Diazotization[10] of 6-acetamido-7-amino-5,8-quinoxalinedione gave another ring closure compound, 1H-triazo[4,5-g]quinoxaline-4,9-dione **(14)** (Scheme 3). 6-Acetamido-7-amino-5,8-quinoxaline dione was synthesized from 6,7-diamino-5,8-quinoxalinedione.[6] Diaminoquinone was formed by amination of dichloroquinone with ammonia readily.[11] However, **1** reacted with ammonia to yield 6,7-dichloro-5,8-quinoxalinol which was a reducted compound.

The compound 1 showed the different reactivity from 2,3-dichloro-1,4-naphthoquinone and 6,7-dichloro-5,8-quinolinedione in some reactions. It was probably caused by electronic effects. A comparison of electron densities in quinolinedione and quinoxalinedione was showed in Figure 1 and Figure 2. The B ring in quinoxalinedione has more positive charge than quinolinedione even though there was one nitrogen difference between them. The electron distribution in heterocycles appeared to affect the reactivity.

The intercalation of compounds with human DNA was the insertion of a planar part of a molecule between two stacked base pairs.[12] The molecule must have 3-4 planar rings and the intercalation complex was parallel to the axis of the helix for an ideal intercalation.[13] We synthesized angular and planar heterocyclic compounds that had 3-4 rings and drew intercalation complexes of synthetic compounds by molecular modeling. As expected, the intercalation complex of planar heterocyclic compound **(9)** between GC/GC base pairs was parallel to the axis of the helix (Figure 3). However, DNA intercalation complex of angular heterocyclic compound **(6)** between GC/GC base pairs did not show the optimum intercalation (Figure 4). So, the planar heterocyclic compound was expected to have antitumor activity.

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# The Molecular Mechanics Evaluation of the Stability of Bridgehead Olefins Containing Medium Rings

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The stability of bridgehead olefins containing 8 and 10 membered rings has been investigated by the MMX molecular mechanics calculation together with the GMMX conformational searching program. A number of 'hyperstable' bridgehead olefins, which have negative olefin strain values, have been found from the calculated values of strain energy and olefin strain for the series of *in-* and *out-* bicyclo[n.3.3]alk-1-ene and *in-* and *out-*bicyclo[n.4.4]alk-1-ene (n=1 to 8). For the bridgehead olefins with 'out' topology, hyperstable olefins were found in the systems having cyclononene or larger rings. For the bridgehead olefins with 'in' topology, hyperstable olefins were found in the systems having cyclodecene or larger rings.

## Introduction

Double bonds at the bridgehead positions have been regarded as unstable and synthetically less accessible. This idea has been known as Bredt's rule, which states that the elimination to give a doule bond in a bridged bicyclic system always leads away from the bridgehead position.[1] Since the pioneering study by Bredt extensive research efforts have been made toward the synthesis, structural study, reactivity, and mechanistic study of strained bridgehead olefins. A number of review articles are now available.[2-4] Most research efforts on the bridgehad olefins, however, have

been directed toward strained smaller cyclic systems. The chemistry of larger ring bridgehead olefins has not been known much and awaits active research. Thus, the continuous interest of the author in the bridgehead olefins[1] has led to explore the large bridgehead olefins.

It is expected that the unavoidable strain involved in the smaller ring bridgehead olefin could be relieved as the ring size becomes larger. To one extreme, when a bridgehead olefin has infinitely large rings, the bridgehead double bond could be considered as a normal acyclic double bond. In case that ring sizes are neither small nor very large, the situation is somewhat complicated. In certain ranges of ring size, bridgehead double bonds become very stable, even more stable than normal acyclic double bonds. This new class of olefins were named 'hyperstable olefins' as Maier and Schleyer.[2] According to their definition, hyperstable olefins contain less strain than the parent hydrocarbons and have negative olefin strain values. Such olefins should be unreactive. Their reduced reactivity, however, is not caused by well known factors such as the steric hindrance or the p-bond energy. Even with this prediction, only limited number of hyperstable olefins have been reported[3-5] and the chem-

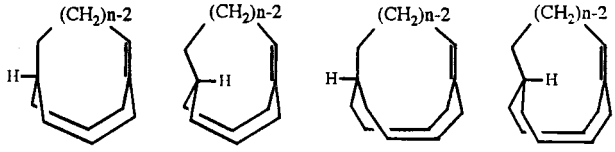


**Chart 1.**

**Table 1.** MMX Calculated Energies (kcal mol) and Derived Values for Bicyclo[n.3.3] Bridgehead Olefins and Corresponding Saturated Hydrocarbons. SE=strain energy, OS=olefin strain.

| Molecule | MMX Energy | $\Delta H_f$ | $\Delta H_r$ | SE | OS |
|---|---|---|---|---|---|
| Bicyclo[3.3.1]non-1(9)-ene (out) | 70.10 | 49.76 | −80.25 | 66.1 | 54.1 |
| Bicyclo[3.3.1]nonane (out,out) | 18.28 | −30.49 | | 12.0 | |
| Bicyclo[3.3.2]dec-1(9)-ene (out) | 52.92 | 26.17 | −51.41 | 48.2 | 25.2 |
| Bicyclo[3.3.2]decane (out,out) | 29.94 | −25.24 | | 23.0 | |
| Bicyclo[3.3.3]undec-1-ene (out) | 43.06 | 9.89 | −34.24 | 37.7 | 8.1 |
| Bicyclo[3.3.3]undec-1-ene (in) | 82.46 | 49.28 | −48.61 | 77.1 | 22.4 |
| Bicyclo[3.3.3]undecane (out,out) | 37.24 | −24.35 | | 29.6 | |
| Bicyclo[3.3.3]undecane (in,out) | 62.28 | 62.28 | | 54.7 | |
| Bicyclo[4.3.3]dodec-1-ene (out) | 41.74 | 2.15 | −21.65 | 35.7 | −4.6 |
| Bicyclo[4.3.3]dodec-1-ene (in) | 60.84 | 21.26 | −33.16 | 54.8 | 7.0 |
| Bicyclo[4.3.3]dodecane (out,out) | 48.51 | −19.50 | | 40.3 | |
| Bicyclo[4.3.3]dodecane (in,out) | 56.10 | −11.90 | | 47.8 | |
| Bicyclo[4.3.3]dodecane (in,in) | 94.09 | 26.09 | | 85.8 | |
| Bicyclo[5.3.3]tridec-1-ene (out) | 38.31 | −7.69 | −10.22 | 31.6 | −16.0 |
| Bicyclo[5.3.3]tridec-1-ene (in) | 46.27 | 0.27 | −22.20 | 39.6 | −4.0 |
| Bicyclo[5.3.3]tridecane (out,out) | 56.52 | −17.91 | | 47.6 | |
| Bicyclo[5.3.3]tridecane (in,out) | 52.49 | −21.93 | | 43.6 | |
| Bicyclo[5.3.3]tridecane (in,in) | 78.65 | 4.23 | | 69.7 | |
| Bicyclo[6.3.3]tetradec-1-ene (out) | 37.11 | −15.31 | −12.40 | 29.8 | −13.7 |
| Bicyclo[6.3.3]tetradec-1-ene (in) | 36.91 | −15.51 | −16.76 | 29.6 | −9.4 |
| Bicyclo[6.3.3]tetradecane (out,out) | 53.12 | −27.71 | | 43.5 | |
| Bicyclo[6.3.3]tetradecane (in,out) | 48.56 | −32.27 | | 39.0 | |
| Bicyclo[6.3.3]tetradecane (in,in) | 63.68 | −17.15 | | 54.1 | |
| Bicyclo[7.3.3]pentadec-1-ene (out) | 36.08 | −22.75 | −14.00 | 28.1 | −12.2 |
| Bicyclo[7.3.3]pentadec-1-ene (in) | 32.00 | −26.83 | −14.21 | 24.0 | −12.0 |
| Bicyclo[7.3.3]pentadecane (out,out) | 50.50 | −36.75 | | 40.3 | |
| Bicyclo[7.3.3]pentadecane (in,out) | 46.21 | −41.04 | | 36.0 | |
| Bicyclo[7.3.3]pentadecane (in,in) | 51.35 | −35.90 | | 41.1 | |
| Bicyclo[8.3.3]hexadec-1-ene (out) | 33.27 | −31.98 | −15.12 | 24.6 | −11.1 |
| Bicyclo[8.3.3]hexadec-1-ene (in) | 30.58 | −34.66 | −14.88 | 21.9 | −11.3 |
| Bicyclo[8.3.3]hexadecane (out,out) | 46.56 | −47.10 | | 35.7 | |
| Bicyclo[8.3.3]hexadecane (in,out) | 44.12 | −49.54 | | 33.2 | |
| Bicyclo[8.3.3]hexadecane (in,in) | 45.61 | −48.05 | | 34.7 | |

**Table 2.** MMX Calculated Energies (kcal mol) and Derived Values for Bicyclo[n.4.4] Bridgehead Olefins and Corresponding Saturated Hydrocarbons. SE=strain energy, OS=olefin strain.

| Molecule | MMX Energy | $\Delta H_f$ | $\Delta H_a$ | SE | OS |
|---|---|---|---|---|---|
| Bicyclo[4.4.1]undec-1(11)-ene (out) | 55.33 | 22.15 | −56.56 | 50.0 | 30.4 |
| Bicyclo[4.4.1]undec-1(11)-ene (in) | 73.56 | 40.38 | −64.39 | 68.2 | 38.2 |
| Bicyclo[4.4.1]undecane (out,out) | 27.19 | −34.41 | | 19.6 | |
| Bicyclo[4.4.1]undecane (in,out) | 37.58 | −24.01 | | 30.0 | |
| Bicyclo[4.4.1]undecane (in,in) | 62.33 | 0.73 | | 54.7 | |
| Bicyclo[4.4.2]dodec-1(11)-ene (out) | 48.87 | 9.28 | −33.22 | 42.8 | 7.0 |
| Bicyclo[4.4.2]dodec-1(11)-ene (in) | 67.97 | 28.38 | −44.79 | 62.0 | 18.7 |
| Bicyclo[4.4.2]dodecane (out,out) | 44.07 | −23.94 | | 35.8 | |
| Bicyclo[4.4.2]dodecane (in,out) | 51.59 | −16.41 | | 43.3 | |
| Bicyclo[4.4.2]dodecane (in,in) | 85.20 | 17.19 | | 76.9 | |
| Bicyclo[4.4.3]tridec-1(11)-ene (out) | 45.61 | −0.39 | −15.73 | 38.9 | −10.5 |
| Bicyclo[4.4.3]tridec-1(11)-ene (in) | 52.73 | 6.72 | −26.20 | 46.0 | 0 |
| Bicyclo[4.4.3]tridecane (out,out) | 58.30 | −16.12 | | 49.4 | |
| Bicyclo[4.4.3]tridecane (in,out) | 54.94 | −19.48 | | 46.0 | |
| Bicyclo[4.4.3]tridecane (in,in) | 83.05 | 8.63 | | 74.1 | |
| Bicyclo[4.4.4]tetradec-1-ene (out) | 49.14 | −3.27 | −9.80 | 41.8 | −17.4 |
| Bicyclo[4.4.4]tetradec-1-ene (in) | 43.25 | −9.17 | −15.17 | 35.9 | −11.0 |
| Bicyclo[4.4.4]tetradecane (out,out) | 68.79 | −12.04 | | 59.2 | |
| Bicyclo[4.4.4]tetradecane (in,out) | 56.49 | −24.34 | | 46.9 | |
| Bicyclo[4.4.4]tetradecane (in,in) | 72.45 | −8.38 | | 62.9 | |
| Bicyclo[5.4.4]pentadec-1-ene (out) | 48.80 | −10.03 | −12.31 | 40.8 | −13.9 |
| Bicyclo[5.4.4]pentadec-1-ene (in) | 39.85 | −18.98 | −13.30 | 31.9 | −13.0 |
| Bicyclo[5.4.4]pentadecane (out,out) | 64.90 | −22.34 | | 54.7 | |
| Bicyclo[5.4.4]pentadecane (in,out) | 55.13 | −32.12 | | 44.9 | |
| Bicyclo[5.4.4]pentadecane (in,in) | 64.12 | −23.13 | | 53.9 | |
| Bicyclo[6.4.4]hexadec-1-ene (out) | 44.27 | −20.97 | −12.33 | 35.6 | −13.9 |
| Bicyclo[6.4.4]hexadec-1-ene (in) | 38.55 | −26.69 | −11.30 | 29.9 | −14.9 |
| Bicyclo[6.4.4]hexadecane (out,out) | 60.36 | −33.30 | | 49.5 | |
| Bicyclo[6.4.4]hexadecane (in,out) | 55.67 | −37.99 | | 44.8 | |
| Bicyclo[6.4.4]hexadecane (in,in) | 54.17 | −39.49 | | 43.3 | |
| Bicyclo[7.4.4]heptadec-1-ene (out) | 42.01 | −29.65 | −14.51 | 32.7 | −11.7 |
| Bicyclo[7.4.4]heptadec-1-ene (in) | 35.22 | −36.44 | −10.59 | 25.9 | −15.6 |
| Bicyclo[7.4.4]heptadecane (out,out) | 55.92 | −44.16 | | 44.4 | |
| Bicyclo[7.4.4]heptadecane (in,out) | 53.05 | −47.03 | | 41.5 | |
| Bicyclo[7.4.4]heptadecane (in,in) | 49.41 | −50.67 | | 37.8 | |
| Bicyclo[8.4.4]octadec-1-ene (out) | 39.80 | −38.28 | −17.42 | 29.8 | −8.8 |
| Bicyclo[8.4.4]octadec-1-ene (in) | 38.32 | −39.75 | −18.18 | 28.3 | −8.0 |
| Bicyclo[8.4.4]octadecane (out,out) | 50.79 | −55.70 | | 38.6 | |
| Bicyclo[8.4.4]octadecane (in,out) | 48.56 | −57.93 | | 36.3 | |
| Bicyclo[8.4.4]octadecane (in,in) | 46.48 | −60.01 | | 34.3 | |

ical consequence of the hyperstability is hardly known. Computational results on the hyperstable olefins by molecular mechanics calculations have been published.[6,10] The results, however, are not systematic and deals with limited number of bridgehead olefins.

One of the best way of computing structures and energies, and other useful properties of molecules, especially for organic molecules, is molecular mechanics calculations (also known as force field calculations).[11] Molecular mechanics calculations have shown reliable output results comparing with X-ray crystallographic data or experimental thermodynamic data. Widely used methods of molecular mechanics are MM2[12] and MM3[13] by Allinger. Many currently used molecular modeling programs are based on the MM2 (or MM3) parameters. Although the conformational study with molecular mechanics is satisfactory, there is an

important problem if we find a real minimum energy conformation (the global minima problem).[14] Trial and error method with applying known conformations could be a solution for smaller molecules that have limited number of significant conformations. However, we should meet with significant difficulty working with large ring systems because of very large number of possible conformations. The stochastic method (or Monte Carlo method) is one way of solving the global minima problem.[15] This method has been applied successfully to examine the conformations of bicyclic ring systems.[9,15]

Major purpose of this paper is finding a relationship between the stability of bridgehead olefins and the ring size. Medium to large rings that contain bridgehead double bond are the primary concern because small ring bridgehead olefins are unstable and well studied. The size of one ring is fixed to cyclooctane (or cyclodecane) in order to remove any ambiguity. The other ring containing bridgehead double bond is fused to 1,5 positions of cyclooctane (or 1,6 positions of cyclodecane) and the size of this ring is varied progressively. Thus bridgehead olefins having bicyclo[n.3.3] and bicyclo[n.4.4] skeletons are selected for the molecular mechanics calculations (chart 1). 'In' and 'out' isomers[16] are treated separately. 'In' isomer, which has a bridgehead proton placed inside the bicyclic system, is very important for larger bicyclic ring systems. For some cases, the 'in' isomer is more stable than the corresponding 'out' isomer provided the bicyclic ring system has enough space inside.[9] Relative stability of 'in' and 'out' isomers will also be discussed in this paper. The MMX force field[17] was used for the energy values. A conformational searching program[18] was also utilized for finding the global minima of larger bicyclic systems.

## Methods

MMX steric energies, heats of formation ($\Delta H_f$), and strain energies (SE) were obtained from the minimum energy conformations by PCMODEL (v. 5.0).[19] MMX force field parameters of hydrocarbons are the same as MM2. Thus, energy values can be directly compared with other literature values derived by MM2 or MM3 force field. Heats of hydrogenation ($\Delta H_h$) were obtained by the difference in the heat of formation between an olefin and its saturated hydrocarbon of 'out' isomer. The olefin strain (OS) was calculated by subtracting the strain energy of the saturated hydrocarbon of 'out' isomer from that of an olefin according to the literature.[9]

The conformational search for finding global minima and some important conformations were performed by GMMX program (v. 1.0).[18,19] Statistical search on both bonds and coordinates routine was used for the search. The output conformations were transferred to PCMODEL and final energies were calculated. Interconversion of 'in' isomers to/from 'out' isomers was observed in some large ring systems during the conformational search. For those systems, the minimum energy conformations were searched by fixing the geometry of bridgehead carbons.

The shape and cartesian coordinates of the resulting conformations are not displayed completely in this paper because they are too voluminous.

## Results and Discussion

Results of molecular mechanics calculations on the bicyclo[n.3.3] bridgehead olefins and bicyclo[n.4.4] bridgehead olefins and the corresponding saturated hydrocarbons (n=1 to 8) are summarize in Table 1 and 2. The MMX energy (also called the steric energy) is the difference in energy between the real molecule and the hypothetical molecule where all the structural values are exactly at their ideal values. The steric energy is the sum of several potential energy terms such as bond stretching, angle bending (together with stretching-bending cross term), nonbonded interaction, and torsional energy terms.[20] Some results could be compared with published values.[10,15] The energy values were in good agreement with each other except for *in*- and *out*-bicyclo[4.4.3]tridec-1(11)-ene. It was found that the struc-

**Table 3.** Proposed Hyperstable Bridgehead Olefins with OS values less than -10 kcal/mol by Molecular Mechanics Calculations and the Number of Minima within 3 kcal/mol by the Conformational Search.

| Molecule | Olefin strain | No. of minima within 3 kcal/mol | No. of probe structures minimized |
|---|---|---|---|
| *out*- bicyclo[4.4.4]tetradec-1-ene | −17.4 | 7 | 4000 |
| *out*- bicyclo[5.3.3]tridec-1-ene | −16.0 | 4 | 8000 |
| *in*- bicyclo[7.4.4]heptadec-1-ene | −15.6 | 11 | 11000 |
| *in*- bicyclo[6.4.4]hexadec-1-ene | −14.9 | 18 | 4000 |
| *out*- bicyclo[5.4.4]pentadec-1-ene | −13.9 | 21 | 4000 |
| *out*- bicyclo[6.4.4]hexadec-1-ene | −13.9 | 6 | 4000 |
| *out*- bicyclo[6.3.3]tetradec-1-ene | −13.7 | 4 | 4000 |
| *in*- bicyclo[5.4.4]pentadec-1-ene | −13.0 | 9 | 8000 |
| *out*- bicyclo[7.3.3]pentadec-1-ene | −12.2 | 8 | 20000 |
| *in*- bicyclo[7.3.3]pentadec-1-ene | −12.0 | 10 | 20000 |
| *out*- bicyclo[7.4.4]heptadec-1-ene | −11.7 | 12 | 20000 |
| *in*- bicyclo[8.3.3]hexadec-1-ene | −11.3 | 16 | 20000 |
| *out*- bicyclo[8.3.3]hexadec-1-ene | −11.1 | 15 | 20000 |
| *in*- bicyclo[4.4.4]tetradec-1-ene | −11.0 | 4 | 4000 |
| *out*- bicyclo[4.4.3]tridec-1(11)-ene | −10.5 | 1 | 1000 |

tures appeared in that paper[10] were those of local energy minima by comparing with the GMMX output structure file.

The conformational search is primarily focused on finding global minima. The default stop setting of GMMX program is satisfactory for that purpose. The number of probe structures manipulated for the default stop setting ranged several hundreds to several thousands depending on the size or the conformational flexibility of each molecule. Reproducible global minima structures were found when checked with extended number (2 to 10 times) of probe structures. More number of probe structures than that of the default stop were necessary for finding higher energy local minima. Table 3 shows the result of conformational search, where the number of minima within 3 kcal/mol and the number of probe structures considered are displayed. The number of probe structures in Table 3 are based on the extended runs. The conformations of global minima usually are not easily identifiable because of the lack of symmetry and uniformity. The cyclooctane ring in many bicyclo[n.3.3] systems has a boat-chair conformation, which is the most stable form of cyclooctane, like the structure in Figure 1b. The cyclododecane ring in bicyclo[n.4.4] systems does not have uniform conformations. Some examples of the global minima searched are displayed in Figure 1.

In the saturated bicyclic hydrocarbons three different topological isomers could exist, which are 'out,out', 'in,out', and 'in,in' isomers. Only one type of these isomers, 'out,out' isomer, is found among small bicyclic systems. This is quite natural because there is not enough cavity inside for the bridgehead hydrogens to exist in small bicyclic systems. As the ring sizes become larger, however, the bridgehead carbons move apart and the 'in' isomer may exist. Interestingly the 'in' isomers are sometimes more stable than the 'out' isomers in some bicyclic systems containing medium and large rings.[10,16] A major reason for this is that the distance between rings are farther apart in the 'in' isomers and the transannular strain, which is very important in medium and large rings, could be reduced. The result of the strain energy (SE) in Table 1 and 2 shows this clearly. For bicyclo[n.3.3]alkanes, 'out,out' isomers are the most stable among the smaller systems (n=1 to 4). On the contrary, *in, out*- bicyclo[5.3.3]tridecane (SE=43.6 kcal/mol) is 4.0 kcal/mol more stable than the corresponding 'out,out' isomer (SE=47.6 kcal/mol). Similar results are found for bicyclo[6.3.3]tetradecane and bicyclo[7.3.3]pentadecane systems. Bicyclo[n.4.4]alkanes show more discernible trend. 'Out,out' isomers are the most stable for bicyclo[4.4.1]undecane and bicyclo[4.4.2]dodecane. 'In,out' isomers are the most stable for bicyclo[4.4.3]tridecane, bicyclo[4.4.4]tetradecane, and bicyclo[5.4.4]pentadecane. 'In,in' isomers are the most stable for bicyclo[6.4.4]hexadecane, bicyclo[7.4.4]heptadecane, and bicyclo[8.4.4]octadecane. Progressive changes of the most stable isomers from 'out,out' to 'in,out' and again to 'in,in' are clearly seen as the ring sizes become larger.

It is worth mention that the interconversion of an 'in' isomer to/from the 'out' isomer could be observed for some large ring systems, not by the inversion of bridgehead carbon but by the dynamic process as shown in Figure 2. Although the existence of such process in real molecules is open to the further research, that would be possible at least for some systems. Such interconversion, known as homeomorphic isomerism,[15] was reported for a sufficiently large bicyclic ring system like bicyclo[6.5.1]tetradecane.[17]

The relative stability between 'in' and 'out' isomers of bridgehead olefins could be found by comparing with their strain energies (Figure 3 and 4). As expected, 'out' isomers are more stable for smaller bridgehead olefins. Differences in the strain energy between 'in' and 'out' isomers become progressively smaller as ring sizes become larger and eventually 'in' isomers are more stable. Among bicyclo[n.3.3] bridgehead olefins, 'in' isomers are more stable for bicyclo[6.3.3]tetradec-1-ene and larger systems (Figure 3). Among bicyclo[n.4.4] bridgehead olefins, 'in' isomers are more stable for bicyclo[4.4.4]tetradec-1-ene and larger systems

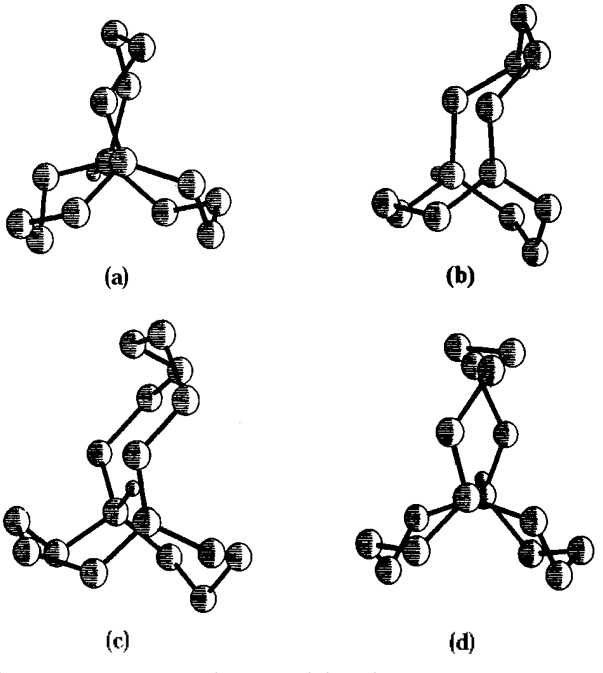


**Figure 1.** Examples of global minima found by GMMX. (a) *out*-bicyclo[4.4.4]tetradec-1-ene. (b) *out*- bicyclo[5.3.3]tridec-1-ene. (c) *in*- bicyclo[7.4.4]heptadec-1-ene. (d) *in*- bicyclo[6.4.4]hexadec-1-ene. Hydrogens except at the bridgehead position are omitted for clarity.

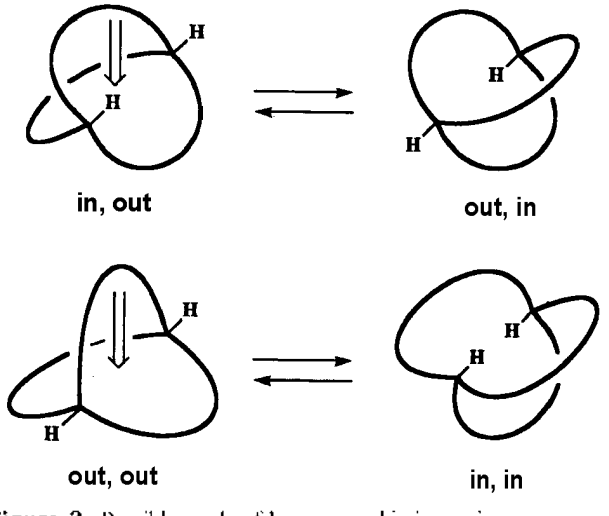


**Figure 2.** Possible mode of homeomorphic isomerism.

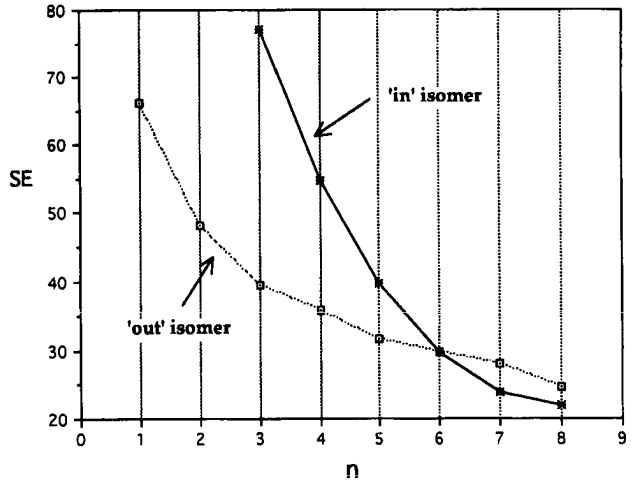


**Figure 3.** Strain energy (SE, in kcal mol) *vs.* chain size (n) for 'in' and 'out' bicyclo[n.3.3] bridgehead olefins.

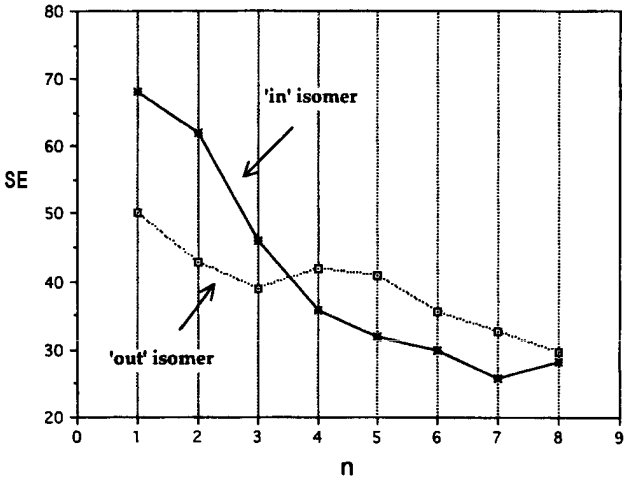


**Figure 4.** Strain energy (SE, in kcal mol) *vs.* chain size (n) for 'in' and 'out' bicyclo[n.4.4] bridgehead olefins.

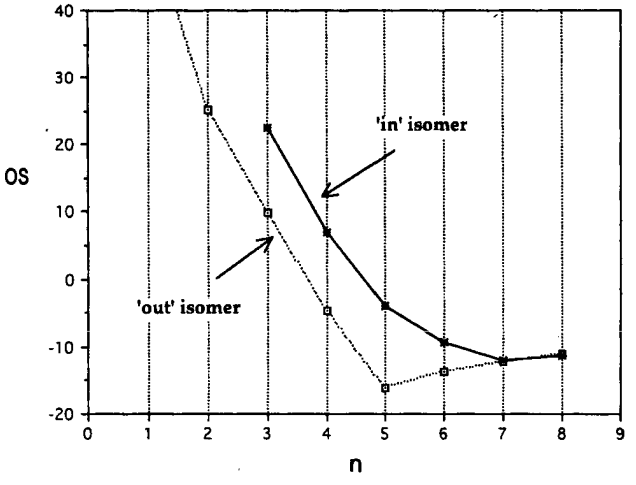


**Figure 5.** Olefin strain (OS, in kcal/mol) *vs.* chain size (n) for 'in' and 'out' bicyclo[n.3.3] bridgehead olefins.

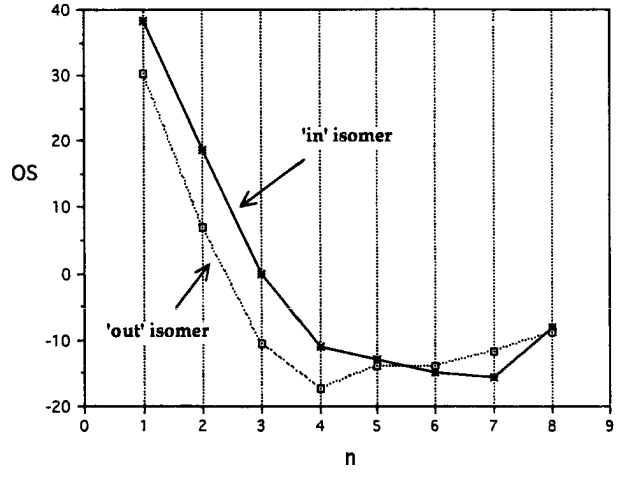


**Figure 6.** Olefin strain (OS, in kcal mol) *vs.* chain size (n) for 'in' and 'out' bicyclo[n.4.4] bridgehead olefins.

(Figure 4).

In order to evaluate the strain involved in the olefins, a new concept other than the strain energy is necessary. Because the strain energy itself is a composite of the strain associated with the double bond and the residual strain associated with the carbon skeleton, we cannot compare the stability of bridgehead double bonds with the strain energy.[5] The 'olefin strain', which is defined as the difference between the strain energy of an olefin and that of its parent hydrocarbon, has been used as an index of olefin stability.[6,10-12] It is generally true that the olefin strain (OS) values of less than 17 kcal/mol are the approximate isolable limit for smaller bridgehead olefins.[6] Bridgehead olefins containing small rings have high OS values and unstable. As ring sizes become larger, OS values decrease and become negative at certain points. Thus the hyperstable olefin emerges.[6,10]

It is now possible to visualize the relationship between the stability and the ring size of bridgehead olefins by the OS values (Figure 5 and 6). Very high strain involved in a small bridgehead olefin decreases rapidly with increasing the ring size at first. After passing the apparent minimum of the olefin strain, the energy increases slowly. It is expected that the OS value becomes close to zero as the chain size goes to very large. The 'in' isomer needs larger ring size for the minimum than the corresponding 'out' isomer. The reason would be that the inside bridgehead hydrogen needs more space between the two bridgehead carbons. The minimum energy bridgehead olefins at each series are as follows (numbers in parentheses are olefin strain values in kcal/mol): *out*- bicyclo[5.3.3]tridec-1-ene (-16.0), *in*- bicyclo[7.3.3]pentadec-1-ene (-12.0), *out*- bicyclo[4.4.4]tetradec-1-ene (-16.4), and *in*- bicyclo[7.4.4]heptadec-1-ene (-15.6).

It was proposed that the stability of a bridgehead olefin is closely related to the ring size of the *trans*- cycloalkene moiety.[13] Although that proposal is qualitatively significant and applicable mainly to small bridgehead olefins, it provides a simple way of comparing the stability with different bridgehead olefins. Minimum energy bridgehead olefins with 'out' topology (*out*- bicyclo[5.3.3]tridec-1-ene and *out*-bicyclo[4.4.4]tetradec-1-ene) both contain cyclodecene rings. Those with 'in' topology contain cyclododecene ring (*in*-bicyclo[7.3.3]pentadec-1-ene) and cyclotrideceне ring (*in*-

**Table 4.** Molecular Mechanics Energy Components of Olefins and the Corresponding Saturated Hydrocarbons.

| Molecule | Olefin strain | Strain energy | Total MMX energy | MMX Energy components | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Stretching | Bending | Stretch-bend | Torsion | van der Waals | Dipole-dipole |
| *out*- bicyclo[4.4.4]tetradec-1-ene | −17.4 | 41.8 | 49.14 | 1.86 | 16.59 | 0.95 | 15.03 | 14.24 | 0.47 |
| *out,out*- bicyclo[4.4.4]tetradecane | | 59.2 | 68.79 | 3.60 | 24.42 | 1.73 | 17.29 | 20.76 | 0 |
| ΔE | | −1.74 | −19.65 | −1.74 | −8.82 | −0.78 | −2.26 | −6.52 | 0.47 |
| *out*- bicyclo[5.3.3]tridec-1-ene | −16.0 | 31.6 | 38.31 | 1.64 | 11.80 | 0.82 | 10.75 | 12.84 | 0.47 |
| *out,out*- bicyclo[5.3.3]tridecane | | 47.6 | 56.52 | 2.27 | 20.78 | 1.26 | 14.68 | 17.52 | 0 |
| ΔE | | −16.0 | −18.20 | −0.63 | −8.98 | −0.44 | −3.93 | −4.68 | 0.47 |
| cyclohexene | −0.2 | 2.4 | 4.57 | 0.21 | 0.36 | 0.05 | 0.16 | 3.30 | 0.48 |
| cyclohexane | | 2.6 | 6.56 | 0.33 | 0.36 | 0.09 | 2.16 | 3.62 | 0 |
| ΔE | | −0.2 | −1.99 | −0.12 | 0 | −0.04 | −2.00 | −0.32 | 0.48 |
| cyclooctene | −3.7 | 10.4 | 13.88 | 0.48 | 2.83 | 0.25 | 4.51 | 5.34 | 0.47 |
| cyclooctane | | 14.1 | 19.42 | 0.57 | 5.44 | 0.37 | 6.45 | 6.58 | 0 |
| ΔE | | −3.7 | −5.54 | −0.09 | −2.61 | −0.12 | −1.94 | −1.24 | 0.47 |

bicyclo[7.4.4]heptadec-1-ene).

The range of ring size for hyperstable bridgehead olefins could be easily identified by Figure 5 and 6. *out*- Bicyclo[4.3.3]dodec-1-ene, *in*- bicyclo[5.3.3]tridec-1-ene, *out*- bicyclo[4.4.3]tridec-1(11)-ene, *in*- bicyclo[4.4.4]tetradec-1-ene, and larger bridgehead olefins at each series have negative olefin strain values. Therefore, 'out' bridgehead olefins containing cyclononene or larger rings would be hyperstable because *out*- bicyclo[4.3.3]dodec-1-ene and *out*- bicyclo[4.4.3]tridec-1(11)-ene both have cyclononene rings. Similarly, 'in' bridgehead olefins containing cyclodecene or larger rings would be hyperstable because *in*- bicyclo[5.3.3]tridec-1-ene and *in*- bicyclo[4.4.4]tetradec-1-ene both have cyclodecene rings.

The cause of hyperstability for the above mentioned bridgehead olefins could be explained by comparing with the energy components of them and related cyclic hydrocarbons in Table 4. Selected for the comparison are the two most hyperstable bridgehead olefins together with cyclooctene and practically stainless cyclohexene. Bending, van der Waals, and torsional components are the major contributor of molecular mechanics energy for *out*- bicyclo[4.4.4]tetradec-1-ene and *out*- bicyclo[5.3.3]tridec-1-ene. The difference of energy (ΔE) between an olefin and the corresponding parent hydrocarbons show the source of hyperstability. The biggest energy change is in the bending component (ΔE values for both bicyclic systems are about − 9 kcal/mol). The van der Waals component (ΔE values of − 6.5 and − 4.7 kcal/mol respectively) and the torsional component (ΔE values of − 2.3 and − 3.9 kcal/mol respectively) also share important contributions. Major reason for the relief of energy from the parent bicyclic alkane to the bridgehead olefin is the change of hybridization at the bridgehead position. Flattening of the bridgehead position by introducing a bridgehead double bond causes significant changes in structure and energy. First, the large-angle strain involved in the medium rings of a bicyclic skeleton could be relieved. This effect is also found in monocyclic medium rings: the minimum energy conformation of cyclooctane has an average C-C-C angle of 116.1° and that of cyclooctene has an average $sp^3$ C-C-C angle of 114.2°. In the same way as monocyclic medium rings, a bridgehead olefin containing medium rings experience relief of large-angle strain. Moreover, a bridgehead double bond could affect all 3 rings in the bridgehead olefin simultaneously, thus the effect is almost tripled. Second, the flat $sp^2$ surface of a double bond is less sterically congested than $sp^3$ centers in medium rings. The transannular strain between hydrogens at the facing carbons is a major strain in medium rings. An $sp^2$ carbon has one less hydrogen than an $sp^3$ carbon and the hydrogen at $sp^2$ carbon places away from the ring junction to become difficult to make transannular interactions. Although the torsional energy values of *out*- bicyclo[4.4.4]tetradec-1-ene and *out*- bicyclo[5.3.3]tridec-1-ene are rather high, the torsional component would be a minor contributor for the hyperstability because the differences of torsional energy (ΔE) do not vary markedly whether an olefin is hyperstable or not.

Among the bridgehead olefins searched, hyperstable olefins in significance having OS values less than − 10 kcal/mol are listed in Table 3. Most of bridgehead olefins in Table 3 have not been synthesized yet. Those systems would be good synthetic targets to investigate the chemistry of hyperstable bridgehead olefins. Only two of them, *in*-bicyclo[5.4.4]pentadec-1-ene[7] and *in*- bicyclo[4.4.4]tetradec-1-ene[8], have been synthesized. Although the chemistry of hyperstable bridgehead olefins have not known very well so far, the results from those compounds synthesized show several interesting features. The unusually sluggish reactivity of *in*-bicyclo[4.4.4]tetradec-1-ene in the catalytic hydrogenation would be due to the hyperstable nature of the compound (OS=-11.0 kcal/mol). In addition, there was no evident reaction when *out*- bicyclo[4.4.4]tetradec-1-ene was treated with dry HCl in variety of solvents, only recovered starting material was obtained.[8] The addition of HCl was observed with *in*- bicyclo[6.3.3]tetradec-1-ene, which is less hyperstable (OS=-9.4 kcal/mol) than *in*- bicyclo[4.4.4]tetradec-1-ene. But the resulting bridgehead chloride spontaneously re-

turned to the starting bridgehead olefin with a loss of HCl.[7] Interestingly, all three bridgehead olefins synthesized produced stable carbocations that contain three-center two-electron C-H-C bonds.[7,8]

Hyperstability would be quite a common feature for large bridgehead olefins. Taxol which has bicyclo[5.3.1]undec-1(10)-ene system was proposed to be slightly hyperstable by MM2 calculations.[24] Bissecododecahedraene was also reported to be hyperstable.[25] Even cycloalkenes of medium to large rings are hyperstable although the extent of hyperstability is not significant (OS values of cycloheptene to cyclotetradecene are usually higher than − 5 kcal/mol with the minimum value of − 7.5kcal/mol in cyclodecene).[10,26]

## Concluding Remark

Although small bridgehead olefins have been studied extensively, the nature and the chemistry of large bridgehead olefins are still hardly known. The hyperstability would be quite a common characteristic for large bridgehead olefins as expected in this paper. Many bridgehead olefins having different ring sizes from those appeared in this paper are expected to show similar stability pattern as shown in Figure 5 and 6. The chemical nature of the hyperstability needs further explorations. Those bridgehead olefins shown in Table 3 would be good targets for synthetic chemists and mechanistic chemists.

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