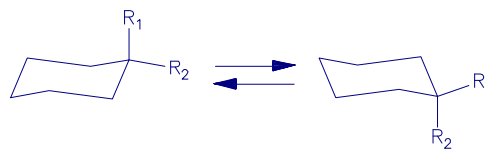


111. In many cases, the axial/equatorial energy difference for single substituents is additive when two substituents are placed on a cyclohexane ring.

Recent evidence (see the cited reference) suggests that this may not hold for 1-alkyl-1-aryl cyclohexanes.

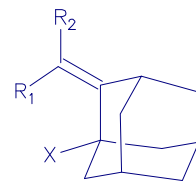
You should calculate the axial/equatorial energy differences for mono-methyl, -tert-butyl, and -phenyl cyclohexane ( $R_1$  = substituent,  $R_2$  = H) and for the various 1,1-disubstituted compounds:  $R_1$  = methyl,  $R_2$  = t-butyl;  $R_1$  = methyl,  $R_2$  = phenyl; and  $R_1$  = t-butyl,  $R_2$  = phenyl. Determine if the single-substituent values are or are not additive; discuss any discrepancies found.

[Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; p 265.]



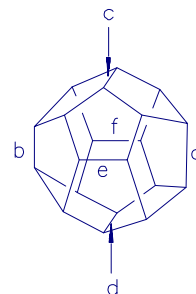
112. In a study reminiscent of that in Problem 90, the solvolysis of some bridgehead allylic adamantyl compounds has been performed. The observed rate differences between Z and E mesylates and chlorides have been rationalized in terms of "F-strain" (steric hindrance between an "inside" methyl and the leaving group) which will differ for the two leaving groups. You should do MM calculations on six molecules: the Z series ( $R_1$  = CH<sub>3</sub>,  $R_2$  = H) where X = Cl, OH, or +; and the E series ( $R_1$  = H,  $R_2$  = CH<sub>3</sub>) where X = Cl, OH, or +; [note: OH is being used as a model for mesylate]. By comparing the calculated  $\Delta H$  for solvolysis of Z and E chlorides and alcohols, confirm or dispute the conclusions cited in the article.

[Takeuchi, K.; Ohga, Y.; Munakata, M.; Kitagawa, T. *Chem. Lett.* **1991**, 2209; see also Takeuchi, K.; Ohga, Y.; Munakata, M.; Kitagawa, T.; Kinoshita, T. *Tetrahedron Lett.* **1992**, 33, 3335; Ohga, Y.; Munakata, M.; Kitagawa, T.; Kinoshita, T.; Takeuchi, K.; Oishi, Y.; Fujimoto, H. *ibid.* **1994**, 59, 4056.]



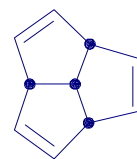
113. Problems 72, 77, and 78 were concerned with dodecahedrane (C<sub>20</sub>H<sub>20</sub>) and related compounds; Problem 109 was concerned with the strain introduced by "pyramidalizing" double bonds. The present question concerns the best (or worst) features of both: you should do MM calculations on dodecahedrane (shown); on its monodehydro derivative (i.e., remove two H's at bond **a** and introduce a double bond); on the didehydro compound (double bonds at **a** and **b**); on the tetrahydro and hexadehydro compounds (double bonds at **a**, **b**, **c**, and **d**; and at **a**, **b**, **c**, **d**, **e**, and **f**, respectively); and finally on the completely dehydro derivative having formula C<sub>20</sub> (a smaller and very strained analog of buckminsterfullerene C<sub>60</sub>).

[Weber, K.; Fritz, H.; Prinzbach, H. *Tetrahedron Lett.* **1992**, 33, 619.]

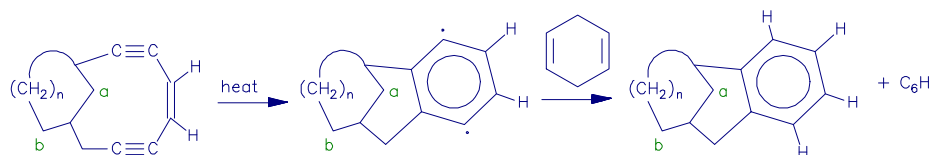


114. Triquinacene (shown to the right) undergoes stepwise addition of three H<sub>2</sub> molecules. The first hydrogenation step is unexpectedly less exothermic than the second and third. The authors cited have done MM and other calculations in an effort to explain this. Your task is to do the MMX calculations on triquinacene and its di-, tetra-, and hexahydro derivatives; to compare your energies, bond distances, dihedral angles, etc. with those in the reference; and to see if you can explain the anomalous heat of hydrogenation.

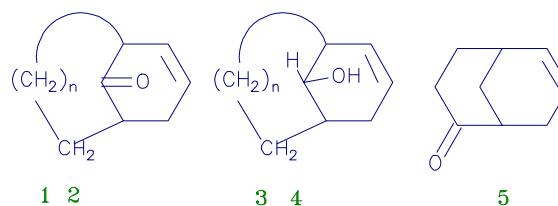
[Storer, J. W.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, 114, 1165.]



115. Naturally occurring bicyclic ene-diyne (general structure shown below)

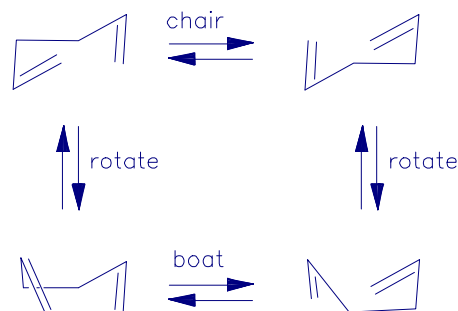


cyclize thermally. In a recent article, the scope of this reaction was measured as a function of bridge length  $n$  and of substituents at positions **a** and **b**. The observed rates correlated quite well with the energies computed for various simple models for the cyclization product. The essence of this MMX problem is to compute the structures and energies of model compounds **1** and **2** ( $n = 1, 0$ ), **3** and **4** ( $n = 1, 0$ ), and **5**. Use the differences in strain energies to confirm or disprove the conclusions drawn on p. 2554-5 of the cited reference.



[Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.]

116. The Cope rearrangement of 1,5-dienes is a well-established reaction. Experiments have established that acyclic compounds react via a chair-like transition state in preference to the boat-like (as illustrated here for the parent case). The difference between the chair and boat transition states has been attributed to various factors. In a recent publication, it is argued that the difference is steric in origin, not electronic. Following the directions on p. 2639-40 of the cited reference, calculate the energies of the chair and boat transition states for 1,5-hexadiene itself (use FXDIS to set the proper  $C_1$  to  $C_6$  separation) and for compounds **20** and **21** in the article (the first of which can react only via the chair, the second by the boat).



Compare your answers with those in Table II (calculated) and  $\Delta\Delta H^\ddagger$  from Table I (experimental). Discuss the factors which make the chair transition state more stable.

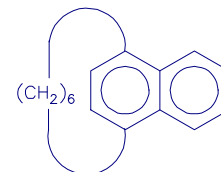
[Shea, K. J.; Stoddard, G. J.; England, W. P.; Haffner, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 2634.]

117. In a recent article, MM2 calculations are performed to see if the experimental rates of epoxidation of unstrained and strained alkenes correlate with the calculated changes in steric energy from reactant to product. This problem entails doing MMX calculations on either: (a) a series of disubstituted alkenes (cis-cyclohexene, -octene, -nonene; trans-cyclooctene, -nonene; norbornene) and the derived epoxides; or (b) a series of trisubstituted alkenes (1-methylcyclopentene, -hexene; ethylidene cyclohexane; cis- and trans-1-methylcyclooctene; anti-Bredt compounds bicyclo[3.3.1]-1-nonene and bicyclo[4.3.1]-1(9)-decene) and the derived epoxides. Then, determine if the change in steric energy for the series you've done correlates with the log of the rate constant for epoxidation (see Table I and Figure 5 in the cited reference). [Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 3044.]

118. A recent paper presents new heats of hydrogenation data for the complete hydrogenation of 1,3,5-hexatriene (E and Z) as well as for all of the hexadienes: 1,3-hexadiene, 1,4-hexadiene, 1,5-hexadiene, 2,4-hexadiene in all of their stereoisomeric forms. From these data are calculated new values for the heats of formation of these various conjugated and unconjugated compounds. This problem requires performing MMX calculations on all of these compounds (plus hexane, the common hydrogenation product) and from these determining the heats of formation and heats of hydrogenation. Compare your results with the experimental values and discuss any differences.

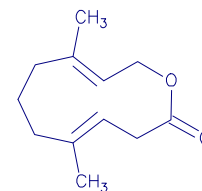
[Fang, W.; Rogers, D. W. *J. Org. Chem.* **1992**, 57, 2294.]

119. Several 1,4-bridged cyclophanes, including [6]-(1,4)-naphthalenophane (shown to the right), have been the subject of experimental and theoretical inquiry. Calculate the heat of formation, strain energy, bond distances, and deformation angles of this structure, relative to those in the unstrained analog, 1,4-dimethylnaphthalene; compare your results with those in Tables I and II of the cited reference. Then do calculations on the carbocations formed by: (a) protonation at C<sub>1</sub>; (b) rearrangement of that ion to the meta-bridged material; and (c) alternative initial protonation at C<sub>2</sub>. Compare your results (for the first two ions) with those in Table IV. Explain why protonation does not occur at C<sub>2</sub> and why the initial ion by protonation at C<sub>1</sub> does not rearrange.



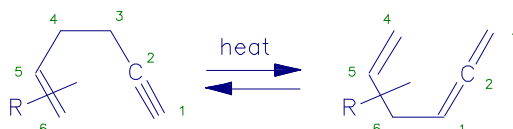
[Tobe, Y.; Takemura, A.; Jimbro, M.; Takahashi, T.; Kobihiro, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **1992**, 114, 3479.]

120. The 11-membered lactone with two E double bonds shown to the right is a major component of the sex pheromone of the Mexican fruit fly. Really! There are four reasonably stable conformations (see Scheme I in the cited article) available for this compound. Use MMX to calculate the energies and structures of the four conformations; comment on similarities and differences between your calculations and those in the article.



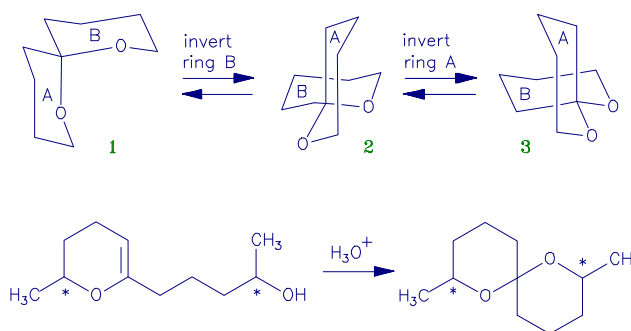
[Wydra, R. L.; Harden, D. B.; Strekowski, L.; Battiste, M. A.; Coxon, J. M. *Tetrahedron* **1992**, 48, 3485.]

121. The Cope rearrangement between 5-hexen-1-yne and 1,2,5-hexatriene (and various derivatives) has been studied experimentally and by computation. Calculate the heats of formation of the parent compounds; of the derivatives with one methyl at C<sub>6</sub>; of the gem-dimethyl (at C<sub>6</sub>); and of the trimethyl (at C<sub>6</sub> and C<sub>5</sub>). Compare your values with those based on Benson's tables of group equivalents, as reported in the article.



[Hopf, H.; Wachholz, G.; Walsh, R. *Chem. Ber.* **1992**, 125, 711.]

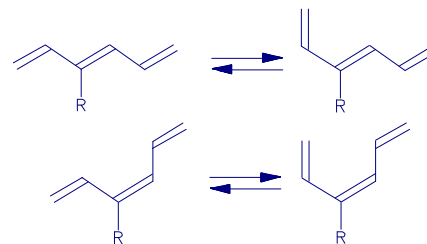
122. The spiro-acetal (shown here) can exist in three favorable conformations: note that in **1**, there are two axial C-O bonds; in **3**, the two axial bonds are C-C; and in **2** there is an axial bond of each kind. Compute the MMX structures and energies of all three. Compare your relative energies with those in the cited reference; comment on the factors that lead to the wide range in energies for three such similar-looking structures.



Then, do calculations on the related dimethyl-substituted acetal formed in the cyclization reaction. Note that there are two stereogenic centers; in fact, cyclization of racemic reactant gives a mixture of R,R + S,S + S,R cyclic products, each one of which can exist in conformations like **1**, **2**, and **3**. The interesting fact is that in one of the diastereomeric products, conformation **1** is preferred; in another it is **2**; and in the third it is **3**. Choose any one of the RR, SS, or SR compounds and do its complete conformational analysis in terms of structures **1**, **2**, and **3**. [If you feel ambitious, do the calculations on all three diastereomers.] Compare your answers with those in the article.

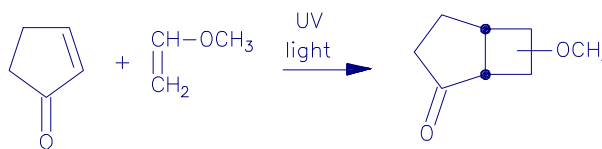
[Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, 75, 604.]

123. An all-planar geometry for 1,3,5-hexatriene gives the best overlap of p-orbitals; two reasonable conformations allow this: the transoid/transoid and the cisoid/transoid. Compute the energies and dihedral angles (from C<sub>1</sub> to C<sub>4</sub> and from C<sub>3</sub> to C<sub>6</sub>) for the triene systems with an E or Z central double bond in each of the two conformations; do the computations for R = H, CH<sub>3</sub> and t-Bu. Compare your results with those in the cited references. Discuss those factors which affect the energy, the angles, and the conformational equilibrium.



[Brouwer, A. M.; Bezemer, L.; Jacobs, H. J. C. *Rec. Trav. Chim. Pays-Bas* **1992**, 111, 138.]

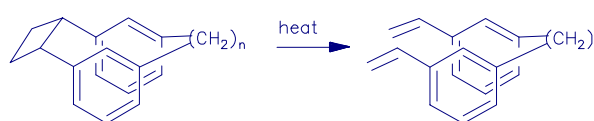
124. The [2 + 2] photocycloaddition of cyclopentenone with methyl vinyl ether can produce four products (differing in regiochemistry and stereochemistry). Calculate the energies of the four structures. Use MMX to estimate the



vicinal coupling constants of the C-H at the carbon bearing the OCH<sub>3</sub> group. Compare your results with the calculated and experimental values in the cited reference.

[Griesbeck, A. G.; Stadtmüller, S.; Busse, H.; Bringmann, G.; Buddrus, J. *Chem. Ber.* **1992**, 125, 933.]

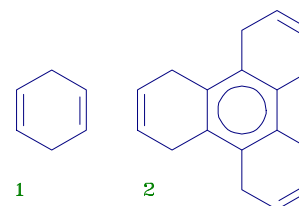
125. The rate of cyclobutane cleavage for a series of meta,meta-cyclophanes has been determined. Use MMX to compute the strain energy of those cyclophanes which have n = 2, 3, 4, and 5; discuss whether strain-relief correlates well with



the rate of reaction. Compare your results with those in the cited reference.

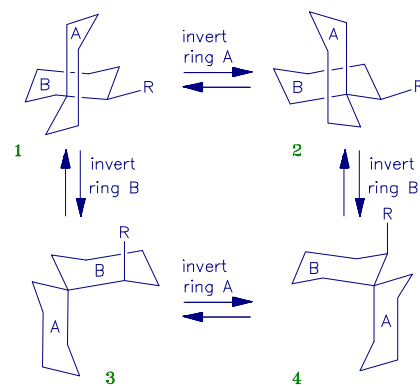
[Nishimura, J.; Wada, Y.; Sano, Y. *Bull. Chem. Soc. Jpn.* **1992**, 65, 618.]

126. The question of whether 1,4-cyclohexadiene is planar or bent has been studied experimentally and by computation. Calculate the energies and geometries of four compounds: 1,4-cyclohexadiene itself (**1**); its mono- and di-benzo fused derivatives (i.e., benzene rings fused at one or both of the double bond positions); and hexahydrotriphenylene (**2**). Compare your answers with those in the cited reference. Suggestion: when doing this sort of MMX problem, you should always begin with a non-planar structure; often a planar structure will minimize as a local minimum, not the most stable structure.

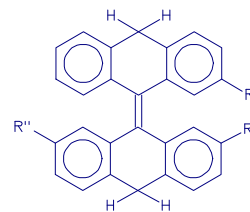


[Rabideau, P. W.; Dhar, R. K.; Fronczek, F. R. *J. Chem. Soc., Chem. Commun.* **1992**, 79.]

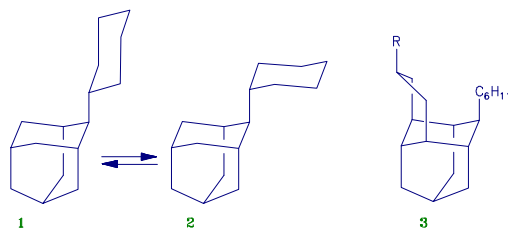
127. The set of conformations (to the right) has been investigated by a version of MM. Note that when  $R = H$ , the four structures are the same. When  $R = CH_3$ , the structures are different: **1** and **2** have an equatorial methyl, but differ in whether the axial substituent from Ring A is CHR (**1**) or  $CH_2$  (**2**); similarly, **3** and **4** have axial methyl, but differ in whether the axial substituent on ring A is CHR (**3**) or  $CH_2$  (**4**). The cited reference has several tables with all of the bond distances, angles, dihedral angles, and energies. Your job is to do a complete MMX analysis of the parent compound ( $R = H$ ) and of the four mono-methyl conformations shown; discuss the factors responsible for the relative energies of the conformations. [Note: this problem is quite similar to the spiroacetal problem number 122.] [Varnali, T. *J. Molec. Struct.* **1992**, 268, 181.]



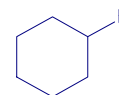
128. The central double bond in the compound to the right is so crowded that it cannot be planar. Two ways for it to relieve the congestion are: (a) by folding and (b) by twisting. Do MMX calculations on both the folded and twisted structures for the parent compounds (all R's = H) and for the dimethyl compounds: trans ( $R = R'' = CH_3$ ,  $R' = H$ ) and cis ( $R = R' = CH_3$ ,  $R'' = H$ ). Compare your results with those in the reference. [Feringa, B. L.; Jager, W. F.; de Lange, B. *Tetrahedron Lett.* **1992**, 33, 2887.]



129. Consider the conformational equilibrium between equatorial (**1**) and axial (**2**) adamantylcyclohexane. In the cited reference, it is alleged that the normal balance (equatorial more stable) can be reversed by having large U-shaped groups which can destabilize the equatorial more than the axial. The article offers a 50-carbon molecule (see **4** in the reference) as an example. In this MMX problem, see if much smaller molecules (such as **3** with  $R = H$  or  $CH_3$  or  $C(CH_3)_3$ ) can also be examples; use your imagination - try other crowded molecules, along the lines suggested in the paper. [Biali, S. E. *J. Org. Chem.* **1992**, 57, 2979.]

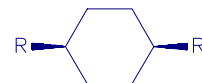


130. Those who do Problem 16 on the axial/equatorial energy differences for the series  $R = Me, Et, iPr, tBu$  will find the "surprising" result that the first three are essentially the same (1.78, 1.82, and 1.72 kcal/mol, respectively) and that the fourth is very large (5.00 kcal/mol). In the cited reference, it is stated "Even though  $CF_3$  is thought of as a small group, it is significantly larger than  $CH_3$  ...". The present MMX Problem is to calculate the axial/equatorial energy differences for the perfluoroalkyl groups ranging from  $R = CF_3$  to  $C(CF_3)_3$ , and to compare the answers with those for the non-fluorinated alkyl groups (available on request). Be sure to do calculations on two different staggered conformations for both  $C_2F_5$  and  $C_3F_7$  in both their axial and equatorial conformations. [Allen, A. D.; Krishnamurti, R.; Prakash, G. K. S.; Tidwell, T. T. *J. Am. Chem. Soc.* **1990**, 112, 1291.]

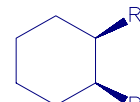


131. An assumption in conformational analysis is that axial/equatorial energy differences for a single

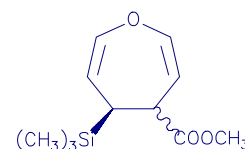
substituent can be applied to molecules in which that same substituent competes with others (the principle of additivity). Using MMX, calculate the relative conformational energies of the chair conformations of cis-1,4-disubstituted cyclohexanes having "symmetrical" groups of very different size ( $R = \text{CH}_3$  and  $R' = \text{t-Bu}$ ;  $R = \text{CF}_3$  and  $R' = \text{C}(\text{CF}_3)_3$ ) and of quite similar size ( $R = \text{CH}_3$  and  $R' = \text{CF}_3$ ;  $R = \text{t-Bu}$  and  $R' = \text{C}(\text{CF}_3)_3$ ). Compare the results with those obtained based on simple additivity arguments and discuss any differences; the MMX equatorial preferences (in kcal/mol) for single substituents [Problems 16 and 130] are:  $\text{CH}_3$  1.78;  $\text{t-Bu}$  5.00;  $\text{CF}_3$  2.87;  $\text{C}(\text{CF}_3)_3$  6.28.



132. Do exactly the same as in Problem 131, but now for the cis-1,2-disubstituted cyclohexanes in which steric interactions between the substituents (in addition to between each substituent and the ring) should become significant. Do the same set of  $R$  and  $R'$  substituents; use the same equatorial preferences for a single substituent as given above.

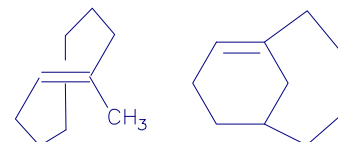


133. Do a complete conformational analysis of both stereoisomers (cis and trans) of the system to the right. For each isomer, calculate the energy and key dihedral angles for four different conformations: i.e., the TMS and ester groups can be axial or equatorial and the ring oxygen can be syn or anti to the TMS. Compare your answers with those in the cited reference. Discuss similarities and differences.



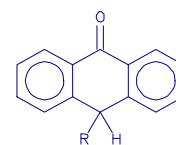
[Chou, W.-N.; White, J. B.; Smith, W. B. *J. Am. Chem. Soc.* **1992**, 114, 4658.]

134. Strained double bonds, like those in 1-methyl-trans-cyclooctene and bicyclo[4.3.1]-1-decene, can be either twisted (non-parallel p-orbitals) or folded or both. Do MMX calculations on these two structures and on both bridgehead alkenes (double bond in the 5- and in the 7-membered ring) of bicyclo[4.2.1]nonene and on bicyclo[3.3.1]-1-nonene. Compare your calculated geometries (concerning distortion of the double bond) with those in Fig. 7 of the cited reference. Discuss similarities and differences.



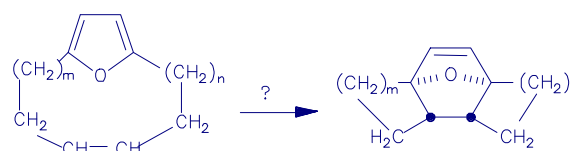
[Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, 114, 4846.]

135. This is a problem reminiscent of number 126. For the anthracenones (shown to the right), calculate the extent of non-planarity of the central ring as  $R$  varies over the series H, Me, Et,  $i\text{Pr}$ ,  $t\text{Bu}$ . Use the measures of nonplanarity suggested in Table I (and the accompanying discussion). Compare your results with those of the cited reference. Discuss similarities and differences.



[Sygula, A.; Sygula, R.; Fronczek, F. R.; Rabideau, P. W. *J. Org. Chem.* **1992**, 57, 3286.]

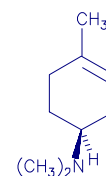
136. Furans are relatively poor Diels-Alder dienes, and never add to unactivated double bonds. Nevertheless, intramolecular versions of this reaction are known (as shown to the right). Using MMX, calculate the energies and geometric parameters of both reactant and product in four isomeric systems:  $m = 2$ ,  $n = 2$ , double bond E or Z; and  $m = 1$ ,  $n = 3$ , double bond E or Z. Compare your answers with those in footnote (22) of the cited reference. Comment on whether your calculations help in understanding why some of these cyclizations occur but others don't.



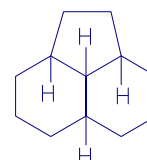
[Marshall, J. A.; Wang, X. *J. Org. Chem.* **1992**, 57, 3386.]



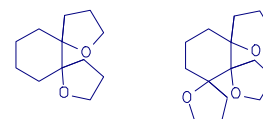
137. The S-(-) tertiary amine to the right (and related compounds, see reference) serve as models for various cationic intermediates in the biosynthesis of certain terpenoids. As such, they are potential inhibitors of the enzymes which catalyze cyclization. Use MMX to calculate the geometry and energy of the important conformations of this compound; compare your answers with those in Fig. 3 of the article.  
[Cane, D. E.; Yang, G.; Coates, R. M.; Pyun, H.; Hohn, T. M. *J. Org. Chem.* **1992**, 57, 3454.]



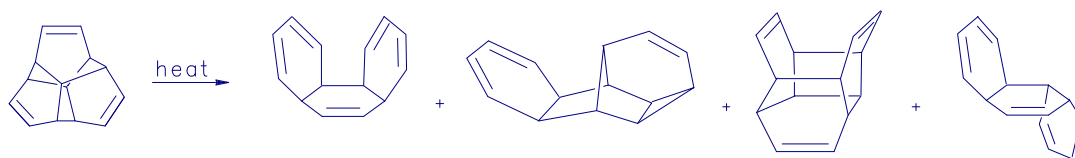
138. The "ufolanes" are structures having one five- and two six-membered rings mutually fused. Unlike the related perhydrophenalenes for which there are only four distinct stereoisomers (Problem 20), there are six distinct isomers (three of which have been synthesized) for the ufolanes. Compute the MMX energies and structures of all six isomers; comment on the sources of the strain which are present in the higher-energy isomers.  
[Boldt, P.; Arensman, E.; Blenkle, M.; Kersten, H.; Tendler, H.; Trog, R.-S.; Jones, P. G.; Döring, D. *Chem. Ber.* **1992**, 125, 1147.]



139. For the dispiro compound to the right, there are two distinct stereoisomers: one has the two oxygens cis; the other has them trans. For the trispiro compound, there are three distinct stereoisomers. All of these isomers, of course, are conformationally mobile. Calculate the relative energies of each chair and its inverted conformation in order to determine where the conformational equilibrium lies; compare your answers with those which have been established experimentally.  
[Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, 57, 3947.]



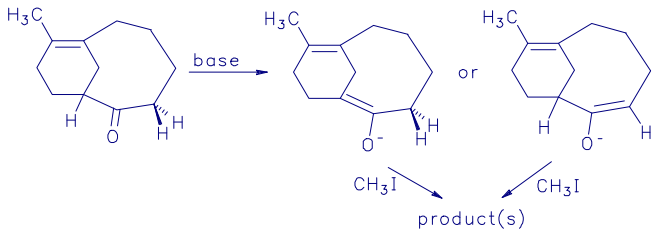
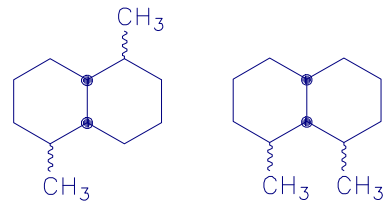
140. Tritwistatriene, a beautifully symmetrical molecule, at 350 °C gives a mixture of four



isomeric products, all  $(CH)_{14}$ . Compute the heats of formation and strain energies of the starting material and of its four reaction products; compare your results with those obtained by MM3 calculations reported in the reference. [Mechanisms for the formation of these products are described in the article.]

[Otten, T.; Müller-Böttcher, H.; Hunkler, D.; Fritz, H.; Prinzbach, H. *Tetrahedron Lett.* **1992**, 33, 4153.]

141. Problem 82 concerned the application of the new MM3 to aldehydes and ketones. In a more recent paper, MM3 calculations have been done on carboxylic acids, esters, and lactones. A reasonable project would be to run MMX calculations (and to compare the results with MM3) on structural parameters (Tables II - VIII), dipole moments (Table XI), and heats of formation (Tables XXII and XXIII) for a series of acids, esters, and cyclic esters.  
[Allinger, N. L.; Zhu, Z. S.; Chen, K. *J. Am. Chem. Soc.* **1992**, 114, 6120.]

142. The bicyclic unsaturated ketone, synthesized by an intramolecular Diels-Alder reaction, serves as a model for Taxol. Enolate formation followed by methylation leads either to alkylation at the bridgehead position or at the alternative  $\alpha$ -position. The authors argue that the bridgehead enolate is formed faster, but that the other enolate is more stable; hence, the proper choice of strong base can control the direction of enolization. This MMX problem consists of two parts: (1) calculate the geometrical parameters of the starting ketone to see if you agree with the authors that the bridgehead proton is removed fastest; (2) calculate the energies of the neutral enols corresponding to the two enolates shown and of the third possible enolate (the geometric isomer of the right-hand structure) to determine which is the most stable. [Shea, K. J.; Sakata, S. T. *Tetrahedron Lett.* **1992**, 33, 4261.]
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143. For each of the dimethyl-substituted cis-decalins shown to the right, there are three distinct stereoisomers (both methyls  $\alpha$ , both  $\beta$ , or one  $\alpha$  and one  $\beta$ ). Each of these, of course, is conformationally mobile. Compute the MMX energies and the distance between methyl groups of both conformations of each the six stereoisomers [for two of the isomers, the inverting conformations are identical]. Compare your results with those in Table I of the reference. Discuss the factor(s) responsible for the position of conformational equilibrium in each compound. [Beeson, C.; Dix, T. A. *J. Org. Chem.* **1992**, 57, 4387.]
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144. Cleavage of a C-C bond in the cubylcarbinyl radical undergoes begins a "cascade" sequence in which a second and then a third bond C-C are broken. Note that the third and fourth structures are allylic radicals (even though only one contributor is indicated). Calculate the energies and geometries of these four radicals and discuss the factors that are involved in each of the three exothermic steps. [Choi, S.-Y.; Eaton, P. E.; Newcomb, M.; Yip, Y. C. *J. Am. Chem. Soc.* **1992**, 114, 6326.]
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