1-C3. Note that this process, occurring with inversion of configuration at C9, arises from the labeled CN* over the diene (i.e., the minor product again).

2. So how does one account for the fact that 73% of the product has the opposite stereochemistry at the migrating carbon? This could well be a case, like those of Baldwin’s and Carpenter’s discussed in class, in which the symmetry-allowed process (either of the two discussed above) is so difficult in terms of atom motion and is so poor in maintaining overlap at the origin and terminus of the \( \pi \)-system that the reaction becomes essentially stepwise diradical in nature. As the C1-C9 bond breaks and C9 goes from sp\(^3\) to sp\(^2\), continuation along the same trajectory gives the inverted sp\(^3\) by the time that bonding occurs at C5 or C3.

3. The unchanging product ratio at different temperatures argues against competing processes with different activation energies and for the creation of the diradical on a broad, flat potential surface, in which its ultimate behavior is determined by the trajectory with which it entered the surface. A least-motion process (avoiding the gymnastics that C9 must engage in if it follows either orbital symmetry route) leads to the 73% product, regardless of whether the reaction is viewed as a 1,5-alkyl shift or a 1,3-alkyl shift.

III.

A. 1. Unlike a Cope rearrangement in which reactants and products are both alkenes, in a Claisen rearrangement one trades two C=C bonds for a C=C and a C=O. The stability of the carbonyl group is a driving force for the reaction.

2. In the following renderings of \( E,E \) compound 1, I’ve tried to show the diene chair and boat arrangements as they actually are (based on molecular models) and not as they were idealized in Handout X. That is, the incipient allylic units are not in parallel planes. In doing this, I was guided by the wise words of Prof. Walter Lwowski (one of the many assistant professors who failed to gain tenure at Yale). When one of my classmates wanted to reduce the gain on an IR spectrometer so as to smooth out the noise, Lwowski admonished him with “In all things scientific, one should seek truth rather than beauty.” The four possible arrangements (two chairs and two boats are shown here. By chair transition state rearrangement, the major product dl-3 is formed. On the next page is shown formation of the minor product dl-4 via the boat TS. Because 1 and 2 differ at only one C=C, the latter will give dl-4 by the chair and dl-3 by the boat.
3. The ZE should behave the same as \(EZ\) and the ZZ should behave the same as \(EE\). In fact, this is observed: \(ZE \rightarrow 4.5\%\) of \(dl-3\) and \(95.5\%\) of \(dl-4\), whereas \(ZZ \rightarrow\) gives \(94.7\%\) and \(5.3\%\) of these products, respectively. [As you might have predicted, the \(EZ\) and \(ZE\) compounds react at the same rate (\(E_a = 28.6\) kcal/mol for each); in contrast, \(EE\) reacts faster than \(ZZ\) (they differ in \(E_a\) by \(1.6\) kcal/mol).]

B. 1. [Do you get the feeling that I've asked this sort of question earlier? Well, you're right - see IIC1 and IIIA1.]

   The equilibrium lies to the right. In the reactant, there are two disubstituted double bonds; the product has two trisubstituted double bonds, which are more stable.

2. Upon examination of molecular models, it becomes clear that meso compound 7 can undergo Cope rearrangement only via a boat transition state; for \(dl\) compound 8, the only possibility is a chair. I've given two drawings of 7's boat arrangement and 8's chair; your drawings may differ if you viewed the structure from a different perspective. Based on the precedents established by Doering, Goldstein, and others, the chair TS is expected to be more stable than the boat, as is seen here by \(\Delta H^\ddagger = 13.8\) kcal/mol. Also, as observed by these chemists (Handout X, p. 5), the more flexible boat leads to \(\Delta S^\ddagger > 0\), whereas the chair has \(\Delta S^\ddagger < 0\). [In retrospect, the answer may not be so simple. The authors of the article on which this question is based have written "The entropies of activation for the chair and boat transition states remain one of the most perplexing aspects of this reaction. The chair transition state is often characterized by a large negative entropy of activation ... However, with the accumulation of additional experimental data, it is clear that the magnitude of \(\Delta S^\ddagger\) is quite system dependent and cannot, at present, be used as a guide for distinguishing between chair and boat topologies."]

IV.

A. 1. a. The NMR spectrum is as expected. Compound 1 (which bears the trivial name hypostrophene) has four olefinic (vinyllic) protons and six aliphatic protons. The ratio of \(\delta 6.1\) to \(\delta 3.2\) should be 4:6 or 1:1.5, exactly as reported. There is no temperature at which any degenerate Cope rearrangement is occurring fast enough to give an averaged spectrum with just one sharp resonance.

   b. Just as Winstein and Berson (Handout IX, p. 12-13) used a deuterium label to detect ring-walking processes that were slow on the NMR time scale, rearrangement does occur with \(1d_2\), as shown by the change in the ratio of vinylic to aliphatic protons from 1:3 at -40°C to 1:1.5 at +35°C. Structure A, before any rearrangement, has two vinylic and six aliphatic protons, thus accounting for the 1:3 ratio. If the cycle of degenerate rearrangements shown here occurs, each deuterium will be equally distributed to the five positions on its ring: 2/5 of the time it will be on a vinylic carbon, 3/5 of the time on an aliphatic carbon. Similarly, the four protons on each ring will be distributed such that 2/5 of the time they are vinylic and 3/5 of the time they are aliphatic. The result is a 1:1.5 area ratio for the protons.

   Here's another way to arrive at the same answer. Each ring has three distinctly different types of carbon labeled a, b, and c in the structure to the right. For the averaged situation, 2/5 of a deuterium is at a, 2/5 at b, and 1/5 at c (for a total of 1 deuterium); at the same time, 8/5 of the protons are at a, 8/5 at b, and 4/5 at c (for a
total of 4 protons). The ratio of vinylic to aliphatic protons, then, is 8/5 : 12/5 or 1:1.5.

2. For compound 2, a complete cycle of Cope rearrangements does not occur. Instead (as with semibullvalene) there are only two isomers in equilibrium. As shown here, the rearranged product is the non-superimposable mirror image of 2; that is, 2 and its enantiomer 2’ are in equilibrium. The result is racemization when the compound is warmed.

B. 1. Through a series of Diels-Alder reactions and retro Diels-Alder reactions (the loss of N2), the product that is shown on the exam results.

2. This compound is a substituted semibullvalene; rapid equilibrium between two identical structures is expected. The sharp resonance at δ 3.17 (3) is for the two methyl esters (6H total); δ 4.79 (2) represents the averaged shift of the four protons (C2,8 and C4,6) which interconvert; and δ 1.17 (3) represents the averaged position of the six protons on the methyl at C1 and the methyl on C5. [This simple spectrum is inconsistent with a static (non-rearranging) structure.]

C. 1. The four isomers are designated using the notations from lecture: B = bridgehead, C = cyclopropyl, VB = vinyl next to bridgehead, VC= vinyl next to cyclopropyl.

2. None! Each has a plane of symmetry. For three isomers (V C V B, V B B, and V C C) the plane goes through the bromines and the carbons to which they’re attached. For C C, the plane lies between the bromines. [Of the twelve isomers, total, there are three that are chiral. These are V C V B (different from the one shown above because it has Br's on different bridges), V C C (also different from that above for the same reason), and V B C (with Br's on different bridges). You can check these out, if you wish.]

3. a. The single isomer of 3 corresponds to V C V B which is the only one that allows for an aromatic ring.

b. As for 4, the saturated version of 3, the most efficient path interconverts the four isomers with just three Cope rearrangements. Each structure, of course, can undergo at total of three Copes; the non-productive ones are not shown.

4. Compound 5 is entirely in the V C V B form, but it can still undergo a degenerate rearrangement as shown here. In the low temperature spectrum δ 7.62(1) and 7.30(1) are for the aromatic protons at C11 and C12; δ 5.93 (m,2) and 5.77 (m,2) are for vinylic protons H2,H8 and H3,H9 in some order or other (which will be clarified when the high temperature spectrum is discussed); 8.328 (t,1) and 2.92 (t,1) are for H5 and H1, in one order or the other; and δ 2.19 (m,2) is for identical protons H4,H10. At high temperature, degenerate rearrangement makes H11= H12, resulting in δ 7.46 at the average of 7.62 and 7.30. Similarly, H2,H8 = H4,H10; the resonance (area 4) at δ 4.06 is the average of 5.93 and 2.19 which settles the uncertainty about the vinylic protons above. The uncertainty is also settled by noting the re-appearance of δ 5.77 (2) (unchanged for H3,H9). Finally, H5 = H1 which accounts for δ 3.10 at the average of 3.28 and 2.92; we still don’t know which is which.